47º

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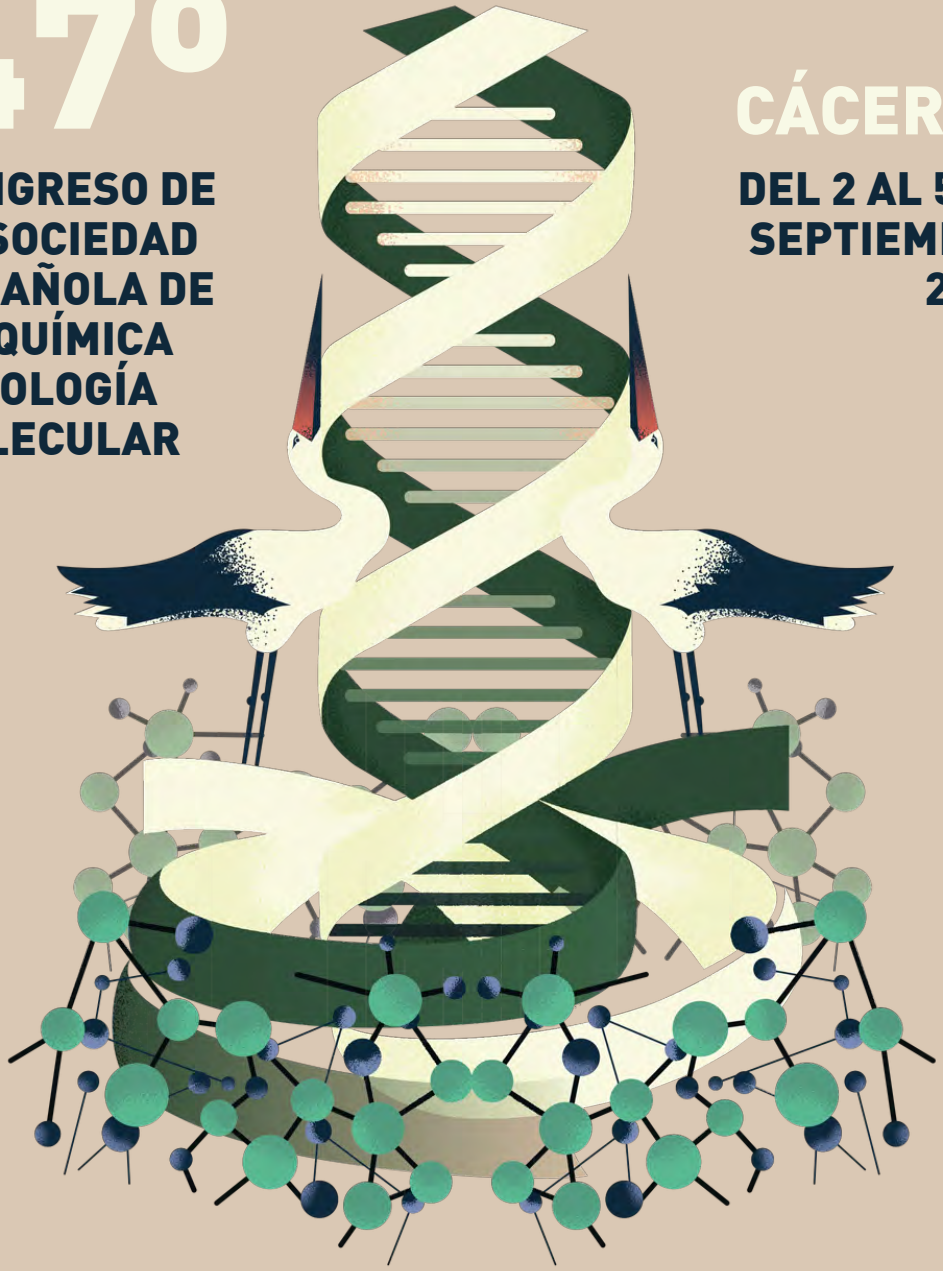

LIBRO DE RESÚMENES

BOOK OF ABSTRACTS

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DIPUTACIÓN DE CÁCERES
ÁREA DE CULTURA Y DEPORTES

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GRUPOS CIENTÍFICOS DE LA SEBBM

ÍNDICE

G10 - 89 - P

Glycaemic control modulates mitochondrial function and leukocyte-endothelium interactions in type 2 diabetes

VICTOR MANUEL VICTOR [1], JULIA CACACE [2], CLARA LUNA-MARCO [3], ALBERTO HERMO ARGIBAY [2], OMAR HERNÁNDEZ LÓPEZ [2], MARÍA PELECHA SALVADOR [2], ALEJANDRO MARTÍNEZ [1], JORDI MOTA [1], ANA JOVER [2], CARLOS MORILLAS [2], MILAGROS ROCHA [2], SUSANA ROVIRA-LLOPIS [2]

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Mitochondrial dysfunction due to electron transport chain overload contributes to oxidative stress and inflammation in type 2 diabetes (T2D). Peripheral blood mononuclear cells (PBMCs) are central to this inflammatory response. This study assessed whether glycaemic control affects mitochondrial respiration, OXPHOS complexes, and inflammation in T2D.

We included 181 individuals: 79 healthy controls, 64 T2D patients with good glycaemic control (HbA1c < 7%), and 38 with poor control (HbA1c > 7%). Basal oxygen consumption rate (OCR) in PBMCs was reduced in the poor control group vs. controls ($p < 0.05$). Maximal respiration and spare respiratory capacity were significantly lower in poorly controlled T2D vs. both other groups ($p < 0.05$). Mitochondrial ROS levels were higher in T2D patients, especially with HbA1c > 7% ($p < 0.001$ vs. controls and HbA1c < 7%).

Mitochondrial complex III and V levels were decreased in the poor control group ($p < 0.05$, $p < 0.01$). Inflammatory markers including MPO, ICAM-1, and VCAM-1 were elevated, particularly in HbA1c > 7% patients ($p < 0.05$ to $p < 0.001$ vs. controls). Neutrophil-endothelial interactions were also enhanced ($p < 0.001$). HbA1c negatively correlated with basal respiration ($r = -0.319$), maximal respiration ($r = -0.350$), and spare capacity ($r = -0.295$).

These findings suggest that poor glycaemic control in T2D impairs PBMC mitochondrial function and increases inflammation, potentially heightening vascular disease risk.

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Keywords: Type 2 Diabetes, HbA1c, Mitochondria, OXPHOS, Inflammation, ROS.

G10 - 92 - P

Herbicide and Amino Acid Synergy: Effects on Yeast Stress Biomarkers

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Employing biological models to study the combined effects of environmentally circulating xenobiotics offers a sustainable approach to understanding their interaction mechanisms with living organisms. Although the use of atrazine (ATZ) and *S*-ethyl-*N*,*N*-dipropylthiocarbamate (EPTC) has been heavily restricted or not approved for agricultural crops in European Union member states, these herbicides remain widely used in several countries that export food to the EU. Furthermore, ATZ and EPTC residues remain elevated in European soil because of consecutive years of agronomic use. However, studies investigating their combined effects in eukaryotic systems are still limited. On the other hand, proline (Pro) protects living cells from stress by neutralizing reactive oxygen species (ROS), such as hydroxyl radical. This study aimed to assess the response of *Saccharomyces cerevisiae,* a unicellular eukaryotic organism, to individuals and combined exposures to EPTC, ATZ, and Pro, with particular emphasis on oxidative stress markers. Combined exposure to ATZ and EPTC triggered distinct responses in *S. cerevisiae* compared to individual treatments. Notably, it resulted in a decrease in total non-protein thiol content, glutathione (GSH) levels, and the activities of glutathione reductase (GR) and cytoplasmic catalase (Ctt), accompanied by an increase in ROS levels. These changes suggest that the dual exposure to EPTC and ATZ induced oxidative stress in *S. cerevisiae*, likely due to the decrease in the antioxidant activities of GR, which regenerates GSH, and Ctt, which scavenges hydrogen peroxide. The presence of Pro in the culture medium reversed the conditions of oxidative stress in terms of non-protein total thiols, ROS, and Ctt activity.

Keywords: Yeast, Thiocarbamates, Triazines, Proline, Reactive Oxygen Species, Glutathione

G10 - 113 - P

The role of the NADPH oxidase NOX4 in regulating mitophagy and oxidative metabolism in liver tumor cells

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The NADPH oxidase NOX4 has been linked to various physiological and pathological processes. Studies from our group showed that silencing NOX4 in liver tumor cells enhances their proliferative and migratory capacity and increases both glycolysis and oxidative phosphorylation. Here we have performed proteomic analysis in two different hepatocellular carcinoma (HCC) cell lines (PLC/PRF/5 and SNU449) where NOX4 was silenced or overexpressed. Results revealed a differential regulation of several autophagy-associated pathways and clear differences in the levels of Sequestome 1 (P62), an autophagy receptor protein. Transcriptomic analyses of autophagy-related genes revealed an opposing expression pattern when NOX4 was overexpressed or silenced, thus reinforcing the regulatory role of NOX4 in this pathway. Consistent with these previous findings, analysis of the autophagic flux revealed induction upon NOX4 silencing and reduction after overexpressing it. Moreover, metabolomic analysis showed that alterations in NOX4 expression resulted in differences in phosphatidylethanolamine levels, known to be directly involved in autophagosome formation. Furthermore, silencing NOX4 resulted in a higher interaction between mitochondria and lysosomes, along with an increased number of phagosomes associated with mitochondria. Evaluation of proteins involved in mitophagy showed a lower expression upon NOX4 overexpression. Interestingly, when inhibiting autophagy with bafilomycin A in NOX4-silenced cells we observed a decrease in the oxidative metabolism, which was increased in these cells. Overall, our findings suggest that loss of NOX4 in HCC tumor cells induces autophagy and mitophagy, which contributes to a switch towards a more efficient oxidative metabolism.

Keywords: NADPH OXIDASES, NOX4, MITOCHONDRIA, AUTOPHAGY, MITOPHAGY, HCC, LIVER CANCER

G10 - 138 - O

High-throughput screening identifies a new potent activator of the mitochondrial calcium uniporter, boosting excitation-bioenergetics-contraction coupling in the heart

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Mitochondrial calcium uptake is an evolutionarily conserved mechanism mediated by the mitochondrial calcium uniporter (MCU). Evidence in preclinical settings suggests that pharmacological regulation of MCU improves the phenotypic outcomes in the context of age-related muscle dysfunction. We have screened a small-compound library containing 1280 well-known molecular targets to identify new potential mechanisms regulating ER to mitochondria Ca^{2+} crosstalk. The screening identified new compounds capable of enhancing histamine-triggered mitochondrial Ca^{2+} transients; among them, CGP7930 was the most potent hit, doubling the activity of the potent MCU activator kaempferol and boosting ER-mitochondrial contacts. Experiments in permeabilized cells exposed to controlled free Ca^{2+} concentrations revealed that CGP7930 is a direct activator of the MCU. Functional genetic analysis on the MCU complex revealed that CGP7930 relies on the activity of MICU1. Computational analysis suggests two potential binding pockets that are currently under functional evaluation. CGP7930 promoted Ca2+-dependent activation of mitochondrial energy metabolism in H9C2 cells and boosted the left ventricle developed pressure in perfused mouse hearts. This was MCU dependent, as MCU KO hearts failed to increase the ventricular contraction force upon CGP7930 perfusion. We conclude that CGP7930 is a new potent activator of the MCU that promotes excitation-bioenergetics-contraction coupling in the heart.

Keywords: Mitochondrial Calcium Uniporter, Calcium Signaling, ER-Mitochondria Crosstalk, Heart

ÍNDICE DE COMUNICACIONES

ÍNDICE

G10 - 83 - O

Mitochondria-associated ER membranes act as platforms to coordinate microglial immunometabolism

Jorge Montesinos, Cristina Antón

G10 - 89 - P

Glycaemic control modulates mitochondrial function and leukocyte-endothelium interactions in type 2 diabetes

Victor Manuel Victor, Julia Cacace, Clara Luna-Marco, Alberto Hermo Argibay, Omar Hernández López, María Pelecha Salvador, Alejandro Martínez, Jordi Mota, Ana Jover, Carlos Morillas, Milagros Rocha, Susana Rovira-Llopis

G10 - 92 - P

Herbicide and Amino Acid Synergy: Effects on Yeast Stress Biomarkers

Gonçalo Nuno Carrasco Sebastião, Isabel Maria Simão Alves-Pereira, Rui Manuel Alves Ferreira

G10 - 113 - P

The role of the NADPH oxidase NOX4 in regulating mitophagy and oxidative metabolism in liver tumor cells

Paula Segalés, Irene Peñuelas-Haro, Gemma Gonfaus-Ortiz, Esther Bertran, Isabel Fabregat

G10 - 138 - O

High-throughput screening identifies a new potent activator of the mitochondrial calcium uniporter, boosting excitation-bioenergetics-contraction coupling in the heart

Elena Caldero-Escudero, Sergio De La Fuente, Marilen Federico, Silvia Romero-Sanz, Silvia Fernandez-Martinez, Paloma Garcia-Casas, Rosalba I Fonteriz, Flavien Bermont, Mayte Montero, Javier Alvarez, Umberto De Marchi, Jaime Santo-Domingo

G10 - 160 - P

NADPH Oxidases and Glutathione Homeostasis Disruption as a Therapeutic Target in Chronic Lymphocytic Leukemia

Laura Yagüe Alonso, Clara García Calvo, Lucía Santos Sendín, Ángel Hernández Hernández

G10 - 163 - P

Amelioration of rotenone-induced Parkinson's disease model in C. elegans by inhibiting the mitochondrial Na+/Ca 2+ exchanger (NCLX) by CGP37157

Silvia Romero-Sanz, Elena Caldero-Escudero, Pilar Álvarez-Illera, Jaime Santo-Domingo, Sergio De La Fuente, Paloma García-Casas, Rosalba I. Fonteriz, Mayte Montero, Javier Alvarez

G10 - 168 - P

Evidence of Rapid Mitochondrial Retrograde Signaling Mediated by PKCs

Silvia Fernandez Martinez, Isabelle Chareyron, Elena Caldero Escudero, Silvia Romero Sanz, Sergio De La Fuente, Rosalba Inés Fonteriz, Mayte Montero, Javier Alvarez, Andreas Wiederkehr, Jaime Santo-Domingo

G10 - 185 - O

Changes Induced by type 2 sodium-glucose cotransporter inhibitors (SGLT2i) in Lymphocytes from Diabetic Kidney Disease patients

Andrea Raposo López-Pastor, Paula Andrés Prado, Clara García Carro, Ana I. Sánchez Fructuoso, Elena Urcelay García, Irene Gómez Delgado

G10 - 191 - P

Aberrant ER-mitochondria communication is a common pathomechanism in mitochondrial disease

Patricia Morcillo Garcia, Khushbu Kabra, Kevin Velasco, Hector Cordero, Sarah Jennings, Orhan Akman, Eric A. Schon

G10 - 218 - P

Transcriptomic analysis of MITF-dependent targets in mast cells revealed a metabolic signature

Laia Ollé, Lihong Song, Margarita Martín, Rosa Muñoz

G10 - 238 - O

Can an acorn cupule extract restore mitochondrial quality in Parkinson's disease models?

Nerea Domínguez Rojo, Mercedes Blanco Benitez, Saray Canales Cortés, Eva Alegre Cortés, Marta Paredes Barquero, Javier Ojalvo Pacheco, Alberto Giménez Bejarano, Enrique Carretero Morán, Pedro Javier Camello Almaraz, Mireia Niso Santano, Patricia Gómez Suaga, Sokhna Yakhine Diop, Ramón Cava, Jose Manuel Fuentes, Rosa Ana González Polo

G10 - 257 - P

Proapoptotic Activity of Acinetobacter baumannii Outer Membrane Proteins in a Yeast Model

Paloma Osset Trenor, Raquel Valero Boix, Markus Proft, Amparo Pascual-Ahuir Giner

G10 - 272 - P

Mitochondrial Sirtuins as Modulators of Innate Immune Signaling: Roles of SIRT3, SIRT4 and SIRT5 in Macrophage Activation

Yara Cuesta Valero, Carolina Meroño Ortega, Javier Traba Domínguez

G10 - 280 - O

The cellular energy status in primary endothelial cells modifies Nrf2 and Foxo3-dependent antioxidant regulation

Leticia Selinger Galant, Andreza Fabro De Bem, María Monsalve Pérez

G10 - 281 - P

Reprogramming Macrophage Identity through Mitochondrial NAD+ Metabolism

Áurea Oliva Herrero, Rosa Belmonte Sánchez, Rubén Rincón Álvarez, Luis González Moreno, Javier Traba Domínguez

ÍNDICE DE AUTORES

ÍNDICE