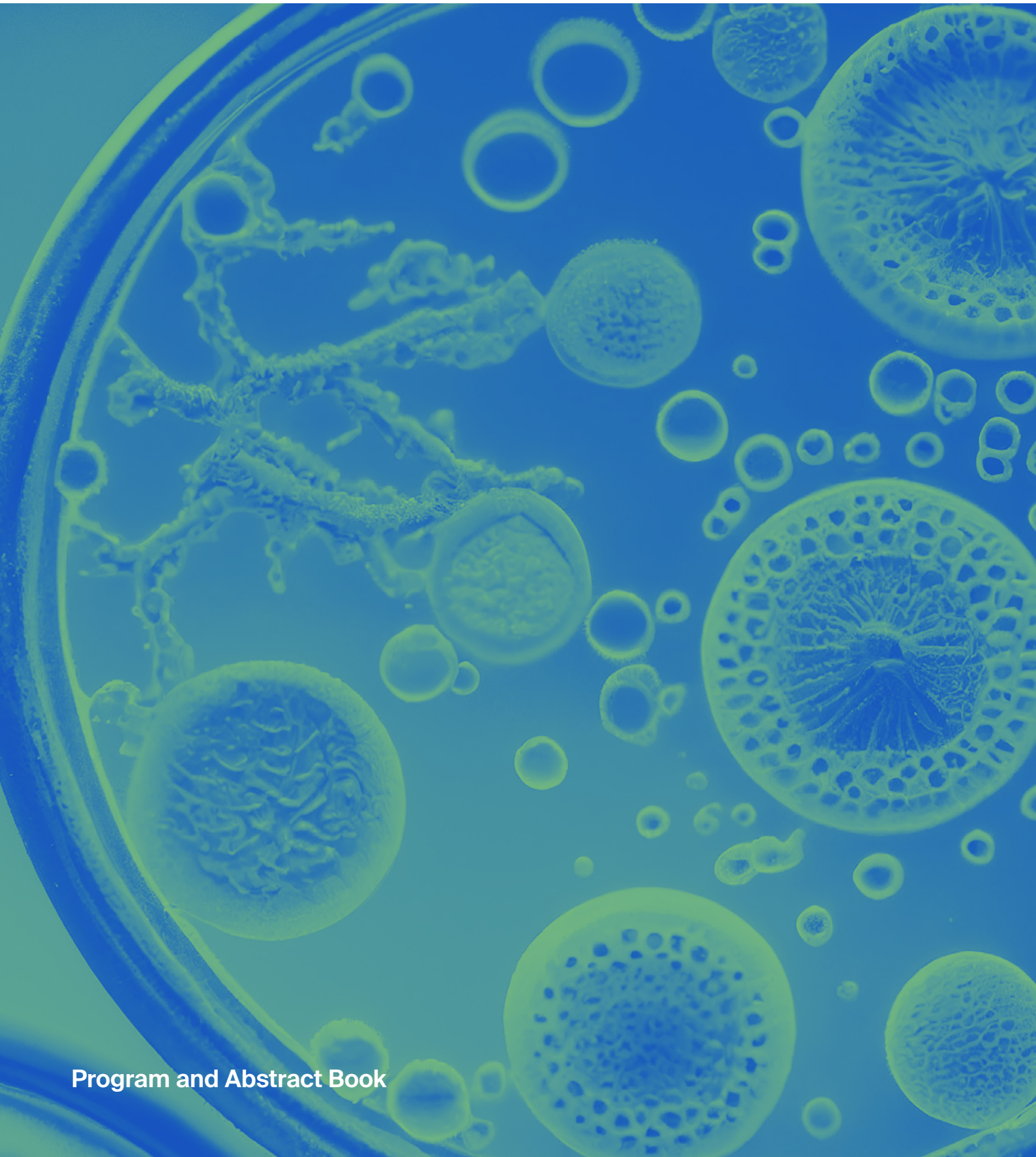
Cells
2025
Conference

The 3rd International Online Conference on Cells

25–27 March 2025 | Online



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The 3rd International Online Conference on Cells: Charming Micro-Insights into Health and Diseases

25–27 March 2025 | Online

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Welcome from the Chair

On behalf of *Cells* (ISSN: 2073-4409; IF: 5.1) I welcome you to our 2025 Virtual Conference. As with our previous 2 conferences of this series, we want to provide a highly interactive platforum for researchers all over the world to discuss major achievements as well as challenges in cell biology. Our goal is to cover a wide range of topics and to get feedback from seasoned researchers and from young investigators. *Cells* is a very dynamic journal with its eyes and ears always open to discoveries and novel emerging directions in cell biology. The goal of our 2025 Virtual Conference is to facilitate interaction between participants and to further advance the highly collaborative spirit of cell biology science. By covering such topics as cellular pathology of cancers, neural cell biology, cellular antivirus immune responses, cell therapies, cellular signaling, cell research in animal models, cellular metabolism, protein quality control, proteasomal degradation and autophagy, *Cells* remains at the forefront of scientific discourse. Over time, *Cells* has gained a reputation as a solid scientific journal, due to its unbiased peer-review process and great attention to every submitted paper.

We are privileged to host the 3rd Online Conference and are looking forward to oral presentations which shed light on complex mechanisms underlying cellular physiology and suggest novel treatment strategies for a wide spectrum of life-threatening pathologies.

Let us exchange provocative ideas, meet collaborators and enjoy the world of science with its incredible surprises and discoveries.

Download the conference flyer and share it with your colleagues!

Prof. Dr. Alexander E. Kalyuzhny
Dental Basic Sciences, UMN Twin Cities, Minneapolis, MN, USA

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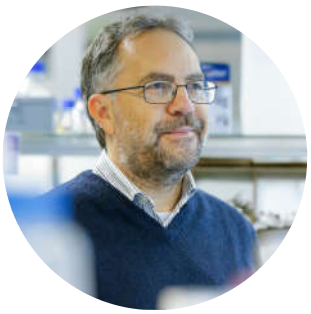
- **Journal Rank:** JCR - Q2 (Cell Biology) / CiteScore - Q1 (General Biochemistry, Genetics and Molecular Biology)
- **Rapid Publication:** manuscripts are peer-reviewed and a first decision is provided to authors approximately 17 days after submission; acceptance to publication is undertaken in 2.6 days (median values for papers published in this journal in the second half of 2024).
- **Recognition of Reviewers:** reviewers who provide timely, thorough peer-review reports receive vouchers entitling them to a discount on the APC of their next publication in any MDPI journal, in appreciation of the work done.
- **Sections:** published in 21 **topical sections**.
- **Companion journal:** ***Organoids***.

Impact Factor: 5.1 (2023); 5-Year Impact Factor: 6.0 (2023)

Keynote Speakers

Prof. Dr. Illana Gozes

The Elton Laboratory for Molecular Neuroendocrinology, Department of Human Molecular Genetics and Biochemistry, Faculty of Medical and Health Sciences, School of Medicine, The Adams Super Center for Brain Studies and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel



Professor Maurizio Molinari

Protein Folding and Quality Control, Institute for Research in Biomedicine (IRB), CH-6500 Bellinzona, Switzerland

Dr. Bilal Hafeez

Department of Immunology and Microbiology, South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX, USA

Professor Ewa Zuba-Surma

Department of Cell Biology, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University, Krakow, Poland

Professor Philippa Mills

Inborn Errors of Metabolism, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

Prof. Dr. Natália Cruz-Martins

Advanced Polytechnic and University Cooperative (CESPU), Faculty of Medicine, University of Porto (FMUP), Porto, Portugal

Invited Speakers

Dr. Luigi Donato

Department of Biomedical, Dental Sciences and Morphofunctional Images, University of Messina, Messina, Italy

Dr. Mario Mauthe

Molecular Cell Biology Section, Department of Biomedical Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Assoc. Prof. Rachid Safi

Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, USA

Professor Giorgio Malpeli

Department of Life Science, Health and Health Professions, Link Campus University, Roma, Italy

Professor Marco Feligioni

Link Campus University, Roma, Italy,
EBRI 'Rita Levi-Montalcini' Foundation, Rome, Italy

Dr. Sarah L. George

Division of Infectious Diseases, Allergy and Immunology, St. Louis University School of Medicine, St. Louis, MO, USA

Dr. Hemant Kumar Mishra

Golden Gate MLabs, San Francisco, CA, USA

Assoc. Prof. Daniel J. Mathew

Department of Animal Science, University of Tennessee Institute of Agriculture, Knoxville, TN, USA

Assoc. Prof. Ahmed Balboula

Division of Animal Sciences, University of Missouri, Columbia, MO, USA

Assoc. Prof. Ilaria Decimo

University of Verona, Verona, Italy

Professor Alan McIntyre

Centre for Cancer Sciences Biodiscovery Institute, University of Nottingham, NG7 2RD Nottingham, UK

Dr. Dindial Ramotar

Biological and Biomedical Sciences, and Division Head, College of Health & Life Sciences Hamad Bin Khalifa University Doha, Doha 34110, Qatar

Professor Simanti Datta

Institute of Post Graduate Medical Education and Research, Kolkata, India

Program at a Glance

	Day 1	Day 2	Day 3
Morning	**Session A.** Cellular Pathology of Cancers		**Session H.** Protein Quality Control, Proteasomal Degradation, and Autophagy Flash poster session
Afternoon	**Session D.** Cell Therapies **Session C.** Cellular Antivirus Immune Responses	**Session E.** Cellular Signaling **Session F.** Cell Research in Animal Models	**Session G.** Cellular Metabolism **Session B.** Neural Cell Biology

Cells 2025 Program

25 March 2025 (Tuesday)

Session A. Cellular Pathology of Cancers

Time: 9:00 (CET, Basel) | 03:00 (EST, New York) | 16:00 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
9:00–9:10	**Prof. Dr. Alexander E. Kalyuzhny** Event Chair	Opening Speech
9:10-9:20	**Prof. Dr. Srinivasan Madhusudan and Prof. Dr. Natália Cruz-Martins** Session Chairs	Welcome from the Session Chairs
9:20-9:50	**Prof. Dr. Natália Cruz-Martins** Keynote Speaker	Dysbiosis and Cancer: What Role Does Diet Play in This Interaction
9:50-10:10	**Prof. Alan McIntyre** Invited Speaker	Investigating tumour molecular adaptation to hypoxia and acidosis
10:10-10:30	**Dr. Dindial Ramotal** Invited Speaker	Loss of Peroxiredoxin 1 leads to ATM instability and defects in DNA damage signaling in response to arsenite exposure
10:30-10:45	**Alessandra Ferraresi** Selected Speaker	Targeting Glycolysis-Dependent Inhibition of Autophagy Reduces Ovarian Cancer Cell Migration and Impairs CAF Phenoconversion
10:45-11:00	**Giuseppina Daniela Naimo** Selected Speaker	Bergapten affects apoptosis through Notch family in colorectal cancer cells
11:00-11:15	**Chiara Lualdi** Selected Speaker	Modulation of Cathepsin D expression drives the growth of neuroblastoma cells in 2D or 3D cultures in response to EGF: analysis in a bona fide model mimicking tumor heterogeneity and metastatic progression
11:15-11:30	**Ankitha Vadi Velu** Selected Speaker	Investigation of cell death mechanisms induced by potential anti-cancer agent MO2455 in leukemia and lymphoma cells
11:30-11:45	**Onyisi Christiana Didamson** Selected Speaker	Photoactivated Aluminium Phthalocyanine Drives Oxidative Stress and Apoptosis in Human Oesophageal Cancer Stem Cells
11:45-12:00	**Jintao He** Selected Speaker	Distinct Characteristics of Brain Metastasis in Lung Adenocarcinoma: Development of High-Confidence Cell Lines

Session D. Cell Therapies

Time: 15:00 (CET, Basel) | 09:00 (EST, New York) | 22:00 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
15:00-15:10	**Prof. Dr. Maciej Kurpisz** Session Chair	Welcome from the Session Chair
15:10-15:40	**Prof. Dr. Ewa Zuba-Surma** Keynote Speaker	Stem cell- derived extracellular vesicles as new generation tools for therapeutic applications in tissue repair
15:40-16:00	**Assoc. Prof. Ilaria Decimo** Invited Speaker	Tumor-Associated macrophages promote tumor innervation and neural repair
16:00-16:20	**Prof. Marco Feligioni** Invited Speaker	Re-Localization of SUMO-1 in Neurons of Alzheimer's Disease (AD) Patients

16:20-16:40	**Dr. Hemant Kumar Mishra** Invited Speaker	Revolutionizing Cancer Treatments through Stem Cell-Derived CAR T/NK Cells for Immunotherapy: Opening New Horizons for the Future of Oncology
16:40-16:55	**BREAK**	

Session C. Cellular Antivirus Immune Responses

Time: 16:55 (CET, Basel) | 10:55 (EST, New York) | 00:00 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
16:55-17:05	**Prof. Ratna Ray** Session Chair	Welcome from the Session Chair
17:05-17:25	**Dr. Sarah George** Invited Speaker	Durability of T cell immunity after dengue vaccination vs. primary and secondary infection
17:25-17:45	**Dr. Simanti Datta** Invited Speaker	Hepatitis B virus inhibits complement C9 synthesis and membrane attack complex formation: implication in disease pathogenesis

26 March 2025 (Wednesday)

Session E. Cellular Signaling

Time: 14:00 (CET, Basel) | 08:00 (EST, New York) | 21:00 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
14:00-14:10	**Dr. Mohammad Asim** Session Chair	Welcome from the Session Chair
14:10-14:40	**Dr. Bilal Hafeez** Keynote Speaker	Clinical significance of targeting ribosome biogenesis for cancer therapy
14:40-15:00	**Dr. Rachid Safi** Invited Speaker	Elucidation of the Mechanisms by Which Cells Recognize and Respond to Different Levels of Steroid Hormones to Elicit Different Biological Responses
15:00-15:15	**Alessandra Galli** Selected Speaker	Exploiting mechanotransductive processes to promote pancreatic β-cell differentiation and function
15:15-15:30	**Sadia Farrukh** Selected Speaker	Parental Biomedical Manifestations and Newborn Telomeres: The Ends with a New Beginning
15:30-15:45	**Concetta Scimone** Selected Speaker	Aberrant methylation events in arteriovenous malformation of the brain
15:45-16:00	**Donghui Yang** Selected Speaker	More than pyroptosis: Cathepsin S is the novel protease for intestinal Gasdermin C
16:00-16:15	**Eleni Petsalaki** Selected Speaker	A novel mechanism for chromatin bridge sensing through the abscission checkpoint in human cells

Session F. Cell Research in Animal Models

Time: 16:15 (CET, Basel) | 10:15 (EST, New York) | 23:15 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
16:15-16:25	**Prof. Dr. Santhi Gorantla and Dr. Susanta K. Behura** Session Chairs	Welcome from the Session Chairs
16:25-16:45	**Dr. Daniel J. Mathew** Invited Speaker	The in vitro produced bovine embryo: Zooming in on the endometrium
16:45-17:05	**Dr. Ahmed Balboula** Invited Speaker	Novel mechanisms regulating chromosome segregation in mammalian oocytes
17:05-17:20	**Jong-Hyuk Lee** Selected Speaker	Cockayne syndrome mice reflect human kidney disease and are defective in de novo NAD biosynthesis
17:20-17:35	**Piotr Krzysztof Jung** Selected Speaker	Advancing Neuroblastoma Research: A 3D Tumorsphere Model to Study GD2 Immunotherapy and Metastasis

27 March 2025 (Thursday)

Session H. Protein Quality Control, Proteasomal Degradation, and Autophagy

Time: 9:00 (CET, Basel) | 03:00 (EST, New York) | 16:00 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
9:00-9:10	**Prof. Dr. Fulvio Mario Reggiori** Session Chair	Welcome from the Session Chair
9:10-9:40	**Prof. Maurizio Molinari** Keynote Speaker	ERAD and ERLAD: The proteasomal and lysosomal clearance of misfolded proteins from the endoplasmic reticulum
9:40-10:00	**Prof. Mario Mauthe** Invited Speaker	A chaperone/proteasome-based fragmentation machinery is essential for aggrephagy
10:00-10:15	**Sofie Lautrup** Selected Speaker	Multi-omics analysis of 267 postmortem human brain samples unveils new mechanisms of brain ageing and Alzheimer's disease
10:15-10:30	**BREAK**	

Flash Poster Session

Time: 10:30 (CET, Basel) | 04:30 (EST, New York) | 17:30 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
10:30-10:35	**Michaela Varone**	p75NTR modulation restores redox metabolism and blunts inflammation in a cell model of Rett syndrome
10:35-10:40	**Rosa D'Angiolo**	New TRPM8 modulators induce melanoma cell death
10:40-10:45	**Viviana Tutino**	Non-Genomic Action of Androgen Receptor in Colorectal Cancer
10:45-10:50	**Carmela Sorrentino**	Targeting TRPM8: A Novel Strategy to Halt Androgen-Driven Invasiveness in Melanoma
10:50-10:55	**Alessia Di Pauli**	(Phospho-)proteomic Signaling Responses of Human Male Germ Cell Lines to Simulated Microgravity and Hypogravity
10:55-11:00	**Fabrizio Fontana**	Dissecting the role of extracellular vesicles in melanoma microenvironment
11:00-11:05	**Luciana Cristina Teixeira**	Effect of modified citrus pectin on DSS-induced colitis in mice
11:05-11:10	**Shatha Alqahtani**	Unravelling the role of AP-1 transcription factor in DNA damage signaling and response (DDR) and platinum and PARP inhibitor resistance in ovarian cancers

Session B. Neural Cell Biology

Time: 15:45 (CET, Basel) | 09:45(EST, New York) | 22:45 (CST Asia, Beijing)

Time (Central European Time)	Speaker	Title
15:45-15:55	**Prof. Dr. George Smith** Session Chair	Welcome from the Session Chair
15:55-16:25	**Prof. Dr. Illana Gozes** Keynote Speaker	Talk: ADNP/davunetide: essential for sex-dependent hippocampal neurogenesis, through male unfolded protein response and female mitochondrial gene regulation
16:25-16:45	**Dr. Luigi Donato** Invited Speaker	Unveiling CACNG8: A Modifier Gene's Role in Retinal Dystrophies Through Structural and Molecular Insights into AMPA Receptor Dysregulation
16:45-17:00	**Lauren Miterko** Selected Speaker	Characterization of developing striatal circuitry in early-onset dystonia
17:00-17:15	**Domenico Mordà** Selected Speaker	Methylation Dynamics of Mitochondrial Stress Response Genes in Retinal Pigment Epithelium under Oxidative Stress Conditions
17:15-17:30	**Daniele Pensabene** Selected Speaker	p75NTR modulation reverses oxidative stress and metabolic derangements in a cell model of Parkinson's disease
17:30-17:45	**Francesco Paolo Zummo** Selected Speaker	Preliminary Investigation of Cerebellar Alterations induced by Cachexia and Endurance Training in C26 Tumor-Bearing Mouse Model
17:45-18:00	**Han Le** Selected Speaker	The role of MICOS in modulating mitochondrial dynamics and structural changes in the brain
18:00-18:10	**Prof. Dr. Alexander E. Kalyuzhny** Event Chair	Closing Speech

Session A. Cellular Pathology of Cancers

sciforum-112415: Analysis of radiosensitization effects of different PARP inhibitors on cancer cells

Barkha Saraswat *, Ankitha Vadi Velu, Zhongming Gao, Ying Tong and Mitsuko Masutani

Department of Molecular and Genomic Biomedicine, CBMM, Graduate School of Biomedical Sciences, Nagasaki University

Poly (ADP-ribose) polymerase (PARP) recognizes single- and double-strand DNA breaks and generates specific signals to facilitate DNA repair. In a genome-wide screening, we identified PARP-1 as a potential target for radiosensitization. PARP-1 is involved in the cellular response to DNA damage, and inhibiting its function can affect the repair process. Additionally, PARP-2, another member of the PARP family, also contributes to DNA repair and affects radiosensitivity. When both PARP-1 and PARP-2 are functionally inhibited, cells become more sensitive to ionizing radiation. In this study, we utilized several clinically approved PARP inhibitors to explore their effects on the radiosensitization in cancer cells. The combined impacts of γ-irradiation and PARP inhibitors on clonogenic cell survival, signal transduction, and cellular senescence were analyzed in cancer cells. We found that most of the PARP inhibitors showed radiosensitization effects on lung adenocarcinoma A549 cells. Rucaparib showed the highest enhancement ratio. Talazoparib showed radiosensitization at the lowest concentration. As a result of a combination of talazoparib and γ-irradiation, we observed an increased level of cellular senescence, accompanied by a decrease in the mitochondrial membrane potential. Our study provides insights into potential therapeutic strategies for enhancing cancer cell sensitivity to radiation. The effect of PARP inhibitors in combination with γ-irradiation on different types of cancer cell lines will also be discussed.

sciforum-112386: Bergapten affects apoptosis through Notch family in colorectal cancer cells

Giuseppina Daniela Naimo *, Giulia Venneri, Martina Forestiero, Adele Elisabetta Leonetti, Loredana Mauro, Maria Luisa Panno and Francesca Giordano

Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Rende, Italy

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide. Its incidence is influenced by genetics, age, lifestyle, and diet factors. Indeed, a balanced diet rich in fiber and regular physical activity can significantly reduce the risk of developing CRC. Functional Foods have aroused considerable interest due to their antiproliferative and anti-cancer effects. Interestingly, bergapten, the main furanocoumarin in bergamot, exhibiting antioxidant properties, has been particularly studied for its ability to inhibit proliferation and induce apoptosis in different tumour cell lines, including CRC. Paradoxically, several reports have highlighted the pro-oxidant effects of natural antioxidant compounds, which increase free radicals and exacerbate oxidative stress. Based on this evidence, we investigated the molecular mechanism by which bergapten may affect survival and ROS production in CRC cells.

Methods

CaCo-2 colorectal adenocarcinoma cells were used as a model to evaluate bergapten anti-cancer effects. ROS production and mitochondrial membrane potential were evaluated through flow cytometry. mRNA levels of stemness, the epithelial-to-mesenchymal transition (EMT), the cell cycle and apoptosis markers were quantified by qRT-PCR. Western blotting was carried out to detect protein levels.

Results

Low doses of bergapten induced a reduction in intracellular ROS levels in CaCo-2 cells, as is generally reported. Unexpectedly, high doses of the furanocumarin promoted a time-dependent significant increase in ROS levels. In CaCo-2 bergapten-treated cells, a reduction in mitochondrial membrane potential, a down-regulation of anti-apoptotic markers, and an increase in pro-apoptotic markers were observed, leading to cytochome C release. In agreement with this, bergapten induced a lowered expression of Cyclin D1, Notch family members, and Survivin compared to untreated cells. Interestingly, the bergapten-induced inhibition of Notch signalling also led to the down-regulation of the EMT, reducing CRC growth and progression.

Conclusions

These results suggest that bergapten, at high doses, may act as a promoter of oxidative stress, favoring antiproliferative effects through the activation of intrinsic apoptosis.

sciforum-115180: Clinicopathological significance of DNA damage signalling and repair (DDR) regulating E3 ubiquitin ligases and de-ubiquitinases in ovarian cancer

amera sheha [1,2,3,*], Emad Rakha [1,2] and Srinivasan Madhusudan [1,4]

[1] Naaz-Coker Ovarian Cancer Research Centre Biodiscovery Institute School of Medicine University of Nottingham UK
[2] Department of Pathology Nottingham University Hospitals Nottingham NG5 1PB UK
[3] Histopathology Department South Egypt Cancer Institute Assiut University Assiut Egypt
[4] Department of Oncology Nottingham University Hospitals Nottingham NG5 1PB UK

Introduction

E3 ubiquitin ligases (EUL) and de-ubiquitinases (DUB) that regulate DDR proteins may influence ovarian cancer pathogenesis. We evaluated DDR-regulating EULs and DUBs in ovarian cancers.

Methods

EULs (DDB2, CUL4A, HLTF, RAD18 and HUWE1) and DUBs (USP5, USP7, USP11 and PSMD14) were immunohistochemically profiled in 331 tumours, and the clinicopathological outcome were analysed. Transcriptomic analysis was completed on a publicly available data set (n=424).

Results

DDB2, USP7 and USP11 expression was nuclear. CUL4A, HLTF, RAD18, HUWE1, USP5 and PSMD14 showed both nuclear and cytoplasmic expression. EULs [low nuclear DDB2 and CUL4A cytoplasmic overexpression] and DUBs [USP5 (nuclear and cytoplasmic) overexpression] were associated with high-grade serous carcinoma ($p = 0.02, 0.003, 0.001, 0.03$, respectively). EULs [low DDB2 nuclear expression ($p = 0.01$) and CUL4A nuclear overexpression ($p = 0.05$)] and DUBs [USP5 cytoplasmic overexpression ($p = 0.05$) and PSMD14 cytoplasmic overexpression ($p = 0.02$)] were associated with advanced-stage tumours. In terms of survival outcomes, EULs [nuclear and cytoplasmic CUL4A ($p = 0.05, 0.001$, respectively), nuclear HLTF ($p = 0.003$) and low-nuclear DDB2 ($p = 0.01$)] and DUBs [overexpression of USP7 ($p = 0.005$), nuclear and cytoplasmic USP5 overexpression ($p = 0.004, 0.04$, respectively), cytoplasmic PSMD14 overexpression ($p = 0.01$), nuclear USP11 overexpression ($p = 0.006$)] were associated with poor progression-free survival (PFS). In a multivariate analysis, advanced stage, cytoplasmic CUL4A overexpression and nuclear USP5 overexpression remain independently associated with worse PFS ($p = 0.02, 0.03$, respectively). At the transcriptomic level, in p53 mutant advanced-stage tumours that received platinum-based chemotherapy (n=424), high *USP5* remains associated with poor PFS.

Conclusion

Our data suggest a complex role of EULs and DUBs in ovarian cancers. USP5 may be an attractive target for patient stratification and therapeutics in ovarian cancer.

sciforum-112420: Development of an evaluation model of flow cytometry for combined effects of anti-cancer drugs using machine learning

Koki Murayama *, Kohei Hayashi, Barkha Saraswat, Ying Tong and Mitsuko Masutani

Dept. Molecular & Genomic Biomed., CBMM, Grad. Sch. Biomed. Sci., Nagasaki Univ.

The analysis of the combined effects of anti-cancer drugs remains limited, especially with DNA quantity data analysis using flow cytometry (FCM). In this study, we aimed to develop a more applicable analytical method combining FCM and machine learning to evaluate the combined effects of anti-cancer drugs more objectively. Human gastric cancer cell lines MKN45, MKN28, and KATO III were treated with platinum-based drugs cisplatin (CDDP) and oxaliplatin (LOHP), both alone and in combination, for 24 hrs. Cells were then fixed and stained with propidium iodide (PI) for DNA content analysis by FCM. A random forest model using Python's scikit-learn was applied to the obtained dataset (comprising four groups: non-drug-treated control, CDDP alone, LOHP alone, and combination). The model successfully distinguished between groups with over 95% accuracy by utilizing not only PI fluorescence intensity but also cell size (with forward scatter, FSC) and internal structural complexity (with side scatter, SSC) as features. An analysis of the combination effects revealed different trends depending on the cell line, with MKN45 showing effects similar to LOHP alone and KATO III showing effects similar to CDDP alone. This novel analytical method enables a more objective evaluation of drug combination effects that are difficult to capture with conventional statistical analysis, potentially contributing to the optimization of future cancer treatment strategies.

sciforum-112512: Dissecting the role of extracellular vesicles in melanoma microenvironment

Gaia Giannitti, Alyssa Julia Jennifer Paganoni, Sara Marchesi, Riccardo Garavaglia, Ivan Preosto and Fabrizio Fontana *

Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Italy

Introduction

Melanoma is an aggressive cancer characterized by a rapid metastatic process. Thus, understanding the mechanisms underlying its progression is urgently needed to improve patient outcomes. In this regard, there is consistent evidence of a tumor-sustaining crosstalk between melanoma and subcutaneous adipose tissue; however, the role of EVs in this communication still needs to be clarified.

Methods

After isolation by SEC, EVs were characterized by NTA, TEM and Western blot analysis. The impact of these particles on melanoma cell growth was evaluated by cell proliferation and colony formation assays, and the effects on metastatic potential were assessed by transwell assay. Melanoma cell stem-like traits, including spherogenic ability, ABCG2 enrichment and vemurafenib response, were investigated by sphere formation assay, flow cytometry and cell viability assay. The metabolic consequences of EV treatment were analyzed by Western blot and cytofluorimetric assays.

Results

We demonstrated that the EVs derived from adipocytes did not alter melanoma cell proliferation, but significantly promoted tumor cell migration and invasion by determining an enrichment in mesenchymal markers, such as N-cadherin and vimentin. In particular, these changes were accompanied by the transition towards a stem-like phenotype, characterized by enhanced spherogenic ability and ABCG2 upregulation. Interestingly, this led to a reduced response to vemurafenib, with diminished apoptotic rates and decreased caspase 3 and PARP cleavage. Mechanistically, an increase in PGC-1α expression was found, resulting in higher mitochondrial mass and activity; of note, the treatment of melanoma cells with XCT790 and SR-18292, two specific inhibitors of mitochondrial biogenesis, successfully counteracted the above EV-related effects, suggesting that this process could be targeted to suppress the EV-mediated interactions between subcutaneous adipocytes and melanoma.

Conclusions

Taken together, these results highlight the crucial role played by EVs in the melanoma microenvironment, highlighting the ability of adipocyte-derived vesicles to sustain melanoma cell aggressiveness via PGC-1α activation.

sciforum-112524: Function of *SNHG12* in early response to boron neutron capture therapy (BNCT) in tumor cells

Zhongming Gao [1,*], Ying Tong [1,2], Barkha Saraswat [1], Shoji Imamichi [1,2,3], Lichao Chen [1], Yu Sanada [4], Minoru Suzuki [4], Masamichi Ishiai [2,3], Shinichiro Masunaga [4] and Mitsuko Masutani [1,2,3]

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BNCT (boron neutron capture therapy) is a cancer therapy combining neutron irradiation and the administration of boron carrier drug, such as ^{10}B-boronophenylalanine (BPA). The clinical application of BNCT has recently been approved for oral and head-and-neck cancers in Japan. To evaluate the therapeutic efficacy and side effects of BNCT for various cancer stages, we evaluated factors related to early responses to BNCT in tumor cells. We showed that the expression of the long noncoding RNA *SNHG12*, a cancer-related molecule, is increased in oral cancer SAS cells after BPA-based BNCT. Here, the biological function of *SNHG12* during BNCT and early cell responses was investigated. We showed that *SNHG12* expression in SAS cells increased significantly after gamma irradiation and treatment with an alkylating agent, methylmethanesulfonate, within 24 hrs. *SNHG12* overexpression triggered a decrease in the sub-G1 apoptotic fraction and increase in S-phase population. We thus hypothesized that *SNHG12* may have a supportive role for cell survival in particular types of DNA damage responses. Furthermore, colony formation assay of SAS cells after BNCT irradiation showed that *SNHG12* knockdown increased the sensitivity of SAS cells to BNCT. Knockdown of *SNHG12* in SAS cells after gamma irradiation decreased the mRNA expression of IAP family protein within 24 hrs. The mechanisms by which *SNHG12* is involved in the early cell response after BNCT will be discussed.

sciforum-112505: Impact of MCT1-Mediated Lactate Uptake on Melanoma Cancer Stem Cells

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Introduction

Lactate significantly influences the metabolism of melanoma by promoting tumor development and progression. However, the role of this metabolite and its main transporter MCT-1 in driving the propagation of melanoma cancer stem cells (CSCs) still needs to be elucidated.

Methods

Experiments were conducted on the A375 and WM115 melanoma cell lines. Cell quiescence was assessed by a proliferation and colony formation assay, cell-cycle and survival analysis (flow cytometry), and Western blotting. The spherogenic ability of tumor cells was evaluated through sphere formation and a propagation assay. The metabolic effects of lactate and AZ3965 treatment were analyzed by flow cytometry and Western blotting.

Results

We found that lactate-treated cells exhibited a quiescent state characterized by reduced proliferation, G1 cell-cycle phase arrest, and P27 upregulation; however, no changes in cell survival or clonogenic efficiency were found, suggesting that this quiescent state was not associated with cell death. More importantly, lactate treatment significantly increased melanoma cells' spherogenic ability and ABCG2 enrichment, two common CSC traits. Mechanistically, lactate was observed to activate PCG1-alpha, leading to enhanced OXPHOS protein expression and mitochondrial mass. Of note, treatment with AZ3965, a specific inhibitor of the lactate transporter MCT-1, significantly suppressed melanoma CSC expansion via PGC1-alpha downregulation.

Conclusions

Lactate plays a key role in sustaining melanoma CSC proliferation and survival. Targeting lactate metabolism via MCT1 inhibition holds promise for novel anti-cancer therapies.

sciforum-112391: Investigation of cell death mechanisms induced by potential anti-cancer agent MO2455 in leukemia and lymphoma cells.

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Poly(ADP-ribose) (PAR) glycohydrolase (PARG) serves as a key enzyme in the hydrolysis of PAR. Deficiency in PARG increases cell death upon exposure to γ-irradiation or treatment with an alkylating agent. This makes PARG a prospective therapeutic target for cancer. Our previous research illustrated that MO2455, leading to PAR accumulation, exerts cytotoxicity on B cell lymphoma cells by disrupting the B cell pathway. In this study, we explored and compared the cellular mechanisms underlying MO2455-induced cell death in histiocytic lymphoma U937, monocytic leukemia THP-1, and T lymphoblastic leukemia CCRF-CEM cells. MO2455 triggered cell death in all cell types at similar concentration ranges. Cell death was observed through the appearances of the apoptotic subG1 fraction and annexin-V+/propidium iodide (PI)- fraction, followed by the annexin-V+/PI+ fraction in U937 cells after MO2455 treatment. U937 cells showed a decreased mitochondrial membrane potential and an early increase in γ-H2AX levels 5 hrs after MO2455 treatment, suggesting a rapid DNA damage and apoptosis induction process. THP-1 also showed an increase in the apoptotic subG1 fraction and then the appearance of the annexin-V+/PI+ fraction. CCRF-CEM showed a rapid induction of the annexin-V+/PI+ fraction. Taken together, MO2455 can effectively induce cell death through some common and distinct processes in various types of lymphoma and leukemia cells.

sciforum-112370: Modulation of Cathepsin D expression drives the growth of neuroblastoma cells in 2D or 3D cultures in response to EGF: analysis in a bona fide model mimicking tumor heterogeneity and metastatic progression

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Neuroblastoma (NB) is a pediatric malignancy originating from the neural crest cells of the sympathetic nervous system, and it often progresses aggressively due to the influence of epidermal growth factor (EGF). Our earlier research demonstrated that cathepsin D (CD) disrupts EGF-driven proliferation in NB cells cultured in 2D by inhibiting the EGFR/MAPK signaling pathway. While this highlights CD's regulatory function in tumor growth, its potential role in metastasis remains unexplored. In order to reproduce tumor heterogeneity, we engineered neuroblastoma (NB) clones with either silenced or overexpressed CD expression and co-cultured the clones in different proportions. We then analyzed the growth of the mixed populations in 2D (adherent) and 3D (suspension) culture conditions to mimic the stages of the metastatic process in response to EGF stimulation. We unexpectedly observed an opposite behavior in 2D and 3D cells with different levels of CD. In particular, cells overexpressing CD demonstrated a greater adaptability to growth in suspension cultures. In contrast, cells with suppressed CD expression exhibited enhanced growth under adherent conditions in two-dimensional environments. Different CD levels lead to different behaviors even during the transition from 3D to 2D: cells that overexpress CD demonstrated an increase in N-cadherin levels, while cells with silenced CD showed a greater propensity to revert to a mesenchymal-to-epithelial-like phenotype, as evidenced by the elevated expression of E-cadherin. The contrasting roles of CD in driving cancer cell growth under 2D and 3D conditions indicate that clonal evolution may favor the emergence of subpopulations with distinct CD levels, optimizing their adaptability to various metastatic niches. This highlights the potential epigenetic regulation of CD as a mechanism supporting survival and proliferation in both substrate-adherent and neurosphere-forming NB cells. Consequently, disrupting the epigenetic control of CD could represent a promising therapeutic approach to hinder NB progression and metastasis.

sciforum-112387: New TRPM8 modulators induce melanoma cell death

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Background And Aim

The global incidence of melanoma is rising steadily. Despite significant advancements in therapeutic options, resistance mechanisms often emerge, leading to disease progression. This event underscores the importance of identifying novel intracellular targets. The transient receptor potential melastatin subtype 8 (TRPM8), a non-selective cation channel with a preference for calcium permeation, is aberrantly expressed in various solid malignancies, including melanoma. Thus, it could represent a promising therapeutic target in melanoma cells.

Methods

Two melanoma cell lines, derived from subcutaneous and lymph node metastases, were utilized to investigate the effects of TRPM8 modulators. Multiple methodologies, including colorimetric assays, Western blotting, immunofluorescence (IF), and confocal microscopy, were employed to assess the biological impact of these modulators.

Results

Time-course experiments demonstrated that TRPM8 modulators induced melanoma cell death. These findings were corroborated by dual-fluorescence IF analyses. Further investigation of the molecular mechanisms revealed that the apoptotic pathway triggered by these modulators involved caspase 3 activation.

Conclusions

Additional studies are necessary to elucidate the regulatory mechanisms of TRPM8 and the resulting calcium influx dynamics. Nonetheless, the identification of novel chemotherapeutic targets with enhanced potency and selectivity may pave the way for innovative melanoma treatment strategies. These approaches hold significant promise for advancing oncology therapeutics.

sciforum-112426: Non-Genomic Action of Androgen Receptor in Colorectal Cancer

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Background-Aim

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related death worldwide. Epidemiological studies demonstrate that men have a higher CRC incidence rate and face worse survival outcomes compared to women. This gender disparity in CRC incidence and outcomes pushed us to explore the mechanisms by which the androgen receptor (AR) may influence its pathology. Interestingly, the roles of the AR in cancer extend beyond traditional hormone-dependent cancers; in fact, in recent years, researchers have identified that AR signaling is also implicated in the progression of other cancers that do not typically respond to hormonal regulation. Understanding how AR mediates CRC's aggressiveness could provide valuable insights that may help to find more effective treatment strategies.

Methods

In this study, we used CRC-derived Caco2, LoVo, and HCT-116 cells, expressing the AR to different extents. A BrdU incorporation assay and the measurement of spheroid growth were used to monitor cell proliferation. Biochemical approaches such as co-immunoprecipitation, immunoblotting, and immunofluorescence show that androgen treatment induces an interaction between the AR and Filamin A and the activation of different effectors without altering AR cell localization.

Results

Our findings demonstrate that, in CRC cells, androgen treatment triggers an interaction between the AR and Filamin A. This complex activates Rac, p70, PKCs, and other proteins, thereby controlling different CRC-derived cells' proliferation. The antiandrogen Bicalutamide and a small peptide, Rh2025u, designed to mimic the AR sequences responsible for the AR/Filamin A interaction, reverse the androgen-induced effects in all cell lines.

Conclusions

This study underscores the significance of the AR in CRC and suggests that variations in androgen levels may influence both the onset and progression of this disease. By elucidating the role of the AR in CRC, this research opens avenues for innovative screening strategies and the development of targeted therapies.

sciforum-112422: Research on the identification of effective radiosensitization target genes in cancer cells

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The development of radiation sensitization methods for cancer cells with low toxicity to normal cells is considered to contribute to improving cancer radiotherapy. To date, a comprehensive approach using an shRNA library has been employed to identify candidate genes for γ-ray sensitization in cancer cells, with a focus on the BACE1 (β-site of amyloid precursor protein (APP)-cleaving enzyme 1) gene. The BACE1 gene mutation has been observed in lung cancer, bone tumors, ovarian cancer, and esophageal cancer. Meanwhile, the effect of inhibiting BACE2 on radiosensitivity, which functions similarly to BACE1 and is upregulated in cancer cells, has not been investigated.

It has previously been reported that the inhibition of BACE1 leads to an increase in γ-H2AX foci, a marker of DNA strand breaks, suggesting its involvement in the early response to DNA damage. To investigate this possibility, BACE1 was knocked down using siRNA in cancer cell lines, and their sensitivity to gamma-irradiation was examined. Also, using siRNA, we evaluated the radiosensitization effect of BACE2 inhibition on cancer cells, which show high BACE2 expression levels.

BACE1 knockdown showed an increased sensitivity to γ-ray irradiation in the cancer cell lines Trex-HeLa, MDA-MB-231, SAOS, U2OS, HeLa, and T98G, whereas BACE1 knockdown did not show a sensitization effect on the normal fibroblast cell line WI-38. BACE1 knockdown showed a greater radiosensitizing effect in HeLa and SAOS cells, which have dysfunctional p53, compared to U2OS cells with normal p53 function. BACE2 knockdown did not exert a radiosensitization effect in cancer cells. These results suggest that BACE1 may be a potential target for radiosensitization in certain cancer cells.

sciforum-112368: Targeting Glycolysis-Dependent Inhibition of Autophagy Reduces Ovarian Cancer Cell Migration and Impairs CAF Phenoconversion

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Introduction

Cancer cells exploit aerobic glycolysis, also known as the Warburg effect, which consists of the fermentation of pyruvate into lactate, even in the presence of oxygen and functioning mitochondria. This metabolic rewiring fuels the uncontrolled growth of the tumor mass and promotes cancer progression. Glycolytic reprogramming occurs not exclusively in cancer cells but also in the stroma, especially in cancer-associated fibroblasts (CAFs), a process that has been named the “reverse Warburg effect”. Autophagy, an evolutionary conserved catabolic process devoted to macromolecular turnover, is often dysregulated in cancer and plays a "double-edged sword" role in regulating the tumor microenvironment.

Methods

To mimic the tumor microenvironment in vitro, we employed IL-6, a pro-inflammatory cytokine abundant in ovarian cancer patients, and we set up an indirect co-culture method by cultivating fibroblasts with the conditioning medium of ovarian cancer cells.

Results

Our work aimed to dissect how the glycolysis/autophagy interplay affects ovarian cancer cell motility and the phenoconversion of CAFs. Our data show that IL-6 induces cancer cell migration only in cases of active glycolysis. On the other hand, nutraceutical resveratrol (RV) inhibits glucose uptake and metabolism while promoting autophagy, collectively hampering cancer cell motility. Moreover, our bioinformatic interrogation of TCGA data shows that patients with a low expression of glycolytic markers and displaying active autophagy exhibit favorable clinical outcomes. Next, we show that the glycolysis-dependent inhibition of autophagy promotes CAF activation. The conditioning medium of the ovarian cancer cells induces the glycolytic reprogramming that is required for CAF activation. Notably, glycolysis inhibition using 2-deoxy-D-glucose (2DG) or RV induces autophagy, which reprograms the CAFs into quiescent fibroblasts.

Conclusions

Taken together, our data support the use of glycolysis inhibitors and/or autophagy inducers as an adjuvant strategy to improve the therapy success rate and limit the risk of metastasis.

sciforum-112811: Unravelling the role of AP-1 transcription factor in DNA damage signaling and response (DDR) and platinum and PARP inhibitor resistance in ovarian cancers

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Background

Hypoxia, common in high-grade serous ovarian cancer (HGSOC) microenvironments, contributes to resistance to platinum-based treatments and PARP inhibitors by activating AP-1 transcription factors. AP-1 promotes proliferation, invasion, metastasis, and angiogenesis, but its role in DNA damage signaling, repair, and resistance mechanisms remains unclear.

Methods

TF activity was assessed in PARP-sensitive and -resistant HGSOC cells (PEO1, PEO1R, OVCAR4) using a luciferase reporter assay. AP-1 subunit (c-JUN, JUND, JUNB, cFOS, FOSL2) expression was analyzed under normoxic and hypoxic (1% O_2) conditions. Immunohistochemistry for JUNB, FOSL2, MRE11, CA-9, and CD-31 was conducted on PEO1 and PEO1R tumor xenografts. CRISPR knockouts of JUNB and FOSL2 were studied for effects on DNA repair gene expression, proliferation, invasion, and cisplatin sensitivity using DNA repair profiling, RNA sequencing, and functional assays. Protein stability and co-immunoprecipitation were analyzed. The clinical significance of FOSL2, JUNB, and MRE11 expression was evaluated in a cohort of 331 ovarian cancer patients.

Results

In platinum/PARP-resistant PEO1R cells, AP-1 transcription activity was elevated compared to PEO1 cells, with JUNB and FOSL2 overexpressed under normoxic and hypoxic (1% O_2) conditions. Tumor xenografts showed high JUNB and FOSL2 in hypoxic regions. Knockout (KO) of JUNB and FOSL2 reduced proliferation and increased cisplatin and olaparib sensitivity, linked to higher double-strand breaks (DSBs), G2/M arrest, and apoptosis. KO cells showed a downregulation of DNA repair genes, including MRE11, which JUNB and FOSL2 interact with to enhance stability. RNA sequencing revealed enriched pathways in platinum response, oxidative phosphorylation, and translation. Clinically, higher FOSL2, JUNB, and MRE11 expression correlated with shorter progression-free survival (PFS) and poorer overall survival (OS).

Conclusion

JUNB and FOSL2 are key players at the intersection of hypoxia and DNA damage response (DDR) in high-grade serous ovarian cancer (HGSOC). They have predictive and prognostic value and may serve as therapeutic targets in platinum/PARP-resistant HGSOC.

Session B. Neural Cell Biology

sciforum-109911: Unlocking the Potential of Non-Neuronal Cell-Derived Extracellular Vesicles in Pain Relief and Neuroprotection

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Introduction

Extracellular vesicles (EVs), including exosomes, are emerging as key mediators of intercellular communication, transferring bioactive molecules such as microRNAs, proteins, and lipids. Among non-neuronal cells, Schwann cells, oligodendrocytes, and satellite glial cells (SGCs) release EVs with distinct neuroprotective and pain-relieving properties. These EVs play critical roles in modulating inflammation, supporting neuronal repair, and regulating pain pathways, offering innovative therapeutic avenues for chronic pain management and neural repair.

Methods

A scoping review was conducted by systematically searching the PubMed, Scopus, and Web of Science databases. Studies published up to November 2024 were screened to identify evidence on Schwann cell-, oligodendrocyte-, and SGC-derived EVs. A total of 15 key studies were included, focusing on their cargo, functional mechanisms, and therapeutic applications.

Results

Schwann cell-derived EVs are enriched with neuroprotective microRNAs such as miR-21 and miR-146a, which reduce pain by regulating inflammation and promoting neuronal survival. They also carry proteins like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), enhancing neuronal repair. Oligodendrocyte-derived EVs deliver proteins such as myelin basic protein (MBP) and proteolipid protein (PLP), which are essential for neuronal stability and repair, as well as superoxide dismutase (SOD), which mitigates oxidative stress. SGC-derived EVs, while also carrying miR-21 and miR-146a, modulate neuronal hyperexcitability and inflammation uniquely through cytokines such as interleukin-10 (IL-10), amplifying their pain-relieving effects.

Conclusion

This review highlights the distinctive roles of Schwann cell-, oligodendrocyte-, and SGC-derived EVs in alleviating pain and supporting neural health. It identifies key research gaps, including the need for standardized methodologies and deeper characterization of EV cargo. These findings emphasize the therapeutic potential of EVs as innovative tools for chronic pain treatment and neural regeneration, underscoring their translational value for future research and clinical applications.

sciforum-111857: Unveiling *CACNG8*: A Modifier Gene's Role in Retinal Dystrophies Through Structural and Molecular Insights into AMPA Receptor Dysregulation

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Introduction

Inherited retinal dystrophies (IRDs) represent a heterogeneous group of genetic disorders characterized by a progressive degeneration of photoreceptors and retinal function, leading to vision loss. Recent research emphasizes the importance of modifier genes in modulating disease phenotypes, with *CACNG8*, which encodes the TARP γ-8 auxiliary subunit of AMPA receptors, emerging as a potential player. TARP γ-8, essential in modulating AMPA receptor function, may influence neural signaling pathways critical for retinal health. This study integrates genetic, molecular, and structural approaches to elucidate CACNG8's role in IRDs, aligning with key themes of cellular signaling and proteasomal degradation.

Methods

A cohort of patients diagnosed with IRDs was subjected to targeted genetic screening for *CACNG8* variants. Genomic DNA was extracted and analyzed using Sanger sequencing. Computational tools such as AlphaFold3 facilitated molecular docking and 3D structural modeling of wild-type and mutant TARP γ-8 protein complexes. Comparative analyses assessed receptor–ligand binding dynamics, hydrogen bond networks, and structural integrity across various *CACNG8* variants, such as p.Arg123Ter and p.Leu96Val-Val102Met. Additionally, in silico predictions evaluated potential disruptions in AMPA receptor signaling pathways.

Results

This study identified several novel and known variants in *CACNG8* associated with altered protein functionality. Structural analysis highlighted significant deviations in receptor–ligand interaction profiles, particularly in mutants like p.Leu96Val-Arg123Ter. These mutations disrupted hydrogen bonding and impaired receptor desensitization recovery, pivotal in retinal synaptic plasticity. Pathway analysis suggested a cascade of signaling defects linked to reduced proteasomal degradation efficiency and impaired protein quality control, likely contributing to neuroretinal degeneration.

Conclusions

This study positions *CACNG8* as a modifier gene within IRD pathophysiology, with specific variants correlating with altered AMPA receptor function and cellular signaling disruption. These findings provide a molecular basis for understanding IRD variability, highlighting the interplay between genetic and proteomic factors in shaping retinal pathology and resonating with emerging themes in cellular neurobiology.

sciforum-113799: Characterization of developing striatal circuitry in early-onset dystonia

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Introduction

Dystonia is a movement disorder characterized by involuntary twisting and sustained postures. Impaired torsinA function causes the neurodevelopmental disorder of early-onset dystonia (DYT-TOR1A). TorsinA is highly expressed during development, and its loss of function during neural maturation impacts circuit development, leading to abnormal movements. Motor symptoms can be improved by lesioning or stimulating the globus pallidus interna (GPi) or administering antimuscarinic medications, implicating basal ganglia and cholinergic neuron involvement.

Methods

We conditionally deleted *Tor1a* from forebrain GABAergic and cholinergic neurons (using Dlx5/6-Cre) to generate overtly symptomatic "Dlx-CKO" mice. Like the neurodevelopmental onset of human DYT-TOR1A, motor abnormalities in Dlx-CKO mice emerge during juvenile development. Electrophysiological alterations found in developing Dlx-CKO striata and cholinergic interneurons (ChIs) motivate our anatomical studies. Using immunohistochemistry, confocal imaging, and neuroanatomical analyses, we characterized striatal ChI morphology and connectivity during development and maturation, with or without cholinergic torsinA re-expression using a novel ChAT-IRES-*Tor1a* construct.

Results

We find that maturing ChIs in Dlx-CKO striata exhibit transient defects in neurite outgrowth and persistent alterations in afferent connectivity that coincide with the onset of abnormal motor behavior. TorsinA re-expression in developing ChIs supports neuronal survival and morphology and promotes proper physiological striatal connectivity.

Conclusions

TorsinA loss-of-function causes morphological and synaptic alterations to maturing ChIs, consistent with a contribution to abnormal motor behavior.

sciforum-112467: Methylation Dynamics of Mitochondrial Stress Response Genes in Retinal Pigment Epithelium under Oxidative Stress Conditions

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Background

Epigenetic modifications, particularly DNA methylation, play a critical role in regulating gene expression under stress conditions. This study investigates the methylation landscape of mitochondrial stress response genes in retinal pigment epithelium (RPE) cells exposed to oxidative stress, focusing on how these changes may drive pathophysiological alterations linked to retinal degenerative diseases.

Methods

Human RPE cells were treated with N-retinylidene-N-retinylethanolamine adduct (A2E) to induce oxidative stress. Whole-genome bisulfite sequencing (WGBS) was employed to profile methylation patterns. Differentially methylated regions (DMRs) were identified and analyzed for enrichment in mitochondrial stress-related pathways using bioinformatic tools, including Bismark, MethylKit, and ClueGO.

Results

Analysis revealed significant methylation changes in key mitochondrial stress pathway genes: 1) Hypomethylation of *PGC1α* and *NRF1*, genes essential for mitochondrial biogenesis and repair, indicating an adaptive response. 2) Hypermethylation of *BCL2* and *HSP70*, associated with decreased anti-apoptotic signaling and impaired mitochondrial protein folding capacity. 3) Identification of novel DMRs in regulatory regions of genes involved in oxidative phosphorylation (e.g., *ND5, COX2*) and antioxidant defense mechanisms (*SOD2, GPX1*). Lastly, 4) clustering analysis of DMRs highlighted enrichment in pathways linked to mitochondrial unfolded protein response (UPRmt) and oxidative stress mitigation.

Conclusion

Oxidative stress induces significant alterations in the methylation profiles of mitochondrial stress pathway genes in RPE cells. These changes likely contribute to mitochondrial dysfunction and cellular apoptosis, underpinning the pathophysiology of retinal degenerative conditions. The identification of key methylation markers provides novel insights into the epigenetic regulation of mitochondrial function and potential therapeutic targets for restoring retinal allostasis.

sciforum-112436: p75NTR modulation reverses oxidative stress and metabolic derangements in a cell model of Parkinson's disease

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Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), mainly affecting the elderly population with an incidence of 1-3%. It is characterized by motor symptoms closely linked to dopaminergic cell death in the *Substantia nigra pars compacta.* From a molecular standpoint, the deposition of Lewy bodies, namely protein aggregates particularly enriched with misfolded α-synuclein, is a typical hallmark of the disease. In addition, recent findings have highlighted cholesterol dysmetabolism as another common peculiarity of PD profoundly contributing to changes in membrane composition and integrity. Notably, p75 neurotrophin receptor (p75NTR) was found to be upregulated in the brains of post-mortem PD patients and associated with a reduction in the expression of pivotal neuroprotective effectors, strongly suggesting a role for this receptor in PD. Given its ability to favor both pro-survival and pro-apoptotic cascades, the synthesis of small p75NTR-binding molecules (i.e. LM11A-31) promoting cell viability over death was of particular interest in research. Hence, the aim of this study was to evaluate whether the pharmacological modulation of p75NTR by LM11A-31 provides neuroprotection in a rotenone-induced cellular model of PD. Our data showed that LM11A-31 promoted cell viability and reduced rotenone-dependent neuromorphological aberrations, as well as α-synuclein downregulation. We also observed that p75NTR modulation counteracted rotenone-dependent cholesterol alterations: specifically, LM11A-31 normalized free cholesterol content, as well as the expression of proteins involved in cholesterol uptake and trafficking. Furthermore, LM11A-31 reduced oxidative stress damage upon macromolecules by both boosting the expression of transcriptional regulators of the antioxidant response and reducing the expression of NADPH-oxidase (NOX) modulatory subunits. Even though further studies are required to better dissect the molecular mechanisms linking p75NTR to PD physiopathology, our data point to p75NTR modulation as a promising therapeutic avenue in PD treatment.

sciforum-112364: Preliminary Investigation of Cerebellar Alterations induced by Cachexia and Endurance Training in C26 Tumor-Bearing Mouse Model

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Cachexia is a syndrome characterized by significant weight loss and is a major complication in cancer development. Despite its importance, there are no effective treatments available. Recently, resistance training has been suggested as a non-pharmacological therapy to prevent muscle atrophy and functional decline in preclinical models. The C26 tumor-bearing mouse model is commonly used, showing progressive muscle and fat loss along with systemic inflammation. However, the impact of these changes on the cerebellum, which is crucial for motor function and balance, remains unclear. In this study, we combined the C26 tumor model with an endurance protocol to investigate cerebellar alterations in sedentary (SED T+) and trained (TR T+) tumor groups compared to sedentary (SED T-) and trained (TR T-) non-tumor groups. The tumor groups were sacrificed at the onset of cachexia to assess the impact of proactive endurance training. After confirming cachexia onset through body weight and strength loss, histological analysis revealed that the cerebellar area was similar across groups. However, a significant reduction in the Purkinje cell layer (PCL) thickness was observed in SED T+ mice. Since PCs are the sole efferent neurons in the cerebellum, we examined their condition using histological analysis, immunohistochemistry, and immunofluorescence by ZIC4 labelling. The PC body size decreased in the tumor groups, while their number was reduced only in TR T+ mice. Interestingly, the SED T+ group exhibited the highest number of PC with abnormal morphology. Additionally, to assess the effects on cerebellar vascularity, we found that tumor groups had an increased number of vessels in the white matter. Altogether, these results suggest that in the C26 tumor mouse model, the cerebellum is affected by PCL hypotrophy with smaller and abnormal PC. Endurance training only partially counteracts these alterations. Further studies are needed to clarify Purkinje cell aberrations due to their crucial role in motor function.

sciforum-114529: The role of the MICOS in modulating mitochondrial dynamics and structural changes in the brain

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Mitochondrial dysfunction is one contributor to aging, and it is implicated in many neurodegenerative diseases, including Alzheimer's Disease (AD). Additionally, age-related vascular and neuronal pathologies may precede AD development. Studies showed that aging correlated with alterations in mitochondrial function and structure. However, how mitochondrial dysfunction affects cellular decline in the brain is still unclear. The mitochondria are regulated by the cristae organizing system (MICOS) complex and mitochondria–ER contact sites (MERCSs) in various organs. In the hippocampus of an AD mice model, researchers have also observed decreases in a MICOS protein, CHCHD6. Therefore, in other vulnerable regions of AD, such as the hypothalamus, dysregulation of the MICOS and MERCSs may lead to mitochondrial dysfunction in the aging process and eventually accelerate AD. Using quantitative polymerase chain reaction, serial block-face scanning electron microscopy, light microscopy, and 3D reconstruction, we found that the gene expression of the MICOS and MERCSs decreased in the aged amygdala and hypothalamus. The mitochondria also had significant morphological changes in the aged hypothalamus. Understanding the importance of the MICOS complex, we investigated mitochondrial homeostasis and observed that the inactivation of MICOS genes disrupted the synaptic transmission in crucial hypothalamic circuits. These results suggested that aging abates mitochondrial dynamics and physiology in the amygdala and the hypothalamus, and the MICOS is necessary for mitochondrial calcium regulation. This study provides targetable therapeutic strategies for aging in the brain, preventing the progression of AD at the early stages.

sciforum-112539: High Cholesterol Levels Promote TNF-α-Dependent Necroptosis In Alzheimer's Disease

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Necroptosis has been reported in post-mortem AD brains; however, the events that regulate this type of inflammatory cell death in AD are not fully understood. Autophagy has been shown to protect cells from necroptotic cell death and act as a negative regulator of necroptosis. Moreover, our previous studies indicate that intracellular cholesterol accumulation can disrupt autophagy function, a pathological hallmark in multiple age-related neurodegenerative diseases, including AD. **This study aims to** evaluate the relationship between high cholesterol levels, altered autophagy, and necroptosis in AD, using primary neurons isolated from APP-PSEN1 mice overexpressing the cholesterol-related transcription factor SREBF2 and dorsal root ganglion neurons (DRGs). **Methods**: Cholesterol enrichment was assessed by incubating the cells with a soluble cholesterol/methyl-cyclodextrin complex (50 mg/ml) for 1h, followed by 4h of recovery. The necroptotic pathway was induced through treatment with TZL (TNFα (60 ng/ml)) plus the SMAC mimetic (LCL-161, 10 mM) and the pan-caspase inhibitor zVAD (10 mM) for different durations. **Results**: Brains from APP-PSEN1-SREBF2 mice exhibited an up-regulated expression of necroptosis-related proteins, specifically RIPK1, RIPK3, and MLKL, which accumulated in the urea-soluble fraction, indicating necrosome assembly. Also, SREBF2 overexpression resulted in increased levels of active phosphorylated RIPK3 and MLKL. Similarly, phospho-RIPK3 and phospho-MLKL levels were significantly elevated in primary neurons derived from the APP-PSEN1-SREBF2 mice compared to wild-type (WT) neurons, even without necroptosis induction. In vitro cholesterol enrichment increased cell death following TZL exposure, which was mitigated by RIPK1 and RIPK3 inhibitors (Necrostatin and GSK'872, respectively). In DRG neurons, phosphorylated RIPK3 and MLKL were constitutively expressed in aged neurons with compromised autophagy. The induction of the necroptotic pathway was prevented by restoring the autophagy function in old neurons. **Conclusions**: Overall, these findings indicate that the activation of the necroptotic pathway and inflammatory cell death in AD may be favored by the increased intracellular cholesterol load and defective autophagy associated with aging.

sciforum-112545: Synergistic Interaction Between Copper Overload and Aβ Peptide enhances Microglial Pro-Inflammatory Response

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Background: Copper (Cu) binds to amyloid beta (Aβ), generating reactive oxygen species (ROS) and altering cholesterol metabolism, leading to accumulation that worsens Alzheimer's disease (AD). Cu near amyloid plaques can mediate inflammation via the NOD-like receptor protein 3 (NLRP3) inflammasome, which activates caspase-1 and interleukin-1β (IL-1β). Whether Cu exacerbates Aβ-induced inflammasome activation and microglial dysfunction remains unclear. **Methods:** Mouse microglia (SIM-A9) were treated with 1 μM Aβ and 100 μM Cu for 24 hours. ROS production was measured using dihydroethidium (DHE). Cholesterol levels were assessed via confocal microscopy and the Amplex Red kit. Inflammasome and phagocytosis proteins were analyzed by Western blot and PCR. Phagocytosis was measured using fluorescent microbeads, while inflammasome assembly was visualized with ASC-GFP speckle formation. **Results:** Cu increased IL-1β and NLRP3 expression, with a synergistic effect observed during Cu+Aβ treatment. Cu and Cu+Aβ elevated total and mitochondrial cholesterol levels while reducing glutathione (GSH). ROS production increased but was mitigated by glutathione ester (GSHee) and mitochondrial antioxidants (MitoTEMPO and MitoQ). Microglial phagocytosis, impaired by Cu and Cu+Aβ, was partially restored by GSHee. Cu also reduced phagocytosis proteins (ABCA7 and CD36) and caused their cytosolic redistribution, leading to decreased phagocytic activity. **Conclusions:** Elevated Cu levels exacerbate Aβ-induced microglial dysfunction by increasing mitochondrial oxidative stress, cholesterol accumulation—both at the cellular and mitochondrial level—and inflammasome activation. These effects impair phagocytosis, contributing to Aβ plaque accumulation and worsening AD pathology.

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Session C. Cellular Antivirus Immune Responses

Session D. Cell Therapies

sciforum-115449: Design of a Nasal Prophylactic for Targeting SARS-CoV-2 Variants with B-escin and Nanoparticles

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The emergence of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) variants continues to challenge global healthcare systems, necessitating the exploration of innovative therapeutic modalities. This study proposes a novel nasal treatment approach leveraging the antiviral properties of Beta-escin (B-escin), a natural compound, in conjunction with gold and silver nanoparticles. B-escin, extracted from horse chestnut seeds, exhibits notable efficacy against coronaviruses, while nanoparticles offer advantageous features for targeted delivery and stability enhancement. Through integrated computational analyses encompassing molecular docking, molecular dynamics simulations, and quantum mechanical calculations, we assess the potential of this combined strategy against prevalent COVID-19 variants, including Alpha, Beta, Gamma, Delta, and Omicron. Specifically tailored for nasal administration, our investigation emphasizes the synergistic interactions between B-escin and nanoparticles, elucidating their collective impact on variant-specific viral targets within the nasal mucosa. The computational results indicate augmented antiviral activity and target specificity when combining B-escin with gold (Au) and silver (Ag) nanoparticles, surpassing individual treatment efficacy. Moreover, we investigate the influence of nanoparticle characteristics, such as size, morphology, and surface functionalization, on the observed synergistic effects. These findings underscore the promise of developing a nasal treatment utilizing natural compounds and nanotechnology, offering a potential frontline defense against the diverse spectrum of SARS-CoV-2 variants.

Session E. Cellular Signaling

sciforum-110431: (Phospho-)proteomic Signaling Responses of Human Male Germ Cell Lines to Simulated Microgravity and Hypogravity.

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Introduction: Access to space has significantly increased over the last decade, and with this comes the need for comprehensive knowledge about the effects exerted by altered gravitational conditions on human physiology and reproductive health. However, it should be highlighted that our knowledge about the effects of altered gravitational force on germ cells is still very poor. In this study, we exploited Reverse-Phase Protein microArrays (RPPAs), a biased (phospho-)proteomic approach, to investigate the impact of simulated microgravity (SμG) and hypogravity (ShG) on two human male germ cell lines, TCam-2 and NT2D1. Methods: TCam-2 and NT2D1 cell lines were exposed to SμG and ShG conditions using a Random Positioning Machine for 3, 24, and 72 hours. RPPA analysis was conducted using a panel of 130 antibodies selected to investigate a broad number of pathways potentially affected by altered gravity conditions. Results: The data analysis revealed that the exposure of both TCam-2 and NT2D1 cells to altered gravity induced significant (phospho-)proteomic changes. In particular, SμG induced early-phase alterations (3–24 hours), mostly characterized by the upregulation of some key regulators of signaling pathways, whereas longer SμG exposure (72 hours) resulted in the downregulation of other signaling proteins. ShG elicited minor changes, mostly characterized by reduced protein expression. The key pathways affected included cytoskeletal dynamics, proliferation, apoptosis, and autophagy. Notably, cell viability was not significantly impacted, suggesting compensating adaptation mechanisms to altered gravitational conditions. Conclusions: These findings indicate that (phospho-)proteomic responses to simulated gravity conditions were transient and non-persistent, demonstrating that human male germ cells exhibit resilience and adaptative capacity to cope with altered gravitational environments. This study provides valuable preliminary insights into the cellular and molecular mechanisms involved in gravity sensing and adaptation, which is crucial for developing countermeasures to ensure reproductive health and functionality during long-duration space missions for astronauts but also for the health of their future offspring.

sciforum-112389: GPER is involved in the resistance to palbociclib in breast cancer cells

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Background

The cyclin dependent kinase (CDK) 4/6 inhibitor palbociclib plus endocrine therapy is an effective treatment for patients with estrogen receptor (ER)-positive and HER2-negative breast cancer (BC). Notwithstanding promising clinical outcomes, intrinsic or acquired resistance frequently arises. Given the established role of cancer-associated fibroblasts (CAFs) in the resistance to chemotherapeutics and the implication of the G-protein estrogen coupled receptor (GPER) in mediating stromal functions, we sought to investigate whether CAFs may contribute to palbociclib resistance in BC cells via GPER.

Methods

MCF7 and T47D BC cells, as well as CAFs isolated from breast tumor tissues, were used as model systems. Docking experiments allowed us to evaluate the potential interaction of palbociclib with GPER. Immunoblotting, gene expression arrays, and gene silencing experiments along with 2D and 3D co-culture assays were performed to evaluate the activation of GPER signaling by palbociclib in CAFs. Investigations on large cohorts of BC patients served to assess new potential stromal targets involved in palbociclib resistance.

Results

First, docking studies showed that palbociclib can interact with the binding site of GPER, like its well-known ligands. Next, we found that in CAFs, palbociclib stimulates the main sensors of GPER activation like ERK1/2 activation and c-Fos up-regulation. To assess the transcriptional changes mediated by palbociclib through GPER in CAFs, we performed a human chemokine gene expression array. Notably, we found that the palbociclib-induced increase of pro-inflammatory genes is no longer evident upon silencing GPER expression. Finally, GPER silencing in CAFs interfered with the capacity of palbociclib to reduce the viability of BC cells in co-culture assays.

Conclusions

Our findings suggest that the activation of GPER signaling in CAFs may contribute to palbociclib resistance in breast cancer cells. On this basis, therapeutic strategies targeting CAFs might enhance the efficacy of palbociclib in BC patients.

sciforum-092831: A novel mechanism for chromatin bridge sensing through the abscission checkpoint in human cells

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Introduction

In the final stages of mitotic cell division, the narrow cytoplasmic canal that connects the two daughter cells is cut, and this is called abscission. However, sometimes chromatin bridges can arise during anaphase and persist in cytokinesis, and these are often the result of incomplete DNA replication or fusions of dicentric chromosomes. Chromatin bridges activate the abscission checkpoint, which is a mechanism that prolongs abscission in order to provide cells with enough time to resolve DNA bridges, and this has been linked to tumorigenesis. The abscission checkpoint prevents chromosome breakage if the cytoplasmic canal is cut, or tetraploidization in the case of furrow regression.

Methods

We performed point mutations in DNA constructs, reduced the levels of endogenous proteins with siRNAs, and used FISH and TUNEL. We also used confocal and time-lapse microscopy.

Results

We recently showed that the Mre11-Rad50-Nbs1 complex activates the ATM kinase, and this activates the Chk2 kinase in order to promote CPC localization to the midbody in cytokinesis with chromatin bridges. In this study, we show that Topoisomerase IIa (Top2a) localizes on DNA knots, which are regions of tangled DNA near the midbody, and creates abortive Top2ccs that are degraded in the proteasome. The degradation of Top2ccs is necessary for the localization of Rad17 on chromatin bridges. Rad17 then recruits the Mre11-Rad50-Nbs1 complex and activates downstream effector proteins to ensure the integrity of the chromatin bridges. Top2a-deficient cells exhibit reduced localization of the Mre11-Rad50-Nbs1 complex, Chk2, and the CPC complex and an increased frequency of broken DNA bridges. Interestingly, bridges derived from dicentric chromosomes do not possess knots or Top2ccs and are incapable of activating the abscission checkpoint.

Conclusions

We identified a new mechanism that cells use to recognize chromatin bridges during cytokinesis by creating abortive Top2ccs located on DNA knots to safeguard genome integrity and protect against tumorigenesis.

sciforum-112390: Aberrant methylation events in arteriovenous malformation of the brain

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Introduction

Arteriovenous malformation of the brain (bAVM) is a vascular condition affecting brain arterioles. It most likely arises due to an impaired expression of vascular differentiation markers that leads failed capillary bed development and, then, to the arteriolar-to-venule direct shunt. In this context, EFNB2 and ephrin-B4 seem to drive arteriovenous differentiation. Although several pathways have been linked to disease development, knowledge on the molecular basis of this phenotype is still very limited.

Methods

Methylome analysis was performed in endothelial cells purified from bAVM in order to identify aberrant methylation patterns in genes controlling vascular development and endothelial cell/vascular smooth muscle cell (VSMC) cross-talk. Human cerebral microvascular endothelial cells (HCMECs) were used as the control. The results were validated by quantitative methylation-specific PCR and quantitative real-time PCR.

Results

Both CpG- and CHG-aberrant methylation events were identified in bAVM endothelial cells. Most differentially methylated loci included noncoding RNA genes. Genes already known to be linked to bAVM development were identified. Interestingly, we focused our attention on the *EPHB1* gene, not yet linked to bAVM onset. Likewise, other differentially methylated genes included transcription factors expressed in VSMCs that regulate the expression of genes involved in endothelial cell differentiation.

Conclusion

Our data allow to identify aberrant methylation events occurring in bAVM endothelial cells when compared to HCMECs. Notably, these genes are clustered in pathways related to vascular homeostasis, as well as to VSMC-- endothelial cell crosstalk, suggesting that an impairment of this interaction plays a prominent role in the loss of vascular differentiation in bAVM phenotypes.

sciforum-112378: Assessment of gene signature deriving from prostate cancer-associated fibroblasts (CAFs)

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Background

The tumor microenvironment plays a pivotal role in shaping tumor aggressiveness and driving disease progression. In this context, the identification of gene signatures characterizing cancer-associated fibroblasts (CAFs) obtained from the two most frequently diagnosed cancers worldwide, such as breast and prostate tumors, may improve outcome prediction and therapeutic strategies for patients.

Methods

The transcriptomes of CAFs isolated from breast and prostate cancer biopsies were analyzed using RNA sequencing. Data from The Cancer Genome Atlas (TCGA) were used to compare the gene expression profiles of CAFs with those of breast and prostate cancer patients. The *clusterProfiler* package was employed to perform pathway enrichment analysis, while the gene signature associated withprostate CAFs was identified by applying K-means clustering. Kaplan--Meier curves and log-rank tests were used to assess the prognostic significance of the signature in prostate cancer patients. A decision-tree classification approach validated the clustering results and the prognostic relevance of the gene signature.

Results

The comparisons of either breast and prostate CAFs transcriptomes or the gene expression landscapes of breast and prostate cancer patients allowed us to construct a gene signature counting 11 genes (IL13RA2, GDF7, IL33, CXCL1, TNFRSF19, CXCL6, LIFR, CXCL5, IL7, TSLP, and TNFSF15) with clinical implications in prostate cancer. Notably, the aforementioned genes are implicated in immune-related transduction pathways. Thereafter, clustering and classification analyses revealed that prostate cancer patients exhibiting low expression levels of these 11 genes are characterized by a worse prognosis with a high prediction accuracy.

Conclusions

The prostate CAFs-related gene signature identified here might serve as a prognostic indicator and might offer a valuable set of biomarkers for improving the management of prostate cancer patients.

sciforum-113560: Exploiting mechanotransductive processes to promote pancreatic β-cell differentiation and function

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Introduction

Pancreatic β-cells, by releasing insulin, play a critical role in the control of glucose homeostasis. In vivo, they reside in the islet niche, which provides a myriad of stimuli derived from the extracellular matrix (ECM) and the neighbouring cells. This multifaceted environment plays a pivotal role in the regulation of pancreas development and in the control of β-cell function. Even though the contribution of chemical stimuli has been widely investigated, the mechanical signals are poorly known. Therefore, the aim of the proposed research was to explore the role of nanotopography in the regulation of β-cell functionality and to investigate the underlying molecular mechanisms.

Methods

Human islets of Langerhans were grown on cluster-assembled zirconia substrates with a tailored roughness mimicking the ECM nanotopography, and flat zirconia substrates were used as controls. The β-cell functionality was evaluated by means of super-resolution fluorescence microscopy, Western blot, and ELISAs and confirmed by shot-gun proteomics.

Results

Quantitative immunofluorescence revealed that β-cells are mechanosensitive and respond to nanotopography through mechanotransduction, which impacts on focal adhesions and cytoskeletal and nuclear organization. These modifications are paralleled by a profound gene reprogramming which promotes the expression of pro-survival and pro-differentiation factors and proteins involved in the regulation of granule trafficking in the islets grown on the nanostructure. In line with these observations, we found that the nanotopography preserves β-cell differentiation and function in long-term cultured islets, as suggested by increased β-cell number, reduced β-cell death, and potentiated glucose-stimulated insulin secretion.

Conclusions

This study provides a better understanding of how mechanical forces contribute to β-cell fate, offering the possibility to harness these mechanisms for promoting β-cell function in physiological and pathological conditions.

sciforum-112003: More than pyroptosis: Cathepsin S is the novel protease for intestinal Gasdermin C

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Gasdermin C (GSDMC), predominantly expressed in the gut, belongs to the Gasdermin (Gsdm) protein family, which only becomes functional after the protease cleavage-mediated release of the N-terminus from their self-inhibited C-terminus. Previous studies have identified caspase 8 as the protease responsible for cleaving human GSDMC in specific cancer cell types, leading to pyroptosis, a form of programmed inflammatory cell death. However, the direct protease that cleaves intestinal GSDMC is unknown. Here, we showed that the protease Cathepsin S (CTSS) is the direct protease for GSDMC. Intriguingly, unlike other Gasdermin N-terminal fragments (GSDMs$^{N\text{-}ter}$), the CTSS-processed GSDMC$^{N\text{-}ter}$ was found to be ineffective in promoting pyroptosis. This ineffectiveness is attributed to an incomplete lipid interaction motif, which limits its ability to disrupt cellular membranes—a hallmark of pyroptosis. Instead, CTSS-processed GSDMC$^{N\text{-}ter}$ localized to and penetrated RAB7^{+} vesicles, which are considered the marker for late endosomes. Consequently, targeting of RAB7^{+} vesicles resulted in the release of endocytic cargo, resulting in enhanced protein production during plasmid transfection and an improved transfectability of cell lines. Furthermore, Rab7 associates with lipid droplets and regulates lysosome recruitment to lipid droplets. We found that CTSS-generated GSDMC$^{N\text{-}ter}$ resulted in impaired lipid droplet breakdown and turnover under starvation conditions. This newly described biological function expands the role of Gsdm beyond pyroptosis and highlight a novel role for Gsdm proteins in modulating Rab7+ vesicles, such as late endosome/lipid droplet functions.

sciforum-112453: Oxidative Stress-Induced Dysregulation of Cytoskeletal Dynamics and Vesicular Trafficking in Retinal Pigment Epithelium: Implications for Retinal Degeneration

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Introduction

The cytoskeleton and trafficking pathway play a pivotal role in maintaining cellular homeostasis, particularly in retinal pigment epithelium (RPE), which is essential for photoreceptor functionality. Dysfunction in these pathways is increasingly recognized as a contributor to retinal degenerative diseases, such as Retinitis Pigmentosa (RP). This study explores transcriptomic alterations in RPE cells under oxidative stress conditions induced by oxidized low-density lipoproteins (oxLDLs).

Methods

Human RPE cells were exposed to oxLDL (100 µg/ml), and transcriptomic analyses were conducted across three time points (0h, 3h, and 6h). RNA-seq was utilized for differential gene expression profiling, and data were analyzed using Gene Set Enrichment Analysis (GSEA) to highlight significantly altered pathways. Focus was given to cytoskeleton-related genes and their association with vesicular trafficking and signal transduction.

Results

Significant changes were observed in genes regulating cytoskeleton integrity, vesicle trafficking, and motor protein function. The key findings include the 1) dysregulation of Retinitis Pigmentosa GTPase Regulator (RPGR), impairing ciliary transport; 2) alterations in actin filament organization and microtubule stabilization, disrupting cellular polarity and vesicular transport; 3) upregulation of genes like FAM161A and RP1, linked to microtubule binding and photoreceptor disk morphogenesis; and 4) progressive collapse of intermediate filaments and junctional complexes affecting RPE--photoreceptor interactions.

Conclusion

Cytoskeleton-related pathways undergo extensive remodeling under oxidative stress, contributing to the pathophysiology of RP. Disruption in vesicular trafficking and cytoskeletal organization underscores the mechanistic link between oxidative stress and retinal degeneration. This study identifies novel targets within the cytoskeleton pathway, providing a foundation for therapeutic exploration in retinal disorders

sciforum-112651: Parental Biomedical Manifestations and Newborn Telomeres: The Ends with a New Beginning

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Background

Telomere biology, even during fetal development, is influenced by parental manifestations that can imprint parental epigenetic marks onto the newborn. The interplay between genes, immune biology, and oxidative stress contributes to age-related non-communicable diseases (NCDs), and the telomere length (TL) dynamics in utero are not fully known. This study investigated the impact of parental biomedical factors, including NCDs, on newborn TL, as well as telomerase genes and immune biology.

Method

Blood samples (n=612) were collected from 204 parent–newborn pairs. Their demographics, socioeconomic status (SES), education, and NCD exposure were assessed. TL was quantified using the T/S ratio via qPCR; telomerase gene (TERC, TERT) polymorphisms were identified through Sanger sequencing; and immune senescence was analyzed using flow cytometry. Multivariate regression was used to analyze the paternal–newborn LTL associations, with p0.05 as the significance threshold.

Results

The mean ages of the mothers and fathers were 27±5.12 and 34±6.36 years, respectively. The newborns of parents aged >30 years old had longer TLs (2.31±1.45; p=0.034). A low SES and blue-collar occupations were correlated with a shorter TL in the parent–newborn pairs (1.5±1.14; p0.05), with higher frequencies of the telomerase CC genotype (TERC: 28%, 41%; TERT: 22%, 37%) compared to those in high-SES and white-collar groups. NCDs and viral pathologies significantly influenced telomere biology (p0.05). The analysis of immune senescence markers showed decreased CD57+ KLRG1+ expression in the newborn T-cells (2.45±4.34; p0.05) compared to those of their parents (3.5±5.49; p=0.04).

Conclusion

Parental biomedical factors and diseases influence newborn telomere biology and immune development in utero, highlighting the importance of mitigating prenatal risk factors.

sciforum-112384: Targeting TRPM8: A Novel Strategy to Halt Androgen-Driven Invasiveness in Melanoma

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BACKGROUND

Melanoma ranks among the most lethal cancers worldwide. Advanced-stage melanoma is treated with various therapeutic strategies, often accompanied by significant side effects. Recent advancements in targeted therapies, particularly those aimed at receptor tyrosine kinases and immune checkpoints, have substantially improved overall survival (OS) and long-term disease control. However, resistance mechanisms frequently develop, leading to disease progression. Consequently, the need for alternative therapeutic approaches for advanced melanoma remains pressing. The transient receptor potential melastatin-8 (TRPM8) channel has emerged as a promising molecular target implicated in the migration and proliferation of malignant cells. However, its specific role in melanoma progression remains unclear.

AIM

This study aims to investigate the effects of novel TRPM8 modulators on androgen-induced migration, invasiveness, and spheroid growth in melanoma cells.

METHODS

Melanoma cell lines with varying malignancy degrees were treated with or without androgens in the presence or absence of newly synthesized TRPM8 modulators. Wound scratch and Boyden's chambers analysis were performed to evaluate cell migration and invasion. The most effective compounds were further tested in melanoma 3D spheroid models.

RESULTS

TRPM8 modulators effectively inhibited the androgen-induced migration and invasion of melanoma cells and reduced the growth of melanoma cell-derived spheroids.

CONCLUSIONS

These preclinical findings highlight TRPM8 as a promising therapeutic target in melanoma, offering potential for innovative treatment strategies to overcome limitations in current therapies.

sciforum-112341: The silencing of the G protein-coupled estrogen receptor (GPER) drives apoptotic death in triple-negative breast cancer cells

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Introduction

The G protein-coupled estrogen receptor (GPER) is known for its ability to mediate rapid estrogen signaling in diverse normal and malignant cell contexts, including breast cancer (BC). Of note, the role of the GPER in promoting pro-tumorigenic traits in triple-negative breast cancer (TNBC) has been suggested. In this study, we sought to provide novel insights into the transcriptionally guided biological behavior of TNBC cells lacking GPER expression.

Methods

GPER knock-out (KO) MDA-MB-231 TNBC cells were obtained using the CRISPR/Cas9 genome editing technology. RNA sequencing (RNA-seq) and Gene Ontology (GO) enrichment analyses served to assess the differentially expressed genes (DEGs) between the GPER KO and wild-type (WT) cells and their biological role. Chromatin immunoprecipitation assays, real-time PCR, immunoblots, immunofluorescence, ELISA, and flow cytometric experiments, as well as the use of RNA interference techniques, allowed us to uncover the molecular routes implicated in the biological features triggered by GPER silencing in the TNBC cells. Survival analyses were performed on TNBC patients ffrom the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) dataset.

Results

The RNA-seq data revealed that GPER silencing in MDA-MB-231 cells induces a pro-apoptotic gene signature. Accordingly, the biological assays demonstrated that GPER KO cells exhibit enhanced mitochondria-dependent apoptotic death with respect to these levels in WT cells. Mechanistically, we found that reduced cAMP levels in GPER KO cells may trigger the activation of the pro-apoptotic JNK/c-Jun/p53/Noxa pathway. In accordance with these results, the bioinformatics analyses on the TNBC patients revealed that high NOXA gene expression levels are associated with better outcomes.

Conclusions

Collectively, our findings unveil the role of the GPER in sustaining anti-apoptotic signals in TNBC cells, thus suggesting this receptor as a potential valuable therapeutic target for preventing the progression of this malignancy.

Session F. Cell Research in Animal Models

sciforum-108239: Advancing Neuroblastoma Research: A 3D Tumorsphere Model to Study GD2 Immunotherapy and Metastasis

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Metastatic neuroblastoma (NB) is one of the most challenging childhood cancers to treat, with a high rate of relapse despite aggressive therapies. Most NB cells express disialoganglioside GD2, a tumor-specific antigen with limited expression in normal tissues. While GD2-targeting monoclonal antibodies have shown promising clinical success, a significant number of patients still experience relapse. This is thought to be due, in part, to heterogeneous or low GD2 expression, which complicates the effectiveness of immunotherapies. However, studying GD2-targeted treatments and metastasis in NB is hindered by a lack of suitable in vitro models. Current 2D culture systems are limited in their ability to mimic the complex environment of metastatic tumors, and murine NB cells typically lose GD2 expression when cultured. To overcome these challenges, I have developed a novel 3D cell culture system known as "tumorspheres." This model allows NB cells to grow in a more physiologically relevant environment and better replicates the conditions of tumor metastasis. Preliminary results demonstrate that tumorspheres retain high GD2 expression and show significant growth and motility within a matrix scaffold, mimicking in vivo tumor behavior more accurately than traditional 2D models. Importantly, these tumorspheres can be formed from a mix of GD2-positive and GD2-negative cells, enabling the study of antigenic heterogeneity and its impact on therapeutic resistance. Additionally, tumorspheres can be implanted subcutaneously into mice to promote in vivo tumor growth, further enhancing their utility as a model for studying neuroblastoma metastasis and immunotherapy. This new 3D model offers a more representative platform for investigating GD2-targeted therapies and tumor metastasis, with the potential to advance our understanding of treatment resistance and lead to more effective strategies for combating metastatic neuroblastoma.

sciforum-112445: The effect of the lipophilic fraction of pequi on extracellular matrix remodeling in skin lesions in mice

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Introduction: The tissue repair process is regulated by various molecular and cellular elements that must be in balance to result in healthy tissue. Pequi oil (Caryocar brasiliense) possesses therapeutic properties that may contribute to this context. Thus, this study evaluated the action of this oil on skin lesions. Methods: Balb/c mice with induced skin lesions were divided into groups (n=5) receiving daily topical applications of saline solution (the Control group) or the lipophilic fraction of pequi (the Treated group). After 3, 7, and 14 days, the animals from each group were sacrificed, and fragments of their injured skin were analyzed using polarization microscopy to evaluate collagen; using Western blot to evaluate matrix metalloproteinase 2 (MMP2); and using a multiplex assay to evaluate tumor growth factor-beta 1 (TGF-β1). CEUA - UFMT 23108.080623/2023-50. Results: In the Treated group, a lower amount of type I collagen was observed on days 3 ($p \leq 0.05$) and 14 ($p \leq 0.001$) and of type III collagen on day 14 ($p \leq 0.001$) compared to these levels in the Control group. Additionally, the Treated group exhibited slightly higher MMP2 expression (not significant) and lower TGF-β1 levels ($p \leq 0.05$) on day 3 compared to the Control, indicating reduced fibrogenic stimulation. Conclusion: These results demonstrate that treatment with pequi oil promotes lower deposition of type I and III collagen in the late stages of skin regeneration, primarily by inhibiting TGF-β1 production in the early stage, suggesting the reduced activation of pathways that could lead to excessive fibrosis. Meanwhile, the stable levels of MMP2 reflect the necessary balance for tissue remodeling. These findings reveal that pequi oil regulates key factors in tissue remodeling, promoting less fibrosis and preserving extracellular matrix balance, highlighting its therapeutic potential for wound management (Financial Support: FAPEMAT 000547-2023).

sciforum-109811: Cockayne syndrome mice reflect human kidney disease and are defective in de novo NAD biosynthesis

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Introduction

Cockayne syndrome (CS) is a rare, premature aging disorder caused by mutations in the CSA and CSB genes, which affect DNA repair and transcription. CS patients frequently exhibit kidney abnormalities, but the molecular mechanisms underlying renal dysfunction remain poorly understood. Recent studies have implicated NAD+ biosynthesis, a critical pathway for cellular metabolism and the stress response, in CS pathogenesis.

Methods

This study utilized CS mouse models to investigate their renal pathology and the role of NAD+ biosynthesis. RNA sequencing was performed to analyze the differential gene expression, with a focus on NAD+ metabolism. Human kidney proximal tubular epithelial cells (HK-2) were used to validate our findings through siRNA knockdown of CSA/B. Our techniques included immunohistochemistry, NAD+ quantification, Western blotting, and chromatin immunoprecipitation (ChIP).

Results

The CS mice exhibited renal atrophy, fibrosis, and tubular epithelial cell abnormalities. RNA sequencing revealed impaired NAD+ biosynthesis pathways, with significant downregulation of quinolinate phosphoribosyl transferase (QPRT), a key enzyme in de novo NAD+ biosynthesis. Mechanistically, CSA/B deficiency stabilized ATF3, a transcriptional repressor, leading to QPRT downregulation and NAD+ depletion. These findings were confirmed in the HK-2 cells, where CSA/B knockdown recapitulated the effects on the QPRT expression and NAD+ levels.

Conclusions

Our study demonstrates that CS-related kidney dysfunction is driven by impaired NAD+ biosynthesis, mediated through ATF3-dependent QPRT repression. These findings provide novel insights into the molecular basis of renal pathology in CS and suggest potential therapeutic strategies targeting NAD+ metabolism for alleviating renal complications.

sciforum-112554: Effect of modified citrus pectin on DSS-induced colitis in mice

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Introduction

Modified citrus pectin (MCP) exhibits diverse biological activities, including anti-proliferative, anti-metastatic, and immunomodulatory effects. Additionally, MCP acts as an antagonist of galectin-3 (Gal-3), a key regulator of inflammation. This study aimed to investigate MCP's therapeutic potential in a murine colitis model induced using dextran sulfate sodium (DSS), focusing on its impact on inflammation and disease severity.

Methods

Male C57BL/6 mice were divided into four groups: a control; DSS (colitis induced through the oral administration of 1.25% DSS in water for 7 days ad libitum); MCP (administered via orogastric gavage for 7 days at 100 mg/kg/day); and MCP+DSS. C57BL/6 Gal-3$^{-/-}$ mice were divided into two groups: control and DSS groups. All of the procedures were approved by the Ethics Committee in Animal Experimentation of UNIFESP (CEUA nº4973090123).

Results

The DSS-treated mice presented significant weight loss on the eighth day and elevated disease activity index scores compared to their respective controls (p0.0001). The DSS and MCP+DSS animals showed significant shortening of the intestines compared to the controls (p0.0001), with increased production of IL-17 and TNF-α. A lack of Gal-3 abolished these effects, showing no changes in gut length or these cytokines between the control and DSS groups. Systemically, the spleens of the Gal-3$^{-/-}$ DSS and MCP+DSS animals were longer than those of the DSS group (p0.01). However, the plasma KC levels increased significantly in the DSS and MCP+DSS groups; again, the lack of Gal-3 abolished these differences between the DSS and control groups.

Conclusion

MCP therapy as a preventive treatment in the development of DSS-induced colitis was not effective. On the other hand, the lack of endogenous Gal-3 mitigates the deleterious effects of SSD-induced colitis, possibly by preventing an increase in IL-17 and TNF-α. Funding: CAPES, CNPq, and FAPESP.

sciforum-112443: Therapeutic properties of pequi lipophilic fraction (*Caryocar brasiliense*) in skin wound repair: modulation of inflammatory and proliferative phases

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Introduction: Pequi (*Caryocar brasiliense*) is a fruit from Cerrado, Brazil, that has important therapeutic properties for the tissue repair of skin wounds. **Methods:** Balb/c mice were subjected to skin lesions and received daily topical treatment with the lipophilic fraction of pequi (Treated group) or saline solution (Control group). Animals from each group were sacrificed at 3, 7, and 14 days post injury (n=5). Macroscopic analyses were performed to assess wound contraction, and peripheral blood was collected for leukocyte quantification. Additionally, skin fragments were used for histopathological analysis (Hematoxylin–Eosin) and for quantification of the expression of the proteins Annexin A1 (AnxA1) and phosphorylated ERK (pERK) using the Western blot technique. CEUA-UFMT 23108.080623/2023-50. **Results**: At 3 days, the Treated animals exhibited a more robust scab on the lesion, providing greater physical and microbiological protection. At 7 days, wound contraction was significantly higher in the Treated group compared to the Control group ($p \leq 0.01$), accelerating wound closure and preventing dehydration and infection risks. In peripheral blood, a higher number of neutrophils, eosinophils, and monocytes were identified in the Treated group compared to the Control group ($p \leq 0.0001$; $p \leq 0.05$; $p \leq 0.05$, respectively), particularly during the early 3-day period. No difference was observed in AnxA1 protein expression between the experimental groups; however, the Treated group showed higher pERK expression at 7 days compared to the Control group ($p \leq 0.05$). **Conclusions**: These data suggest that pequi oil acts as an effective modulator of the inflammatory phase, by inhibiting leukocyte transmigration, and of the proliferative phase, through the activation of the ERK pathway, preparing the tissue for regeneration without altering AnxA1 levels. Thus, it is evident that the lipophilic fraction of pequi accelerates tissue repair by modulating the inflammatory and proliferative phases, promoting more efficient healing. (Financial Support: Fapemat 000547-2023; CAPES 88887.976959/2024-00).

sciforum-111507: Annexin A1 deficiency increases liver damage and metabolic alterations in mice with type I diabetes

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Diabetes mellitus (DM) is a global public health issue causing systemic dysregulations, including severe liver complications. Type 2 diabetes (DM2) patients show elevated annexin A1 (AnxA1) levels, and in murine DM2 models, AnxA1 mitigates insulin resistance effects like hepatosteatosis. However, its role in DM1 is underexplored. This study investigates AnxA1's role in hepatocyte biology in a streptozotocin (STZ)-induced DM mouse model. Male C57BL/6 mice (WT and AnxA1-/-) were divided into control (CTR) and DM groups. DM was induced via STZ injection (65 mg/kg for 5 days). After 12 weeks, livers were collected for analysis. DM WT and AnxA1-/- mice showed weight loss and increased blood glucose, reflecting typical diabetic metabolic disruptions. Morphological evaluations revealed normal hepatocytes in WT CTR mice, while 70% of AnxA1-/- CTR mice showed cytoplasmic vacuolation. In DM groups, 50% of WT mice had vacuolated, damaged hepatocytes, increasing to 75% in AnxA1-/- DM mice, highlighting AnxA1's protective role. Hepatocyte glycogen levels were lower in DM mice, especially AnxA1-/-. Collagen deposition in the centrolobular veins and portal triads was higher in AnxA1-/- DM mice, indicating worsened fibrosis without AnxA1. Both DM WT and AnxA1-/- livers showed reduced fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor A (VEGF-A), suggesting impaired regeneration. Inflammation varied between genotypes: WT DM mice had higher IL-10 and TNF-α, while AnxA1-/- DM mice showed increased monocyte chemoattractant protein-1 (MCP-1). Oxidative stress markers indicated increased reactive oxygen species (ROS) in AnxA1-/- DM hepatocytes, with differing trends in superoxide dismutase (SOD) and catalase (CAT) activities. Metabolites linked to the tyrosine, malate-aspartate, taurine, and hypotaurine pathways stood out in AnxA1 knockout mice, suggesting that these pathways are key in AnxA1-deficient mice. This highlights AnxA1's role in liver protection under diabetic conditions.

Session G. Cellular Metabolism

sciforum-110467: Alpha-ketoglutarate dehydrogenase (KGDH): an update on its redox regulation and importance in generating mitochondrial reactive oxygen species (mtROS) in hepatocytes

Ryan Mailloux

Ryan J. Mailloux, Associate Professor and Director of the School of Human Nutrition, Faculty of Agricultural and Environmental Science, McGill University.

The regulated production of mitochondrial reactive oxygen species (mtROS) is vital for maintaining optimal liver health. The mtROS-mediated maintenance of cell function(s) is through the induction of oxidative eustress signals, which are transmitted through the site-specific cysteine modifications. By contrast, the sustained overgeneration of mtROS triggers oxidative distress, resulting in the manifestation of metabolic diseases like non-alcoholic fatty liver disease (NAFLD) and the progression of cancer. Therefore, it is crucial to understand precisely how mitochondria generate mtROS, how its production is regulated, and how dysfunction in these regulatory mechanisms may cause NAFLD and its related disorders. Complexes I and III of the electron transport chain (ETC) are viewed as the primary mtROS sources in mammalian cells. However, we recently generated compelling evidence showing that TCA cycle enzyme α-ketoglutarate dehydrogenase (KGDH), and not the ETC, is the main mtROS supplier in hepatocytes. We found that KGDH is a main mtROS source when hepatic mitochondria are fueled with oxidizable substrates and is a main source of oxidative stress in the livers of mice subjected to dietary fat overload. Additionally, we discovered that mtROS generation by KGDH is controlled by reversible protein S-glutathionylation, which is catalyzed by glutaredoxin-2 (Glrx2). In this context, the oxidation of the glutathione (GSH) pool S-glutathionylates KGDH to shut down mtROS generation. This creates a self-contained negative feedback loop for the redox regulation of mtROS production. Recently, we showed that the manipulation of the Glrx2 pathway protects from diet-induced NAFLD development through the dynamic inhibition of KGDH-mediated mtROS hyper-generation by S-glutathionylation. In this presentation, I will elaborate on the importance of these findings in understanding the manifestation of NAFLD and how the targeted and dynamic redox modification of KGDH with mitochondria-targeted drugs can mitigate the onset of this disease through the dynamic inhibition of mtROS hyper-production by redox modifications.

sciforum-106761: Brain pericytes: from origins to implications in cell–cell communication within the neurovascular unit

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The BBB is a natural barrier located in the endothelial cells of the cerebral microvessels (BMECs) that restricts exchanges between the bloodstream and the cerebral parenchyma. The integrity of the BBB is vital for preserving cerebral homeostasis, and neuroinflammatory processes alter the physical and/or metabolic properties of this barrier. The brain pericyte, which shares a common basement membrane with BMECs, has been shown to be a major cell type involved in the induction and maintenance of the BBB's main features. This presentation will review the role and intercellular interactions of human brain pericytes (hBPs) with the cells of the neurovascular unit, and particularly BMECs, based on data generated within the lab using proteomics, cell physiology, and studies of extracellular vesicles (EVs). The protein pattern of hBPs is modified once they are cocultured with BMECs, highlighting a metabolic switch induced by BMECs on hBPs. A stimulation of EV biogenesis is observed, indicating a potential need for a hBP-derived cell–cell communication through EVs. The mechanisms of interaction between BMECs and hBP-derived EVs are in favor a clathrin-coated pit-mediated endocytosis. Under inflammation, hBP-derived EVs exhibit a modified protein pattern compared to untreated EVs and induce a dysregulation of trans-endothelial electric resistance (TEER) on BMECs.

Despite their former reputation as a contaminant for BBB modeling in vitro, hBPs remain of importance for maintaining the BBB phenotype. BMECs also modulate the functions and developmental fates of hBPs. This work opens perspectives on the role of hBP-derived EVs on BBB feature regulation.

sciforum-112382: Dysfunctional Cellular Energy Metabolism is a Premorbid Characteristic of Late-Onset Alzheimer's disease

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Age is the main risk factor for late-onset Alzheimer's disease (LOAD) and all processes in normal aging also occur in LOAD pathology. While some factors appear to be more specific to LOAD and may be genetically determined, others are acquired through the aging process. Because bioenergetic metabolism is among the most fundamental features of cell functions, changes thereof have profound effects on every aspect of aging. In both fibroblasts and induced pluripotent stem cell (iPSC)-derived immature and mature brain cells of subjects with LOAD, we observed bioenergetic substrate deficiencies, including reductions in the redox agent nicotinamide adenine dinucleotide (NAD) or glucose uptake and metabolism, and alterations of associated bioenergetic-dependent cell functions. These data suggest that dysfunctional bioenergetics is an inherent cell-specific and cell-autonomous risk factor in LOAD. Together with findings from the brains of normally aging individuals or patients with LOAD, our data support the view that in LOAD, inherent cell-metabolic dysfunctions may occur in development and early life, altering the trajectory of the normal aging process in youth and middle-age, and predisposing neuropathological events that lead to symptomatic features of LOAD later in life. Our studies seek to further identify and characterize the cellular mechanisms underlying LOAD-associated bioenergetic abnormalities. The results of these studies may reveal targets and methods for treating individuals at risk for LOAD before illness develops or delaying disease onset and progression later in life.

sciforum-112439: p75NTR modulation restores redox metabolism and blunts inflammation in a cell model of Rett syndrome

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Rett syndrome (RTT) is a neurological disorder with an early onset, primarily affecting females, and is characterized by severe cognitive and physical impairments. RTT is no longer regarded as an exclusively neurological disease; rather, it is now considered a multisystem syndrome that affects the brain and several other tissues/organs. Recent research suggests that disruptions in redox homeostasis and heightened inflammatory responses are of pivotal importance with regard to the disease's clinical manifestations. Notably, emerging evidence points to the p75 neurotrophin receptor (p75NTR) as a regulator of oxidative stress (OS) and inflammation.

The objective of this study is to explore the impact of modulating p75NTR through the use of the small molecule LM11A-31 on fibroblasts derived from RTT patients. Fibroblasts were treated with 0.1 μM of LM11A-31 for 24 hours, and analyses were conducted through qPCR, immunofluorescence, ELISA, and Western blotting.

The results reveal that LM11A-31 significantly mitigates OS markers in RTT fibroblasts. Specifically, p75NTR modulation restored protein glutathionylation and reduced the expression of the pro-oxidant enzyme NADPH-oxidase 4 (NOX4). Moreover, LM11A-31 blunted the expression of pro-inflammatory mediators while simultaneously normalizing transcription factors involved in antioxidant response and inflammatory response.

These results suggest that targeting p75NTR with LM11A-31 may offer a potential therapeutic avenue for restoring redox balance and alleviating inflammation in RTT patients. The use of a p75NTR modulator, such as LM11A-31, could be more effective for treating RTT by targeting key processes, addressing multiple aspects of the disease simultaneously. Further research should be directed towards a more detailed investigation of the molecular mechanisms and the corroboration of these findings in in vivo models.

Session H. Protein Quality Control, Proteasomal Degradation and Autophagy

sciforum-115084: Intrinsic Disorder in Autophagy-Related Proteins: Insights for Therapeutic Development

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Autophagy is a crucial cellular process that maintains homeostasis by degrading and recycling intracellular components. A network of autophagy-related proteins orchestrates this process, many of which exhibit intrinsic disorder. Intrinsically disordered proteins (IDPs), lacking stable three-dimensional structures, possess structural flexibility, which enables dynamic interactions and diverse biological functions.

In this study, we analyzed 95 autophagy-related proteins from the Human Autophagy Database (HADb) and UniProt using sets of bioinformatics tools like ESpritz and leveraging datasets trained on X-ray, NMR, and DisProt. Our findings revealed that these proteins are significantly enriched with intrinsically disordered protein regions (IDPRs), particularly in key functional roles such as cargo recognition (e.g., SQSTM1, NBR1), autophagosome formation (e.g., ATG8, ATG12, WIPI1), and lysosomal degradation. Remarkably, proteins such as Beclin-1, LC3, and ATG9 exhibited high levels of intrinsic disorder, underscoring their critical regulatory roles.

The statistical analysis demonstrated that 80.21% of autophagy-related proteins contain at least one disordered region longer than 30 amino acids, and 65.97% have regions exceeding 50 amino acids. A total of 159 long disordered regions (greater than 30 amino acids) and 100 very long disordered regions (greater than 50 amino acids) were identified, emphasizing their functional relevance. Proteins like SPO95817 and SPP35638 showed extreme levels of disorder, with a mean percentage disorder above 90%, while others, such as SPP51809, exhibited minimal disorder, highlighting the variability within the autophagy-related proteome.

These results reinforce the critical role of IDPs in mediating transient and dynamic interactions that are essential for autophagy. This study advances our understanding of the molecular dynamics of autophagy-related proteins and provides a foundation for developing disorder-targeted therapeutic strategies. Such strategies hold potential for addressing neurodegenerative diseases, cancers, and other disorders linked to autophagic dysregulation.

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