SMB

IX Congreso de la Rama de Transducción de Señales

1-4 de octubre de 2023 / Acapulco, Guerrero

Comité organizador:
Dr. Luis Enrique Arias Romero (FES Iztacala-UNAM),
Dra. Olga Villamar Cruz (FES Iztacala-UNAM)
Dra. Patricia Juárez Camacho (CICESE)
Dr. Eduardo Castañeda Saucedo (UAGro)

Facultad de Estudios Superiores IZTACALA

CICESE

UAGro

CONACYT

Consejo de Ciencia, Tecnología e Innovación del Estado de Guerrero

informes al correo: smb_ts@ifc.unam.mx

Comité Organizador

Luis Enrique Arias Romero
FES Iztacala, UNAM

Olga Villamar Cruz
FES Iztacala, UNAM

Patricia Juárez Camacho
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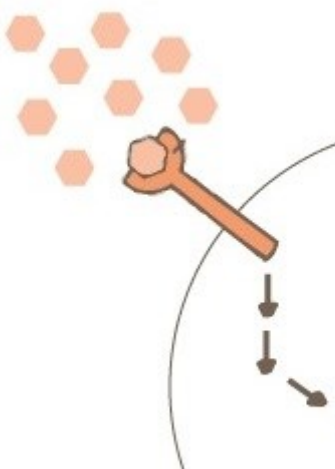
Eduardo Castañeda Saucedo
Universidad Autónoma de Guerrero

Congress Website

https://smb.org.mx/ix-congreso-de-la-rama-de-transduccion-de-senales/



Patrocinadores:

Facultad de Estudios Superiores IZTACALA

50 ANIVERSARIO CICESE

UAGro

CONAHCYT
CONSEJO NACIONAL DE HUMANIDADES CIENCIAS Y TECNOLOGÍAS

SDI SECRETARÍA DE DESARROLLO INSTITUCIONAL

Coordinación de la Investigación Científica

AccesoLab

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Domingo 1º de octubre

Las conferencias se llevarán a cabo en el Salón “Costa Azul”

La sesión de carteles en el Salón “Punta Diamante”

17:30 – 18:00 **Inauguración**

18:00 – 18:30 **Presentación del libro**

Nuevas Tendencias de investigación en la señalización celular en la era post-COVID

Editores: Dr. Jesús Alberto Olivares Reyes
Dra. Angélica Rueda y Sánchez de la Vega

Presenta: Dra. Guadalupe Reyes Cruz. Cinvestav Zacatenco

18:30 – 19:30 **Conferencia Magistral**

G protein-coupled receptors: phosphorylation, signaling, and trafficking

Dr. Jesús Adolfo García Sáinz
Instituto de Fisiología Celular, UNAM

19:30 – 21:00 *Coctail de Bienvenida*
Lugar: Terraza “Alberca Tapanco”

Lunes 2 de octubre, 2023

9:00 – 11:00 **Simposio 1 RECEPTORES**

9:00 – 9:40 *Decoding the Role of Adhesion G Protein-Coupled Receptors Latrophilins in Neurodevelopmental Disorders and Cancer*
Dr. Antony A. Boucard. Cinvestav – Zacatenco

9:40 – 10:20 *Betaglicano y endoglina, más que co-receptores, eminencias grises del señalamiento por TGF-beta*
Dr. Fernando López Casillas. Instituto de Fisiología Celular, UNAM

10:20 – 11:10 **Plenaria 1**

Systemic effects of pathological bone destruction in cancer: role of ryanodine receptor remodelling
Dr. Theresa A. Guise
The University of Texas MD Anderson Cancer Center, Houston, Texas

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11:10 – 11:30 RECESO

11:30 – 13:00 **Sesión 1** **Presentación de trabajos de estudiantes**

11:30 – 11:50 *Dysregulation of p53 regulation on TLR3 in cellular models of Prostate Cancer induced by sodium arsenite*
Nancy Cecilia Pacheco Castillo. Universidad Autónoma de San Luis Potosí / INMEGEN

11:50 – 12:10 *Effect of Corticotropin-Releasing Factor (CRF) on the MAPK pathway activation induced by Insulin-like Growth Factor-1 (IGF-1) in CHO-K1 cells*
Carlos de Jesús Quiróz. Cinvestav IPN Zacatenco

12:10 – 12:30 *Effect of heterosteroids derived from sapogenins in PI3K/AKT/mTOR and apoptosis pathways in breast cancer cells*
Nadia Leney Olazo Márquez. Benemérita Universidad Autónoma de Puebla

12:30 – 12:50 *Regulation of Lysophosphatidic acid receptor 3*
Karina Helivier Solís González. Instituto de Fisiología Celular, UNAM

13:00 – 14:00 **Plenaria 2**

Unravelling the molecular and cellular mechanisms governing breast cancer metastasis
Dr. Jean Francois Cote
Montreal Clinical Research Institute

14:00 – 15:30 COMIDA

15:30 – 17:30 **Simposio 2** **SEGUNDOS MENSAJEROS**

15:30 – 16:10 *A novel mechanism for PKC to regulate agonist-induced calcium oscillations*
Dr. Agustín Guerrero Hernández. Cinvestav IPN – Zacatenco

16:10 – 16:50 *Alteration of signals that regulate appetite and regulatory effect of curcumin in diabetes*
Dra. **Mónica Espinoza Rojo.** Universidad Autónoma de Guerrero

16:50 – 17:30 *Study of the effect of biotic and abiotic stress on signal transduction mechanisms in two plant suspension cells cultures*
Dra. Teresa Hernández Sotomayor. Centro de Investigación Científica de Yucatán

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17:30 – 18:30 **Plenaria 3**

Regulation of stem cell activity, endocrine resistance and metastasis

Dr. Robert Clarke
Manchester Cancer Research. University of Manchester

18:30 – 20:30 **Sesión de Posters 1**

Martes 3 de octubre, 2023

9:00 – 11:00 **Simposio 3 EFECTORES**

9:00 – 9:40 *El fascinante mundo de las WNKs, la hipertensión arterial, la actividad neuronal y la regulación del volumen celular*

Dr. Gerardo Gamba Ayala. Instituto de Investigaciones Biomédicas, UNAM. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

9:40 – 10:20 *RhoGEFs as effectors of chemotactic cell migration*

Dr. José Vázquez Prado. Cinvestav IPN – Zacatenco

10:20 – 11:00 *Receptor de Estrógeno y Nuevos Co-reguladores*

Dr. Alejandro Zentella Dehesa. Instituto de Investigaciones Biomédicas, UNAM / Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

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11:00 – 11:30 RECESO

11:30 – 13:00 **Sesión 2 Presentación de trabajos de estudiantes**

11:30 – 11:50 *Regulation of mitochondrial metabolism by autophagy supports leptin-induced cell migration*
Alin García Miranda. Universidad Autónoma de Guerrero

11:50 – 12:10 *Multi-targeting of signaling networks by miR-204 inhibits angiogenesis and vasculogenic mimicry in CD44+/CD34- breast cancer stem-like cells*
César López Camarillo. Universidad Autónoma de la Ciudad de México

12:10 – 12:30 *Anabolic effect of novel saponin-derived heterosteroids on skeletal muscle*
Amairani Domínguez Bahena. Benemérita Universidad Autónoma de Puebla

12:30 – 12:50 *The Pak1-CaMKII Signaling Pathway: Implications for Breast Cancer Progression and Therapeutic Targeting*

Héctor Iván Saldivar Cerón. Facultad de Estudios Superiores-Iztacala, UNAM

13:00 – 14:00 **Plenaria 4**

Unique Metabolic Effects of KRAS G12V in Colorectal Cancer Cells
Dr. Jonathan Chernoff
Fox Chase Cancer Center

14:00 – 15:30 COMIDA

15:30 – 17:30 **Simposio 4 SEÑALIZACIÓN A NÚCLEO**

15:30 – 16:10 *BRCA1 mutations in cancer: implications for DNA repair and therapeutics*

Dr. Neil Johnson. Fox Chase Cancer Center

16:10 – 16:50 *Hypoxia Inducible Factors are essential promoters of malignant phenotype and resistance to treatment in colon cancer*

Dra. **Martha Robles Flores.** Facultad de Medicina, UNAM

16:50 – 17:30 *Identification of Key Genes and Pathways Involved in Tissue Regeneration through Comparative Transcriptomics*

Dr. Ernesto Soto Reyes. Universidad Autónoma Metropolitana-Cuajimalpa

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17:30 – 18:30 **Plenaria 5**

New insights into prostate cancer
Dr. Daniel Metzger
Institut de Génétique et de Biologie Moléculaire et Cellulaire. CNRS

18:30 – 20:30 **Sesión de Posters 2**

Miércoles 4 de octubre, 2023

9:00 – 11:00 **Simposio 5** **SEÑALIZACION EN SISTEMA INMUNE**

9:00 – 9:40 *Molecular mechanisms involved in the TGF-b response in T lymphocytes*

Dra. Paula Licona Limón. Instituto de Fisiología Celular, UNAM

9:40 – 10:20 *Signal transduction by antibody Fc receptors in human neutrophils*

Dr. Carlos Rosales Ledezma. Instituto de Investigaciones Biomédicas, UNAM

10:20 – 11:00 *Human T Cell Activation: New Kids on the...Pathway*

Dr. Genaro Patiño López. Hospital Infantil de México. Federico Gómez

11:00 – 11:30 RECESO

11:30 – 13:00 **Sesión 3** **Presentación de trabajos de estudiantes**

11:30 – 11:50 *Metabolic Syndrome impairs Akt activation by Urocortin 2 in Adipocytes*
Daphne Esperanza Cruz Villarreal. Cinvestav IPN Zacatenco

11:50 – 12:10 ***C**racking the TGF-beta Code: Exploring the Significance of Smad7 and T Cell Subsets in the Complex Tumor Microenvironment*
Eugenio Contreras Castillo. Instituto de Fisiología Celular, UNAM

12:10 – 12:30 *BFNB enhance hair growth in C57BL/6 mice through the induction of EGF and FGF7 factors and the PI3K-AKT-β-catenin pathway*
Salvador Pérez Mora. Escuela Nacional de Medicina y Homeopatía, IPN

12:30 – 12:50 *Towards an integrative model of CD4 T cell activation, regulation and function*
Leonor Huerta Hernández. Instituto de Investigaciones Biomédicas, UNAM

13:00 – 14:00 **Plenaria 6**

The Class I Myosins represent highly versatile proteins mediating different functions in the cells of the immune system

Dr. Leopoldo Santos Argumedo
Cinvestav IPN Zacatenco

14:00 – 14:30 **Clausura**

Presentación de posters

Números nones: Lunes 2 de octubre

Números pares: Martes 3 de octubre

EFECTORES: cinasas, protesínas adaptadoras, adenilato ciclasas, fosfolipasas …….

1.	**Protein kinase C alpha (PKCα) fragmentation. Possible role of metalloproteinases.** Alcántara-Hernández Rocío, Hernández-Espinosa David Alejandro, Hernández-Méndez Aurelio and García-Sáinz, J. Adolfo. Instituto de Fisiología Celular, UNAM
2.	**Thrombin-induced NFκB activation in retinal pigmented epithelium cells (RPE).** *Daniela* Alejandra Alvarado Fernández, Irene Lee Rivera, Edith Catalina López Hernández, Ana María López Colomé. Instituto de Fisiología Celular, UNAM
3.	**ROS-dependent Inhibition of PMCA Activity Drives Allyl Isothiocianate-Induced Ca^{2+} Signals and Nitric Oxide Release in the Human Cerebrovascular Endothelial Cell Line, hCMEC/D3.** Roberto Berra Romani, Valentina Brunetti, Giorgia Pellavio, Teresa Soda, Umberto Laforenza, Giorgia Scarpellino, and Francesco Moccia**.** Benemérita Universidad Autónoma de Puebla
4.	**Protein kinase C regulates fibrosis induced by Transforming Growth Factor β3 (TFGβ3) in human hypertrophic myofibroblast.** Alejandro Cabrera-Wrooman, Nadia Mireya Murillo-Melo, Renata Ghenno-Manrique, Rene Abarca-Buis, Francisco Ferreira. Laboratorio de Tejido Conjuntivo. Instituto Nacional de Rehabilitación
5.	**Chlorogenic acid modulates dopamine levels in a model of strial neurodegeneration.** Cantero-Téllez, A., Rodríguez-Córdova, V.M. and Hernández-Echeagaray, E. FES Iztacala. UNAM
6.	**Testosterone enhances, via a genomic pathway, airway smooth muscle relaxation induced by ATP and UTP.** Abril Carbajal García, Jorge Eduardo Reyes García, María Fernanda Casas Hernández, Luis Manuel Montaño Ramírez. Facultad de Medicina. UNAM
7.	**Analysis of LIMK1 and COFILIN phosphorylation in the hippocampus of the C58/J mouse model of autism during estrous cycle.** Miriam Yesenia Cortés Sánchez, Isabel Cristina Barón Mendoza, Montserrat Mejía Hernández, Mónica Martínez Marcial and Aliesha Araceli González Arenas. Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
8.	**Role of PKCs in the negative regulation of the insulin pathway by resveratrol**. Karla Daniela Hernandez-Gonzalez, Judith Hernandez-Aranda & Jesús Alberto Olivares-Reyes. Department of Biochemistry, Center for Research and Advanced Studies of the National Polytechnic Institute, Cinvestav. IPN
9.	**The RTKs and ERK1 are involved in the KCl-induced contraction in guinea pig airway smooth muscle.** Eva Herrera Alcibar, Betina Sommer Cervantes, Lizet Ocampo Monzalvo, Vanesa Alarcón Barcena, Enrique Castillo Henkel, Ruth López Mayorga and Verónica Carbajal Salinas. Instituto Nacional de Enfermedades Respiratorias “Ismael Cosío Villegas”.
10.	**Activación de la calpaína-10 en respuesta a pulsos de glucosa.** Adriana Juárez Nájera, Juan Pablo Pánico Molina, Monserrat Sordo Cedeño, Andrea Díaz Villaseñor, Marcia Hiriart Urdanivia, Patricia Ostrosky Wegman, Ana María Salazar Martínez. Instituto de Investigaciones Biomédicas, UNAM

11.	**c-kit influences CXCR4, α4β1 integrins expression in leukaemic lymphoblasts.** Ruth Angélica Lezama Palacios, Zoraida Silva Sánchez, Jorge Rigoberto Bautista Secun. Escuela Nacional de Ciencias Biológicas, Departamento de Morfología. Instituto Politécnico Nacional
12.	**Possible Involvement of Pak1 and CaMKII in Insulin Secretion by Pancreatic Beta Cells.** Nely Gisela López Desiderio, Olga Villamar Cruz, Luis Enrique Arias Romero, Héctor Iván Saldívar Cerón, Jazmín García-Machorro, Estefania Isay Martínez Acosta. Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México
13.	**Thrombin-induced activation of focal adhesion proteins in the Retinal Pigment Epithelium (RPE).** Katya Manzanita Quintero, Irene Lee Rivera, Edith Catalina López Hernández, Ana María López Colomé. Instituto de Fisiología Celular, UNAM
14.	**Thrombin-induced cytokine secretion on retinal Müller glia.** Naomi Vargas Martínez, Irene Lee Rivera, Gabriela Rodríguez Rodríguez, Ángel Alfonso Zaraín Herzberg, Ana María López Colomé. Instituto de Fisiología Celular, UNAM
15.	**Identificación *in silico* e *in vitro* de proteínas tipo caspasa 3 en *G. intestinalis.*** María Cristina Villa Medina, Héctor Samuel López Moreno, Ulises Vega Castillo, Claudia del Rosario León Sicairos. Facultad de Ciencias Químico-Biológicas. Universidad Autónoma de Sinaloa

ESTRUCTURA Y FUNCIÓN DE RECEPTORES

16.	**EGF-receptor phosphorylation and downstream signaling are activated by genistein during subacute liver damage.** Erick Ayala-Calvillo, Elizabeth Álvarez-Ayala and Lourdes Rodríguez-Fragoso. Facultad de Farmacia, Universidad Autónoma del Estado de Morelos
17.	**Progesterone receptor has a role in choriocarcinoma cells and placental steroidogenesis.** Paola Díaz-Carrillo, Sofía Olvera-Sánchez y Federico Martínez. Facultad de Medicina, UNAM
18.	**TRPV4 activation during guinea pig airway smooth muscle contraction promotes Ca2+ and Na+ influx.** Jorge Eduardo Reyes García, Abril Carbajal García, María Fernanda Casas Hernández, David Arredondo Zamarripa, Luis M. Montaño Ramírez. Departamento de Farmacología, Facultad de Medicina, UNAM
19.	**Latrophilin-1 is involved in sperm-ovum interaction in mice.** Ana Lilia Roa-Espitia**,** Lesli DennisTafoya Domínguez, Irma Jiménez Morales y Enrique Othón Hernández-González. Departamento de Biología Celular, CINVESTAV-IPN
20.	**Relationship of oxidative damage with the expression of the insulin receptor, during brain and peripheral insulin resistance in a model of obesity.** Elena Salazar-Hernández, Óscar Ezequiel Bahena-Cuevas, Gema Damián-Sanchez, Linda Esther Morales-García, Manuel Sánchez-Alavez, Yaccil Adilene Flores-Cortez, Estefanía Salinas-Bautista, Lucio Villalva-Cruz, Martha Isela Barragán-Bonilla, Juan Miguel Mendoza-Bello, Mónica Espinoza-Rojo. Facultad de Ciencias Químico Biológicas. Universidad Autónoma de Guerrero

PROTEINAS G

21.	**Genetic screen for the identification of multicopy suppressor genes in the *Saccharomyces cerevisiae npa3G70A* mutant strain.** Andrea Yunuen Delgado-Toledo, Alejandro De Las Peñas, Lina Riego-Ruiz, Mónica R. Calera, Roberto Sánchez-Olea. Instituto de Física, Universidad Autónoma de San Luis Potosí
22.	**The GPN-loop GTPase Gpn3 is mobilized between the cytoplasm and cell nucleus.** Sonia Griselda Peña-Gómez, Dulce M. Pérez-Rodríguez, Cristhian Raúl Vega-Palomo, Yolanda

	Rebolloso-Gómez, Roberto Sánchez-Olea, Mónica R. Calera. Instituto de Física, Universidad Autónoma de San Luis Potosí.
23.	**Glycine effects on GPR3, GPR6 and GPR12 expression in Wistar rat neonatal neurons primary culture.** Moisés Sánchez Coria, Karla Aidee Aguayo-Cerón, Rocío Alejandra Gutiérrez Rojas, Cruz Vargas-De-León, Rodrigo Romero-Nava. Escuela Nacional de Ciencias Biológicas. Instituto Politécnico Nacional
24.	**RAC1 stabilizes membrane domains in the acrosomal region throughout the actin cytoskeleton.** Ana L. Roa-Espitia AL, Fabrizio E. Moreno Bravo, Dennis Tafoya Domínguez Reyna C. Fierros Pastrana y Enrique O. Hernández-González. Departamento de Biología Celular, CINVESTAV. IPN
25.	***In silico* molecular docking analysis of small chemical compounds on the GTP-binding site of the GPN-loop GTPase Npa3.** Cristhian Raúl Vega-Palomo, Julio A. Muñiz-Luna, Mónica R. Calera, Roberto Sánchez-Olea. Instituto de Física, Universidad Autónoma de San Luis Potosí

TRANSDUCCIÓN DE SEÑALES Y BIOLOGÍA DE SISTEMAS

26.	**Influence of Branched-Chain Amino Acids on the Mechanistic Target of Rapamycin complex 1 (mTORC1) through the AMPK and SestrinA Pathways in *Centropomus viridis* Brain Cells.** Maria Jose Soto Lopez, Anaguiven Avalos Soriano, Alejandra García Gasca, Crisantema Hernandez. Laboratory of Molecular and Cellular Biology. Research Center for Food and Development. Mazatlán, Sinaloa
27.	**Analysis of the global expression of genes related to appetite regulation in the hypothalamus of obese mice treated with resveratrol.** Brenda de la Cruz-Concepción, Gema Damian-Sánchez, Adilene Flores-Cortez, Elena Salazar-Hernández, Lucio Villalba-Cruz, Gize Jaqueline Barbosa-Solis, Juan Miguel Mendoza-Bello, Freddy Omar Beltrán-Anaya, Mónica Ramírez-Ruano, Monica Espinoza-Rojo. Laboratorio de Biología Molecular y Genómica, Facultad de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero
28.	**Comparative transcriptome analysis reveals key epigenetic targets in SARS-CoV-2 infection.** Aylin Del Moral-Morales, Marisol Salgado-Albarrán, Erick I Navarro-Delgado, Nicolas Alcaraz, Jan Baumbach, Rodrigo González-Barrios, Ernesto Soto-Reyes. Departamento de Ciencias Naturales, Universidad Autónoma Metropolitana-Cuajimalpa
29.	**Curcumin improves redox status and insulin sensitivity in the periphery and decreases leptin receptor expression in nucleus arcuate in obese diabetic mice.** Yaccil Adilene Flores-Cortez, Estefania Salinas-Bautista, Ruth Yareli Calvario, Elena Salazar-Hernández, Lucio Villalba-Cruz, Gize Jacquelin Barbosa-Solis, Juan Miguel Mendoza-Bello, Karen Cortes-Sarabia, Brenda De la Cruz-Concepción, Mónica Ramirez-Ruano, Mónica Lamas-Gregori, Mónica Espinoza Rojo. Facultad de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero
30.	**Role of the Renin Angiotensin System in obesity as a predictor of mortality in patients with SARS-CoV-2 pneumonia.** Lia Leslie Granciano Cano, Nathaly Solanilla Pabón, María de los Ángeles Granados-Silvestre, Katia Avilés-Pinto, María Alicia Mejía-Blanquel, María Guadalupe Ortiz-López, Goreti Nieto Velázquez, Katy Sánchez-Pozos. División de Investigación, Hospital Juárez de México
31.	**MAPK signaling pathway is involved in the steroidogenesis regulation in choriocarcinoma cells.** Sofía Olvera-Sánchez and Federico Martínez. Departamento de Bioquímica, Facultad de Medicina, Universidad Nacional Autónoma de México
32.	**Expression of connexin 43 in neurons of the superior cervical ganglia.** Elia Martha Pérez Armendáriz, Beatriz Hernández, Lourdes Cruz Miguel, E. Verazas, Sofia Téllez Alonso, Oscar

	Lara Zacarías. Laboratorio de Sinapsis Eléctricas, Unidad de Investigación en Medicina Experimental, Torre de Investigación, Facultad de Medicina, UNAM
33.	**Repurposing of approved drugs for the inhibition of PTP1B in type 2 diabetes therapy.** Ximena V. Sánchez-Nava, Olga Villamar-Cruz, Karen Pelcastre-Guzmán, Héctor I. Saldivar-Cerón, Marco A. Loza-Mejía, and Luis E. Arias-Romero. Unidad de Investigación en Biomedicina (UBIMED). Facultad de Estudios Superiores-Iztacala, UNAM
34.	**Evaluation of the modulatory effect produced by the G-1-F-2 mixture on cortico-striatal synapses.** Daniel Alonso Villarreal y Elizabeth Hernández Echeagaray. Unidad de Investigación en Biomedicina, DIP, FES-I, UNAM

TRANSDUCCIÓN DE SEÑALES Y CÁNCER

35.	**Differential effect of NO on metastatic potential in triple negative breast cancer cells, MDA-MB-231.** Osiris Evelyn A. Carrillo, Julieta López-Cuevas, Eduardo Monjaraz-Guzmán Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla
36.	**Interaction between LPA1-PKCα-PR in Glioblastoma.** Arcos-Montoya Denisse, González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, UNAM
37.	**The role of the estrogen receptor β on the metastatic potential in the MDA-MB-231 cell line.** Rubén Avalos-López, Julieta López-Cuevas, Eduardo Monjaraz-Guzmán. Instituto de Fisiología, BUAP
38.	**Purinergic system on the proliferative capacity of PC-3 prostate cancer cells.** Susana G. Barrientos-Robledo, Rubén Avalos-López, Osiris E. Aparicio-Carrillo, Julieta López-Cuevas, Eduardo Monjaraz-Guzmán. Institute of Physiology, BUAP
39.	**Lysophosphatidic acid promotes stemness of glioma cells via SOX2 and OCT4**. Claudia Bello-Alvarez, Angel Rubio-Galicia, Marisol De la Fuente-Granada, Marco A. Velasco-Velázquez and Aliesha González-Arenas. Instituto de Investigaciones Biomédicas. UNAM
40.	**PI3Kβ and effectors form an agonist-dependent signaling complex integrated by the RacGEF P-Rex1**. Yarely Mabell Beltrán-Navarro, Rodolfo Daniel Cervantes-Villagrana, Dante Gustavo Juan-Guadarrama, Yazmin Torres-Santos#, Guadalupe Reyes-Cruz# and José Vázquez-Prado. Departments of Pharmacology and Cell Biology, Cinvestav-IPN
41.	**The canonical Wnt pathway is involved in chemoresistance and cell cycle arrest in spheroids from colon cancer cell lines.** Paola Briseño-Díaz, Angela Patricia Moreno-Londoño , María Cristina Castañeda-Patlán , Miguel Angel Sarabia-Sánchez , Marina Macías-Silva and Martha Robles-Flores. Facultad de Medicina, Universidad Nacional Autónoma de México
42.	**Increased HIF-α levels in a cell line derived from a FeNTA-induced RCC tumor resemble that observed in the experimental and human neoplasms.** Jorge Luis Copado-Romero, José Dolores Solano-Becerra, Patricia Curiel-Muñiz María Elena Ibarra-Rubio. Faculty of Chemistry, UNAM
43.	**Effect of Il-2 in the expression and activity of STAT1 in cervical cancer cell lines.** Erika Anayatzin Covarrubias Negrete, Isabel Soto Cruz, Arturo Valle Mendiola, Fernando Abdias López Alva. Facultad de Estudios Superiores Zaragoza, UNAM
44.	**Effect of interleukin 1β (IL-1β) on proliferative capacity and temozolomide resistance in human glioblastoma cells, U-87 MG.** Selene Cruz Cantero- María Julieta López Cuevas- María de los Ángeles Manzano Hernández- Eduardo Monjaraz Guzmán. Benemérita Universidad Autónoma de Puebla
45.	**Effect of resistin on cell migration and activation of p38MAPK and ERK1/2 in MCF7 and MDA-MB-231 breast cancer cells.** Reyna Lizeth Cuachirria Espinoza, Monserrat Olea

	Flores, Rafael Hernández Barragán, César Sotelo Leyva, Napoleón Navarro Tito. Facultad de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero
46.	**Effect of Pentoxifylline and Norcantharidine on endoplasmic reticulum stress in 3D cultures of B16F1 cells.** María Lilia Domínguez-López, José Luis González-Quiroz, Juan Moisés Ocampo-Godínez, Victoria Noemi Hernández-González, Ruth Angélica Lezama, Armando Vega-López, Elba Reyes-Maldonado, José Pablo Romero-López. Escuela nacional de Ciencias Biológicas. IPN
47.	**Encapsulation and characterization of a TGF-β inhibitor as a therapy for triple-negative breast cancer.** Claudia Alcira Espinoza-González, Pierrick GJ Fournier, Rafael Vazquez-Duhalt, MV Villagrana-Escareno, LR Arriaga3, Patricia Juárez. Centro de Investigación Científica y de Educación Superior de Ensenada – CICESE. Centro de Nanociencias y Nanotecnologia CNyN–UNAM
48.	**Apoptosis induction via ROS by tetrahydroxyquinone on human colorectal adenocarcinoma cell line HT-29.** Ximena Alejandra Flores Arévalo, Mario Eduardo Cano González, Peter Knauth & Zaira del Rocío López López. Centro Universitario de la Ciénega, Universidad de Guadalajara
49.	**Role of STAT5 in energy mitochondrial metabolism genes regulation in cervical cancer cells stimulated with Interleukin 2.** Rubén-Alejandro Fuentes-Pascacio, Arturo Valle-Mendiola, Adriana Gutiérrez-Hoya, Benny Weiss-Steider, Isabel Soto-Cruz. FES Zaragoza, Universidad Nacional Autónoma de México
50.	**DNA Methylation-associated expression of the Ca^{2+} signaling genes in breast cancer cell lines during the epithelial-to-mesenchymal transition.** Pablo Sinuhé Gómez González, Ángel Salmerón Hernández, Gabriela Rodríguez Rodríguez, Ángel Zarain Herzberg Departamento de Bioquímica. Facultad de Medicina UNAM
51.	**Regulation of proliferation and transcriptome of prostate cancer cells by Menadione and Cabazitaxel.** Ana Laura Gómez-Rosas, Sandra Romero-Córdoba, Mariana Segovia-Mendoza, Nancy Noyola-Martínez, Nayeli Torres-Ramírez, Mitzi García-Olivares, Diana C. Castro-Rodríguez, Ali Halhali, David Barrera. Departamento de Biología de la Reproducción, INCMNSZ
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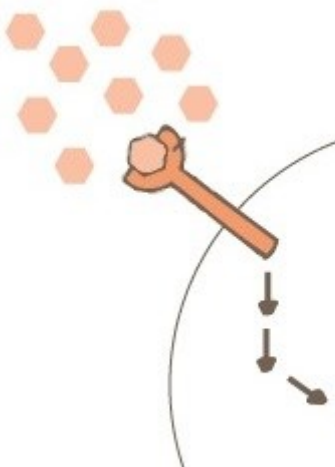
G protein-coupled receptors: phosphorylation, signaling, and trafficking. J. Adolfo García-Sáinz. Instituto de Fisiología Celular, Universidad Nacional Autónoma de México. Ciudad Universitaria, Ciudad de México 04510. México. Email: agarcia@ifc.unam.mx

G protein-coupled receptors (GPCRs) are the most abundant family of membrane proteins, consisting of approximately 800 members in Homo sapiens, and have been divided into different families based on genomic and structural information. Most of these receptors belong to the Rhodopsin family. These receptors are characterized by seven transmembrane domains, joined by intracellular and extracellular loops; their amino terminus is located extracellularly, whereas the carboxyl tail is intracellular.
Our laboratory is mainly interested in α_1-adrenergic receptors and some receptors for bioactive lipids. Phosphorylation seems to be a critical event in signaling and vesicular trafficking. Current ideas indicate that the initial signaling is mediated through interaction with G proteins that modulate effector proteins that regulate the concentration of second messengers. Receptor phosphorylation by different protein kinases triggers interaction with β-arrestins that block interaction with G proteins (inducing desensitization) and facilitates receptor association to clathrin and receptor internalization. Interestingly, a signaling switch occurs during these events, and a second wave of signaling occurs in the endosomes mediated through β-arrestins and other proteins.
Evidence also indicates that receptors can be phosphorylated at different sites and that such sites determine the internalization process and the endosomal signaling, which results in different actions in distinct tissues and through the action of various types of agonists (full, partial, inverse, and biased, among others). This process is frequently referred to as the "phosphorylation bar-code hypothesis".
We have studied these aspects for some receptors, and our data indicate that receptors are phosphorylated in distinct, generally non-conserved (even among subtypes) residues and that receptors migrate through distinct endosomal compartments, guided by the interaction with different Rab GTPases.
We have also used substitution of amino acids found phosphorylated in mass spectrometry analysis for non-phosphorylatable residues, which is helping us to define the roles of domains (intracellular loops, carboxyl tail) or clusters of sites in these domains in the signaling events, desensitization, internalization, and recycling to the plasma membrane.

Research in our laboratory is partially supported by Grants for CONAHCYT (Fronteras 6676) and DGAPA-UNAM (IN201221).



Decoding the Role of Adhesion G Protein-Coupled Receptors Latrophilins in Neurodevelopmental Disorders and Cancer

Antony A. Boucard

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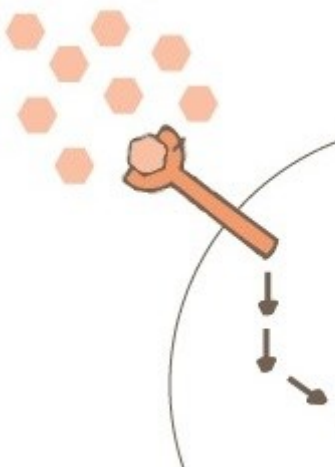
Adhesion molecules/G protein-coupled receptors Latrophilins have emerged as critical determinants of synapse formation in the brain. These cell adhesion molecules conveniently located at the interface between the cell membrane and the extracellular milieu define cell movements or anchoring by establishing heterophilic or homophilic contacts with molecular components of surrounding cells or matrix, thus allowing context recognition. Thus, the proper dissection of the molecular adhesion function of Latrophilins is warranted to further our understanding of tissue formation. Here, we will discuss hierarchical adhesion functions exerted by the three mammalian isoforms of Latrophilins by gaining insights from ligand recognition/selectivity, alternative splicing, and signaling specificity. Association with neurodevelopmental disorder and cancer will come from insights gained by our evaluation of disease-related genetic variants affecting Latrophilin-3 isoform in which we identified specific defects in signaling cascades underlying actin cytoskeleton remodeling events. In addition to presenting recent advances, we will highlight the many challenges that lie ahead to uncover the role of these prototypical adhesion G protein-coupled receptors and their pharmacological targeting for alleviating symptoms underlying neurological disorders and cancer.

Área: Estructura y función de receptores



Betaglicano y endoglina, más que co-receptores, eminencias grises del señalamiento por TGF-beta.

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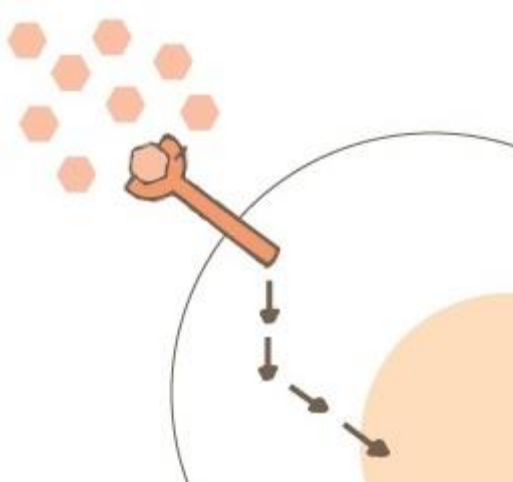
Se suele llamar "eminencia gris" a aquella persona que ejerce una extrema injerencia sobre el aparato y las decisiones de un gobierno. Influencia que ejercen desde las sombras, tras bastidores. Cuando se analizan las propiedades y funciones del betaglicano y la endoglina, percibimos ese discreto ejercicio del poder en las acciones de factores de la familia del TGF-beta. En este trabajo discutiremos casos específicos de como el betaglicano influye en “decisiones” del TGF-beta durante el desarrollo embrionario del pez cebra y de otros factores ajenos a esta familia durante la oncogénesis. También se discutirá la versatilidad estructural del betaglicano, la cual le permite actuar en diversos escenarios celulares, muchas veces con efectos contradictorios, dando sustento a fenotipos pleiotrópicos aun no explorados a cabalidad.

Mi laboratorio recibe apoyo de PAPIIT-DGAPA-UNAM (proyecto IN204620)



Systemic effects of pathological bone destruction in cancer: role of ryanodine receptor remodelling

Theresa A. Guise
Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine.
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Los receptores de rianodina (RyR) se encuentran en la membrana del retículo sarcoplásmico/endoplásmico y son responsables de la liberación de $Ca^{2}+$ de las reservas intracelulares durante el acoplamiento de excitación-contracción tanto en el músculo cardíaco como en el esquelético.
Hay tres isoformas de RyR en mamíferos conocidas: RyR1, RyR2 y RyR3. RyR1 se detectó por primera vez en el músculo esquelético. RyR2 se encontró por primera vez en los músculos cardíacos y RyR3, anteriormente denominada isoforma cerebral, se encontró en el cerebro. RyR1 es la isoforma examinada más a fondo debido a sus altos niveles de expresión y a su facilidad de purificación a partir del músculo esquelético. En los vertebrados no mamíferos, RyRα y RyRβ son altamente homólogos a las tres isoformas de los mamíferos. Se han identificado RyR en *Drosophila melanogaster*, *Caenorhabditis elegans* y *Homarus americanus*.
Las mutaciones tanto en RyR1 como en RyR2 están asociadas con una serie de enfermedades humanas. Las mutaciones en el gen RYR1 están presentes en varias enfermedades musculares, debilitando al músculo y algunas de ellas pueden ser potencialmente mortales, incluidas la hipertermia maligna, la rabdomiólisis por esfuerzo inducida por calor/ejercicio, la enfermedad del núcleo central, la enfermedad multiminicore y las parálisis periódicas atípicas. Los RyR2 están asociados con taquicardia ventricular polimórfica catecolaminérgica y displasia arritmogénica del ventrículo derecho tipo 2. Hoy en día se han identificado alrededor de 300 mutaciones y se han relacionado con enfermedades asociadas con RyR.
En esta charla discutiremos sobre el papel de la remodelación del receptor de rianodina, y sus efectos sistémicos en la destrucción ósea patológica en el cáncer.

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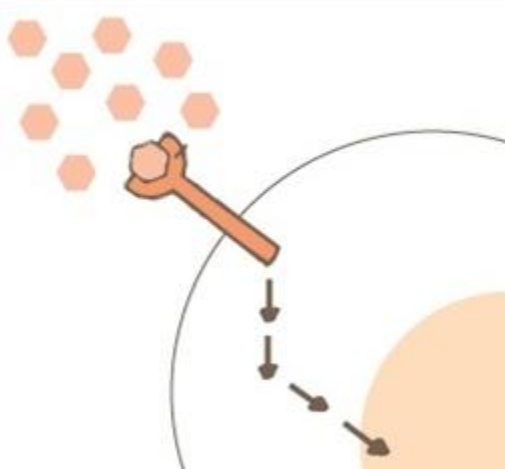

Unravelling the molecular and cellular mechanisms governing breast cancer metastasis

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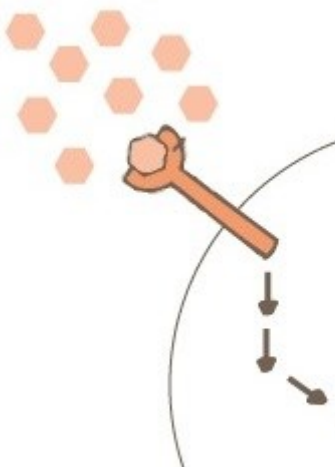
Progression of breast cancer to a metastatic disease correlates with poor patient outcome. We are interested in understanding the molecular and cellular mechanisms that promote cell migration, invasion, and homing of disseminated cancer cells into secondary organs. In the first part of the presentation, we will overview some of the functions of the receptor tyrosine kinase AXL in HER2+ breast cancer metastasis. In the second part, we will focus on the outcome of disseminated cancer cells in secondary organs and how they can adopt dormant characteristics or instead progress to form overt metastases. Halting breast cancer metastatic relapses following primary tumor removal and the clinical dormant phase, remains challenging, due to a lack of specific vulnerabilities to target during dormancy. To address this, we conducted genome-wide CRISPR screens on two breast cancer cell lines with distinct dormancy properties: 4T1 (short-term dormancy) and 4T07 (prolonged dormancy). We discovered that loss of class-III PI3K, Pik3c3, revealed a unique vulnerability in 4T07 cells. Surprisingly, dormancy-prone 4T07 cells exhibited higher mTORC1 activity than 4T1 cells, due to lysosome-dependent signaling occurring at the cell periphery. Pharmacological inhibition of Pik3c3 counteracted this phenotype in 4T07 cells, and selectively reduced metastasis burden only in the 4T07 dormancy prone model. This mechanism was also detected in xenografts from human breast cancer patients, supporting that it may be relevant in humans. Our findings suggest dormant cancer cell-initiated metastasis may be prevented in patients carrying tumor cells that display PIK3C3-peripheral lysosomal signaling to mTORC1. Collectively, these studies reveal novel therapeutic intervention options to limit breast cancer metastases.



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A novel mechanism for PKC to regulate agonist-induced calcium oscillations

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Agonist-induced calcium signaling generates oscillatory increases in the cytoplasmic calcium concentration ($[Ca^{2+}]_i$). These $[Ca^{2+}]_i$ oscillations involve three distinctive steps: 1) the activation of IP_3R, 2) the IP_3R inactivation, and 3) the IP_3R resensitization. The first step involves the agonist-induced IP_3 production by stimulating PIP_2 hydrolysis in IP_3 and diacylglycerol (DAG); the former activates the IP_3R, an endoplasmic reticulum (ER) Ca^{2+} release channel. The second step requires the rise of the $[Ca^{2+}]_i$ resulting in the inactivation of the IP_3R, and the third step involves SERCA pump activity to replenish the ER Ca^{2+} store and to resensitize the IP_3R. DAG and Ca^{2+} activate protein kinase C (PKC), negatively regulating $[Ca^{2+}]_i$ oscillations. The store-operated Ca^{2+} entry (SOCE) is the typical ER Ca^{2+} replenishment mechanism in non-excitable cells that involves the interaction of two different types of proteins, Orai channels and STIM protein. The latter possesses a Ca^{2+} binding domain (EF-hand) facing the luminal side of the ER. The $[Ca^{2+}]_{ER}$ reduction results in the oligomerization and unfolding of STIM proteins to mechanically activate the Orai1 channel at the plasma membrane and the ensuing Ca^{2+} entry. Finally, the activity of the SERCA pump reloads the ER Ca^{2+} store, facilitating the IP_3R resensitization.

We have demonstrated that PKC-mediated phosphorylation of S27 and S30 residues of the Orai1 (O1) channel increases its association with the IP_3R, inhibiting its Ca^{2+}-releasing activity. Moreover, the Orai1 channel phosphomimetic mutant O1-S27D/S30D inhibits agonist-induced Ca^{2+} release even in the presence of a PKC inhibitor, while O1-S27A/S30A mutant cannot mimic the effect of the Orai1 channel wild-type. Furthermore, the nonfunctional Orai1-E106A mutant still inhibits the agonist-induced Ca^{2+} release. The activation of purinergic receptors with ATP (10 μM) resulted in an oscillatory increase of the $[Ca^{2+}]_i$ in 90% of cells, while the remaining 10% displayed $[Ca^{2+}]_i$ transient elevation. Overexpression of Orai1 channels increased the number of cells showing a transient $[Ca^{2+}]_i$ response. However, O1-wt and O1-S27D/S30D decreased while O1-S27A/S30A increased the frequency of oscillatory $[Ca^{2+}]_i$ responses [1].

Two approaches were used to study the role of Ca^{2+} entry via Orai1 channels in oscillatory $[Ca^{2+}]_i$ responses. 1) Membrane depolarization with high K^+ inhibited $[Ca^{2+}]_i$ oscillations for all mutants resulting in a transient $[Ca^{2+}]_i$ response. 2) The introduction of E106A mutation in all Orai1 to produce dominant negative, null ion channels. The overexpression of O1-S27D/S30D/E106A resulted in an increased frequency of non-responding cells and decreased frequency of oscillatory $[Ca^{2+}]_i$ responses, while O1-S27A/S30A/E106A displayed a larger amplitude of the transient $[Ca^{2+}]_i$ response. These data argue for PKC inhibiting oscillatory $[Ca^{2+}]_i$ responses by phosphorylating the Orai1 channel, and this, in turn, stabilizes the Ca^{2+} entry-dependent IP_3R inactivated state. It appears then that the Orai1 channel, besides its well-known role in allowing Ca^{2+} entry and refilling of the ER Ca^{2+} store, its phosphorylated form plays a novel role in stabilizing the IP_3R inactivated state and inhibiting the oscillatory $[Ca^{2+}]_i$ response.

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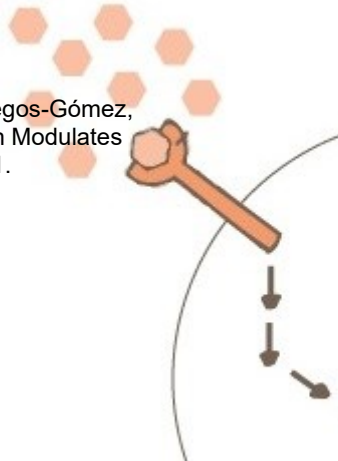

Alteration of signals that regulate appetite and regulatory effect of curcumin in diabetes.

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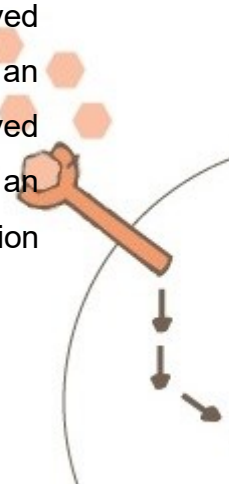
Diabetes is a disease with high prevalence worldwide. This disease is characterized by hyperglycemia and oxidative stress. In this condition, appetite- mediating signals are altered in the adipose tissue, bloodstream, and the hypothalamus. In this study was to evaluate the effect of curcumin (Cur) on diabetic hyperphagia, glucose level, and the expression of neuropeptide Y (NPY), proopiomelanocortin (POMC), and levels of oxidative stress markers, in Wistar rats (two-days-old male) which were injected with streptozotocin. At 10 weeks-of-age diabetes was confirmed, and the antioxidant was orally administered for 4 weeks. Food intake and body weight were measured daily. Blood glucose, oxidative stress markers, insulin tolerance, insulin, leptin and ghrelin concentration were evaluated at the end of the treatment. NPY and POMC expression in arcuate nucleus was determined by immunofluorescence. Diabetic rats had fasting hyperglycemia, hyperphagia, insulin resistance, altered plasma insulin and leptin levels, increased oxidative stress, increased expression of NPY and decreased POMC. Cur had a hypoglycemic effect, attenuated oxidative stress, and promoted downregulation of NPY expression without affecting hyperphagic behavior. On the other hand, we analyzed the level of gene expression by RNA sequencing (RNAseq) in samples of RNA hypothalamic. Throught KEGG (Kyoto Encyclopedia of Genes and Genomes) analyses we observed that Cur regulated the expression of genes which were altered in diabetes. This has an impact on the pathways that regulate appetite, on proteasome, on the pathways involved in neural communication, and on oxidative phosphorylation. Therefore, the Cur had an important effect on appetite signaling pathways and may regulate altered gene expression in diabetes.



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Study of the effect of biotic and abiotic stress on signal transduction mechanisms in two plant suspension cells cultures

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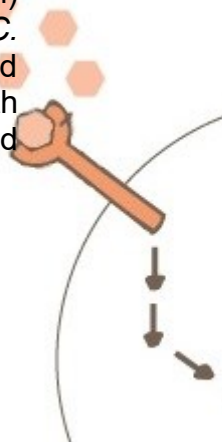
Aluminium (Al) is the most abundant metal on Earth. It represents 7% of the all elements. The toxicity produced by this metal is widely documented in tropical acid mineral soils. It is the major factor limiting the productivity of crop species. Coffee is one of the most important crops economically worldwide mainly due to the production of the secondary metabolite caffeine. In the other hand, the fruits of the habanero chili pepper belong to the species *Capsicum chinense* Jacq. Habanero chilies are relevant for the economy due to their high demand and agricultural production. However, this crop as well as coffee are affected by different types of biotic and abiotic stress. We have developed a biological model in which suspension cells of *Coffea arabica* and *Capsicum chinense* have been used.

Particularly, we paid attention to Phospholipase type C (PLC), and we evaluated the PLCs transcription profile in coffee suspension cells from 14 days of culture that were treated or not with 100 µM to $AlCl_3$ for 30s or 3h. *CaPLC1* and *CaPLC2* did not showed change after the treatment. In contrast, *CaPLC3* and *CaPLC4* showed specific profile, down- and up-regulated, respectively. We obtained coffee PLC´s by heterologous expression using pColdII vector in *E. coli* BL21star strain, they were purified by affinity using Ni-NTA column and we found that Al-treatment in vitro, also affects PLC2 activity but not PLC4. Also, we obtained PLCs constructions (promTUB::PLC::mGFP) to visualize PLCs subcellular localization during $AlCl_3$ treatments. When YFP-$PH_{PLC\delta1}$ (PIP_2 biosensor) was transfected into coffee protoplast, a fluorescence signal changes near to polar growing point was showed, but when they were treatment with Al^{3+} this signal was not detected. With these data, the PLC role into signal-transduction process in response to aluminum stress should be established. In the other hand, morphological changes were evident 24 hours after inoculation (hai) of *C. chinene* cells with the microbial consortium, which consisted primarily of *C. ignotum*. High levels of diacylglycerol pyrophosphate (DGPP) and phosphatidic acid (PA) were found around 6 hai. These metabolic changes could be correlated with high transcription levels of diacylglycerol-kinase (*CchDGK1* and *CchDG31*) at 3, 6 and 12 hai and also to pathogen gene markers, such as *CchPR1* and *CchPR5.*



Regulation of stem cell activity, endocrine resistance and metastasis

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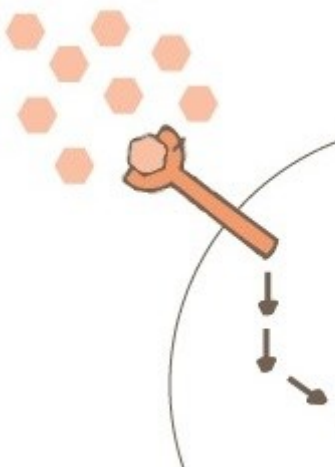
ER+ breast cancer is often successfully treated with endocrine therapies and more recently CDK4/6 inhibitors. In order to discover resistance mechanisms, we studied the tumour cells that survive anti-estrogen therapies such as tamoxifen and fulvestrant.

We found that tamoxifen and fulvestrant therapy-resistant cells have cancer stem cell (CSC) attributes such as aldehyde dehydrogenase (ALDH) enzyme activity, mammosphere colony formation ex vivo and tumour initiation in vivo. We established that these CSC activities are regulated by pathways downstream of JAGGED/NOTCH4 receptor, the interleukin (IL) 1beta/IL1 receptor, and IL6/STAT3 signalling.

Emerging data implicate these signalling pathways in metastatic progression, and in both endocrine and CDK4/6 inhibitor therapy resistance. Targeting them in combination with current therapies has the potential to improve clinical outcomes.



El fascinante mundo de las WNKs, la hipertensión arterial, la actividad neuronal y la regulación del volumen celular.

Dr. Gerardo Gamba
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Las cinasas de serina treonina conocidas como WNK (Kith No [K]Lysine) fueron descubiertas en el año 2000 y denominadas WNK por la ausencia de la lisina catalítica en el subdominio II de la región cinasa, como ocurre normalmente. Esta familia está formada por cuatros genes que codifican para las WNK1 a 4. La WNK2 es casi exclusiva del sistema nervioso central. Las WNK1, WNK3 y WNK4 son de distribución en diversos tejidos.

Las WNKs cobraron particular importancia para la medicina en el año 2001 en que fue demostrado que una enfermedad hereditaria, autosómica dominante, que cursa con hipertensión arterial e hiperkalemia, justamente conocida como Hipertensión Hiperkalémica Familiar (HHF), es debida en algunas familias a deleciones intrónicas del gen que codifica para la WNK1 y en otras familias a mutaciones puntuales en una región acídica de WNK4, que está particularmente conservada entre las WNKs. Años más tarde fue demostrado que en otras familias la enfermedad se debe a mutaciones puntuales en dos genes que codifican para las proteínas CUL3 y KLHL3 que juntas forman un complejo de ligasa de ubiquitina tipo RING. Las mutaciones en CUL3 o KLHL3 producen una enfermedad más grave y de inicio más temprano, lo que tiene sentido ya que el complejo CUL3/KLHL3 es quien reconoce a las WNKs para ser ubiquitinadas y por tanto destruidas. La región acídica mutada en WNK4 es justamente el sitio de reconocimiento de la cinasa por el complejo CUL3/KLHL3.

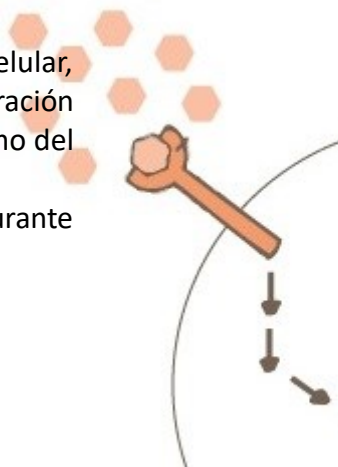
En los últimos 20 años las WNKs han sido materia de intensa investigación por diversos grupos por su importancia en enfermedades cardiovasculares y neurológicas. Las deleciones del intrón 1 de WNK1 producen HHF porque permite la expresión ectópica de la cinasa en el túbulo contorneado del riñón en donde normalmente no se expresa. En cambio, mutaciones puntuales en un exón particular de la WNK1 produce una enfermedad neurológica conocida como neuropatía sensora hereditaria tipo II.

La WNK1 controla la concentración de cloruro intraneuronal y, por lo tanto, el tipo de respuesta a neurotransmisores que actúan en canales de cloro en la membrana postsináptica (GABA).

Dado que el interés principal de mi laboratorio es la fisiología de la reabsorción renal de sal y la hipertensión arterial, hemos participado con aportaciones sobre cómo funcionan las WNKs, con lo que ahora tenemos una visión bastante clara de cómo se regula el transportador de NaCl en el riñón y su importancia a la hipertensión arterial.

Por otro lado, las WNKs también tienen que ver con la regulación del volumen celular, probablemente a través de la WNK3. Las WNKs son las cinasas sensoras de la concentración de cloruro intracelular, ya que su actividad se modula directamente por el Cl^-, así como del volumen celular.

Todas estas acciones y mecanismos de regulación de las WNKs serán presentadas durante el simposio.



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RhoGEFs as effectors of chemotactic cell migration

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Cells dynamically adjust their shape to migrate in response to chemotactic factors. The process involves the constant assembly and disassembly of cytoskeletal supramolecular structures guided by Rho GTPases. These molecular switches are activated by Rho guanine nucleotide exchange factors (RhoGEFs), which are sophisticated multidomain proteins that control morphological behavior of migrating cells. RhoGEFs are characterized by phylogenetically conserved catalytic modules flanked by structurally diverse domains that maintain intramolecular control and respond to chemotactic cues. In general terms, RhoGEFs are regulated by phosphorylation and direct interactions with transducers and phosphorylated lipids at the plasma membrane. Due to their strategic position in the signaling cascades that drive dynamic Rho GTPase signaling, cytoskeletal remodeling and cell migration, RhoGEFs have a central role in pathological cell migration, as in the case of metastatic dissemination of cancers cells, exacerbated by the actions of oncogenic proteins.

To understand how RhoGEFs integrate chemotactic signaling cascades relevant in endothelial and metastatic cancer cells, particularly those involving receptors coupled to heterotrimeric G proteins and tyrosine kinase receptors, we have focused on the role of RhoGEFs as signaling platforms that integrate chemotactic inputs. We have revealed novel mechanisms by which RhoGEFs are regulated by heterotrimeric G proteins, PKA and mTOR kinases. To characterize the regulatory mechanisms restricted to RhoGEF catalytic modules, we have studied the cellular and molecular effects of constitutively active RhoGEF constructs. In addition, we have pursued systematic data mining strategies to address the broad potential and clinical significance of RhoGEFs as signaling nodes in relevant cancer settings, this approach led us to identify signaling signatures, associated to the expression of various RhoGEFs, statistically linked to the clinical outcomes of cancer patients.

Our studies contribute to put the spotlight on RhoGEFs as strategic effectors of oncogenic signaling cascades linked to metastatic cancer cell dissemination and preview them as targets of antimetastatic precision therapies.

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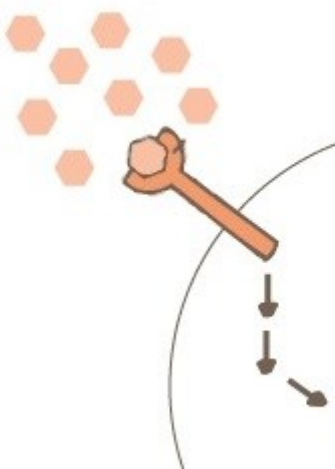

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Receptor de Estrógeno y Nuevos Co-reguladores

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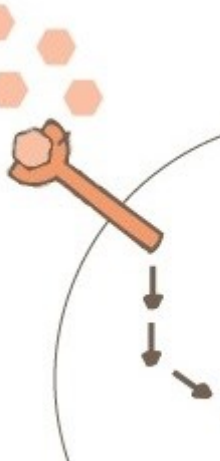
RESUMEN

El receptor de estrógenos alfa (ERα) pertenece a la familia de receptores nuceares que regulan supervivencia, proliferación, diferenciación , muerte celular, homeostasis y reproducción. La isoforma alfa del ER ha emergido como un regulador central de cáncer de mama y de ovario. La unión de estradiol al ERα promueve su unión a más de 1000 elementos de respuesta en el genoma, a los que se unen co-activadores transcripcionales como NCOA1/3 y acetil transferasas de histonas como CBP/p300 que acetilan a H3K27. El descubrimiento de los moduladores selectivos de estos receptores como el tamoxifeno llevó a postular un modelo en el que la unión de estos moduladores al ERα estabiliza una conformació que ahora le permite interaccionar con co-represores como NCOR1 que atenúan la actividad transcripcional del ERα reclutando desacetilazas de histonas como HDAC5 y promoviendo de la metilación de islas CpG en regiones promotoras de genes activados por el ERα. La aparición de resistencia a tamoxifeno ha promovido un análisis más detallado de los mecanismos asociados a estos co-represores revelando una complejidad inesperada en la que participan reguladores transcripcionales como FOXO1 o SOX9 que se consideraban ajenos a la regulación del ERα. A estos sistemas se han sumado elementos de la via Hippo como el factor de transcripción TEAD1 que puede heterodimerizar con el ERα y estabilizar la unión a sus elementos de respuesta. La activación del regulador transcripcional de la misma vía Hippo, YAP, hace que se una a TEAD1 desplazando al ERα de su elemento de respuesta. Estas interacciones motivaron la búsqueda de otro tipo de reguladores epigenéticos, llevando a la identificación de la enzima peptidil-arginil deiminasa-2 (PAD-2) cuya actividad estabiliza la unión del ERα al nucleosoma que presenta el elemento de respuesta específico para el receptor de estrógenos. A este grupo de reguladores transcripcionales se ha sumado otros como la proteína inducida por interferon (ISG12) y la proteína de andamiaje NHERF2. Mientras que ISG12 se encuentra asociada a la membrana nuclear, NHERF2 se puede encontrar tanto en el citoplasma como en el nucleoplas. En resumen, el ERα interactúa con una gran diversidad de reguladores transcripcionales y proteinas en el nucleoplasma, la envoltura nuclear y el citoplasma en forma dinámica creandose un sistema de regulación dinámico y complejo. Un mejor entendimiento de este sistema permitirá enfrentar la resistencia a la terapia anti-estrogénica de forma más racional y eficaz.



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Unique Metabolic Effects of KRAS G12V in Colorectal Cancer Cells

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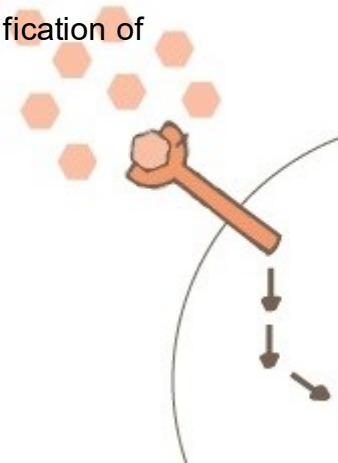
Abstract

Oncogenic KRAS mutations are prevalent in colorectal cancer (CRC) and are associated with poor prognosis and resistance to therapy. There is a substantial diversity of KRAS mutant alleles observed in CRC, and emerging clinical and experimental evidence suggests that each mutation differently influences the clinical properties of disease and response to therapy. Although there is some evidence to suggest biological differences between mutant various KRAS alleles, these are yet to be fully elucidated. One approach to study allelic variation involves the use of isogenic cell lines that express different endogenous Kras mutants. Here, we generated Kras isogenic Apc-/- mouse colon epithelial cell lines using CRISPR-driven genome editing to alter the original G12D Kras allele to G12V, G12R, or G13D. We used these cell lines to perform transcriptomic, proteomic, and metabolomic analyses to compare different signaling properties between these mutants. All screens indicate significant differences in pathways relating to cholesterol and lipid regulation. We found that these processes are upregulated in G12V lines through increased expression of nuclear SREBP1 and higher activation of mTOR. Furthermore, G12V cells showed higher expression of ACSS2 and ACSS2 inhibition sensitized G12V cells to MEK inhibition. These observations highlight functionally significant differences between the signaling properties of KRAS mutations. Further exploration of these pathways may prove to be valuable for understanding how specific KRAS mutants function, and for identification of novel therapeutic opportunities in CRC.



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BRCA1 mutations in cancer: implications for DNA repair and therapeutics

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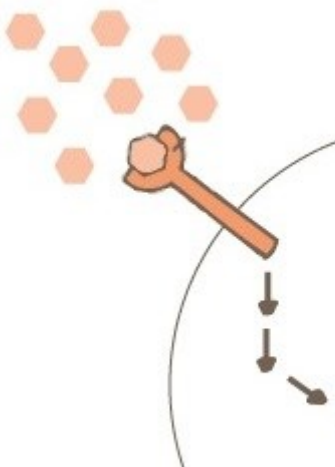
Abstract

Individuals that harbor a single *BRCA1* mutation-containing allele in their germline develop normally, but are predisposed to breast and ovarian cancer. Our research involves investigating factors that enable cells containing *BRCA1* mutations to carry out homologous recombination (HR) DNA repair and survive DNA damaging agent chemotherapy. We are examining the ability of mutant BRCA1 proteins to contribute to HR in both cancer cell line models and genetically engineered mouse models. In this seminar, I will discuss recent work examining DNA repair pathway choice. HR-deficiency induces a dependency on DNA polymerase theta (Polθ/Polq)-mediated end joining, and Polθ inhibitors (Polθi) are in development for cancer therapy. BRCA1 and BRCA2 deficient cells are thought to be synthetic lethal with Polθ, but whether distinct HR gene mutations give rise to equivalent Polθ-dependence, and the events that drive lethality, are unclear. In our work, we utilized mouse models with separate Brca1 functional defects to mechanistically define Brca1-Polθ synthetic lethality. We find that a process called DNA end resection is a critical determinant of Polθi sensitivity in HR-deficient cells, and should be considered when selecting patients for clinical studies.



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"Hypoxia Inducible Factors are essential promoters of malignant phenotype and resistance to treatment in colon cancer"

Martha Robles Flores, María Cristina Castañeda Patlán, Abril Saint-Martin Castellanos, Andrea Sánchez Collado, Eduardo Alvarado Ortiz, Alejandro López Mejía.
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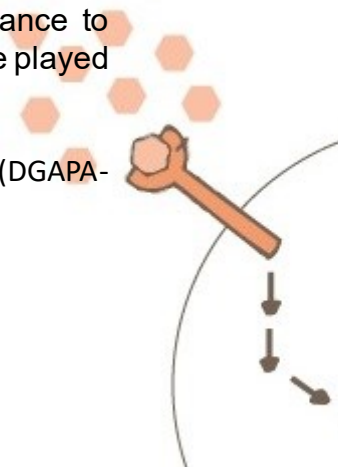
Hypoxia resulting in nutrient depletion is a hallmark of the tumoral microenvironment. Cellular adaptation to hypoxia is primarily mediated by a family of master transcriptional regulators: HIF-1α, HIF-2α, and HIF-3α, which play key roles in many crucial aspects of cancer biology. Remarkably, in cancer cells, HIFs upregulation also occurs under normoxic conditions because its expression is induced by deregulated oncogenic signaling by several mechanisms in an O_2-independent manner. Notably, hypoxia and the accumulation of HIFs in tumors have been associated with therapeutic resistance and with autophagy establishment.
To investigate the roles played by each HIF-α in colon cancer, we induced the stable knockdown expression of each one and explore the effects derived of this on malignant phenotype, autophagy establishment and drug resistance to treatment in colon cancer cells. We found that under normoxic conditions, malignant cells co-express HIF-1α, HIF-2α and HIF-3α and exhibit increased basal levels of autophagy, compared with non-malignant cells. We observed significant differences in stability of HIF-α protein subunits: while HIF-1α and HIF-2α display short half-life (<1 hr), HIF-3α protein displays much higher stability (~ 6 hrs) under normoxic conditions. Knockdown of each HIF-α expression resulted in increased autophagic and apoptotic cell death, indicating that the survival of cells is HIF-dependent. Cytotoxic-induced cell death was significantly increased by knockdown of HIFs but not by autophagy inhibition. Strikingly, although malignancy-resistant cells were sensitized to death by nutrient stress, the combination with HIF-2α depletion, but not with HIF-1α depletion, induced severe cell death. Oxidative stress levels were significantly increased as a result of HIF-2α specific inhibition or silencing suggesting that this may contribute to sensitize cells to death. The in vitro results were confirmed in vivo using a xenograft mouse model. We found that coordinated autophagy and mTOR inhibition enhanced cell death and induced tumor remission only in HIF-2α -silenced cells. Finally, using a specific HIF-2α inhibitor alone or in combination with drugs in patient-derived primary colon cancer cells, overcame their resistance to chemotherapeutic drugs (5-FU or CCI-779), thus emphasizing the crucial role played by HIF-2α in promoting chemoresistance and cell survival.

Funding: supported by grants from Universidad Nacional Autónoma de México (DGAPA-UNAM IN229420 and IV200220) and from CONACYT (FOSSIS 2017-289600).



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Identification of Key Genes and Pathways Involved in Tissue Regeneration through Comparative Transcriptomics

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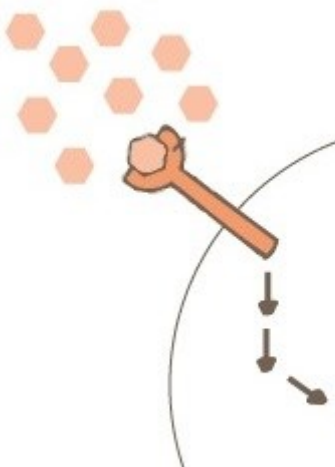
The axolotl is an animal with remarkable regenerative abilities, making it an ideal model for studying potential regenerative therapies in mammals, including humans. However, the molecular mechanisms involved in regeneration remain unclear. We conducted a transcriptomic analysis of juvenile axolotls' limbs and their blastema and compared the results with aged axolotls that failed to regenerate after amputation. We identified a set of genes involved in cell differentiation, migration, cartilage development, bone morphogenesis, and extracellular matrix remodeling. Four highly expressed genes (*FSTL1, ADAMTS17, GPX7*, and *CTHRC1*) were identified in regenerating tissue, but underexpressed in aged axolotls. Structural and homology analysis showed that these genes are conserved and have important roles in development, bone morphogenesis, and cartilage formation. Our findings propose a novel set of key axolotl genes involved in tissue regeneration that could be a starting point for further studies in other vertebrates.



New insights into prostate cancer

Daniel Metzger

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Prostate cancer (PCa) is the second most commonly diagnosed neoplasia in men worldwide and one of the major causes of cancer-related death. It is a heterogeneous disease with a slow progression and a highly variable clinical outcome. The initial step in the malignant transformation of prostatic epithelial cells is the development of precancerous lesions termed prostatic intraepithelial neoplasia (PIN), which may progress to adenocarcinoma and become metastatic. Serum prostate specific antigen (PSA) is a widely used biomarker for prostate cancer diagnosis. However, it does not predict whether tumors will remain indolent or become clinically aggressive. Its systematic use is suspected to lead to over-diagnosis and over-treatment, and thus is under intensive debate. Localized PCa can be cured by radical prostatectomy or radiotherapy, but these interventions may induce side effects. Metastatic PCa is treated by androgen deprivation therapy, but although initially effective, progression to castration-resistant PCa occurs in most patients, for whom the therapeutic arsenal is limited.
The tumor suppressor genes *PTEN* and *TP53* are among the most frequently altered genes in prostate cancer. PTEN mutations have been identified in 10–15% of all prostate tumors and in up to 60% of advanced prostate cancers, whereas inactivation of TP53 has been suggested to be a late event during prostate cancer progression.
To provide insights to prostate tumor evolution, we generated genetically engineered mice, in which *TP53* and/or *Pten* are selectively inactivated in prostatic luminal cells after puberty. Data showing that these mice faithfully reproduce the human disease and are powerful tool to identify molecular and cellular mechanisms underlying prostate cancer progression, as well as biomarkers of tumorigenesis and new therapeutic strategies will be presented.

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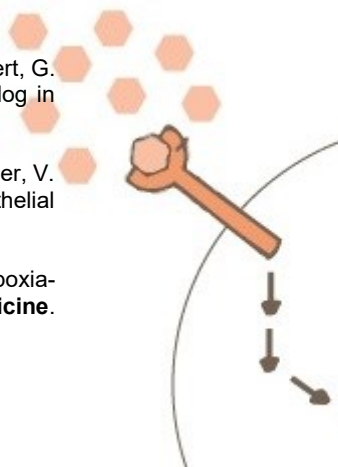

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Molecular mechanisms involved in the TGF-b response in T lymphocytes.

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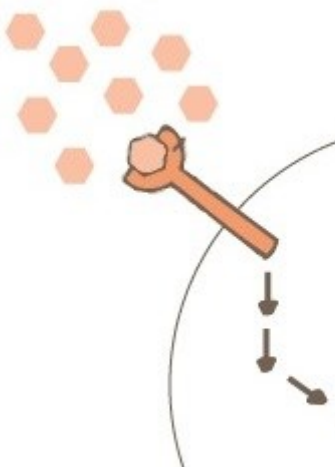
TGF-β is pleiotropic cytokine able to regulate T cell differentiation and effector phenotypes. In particular, it can induce the differentiation and function of regulatory T cells (Tregs) while it inhibits effector functions of cytotoxic CD8 T cells (CTL) among others. TGF-β signaling depends on serine/threonine kinase receptors that phosphorylate Smad2 and Smad3, to allow interaction with the common Smad: Smad4. This Smad2/3/4 complex was considered the main signal transduction element in the pathway. However, the transcriptional intermediary factor 1 γ (TIF1γ) was recently shown to interact with Smad2/3, leading to a distinctive gene expression profile and cell fate downstream of the TGF-β signaling. The objective of this work is to elucidate the role of TIF1γ in the differentiation, cell function, and stability of Tregs and CTL cells. Using different conditional mouse models we demonstrated that under homeostatic conditions, TIF1γ is dispensable for Treg and CTL generation. However, it is required for the maintenance of Treg suppressive functions and stability under inflammatory conditions, both in in vivo and in vitro models. TIF1γ is also important for the cytotoxic activity of CD8 T cells in vivo and controls differential expression of effector molecules in these cells. We also identified increased proliferative capacity of T cells lacking TIF1γ expression. Our data suggests that the phenotype observed could be dependent on two key functions of TIF1γ, its role as an ubiquitin ligase and its regulatory capacity as an epigenetic modulator.



Signal transduction by antibody Fc receptors in human neutrophils.

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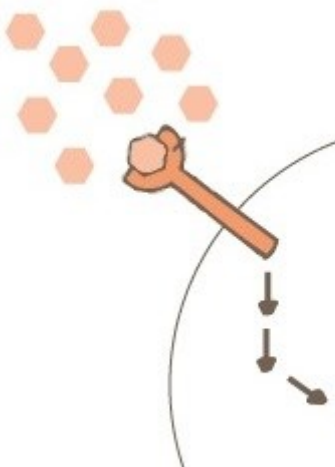
Neutrophils are fundamental cells in host defense. These leukocytes are quickly recruited from the blood to sites of infection or tissue damage. At these sites, neutrophils initiate several innate immune responses, including phagocytosis, production of reactive oxygen species, degranulation to release proteases and other antimicrobial compounds, production of inflammatory mediators and formation of neutrophil extracellular traps. In addition to their role in innate immunity, neutrophils are now recognized as cells that also regulate adaptive immunity, via interaction with dendritic cells and lymphocytes. Neutrophils also respond to adaptive immunity by interacting with antibody molecules. Indeed, antibody molecules allow neutrophils to have antigen-specific responses. Neutrophils express different receptors for antibodies. The receptors for IgG molecules are known as Fc gamma receptors. Upon Fc gamma receptor aggregation on the cell membrane, these receptors trigger distinct signal transduction cascades that activate particular cellular responses. Human neutrophils express two unique Fc gamma receptors that initiate discrete signal transduction pathways to activate particular cellular responses. The Fc gamma RIIa induces phagocytosis and L-selectin shedding. In contrast, the Fc gamma RIIIb induces integrin activation and neutrophil extracellular trap (NET) formation.



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Human T Cell Activation: New Kids on the...Pathway

Mario Morales-Martínez[1], David Andón García[1], Karla Aimee Patiño-Santiago[1], Abrahan Hernández-Hernández[2] and Genaro Patiño-López *[1]

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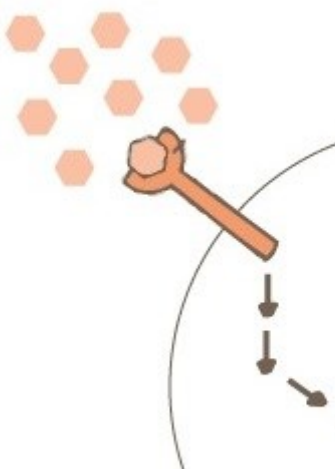
T-cell activation is a central process of the adaptive immune response and is the result of the close communication between the Antigen Presenting Cell (APC) and the T lymphocyte. T-cell activation has been widely studied and is currently well understood, nevertheless with the use of new technologies like, microarray gene expression, whole exome sequencing, RNA-seq, etc., these biological pathways have been updated with the addition of several proteins, microRNAs or lncRNAs, complementing the protein interactome previously reported. In this work we aimed to identify new players in early T cell activation, for this, we reviewed and analyzed results of microarray gene expression datasets reported in the public database GEO-NCBI. Using data from GSE136625, GSE50971, GSE13887, GSE11989 and GSE902 we performed different comparisons using R and GEO2R, to identify upregulated proteins upon T-cell activation that have no previous reports to participate in immune related functions, particularly in T-cell activation. Interestingly among many candidates we identified at least two lncRNAs with high expression upon T-cell activation that let us suggest could be involved in the regulation of T-cell activation. Further in vitro studies are warranted to confirm the proposed roles in T cell activation for the different candidates here reported. Funding: CONACYT grant #320456 from the Fondo Ciencia de Frontera 2022



The Class I Myosins represent highly versatile proteins mediating different functions in the cells of the immune system.

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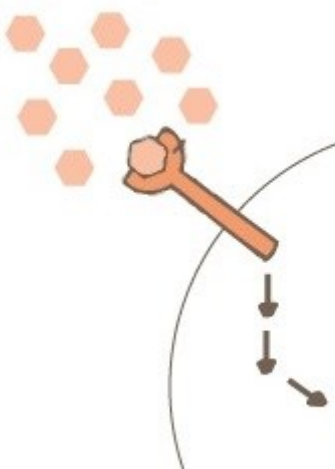
Class I myosins are monomeric proteins involved in actin polymerization, cell motility, cell shape control, sensory transduction, and vesicular trafficking. Eight class I myosins are expressed in humans and mice, encompassing six short-tailed (Myo1a, Myo1b, Myo1c, Myo1d, Myo1g, and Myo1h) and two long-tailed (Myo1e and Myo1f) myosins. Both short-tailed and long-tailed myosins have a TH1 (tail homology) domain enriched with basic amino acids, thus permitting their interaction with the plasma membrane. Long-tailed myosins also have a TH2 domain rich in prolines and a TH3 domain corresponding to an SH3 domain. In immune cells, those proteins also form and maintain immunological synapse-related signaling. Thus, these proteins are master regulators of actin cytoskeleton dynamics in different scenarios. Although the localization of class I myosins has been described in vertebrates, their functions, regulation, and mechanical properties still need to be better understood. This presentation will summarize our current understanding of class I myosins in leukocytes. We will present evidence of their role in B-cell functions, such as adhesion and migration, macrophage differentiation, and participation in gamma-delta T-cell recruitment to mucosal tissues summarizing the work of our laboratory during the last 20 years.



Sesiones Orales Estudiantes

Dysregulation of p53 regulation on TLR3 in cellular models of Prostate Cancer induced by sodium arsenite.

Nancy C. Pacheco-Castillo, Vanesa Olivares-Illana, Erik Tokar, S. Eréndira Avendaño-Vázquez y Claudia Escudero-Lourdes.

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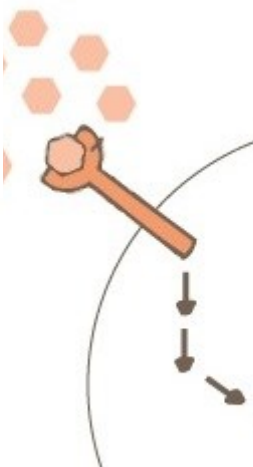
Out of different types of cancer, Prostate Cancer (PCa) is the second leading cause of death in males worldwide, with a survival rate of less than 30% in advanced stages, because development of chemoresistance and androgen-independent tumor growth. For this reason, in advanced stages, the use of different immunotherapies is suggested, including the activation of the Toll-like receptor 3 (TLR-3), whose expression is mainly regulated by the transcription factor and tumor suppressor p53. Human exposure to inorganic arsenic (iAs), a common environmental contaminant worldwide, is clearly associated with the development of PCa. We had demonstrated that iAs causes malignant transformation of prostate epithelial cell line RWPE-1, and iAs decreases the expression and activation of TLR3 by its synthetic ligand poly-inosine-poly citidine (Poly I:C, PIC) used in immunotherapy for PCa. With this evidence, it could be expected that iAs exposure leads to a decreased p53 protein, leading in turn to a significant decrease in TLR3 expression. This is supported by studies conducted on a keratinocyte cell line, describing that exposure to iAs leads to p53 down regulation and a significant increase in the p53 negative regulator, MDM2 protein (Zhao Y. et al, 2020). In present study, we used two PCa cell models generated from epithelial prostate cell lines (RWPE-1 and HPrEC), exposed to 5 and 3 µM of iAs for 30 weeks, respectively. In these cell models, we determined the expression of TLR3, p53, and MDM2 at transcript and protein levels. The results showed that in both cell lines, although TLR3 and MDM2 expression was significantly decreased, p53 expressionsignificantly increased with prolonged exposure to iAs. This expression pattern was also observed in transcriptomic results obtained from RWPE-1 cells exposed to iAs. The transcriptomic study also showed that other p53 target genes, including other TLRs such as TLR1, TLR9, and TLR10, and the genes Icam 2, Cx3cl1, Isg15, and CdK1nA, were also significantly decreased. These observations strongly suggest that in these PCa models, nevertheless p53 overexpression, the protein is not exerting its functions as transcription factor; therefore, it is important to determine its binding and activation capacity over its target genes promoters.



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Effect of Corticotropin-Releasing Factor (CRF) on the MAPK pathway activation induced by Insulin-like Growth Factor-1 (IGF-1) in CHO-K1 cells.

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The insulin-like growth factor-1 receptor (IGF-1R) belongs to the receptors tyrosine kinase (RTKs) family and participates in cellular processes such as proliferation, differentiation, and survival by activating the MAPK pathway[1]. The effects of this pathway are reduced in psychiatric disorders such as depression, anxiety, and Alzheimer's disease[2]; however, the molecular mechanism is not clear, but it is known that chronic stress has an important role in developing these pathologies. During this condition, dysregulation of the hypothalamic-pituitary-adrenal axis (HPA), an critical system during the neuroendocrine stress response, has been reported[3]. This deregulation is associated with increased concentrations of corticotropin-releasing factor (CRF) (the main physiological regulator of the HPA axis) and overactivation of CRF type 1 receptor (CRF_1R), a member of the G protein-coupled receptors (GPCRs) family[4]. Evidence to date suggests that CRF_1R inhibits IGF-1 release in rat granulosa cells[5]; furthermore, it is known that chronic activation of GPCRs can desensitize members of the RTK family[,6]. Therefore, this work aims to determine the role of CRF in the molecular mechanism of regulating the MAPK pathway mediated by IGF-1. We used Chinese hamster ovary cells (CHO-K1), a cell model expressing IGF-1Rs and transiently transfected with the HA-$hCRF_1R$ by using Lipofectamine 2000. The transfected cells were preincubated with CRF (using different times and concentrations) and stimulated with IGF-1. The results showed that CRF specifically reduced IGF-1-induced ERK1/2 Thr^{202}/Tyr^{204} phosphorylation. Similarly, CRF inhibited IGF-stimulated IGF-1R and Shc tyrosine phosphorylation. We also observed that by using rapamycin and SP600125, two selective inhibitors of mTOR and JNK, respectively, the inhibitory effect of CRF on the IGF-induced ERK1/2 phosphorylation was prevented. Altogether, these results suggest that CRF regulates the actions of IGF-1 by reducing the activation of the MAPK pathway, most likely at the level of IGF-1R and its adapter substrate Shc. In this proposed regulatory mechanism, the participation of JNK and mTOR is important, and we are currently continuing to study how both kinases may be acting.

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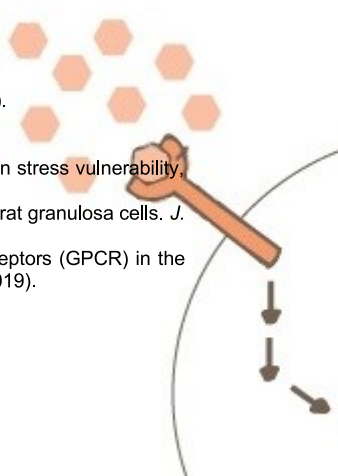

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Effect of heterosteroids derived from sapogenins in PI3K/AKT/mTOR and apoptosis pathways in breast cancer cells

Nadia Ieney Olazo Márquez, Maura Cárdenas García, María Guadalupe Hernández Linares, Ivet Etchegaray Morales, Sylvain Bernés

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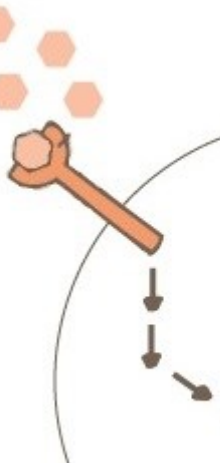
Transducción de señales y cáncer

Introduction. Cancer is one of the main causes of mortality worldwide and breast cancer is the most common both worldwide and in Mexico, therefore, treatment options such as heterosteroids, continue to be investigated. New sapogenin derived heterosteroids were synthesized at the Laboratorio de Investigación del Jardín Botánico de ICUAP, BUAP and molecular docking was performed with their protein targets to establish the effect on signaling pathways altered in cancer such as PI3K/AKT/mTOR and apoptosis, and their antiproliferative effect was determined in MDA-MB-231 and MCF-7 cell lines. **Aim**. To analyze by molecular docking the interactions of heterosteroids derived from sapogenins on proteins from PI3K/AKT/mTOR and apoptosis pathways and to evaluate the antiproliferative effect in breast cancer cells. **Materials and Methods.** Molecular docking was performed on AutoDock Tools with ten new heterosteroids and PI3K, AKT, caspase 3, caspase 7, caspase 9, Bcl-XL, p53 and PARP1. Their effect was determined on MDA-MB-231 and MCF-7 and flow cytometry was performed on MDA-MB-231 to stablish if caspases 3 and 7 were expressed after treatment. **Results.** Molecular docking showed interactions between PARP1-D8, PARP1-D9, caspase 3-D10, caspase 3-D11, caspase 7-D10, caspase 9-D11, p53-D11, PI3K-D7, D8, D10, D11, D12, AKT-D7, and AKT-D12. The best interactions were between PARP1-D9 (-10.29 kcal/mol), caspase 3-D10 (-9.46 kcal/mol), PI3Kα-D8 (-9.86 kcal/mol) and PI3Kγ-D8 (-9.08 kcal/mol). Then, D8, D9 and D10 were tested on breast cancer cell lines finding that best IC_{50} on MCF-7 was D10 with 3.29 µM and on MDA-MB-231 was D9 with 2.88 µM. Flow cytometry showed that treatment of D8, D9, D10 and D11 expressed caspase 3 and 7 meaning that they can cause cell death of MDA-MB-231 through their activation. **Conclusion.** The new heterosteroids could inhibit PI3K/AKT/mTOR pathway and activate apoptosis through the interaction between PI3K and caspases, also D9 could inhibit PARP1. In MDA-MB-231 cell line, D8, D9, D10 and D11 activate caspases 3 and 7 expression.

Keywords: breast cancer, heterosteroids, sapogenins



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Regulation of Lysophosphatidic acid receptor 3

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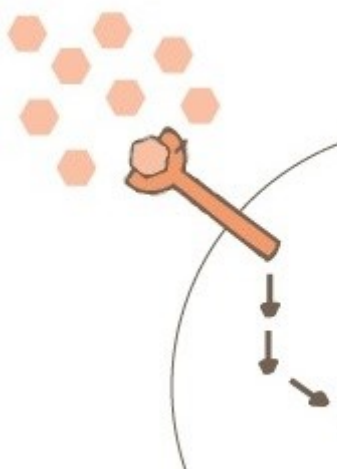
The lysophosphatidic acid receptor type 3 belongs to the lysophosphatidic acid receptor sub-family, a member of the G protein-coupled receptor superfamily, consisting of 7 transmembrane domains. These receptors can activate two types of G proteins (Gαq and Gαi/o), thus triggering the activation of downstream signaling pathways, which promotes the participation of this receptor in many physiological functions, as well as pathological processes. However, despite the wide relationship of the receptor with these functions, the mechanism by which the receptor could be regulating these processes is not known, with certainty, so far. Studies carried out in the laboratory have shown that this receptor is phosphorylated when activated by lysophosphatidic acid. This event becomes relevant if we consider that for various GPCRs phosphorylation could be involved in the activation of downstream signaling pathways and promoting the modulation of a plethora of functions. Our main objective for this work was to study the regulation of the LPA3 receptor, as well as the sites in which it is phosphorylated under basal conditions and when it is stimulated. We were able to determine that the LPA3 receptor has 11 phosphorylation sites and that they were located in the intracellular bundle 3 and the carboxyl-terminus. According to *in silico* studies, these sites are considered important for the binding of the β-arrestin, protein to the receptor, an event known to have an impact on its regulation. Additionally, we demonstrated that the LPA3 receptor has a differential pattern of phosphorylation under the distinct conditions studied. This study suggests that the found phosphorylated sites are, probably, sites for the binding of β-arrestin. Mutation of these sites could have an impact on the internalization and activation of signaling pathways that are involved in physiological functions and physiopathological roles.

This research was partially supported by Grants from CONACYT (Fronteras 6676) and DGAPA (In201221). K. Helivier Solis is a PhD student of the Programa de Ciencias Biomédicas.



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Regulation of mitochondrial metabolism by autophagy supports leptin-induced cell migration

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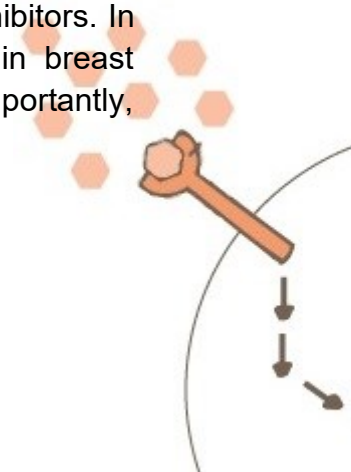
ABSTRACT
Leptin is an adipokine secreted by adipose tissue, which promotes tumor progression by activating canonical signaling pathways such as MAPK/ERK. Recent studies have shown that leptin induces autophagy, and this process is involved in leptin-induced characteristics of malignancy. Autophagy is an intracellular degradation process associated with different hallmarks of cancer, such as cell survival, migration, and metabolic reprogramming. However, its relationship with metabolic reprogramming has not been clearly described. The purpose of this study was to determine the role of leptin-induced autophagy in cancer cell metabolism and its association with cellular proliferation and migration in breast cancer cells. We used ER^+/PR^+ and triple-negative breast cancer cell lines treated with leptin, autophagy inhibition, or mitochondrial metabolism inhibitors. Our results show that leptin induces autophagy, increases mitochondrial ATP production and mitochondrial function in ER^+/PR^+ cells. Importantly, autophagy was required to maintain metabolic changes and cell proliferation driven by leptin. In triple-negative cells, leptin did not induce autophagy or cell proliferation but increased glycolytic and mitochondrial ATP production, mitochondrial function, and cell migration. Interestingly, in invasive breast cancer cells, autophagy was required to support metabolic changes and cell migration. Finally, our data demonstrates that autophagy inhibition decreased cellular migration similar to mitochondrial inhibitors. In conclusion, leptin-induced autophagy supports mitochondrial metabolism in breast cancer cells as well as glycolysis in triple negative breast cancer cells. Importantly, leptin-induced mitochondrial metabolism promoted cancer cell migration.



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Multi-targeting of signaling networks by miR-204 inhibits angiogenesis and vasculogenic mimicry in CD44+/CD34- breast cancer stem-like cells

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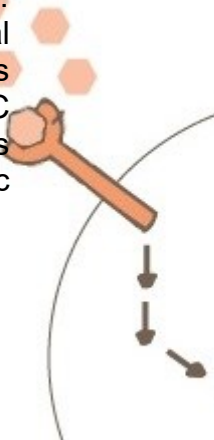
Abstract

MicroRNAs-based therapies targeting multiple signaling pathways represent an attractive approach in cancer. Vasculogenic mimicry (VM) was described as a novel blood and oxygen supply mechanism in which tumors can feed themselves, operating in an independent route or simultaneously with classical angiogenesis. VM involves the formation of patterned three dimensional (3D) vascular channel- like structures by tumor cells changing our traditional assumption that angiogenesis is the only mechanism by which tumors acquire blood and nutrients. VM has been associated with poor prognosis and metastasis in cancer patients.

Here, we uncovered a miR-204 cooperative targeting of multiple signaling transducers involved in VM and angiogenesis in breast cancer stem-like cells. Our data showed that invasive triple negative MDA-MB-231 and Hs-578T breast cancer cells efficiently undergoes extracellular matrix (ECM)-associated VM after hypoxia. Ectopic restoration of miR-204 in MDA-MB-231 and Hs-578T stem-like cells leads to a potent inhibition of VM and reduction of number of branch points and patterned 3D channels. In addition, angiogenesis of HUVEC cells induced by tumor cells was significantly abolished by miR-204. Further analysis of activation state of multiple signaling pathways using Phosphorylation Antibody Arrays revealed that miR-204 reduced the expression and phosphorylation levels of 13 proteins involved in PI3K/AKT, RAF1/MAPK, VEGF, and FAK/SRC cell signaling. In agreement with phospho-proteomic profiling, VM was impaired following pharmacological administration of PI3K and SRC inhibitors. Mechanistic studies confirmed that miR- 204 exerts a negative post-transcriptional regulation of PI3K-α and c-SRC proto- oncogenes. Moreover, overall survival analysis of a large cohort of breast cancer patients indicates that low miR-204 and high FAK/SRC levels of were associated with worst outcomes. In conclusion, our study provides lines of evidence indicating that miR-204 may exerts a fine-tuning regulation of the synergistic transduction of PI3K/AKT/FAK mediators critical in VM formation and angiogenesis.



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Anabolic effect of novel saponin-derived heterosteroids on skeletal muscle

Amairani Domínguez Bahena, Raisa Oves García, Adrián Mendoza Montalvo, Linda Fabiola Pérez Pérez, Maura Cárdenas García, María Guadalupe Hernández Linares, Gabriel Guerrero Luna, Sylvain Bernés.

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Transducción de señales y diferenciación celular

Introduction. Skeletal muscle tissue can get atrophy disease when protein synthesis is less than degradation process, leading to muscle atrophy; this condition has been directly linked to diseases such as cancer, AIDS and heart failure, affecting the quality and length of life of affected individuals. The use of heterosteroids derived from saponins has been investigated, demonstrating an anabolic effect on muscle. Currently, new heterosteroids have been synthesized that can exert an anabolic effect on atrophied human muscle cells. Among the most important signaling pathways controlling muscle hypertrophy is the IGF1-activated pathway, while on the atrophy side, one of the most prominent pathways is that activated by myostatin, an important negative regulator of muscle.

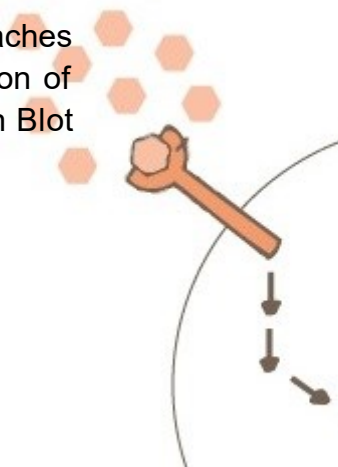
Objective. Determine the effect of new heterosteroids on skeletal muscle through muscle regulatory pathways.

Methodology. Skeletal muscle anabolic and catabolic signaling pathways were modeled and subsequently the interaction of new heterosteroids with PI3K, mTOR, GSK3β, MAPK and ERK1/2 proteins was determined by molecular docking in AutoDock. Finally, their anabolic activity was tested in a skeletal muscle cell line.

Results. It was found that heterosteroids can regulate both the hypertrophic and atrophic pathway in muscle by interacting with some of the main proteins such as PI3K, mTOR, GSK3β, MAPK and ERK1/2 from *in silico* simulation and molecular docking . It was found *in vitro* that the most promising compounds were D8 by increasing cell viability 63% with respect to the control and OXH >150%.

Perspectives. We will continue with the simulation based on molecular approaches to test all the new heterosteroids synthesized, in addition to the quantification of specific markers of muscle mass regulation by means of Bradford and Western Blot assays, in order to confirm the anabolic effect of the new compounds *in vitro*.

Keywords: heterosteroids, skeletal muscle, anabolic



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Title: **"The Pak1-CaMKII Signaling Pathway: Implications for Breast Cancer Progression and Therapeutic Targeting"**

Héctor I Saldivar-Cerón[1,2], Olga Villamar-Cruz[1], Claire M Wells[3], Ibrahim Oguz[3], Federica Spaggiari[3], Jonathan Chernoff[4], Genaro Patiño-López[5], Sara Huerta-Yepez[6], Mayra Montecillo-Aguado[6], Clara M Rivera-Pazos[6], Marco A Loza-Mejía[7], Alonso Vivar-Sierra[7], Paola Briseño-Díaz[2], Alejandro Zentella-Dehesa[8,9], Alfonso Leon-Del-Rio[8], Alejandro López-Saavedra[10], Laura Padierna-Mota[11], María de Jesús Ibarra-Sánchez[9], José Esparza-López[9], Rosaura Hernández-Rivas[2], Luis E Arias-Romero[1]

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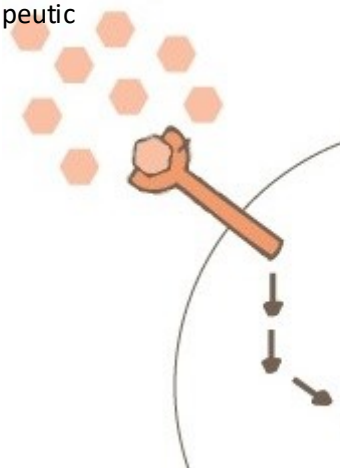
Abstract:

p21-Activated kinase-1 (Pak1) plays a critical role in breast cancer development and is frequently overexpressed in tumor cells. In this study, we investigate the interaction between Pak1 and the Calcium/Calmodulin-dependent Protein Kinase II (CaMKII) and its impact on breast cancer progression. We demonstrate that Pak1 phosphorylates and activates CaMKII, and inhibition or depletion of Pak1 leads to reduced CaMKII activity. Our analysis of human breast cancer samples reveals a strong correlation between Pak1 and CaMKII expression. Furthermore, simultaneous inhibition of Pak1 and CaMKII with small-molecule inhibitors synergistically induces apoptosis, particularly in Her2-positive and triple-negative breast cancer (TNBC) cells. Combination treatment significantly impairs proliferation, migration, and invasion in 3D cell cultures of TNBC cells. In a TNBC xenograft mouse model, co-administration of Pak1 and CaMKII inhibitors results in a substantial delay in tumor growth. These findings uncover a crucial signaling pathway from Pak1 to CaMKII that drives the proliferation, migration, and invasion of breast cancer cells, suggesting novel therapeutic strategies for breast cancer treatment.



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Metabolic Syndrome impairs Akt activation by Urocortin 2 in Adipocytes

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The family of corticotropin-releasing factor (CRF) peptides is involved in a wide range of physiological processes to mount appropriate stress responses. This system plays a key role in regulating the hypothalamic-pituitary-adrenal axis, which leads to the release of the adrenocorticotropic hormone and, subsequently, corticosteroids. Therefore, alterations in this system have been associated with various emotional, behavioral, feeding, and metabolic disorders. This family is composed of four related peptides: CRF and Urocortins 1, 2, and 3 (Ucn1, Ucn2, and Ucn3), which bind to CRF type 1 and type 2 receptors (CRF_1R and CRF_2R)[1]. Although this system has been mainly described in the CNS, it has also been found in other organs and tissues, such as skeletal muscle, heart, pancreas, and adipose tissue. In adipose tissue, where CRF_2R, Ucn2, and Ucn3 are mainly expressed[2], the physiological actions of this system are not fully described, and the role of urocortins in insulin resistance and metabolic syndrome (MetS) is unknown. MetS is a group of metabolic disorders that increase the risk for developing cardiovascular disease and type 2 diabetes associated with visceral adipose tissue alterations and insulin resistance[3]. It is known that CRF_2Rs activate cAMP/PKA, PLC/IP3/Ca^{2+}, PI3K/Akt, and the mitogen-activated protein kinases (MAPKs) signaling pathways. Besides, depending on the cellular model, MAPKs and Akt activation may involve several signaling molecules and receptor tyrosine kinases (RTKs) transactivation. Therefore, we aimed to study the effect of Ucn2 in adipocytes 3T3-L1 and adipocytes isolated from epididymal tissue of a Wistar rat model of MetS to characterize the role of Ucn2 in the insulin resistance and MetS. In cell culture, our data indicated that the activation of Akt is induced by Ucn2 independent of insulin receptor activation. Using specific kinase inhibitors, we demonstrated that Akt activation in response to Ucn2 was dependent on Src, PI3K, and EGFR transactivation. Moving on to the animal model, MetS rats exhibited abnormalities in glucose metabolism and biochemical parameters, indicative of metabolic dysfunction. Interestingly, an impaired response in Akt activation was observed in MetS adipocytes treated with Ucn2. Lastly, the pathophysiology of adipose tissue in MetS could alter the signaling of CRF_2R, although these results need to be confirmed with additional studies.

This research was supported by a CONAHCYT scholarship grant CVU:1002080 to D.E.C-V, and Conacyt Grant #A1-S-9082 (Fondo Ciencia Básica 2017-2018) to A.R.

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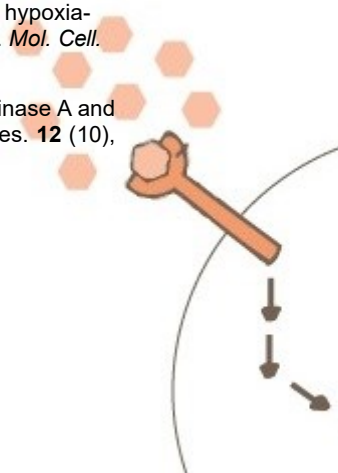

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Cracking the TGF-beta Code: Exploring the Significance of Smad7 and T Cell Subsets in the Complex Tumor Microenvironment

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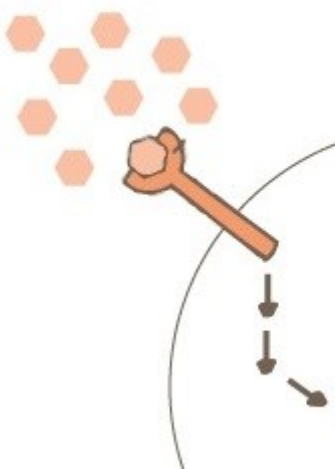
Within the antitumoral immune response, a wide range of immune cells, including T lymphocytes, play crucial roles. CD4+ helper T cells and CD8+ cytotoxic T cells exert antagonistic functions, either promoting or regulating tumor growth. TGF-β is a cytokine enriched in the tumor microenvironment that regulates positively or negatively the effector function of T lymphocytes. TGF-β signals through pairs of type I and type II receptors, inducing the phosphorylation of R-Smads (Smad2/3). R-Smads interact with Smad4, translocating to the nucleus and regulating gene expression. The pathway is regulated by various mechanisms, including the ones exerted by Smad7. For instance, Smad7 not only blocks the phosphorylation and activation of Smad2 but also promotes the degradation of type 1 TGFbeta receptor. In this study, our objective was to investigate the impact of Smad7 depletion in different T cell subsets within the tumor microenvironment. Strikingly, depleting Smad7 in all T cell compartments (CD4 Cre), encompassing CD4, CD8 T cells, and Tregs, resulted in significantly increased tumor growth. This phenotype was accompanied by reduced infiltration of cytotoxic CD8 T cells and enhanced suppressive capacity of Tregs. To gain further insights into the contribution of Smad7 in specific T cell subsets, we generated conditional knockout animals where Smad7 was specifically depleted in CD8 T cells (CD8 Cre) or Treg cells (CD4 Cre). Interestingly, in both cases, the absence of Smad7 in the cytotoxic compartment or Tregs led to heightened tumor growth. In conclusion, these findings indicate that augmenting TGF-β signaling in T cells by eliminating its negative regulator has both positive and negative consequences. It suppresses cytotoxic T cells while potentiating the functions of Tregs, highlighting the intricate balance within the tumor microenvironment.



BFNB enhance hair growth in C57BL/6 mice through the induction of EGF and FGF7 factors and the PI3K-AKT-β-catenin pathway

Salvador Pérez-Mora1, María del Consuelo Gómez-García1, Juan Ocampo-López2, David Guillermo Pérez-Ishiwara1*
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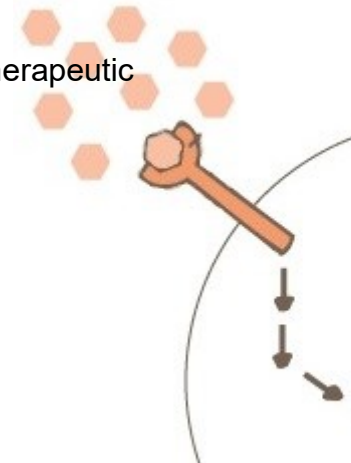
Introduction. Alopecia affects approximately 50% of men and 30% of women worldwide. Currently, Minoxidil and finasteride are the only FDA-approved treatments for this condition, however, they have adverse side effects. Therefore, the aim of this study was to investigate the potential effects of a nanostructured formulation derived from the bioactive fraction of *Bacopa procumbens* (BFNB) on promoting hair growth in a murine model.
Methodology. C57BL/6 mice were depilated on their back and head and received topical applications of BFNB for 30 days. Minoxidil was used as a positive control, and the vehicle served as a negative control.
Results. Characterization of the follicular phases and histomorphological analysis showed that topical application of BFNB for 15 days significantly increased pigmentation and hair growth on the back and head of mice. Furthermore, mice treated with BFNB exhibited an acceleration of the follicular cycle phases, as well as an increase in the number of follicles, hair length, and diameter compared to those treated with minoxidil. Molecular characterization revealed that BFNB upregulates the protein expression of growth factors such as epidermal growth factor (EGF) and fibroblast growth factor 7 (FGF7). This, in turn, activates the PI3K-AKT-β-catenin signaling pathway, along with an increase in the expression of crucial proteins involved in cellular proliferation, including PCNA, KI-67, Cyclin D1, and Cyclin E. These results demonstrate the role of BFNB in regulating the cell cycle and proliferation, which are crucial events for hair regeneration.
Conclusion. Our results suggest that BFNB could be an effective therapeutic alternative to stimulate hair growth and promote its health.



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Towards an integrative model of CD4 T cell activation, regulation and function

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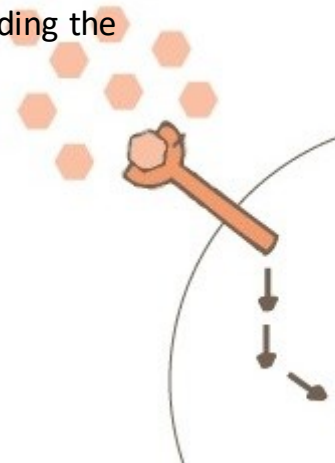
Background: The adaptive immune response initiates after the interaction of the T-cell antigen receptor/CD3 complex (TCR) with an MHC-peptide molecule in the presence of costimulation and cytokines. Downstream activation signals are induced, and they are reinforced, amplified and diversified by a complex network of biochemical interactions resulting in cell proliferation and effector functions. **Objective**: To design a model of downstream TCR and CD28 signaling processes, representing the main early biochemical events involved in T cell activation, regulation, and metabolic changes, in order to construct an interactive framework for simulation of T cell activation. **Methods:** The model includes the anergy factor Ndrg1, modulation of activation by CTLA-4, and the activity of the AMPK nutrient sensor, as intrinsic actors of the activation process. A continuous fuzzy logic approach was employed, so modeling allowed the input of variable levels of stimulating conditions (e.g, levels of cytokines) and activity times of nodes. It also outlined gradual behaviors of the output elements (like AP-1, NFAT and NFκB transcription factors). **Results**: The model generates the dynamics of the activation signals generated by TCR and CD28, and the induction of anergy due to Ndrg1 expression in the absence of co-stimulation. It also reproduces the activation of CTLA-4 and its competition with CD28 by binding to CD80/86 co-stimulating molecules, leading to the arrest of activation. The activity of AMPK, in combination with cytokines, induces the polarization of the cell metabolism towards glycolysis or oxidative phosphorylation, promoting differentiation to effector cell subsets (Th1, Th2, Th17, Treg and TFH). The model described the effect of nutrients, hypoxia and anti-inflammatory compounds, as well as the intrinsic hierarchy in the induction of the different effector phenotypes. **Conclusion:** The model represents a conceptual framework for the integration and prediction of relevant processes regarding the function of CD4 T cells during an immune response.



Resúmenes Sesiones de Carteles

1-4 de octubre de 2023 / Acapulco, Guerrero

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Protein kinase C alpha (PKCα) fragmentation.

Possible role of metalloproteinases.

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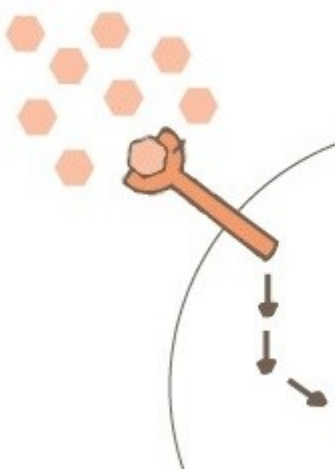
Abstract

Regulation of proteins by degradation is crucial for their function and participation in signal transduction pathways. Protein kinase C (PKC) activation is a fundamental element in the signaling pathways of many G protein-coupled receptors (GPCRs) involved in proliferation, differentiation, and metabolism. There are at least 12 PKC isoforms classified into three groups: a) conventional, b) new, and c) atypical; members of the first two classes are activated by calcium and DAG and by phorbol esters such as phorbol-myristate acetate (PMA) due to do its DAG-like structure.

The activation of PKC by PMA induces its rapid translocation to the plasma membrane (minutes) and also induces the decrease of its expression or “down-regulation” at longer times (hours).

In this work, we study the role of zinc-dependent proteases of the metalloproteinase (MMPs) family on the downregulation of PKCα. *In silico* analysis showed that PKCα has four putative MMPs-catalyzed cleavage sites (three sites by MMP2/9). Confocal microscopy studies suggest that PKCα-GFP colocalizes with both MMPs. Interestingly, 1 μM PMA treatment progressively decreased PKCα abundance, starting at 3 and up to 24 hours, whereas PKCζ expression did not change. We are currently performing western blot experiments to determine whether PKCα degradation by PMA treatment is blocked by specific MMP2/9 inhibitors and/or proteasome inhibitors.

Project supported by CONAHCYT Fronteras 6676, and DGAPA IN201221



Thrombin-induced NFκB activation in retinal pigmented epithelium cells (RPE).

Daniela Alejandra Alvarado Fernández, Irene Lee Rivera, Edith Catalina López Hernández, Ana María López Colomé

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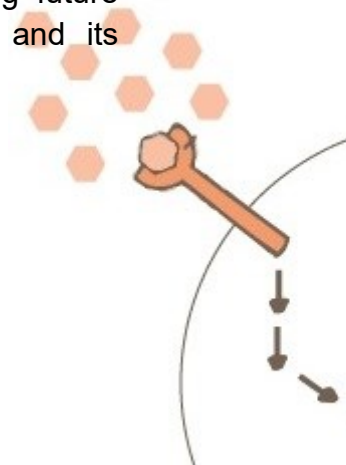
Thrombin is a serine/threonine protease, which contributes to the inflammatory process and induces the transformation, proliferation, and migration of retinal pigmented epithelium cells (RPE). Previous work in the lab suggests that the nuclear factor kappa light chain enhancer of activated B cells (NFκB) plays a major role in these processes. This is an ubiquitous transcription factor known for its role in the regulation of inflammation, proliferation, differentiation, and development. In particular, since thrombin is a pro-inflammatory factor, this work aims to determine the molecular mechanisms involved in NFκB activation in RPE cells.

The NFκB activation and translocation from the cytoplasm to the nucleus is dependent on the removal of IκB, which is bound to NFκB dimers. In response to stimulation, IκB is phosphorylated and releases NFκB, which upon translocation to the nucleus acts as a transcription factor. In previous studies, it has been shown that thrombin induces NFκB activation, via PI3K/Akt pathway in epithelial-like 293T cells and lung epithelial cells A549. In RPE cells, however, these mechanisms have not been elucidated. As this transcription factor is crucial for the inflammatory processes such as cytokine secretion and cell proliferation in response to injury, the objective of this work is to determine the effect of thrombin on IκB activation and degradation in the retinal pigmented epithelium (RPE) cells. For this purpose, the Western Blot technique was used. We observe the maximum level of phosphorylation at 15 minutes, and degradation appears to peak 30 minutes after stimulation. We also determined that the effect of thrombin is specific by using pharmacological tools, such as Hirudin and PPACK, as thrombin inhibitors.

In conclusion, thrombin induces IκB phosphorylation in a specific manner and promotes its degradation in retinal pigmented epithelium cells (RPE). The determination of the molecular mechanism regulating IκB, may help us to elucidate how NFκB is activated, and therefore, can be important for developing future therapeutic treatments for diseases involving this transcription factor and its subsequent role in inflammation of the retina.



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ROS-dependent Inhibition of PMCA Activity Drives Allyl Isothiocianate-Induced Ca^{2+} Signals and Nitric Oxide Release in the Human Cerebrovascular Endothelial Cell Line, hCMEC/D3

[1]Roberto Berra Romani, [2]Valentina Brunetti, [2]Giorgia Pellavio, [4]Teresa Soda, [3]Umberto Laforenza, [3]Giorgia Scarpellino, and [2]Francesco Moccia

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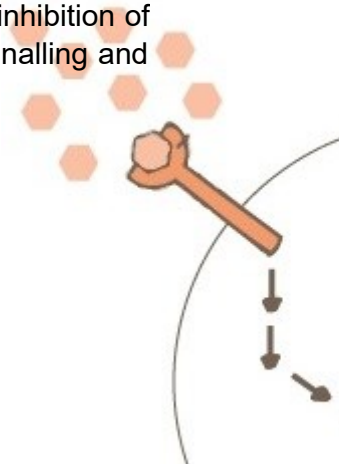
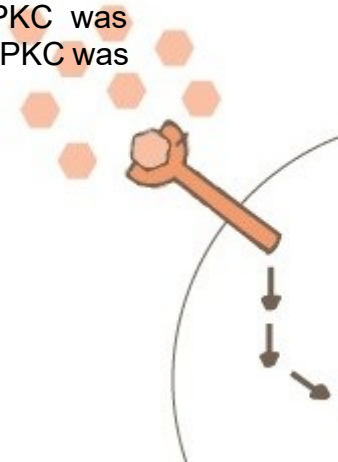
Nitric oxide (NO) represents a crucial mediator to regulate cerebral blood flow (CBF) in human brain both under basal conditions and in response to somatosensory stimulation. An increase in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) stimulates the endothelial NO synthase to produce NO in human cerebrovascular endothelial cells. Therefore, targeting the endothelial ion channel machinery could represent a promising strategy to rescue endothelial NO signalling in traumatic brain injury and neurodegenerative disorders. Allyl isothiocyanate (AITC), a major active constituent of cruciferous vegetables, was found to increase CBF in non-human preclinical models, but it is still unknown whether it stimulates NO release in human brain capillary endothelial cells. In the present investigation, we showed that AITC evoked Ca^{2+}-dependent NO release in the human cerebrovascular endothelial cell line, hCMEC/D3. The Ca^{2+} response to AITC was shaped by both intra- and extracellular Ca^{2+} sources, although it was insensitive to the pharmacological blockade of Transient Receptor Potential Ankyrin 1, which is regarded among the main molecular targets of AITC. AITC-evoked Ca^{2+} signal was triggered by the production of cytosolic, but not mitochondrial, reactive oxygen species (ROS), and was supported by store-operated Ca^{2+} entry (SOCE). Conversely, the Ca^{2+} response to AITC did not require Ca^{2+} mobilization from the endoplasmic reticulum, lysosomes, or mitochondria. However, pharmacological manipulation revealed that AITC-dependent ROS generation inhibited plasma-membrane Ca^{2+}-ATPase (PMCA) activity, thereby attenuating Ca^{2+} removal across the plasma membrane and resulting in a sustained increase in $[Ca^{2+}]_i$. In accord, AITC-evoked NO release was driven by ROS generation and required ROS-dependent inhibition of PMCA activity. These data suggest that AITC could be exploited to restore NO signalling and restore CBF in brain disorders featured by neurovascular dysfunction.



Protein kinase C regulates fibrosis induced by Transforming Growth Factor β3 (TFGβ$_3$) in human hypertrophic myofibroblast

Alejandro Cabrera-Wrooman[1], Nadia Mireya Murillo-Melo[2], Renata Ghenno-Manrique[2], Rene Abarca-Buis[1], Francisco Ferreira[3]. Laboratorio de Tejido Conjuntivo[1], Laboratorio de Medicina Genómica[2], Centro Nacional de Investigación y Atención de Quemados[3]. Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra". Calzada México-Xochimilco 289, Coapa, Arenal Tepepan, 14389 Ciudad de México, México. 59991000 ext: 14706 aca_w@yahoo.com.mx

Many situations can cause skin injuries, and most human skin wounds heal through the process of scaring. Impaired wound healing and excessive scarring (fibrosis) is characterized by the excessive accumulation of dysfunctional extracellular matrix, which hinders tissue regeneration and the complete restoration of structures and function during wound healing. TGF-*β* signaling has been implicated in these processes, indicating that targeting the TGF-*β* pathway with therapeutic agents may enhance wound healing and improve the outcome of scarring. There are three isoforms of TGF-*β* family (TGF-*β*1, 2 and 3), each with a distinct role in the wound healing process. TGF-*β*1 is the most prevalent isoform and maybe the most biologically relevant. In contrast to TGF-*β*1, TGF-*β*3 may be have an anti-fibrotic effect during wound healing. The signaling of the TGF-*β* occurs through its membrane receptors, activating SMAD pathways. The specific role of the TGF-*β*3 in the development of the hypertrophic scar is not yet clear. The aim of this work is to investigate the role of PKC in the development and regulation of fibrosis in human hypertrophic myofibroblasts isolated from biopsies of patients with hypertrophic scars. The results showed an increase of RNA expression of α-sma, collagen I and TGF-*β*1 in myofibroblast. When myofibroblast were stimulated with TGF-*β*1, both the RNA expression and protein levels of PKC increased in comparison to fibroblasts. Interestingly, fibroblast increased PKC levels with TGF-*β*3 stimulation but not with TGF-*β*1. However, PKC RNA expression did not show any changes. The levels of MAPK increased in myofibroblast, and its localization was observed inside the nucleus. Furthermore, MAPK RNA expression increased in both line cells with TGF-*β* incubation, but not with TGF-*β*3. Intriguingly, inhibition of PKC with bisindolylmaleimide (BIM) resulted in decreased MAPK RNA expression with TGF-*β*3 and TGF-*β*1. On the other hand, without any stimulus, AKT levels were high in myofibroblast, and both stimuli increased the proteins levels. However, BIM decreased AKT levels in myofibroblast. Conclusions: Activation of the TGF-*β* receptor led to the activation of MAPK and AKT in both cell lines. PKC was specifically activated by TGF-*β*1 stimulation in myofibroblasts. Additionally, PKC was involved in regulating the expression of Collagen I in both line cells.



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CHLOROGENIC ACID MODULATES DOPAMINE LEVELS IN A MODEL OF STRIAL NEURODEGENERATION.

Cantero-Téllez, A., Rodríguez-Córdova, V.M. and Hernández-Echeagaray, E.

The striatum, an integral part of the central nervous system, plays a crucial role in regulating voluntary movements. The degeneration of its neuronal components has been linked to the development of various neurodegenerative diseases.

One commonly employed model for studying the alterations that occur during striatal neurodegeneration involves the use of 3-nitropropionic acid (3-NP). This toxin blocks mitochondrial complex II, leading to impaired functioning of the electron transport chain, resulting in a deficit of ATP production. Additionally, it triggers an increased production of reactive oxygen species and excitotoxicity mechanisms, ultimately leading to neuronal death.

Emerging research suggests that antioxidants may offer potential benefits in preventing the changes triggered by neurodegeneration. A prominent antioxidant, chlorogenic acid (CGA), which is abundant in the foods we consume daily, has demonstrated neuroprotective properties. Studies have shown that CGA can reduce apoptotic markers, enhance cognitive capacity, and decrease toxic and genotoxic markers in in vitro and in vivo models of neurodegeneration. In vitro experiments have suggested a modulation of Dopamine (DA) release, but this has not been tested in vivo experiments.

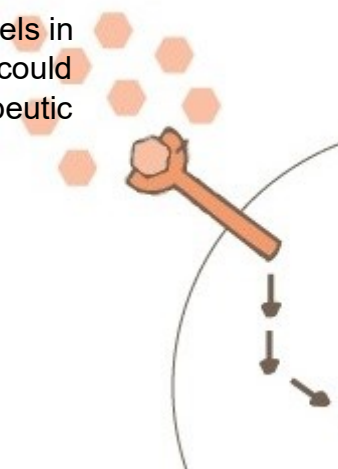
With this background in mind, the objective of our study was to determine if CGA could influence DA and Serotonin (5-HT) levels in a model of striatal degeneration induced by 3-NP.

To achieve this objective, we utilized a neurodegeneration model based on the use of 3-NP in 5-week-old C57BL6 mice. The mice were treated with 3-NP (15mg/kg), CGA (100mg/kg), or a combination of every 24 hours for 5 days. After the treatment period, we obtained samples from the striatum and frontal cortices to measure dopamine, serotonin, and their metabolite levels.

Our findings revealed that while CGA did not cause any significant changes in the levels of 5-HT or its metabolites, it did result in an increase in DA levels in CGA group in the frontal cortex. This indicates that CGA differentially modulates DA levels in the frontal cortex.

In conclusion, our study sheds light on the effects of CGA in influencing DA levels in the frontal cortex during striatal degeneration. Further research in this area could lead to a better understanding of the properties of CGA and its potential therapeutic implications for neurodegenerative diseases.

This work was supported by PAPIIT IN 216721



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Testosterone enhances, via a genomic pathway, airway smooth muscle relaxation induced by ATP and UTP.

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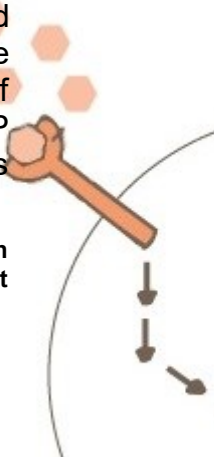
Abstract:

Airway smooth muscle (ASM) relaxation is mediated by circulating catecholamines through the adrenergic system. However, several chemical mediators can alter ASM tone, such as adenosine triphosphate (ATP) and uridine triphosphate (UTP). Initially, they induce contraction, and when they reach the maximum response, they cause ASM relaxation. ATP and UTP act on P2-type purinergic receptors coupled to G proteins (P2Y). Activation of P2Y receptors leads to an increase in intracellular Ca^{2+} concentration, which promotes the synthesis of prostaglandin E_2. This mediator favors the enhancement of cyclic adenosine monophosphate (cAMP) and consequently the activation of protein kinase A (PKA). PKA promotes the opening of K^+ channels, hyperpolarization of the plasma membrane, and consequently ASM relaxation. The major K^+ channels involved in this process are high-conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) and delayed rectifier voltage-gated channels (K_V). They can be activated via the cAMP-PKA pathway. An association between androgens and asthma disease has been widely documented. In childhood, asthma symptoms are more common in boys than in girls. This phenomenon reverses at puberty when symptoms decrease, and plasma concentrations of testosterone (TES) increase in young men. Androgens are known to exert their physiological effects via genomic and non-genomic pathways. Genomic effects depend on the androgen receptor (AR) to modulate transcription and protein synthesis, whereas nongenomic effects occur over a short period of time and are independent of AR activity. This project aimed to investigate the signaling pathway by which TES might enhance relaxation induced by ATP and UTP, possibly through a genomic effect. Chronic incubation of guinea pig trachea with TES (40 nM for 48 hours) enhanced ATP- and UTP-induced relaxation. In tracheal myocytes, chronic incubation with TES increased ATP- and UTP-elicited K^+ currents (IK^+), which were abolished by flutamide (AR antagonist). The ATP- and UTP-induced increase in IK^+ was blocked by 4-aminopyridine and iberiotoxin, suggesting that K_V and BK_{Ca} are involved in the TES potentiation effect. In conclusion, chronic exposure to physiological levels of TES in guinea pig ASM promotes increments in K^+ currents, favoring ATP and UTP responses, and likely limits the severity of asthmatic exacerbations in teenage boys and men.

This work was partially funded by the Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT), UNAM (IN200522) to L. M. Montaño. In addition, L. M. Montaño received a grant from the Consejo Nacional de Ciencia y Tecnología, México (CF -137725).



Analysis of LIMK1 and COFILIN phosphorylation in the hippocampus of the C58/J mouse model of autism during estrous cycle.

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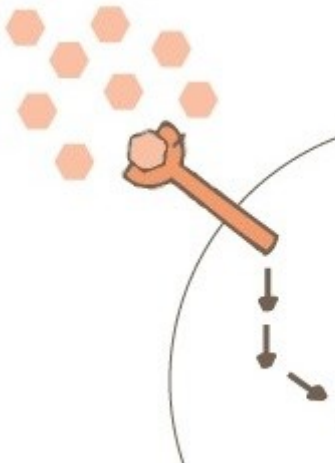
Autism spectrum disorder (ASD) is a neurodevelopment disorder characterized by deficits in communication and social interaction, restricted interests, and repetitive behaviors. Although the ASD etiology remains unclear, it is known that the prevalence of ASD is higher in males than I females, with a ratio of 4:1.The gender difference in the prevalence of ASD is related to genetic and neurobiological factors. Notably women with ASD have a higher prevalence of endocrine comorbidities compared to neurotypical women.

Hormonal fluctuations during the menstrual /estrous cycle have been shown to promote changes in structural plasticity in the hippocampus, characterized by variations in dendritic spine density depending on the phase of the cycle and hormone levels such as estrogen.

Estradiol plays a crucial role in modulating hippocampal structural plasticity by activating selective membrane-associated receptors. It influences the function of important proteins involved in actin cytoskeleton that impact in dendritic spines formation such as Cofilin. Cofilin a potent regulator of actin filament dynamics, undergoes phosphorylation by LIMK kinase, leading to actin filament polymerization. This process is a significant mechanism in dendritic spine formation.

Previous data obtained from females of the C58/J murine model of autism , for which the day of the estrous cycle was not determined, showed differences in the amount of phosphorylated Cofilin compared to C57BL/6J wild type strain females. Therefore, the objective of this study was to analyze the phosphorylation levels Cofilin and LIMK proteins in the hippocampus of C58J females across each phase of the estrous cycle. This analysis aimed to investigate the impact of endogenous estrogen levels on neuronal structure in ASD .



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Role of PKCs in the negative regulation of the insulin pathway by resveratrol

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Resveratrol (3,5,4'-trihydroxy-trans-stilbene)(RSV) is a polyphenol present in a wide variety of red fruits and wine. Different preclinical studies show that RSV exerts protective effects in models of diseases such as obesity, diabetes mellitus, cancer, and other cardiovascular diseases(1). The positive effects of this compound have been associated with its antioxidant activity through changes in the expression and activity of proteins that produce or metabolize reactive oxygen species (ROS). However, the direct scavenging of free radicals by RSV is known to be significantly less compared to other antioxidants, and there is also controversy about its effects on metabolic tissues(2). In our laboratory, the effect of RSV on the insulin pathway was evaluated in C9 liver cells from normal rat tissue and Hepa 1-6 cells derived from mouse hepatoma. An inhibitory effect of the PI3K/Akt signaling pathway, associated with the metabolic functions of insulin, was found. RSV caused decreased phosphorylation in Tyr^{1158} of the insulin receptor (IR) and Ser^{473} in the Akt protein in both cell lines. On the contrary, the effects of RSV on the MAPKs pathway were dual, an increase in ERK1/2 phosphorylation was observed in C9 cells and a decrease in Hepa1-6, the latter coinciding with reports of the anticancer effect of RSV(3). The effects of RSV in the PI3K/Akt pathway and the MAPKs are associated with the positive regulation of the PKC isoforms, which was corroborated by inhibiting the activity of classic and new PKCs. PKC inhibition prevented RSV-induced effects on IR, Akt, and ERK1/2 phosphorylation. The effect of polyphenol on the phosphorylation of the PKCα (Ser^{657}), PKCδ (Ser^{643}), and PKCε (Ser^{729}) isoforms was also evaluated, observing an increase in Ser residue phosphorylation in the three isoforms. Immunoprecipitation assays also showed that RSV promotes the interaction of IR with the PKCα and PKCε isoforms. The results of this study demonstrate that RSV inhibits the PI3K/Akt signaling pathway and may favor MAPK activity through a mechanism that involves the activation of different PKC isoforms to promote the interaction of IR with PKCs.

Funding
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The RTKs and ERK1 are involved in the KCl-induced contraction in guinea pig airway smooth muscle.

Eva Herrera Alcibar[1], Betina Sommer Cervantes[1], Lizet Ocampo Monzalvo[1], Vanesa Alarcón Barcena[1], Enrique Castillo Henkel[2], Ruth López Mayorga[2] and Verónica Carbajal Salinas[1].

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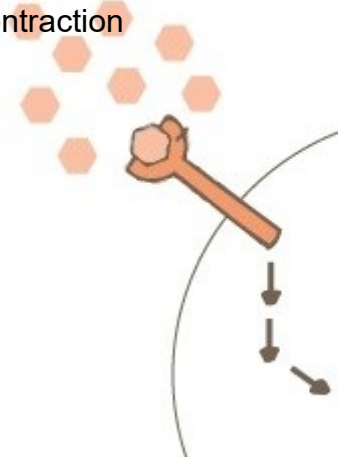
The contraction of airway smooth muscle (ASM) is given by the activation of receptors coupled to G proteins, where second messengers are involved, generating an increase in intracellular calcium. The contraction is also given by the depolarization of the cell membrane allowing the entry of calcium through the activation of L-type voltage dependent calcium channels. Potassium chloride (KCl) has been used as a pharmacological tool that induces depolarization of the cell membrane generating contraction and this induces the activation of different signaling pathways. **Aim:** We evaluated the involvement of receptor tyrosine kinase (RTKs) and ERK1/ERK2 in KCl-induced contraction in the airways smooth muscle of the guinea pig. **Methods.** Guinea pig tracheal rings were precontracted with 20 mM KCl, then pre-incubated with genistein or ST638 (10 μM, inhibitor of RTKs), PD98059 (5, 10 or 32 μM, inhibitor of MEK) and FR180204 (5, 10 or 32 μM, inhibitor of ERK1/ERK2) and a second response of 20 mM KCl was given. Afterwards, KCl-stimulated tissues were homogenized, and Western Blots were carried out to evaluate the participation of phosphorylated ERK1/ERK2 in the contraction. **Result:** We found that genistein, ST638, and PD98059 decrease contraction responses induced by 20 mM KCl, however, with FR180204 only 32 μM decreases contraction significantly. In the densitometry analysis we found a decrease in the phosphorylation of ERK1/ERK2 when RTKs were inhibited; when MEK and ERK inhibitors were used, we observed a decrease in ERK1 phosphorylation. **In conclusion** receptor tyrosine kinase and ERK1 participated in the contraction induced by 20 mM KCl in guinea pig tracheal smooth muscle.



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Activación de la calpaína-10 en respuesta a pulsos de glucosa

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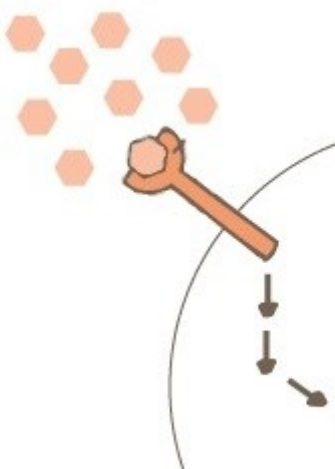
Introducción. La calpaína-10 es una proteasa de cisteína que aumenta la captación de glucosa inducida por insulina al promover el tráfico de GLUT4 en adipocitos y mioblastos (1,2). De manera similar, en células linfoides, la calpaína-10 regula la abundancia de GLUT1 y la captación de glucosa inducida por cambios en la concentración extracelular de glucosa (3). **Objetivo.** Evaluar la participación de la calpaína-10 en respuesta a pulsos de glucosa en células linfoides. **Metodología.** En este estudio se establecieron modelos de silenciamiento génico en las células Jurkat con un *shRNA* contra CAPN10 ($CAPN10^{shRNA}$) o contra un gen control ($Control^{shRNA}$). El silenciamiento se validó al medir la abundancia proteica y el mRNA de calpaína-10 por western blot y qPCR respectivamente. La actividad general de las calpaínas y los cambios en la concentración intracelular de calcio en respuesta a pulsos de glucosa se evaluaron al medir la hidrólisis de un sustrato fluorogénico de las calpaínas, y la fluorescencia del colorante Fluo-8, respectivamente. El efecto de los pulsos de glucosa en la abundancia proteica de Akt, pAkt y calpaína-10 se determinó por Western blot. **Resultados.** Los resultados muestran que la alta glucosa genera un aumento en la actividad general de las calpaínas dependiente de la presencia de calpaína-10. Los pulsos de glucosa no producen cambios en la concentración intracelular de calcio, ni en la abundancia proteica de Akt y pAkt. La abundancia de calpaína-10 aumenta con alta glucosa. **Conclusión.** En células linfoides, los pulsos con alta glucosa no activan la vía canónica, pero inducen la activación y el aumento en la abundancia proteica de la calpaína-10.

Agradecimientos. Este trabajo recibió financiamiento de PAPIIT-UNAM proyecto IN205621.



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c-kit influences CXCR4, α4β1 integrins expression in leukaemic lymphoblasts.

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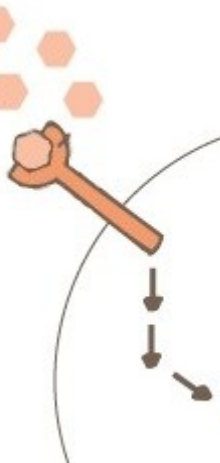
Acute lymphoblastic leukaemia (ALL) often presents with a high proliferation rate of pre-B lymphoblasts. These lymphoblasts mobilize from the bone marrow to the peripheral blood and lymphatic system; as proliferation advances, they infiltrate the liver, spleen, lymph nodes, testes and central nervous system. The ability to move from the blood and/or lymphatic circulation to extra-medullary sites implies that these cells cross vascular barriers, which suggests they acquire signals that mediate leukocyte migration . Among these signals are chemokine SDF-1 and CXC chemokine receptor 4 (CXCR4), which are related to the retention and release of haematopoietic stem cells (HSCs) and leukocytes. CXCR4 signalling has been linked with c-kit receptor and α4-integrin in the retention and release of HSCs. The ckit receptor exhibits tyrosine kinase activity and is associated with cell proliferation and differentiation. Integrins are transmembrane heterodimers that act synergistically with growth factor receptors, mediating cell adhesion, migration, proliferation and differentiation. In particular, α4β1-integrin has been reported to be expressed in HSCs and lymphocytes. In this study, we tested whether the cKit receptor influences the expression of CXCR4 and α4β1 integrins via CXCR4 and whether CXCR4 directly influences the expression of these same integrins in leukaemic lymphoblasts. We found that in leukaemic lymphoblasts, activation of cKit induced a 2.1-fold increase in CXCR4 expression. Likewise, we observed that activation of cKit increased α4 integrin expression 4.2-fold; inhibiting CXCR4 decreased α4 integrin expression 1.7-fold compared to that observed in lymphoblasts treated with SCF alone. We also observed that ckit activation increased β1 integrin expression 1.8-fold; and inhibiting CXCR4 decreased β1 integrin expression. On the other hand, when we assessed whether CXCR4 activation influences the expression of α4β1 integrins, we found that CXCR4 activation increased α4 expression 2.1-fold and β1 expression 1.3-fold. Our results indicate that in leukaemic lymphoblasts cKit and CXCR4 receptor activation alone induce an increase in α4β1 integrin expression and that cKit increases CXCR4 expression and influences α4β1 integrin expression via CXCR4.



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"Possible Involvement of Pak1 and CaMKII in Insulin Secretion by Pancreatic Beta Cells".

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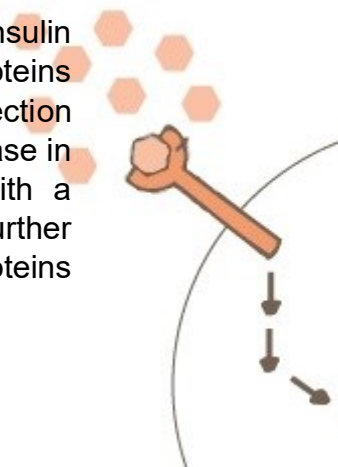
Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by elevated blood glucose levels due to insulin resistance and decreased insulin secretion by pancreatic beta cells. Insulin secretion is regulated by a series of intracellular processes involving different proteins and enzymes.

The objective of this study was to investigate the potential cooperation between two enzymes, Pak1 and CaMKII, which participate in different phases of insulin secretion, in pancreatic beta cells. Using indirect immunofluorescence, we observed that Pak1 and CaMKII co-localize and form a protein complex in the beta pancreatic cell line Beta-TC-6, but only when stimulated with 20 mM of glucose and not with low levels of glucose (4 mM).

Furthermore, we conducted an experiment where we pharmacologically inhibited Pak1 with Frax-1036 and CaMKII with KN-93. We evaluated insulin secretion using the ELISA technique and observed a significant decrease in insulin secretion in both conditions. Interestingly, there was a trend towards suppression when both enzymes were inhibited simultaneously.

In addition, we analyzed the mRNA expression levels of Pak1 and CaMKII in human beta cells obtained from healthy individuals, pre-diabetic individuals, and diabetic patients. Our results demonstrate that Pak1 and CaMKII expression is increased in pre-diabetic and diabetic patients. Interestingly, the expression of these proteins is initially upregulated in pre-diabetes, possibly as a compensatory mechanism, but returns to baseline values in T2DM, likely due to the destruction of beta cells, which is a key aspect of T2DM pathophysiology.

In conclusion, these findings suggest that Pak1 and CaMKII may play a role in insulin secretion by pancreatic beta cells. Moreover, the overexpression of these proteins in pathological conditions implies their potential utility as markers for early detection of pre-diabetes and T2DM. Our experimental data showed a significant decrease in insulin secretion when pharmacologically inhibiting Pak1 and CaMKII, with a tendency towards suppression in the combined inhibition condition. Further investigations are warranted to elucidate the precise involvement of these proteins in insulin secretion and explore their clinical implications.



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Thrombin-induced activation of focal adhesion proteins in the Retinal Pigment Epithelium (RPE)

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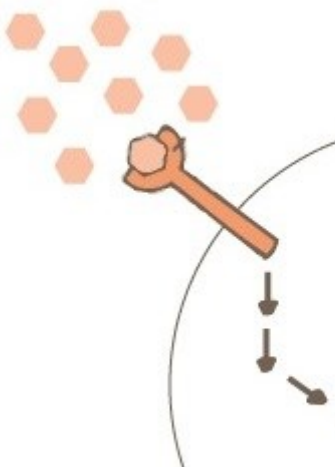
The retinal pigment epithelium (RPE) is a monolayer of pigmented cells that, along with Bruch´s membrane, form the outer blood-retinal barrier; when damaged, photoreceptors die in consequence. One of the diseases affecting the RPE is proliferative vitreoretinopathy (PVR); where some RPE cells transform and migrate into the vitreous cavity and underneath the retina, forming a layer of cells that is capable of detaching the retina.

In previous studies, it has been shown that thrombin's activity increases in the vitreous cavity of patients with PVR, which can induce cell migration. This process involves the assembly and disassembly of focal adhesion proteins such as focal adhesion kinase (FAK), Paxillin and proline-rich tyrosine kinase 2 (Pyk2). Previous work in the laboratory has shown that thrombin activates FAK, resulting in increased RPE cell migration. This suggests that other proteins involved in focal adhesions, such as Paxillin y Pyk2 are also activated by this protease. Therefore, the aim of this project is to determine the effect of thrombin on the phosphorylation of these proteins. Paxillin and Pyk2 activation was assessed by Western Blot in RPE primary cultures. Using thrombin concentration curves, we determined that the activation peak corresponds to a 5U/ml concentration for both proteins. Also, we evaluated activation from 2 to 30 minutes of stimulation and found maximum phosphorylation at 5 minutes.

In conclusion, thrombin promotes the assembly of focal adhesions by inducing the phosphorylation of key proteins, which may result in increased RPE cell transformation and migration. The determination of optimal timing and thrombin concentration for the induction of these proteins, can be of importance to develop future therapeutic treatments for diseases such as PVR or to prevent the deleterious effects of retinal detachment on photoreceptor death.



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Thrombin-induced cytokine secretion on retinal Müller glia

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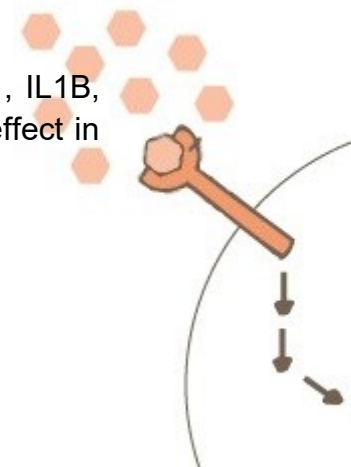
Müller cells are the main type of glia in the vertebrate retina. These cells are involved in the maintenance of tissue structure, homeostasis, damage detection, inflammation, and induce protection and repairment responses. In the presence of injury or disease, Müller cells activate and produce gliosis. This process is characterized by morphological and physiological changes that involve the release of proinflammatory cytokines, among other factors, which, can promote retinal degeneration in the long term.

Similarly, upon the rupture of the blood-retinal barrier, the retina comes in contact with blood serum components, including thrombin. It has been observed that thrombin, a pro inflammatory factor, induces gliosis in Müller cells. Moreover, in the pigmented epithelium of the retina it has been observed that this protease induces cytokine secretion, that appears to depend on NF-kB. In addition, thrombin also triggers MAPK and PKC signaling pathways, which might be important for the release of pro inflammatory factors.

The aim of this study was to understand the mechanisms by which thrombin induces cytokine secretion in retinal Müller glia. We worked with MIO-M1 cell line, stimulated with thrombin for 24 and 48h. Cytokine expression was evaluated by qRT-PCR. It was found that thrombin induces the expression of: CCL2, CXCL1 and IL1A at 24h of stimulus; whereas IL1A and IL1RN were induced after 48h of stimulation. Thrombin specificity was assessed using two specific pharmacological inhibitors: Hirudin and PPACK, which were found to inhibit thrombin-induced cytokine expression. To evaluate the participation of the aforementioned signaling pathways in cytokine expression, their specific pharmacological inhibitors, U0126 for MAPK, Ro32-4032 for PKC and BAY11-7082 for NF-kB, were used.

In conclusion, thrombin induces the expression of CCL2, CXCL1, IL1B, IL1A and IL1RN in a specific manner, which could mediate thrombin's effect in gliosis induction.



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Identificación *in silico* e *in vitro* de proteínas tipo caspasa 3 en *G. intestinalis*

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Palabras clave: ***Giardia intestinalis, caspasas, separasa, transaminasa de anclaje GPI***

Introducción. *Giardia intestinalis* es un parásito protozoario amitocondriado, causante de la Giardiasis, una de las principales causas de diarrea en todo el mundo, por ello los datos moleculares sobre su muerte celular, en especial las involucradas en la vía de apoptosis son de gran relevancia terapéutica. Nuestro grupo de investigación identificó en *G. intestinalis* al ortólogo de la endonucleasa activada por caspasas (CAD) denominada GCAD, así como su inhibidor (ICAD) homólogo o IGCAD (1). En eucariotas superiores se ha observado que caspasa-3, escinde a ICAD. Otras proteínas diana de caspasa-3 son las flipasas que al ser escindidas exponen extracelularmente a fosfatidilserina (2). Por ello, nuestro objetivo fue la búsqueda *in silico* e *in vitro* de proteasas ortólogas a caspasa-3 en de *G. intestinalis.*

Metodología. Se utilizó la secuencia pro-caspasa-3 (GenBank NP_004337.2) de *Homo sapiens* para realizar la búsqueda en el proteoma de *G. intestinalis* mediante DELTA-BLAST. Se predijo la estructura terciaria de las proteínas mediante Robetta (3), las estructuras se editaron en UCSF Chimera (4). Se realizó un *Western blot* para la detección *in vitro* de proteínas tipo caspasa 3 en el extracto crudo de proteínas de *G. intestinalis* cepa WB (ATCC 30957).

Resultados. Se identificaron *in silico* la separasa (GenBank ESU44720.1) y la transaminasa de anclaje GPI (GenBank XP_001707708.1) de *G.intestinalis*, con un porcentaje de identidad del 39.47 % y 31.25 %, respectivamente. Ambas contienen un dominio tipo caspasa. Se logró la detección de proteínas tipo caspasa *in vitro* con un peso molecular de 250, 150 y 50 kDa. De las cuales, la que podría coincidir en peso molecular es la separasa de 178 kDa, no obstante, se necesita verificar su secuencia. Las proteínas de 50 y 250 kDa podrían ser proteínas ortólogas a caspasa 3 sin reporte previo.

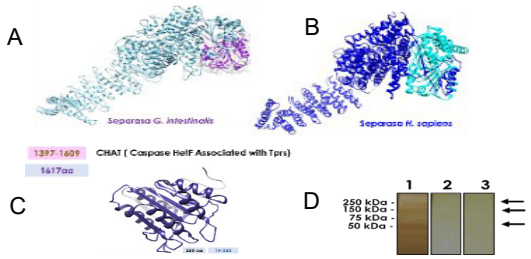

Figura 1. A) Estructura de la separasa de *G. intestinalis*, dominio catalítico tipo caspasa se resalta en morado (residuos 1397-1609). B) Estructura cristalizada de la separasa de *H. sapiens*, dominio catalítico tipo caspasa en azul cian. C) Estructura de la transaminasa de anclaje GPI, dominio catalítico tipo caspasa en azul marino. D) Identificación inmunoquímica de proteínas ortólogas a caspasa 3 en el proteoma de *Giardia intestinalis.*

Conclusiones. Se identificaron *in silico* e *in vitro* proteínas ortólogas a caspasa 3.

Agradecimiento. Al fondo CB-2014-240185, por el financiamiento de este proyecto.

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ESTRUCTURA

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EGF-receptor phosphorylation and downstream signaling are activated by genistein during subacute liver damage.

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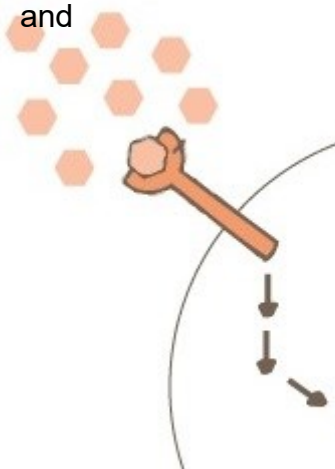
The chemically-induced hepatotoxicity is followed by compensatory liver regeneration, which involves an interplay of several signaling pathways. The epidermal growth factor receptor (EGFR) plays an important role on hepatic protection in acute and chronic liver injury. Previous studies have demonstrated that genistein is an inhibitor of protein-tyrosine kinases, attenuating growth factor and cytokine, as EGFR ligands. Therefore, the aim of the present study was to investigate the role of genistein on EGFR expression, phosphorylation and signaling pathway in a CCl4-induced subacute liver injury model of rats.
We used male Wistar rats that were randomly divided into four groups: (1) Control; (2) Genistein 5 mg/kg per oral; (3) Subacute liver damage induced by CCl4 4 mg/kg subcutaneously; and (4) Animals received CCl4 and genistein at the dosage indicated. The effect of genistein on EGFR expression, phosphorylation and signaling pathways were investigated by western blot and densitometric analyses. Histological changes were evaluated on slices stained with Hematoxylin-Eosin and Masson´s trichromic, as well as an immunohistochemical analysis for proliferating cell nuclear antigen (PCNA). Additionally, pro-inflammatory cytokines and liver enzymes were quantified.
Our study showed that genistein increased EGFR expression, EGFR-specific tyrosine residues phosphorylation (pY1068-EGFR and pY84-EGFR), signal transducer and activator of transcription phosphorylation (pSTAT5), protein kinase B phosphorylation (pAKT) and PCNA in animals with CCl4-induced subacute liver damage. Therefore, our results suggest that genistein can transactivate EGFR and activate downstream cell signaling subacute liver damage. It was found a significant reduction of pro-inflammatory cytokines in serum from animals with subacute liver damage treated with genistein. Those effects were reflected in an improvement in the architecture and liver function.
In conclusion, genistein can induce a transactivation of EGFR leading to downstream cell signaling pathways as early events associated with regeneration and hepatoprotection following subacute liver damage.



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Progesterone receptor has a role in choriocarcinoma cells and placental steroidogenesis

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Progesterone receptor (PR) plays a critical role during pregnancy but its role in the of steroidogenesis is unknown. In the human placenta isoforms of PR have been described (PR-A, B and C), which sharing the substrate-binding domain (1). Recently, a mitochondrial PR (PR-M) was identified and associated with spermatozoa activation and myometrial growth, both activities respond to progesterone concentrations (2). In our laboratory we identified the PR-M in isolated mitochondria from syncytiotrophoblast or choriocarcinoma cells (JEG-3). The PR-M was in the outer mitochondrial membrane, suggesting that it could be associated to the steroidosome, a multiproteic complex with the P450scc chain which regulate the steroidogenesis.

The objective of this work is determining the role of PR-M as a possible modulator of placental steroidogenesis. The JEG-3 cells were incubated 24, 48 or 72 h with 10 nM P4 or 15 µM RU486, a progesterone receptor antagonist. Progesterone was quantified by ELISA, and protein expression of PR, P450scc, 3BHSD and HSP60 by western blot. Immunoprecipitation assay was performed with isolated mitochondria and the PRs identified by western blot.

The results showed the four PR isoforms in the cell lysate and isolated mitochondria; while in the mitochondrial immunoprecipitation a band of 37 kDa was identified, which corresponds to PR-M. When the cells were incubated with RU486, the P4 concentration in the culture medium decreased 20% at 24 h, while at 72 h the progesterone increase about 40%. In the presence of exogenous P4, its concentration in the medium increased by 40% at 24 h, but decreased with time, reaching the control value at 72 h. To determine if antagonist effect displaces the agonist effect or vice versa, cells were incubated with RU496 or exogenous P4 during 24 h followed by the addition of exogenous P4 or RU486 for another 24 h. The results showed that the inhibitory effect of exogenous P4 prevails over the stimulatory effect of RU486, in the same way that RU486 over exogenous P4. The data suggest that changes in the P4 concentration could be associated with the modulation of the P450scc or HSP60 expression. However, preliminary experiments with isolated mitochondria from human placenta suggest that PR-M could have also a local effect modulating the P4 synthesis thought the activity of proteins involved in the first steps of steroidogenesis.

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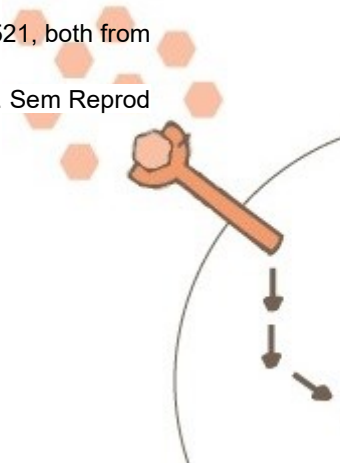

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TRPV4 activation during guinea pig airway smooth muscle contraction promotes Ca^{2+} and Na^{+} influx.

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Abstract:

Airway smooth muscle (ASM) contraction is determined by the increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) caused by release from the sarcoplasmic reticulum (SR) or by extracellular Ca^{2+} influx. The major channels involved in Ca^{2+} influx in ASM cells are L-type voltage-dependent Ca^{2+} channels (L-VDCCs) and nonselective cation channels (NSCCs). Transient receptor potential vanilloid 4 (TRPV4) is a NSCC recently studied in ASM. TRPV4 is activated by warm temperatures, osmotic and mechanical stimuli, such as muscle contraction. We investigated the possible activation of TRPV4 by histamine (His)- or carbachol (CCh)-induced contraction in guinea pig ASM. In single myocytes, TRPV4 agonist (GSK1016790A, 32 nM) evoked an increase in $[Ca^{2+}]_i$ characterized by a slow onset and a plateau phase. The TRPV4 antagonist (GSK2193847) decreased channel activity by 94%, whereas Ca^{2+}-free medium abolished the Ca^{2+} response induced by GSK1016790A. Stimulation of tracheal myocytes with GSK1016790A induced Na^{+} influx that was blocked with the antagonist GSK2193847. Na^{+} influx is responsible for plasma membrane depolarization and L-VDCCs opening. D-600, a blocker of L-VDCCs decreased the Ca^{2+} response induced by the TRPV4 agonist. ASM cells stimulated with His or CCh produced a transient Ca^{2+} peak followed by a sustained plateau. GSK2193847 significantly reduced the Ca^{2+} peak and the Ca^{2+} plateau triggered by His or CCh. In tracheal rings, the addition of cumulative concentrations of the agonist GSK1016790A elicited ASM contraction, which was reduced by D-600. TRPV4 blockade shifted the concentration-response curve to His and CCh to the right and reduced the maximal contraction response. Finally, activation of TRPV4 in single myocytes increased the SR-Ca^{2+} refill. We conclude that contraction of ASM cells after their stimulation with His or CCh promotes TRPV4 activation and subsequent influx of Ca^{2+} and Na^{+}, and the opening of L-VDCCs. The entry of Ca^{2+} into ASM cells via TRPV4 and L-VDCCs contributes to smooth muscle contraction.

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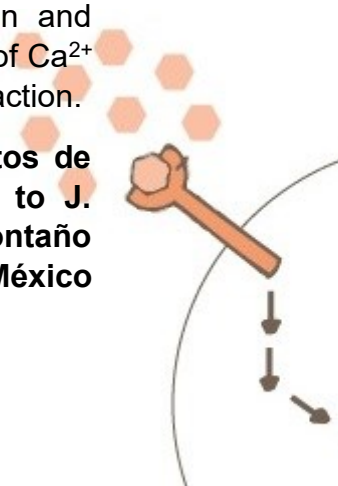

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Latrophilin-1 is involved in sperm-ovum interaction in mice

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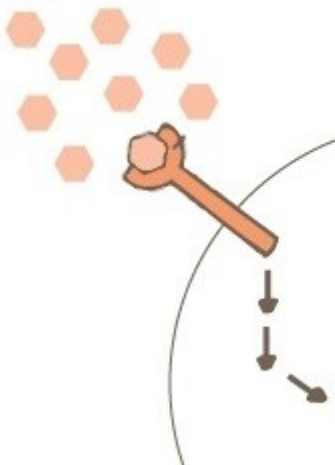
Introduction. Mammalian fertilization is completed through the interaction between the sperm and the ovum, a process mainly mediated by adhesion and membrane fusion proteins found on the surface of the gametes. Both gametes have proteins on their surface that are unique. Despite their importance, only three essential proteins for the adhesion and fusion of the sperm cell membrane with that of the egg cell are known: IZUMO1, Fertilin and SPACA6 in the sperm cell, JUNO in the egg cell and C9 in both gametes. Despite the fundamental importance of sperm-ovum interaction, little is known about what happens at the molecular level. Another candidate protein in the sperm-ovum adhesion process is latrophilin-1, a member of the latrophilin family (LPHN). LPHNs are part of a still unexplored family of receptors comprising three isoforms, LPHN1, LPHN2, and LPHN3, and belong to a unique branch of G protein-coupled receptors (GPCRs) called adhesion GPCRs (aGPCRs).
Objective. The present work was to detect and immunolocalize LPHN1 in mouse sperm and determine its possible participation in sperm-ovule interaction.
Results. LPHN1 was identified by western blot as a 60 kDa protein in whole mouse spermatozoa extracts. LPHN1 was immunolocalized in the acrosome, equatorial and middle parts of the flagellum. Its location did not change during capacitation and the acrosome reaction (AR). Sperm (30 X 103 sperm/mL) were incubated with the anti-LPHN1 antibody for 30 min, added to the ova, and incubated for 4 hours. The results show that the antibody inhibited the sperm-ovule interaction concerning the control. Similar results were obtained when a blocking peptide was used.
Conclusion. Latrophilin 1 is present on the surface of mouse spermatozoa, and the blocking results of this adhesion protein suggest its partition in the sperm-ovum interaction.
CONAHCYT CB-284183



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RELATIONSHIP OF OXIDATIVE DAMAGE WITH THE EXPRESSION OF THE INSULIN RECEPTOR, DURING BRAIN AND PERIPHERAL INSULIN RESISTANCE IN A MODEL OF OBESITY

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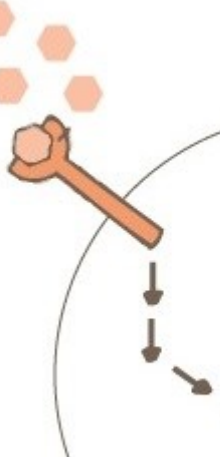
Introduction: Insulin resistance consists in improper response of body cells to insulin signals. This leads to reduced glucose uptake and increased blood sugar levels. The development of insulin resistance implies molecular events, including reduced expression and/or activation of the insulin receptor (IR) and its downstream signaling molecules. In the case of brain insulin resistance, there is a decrease in thermogenesis, weight gain and cognitive processes (memory and learning). Stress and oxidative damage have also been suggested as factors involved in the insulin resistance. However, the relationship between oxidative damage and the IR expression is not well understood. **Aim:** To evaluate the level of oxidative damage during the development of brain and peripheral insulin resistance, as well as to relate the damage to the IR expression *in vivo* model of obesity. **Methodology:** 3-month-old C57BL/6 male mice were fed high-fat diet (HFD), high-carbohydrate diet (HCD), and standard diet (STD) for 1, 2, and 3 months (n=6). The evaluation of oxidative damage to lipids was detected by malondialdehyde (MDA); protein damage was performed by carbonylated proteins (PCO); and antioxidant system evaluation was performed by measuring the enzymatic activity of glutathione peroxidase in cerebral cortex, plasma, white adipose tissue (WAT) and brown adipose tissue (BAT), with spectrophotometric techniques. Oxidative DNA damage, represented by the presence of 8-hydroxydeoxyguanosine (8-OHdG), was determined in plasma by ELISA. The IR expression in cerebral cortex, hypothalamus, and BAT was determined by western blot. **Results**: *Evaluation of oxidative damage and IR expression at the brain.* In mice fed for 1 month with HFD or HCD: the amount of MDA was lower in cerebral cortex of HFD-fed mice. In mice fed for 2 months with HFD or HCD: the amount of PCO was higher in HCD-fed mice. In mice fed for 3 months with HFD or HCD: the IR expression was higher in cerebral cortex HCD-fed mice,and was lower in hypothalamus HCD-fed mice. *Evaluation of oxidative damage and expression of the IR at peripheral level*. In mice fed for 1 month with HFD or HCD: a) the amount of MDA in plasma was higher in mice fed with HFD, b) the amount of PCO in plasma and WAT was higher in mice HFD-fed. In mice fed for 2 months with HFD or HCD: a) the amount of MDA in WAT was higher in mice fed with HFD, b) receptor expression was significantly increased in BAT from HFD-fed mice. **Conclusions:** The HCD induces protein oxidative damage in cerebral cortex, but this result is not related with IR expression, while HFD induces the oxidative damage at the peripheral level. Despite the increase in IR by HFD in BAT, this result is not related to the presence of oxidative damage.



PROTEÍNAS G

Genetic screen for the identification of multicopy suppressor genes in the *Saccharomyces cerevisiae npa3G70A* mutant strain.

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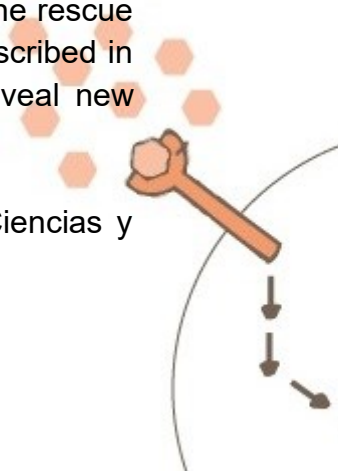
Npa3 is a GTPase that belongs to the GPN subfamily and is an essential protein in the yeast *Saccharomyces cerevisiae.* Npa3 is required for the nuclear accumulation of RNA polymerase II (RNAPII) in both the yeast *S. cerevisiae* and human cells (Forget et al., 2010. *Mol Cell Proteomics 9*:2827). An analysis performed by our group using public databases revealed that transcription of the *NPA3* gene is regulated in a similar way to genes whose products are known to participate in ribosomal biogenesis (https://yeastgenome.org/, SPELL). This observation stimulated us to investigate a possible participation of Npa3 in other cellular processes and molecular pathways, including ribosomal biogenesis.

Since Npa3 is an essential protein, it is not possible to inactivate the *NPA3*gene to study its cellular functions. To achieve this goal, strains of *S. cerevisiae* that express mutant versions of Npa3 with a partial loss of function (hypomorphic) have been generated. In the *npa3G70A* strain RNAPII is distributed throughout the cell and not only in the cell nucleus, as observed in wild type cells; cell size is increased and proliferation is slower, compared to the control strain (Forget et al., 2010. *Mol Cell Proteomics 9*:2827). To gain insight into the molecular processes controlled by Npa3 in the cell we set out to identify genetic suppressors of these phenotypes. As a first step to achieve this goal, we are generating a genomic library in a high copy number plasmid representing the complete genome of *S. cerevisiae*. We have optimized the experimental conditions to reproducibly obtain an enriched fraction in 8-12 kb fragments when digesting genomic DNA with the four nucleotide-cutter enzyme Sau3A1. These fragments are being ligated into the *Bam*HI-digested, SacB-containing and cip-treated pRS426 high copy plasmid to electroporate DH10B competent cells. With this genomic library we will subsequently perform the rescue experiments to identify those genes able to suppress the phenotypes described in the *npa3G70A* mutant strain. The identity of these suppressors will reveal new molecular pathways that require Npa3 to function appropriately.

This work was supported by the Consejo Nacional de Humanidades, Ciencias y Tecnologías, grant number A1-S-21070 (to RSO).



The GPN-loop GTPase Gpn3 is mobilized between the cytoplasm and cell nucleus.

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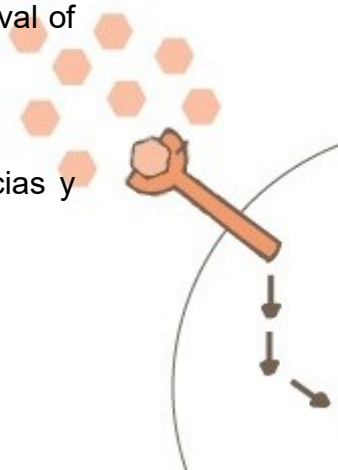
The essential GPN-loop GTPase Gpn3 is required for the biogenesis and nuclear targeting of RNA polymerase II (Calera et al., 2011, BBA 1813:1708-1716). We have previously shown that although Gpn3 is a cytosolic protein, it accumulates in the nucleus in the presence of leptomycin B, a chemical inhibitor of the exportin Crm1. This finding indicates that Gpn3 is constantly mobilized between the cytoplasm and cell nucleus. Crm1 recognizes short hydrophobic sequences known as nuclear export sequence (NES) in the cargo proteins, followed by the transport of the Crm1/substrate protein complex across the nuclear pores to the cytoplasm. In this study, we identified the functional NES sequences in Gpn3 and investigated the importance of nucleocytoplasmic shuttling of Gpn3 in human mammary epithelial cells MCF-12A. Site-directed mutagenesis was performed by pcr to change conserved hydrophobic residues in putative NES sequences to alanine. The subcellular distribution of these Gpn3 mutants was assessed by immunofluorescence. We identified the NESs responsible for nuclear export of the GTPase Gpn3. Also, we showed the synergistic effect of double NES mutants in the nuclear accumulation of this protein. Additionally, we demonstrated that survival of MCF-12A cells was dependent on an intact Gpn3 nucleocytoplasmic shuttling.

This work was supported by the Consejo Nacional de Humanidades, Ciencias y Tecnologías, grant number A1-S-21070 (to RSO).



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Glycine effects on GPR3, GPR6 and GPR12 expression in Wistar rat neonatal neurons primary culture

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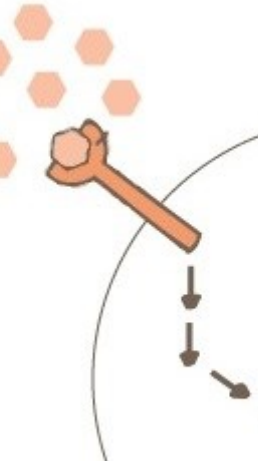
Abstract

Introduction Glycine acts as a neurotransmitter in the central nervous system and has multiple functions in the peripheral and nervous tissues such as antioxidant, anti-inflammatory, cryoprotective and immunomodulatory. The Alzheimer's disease is a brain disorder that is direct associated to the memory decrease and degeneration to realize the simplest tasks; this disease is progressive and affect the cognitive functions, as the way of behaving, the character or the memory. The associated receptors that some investigations provide to Alzheimer's disease are glutamate receptors, GABA receptors and other receptor associated is the nerve growth factor receptor-interacting protein, which is found in nerve cells, GPR3, GPR6, GPR12 increases APP (amyloid precursor protein) and amyloid plaques in brain, also a primordial factor are the IL-1, IL-4 cytokines, associated to neuroinflammation. **Objective** To analyse the glycine participation in a primary astrocytes culture gene expression profile of NRF2 and orphan receptors GPR3, GPR6, GPR12. To evaluate the glycine effect in the A1 and A2 phenotype differentiation in astrocytes. **Methods** Primary astrocyte cultures from Wistar rats. Briefly, cerebral cortices of newborn Wistar rats were removed and mechanically dissociated in Buffer. The cortices were cleaned of meninges and mechanically dissociated by sequential passage through a Pasteur pipette. The cells were plated in 24 well- plates (4 x10^5 cell per well) in DMEM/F12 supplemented with 10% foetal bovine serum and medium,1% antibiotic and antimycotic. The astrocytes cell was stimulated with Glycine (1mM, 10mM, 20mM) for two span times 1 hour and 24 hours. The gene expression of IL-1b, IL-4b, LPS and beta- amyloid was measured by RT-qPCR. **Results** Our results showed that glycine decreased the beta amyloid concentration and the orphan gene expression in vitro and glycine reverts the gene expression of GPR6 **Conclusion** Our conclusion the Glycine may be related to a decrease in Amyloid-beta concentration and neuro inflammation. Beta-amyloid does not realize the paper of antibiotic and increases inflammation and concentration of the beta-amyloid formed as plaques. Glycine provides of cytokines synthesis.

Keywords: Alzheimer's disease, orphan receptors, neurons.



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RAC1 STABILIZES MEMBRANE DOMAINS IN THE ACROSOMAL REGION THROUGHOUT THE ACTIN CYTOSKELETON

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INTRODUCTION. The formation and remodeling of the actin cytoskeleton in the spermatozoon is a critical process that occurs during sperm capacitation and is essential for acquiring fertilizing capacity. This actin cytoskeleton forms a barrier that prevents premature acrosomal reaction and is essential for the migration of proteins for fertilization, as in the case of Izumo. Rac1 has been related to the stability of membrane domains of different cells. Rac1 structures the actin network and is associated with the plasma membrane of capacitated sperm, stabilizing the plasma membrane by binding through filamin-1, which positions different transmembrane proteins such as receptors, ion channels and adhesion molecules, forming a new domain where different signaling molecules are required for RA.
OBJECTIVE. To elucidate the participation of Rac-1 in stabilizing membrane domains in the acrosomal region.
RESULTS. During capacitation, the actin cytoskeleton is restructured in the apical region of the acrosome. When spermatozoa were capacitated in the presence of a Rac1 inhibitor (NSC23766), remodeling of the actin cytoskeleton was inhibited. The actin cytoskeleton is disrupted and disperses throughout the acrosomal domain. Consequently, integral membrane proteins not changing location during capacitation, such as integrins β1, β2, and ankyrins B and G, were dispersed throughout the acrosome. Others, such as the TMEM16A chlorine channel, did not experience changes.
CONCLUSIONS. The actin cytoskeleton structured by Rac1 is essential for maintaining the stability of membrane domains in the acrosomal region of spermatozoa, as shown by the change in localization of the integrin β1, integrin β3, as well as ankyrins B and G. In the case of the Cl-TMEM16A channel, it is probably anchored to a different type of membrane domain.
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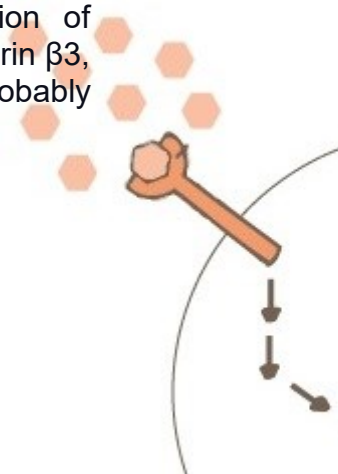

In silico molecular docking analysis of small chemical compounds on the GTP-binding site of the GPN-loop GTPase Npa3.

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Npa3 is the yeast orthologue of human Gpn1. Npa3 is an essential protein that belongs to the GPN-loop family of GTPases. The best well-known function of Npa3/Gpn1 is to participate in the nuclear accumulation of RNA polymerase II in both, human and *Saccharomyces cerevisiae* yeast cells (Forget et al., 2010, Mol Cell Proteomics 9:2827). As very little is known on the molecular and cellular functions of Npa3, the identification of specific small chemical inhibitors would be a very powerful tool to facilitate the study of this GTPase. In this study, we performed computational molecular docking experiments on the GTP-binding site in the crystallographic structure of monomeric Npa3 in an open conformation (Niesser et al., 2015, Mol Cell Biol 36:820) employing a total of 74,167 compounds derived from libraries designed as nucleoside mimetics and anticancer compounds. Compounds with the best binding affinity and those that, according to its binding mode, could potentially interfere with the interaction between Npa3 and GTP were selected. Subsequently, the interactions between lead compounds and Npa3 were studied in more detail, allowing us to identify the critical residues in Npa3 mediating this interaction. In order to improve their binding affinity and to identify new binding modes, we also generated isosters by geometric similarity based on the leading compounds. We were able to increase the binding affinity of some compounds, as well as to identify molecules with higher binding affinity than GMPPCP (non-hydrolyzable analogue of GTP). Interestingly, some of these compounds interact with residues of the insertion I, a region found exclusively in the GPN-loop GTPases. Thus, we propose these compounds as potential competitive inhibitors of the hydrolytic activity of Npa3.

This work was supported by the Consejo Nacional de Humanidades, Ciencias y Tecnologías, grant number A1-S-21070 (to RSO). We also thank the Laboratorio Nacional de Supercómputo del Sureste de México grant number 202201035N (MRC).

TS BIOL SISTEMAS

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EVALUATION OF THE MODULATORY EFFECT PRODUCED BY THE G-1-F-2 MIXTURE ON CORTICO-STRIATAL SYNAPSES.

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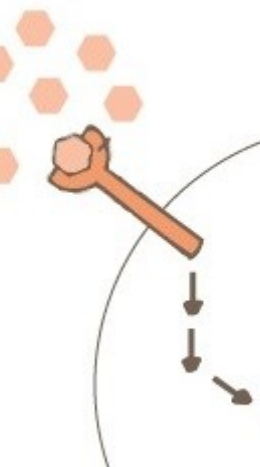
Galphimia glauca, commonly known as "Calderona amarilla," is a native plant species in México with a history of use in traditional Mexican medicine for its sedative and tranquilizing properties attributed to its psychotropic effects. The active compounds in *Galphimia glauca*, referred to as "Galphimines," notably Galphimine-B (G-B) and Galphimine-A (G-A), are recognized as the primary contributors to the plant's neurological depressant effects. Specifically, G-B has been observed to inhibit neuronal firing rates in the ventral tegmental area and hippocampus, while G-A dose-dependently suppresses neuronal responses in the basolateral amygdala. Remarkably, the systemic effects of these compounds closely resemble those of standard anxiolytic agents. Despite this knowledge, the precise mechanism of action and neural circuits engaged in the depressant effects of G-B and G-A remain unexplored. Although several theories propose an association with GABAergic neurotransmission systems, no conclusive literature exists on this matter.

In this study, we employ electrophysiological field potential recordings to shed light on the impact of a mixture containing G-B and G-A (referred to as mixture G-1-F-2) on cortico-striatal synaptic activity. Contrary to the prevailing hypothesis involving GABAergic systems, our findings challenge this notion. The G-1-F-2 mixture induces an enhancement in the amplitude of the cortico-striatal population synaptic spike, driven by a combination of glutamatergic and GABAergic components. To comprehensively understand this modulatory effect, we investigate its interaction with the GABAA receptor positive allosteric modulator (Diazepam) and the non-competitive antagonist of NMDA receptors (Memantine). Our experimental outcomes demonstrate that the effect triggered by the G-1-F-2 mixture, comprising Galphimine-B and Galphimine-A, does not operate through GABAergic neurotransmission systems, specifically not at the diazepam binding site on GABAA receptors. Instead, the observed impact of these compounds aligns more closely with glutamatergic neurotransmission systems, particularly implicating NMDA receptors.This study was partially funded by DGAPA-PAPIIT Grant IN 216721 and Institutional support. DAV received a scholarship from CONACyT.

Keywords: Galphimine, NMDA, $GABA_A$



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Influence of Branched-Chain Amino Acids on the Mechanistic Target of Rapamycin complex 1 (mTORC1) through the AMPK and SestrinA Pathways in *Centropomus viridis* Brain Cells

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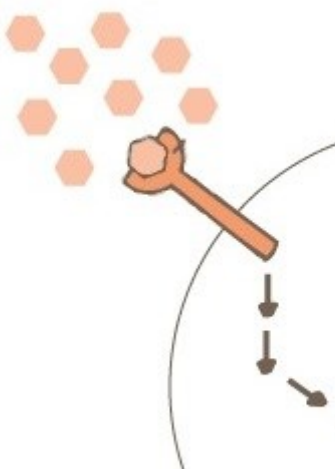
The mechanistic target of rapamycin (mTOR) is the kinase subunit of the multiprotein complexes mTOR1 (mTORC1) and mTORC2. It performs vital physiological functions in the cell, as it controls anabolic and catabolic processes in response to extracellular signals, nutrients, energy, and stress conditions. It determines changes of catabolic and anabolic processes in most eukaryotes based on the individual amino acids detected by the intracellular sensors of L-Leucine. The mTOR system and its amino acid sensors are poorly studied in teleost fish and aquaculture animals; in the present study we evaluated the effect of branched-chain amino acids (BCAAS) at different concentrations on gene expression of proteins upstream of mTORC1 in a brain cell culture generated from the sea bass *Centropomus viridis*. The MTT assay was used to evaluate the biosafety and cytotoxicity of BCAAS on *C. viridis* brain cells. The results showed that BCAAS treatments did not affect the proliferation or viability of these cells even at the highest concentrations (5000-10000mg/mL). Subsequently, the effect of BCAAS (1000 mg/mL) on the expression of *SestrinA*, *TOR, Raptor, AMPK, RagA, RagC*, and *Rheb* was evaluated. The results suggest that the mTOR pathway and its amino acid sensors is a conserved pathway throughout evolution, and is present in the brain cells of *C. viridis*. Further studies are required on appetite-satiety cycle regulation, neuropeptides, protein nutrition, amino acid profiles and their role in aquaculture nutrition.

Keywords: Cell Culture, mTOR, SestrinA,



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Analysis of the global expression of genes related to appetite regulation in the hypothalamus of obese mice treated with resveratrol

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Abstract

The pathogeny of obesity is very complex, one of the main causes in its development involves the excessive intake of lipids, related to the modern lifestyle. Oxidative stress is highly correlated with inflammation, metabolic abnormalities, and appetite dysregulation. Dietary antioxidant compounds such as resveratrol have been used as effective and safe nutraceutical strategies to regulate oxidative stress and appetite. An obesity model was developed in C57BL/6 mice from a high-fat diet, oral resveratrol treatment was administered for 4 weeks with an esophageal cannula, total RNA extraction from the hypothalamus was performed with the Trizol technique, and analyzed the level of gene expression by RNAseq, the results indicate that RSV has an important role in the regulation of appetite signaling pathways, thermogenesis, and neuronal communication.

Keywords: Oxidative stress, obesity, resveratrol, hypothalamus, thermogenesis, RNAseq.

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Comparative transcriptome analysis reveals key epigenetic targets in SARS-CoV-2 infection

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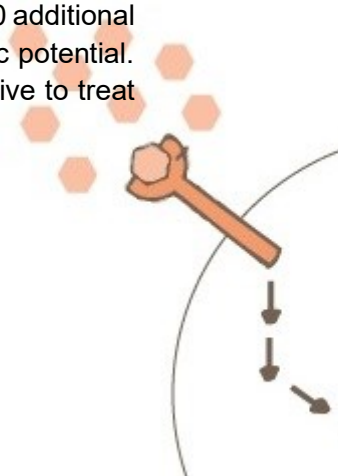
Abstract

COVID-19 is an infection caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2), which has caused a global outbreak. Current research efforts are focused on the understanding of the molecular mechanisms involved in SARS-CoV-2 infection in order to propose drug-based therapeutic options. Transcriptional changes due to epigenetic regulation are key host cell responses to viral infection and have been studied in SARS-CoV and MERS-CoV; however, such changes are not fully described for SARS-CoV-2. In this study, we analyzed multiple transcriptomes obtained from cell lines infected with MERS-CoV, SARS-CoV, and SARS-CoV-2, and from COVID-19 patient-derived samples. Using integrative analyses of gene co-expression networks and de-novo pathway enrichment, we characterize different gene modules and protein pathways enriched with Transcription Factors or Epifactors relevant for SARS-CoV-2 infection. We identified EP300, MOV10, RELA, and TRIM25 as top candidates, and more than 60 additional proteins involved in the epigenetic response during viral infection that has therapeutic potential. Our results show that targeting the epigenetic machinery could be a feasible alternative to treat COVID-19.



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Curcumin improves redox status and insulin sensitivity in the periphery and decreases leptin receptor expression in nucleus arcuate in obese diabetic mice.

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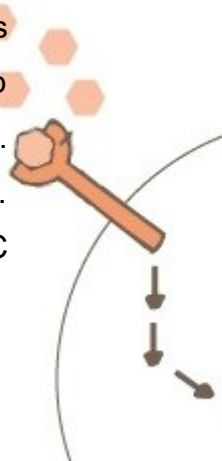
Introduction: Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia, insulin resistance and oxidative damage, one of the main risk factors for its development is obesity. Leptin and Lep-Rb are proteins involved in appetite regulation, which are altered during obesity, diabetes and oxidative stress. Oxidative stress plays an important role in the development of hyperphagia by inducing oxidative damage to the molecules responsible for appetite regulation, such as alterations in leptin and Lep-Rb. It is essential to evaluate natural compounds with antioxidant capacity that regulate the expression of both proteins, through the reduction of oxidative stress. **Objective**: To evaluate the effect of curcumin on oxidative damage and leptin levels in adipose tissue, as well as Lep-Rb in hypothalamus of diabetic mice. **Material and methods:** Male mice of the C57BL/6 strain were injected with 70 mg/kg of STZ i.p. and fed with HFD for 8 weeks. Experimental groups were: control (C), control treated with curcumin 50 mg/kg (C+CUR), diabetic (D) and diabetic treated with curcumin 50 mg/kg (D+CUR). The concentration of malondialdehyde (MDA), protein carbonyl (PCO), glutathione peroxidase (GPX), total antioxidant capacity (TAC) and leptin were determined in white vsiceral (WAT) and brown (BAT) adipose tissue. Transcardiac perfusion was performed to obtain the brain and to evaluate Lep-Rb in hypothalamus by immunofluorescence. **Results**: Diabetic animals presented hyperglycemia, insulin resistance and obesity. An oxidative state (elevated MDA, decreased PCO, GPX and TAC) was observed in WAT of diabetic mice, but not in BAT. Curcumin reduced oxidative damage markers such as MDA and PCO, additionally curcumin improves insulin sensitivity. The diabetic group showed elevated Lep-Rb expression and decreased in the curcumin-treated group. **Conclusion**: Curcumin improves insulin sensitivity, but has no effect on body weight. Curcumin has antioxidant effect on WAT and decreases Lep-Rb expression in the ARC of obese diabetic mice.



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Role of the Renin Angiotensin System in obesity as a predictor of mortality in patients with SARS-CoV-2 pneumonia

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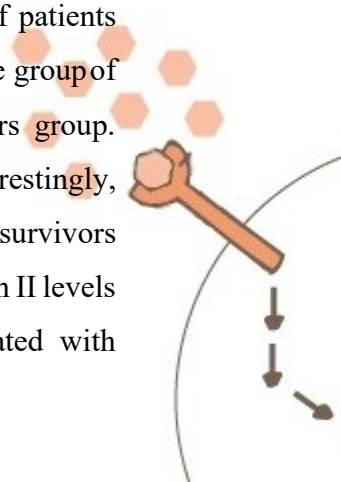
Introduction. An outbreak of COVID-19 disease appeared in Wuhan, China, in December 2019, since this time the disease has spread globally. SARS-CoV-2 viruses bind to the cell surface via its S protein and enter to the cells through angiotensin-converting enzyme 2 (ACE2), expressed in the lungs, heart, vasculature, intestines, or kidneys. Thus, ACE2 expression increases in patients infected with SARS-CoV-2 in airway epithelium and immune cells, with the worst outcomes in patients with hypertension, diabetes, and obesity. In Mexico, there is currently a growing problem of obesity with a prevalence of 30.5% in men and 40.2% in women over 20 years of age. With the arrival of the SARS-CoV-2 pandemic and the development of severe pneumonia with high mortality, obesity was consolidated as a major risk factor for developing greater severity, even in young patients with no other comorbidities. **Objective.** This study aimed to evaluate whether Renin Angiotensin System in obese patients was associated with mortality in patients with SARS-CoV-2 pneumonia in the emergency department of Hospital Juarez de Mexico. **Material and methods.** An observational and cross-sectional study was performed. Renin, angiotensin I, angiotensin II and aldosterone were determined by Enzyme-Linked Immunosorbent Assay (ELISA) according to manufacturer´s instructions. The results were described with frequencies and percentages for qualitative variables. In the case of quantitative variables, the Kolmogorov-Smirnov test was used to determine data distribution. **Results.** One hundred forty-five subjects were included in the study. The individuals were grouped in survivors and non-survivors. The 45.5% of patients survived and 54.5% died. The 53.3% was not vaccinated against SARS-CoV2. In the group of non-survivors, the 88.6% needed mechanic ventilation vs. 18.2% in the survivors group. Obesity was not related with renin angiotensin system levels nor with mortality. Interestingly, angiontensin I and aldosterone plasma levels were significantly increased in non-survivors compared with survivors ($p < 0.05$). There were no differences in renin and angiotensin II levels between two groups. **Conclusions**. The Renin Angiotensin System was associated with mortality in patients with SARS-CoV-2 pneumonia independently of obesity status.



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MAPK signaling pathway is involved in the steroidogenesis regulation in choriocarcinoma cells

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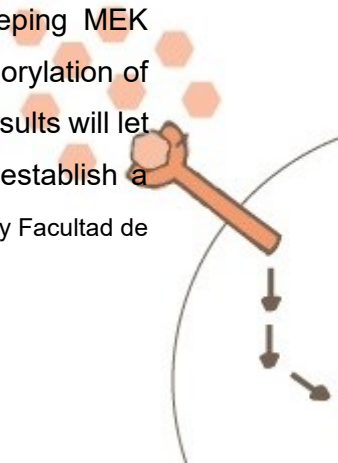
The steroid synthesis in placental cells requires the steroidosome and the signalosome, which contain the enzymes involved in steroidogenesis and the signal transduction elements associated with the PKA pathway. Preliminary data showed that inhibition of MEK1/2 with U0126 decreases the P4 concentration, in the same way as when PKA is inhibited with H89. In this sense, to determine if there is crosstalk between the PKA/MAPK kinase pathways involved in the regulation of steroid synthesis, inhibitors of MEK1/2 activity (U01216 and MEK162) were used. Choriocarcinoma cells (JEG3) were incubated with U0126 or MEK162. P4 concentration was quantified and the proteins phosphorylation from MAPK cascade were analyzed by western blot. The determine the possible synergic effect of PKA and MAPK signaling cascade on P4 synthesis, cells were incubated with H89, U0126 or MEK162 for 24 h followed by the addition of H89, U0126 or MEK162 for other 24 h. The results shown that P4 synthesis decreases 30% in the presence of H89, U0126 or MEK126. The complementary addition of inhibitors did not modify the P4 synthesis. The addition of cAMP to cells preincubated with inhibitors reestablishes partially the production of P4, suggesting that PKA pathway is the main signal for steroidogenesis. U0126 and MEK162 decreased P450scc expression, ERK1/2 phosphorylation and P4 concentration. Contrary to this, p-ERK1/2 increased with cAMP and H89, but P450scc expression was not modify. The results suggest that the cAMP support MEK activity through Rap/Raf, and the inhibition of PKA in turn inactivates a phosphatase, thus keeping MEK phosphorylated. The effect can be reflected at nuclear level, preventing the phosphorylation of transcription factors associated with the expression of steroidogenic proteins. The results will let us identify proteins of cell signaling which modulate steroidogenesis and further establish a possible mechanism of signal transduction. Acknowledgements: This work was supported by Facultad de Medicina and DGAPA-PAPIIT IN200521, both from UNAM.



Expression of connexin 43 in neurons of the superior cervical ganglia. Elia Martha Pérez Armendariz, Beatriz Hernández, Lourdes Cruz Miguel, E. Verazas, Sofia Tellez Alonso, Oscar Lara Zacarias. Laboratorio de Sinapsis Eléctricas, Unidad de Investigación en Medicina Experimental, Torre de Investigación, Facultad de Medicina, UNAM. Av. Universidad 3000, Circuito Universitario S/N, Ciudad Universitaria, 04318. e-mail: emperezarmendariz@gmail.com

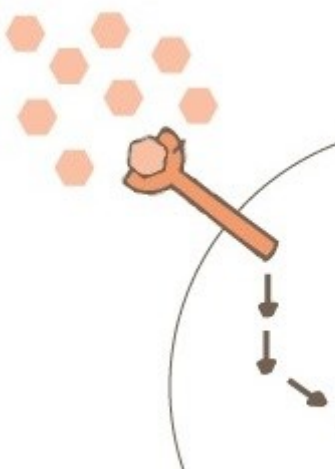
SUMMARY

The superior cervical ganglion (SCG) receives innervation from motor neurons of the spinal cord, which in turn are innervated by nerve fibers coming from the suprachiasmatic nucleus. The SCG innervates different organs of the head and neck, including the pineal gland. Stimulation of noradrenergic receptors in the pineal gland modulates the production of melatonin. Melatonin in turn modulates the sleep-wake cycle and synchronizes different other hormones and metabolic rates. In the rat, SCG ablation generates different metabolic alterations and induces an increase in the index of weight gain with respect to food intake.

The SCG is made up of thousands of neurons surrounded by satellite glial cells (sGCs), nerve fibers, and blood vessels. It has been described that the sGCs of the SCG are electrically coupled and that the degree of coupling is increased by Ach. In addition, dye transfer and electrical coupling between cultured SCG neurons has been described. However, the molecular components that underlay direct intercellular communication between these cells have been scarcely studied.

In vertebrates, it is known that electrical coupling results from the expression of intercellular channels mainly formed by the family of homologous proteins known as connexins (Cxs) (20 in the mouse). It is also known that specific functional and biophysical properties of gap junction channels result form their molecular composition. Genetic alterations in the Cxs family have been found to be associated with human pathology.

Recently it was found that sGCs of the SCG express connexin 43 (Cx43). In the present study, by incubating both male and female GCS sections with anti-Cx43 combined with fluorescence microscopy, we found that Cx43 protein is expressed in SCG neurons. In addition, we did not find sexual differences in the relative levels of Cx43 transcripts using real-time PCR studies. The possible physiological implications of these findings are discussed. **Acknowledgments:** Grant num. PAPIIT IN229623, DGAPA UNAM.



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Repurposing of approved drugs for the inhibition of PTP1B in type 2 diabetes therapy

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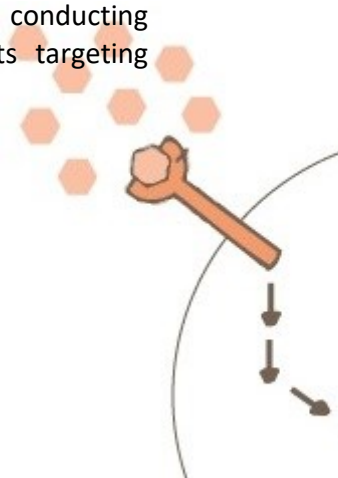
Abstract

PTP1B is a ubiquitous and abundant intracellular enzyme encoded by the protein tyrosine phosphatase non-receptor type 1 (PTPN1) gene. In humans, it is located at chromosome 20q13.1, in a region that has been associated with diabetes and obesity. During the lastyears, several reports have shown that PTP1B acts as a critical negative and positive regulator of numerous signaling cascades. Initial *in vitro* evidence suggested that PTP1B was a negative regulator of the Insulin Receptor (IR) and its downstream signaling pathways. Over the past years, numerous modulators of PTP1B have been reported. However, only a few have been tested in clinical trials. One of these drugs is trodusquemine, a small-molecule inhibitor that binds to PTP1B in a reversible and selective manner. Unfortunately, due to its poor bioavailability, this inhibitor was discontinued. Therefore, this study aimed to identify new catalytic-approved inhibitors of PTP1B that can be used in diabetes therapy.

A screening of 2094 drugs from the e-Drug3D FDA- approved drug database (https://chemoinfo.ipmc.cnrs.fr/MOLDB/index.php) was conducted to assess their repurposing potential using molecular docking. The three drugs with higher theoretical affinity were selected for performing molecular dynamic simulations, confirming their stable interactions with PTP1B and *in vitro* assays. Altogether, our results may serve as theoretical guidance for further conducting experimental-based preclinical studies necessary for developing therapeutic agents targeting PTP1B.



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Differential effect of NO on metastatic potential in triple negative breast cancer cells, MDA-MB-231.

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Nitric Oxide (NO) is a biological signaling molecule, involved in both normal and pathological cellular processes, including cancer. Several studies show a positive correlation between the level of expression of nitric oxide synthase type 2 (NOS-2) with the degree of malignancy of different types of cancer, suggesting the participation of NO in tumor development and progression, highlighting the case of breast cancer.

The purpose of this project was to investigate whether the chronic presence of NO affects the metastatic potential of breast tumor cells, evaluating three properties: proliferative, migratory, and chemo-resistance to doxorubicin. For this, the MDA-MB-231 cell line, representative of the triple negative breast cancer subtype, was used as an experimental model, which was maintained under standard culture conditions.

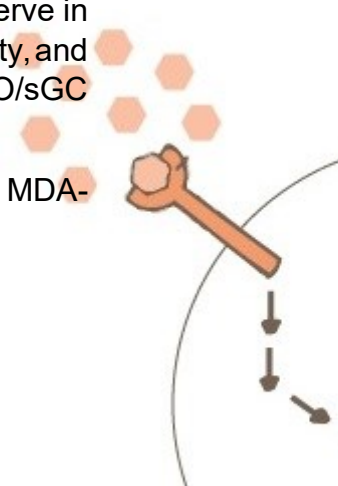
Initially, it was observed that the presence of NOC-18 increases nitrite levels more than 5 times compared to the control condition, validating its use as an effective NO donor. To assess the proliferative capacity, we determined by RT-PCR the expression level of the mRNA encoding Ki-67, a nuclear marker of cell proliferation, observing a significant increase of almost two times with NOC-18 respect to the control condition.

The migratory capacity was evaluated by assays in transwell chambers, and unlike what we observed regarding proliferative capacity, the presence of NOC-18, significantly reduces the migratory capacity of MDA-MB 231 cells, reaching 30% of the value observed in the control condition. On the other hand, the capacity for chemo-resistance to doxorubicin was evaluated by MTT assays. In this case, NOC-18 does not modify the chemosensitivity of MDA-MB 231 cells to the cytotoxic effect exerted by doxorubicin.

The use of ODQ, soluble guanylate cyclase (sGC) inhibitor, allowed us to observe in a preliminary way, that the stimulatory effect of NO on the proliferative capacity, and the inhibitory effect, on the migratory capacity, is independent of the NO/sGC pathway.

These results suggest a differential effect of NO on the metastatic potential in MDA-MB 231 cells.

Keywords: Breast Cancer, Nitric Oxide (NO), metastatic potential.



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Interaction between LPA_1-PKCα-PR in Glioblastoma

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Introduction

Glioblastomas (GBs) are the most common, aggressive, and lethal malignant brain tumors of the central nervous system (CNS). It has been previously reported that progesterone receptor (PR) is overexpressed when compared to tumors of lower malignancy grades. Furthermore, blocking this receptor with the antagonist RU486 results in decreased proliferation, migration, and invasion of GB-derived cell lines. In *in vivo* models, the size of tumors derived from heterotopic and orthotopic xenografts of human or murine GB decreases by 50% after treatment with RU486.

On the other hand, the Lysophosphatidic Acid Receptor 1 (LPA_1) receptor belongs to the family of G-protein-coupled receptors. This receptor has been associated with GB malignancy, as its activation has been observed to induce tumor progression and migration in GB-derived cells. The expression of LPA_1 is increased in this type of tumor, and its activation enhances signaling pathways that promote tumor progression. Interestingly, antagonism of the LPA_1 receptor reduces the number of mitotic cells and tumor volume by 50%. In our laboratory, we have demonstrated that the endogenous ligand of LPA_1, lysophosphatidic acid (LPA), induces phosphorylation of PR at Serine 400 via protein kinase alpha (PKCα).

Objective

Determine if PR and LPA_1 receptors can interact and if the interaction is mediated by PKCα.

Methodology

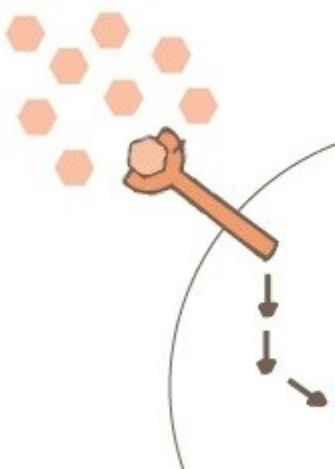
Protein interaction will be determined using the Proximity Ligation Assay (PLA) which is based on the recognition of two proteins through primary antibodies. Subsequently, cells will be incubated with secondary antibodies labeled with oligonucleotides. If they are within a distance <40 nm, they will be able to hybridize with a complementary sequence, resulting in the formation of a template that will be amplified and bound with fluorescence-labeled probes. As a result, the signal will be observed as fluorescent dots. Localization will be evaluated using stereology.

Results

Using the U251 cell line derived from human GB, we were able to observe that under basal conditions (10% FBS in DMEM), the PR and LPA_1 receptors can interact at a distance <40 nm both in cytoplasm and in a perinuclear manner. We suggest that this interaction may be mediated by PKCα, therefore, the interaction will be evaluated by inhibiting PKCα with Gö6983.

Keywords

Glioblastoma, Progesterone Receptor, Lysophosphatidic Acid Receptor 1.



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The role of the estrogen receptor β on the metastatic potential in the MDA-MB-231 cell line

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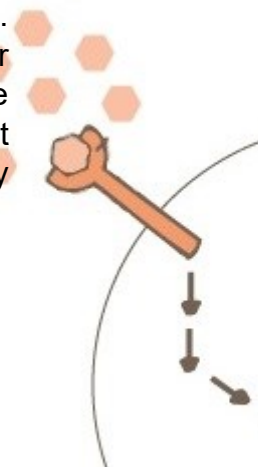
Estrogens take part of various cellular processes, both under normal and pathological conditions, including cancer. The effect of estrogens is mediated by two types of intracellular receptors (ERα and ERβ) and one transmembrane (GPER30). One of the main targets of estrogens are the epithelial cells of the mammary gland, observing that the activation of ERα stimulates its proliferative capacity, while the activation of ERβ exerts the opposite effect, considering a physiological balance the level of expression of estrogen receptors. Cells from triple-negative breast cancer do not express ERα, but do express ERβ abundantly, and the effect that activation of said receptor could be having on the metastatic potential of breast cancer cells is unknown in detail. The central purpose of this work was to investigate whether chronic ERβ activation affects the metastatic potential of breast tumor cells, evaluating two properties: proliferative and migratory. For this purpose, the MDA-MB-231 cell line, representative of the triple negative breast cancer subtype, was used as an experimental model, which was maintained under standard culture conditions. Initially, it was observed by RT-PCR that MDA-MB 231 cells over-express the mRNA encoding ERβ compared to MCF-7 and MCF-10A cells, validating that the expression level of ERβ, is positively correlated with the degree of malignancy of the tumor. To evaluate the proliferative capacity, we determined by RT-PCR, the expression level of the mRNA that codes for Ki-67, a nuclear marker of cell proliferation, in the presence and absence of 17β-Estradiol (nonspecific agonist) or DPN (selective agonist), observing a significant increase in the two conditions with respect to the control condition. The migratory capacity was evaluated by assays in transwell chambers and wound closure, observing that the activation of ERβ significantly favors the migratory capacity of MDA-MB 231 cells. In a complementary way, we evaluated whether the increase in the capacity migration of MDA-MB 231 cells, was accompanied by a change in the expression levels of the mRNA encoding different transcription factors associated with the epithelial-mesenchymal transition. RT-PCR assays showed that MDA-MB-231 cells in the presence of 17β-Estradiol or DPN over-express the mRNA encoding Snail-1, Snail-2 and Zeb-1, ensuring the mesenchymal phenotype, condition that favors cell migration. These results suggest a new role for ERβ in the progression and development of breast cancer, most likely providing a new drug target.

Keywords: Cancer, metastatic potential, estrogen receptor.



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Purinergic system on the proliferative capacity of PC-3 prostate cancer cells.

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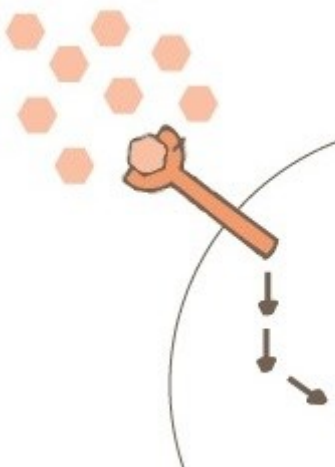
Prostate cancer (CaP) is the neoplasia with the highest incidence and mortality rate in the adult male population both worldwide and nationally. Metastasis is responsible for more than 90% of deaths caused by PCa. The ability to identify extracellular factors present in the tumor microenvironment that regulate the migratory and invasive capacity of tumor cells has generated great interest. In this context, it has been observed that Adenosine, present in the tumor microenvironment, is capable of influencing tumor development and progression. Adenosine extracellular levels depend fundamentally on ATP hydrolysis, which involves the participation of two ecto-nucleotidase enzymes , CD39 and CD73, respectively in that order. Adenosine, for its part, can bind specifically to four different purinergic receptors of the P_1 family, which are identified as A_1, A_{2A}, A_{2B} and A_3. The A_1 and A_3 receptors are coupled to Gs proteins, while the A_{2A} and A_{2B} receptors are coupled to G_i proteins. The activation of any of these receptors modifies the intracellular levels of AMP_c, which, being a second messenger, is responsible for activating different intracellular signaling pathways, which could influence the migratory capacity of tumor cells. Therefore, the objective of this work is to determine if the activation of the purinergic system, made up of the ectonucleotidases CD39 and CD73, as well as the P_1 receptors purinergic, affects the migratory and proliferative capacity of PC-3 cells. The PC-3 cell line was maintained under standard culture conditions. Initially, we determined by endpoint RT-PCR that PC-3 cells express the mRNA that codes for the different elements of the purinergic system , this being differential expression. For the migration assay, Transwell chambers were used, PC-3 cells were treated for 48 h with 50 μM (P_1 receptor agonist) and 1 μM caffeine (P_1 receptor antagonist). The results we obtained show that the blockade of P_1 receptors by caffeine increases the migratory capacity of PC-3 cells by more than 70%, while Adenosine practically does not modify it. These results suggest a new role for elements of the purinergic system in the progression and development of prostate cancer, most likely providing new drug targets.

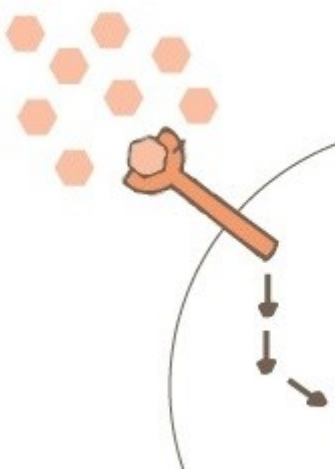


"Lysophosphatidic acid promotes stemness of glioma cells via SOX2 and OCT4."

Claudia Bello-Alvarez, Angel Rubio-Galicia, Marisol De la Fuente-Granada, Marco A. Velasco-Velázquez and Aliesha González-Arenas*

Abstract

Glioblastomas (GB) are the most common and deadly primary brain tumors in adults. The therapy of choice for these patients has not changed in over 10 years and offers a survival rate of approximately 12 months. Lysophosphatidic acid (LPA) is a bioactive lipid that regulates a wide range of signals, including Akt, MAPKs, and PKC activation through interaction with six G protein-coupled receptors (LPA1-6). The role of LPA in cancer has been extensively studied and has been shown to induce the expression of transcription factors associated with cancer cell stemness, such as SOX2 and OCT4. However, there is no data on the involvement of LPA in stemness signaling pathways in GB cells. In this study, we evaluated the effect of LPA on the sphere culture of U251, U87 and C6 cell lines derived from human and murine glioblastoma, respectively. First, we isolated glioblastoma stem cells through sphere culture of the U251, U87, and C6 glioma-derived cell lines. We then established the distribution of the spheres by grouping them into three size ranges: 25-60 µm, 75-100 µm, and greater than 100 µm. Treatment with LPA increased the sphere-forming efficiency (SFE) in all three cell lines and in all sizes, while treatment with Ki16425 (Ki) (LPA 1-3 inhibitor) decreased the SFE by greater than 100 µm. Interestingly, the decrease and increase in SFE were accompanied by decreased and increased expression of the transcription factors SOX2 and OCT4. The comparison between Ki (LPA1-3 inhibitor) and AM095 (AM) (LPA1 inhibitor) treatments suggests that the type of receptor involved in the LPA effect (LPA1, 2 or 3) is determined by the cellular context. Treatment of glioblastoma cells cultured under nonadherent conditions with LPA increased the phosphorylation of ERK kinase, which in turn positively regulates the transcription factors SOX2 and OCT4. The results of this work suggest that LPA increases the stemness of glioma-derived cells by increasing the expression of SOX2 and OCT4.



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PI3Kβ and effectors form an agonist-dependent signaling complex integrated by the RacGEF P-Rex1

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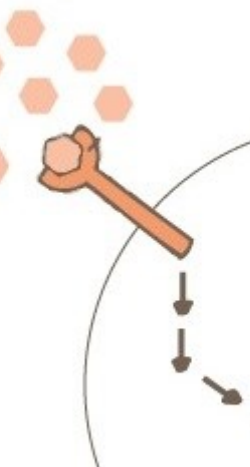
PI3Kβ is an effector of G protein coupled receptors and tyrosine kinase receptors that produces PIP_3 (phosphatidylinositol 3,4,5-trisphosphate), a lipidic second messenger that supports the activation of P-Rex1, a guanine nucleotide exchange factor for the Rac GTPase. This pathway is activated in response to chemokines and growth factors, promoting the formation of lamellipodia and cell migration. P-Rex1 PH domain directly interacts with PIP_3, establishing a functional link between PI3Kβ and P-Rex1. Since P-Rex1 possesses multiple domains able to interact with different signaling proteins, like G$\beta\gamma$ and mTORC2, we aimed to clarify if P-Rex1 could serve as a platform for PI3Kβ and its effectors. In addition, to reveal potential P-Rex1 signaling partners, we seek to identify an oncogenic transcriptional signature integrated by *PREX1*. Through data mining of public transcriptomic databases, we identified 24 signaling genes as part of a transcriptional signature linked to high *PREX1* expression in breast cancer cell lines and patients. These genes were essential in cancer cells in which also P-Rex1 and components of the PI3K/mTORC2/Akt pathway were essential. As a signaling signature, *PREX1* and its coessential partners were significantly coexpressed in *ESR1*$^+$ epithelial cells. Our results suggest the existence of a multiprotein complex integrated by P-Rex1 relevant in breast cancer cells. Experimentally, we found that p110β, the catalytic subunit of PI3Kβ, Rictor and Akt1 coimmunoprecipitated with endogenous P-Rex1 in MCF-7 breast cancer cells stimulated with SDF-1. Reciprocal coimmunoprecipitation experiments confirmed that P-Rex1 was an endogenous interactor of PI3Kβ. As a signaling platform, P-Rex1 facilitated Akt signaling, as indicated by the lower response of Akt in P-Rex1 knockdown MCF-7 cells stimulated with SDF-1 or HGF. Hence, P-Rex1 functions as an agonist-dependent signaling platform for the PI3Kβ/mTORC2/Akt1 pathway, and integrates a transcriptional signature with coessential effectors, postulated as potential functional partners relevant in breast cancer.



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The canonical Wnt pathway is involved in chemoresistance and cell cycle arrest in spheroids from colon cancer cell lines.

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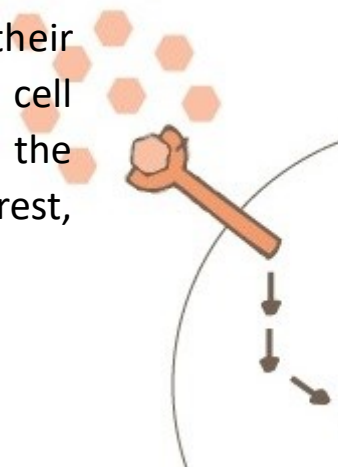
The presence of cancer stem cells (CSC) is associated with chemoresistance. 5-fluorouracil (5FU) is the first-line chemotherapy against colorectal cancer. However, its efficacy may be limited by induction drug resistance in tumor cells. This work aimed to investigate the role played by the canonical Wnt/B-catenin pathway in CSCs and resistance to 5FU treatment. The Wnt pathway plays a key role in CRC development and progression, but it is not clearly established how it is involved in the resistance of CSCs to treatment. Using tumor spheroids as a model for CSC enrichment of CRC cell lines, we found that 5FU induces death, DNA damage, and quiescence. Activating the Wnt canonical pathway with Wnt3a in RKO spheroids decreased 5FU-induced cell death. However, the Wnt/B-catenin pathway, inhibited by Adavivent alone or in combination with 5FU in spheroids with aberrant activation of this pathway, produced a severe cytostatic effect, compromising their clonogenic capacity and decreasing the expression of stem cell markers. Surprisingly, this combination treatment also induced the survival of a small cell subpopulation that could come out of arrest, recover SOX2 levels, and regrow after treatment.



The role of Hypoxia inducible factor-3α in colon cancer

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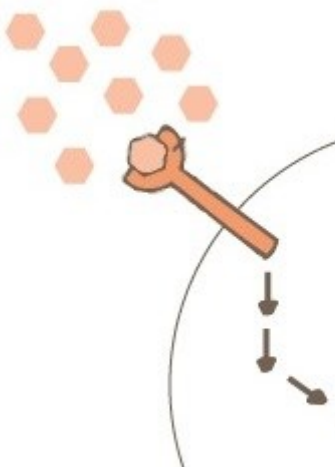
Colorectal cancer is one of the most common malignant neoplasms in terms of incidence around the world and is the second cause of death from cancer. Hypoxia is a hallmark of the tumor microenvironment. Cellular adaptation to hypoxia is primarily mediated by a family of transcriptional regulators: HIF-1α, HIF-2α, and HIF- 3α. In contrast to HIF-1α and HIF-2α, a specific role for HIF-3α in cancer biology has not yet been established. The aim of this study is to elucidate the role of HIF-3α in colon cancer.

Three lines of malignant colorectal cancer (RKO, SW480 and SW620), one non-malignant (112CON), normal tissue and tumor tissue derived from colon cancer patients were evaluated to examine HIF-3α expression by Western Blot. Data Analysis from "Progno Scan" was carried out to analyze the correlation between HIF- 3α mRNA expression and cancer progression. Knockdown of HIF-3α expression was carried out using a lentiviral system in the three malignant cells to investigate the effects of its silencing on malignant phenotype maintenance: cell viability, colony formation, β-catenin-transcriptional activity activation and the basal autophagia activity. We found that HIF-3α is overexpressed under normoxia conditions in all cell cancer lines and tumor tissue sample compared with non-malignant cells and normal epithelium tissue. Kaplan-Maier analysis showed that overexpression of HIF-3α correlates with a patient's lower survival rate and a poor prognosis with different cancer types. Cell viability and migration were decreased in all three malignant lines with HIF-3α knockdown compared with normal HIF-3α expressing cells. Consistent with this, Annexin-V evaluation showed an increase in apoptotic rate in cells depleted of HIF-3α compared to control cells. In addition, HIF-3α silencing also decreased clonogenic capacity, increased basal autophagy and increased activation of canonical Wnt pathway in colon cancer cells.



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Increased HIF-α levels in a cell line derived from a FeNTA-induced RCC tumor resemble that observed in the experimental and human neoplasms

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Despite renal cell carcinoma (RCC) is the most frequent renal neoplasm in adults, little is known about the molecular mechanisms involved in its development and progression. Ferric nitrilotriacetate (FeNTA)-induced RCC rat model has been used as a good alternative for the study of this type of cancer *in vivo*, and the experimental tumors derived are histologically identical to those of human clear cell RCC (ccRCC), the most common subtype. Although *in vivo* models are valuable approaches for representing the complexity of biological systems, they are expensive and time-consuming. Thus, we developed a cell line named RC5E, derived from a tumor obtained with the aforementioned model.

An increase in the oxygen sensitive alpha subunit of the hypoxia-inducible factor (HIF-α) levels is one of the most common alterations in human ccRCC, increase that has been explained by an inactivation of pVHL gene, present in more than 70% of the cases, since pVHL ubiquitinates HIF-α for proteasomal degradation. However, these high levels have been observed even with an apparently functional pVHL.

Therefore, in the present study, the levels of HIF-1α and 2α were determined under normoxia conditions in the RC5E cell line and compared against data from NRK-52E, a non-tumoral rat renal epithelium cell line. A statistically significant increase was observed in the amount of both HIF-α isoforms in RC5E cells, the same behavior previously determined for the tumor samples obtained with the *in vivo* experimental model. Additionally, despite pVHL has been previously detected in the FeNTA induced tumors, the RC5E cells HIF-α levels were similar to those exhibited by 786-O, a human *VHL* $^{-/-}$ RCC cell line. These data suggest that a VHL-independent mechanism for HIF-α stabilization may be involved.

Altogether our results show that this *in vitro* model can work as a feasible first approach for exploring molecular mechanism implicated in RCC, that could be later proved on *in vivo* models.

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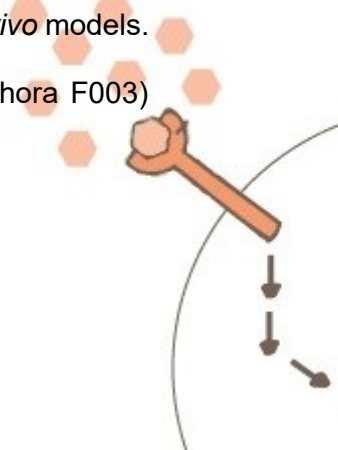
Key words: HIF-α, Renal cell carcinoma, *in vitro*.



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Effect of Il-2 in the expression and activity of STAT1 in cervical cancer cell lines.

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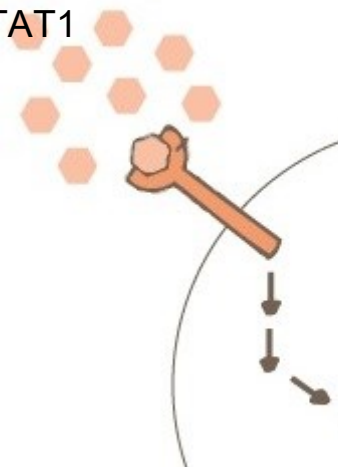
Abstract:

Cancer is a process of uncontrolled growth and spread of abnormal cells, cervical cancer is a type of cancer that originates in the cells that line the cervix, cervical cancer was reported in 2020 as number 4 in incidence in women from all over the world and the third in death, and as the number 2 in Mexico.

IL-2 has been used as an effective immunotherapy against melanoma for approximately 20 years, through the activation of the JAK/STAT pathway. The JAK/STAT pathway is involved in numerous physiological cellular processes, such as proliferation, differentiation, apoptosis, and regulation of the immune system; however, aberrant regulation of STAT can lead to pathological events, including malignant cell transformation and metastasis. STAT1 plays important roles in cytokine-induced signaling pathways and can act as an antiviral and antibacterial mediator, growth inhibitor, and inducer of apoptosis.

Some authors suggest that HPV16 E6 protein mediates STAT1 transcription by activating STAT3 in cervical cancer or STAT1 and STAT3 may compete for the same receptor docking sites.

On that basis, an assay was carried out to observe the phosphorylation of STAT1 in which a greater phosphorylation of STAT1 was observed at 35 minutes of treatment with 100U/mL of IL-2 and in the case of treatment with 10U/mL of IL -2 does not increase STAT1 phosphorylation.



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Effect of interleukin 1β (IL-1β) on proliferative capacity and temozolomide resistance in human glioblastoma cells, U-87 MG

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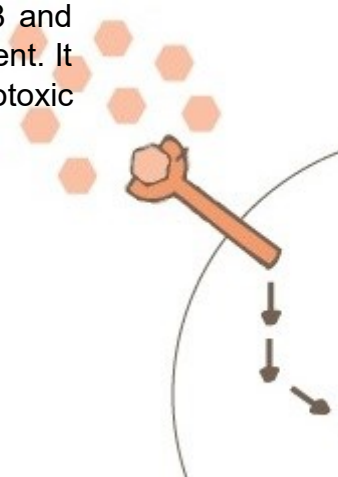
Glioblastoma multiforme (GBM) is the most common and aggressive malignant brain tumor in adults, with a median survival of only 15 months after initial diagnosis. Temozolomide (TMZ) is the most widely used treatment for GBM, however a high percentage of patients develop resistance to the treatment, without understanding the detailed molecular mechanism involved. Nevertheless, it has been demonstrated that inside the tumor's microenvironment high levels of growth factors and cytokines exist, signaling molecules that in other types of neoplasms (breast and prostate cancer, for example), promote tumor cells to present resistance to the cytotoxic effect exerted by doxorubicin and placlitaxel. According to this evidence, the aim of the present paper is to determine whether the presence of IL-1β, a pro-inflammatory cytokine, is able to adversely impact the cytotoxic effect exerted by TMZ in cells derived from human glioblastoma multiforme, for which the U-87MG cell line was used as an experimental model. U-87 MG cells were maintained in standard culture conditions at different concentrations of IL-1β (1, 5, 10, 20 and 40 ng/ml) and for different treatment duration (8, 12 and 24 h), in presence and absence of TMZ. Cell counting and survival assays were performed in the presence and absence of IL-1β and TMZ, to evaluate whether IL-1β treatment had effects on cell proliferation and over the cytotoxic effect exerted by TMZ. In a complementary manner, the expression levels of mRNA coding for BIRC3 and BIRC5 (anti-apoptotic proteins) were evaluated by end-point RT-PCR. The results obtained showed that chronic presence of IL-1β increases the proliferative capacity of U-87 MG cells, associated with a parallel increase in the expression levels of mRNA coding for BIRC3 and BIRC5. This effect is dependent on both concentration and duration of treatment. It was also observed that pretreatment with IL-1β significantly reduces the cytotoxic effect exerted by TMZ on U-87 MG cells.



Effect of resistin on cell migration and activation of p38MAPK and ERK1/2 in MCF7 and MDA-MB-231 breast cancer cells

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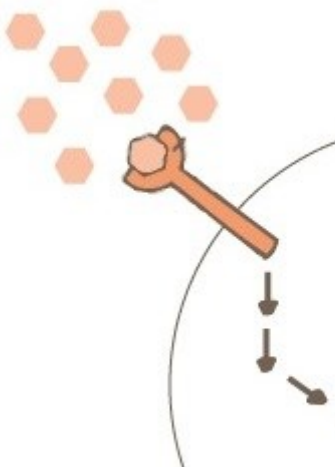
Area: Signal transduction and cancer

Breast cancer is the leading cause of cancer death in women worldwide. Obesity increases the risk of breast cancer through dysregulated secretion of proinflammatory cytokines and tumor adipokines that induce an inflammatory breast microenvironment. Resistin is a novel adipokine in breast cancer because it is secreted by adipocytes and primarily by immune cells. The resistin study will provide an overview in which obesity-induced chronic low-grade inflammation contributes to breast cancer progression. However, the molecular mechanisms by which resistin acts in breast cancer are unknown. Therefore, this research aimed to evaluate the effect of resistin on cell migration and activation of p38MAPK and ERK1/2 in the breast cancer lines MCF7 and MDA-MB-231. By wound closure assays, we evaluated cell migration and activation of p38MAPK, and ERK1/2 was determined by Western blot. The results show that resistin increased cell migration in MCF7 and MDA-MB-231 breast cancer cells. In addition, it was observed that resistin promoted the activation of p38MAPK and ERK1/2. These findings suggest that resistin induces the activation of MAPKs involved in cell migration in breast cancer cells.

Keywords: breast cancer; resistin; migration; MAPKs



Effect of Pentoxifylline and Norcantharidine on endoplasmic reticulum stress in 3D cultures of B16F1 cells.

***María Lilia Domínguez-López**; José Luis González-Quiroz; Juan Moisés Ocampo-Godínez; Victoria Noemi Hernández-González; Ruth Angélica Lezama; Armando Vega-López; Elba Reyes-Maldonado; José Pablo Romero-López.

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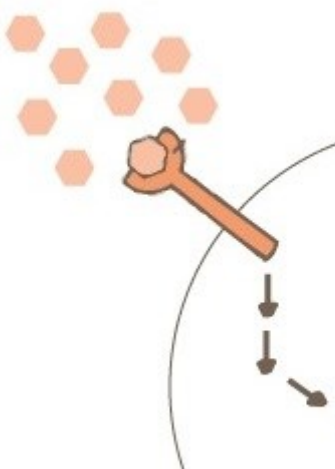
Melanoma is the main skin cancer. In advanced stages, the current treatment has shown low effectiveness causing poor prognosis for patients. Endoplasmic reticulum (ER) stress is a mechanism which support to control proteins synthesis. In chronic ER stress conditions, cell death pathways are activated. Therefore, ER stress has been proposed as a possible therapeutic target in cancer. Autophagy maintains cellular homeostasis and acts as a cellular survival mechanism in starved cells. In cancer cells, autophagy avoids apoptosis by treatments such as chemotherapy. Pentoxifylline (PTX) and Norcantharidine (NCTD) have shown to induce ER stress and activate apoptosis in tumoral cells. In this work, we propose to determinate the effect of both drugs in spheroids of B16F1 melanoma cells. Spheroids were performed by the hanging drop technique using $1x10^3$ cells. Spheroids were treated with PTX, NCTD, combination of both, and the control without stimulus at three times 6, 24 and 48 hours. Furthermore, we used Tunicamycin and Rapamycin as positive controls of ER stress and autophagy respectively. As ER stress markers were evaluated BiP and CHOP, and as autophagy markers were used Beclin-1 and LC3I/II by Western blot. We observed microscopically morphological changes in the proliferative zone cells of the spheroids treated with PTX, NCTD and both drugs. In addition, we observed a higher expression of BiP and CHOP in the spheroid's cells treated with the three drug conditions at 48 hours. LC3II showed less expression with NCTD and the drugs combination at 6 hours.



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Encapsulation and characterization of a TGF-β inhibitor as a therapy for triple-negative breast cancer.

Claudia Alcira Espinoza-González[1,2], Pierrick GJ Fournier[1], Rafael Vazquez-Duhalt[2], MV Villagrana-Escareño[2], LR Arriaga[3], Patricia Juárez[1].

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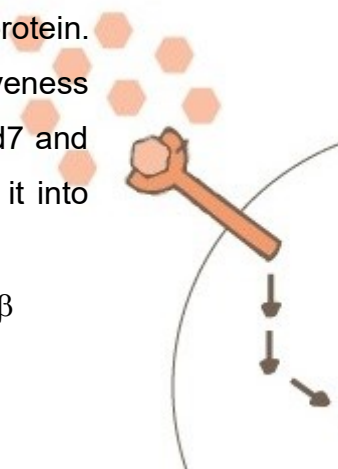
Triple-negative breast cancer (TNBC) is an aggressive type of breast cancer that does not have any of the receptors commonly found in breast cancer. In Mexico, TNBC represents 17% of all breast cancer cases and is associated with high mortality due to the few available treatments. Regular hormonal therapy is ineffective in treating TNBC. However, chemotherapy can be used as an alternative, although it may cause various side effects. There is a need for further research to develop new therapeutic strategies to improve the treatment of this terrible disease. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that plays a crucial role in controlling cell proliferation and differentiation. In the early stages of tumor development, TGF-β limits tumor growth by activating pathways that inhibit cell proliferation and promote apoptosis. Smad7 is a negative regulator of TGF-β. Controlled overexpression of Smad7 in cancer cells has been reported to inhibit TGF-β signaling pathways that reduce melanoma skin cancer growth and metastasis. Therefore, in this project, we propose to develop therapeutic nanoparticles to downregulate TGF-β signaling in TNBC tumors. We use viral nanocarriers and liposomes to encapsulate the mRNA encoding the Smad7 protein. Then, we characterize their effectiveness in regulating the growth and invasiveness of cancer cells in vitro and in vivo. We are currently producing mRNA Smad7 and encapsulating it in BMV particles and liposomes as nanocarriers to deliver it into cancer cells.

Keywords: mRNA at nanocarrier, therapy of breast cancer, inhibition of TGF-β



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Apoptosis induction via ROS by tetrahydroxyquinone on human colorectal adenocarcinoma cell line HT-29

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Abstract:

Tetrahydroxyquinone (THQ) is a highly redox active molecule that can induce the production of Reactive Oxygen Species (ROS), nevertheless its potential as anticancer drug has not been well studied. ROS generation is an important factor to control cellular biochemical processes as well as to induce cytotoxicity in cancer cells. Mainly the toxicological properties of THQ are due to its ability to autoxidize generating superoxide anion radicals ($O_2 \bullet^-$), semiquinone radicals and rhodizonic acid (RDZ). In the present study we observed that THQ induces apoptosis in the human cell line HT-29. Cytotoxic assays were carried out with different concentrations of THQ (0.01, 0.1, 0.2 & 0.3 mg/mL), the viability of HT-29 was evaluated by WST-1 technique and trypan blue staining. Then ROS generation was determined by a fluorescence method using 2,7-dichlorodihydrofluorescein diacetate ($DCFH_2$-DA). The intracellular accumulation of RDZ was investigated by UV-vis spectrophotometry and induction of apoptosis was determined with Annexin V-FITC. We observed that THQ has a LD_{50} = 0.075 mg/mL. Moreover, THQ causes ROS production and induces apoptosis. We concluded that THQ is taken up by the cell, then in the cytosol it is oxidized to RDZ, concomitant ROS generation induced apoptosis. It is possible that the generated ROS activated p53 and/or c-Jun N-terminal kinase (JNK) which, in turn, activated pro-apoptotic Bcl-2 protein.

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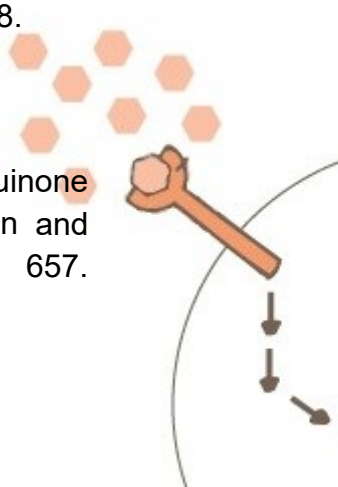

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Loss of the tumor suppressor miR-122 promotes cell migration and up-regulation of BORIS/CTCFL in triple-negative breast cancer

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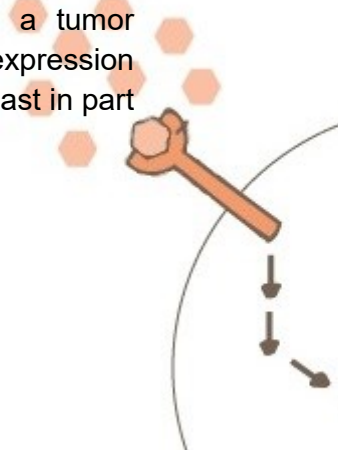
Abstract

miRNAs are endogenous short non-coding RNAs that regulate the expression of target genes post-transcriptionally. In human cancer, miRNAs are key regulators of pathways to promote or suppress carcinogenesis. miR-122 is aberrantly expressed in breast cancer having a role as both tumor suppressor and oncomiR. In triple-negative breast cancer (TNBC) the function of miR-122 is still unclear. This study was conducted to better understand the molecular mechanism behind miR-122 in TNBC, mainly its role on the chemotherapy response. The expression and clinical association of miR-122 in TNBC patients submitted to neoadjuvant chemotherapy (NAC), and the differentially expressed genes (DEG) were evaluated throughout bioinformatic analysis using the TNBC-related RNA-seq from TCGA and KM-plotter datasets. The functional analysis of miR-122 in TNBC cells were performed by knockdown or overexpress miR-122 by cell transfections, RT-qPCR, immunoblot, cell viability and cell migration assays. Results showed that the loss of miR-122 expression in TNBC patients was associated with tumor recurrence but not with pathologic complete response after NAC. The loss of miR-122 allows the activation of gene co-expression network highly related with advanced stage, poor prognosis, and worse outcome. The gene co-expression network was enriched in genes associated to migration, invasion, stem phenotype and cell differentiation. Among gene co-expressed, the DNA-binding protein BORIS was identified as target gene of miR-122. Functionally, exogenous overexpression of miR-122 modulated the cell migration and BORIS expression in the TNBC cells. In addition, BORIS promoted a gene expression profile related to cell differentiation and cytoskeletal components in TNBC patients. In conclusion, miR-122 is a tumor suppressor in TNBC that negatively regulates cell migration. Loss of miR-122 expression promotes overexpression of genes to favor cell differentiation and migration, at least in part by regulates BORIS expression.

Keywords: tumor suppressor, miR-122, BORIS, chemotherapy, TNBC



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Role of STAT5 in energy mitochondrial metabolism genes regulation in cervical cancer cells stimulated with Interleukin 2

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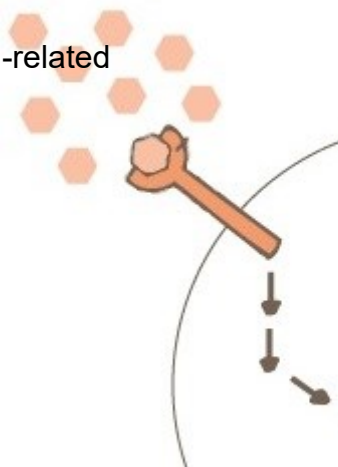
Cervical cancer (Cacu) is second in incidence and death in women in Mexico. An important risk factor in Cacu is the chronic infection with human papillomavirus (HPV); this infection can change the regulation of the cell cycle, and normal cells transform into cancer cells and, with this, acquire new characteristics. We have demonstrated that cervical cancer cell lines produce IL-2, and the IL-2 receptor is present in these cell lines. Also, the JAK/STAT pathway is active in Cacu cell lines since JAK3, STAT3, and STAT5 increase their phosphorylation in response to 10 IU/mL of IL-2, thus increasing cell proliferation. Another hallmark of cancer cells is metabolic reprogramming. Mitochondria plays a vital role in this regulation, specifically genes related to the electron transport chain (ETC). However, the role of the STAT proteins in the metabolic reprogramming of Cacu cells is not known. We analysed the role of STAT5 in regulating ETC-related genes in mitochondria in response to IL-2. We demonstrate that STAT5 is localised in mitochondria in a basal form; after the stimulation of cervical cancer cell lines with 10 IU/mL of IL-2, there is an increase in activation and the translocation of STAT5 to mitochondria. Also, our results show that the treatment with 10 IU/mL of IL-2 decreases the transcription of ETC-related genes, specifically UQCRC1, NDUFV1 and ATP5FB1. These results suggest that IL-2/JAK/STAT signalling pathway can regulate metabolism-related genes, specifically ETC genes.
These results suggest that STAT5 may be a negative regulator for ETC-related genes and contribute to the metabolic switch in cervical cancer cells.



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DNA Methylation-associated expression of the Ca^{2+} signaling genes in breast cancer cell lines during the epithelial-to-mesenchymal transition

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DNA methylation is a main epigenetic modification that regulates gene expression by the methyl group addition to a cytosine present in DNA, methylation occurs mainly in CpG dinucleotides that are present in repetitive regions and promoter regions of genes, this reaction is catalyzed by the DNA methyltransferases (DNMTs) family [i]. Promoter hypermethylation causes the silencing of gene expression and this phenomenon is highly associated with breast cancer where enhances tumor progression through epithelial-to-mesenchymal transition (EMT) targeting DNMTs as a therapeutic target for metastatic cancer treatment [ii]. The use of growth factors such as TGF-β and EGF allowed the establishment of EMT induction model (iEMT) that produces changes in the expression of E-cadherin (*CDH1*) and fibronectin (*FN1*) genes that are widely used as biomarkers of cell differentiation status. Analysis of public sequencing data had identified genes involved in Ca^{2+} signaling with differential expression in tumor samples and breast cancer cell lines compared to healthy mammary tissue being the family of cadherins one of the main expressions silenced associated with hypermethylation[iii]. Results obtained by RT-qPCR in our laboratory show that the gene expression of *DSG3* tends to decrease in the presence of iEMT in MCF10A cells however after 5-azacytidine (5-aza) administration gene expression increases at basal levels. In addition, *DSC3*, *DSG3* and *PCDH18* genes also show increased expression after resveratrol (RSV) administration where total restoration of their expression is observed even in the presence of the iEMT, due to this our results suggest that the use of inhibitors of DNMTs such as 5-aza and RSV could reverse methylation-mediated gene silencing in breast cancer cell lines during EMT.

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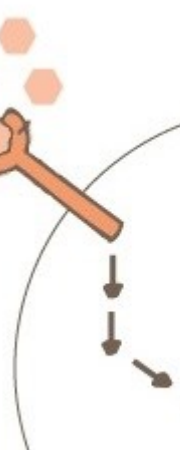

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Regulation of proliferation and transcriptome of prostate cancer cells by Menadione and Cabazitaxel

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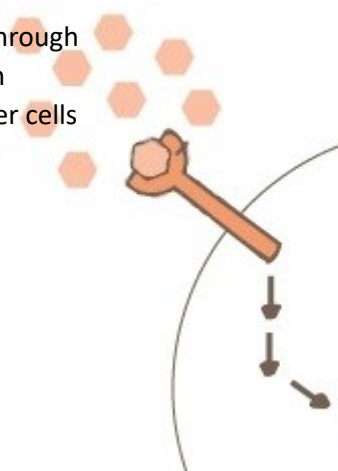
Abstract:

Introduction: Menadione (VK3) is a synthetic derivative of vitamin K with potential antitumoral effects, while cabazitaxel (CBZ) belongs to the taxane family and is used as second-line treatment for prostate cancer (PCa). Therefore, both are considered chemotherapeutic compounds. Several reports indicate that VK3 and CBZ present independent antineoplastic effects. In fact, VK3 has been reported to induce apoptosis and inhibit the proliferation of tumor cells, whereas CBZ is an antimitotic drug that inhibits microtubule dynamics. The combination of two or more treatments may lead to increased efficacy, permitting lower doses of the molecules, which could be an option effective against PCa with minimal side effects. Nowadays, there is no information regarding the combinatory effects of these two compounds and their implications in signal pathways in human prostate cancer cell lines. **Aim:** To study the effects of VK3, CBZ and their combination (COMB) upon the proliferation and transcriptome of prostate cancer cells. **Methodology:** To determine the effects of the indicated compounds on cell proliferation, we seeded 2000 cells of PC-3 and DU145 in 96 wells culture plates. After 24 h of culture, cells were incubated with CBZ (0.1, 0.25, 0.5 and 1 µM), VK3 (1.25, 2.5, 5 y 7 µM) or their COMB (VK3 [5 µM] and

CBZ [0.25 µM]) during 72 h. After this time, cell proliferation was evaluated by sulforhodamine B (SRB) assay. To identify the differentially expressed genes(DEG) after each treatment, 150 000 PC-3 cells were seeded in six wells culture plates, incubated for 24 h with each treatment and total RNA samples were analyzed using a Clariom D human microarray, followed by bioinformatic analysis. **Results:** Our data showed that VK3 and CBZ significantly inhibited the proliferation of both cell lines in a dose-response manner. Remarkably, the COMB treatment resulted in significant inhibition of cell proliferation in comparison to independent treatments. Microarray analyses revealed a set of DEG (log fold change ± 0.7 and $P < 0.05$) for each treatment. Venn diagrams showed that most of the DEG were dependent for each treatment. Among the DEG, we found that the COMB treatment significantly stimulated the IL-24 synthesis, which could be related to growth cell inhibition through increased production of reactive oxygen species (ROS). **Conclusion:** As compared with each compound, the COMB treatment was more effective for inducing cell death of prostate cancer cells probably by ROS production.

This work was partially supported by CONAHCyT, México [grant number 282770]. ALGR has a scholarship from CONAHCyT and NNM from FunSaEd No.



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UVB and UVC inhibits cellular processes related to carcinogenesis in cervical cancer cell lines

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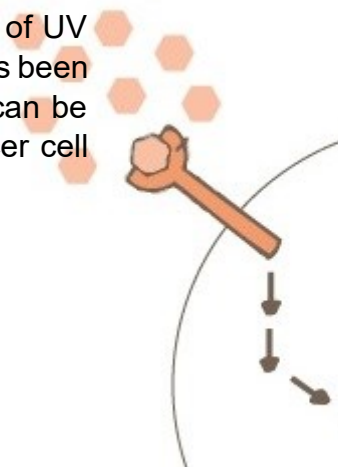
The interaction of UV and cell generates free radicals producing cell death, senescence and proliferation alteration among other cell processes changes. UVB and UVC potentially could be used in therapy as an alternative for common radio and chemotherapy. In this work we where interested in seeking the quantity of UV necessary to inhibit cell proliferation and induce cell death. Therefore we make a dose-response and temporal time experiment at different doses of UVB and UVC. Interestingly we find that UVB and UVC present almost the same effect at a similar energy in SiHa, HeLa, C4.1, C33A and Calo cell proliferation. UVB treatment arrest SiHa cells in S phase in a dose-response shape. Cell migration and invasion shows inhibition since 15 sec of UV exposition showing a profound effect at 25 sec of UV treatment. These UVB cell effects seams protein p53 dependent because it has been shown an increase dependent of UVB doses. These results show that UV can be used for inhibit cellular processes related to carcinogenesis in cervical cancer cell lines opening the possibility to cancer patients.



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Determination of autophagy and apoptosis in SiHa and HeLa cells treated with IL-2 and anti-CD95

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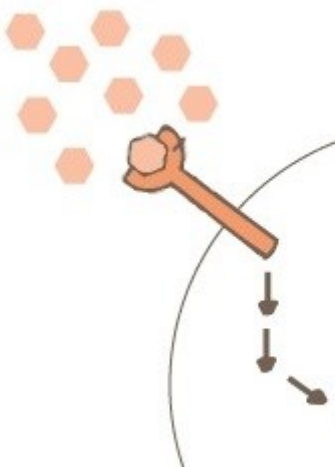
Programmed cell death induced by the CD95 receptor plays an important role in the elimination of damaged, infected and transformed cells. However, in HPV-positive cervical tumour cells, high expression of this receptor and high resistance to the induction of apoptosis have been reported. These data could indicate that stimulation of the CD95 receptor could activate the non-canonical pathway, a pathway that in other types of cancer is associated with survival, metastasis, and proliferation processes. On the other hand, our work group has reported that IL-2 has a dual role on cervical tumor cells, inducing or inhibiting their proliferation when they are treated with high and low doses, respectively. Because of this, we decided to evaluate whether treatment of cervical tumour cells with IL-2 (10 and 100 IU/mL), agonist anti-CD95 antibodies, and together affect proliferation, apoptosis, and autophagy. The determinations were made by crystal violet, flow cytometry and confocal microscopy. We found that IL-2 induces or inhibits proliferation depending on the dose. Cervical tumour cells express CD95 as well as its ligand; treatment with anti-CD95 promotes cell proliferation. The doses of IL-2 and anti-CD95 used do not induce apoptosis, but the joint treatments of IL-2 plus CD95 promote the accumulation of LC3B fluorescent foci, that is, autophagosomes, structures inherent in the autophagic process. Our results demonstrate the pleiotropic role of IL2 in cervical tumor cells, 100 IU of IL2 negatively regulates proliferation, while 10 IU induces the opposite. Apparently the expression of CD95 and its ligand play a pro-survival role. In addition, the accumulation of the LC3B protein through the stimulation of IL-2 plus CD95 is related to the increase in cell proliferation and also as a possible cytoprotective process mediated by autophagy.



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The calcium-activated chloride channel TMEM16A promotes sphingosine 1-phosphate-induced migration in HEK293 cells via the RhoA/ROCK/MLC pathway.

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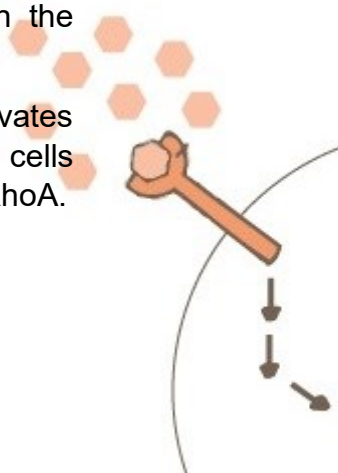
BACKGROUND: Previous proteomics experiments indicated an association between TMEM16A and the small GTPase RhoA, known to regulate both actin and myosin and thereby cell motility. Since RhoA is activated downstream the sphingosine-1-phosphate receptor (S1PR) to initiate cell migration and overexpression of TMEM16A either promote or inhibit cell proliferation and migration in cancer cells, we investigated whether S1PR stimulation could promote migration of HEK293 cells expressing TMEM16A by activating the RhoA signaling pathway.

METHODS: Wild type (mTMEM16A-3Xflag) and mutant (R429P hTMEM16A) channels were expressed in HEK293 cells using lipofectamine. Proteins were extracted 48 h post-transfection and quantified by the Bradford method. The mTMEM16A-3XFlag-RhoA interaction was assessed by co-immunoprecipitation (Co-IP). Whole cell Cl^- currents were recorded 24 h post-transfection using the patch-clamp technique. Phosphorylated ROCK and MLC proteins were detected and quantified by Western blot. RhoA signaling in HEK293 cells was induced by stimulating endogenous S1PRs. Cell migration was quantified using the wound healing assay as follows. First a gap was made in a cell monolayer with a pipette tip and then the gap area was imaged at 0, 3, 6, 9, 12, and 24 h using a camera attached to a Nikon inverted microscope.

RESULTS: Co-IP showed that TMEM16A interacts with endogenous RhoA. We found that S1P (10 μM) activates RhoA but not TMEM16A, despite increasing the intracellular calcium concentration. Also, S1P promoted the migration of HEK293 cells transfected with the wild-type TMEM16A, which was attenuated by the ROCK inhibitor, Y-27632. Conversely, S1P increased the migration of cells expressing the tumor associated R429P mutant. Despite this, the total expression of RhoA and phosphorylated MLC decreased, while phosphorylated ROCK increased in the presence of the mutant channels.

CONCLUSIONS: Our data suggest that in the presence of TMEM16A, S1P activates the RhoA/ROCK/MLC signaling pathway during HEK293 cells migration, but in cells expressing the R429P oncogenic mutant migration rely on ROCK but not on RhoA.

KEYWORDS: TMEM16A, RhoA, cell migration. Support: CONACYT 1308052.



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Effect of the IFC-305 in B-cell Acute Lymphoblastic Leukemia cell lines on the PI3K/Akt/mTOR pathway

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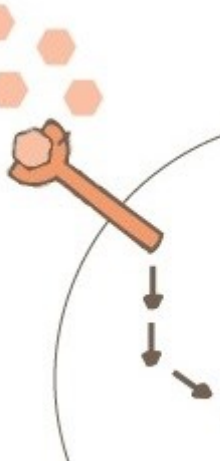
Abstract

B-cell acute lymphoblastic leukemia (B-ALL) is a type of hematologic cancer caused by the malignant transformation of precursor B cells that proliferate uncontrollably in bone marrow, peripheral blood, and extramedullary sites. The PI3K/Akt/mTOR signaling pathway in B-ALL is hyperactivated, promoting proliferation of leukemic cells and resistance to treatment. Among the new alternatives for cancer treatment is an adenosine derivative, IFC-305, which has been studied in hepatocellular carcinoma (HCC) where it has been seen to prevent and reverse cirrhosis in animal models, has an anticarcinogenic effect, induces autophagy in vivo and in vitro. While in hepatic stellar cells, the levels of the phosphorylated proteins AKT and P70S6K decrease.

The objective of this project is to evaluate the effect of IFC-305 on the activation of the PI3K/Akt/mTOR pathway, autophagy, and apoptosis in B-ALL cell lines. For this, it was first determined that IFC-305 has a cytotoxic effect on the three B-ALL cell lines: REH, Nalm6 and SUP-B15, and the inhibitory concentration 50 (IC50) of the compound was determined in each cell line, which varied between each one, suggesting that the effect could depend on the molecular characteristics of each cell line. Subsequently, it was determined in vitro that there is a synergistic effect between IFC-305 and two mTORC1 inhibitors Everolimus and Gedatolisib at 24 and 48 hours of treatment. It was found that when IFC-305 is added together with Everolimus or Gedatolisib there is a statistically significant decrease in the survival of leukemic cells compared to when only one is added. To assess the effect of IFC-305 on the PI3/AKT/mTOR signaling pathway, the levels of total and phosphorylated PI3K, AKT, mTOR, and P70S6 proteins were determined. The results show that the greatest effect of IFC-305 is on the mTOR protein phosphorylated at Ser2448 and Ser2481 residues in all cell lines. In addition, when evaluating the effect of IFC-305 on the autophagy process by determining the levels of protein Beclin-1 (induction of autophagy) and p62 (autophagic flow), it was found that in the three cell lines it favors the induction and flow of this process.

These results suggest that IFC-305 has a cytotoxic effect and on the PI3K/AKT/mTOR signaling pathway in B-ALL cell lines through its activity on the phosphorylated mTOR protein, also favoring the autophagy process that could help control hyperproliferation of leukemic cells and, in turn, eliminate them through autophagy.



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Differential Proliferation, Migration, and Invasion Effect of the Alanine, Methionine, Glycine, Asparagine, Phenylalanine, Tyrosine, Valine, and Tryptophan-naphthoquinones in Immortal and Tumorigenic Cervical Cell Lines

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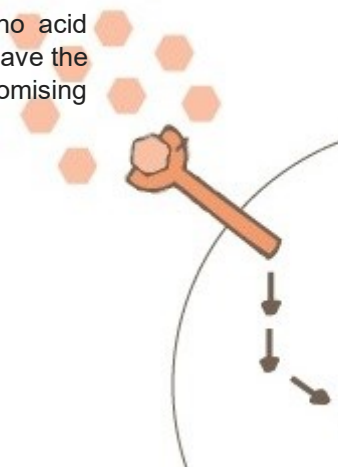
We synthesized chloride and non-chloride Alanine, Methionine, Glycine, Asparagine, Phenylalanine, tyrosine, valine, and tryptophan-naphthoquinones achieving 78–95% yields. The newly synthesized compounds were tested in HPV positive and negative as well as in immortal and tumorigenic cell lines to observe the effects in different cellular context simulating precancerous and cancerous status and the participation of cell signaling p53-miR-34 pathway. A dose-response was performe to determine the IC50 of newly synthesized compounds in SiHa (Tumorigenic and HPV16 positive), CaLo (Tumorigenic and HPV18 positive), C33-A (Tumorigenic and HPV negative) and HaCaT (Keratinocytes immortal HPV negative) cell lines and to evaluate migration, invasion and p53-miR-34 system expression. Interestingly, a differential effect with non-chloride and chloride naphthoquinone amino acid derivatives in tumorigenic versus non tumorigenic cells in proliferation, migration and invasion was observed. The effects elicited by naphthoquinone amino acid derivatives were independent of p53 and miR-34 family expression. Considering all naphthoquinone amino acid derivatives that our group synthesized, it seems that hydrophobic and aromatic amino acids have the greatest effect on cell proliferation, migration and invasion inhibition. These results show promising compounds for cervical cancer treatment.



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Comparison of total phosphorylation in cervical cancer cells cultured in monolayer and in a three-dimensional system

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Abstract:

The cancer is a process of uncontrolled growth of abnormal cells that spread beyond their usual limits. Cervical cancer is a type of cancer that originates in the cervix cells, this type of cancer is classified by the appearance it presents when observed under a microscope in the laboratory.

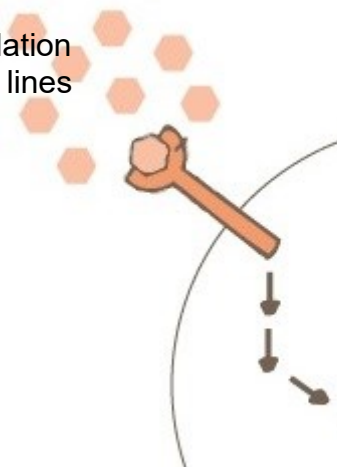
The two most common types are squamous cell carcinoma and adenocarcinoma, with squamous cell carcinoma found mostly in 90%. GLOBOCAN reported in 2020 that cervical cancer is the fourth in incidence in women around the world and the third in death, and as number 2 in Mexico, despite efforts to eradicate the disease, each year it is increasing. High-dose IL-2 therapy has been used as an effective immunotherapy against melanoma for approximately 20 years, through the activation of the JAK/STAT pathway.

Our work group was show that cervical cancer cells express a functional IL-2R and is capable activate JAK/STAT pathway, this pathway is involved in numerous physiological cellular processes, such as proliferation, differentiation, apoptosis, and regulation of the immune system; however, aberrant regulation of STAT can lead to pathological events, including malignant cell transformation and metastasis.

Monolayer cell cultures have been the standard for cancer biology research, however their ability to accurately reflect the molecular mechanisms of tumors occurring in vivo is limited. Three-dimensional culture systems are becoming increasingly popular due to their ability to mimic tissue-like structures more effectively than monolayer cultures, facilitate the possibility to better recapitulate several of the biological and molecular characteristics of tumors *in vivo*, such as cancer cells heterogeneity, cell-extracellular matrix interactions, development of a hypoxic microenvironment, signaling pathway activities depending on contacts with extracellular matrix, differential growth kinetics, more accurate drugs response, and specific gene expression and epigenetic patterns.

On that basis, the comparison of total protein phosphorylation in cervical cancer cells cultured in monolayer and in a three-dimensional system was performed.

The objective of this project is determinate the state of total tyrosine phosphorylation after stimulation with 10 and 100 U/mL of IL-2 in different cervical cancer cell lines cultured in 2D and 3D.



Nuclear accumulation of Rac1 increases proliferation and migration in HaCat cells

Dana Clarissa Maldonado Fuentes, Fernanda Donaji Memije Soto, Yunue Bello Gálvez, Juan Carlos Juárez Cruz, Carlos Ortuño Pineda, Mónica Ramírez Ruano, Eduardo Castañeda Saucedo

Laboratorio de Biología Celular del Cáncer. Facultad de Ciencias Químico-Biológicas. Universidad Autónoma de Guerrero. Ciudad Universitaria Sur. Av. Lázaro Cárdenas s/n. Col. La Haciendita. CP. 39087.

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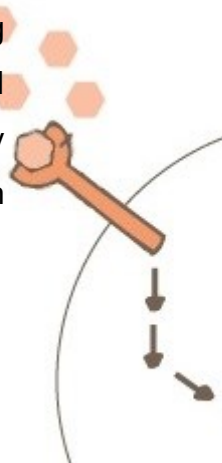
Abstract

RAC1 GTPase modulates a variety of cellular processes. Its activity is regulated by interaction with a plethora of regulatory and effector proteins. Importantly, RAC1 subcellular localization plays a key role in regulating its functions. RAC1 has a functional nuclear localization signal, however, the mechanisms controlling RAC1 translocation to the nucleus and its functions within this compartment have not been completely elucidated. In addition, it has been suggested that nuclear RAC1 may play a role in carcinogenesis. The goal of this work is to explore the potential role of nuclear RAC1 as a regulator of cell proliferation and migration. Constitutively active RAC1 mutants that accumulate in the nucleus (EGFP-L61Rac1$^{\Delta AAX}$), that lack the NLS and are sequestered in the cytoplasm (EGFP-L61Rac1^{KTail}), or a RAC1 version that can shuttle between nucleus and cytoplasm (EGFP-L61Rac1) were expressed in HaCat cells. Cell proliferation was evaluated by MTT assays and cell migration was evaluated by wound healing assay and video-microscopy. Changes in gene expression were evaluated by RNAseq and RT-PCR. We found that cells expressing the RAC1 mutant that accumulates in the nucleus have increased proliferation and migration compared to cells expressing the cytoplasmic RAC1 mutant. Preliminary RNAseq analysis shows that nuclear accumulation of RAC1 results in deregulation of several genes involved in proliferation and migration.



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Effect of Toll-like receptor 4 (TLR-4) activation by LPS on the migratory and proliferative capacity of prostate cancer tumor cells, PC-3.

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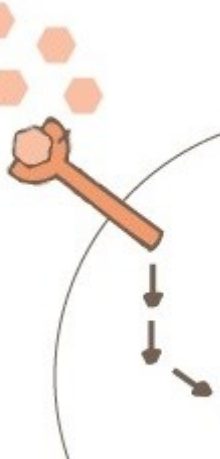
Prostate cancer (PCa) is the neoplasm with the highest incidence and mortality rate in the adult male population. More than 90% of the deaths caused by PCa are due to the presence of metastases in bone, lung and brain. There has been extensive research on the factors present in the tumor microenvironment that favor the process of metastasis, with inflammatory processes being the most widely studied and related to this process. Several evidences show that tumor cells are able to synthesize and release pro-inflammatory cytokines into the tumor microenvironment, favoring tumor development and progression. One of the main membrane receptors related to the inflammatory response of both immune system cells and tumor cells is the Toll-like receptor 4 (TLR-4), which when activated by LPS or other endogenous ligands, triggers signaling pathways aimed at the production of pro-inflammatory cytokines. Chronic activation of TLR-4 in prostate epithelial cells is known to promote proliferation, migration, survival and tumor transformation. TLR-4 is overexpressed in PCa cells; however, it is unknown whether its activation by LPS is able to favor its metastatic potential. Therefore, the aim of the present work is to determine whether chronic activation of TLR-4 with LPS affects the migratory and proliferative capacity of PC-3 cells. The PC-3 cell line was maintained under standard culture conditions. For the migration assay, Transwell chambers were used, PC-3 cells were treated for 48 h with LPS at different concentrations (0.25, 0.5, 1, 5 and 10 µg/ml), in the presence and absence of an inhibitor of NF-kB (PDTC), and the expression levels of mRNA coding for MMP-2 and -9 were evaluated by RT-PCR. For the proliferation assay, cells were counted in a hematocytometer using trypan blue and the expression level of mRNA coding for Ki-67 was evaluated by RT-PCR. Complementarily, we evaluated whether TLR-4 silencing affected the proliferative and migratory capacity of PC-3 cells. The results obtained show that chronic activation of TLR-4 by LPS favors both the proliferative and migratory capacity of PC-3 cells. These effects induced by TLR-4 depend on NF-kB, since when its specific inhibitor is simultaneously incubated with LPS; the stimulatory effect of LPS is prevented. The specific silencing of TLR-4 reduces the migratory and proliferative capacity of PC-3 cells, making clear the participation of this receptor in the metastatic potential of prostate cancer cells.



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"Evaluation of the co-expression of PAK1 and ABL1 oncoproteins in human breast cancer samples"

Estefanía Isay Martínez Acosta, Olga Villamar Cruz, Nely Gisela López Desiderio, Hector Iván Saldivar Cerón, Luis Enrique Arias Romero.
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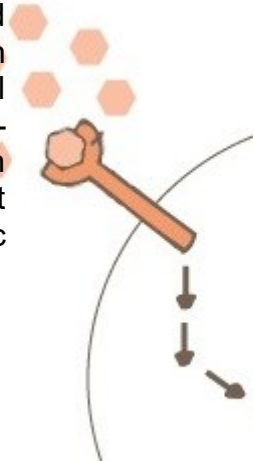
Breast cancer is one of the most common malignancies among women and is the fifth leading cause of cancer-related deaths. In Mexico, breast cancer is the leading cause of cancer-related deaths among women. Breast carcinomas can be stratified into different entities based on clinical behavior, histologic features, and/or by biological properties. Molecular stratification based on gene expression profiling revealed that breast cancers could be classified in so-called intrinsic subtypes (luminal A and B, HER2-enriched and triple negative breast cancer), which mostly corresponded to hormone receptor and HER2 status. In addition, immunohistochemical analysis of other proteins in tumor samples has allowed the identification of new biomarkers and therapeutic targets.

In this regard, we analyzed the co-expression of PAK1 and ABL1, two oncogenic kinases that are commonly overexpressed in breast cancer cell lines and human tumor samples with an aggressive phenotype. To do this, we designed a tissue microarray (TMA) that contains 295 breast tumor samples. These TMAs were stained for ABL1 or PAK1, Immunohistochemically stained samples were digitalized and protein expression analysis of each tissue section was performed by digital pathology using a ScanScope CS digital processor. Finally, in the statistical analysis, we evaluated PAK1 and ABL1 expression levels according to histological grade, molecular subtype, and patient survival.

Overall, both PAK1 and ABL1 showed higher expression levels in tumor samples than in non-transformed adjacent tissue ($p < 0.0001$). The results of these analyses proved that PAK1 and ABL1 are co-expressed in breast cancer human samples, both at cytoplasmic and nuclear levels. All the breast cancer intrinsic subtypes samples co-expressed both proteins. Interestingly, ABL1 is overexpressed in tumors with more advanced histological grades. In addition, the survival analysis showed that co-expression of both proteins is related to a worst prognosis. For the correlation analysis, we obtained an $r=0.48$ for all the samples and an $r=0.68$ for the luminal B/HER2+ subtype. In conclusion, we demonstrated that PAK1 and ABL are co-expressed in human breast cancer samples, that there is an association between overexpression, advanced histological grades and lower survival rates. Our result suggest that PAK1 an ABL1 might be used as prognostic markers or therapeutic targets.



Interaction between Wnt and lysophosphatidic acid (LPA) receptor signaling pathways in colon cancer

Juan Carlos Martínez Morales*, M. Cristina Castañeda-Patlán, Marco Antonio Morquecho León, Teresa Romero Ávila, Jesús Adolfo García-Sáinz and Martha Robles Flores

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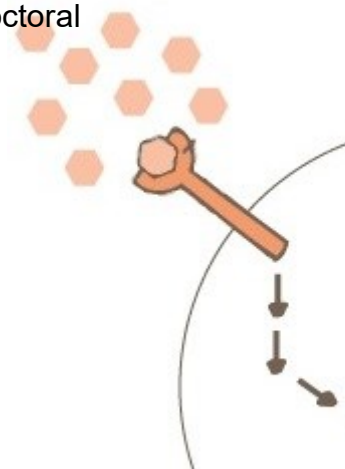
Colorectal cancer is the third cause of death from cancer worldwide. Aberrant canonical Wnt signaling is a hallmark of this type of cancer. It has been reported that LPA is a “bioactive lipid” and its G-protein -coupled receptors may play different roles in colon cancer inducing cell proliferation, migration, survival, and angiogenesis.

LPA receptors expression changes under malignant conditions: we found that while $LPAR_1$ and $LPAR_2$ are expressed at low levels in non-malignant 112CoN cells, RKO malignant cells overexpress $LPAR_1$ and $LPAR_2$ and SW480 cancer cell line only overexpress $LPAR_1$. We also found that LPA and Wnt3A induce a strong ERK activation in all colon cell lines that were not additive. LPA and Wnt3a were both able to stimulate β-catenin transcriptional activity and the β-catenin phosphorylation at S552 and S675 residues, again in an apparently non- additive manner. In addition, we found that $LPAR_1$ and the Wnt effector Dvl3 interact in RKO cells, and we are currently investigating if this interaction occurs via PDZ-interacting motifs located in both proteins.

Supported by grants from Universidad Nacional Autónoma de México (PAPIIT IN229420). Juan Carlos Martínez Morales was granted with a Postdoctoral Fellowship by DGAPA, UNAM, México.



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TGF-β/SMAD canonical pathway induces the expression of transcriptional co-factor TAZ (WWTR1) in liver cancer cells

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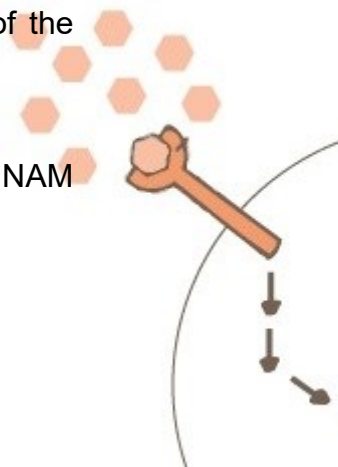
ABSTRACT

The TGF-β and Hippo pathways have a physiological relevance in health and disease, as they regulate multiple homeostatic processes from development to adulthood. In the liver, a major crosstalk between TGF-β and Hippo pathways is critical for organ size control, hepatic regeneration, and hepatocarcinogenesis. TGF-β and Hippo pathways are tumor suppressors in hepatocytes, as both inhibit cell proliferation and maintain homeostasis, and are also essential players in liver regeneration, although they may promote hepatic cancer when their signaling pathways become altered. The transcriptional co-factor TAZ, also named WWTR1, is a downstream effector of Hippo pathway and plays a key role in the maintenance of liver physiological functions. However, the upregulation of *TAZ* expression has been associated with liver cancer progression. Recent evidence shows crosstalk of TGF-β and Hippo pathways, since TGF-β modulates *TAZ* expression through different molecular mechanisms in a cellular context-dependent manner. Previous reports demonstrate that TGF-β regulates TAZ gene expression mainly through SMAD-independent pathways or in synergy with other cytokine pathways. However, it was unclear if TAZ was a direct target gene of the canonical TGF-β signaling pathway. Here, we reported that the TGF-β cytokine through its canonical SMAD pathway induces TAZ gene expression, and subsequently increases TAZ protein levels in HepG2 cells, a model of cancerous hepatocytes. We analyzed *TAZ* gene promoter and identified SMAD binding elements. Our results show that TAZ transcriptional co-factor is a primary target of TGF-β/SMAD signaling, one of the main pathways altered in liver cancer.

This work was supported by grant No. IN208118 from PAPIIT/DGAPA/UNAM (MMS), and grant No. 304023 from CONACyT (GVV/MMS).



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Effect of the Insulin-like growth factor system (IGF) on the proliferative capacity of non-small cell lung cancer cell line (A549).

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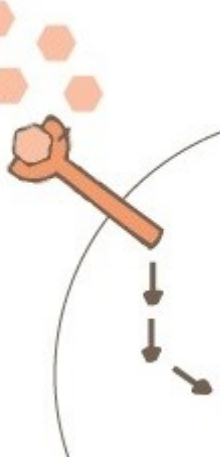
Insulin-like growth factors (IGF) are a set of elements of protein nature, with high sequence similarity to insulin, which physiologically participate in the normal development of an individual. However, its participation in the progression of various types of cancer has been widely documented. Lung cancer is the leading cause of cancer mortality worldwide, according to GLOBOCAN 2020 data. It is classified into two types: a) non-small cell lung carcinoma (NSCLC) and, b) carcinoma of the small cell lung. The NSCLC represents 75% of the total lung cancer cases.

In this context, the aim of the present work is to determine if the IGF signal transduction system exerts an effect on the proliferation of non-small cell lung cancer cell line (A549 cells). The A549 cell line was maintained under standard culture conditions. For proliferation assay, A549 cells were treated for 72 h with IGF1 or IGF2 at different concentrations (100 or 200 ng/mL), at the end of the treatment period, cell count was performed using Countess® II Automated Cell Counter (*Invitrogen*). We also evaluated the expression of molecular targets, at mRNA level, associated with the proliferation and apoptosis by RT-PCR.

Our results indicate that the chronic presence of IGF1 exacerbates the proliferative capacity of A549 cells, positively associated with an increase in the level of expression of Ki67, Birc3 and survivin 3.

A549 cells express the mRNA for IGF1R, a specific receptor for IGF1. Activation of this receptor, which has intrinsic tyrosine kinase activity, triggers two signaling pathways: the PI3K/AKT pathway and the MAPK pathway. We show that the blocking either of the two pathways has a negative impact on their proliferative capacity. With the results obtained, IGF1/IGF1R complex could be proposed as new pharmacological targets for the treatment of NSCLC.



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Interferon-stimulated gene 15 and ISGylation are upregulated in glioblastoma.

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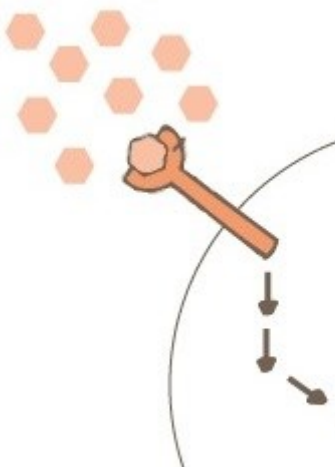
ISG15 (interferon-stimulated gene 15) is a 15 kDa protein consisting of two ubiquitin-like domains, which acts as a post-translational modifier by covalently binding to its target proteins through a catalytic process called ISGylation. The *ISG15* expression is deregulated in some cancer types, however, it has not been fully studied in brain tumors. This work focused on glioblastoma, a highly aggressive and invasive malignant brain tumor. The ISG15/ISGylation profile in glioblastoma cells and its modulation by the IFN-γ signaling pathway were determined by western blotting. The expression of *ISG15* and ISGylation system elements in glioblastoma samples was also evaluated *in silico*. By immunohistochemistry, ISG15 levels were detected in glioblastoma samples, and the effect of *ISG15* expression on patient survival was analyzed. Our results indicate that IFN-γ signaling increases ISG15/ISGylation levels. This result is relevant because high levels of ISG15 are detected in glioblastoma compared to healthy brain tissue, being associated with shorter survival time. Therefore, our results suggest that high levels of ISG15/ISGylation may promote glioblastoma progression.

This research was supported by UACM-CCyT (CCyT-2022-08). KHM-A is a student of Posgrado en Ciencias Genómicas-UACM. KHM-A is recipient of a fellowship from CONAHCyT.



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Study and characterization of an Adenosine derivative, as a potential treatment of bone metastasis

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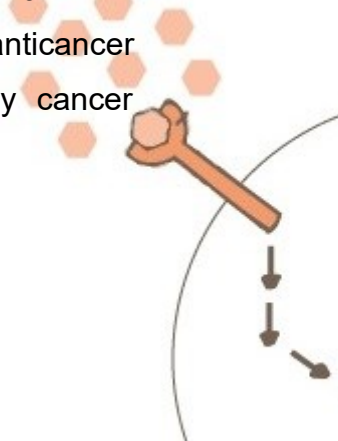
Breast cancer is the highest incidence and the main cause of death caused by cancer in women. Although the prognosis for some patients may be favorable due to early detection and treatment, there is still no therapy to cure breast cancer bone metastasis. Adenosine and its derivatives have demonstrated their relevance in the control of proliferation, immune response, and apoptosis in different types of cancer. In this project, we evaluated the anticancer potential of a derivate of Adenosine (derAde) in breast cancer cells *in vitro*, and in an *in vivo* model of bone metastasis. To evaluate the effect of derAde on the cell proliferation of 4T1 murine breast cancer cells by MTT assay. The drug inhibited the proliferation of 4T1 cells in a dose-dependent manner. To understand the underlying mechanism, we evaluated the apoptosis and the cell cycle of 4T1 cells in the presence or absence of derAde by flow cytometry. Results showed that after 24 hours of exposure to the drug, the effect on apoptosis is minimal. However, we found that 4T1 cells were arrested in the G0/G1 phase of the cell cycle. We use a wound-healing assay to measure the effect of the adenosine derivative on 4t1 cell migration. We found that after 24 hours of exposure to the drug, the migration of the 4T1 cell line decreases significantly at a concentration of 5 to 20 mM. Evaluation of the effects of derAde on an *in vivo* model of bone metastasis are in progress. Our findings suggest that derAde has anticancer potential effects and could be a potential therapeutic agent to delay cancer progression.



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Epidermal growth factor (EGF) potentiates migration of MDA-MB 231 breast cancer cells by increasing voltage-gated sodium and calcium channels expression.

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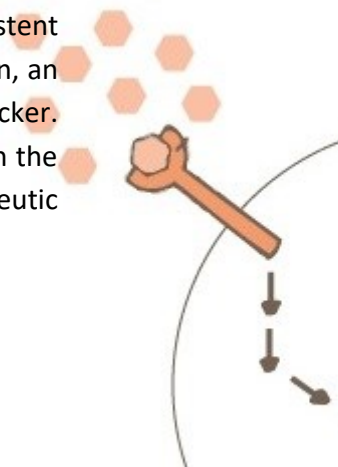
Introduction: Breast cancer is one of the leading causes of death worldwide and is the result of dysregulation of various signaling pathways in mammary epithelial cells. Triple-negative breast cancer (TNBC) represent 15 to 20% de all cases of breast cancer, presents the most aggressive phenpotype and the worst prognosis of survival. These tumor cell are characterized by being negative for the expression of ERα, PR and HER2, so the re is not efficient pharmacological treatment so far. The mortality rate in patients suffering TNBC is high because the tumor cells have a prominent invasive capacity towards the surrounding tissues. These cells overexpress the receptor to EGF, whose activation exacerbates its metastatic potential and the molecular mechanisms involved are still unknow. Previous studies carried out in tumor cell models show that voltage-gated ion channels may be important molecular actors that contribute to the migratory and invasive capacity of the tumor cells. ***Methods:*** In this study, by using an experimental strategy that combines cell and molecular biology assays with electrophysiological recording, we sought to determine whether the voltage-dependent sodium and calcium channel regulates the migratory capacity of the human breast cancer cell line MDA-MB 231, when cells are maintained in the presence of epidermal growth factor (EGF), as an inductor of the epithelial- mesenchymal transition. ***Results:*** Our data show that EGF stimulates the migratory capacity of MDA-MB 231 cells, by regulating the functional expression of sodium and calcium channels. Consistent with this, the stimulatory actions of the EGF were prevented by the use of tetrodotoxin, an Na+ channel selective blocker, as well as nimodipine, an Ca2+ channel selective blocker. ***Conclusions:*** The understanding of molecular mechanisms, such as the EGF pathway in the progression of breast cancer is fundamental for the design of more effective therapeutic strategies for the disease.



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Analysis of *TRIM25* gene expression in glioblastoma

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Introduction. Glioblastoma is the most aggressive brain tumor. The molecular bases of glioblastoma are not completely defined. We are studying the TRIM25 protein in the glioblastoma context.

TRIM25 belongs to a large family of proteins called tripartite motif-containing (TRIM) characterized by possessing in the N-terminal region a RING domain, 1 o 2 b-box domains, and a coiled-coil domain (CCD). The RING domain of TRIM25 has E3 ligase activity for ubiquitin and ISG15[1], participating in ubiquitination and ISGylation. Protein ISGylation is a novel posttranslational modification increased in glioblastoma[2]. *TRIM25* overexpression has been associated with various types of cancer, promoting cell growth; however, it is not yet known whether *TRIM25* plays a role in the progression of glioblastoma.

Objective. Analyze *TRIM25* expression in human glioblastoma samples and normal brain tissue samples.

Material and Methods. Using the UALCAN, GEPIA, Oncopression, and GENT2 database, *TRIM25* expression was analyzed in brain tissue derived from glioblastoma patients compared to normal brain tissue.

Results. *TRIM25* expression was statistically higher in brain tissue with glioblastoma than in normal brain tissue.

Using Kaplan Meier survival analysis, it was shown that a higher expression of *TRIM25* is related to a lower survival rate of glioblastoma patients.

Conclusion. This study showed that *TRIM25* is upregulated in glioblastoma tissue, correlating with lower survival time.

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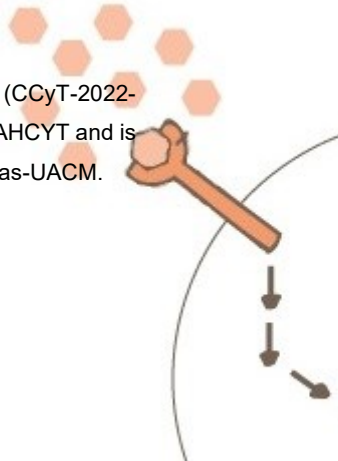

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ATP at low concentrations stimulates the proliferative capacity of non-small cell lung cancer cells A549.

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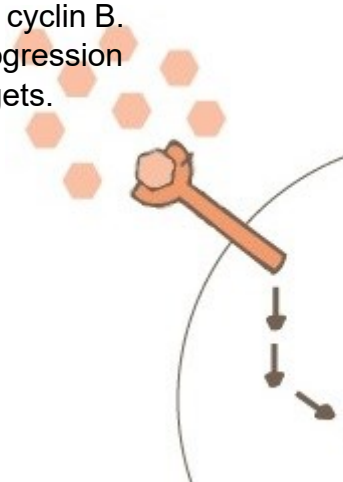
Lung cancer (LC) is the neoplasm with the highest incidence and mortality rate in the adult population, both globally and nationally. Metastasis is responsible for over 90% of deaths caused by LC. There has been great interest in identifying extracellular factors present in the tumor microenvironment that regulate the proliferative capacity of tumor cells and thus promote metastasis. In this context, it has been observed that ATP, present in the tumor microenvironment, can influence the development and progression of the tumor in a differential manner. Tumor cells can release ATP into the extracellular environment, and these levels of ATP are maintained when the activity of ectonucleotidase enzymes is reduced. ATP can specifically bind to ionotropic purinergic receptors (P2X) and metabotropic receptors (P2Y).

The objective of this study is to determine whether the presence of low concentrations of ATP affects the proliferative capacity of lung cancer-derived cells, using the A549 cell line as an experimental model. For cell counting, A549 cells were maintained in the presence and absence of 1 μM ATP to evaluate whether treatment with a low concentration of ATP affects cell proliferation. In addition, the expression levels of mRNA encoding different molecular markers of cell proliferation and survival, such as Ki-67, Bcl-2, cyclin B, and Bax, were evaluated by endpoint RT-PCR. The results obtained show that the chronic presence of 1 μM ATP increases the proliferative capacity of A549 cells almost two-fold compared to the control condition. This effect is associated with a significant increase in the expression levels of mRNA encoding Ki-67 and Bcl-2, and a tendency towards an increase in cyclin B. These results suggest a new role for purinergic system elements in the progression and development of lung cancer, likely providing new pharmacological targets.



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Effect of molecular iodine supplementation on the invasion capacity of SK-N-BE(2) neuroblastoma xenografts.

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Cancer is one of the leading causes of childhood mortality. Neuroblastoma (NB) is an extracranial solid tumor of undifferentiated cells of the neural crest. It is characterized by high cellular heterogeneity, resistance, recurrence, and metastatic progression highly associated with the presence of cancer stem cells (CSC). This population is related to an apoptosis decrease, increased DNA damage repair, and chemoresistance.

Previous work has demonstrated that supplementation with micromolar doses of molecular iodine (I_2) exerts antineoplastic effects by inducing apoptotic and differentiation mechanisms in various cancer cells such as breast, prostate, and neuroblastoma. Its pathways are associated with its oxidant/antioxidant capacity by disrupting the mitochondrial membrane potential (MmpΨ), releasing apoptotic proteins (Bax/Bcl-2), or activating PPARγ receptors to induce the expression antitumor and differentiation factors. This project aimed to evaluate the effect of I_2 on the tumor formation capacity and the potential for invasion from xenografts of SK-N-BE(2) cells generated with monolayer cells and/or neurospheres (enrichment of cancer stem cells).

Our results showed I_2 supplementation increased the expression of PPARγ receptors regardless of the culture condition. In addition, I_2 supplementation decreased the incidence and the volume of tumors from progenitor cells (3505 ± 310.6 vs. 2090 ± 580.6 mm^3) and tumors from neurospheres (9268 ± 1036 vs 2972 ± 658.1 mm^3). In addition, I_2 reduced the expression of the STEM marker CD44 by 29%, as well as the expression of VEGF, and extravascular erythrocytes, and the expression of genes associated with an invasive potential (WNT, MMP9, and VIM) in neurosphere tumors.

Based on our results, I_2 can reduce the potential for invasion in neuroblastoma xenografts from both parental and stem populations. Further research is needed to fully comprehend the specific interactions between I_2 and the loss of intrinsic stem cell characteristics. These results suggest the feasibility of conducting clinical studies with I_2 supplements to enhance conventional therapies, leading to better therapeutic outcomes and fewer side effects.

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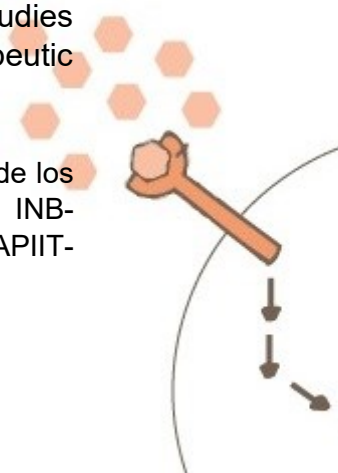

Endosomal PI(3)P, generated by VPS34 and PI3K-C2α, is required for CaSR-promoted Rab27B activation and secretion of cytokines and chemotactic factors.

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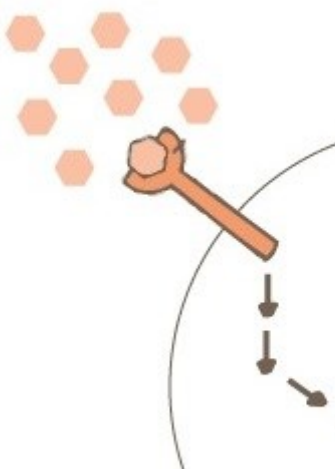
The proper coordination of vesicular trafficking requires the participation of molecules, such as Rab GTPases and phosphoinositides. Phosphatidylinositol 3-phosphate (PI(3)P) is the characteristic phosphoinositide of early and sorting endosomes; it is mainly generated by the action of VPS34, a class III phosphatidylinositol 3-kinase (PI3K). However, the 20% of PI(3)P endosomal is produced by PI3K-C2α, a class II PI3K, which is important for Rab11 activation. Although Rab11$^+$ endosomes are destined for slow recycling pathways, the involvement of PI(3)P in secretory events is still unknown. We recently demonstrated that, in breast cancer cells, secretion of IL-6, angiogenic and chemotactic factors is regulated by the calcium-sensing receptor (CaSR), a class C GPCR. In this process, vesicular trafficking of CaSR, with the participation of Rab11 endosomes, and activation of PI3K/AKT signaling pathways, is essential. Therefore, this work has been focused to study the importance of PI(3)P produced from VPS34 and PI3K-C2α in the CaSR-promoted Rab27B GTPase activation and secretion of cytokines and chemotactic factors. Our results demonstrate that PI(3)P originated from class II and class III PI3K, is necessary for Rab27B activation and the secretion of chemotactic factors, IL-1β, IL-8, and IL-6 upon CaSR stimulation. Nonetheless, endosomal AKT signaling trigger by CaSR appears to be more related to the PI(3)P population originated by VPS34. Altogether, this work shows the importance of PI(3)P in a possible link between slow recycling pathways and Rab27B-directed secretory pathways mediated by de CaSR.

This work was supported by CONACyHT FORDECYT-PRONACES grant 1794 and Fellowships No. and 723795.



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Role of STAT3 on the regulation of critical genes for metabolic rearrangement in cervical cancer cells in response to IL-2 treatment

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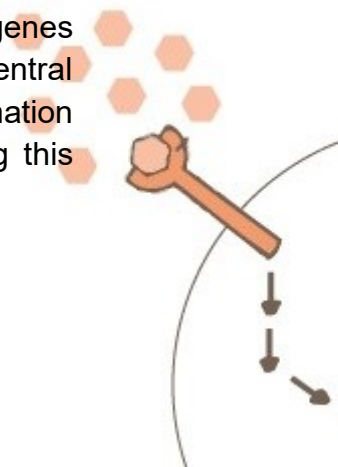
In Mexico, cervical cancer is the second leading cause of cancer death in women. Cervical cancer is associated with human papillomavirus infection, which modifies cells to acquire transformed characteristics such as uncontrolled proliferation and reprogramming their energy metabolism to maintain rapid and uncontrolled growth. This characteristic of tumor cells showing a high glycolysis ratio while growing even under normoxic conditions correlates with increased expression of glycolytic enzymes and glucose transporters. It is important to note that the JAK/STAT pathway relates to cell proliferation in cervical cancer, so activating the STAT3 and STAT5 proteins by tyrosine phosphorylation is essential to initiate their function. Therefore, in this work, we evaluated the role of STAT3 on the expression of critical genes that are characteristic of the metabolic change in tumor cells. We demonstrate that treatment with 10 IU/mL of IL-2 increases the activation of STAT3 by phosphorylation on Y705 and S727, also on cell proliferation. Thus, its activity as a transcription factor increases the transcription of the PDK1, HIF-1α and GLUT1 genes. On the other hand, we also observe that mitochondrial genes UQCRC1 and NDUFV1 decrease after the treatment with 10 IU/mL of IL-2, suggesting that STAT3 can also have a role of a negative transcription regulator. Altogether, these results suggest the fundamental role of STAT3 as a transcription factor on some critical genes in the Warburg effect necessary to continue the cell cycle and increase cell proliferation. Furthermore, the increase in PDK1, HIF-1α and GLUT1, and the decrease on UQCRC1 and NDUFV1 demonstrates the importance of these genes for tumor maintenance and progression and that these genes are the central regulators of the energy-obtaining pathways of the transformed cell. The information generated in this project suggests that STAT3 may be a target for treating this cancer.



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STAT3 role in the autophagy activation in cervical cancer cells treated with high doses of IL-2 and DDP

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Cervical cancer is the fourth cancer in prevalence and mortality at Mexico and the principal treatment is cisplatin, however above of 40% of patients present chemoresistance, because of these new alternative therapies were developed such as immunotherapy this consists in administration of some cytokines like IL-2, IL-15, IL-7, IL-12, IL-21 for immune system activation and improve cancer cells elimination.

However cervical cancer cells can respond to IL-2 stimulus with a different behavior, at low doses of IL-2 it induces the activation of some transcription factors such as STAT3 which is involucrate with important process in cancer proliferation, survival and chemoresistance, in the other hand high doses of IL-2 induces cell cycle arrest in G1 phase but interestingly it has a protective role before DDP stimulus.

In this work our objective is to determine the role of STAT3 activation in cervical cancer cells with previous IL-2 treatment at high and low doses and STAT3-chemoresistance induction.

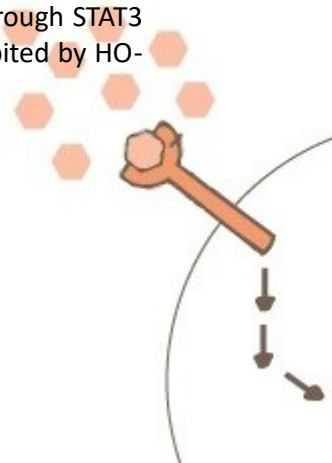
We determine DDP IC50 for both cell-lines HeLa 6.9µM and SiHa 5.1µM and observed same behavior of HeLa and SiHa cell-lines before IL-2 treatment low doses (10UI/mL) increment proliferation, and high doses (100UI/mL) decrease it, while high doses of IL-2 with DDP treatment augment HeLa proliferation in SiHa doesn't show the same answer.

Also determine IC50 HO-3867 that is an inhibitor of STAT3 phosphorylation in HeLa cells 3.7µM and increase with IL-2 low doses treatment 9.2µM.

LC3B was determined by confocal microscopy, and we observed the signal augment when we treated HeLa cells with high doses of IL-2 and DDP, meanwhile SiHa we didn't observe the same behavior.

We also determine apoptosis in HeLa cells and we observed an retardment of apoptosis process when we administrated high doses of IL-2 and DDP in regard to a IC50-DDP treated control and then apoptosis reestablished with administration of HO-3867 what suggest pSTAT3 is the responsible of activation of autophagy via and its chemoresistance mechanism.

We conclude that high doses of IL-2 protect cells from DDP cell-death induction, and this trough STAT3 activation, allegedly by autophagy induction, however when STAT3 phosphorylation is inhibited by HO-3867 DDP apoptosis induction is reestablished.



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Histone acetylation-associated expression of the Ca^{2+} signaling genes in an Epithelial Mesenchymal Transition model in breast cancer cell lines

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Breast cancer occupies the first place in cancer mortality in females worldwide, where metastasis is involved in 90% of all cases. Metastasis is in part regulated by the Epithelial-Mesenchymal Transition (EMT), where epigenetic mechanisms regulate gene expression to induce the transition between states. Inhibition of epigenetic mechanisms mitigates the acquisition of mesenchymal phenotypes in breast cancer cells (Skrypek et al., 2017). Histone deacetylases (HDACs) remove acetylation marks from histones and play a critical role in chromatin remodeling. Because histone acetylation is associated with open chromatin and gene activation, HDACs typically mediate gene repression(Li & Seto, 2016). HDAC inhibitors have had antitumoral effects such as induction of apoptosis, deregulating cell cycle de-repressing differentiation genes, etc. Nevertheless, their effects appear to differ between tumor types (Guerra & Cichowski, 2019). Another major mechanism involved in the regulation of the EMT is calcium ion (Ca^{2+}) signaling. Recently, we demonstrated that the expression of the genes involved in Ca^{2+} signaling is altered in breast cancer samples and cell lines, and their expression is modulated by histone acetylation (Hernández-Oliveras & Zarain-Herzberg, 2021). Panobinostat (LBH) is an FDA-approved pan-inhibitor of HDACs and has been used as an adjuvant in the treatment of peripheral T-cell lymphomas (PTCL) (Eckschlager et al., 2017). This work aims to study the changes in expression and the epigenetic regulation of genes involved in Ca^{2+} signaling on an EMT model in breast cancer cell lines and non- tumoral breast cells under an LBH treatment.

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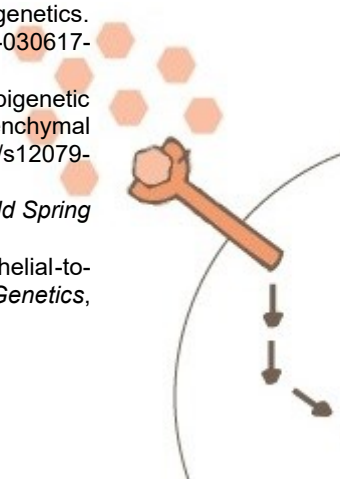

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Calcium sensing receptor activates PKCζ and the Rac exchange factors Dock180 and VAV2 to promote metastatic breast cancer cell migration and invasion

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Calcium-sensing receptor (CaSR), a G protein-coupled receptor, has been found overexpressed in breast cancer patients and preclinical data indicate that in might contribute to bone cancer metastasis by promoting secretion of protumoral agonists within the tumor microenvironment and by driving cancer cell migration. We recently demonstrated that CaSR activates Rac and cell migration via the Gβγ-PI3K- mTORC2 pathway. Given that some isoforms o protein kinase C (PKC), which have been linked to breast carcinogenesis, are effectors of mTORC2, we investigated the hypothetical role of these kinases in the mechanism by which CaSR promotes mTORC2-dependent cell migration and invasion. We show evidence that CaSR activates PKC-ζ, which was predominant compared to classical and novel PKCs. The effect occurred via the G*i* and Gβγ-PI3K signaling pathway. Once activated by CaSR, PKC-ζ stimulated the small GTPase Rac and guanine nucleotide exchange factors specific for this GTPase, including Dock180 and VAV2, both of which contain putative PKC-ζ phosphorylation sites, and were found by analysis *in silico* data mining. The PKCζ/ Dock180,VAV2/Rac1 signaling axis participated in CaSR- dependent cell migration and invasion in metastatic MDA-MB-231 breast cancer cells. These results support ongoing initiatives to establish CaSR as a potential therapeutic target in metastatic breast cancer.

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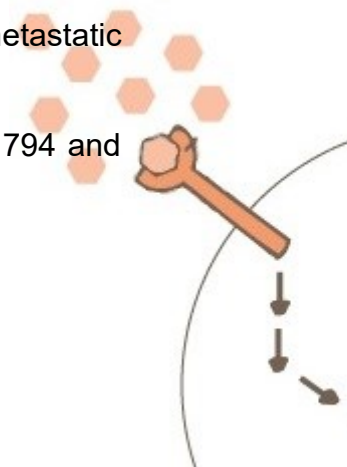

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"Relationship of IL-1β in the regulation of proliferation and inhibition of apoptosis phatway Akt/Src/ NF-kB in leukemic lymphoblasts."

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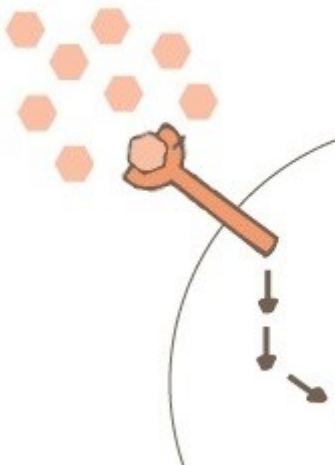
In the relationship between cancer development and the immune system, the formation of a tumor microenvironment stands out, within which proinflammatory molecules such as IL-1 beta have been related to carcinogenesis and metastasis. These proinflammatory cytokines are known to regulate important signaling pathways capable of activating transcription factors such as NF-kB which regulate the expression of genes coding for proteins involved in apoptosis and proliferation. So far in acute lymphoblastic leukemia (ALL), the effect of proinflammatory cytokines has not been reported. Therefore, we investigated in leukemic lymphoblasts the relationship of IL-1 beta in the regulation of proliferation and inhibition of apoptosis. For which we analyzed in a leukemic lymphoblast cell line of LAL patient whether IL-1 beta induces the activation of Akt, Src and NF-kB and subsequently evaluated whether IL-1 beta influences the expression of Bcl-2, cIAP1 and cyclin D1 proteins pathway Akt/Src/NF-kB by flow cytometry, proliferation analysis (mitochondrial activity) and Annexin V expression. We found that IL-1 beta in leukemic lymphoblasts induces 3.9 increase in Akt activation, Src 2.0 increase, NF-kB 3.7 increase with respect to the control. When analyzing the effect of IL-1 beta on cyclin D1 expression; we observed that IL-1 beta induces 2.99 increase in cyclin D1 expression with respect to the control, pathway Akt/ Src/ NF-kB. With respect to Bcl-2 expression, we found that IL-1 beta induced a 2.3 increase in Bcl-2 expression and a 3.7 increase in cIAP1 expression with respect to the control, pathway Akt/Src/NF-kB. When analyzing whether IL-1 beta affected lymphoblast proliferation, we found that this interleukin significantly increased proliferation at all culture times examined. As for the effect of IL-1 beta on the regulation of lymphoblast apoptosis, we observed that this cytokine inhibited apoptosis at the different culture times tested. Our results indicate that IL-1 beta in leukemic lymphoblasts regulates proliferation pathway cyclin D1/NF-kB/Src/Akt in addition to inhibiting apoptosis pathway Bcl-2, cIAP1/NF-kB/Src/Akt; these data are useful since they show possible therapeutic targets for the treatment of acute lymphoblastic leukemia. They also suggest that an inflammatory environment could favor the development of LAL.



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Expression of SPARC and Runx2 genes in the osteogenic differentiation of mesenchymal stem cells cultured on silica scaffolds as a possible proposal for clinical application.

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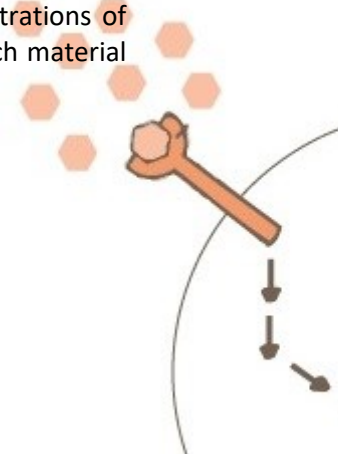
Área: Transducción de señales y diferenciación celular

The expression of the SPARC and Runx2 genes in the differentiation of mesenchymal stem cells (MSCs) cultivated on silica scaffolds as an in vitro study model that allows knowing the efficacy of these materials in terms of their viability and the possibility of their use in bone regeneration; therefore, has important clinical relevance. The genes involved in bone differentiation are two major genes that orchestrate osteogenesis signaling. On the one hand, Runx2 is a transcription factor for increased recognition of the osteogenic lineage by immature osteoblasts. Another gene, called SPARC, encodes a protein secreted by osteoblasts during bone formation; it is one of the most abundant non-collagenous proteins expressed in mineralized and non-mineralized tissues.

In the present work, the expression of the mentioned genes was evaluated on cultures of mesenchymal stem cells seeded on scaffolds of different combinations of silica. Wells were seeded with silica composition scaffolds and others (B, Na2O, and Al2O3). As a gold control, cuboidal bone grafts were used in a 6-well plate at a density of 0.3x10^6 cells, and a double negative was cultured in the same plate. Culture conditions were DMEM-F12+Glutamax (Gibco), 10% Fetal Bovine Serum (SFB, Gibco) and 1X Antifungal-Antibiotic (Gibco). The cultures remained in an incubator at 5% CO2 and 37 °C until reaching 80% confluence. Subsequently, 2 mL of osteogenic medium (250 µm ascorbic acid, 100 nm dexamethasone, and 10 mm β-glycerol-phosphate) were added to the plate with CTM.

After 3 days, the supernatant was decanted, fresh culture medium from normal use was added, and culture was continued for 21 days to allow differentiation. Subsequently, the cells in the scaffolds were lysed with TRIZOL to obtain the total RNA, and in this way, an RT-PCR was carried out with the SPARC and Runx2 primers. The results showed that cells have the ability to differentiate on silica scaffolds, in addition to the fact that the composition of the material directly influences the adhesion and differentiation of MSCs (revealed by the expression of genes involved in osteogenic differentiation). These findings contribute to the description of the ability of scaffolds of different concentrations of silica to improve cell differentiation conditions, and from these results, it can be seen which material may be more suitable for use in the clinical field for bone regeneration.

Keywords: mesenchymal stem cells, osteogenesis, silica scaffolds



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Deciphering the neuroprotective role of a *Malva parviflora* extract in an *in vitro* model of cholinergic neurons

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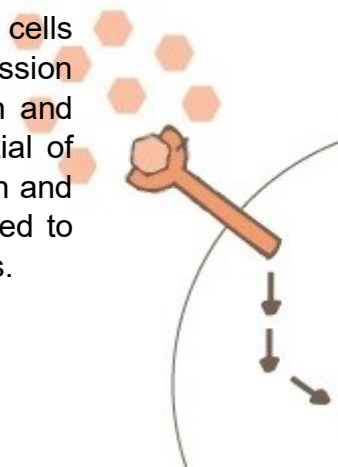
A natural plant compounds hold significant pharmacological potential for treatment of neurological diseases due to their neural induction and regeneration properties. Compounds such as polyphenols, flavonoids and coumarins have neural induction effects by regulating Brain-Derived Neurothophic Factor (BDNF), a protein involved in growth, maintenance, survival and synaptic plasticity, and phenotypic maturation of developing neurons.

BDNF, due to its role in neuronal differentiation and plasticity, has been identified as a therapeutic target for delaying or reversing the neurodegenerative process in cholinergic neurons. Cholinergic neurons play a pivotal role in brain functions, including cognitive mechanisms and regulation of signaling throughout the cerebral cortex. The degeneration of cholinergic function is one of the major processes during the pathophysiology of Alzheimer's disease (AD), reducing the synaptic availability of acetylcholine (ACh). ACh, synthesized by the enzyme choline acetyltransferase (ChAT), modulates neuronal proliferation and differentiation during early development through muscarinic and nicotinic acetylcholine receptors.

Previous studies conducted in our laboratory reported the neuroprotective effect of the hydroalcoholic extract of *Malva parviflora* (EHMp), a plant rich in polyphenols, flavonoids and coumarins widely used in traditional medicine in America and Africa. EHMp has been shown to ameliorating cognitive decline in AD mouse models. Given the degeneration of cholinergic neurons in AD and the positive effects of EHMp on memory in AD mouse models, we aimed to evaluate whether EHMp induces neuronal differentiation in an *in vitro* model of cholinergic neurons. The cholinergic neuroblastoma cell line SN56 was chosen as our study model. Our findings revealed that exposure of SN56 line to 200 µg/mL of EHMp induced a change in cell morphology, leading to three fold increasing in the percentage of branched cells compared to the control. Importantly, this increase correlates with high expression of ChAT and BDNF mRNA, which are markers associated to differentiation and plasticity of cholinergic neurons. Overall, these findings highlight the potential of natural plant compounds, such as EHMp, in promoting neuronal differentiation and plasticity, particularly in cholinergic neurons. Further investigation is warranted to explore the signaling pathways modulated by the EHMp in cholinergic neurons.



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TNFR1 and TNFR2 knockdown modulates the anti-inflammatory response in adipocytes 3T3-L1 cells

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Abstract

Introduction Glycine is an amino acid with anti-inflammatory effects, strongly reduces the serum levels of pro-inflammatory cytokines and increases the levels of anti-inflammatory cytokines. Other studies described that 3T3-L1 differentiated to adipocytes of obese mice, glycine decreased gene expression and serum levels of TNF-α and IL-6, modified the balance of PPARs, and inhibited activation of NF-κB pathway induced by TNF-α through modulation of IKKs. However, the glycine mechanism involved in this inhibitory action is still unknown. TNF-α has two receptors: TNF-α receptor 1 (TNFR1a, Tnfrsf1a gene) and TNFR2 (TNFR1b, Tnfrsf1b gene), which could be modulated by glycine, but more studies are needed to find the possible mechanism or signalling pathway. **Objective** To analyse the effect of glycine in the expression of cytokines in adipocytes differentiated from 3T3-L1 cells silenced with the siRNA TNFR1a and TNFR1b. **Methods** The cell culture of 3T3-L1 was made in 6 wells plate (4 x10^5 cell per well) in DMEM/F12 medium supplemented with 10% New Born Calf Serum and 1% penicillin, streptomycin, and amphotericin B. Cell differentiation of fibroblasts into adipocytes was induced adding a cocktail with murine insulin, dexamethasone, and methyl-isobutyl-xanthine. The medium was replaced 48 hours with DMEM supplemented with insulin. Adipocytes cells were transfected with siRNA for the TNF1a (Tnfrsf1a) and TNF1b (Tnfrsf1b) receptors, using lipofectamine 2000 as a vehicle of siRNA, and were incubated in Opti-MEM. Transfected cells were treated with glycine (10 mM) for two span times 1 hour and 24 hours. The gene expressions of TNF-a, IL-1, IL-6, and IL-10 and AdipoQ were measured by qRT-PCR. **Results** Glycine decreased the expression of TNF-a and IL-1 through the TNFR1 in the other hand IL-10 increased when glycine acts together with TNF1a siRNA. **Conclusion** Glycine may be modulating the secretion of cytokines pro-inflammatory in adipocytes through the Tnfrsf1a siRNA.

Keywords: Citokynes, adipocytes cells, inflammation.

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Regulation of MRTF-A promoter region by YAP/TAZ transcriptional cofactors

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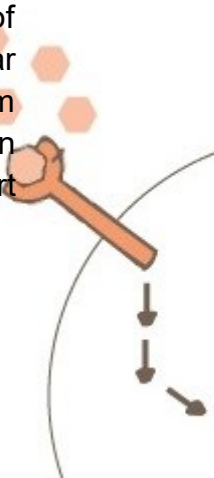
MRTFA is a transcriptional cofactor implicated in many physiological processes such as migration, differentiation, extracellular matrix formation and participates in mechanotransduction in order to maintain cellular homeostasis. The principal mechanism that regulates this cofactor depends on the actin polymerization. Thus, any stimulus that induces the formation of actin filaments promotes MRTFA protein to translocate to the nucleus and regulate the transcription of its target genes. Despite this cofactor being associated with pathologies like cancer and fibrosis in many tissues, there is not enough information about the transcriptional regulation of MRTFA. Currently, there is evidence that *mrtfa* transcriptional regulation could be mediated by YAP; another transcriptional cofactor that is regulated by actin polymerization as well. This regulation is mediated by the transcriptional factor TEAD. There is a report that found out regulatory elements of TEAD near to exon one of *mrtfa* in rat, human and mouse species. Different transcriptional variants of *mrtfa* have been described, however, there is not a consensus about the initial genomic exons present in the *mrtfa* variants. So, it is difficult to identify possible different transcriptional start sites with new regulatory elements in the promoter region of *mrtfa*.

For this reason, we identified all transcriptional variants of *mrtfa* reported in the NCBI database in an effort to facilitate the analysis and localization of presumed promoter regions among the variants and localized the potential TEAD binding elements (TBE). We found that these sites are close to exon two and not to exon one, as previously reported. In the case of rat *mrtfa*, there are two transcriptional variants that start in exon two and this TEAD motif could be functional. In humans, there are not any variants that start in exon two. So, we delimited a promoter region of human *mrtfa* using the previous evidence of chromatin relaxation marks, immunoprecipitation of RNA polymerase II and regions with CG rich sequences. This promoter region is near to genomic exon one where we identified two possible TBE upstream and downstream to transcriptional start site of three variants of MRTFA. Also, we identify the expression of all variants of MRTFA in both human and rat by RT-PCR assay in order to support the viability of functional *mrtfa* promoter regions.



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MRTF-A/B transcriptional cofactors activation in response to extracellular mechanics in primary rat hepatocytes

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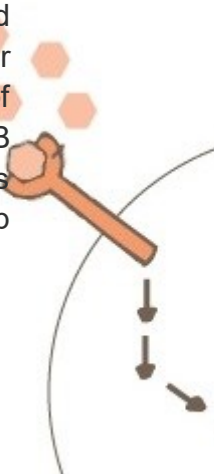
Hepatocytes constitute the liver parenchyma, hence they perform vital processes such as the metabolism of biomolecules. They have a unique polarity generated by intracellular lumen (canaliculi) and sinusoidal extracellular matrix (ECM) interactions. Intercellular forces and ECM properties change in some pathologies such as fibrosis where the stiffness and fibrillar collagens deposits increase substantially. Stiffness and loss of polarity are associated with the loss of the hepatocytes phenotype *in vitro*, together with alterations in their metabolic functions, as a consequence. These changes are relevant due to the hepatocytes capacity of mechanical response in a process known as *mechanotransduction.*

Myocardin-related transcription factors A and B (MRTF-A/B) are transcriptional cofactors involved in cytoskeleton dynamics as a consequence of their target genes such as actins, tubulins and integrins. They are controlled by the cytoskeleton as well because of their interaction with G-actin which negatively regulates in a feedback loop. Also, it has been shown that MRTF-A/B are physiologically active in the liver and its upregulation have been mainly associated in liver fibrosis, mainly to their role in hepatic stellate cells activation. However, it is unknown their role in hepatocytes as well as its regulation given by their different interactions. Therefore, to elucidate this problem, the aim is to study the activation of MRTF-A/B as well as to detect protein interactions of MRTF/A-B of primary fresh hepatocytes and on long-term culture.

We have found a noticeable MRTF-A/B mRNA and protein levels upregulation in primary rat hepatocytes since the first day of standard stiff culture (polystyrene petri dish), as well as an mRNA upregulation of their target genes. Also, we found a a nuclear accumulation of MRTF-A/B in primary hepatocytes in a time dependent manner; however MRTF-B was slightly more cytoplasmic retained even at 72 h of culture. Similarly, stiffness also caused the increase in the MRTF-A/B nuclear accumulation, and it was more accentuated for MRTF-A even. This probably reflects differences in their regulation, as a consequence of modifications in their protein interactions. To clarify this, immunoprecipitations of MRTF-A/B were performed in order to characterize unknown interactions with MS/MS. The results obtained in this project highlights the activity of MRTF-A/B in hepatocytes and points up the relevance of searching the regulatory mechanisms of MRTF-A/B in hepatocytes



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Differential effect of exosomes secreted by astrocytes cultured in high glucose on viability in neurons and astrocytes

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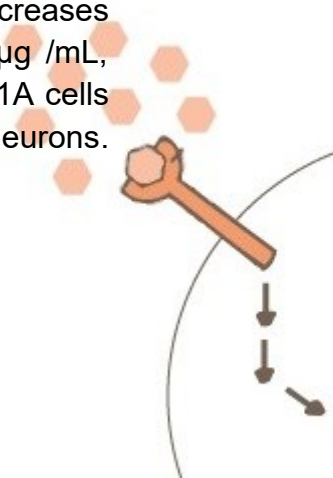
Introduction. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, which causes neuronal damage, a phenomenon known as glucose neurotoxicity. Astrocytes are a type of glial cells that respond to any attack on the CNS through a process called reactive astrogliosis which, under conditions of chronic damage, can contribute to the progression of neurological diseases. Astrocytes secrete exosomes that function as modulators of cell communication by transmitting protective signals, however, they can also contribute to the spread of pathogenesis or neuronal damage. **Objective:** To analyze the effect of exosomes secreted by astrocytes cultured in normal and high glucose on viability in astrocytes and neurons. Methodology: C8-D1A cells were cultured for 7 days with normal (5.5 mM) and high (25 mM) glucose treatments to isolate exosomes by differential ultracentrifugation. To confirm the isolation of exosomes, the constitutive proteins CD63 and annexin V were detected by western blot, the size of the exosomes was analyzed by transmission electron microscopy (TEM), and the uptake of exosomes was observed by immunofluorescence, staining at exosomes with PKH67. Finally, the MTT assay was performed on astrocytes and neurons stimulated for 24 hours with exosomes derived from astrocytes cultured in normal and high glucose. **Results:** In the exosomes secreted by C8-D1A cells cultured in normal and high glucose, the CD63 and Annexin V proteins are present. The presence of exosomes characterized as double-membrane vesicles with an approximate size of 100 nm was demonstrated. In addition, the labeling with the PKH67 dye was carried out, and it was observed that after 24 hours, the exosomes were incorporated into the cells. A statistically significant decrease in viability was observed in C8-D1A cells stimulated with astrocyte exosomes grown in high glucose (20 µg/mL; 20.6%; $p<0.05$). Meanwhile, cell viability of neurons also decreases with exosome exposure from astrocytes cultured in high glucose (20 µg/mL, 14.09%; $p<0.01$) and increases with exosome exposure from astrocytes cultured in normal glucose (10 µg /mL, 8.5%; $p<0.05$). **Conclusion:** Stimulation with exosomes secreted by C8-D1A cells cultured in high glucose decreases viability in astrocytes and neurons.
Acknowledgments: CONAHCyT-Mexico for financing project A1-S-34290.



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Traction force microscopy analysis in primary hepatocytes cultured soft substrates

María Guadalupe Martínez-Arellano[1], Daniel Pérez-Calixto[1], Diana Cristina Pinto-Dueñas[2], Beatriz Díaz-Bello[1], Lorenza González-Mariscal[2] and Genaro Vázquez-Victorio[1]

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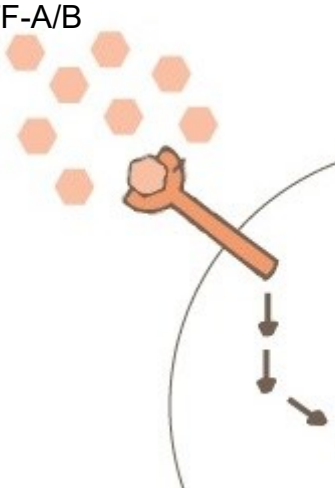
Hepatocytes exert mechanical forces with their surrounding environment, through cell adhesions, and this is important for liver functions. Any modification of the mechanical environment has a remarkable role in hepatic cell differentiation resulting in the development of diseases such as liver fibrosis. Unfortunately, measuring mechanical forces in vivo and in vitro is not quantitatively accurate, so there is huge delay in studying the impact of mechanical forces involved in the regulation of many cellular processes. Being able to quantify these forces allows us to understand different biological responses that derive from the relationship of cells with the extracellular matrix.

In this work, these stresses (forces) or tractions were evaluated by implementing an interface adapted for traction force microscopy (TFM) analysis of primary hepatocyte cell aggregates on substrates with controlled stiffness having a elastic modulus of 10 kPa after 24 and 72h of culture. Also, hepatic aggregates cultured on stiff substrates were found to have a larger cell area compared to those on soft substrates. We were able to measure traction forces (Pa) and deformations on the substrates. This is the first time that TFM is implemented here and it is a reference to implement in other laboratories in México. Additionally, we evaluated the role of MRTF transcriptional cofactors in traccion forces using the inhibitor CCG-203971, specific for MRTF-A/B activation.



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Physics constraints and geometric confinement influence on the primary hepatocytes phenotype.

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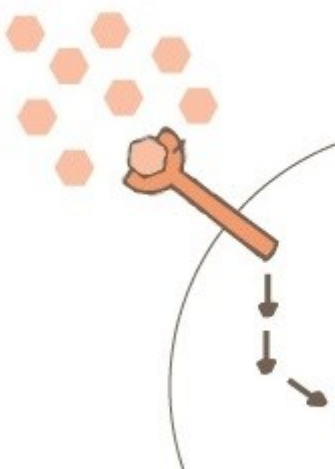
Abstract

The tissue microenvironment is composed of a wide range of physical constraints that play a significant role on the behavior, phenotype and function of cells. Some physical properties at the local level such as stiffness and geometry of extracellular matrix could help to improve the phenotype maintenance since the disruption of these parameters may induce an atypical response of cells. In this work we present a comparison among different biomimetic culture platforms in order to maintain hepatocytes phenotype. A polyacrylamide controlled stiffness hydrogels was used to culture primary rat hepatocytes to visualize their collective behavior. We observed that in soft substrates the cells formed clusters, unlike on stiffer substrates, where they formed a monolayer. Another observation was that soft substrates improve the maintenance of phenotype in opposite behavior to stiffer substrates that favors a differentiated state. Furthermore, we confine hepatocytes in a microfluidic channel conjugated with an ECM protein mixture. After 24 h of culture the monolayer was coated with a matrigel layer and a flow rate of 30 μL/h was set. We observed an improvement of phenotype hepatocytes markers after several days of culture. Finally, we observed that the collective dynamics of the monolayer within the microfluidic channel presents a stable state with the flow against the static culture.



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Organ-on-a- Chip Development

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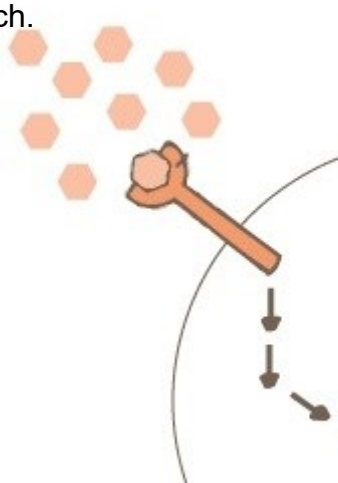
Abstract– An organ-on-a-chip is a microfluidic device for culturing cells in continuously perfused micrometer-sized chambers, in order to recapitulate model physiological functions of tissue or organs. In this work, a liver organ-on-a-chip was fabricated, taking into account the physicochemical characteristics of a liver lobule. Simulation of fluid flow in the microfluidic device was performed by finite element analysis using Comsol Multiphysics 5.5 © software. Subsequently, the device was fabricated using an optically transparent polymer, polydimethylsiloxane (PDMS) applying a cast-replica process from a CNC-molded PMMA mold. To allow for adequate adhesion of extracellular matrix protein, the surface was functionalized with sulfo-SANPAH/UV/O3. The surface was then characterized physicochemically by X-ray spectroscopy (XPS), contact angle and SEM. The optimal combination of extracellular matrix protein which promoted cell monolayer formation was a mixture of collagen and fibronectin. For biological characterization, human liver endothelial cells were used and culture medium was perfused into the device at a volumetric flow rate of 2 µL/min by peristaltic pump assembly. The cultured cells exhibited a high percentage of cell viability in static and flow conditions. Additionally, a two-channel device for hepatocyte culture was fabricated. Finally, the physicochemical and biological characterization of the two-channel microfluidic device demonstrated that it can recapitulate the adhesion and flow conditions necessary for liver endothelial cell functionality, making it a useful tool for research use as an organ-on-a-chip in vitro model.

Keywords – organ-on-a-chip, LSEC, cell morphology, contact angle & laminar flow.

Acknowledgments – To Cindy Peto for support in SEM measurement, Conacyt 304023 & PAPIIT IN219721 for the funding granted to carry out the research.



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Influence of the extracellular matrix geometry on lung mesenchymal cells behavior

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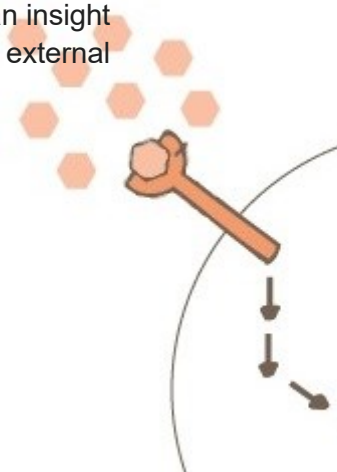
Abstract

The cell microenvironment is composed of a wide range of mechanical stimuli that play a crucial role on phenotype, behavior and function of cells. Some physical properties at local level, such as: stiffness and geometry of extracellular matrix components can be modified by the cells. In the right values these characteristics allow to improve environmental homeostasis and any disturbance of these parameters may induce an aberrant cell response. Since alterations in collective behavior are associated with pathological processes such as cancer metastasis and fibrosis, it is necessary to study and characterize topological and mechanical intrinsic properties of cellular microenvironment, as well as how those properties influence the collective dynamics (long range directional order, self-organization) of cells that form organs and tissues. In order to elucidate the impact of the stiffness and geometry of the extracellular matrix on cells collective dynamics, mesenchymal cells (fibroblast) were seeded on alveoli-shaped structures of polyacrylamide hydrogels. Morphological and mechanical hallmarks were detected, visualized and quantified by optical microscopy and immunofluorescence assays. An heterogeneous mechanical response of the cell layer associated with the stiffness and geometric constraints of the substrates were observed. The collective dynamics was approached by modeling the fibroblasts as an active nematic liquid crystal that presents a long range directional order. We observed a decrease in activity of the cells seeded on stiffer hydrogels together with the emergence of topological defects. Whereas in soft gels the activity increased, interfering with the collective nematic order. These results could provide an insight towards the understanding of cellular response to the combined influence of several external stimuli in different pulmonary pathologies.



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The calcium-sensing receptor (CaSR) regulates the acrosomal reaction and sperm viability through the PI3K/Akt pathway in guinea pig sperm

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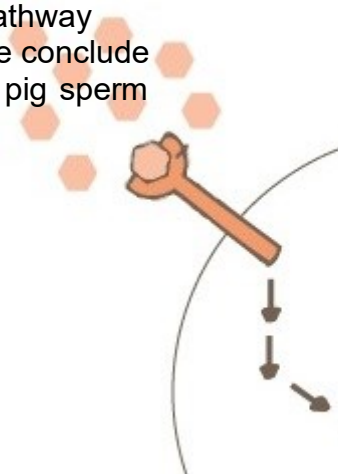
Freshly ejaculated mammalian sperm are not yet capable of fertilizing the oocyte; this ability is acquired within the female reproductive tract, and they undergo the processes of capacitation and acrosomal reaction. Ca^{2+} is critical in mobility, capacitation, and the acrosome reaction. The CaSR plays a role in signalling by detecting extracellular Ca^{2+} levels. In spermatozoa, the CaSR is related to motility, the phosphorylation of tyrosine residues, the integrity of the acrosome, and, in addition, its inhibition decreases sperm viability. The PI3K/Akt pathway has been reported to be important in sperm survival by preventing caspase activation. Therefore, the project's objective is to determine the participation of CaSR in activating the PI3K/Akt pathway and its relationship with sperm survival, as well as in the capacitation and acrosomal reaction processes in guinea pig sperm. The role of the CaSR PI3K and Akt proteins was determined using specific inhibitors and analyzing how their inhibition affects physiological processes and sperm viability. The results obtained so far show the presence of CaSR in the midpiece of the flagellum; we also observed that inhibition of CaSR by a catalytic agent (NPS2143) or its activation by a calcimimetic agent (Ac265347) accelerates the capacitation and increases the acrosomal reaction, the latter being dependent on Ca^{2+}. This phenomenon can be explained because we observed that CaSR inhibition increases the rate of calcium uptake, increasing the concentration of intracellular Ca^{2+}.

On the other hand, we determined the presence of Akt1/2/3 and its activation at early times of capacitation, which NPS2143 inhibits. In addition, we observed that the inhibition of Akt and CaSR leads to an increase in the Ca^{2+}-dependent acrosomal reaction. Finally, we observed that inhibiting the CaSR or the PI3K/Akt pathway increases the activation of caspase 3/7 during capacitation. Therefore, we conclude that the CaSR regulates the acrosomal reaction and viability in guinea pig sperm through the PI3K/Akt pathway. CONAHCYT CB-284183.



Regulation of MRTF-A/B and YAP/TAZ proteins by stiffness using a CCl4-treated liver model

Brenda Selene Torres-Ortiz[1], Jorge Carretero-Ortega and Genaro Vázquez-Victorio[1]
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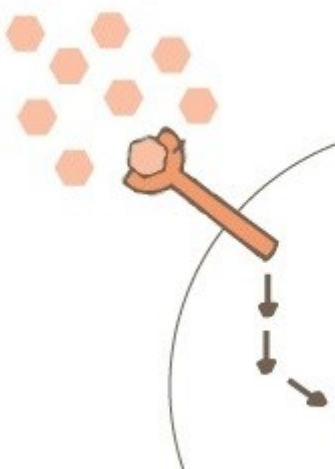
The liver is an essential organ that performs a broad range of biochemical functions with a huge ability of regeneration caused by acute damage. However if damage is maintained, this ability is reduced due to the deposition of extracellular matrix in a disorganized manner in the hepatic tissue. This causes the loss of several hepatic functions besides affecting the architecture of the hepatic lobule and compromising its function. Also, hepatocytes react to biochemical stimuli, detect and respond to mechanical stimuli. These cellular responses involve the reorganization of the actin cytoskeleton then affecting cell morphology, orientation, polarity, migration and gene expression.

Myocardin-related transcriptional factors (MRTF-A/B) and Yes-associated protein (YAP), as well as its paralog TAZ protein, translocates to the nucleus to regulate gene transcription as a consequence of actin cytoskeleton dynamics. MRTF protein family members bind to YAP and TAZ through a conserved motif and domain present in both proteins. This interaction allows MRTF to be recruited to the TEAD-YAP transcriptional complex enhancing its transcriptional activity in both directions. The goal of this project is to evaluate the activation of MRTF-A/B and YAP/TAZ target genes through RT-PCR in health and fibrotic liver using CCl4 model in rats. We found out that in fibrotic livers, MRTF-A/B and YAP/TAZ target genes increased compared to normal livers. This increment correlated with the upregulation of MRTF-A/B and YAP/TAZ proteins. Additionally, we measured the stiffness in normal and fibrotic livers to evaluate the relation of mechanical modifications with the activation of mechanical sensitive transcriptional cofactors.



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Regulation of *PGR* gene expression in immortalized human endometrial stromal cells

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Background: Decidualization is a complex process that involves the transformation of the endometrial stroma into a receptive state, which is crucial for establishing and supporting pregnancy. *In vitro* decidualization is induced by estradiol (E2), cyclic adenosine monophosphate (cAMP), and the synthetic progestin medroxyprogesterone (MPA). The progesterone receptor (PGR) plays a pivotal role in regulating decidualization, and alterations in its expression are linked to endometrial pathologies, such as endometriosis, implantation failure, recurrent pregnancy loss, and infertility. However, the mechanisms governing *PGR* expression in endometrial stromal cells during decidualization are not fully understood. Therefore, the present study aimed to identify the mechanisms of *PGR* expression regulation in immortalized human endometrial stromal cells.

Methods: Immortalized human endometrial stromal cells (T-hESC, ATCC, CRL4003) were exposed to E2, MPA, and/or cAMP at different time points to evaluate the expression of *PGR* isoforms *(PGR-AB* and *PGR-B)*. To understand the underlying action mechanisms of the decidualization stimulus components, we examined the effect of estrogen receptors and PGR antagonists, as well as a Protein Kinase A (PKA) inhibitor.

Results: The expression of *PGR-AB* and *PGR-B* was induced after 24 h of treatment with E2 + MPA + cAMP (EMC) compared to the vehicle. Surprisingly, the induction of both *PGR* transcripts was more pronounced with cAMP stimulus and RU486 + EMC combination compared to EMC alone. Furthermore, the induction observed with EMC was blocked by the H-89 PKA inhibitor.

Conclusion: This study provides evidence that cAMP plays a crucial role in inducing the expression of *PGR-AB* and *PGR-B* during *in vitro* decidualization.

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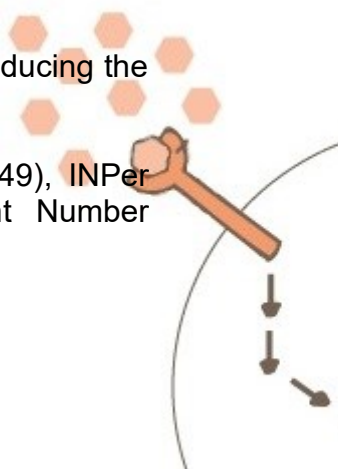

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Anti-inflammatory effect of novel sapogenin-derived heterosteroids as regulators of the IL-6/JAK/STAT3 pathway in skeletal muscle cells.

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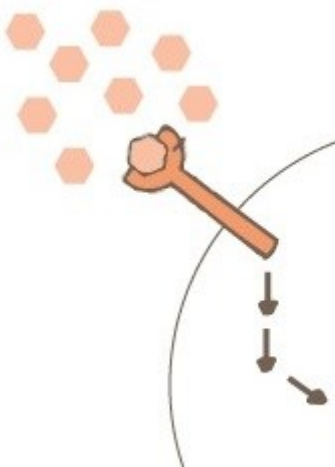
Introduction: Inflammation and anabolic activity play important roles in skeletal muscle cells. Inflammation is a natural response of the body to injury or tissue damage. In the case of skeletal muscle cells, inflammation can be triggered by muscle injury, intense exercise or disease. During inflammation, cytokines are released, which recruit immune cells, such as neutrophils and macrophages, to the site of injury. The impact of inflammation on skeletal muscle cells can be both beneficial and detrimental. Acute inflammation can trigger repair and regenerative responses in muscle cells. Macrophages, for example, can clear damaged tissues and secrete growth factors that promote the proliferation and differentiation of satellite muscle cells, which are the cells responsible for muscle regeneration. Prolonged inflammation can interfere with the function and regenerative capacity of muscle cells, which can contribute to loss of muscle mass (atrophy) and decreased physical performance.

The intricate network of MAPK/RK, IL-6/JAK/STAT3 and PI3K/Akt/mTOR signaling pathways are involved in the regulation of cytokine release. Our research group synthesized ten new sapogenin-derived heterosteroids targeting MAPK, PI3K, mTOR, AKT1, JAK and EGFR, and evaluated their anti-inflammatory activity in skeletal muscle cells. Objective: To evaluate IL4 and Il10 interleukins in skeletal muscle cells treated with novel heterosteroids.

Modeling and simulation of MAPK/RK, IL-6/JAK/STAT3 and PI3K/Akt/mTOR pathways for the selection of potential targets. 2. Design of new heterosteroids. 3. Molecular docking of heterosteroids with target proteins. Evaluation of interleukins 4 and 10 levels in skeletal muscle cells treated with the novel heterosteroids. Conclusions: Knowledge of the signaling pathways that regulate the release of anti-inflammatory interleukins during the inflammatory process in skeletal muscle cells is of great importance for the control of inflammation, maintaining the balance between inflammation and repair, as well as the development of new specific anti-inflammatory drugs.



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Enhanced proinflammatory cytokine signaling in the hippocampus of a murine model of idiopathic autism

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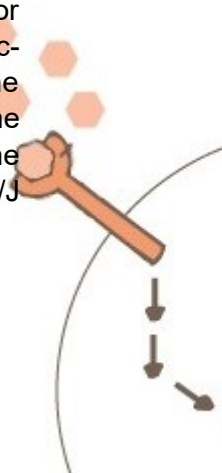
Abstract

Autism spectrum disorder (ASD) comprises a complex and heterogenous array of neurodevelopmental disorders that are characterized by communication and language impairments, as well as repetitive behaviors or restricted interests. Immune system hyperactivation is a biological feature that has been extensively described in a subset of individuals with ASD.

For instance, the proinflammatory cytokines interferon-gamma (IFN-γ) and tumor necrosis factor-alfa (TNF-α), and chemokines like the macrophage chemoattractant protein 1 (MCP-1), are reported to be upregulated in the central nervous system (CNS) and peripheral tissues of individuals with ASD, pointing towards a generalized alteration of inflammatory signaling in this disorder. Moreover, peripheral blood mononuclear cells (PBMC) of individuals with ASD show an enhanced content of the Janus kinase 1 (JAK1) and its phosphorylated form (p-JAK1), indicating a basally reactive immune cell phenotype associated with ASD.

Several animal models have been proposed for studying the molecular alterations implicated in the development of autistic-like traits. The inbred mouse strain C58/J shows a low social preference along with repetitive behaviors. Here we found that male adult mice of the C58/J strain show a significant basal increase in the hippocampal content of the cytokine IFN-γ, when compared with a control strain. Accordingly, we found that autistic-like mice exhibit changes in the hippocampal content of proteins JAK1/STAT3 compared to a neurotypical strain, in addition to changes in their phosphorylation, pointing towards an overactive immune phenotype in the C58/J mice.

We also found a basally increased content of the macrophage chemoattractant protein 1 (MCP-1) in the same brain region of autistic-like mice, when compared to a control strain. MCP-1 acts by promoting the recruitment of myeloid cells, mainly macrophages. Microglia are the major population of macrophages residing in the CNS and perform several immune- and synaptic-related tasks in the brain parenchyma; hence we sought to evaluate this cell population in the hippocampus of autistic-like mice. We observed a significant increase in microglial density in the CA1 region and the dentate gyrus of the hippocampus of autistic-like mice, suggesting that the cell signaling mediating microglial recruitment may be upregulated in the hippocampus of C58/J mice.



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The deletion of Smad7 enhances the inhibitory effect of TGF-β on the effector functions of CD8⁺ T lymphocytes.

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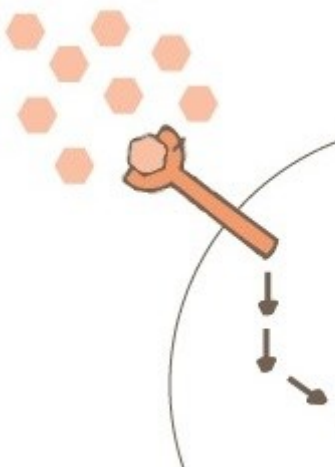
CD8⁺ T cells are very important for immune defense against intracellular pathogens, including viruses and bacteria, and for tumor surveillance. Transforming growth factor β (TGFβ) is a potent immunosuppressive cytokine known to regulate several CD8⁺ T cell functions. It restrains the expression of IFNγ, granzyme B, and perforin, which are essential for CD8⁺ T cell effector functions. Additionally, TGFβ elicits cell cycle arrest and apoptosis in effector CD8⁺ T cells. Smad proteins are the main intracellular mediators of the canonical TGFβ signaling pathway. This pathway is initiated when one of the three isoforms of TGFβ binds to TGFβR2, which recruits and phosphorylates TGFβR1. TGFβR1 then phosphorylates Smad2 and Smad3. Subsequently, Smad4 is recruited, and together with Smad2 and Smad3, translocates into the nucleus to regulate the transcription of TGFβ target genes. Smad7 serves as a negative regulator of canonical TGFβ signaling by inducing the degradation of TGFβR1. In this study, our objective was to elucidate the role of Smad7 in the effector functions of CD8⁺ T cells. Using animals with conditional deletion of Smad7 in the T lymphocyte compartment (CD4 Cre), we discovered that Smad7-deficient CD8 lymphocytes are more sensitive to TGFβ inhibition. Interestingly, in vitro experiments showed that in the presence of TGFβ, there is a decrease in the proliferative capacity of CD8 T lymphocytes lacking Smad7 (Smad7KO) and a reduction in the expression of effector molecules such as IFNγ, granzyme B, and perforin.



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The LPI/GPR55 axis induces chemotaxis and significant transcriptional changes in Mast Cells

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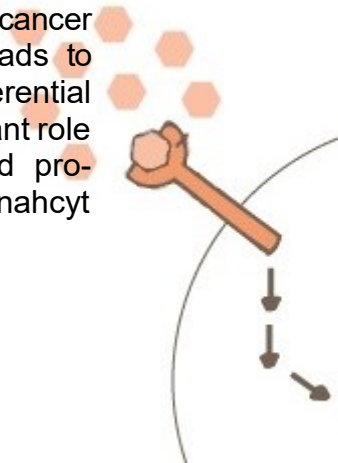
Mast cells (MC) are central players in allergic reactions and innate immune inflammatory responses and are also active elements in tumor environment, orchestrating pro-angiogenic and pro-fibrotic events leading to tumor growth and immune evasion. To date, chemical mediators leading to MC recruitment to solid tumors and the effect of those chemoattractants on their capacity of cytokine synthesis have not been full described. In the present work, we sought to investigate the possible role of the bioactive lipid lysophosphatidylinositol (LPI) on MC chemotaxis, cytokine production and gene expression. Utilizing murine bone marrow-derived mast cells (BMMCs), we found that LPI did not cause degranulation, but slightly increased FcεRI-dependent β-hexosaminidase release. However, LPI induced strong chemotaxis together with changes in LIM kinase (LIMK) and cofilin phosphorylation. LPI also promoted modifications to actin cytoskeleton dynamics that were detected by an increase in cell size and interruptions in the continuity of the cortical actin ring. Chemotaxis and cortical actin ring changes were dependent on GPR55 receptor activation since the specific agonist O1602 mimicked the effects of LPI and the selective antagonist ML193 prevented them. LPI and O1602-dependent stimulation of BMMC also led to VEGF, TNF, IL-1β , and IL-1α mRNA accumulation, but, in contrast with chemotaxis related processes, the effects on cytokine transcription were dependent on GPR55 and cannabinoid (CB) 2 receptors, since they were sensitive to ML193 and to the specific CB2 receptor antagonist AM630. RNA-Seq analysis of O1602-treated MCs showed changes on close to 500 genes. Upregulated genes were related to spliceosome activation, HIF-1α-dependent pathway and phagocytosis, whereas downregulated genes were related to innate immune responses. Remarkably, GPR55-dependent BMMC chemotaxis was observed towards conditioned media from distinct mouse and human cancer cells. Our data suggest that LPI induces the chemotaxis of MCs and leads to transcriptional changes and cytokine production in MC *in vitro* with the differential participation of GPR55 and CB2 receptors. These effects could play a significant role in the recruitment of MCs to tumors and the production of MC-derived pro-angiogenic factors in the tumor microenvironment. Project supported by Conahcyt Project CF-2019-51488.



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LRBA is important for a proper NF-κB activation in B cells driven by BCR signalling

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Field of knowledge: Transduction of signals in the Immune System

Key words: NF-κB, B cells, B-cell Receptor.

Lipopolysaccharide-Responsive Beige-like anchor (*LRBA*) is a scaffolding protein whose deficiency is associated with an inborn error of immunity like common variable immunodeficiency. Patients with LRBA deficiency have a heterogeneous clinical presentation that includes hypogammaglobulinaemia, reduction of B cells and T regulatory cells, recurrent infections, and autoimmune diseases. Studies have demonstrated the importance of LRBA in the recycling of CTLA-4 on Treg cells, however, its action on B cells remains unknown. The porpoise of this work is to identify the function of Lrba in B-cell receptor (BCR) signalling.

Mice deficient of Lrba (*Lrba*$^{-/-}$) have a higher proportion of Trasitional 1 B cells on spleen; it shows reduced B cell proliferation and an increased apoptosis, in response to activation B through BCR crosslinking. Immunoblot and confocal microscopy reveals an increased activation of p50, p65 and IκBα (components of canonical pathway of NF-κB) in *Lrba*$^{-/-}$ B cells under basal conditions. Preliminary co-immunoprecipitation assays suggest an interaction between Lrba and components of B cell signalling: PLC-γ, p65 and ERK2. Those results suggest the participation of Lrba in BCR signalling regulation.

Finally, cytometry analysis has shown a reduced levels of membrane and cytoplasmic IgM in Lrba$^{-/-}$ B cells, hence Lrba could be important for the recycling BCR, not only CTLA-4 in T regulatory cells. Lasted studies are focused on the physiological importance of those findings.

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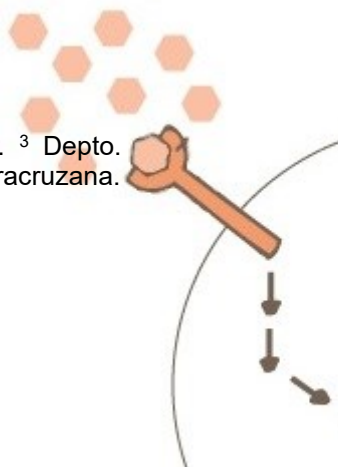

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"Study of the role of the urate transporter ABCG2 in the regulation of the immune response in knockout models of human colon and kidney cells"

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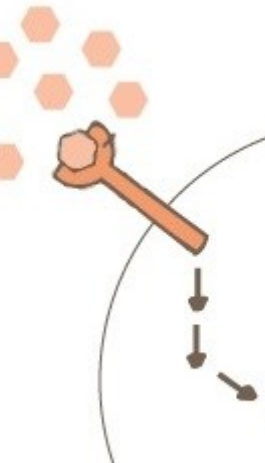
Introduction.- Gout is a multifactorial metabolic disease, characterized by intra articular pain attacks due to inflammatory activation induced by monosodium urate (MSU) crystals. These crystals accumulate due to the patient's frequent hyperuricemia. ABCG2 is a membrane transporter protein that clears uric acid mainly in the intestine and kidney. *ABCG2* gene has been related to hyperuricemia and gout due to polymorphism studies in different populations, however its role in the development and progression of the disease is not clear, a recent study where *ABCG2* gene was silenced in THP1 cells stimulated with MSU, it suggested a possible role of *ABCG2* in the negative regulation of inflammation in gout. **Objective**.- To study the role of *ABCG2* as a possible regulator of inflammation induced by the presence of MSU crystals and soluble uric acid (sUA) crystals in two *in vitro* models of gout. **Methodology**.- Until now cultures of the human colon HCT15 and the kidney cell line HEK293T was been grown in specific media until the day of the tests with or without activation with MSU for 48 hours. Genome editing of cultures of these same cells was performed using the CRISPR CAS9 recombinant protein to silence the *ABCG*2 gene with Edit R- human *ABCG2* crRNA and track RNA. The identification of transfected cells with non-functional *ABCG2* will be through growth in culture plates to evaluate the gene and protein expression of *ABCG2*, later sequencing of the target area will be carried out. Activation assays with MSU of the cells silenced for 48 h will be carried out, later the expression of inflammation and *ABCG2*, *IL-1*beta, *IL-6*, *S-100*, *p53, NFkB* and *TL3* genes will be analyzed by immunofluorescence, westen blot and real-time PCR. **Preliminar results**.- Until now, transfected cells and not transfected cells have been stimulated with MSU and SUA, we observed that vesicles with internal crystals are formed in the colon HCT15 cells after 24 hours of exposure with MSU. *ABCG2 ,S-100* and *p53* gene expression was measured without finding differences in expression at 24 and 48 hours by immunofluorescence. Transfected HCT15 cells had higher expression of phosphorylated p53 than non-transfected cells without stimulation. **Conclusions**.- Human colon and kidney non transfected cells respond to the presence of MSU by forming vesicles with MSU crystals without finding differences in the expression of *ABCG2* at the exposure times used up to now. The transfected HCT15 cells maintain their normal growth with active p53 expression.



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"Monomers of *Vibrio cholerae* VCC, induced activation of p38, ERK and NFkB in THP-1 macrophages"

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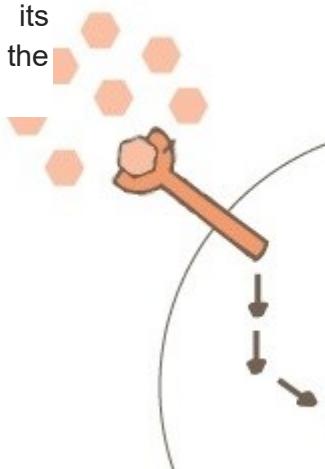
The *Vibrio cholerae* cytolysin (VCC) is part of the pathogenesis of cholera disease, the gastrointestinal diarrhea caused by non-O1 *Vibrio cholerae*, strains unable to produce the cholera toxin (CT). VCC is part of the family of beta pore forming toxins (β-PFT). The monomer of VCC, shows β structure, which assembles together another 6 β structures, accomplishing a heptameric structure forming a β barrel. In this study VCC shows a significant activating effect, starting the pro-immflamatory response through regulation of the MAPKs signalling pathway. Besides VCC activates the transcription factor NF-κB, necesario to the assembly of the inflammasome NLRP3 platform, whose role is starting the molecular mechanisms of inflamation, producing IL-1B with the resulting pyroptotic cell death. OBJECTIVE: Identify the onset of the innate immune response induced by the monomer of VCC, through activation of the MAPKs pathway (p38, ERK) pathway and promoting the transcription of NF-kB allowing the assembly of the inflammasome molecular platform. MATERIALS and METHODS: THP-1 macrophages were treated with VCC (40 pg/mL) and results were observed at 0, 10, 15, 30 y 60 min. The kinetics of p38 and ERK were evaluated by Western Blot. The transcriptional activation of NFkB was estimated by RT-PCR. RESULTS: Phosphorylation of p38 (activation) showed increments at 15 and 30 min; likewise the highest phosphorylation of ERK occurs at 30 min. Besides, here is shown that the monomer of VCC stimulated the transcriptional activation of the transcription factor NF-κB, with important implications in the onset of the inflammatory response. CONCLUSION: Participation of MAPK was induced by treatments with VCC in the first hour, demonstrated by increasing of the proteins p38 and ERK. To establishing that the monomer of VCC truly activates NF-kB through the MAPK pathway, the p50 (NF-κB) was quantitatively determined, showing that this transcription factor increases with time, consistent with its responsibility of starting the innate immune pro-inflamatory response and the pyroptotic cell death of the macrophages.



Altered content of pro-inflammatory cytokines and NF-kB activation in the prefrontal cortex of autistic-like C58/J mice.

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Área: transducción de señales en células del sistema inmune

Autism spectrum disorder (ASD) comprises a set of neurodevelopmental disorders, which affect communication, social interaction and present repetitive behaviours. Although the etiology of ASD remains unclear, there is increasing evidence indicating the presence of neuroinflammation, characterized by reactive glial cells and the production of inflammatory mediators, which could promote to its physiopathology. Indeed, some findings show increased levels of pro- and anti- inflammatory cytokines, as well as the density of reactive glial cells, across different brain regions in individuals with ASD.

Findings from our laboratory showed increased IFN-γ and MCP-1 (CCL2) content in the hippocampus, as well as increased microglial density at the same region in autistic-like mouse strain C58/J compared to a wild-type mouse strain. Since some studies have evaluated the levels of different inflammatory markers in different regions of individuals with ASD and have found that their levels vary depending on the region, we decided to further evaluate the presence of neuroinflammatory markers and processes. In this study, our aim was to evaluate the microglial density and the levels of major proinflammatory cytokines in the prefrontal cortex (PFC) of autistic-like mice C58/J. Our data show an increased microglial density in the PFC accompanied by a decreased TNF-α content, while the IFN-γ content in the same region remains unchanged.

These findings could be related with a deregulation of NF-kB and JAK/STAT signalling pathways, as well as the production of pro- and anti- inflammatory cytokines. Therefore, it is important to assess the levels of the p-p65 protein and IKB protein contents at the PFC and determine if there is a downregulation of the NF-kB pathway resulting in a decrease of proinflammatory cytokines such as TNF- α, IL-6 or IL-1β.

Keywords: neuroinflammation, NF-kB, autism

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Evaluation of Artificial Virus-Like Particles (AVLPS) as a new alternative of delivery systems for veterinary vaccines

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Introduction

The Porcine Epidemic Diarrhea Virus (PEDV) is a lethal coronavirus causing a severe intestinal infection in piglets (1). Vaccination is one of the main strategies to combat viral infections. Few vaccines against PEDV currently exist: one is based on inactivated virus isolated from Colorado, USA; another is based on mRNA that must be stored frozen to prevent degradation. However, some PEDV strains do not generate cross immunity, particularly the INDEL strains that have been reported in our country (2). The main objective of this work is to develop an mRNA vaccine against a Mexican PEDV using Artificial Virus-Like Particles (AVLPs) as delivery systems. The first part of the project consisted of evaluating the ability of AVLPs to transfect HEK and THP-1 cells. Subsequently, we performed a phylogenetic analysis of PEDV strains isolated in Mexico and analyzed peptide sequences that generate neutralizing antibodies. Our preliminary results indicate that AVLPs are an attractive alternative as delivery systems.

Materials and methods

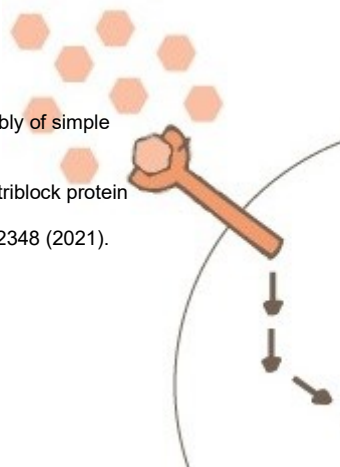
PRODUCTION OF FLUORESCENT DNA AND AVLPs: Fluorescent DNA was produced by PCR using $ATTO_{590}$-conjugated oligonucleotides. For the design of the AVLPs we used mixtures of the fluorescent DNA with the recombinant proteins: C4-BK12 (diblock) and C4-S10-BK12 (triblock) developed by Dr. Armando Hernández of the IQ-UNAM (3, 4).
TRANSFECTIONS: HEK-293 and THP-1 cells were seeded using 96-well plates. The AVLPs were used 24 h after their assembly in OPTI-MEM medium. Lipofectamine 2000 with fluorescent DNA and fluorescent DNA alone were used as transfection controls. Then, we stained the nuclei with hoechst 33342 and cells were observed under a fluorescence microscope (Cytation). Finally, brightfield and fluorescence images were obtained to assess the transfection efficiency of the different AVLPs.

Results and discussion

The $ATTO_{590}$-conjugated DNA served to demonstrate the cells transfected with the AVLPs. Our preliminary results have shown that AVLPs are good nucleic acid transfection vehicles. The next step will be to evaluate their delivery effect on mRNA sequences encoding for 3 PEDV peptides found at the N-terminus of the spike (S) protein.

Conclusion

Our preliminary results have shown that AVLPs are good vectors for transporting and introducing nucleic acids into cultured cells.



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