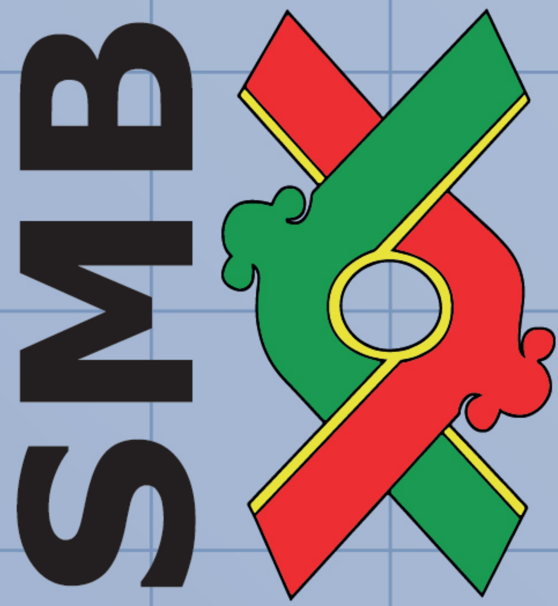

XXIII CONGRESO DE BIOENERGÉTICA Y BIOMEMBRANAS

October 22-26, 2023 - Atlixco, Puebla, México

SOCIEDAD MEXICANA DE BIOQUÍMICA

Organizing Committee

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SOCIEDAD MEXICANA DE BIOQUÍMICA, A.C.

XXIII CONGRESO DE BIOENERGÉTICA Y BIOMEMBRANAS

ORGANIZING COMMITTEE

NATALIA CHIQUETE FÉLIX
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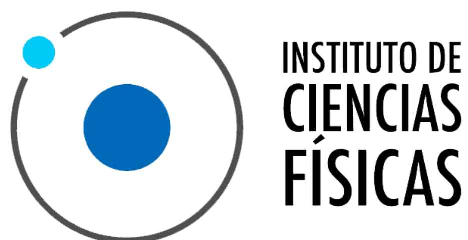
SPONSORS



AGRADECEMOS AL CONSEJO NACIONAL DE HUMANIDADES, CIENCIA Y TECNOLOGÍA (CONAHCYT) POR EL APOYO OTORGADO A LA SOCIEDAD MEXICANA DE BIOQUÍMICA PARA LA ORGANIZACIÓN DE ESTE EVENTO, MEDIANTE EL PROYECTO NÚMERO 318661 "APOYO PARA LA ORGANIZACIÓN DE LOS CONGRESOS NACIONALES DE LA SOCIEDAD MEXICANA DE BIOQUÍMICA, A.C." DENTRO DE LA CONVOCATORIA "FORTALECIMIENTO DE ACTIVIDADES VINCULADAS CON LA PROMOCIÓN, DIFUSIÓN Y DIVULGACIÓN DE LAS HUMANIDADES, CIENCIAS, TECNOLOGÍAS Y LA INNOVACIÓN: ACADEMIAS Y SOCIEDADES CIENTÍFICAS 2021".

Bienvenida

La Rama de Bioenergética y Biomembranas fue uno de los subgrupos pioneros en la Sociedad Mexicana de Bioquímica, que actualmente cuenta con 44 años de experiencia en la organización de reuniones bianuales. Sus fundadores, los Dres. Carlos Gómez Lojero, Armando Gómez Puyou y Antonio Peña Díaz, compartieron desde los inicios de la Rama su amplia experiencia académica con las siguientes generaciones.
Esperamos con gran entusiasmo esta reunión, ya que no solo compartimos y discutimos resultados de investigaciones científicas de alto nivel, sino que también disfrutamos de la compañía de todos los asistentes.
Una característica destacada y de gran interés en la comunidad científica de esta reunión es que se otorga prioridad a los estudiantes de todos los niveles (licenciatura, maestría y doctorado) para presentar y discutir sus proyectos de investigación con científicos consolidados, tanto nacionales como internacionales y de gran renombre. En muchos casos, conocer a los integrantes de la Rama, les abre oportunidades a los estudiantes para realizar estancias de investigación durante sus estudios de posgrado.
En esta ocasión, el comité organizador ha diseñado un programa que incluye la participación de investigadores mexicanos y extranjeros, quienes impartirán seis conferencias magistrales y un simposio sobre "Enfermedades Metabólicas". Además, se llevarán a cabo ponencias orales y discusiones con carteles, siendo la mayoría de estas presentaciones realizadas por estudiantes en diversas áreas de la Rama.
Esta edición será especialmente significativa, ya que rendiremos homenaje póstumo a tres científicos muy queridos de nuestra Rama: los Dres. Georges Dreyfus, Marietta Tuena y Jorge Cerbón. Estos distinguidos investigadores contribuyeron al sueño de establecer una comunidad de Bioenergética y Biomembranas en México, compartiendo sus enseñanzas y conocimientos para formar a las futuras generaciones de investigadores.
Llegamos a la XXIII Reunión después de haber celebrado la edición anterior de forma híbrida durante la pandemia. Es un gran honor para el comité organizador poder reunirse nuevamente de forma presencial como una familia científica para discutir y aprender sobre las nuevas investigaciones en el campo.
También se llevará a cabo la sexta entrega de la Medalla José Laguna García, con el fin de reconocer la trayectoria de un investigador joven y un investigador consolidado en el área de la Bioenergética y las Biomembranas.

¡Les damos la más cordial bienvenida a Atlixco, Puebla! Esperamos que todos aportemos lo mejor de nosotros para hacer de esta reunión una experiencia inolvidable.

Comité Organizador

Natalia Chiquete Félix
Miriam Vázquez Acevedo
Carlos Muñoz Garay

MEDALLA "JOSÉ LAGUNA GARCÍA"

ESTA MEDALLA SE OTORGA POR LA RAMA DE BIOENERGÉTICA Y BIOMEMBRANAS A DOS MIEMBROS QUE SE HAN DISTINGUIDO POR LA CALIDAD DE SUS TRABAJOS DE INVESTIGACIÓN, SUS CONTRIBUCIONES EN EL ÁREA Y SU PARTICIPACIÓN EN LAS ACTIVIDADES ACADÉMICAS DE LA RAMA.

PREMIADOS EN 2021
DRA. MARINA GAVILANES RUÍZ
DR. MANUEL GUTIÉRREZ AGUILAR

PREMIADOS EN 2019
DRA. XÓCHITL PÉREZ MARTÍNEZ
DRA. ISABEL BAEZA RAMÍREZ

PREMIADOS EN 2017
DR. OSCAR FLORES HERRERA
DR. SALVADOR URIBE CARVAJAL

PREMIADOS EN 2015
DR. JOSÉ DE JESÚS GARCÍA TREJO
DR. RAFAEL MORENO SÁNCHEZ

PREMIADOS EN 2013
DR. HELIODORO CELIS SANDOVAL
DRA. VICTORIA CHAGOYA DE SÁNCHEZ
DR. EDMUNDO CHÁVEZ COSSÍO
DR. CARLOS GÓMEZ LOJERO
DR. ARMANDO GÓMEZ PUYOU
DR. ANTONIO PEÑA DÍAZ
DRA. MARIETTA TUENA SANGRI

PREMIADOS EN 2023
DR. FEDERICO MARTÍNEZ MONTES
DR. CHRISTIAN CORTÉS ROJO

MIEMBROS DEL JURADO EN 2023
DR. OSCAR FLORES HERRERA
DRA. SOBEIDA SÁNCHEZ NIETO
DRA. ADRIANA MUHLIA ALMAZÁN

Medalla José Laguna García, acuñada en el 2013

Cuño Anverso: Efigie del Dr. José Laguna, con la leyenda “JOSÉ LAGUNA GARCÍA 1921-2011”.

Cuño Reverso: Formando una espiral, la leyenda “POR SUS CONTRIBUCIONES A LA BIOENERGÉTICA Y A LAS BIOMEMBRANAS”. En el origen de la espiral, el símbolo $X{\sim}P$, representando el intermediario fosforilado de alta energía de la hipótesis de E.C. Slater (1953) y en el final de la espiral, el símbolo $\Delta\mu H^{+}$, representando la fuerza protón-motriz de la hipótesis quimiosmótica de Peter Mitchel (1961).

Metal: Bronce

Peso: 125 g

Diámetro: 6 cm

Diseño: Miguel Gómez Counahan

Troquelado: “ARTE Y ESCULTURA FIDIAS”, México

LINEAMIENTOS PARA EL OTORGAMIENTO DE LA "MEDALLA JOSÉ LAGUNA GARCÍA"

La "Medalla José Laguna García" fue acuñada *ex profeso* en el 2013 para honrar la memoria del Dr. José Laguna, quien fuera pionero de la bioquímica moderna en México, uno de los fundadores de la Sociedad Mexicana de Bioquímica (SMB) y mentor de muchos de los miembros que integraron la primera generación de investigadores que cultivaron el estudio de la Bioenergética y de las Biomembranas, generando así la corriente más activa de investigación en esta área en nuestro país.

- **Objeto del reconocimiento**

La "Medalla José Laguna García" fue concebida para preservar y estimular la investigación en el área de la bioenergética y las biomembranas. Este reconocimiento lo otorgará la Rama de Bioenergética y Biomembranas de la SMB (de aquí en adelante denominada como "la Rama") a miembros distinguidos de la comunidad que llevan a cabo investigación en alguna de estas dos áreas del conocimiento. Se otorga en dos modalidades, la primera a la trayectoria de científicos consolidados y la segunda como un estímulo a las contribuciones realizadas por científicos más jóvenes.

- **Académicos que pueden hacerse acreedores a este reconocimiento**

En su primera edición la medalla se otorgó a investigadores que cultivaron la Bioenergética en sus inicios y que colaboraron con la creación y desarrollo de la Rama. Bianualmente se entregan dos reconocimientos "Medalla José Laguna García", una de ellas a un miembro de la Rama que cuente con una trayectoria fructífera de investigación, que haya contribuido de manera notable a profundizar el conocimiento en el campo y que haya mantenido una actividad académica sostenida en la Rama. La segunda medalla se le otorga a un miembro de la Rama menor de 50 años que haya participado con constancia en las actividades académicas de ésta y que haya realizado contribuciones relevantes en este campo.

- **Procedimiento para la concesión del reconocimiento**

- No se emitirá convocatoria alguna para concursar por el reconocimiento "Medalla José Laguna García", tampoco se recibirán solicitudes institucionales o personales apoyando a un determinado candidato.
- Los merecedores de este reconocimiento honorario serán seleccionados directamente por el jurado, en función de los estudios, investigaciones y/o entrevistas que el propio jurado realice sobre la calidad de las contribuciones

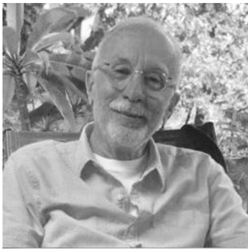
científicas que han llevado a cabo los miembros de la Rama, tomando en cuenta asimismo su probidad académica y moral.

- La entrega del reconocimiento "Medalla José Laguna García" se hará exclusivamente en la Reunión o Congreso bianual de la Rama. Quedará a juicio del Comité Organizador de la Reunión de la Rama escoger, dentro del programa académico, el momento apropiado en que se efectuará la ceremonia de entrega de las medallas. Será prerrogativa del Comité Organizador invitar o no, a alguno de los premiados a impartir una conferencia dentro del programa científico de la reunión.
- El jurado que otorgará la medalla en su siguiente edición será elegido durante la Reunión previa de la Rama, de la misma forma en que se elige al Comité Organizador para la siguiente Reunión.
- El jurado quedará conformado por tres personas, todos ellos integrantes reconocidos y asiduos a las reuniones de la Rama. Al menos uno de ellos deberá haber participado en un Comité Organizador de alguna Reunión. Los miembros del Comité Organizador de la Reunión en turno no podrán ser a la vez miembros del jurado durante ese mismo periodo.
- Los miembros del jurado desarrollarán sus actividades de forma honoraria, sin percibir retribución económica alguna. Además, organizarán sus sesiones y deliberaciones de la manera que mejor convenga a sus intereses. En caso de que algún miembro del jurado esté incapacitado para realizar sus funciones, el Comité Organizador de la Reunión en funciones será el encargado de seleccionar e invitar a algún otro integrante de la Rama para que ocupe el puesto vacante.
- Uno de los miembros del jurado deberá permanecer como integrante en el siguiente jurado, con el fin de preservar los antecedentes de los procedimientos y criterios de selección. El integrante que permanecerá en funciones en una segunda ocasión será seleccionado por mutuo acuerdo del jurado anterior. En la reunión subsecuente de la Rama se elegirán a dos nuevos miembros para integrar el siguiente jurado y así sucesivamente.
- El jurado dispone de más de un año y medio para llevar a cabo sus deliberaciones y deberá emitir su fallo al menos tres meses antes de la fecha en que se lleve a cabo la Reunión de la Rama, haciéndolo del conocimiento únicamente del Comité Organizador. Así mismo, será el propio Comité Organizador el encargado de informar a los colegas seleccionados que se hicieron acreedores al reconocimiento y convocarlos a la ceremonia de entrega.
- El fallo del jurado será inapelable.
- Ninguno de los dos firmantes de este documento puede hacerse acreedor al reconocimiento.
- No podrá otorgarse la medalla en forma póstuma.

- No podrá otorgarse este reconocimiento a científicos externos a la Rama que no hayan tenido una participación relevante y sostenida en la vida académica de la propia Rama.
- No se le podrá otorgar la "Medalla José Laguna García" a una persona que ya fue distinguida con este reconocimiento.
- En las memorias de la Reunión de la Rama ulteriores se incluirán en orden alfabético, por una parte, los nombres de los científicos distinguidos con la medalla, tanto de la Reunión correspondiente como de las anteriores y por otra, los nombres de los miembros del jurado del año correspondiente.
- El financiamiento, la responsabilidad de la manufactura y la disponibilidad de las medallas para cada ceremonia de entrega, estarán a cargo de los abajo firmantes. Por lo tanto, la responsabilidad de elaborar las medallas no recaerá sobre los miembros del Comité Organizador de la Reunión de la Rama.
- El reconocimiento "Medalla José Laguna García" no podrá otorgarse en ninguna otra instancia académica o social fuera del ámbito de la Rama.
- Estos lineamientos se publicarán, en lo sucesivo, en las memorias de cada Reunión de la Rama. Cualquier situación no contemplada en éstos será resuelta por el pleno del jurado, consultando, si así lo consideran necesario, con los miembros del Comité Organizador de la Reunión de la Rama o con integrantes de jurados anteriores.

México D.F., Febrero de 2015

Georges Dreyfus
Diego González Halphen



Recordando a Georges Dreyfus, distinguido miembro de nuestra comunidad bioenergética.

El 26 de septiembre de 2023 nos abandonó Georges Dreyfus, dejando un gran vacío en aquellos que lo conocimos, familiares, amigos, colegas y estudiantes.

Georges siempre consideró un privilegio ser un científico en un país donde la ciencia se considera un lujo y no una necesidad. Por eso apreciaba tanto pertenecer a la UNAM y también a la Sociedad Mexicana de Bioquímica (SMB), asistiendo asiduamente a muchas Reuniones de la Rama de Bioenergética y Biomembranas y organizando la sexta reunión de nuestra Rama en Taxco, Guerrero (1989). Cuando trabajó en la mesa directiva de la SMB (1995-1999), organizó dos congresos nacionales de nuestra sociedad (Manzanillo, Colima, 1996 y Mérida, Yucatán, 1998). A pesar de su genuina aversión hacia los premios y reconocimientos, instauró la distinción Medalla José Laguna para la Rama de Bioenergética, la cual tiene la particularidad de ser un reconocimiento que otorga la propia comunidad, sin mediar convocatoria alguna. Quizá la única distinción en nuestro país que le cae inesperadamente a los galardonados, sin que ellos mismos lo hayan solicitado expresamente.

Siendo estudiante participó en investigación en la Facultad de Medicina tanto en los Departamentos de Cirugía Experimental como en el de Bioquímica/Inmunología. Después de terminar la carrera de Médico Cirujano, tuvo una breve incursión en el área de las neurociencias (1979), trabajando en el laboratorio del Dr. René Drucker Colín, en el entonces Centro de Fisiología Celular. Después se integró al grupo de los Dres. Marietta y Armando Gómez Puyou, contribuyendo a la caracterización del inhibidor natural de la ATP sintasa mitocondrial. Realizó una estancia posdoctoral en Grenoble, Francia, donde continuó investigando la misma enzima en el laboratorio de Pierre Vignais. A su regreso en 1982, se reincorporó al IFC e inició su carrera como investigador independiente estudiando a la ATP sintasa por aproximadamente diez años, una enzima clave en los procesos bioenergéticos. Después de una estancia sabática en el laboratorio del Dr. Robert Macnab en la Universidad de Yale (1992), se entusiasmó por conocer los secretos de otra máquina molecular rotatoria movida por el gradiente electroquímico de protones, el flagelo bacteriano. A su regreso a México comenzó a estudiar la estructura, función y regulación del flagelo de la bacteria fotosintética *Rhodobacter sphaeroides*, entusiasmando a colegas y estudiantes a trabajar en este sistema. Sus manuscritos científicos siempre fueron claros y al punto, describiendo sus resultados con precisión y sin pretensiones. Entre los descubrimientos más notables que hizo el grupo, fue identificar un segundo operón que codifica y regula al flagelo de la alfa-proteobacteria *R. sphaeroides*, probablemente adquirido de una gamma-proteobacteria por transferencia horizontal.

Georges Dreyfus dedicó su vida a la UNAM, como investigador y en su momento como director del Instituto de Fisiología Celular (1993-2001) periodo en que trabajó con enorme entusiasmo por su comunidad. Durante su gestión, además, se hicieron varias contrataciones de investigadores jóvenes independientes y se afinaron las políticas de contratación; promovió los nombramientos de nuestros investigadores fundadores a eméritos; participó en la conformación del entonces nuevo Doctorado en Ciencias Biomédicas y tuvo que sortear la larga huelga de nueve meses del movimiento estudiantil de 1999-2000, que trastocó duramente la vida académica de la UNAM y del instituto.

La muerte sorprendió a Georges Dreyfus cuando se encontraba en su año sabático, trabajando en una revisión sobre el flagelo de *R. sphaeroides*. Será siempre recordado con gran afecto por nuestra comunidad bioenergética.

Diego González Halphen, octubre, 2023

Dr. Marietta Tuena: A Lifetime of passion, joy, and dedication in science

Marina Gavilanes Ruiz. Depto. de Bioquímica, Conjunto E, Facultad de Química, UNAM. Cd. Universitaria. 04510, Cd. de Mexico, Mexico. gavilan@unam.mx; 55 5622 5376

Dr. Marietta Tuena, born to Italian parents in the southern Mexican city of Chetumal, stands as a respected, admired, and beloved figure among the pioneering generation of Mexican biochemists. Her Italian heritage infused her with a festive and effervescent personality, radiating boundless energy, particularly evident in her laboratory endeavors—a realm she dedicated approximately six decades of her life.

During her medical studies, Dr. Tuena initiated a social service mission in the countryside, where she found herself the sole caretaker of health services amid profound resource scarcity. Soon, she would realize that her true calling lay in the captivating world of research, eclipsing her initial aspirations in Medicine. This coincided with the beginning of a lifelong partnership with Dr. Armando Gómez-Puyou, who was her collaborator, editor, and husband. Within this productive and affectionate union, she emerged as the driving force, an indispensable element in every energy-demanding process.

Together, they embarked on a journey through three distinct research domains spanning nearly half a century. The energy transduction of biological membranes, especially mitochondrial membranes, occupied the many first years of their productive research. Then, they transitioned to studies on the water role on the catalysis of energy transducing enzymes. Later, they indeed sat to analyze what was a field that was more challenging and affordable. Then, they ventured into the intricate field of protein structure analysis. Once, answering my question about which was the most interesting and better research project they had ever had, Dr. Gomez-Puyou confessed: the one at the present time, whatever it is. However, Dr. Tuena´s favorite and always pet-topic was the mitochondrial H^+-ATPase, her first scientific love. This enzyme and its inhibitor protein occupied her hands, her devotion, her mind and her heart. She continuously published and gave talks on this enzyme along her life.

One of the enduring legacies of Dr. Tuena and her husband´s scientific journey lies in the contagious fervor and mystical nature of the experimental everyday work that they shed on us (their students, collaborators, as they used to name us). We are forever labeled with the dedication, commitment, discipline and the rigor tags they imprinted on us. This legacy is both an honor and a responsibility… Much to thank and to accomplish. It is a duty; it has been a pleasure.

Today, we have the privilege of hearing from Dr. Jose de Jesus Garcia-Trejo, whom I consider Dr. Tuena's closest collaborator in the H^+-ATPase issues. He has further advanced the study of the catalytic mechanism of this enzyme, a passionate pursuit he shared with Dr. Tuena.

MGR work is supported by DGAPA, UNAM (PAPIIT IN222621) and Facultad de Quimica (PAIP 5000 9115).

Bioenergetics according to Prof. Marietta Tuena Sangri

Prof. José J. García Trejo
Faculty of Chemistry, UNAM

Prof. Marietta Tuena Sangri, (November 12, 1935-February 3, 2023) was, besides an authority in the fields of Bioenergetics, ATP synthase, enzymology, and the structure and function of proteins, she was also an advisor of countless graduate students at UNAM in Biochemical Sciences, many of whom we owe our most important scientific training to her. Prof. Marietta Tuena Sangri is not only a MD doctor, she is “The Professor”. I always preferred to write her name without her married name because although she called herself “Marietta Tuena de Gómez Puyou”, she used that more for her numerous international frontier articles in science. In her laboratory, in her home, and in her country, I always realized that she was not, and she did not want to appear to be an extension of her husband. Prof. Marietta Tuena Sangri, in addition to her countless articles and high-level contributions in Bioenergetics and the regulation of the mitochondrial ATP synthase, she was awarded the National University Award of UNAM, and as Emeritus Researcher at UNAM and at the National System of Researchers (SNI of the still named National Council of Sciences of Mexico or “CONACyT”) for her own merits. Prof. Marietta Tuena Sangri was not only a pioneer of Biochemistry and Bioenergetics in Mexico, but also a major pillar or basement of the national and international Biochemistry, and with her sad departure a great part of the best era of Biochemistry in our country and abroad is lost forever. Sadly, there is a risk that the scientific structure she built in Mexico, based on her experiments and tireless pipetting until the last of her days, based on scientific seminars, articles, thesis direction and advice, her great dissemination work at conferences, colloquiums, workshops, etc., all her legacy could be lost. It has been our mission as her former direct students to support and maintain her great legacy, but the risk still remains that this great legacy will crumble in the near future with any tremor with the new generations who surely do not know who she is, and how, thanks to her and to other great researchers, they can work in their laboratories on what in theory students like the most, which must be doing experiments and science. Prof. Marietta Tuena Sangri always invested all her personal mitochondrial ATP in her work, just as we, her former students, do now. It is up to the new generations not to invest the minimum of their own ATP, as sometimes seems to be, but to put all of this personal ATP to work as much as possible in their respective laboratories, only then her great legacy will be maintained, and only then will we be able to do cutting-edge science, and we will be able to honor her properly. Let's hope the national Bioenergetics will not be lost by investing the minimum of the personal ATP of the new generations of our country, but instead they will keep her great legacy with hard and good work, and with solid Bioenergetics in Mexico.

Jorge Cerbón Solórzano - *in memoriam*

El Dr. Jorge Cerbón Solórzano nació en la Cd. de México el 20 de marzo de 1930, para inicios de 1980´s ya se le había otorgado diferentes distinciones. Destacando el Premio Nacional de Ciencias Físico-Matemáticas y Naturales (1977), máximo reconocimiento del Gobierno a las ciencias y las artes de nuestro país. Además de múltiples reconocimientos en el Instituto Politécnico Nacional como la presea Miguel Othón de Mendizábal, "Egresado Distinguido" de la Escuela Nacional de Ciencias Biológicas en 1979, el diploma Lázaro Cárdenas en 1981 y dar su nombre al edificio 6 del CECYT.

Entre los emblemas que se le reconocen al Dr. Cerbón, resalta el curso que impartió por años en el tema de lípidos y membranas; curso temido por el estudiantado. Sin embargo, a lo largo del curso dejaba claro su genuino interés en formar y sembrar el aprendizaje en sus estudiantes. En el curso guiaba a sus estudiantes cuidadosamente por el difícil mundo de los lípidos, desde sus legendarias gráficas de sistemas binarios y ternarios, hasta los modelos de membrana y su estructura-función celular. Durante el curso quedaba clara su amplia y contundente experiencia en la academia y la investigación.

El Dr. Cerbón trabajó en tres áreas principales: la microbiología en sus aspectos fisiológicos y bioquímicos, la biofísica y la dinámica metabólica de las membranas biológicas, la dinámica de fosfolípidos y de esfingolípidos en la generación de segundos mensajeros. Del Doctor destacaba su intuición; la oportunidad de las ideas; su atrevimiento con los experimentos; su tesón casi infinito al seguir una idea. Estas cualidades explican completamente la trascendencia de su trabajo. Cerbón inició sucarrera científica enla Unidad de Neumología del IMSS estudiando métodos diagnósticos dela tuberculosis y las características bioquímicas de las membranas y la pared que recubre al microorganismo productor de la tuberculosis.

En 1954 publicó su primer trabajo científico. En 1963 fue invitado a una estancia en el National Institute of Arthritis and Metabolic Diseases del NIH, donde realiza los primeros estudios de Resonancia Magnética Nuclear (RMN) del agua, en células, membranas lipídicas y organismos vivos. Ingresó al Depto. de Bioquímica el 1 dejulio de 1965 y fue un pilar indiscutible, dirigiéndolo por más de 10 años con gran cariñoy lealtad al Departamento. Deigual forma el Dr. Cerbón siempre encontró la forma yel tiempo para ayudar al desarrollo de la ciencia y la academia del País.

El Dr. Cerbón perteneció al Consejo Consultivo de Ciencias y trabajó con varias asociaciones científicas como la Academia Mexicana de Ciencias, la Asociación Mexicana de Microbiología, la American Society for Microbiology, el Biomembranes Group de la Biophysical Society, la American Society of Biochemistry and Molecular Biology, la International Union of Biochemistry, la International Union for Pure and Applied Biophysics, fue Chairman del Scientific Exchange Committee de la Asociación Panamericana de Sociedades de Bioquímica, Organizó el Simposio Internacional de Biomembranas en el X Congreso Internacional de Microbiología, el 1er Curso Latinoamericano sobre Bioquímica de plantas (OEA), y fue Presidente dela SMB (1977-1979).

Sus convicciones y forma detrabajar lo obligaban a tener una posición muy clara en contra delos trabajos multiautor y una idea estricta sobre la distribución de créditos, defensor arduode la disciplina filosófica y humanística. Él Dr. Cerbón ingresó a la Escuela Nacional de Ciencias Biológicas en 1947 donde se graduó de Quím. Bacteriólogo en 1951. En 1961 inició sus estudios de doctorado en la propia Escuela Nacional de Ciencias Biológicas dondeobtiene en 1963 el doctorado con especialidad de Microbiología. De 1955 A 1957 realizó estancia en el Depto. de Fisiología de la Esc. de Med. de la UNAM, en la Unidad de Patología.

Investigador Emérito por el Sistema Nacional de Investigadores en 1996 y Profesor Emérito por el CINVESTAV en 1997, El Dr. Cerbón es orgullo y profesor insignia del Depto. de Bioquímica. Por esa época publicó trabajos en los que se demostró la distribución asimétrica de fosfolípidosen la membrana plasmática, su dinámica metabólica y su importancia en la determinación del pH

interfacial y del potencial transmembranal, además del papel de los lípidos en la actividad de proteínas de transporte de metabolitos celulares. También se enfocó en el estudio de la función de los esfingolípidos en la regulación del ciclo celular, mediante técnicas de lipidómica.

(Texto modificado del discurso pronunciado el viernes 9 de julio de 2010 para la ceremonia de Homenaje al Dr. Cerbón por sus 45 años en el Departamento de Bioquímica del CINVESTAV)

XXIII Reunión Bioenergética y Biomembranas

October 22 - 26, 2023

TIME	SUN October 22th		MON October 23th	TUES October 24th	WED October 25th	THURS October 26th
7:30 - 9:00	Arrival		Breakfast	Breakfast	Breakfast	Breakfast
9:00 - 10:00			Magistral Conference I Xochitl Pérez	Magistral Conference III Jean Pierre Mazat	Magistral Conference V Edward Dennis	
10:00 - 11:30			Oral Session I	Oral Session IV	Oral Session VII	Check out
11:30 - 12:00			Coffee Break	Coffee Break	Coffee Break	Departure
12:00 - 13:00			Oral Session II	Oral Session V	Magistral Conference VI Maria Isabel Hernández	
13:00 - 14:00	Registration and Check in		*In memoriam* Marietta Tuena	*In memoriam* Jorge Cerbón	Oral Session VIII	
14:00 - 16:00		Lunch	Lunch	Lunch	Lunch	
16:00 - 16:30	Welcome ceremony		Magistral Conference II Benjamín Podbilewicz	Magistral Conference IV Luis González de la Vara	Magistral Conference VII Oxana Dobrovinskaya	
16:30 - 17:00	Cultural Conference Hugo García Capistrán					
17:00 - 17:30			Coffee Break	Oral Session VI	Oral Session IX	
17:30 - 18:00	Coffee Break		Oral Session III			
18:00 - 18:30	*In Memoriam* Georges Dreyfus			Poster Session and Coffee Break	Coffee Break	
18:30 - 19:00					Closing Ceremony	
19:00 - 19:30	José Laguna´s Medal Award		Free time			
19:30 - 20:00	Welcome Cocktail					
20:00 - 22:00			Dinner	Dinner	Dinner and Farewall Party (20:30 - 1:30)	

Sunday October 22th

13:00 – 16:00 **Registration**

14:00 – 16:00 **Lunch**

16:00 – 16:30 **Welcome Ceremony**

16:30 – 17:30 **Cultural Conference**

La región Puebla – Tlaxcala en la época prehispánica.
Breve desarrollo cultural
M.C. Hugo García Capistrán
Facultad de Filosofía y Letras, UNAM

Chair: Manuel Gutiérrez. Facultad de Química, UNAM

17:30 – 18:00 **Coffee Break**

18:00 – 19:00 **In memoriam Georges Dreyfus**

Dr. Diego González Halphen
Instituto de Fisiología Celular. UNAM
Dr. Iván Ortega Blake
Instituto de Ciencias Físicas, UNAM
Dr. Bertha González Pedrajo
Instituto de Fisiología Celular. UNAM

19:00 – 19:30 **José Laguna´s Medal Award Ceremony**

19:30 – 22:00 **Welcome Cocktail**

Monday October 23rd

7:30 – 9:00 **Breakfast**

9:00 – 10:00 **Magistral Conference I**

Biogenesis of mitochondrial respiratory complexes: interplay between nuclear and mitochondrial genes

Dr. Xochitl Pérez Martínez
Instituto de Fisiología Celular, UNAM

Chair: Miriam Vázquez Acevedo
Instituto de Fisiología Celular, UNAM

10:00 – 11:30 **Oral Session I**
Chair: Manuel Gutiérrez Aguilar
Facultad de Química, UNAM

10:00 – 10:15 The mitochondrial uncoupling proteins from the cannonball jellyfish and the effect of temperature on their genes expression.
Edgar Gamero Mora, and Adriana Muhlia Almazan. Bioenergetics and Molecular Genetics Laboratory, Centro de Investigacion en Alimentación y Desarrollo, A. C.

10:15 – 10:30 The *Killer* system of *Saccharomyces cerevisiae* reveals strengths and weaknesses in the interaction with *Pseudomonas aeruginosa*: battle at the plasma membrane.
Jennifer Andrea Uribe López, Morales Tlalpan V, Campos Guillen J, Cervantes Chávez JA, García-Gasca T. and Saldaña C. Laboratorio de Biofísica de Membranas y Nanotecnología. Facultad de Ciencias Naturales. Universidad Autónoma de Querétaro

10:30 – 10:45 Culture optimization and mitochondrial complex I characterization from the diatom *Phaeodactylum tricornutum*.
Gloria Vargas Romero, Zhaida Aguilar-Gonzalez, Girian Jaguer García, Sofía Laguna Soria, Mónica Rodríguez Bolaños, Pierre Morsomme, Hervé Degand, Pierre Cardol, Héctor V. Miranda Astudillo. Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, UNAM

10:45 – 11:00 Insights into the cooperation of NAC and RAC as part of the mitochondrial protein import mechanism.
José Ernesto Bravo Arévalo, Ariann E. Mendoza Martínez & Soledad Funes. Departamento de Genética Molecular. UNAM

11:00 – 11:15 Characterization of genetic factors that promote the allotopic expression of the yeast mitochondrial *cox2* gene.
Felipe Nieto Panqueva, Miriam Vazquez Acevedo, Patrice Paul Hamel and Diego Gonzaléz Halphen. Instituto de Fisiología Celular, UNAM

11:15 – 11:30 Unraveling the Interaction Mechanism between the ATPase and its Central Stalk in the Type III Secretion System of enteropathogenic *Escherichia coli.*
Amin Mora Garcia, Ángel Andrade, Norma Espinosa, Mariana Romo-Castillo and Bertha González-Pedrajo. Instituto de Fisiología Celular, UNAM

11:30 – 12:00 **Coffee Break**

12:00 – 13:00 **Oral Session II**
Chair: Norma Silvia Sánchez
Instituto de Fisiología Celular, UNAM

12:00 – 12:15 Optimization of paramylon production in *Euglena gracilis* using different light spectra.
Zhaida Itzel Aguilar González, Gloria Vargas-Romero, Sofía B. Laguna-Soria, Héctor V. Miranda-Astudillo. Departamento de Biología Molecular y Biotecnología. Instituto de Investigaciones Biomédicas, UNAM

12:15 – 12:30 Development of species-specific light harvesting complexes in *Euglena gracilis.*
Héctor Vicente Miranda Astudillo and Pierre Cardol. Departamento de Biología Molecular y Biotecnología. Instituto de Investigaciones Biomédicas, UNAM

12:30 – 12:45 ATP synthase as a pharmacological and antimicrobial target.
Enrique García Hernández, Luis Fernando Cofas Vargas, Jesús Antonio Rauda-Ceja. Instituto de Química, UNAM

12:45 – 13:00 Complex I inhibition by metformin in rat kidney mitochondria depending on sex.
Diana Elisa Cruz Vilchis, Stefanie Paola López Cervantes, Giovanni

García Cruz, Mercedes Esparza Perusquía, Oscar Flores Herrera. Laboratorio $3^{6}/_{4}$, Departamento de Bioquímica, Facultad de Medicina, UNAM

13:00 – 14:00 **In Memoriam Marietta Tuena**
Dr. Marina Gavilanes Ruiz
Dr. José de Jesús García Trejo
Facultad de Química, UNAM

14:00 – 16:00 **Lunch**

16:00 – 17:00 **Magistral Conference II**

Mechanisms and origins of egg-sperm fusion in plants, parasites and mammals

Dr. Benjamín Podbilewicz
Department of Biology, Technion- Israel Institute of Technology, Haifa, Israel

Chair: Diego González Halphen
Instituto de Fisiología Celular, UNAM

17:00 – 17:30 **Coffee Break**

17:30 – 19:00 **Oral Session III**
Chair: Christian Cortés Rojo
IIQB. Universidad Michoacana de San Nicolás de Hidalgo

17:30 – 17:45 Conformational changes on the estrogen-related receptor probed by Gaussian accelerated molecular dynamics.
Lenin Domínguez Ramírez, Paulina Cortes-Hernandez. Centro de Investigación Biomédica de Oriente

17:45 – 18:00 Exploring Slm35 and Atg32 functions in mitophagy and oxidative stress response in *Saccharomyces cerevisiae*.
Ariann Elizabeth Mendoza Martínez, Hernán Romo Casanueva, Hilario Ruelas y Soledad Funes. Instituto de Fisiología Celular, UNAM

18:00 – 18:15 Novel insights in the production of the *Killer* toxin *K*1 in *Saccharomyces cerevisiae*: a relation in volume regulation.
Amairani Chávez Vega, Morales Tlalpan V, Arellano Carbajal F., Cervantes Chávez J, López Meza J, Ferriz Martínez R, and Saldaña C. Laboratorio de Biofísica de Membranas y Nanotecnología. Facultad de Ciencias Naturales. Universidad Autónoma de Querétaro

18:15 – 18:30 The translational activator Mss51 has conserved function in different yeast species.
Yolanda Margarita Camacho Villasana, Ulrik Pedroza Dávila, Aldo E. García Guerrero and Xochitl Pérez Martínez. Departamento de Genética Molecular, Instituto de Fisiología Celular. UNAM

18:30 – 18:45 Analysis of the transit peptides of the proteins whose final destiny are the colorless plastids of the chlorophycean alga *Polytomella parva*.
Sergio Fuentes Hernández, Vázquez Acevedo Miriam, Santillán Torres José Luis and González Halphen Diego. Instituto de Fisiología Celular. UNAM

18:45 – 19:00 Mitochondrial morphology transition assessment in *Arabidopsis thaliana*
Bryan Ocampo Hernández, *Manuel Gutiérrez Aguilar*. Departamento de Bioquímica, Facultad de Química. UNAM

20:00 – 22:00 **Dinner**

Tuesday October 24th

7:30 – 9:00 **Breakfast**

9:00 – 10:00

Magistral Conference III

Small is beautiful: C2M2NF, a quantitative stoichiometric core model to study the rewiring of metabolism in proliferating cells

Jean Pierre Mazat
IBGC CNRS UMR 5095 & Université de Bordeaux. France

Chair: Salvador Uribe Carvajal
Instituto de Fisiología Celular, UNAM

10:00 – 11:30 **Oral Session IV**
Chair: Yolanda Margarita Camacho Villasana
Instituto de Fisiología Celular, UNAM

10:00 – 10:15 The ancient respirasome
Mercedes Esparza Perusquía and Oscar Flores-Herrera. Laboratorio 3⁶/₄, Departamento de Bioquímica, Facultad de Medicina, UNAM

10:15 – 10:30 Is the assembly pathway of mitochondrial supercomplexes conserved among species?
Sofía Beatriz Laguna Soria, Anaiza Rico-Luna, Mercedes Esparza Perusquía, Oscar Flores Herrera, Héctor Vicente Miranda Astudillo. Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, UNAM

10:30 – 10:45 Identification of the critical residues of the ζ subunit as inhibitor of the F_1F_O-ATPase of Paracoccus denitrificans at its very N-terminus and globular domains
José J. García Trejo, Gilberto Garduño Javier, Oliver Sotelo Serrano, Emiliano Salinas López, Raquel Ortega Muñoz, Nallely Cabrera González, Héctor A. Martínez Torres, Mariel Zarco Zavala, and Hiroyiki Noji. Facultad de Química, UNAM

10:45 – 11:00 Changes in glycerol-3-phosphate metabolism are early events during palmitic acid-induced metabolic reprograming in U937-derived macrophages
Luis Alberto Luévano Martínez, Victor Baylon Valdez, Diana Bonilla Ruelas, Marion E.G Brunck, Gerardo García-Rivas. Tecnologico de Monterrey, Centro de Investigación Biomédica, Hospital Zambrano Hellion, TecSalud. The Institute for Obesity Research

11:00 – 11:15 The Colorful Guardians: Carotenoids of R. Mucilaginosa Defend Against Oxidative Stress
Ofelia Alejandra Mendez Romero, Edson Mosqueda Martínez, Natalia Chiquete Félix, Salvador Uribe Carvajal. Departamento de Genética Molecular, Instituto de Fisiología Celular, UNAM

11:15 – 11:30 Kinetic characterization of respirasomes from *Yarrowia lipolytica*
Giovanni García Cruz, Mercedes Esparza Perusquía, Stefanie Paola López Cervantes, Federico Martínez, Juan Pablo Pardo, and Oscar Flores Herrera. Laboratorio 3 $^{6}/_{4}$, Departamento de Bioquímica, Facultad de Medicina, UNAM

11:30 – 12:00 **Coffee Break**

12:00 – 13:00 **Oral Session V**
Chair: Enrique Chávez Jiménez
Instituto de Fisiología Celular, UNAM

12:00 – 12:15 Effect of insulin resistance on the metabolism-insulin secretion coupling in pancreatic islets of Wistar rats.
Diana Moroni Gonzalez, Victor E. Sarmiento Ortega, José E. Avelino Cruz, Samuel Treviño. Faculty of Chemical Sciences, BUAP

12:15 – 12:30 Dexamethasone-induced switch to fatty acid oxidation and autophagy/mitophagyare essential for T-ALL glucocorticoid resistance.
Miguel Olivas Aguirre, Jesús Pérez Chávez, Liliana Torres López, Arturo Hernández Cruz, Igor Pottosin, Oxana Dobrovinskaya. Centro Universitario de Investigaciones Biomédicas, Universidad de Colima

12:30 – 12:45 Tissue-specific characteristics of the mitochondrial permeability transition pore in rats.
Mauricio Reyes Becerril, Carolina Ricardez García, Ofelia Méndez Romero, Natalia Chiquete Félix, Angélica Ruiz Ramírez and Salvador Uribe-Carvajal. Departamento de Genética Molecular, Instituto de Fisiología Celular, UNAM

12:45 – 13:00 Intervention into the dynamics of intracellular Ca^{2+} improves the NK cells anticancer activity.
Igor Pottosin, Miguel Olivas-Aguirre, Laura Hadit Cruz-Aguilar, Oxana Dobrovinskaya. Centro Universitario de Investigaciones Biomédicas, Universidad de Colima

13:00 – 14:00 **In Memoriam Jorge Cerbón**
Dr. José Víctor Calderón Salinas
Dra. Emeli Cortina Ramírez
Cinvestav Zacatenco IPN

14:00 – 16:00 **Lunch**

16:00 – 17:00 **Magistral Conference IV**

The H + -transporting ATPases in plant cell plasma membranes, and their circumstance

Luis González de la Vara
Departamento de Biotecnología y Bioquímica.
Cinvestav Irapuato. IPN

Chair: Marina Gavilanes Ruiz
Facultad de Química, UNAM

17:00 – 18:00 **Oral Session VI**
Chair: Mercedes Esparza Perusquía
Facultad de Medicina, UNAM

17:00 – 17:15 Kinetics characterization of the F_1F_O-ATP synthase dimer and monomer from *Yarrowia lipolytica.*
Alejandro Cruz Cárdenas, Giovanni García Cruz, Mercedes Esparza Perusquía, Oscar Flores Herrera. Laboratorio 3⁶/₄, Departamento de Bioquímica, Facultad de Medicina, UNAM

17:15 – 17:30 Functional and structural characterization of the endogenous zeta (ζ) inhibitor of the F_1F_O-ATPase in photosynthetic α-proteobacteria.
Jorge Brito Sánchez, Raquel Ortega, Claudia Peña Segura y José J. García Trejo. Facultad de Química, UNAM

17:30 – 17:45 Role of the δ subunit of the F1-ATPase sector in the colorless alga *Polytomellaparva* in the regulation of the hydrolytic activity of the complex.
Marcos Ostolga Chavarría, Héctor Vicente Miranda Astudillo, Miriam Vázquez Acevedo y Diego Gonzalez Halphen. Instituto de Fisiología Celular, UNAM

17:45 – 18:00 Mitochondrial ATP synthase structure diversity and catalytic activity.
Anaiza Rico Luna, Sofía Beatriz Laguna Soria, Gloria Vargas Romero, Héctor Vicente Miranda Astudillo. Departamento de Biología Molecular y Biotecnología, Instituto de Investigaciones Biomédicas, UNAM

18:00 – 20:00 **Poster Session**

20:00 – 22:00 **Dinner**

Wednesday October 25th

7:30 – 9:00 **Breakfast**

9:00 – 10:00

Magistral Conference V

Membrane Allostery and Unique Hydrophobic Sites Promote Enzyme Substrate Specificity

Edward Dennis
School of Medicine, University of California

Chair: Brandt Bertrand
Instituto de Ciencias Físicas, UNAM

10:00 – 11:30 **Oral Session VII**
Chair: Ariann Elizabeth Mendoza Martínez
Instituto de Fisiología Celular, UNAM

10:00 – 10:15 Effect of high temperatures on phenotypes and gene expression of heat shock protein in plants lacking MPKs or with sphingolipid imbalance.
David F. Barrera Gómez, I. Giordano Ponce Pineda, Laura Carmona Salazar, B. García Ponce de León, A. Arturo Guevara García, Edgar B. Cahoon & Marina Gavilanes Ruiz. Departamento de Bioquímica, Facultad de Química, UNAM

10:15 – 10:30 Contribution of sphingolipid Δ8 unsaturation on plasma membrane fluidity from Arabidopsis leaves during cold acclimation.
Laura Carmona Salazar, LeidyZaibeth Cruz Martínez, Dora Cano Ramírez, Edgar B. Cahoon and Marina Gavilanes Ruiz. Departamento de Bioquímica, Facultad de Química, UNAM

10:30 – 10:45 It is capable the mitochondria to regulate its own membranal fatty acids composition?
Jorge Escutia Martínez, Ricardo Mejía Zepeda. Facultad de Estudios Superiores Iztacala. UNAM

10:45 – 11:00 Fatty acids and protein profiles of the inner and outer mitochondrial membranes in diabetes.
Ramiro Perusquia García, Ricardo Mejía Zepeda. Facultad de Estudios Superiores Iztacala. UNAM

11:00 – 11:15 The importance of the C-terminal of cornichon homologuesin plants and yeast.
Omar Pantoja, Yáñez Domínguez C, Lagunas Gómez D, Bezanilla M, Barlowe C. Instituto de Biotecnología, UNAM

11:15 – 11:30 Kramers theory of rate reactions and yeast alcohol dehydrogenase kinetics.
Juan C. González Castro and José G. Sampedro. Laboratorio de Biofísica de Proteínas. Instituto de Física, UASLP

11:30 – 12:00 **Coffee Break**

12:00 – 13:00 **Metabolic Diseases Symposium**

Magistral Conference VI

Mitochondrial fusion proteins are a hub in phospholipid synthesis and metabolism

Maria Isabel Hernández

Chair: Gerardo García Rivas
TecSalud. The Institute for Obesity Research

13:00 – 14:00 **Oral sesión VIII**
Chair: Luis Alberto Luévano Martínez
TecSalud. The Institute for Obesity Research

13:00 – 13:15 Effect of estradiol on Ca^{2+} handling proteins and mitochondrial activity in hypertrophied H9c2-derived cardiac myotubes.
Silvia A. López Morán, Christian Silva Platas, Luis A. Luévano Martínez, Julio Altamirano, Gerardo García Rivas. Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud

13:15 – 13:30 Cannabidioltreatment on 3T3-L1 pre-adipocytes modify lipid droplet accumulation during white-like adipocytes differentiation.
*Helen Yarimet Lorenzo Anota***,** Antonio Sansen, Silvia López, Luis Luevano, Eduardo Vázquez Garza, Rebeca Pérez Cabeza de Vaca, Isidro Valdéz Bello, Raquel Sánchez Ramírez, Karla Mayolo Deloisa, Jorge Benavides Lozano, Marco Rito Palomares, Gerardo García Rivas, Omar Lozano. Tecnológico de Monterrey, The Institute for Obesity Research, Monterrey

13:30 – 13:45 The excitation-contraction coupling is profoundly altered in ventricular cardiomyocytes of a novel model of HFpEF.
Abraham Méndez Fernández, Leandro A. Díaz Zegarra, Ángel E. Fernández, Felipe Salazar Ramírez, Alejandro E. Aiello, Gerardo García Rivas. Tecnológico de Monterrey, Institute for Obesity Research, Hospital Zambrano Hellion, TecSalud, Monterrey

13:45 – 14:00 Increased oxidative stress mediated by catecholamine-induced mitochondrial calcium overload leads to mitochondrial and cellular dysfunction, ultimately promoting arrhythmia generation.
Felipe Salazar Ramírez, Judith Bernal Ramírez, Luis A. Luévano Martínez, Christian Silva Platas, Gerardo García Rivas. Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey and Institute for Obesity Research. Hospital Zambrano-Hellion

14:00 – 16:00 **Lunch**

16:00 – 17:00 **Magistral Conference VII**

Mitochondria in malignant transformation to the acute lymphoblastic leukemia and their potential as a therapeutic target

Oxana Dobrovinskaya

Chair: Natalia Chiquete Félix
Instituto de Fisiología Celular, UNAM

17:00 – 18:00 **Oral Session IX**
Chair: Adriana Muhlia Almazán
Centro de Investigación en Alimentación y Desarrollo

17:00 – 17:15 Effect of metformin on the inhibition of complex I in the liver, brain, and heart of male and female rats.
Stefanie Paola López Cervantes, Diana Elisa Cruz Vilchis, Giovanni García Cruz, Mercedes Esparza Perusquía, and Oscar Flores Herrera. Laboratorio 3$^{6}/_{4}$, Depto. Bioquímica, Facultad de Medicina, UNAM

17:15 – 17:30 Histology of renal tumors, and analysis of the fatty acids composition of the tissue and its mitochondria.
Avendaño Briseño Karla Alejandra, Figueroa García María del Consuelo, and Mejía Zepeda Ricardo. Facultad de Estudios Superiores Iztacala. UNAM

17:30 – 17:45 Tamoxifen interacts with cyclophilin-D at the cyclosporine A-binding domain and sensitizes leukemic cells to cannabidiol.
Liliana Torres-López, Miguel Olivas-Aguirre, Igor Pottosin, Oxana Dobrovinskaya. Centro Universitario de Investigaciones Biomédicas, Universidad de Colima

17:45 – 18:00 B-NIPOx is a new drug effective in the chronic phase of experimental Chagas disease in mice.
Carlos Wong Baeza, Giovanna Berenice Barrera Aveleida, Anahi Sotelo Rodríguez, Edgar Iván Galarce Sosa, Jesús Elías Isidro Magallán, Claudia Albany Reséndiz Mora and María Isabel Baeza Ramírez. Laboratorios de Biomembranas y de Enzimología, Escuela Nacional de Ciencias Biológicas, IPN

18:00 – 18:30 **Coffee Break**

18:30 – 20:00 **Closing Ceremony**

20:30 – 1:30 **Dinner and Farewell Party**

CULTURAL CONFERENCE

La región Puebla-Tlaxcala en la época prehispánica. Breve desarrollo cultural

Hugo García Capistrán
Facultad de Filosofía y Letras
Universidad Nacional Autónoma de México

La gran área cultural llamada Mesoamérica ha sido dividida en diversas subáreas para su estudio. Una de estas subáreas es llamada el Altiplano Central mexicano, dicha subárea se compone de distintas regiones geográficas donde se desarrollaron varias sociedades prehispánicas: la Cuenca de México, espacio que albergó asentamientos importantes como Cuicuilco, Tlatilco, Tlapacoya, Teotihuacan y Tenochtitlan-Tlatelolco; por otro lado tenemos el valle de Morelos, donde también existieron varios sitios relevantes, como Chalcatzingo y Xochicalco; el Valle de Toluca, donde encontramos el sitio arqueológico de Teotenango, la antigua ciudad de Tollocan y otros asentamientos; los Valles del Mezquital y Tulancingo en Hidalgo, donde podemos encontrar varios ejemplos de sitios rupestres, así como la importante ciudad tolteca de Tula-Xicocotitla, por último el Valle de Puebla-Tlaxcala.

El Valle de Puebla-Tlaxcala, objeto de esta presentación, fue una importante región cuyas características fisiográficas permitieron el desarrollo de varios asentamientos prehispánicos que fueron protagonistas de la historia prehispánica. La conferencia presentará un desarrollo general de los principales asentamientos prehispánicos de la región, especialmente de los sitios de Tlalancaleca, Tetimpa, Cacaxtla-Xochitécatl, Cholula y Tlaxcala. El objetivo es brindar un panorama muy general de los desarrollos socio-culturales de las diferentes sociedades prehispánicas que se asentaron en esta región.

MAGISTRAL CONFERENCES

Biogenesis of mitochondrial respiratory complexes: an interplay between nuclear and mitochondrial genes.

Xochitl Pérez Martínez, Yolanda Camacho Villasana, Ulrik Pedroza Dávila, Aldo García Guerrero, Rodolfo García Villegas, Daniel Flores Mireles.

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Except for Complex II, all the respiratory complexes and the ATPase synthase have subunits encoded by nuclear and mitochondrial genes, while Complex II subunits are exclusively encoded in the nucleus. Coordination of mitochondrial and cytosolic subunits assembly, and addition of prosthetic groups is a highly regulated process that requires several subunit-specific factors, as well as general factors. In the present work we will present some of our recent understanding on how synthesis and assembly of subunits Cox1 (from Cytochrome *c* oxidase) and Cyt*b* (from bc_1 complex) occur in *Saccharomyces cerevisiae* mitochondria. We will discuss the role of the carboxyl terminal region of Cox1 and Cyt*b* on their own biogenesis and on cytochrome *c* oxidase, bc_1 complex and supercomplexes biogenesis. In addition, we will discuss how complex II assembly is downregulated by defects on the other respiratory complexes, even if all complex II subunits are imported from the cytosol.

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Keywords: Mitoribosome, yeast, respiratory complexes

Mechanisms and origins of egg-sperm fusion in plants, parasites and mammals

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Fusion between gametes is essential for sexual reproduction. It is widely accepted that sex is an ancient trait of eukaryotes and was probably present in their last common ancestor. Archaea (prokaryotes without nuclei) are the progenitors of the eukaryotic nucleocytoplasm and current evidence suggests that cell fusion probably originated in archaea. Indeed, sex-like exchange of genetic material via fusion is known to occur in archaea from the Dead and Mediterranean seas. These archaea can form cytoplasmic bridges visible by electron microscopy that then enable large-scale eukaryotic-like recombination. However, neither molecular nor cellular mechanisms of cell fusion have been described in archaea. A few types of protein machineries that are both necessary and sufficient to fuse eukaryotic cells (fusogens) have been identified and studied. Our lab discovered the first one, EFF-1 from *C. elegans,* that is now known to be a member of a diverse protein family. In eukaryotes, sexual reproduction depends on the GCS1(HAP2) plasma membrane protein that is necessary and sufficient for gamete fusion. GCS1 proteins from protists (both free-living and parasitic), plants and invertebrates are related to class II viral glycoproteins (e.g. from Zika and Dengue viruses) and have structural and functional similarity to fusion proteins from animals (e.g. EFF-1 and AFF-1 from *C. elegans*). We named this family of fusogens from gametes, enveloped viruses and somatic cells **Fusexins**: fusion proteins essential for sexual reproduction and exoplasmic merger of plasma membranes. More recently **we found fusexins in archaea and determined the crystal structure of the prokaryotic Fsx1. Moreover, Fsx1 can fuse heterologous mammalian cells demonstrating that they are fusogens. To understand the origin of eukaryotic sexual reproduction** we study the functions and evolutionary history of Fsx1 and we also found that the mouse sperm adhesion protein IZUMO1 is also a fusogen that is unrelated to fusexins. Thus, different families of fusogens can fuse gamete plasma membranes essential for sexual reproduction.

Small is beautiful: C2M2NF, a quantitative stoichiometric core model to study the rewiring of metabolism in proliferating cells.

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Keywords: Model of central carbon and nitrogen metabolism, Flux Balance Analysis, Glutamine, mitochondria, NADH reoxidation. One-carbon Metabolism. An average cancer cell.

Genome-scale models of metabolism (GEM) are now used to study how metabolism varies in different physiological conditions or environments. However, the great number of reactions involved in GEM makes it difficult to understand the results obtained in these studies. In order to have a more understandable tool, we developed a reduced metabolic model of central carbon and nitrogen metabolism, C2M2N with 77 reactions, 52 internal metabolites and 3 compartments, taking into account the actual stoichiometry of the reactions, including the stoichiometric role of the cofactors and the irreversibility of some reactions. In order to adequately model OXPHOS operation, the proton gradient through the inner mitochondrial membrane is represented by two pseudo-metabolites DPH (ΔpH) and DPSI ($\Delta\psi$).

To illustrate the interest of such a reduced model of metabolism in mammalian cell, we used Flux Balance Analysis (FBA), to systematically study all the possible fates of glutamine in central carbon metabolism. Glutamine is the most abundant amino acid in plasma and has long been recognize to be essential in the proliferation of most cells, particularly of cancer and immune cells.

Our analysis shows that glutamine can supply carbon sources for cell energy production (ATP synthesis) and can be used as a carbon and nitrogen sources to produce essential metabolites: nucleotides, amino acids and fatty acids. We give the maximal yield of these syntheses and compare them with the same yield on glucose as sole source of carbon.

In addition we study the sharing between glucose and glutamine for the formation of proliferating cell biomass according to ammonia microenvironment.

Our core model allowed us to clarify the mechanisms underlying the Warburg effect and the different metabolic phenotypes according to mutations in different respiratory complexes.

More recently, we incorporated in our model the one-carbon metabolism in cytosol and in mitochondria (C2M2NF with 100 reactions). With this model, we were able to demonstrate the importance of serine and glycine exchange of cancers cells with their environment.

In all our simulations, it clearly appears that the reoxidation of NADH is the great challenges of proliferating cells.

Work is now in progress in our group to develop different theoretical approaches with the same core model: calculations of the elementary flux

modes (EFMs), dynamical system of differential equations describing the variations of metabolites in the rewiring of metabolism, metabolic control analysis to detect the relevant therapeutic reactions, study of metabolic consortia etc.

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The H^+-transporting ATPases in plant cell plasma membranes, and their circumstance

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Plant cells have an electrochemical H^+ gradient across their plasma membranes due to the activity of plasma membrane H^+-transporting ATPases (PM H^+-ATPases). This gradient provides the energy for nutrient absorption in roots, cell expansion, stomata opening, etc. In this talk, we'll summarize the knowledge about the structure and kinetic mechanisms of these ATPases, as well as the control of their activity by phosphorylation and interactions with other proteins. In our laboratory, hundreds of proteins in beetroot (*Beta vulgaris*, Caryophyllales) plasma membrane were identified by mass spectrometry; two H^+-ATPase isoforms: PMA1 and PMA4, among the most abundant. These ATPases associate forming from dimers to very large (~70S) complexes. Other plasma membrane proteins could interact with PM H^+-ATPases including several protein kinases that could phosphorylate them thereby controlling their activities. However, no one protein appeared to form stable associations with these H^+-ATPases in all conditions. When beetroots were submitted to hypoxia by flooding, the sizes of H^+-ATPase protein complexes change. At present, we are studying the lipid composition of plasma membranes from flooded beetroots to correlate it with those changes. Finally, we are studying the possible roles of PM H^+-ATPases in the morphological responses to flooding of three *Amaranthus* species.

Membrane Allostery and Unique Hydrophobic Sites Promote Enzyme Substrate Specificity

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Lipidomics coupled with molecular dynamics reveal unique phospholipase A2 specificity toward membrane phospholipid substrates. We discovered unexpected headgroup and acyl-chain specificity for three major human phospholipases A2. The differences between each enzyme’s specificity, coupled with molecular dynamics- based structural and binding studies, revealed unique binding sites and interfacial surface binding moieties for each enzyme that explain the observed specificity at a hitherto inaccessible structural level. Surprisingly, we discovered that a unique hydrophobic binding site for the cleaved fatty acid dominates each enzyme’s specificity rather than its catalytic residues and polar headgroup binding site. Molecular dynamics simulations revealed the optimal phospholipid binding mode leading to a detailed understanding of the preference of cytosolic phospholipase A2 for cleavage of proinflammatory arachidonic acid, calcium-independent phospholipase A2, which is involved in membrane remodeling for cleavage of linoleic acid and for antibacterial secreted phospholipase A2 favoring linoleic acid, saturated fatty acids, and phosphatidylglycerol

Mitochondrial fusion proteins are a hub in phospholipid synthesis and metabolism

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The mitochondrial fusion protein Mitofusin 2 (Mfn2) plays a key role in the maintenance of normal mitochondrial metabolism and endoplasmic reticulum function. Here, we show that Mfn2 protects against liver disease. Our results show that hepatic Mfn2 is downregulated in non-alcoholic steatotic patients. Moreover, this downregulation is larger when the steatosis progress to Non-alcoholic steatohepatitis (NASH). To corroborate this data, a mouse model of lipid accumulation with high fat diet (HFD) was explored. Our results show a downregulation of Mfn2 levels in liver also in the mouse model. To go further and evaluate the levels of Mfn2 in NASH in mice, methionine-choline deficient diet (MCD) was assessed. The results showed lowest levels of Mfn2 in liver of MCD treated mice than in HFD treatment. Interestingly, liver-specific Mfn2 ablation in mice caused inflammation, fibrosis (NASH-like phenotype) that progress to liver cancer with age. Overall, the data presented here strongly suggests that Mfn2 constitutes a new target not only for liver cancer but for the treatment of NASH.

Mitochondria in malignant transformation to the acute lymphoblastic leukemia and their potential as a therapeutic target

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Acute lymphoblastic leukemia (ALL) comprises a heterogeneous group of hematologic malignancies, arising from diverse genetic alterations in the early lymphocyte development. ALL represents a public health problem in Mexico that requires new therapeutic strategies to improve existing protocols, combat chemoresistance and relapse. Malignant transformation is tightly linked to metabolic reprogramming, to support the increased energy request of continuously growing and proliferating tumor cells. Mitochondria, which exert central bioenergetic function in a healthy cell, is a key regulator of oncogenic metabolic reprogramming. This talk will focus on the role of mitochondria in leukemogenesis as well as in development of chemoresistance in ALL. First, mitochondria determine the bioenergetic profile of a leukemic cell through an interplay and flexible switch between aerobic glycolysis and mitochondrial oxidative phosphorylation (OXPHOS), ensuring therefore a rapid anabolism. Voltage-dependent anion channel (VDAC) in the outer mitochondrial membrane (OMM) is an important regulator of such plasticity. Next, leukemic cells possess a characteristic profile of proteins from the Bcl-2 family that interact specifically one with other and with VDAC. These interactions ensure a high metabolic rate and an antiapoptotic status of tumor cell. Mitochondria are main source of the reactive oxygen species (ROS) generation, which can activate some oncogenic signaling pathways. Finally, ATP and ROS production as well as survival/apoptosis balance are under the control of mitochondrial Ca^{2+} uptake. Accordingly, a novel class of anticancer compounds, named mitocans, which target mitochondria at distinct crucial points was developed. Our group has identified several small molecule compounds, which primarily target leukemic mitochondria. One is phenolic compound cannabidiol (CBD), no psychoactive cannabinoid, which rapidly enters the cell, bind to VDAC, turning it to the highly Ca^{2+} permeable “closed” state, provoking Ca^{2+} uptake mediated by mitochondrial Ca^{2+} uniporter MCU, mitochondrial Ca^{2+} overload, formation of stable mitochondrial permeability transition pore (mPTP,) enhanced ROS production and release of pro-apoptotic factors, culminating in cell death. ALL of T lineage (T-ALL) was the most sensitive to CBD among different types of tumors testing. Stromal bone marrow cells and resting T lymphocytes were resistant to CBD. Testing of natural phenolic compounds revealed two other molecules, curcumin and quercetin, which share the same mechanism with CBD, albeit with a lower affinity/potency, and displayed in addition the uncoupling activity. Notably, CBD demonstrated synergism with several conventional chemotherapeutic drugs, such as tamoxifen (TAM), dexamethasone (DEX), doxorubicin.

Interestingly, TAM sensitizes T-ALL to mitocans binding to cyclophilin D and arresting the formation of the mPTP. Recently, we have demonstrated that treatment of T-ALL with DEX caused metabolic reprogramming towards increased fatty acid oxidation (FAO) to overcome decreased glycolysis and glutaminolysis. Then targeting FAO as well as use of mitocans may represent the novel strategy to overcome glucocorticoid resistance in ALL.
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ORAL SESSIONS

Insights into the cooperation of NAC and RAC as part of the mitochondrial protein import mechanism

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Around 99% of mitochondrial proteins are synthesized in cytosolic ribosomes and then imported into mitochondria through a process called mitochondrial import. It has been shown that the NAC complex (Nascent Polypeptide-Associated Complex) participates in early stages of mitochondrial import by physically associating with the ribosome exit tunnel. In Saccharomyces cerevisiae, there are two genes encoding two β-NAC subunits (β1-NAC and β2-NAC) due to a genomic duplication event. As a result, in yeast both NAC heterodimers (αβ1-NAC and αβ2-NAC) interact with mitochondrial outer membrane proteins and influence the import of specific mitochondrial substrates.
Yet, despite the role of the NAC complex in mitochondrial import, the phenotypic effects of NAC absence in yeast are barely detectable, which suggests the existence of compensatory mechanisms. One such compensatory system may be the Ribosome-Associated Complex (RAC), which involves a system based on Hsp70 chaperones (Ssz1, Zuo1, Ssb1, and Ssb2). RAC may operate in conjunction with NAC to facilitate the transfer of mitochondrial proteins from the cytosol to mitochondria as it has been shown that Hsp70 chaperones can interact with Tetratricopeptide Repeat (TPR)-rich mitochondrial outer membrane receptors like Tom20, Tom70, and Tom71.
So far, we have found that the elimination of elements from NAC or RAC has differential effects on cell physiology: while the absence of NAC triggers the activation of the mitochondrial retrograde response pathway, the removal of the Ssb1/2 chaperones from RAC possibly induces the activation of general proteostasis mechanisms dependent on the TORC1 complex. Additionally, we have observed differential sensitivity to endoplasmic reticulum stress and variations in the utilization of respiratory carbon sources like ethanol. Finally, we identified a differential impact on the import of mitochondrial proteins such as Sod2.

The mitochondrial uncoupling proteins from the cannonball jellyfish and the effect of temperature on their genes expression

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Mitochondrial uncoupling proteins (UCPs) are involved in properly functioning of the electron transport chain, thermogenesis, and protection against reactive oxygen species. Because of their crucial role, they are widely distributed through the eukaryotic tree of life. In the animal kingdom, there is strong evidence of five UCPs (UCP1 to UCP5), all with records in vertebrates, but only two were reported in invertebrates (UCP4 and UCP5). Therefore, scarce information exists about those ancestral non-bilaterian animals, such as the cannonball jellyfish (*Stomolophus* sp. 2) that have shown interesting bioenergetic abilities allowing them to conquer the ocean facing global warming. The study aimed to understand these animals' diversity and function for the first time. The results indicate that *Stomolophus* sp. 2 possesses three UCPs: UCP4, UCP5, and a novel UCP (hereinafter referred to as UCPcn). The jellyfish transcripts and deduced proteins show the conserved characteristics of the mitochondrial anion carriers family; the obtained phylogenetic tree shows that the UCPs from *Stomolophus* sp. 2 groups in two major monophyletic clades, one including UCP4 and UCP5, and the other clustering UCPcn with those mainly mammalian representatives UCP1 to UCP3.
The relative quantification of mRNA levels was addressed at different temperatures, and results indicate that UCP4 presented the highest expression levels, followed by UCPcn and UCP5, and all UCP transcripts show lower expression at 33 °C. The results support the hypothesis that UCPs are less diverse in invertebrates than in vertebrates; this suggests an early origin of UCP4 and UCP5 and a recent origin of the exclusive vertebrate UCPs and UCPcn. Moreover, discovering the UCPcn and unveiling its close phylogenetic relationship to vertebrate UCPs1-3 could indicate that UCPcn has a similar function to that of UCP1-3. Furthermore, the information on mRNA expression level is a basis for future research on the UCPs functions, including non-thermogenic roles in ectothermic animals.

Unraveling the Interaction Mechanism between the ATPase and its Central Stalk in the Type III Secretion System of enteropathogenic *Escherichia coli*

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Type III secretion systems (T3SSs) are essential interaction mediators between multiple bacterial pathogens (such as *Salmonella*, *Pseudomonas*, and enteropathogenic *E. coli*: EPEC) and host cells. Injectisomes or virulence T3SSs, allow bacteria to inject effector proteins directly into the cytoplasm of the host cell. EPEC injects these proteins to subvert host cell signaling pathways for its benefit. The injectisome is a nanomolecular machine consisting of more than 20 proteins. The components of this complex structure are grouped in extracellular appendages, basal body and cytoplasmic components. Among the cytoplasmic components are those that constitute the ATPase complex. The EscN protein is the catalytic subunit, which is required to unfold and target substrates for secretion, and forms the ATPase complex together with EscL and EscO. EscL forms a peripheral stalk and negatively regulates the ATPase activity of EscN. In contrast, EscO forms the central stalk and stimulates the ATPase enzymatic activity of EscN. ATP hydrolysis by the EscN-EscO complex is predicted to activate the conversion of the proton motive force into protein export, through an interaction between EscO and the export gate component EscV. However, the molecular mechanisms leading to central stalk ATPase-mediated activation of the T3SS are not fully understood.

In this work, we undertook a bioinformatics analysis of the ATPase EscN and the central stalk EscO complex. Accordingly, we found two interaction regions of EscO in its N-terminal domain (NTD) and C-terminal domain (CTD) with the CTD of EscN. Using a type III protein secretion assay and yeast two-hybrid experiments, we evaluated the importance of these domains in the interaction between these proteins and the activation of the ATPase activity for protein secretion.

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Characterization of genetic factors that promote the allotopic expression of the yeast mitochondrial *cox2* gene

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Subunit 2 (Cox2) of cytochrome c oxidase (C*c*O) was allotopically expressed in the yeast *Saccharomyces cerevisiae* (Supekova et al., 2010). The recombinant Cox2 protein contains, in order, a mitochondrial targeting sequence (MTS) derived from the integral membrane protein Oxa1; a leader peptide (LP) required for its integration into the inner membrane, two highly hydrophobic transmembrane domains (TMS1 and TMS2), and a long hydrophilic C-terminal domain. The presence of a W56R point mutation in TMS1 is necessary to reduce its overall hydrophobicity of the membrane domain and allow the import of Cox2 into mitochondria. Upon entering the mitochondria, the precursor is proteolytically matured, incorporated into the inner mitochondrial membrane (IMM) and functionally assembled in C*c*O. The Cox2W56R precursor restores the growth of a *Δcox2* null mutant on non-fermentable carbon sources up to 60% of the wild-type strain (Cruz-Torres et al., 2012). In this work, using strains expressing Cox2W56R integrated into the nucleus (low copy number), or from a 2μ plasmid (high copy number) we aimed to investigate if the deletion or overexpression of specific genes could enhance the import of allotopic Cox2 into mitochondria, thereby facilitating the growth of the null mutant in respiratory media. Our experimental strategy involved three approaches, with one dedicated to studying Mgr2, a quality control factor that modulates the sorting of precursor proteins based on their hydrophobicity during translocation through the inner membrane complex TIM23 (Gebert et al., 2012). When the *COX2W56R* gene was expressed in the absence of *MGR2*, Cox2W56R levels were decreased. Contrary to our expectations, overexpressing *MGR2* from a multicopy plasmid, also decreased the levels of mature Cox2W56R. These findings led us to conclude that the stoichiometry of Mgr2 is crucial for TIM23 function, and its absence alters the import of hydrophobic precursors. We also conclude that the allotopic protein Cox2W56R is imported through the TIM23 translocation complex, in a process that involves the interplay of both of its functional sub-complexes: $TIM23^{MOTOR}$ (without Mgr2) and $TIM23^{SORT}$ (with Mgr2). We propose a model for the biogenesis of Cox2W56R, where the concerted action of $TIM23^{MOTOR}$ and $TIM23^{SORT}$ are essential for the correct ordering of the TMS1 and TMS2 transmembrane stretches of Cox2W56R respectively, allowing the protein to reach the same final functional topology that is attained by orthodox Cox2 synthesized inside mitochondria. Moreover, Mgr2 plays a critical role in the lateral release of TMS2 within the inner mitochondrial membrane (IMM), leading to the subsequent exposure of the C-terminal hydrophilic domain in the mitochondrial intermembrane space (IMS). The final topology facilitates the proper insertion of the enzyme's CuA binuclear center.

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The *Killer* system of *Saccharomyces cerevisiae* reveals strengths and weaknesses in the interaction with *Pseudomonas aeruginosa*: battle at the plasma membrane

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Abstract:
P. aeruginosa is a pathogenic microorganism and main agent of nosocomial infections with high morbidity and mortality rate in patients with cystic fibrosis and immunocompromised patients; this bacterium has a genome of approximately 5.5 - 7 Mbps, which allows the bacterium to develop a great metabolic versatility, wide adaptability to environmental changes and a large arsenal of resistance mechanisms (Pang et al., 2019). Very little research has been conducted on the competition that *S. cerevisiae* has with *P. aeruginosa*, and it has been studied with different approaches and methodologies. Zahra Dehghan Zadeh in 2021 reported that *S. cerevisiae* S3 can inhibit the expression of some virulence factors of *P.* aeruginosa strain PAO1, specifically the *apl* (alkaline protease) and *lasB* (elastase) genes being affected (Dehghanzadeh et al., 2021). On the other hand, Rafat Zrieq in 2015 by means of a genome screen of *P. aeruginosa* strain PA14, identified effector proteins that alter some cellular processes of *S. cerevisiae*, impairing its growth (Zrieq et al., 2015). Our research focuses on studying how two different strains of *P. aeruginosa* are affected by the *K*1 toxin produced by *S. cerevisiae Killer*. In parallel, we also studied the effect of cytotoxic metabolites produced by the two *P. aeruginosa* strains on *K*1 toxin-producing *S. cerevisiae* and non-*K*1 toxin-producing *S. cerevisiae*. Using the cytotoxic metabolites secreted by the yeast and the bacteria in their culture medium, we evaluated how these affect the growth of both microorganisms, developing an antagonistic effect or stimulation of the same growth. The experiments were performed in different culture media and with two strains of *P. aeruginosa* to determine if the environment where the cytotoxic competition develops and the metabolic and genetic capabilities of both microorganisms can develop differences in their competition, being benefited or affected by one of them. Our results open the panorama to new lines of research that can help to understand the mechanism of action that *K*1 has on *P. aeruginosa* and the metabolites secreted by *P. aeruginosa* on *S. cerevisiae*; identifying molecular targets and cellular processes that activate or inhibit the expression of genes in these microorganisms and how this affects or benefits the pathogenicity and resistance processes of *P. aeruginosa* (Uribe López JA., 2023). The main objective is to consider new alternative strategies to the use of antibiotics and bactericides already considered resistant to *P. aeruginosa*.

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Culture optimization and mitochondrial complex I characterization from the diatom *Phaeodactylum tricornutum*

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Mitochondrial NADH:ubiquinol oxidoreductase is the larger membrane complex involved in the respiratory chain. Structurally, this enzyme can be described as two large domains, one embedded in the membrane, involved in proton translocation, while the second domain protrudes from the membrane and it is involved in the electron transfer process. Historically, the mitochondrial complex I from two model organisms, *Bos taurus* and *Yarrowia lipolytica* has been studied and characterized in detail giving a slightly similar shape, however, with the recent inclusion of other organisms like *Polytomella sp* [1], *Arabidopsis thaliana* [1], and *Euglena gracilis* [2], divergent structures with extra domains have been described.
Diatoms are an important group of organisms with a major role in ecological and biotechnological fields. The contribution as primary producers of this group of organisms is equivalent to the one of all the rainforests in the planet. An important cooperation between the two major energetic routes, *i.e.* mitochondrial respiration and photosynthesis, has been characterized [3], nevertheless, no detail description of the composition of the any complex involved in the oxidative phosphorylation system has been described so far. In the present work we showed the optimization of the *Phaeodactylum tricornutum* culture in laboratory conditions and the purification and characterization of the mitochondrial complex I from this species.
P. tricornutum was cultured in ESAW medium in an Antares I photobioreactor with 12:12 photoperiod using green-enriched light [4], and total membranes were prepared. Mitochondrial complex I was extracted with N-dodecyl-beta maltoside and purified using two steps of liquid chromatography followed by native electrophoresis. The polypeptide composition was solved using a 3D gel system [2], and the identification of the different subunits was made by LC-ESI-Q-TOF-MS quantitative analysis. Our results showed a smaller functional complex compared with other organisms with the presence of several linage-specific subunits.

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Optimization of paramylon production in *Euglena gracilis* using different light spectra

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The carbohydrate β-1,3-glucan, also known as paramylon, is the reserve carbohydrate present in Euglenozoa group. This compound consists in a D-glucose polymer and has relevant importance in pharmaceutical and biotechnological fields. Several applications have been described so far: obesity treatment when it is used as insoluble fiber [1], healing coadjuvant in acute liver injury [2], antimicrobial activity and immune system stimulation [3]. *Euglena gracilis* is known by its diverse metabolic capacity that allows it to grow autotrophically, heterotrophically and photo-heterotrophically using a large number of organic substrates, *e.g.* acetate, ethanol, pyruvate, propionate, lactate, succinate, glutamate and glucose. Paramylon production in this species can be as far as 80% of the total dry mass [4].
In the present work, we are focused on autotrophically paramylon production in *E. gracilis* by the adaptation of its photosynthetic machinery using several specific wavelengths: 400nm, 440nm, 469nm, 520nm, 635nm, 730nm and 850nm, as well as, complete spectrum lights: 30 000K, 10 000K, "full-spectrum", warn and cold light. The organism was grown on tris-phophate minimum medium (TMP) supplemented with a mix of vitamins (biotin 10^{-7}%, B12 vitamin 10^{-7}%, and B1 vitamin 2×10^{-5}% (w/v)). Our results show a huge increase of paramylon production with far-red (720-730nm) adapted cells compared to white cold light [5].

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Complex I inhibition by metformin in rat kidney mitocondria depending on sex

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Metformin (MTF) is a first-line treatment for diabetes type 2 due to its safety and low cost. Lots of people use metformin all around the world and yet there are still many questions about its mechanism of action. In the early 2000s, specific inhibition of mitochondrial complex I by metformin was proposed (Szymczak *et al.,* 2022), suggesting that the inhibition of NADH oxidation blocks the electron input to the respiratory chain, decreasing the ATP:ADP and ATP:AMP ratios, which activates AMPK cell signaling. However, the IC_{50} for isolated complex I inhibition by MTF was about 20 mM (Vial *et al.*, 2019), but its plasmatic and tissue concentration is around 10 and 40 μM, respectively (He *et al.*, 2015). Interestingly, MTF is dispensed in men and women in different treatment concentrations (de Vries *et al.,* 2020). Our work team was curious about these observations and decided to study the effect of MTF on the mitochondrial function of the kidney, the organ involved in the elimination of this drug. We isolated kidney mitochondria from both male and female Wistar rats of approximately 250 g to evaluate complex I inhibition using different concentrations of MTF. As a first approximation, the mitochondrial oxygen consumption was determined. Respiration of female kidney mitochondria was inhibited by MTF at the micromolar range with an IC_{50} = 40 μM, while males need a more elevated concentration of the drug to inhibit complex I. This result indicates three conclusions: 1) the IC_{50} for complex I inhibition determined in this work was in the range of concentration determined in the kidney; 2) the function of complex I integrated into mitochondria is quite different to isolated complex I; and 3) female mitochondria were more sensible to inhibition with MTF than male mitochondria. This is the first observation about the role of sex in the MTF inhibition of complex I, which could be the answer to different clinical treatments used in women and men.

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ATP synthase as a pharmacological and antimicrobial target

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In addition to its classical role in ATP production within the mitochondria, ATP synthase located in plasma membranes plays a crucial role in regulating multiple physiological processes, including lipid metabolism, cell differentiation, survival, and proliferation, and pH regulation. Consequently, malfunction of this enzyme has been implicated in the development and establishment of various diseases in humans. Moreover, the emergence of antibiotic resistance has led to ATP synthase becoming an increasingly important pharmacological target by undermining bacterial bioenergetics. Notably, a specific antibiotic has been developed to combat *Mycobacterium tuberculosis* by targeting ATP synthase. Despite its potential as a therapeutic target for various diseases and infections, the pharmacological potential of ATP synthase remains largely unexplored. In modern medicine, the identification and validation of new therapeutic targets are essential to address diseases that lack effective cures or have treatments with significant side effects. Unlike drugs that target protein active sites (which constitute about 99.5% of those approved for clinical use), allosteric-type drugs bind to less-conserved pockets, enabling more selective modulation of the desired targets. Allosteric sites lacking endogenous binders (non-functional allosteric sites) are particularly attractive as they require less binding power than drugs targeting functional allosteric or orthosteric sites. The existence of a wide variety of endogenous and exogenous inhibitors that bind to transiently formed sites during the enzyme's catalytic cycle presents a valuable opportunity for the development of species-specific drugs. In this study, we present an in-silico characterization of the inhibitor-binding energy and stereochemical properties of these sites. By doing so, we hope to contribute to the field of combating antibiotic resistance and addressing the challenges posed by multidrug-resistant microorganisms and to the treatment of human diseases in which ATP synthase is involved. Using information derived from molecular dynamics simulations and methods based on machine learning and simulated evolution, we have successfully engineered innovative lead molecules. These compounds include both drug and peptide-type agents that demonstrate a remarkable ability to inhibit the catalytic activity of ATP synthase from *Escherichia coli*, an ESKAPEE microorganism (Ruiz-Blanco et al., 2021; Avila-Barrientos et al., 2022; Cofas-Vargas et al., 2022).

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Development of species-specific light harvesting complexes in *Euglena gracilis*

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Oxygenic photosynthesis converts sunlight energy into chemical energy sustaining directly or indirectly most life on Earth. Photochemical reactions of oxygenic photosynthesis occur in two membrane-embedded complexes, Photosystem II (PSII) and I (PSI). Each one comprises a core complex, including a reaction center and structural subunits, together with an inner antenna. Both photosystems process different wavelengths and cooperate during photosynthesis. Excess of light induces damage mainly to PSII. Still, PSI is also subject to photoinhibition, particularly at low temperature. Because of these reasons, photosynthetic organisms must find equilibrium between collecting enough photons under low light conditions and avoiding photodamage at high light. In green plants, one of the developed mechanisms for light adaptation is the presence of “red” or “low energy” chlorophylls, connected to photosystem I while photoprotection driven by thermal dissipation of absorbed light.

Euglena gracilis, a secondary green flagellate, possesses a chloroplast acquired through a secondary endosymbiosis with green algae, by this reason an additional third chloroplast envelope membrane is present, however their thylakoid membranes do not associate in stacking form as grana regions as in primary plastids. Differences in spectral properties with light condition have been described [1,2] probably mediated by a common antenna system used by both photosystems consisting of LHCA and LHCII proteins [2,3]. *Euglena* LHCs can be arranged into 8 groups of LHCBM (I-VIII) that are related to various LHCII sequences of primary green eukaryotes. In contrast, all so-called LHCA proteins of *Euglena* form a cluster group within the LHCII tree[4,5]. *Euglena* contains the xanthophyll cycle pigments, diadinoxanthin and diatoxanthin, but neither lutein, fucoxanthin nor pigments of the violaxanthin cycle are present, while the amount of chlorophyll *b* relative to chlorophyll *a* is relatively low [6].

Here, combining phylogenetic, biochemical, structural, and functional studies, we reveal that *Euglena gracilis,* exhibits consistent low- and far-red-light adaptations. We demonstrate that thermal dissipation ability has been lost, while a red-shifted chlorophyll *a*-containing LHCE antenna complex is abundant in light-limiting growth conditions. Sixty years after the first observation of changes in spectral properties of *E. gracilis* cells in function of light in culture [1], we therefore identified the antenna complex responsible for it. Finally, this unique LHCE complex, and not the classical $LHCII_3$ antenna, is involved in the state transition mechanism around PSII as an adaptation against light changes in this organism.

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The translational activator Mss51 has conserved function in different yeast species

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The mitochondrial mRNAs in yeast lack a Shine-Dalgarno sequence to assist the mitoribosome in locating the *AUG* start codon. Instead, mitochondrial mRNAs have long 5' untranslated regions (5'-UTR) where translational activators act to direct the mitoribosome to the *AUG* codon. Each mitochondrial gene contains its specific set of translational activators that physically interact with the 5'-UTR and with the mitoribosome. (Fox *et al* 1990, Ott *et al* 2016).

Cytochrome *c* oxidase (C*c*O) contains three mitochondrial encoded subunits Cox1, Cox2 and Cox3 which form the catalytic core of the enzyme. Cox1 is the largest subunit of the C*c*O, and it is an essential subunit of the catalytic core and for the C*c*O assembly. Mss51, along with other nuclear factors, promotes *COX1* mRNA translation at the level of initiation and probably elongation (Perez-Martínez *et al* 2003). In addition, it interacts with the Cox1 C-terminal region, and this interaction is essential for the first assembly steps of the C*c*O (Shingú-Vázquez *et al* 2010, Garcia-Villegas *et al* 2017). Thus, Mss51 has translational activator and chaperone functions to coordinate the synthesis and assembly of Cox1 (Pérez-Martínez et al, 2003, Shingú-Vázquez 2010, García-Villegas et al 2017).

In order to gain new insights into Mss51 function, we studied the chaperone and translational activator function were conserved in orthologues from other yeast species. Therefore, we cloned in a yeast expression vector five *MSS51* gene orthologues to evaluate if they were able to complement and rescue the respiratory phenotype of a *mss51Δ* mutant in *S. cerevisiae* cells. We used the mitochondrial reporter *ARG8*^{m} inserted at the *COX1* locus (Perez-Martínez et al 2003) to test the capacity of the Mss51 orthologues to complement the chaperone and the translation activities. We found that the *K. lactis* and *C. glabrata* orthologues complemented both activities, while in *Y. lipolytica* and *D. hansenii* orthologues were able to just rescue the chaperone activity. We conclude that not all yeast Mss51 orthologues have a dual function on Cox1 biogenesis, but the chaperone activity seems to be a constant in most species. Based on our findings, we aim to study which domains are necessary for chaperone or for translational activator functions by using a phylogenetic approach.

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Novel insights in the production of the *Killer* toxin *K*1 in *Saccharomyces cerevisiae*: a relation in volume regulation

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The *Killer* phenotype of *Saccharomyces cerevisiae* is characterized by the production of a toxin capable of inhibiting the growth of sensitive strains that do not produce it[1]. This symbiotic system between two dsRNA viruses and yeast has been known for the last decades, in which knowledge has been generated about its origin, mechanisms of action and the different variables that affect the system, among which stand out: the type of protein Killer, pH, temperature, the relationship between the producing strain and the sensitive strain, as well as the culture media and inducing media[2]. Another of the best-studied cellular processes in *S. cerevisiae* is its adaptation to osmotic changes and its regulation of cell volume through the HOG signaling pathway, which is characterized by generating the cellular response to hyperosmotic stress activating the transcription of associated genes, cell cycle arrest, conformational changes in the chromatin and, in general, different steps of the transcriptional process[3]. In this study, the production of the *Killer* *K*1 toxin of the 42300 strain[4] was evaluated under the effect of osmotic shock (1 M KCl) and the volume regulation capacity during it, using a new inducing medium with a high Fe^{+3} concentration[5]. The results indicate that during the osmotic shock event and high Fe^{+3} concentrations, the production of the *Killer* toxin is enhanced while a change in the edition of the mRNA encoding the *K*1 toxin is caused. Taking all this into account, it has been possible to obtain a greater production of the *Killer* toxin at different times of the study.

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Conformational changes on the estrogen-related receptor followed by GaMD

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Abstract
The estrogen-related receptor (ESRRA) is one member of the superfamily of orphan nuclear receptors. It is a protein of 423 residues (Uniprot P11474) that shares a general structure common to these receptors: a N-terminus domain, a DNA-binding domain (DBD), a hinge and a ligand binding domain (LBD). ESRA is the most abundant member of this family in terms of protein expression. It has a known role in the regulation of the energetic metabolism in several cell types.
In the current work, we will focus on the LBD domain, specifically, its conformation in the absence and presence of ligands. ESRRA is known for not requiring a ligand to actívate gene expression. That is, it is constitutively active. Our aim is to understand the mechanisms that keep it in an active state, in an agonistics state so we can identify ligands with an antagonistic or reverse agonist effect. We will employ in silico methods such as molecular dynamics and gaussian accelerated molecular dynamics.

Keywords: molecular dynamics, conformational changes, drug design

Material and methods.
XRD structures 2PJL and 1XB& were used. Prior molecular dynamics, ions, ligands and wáter molecules were removed. Hydrogens and charges were added using tleap from the Amber22 suite. We employed the ffS19B forcefield for the proteins. Ligans structure and charges were optimized using ab initio quantum mechanics with Gaussian at the B3LYP/6-311g* level. For the simulations, the qm results were processed to fit gaff2.

The water model used is OPC. Gaussian accelerated molecular dynamics with dua boost were ran for 1 microsecond in triplicates. Normal molecular dynamics were ran for 500 ns

Results.
Our results show that in normal molecular mechanics, the empty binding site of 2PJL remains stable. Under GaMD the site collapses, showing a transition to the empty forn (1XB7). The carboxyl-terminus remains stable suggesting the binding to regulatory peptides is an induced fit mechanism.
Empty strucutres of the 1XB7 remain stable during the simulations, not showing any change associated with binding. As for regulatory peptides, an induced fit mechanism may be at play.
Ligand binding energetics is similar under both types of simulation suggesting the conformational changes due to ligands are stable.

Analysis of the transit peptides of the proteins whose final destiny are the colorless plastids of the chlorophycean alga *Polytomella parva.*

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During evolution, some plants and algae have lost the capacity to carry out photosynthesis. The chlorophycean alga *Polytomella parva* lost its photosynthetic machinery and adapted a heterotrophic lifestyle. Thus. *P. parva* now exhibits colorless plastids that are metabolically active, exhibiting synthesis of starch, lipids, and amino acids. The transcriptome of the colorless alga has revealed the presence of orthologs of the chloroplast TIC-TOC import machinery, indicating the presence of protein import components in these plastids. In addition, *P. parva* is unique in the sense that it lacks a plastid genome. Therefore, it has been suggested that all the proteins present in the algal colorless plastids must be synthesized in the cytosol and internalized into the plastid.
Transit peptides (TPs) are present in several proteins that are destined to be imported into organelles. These amino acid sequences are localized in the N-termini of the precursor proteins and are recognized by the protein translocation machineries present in each organelle. Although no consensus sequences have been identified in TPs, they do contain some defined biochemical characteristics that allow them to direct the precursors to specific cell targets.
Here, we characterized the TPs of precursors targeted to the colorless plastids of *P. parva* (Fuentes-Ramírez y col., 2021). Several *in silico* analyzes were carried out, using bioinformatic tools of public domain. We found that the TPs of *P. parva* are like the chloroplast targeting peptides (cTPs) of the green alga *C. reinhardtii,* a photosynthetic close relative of *Polytomella*. The TPs exhibit similar characteristics in structure, size, and processing sites. Nevertheless, they show differences in their preference towards basic residues, exhibiting more lysines in Polytomella and more arginines in Chlamydomonas. The sequence of the TP´s from 73 proteins that belong to the *P. parva* colorless plastid were identified using different algorithms. The predicted processing sites match many of the ones found in the green alga, some of which have been experimentally verified.

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Mitochondrial morphology transition assessment in *Arabidopsis thaliana*

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Abstract

Mitochondria are energy-producing reactors in eucaryotic organisms. These organelles have several roles in metabolism and cell death. For example, during environmental stressors such as heat shock or calcium overload, a mitochondrial permeability transition pore (PTP) opens causing cell death. Various reports have shown that PTP opening collapses ion gradients across inner mitochondrial membranes in mammalian mitochondria. However, less is known about the occurrence of PTPs in plants. Some authors have proposed that a Mitochondrial Morphology Transition (MMT) can be an *in vivo* indicator of PTP opening. Here we establish a potential link between PTP and MMT through mitochondrial stress assays in the model organism *Arabidopsis thaliana* expressing a mitochondrially targeted GFP. Our results show calcium ions, benzodiazepine analogues and cyclosporin A can regulate PTP-MMT.

Exploring Slm35 and Atg32 functions in mitophagy and oxidative stress response in *Saccharomyces cerevisiae*

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Mitophagy is a process involving selective mitochondrial degradation modulated in yeast by the specific receptor protein Atg32. Despite the large amount of data regarding the relevance of Atg32 and its essentiality for mitophagy, little is known on the molecular signals that trigger the initiation of the process. In this work, we focus on the relevance of oxidative stress for mitophagy. In addition to Atg32, our work is centered in the mutant protein Slm35, a mitochondrial protein previously identified as a negative regulator of mitophagy. A mutant lacking *SLM35* gene, exhibits increased mitophagic flux and higher resistance to oxidative stress compared to the wild-type strain, suggesting a potential correlation between mitophagy and oxidative stress resistance. To further understand this, we evaluated a GFP-tagged version of Slm35 during the stationary phase with glucose as a carbon source and under oxidative stress conditions where Slm35 showed elevated protein levels. In contrast, reduced Slm35-GFP levels were observed in respiratory carbon sources like lactate or synthetic medium without amino acids, associated with mitophagy. However, the increased mitophagy in this mutant seems independent of Atg32 editing by the mitochondrial protease Yme1, a step previously reported as a requisite for Atg32 activation and mitophagy initiation.

In contrast, in a *Δatg32* mutant which lacks mitophagic flux, no resistance or sensitivity to oxidizing agents was observed. However, work from other groups reported that treatment with the antioxidant N-acetylcysteine (NAC) reduced mitophagic flux in yeast, indicating a precise regulation likely mediated by reversible and specific oxidation of cysteine thiol groups in proteins. Following this idea, we generated Atg32 variants where each cysteine was replaced by alanine. It was surprising that the absence of C288 resulted in significantly reduced mitophagic flux under prolonged respiratory growth and nitrogen starvation. This emphasizes the importance of C288 in Atg32 for complete mitophagy induction and supports a redox regulation mechanism for this process.

Identification of the critical residues of the ζ subunit as inhibitor of the F_1F_O-ATPase of Paracoccus denitrificans at its very N-terminus and globular domains

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The ζ subunit is the main natural regulatory factor of the ATP synthase of *Paracoccus denitrificans* and related α-proteobacteria. Its major role as inhibitor of the F_1FO-ATPase was demonstrated by a null PdΔζ mutant in which the ζ gene was replaced by an antibiotic (kanamycin) resistance gene [1]. The PdΔζ mutant showed a severe delay in growth in respiratory media where all the cellular ATP comes from the ATP synthase. Besides this ζ knockout, other ζ mutants constructed in our laboratory has been some N-terminal deletion mutants in which we demonstrated that the inhibitory domain of the ζ subunit is located in the first 14 N-terminal residues, since genetic removal of these 14 aa residues eliminated completely the inhibitory function of ζ, while preserving its binding to the PdF_1-ATPase [2]. This 14-residues inhibitory N-terminus was confirmed as the inhibitory domain of ζ by model building and docking analysis [3] and by crystallographic resolution of this N-terminal inhibitory domain of ζ bound to the full PdF_1FO-ATP synthase of P. d*enitrificans* [4]. This ζ N-terminus therefore undergoes an important transition from an Intrinsically Disordered Protein Region (IDPr) observed in the soluble structure of Pd-ζ (PDB_id 2LL0) to an ordered inhibitory ζ-helix (PDB_id 5DN6). Although we knew that the inhibitory domain of ζ is within its fist 14 N-terminal residues, we ignored if the critical inhibitory domain of ζ could be even shorter than these 14 residues and limited to a few N-terminus ones. We also wished to identify other key residues of ζ outside this inhibitory N-terminus that are more or less preserved in the globular domain of the ζ protein family, and that are likely involved in a low affinity ADP/ATP binding site, according to our latest docking and molecular dynamics studies. We therefore carried out site-directed mutagenesis to remove the first 4 and 8 N-terminal residues of Pd-ζ and to make single site mutants of alanine scanning in order to identify the critical residues of the very N-terminus and globular domains of the ζ subunit. This was carried out by PCR mutagenesis in the case of the N-terminal mutants, and by quickchange PCR in the case of the central domain mutants. The functional results of these mutants, after their respective overexpression, purification, and reconstitution into the PdF_1-ATPase lacking its endogenous ζ subunit, showed that the main inhibitory aminoacids are limited the first 4 aminoacid residues, making this the first F-ATPase inhibitor with the first 4 N-terminus residues as the main inhibitory domain. Besides, we identified another key residue in the globular domain that is important for inhibition, but since it is not in the N-terminus, but in the globular domain, it is likely to modify the ζ ATP/ADP binding site affinity and thus affecting the inhibitory function of ζ indirectly. The important novel functional and structural implications of these mutants for the control of the ATP synthase of P. *denitrificans* and other α-preotobacteria by the ζ subunit are discussed.

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The ancient respirasome

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Paracoccus denitrificans, an α-proteobacteria, resembles more closely a mitochondrion than other bacteria do. A feasible evolutionary transition from the plasma membrane of an ancestral aerobic bacterium resembling *P. denitrificans* to the mitochondrial membrane have been suggested (John *et al.,* 1975). The Electron Transport Chain of *P. denitrificans* is constituted by the NADH-Q oxidoreductase (complex I), the succinate-Q oxidoreductase (complex II), the QH_2-cytochrome c oxidoreductase (complex III), and the cytochrome c oxidase (complex IV); all of them are embedded in its plasma membrane with their catalytic regions oriented to the cytoplasm (John *et al.,* 1977). Because these complexes are constituted by a few polypeptide chains, are considered as a simplified version of those present in eukaryotes; however, can use NADH or succinate as high-potential electron donors to carry out the proton-motive force (Δp), which is used by F_1F_O-ATP synthase to produce ATP. In our laboratory we are interested in the study of supercomplexes, particularly the respirasome which is constituted by the complexes I, III_2, and IV, oxidize NADH and reduce oxygen. There is a stable interaction between these complexes and the inhibition of complex III_2 or IV avoid NADH oxidation by complex I, even if coenzyme Q or cytochrome c are added, indicating a functional intercommunication among them. To get inside in the functional history of the respirasome, we decide to study the respirasome of *P. denitrificans*, the ancient respirasome. The PD1222 strain of *P. denitrificans* was grown and plasma membrane vesicles were isolated as described by Morales-Ríos *et al.,* 2010. Respirasome and free complex I were solubilized with digitonin and isolated as described by our group (Reyes-Galindo *et al.,* 2019). The activities of complex I and IV from *P. denitrificans* respirasome was located at upper zone of the BN-PAGE gel (3.5 - 7.25% acrylamide), showing a higher molecular weight than respirasome from bovine heart mitochondria. The NADH dehydrogenase activity from the *P. denitrificans* respirasome was inhibited separately by rotenone, antimycin A, or cyanide, suggesting that this “megacomplex” showed a similar functional intercommunication among complex I, III_2, and IV as observed in *Ustilago maydis* respirasome (Reyes-Galindo *et al.,* 2019).

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Kinetic characterization of respirasomes from Yarrowia lipolytica

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Abstract:
Inside the internal mitochondrial membrane, the respiratory complexes could associate into structures called "supercomplexes". Respirasomes are a type of supercomplexes constituted by complexes I, III2, and IV and have the capacity of oxidized the NADH and transfer electrons to oxygen, reducing it into water. Simultaneously to electron flux, respirasome translocates protons from the matrix to the intermembrane space generating a proton motriz force that used the complex V for the ATP synthesis. It has been shown that the interaction between the complexes that form the respirasomes increases their activity and affinity for substrates and reduces the production of reactive oxygen species (ROS; Reyes-Galindo *et al.*, 2019). Additionally, the regulation of respirasomal NADH:DBQ oxidoreductase activity by the functional communication between complexes I:IV and I:III2 has been identified. However, kinetics characterization of respirasome has been done in Ustilago maydis. To increase knowledge about the role of respirasome in mitochondrial function, it is necessary to study it from a new organism. In this work, the respirasome from *Yarrowia lipolytica*, a dimorphic yeast from the phylum *Ascomycota*, was solubilized, isolated, and kinetically characterized. *Y. lipolytica* cells were grown in YD medium and disrupted with 0.5 mm glass beads for mitochondria isolation. Briefly, the cells were isolated by differential centrifugation, they were placed at 50% volume in the Bead-Beater with the rest of the volume of glass beads, we made five pulses of 20 seconds at 4°C, with one rest minute between each pulse, and they were centrifuged at 4,667 *g*, the supernatant was recovered and centrifuged at 17,227 *g* to finally obtain the mitochondria. The supercomplexes and complexes solubilization curve with digitonin showed that the ideal ratio was 3 mg digitonin:1 mg protein; then we made a continuous sucrose gradient from 16% to 44% to isolate the respirasomes in their active form. The BN-PAGE analysis of the gradient fractions showed that respirasomes were located at the bottom of the gradient, while free-complex I was in the middle. These fractions were used for the spectrophotometric characterization assays of the respirasome and free-complex I, where we could obtain the kinetic parameters for each one, determining their NADH dehydrogenase activity at 340 nm, using DBQ and cytochrome c as substrates. The parameters obtained were the followings: Vmax= 947 ± 146 and 847 ± 102 nmol NADH oxidized/min·mg total protein; KM(NADH)= 37 ± 13 and 42 ± 12 μM; KM(DBQ)=108 ± 38 and 36 ± 13 μM from respirasome and free-complex I respectively. Also, we studied the effect of the specific inhibitors of the transport chain in the free CI and the respirasomes. As well, we quantify the oxygen consumption by the

respirasome in Vmax conditions, then we determine the stoichiometry of reduced oxygens per each NADH oxidized, the ratio is 1.93 while the theoretical ratio is 2.0.

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Is the assembly pathway of mitochondrial supercomplexes conserved among species?

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Historically, the study of the organization of the respiratory chain complexes has been separated in two principal theories: the "fluid" model, which proposes a free diffusion of the oxidative phosphorylation components in the inner mitochondrial membrane (1) in accordance with the fluid mosaic model, in contrast, the "solid" model postulates a physical association between the respiratory chain complexes (2) that promotes the efficiency of their activity. This last model got one of its main support with pioneer studies developed by the group of Hermann Schägger based on blue native polyacrylamide gel electrophoresis and the use of non-ionic detergents to isolate membrane proteins from bovine mitochondria. Since then, several associations with different stoichiometries have been evidenced in mitochondria from different species studied so far. The mitochondrial respirasome, a supercomplex resulted of the union of complexes I, III_2 and IV, is capable to perform the entire process of "respiration", *i.e.* the transfer of electrons from the NADH to the molecular oxygen, coupled with the formation of a proton motive force (PMF), this PMF is used by ATP synthase complex to synthetize ATP.
In the present study, we are focused on the determination of the assembly pathway of mitochondrial supercomplexes from five species among different eukaryotic linages: *Polytomella parva* (Chloroplastida), *Euglena gracilis* (Discoba), *Ustilago maydis* (Opisthokonta), *Phaeodactylum tricornutum* (Stramenopila) and *Paramecium multimicronucleatum* (Alveolata). After mitochondria preparation, the native supercomplexes were extracted using mild detergents, *e.g.* digitonin (sigma) and glycodiosgenin 101 (Anatrace), and solved by blue native electrophoresis. Our results so far, indicate the putative assembly pathway from *Euglena gracilis* (4), *Polytomella parva* and *Ustilago maydis.*

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Changes in glycerol-3-phosphate metabolism are early events during palmitic acid-induced metabolic reprograming in U937-derived macrophages.

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Abstract.
Macrophages chronically exposed to saturated fatty acids, especially those in adipose tissue, present a pro-inflammatory phenotype with a characteristic foamy morphology. This characteristic is due to the presence of large cytoplasmic lipid bodies occasioned by the uptake of excess circulating lipids. These organelles are constituted by a lipid core formed by triacylglycerols and cholesteryl derivatives. Palmitic acid, as one of main fatty acids present in the organism, is a potent inducer of the inflammatory phenotype in macrophages. However, an acute exposure to this fatty acid is unable to activate a pro-inflammatory phenotype although it is enough to induce a metabolic reprograming including the formation of small lipid bodies. In this work, we used an *in vitro* model of monocyte-derived macrophages to unravel the early stages of metabolic reprogramming observed in macrophages exposed to palmitic acid. We observed that a partial inhibition of the glycerol-3-phosphate shuttle is necessary for supplying glycerol-3-phosphate, a glycolytic metabolite, for triacylglycerol biosynthesis. Furthermore, we characterize an alternative pathway to increase the concentration of glycerol-3-phosphate involving an aquaporin and glycerol kinase. Finally, our results suggest that lipid bodies biogenesis increases as a mechanism to buffer excessive palmitic acid without inducing a pro-inflammatory program. Moreover, we observed that macrophages chronically expose to palmitic acid effectively upregulate the production of inflammatory cytokines.

The Colorful Guardians: Carotenoids of R. Mucilaginosa Defend Against Oxidative Stress.

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Rhodotorula sp. yeasts can withstand high salt concentrations, UV radiation, low temperatures, and heavy metal pollution. These extremophile organisms produce carotenoids. Most studies have focused on enhancing the synthesis of these substances with industrial applications in mind. This has been achieved using various substrates and/or stressors. The physiological effects of carotenoids' in this yeast are still poorly defined. Thus, we decided to investigate whether carotenoids protect *Rhodotorula mucilaginosa* from extreme conditions. To do this, carotenoid production was inhibited by diphenylamine (DPA) and menadione was added to promote oxidative stress. Carotenoids were also grown in both fermentative (YPD, dextrose) and non-fermentative (YPLac, lactate) media. *R. mucilaginosa* produced greater biomass (2.1-fold) in YPD than in YPLac. Carotenoid concentrations were greater in YPLac than in YPD. Nonetheless, these protected cells against reactive oxygen species (EROs) as evidenced by our DPA experiments.

Effect of insulin resistance on the metabolism-insulin secretion coupling in pancreatic islets of Wistar rats

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The classic model of stimulus - insulin secretion, has glucose as its primary metabolic inducer, whose oxidative metabolism is coupled to a series of events that involve the increase in mitochondrial ATP, the depolarization of the plasma membrane and the influx of extracellular calcium, which It results in the mobilization and secretion of insulin granules. It has been described that deregulation in any of these processes leads to altered insulin secretion, and therefore constitutes a predisposing factor for the development of resistance to the hormone and its progression to chronic-degenerative diseases such as type 2 diabetes. Hipercarloric diet, has been associated with insulin resistance through mechanisms of oxidative stress and inflammation. However, its effect on the regulation of insulin secretion-stimulus processes is not known. The objective of this work was to analyze the key points of the canonical pathway of hormone secretion in primary islets of an animal model of insulin resistance induced by hipercarloric diet. Male Wistar rats were randomly assind to form Control (Diet 5001 + water *ad libitum*) and Hipercaloric group (Hipercaloric diet + water *ad libitum*). At the end of 3 months of treatment, the islets were isolated and with them the following tests were carried out: glucose-mediated insulin secretion in vitro, analysis of the dynamics of calcium fluxes and mitochondrial membrane potential in real time using the fluorescent indicators Fluo-4 am and TMRE respectively and finally, the ATP production and the oxygen consumption rate (OCR) in the islets were analyzed; all measurements were performed under basal conditions of 5mM glucose and later with stimulation at 16mM glucose. The results show that the hipercaloric group increases insulin secretion per stimulus, accompanied by differences in pattern of oscillations and the amplitude of the response in calcium flux. In the case of the mitochondrial membrane potential, a difference was also found in the response, which precedes the mobilization of calcium flux by a few seconds. Finally, an increase in OCR and ATP production from oxidative phosphorylation was observed, which was greater in stimulatory than basal conditions (16mM vs 5mM glucose). With the above results, we can conclude that Hipercaloric diet induces key modifications in the glucose-stimulated insulin secretion mechanism, which alters the pattern of insulin secretion in animals, promoting hyperinsulinemic states that promote the development of insulin resistance.

Dexamethasone-induced switch to fatty acid oxidation and autophagy/mitophagy are essential for T-ALLglucocorticoid resistance

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ALL is a highly aggressive subtype of leukemia that affects children and adults. Glucocorticoids (GCs) are a critical component of the chemotherapeutic strategy against T-ALL. The presence of resistance to GC therapy and subsequent recurrent disease require novel strategies to overcome them. In this work we analyzed the effects of dexamethasone (Dex), one of the main GCs used in ALL treatment, on two T-ALL cell lines: resistant Jurkat and unselected CCRF-CEM, representing a mixture of sensitive and resistant clones. In addition to the traditional nuclear targeting, we observed a massive accumulation of Dex in mitochondria. Dex-treated leukemic cells suffered a metabolic reprogramming from glycolysis and glutaminolysis towards lipolysis and increased fatty acid oxidation (FAO), along with the hyperpolarization of mitochondrial membrane potential and ROS production. Dex provoked mitochondrial fragmentation and induced autophagy/mitophagy. Mitophagy preceded cell death in susceptible populations of CCRF-CEM cells while serving as a pro-survival mechanism in resistant Jurkat. Accordingly, prevention of FAO or autophagy greatly increased the Dex cytotoxicity and overcame the GC resistance. Dex acted synergistically with mitochondria-targeted drugs, curcumin, and cannabidiol. Collectively, our data suggest that GCs treatment should not be neglected even in apparently GC-resistant clinical cases. Co-administration of drugs targeting mitochondria, FAO, or autophagy can help to overcome GC resistance.Financial support: PRONAII “Leucemia infantil”, grant # 303072 to OD.

Intervention into the dynamics of intracellular Ca^{2+} improves the NK cells anticancer activity

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Ca^{2+} is universal signaling element, which controls multiple cellular functions. Its intracellular concentration, $[Ca^{2+}]_i$, at any moment is defined by the balance of uptake, extrusion and buffering. During signaling Ca^{2+} entry increases so does also $[Ca^{2+}]_i$. In excitable cells Ca^{2+} entry is mainly mediated by voltage-dependent Ca^{2+}-selective channels activated by membrane depolarization, Ca_v. In non-excitable cells dominates store-operated Ca^{2+} entry, SOCE, which is characterized by an inward rectification, with Ca^{2+} influx increasing in a non-linear fashion when voltage is made more negative. This underlies the basic difference in the interaction with partner Ca^{2+}-activated K^+ channels: opening of these channels in a response to increased $[Ca^{2+}]_i$ provokes K^+ efflux and membrane *hyperpolarization*; it results in closure of Ca_v but, in contrast, potentiates SOCE. In human lymphocytes (B, T and natural killer NK cells) the only KCa channel present is of KCa3.1 type. We applied a specific blocker of KCa3.1, NS6180, to NK cells and analyzed its effect on $[Ca^{2+}]_i$. Firstly, NS6180 caused an abrupt decrease of resting $[Ca^{2+}]_i$. This may be expected on theoretical background as Ca^{2+} entry should decrease, and the balance should be changed. But typically other types cells withstand such challenge and resting $[Ca^{2+}]_i$ changes insignificantly. Moreover, NS6180 significantly (by 15-30%) suppressed SOCE as well as Ca^{2+} increase in a response to the presentation of target cells (here, acute lymphoblastic leukemia Jurkat cells) and activating interleukin IL-15. Patch-clamp experiments evidenced that at the rest less than 30% of NK cells express KCa3.1 current. Therefore, this population response came close to theoretical limit, implying a very strong cooperation between SOCE and KCa3.1 in NK cells. It is considered that anticancer cytotoxicity of NK cells is proportional to the degranulation, the discharge of lytic granules towards target cells. Degranulation strongly depends on SOCE and $[Ca^{2+}]_i$. Consequently, NS6180 caused an abrupt decrease of degranulation by NK cells, induced by a contact with target Jurkat cells. Yet, in time (after 1 hr), the usage of the reserve of lytic granules approached this in control. And the death toll of target cells after this time point started to exceed this in control, so that at 8 hr only 10% of Jurkat cells stayed alive *vs* 30% in control. We concluded that the release of lytic granules in control was exaggerated. Indeed, only few granules were shown to be sufficient to kill target cells. Slowing down the degranulation by KCa3.1 block allowed killing of a greater number of target cells in time. Supported by CONACYT Fronteras de Ciencia-2019 #21887 grant to IP.

Tissue-specific characteristics of the mitochondrial permeability transition pore in rats

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In the inner mitochondrial membrane (IMM) the prescence of a permeability transition pore (PTP) has been reported. When open, PTP dissipates ion gradients and the transmembrane electric potential ($\Delta\Psi$) across IMM. As a result, excess Ca^{2+} is released from the mitochondrial matrix. If PTP does not close, mitochondria suffer outer membrane disruption, loss of cytochrome *c* and eventual cell death. Flickering, defined as the rapid opening and closing of PTP, has been reported in heart, which undergoes frequent, large variations of [Ca^{2+}]. In contrast, in tissues that undergo depolarization events less frequently, such as the liver, PTP would not need to be as dynamic. It follows that these tissues would not be as resistant to stress. To evaluate this hypothesis, it was decided to follow the reversibility of the permeability transition (PT) in isolated mitochondria from two different tissues: the heart and the liver. It was observed that in heart mitochondria PT remained reversible for longer periods and at higher Ca^{2+} loads than in liver mitochondria. This was evaluated measuring the oxygen consumption rate, organelle swelling, ROS production, and Ca^{2+} retention capacity.

Functional and structural characterization of the endogenous zeta (ζ) inhibitor of the F_1F_O-ATPase in photosynthetic α-proteobacteria

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The F_1F_O-ATP synthase is a multiprotein complex that synthesizes or hydrolyzes ATP, and its non-regulated F-ATPase activity can be deleterious. To prevent the spurious F_1F_O-ATPase activity, different endogenous subunits act as inhibitory natural regulators. In α-proteobacteria this regulator is the zeta (ζ) subunit [1; 2; 3]. ζ is unique to the α-proteobacteria class [3], a diverse group that includes free-living bacteria (*Paraccocus denitrificans*), plant endosymbionts (*Rhizobium etli, Sinorhizobium meliloti*), mammalian pathogens (*Brucella canis*), endosymbionts or obligate intracellular parasites (*Wolbachia pipientis*, *Rickettsia ricketsii*), non-sulfur purple photosynthetic bacteria (*Rhodospirillum rubrum, Cereibacter sphaeroides*), etc. [4]. Homologous (on its own F_1F_O-ATPase) or heterologous (on F_1F_O-ATPases of other organisms) inhibition has been demonstrated for the *P. denitrificans'* ζ (Pd-ζ), *Jannaschia sp.* ζ (Js-ζ) [4], and *C. sphaeroides'* ζ (order Rhodobacterales) (Cs-ζ) [5], on the F_1F_O-ATPases of *P. denitrificans*, *Rhodobacter capsulatus*, and *C. sphaeroides*, and with the ζ subunit of *S. meliloti* (Sm-ζ) on the F_1- and F_1F_O-ATPases of *P. denitrificans*. However, Sm-ζ has lost its homologous inhibitory function. On the other hand, *Ricketssia ricketsii* and *Wolbachia pipientis*, have lost the gene encoding ζ [5]. The latest functional and evolutionary results agree with our current hypothesis in that there is a trend to lose the ζ ORF and/or its inhibitory function in parasitic or symbiotic α-proteobacteria, respectively, whereas ζ of free-living α-proteobacteria preserves it´s intrinsic inhibitory function [5]. Demonstrating that the inhibitory function of the ζ subunit of *R. rubrum* (Rr-ζ), a free-living photosynthetic bacterium, is conserved, would support further this hypothesis and also the AlphaFold model of Rhodospirillales' ζ showing it´s inhibitory α-helical extended conformer. The objective of the present work was to determine if the inhibitory function of ζ is conserved in photosynthetic α-proteobacteria evolutionarily distant from *C. sphaeroides*, as in the case of *R. rubrum*, and to characterize and compare the kinetics of F-ATPase inhibition by Cs-ζ and Rr-ζ. Recombinant Rr-ζ and Cs-ζ were purified for *R. rubrum* and *C. sphaeorides* to carry out F_1F_O-ATPase inhibition assays. It was observed that Rr-ζ inhibits its own ATPase with an IC_{50} of 15.33 μM. While Cs-ζ inhibits its F-ATPase with an IC_{50} of 9.57 nM. Furthermore, Cs-ζ showed a 45.8-fold higher affinity than Pd-ζ for its F-ATPase. These differences may obey changes in the primary structure of the ζ subunits, especially in the inhibitory N-terminal region. In conclusion, it was shown that Rr-ζ preserves its inhibitory function with a very low affinity for its F-ATPase, supporting our hypothesis of keeping the inhibitory function of ζ in free-living α-

proteobacteria [5]. The latest results showed a Rr-ζ dimer formed by a unique interchain cystine fomed between two Rr-ζ monomers, which is absent in the ζ subunits from the other α-proteobacteria. This could add a redox regulation of Rr-ζ, we are assesing this phenomenon *in vitro* and *in vivo* to resolve its putative important biological relevance.

Palabras Clave: ATP synthase, ζ subunit, photosynthetic α-proteobacteria.

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Kinetics characterization of the F_1F_O-ATP synthase dimer and monomer from *Yarrowia lipolytica*

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The F_1F_O-ATP synthase is the last complex in the oxidative phosphorylation pathway that uses the electrochemical gradient of protons to impulse ATP synthesis, the fuel for almost all metabolic pathways of the cell [1]. The F_1F_O-ATP synthase can be found in a monomer (V_1) as well as a dimer (V_2) state; the last one has a role in the mitochondrial cristae architecture. The kinetics characterization of the V_2 from *Ustilago maydis* and Polytomella sp suggest that interface monomer-monomer have an important role in the activity of the oligomer [2, 3]. Nevertheless, it is necessary to explore new biological sources to get a general view of the function of the V_2. In this work, we isolated the V_1 and V_2 of the F_1F_O-ATP synthase from *Yarrowia lipolytica*, a strictly aerobic yeast [4] that depends on oxidative phosphorylation for its supply of ATP. The V_1 and V_2 were solubilized with digitonin (3:1 ratio, g digitonin/g protein), isolates, and their ATPase activity was performed as described [2]. The ATPase activity was determined using a coupled reaction following the oxidation of NADH ($\varepsilon_{340\ nm} = 6.22\ mM^{-1}\cdot cm^{-1}$). Our preliminary results suggest a V_{max} value of 0.84 ± 0.06 μmol ATP hydrolyzed·min^{-1}·mg protein^{-1} and a K_m = 0.21 ± 0.08 μM for V_1. In the presence of DDM, the V_1 showed V_{max} and K_m values of 0.81 ± 0.05 μmol ATP hydrolyzed·min^{-1}·mg protein^{-1}, and 0.76 ± 0.22 μM, respectively. The V_{max} values agree with the reported for the V_1 from *Ustilago maydis* [2].

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Role of the δ subunit of the F1-ATPase sector in the colorless alga *Polytomella parva* in the regulation of the hydrolytic activity of the complex

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The ATP synthase is a multiprotein enzymatic complex that plays a central role in energy production, catalyzing the phosphorylation of ADP by inorganic Pi to form ATP. This enzyme is present in the plasma membrane of bacteria, in the thylakoid membrane of chloroplasts, and in the membranes of mitochondrial cristae[1]. Under conditions where the electrochemical gradient is diminished, either due to the absence of oxygen or the presence of uncouplers, this complex can carry out the opposite reaction, hydrolyzing ATP coupled with proton pumping as a mechanism aimed to restore the membrane potential[2]. However, due to the risk of cellular ATP loss, there are several mechanisms responsible for controlling the hydrolytic activity of this enzyme. Natural inhibitors of the ATP hydrolysis in most mitochondrial ATP synthases, such as the inhibitory IF1 peptide have been described. The ATP synthase of the chlorophycean colorless alga *Polytomella parva* shows unique characteristics, such as the presence of atypical subunits not found in the enzyme of other eukaryotic lineages[3]. In vitro assays have shown that the hydrolytic activity of this complex is low compared to its counterpart in bovine and yeast[4]. However, there is no report (biochemical or structural) of the presence of a natural inhibitor in the algal enzyme. In addition, some treatments, such as incubation of the enzyme at high temperature, allow the dissociation of the F1 sector, leading to a strong increase in hydrolytic activity[5]. Bioinformatics approaches using alignment of homologous subunit sequences identified the presence of an extension in the N- terminal region of the δ subunit, which seems to be present only in the lineage of green algae. Predictions of the structure of the δ subunit of the alga *Chlamydomonas reinhardtii* with Alphafold2 suggest that the N-terminal region is the most flexible or dynamic zone of the protein, making it likely that this region is prone to undergo some conformational changes that allow it to reach the beta subunit and control the hydrolytic activity of the complex. Therefore, one of the main objectives of this project is to try to elucidate the role that the δ subunit may play controlling the hydrolytic activity of the ATP synthase of the colorless alga.

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Mitochondrial ATP synthase structure diversity and catalytic activity

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Rotary ATPases are one of the principal players in energy transduction among all living organisms. Inside this group, F_1F_O ATP synthase and A1Ao-ATPase use a proton motive force to synthesize ATP, while V1Vo-ATPase consumes ATP to pump H+ across the vacuolar membrane. F-ATPases are multiproteic complexes composed of a membrane-embedded region, which is involved in proton translocation and in the rotational mechanism of the complex; a region that protrudes from the membrane, which traduces the rotation of the central stalk to conformational changes in the catalytic region that favor ATP synthesis; and one peripheral stalk which maintains the catalytic region relatively static compared with the central stalk.[1]
These enzymes are found in bacteria plasma membranes, thylakoids membrane of chloroplasts, and in the inner mitochondrial membrane. Unlike bacterial and thylakoid ATP synthases, the structural and functional unit of mitochondrial ATP synthase is the dimer. In recent years, with the incorporation of new study species, it has been described that the mitochondrial complex V presents a large structural diversity, mainly in the transmembrane region and in the peripheral stalk. This affects the stability of the dimer and modifies the ultrastructure of the mitochondrial cristae.2 These discoveries lead us to ask if the structural differences observed in the complex V of phylogenetically separated organisms modify the overall catalytic activity of this enzyme. Therefore, this project seeks to compare the hydrolysis activity of the dimeric complex V from *Polytomella parva* (Chloroplastida), *Euglena gracilis* (Discoba), *Saccharomyces cerevisiae* (Opisthokonta), *Phaeodactylum tricornutum* (Stramenopila) and *Paramecium multimicronucleatum* (Alveolata). After cell culture of the above-mentioned organisms, complex V would be extracted with mild detergents and purified by a two-step liquid chromatography. Finally, catalytic activity of the purified dimer would be assessed by a coupled assay of ATP hydrolysis.

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Effect of high temperatures on phenotypes and gene expression of heat shock protein in plants lacking MPKs or with sphingolipid imbalance

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High temperatures have a detrimental impact on plant and agricultural development, productivity and yield. The production of heat shock proteins (HSPs) is a plant-adaptation process for dealing with high temperatures and acquiring thermotolerance. Signaling molecules, such as certain sphingolipids, are produced in response to temperature increases, and they also contribute to the remodeling of the plasma membrane. The most abundant sphingolipids in plants include trihydroxylated long-chain bases (LCBs). Some of them are second messengers in the route to programmed cell death. It has not been investigated if the signaling sphingolipids are associated to HSPs and HSF (heat stress transcription factor) expression in the response to high temperatures. It has also been reported that the activation of mitogen-activated protein kinases (MAPKs), MPK3 and MPK6, contributes to signaling in response to high temperatures. To test sphingolipids and MPKs participation, we studied the effects of high temperatures on seedlings with altered sphingolipid composition (mutant lines *sld1 sld2, sbh1-1*) and lacking the kinases MPK3 and MPK6 (lines *mpk3* and *mpk6*). Six-day-old seedlings were grown in Gamborg media at 22°C and 8 h dark/16 h light. Then, they were exposed to different treatments, all in dark conditions: control (22 °C), acclimation (37 °C for 2 h), challenge (45 °C for 2 h), and acclimation plus challenge (37 °C for 2 h, 22 °C for 2 h, and 45 °C for 2 h). After treatments, phenotypes were assessed by image recording and quantitation of number of lateral roots, root hairs, and color of the leaves. It was observed that at high temperature (45 ºC), seedling growth decreased in all genotypes and leave color became chlorotic at different extent in the wt and the mutants, but *sld1 sld2* green leaves were resistant to chlorosis. This

same heat condition prevented the elongation of the primary root in all genotypes. However, this effect was partially mitigated by the acclimation pre-treatment (37 °C) in *sld1 sld2, sbh1*-1 and *mpk3*. The number of lateral roots decreased with moderate heat (acclimation, 37 ºC) in wt and *sbh1-1* seedlings but not in the other genotypes. However, high temperature (45°C) inhibited the development of lateral roots in all genotypes. These results show that unsaturated sphingolipids (*sld1 sld2* line) are involved in the basal and acquired thermotolerance to high temperatures. We analyzed the transcript levels of the HSP70-4, HSP70-5, HSP70-14 and HSFA2 protein genes using RT-qPCR in order to identify the link between sphingolipids and the heat shock response.

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Contribution of sphingolipid Δ8 unsaturation on plasma membrane fluidity from Arabidopsis leaves during cold acclimation

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Some plant species develop a mechanism of freezing tolerance through a pre-exposure to non-freezing temperatures, which is called cold acclimation (Miura and Furumoto 2013 Int J Mol Sci. 14:5312). One response of cold acclimation is the remodeling of the plasma membrane (PM), which consists, among other modifications, in an increase of fatty acid unsaturation in order to promote greater fluidity (Uemura et al. 1995 Plant Physiol. 109:15). Sphingolipids represent up to 60% of the lipid composition of plant PM, which can contribute to the order and fluidity of the bilayer (Cacas et al. 2016 Plant Physiol. 170:367-384). Sphingolipid structure consists of a hydrophobic long-chain base (LCB) of 18C which C2 amidates a fatty acid and with the C1 binding a polar head. The LCB is an amino alcohol which hydroxyl groups and double bounds (Δ4 and Δ8) varying in number, position, and stereochemistry (Pruett et al. 2008 J Lipid Res. 49:1621). Between 85-90% of the LCB from Arabidopsis leaves contain a double bond in Δ8 unsaturation as a product of two LCB desaturases (SLD1 and SLD2) (Chen et al. 2012 Plant J. 69:769). In this study, we used *sld1 sld2,* a double mutant, to evaluate the contribution of LCB Δ8 unsaturation to the PM fluidity and to freezing tolerance. We purified PM from leaves of wild type and *sld1 sld2* mutant plants exposed to non-acclimation (NA, 22 ℃, 7 days) or acclimation (AC, 4 ℃, 7 days) treatments. Membrane fluidity was determined by measuring the fluorescence polarization (FP) of the probe TMA-DPH (Cano-Ramirez et al. 2021 Cells 10:2778). Wild type AC plants showed 80% survival to freezing temperatures as compared to NA plants. FP curves showed that PM from wt AC plants had lower FP values than the NA plants, indicating a more fluid membrane. NA mutant plants exposed to -20 °C did not survive 0%, while AC plants produced lower survival values 60-70% when compared to the wild type AC plants. The FP profile in the *sld1 sld2* mutant did not show differences between AC and NA mutant plants, nor with respect to wt NA plants. These results indicate that LCB desaturases may contribute to promote fluidification of PM during cold acclimation, which may favor freezing tolerance.

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It is capable the mitochondria to regulate its own membranal fatty acids composition?

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It is known that the membranes are dynamic entities that change its structure and composition under different stressful conditions such as the diabetes. It is of great relevance to understand the mechanisms involved in the regulation of membranes composition in order to know their function, such as those of mitochondria. Recently, it was introduced the idea that apparently, the Mitochondria Associated Membranes (MAMs) are the responsible for regulating the mitochondrial membranes. In this research we are interested in generating information related with the regulation of mitochondrial membrane lipids, particularly the fatty acids composition (FAC). The fatty acids composition of the MAMs will be alike to mitochondrial FAC during a stressful condition, which suggests that the mitochondrial FAC is being mainly regulated by the MAMs. Objective. Using a stressful condition such as the diabetes, we will try to find out evidence that indicates that the FAC of mitochondria is regulated trough the MAMs. Methods. Wistar rats were used in this study for inducing severe hyperglycaemia by an intraperitoneal injection of streptozotocin. A group of rats was sacrificed every week (0, 7, 15 and 30 days). From each animal it was obtained a sample of homogenized tissue, and Endoplasmic Reticulum, MAMs, and mitochondria by differential centrifugations. The fatty acids composition was analyzed by gas chromatography and the statistical analysis by two-ways ANOVA. Results. It was found that the MAMs and mitochondria of animals with hyperglycaemia are different at 15 days, but at 30 days there are not differences, which can be due to the severe and prolonged stress these mitochondria were exposed to, driving MAMs to take control of the mitochondria FAC. Conclusion. The MAMs participate more actively in the regulation of mitochondrial FAC at specific moments, both by aging and stressful conditions, which suggest that in mitochondria still could exist an unknown mechanism that participate in the regulation of its fatty acids composition as an alternative way to what happened in MAMs at specific moments of the age and the stressful condition, in fact, a mitochondrial Fatty Acids Synthase has been recently reported.

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Kramers theory of rate reactions and yeast alcohol dehydrogenase kinetics

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All chemical reactions occur through interaction between the reactants, and the subsequent crossing of the transition state; i.e., a minimum energy barrier known as the activation energy (E_a). Enzymes perform catalysis (or the increase of rate reaction) by lowering the energy barrier. Nonetheless, physical factors may increase/decrease the E_a. In this regard, Hendrik Anthony Kramers stated in his theory of rate reactions (1940) that the increase of friction (viscosity) of the medium may lead to a decrease of the rate (k) of the chemical reaction. Recently, this theory has been applied to enzyme catalysis, which considers that any environmental factor affecting friction of the medium may modulate enzyme catalysis when a component diffusive process is present in the catalytic mechanism. To prove what has been stated by Kramers theory, the dehydrogenation reaction of ethanol to acetaldehyde was considered. The reaction is catalyzed by alcohol dehydrogenase (ADH) from *Saccharomyces cerevisiae*. ADH catalysis was studied at different temperatures (5 to 30 °C), and in the presence of the disaccharide trehalose at physiological concentrations; which increases medium viscosity. Trehalose is produced by *S. cerevisiae* under stress conditions and allows yeast survival. Reaction rates were measured and analyzed using the Michaelis-Menten equation, and the maximum velocity relationship to medium viscosity according to Kramers´ equation was determined.

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The importance of the C-terminal of cornichon homologues in plants and yeast

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It is estimated that 20-30% of the proteome from eukaryotic cells employs the secretory pathway to either reach the extracellular space or some of the cell membranes. Correct protein targeting is important as membrane proteins are responsible to confer the selectivity or specificity to cellular organelles. Besides the well-established role for the COPII components (Sec12, 13, 23, 24, 31, Sar1, etc.) in structuring and activating protein trafficking through the COPII vesicles, additional membrane associated proteins have been identified. Among these proteins, the cornichon/Erv14 family function as cargo receptors. In contrast to animal cornichon homologs, plant and yeast proteins possess an acidic domain at the C-terminal that functions in establishing protein/protein interactions with their cargoes for their correct targeting. Results will be presented on the importance of the C-terminal to select cargo proteins and to structure COPII vesicles.

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Fatty acids and protein profiles ofthe inner and outer mitochondrial membranes in diabetes

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Previous research hasshown that Diabetes Mellitus(DM)modify the lipid and protein metabolism at different levels, from whole cells to subcellularstructures. As is known, the eukaryotic cellsare full of membranous organelles, making them vulnerable to the changes in its lipid and protein composition by metabolic alterations originated by pathologies like DM. The mitochondria areorganellescomposed of two membranes, the inner membrane (IM) and the outer membrane (OM); also, itis the powerhouse of the cell, making about 95% of the ATP thanks to the electron transport chain(ETC)and the oxidative phosphorylation(OXPHOS). These processes(the ETC and OXPHOS) take placewithin the inner membrane, so, changes on the micro conditions of the membranecanalter or even stop them. In this study we evaluatedthe alterations of the Fatty Acidcomposition(FAc) andprotein profile of the outer and inner membranes of the liver's mitochondria on Wistar rats, under the experimental model of Type 1 Diabetes Mellitus(T1DM).

Methods: 2 months old Wistar ratswere induced to T1DMusing streptozotocin. The rats wereeuthanizedafter one moth and liver's mitochondriawereisolated by differential centrifugation and mitochondrial respiration was evaluated. To obtain the OM and IM, we usethe method of sucrose gradient ultracentrifugation. The FAc was determinated by gas chromatographyandthe protein profileby SDS-PAGEin both,the OM and IM.

Results:we found that T1DM modifyboth the OM and IM FAc:In theOM, the essential FA like arachidonic, eicosapentaenoic and, docosahexaenoic, have an increase in its percentage,and short-chain FA have a decrease proportionbut, the interestingly, total saturated fatty acids (SFA) and unsaturated fatty acids (UFA) do not change between groups; In the IM, the FAc is moreheterogenous, showing not trend at all between FA but, as in the OM, the summatory of SFA and UFS remainsthe same. Also,the protein profilein both the OM and IMis also modified by the T1DM. Finally, we found that mitochondrial respiration is enhanced as a consequence of DM1, respiration with and without ADP is almost one third higher in the diabetic group compared to the normoglycemicone. We infer that the lipid andprotein modifications of theOM and the IMaffectthe efficiency and/or thefunctionality of the ETC and OXPHOS. We suggest that more research is needed to verify this assumption.

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Effect of estradiol on Ca^{2+} handling proteins and mitochondrial activity in hypertrophied H9c2-derived cardiac myotubes

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Background: Pathological cardiac hypertrophy is a chronic degenerative process, characterized by structural changes, alterations in Ca^{2+} handling, and mitochondrial impairment. Cardiovascular diseases (CVD) are less prevalent in females compared to males. However, at post-menopause, the prevalence increases drastically in women. This suggests that estradiol plays an important cardioprotective role. However, the precise role of estradiol on Ca^{2+} handling and mitochondrial metabolism is not completely understood.
Methods: We developed a model of hypertrophied myotubes with angiotensin II (Ang II), and retinoic acid was used to contribute a cardiac-like differentiation. It was used as a pre-treatment of 17-β estradiol (17-βE2) and estrogen receptor inhibitor ICI-182,780 to determine if sex hormones correlate to changes in the expression of the main Ca^{2+} handling proteins, mitochondrial activity, and pathological cardiac remodeling. Cell hypertrophy was determined by cell area using calcein AM under confocal microscopy. Changes in the expression of the main cellular and mitochondrial Ca^{2+} handling proteins, pathological remodeling, and inflammation markers were evaluated by real-time PCR. Mitochondrial activity was assessed with oxygen consumption using a High-Resolution oximeter.
Results: It was observed that Ang II treatment generated hypertrophy, and it was prevented with a 17-βE2 pre-treatment in a dose-dependent manner. Ang II increased brain natriuretic peptide gene expression, which was significantly reduced with 17-βE2. Ang II increased IL-6 gene expression that tends to reduce with 17-βE2. Regarding Ca^{2+} handling proteins, there was a significant decrease in the SERCA2a/PLB ratio in the group treated with Ang II, whose statistical significance was lost in the group treated with Ang II and 17-βE2.
Conclusion: These results suggest that pretreatment with 17-βE2 in hypertrophied myotubes derived from H9c2 cells prevents structural and molecular damage induced by Ang II. The importance of studying the proteins that manage Ca^{2+}, mitochondrial activity, and its relationship with 17-βE2 in the study of pathological hypertrophy using differentiated myotubes is highlighted.

Cannabidiol treatment on 3T3-L1 pre-adipocytes modify lipid droplet accumulation during white-like adipocytes differentiation

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Adipose tissue browning consists in a promotion of white fat depots into thermogenic active adipocytes, currently it is a promising therapeutic target to increase energy expenditure and counteract weight gain in the context against obesity. Cannabidiol (CBD) a major non-psychotropic phytocannabinoid of *Cannabis sativa* with proven properties as an anti-inflammatory and immunomodulator compound. Recently, CBD showed browning in adipocytes. However, phenotype, effector function and metabolic changes are not yet demonstrated. Thus, this study aims to evaluate the effect of CBD administration on 3T3-L1 pre-adipocytes during white-like adipocyte differentiation; particularly, phenotype, effector functions and metabolic changes. First, cell viability was assessed by cellular metabolism on pre-adipocytes at 24, 48 and 72h of treatment, showing that at low CBD concentrations (0.5 - 10 μM) does not modify this function. Intracellular lipid droplets and triglycerides content were assessed, finding that CBD at 0.5, 5 and 10 μM decreased intracellular lipid droplet accumulation and triglycerides content after 10 days of administration. Adipocyte phenotype was evaluated by gene (PCG1-α, PPAR-γ, UCP-1, and TFAM) and protein (ASC-1, Eva-1, Pref-1, and CD40) expression. Preliminary data demonstrates that CBD promotes surface and gene markers associated with adipocyte browning. In addition, changes with oxygen consumption rate and mitochondrial reactive oxygen species were observed. In conclusion, our data demonstrate that CBD plays dual modulatory roles as inductor of brown-like adipocyte phenotype as well as promoting lipid metabolism. These results point out CBD as a potentially promising therapeutic agent for treating obesity.

The excitation-contraction coupling is profoundly altered in ventricular cardiomyocytes of a novel model of HFpEF

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Background. Even though heart failure with preserved ejection fraction (HFpEF) represents roughly half of the total cases of heart failure, it is only recently that *bona fide* animal models of HFpEF have been developed. To a large extent, this is behind the lack of understanding of HFpEF pathophysiology. In the present study, we aimed to characterize the excitation-contraction coupling process in a novel mouse model of HFpEF.
Methods. HFpEF animals consisted in mice fed with a high-fat diet and exposed to L-NAME for eight weeks. Controls (CTRL) were fed with a standard chow diet. Action potentials and L-type Ca^{2+} current of ventricular cardiomyocytes were recorded via patch clamp. Ca^{2+} transients, Ca^{2+} sparks, and the sarcoplasmic reticulum Ca^{2+} content were all measured in Fluo-4-loaded myocytes by confocal microscopy imaging. The T-tubule system was studied in micrographs of di-8-ANNEPS-loaded myocytes.
Results. HFpEF myocytes exhibited a dramatic enlargement of the duration of the action potential (APD90 was 2.2 times higher than CTRL). Interestingly, the amplitude of Ca^{2+} transients was slightly higher, which, however, could not be explained by increases in either L-type Ca^{2+} current or sarcoplasmic reticulum Ca^{2+} content. Notably, microscopic releases of Ca^{2+}, known as Ca^{2+} sparks, also exhibited a larger amplitude in HFpEF. Of physiological relevance, HFpEF myocytes were characterized by a delayed Ca^{2+} reuptake (increased T50). This last feature was paralleled by a slower re-lengthening rate, which may manifest as overt diastolic dysfunction in the left ventricle as a whole. Finally, the release of Ca^{2+} occurred in a less synchronic manner during HFpEF Ca^{2+} transients, despite the T-tubule system regularity and density were both preserved.
Conclusion. Ca^{2+} dynamics of cardiomyocytes of a preclinical model of HFpEF suggested an impairment in cytosolic Ca^{2+} reuptake, which may underlie diastolic dysfunction at the left ventricle level. Further research is warranted on the sarcolemmal NCX activity in order to provide a more thorough understanding of the excitation-contraction coupling in HFpEF.

Increased oxidative stress mediated by catecholamine-induced mitochondrial calcium overload leads to mitochondrial and cellular dysfunction, ultimately promoting arrhythmia generation.

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Background: Ventricular arrhythmias are a significant cause of mortality in cardiovascular patients. High levels of catecholamines have been associated with the development of ventricular arrhythmias, and no intervention has been efficient in reducing mortality since β-blockers. Mitochondrial Ca^{2+} transport is necessary for an adequate adrenergic response; however, constant adrenergic stimulation leads to mitochondrial Ca^{2+} overload and mitochondrial dysfunction. In this study, we assessed the role of mitochondrial Ca^{2+} transport and its modulation in arrhythmia generation in a model of catecholamine overload.
Methods: The study followed the national laboratory animal use and care guidelines. 12-15-week-old C57bl/6 male mice received Ru360, a mitochondrial Ca^{2+} transport inhibitor, or normal saline via IV, and a baseline ECG was recorded. Afterward, Isoproterenol (ISO) at a dose of 400mg/kg was administrated subcutaneously, and ECG recording was kept for another 20 minutes. Finally, hearts were excised, and cardiomyocytes and mitochondria were isolated for further characterization.
Results: Animals administered with ISO developed ventricular tachycardia and fibrillation. This was completely prevented in the group treated with Ru360. Mitochondria from the ISO group had a higher Ca^{2+} content, indicating Ca^{2+} overload, which was associated with a compromised function and membrane integrity as evidenced by a lower respiratory control ratio, Ca^{2+} retention capacity, mitochondrial membrane potential and a faster rate of mitochondrial membrane potential loss upon a Ca^{2+} insult; all of which were preserved or partially preserved in the Ru360 group. We observed elevated oxidative stress, higher peroxide production, electron leak, and ROS oxidative damage in the ISO group. Remarkably, mitochondrial proteome showed an increase in ROS-driven oxidative post-translational modifications. Redox unbalance was associated with a loss of cellular Ca^{2+} homeostasis demonstrated by an increase in abnormal activity during Ca^{2+} transients and a more dispersed transient front, findings which were again prevented by inhibiting mitochondrial Ca^{2+} transport with Ru360.
Conclusion: These results imply that oxidative stress induced by mitochondrial Ca^{2+} overload is fundamental for arrhythmia generation in catecholamine overload. In this sense, mitochondria homeostasis could be a potential new target for developing new anti-arrhythmic therapies.

Histology of renal tumors, and analysis of the fatty acids composition of the tissue and its mitochondria

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It has been seen that the administration of long- chain omega 3 fatty acids (LCω3) to Wistar rats, induced to Type 2 Diabetes Mellitus (DM2), promotes the development of renal tumors. Little is known about this model of renal tumors and we are working on describing and characterizing it. For this study, we were mainly interested in mitochondrial fatty acids composition because of its correlation with the mitochondrial respiration, but also we studied the fatty acids composition of total tissue and the histological characteristics.
DM2 was induced in 48 hours-old newborn male Wistar Rats by an intraperitoneal injection of STZ. The LCω3 were administered directly into the mouth of the rats. When evidence of tumors was detected, the organisms were anesthetized, euthanized and kidneys were removed, the samples were collected for histological analysis and the remaining tissue was homogenized. Mitochondria were isolated by differential centrifugation. The fatty acids composition of tissue (and its mitochondria) was analyzed by gas chromatography.
By macroscopic observation, the renal tumor model was successfully obtained in 50% of the experimental organisms with LCω3 supplement and DM2 induction, but microscopic analysis reveals that 100% of these animals had neoplastic architecture and the presence of clear cells, characteristic of renal carcinoma. We also found in kidney that the bigger the tumor, the lower the arachidonic acid proportion, and the higher the palmitic acid proportion, both in total tissue and isolated mitochondria. As a result, the Unsaturated to Saturated Fatty Acids Ratio (U/S), decreased.
In conclusion, the LCω3 are involved in the development of the renal tumors in rats with DM2. The tumors appear to correspond to clear cell renal carcinoma. In macroscopically apparent renal tumors, the size of tumors is closely related with the fatty acid composition of total tissue and mitochondria, but microscopically apparently not.
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Effect of metformin on the inhibition of complex I in the liver, brain, and heart of male and female rats

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Metformin (MTF) is an antihyperglycemic agent used to treat type II diabetes. MTF lowers blood glucose levels by suppressing hepatic gluconeogenesis and stimulating glucose uptake in skeletal muscle and adipose tissue. It has been suggested that the mechanism of action of MTF is the inhibition of complex I, this interrupts mitochondrial respiration and decreases ATP synthesis, causing cellular energy stress and elevation of the AMP/ATP ratio. These changes result in AMPK activation, a primary metabolic sensor. It is important to highlight that MTF only exerts a weak and reversible selective inhibition of isolated complex I (IC50 ~20 mM). However, the pharmaceutical dose of MTF only achieves plasma concentrations of 10 to 40 μM. Based on this, we wonder if micromolar MTF concentrations are enough to achieve inhibition of mitochondrial complex I in the liver, brain, and heart tissues of 250 g male and female Wistar rats. Mitochondrial oxygen consumption from female rats was inhibited with micromolar MTF concentrations, while male mitochondrial respiration was inhibited at millimolar concentrations. Permeabilization of mitochondria with triton X-100 confirms that MTF blocks respiration through complex I inhibition. Our data showed a genre-selective effect of MTF on complex I inhibition, resembling the different doses used in female and male treatment.

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Tamoxifen interacts with cyclophilin-D at the cyclosporine A-binding domain and sensitizes leukemic cells to cannabidiol

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T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive ALL with poor prognosis, low survival, and high recurrence rate. Thus, new strategies have been sought to overcome resistance to chemotherapy. One of these strategies involves drugs, which target mitochondria (mitocans). Tamoxifen (TAM) is traditionally used in clinic for the treatment of estrogen receptor-positive (ER+) breast cancer. However, several “off-target” effects have been reported for TAM, many of them related to mitochondria. Recently, we have shown that cannabidiol (CBD) possesses mitocan activity. It directly interacts with voltage-dependent anion channel (VDAC) favoring highly Ca^{2+} permeable state, which leads to a formation of the mitochondrial permeability transition pore (mPTP), cytochrome C (Cyt-C) release and cell death.
In the present work we demonstrated that TAM and CBD act synergistically, increasing cell death in T-ALL cell lines. mPTP inhibitor cyclosporine A (CsA) and TAM limited the CBD-induced Cyt-C release. Whereas CBD alone induces transient mitochondrial calcium ($[Ca^{2+}]m$) overload, in cells pre- or co-incubated with TAM, CBD induces a sustained $[Ca^{2+}]m$ response, similar to that caused by pre-incubation with CsA. After $[Ca^{2+}]m$ overload caused by CBD and the formation of the mPTP, the dissipation of the mitochondrial membrane potential ($\Delta\Psi m$) occurs, whereas pre-incubation with TAM or CsA limited the CBD-induced $\Delta\Psi m$ loss. All these findings indicate that TAM inhibits the mPTP formation. Moreover, in *silico* analysis demonstrated that TAM interacts with cyclophilin-D (Cyp-D, isoform expressed in mitochondria) at the same site as CsA. Therefore, TAM acts as an analog of CsA, inhibiting the mPTP formation through the direct interaction with Cyp-D.
Our results provide a mechanistic basis for the synergistic action of two drugs, TAM and CBD, already approved by the FDA for the treatment of other diseases and which can be redirected to improve the treatment of T-ALL.

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Keywords: leukemia; cannabidiol; tamoxifen

B-NIPOx is a new drug effective in the chronic phase of experimental Chagas disease in mice

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Chagas disease, or American Trypanosomiasis, is caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) and represents a significant public health problem, which is endemic in Latin America and emerging in the rest of the world. Currently, only two drugs are available for its treatment, Benznidazole, and Nifurtimox, which are partially effective in the chronic phase of the disease, generate several side effects, and there are a lot of *T. cruzi-resistant* strains. Glycolysis is the main metabolic pathway used by *T. cruzi* to obtain its energy, with NADH + H^+ being reoxidized by an enzyme (α-hydroxy acid dehydrogenase isozyme II, HADH-II) with no human analogs. We previously designed and synthesized N-isopropyl oxamic acid (NIPOx), which is structurally analogous to the enzyme's main substrate and an excellent HADH-II inhibitor. However, it is a polar molecule and does not cross the parasite membrane. In this study, we synthesized the benzyl ester of NIPOx (B-NIPOx), which is a non-polar molecule that crosses cell membranes. B-NIPOx had higher *in vitro* trypanocidal activity on epimastigotes and trypomastigotes than Benznidazole and Nifurtimox; it was more effective to reduce blood parasitemia and amastigote nests in infected mice and, in contrast to the reference drugs, it prevented the development of Chagasic enteropathy since B-NIPOx prevented the thickening of the inner circular muscle layer of the large intestine of these mice, as well as its infiltration by leukocytes and its loss of nitrergic neurons, which are characteristic events of Chagasic enteropathy. Our results suggest that B-NIPOx could be used for the treatment of acute and chronic Chagas disease.

POSTER SESSIONS

1

Extremophile yeast growth on minimal medium using glutamine as sole carbon source

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Modeling microorganisms to study cancer is in constant progress. Currently, there are several models and the most widely used is *Saccharomyces cerevisiae.* However, this model allows information to be obtained only under limited, specific conditions. Cancer cells proliferate on glutamine alone, even under genotoxic, oxidative and nutritional stress. Gln is used as a nitrogen source to the biosynthesis of amino acids and nucleotides, and it is a carbon source that replenishes lipids, carbohydrates and tricarboxylic acid cycle (TCA) intermediates. Some unconventional yeasts possess the ability to grow in extreme environments that are inhospitable to other organisms, and they may possess characteristics that make them potential models for the study of cancer. It was decided to examine whether unconventional yeasts (*Rhodotorula mucilaginosa* and *Debaryomyces hansenii*) may be suitable models for the study of cancer. To corroborate this, yeasts were grown in a minimal medium using different concentrations of glutamine. *R. mucilaginosa* exhibited higher capacity to grow on minimal glutamine-supplemented media than *D. hansenii*, while *S. cerevisiae* showed little, if any growth. These results suggest that *R. mucilaginosa* may be a rapid and easy glutamine metabolism assay alternative as compared to cancer cells.

2

The use of thioflavin T for the estimation and measurement of the plasma membrane electric potential difference in different yeast strains

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The cationic dye thioflavin T (ThT) was previously used in baker's yeast to develop a method to estimate the electric plasma membrane potential difference (PMP) by changes in fluorescence, and to obtain actual values from the accumulation of the dye, considering important correction factors like the binding to the internal components of the cell. However, it was considered important to explore whether the method developed could be applied to other yeast strains, such as other strains of *Saccharomyces cerevisiae* (W303-1A and FY833), as well as with non conventional yeasts: *Debaryomyces hansenii*, *Candida albicans*, *Meyerozyma guilliermondii* and *Rhodotorula mucilaginosa*. We also proposed alternative ways to estimate the PMP by using flow cytometry and a multi-well plate reader.

Results of the estimation of the PMP by the fluorescence changes under different conditions were adequate with all the strains. Consistent results were also obtained with several mutants of the main monovalent transporters, validating ThT as a monitor for PMP estimation.

3

Mitochondrial changes in B cell response against non-bilayer phospholipid arrangements

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Mitochondria play a crucial role in B cell fate determination by metabolic changes associated with differences in mitochondrial membrane potential ($\Delta\Psi m$) and mt-ROS production, influenced by the fusion and fission of the mitochondrial membranes. B cell response against lipidic antigens can lead to the production of high-affinity IgG antibodies; this can occur if cell membrane lipids present antigenic properties when they form stable non-bilayer phospholipid arrangements (NPAs), which can be induced by some drugs such as chlorpromazine. Stable NPAs induce B cell activation that can respond by germinal center pathway where distinct B cell subsets are generated, including memory B cells and plasma cells that produce anti-lipid NPA IgG antibodies, which are present in autoimmune diseases such as Systemic Lupus Erythematosus (SLE). We analyzed the differences in mitochondrial dynamics, $\Delta\Psi m$ and mt-ROS from B cells in a murine model resembling human SLE by flow cytometry. We found that germinal center B cells have fused mitochondria with increased $\Delta\Psi m$, which indicates that they efficiently lead their metabolism to oxidative phosphorylation. Differentiation into memory B cells occurs in cells with increased mitochondrial mass and $\Delta\Psi m$. In contrast, mitochondrial fission and decreased $\Delta\Psi m$ promote plasma cell differentiation. These events result from changes in mt-ROS production; however, little is known about how mt-ROS contributes to B cell activation and differentiation to enable an effective immune response.

4

Characterization of the mitochondrial function in renal tissue in an HFpEF mice model

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Backgroud: Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome whose main risk factors include older age, diabetes, dyslipidemia, obesity, and hypertension. Regardless of its increased incidence, there is no clear evidence that pharmacologic therapy, diet, or other therapies reduce mortality risk. Since chronic kidney disease (CKD) shares similar risk factors, these diseases are frequently co-diagnosed, representing a poor prognostic indicator for the patient. Also, CKD in an HFpEF patient limits the pharmacological treatment options for HFpEF. The cross-talking between the heart and kidneys in HFpEF is relevant since impaired renal function contributes to HFpEF development. The role the kidney plays in a systemic process involving inflammatory, microvascular, and cardiac components; might be linked to metabolic and systemic derangements in circulating factors caused by renal dysfunction. This might lead to an activated systemic inflammatory state and endothelial dysfunction, leading to cardiac fibrosis and hypertrophy.
Methods: By using a *double-hit* model of hypertension and obesity, we developed an HFpEF mice model where we could assess the renal function and the bioenergetics of renal tissue.
Results: After eight weeks of progression of the HFpEF model, animals developed an increase in adipose tissue, hypertension, hypercholesterolemia, and hypertriglyceridemia. Also, cardiac function was importantly altered, while the ejection fraction did not change between control and HFpEF animals. In contrast, the kidneys showed slight atrophy in the HFpEF animals. By measuring the mitochondrial respiration in kidney homogenates, we identify a tendency to decrease the respiratory control. Besides, the HFpEF group showed an increase in the maximal respiratory capacity after adding an uncoupling agent; however, no changes were observed in the mitochondrial mass.
Further characterization of the renal function in this model may provide new insight into the cross-talk link between both systems and may contribute to identifying new therapeutic targets.

5

Molecular description of ascaphin-8 affinity towards different bacterial membranes and the effect of C-terminal amide moiety on selectivity

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Summary:

We investigated the molecular basis for the potency and selectivity of the antimicrobial peptide ascaphin-8 towards archetypes of gram-negative and gram-positive bacterial lipid membranes. We also describe how C-terminal amidation influences the peptide´s mechanism of action enhancing activity while diminishing its selectivity. Both peptides presented greater affinity towards the gram-positive model due to overall greater negative charge distribution of the lipid bilayer. Fewer but stronger electrostatic interactions between ascaphin-8.NH2 and lipid bilayers systems translated into greater affinities compared to its non-amidated counterpart, as corroborated in vitro fluorescence spectroscopy of calcein leaking from liposomes and previously reported microbial assay. Likewise, ascaphin-8.NH2 modified area per lipid to a greater extent; interestingly, membrane thickness was unaffected. In all cases ascaphin-8 as monomer induced membrane perturbations generating a small "water channel", along with the flow of ions. The C-terminal amide moiety seemed to influence/improve water penetration into the bilayer center, that subsequently resulted in the conformational changes of the peptide.

Lipid/peptide systems for molecular dynamics simulations were mounted and ran as described by [1]. Analysis was carried out as described by [2].

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6

Adenosine-derived compound IFC-305 restores mitochondrial bioenergetics at complex I in an *in vivo* model of hepatocellular carcinoma

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The hepatocellular carcinoma (HCC) most often is a result of cirrhosis; a chronic degenerative disease of tissue structure and liver function considered as irreversible. It has been shown that these liver diseases present high gene dysregulation, in addition to a loss of energy production in the form of ATP due to mitochondrial dysfunction. This dysfunction is reflected in a malfunction of the electron transport chain complexes (ETC), highlighting complex I for being the first acceptor of electrons donated by the citric acid cycle within the mitochondria. This organelle is in charge of regulating the energy state, the redox state and the metabolism of the cell, which makes it a therapeutic target for cancer. The IFC-305 compound is a salt derived from adenosine nucleoside. In previous studies, has been shown that this compound serve as a hepatoprotective agent and recover the normal hepatic function. For this reason on this scientific study was decided to evaluate the activity of complex I of the electron transport chain in a mouse model of hepatocellular carcinoma induced with diethylnitrosamine (DEN). A murin model was used divided in 4 groups, it was developed in 2 stages, control C group (C), control with IFC-305 (IFC-305), cancer progession (DEN) and cancer progression treated with IFC-305 (DEN/IFC-305). The reduction of 2,6-dichloroindophenol (DCPIP) was used to quantitatively determine the activity of complex I in the mitochondria isolated from the livers of the four groups and the technique of High Resolution Gels (hrCN-PAGE), in which NADH was used as a substrate and tetrazolium nitrate (NBT) was used as an indicator of reduction to NAD+. Both cases showed a general trend towards recovery of mitochondrial function and greater efficiency of complex I in the cancer progression group supplied with DEN and subsequently treated with the IFC-305 compound compared to the control group. Concluding that IFC-305 contributes to reestablish the normal functioning of the mitochondrial complex I and with it increases the production of ATP to normal levels in the mitochondria of hepatocellular carcinoma cells, to improve its metabolic functioning and to compensate liver damage.

7

Effect of chronic consumption of a high-carbohydrate diet on the mitochondrial efficiency of the frontal cortex of male Wistar rats

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Introduction: The intake of hypercaloric diets and/or reduced energy expenditure due to a sedentary lifestyle leads to a positive energy balance, promoting the development of insulin resistance (IR), metabolic syndrome (MS), obesity, diabetes, and currently, it also has been associated with neurodegenerative diseases development. In common, these abnormalities are closely related to mitochondria alterations; however, it has not been thoroughly studied. **Methodology:** Two groups of male Wistar rats (n=5, 1-month-old, and weighing 100 g) were fed for 120 days with a high-carbohydrate diet (Patent: MX/E/2013/047377) or regular chow (NCD; LabDiet 5001; diet for laboratory rodents). At the end of feeding, metabolic characterization was performed. Glucose, triglycerides, insulin, cholesterol, and its fractions were quantified using commercial kits. HOMA-IR and Matsuda–DeFronzo insulin sensitivity indexes were calculated. From a frontal cortex sample, mitochondrial supercomplexes were analyzed by western blot or in-gel activity; PGC-1α was assessed by western blot, and ATP quantification was performed using a commercial kit based on glycerol phosphorylation. **Results:** Wistar rats fed high carbohydrate content developed MS characterized by hyperglycemia, hyperinsulinemia, dyslipidemia, and IR. In rats with MS, PGC-1α expression did not show statistically significant changes in the frontal cortex. However, western blot and in-gel activity evidenced that the expression and activity of individual complexes are favored over supercomplexes in the frontal cortex. Finally, in our model, the frontal cortex ATP content increased significantly. **Conclusion:** MS modified the expression and activity of mitochondrial complexes and supercomplexes in the frontal cortex; the changes generated in energy efficiency seem to favor maintaining and even increasing ATP concentration.

Keywords: supercomplexes, frontal cortex

8

Interleukin 6 in skeletal muscle: a double-edged sword, contraction and fatigue in slow and rapid muscle

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Skeletal muscle is one of the largest tissues in the human body, representing from 35 to 42 percent of the body weight in adulthood. It has transcendental mechanical and metabolic functions. Skeletal muscle is divided into fast and slow muscle depending on various histological and metabolic features. Fast skeletal muscle (FSM) owns a glycolytic metabolism and is sensible to fatigue; whereas slow skeletal muscle (SSM) has an oxidative metabolism and resistance to fatigue. We define fatigue as a reversible decline in force production after a constant stimulus. Interleukin 6 (IL-6) is a pleiotropic cytokine with immune and endocrine functions. Because of its overexpression in inflammatory states, it has been identified as a proinflammatory cytokine but in recent years its anti-inflammatory and regenerative effect as myokine has arouse curiosity. During exercise skeletal muscle folds IL-6 secretion up to 100 times its baseline value, stimulating lipolysis, improving glucose metabolism, and helping in the adaptations skeletal muscle undergoes throughout exercise. Although new discoveries regarding IL-6 as an ambivalent cytokine have been done, its effects in skeletal muscle contraction force and fatigue remain scarcely understood. The purpose of this study is to assess the effect of exogenous IL-6 on skeletal muscle's contraction force registered through electrophysiological methods on isolated rat muscles. We will use isolated Extensor Digitorum Longus (EDL) and Soleus muscles of young male and female Wistar rats weighting 250 to 300 grams obtained from the Universidad Autónoma de México's vivarium. Once isolated we will place them in an electrophysiological chamber, fast and slow muscles will undergo a single twitch and a tetanic fatigue protocol with increases of IL-6 in the medium. Mechanical properties between muscles with and without IL-6 will be compared to elucidate IL-6 effects on skeletal muscle. In consequence, this will pave the way for further studies regarding the importance of IL-6 in the skeletal muscle's mechanical properties.

9

In anaerobiosis the mitochondrial respiratory chain from *Rhodotorula mucilaginosa* probably uses Fumarate Reductase as a final electron acceptor

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In anaerobic conditions, different organisms express an electron transport chain that uses different molecules as final electron acceptor. Some of these are nitrate and fumarate. Under anaerobiosis, fumarate reductase (FR) may be the final acceptor in of anaerobic respiration in bacteria such as Helicobacter pylori and Escherichia coli, in protozoa such as Trypanosoma, Plasmodium, and Leishmania, and in helminths including C. elegans. The extremophile yeast Rho*dotorula mucilaginosa* may be found in environments such as ice glaciers, heavily contaminated waters, soils, food, and skin where oxygen concentrations may vary widely. *Rhodotorula* has a branched respiratory chain (RC) expressing alternative NAD^+ oxido-reductases (both ND2i and ND2e) and an alternative oxidase (AOX) (Castañeda-Tamez P et al., manuscript in preparation). In addition, when subjected to hypoxia or anaerobiosis, fumarate reductase (FR) may catalyze the reduction of fumarate to succinate allowing the cell to survive. Here, Complex I oxidizes NADH and reduces quinone pumping protons and then FR reoxidizes quinol to reduce fumarate, yielding succinate. In isolated mitochondria from *R. mucilaginosa*a FR was detected by clear-activity PAGE and its identity was confirmed by mass spectroscopy. FR expression/activity was higher in the non-fermentative carbon source lactate (YPLac). FR might be important for *Rhodotorula* survival in extreme environments.

10

Polydatin prevents electron transport chain dysfunction and excessive ROS production by decreasing cardiolipin loss and lipid peroxidation in liver mitochondria exposed to iron overload.

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Many genetic and age-related diseases are characterized by disruption of iron homeostasis and mitochondrial iron overload. As iron catalyzes the generation of hydroxyl radical, iron overload leads to mitochondrial oxidative stress, bioenergetic collapse, cell death, and tissue injury. Thus, molecules diminishing oxidative stress in mitochondria may have a therapeutic potential to counteract iron overload – related diseases. In this regard, oxidative damage to cardiolipin is a potential target to counteract mitochondrial damage as this phospholipid is highly prone to oxidative damage, and it is essential for the structure and function of the electron transport chain (ETC). On the other hand, polydatin, a polyphenol derived from resveratrol, has been proposed as a promissory treatment for liver-related diseases, besides it has been successfully used in preclinical and clinical studies for the treatment of cardiovascular diseases. Thus, we aimed to test if polydatin protects the function of the ETC in liver mitochondria under iron overload by decreasing lipid peroxidation and attenuating the loss of cardiolipin and cytochromes. Rat liver mitochondria were incubated with 50 µM Fe^{2+} by 30 min. Then, it was assessed lipid peroxidation, cardiolipin content, cytochrome levels, activity of ETC complexes and ROS generation. Incubations with 100 µM polydatin were done 15 min before incubation with Fe^{2+}. Fe^{2+} induced a four-fold increase in lipid peroxidation, decreased more than four-fold the levels of cardiolipin, and diminished the content of cytochromes $c+c_1$, b, and $a+a_3$. Moreover, Fe^{+2} decreased in a variable degree the activity of all the ETC complexes, while increasing several times the levels of ROS. Polydatin decreased lipid peroxidation at the levels of control, increased twofold the levels of cardiolipin in comparison to Fe^{+2} - treated mitochondria, and normalized cytochromes levels. Furthermore, polydatin enhanced the activities of all the ETC complexes in some cases even above the levels of control, besides it fully diminished ROS generation. Overall, these results suggest that a mechanism of action of polydatin in diseases involving iron overload in mitochondria may involve diminution of oxidative damage to mitochondrial membranes and cardiolipin, thereby protecting from cytochrome loss, augmenting the electron flow through the ETC, and decreasing ROS levels.

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Distinctive phenotypic, functional and molecular hallmarks between HFpEF and HFrEF

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Background. Depending on the left ventricle ejection fraction (EF), heart failure (HF) can be classified as HF with reduced (<40%) and preserved (>50%) EF (HFrEF and HFpEF, respectively). These two clinical syndromes result from different etiologies that give rise to distinctive remodeling patterns. Of note, HFrEF pharmacotherapy is often ineffective for HFpEF. In this study, we aimed to compare two preclinical models (HFrEF vs. HFpEF) in terms of their phenotype, functional features, and molecular signatures.

Methods. HFrEF animals consisted in mice exposed to angiotensin II and L-NAME, whereas HFpEF mice were fed with a high-fat diet combined with L-NAME exposure. Controls received a standard chow diet. Left ventricle function was invasively evaluated after which the heart was retrieved for histopathological and molecular analysis. Ca^{2+} dynamics was studied in confocal microscopy line scans recorded in isolated ventricular cardiomyocytes. Mitochondrial membrane potential was evaluated with TMRE dye. Gene expression was assessed via qPCR, while immunoblot was used to measure acetyl-lysine profiles and sirtuin levels.

Results. Both HFrEF and HFpEF mice exhibited impaired function of the left ventricle, manifested as increased systolic and diastolic pressures, and an elevated stiffness index. As expected, the HFrEF group had a marked drop in EF, while it remained unaffected in HFpEF mice. Structurally, cardiomyocytes cross-sectional area in HFrEF was two times as high as in controls, whereas only a modest degree of hypertrophy was determined in HFpEF. While the amplitude of Ca^{2+} transients was slightly higher in HFpEF myocytes, it was reduced in HFrEF. In either case, Ca^{2+} reuptake was similarly affected. Expression of BNP and COL1A was increased in the cardiac tissue of HFrEF mice, while no changes were found in the HFpEF group. On the other hand, the expression profile of pro-inflammatory (IL-1B, IL-6, TNF) and anti-inflammatory (IL-10) cytokines indicated a similar degree of inflammation in both HF models. Mitochondrial membrane potential was reduced in both HF models. Finally, the HFpEF heart's abundance of acetylated lysine residues was three times as large as the control, while a two-fold increase was found in HFrEF.

Conclusion. Whereas inflammation and Ca^{2+} mishandling are shared features of both HFrEF and HFpEF myocardium, there are some signatures unique to each syndrome. Namely, the degree of hypertrophy and maladaptive remodeling is more severe in HFrEF, while protein acetylation appeared to be higher in HFpEF.

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Evaluation of Nano-carriers for Drug Delivery

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Currently, the development of drug delivery and transportation systems has been the subject of high interest. Research in these areas has rapidly expanded in recent years, accompanied by the development of novel techniques for sample measurement and analysis. Nano-carriers have emerged as viable delivery mechanisms due to the versatility they exhibit. For instance, it has been discovered that utilizing liposomal formulations as drug delivery systems in controlled release offers increased safety and reduced collateral damage. In the biophysics laboratory at ICF-UNAM, liposomal formulations are being investigated as a means of delivering broad-spectrum polyene antifungals, such as Amphotericin B (AmB), and its derivative, the methyl ester di-chlorate of L-histidine of Amphotericin B, known as A21. It presents characteristics like higher water solubility and reduced collateral toxicity. This study focuses on liposomal formulations for drug administration due to their unique properties and ease of preparation. Two formulations with different lipid mixtures, labeled as L0 and L1, were prepared for both AmB and A21. The obtained formulations were characterized using the Tunable Resistive Pulse Sensing (TRPS) technique to evaluate their zeta potential and size. The impact of various ultrasonic agitation times and concentrations on these formulation parameters, with and without drugs, was assessed.

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Tγδ cells participation in the development of a lupus-like disease in mice triggered by stable NPAs

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a variable clinical phenotype, where the mechanisms that led to its development are not yet fully understood(1). In our research group, we have proposed that SLE and other autoimmune diseases are related to cell membrane alterations, where stable non-bilayer phospholipid arrangements (NPA) induce the formation of autoantibodies(2). On the other hand, it has been described that Tγδ cells participate in the pathogenesis of SLE by secreting specific cytokines(3) and can also respond against lipid antigens(4). In the present work, we studied the participation of Tγδ cells in the development of lupus in mice (BALB/c) induced by stable NPA. Tγδ cells from the spleen and mesenteric lymph nodes were analyzed by flow cytometry to evaluate their activation, cell cycle, mitochondria type, and cytokine production after 5, 10, and 15 days of stable NPA administration. A statistically significant increase in the absolute number of Tγδ cells from the spleen was detected in mice administered with liposomes bearing NPA compared to those that received saline solution. This increase was also observed in the production of IFNγ and IL-4 by Tγδ cells of both lymphoid organs. We also found that a higher percentage of Tγδ cells from mice administered with NPA were in the active phases of the cell cycle and exhibited fissioned mitochondria. Our data suggest that Tγδ cells participate in the processes that enable the establishment of the adaptive response and are possibly involved in the production of antibodies against lipids.

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The Branched Respiratory Chain of the Jellyfish *Stomolophus* sp.2 as an Adaptative Response to Climate Change

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Abstract
Jellyfish are ancestral organisms with a long evolutionary history on the planet. As survivors of natural phenomena and anthropogenic activities, these organisms present biochemical adaptations that have allowed them to adapt to the environment. It is suggested that jellyfish have specialized mechanisms for energy production under environmental stress conditions, such as climate change. Jellyfish, when exposed to temperature changes caused by climate change, display a series of metabolic responses that allow them to survive. In the cannonball jellyfish *Stomolophus* sp.2, it is known that the increase in seawater temperature is related to the rise in the metabolic rate of the polyps (asexual phase) and in their reproduction rate, resulting in the formation of jellyfish blooms. The energetic metabolism of jellyfish has yet to be studied. The bell cells of *Stomolophus* sp.2 are known to produce high levels of ATP even at elevated temperatures.

Therefore, we characterized the electron transport chain. Four alternative enzymes were identified as part of a branched respiratory chain (external-NDH2, internal-NDH2, AOX, mitGPDH), allowing the mitochondrion to maintain its membrane potential and constant energy production during thermal-stress conditions. In addition, changes in transcripts abundance resulting from jellyfish transcriptomes exposed to different temperatures (18, 23, and 33 C) were evaluated, and it was found that temperature promotes significant changes in gene expression of the four alternating enzymes. The branched respiratory chain of *Stomolophus* sp.2 is suggested as an adaptive response to face environmental challenges, allowing the organisms to face global warming successfully.

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Mitochondrial kidney dysfunction during NAFLD decreases by *Eryngium carlinae* ethanol extract administration

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Nonalcoholic Fatty Liver Disease (NFLD) is a clinical syndrome characterized by the excessive fat accumulation in the liver and hepatic cellular degeneration even in the absence of alcohol consumption. The histologic spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, and cirrhosis. NAFLD and chronic kidney disease (CKD) are worldwide public health problems, affecting up to 25-30% (NAFLD), and up to 10-15% (CKD) of the general population. Recently, it has also been established that there is a strong association between NAFLD and CKD, regardless of the presence of potential confounding diseases such as obesity, hypertension and type 2 diabetes. Recent evidence suggests that associated factors such as metabolic syndrome, dysbiosis, unhealthy diets, platelet activation and processes associated with ageing could also contribute mechanisms linking NAFLD and CKD.

Eryngium carlinae is a traditional herbal medicine in Mexico, commonly known as “Frog herb”. Previous research has shown that species of this genus contain a wide variety of secondary metabolites with bioactive potential, including flavonoids, saponins, triterpenes, coumarins, and derivatives of rosmarinic acid, polyacetylenes, and essential oils. Actually, reported that *Eryngium carlinae* administration has shown beneficials effects to regulate blood pressure, hypoglycemic and hypolipidemic effects in diabetic rats.

The aim of this work was to identify alterations in electron transport chain (ETC) function of kidney mitochondria in rats with NAFLD and the evaluation of the effects of *Eryngium carlinae* ethanolic extract intake in these alterations.

We found an increase in the body weight, consumption of oxygen mitochondrial, in the activity of complex II+III as well as in the membrane potential in groups where the *Eryngium carlinae* ethanolic extract was administered during induction of the NAFLD. These data suggest that the of *Eryngium carlinae* ethanolic extract administration has a protective effect delaying the kidney damage during the development of NAFLD in rats.

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An adenosine derivative promotes mitochondrial supercomplexes reorganization and restoration of mitochondria structure and bioenergetics in a DEN-induced HCC model

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Abstract: Hepatocellular carcinoma (HCC) has become highly relevant in oncology research due to its high mortality rate and difficult diagnosis and treatment. Most chronic liver diseases, including HCC, are characterized by bioenergetics deterioration associated with dysfunctional mitochondria. Hepatic mitochondria have unique features compared to other organs since this central organelle integrates the hepatic metabolism of carbohydrates, lipids, proteins, and energy production. However, no data are available about the relationship between mitochondrial supercomplexes formation and the ATP production rates in HCC. Our group has developed an adenosine derivative, IFC-305, proposed as a potential HCC treatment capable of improving mitochondrial dynamics. Since the effects of this compound on the mitochondrial architecture and energy production in HCC remain unclear, we aimed to determine the role of IFC-305 on mitochondrial structure and bioenergetics in a sequential cirrhosis-HCC model. Our results showed that IFC-305 administration in DEN-induced HCC in rats diminished the number and size of liver tumors, reduced tumoral markers expression in hepatic tissue and AFP serum levels, and reestablished the typical hepatic tissue architecture. In addition, it exhibited a reduction in the mitochondria number with recovery of the mtDNA/nDNA ratio and mitochondrial length when compared with HCC condition. Also, IFC-305 increased cardiolipin and phosphatidylcholine levels and promoted the reorganization of high molecular weight mitochondrial supercomplexes (hmwSC) (V2, I+III2+IV, I+III2+IV2, and I+III2+IV3). Furthermore, the expression levels of hmwSC assembly-related genes were correlated with the changes in the mitochondrial structure. Additionally, administration of IFC-305 in HCC modified the expression of several genes encoding elements of complexes I, II, III, IV, and V; and also increased the ATP levels by recovering the complex I, III, and V activity. We suggest that IFC-305 restores the mitochondrial bioenergetics in HCC by normalizing the number, structure, and functionality of mitochondria, possibly as part of its hepatoprotective mechanism of action.

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Modification of mitochondrial functions in a metabolic syndrome model and the effect of the drug IFC 305

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Metabolic syndrome is considered a global epidemic caused by high-calorie diets and physical inactivity. It is characterized by multiorgan failure, with one of the main affected organs being the liver, which is the focus of this project. The metabolic syndrome was induced from a high-fat model that consisted of a high-fat diet (37% carbohydrates and 45% fats plus 410 cal/l in drinking water) for 16 weeks in Wistar rats, in which the effect of the drug IFC-305 was tested. It should be noted that mitochondria were obtained from frozen liver tissue samples.

Previous studies of chronic hepatotoxicity models of cirrhosis and hepatocellular carcinoma have shown that they cause energy deficiency in mitochondria, redox state imbalance, and an increase in oxidative stress that alter mitochondrial function, metabolism, and dynamics. Based on this, a predominant role of mitochondria has been observed in response to an increase in energy intake. Therefore, the objectives of this project were to measure the activity of complexes I, II, III through a spectrophotometric method and ATPase through native gels of the electron transport chain to evaluate mitochondrial function. Another objective was to measure mitochondrial area, circularity, and count the number of mitochondria per field of electron microscopy images, as well as determine the presence of DRP1 and MFN2 to evaluate whether there is an imbalance in mitochondrial dynamics in any of the processes that compose it through the Western blot method.

The results obtained so far show a significant reduction in activity in complexes I and II in the high-fat diet group and a significant recovery when treated with IFC-305. There were no significant differences in activity for complex III and ATPase, but there was a tendency to increase with IFC-305 treatment. On the other hand, the analysis of mitochondrial morphology showed that mitochondria in the high-fat model had a significant increase in circular mitochondria. There was a tendency for recovery with IFC-305 of the elongated form of the mitochondria. There were no significant differences in mitochondrial area and number between treatments.

So far, the metabolic syndrome model indicates that a high-fat diet compromises the ability to generate energy through the electron transport of complexes I and II, suggesting that the model may be negatively impacting cell energy efficiency. The administration of the drug IFC-305 shows a beneficial impact on the recovery of damage caused by the metabolic syndrome model in the evaluated parameters of mitochondria.

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

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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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Mitochondrial iron homeostasis is disrupted in a murine model of obesity

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Iron is an essential metal found in several metalloproteins involved in respiration, oxygen transport, control of oxidants and DNA maintenance. Because of its redox properties, its homeostasis is strictly regulated at several levels to avoid cellular toxicity. Accumulating evidence shows that obesity predisposes individuals to alteration in iron homeostasis leading to low-grade anemia due to iron overaccumulation in non-hematopoietic tissues mainly in liver. Mitochondria plays a key role in iron homeostasis since within this organelle two important cofactors are synthesized, i.e., iron-sulfur clusters and hemes, besides its role as an important iron storage site. However, despite the evidence showing iron homeostasis alterations in obesity, the information concerning the role that mitochondria play in iron homeostasis under this metabolic status is scarce. In this work, we study how mitochondrial iron is handle in a mouse model of obesity. We found that total cell heme content decreases, indicating that heme biosynthesis could be compromised. Additionally, we found that ferrochelatase, the last step of the heme biosynthesis pathway, and frataxin, an important mitochondrial iron chaperone involved in iron-sulfur cluster and heme biosynthesis, were downregulated. Moreover, liver mitochondria from obese mice present lower activities of several enzymes containing iron-sulfur clusters and heme like aconitase, succinate dehydrogenase and cytochrome *c* oxidase

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Evaluation of mitochondrial dysfunction and oxidative stress in the liver of mice with induction of heart failure with preserved ejection fraction (HFpEF)

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Non-alcoholic fatty liver disease (NAFLD) and heart failure with preserved ejection fraction (HFpEF) are among the most common chronic liver diseases and the main form of heart failure (HF), respectively. NAFLD is closely associated with HFpEF, sharing common risk factors just as systemic inflammation, increased adipose tissue, dyslipidemia, steatosis, and metabolic dysfunction. Both diseases have been linked to high-fat and high-sugar diets. Mitochondrial dysfunction is involved in these alterations in other metabolic diseases, However, mitochondrial dysfunction in liver has not been evaluated in HFpEF. Thus, we induced HFpEF in C57BL/6 mice by feeding with a high-fat, high-sugar standard diet (DIO Rodent Purified Diet w/60% Energy from fat – Blue) and L-NAME in the drinking water by eight-weeks. Control mice (CTRL) were feeding with standard rodent diet. Mitochondria were isolated by differential centrifugation, and mitochondrial function was evaluated by measuring respiration in states 4 and 3 using a high-resolution respirometer (Oxygraph, Oroboros Instrument). Although not statistical differences were observed in respiration between the HFpEF and CTRL groups, there was a trend to decreased respiration in the HFpEF group. The activities of mitochondrial electron transport chain complexes (complexes I to IV) were assessed spectrophotometrically, employing adequate substrates and inhibitors for each complex. The activities of complexes II and III were lower in the HFpEF group than in the CTRL group. Regarding to oxidative stress, lipid peroxidation and cardiolipin levels were measured. No discernible differences were noted between the CTRL and HFpEF groups. Despite it may be a probable association between NAFLD and HFpEF, it is probable that hepatic damage it is not fully evident with the 8-week treatment with the high fat diet. Therefore, further evaluation of the model at 12 weeks is deemed necessary for better assessment of significant differences in oxidative stress.
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IL10RB, IL2RG, TNFRSF1A expression in neutrophil membranes in patients with chronic inflammation with rheumatoid arthritis

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Abstract: Chronic inflammation is defined as gradual, persistent, and prolonged inflammation that lasts from months to years (Pahwa *et al.*, 2022). Chronic inflammatory diseases, such as autoimmune diseases, diabetes mellitus, atherosclerosis, negatively impact on patients' quality of life. Recent literature describes a prominent and significant role of neutrophils in chronic inflammation. Recruitment of neutrophils to sites of chronic inflammation stimulates the inflammation cascade through the formation of neutrophil extracellular traps (NETs) and the release of serine proteases (Herrero-Cervera *et al.*, 2022). Ultimately, this activates additional immune complexes and therefore fuels the chronic inflammation process. IL10RB, IL2RG, TNFRSF1A are three surface cytokine receptors expressed on neutrophils that are worth analyzing due to their impact on the chronic inflammation cascade. IL10RB is an accessory chain necessary for the active IL-10 receptor complex. Co-expression of IL10RB and IL10RA surface cytokine receptors is essential for IL10-induced signal transduction. IL2RG is a necessary signaling element of many interleukin receptors, such as IL-2, IL-4, IL-7, and IL-21. TNFRSF1A is found both in membrane-bound and soluble forms that interact with its ligand, tumor necrosis factor alpha. Its activation is a factor in cell survival, apoptosis, and inflammation. The expression of these proteins in neutrophils has been confirmed by our group analyzing the GSE213313 database (2023). Additionally, IL10RB, IL2RG, TNFRSF1A, have been linked with disease activity, severity, and genetic upregulation in patients with rheumatoid arthritis (RA) in serum samples and synovial tissue samples (Lopez-Pedrera *et al.*, 2022; Feng *et al.*, 2023; and Perik-Zavodskaia *et al.,* 2023). Therefore, we aim to analyze the expression of the aforementioned surface cytokine receptors in neutrophils to determine regulatory processes during the pathophysiology of chronic inflammation in RA, one of the most common autoimmune diseases worldwide. These results may offer valuable insight for future RA diagnosis, treatment, and upcoming research in this field.

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Phyletic distribution and natural history of accessory subunits e, g, i/j and k that participate in dimeric/oligomeric F_1F_O ATP synthase arrangements

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F_1F_O ATP synthase is widely conserved in bacteria, mitochondria, chloroplasts, and even some archaea. The ATP synthase, particularly the mitochondrial one, can be found in dimeric/oligomeric arrangements. The dimeric or oligomeric arrangements are organized in rows inducing membrane invaginations called mitochondrial cristae. Different model organisms have allowed the identification of several dimers that vary in subunit composition, curvature angle between monomers as well as their supramolecular organization. The dimer of the F_1F_O ATP synthase (V_2) present in mammals and fungi is mainly stabilized by the subunits e, g and b, as well as the subunits i/j and k according to the obtained models.
The seemingly ubiquitous presence of V_2 in eukaryotes led us to ask: How were the subunits that participate in the dimerization of F_O of the mitochondrial F_1F_O ATP synthase recruited? What is its natural history and phylogenetic distribution of the subunits responsible for F_O dimerization?
To answer these questions, we obtained the available sequences from both NCBI and Pfam for the subunits of interest. Duplicated, outdated sequences were cleaned and the most conserved isoform per gene was selected to obtain phylogenetic trees. We also performed an analysis of the presence/absence of the subunits of interest by searching 1110 refseq genomes of eukaryotic organisms. Finally, the already cleaned and aligned sequences were used to generate conserved amino acid sequence logos. The results obtained showed a wide presence of the e and g subunits within ophistokonta, amebozoa, archaeoplastida and other protists. The GXXXG motif and other previously found key positions are even present in more divergent taxa. The i/j and k subunits, on the other hand, were found only in fungi.
Neither the e nor g subunit was found within microsporidia, discosea and archamoebae. These taxa are distinguished by possessing mitochondria-related organelles (MRO) instead of mitochondria. Interestingly. e and g subunits also showed high divergence and a high redundancy of homologs in plants and animals.
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NKT cells and Tγδ lymphocytes activity against bacterial and non- bacterial lipids

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Lipids are essential macromolecules in organisms, beyond their structural role they were not considered relevant in diseases. However, recent studies have reported their involvement in several diseases, both infectious and autoimmune, including lupus. The *Mycobacteryum tuberculosis* (MTB) cell wall is a contributing factor to the establishment of infection, since it provides resistance to different agents. One of the main components of the MTB cell wall are lipids. NKT cells and Tγδ lymphocytes are unconventional cells capable of generating a response to self and non-self lipid antigens through cd1 molecules. In this work we will evaluate the response of NKT cells and Tγδ lymphocytes to lipids isolated from *Mycobacterium tuberculosis* H37Rv and compare this response with a lupus-like murine model based on lipids. Activation, cell cycle and cytotoxicity parameters will be discerned using flow cytometry.

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Evaluation of Redox status and inflammatory markers in plasma of female professional athletes

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Exercise enhances the physiological demand of the body, increasing oxygen consumption and excess of metabolites that need to be further disrupted or excreted. The Redox balance in plasma and inside cells plays a transcendental role in order to keep the body functioning at optimal conditions during long periods of exercise (more than 30min). Lately the concept of Oxinflammation has emerged since redox balance and inflammation are two processes that cannot be separated from each other. Therefore, the release of myokines such as IL-6 and Reactive oxygen species (ROS) during exercise is a fully connected process, however not necessarily undesirable. IL-6 when considered as an autocrine myokine has benefits for muscle contraction performance and tissue protection. Its secretion depends on the Redox status of the extracellular environment and is therefore necessary for proper exercise performance, but without reaching extreme values. In this study we aim to evaluate the redox status and IL-6 plasma concentrations of female professional athletes before and after a 2h training. We aim to associate these dependent variables with training performance quality, hormone concentrations and anthropometric variables in order to find out if any of these parameters could be associated with the variations of both outcomes and the performance of exercise. For this we are going to use blood samples of at least 10 female professional athletes, isolate through centrifugation the plasmatic phase and evaluate 3 different parameters: hormone parameters, IL-6 concentration and Redox status. Anthropometric parameters are going to be measured by Impedance and the quality of training performance is going to be evaluated by a survey of the Coach. We hope to achieve this at least during three training sessions.
This work intends to find out variables affecting the oxinflammation status of the athletes and hopefully give some nutritional recommendations that could help optimize training performance by the consideration of their biochemical and endocrine parameters.

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Mitochondrial HCN3 channel protects against oxidative stress by stimulation of mitophagy and apoptosis in renal proximal tubule cells

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Abstract:
The family of hyperpolarization-activated and cyclic nucleotide gated channels (HCN1-HCN4), known as pacemaker channels in nervous and cardiac cells, constitutes a pathway for the uptake of Na+, K+ and NH4+ in the kidney (Carrizosa et al. 2011; López et al. 2016). HCN channels are also localized in mitochondria (mitoHCN) of rat and human kidney. MitoHCN regulates the membrane potential (ΔΨm), oxygen consumption and ATP synthesis in mitochondria (León et al. 2019; Padilla et al. 2020). MitoHCN3 is abundant in the luminal membranes and mitochondria of the proximal tubule cells and its degradation is accelerated in lysosomes under metabolic acidosis (MA), a common condition in chronic renal disease (López et al. 2020). In MA, the production of reactive oxygen species (ROS) increases and depends on ΔΨm, which can trigger mitophagy and/or cell apoptosis. In this work we study the role of mitoHCN3 in the regulation of ROS production, mitophagy and apoptosis in renal proximal tubule cells (NRK-52E). MitoHCN3 was pharmacologically inhibited with ZD7288 for 24h in conditions where ROS production mitophagy and apoptosis are augmented (acidosis and cytotoxicity with cisplatin). Western blot, spectrofluorometry and flow cytometry techniques were used. Inhibition of MitoHCN3: a) increased ROS levels in both basal and acidotic conditions, b) decreased the abundance of Beclin-1, LC3βII and Parkin-2 in acidosis, c) increased apoptosis in cells incubated with cisplatin, and d) depolarized the ΔΨm in basal and cisplatin conditions. Our results suggest that K+ leak through mitoHCN3 channels contribute to mitophagy and protect against ROS production and apoptosis by ΔΨm regulation in renal cells.

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Effect of chemical inhibitors on the recombinant G6PD::6PGL fused protein of the parasite *Trichomonas vaginalis*

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Abstract:

Trichomoniasis is a sexually transmitted disease (STD) caused by the protozoan *Trichomonas vaginalis*. This infection is very common in the world, with an incidence of around 270 million people affected per year and an estimated prevalence of 8.1% for women and 1.0% for men. *T. vaginalis* uses carbohydrates as its main source of energy, and the glycolytic, pentose phosphate pathway is also important in the metabolism of *T. vaginalis*. In this pathway, glucose-6-phosphate dehydrogenase (G6PD) is a key enzyme that catalyzes the first step. The G6PD protein of *T. vaginalis* differs in length and amino acid sequence with respect to human G6PD because it has been reported that in *T. vaginalis* the gene that codes for G6PD are fused with the gene for 6- phosphogluconolactonase (6PGL) to give rise to a fused G6PD::6PGL enzyme, so the structure of the G6PD::6PGL enzyme is different from that of the human G6PD protein. In this project, the inactivation of the fused recombinant protein G6PD::6PGL of *T. vaginalis* with chemical compounds was studied to propose this protein as a possible pharmacological target, by taking advantage of the differences with the human G6PD enzyme. Functional and structural assays were carried out on the recombinant G6PD::6PGL fused enzyme from the parasite *T. vaginalis*. From a library of 55 chemical compounds, four compounds (JMM-3, CNZ-3, CNZ-17, and MCC-7) were selected that exerted greater than 50% inhibition on the enzyme. Determination of the IC50 calculated for the four compounds indicated values of 155.1, 93, 356, and 260 μM respectively. These IC50 values were used to obtain the second-order inactivation constant (k2) of each of them, their reactivity indicated values of 0.32, 0.63, 0.34, and 0.38 M^{-}

$^{1}s^{-1}$ for compounds JMM-3, CNZ- 3, CNZ-17, and MCC-7. Subsequently, a series of structural tests were carried out to determine changes in the secondary and tertiary structure of the G6PD::6PGL protein in the presence of the inhibitors. Circular dichroism assays indicated that the compounds affect the secondary structure of the protein which correlates with the loss of catalytic activity. The evaluation of the tertiary structure of the G6PD::6PGL protein in the presence of the four compounds showed a change in the microenvironment of the tryptophan residues, as well as in the hydrophobic zones when evaluated by intrinsic and extrinsic fluorescence.

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Mitochondrial bioenergetics is compromised in a preclinical model of cardiometabolic heart failure

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Background. Heart failure (HF) stands as a top cause of death and disability worldwide. In particular, cardiometabolic heart failure with preserved ejection fraction (HFpEF) can be conceived as the cardiac manifestation of a systemic metabolic disturbance, typically, driven by obesity. In the present study, transcriptomic data from the heart suggested that mitochondria may be central to cardiometabolic HFpEF. Functional assays confirmed bioenergetic impairment in the cardiomyocytes of HFpEF animals.
Methods. HFpEF animals consisted in mice fed with a high-fat diet and exposed to L-NAME during either five or eight weeks. Controls (CTRL) received a standard chow diet. Gene expression of the heart was assessed via next-generation-based RNA-seq and qPCR. High-resolution respirometry was used to quantify the oxygen consumption of ventricular cardiomyocytes. Mitochondrial membrane potential was assessed by confocal microscopy imaging in TMRE-loaded myocytes.
Results. HFpEF animals were characterized by increased body weight, visceral fat accumulation, hypertension, and diastolic dysfunction. At the heart level, RNA-seq uncovered 1535 differentially-expressed genes (DEGs), for HFpEF vs. CTRL. 146 DEGs (142 down-regulated in HFpEF) were contained in the GO-CC “mitochondrion” term, mostly affecting respiratory complexes I, IV, and V in a time-dependent progressive manner. Consistently, high-resolution respirometry revealed that the maximal capacity of the electron transfer system was compromised in HFpEF myocytes along with an increased leak respiration. Confocal microscopy imaging showed a diminished mitochondrial membrane potential, which may limit the energy supply to fuel myocyte relaxation and ultimately underlie diastolic dysfunction at the heart level.
Conclusion. Our findings suggest for the first time impaired mitochondrial bioenergetics in the cardiomyocytes of a murine model of cardiometabolic HFpEF.

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The ζ subunit from the F_1F_O-ATP synthase of *Sinorhizobium meliloti* is pH sensitive as reveiled by 2D-NMR

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The F_1F_O-ATP synthase is a multi-protein complex that is in charge of synthesizing more than 90 % of the cellular ATP, and this enzyme is represented in the three domains of life. Under particular conditions, this enzyme can also hydrolyze ATP, which can be adverse for organisms. Because the complete hydrolysis of ATP will have as an outcome cellular death, this ATPase activity is regulated by several mechanisms. Here we will focus on the regulatory subunits: ε for most bacteria, IF_1 for the mitochondrial enzyme, and ζ for the α-proteobacteria. The regulatory mechanism of the e subunit is that of a sensor of concentration of ATP, in which when in the cytoplasm of bacteria if the concentration of ATP is low, the e subunit will have a conformational change, where its C-terminus will adopt an extended conformation and inhibit the ATPase activity of the enzyme. The mitochondrial IF_1 subunit has a pH-sensitive mechanism in which it is tetramerized in basic pH. It is in a non-inhibitory conformation, but oxygen is scarce when the conditions are adverse. There is no proton pumping by the electron transport chain; the influx of protons by the F_O channel of the enzyme into the mitochondrial matrix acidifies the pH of the matrix, which then subsequently IF_1 will adopt a dimeric inhibitory conformation, ensuing the inhibition of the ATPase activity. The case of the ζ subunit is particular, as it is known to bind ATP, but how the binding of ATP in the regulatory mechanism is still unknown. More so, as we were determining the structure by NMR of the ζ of the α-proteobacteria *Sinorhizobium meliloti* (PDB ID 7VKV) using a double-labeled 13C, 15N, we found that at different pHs, there were chemical shifts, which indicate movements of the subunit, indicating it is pH sensitive. Here we will show our ^{1}H, ^{15}N-HSCQ data on the ζ subunit from *Sinorhizobium meliloti*.

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The secretion and activity of *K*1 killer toxin are triggered by the interaction of *Killer* / sensitive in growth assays

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In 1963 the first evidence of a killer yeast was shown, since then several killer toxins have been discovered, not only in *S. cerevisiae* but also in other fungi (Rodríguez-Cousiño et al., 2017). One of the most studied *killer* toxins of *S. cerevisiae* is *K*1, whose viral origin is codified by ScV-M1 also known as *killer* 1 virus, its product is a preprotoxin (pptox) containing four subunits: δ, α, γ, and β from which δ and γ are removed, leading to an "immature" α-β dimer joined by one or three disulfide bonds (Gier et al., 2020). The most accepted mechanism of killing occurs when β recognizes the 1-6-β-D-Glucan, leading α to interact with the target TOK1 (Sesti et al., 2001). Previous studies from our lab demonstrated the importance of pH regulation on the activity of *K*1 over sensitive strains, showing the highest effect at pH 4.7. However, little is known about the role of the sensitive strain in the killer system. In the present study, the role of the sensitive strain during the interaction *Killer*/sensitive was demonstrated. Two control conditions (YPD, and Inductor Media) were tested (Growth, killing zone, and Total protein) to compare the *K*1 yield over 75 hrs, and agar plate pH 4.7 inhibition zone assays were also performed to corroborate the *killer* effect. To know if the interaction between the two strains is necessary to induce or increase the *K*1 production, an independent co-culture was set along a modified Kirby-Bauer assay, increasing the interaction distance between the growth spots of *Killer* from the sensitive. The *K*1 dynamics on YPD and Inductor media were very similar in total protein secretion to the media (1.4 µg and 1.2 µg) and killing zone (0.140 cm^2 and 0.139 cm^2 respectively). Interestingly, the coculture showed increased total protein secretion at 24 hrs with no difference in the inhibition zone. However, the distance assays showed that the presence of the sensitive strain is necessary to induce the *killer* effect, even in those in which the distance was 1 mm away from each other. These data strongly suggest the importance of the interaction between the *Killer* and the sensitive strain at the activation phase. The role of the sensitive strain seems to be the signalization for the killer strain to activate the immature state of *K*1, meanwhile, the *Killer* strain keeps a constant production yield, ready to attack when the sensitive is present in the environment.

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Evaluation of the signaling pathway involved in the cardioprotective effect of cannabidiol (CBD) dependent on mitochondrial calcium handling and PPARγ activation in hypertrophic cardiac myoblasts

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Background: Cardiac hypertrophy is a crucial component in heart failure, hence its wide attention as a molecular target and the interest to study its molecular mechanism involved. On the other hand, CBD a phytocannabinoid, has been reported to activate various receptors, including peroxisome proliferator-activated receptors (PPARs), which are also implicated in the development of pathological hypertrophy. In this study, we investigate if CBD anti-hypertrophic activity depends on PPARγ activation.

Methods: We used rat H9c2 myoblasts to investigate the effects of CBD on cardiomyocyte hypertrophy. To induce hypertrophy, the cells were treated with Angiotensin II (Ang. II), subsequently, CBD was administered to the hypertrophied cells. Mitochondrial Ca^{2+} handling was evaluated using Calcium green dye, and mROS were evaluated using mitoSOX. Mitochondrial activity was evaluated using oximetry. Moreover, we used specific PPARγ inhibitors to evaluate the potential cardioprotective effect. To quantify the changes, we measured the expression levels of hypertrophy biomarkers (BNP, COL 1) and PPAR isoforms using qPCR. To evaluate one of the signaling pathways that could be involved, AMPK was performed by Western Blotting.

Results: Our findings indicate that the administration of CBD to hypertrophied cardiac myoblasts treated with Ang. II leads to a reduction in cell size and other biomarkers associated with hypertrophy. CBD also reduced mROS production and reduce mitochondrial calcium uptake by regulating the mitochondrial calcium uniporter activity observed in hypertrophic cells. Of note, mitochondrial calcium overload triggered by a mitochondrial Na+/Ca2+ exchanger blocker resulted in hypertrophy and inflammation regardless of CBD administration. Moreover, hypertrophy on cardiac cells revealed a 3-fold increase in MCU overexpression. Under this condition, the respiratory control ratio was reduced by 30% concomitant with a reduction of calcium retention capacity and mitochondrial dysfunction. Notably, this cardioprotective effect of CBD appears to be dependent on the PPARγ molecule, as blocking it abolishes the observed effects. These results strongly suggest that CBD exerts its beneficial impact on cardiomyocytes through its interaction with PPARγ. In addition, molecular docking simulations indicate that CBD conformation was allocated near the activation function-2 helix in PPARγ.

Conclusion: These findings open up the possibility of using CBD and modulation of PPARγ receptors as a therapeutic strategy to prevent or reverse cardiac hypertrophy. However, further understanding of the hypertrophic inhibition mechanisms and the specific signaling pathway is necessary to develop innovative therapeutic interventions.

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Role of voltage-gated L-type Ca^{2+} channel (ICa.L) and ryanodine receptor (RyR2) in the effect of the noisy stimulus on Ca^{2+} dynamics of cardiomyocytes

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Abstract:
Noise is an intrinsic property of physiological systems, affecting the nervous and cardiovascular systems[1]. It has experimentally been shown that noise enhances the homeostatic function of the blood pressure regulatory system. Recently, we demonstrated low levels of noisy stimulation improve calcium dynamic[2] and contractile response in cardiomyopathy model cells. However, the mechanisms underlying this general phenomenon remain to be characterized. We have investigated the role of voltage-sensitive molecules such as voltage-gated L-type Ca^{2+} channel (*I*Ca.L) and ryanodine receptor (RyR2) on the Ca^{2+} dynamics of cardiomyocytes in response to a noise stimulus. Mouse cardiomyocytes were isolated using the simplified, Langendorff-free method3. A pharmacological inhibition of *I*Ca.L and RyR2 was performed, and Ca^{2+} dynamics parameters were obtained using imaging signals by epifluorescence microscopy. Cardiomyocytes were stimulated with a train of five pulses of 20V and 5ms duration using a function generator programmed in LabVIEW and a data acquisition board and applied by two platinum electrodes. Amplitude, frequency, and noise level are controlled. We found that the baseline results showed that with a 20% noise level, the Ca^{2+} transient amplitude, rise rate, and decay 50% improved. The individual inhibition of *I*Ca.L and RYR2 by amlodipine and ryanodine decreased the Ca^{2+} transients by at least 50%. However, the *I*Ca.L inhibition changed when 10 and 20% noise levels were added to the stimulus since the Ca^{2+} transients were retrieved, reaching the basal response without inhibition. We proposed that the noisy stimuli may induce fluctuations in the membrane potential, increasing the probability of opening of *I*Ca.L and, therefore, improving the intracellular Ca^{2+} dynamics. We drew this conclusion with reservation. These findings have improved our understanding of the molecular mechanism regulated by noisy stimulus in cardiomyocytes.

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IFC-305 treatment inducesapoptosis inHepG2 cells

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Hepatocellular cancer(HCC)is a type of liver cancer, causedby several factors such as cirrhosis, virus hepatitis B, virus hepatitis C, and others.InHCC, there is an imbalance between cell proliferation and cell death. In the case of apoptosis can be evaded either by alterations in the signaling pathways that regulate it or by mutations.On the other hand, the effectivenessof treatmentsor development resistance to treatment is a problem in liver cancer so it is necessary to research more effective therapies. There are studies about adenosine derivate or IFC-305as hepatoprotection, previous studies have shown that IFC-305 treatmentcouldregulate mitochondrial dynamicsand autophagy in rat modelsof livercancer induced by DEN, however, itisunknown if apoptosis is part ofits mechanism of action.
Thisstudy usedHepG2 cells(cells derivate from liver cancer),and a time course was performed with the IFC-305 treatment (1 and 5mM)to evaluatethe mRNA and protein of Bak and Bcl-2. Bak expression levels increase in both IFC-305 concentrations, however, this increase is greater with 5mM at 3 hours. On the other hand, we determinewhether the expression levels of Bcl-2 (anti-apoptotic protein) were also modified. When performing the RT-qPCR, it showed that the expression of Bcl-2 is decreased with respect to the time of treatment with IFC-305, this decrease isgreater with 5 mM at 24 hours. The results suggest that IFC-305 treatment is modulating the expression levels of Bak and Bcl-2.
To corroborate if the abundance of proteinsrelated to apoptosisis also modified,we perform a western blot. The abundance of Bak is increased at 48 hours, while the Bcl-2 protein is decreased at 12 hours with 1mM IFC-305, however, in the IFC-305 5mM treatment, the abundance of Bak isdecreasedat 6 hours. The results suggest that there are changes in the expression of Bak and Bcl-2 with IFC-305. To determine if apoptosis is activated cleavedcaspase 3was evaluated, showing that it was cleavedafter 24 hours with the 5 mM IFC-305 treatment.The mitochondrial dynamic is important for regulating apoptosis so we evaluated DRP-1 and MFN2, it is shown that there are changes in the abundance with respect to IFC-305 treatment and time evaluated.Moreover, we showed that there is a reduction in the formation colony of HepG2 cells and this decrease is higher in correlation with IFC-305 concentration. Taken together, the results suggest that treatment with IFC-305 could promoteapoptosisin HepG2 cells.

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Molecular interactions and quantitative descriptors of Maximin 3 with different lipid membrane archetypes

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Maximin 3 (Max3) is a cationic antimicrobial peptide (GIGGKILSGLKTALKGAAKELASTYLH-COOH) that is found in skin secretions and the brain of the Chinese red-belly toad Bombina maxima. Up-to-date, the molecular interactions that govern its antimicrobial activity and membrane specificity are still unknown. In this research we implemented all-atom (AA) molecular dynamics simulations (MDs) and liposomal formulations to gain insight into the molecular interaction of Max3 with bacterial, mammal and fungal membrane archetypes. Molecular details revealed how the peptide modifies local lipid organization. Max3 draws the polar heads of the phospholipids towards the center of the bilayer inducing membrane thinning and increases area per lipid. Additionally, lipid acyl chain order decreases in the vicinity of the polar head. Membrane thinning led to the generation of a small water channel using the lysine residues located on the hydrophilic face of the α-helix as a “stairway”. Electrostatic free energy calculations show that Max3 in transmembranal state (TM-State) has a higher affinity for bacterial membrane than for sterol-rich membranes. Peptide-induced calcein leakage experiments demonstrated that Max3 has high activity and selectivity towards bacterial membranes, and low activity towards sterol-enriched systems (mammalian and fungal models). Some of the analyses presented in this work could be useful parameters for machine learning protocols as predictors of membrane active peptide activity and selectivity to specific membranes.
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DESIGN OF PEPTIDE INHIBITORS OF PM1:PM2 MEMBRANE PROTEIN INTERACTIONS OF THERAPEUTIC INTEREST IN CANCER

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In recent decades, the development of new cancer treatments has been specifically directed against proteins involved in the development of the disease, such as the case of antibodies such as trastuzumab that can inhibit the activity of the factor two membrane receptor. of epidermal growth (HER2 or ERBB2), involved in the process of cell replication. In the specific case of HER2, the antibodies or drugs used as treatments usually inhibit the receptor by binding to its extra- or intracellular domain. The reason why mutations in the epitope and the inability to cross the cytoplasmic membrane are the main causes of the decrease in anticancer activity. In this work, bioinformatics tools were used to design using the antimicrobial peptide VC15 as a template and peptides from anticancer and antimicrobial databases to design "*in sillico"* short peptides with the ability to inhibit the activity of HER2 by binding to the transmembrane region of the receptor**.** Several databases and bioinformatic platforms were used such as PPIMem, Regex101, Chimera, GRAMM, CancerPPD, CAMP, DRAMP, BDASSP, Vina and bash, Marvin Sketch editor, Open Babel, MOL2 Autodock Vina, protein.plus viewer, CancerAPP, FMAP de membranom, AntiCP 2.0, CAMPR3 ToxiPrend, HemoPI, peptide cutter Allergent, and AllerTop. A total of 157 mutants were obtained, of which 73 were obtained by superposition of the receptors with VC15 and 84 by comparison of the consensus receptors sequences and the selected anticancer peptides. Five generated mutants presented a good interaction energy with Her2 receptor these sequences are VC15-2HA-7RH-10QRKRN (-6.7 Kcal/mol), VC15-10QRKRN (-5.7 Kcal/mol), VC15- 11(-8.9), VC15-12 (-6.7 kcal/mol) and VC15-66 (-6.0 kcal/mol). The best candidates to inhibit the PM1:HER2 interaction are the mutuals VC15-12 with an interaction energy of -6.7 Kcal/mol, VC15-156 with an interaction energy of -4.7 Kcal/mol, and VC15-157 with -4.8 Kcal/mol. mole These are also the candidates that have better interaction and penetration into the membrane, making interaction with HER2 more likely.

Z González, M Adame, E Cuevas, G Corzo, E Villegas, "Antimicrobial activity of cationic peptide VC15 obtained from the proteolysis of Pin2", Toxicon, Vol. 182, pag. S21, 2

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Metabolic energetic alterations on fatty liver disease in a heart failure with preserved ejection fraction preclinical model

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Background: Non-Alcoholic Fatty Liver Disease (NAFLD) and non-alcoholic steatosis have ventricular heart disease that often manifests clinically as Heart Failure of Preserved Ejection Fraction (HFpEF). HFpEF with NAFLD prevalence could reach 50%, and half of these patients also course with advanced fibrosis, but nowadays, it is not described which clinical entity appears first during a time course of patient evolution, either the molecular or cellular mechanisms related with. Besides frequency, there is no specific treatment for these metabolic diseases. The experimental induction of HFpEF has been achieved by a model of cardiometabolic disease induced by hypertension and a high-fat diet, which produces ventricular dysfunction and systemic modifications, physiologically mimicking what occurs in the metabolic syndrome, that could be followed through time. This model has widely characterized cardiac dysfunction. However, it is unknown if NAFLD is recapitulated in this model, similar to patients with HFpEF during time evolution.

Methods: We analyzed C57BL/6 mice in 3 groups, controls, and 8 and 12 weeks of HFpEF, for which serum and liver tissue were extracted. We evaluated serum parameters of HDL, LDL, TG, ALT, AST, albumin, and protein. In liver tissue, we assessed the presence of steatosis and fibrosis with H/E and Masson. Triacylglycerols (TG) and cholesterol were quantified, evaluation of mitochondrial function, oxidative stress markers, LPO, inflammatory and lipidic markers associated with fatty acids metabolism.

Results: HFpEF mice presented alterations regarding the function of the left ventricle, impairment in diastolic pressures, high stiffness index, and pulmonary congestion. As expected, HFpEF mice exhibited no differences in ejection fraction. The cross-sectional area of the cardiomyocytes showed hypertrophy. Liver tissue micrographs showed the presence of micronodular steatosis in animals with HFpEF without forming fibrotic bridges or changes at the parenchyma level. We observed a significant difference between groups for TG and LDL serum values. Likewise, a notable increase in TG accumulation in liver tissue is observed. However, this accumulation of lipids does not induce remarkable mitochondrial damage as respiratory control or mitochondrial phosphorylating efficiency at eight weeks, but other metabolic and energetic changes over hepatic tissue are manifested until 12 weeks of HFpEF development.

Conclusions: Due to a high-fat diet and hypertension, dyslipidemia was demonstrated. Hepatic liver turnover and changes over metabolic energetic function are time-course dependent and related to intracellular lipid overaccumulation, suggesting liver damage associated with HFpEF, but in a chronicle way.

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Characterization of the Function of the Tef4 Factor in Yeast Mitochondria

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The eukaryotic elongation factor 1Bγ (eEF1Bγ) belongs to the eEF1 complex, whose function is to deliver amino acids to the ribosome during cytosolic translation. In yeast, it has two isoforms encoded by the genes *TEF3* and *TEF4*. Deletion of both isoforms has no impact on translation, suggesting that they may function solely as structural proteins. Recent studies using yeast mitochondria proteomes have revealed the presence of several cytosolic translation factors in mitochondria, raising questions about their functions within this organelle. One such factor that could be associated with mitochondria is the isoform Tef4, encoded by *TEF4*. To confirm the localization of Tef4, we obtained highly purified mitochondria and successfully identified Tef4 as a component of mitochondria. Currently, we are investigating its specific localization within this organelle.

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Kill me if you can: the long-lived yeast *Rhodotorula mucilaginosa*

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Organisms that age slowly provide important information to understand the mechanisms underlying the normal aging process. Evolution-conserved pathways regulate aging. Modifying individual genes within these pathways can dramatically prolong life, slowing aging. Some long-lived mutants are impressive, e.g., *Heterocephalus glaber* (naked rat) or *Hydra vulgaris* (hydra) exhibit exceptionally long lifespans. Regretfully, these long periods make studies complicated and expensive. Thus a viable alternative may be *Rhodotorula mucilaginosa.* This extremophile yeast may survive for very long periods under stress. It also has a versatile metabolism, expressing a branched respiratory chain and synthetizing carotenoids. The objective of this work is to evaluate whether the *R. mucilaginosa* yeast is a useful long-lived organism model by comparison with *S. cerevisiae* at different aging stages where we will perform viability tests, mitochondrial function, reactive oxygen species (ROS) production, ATP content, membrane potential, antioxidant enzyme activity and carotene quantification.

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Immonumodulator Effect of Cannabidiol in Macrophages Activated with Palmitic Acid

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Macrophages can be differentiated in two main subsets M1 (pro inflammatory) and M2 (anti-inflammatory). This plasticity, allows macrophages to adapt to various physiological and pathological conditions, contributing to the maintenance of tissue homeostasis and the resolution of inflammatory states. Fatty acids, such as palmitic acid, can influence the polarization of macrophages and its relationship with macrophages is a subject of interest in the context of inflammation and contribute to insulin resistance, potentially impacting metabolic diseases including obesity and diabetes. In chronic inflammation, macrophages produce and release pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) resulting in more inflammation, macrophages engulf large quantities of triglycerides, leading to collateral damage and exacerbation of this inflammatory state. Cannabidiol (CBD), a non-psychoactive compound derived from *cannabis sativa,* has gained considerable attention for its potential therapeutic properties, including its anti-inflammatory effects.

CBD interacts with several of receptors and signaling molecules that help to regulate physiological process, including inflammation and immune responses, reducing the production of cytokines like TNF-α, IL-1β and IL-6. CBD antioxidant properties can ameliorate oxidative stress within macrophages. Oxidative stress can contribute to inflammation and tissue damage, but CBD´s properties can neutralize harmful free radicals as protective effects.

In this work, we studied the effect of CBD in macrophages metabolically activated. Human monocytes, U937 cells, were differentiated to macrophages by phorbol myristate acetate during 3 days and treated with palmitic acid ± CBD during 24 hours. Preliminary data indicate that triglycerides accumulate in metabolically activated macrophages, with CBD reverting this change. Production of pro- and antiinflammatory cytokines were analyzed, showing that CBD reduced the former compared to metabolically activated macrophages. Oxygen consumption rate revealed that CBD is able to modulate macrophage activation.

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Alternative components can help against oxidative stress

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Abstract:

Rhodotorula mucilaginosa is an oleaginous yeast that has been isolated from a wide variety of extreme environments, such as high pressure, high salt concentration, low temperature and heavy metal contamination. Carotenoids and lipids produced by *Rhodotorula* are of great interest to the pharmaceutical, cosmetic and biofuel industries. *R. mucilaginosa* has been tested against different types of stress such as osmotic, oxidative and low temperatures, observing an increase in antioxidant enzyme activity and in the production of carotenoids and lipids. Several yeast species react to stress modifying the composition of their branched respiratory chains enduring stress situations better. The respiratory chain in *R. mucilaginosa* is branched, expresses at least two type II NADH dehydrogenases (NDH2), one internal and one external plus the presence of an alternative oxidase (AOX). Branching could be useful for survival and tolerance to adverse conditions where *R. mucilaginosa* has been isolated. Therefore, the effect of different oxidative stress inducers was evaluated after inhibiting the alternative components of the respiratory chain of *R. mucilaginosa* to verify that the alternative components are an essential factor for resistance to oxidative stress.

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The ancillary subunit KChIP2c modulates the inhibitory effect of sertraline on Kv4.2 channels

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Kv channel-interacting proteins (KChIP) is a family of ancillary subunits that co-assemble with Kv channels to modulate their biophysical properties. KChIP2 is the only isoform expressed in the heart, with KChIP2c being the most abundant. In this tissue, KChIP2c co-assembles with Kv4.2 channels to underlie the fast-inactivating transient outward current (I_{tof}). Sertraline, a selective serotonin reuptake inhibitor, is an antidepressant drug that has been reported being able to induce cardiac toxicity at therapeutic doses. However, the mechanism by which sertraline induces this toxicity and the potential involvement of KChIP2c in such mechanism have not been investigated. In this study, we observed that sertraline inhibited both Kv4.2 and Kv4.2/KChIP2c channels in a concentration-dependent but voltage-independent manner. The drug had higher affinity (~4-fold) for the heteromeric channels (IC50 ~ 3.9 μM and 1.1 μM for Kv4.2 and Kv4.2/KChIP2c channels, respectively). In addition, sertraline accelerated the activation of both homomeric and heteromeric channels, but it differentially modulated the inactivation process, where the drug speeded up the fast component of channel inactivation of Kv4.2 channels, but accelerated the slow component of Kv4.2/KChIP2c. Our data show that the effect of sertraline on Kv4.2 channels is modulated by the presence of KChIP2c, and also emphasize that the actions of drugs on Kv channels should be evaluated in the presence of the ancillary subunit, considering their tissue-specific expression pattern.

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Identification of conventional dendritic cells in a lupus-like mouse model induced with non-bilayer phospholipid arrays

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Conventional dendritic cells are highly efficient in maintaining self-tolerance and prime T-helper lymphocyte responses. Since they are central modulators of immune tolerance and activators of innate and adaptative immune responses, they have been associated with autoimmune diseases. Systemic Lupus Erythematosus (SLE) is an autoimmune disease that causes systemic inflammation characterized by the loss of self-tolerance and production of different autoantigens as lipid autoantibodies.
Previously we developed a model of Lupus Like (LL) in mice through the induction of liposomes with non-bilayer phospholipid arrays (NPA), demonstrating that these have antigenic properties and could be participating in the development of the disease. In this work, we identified conventional dendritic cells and determined their role in the development of lupus induced with NPA´s. NPA's were induced with 3mM chlorpromazine and were characterized by flow cytometry and Nanoparticle Tracking Analysis (NTA) with Nanosight NS300. The inoculation of NPA's in BALB-/c female mice established the LL model. Dendritic cells and cytokine production were identified in splenocytes labeled with specific fluorochrome antibodies. The Mann-Whitney U statistical test (P0.05) was used for data analysis.

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Enhancement of Amphotericin B channel activity by applied pressures, in the range of MSchannels activation, in ergosterol containing membranes

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For over 70 years, Amphotericin B (AmB), a polyene antibiotic, has been used for the treatment of severe invasive fungal infections. However, its clinical use is limited due to substantial collateral toxicity. The exact mechanism of AmB's action at the membrane level is still a subject of debate, with the prevailing hypothesis being the formation of membrane pores. The activity of these pores is influenced by various factors, including membrane lipid composition, sterol presens, relative concentration to lipids, membrane phase and presences of domains. In this study, we investigated the effect of applied normal pressure on the activity associated with AmB channels. Our findings demonstrate that an increase in applied pressure enhances the activity of AmB channels in a monotonous manner from 50 mmHg to 250 mmHg. We attribute this enhanced activity to structural changes in the membrane induced by the applied pressure. These results provide further support for the notion that membrane structure plays a crucial role in the action of AmB.

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Molecular cloning and functional characterization of two novel $GABA_AR$-like subunits from red swamp crayfish *Procambarus clarkii*

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Abstract

$GABA_A$ receptors are responsible for mediating fast synaptic inhibitory transmission in the central nervous system from vertebrates and invertebrates. In this work, we cloned and functionally expressed two novel $GABA_A$ receptor subunits from *Procambarus clarkii* crayfish. These subunits were named $PcGABA_A$-α and $PcGABA_A$-$\beta2$. Bioinformatic analysis revealed that these subunits are homologous to $PcGABA_A$-β subunit, which was previously characterized in our laboratory. Remarkably, $PcGABA_A$-α and $PcGABA_A$-$\beta2$ shared a significant degree of homology to *Drosophila melanogaster* subunits GRD (GABA and glycine-like receptor subunits of Drosophila) and LCCH3 (ligand-gated chloride channel homolog 3), respectively. Electrophysiological recordings showed that the expression of the novel subunits, either alone or in combination, failed to form functional homo- or hetero-pentameric receptors. However, co-expression of $PcGABA_A$-α with $PcGABA_A$-β evoked chloride and sodium currents that accurately reproduced the time course of the GABA-evoked currents in the X-organ neurons from *P. clarkii* crayfish. These findings suggest that these GABA subunits combine to form two types of GABA receptors, one with an anionic selectivity filter while the other preferentially permeates cations. Interestingly, $PcGABA_A$-$\beta2$ and $PcGABA_A$-β co-expression yielded a chloride current with persistent desensitization that was inhibited by picrotoxin. Finally, RT-PCR amplifications revealed that $PcGABA_A$-α is predominantly expressed in the crayfish nervous system, whereas $PcGABA_A$-$\beta2$ is found in both muscle and the nervous system. These findings provide the first evidence of a neural GABA-gated cationic channel in the *P. clarkii* crayfish, increasing our understanding about the role of these new GABA receptor subunits in native heteromeric receptors.

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A novel characterization of local structure and dynamics of multicomponent bilayers through Transfer Entropy and Graph Theory analyses

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Cellular processes rely on signaling to initiate various activities, often involving the transmission of information to trigger these events. While conventional biochemical signaling pathways typically involve specific molecule arrival, allosterism introduces conformational changes in one site that affect another at a topographically distinct site. The application of transfer entropy (TE) has recently enhanced our understanding of these phenomena. In the case of biological membranes, the lipid raft hypothesis postulates that lipid-lipid interactions can laterally organize them into domains of distinct structures, lipid/protein compositions, and functions; nonetheless, the difficulties of experimentally observing nano-scale dynamic structures have prevented a full characterization. Furthermore, the time required for the spontaneous formation of a raft from an arbitrary initial configuration is still beyond the current capacity of molecular dynamics (MD) simulations. Moreover, the standard tools to analyse MD trajectories are aimed at describing the properties of the whole simulated system. In this work, TE is shown to provide a quantitative tool to evaluate the influence that instantaneous fluctuations of lipid tails have on each other, thus to assess emergent collective behaviors. TE analyses were conducted on all lipid pairs within three distinct MD trajectories of bilayers, each characterized by a specific composition: one with a 55:45 POPC:PSM mixture, a second with a 45:35:20 POPC:PSM:Cholesterol mixture, and a third with a 35:30:35 composition. Leveraging TE results, a directed graph is constructed to facilitate the evaluation of emergent system properties. From the comparison of the results, it is inferred that lipid behavior becomes more intertwined at higher cholesterol concentrations. This methodology can be extended to various different lipid mixtures to study how motion fluctuations can convey structural and dynamic information from one region of a bilayer to another.

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Physical membrane changes in antimicrobial peptides interaction: a molecular dynamics study

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Antimicrobial peptides constitute a category of dynamic biomolecules capable of inducing mortality in numerous microorganisms. Their remarkable capacity to proficiently eradicate bacteria is particularly captivating, especially considering the escalating prevalence of antimicrobial resistance witnessed with contemporary antibiotics. An example is Pin2, a 24-residue antimicrobial peptide with a broad spectrum of activity, sourced from the venom of *Pandinus imperator*. Nevertheless, its toxicity and limited stability against bacterial and human proteases have been clearly demonstrated (Carmona *et al.,* 2013). A 15-residue fragment (VC15) from Pin2 *Pseudomonas* aeruginosa's protease digestion was detected and displayed activity against Gram-positive bacteria and low toxicity to human erythrocytes. However, its activity against Gram-negative bacteria was weaker than Pin2. This study aimed to enhance variants via a structure-function approach using VC15 as a base template. Optimal variants were selected based on the potential to modify the antimicrobial peptide's primary target: the membrane. The PPM web server measured these parameters by identifying low interaction energy and high penetration variants through a Gram-negative membrane model. Then, a 500 ns molecular dynamics simulation analyzed initial interactions and transmembrane behavior. Alterations in membrane thickness, area per lipid (APL), and permeability indicated potential membrane damage. In short, VC15RH exhibited favorable membrane energy interaction (-10.9 kcal/mol) among the variants. It reduced the membrane thickness by 2.48 Å and altered the APL by 43.3 $Å^2$. Furthermore, in the study of its transmembrane state, VC15RH was found to impact the water density within the membrane core, a factor related to membrane permeability. In conclusion, these findings make VC15RH an intriguing theoretical peptide that merits further laboratory testing to assess its antimicrobial activity and toxicity.

Keywords: Antimicrobial peptides, Membrane, Gram negative, Structure-function of membrane proteins

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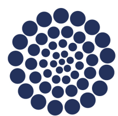

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