INTERNATIONAL CONGRESS ON NEUROINFLAMMATION, AGING AND NEURODEGENERATIVE DISORDERS

XIX CIBERNED ANNUAL FORUM

FIRST JOINT MEETING CIBERNED/CIBERFES

Organized by

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With the collaboration of

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SESSION: 1
POSTER#1

INTRODUCED BY: Laia Lidón.

PRINCIPAL INVESTIGATOR: Alberto Lleó.

RESEARCH AREA: CIBERNED.

TITLE: Altered miRNA expression in Alzheimer's disease synapses postmortem.

AUTHORS: Laia Lidón, Xuanyang Bai, Raúl Núñez-Llaves, Danna Perlaza, Alba Cervantes-González, Sònia Sirisi, Oriol Dols-Icardo, Alberto Lleó, Olivia Belbin.

ABSTRACT: Synapse degeneration occurs early in Alzheimer's disease (AD) and is the major neuropathologic correlate of cognitive impairment. MicroRNA (miRNA) regulate synaptic plasticity and play a role in AD pathogenesis. The aim of this study was to characterize miRNA dysregulation at AD synapses in post-mortem brain tissue and explore the specificity for AD.

Homogenates and synaptosomes were prepared and total RNA was extracted to quantify 751 miRNA in an exploratory study from 10 AD and 10 control (CTL) temporal cortex tissues. Then we quantified 9 miRNA across 3 brain regions (anterior cingulate, temporal and prefrontal cortex) from 5 CTL, 5 AD and 5 non-AD tauopathy (TAU) cases in a follow-up study. We compared the synapse-related Gene Ontology associated with genes targeted by synaptic (expressed in 2 or more synaptosomes) and non-synaptic miRNA.

Targets of the synaptic miRNA were enriched for 16 synaptic pathways, while targets of non-synaptic miRNA were enriched for 8 synaptic pathways. We found miR-132-3p, miR-132-5p and miR-212-3p under-expressed and miR-181a-3p and miR-1260a over-expressed in AD vs CTL synaptosomes ($p<0.001$). We selected the 9 miRNA with the lowest p-value for the follow-up study and we validated the down-regulation of miR-132-3p (FDR=0.003, FDR=0.001) and miR-212-3p (FDR=0.02, FDR=0.03) in AD temporal cortex synaptosomes.

This study confirms the under-expression of miR-132-3p and miR-212-3p in AD synaptosomes that is specific to a brain region with high AD pathology and is not observed in another common cause of neurodegenerative dementia. Future studies will focus on the use of these miRNA as therapeutic targets for AD.

SESSION: 1
POSTER#2

INTRODUCED BY: María Cristina Ortega.

PRINCIPAL INVESTIGATOR: Diego Clemente.

RESEARCH AREA: CIBERNED.

TITLE: Deciphering the role of extracellular vesicles from myeloid-derived suppressor cells in the clinical severity of experimental multiple sclerosis.

AUTHORS: María Cristina Ortega, Cristina Martos-Polo, Pilar García-Llorena, Rocío del Carmen Bravo-Miana, Ángela Marquina-Rodríguez, Virginia Vila-del Sol, David Otaegui, Diego Clemente.

ABSTRACT: INTRODUCTION: Multiple Sclerosis (MS) is an immune-mediated demyelinating CNS disorder. Some patients experience a highly active disease poorly controlled by existing medications. Cell-based therapies with myeloid-derived suppressor cells (MDSCs) offer a promising alternative due to their ability to suppress T-cells in the experimental autoimmune encephalomyelitis (EAE) MS model. Notably, a reduced number and impaired function of MDSCs are associated with more severe EAE. Extracellular vesicles (EVs) have emerged as a safer alternative to cell transplants. In this work, we investigated whether EAE severity alters the molecular cargo and immunosuppressive activity of MDSC-derived EV (MDSC-EVs).

METHODS: MDSCs were isolated from EAE mice with mild or severe diseases. After 24h in culture, EVs were extracted from supernatants using optimized protocols combining centrifugation and size-exclusion chromatography. MDSC-EVs were analysed for surface markers and transcriptomic content, and their immunosuppressive function was evaluated via co-culture with MOG-stimulated splenocytes.

RESULTS: MDSC-EVs shared around 25% of their mRNAs with parental MDSCs. Transcriptomic and miRNA analysis revealed 326 differentially expressed genes (DEG) and 13 DE miRNAs between EVs derived from mild versus severe EAE mice. GO analysis linked DEGs to T-helper cytokine production. MDSC-EVs showed consistent expression of Ly-6C and HSP70 regardless of severity, with CD81 expression upregulated in EVs from severely affected EAE mice. Interestingly, MDSCs-EVs impaired lymphocyte proliferation to a similar extent than MDSCs, independently of clinical severity.

CONCLUSIONS: Our findings suggest that disease severity influences the molecular cargo. The optimized isolation protocol yields biologically active EVs, supporting their potential as cell-free therapeutic strategy for MS.

SESSION: 1
POSTER#3

INTRODUCED BY: Katherine T. Herrera Panchi ; Alba Elias Tersa.

PRINCIPAL INVESTIGATOR: Eduardo Soriano.

RESEARCH AREA: CIBERNED.

TITLE: Reelin regulates microglial activation phenotypes and boosts phagocytic activity in Alzheimer's Disease.

AUTHORS: Angel Marquez-Galera, Aysha M Bhojwani-Cabrera, Lluís Pujadas, José P. López-Atalaya, Eduardo Soriano, Yasmina Manso.

ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline. AD is characterized by amyloid-beta (Aβ) plaque deposition, neurofibrillary tangles, and neuroinflammation. Reelin, an extracellular matrix glycoprotein, plays a pivotal role in neural development and adult plasticity. Our research, along with others, demonstrates its multifaceted impact on AD, including hindering amyloid aggregation, reducing P-Tau pathology and amyloid production, and preserving cognitive function. Microglia, the brain's immune cells, are key responders to brain damage in AD. They bind to Aβ oligomers through various receptors, leading to their activation, proliferation, increased phagocytosis, and cytokine production. Given that microglia express Reelin receptors, we used immunohistochemical approaches coupled with confocal imaging to determine whether Reelin modulates microglial activation phenotype and enhances Aβ phagocytosis. By combining the J20 AD model with either Reelin gain- (J20OE) or loss-of-function (J20KO) mouse models, we analyzed various homeostatic (Tmem119, P2RY12) and activation phenotype markers (TREM2, IFTM3, CD68, etc). Our results indicate that Reelin overexpression enhances microglial recruitment to dense-cored amyloid deposits and increases microglial-mediated Aβ phagocytosis in J20OE mice compared to control mice. Additionally, single-cell RNA sequencing (scRNA-seq) of purified microglial cells revealed distinct microglial subpopulations in response to Reelin levels. Our findings highlight Reelin's role in modulating microglial phenotype and activity, enhancing their ability to phagocytose and eliminate Aβ species, revealing a novel mechanism for Aβ reduction.

SESSION: 1
POSTER#4

INTRODUCED BY: Rodrigo Barderas Manchado.

PRINCIPAL INVESTIGATOR: Teresa Moreno Casbas.

RESEARCH AREA: CIBERFES.

TITLE: COGNITIVE SCREENING TOOLS IN SPANISH FOR MILD COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS.

AUTHORS: R. Barderas Manchado, A. Ropero Sánchez, G. Escudero Pérez, P. Lozano González, O. Alonso del Cura, L. Camacho Montaño, M. Pascual García, R. Sánchez Ruano, C. Martín Saborido, T. Moreno Casbas.

ABSTRACT: Background: Mild Cognitive Impairment (MCI) represents the earliest stage of a chronic and degenerative condition, often undetected, impacting individuals, families, and healthcare systems. Early detection is critical to initiate timely interventions. However, the accuracy and consistency of MCI screening tools in Spanish-speaking populations remain uncertain, limiting effective screening.

Objectives: This systematic review aims to identify cognitive screening tools validated in Spanish for detecting MCI in individuals aged 50 years and older and to evaluate their diagnostic accuracy in terms of sensitivity, specificity, AUROC, and cut-off scores. It also seeks to determine which tool, or combination of tools, provides the highest validity for early MCI detection.

Methods: Following PRISMA guidelines and the PIRD framework, a systematic search was conducted across seven databases (CINAHL, Embase, PsycInfo, PubMed, ScienceDirect, Scopus, and Web of Science), covering studies published in English or Spanish between 2015 and 2025. Inclusion criteria were: Spanish-speaking adults aged ≥50, cognitively unimpaired or diagnosed with MCI per DSM-5 criteria, and use of Spanish-validated cognitive screening tools. Eligible studies were quantitative or mixed-methods, reporting diagnostic accuracy measures. Studies involving non-cognitive tools, tools not validated in Spanish, or participants with confounding comorbidities, institutionalization, or major barriers to questionnaire completion were excluded. Secondary literature, grey literature, non-original articles, and case reports were also excluded.

Conclusion: This review will synthesize current evidence on Spanish-validated MCI screening tools and their diagnostic performance. Findings will inform clinical decision-making and support the selection of the most accurate tools for early MCI detection in Spanish-speaking populations.

SESSION: 1
POSTER#5

INTRODUCED BY: Laura Carrero.

PRINCIPAL INVESTIGATOR: Eva Carro.

RESEARCH AREA: CIBERNED.

TITLE: Altered Clock Gene Expression in Female APP/PS1 Mice and Aquaporin-Dependent Amyloid Accumulation in the Retina.

AUTHORS: Laura Carrero, Desiree Antequera, Ignacio Alcalde, Diego Megías, Lara Ordoñez-Gutiérrez, Francisco Wandosell, Cristina Municio, Eva Carro.

ABSTRACT: Alzheimer's disease (AD), the most prevalent form of dementia, is a neurodegenerative disorder characterized by different pathological symptomatology, including disrupted circadian rhythm. The regulation of circadian rhythm depends on the light information that is projected from the retina to the suprachiasmatic nucleus in the hypothalamus. Studies of AD patients and AD transgenic mice have revealed AD retinal pathology, including amyloid-β (Aβ) accumulation that can directly interfere with the regulation of the circadian cycle. Although the cause of AD pathology is poorly understood, one of the main risk factors for AD is female gender. Here, we found that female APP/PS1 mice at 6- and 12-months old display severe circadian rhythm disturbances and retinal pathological hallmarks, including Aβ deposits in retinal layers. Since brain Aβ transport is facilitated by aquaporin (AQP)4, the expression of AQPs were also explored in APP/PS1 retina to investigate a potential correlation between retinal Aβ deposits and AQPs expression. Important reductions in AQP1, AQP4, and AQP5 were detected in the retinal tissue of these transgenic mice, mainly at 6-months of age. Taken together, our findings suggest that abnormal transport of Aβ, mediated by impaired AQPs expression, contributes to the retinal degeneration in the early stages of AD.

SESSION: 1
POSTER#6

INTRODUCED BY: Carmen Mª Alburquerque Pastor.

PRINCIPAL INVESTIGATOR: Externo.

RESEARCH AREA: EXT.

TITLE: From Olive Oil Waste to Brain Shield: Liposomal Hydroxytyrosol as a Neuroprotective Agent.

AUTHORS: Carmen Mª Alburquerque Pastor, David Auñón Calles, Estrella Núñez Delicado, José Antonio Gabaldón Hernández.

ABSTRACT: Olive oil is one of the most distinguished food due to its nutritional properties and high economic value (1). During its extraction process, a large amount of waste is generated, which is rich in bioactive compounds but may pose an environmental concern (2). Among these compounds, phenolic compounds such as hydroxytyrosol (HT) stand out due to their antioxidant, anti-inflammatory and neuroprotective properties (3).

In this study, hydroxytyrosol encapsulated in liposomes (which enhances therapeutic benefits while minimizing toxicities and side effects (4)) was used to evaluate its neuroprotective potential in the SH-SY5Y cell line (ATCC® CRL-2266). For this purpose, a cell viability assay was performed, considering two experimental groups: (1) non-neurodegenerative cells and (2) neurodegenerative cells treated with 6-hydroxydopamine (6-OHDA).

The results showed that when free HT was applied at concentrations higher than 6.25 mg/L, neurodegenerative cells viability was significantly lower compared to the control, which indicated that at high concentrations it could be cytotoxic. However, when neurodegeneration was induced, cell viability increased at concentrations below 6.25 mg/L, indicating protection against neurodegeneration. Futhermore, when HT encapsulated in liposomes was added, the viability of neurodegenerated cells increased by 75% compared to the control, enhancing the protection against 6-OHDA induced neurodegeneration.

In conclusion, liposome-encapsulated HT enhances cell viability in neurodegenerative models, demonstrating its protective potential. Its encapsulation optimizes therapeutic effects, avoiding cytotoxicity and suggesting a promising strategy for the prevention of neurodegenerative diseases.

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SESSION: 1
POSTER#7

INTRODUCED BY: Daniel Carnicero-Senabree.

PRINCIPAL INVESTIGATOR: Antonio Cuadrado Pastor.

RESEARCH AREA: CIBERNED.

TITLE: Role of transcription factor NRF2 in the maintenance of synaptic homeostasis.

AUTHORS: Daniel Carnicero-Senabre, Mariana A. Barata, Antonio Cuadrado, Cláudia G. Almeida, Ana I. Rojo.

ABSTRACT: Introduction: Failure to translate successful neuroprotective preclinical data to a clinical setting in Alzheimer's disease (AD) indicates that amyloidopathy and tauopathy alone provide an incomplete view of disease. Here, we evaluated the relevance on synapses of additional homeostatic deviations that result from loss of activity of NRF2, a transcription factor that regulates the expression of over 250 genes, including those related to protection against oxidative stress, whose activity declines with ageing.

Methods: We have employed immunofluorescence techniques to quantify synapses both in primary cultures and in brain slices. To analyse synaptic composition by western blotting, we have isolated synaptosomal fractions. To determine lipidic composition, we have carried out untargeted lipidomics of whole hippocampus or the synaptosomal fraction of neurons in culture or from hippocampal lysates.

Results: Therefore, we evaluated the impact of NRF2 activity on synaptic architecture and composition by measuring synaptic contacts, both excitatory and inhibitory, in primary neurons and in brain tissue from NRF2-WT and knock-out mice. Our findings revealed that the absence of NRF2 modified the molecular composition of the synapse and impacted glutamate and calcium signaling. Moreover, these alterations were concomitant with changes in the synaptic lipidome with an upregulation of certain ether-lipid species. To address whether ether bonds in lipids could have functional effects on synapses, we treated primary cultures and organotypic slices with an ether-linked lipid precursor (HG) and observed that synaptic contacts were impaired. However, activation of NRF2 with 6-MSITC prevented synaptic loss.

Conclusions: In conclusion, NRF2 emerged as a crucial modulator of synaptic homeostasis, providing a new avenue for exploring its potential as a therapeutic target for neurodegenerative diseases characterized by progressive synaptic loss, such as AD.

SESSION: 1
POSTER#8

INTRODUCED BY: Pedro González-Romero.

PRINCIPAL INVESTIGATOR: Mª Ángeles Rol de Lama.

RESEARCH AREA: CIBERFES.

TITLE: Assessing circadianity of sleep and motor activity when diabetes and frail phenotypes coexist.

AUTHORS: Pedro González-Romero, Juan Antonio Madrid, Carlos Cano Gutierrez, Daniela Rey, Samir Aruachan, María Ángeles Rol.

ABSTRACT: Introduction: People affected by type 2 diabetes (T2DM) are prone to worse circadian health. Besides, an association between frailty prevalence and circadian disturbances has been described recently. This study aimed to evaluate the circadian state at different levels of glycemic control and frailty.

Materials and Methods: Ambulatory circadian monitoring was performed in 111 older adults (≥65 years), diagnosed with T2DM and a prefrail/frail phenotype according to Fried criteria. Participants were grouped as follows: Controlled Glycemia (HbA1c <7%, Prefrail CG n=45, Frail CG n=18) and Non-Controlled Glycemia (HbA1c ≥7%, Prefrail NCG n=31, Frail CG n=17). A Two-Way ANOVA was conducted, evaluating jointly how glycemia and frailty affect circadian patterns of sleep and motor activity variables (TM: Time in Movement; MI: Movement Intensity).

Results: Motor activity during night was significantly delayed in NCG participants (TM-hL5, F=10.72, p=0.001; MI-hL5, F=4.43, p=0.038) and in Frail elders (TM-hL5, F=5.41, p=0.022; MI-hL5, F=8.03, p=0.006). Moreover, only in the NCG group, daytime activity phase occurred later in Frail participants than in Prefrail ones (TM-hM10, F=4.02, p=0.047; MI-hM10, F=4.49, p=0.036). Contrast between day and night for motor activity was lower in NCG group compared to CG group, due to higher TM levels at night (AT index: TM-vL5/MI-vM10, F=7.94, p=0.006). Consistently, sleep depth (vM5, F=5.85, p=0.017) and regularity (IS, F=6.03, p=0.016) were reduced in NCG group.

Conclusions: Activity phase is related to both glycemic control and frailty in older adults with T2DM and frailty. However, the amplitude values of activity and sleep seem to be mainly affected by glycemia.

SESSION: 1
POSTER#9

INTRODUCED BY: Azucena Pérez-Cañamás.

PRINCIPAL INVESTIGATOR: Isabel Fariñas.

RESEARCH AREA: CIBERNED.

TITLE: mGluR4–Npdc1 complex mediates a-synuclein fibril-induced neurodegeneration.

AUTHORS: Mingming Chen, Leire Almandoz-Gil, Nabab Khan, Si Jie Tang, Allyson Ho, Erik C. Gunther, Stephen M. Strittmatter.

ABSTRACT: Fibrils of misfolded a-synuclein (a-syn) accumulate in Parkinson's disease and other synucleinopathies, spreading between cells to template further misfolding and drive neurodegeneration. a-syn fibril entry into healthy neurons is recognized as a key step in the disease process but remains ill-defined mechanistically. Here, we comprehensively assessed the membrane proteome for binding of a-syn fibrils. Expression cloning identified mGluR4 and Npdc1 as plasma membrane proteins expressed by substantia nigra neurons capable of supporting high affinity a-syn fibril binding. Moreover, mGluR4 and Npdc1 cellular signaling functions were titrated by the presence of extracellular fibrillary a-syn. While striatal a-syn fibril injection led to nigral dopamine neuron loss in wild type mice, deletion of either Grm4 or Npdc1 provided protection of dopamine neurons. We observed mGluR4 and Npdc1 to form a complex that regulates mGluR4 signaling. Cultured neurons lacking both Grm4 and Npdc1 fail to bind a-syn fibrils, to accumulate phosphorylated a-syn and to lose synapses. Transheterozygous Grm4, Npdc1 mice showed protection from nigral neuron loss after striatal a-syn injection, demonstrating genetic interaction between the two binding proteins. On a transgenic a-syn A53T background, double Grm4, Npdc1 heterozygosity robustly increased mouse survival, motor function and spinal motoneuron number. Thus, a cell surface mGluR4–Npdc1 complex participates in a-syn neurodegeneration.

SESSION: 1
POSTER#10

INTRODUCED BY: Fernando Cardona.

PRINCIPAL INVESTIGATOR: Jordi Pérez Tur.

RESEARCH AREA: CIBERNED.

TITLE: Development of a cellular model to study the role of inflammation and complement function in Alzheimer's disease.

AUTHORS: Florencia Balverde, Bianca Moraru, Jordi Pérez-Tur, Fernando Cardona.

ABSTRACT: Alzheimer's disease is the leading cause of dementia worldwide, characterised by progressive cognitive impairment and neuronal loss. Although β-amyloid plaques and neurofibrillary tangles have been considered the major triggers, recent studies highlight chronic neuroinflammation as a key component of its pathophysiology. In particular, prolonged activation of microglia and astrocytes contributes to synaptic dysfunction and disease progression. However, conventional cellular models do not allow studying neuron-glial cell interactions under physiological conditions.

To overcome this limitation, an indirect triple co-culture model was developed using human cell lines co-cultured in the Transwell® system. This model consists of SH-SY5Y neurons, differentiated to a cholinergic phenotype, HMC3 microglia, and 1321N1 astrocytes. The model was treated with lipopolysaccharide (LPS) or β-amyloid oligomers ($A\beta_{1-42}$) and modulation of CR1 complement receptor gene expression, a risk factor related to the complement system associated with AD in GWAS studies.

LPS exposure induced an overt inflammatory response without affecting cell viability, whereas treatment with $A\beta_{1-42}$ significantly reduced viability, especially under conditions of CR1 overexpression. The expression of key genes such as IL-6, TGF-β, BDNF, C3, and CR1 itself was differentially modulated depending on the experimental conditions, correlating with the inflammatory signals used.

These results validate the use of this triple co-culture system as a physiologically relevant model to study inflammatory processes in Alzheimer's disease and reveal a functional role for CR1 and the complement system in the cellular response to $A\beta_{1-42}$ pathological stimuli.

SESSION: 1
POSTER#11

INTRODUCED BY: Marta Antequera.

PRINCIPAL INVESTIGATOR: Juan Pedro Bolaños.

RESEARCH AREA: CIBERFES.

TITLE: Astrocyte metabolism as an epigenetic regulator of neural functions during cognitive decline.

AUTHORS: Marta Antequera, Darío García-Rodríguez, Zaki Saati-Santamaría, Estefanía Prieto-García, Cristina Andres-Lacueva, Juan P. Bolaños.

ABSTRACT: In recent decades, increasing life expectancy has led to a growing prevalence of cognitive impairment and related brain diseases. Normal aging entails metabolic alterations that are associated with a decline in cognitive performance (1). Astrocytes have direct access to brain vasculature, acting as sensors of systemic changes to provide metabolic and functional support to neurons. These cells produce lactate, acetyl-CoA and β-hydroxybutyrate –key metabolites that serve as energy substrates or metabolic precursors to sustain cognitive performance (2, 3). Moreover, these metabolites are known to induce post-translational modifications (PTMs) of histones and thereby modulate gene expression in a metabolism-dependent manner (4).

In this context, lifestyle is a modifiable factor with a high influence on brain metabolism. Our work investigates the impact of aerobic exercise on the metabolism-driven epigenetic modifications of histones in astrocytes.

Preliminary DNA ChIP-Seq analyses of astrocytes isolated from mice subjected to six weeks of aerobic exercise reveal alterations in chromatin acetylation patterns. These changes correlate with systemic metabolic changes in the use of glucose and fatty acids, as well as improving long-term cognitive performance. Our findings suggest a potential link between astrocytic metabolism and cognitive decline mediated by epigenetic mechanisms, offering new insights into the molecular basis of age-related cognitive decline.

Bonvento & Bolaños (2021) Cell Metabolism, 33 (8), 1546-1564

Herrero-Mendez, A. et al. (2009) Nature Cell Biology, 11 (6), 747-752

Morant-Ferrando, B. et al. (2023) Nature Metabolism, 5, 1290-1302

Boon, R. et al. (2020) Nature Metabolism, 2, 1190-1203.

SESSION: 1
POSTER#12

INTRODUCED BY: Ines Moreno-Gonzalez.

PRINCIPAL INVESTIGATOR: Antonia Gutiérrez.

RESEARCH AREA: CIBERNED.

TITLE: Peripheral administration of blood from tauopathy mouse model enhances associated pathology.

AUTHORS: Jesus Garcia-Martin, Laura Vegas-Gomez, Maria Angeles Arredondo-Alcala, Antonia Gutierrez, Claudia Duran-Aniotz, Ines Moreno-Gonzalez.

ABSTRACT: Alzheimer's disease (AD) is characterized by the pathological accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau in the brain. Although these tau aggregates have also been detected in different peripheral tissues, their contribution to central tau pathology remains unclear. In this study, we assess the potential role of blood from transgenic mice with P301S human tau mutation, a tauopathy well-characterized model, in exacerbating brain tau-associated neurodegeneration after peripheral administration. Aged P301S mice served as donors, and their blood was injected into young P301S mice via intraperitoneal and intravenous injections. Behavioral, biochemical, and histological assessments were performed to evaluate the effects of peripheral blood exposure on cognitive and motor impairment, tau pathology, and glial response. Our results indicate that peripheral blood inoculation from tauopathy mice promotes tau deposition in the hippocampus, increases glial response, and exacerbates motor deficits in recipient mice. These findings sustain the hypothesis that peripherally administered blood from affected individuals contributes to the progression of tau-associated pathology in the brain, highlighting the need for further investigation into the mechanisms by which peripheral tau influences central neurodegenerative processes, as well as the development of therapeutic strategies targeting tau dissemination in AD and related tauopathies.

SESSION: 1
POSTER#13

INTRODUCED BY: Valle Palomo.

PRINCIPAL INVESTIGATOR: Ana Martínez.

RESEARCH AREA: CIBERNED.

TITLE: Selective and Multiplexed Cytoplasmic TDP-43 Labelling withCd-Se Quantum Dots.

AUTHORS: Paula Fernández-Gómez, Carlota Tosat-Bitrián, Tania Marugán, Laura Fernández-Hernández, Alicia Cano, Jose A. Martinez-Mulero, Juan I. López-Carbonero, Ana Martínez, Jaime Pignatelli, Silvia Corrochano, Valle Palomo.

ABSTRACT: Semiconductor quantum dots (QDs) provide unique photophysical properties for biomarker detection in complex diseases. Here, we demonstrate that QDs enable cytoplasmic selective, multiplexed detection of four neurodegeneration related proteins, including TAR DNA-binding protein 43 (TDP-43), in patient-derived lymphoblasts. This approach distinguished control, disease, and treated lymphoblast samples via immunofluorescence microscopy with high specificity. Leveraging this selective staining, we implemented flow cytometry for high-throughput quantitative classification of patient samples, offering a scalable alternative to conventional imaging techniques. This technique was additionally implemented in primary lymphocytes, assessing their potential of accurately monitoring TDP-43 in Amyotrophic Lateral Sclerosis (ALS) and other neurodegenerative diseases. In mouse hippocampal tissue, QDs maintained cytoplasmic selectivity, underscoring their versatility across biological systems. Compared to organic fluorophores, QDs enhance sensitivity, improve signal stability, and enable simultaneous biomarker quantification, broadening their potential for clinical diagnostics and personalized medicine. These findings establish QDs as powerful tools for neurodegeneration research, disease monitoring, and early biomarker discovery, with potential applications in translational neuroscience and precision medicine.

SESSION: 1
POSTER#14

INTRODUCED BY: Karolina Zimkowska.

PRINCIPAL INVESTIGATOR: Jose Antonio del Río.

RESEARCH AREA: CIBERNED.

TITLE: Biochemical and functional analysis of P301L Tau in human brain cortical organoids mimicking tauopathies of the FTLD spectrum.

AUTHORS: Karolina Zimkowska, Marc Riu-Villanueva, Pol Picón-Pagès, Irene Fernandez-Carasa, Jorge Oliver-De La Cruz, Pere Roca-Cusachs, Antonella Consiglio, José Antonio del Río.

ABSTRACT: The P301L mutation in the MAPT gene, encoding the microtubule-associated protein tau, is a well-characterized pathogenic variant linked to a subset of inherited neurodegenerative tauopathies. This single amino acid substitution-from proline to leucine at position 301-alters tau's normal function of stabilizing microtubules, leading to its pathological aggregation into insoluble fibrils. These aggregates are central to the formation of neurofibrillary tangles, a hallmark of diseases such as Frontotemporal Dementia with Parkinsonism linked to chromosome 17 (FTDP-17), and to a lesser extent, Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD). Although rare in the general population, the P301L mutation accounts for approximately 25-40% of familial FTDP-17 cases with confirmed MAPT mutations, with over 60 families identified worldwide, particularly in Europe, North America, and parts of Asia. In contrast, the P301L MAPT mutation has also been identified in rare cases presenting clinical features overlapping with PSP and CBD. However, such associations represent a minority of tauopathy cases and often reflect diagnostic overlaps within the broader FTLD-tau spectrum.

Tau pathology in P301L-associated tauopathies preferentially affects the frontal and temporal cortices and subcortical regions such as the basal ganglia and brainstem nuclei. At the cellular level, the mutation predominantly impacts excitatory glutamatergic neurons and astrocytes, contributing to synaptic loss, impaired neuronal connectivity, and glial dysfunction. These disruptions ultimately compromise network integrity and cognitive-emotional processing, aligning with the clinical phenotypes observed in affected individuals.

In this study, we employ human cortical brain organoids (hCBOs) derived from pluripotent stem cells to model the biochemical and functional consequences of P301L tau expression. This system enables a high-resolution investigation of tau aggregation, neurotoxicity, .

SESSION: 1
POSTER#15

INTRODUCED BY: Ana Castillo-Luna.

PRINCIPAL INVESTIGATOR: Externo.

RESEARCH AREA: EXT.

TITLE: Development and validation of an analytical method for the determination of Advances Glycation End Products in human biofluids.

AUTHORS: Ana Castillo-Luna, Feliciano Priego-Capote.

ABSTRACT: Advanced Glycation End Products (AGEs) are a heterogeneous group of compounds that can be found in biofluids by endogenous and exogenous sources. These compounds are formed by the Maillard reaction which implies a non-enzymatic reaction between reducing sugars and molecules with free amino groups such as peptides, proteins, etc.

The biochemical relevance of AGEs and their levels may be of interest in the study of metabolic disorders as well as in other pathologies related to inflammation and oxidative stress, including neurodegenerative and cardiovascular diseases and type 2 diabetes mellitus. Recent research studies confirm that a high concentration of AGEs in our body increases the predisposition to suffer from chronic diseases such as renal failure, Alzheimer's disease, among others.

Over years, many methods have been developed to detect and quantify individual or similarly structured AGEs (for instance, glyoxal and methylglyoxal). Nevertheless, there is no unique methods that include the main AGEs such as glyoxal, methylglyoxal, 3-deoxyglucosone, Nε-carboxyethyl-lysine, Nε-carboxymethyl-lysine, arg-pyramidine, pyrraline, glyoxal-lysine and methylglyoxal-lysine dimer and glyoxal and methylglyoxal hydroimidazolone. For these reasons, a method for their joint analysis in human biofluids has been developed based on a derivatization reaction and determination with an LC-MS/MS device. We used o-phenylenediamine as derivatization reagent for the detection of glyoxal, methylglyoxal and 3-deoxyglucosone. The optimized method was applied to several human biofluids to determine physiological levels. We have detected and quantified AGEs concentrations in the ng/mL and pg/mL range in the different biofluid samples.

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SESSION: 1
POSTER#16

INTRODUCED BY: Vicente Roca Agujetas.

PRINCIPAL INVESTIGATOR: Javier Vitorica.

RESEARCH AREA: CIBERNED.

TITLE: MITOCHONDRIAL STRESS MEDIATES A PRO-INFLAMMATORY AND SENESCENT MIRCOGLIAL PROFILE IN ALZHEIMER'S DISEASE.

AUTHORS: Vicente Roca Agujetas, Jorge Moreno Fernández , Rocío Díaz González, Cristina Núñez Díaz, Carmen Romero Molina, Sebastián Jiménez Muñoz, Cristina Muñoz Castro, María Manfredi Lozano, Nicolás Capelo Carrasco, Clara García Mayor, Alberto Pascual, Antonia Gutiérrez, Marisa Vizuete, Javier Vitorica.

ABSTRACT: Introduction and Methods

Microglial phenotype during Alzheimer's Disease (AD) continuum is under debate. At early stages, a protective phenotype with the typical DAM profile would participate in plaque compaction and Aβ degradation. Instead, human AD microglia (HAM) show an enhance aged/degenerative profile, supporting a microglial dysfunction as a central mechanism in AD aetiology. Recent findings from our lab described that peri-plaque microglia are highly reliant on oxygen levels and mitochondrial integrity. Nevertheless, mitochondrial implication in aged microglia during the disease progression remains unclear. Therefore, we aimed to analyse the mitochondrial contribution to microglial phenotype changes in APP-based transgenic mice at different ages and in vitro microglial cells, focusing on the pro-inflammatory type-I IFN pathway and senescence.

Results

Isolated active microglia from aged APP mice displayed a significant induction of the oxidative phosphorylation transcriptomic signature, but, at the same time, an increase in the hypoxia gene set. This contradictory induction correlates with a rise in the mitochondrial ROS production and the expression of the antioxidant machinery. Likewise, electron microscopy images exhibited mitochondrial morphological abnormalities in hippocampal peri-plaque microglia from these mice. Moreover, aged, and active microglia exhibited a significant increase of gene sets of type-I IFN pathway and senescence-associated secretory phenotype (SASP). In vitro experiments with Aβ-exposed BV2 cells and murine primary microglia confirmed a significant induction of type-I IFN and senescence pathways, only following a mitochondrial insult caused by the inhibition of complex III of the mitochondrial respiratory chain by Antimycin A.

Conclusion

Altogether, these results suggest that amyloid pathology accumulation triggers a shift in microglia towards a pro-inflammatory and senescent profile associated with mitochondrial stress.

SESSION: 1
POSTER#17

INTRODUCED BY: Alejandra M Arroyo García.

PRINCIPAL INVESTIGATOR: Jose Javier Lucas.

RESEARCH AREA: CIBERNED.

TITLE: C-terminal TAF1 alteration in demyelinating diseases.

AUTHORS: Alejandra M Arroyo, Claudia Rodríguez, Laura Planas, Aurora Pujol, Jose J Lucas.

ABSTRACT: Introduction: The TATA-box binding protein associated factor 1 (TAF1) is the largest subunit of the general transcription factor IID. This protein has been implicated in neural diseases such as X-linked intellectual disability syndrome (XLID) or X-linked dystonia-parkinsonism (XDP), and recently we have also described a role in multiple sclerosis (MS). More precisely, we found an underrepresentation of the C-terminal region of TAF1 in postmortem brain tissue from individuals with MS1. Genetically modified mice mimicking such TAF1 alteration (Taf1d38) exhibit an MS-like phenotype with progressive motor disability, CNS-resident neuroinflammation in white matter tracts and progressive demyelination1. Thus, we hypothesize a role for TAF1 in other demyelinating diseases such as adrenoleukodystrophy (ALD). ALD is a rare peroxisomal disorder caused by mutations in the ABCD1 gene, leading to the abnormal accumulation of very long-chain fatty acids (VLCFAs). This results in progressive damage of the CNS white matter, adrenal glands and testes.

Materials and Methods: We analyzed postmortem brain tissue from patients with ALD, including both the childhood cerebral form and the adult-onset adrenomyeloneuropathy (AMN), as well as from Abcd1−/y/Abcd2−/− double-knockout mice model (DKO mice) that mimic the disease due to the disruption of the ABCD1 gene without ABCD mediated compensation2.

Results: We found a decrease in the C-terminal levels of TAF1 without changes in total TAF1 levels in both AMN samples and DKO mice.

Conclusion: We conclude that alterations in the C-terminal region of TAF1 may be common to additional demyelinating diseases apart from MS.

Bibliography

1 Rodríguez-López, et al. doi: https://doi.org/10.1101/2024.08.23.609325

2 Vasireddy et al. doi: https://doi.org/10.1016/j.omtm.2024.101354.

SESSION: 1
POSTER#18

INTRODUCED BY: María Angeles Arévalo Arévalo.

PRINCIPAL INVESTIGATOR: María Ángeles Arevalo.

RESEARCH AREA: CIBERFES.

TITLE: IGF1 RESCUES THE PHAGOCYTIC CAPACITY OF AGED MICROGLIA IN MALE MICE AFTER TBI.

AUTHORS: Daniela Grassi, Alvaro Bautista-Abad, Daniel Pinto-Benito, Danny Ganchala, María-José Bellini, María-Angeles Arévalo.

ABSTRACT: Myelin debris constitutes a barrier to axonal regeneration and functional recovery. Microglia is crucial for clearing myelin debris. Aging produces decreased IGF-1 expression, as well as microglial dysfunction, impairing recovery after injury. Therefore, identifying new targets to enhance microglial phagocytosis represents a therapeutic strategy aimed at repairing brain tissue. Here we examine the effect of IGF-1 gene therapy on microglial response in a traumatic brain injury model (TBI) in aged mice.

Animals received intramuscular injections of an adenoviral vectors carrying IGF-1 cDNA or PBS. Two weeks later, they underwent TBI and were sacrificed a week later. The microglial phagocytic capacity was evaluated by immunocytochemistry, quantifying the denaturalized myelin basic protein (dMBP) density in IBA1-positive cells using IMARIS software.

Microglial myelin uptake is greater in young female than in male mice. In aged animals, microglial myelin phagocytosis was lower than in young animals and sex differences disappeared. IGF-1 gene therapy showed sex-specific effects: it restored the microglia phagocytic capacity in males. However, in females it induced morphological changes toward a more reactive phenotype. Multifactorial analysis shows that the four experimental groups are separated within a space defined by three variables: IBA1 volume, integrated dMBP density, and IBA1 sphericity. The four ellipses delineating the 95% confidence regions do not overlap, underscoring the separation between groups and indicating that IGF-1 significantly modulates microglial morphology and phagocytosis.

In summary, our study shows that IGF-1 therapy improves microglia phagocytosis in aged males, but transforms them into foam-like morphology in females, blocking the increase in phagocytosis. .

SESSION: 1
POSTER#19

INTRODUCED BY: Amaia Lopez de Arbina.

PRINCIPAL INVESTIGATOR: Externo.

RESEARCH AREA: EXT.

TITLE: Manganese Supplementation Rescues Mitochondrial DNA replication in the Absence of ER-Mitochondrial Contact Sites.

AUTHORS: Amaia Lopez de Arbina, Mikel Muñoz Oreja, Laura Mosqueira Martín, Diego Perez Rodriguez, Ainara Vallejo-Illarramendi, Antonella Spinazzola, Ian Holt.

ABSTRACT: Mitochondrial dysfunction contributes to the development of a variety of neurodegenerative diseases. A growing body of research highlights disrupted endoplasmic reticulum-mitochondria contact sites (ERMCS) in conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis with frontotemporal dementia (ALS/FTD). ERMCS are essential hubs for the regulation of numerous mitochondrial processes, including mitochondrial DNA (mtDNA) maintenance and replication. However, the specific endoplasmic reticulum factors involved in this regulation remain largely unexplored.

We have shown that the repression of ER lipid raft-associated protein 2 (ERLIN2) leads to a reduction in contact sites and inhibits mtDNA replication. Similarly, the repression of the ER-mitochondrial bridging protein GRP75 and Reticulon 4 results in analogous effects, suggesting that a deficiency of ERMCS impairs mtDNA synthesis. A critical role of ERMCS is the transfer of calcium from the ER to the mitochondria via the mitochondrial calcium uniporter (MCU). And, notably, inhibiting MCU also hampers mtDNA synthesis. Furthermore, MCU is responsible for transporting manganese in addition to calcium, and supplementing manganese has been shown to restore mtDNA replication in cells with diminished ERMCS or inhibited MCU. These findings propose a model in which the endoplasmic reticulum regulates mtDNA replication by controlling manganese supply to the mitochondria.

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SESSION: 1
POSTER#20

INTRODUCED BY: Andrea Sainz Prado.

PRINCIPAL INVESTIGATOR: Carlos Matute.

RESEARCH AREA: CIBERNED.

TITLE: Myelin-derived fatty acids ameliorate pathology in human cortical organoids originating from Alzheimer's disease.

AUTHORS: Andrea Sainz, Alicia Pellitero, Alberto Pérez-Samartín , Carlos Matute.

ABSTRACT: Aging alters myelin structure and function. This is particularly aggravated in Alzheimer's disease (AD) whose main risk factor is brain aging. As we recently provided evidence of myelin being an energy source (10.1038/s42255-025-01244-7), we have challenged the idea that deficient metabolic support of aged myelin may contribute to AD onset and progression. To that end, we generated human cortical organoids derived from iPSCs originating from a female patient with sporadic AD. Organoids were characterized across developmental stages using immunofluorescence for neural and glial lineage markers (e.g., SOX2, MAP2, S100β, Tuj1, CTIP2), ensuring proper regional identity and maturation. Multiple pathological parameters, including myelination, tau hyperphosphorylation, astrocytic reactivity, and neuronal viability, were assessed with immunofluorescence and western blot. Analysis of live 4-month-old organoids using redox-sensitive fluorescent probes showed that myelin-derived fatty acids robustly attenuate oxidative stress. In turn, fatty acids significantly reduced phospho-Tau levels in those organoids. Ongoing experiments are exploring the impact of fatty acids in neuronal networks with live calcium imaging and microelectrode arrays. Together, these initial findings provide evidence that energy substrates derived from myelin may alleviate AD pathology. Furthermore, these data raise the question as to whether aged myelin may be a key factor in AD onset and progression.

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Supported by CIBERNED, MICINN, Gobierno Vasco and EITB-Maratoia.

SESSION: 1
POSTER#21

INTRODUCED BY: Alberto Giménez-Bejarano.

PRINCIPAL INVESTIGATOR: Jose Manuel Fuentes.

RESEARCH AREA: CIBERNED.

TITLE: A myotonic dystrophy type 1 in vitro model replicates autophagy perturbances observed in patient-derived fibroblasts.

AUTHORS: Enrique Carretero Morán, Eva Alegre Cortés, Javier Ojalvo Pacheco, Marta Paredes Barquero, Mercedes Blanco Benítez, Nerea Domínguez Rojo, Héctor Foronda Herrera, Saray Canales Cortés, Rosa Ana González Polo, Mireia Niso Santano, Sokhna M.S. Yakhine Diop , José Manuel Fuentes Rodríguez, Patricia Gómez Suaga.

ABSTRACT: Introduction

Unstable repeat expansions in non-coding regions of certain genes are linked to several hereditary neurological and neuromuscular diseases, including myotonic dystrophy type 1 (DM1). DM1 is the most common form of muscular dystrophy in adulthood. It is caused by a CTG repeat expansion located in the 3' untranslated region of the DMPK gene (DM1 CTGexp). Autophagy is a lysosomal degradative pathway that digests cellular components such as defective proteins or organelles and alterations on this pathway have been extensively linked to DM1.

Materials and Methods

Using transient transfection in cell lines of a DM1 minigene containing the human DMPK genomic sequence with exons 11-15 and 960 interrupted CTG repeats, we have characterized DM1 CTGexp-mediated changes in autophagy flux and signalling, including mTOR and AMPK signalling pathways.

Results

DT960 transfected cells showed similar alterations in autophagic flux and in the endo-lysosomal compartments than DM1 patient cells, as previously described by others.

Conclusions

Transient transfection in cell lines of the DM1 minigene DT960 replicates autophagic-lysosomal phenotypes observed in DM1 fibroblasts. We propose this in vitro model as a possible tool for high-throughput screening of molecules targeting the above effects.

SESSION: 1
POSTER#22

INTRODUCED BY: Marta C Alonso-Moreno.

PRINCIPAL INVESTIGATOR: Maria Llorens.

RESEARCH AREA: CIBERNED.

TITLE: Regional differences in dendritic spine morphology and excitatory input in hippocampal and entorhinal cortex regions of an Alzheimer's disease mouse model.

AUTHORS: Marta C Alonso-Moreno, Asta Kastanauskaite, Carla B Rodríguez-Moreno, Julia Terreros-Roncal, Jesús Avila, Javier Defelipe, María Llorens-Martín.

ABSTRACT: Alzheimer's disease (AD) is characterized by cognitive deficits and synaptic dysfunction.

The hippocampal trisynaptic circuit, which includes the entorhinal cortex (EC), dentate gyrus, and the hippocampal CA3 and CA1 regions, plays a critical role in learning and memory. Within this circuit, dendritic spines, essential for synaptic plasticity, vary in shape and density. This study examined dendritic spine morphology and density in the apical and basal dendrites of principal neurons in the CA1, CA3, and EC regions of wild-type (WT) mice and a murine model overexpressing GSK-3β. Using intracellular Lucifer yellow injections and VGLUT1 labeling, WT mice showed distinct spine distributions in apical and basal dendrites. CA3 basal dendrites exhibited a reduced density of thin spines, while EC dendrites showed increased density and a higher percentage of mushroom spines. In the AD model, region-specific alterations included reduced spine density, a higher percentage of thin spines and fewer mushroom spines in CA1 dendrites. CA3 basal dendrites displayed increased density of stubby spines while basal EC dendrites showed reduced density and percentage of mushroom spines. Additionally, a decrease in excitatory input was observed in apical and basal CA1 dendrites and in basal CA3 dendrites in the AD model. These findings suggest a shift from mature mushroom spines to immature thin spines, and a loss of excitatory synapses in specific hippocampal regions, pointing to disrupted synaptic plasticity. The study emphasizes the importance of understanding regional differences in dendritic spine alterations, highlighting a selective impact of AD on distinct hippocampal areas.

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SESSION: 1
POSTER#23

INTRODUCED BY: Javier Fernández Ruiz.

PRINCIPAL INVESTIGATOR: Javier Fernandez Ruiz.

RESEARCH AREA: CIBERNED.

TITLE: Induction of experimental parkinsonism in GPR55-knockout mice resulted in an attenuated pathological phenotype suggesting the interest of GPR55 inactivation as a potential therapy in this disease.

AUTHORS: Santiago Rodríguez-Carreiro, Mª Carmen Nogales, Sara Pardo, Evi Gheysens, Elisa Navarro, Javier Fernández-Ruiz.

ABSTRACT: Parkinson's disease (PD) is the most common neurodegenerative disorder affecting the basal ganglia and the control of movement. Therapies only cover symptom alleviation, then lacking effective disease-modifying treatments. Cannabinoids have been broadly investigated as potential neuroprotectants in PD. Recent experimental evidence supports that GPR55, an atypical cannabinoid receptor, may be a new pharmacological target given that it is altered in this disease. The present study investigated the progression of the pathological phenotype after inducing experimental PD in GPR55-deficient mice. In a first experiment, we unilaterally inoculated (A53T)α-synuclein into the right substantia nigra using AAV9 technology and subjected these mice to behavioral testing and histopathological analysis. Our data indicated that the (A53T)α-synuclein-induced impairment in motor performance was apparently lower in mice lacking GPR55 than in wildtype animals. This difference was consistent with a reduced loss of tyrosine hydroxylase-labelled neurons in GPR55-deficient mice compared to wildtype animals, although such difference was not so evident in the analysis of glial reactivities. Mostly similar results, although to a lower extent, were found in a second experiment aimed at elucidating whether such differences were also evident in 6-hydroxydopamine-lesioned mice. Interestingly, in both experiments, the differences found between genotypes occurred in males but resulted to be more evident in females. In conclusion, our results proved that the absence of GPR55 attenuated the disease progression in two models of PD. This indirectly suggests that GPR55 may contribute to PD pathogenesis, so that its pharmacological inactivation may work as a therapeutic strategy in this disease.

Supported by a grant from Michael J. Fox Foundation (reference MJFF-022552).

SESSION: 1
POSTER#24

INTRODUCED BY: Alba Pereda-Velarde.

PRINCIPAL INVESTIGATOR: Jordi Alberch.

RESEARCH AREA: CIBERNED.

TITLE: Astrocyte-derived mitochondria, a potential threat for striatal neurons in Huntington's disease.

AUTHORS: Laura Lopez-Molina, Nadia di Franco, Laura Valls-Roca, Mariona Guitart-Mampel, Gloria Garrabou, Silvia Gines.

ABSTRACT: Mitochondrial dysfunction plays a central role in the pathogenesis of several neurodegenerative diseases. In Huntington's disease (HD) -an inherited neurodegenerative disorder characterized by progressive psychiatric, cognitive and motor impairments -mitochondrial abnormalities are particularly prominent. These defects, alongside other cellular alterations, are especially evident in striatal neurons, the primary neuronal population affected in HD.

Under normal physiological conditions, astrocytes and neurons engage in a process known as transmitophagy, involving the intercellular transfer and degradation of mitochondria. This exchange supports neuronal health and metabolism. However, the role of transmitophagy in neurodegenerative diseases like HD remains poorly understood.

Our research aims to elucidate the effects of transmitophagy from striatal astrocytes to striatal neurons in the R6/1 mouse model of HD. We first characterized mitochondrial function and network integrity in primary cultures of R6/1 astrocytes, followed by examining how the transfer of astrocytic mitochondria influences cultured striatal neurons. Our findings reveal that mitochondria in R6/1 astrocytes display abnormally accelerated respiration and elevated mitochondrial oxidative stress, despite maintaining normal mitochondrial membrane potential. Interestingly, these astrocytes release mitochondria into the extracellular media, which are subsequently internalized by striatal neurons. Upon internalization of R6/1-derived astrocytic mitochondria, striatal neurons exhibit elevated levels of reactive oxygen species (ROS) and defective neuronal branching. These observations suggest that, in the context of HD, transmitophagy may contribute to neuronal dysfunction and exacerbate neurotoxicity. As such, targeting this process could offer a novel therapeutic avenue for HD

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SESSION: 1
POSTER#25

INTRODUCED BY: Nozha Borjini.

PRINCIPAL INVESTIGATOR: Rafael Fernández Chacón.

RESEARCH AREA: CIBERNED.

TITLE: Microglial dynamics and lipofuscin clearance in a Kufs disease mouse model: impact of microglial elimination.

AUTHORS: Nozha Borjini, Santiago López-Begines, Carmen Paradela Leal, Alberto Pascual Bravo, Francisco Javier Vitorica Ferrández, Rafael Fernández-Chacón.

ABSTRACT: Autosomal-dominant adult-onset neuronal ceroid lipofuscinosis (CLN4), or Kufs disease, is a rare neurodegenerative disorder caused by mutations in DNAJC5, which encodes the synaptic co-chaperone Cysteine String Protein α (CSPα). These mutations result in pathological accumulation of neuronal lipofuscin and granular osmiophilic deposits (GRODs), key hallmarks of the disease. Using transgenic mouse models expressing wild-type or mutant CSPα (Thy1-GFP-CSPα-L115R), we observed autofluorescent lipofuscin aggregates closely associated with microglial processes. Immunofluorescence and 3D-reconstruction revealed moderate microglial activation in mutant mice, with increased neuron-microglia interactions and phagocytosis of lipofuscin-laden neurons. Further analysis showed elevated CD68 levels in microglia, and electron microscopy confirmed enhanced phagocytic activity, with darkened microglia actively internalizing lipofuscin. These findings suggest microglia may play a central role in lipofuscin clearance. To explore their role in disease progression, we depleted microglia using PLX3397, a CSF1R tyrosine kinase inhibitor and FDA-approved drug. We are assessing motor function and lipofuscin levels in treated mice, along with astrocytic involvement, to determine the impact of microglial depletion. This work aims to clarify whether modulating microglial activity may offer a therapeutic strategy to slow CLN4 progression.

Supported by grant PID2022- 138957NB-I00 funded by the Spanish Agencia Estatal de Investigación and Ministerio de Ciencia, Innovación y Universidades (MICIU/AEI/10.13039/501100011033) and European Regional Development Fund (ERDF), CIBERNED, Institute of Health Carlos III and Plan Propio de Investigación de la Universidad de Sevilla Contrato Acción II.4 PPIT.

SESSION: 1
POSTER#26

INTRODUCED BY: Ruben López Vales.

PRINCIPAL INVESTIGATOR: Xavier Navarro.

RESEARCH AREA: CIBERNED.

TITLE: ALS-linked SOD1G93A mutation disrupts microglial functions in a cell-autonomous manner in human ESC-derived microglia in vitro.

AUTHORS: Joana Garcia-Garcia, Gisele Priscila Soares, Juan Alberto Ortega, Rubèn López-Vales.

ABSTRACT: Microglia are known to contribute to ALS pathogenesis. Mutations in the SOD1 gene, a genetic cause of ALS, have enabled the development of mouse models. However, the commonly used SOD1G93A mouse model overexpresses human mutant SOD1, complicating efforts to fully understand its cell-type-specific effects. Additionally, species differences, particularly in microglia, limit the translation of findings from mice to humans, as mouse microglia lack the full spectrum of human microglial states and expression of disease-associated genes. The ability to generate human microglia from stem cells and edit genes now allows more precise evaluation of genetic influences on cellular phenotypes.

We investigated how mutant SOD1 affects microglial function using a CRISPR/Cas9-engineered isogenic human embryonic stem cell (ESC) line carrying the SOD1G93A mutation. Microglia derived from these ESCs were characterized and compared to isogenic controls. We examined cytokine expression, phagocytosis, and metabolism in baseline and pro-inflammatory conditions.

SOD1G93A microglia exhibited altered basal cytokine profiles and heightened reactivity to LPS stimulation. Phagocytic function was impaired, as shown by reduced digestion of pHrodo-labeled myelin debris. Cell metabolism, assessed by Seahorse analysis, was also affected. Finally, conditioned media (CM) from SOD1G93A microglia showed increased neurotoxicity toward control iPSC-derived motor neurons under both basal and inflammatory conditions.

Overall, our findings reveal a cell-autonomous microglial dysfunction caused by mutant SOD1 in a human stem cell-based model, providing insight into microglia's role in ALS pathogenesis.

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SESSION: 1
POSTER#27

INTRODUCED BY: Anabel Saez-Mas.

PRINCIPAL INVESTIGATOR: Oscar Fernandez-Capetillo.

RESEARCH AREA: CIBERNED.

TITLE: Ribosomopathies at the core of aging and neurodegeneration.

AUTHORS: Anabel Sáez-Mas, Guillermo de la Vega-Barranco, Iván Ventoso, Vanesa Lafarga, Óscar Fernández-Capetillo.

ABSTRACT: Aging is the major risk factor for neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS). Recent work in our lab has shown that the most common genetic alteration in ALS, a hexanucleotide expansion in C9ORF72, generates arginine-rich peptides that, when expressed ubiquitously in adult mice, lead to premature aging. Mechanistically, this progeroid phenotype is associated to a widespread accumulation of orphan ribosomal proteins, which is a hallmark of ribosomopathies. Consistent with this model, reducing ribosome biogenesis by targeting of MYC or mTOR, alleviates the pathologies triggered by R-rich peptides and extended the mouse lifespan. These data suggest a shared mechanism for ALS and aging, driven by a dysfunctional accumulation of ribosomal proteins.

We now want to explore whether these observations are only relevant in the context of R-rich peptides, or if they are extensive to other genetic or environmental cases of ALS. Specifically, we are investigating the mechanism of toxicity mechanism of an environmental toxin, L-BMAA, the bioaccumulation of which has been associated with the outbreak of different geographical clusters of ALS worldwide. Our preliminary data supports a convergent mechanism of toxicity for L-BMMA and R-rich peptides, supporting that the loss of ribosomal proteostasis might be a shared phenomenon in ALS. .

SESSION: 1
POSTER#28

INTRODUCED BY: Beatriz García Fontana.

PRINCIPAL INVESTIGATOR: Manuel Muñoz Torres.

RESEARCH AREA: CIBERFES.

TITLE: Alkaline phosphatase as potential biomarker of muscle function. A pilot study in patients with hypophosphatasia .

AUTHORS: Maria del Carmen Andreo López, Victoria Contreras Bolívar, Luis Martínez Heredia, Francisco Andújar-Vera, Diego Becerra García, Trinidad González-Cejudo, Sheila González-Salvatierra, Cristina García-Fontana, Beatriz García-Fontana, Manuel Muñoz-Torres.

ABSTRACT: Background: Alkaline phosphatase (ALP) deficiency, as seen in hypophosphatasia (HPP), has been linked to impaired bone mineralization and reduced physical performance. However, the potential role of ALP in muscle function has not been fully explored.

Methods: We conducted a cross-sectional study in 34 adults with HPP and 34 healthy controls matched by age, sex, and body mass index. Muscle strength was assessed using handgrip strength (HGS), considering values below the 10th percentile of the Spanish population as low strength. Muscle mass was evaluated using dual-energy X-ray absorptiometry (DXA) and morphometric ultrasound. Bone mineral density (BMD) was measured at the lumbar spine, femoral neck, and total hip.

Results: The prevalence of low muscle strength was significantly higher in the HPP group compared to controls (30% vs. 6%; p=0.009). HGS was lower in the HPP group (p=0.039) and showed a positive association with ALP levels, femoral neck BMD, leg circumference, and fat-free mass, and an inverse association with tricipital skinfold. Subjects with ALP levels below the sex-adjusted median (31 IU/L in women and 43 IU/L in men) had a significantly higher risk of low muscle strength, independent of HPP diagnosis. ALP remained independently associated with HGS (p=0.005), and predictive models combining ALP with fat-free mass index showed strong discriminative ability, with AUC values of 0.8 in men and 0.9 in women.

Conclusions: Circulating ALP levels are independently associated with muscle strength and may represent a useful biomarker for the early detection of muscle dysfunction.

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SESSION: 1
POSTER#29

INTRODUCED BY: Laura Guzman.

PRINCIPAL INVESTIGATOR: Antoni Camins.

RESEARCH AREA: CIBERNED.

TITLE: Role of Reelin in synaptic preservation and complement-mediated pruning in Alzheimer Disease.

AUTHORS: Laura Guzman, Maria Angeles Llanos, Alba Elias-Tersa, Katherine Herrera, Antoni Camins, Lluis Pujades, Eduardo Soriano, Yasmina Manso.

ABSTRACT: Reelin, a large extracellular glycoprotein, plays a crucial role in regulating adult synaptic plasticity by modulating dendrite growth and dendritic spine formation. Synapse loss is an early event in Alzheimer's disease (AD) and strongly correlates with cognitive decline. The abnormal accumulation of complement cascade molecules, such as C1q, at synaptic sites is believed to drive the excessive microglial-mediated pruning observed in AD. Data from our group indicates that Reelin modulates microglia phenotype and reactivity to amyloid plaques by enhancing Aβ phagocytosis. Therefore, we hypothesize that Reelin, by modulating microglia activation phenotype, could prevent from aberrant microglia-mediated synaptic pruning in AD preclinical models.

To characterize the role of Reelin in synaptic integrity, we analyzed three key synaptic markers (PSD95, Homer, Synaptophysin) in AD preclinical mouse models (J20 amyloidosis model) with either Reelin gain or loss-of-function. Using immunohistochemistry and high-resolution microscopy, we assessed whether Reelin modulates the expression of presynaptic and postsynaptic proteins, their colocalization, and the accumulation of complement system markers (C1q) in the hippocampus, specifically in the CA1, stratum lacunosum-moleculare, and dentate gyrus regions.

Our results demonstrate that Reelin modulates synaptic protein levels and C1q deposition suggesting that Reelin may serve as a promising therapeutic target for AD.

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SESSION: 1
POSTER#30

INTRODUCED BY: Juan Antonio Garcia Leon.

PRINCIPAL INVESTIGATOR: Antonia Gutiérrez.

RESEARCH AREA: CIBERNED.

TITLE: Human iPSCs-Derived Astrocytes from APOE4/4 Alzheimer´s Patients Exhibit a Senescent Phenotype.

AUTHORS: Juan Antonio Garcia Leon, Laura Caceres Palomo, Elisabeth Sanchez Mejias, Laura Trujillo Estrada, Elba Lopez Oliva, Ines Moreno Gonzalez, Javier Vitorica, Antonia Gutierrez.

ABSTRACT: Background:

Alzheimer's disease (AD) is characterized by a complex pathology, not fully resolved yet. This fact, together with the lack of reliable models, has impeded the development of effective targeted therapies to the clinic. Glial dysfunction has been proposed to be a key factor in AD pathogenesis, but this cannot be properly modeled using the available transgenic models, so we hypothesized that glial cells derived from human induced pluripotent stem cells (iPSCs) from AD patients can serve as a better platform for studying this neurodegenerative disease.

Methods:

Human iPSC-derived astrocytes from AD APOE4/4 patients and cognitively unimpaired age-matched individuals (CTRL) APOE3/3 were differentiated. Their phenotype was evaluated employing immunofluorescence, confocal imaging, flow cytometry, RT-qPCR and functional assays.

Results:

Astrocytes derived from APOE4/4 AD patients present features of cellular senescence like decreased expression of the proliferation marker ki67, elongated mitochondria and increased expression of senescence markers compared to CTRL astrocytes. AD astrocytes also express the senescence-associated secretory phenotype (SASP) and show reduced neuronal support capacity, revealing a dysfunctional state directly implicated in AD pathology.

Conclusions:

These results suggest that human AD astrocytes present an intrinsic senescent phenotype which compromise their neuroprotective properties. Elucidating the mechanisms underlying astroglial dysfunction might lead to the identification of potential therapeutic targets for future treatments.

Supported by ISCiii grants, co-financed by FEDER funds from EU, PI21/00915 and PI24/00274 (AG) and PI21/00914 and PI24/00308 (JV), collaborative Ciberned grant PI2022/01 (to AG and JV), Sumaira Foundation TSF_SPARK_2023_03 (JAGL) and IBIMA-Plataforma Bionand Innovative Funds INN24_02 (JAGL).

SESSION: 1
POSTER#31

INTRODUCED BY: Laura Martins-Almeida.

PRINCIPAL INVESTIGATOR: David Otaegui.

RESEARCH AREA: CIBERNED.

TITLE: Development of an in vitro model of monocyte-derived microglia to study neuroinflammation and neurodegeneration.

AUTHORS: Laura Martins-Almeida, Andrea Iribarren-López, Hirune Crespillo-Velasco, David Otaegui, Ainhoa Alberro.

ABSTRACT: Introduction: Microglia, the cellular component of the immune system in the CNS, play an important role in neuroinflammation and neurodegeneration. These cells perform different functions depending on the surrounding environment and they are known to be implicated in signaling and myelin degrading processes. However, most microglial studies have been carried out in animal models, immortalized cells or postmortem samples and, therefore, their functions in the human brain are not well understood. For instance, in multiple sclerosis (MS) – an immune-mediated demyelinating disease of the CNS – microglia have been found in active lesions but their role are not completely described.

Materials and Methods: We are developing an in vitro model to generate human induced microglia-like (iMG) cells. Peripheral blood mononuclear cells (PBMCs) were isolated and cultured with GM-CSF and IL-34 to differentiate monocytes into iMG. To characterize iMG we used immunofluorescence and acquired the images with Epifluorescence Microscope Axio Observer 7.

Results: We are setting up the model testing different culture conditions, like density of plated cells, types of plate coating and differentiation endpoints. So far, around 300,000 of plated cells in a 96 well plate, a matrigel coating and 11/14 days of differentiation have proved to be the best conditions for obtaining iMG. These cells are positive for Iba1 and the microglia specific marker P2RY12.

Conclusions: This model will shed light on the functions of human microglia and their implication in MS and could be applied to other neurodegenerative diseases.

SESSION: 1
POSTER#32

INTRODUCED BY: Arnaldo Parra Damas.

PRINCIPAL INVESTIGATOR: José Rodríguez Álvarez.

RESEARCH AREA: CIBERNED.

TITLE: Age-related changes in the excitatory translatome of Alzheimer's disease transgenic mice.

AUTHORS: Arnaldo Parra-Damas, Maria Dolores Capilla López, Angel Deprada, José Rodríguez Álvarez, Carlos A. Saura.

ABSTRACT: Neuronal protein synthesis is finely regulated both spatially and temporally. However, how mRNA translation is affected in vulnerable neuronal populations during age-related neurodegeneration, such as Alzheimer's disease (AD), remains unknown. Here, we investigated age-associated changes in neuropathology, behavior, bulk hippocampal gene expression, and in the translational profile of hippocampal excitatory neurons of 6 y 9-month-old APP/Tau mice, a model of AD neuropathology exhibiting age-dependent amyloidosis, tau pathology, and neurodegeneration. Bulk RNA-seq profiling in the hippocampus of 6-month-old APP/Tau mice revealed differential expression of 1037 genes related to inflammation and synaptic pathways, coinciding with early spatial learning deficits, accumulation of synaptic tau, and intraneuronal amyloid beta peptide (Aβ). At 9 months, we detected exacerbated transcriptional changes affecting 5985 genes in the hippocampus of APP/Tau mice, including immune, astrocytic, microglial and 63 AD-risk genes, coinciding with increased tau pathology and accumulation of amyloid plaques. Translational profiling of hippocampal CaMKIIα excitatory neurons in RiboTag transgenic mice, comprising controls (CaMKIIα-Cre;RiboTag) and APP/Tau;CaMKIIα-Cre;RiboTag mice, revealed altered transcripts related to synaptic function, brain aging, and neuronal proteinopathies in 9-month-old APP/Tau RiboTag mice. Taken together, our findings indicate that concomitant Aβ and tau pathologies induce progressive hippocampal synaptic dysfunction by disrupting transcription and translation in excitatory neurons.

SESSION: 1
POSTER#33

INTRODUCED BY: Rodrigo Barderas.

PRINCIPAL INVESTIGATOR: Teresa Moreno Casbas.

RESEARCH AREA: CIBERFES.

TITLE: Novel 6xHis/HaloTag Mammalian Expressed Autoantigens for the Detection of Humoral Response with Multiplexed Electrochemical Biosensors: A Breakthrough in Colorectal Cancer and Alzheimer's Disease Personalized Diagnostics.

AUTHORS: Eloy Povedano, María Garranzo-Asensio, Ana Montero-Calle, Alejandro Valverde, Pablo Dalmasso, Pablo San Segundo-Acosta, Olga Cano, Mónica Vázquez, Vicente Mas, María Jesús Fernández-Aceñero, Gustavo Rivas, José M. Pingarrón, Susana Campuzano, Rodrigo Barderas.

ABSTRACT:

Introduction: Chronic diseases are among the leading global causes of mortality and frailty. Colorectal cancer (CRC) and Alzheimer's disease (AD) are highly prevalent chronic conditions associated with significant clinical and economic burden. This highlights the urgent need for early and accurate diagnostic strategies using innovative, minimally invasive tools to improve patient outcomes and reduce healthcare costs.

Materials and Methods: This study presents the development of biosensing platforms as cost-effective, minimally invasive, and sustainable alternatives to traditional diagnostic methods for CRC and AD. The platforms are designed to detect disease-specific humoral responses using full-length autoantigens expressed in mammalian cells as fusion proteins: 6xHis at the N-terminus for purification and HaloTag at the C-terminus for covalent immobilization onto chloroalkane-modified magnetic beads (MBs). After purification via the 6xHis tag, autoantigens are immobilized on MBs through the HaloTag, enabling selective capture of CRC- and AD-associated plasma autoantibodies.

Results: The CRC biosensor incorporated seven disease-specific full-length autoantigens, while the AD bioplatform combined three full-length proteins and four peptides specific to AD. Detection was performed using amperometric measurements on disposable multiplexed screen-printed carbon electrodes, with HRP-conjugated secondary antibodies and the hydroquinone/hydrogen peroxide system. The platforms effectively discriminated between healthy individuals and patients with CRC or AD. ROC curve analyses confirmed the robust diagnostic performance of both systems.

Conclusions: The developed biosensing platforms demonstrated reliable, minimally invasive detection of CRC and AD through plasma autoantibody profiling. Their performance supports their application in early disease diagnosis and personalized medicine, offering a valuable approach for liquid biopsy-based screening.

SESSION: 1
POSTER#34

INTRODUCED BY: Antonio Camins.

PRINCIPAL INVESTIGATOR: Antoni Camins.

RESEARCH AREA: CIBERNED.

TITLE: Two blood isoforms' levels of ADAM10 in different types of dementia.

AUTHORS: Patrícia R Manzine, Mantellatto Grigoli, Paulo Caramelli, Vitor Tumas, Fabiana de Souza Orlandi, Márcia Regina Cominetti, Miren Ettcheto, Antonio Camins.

ABSTRACT: A disintegrin and metalloproteinase protein 10 (ADAM10) is the main alpha-secretase involved in the non-amyloidogenic cleavage of amyloid precursor protein (APP). ADAM10 exists in multiple isoforms, including the membrane-bound form (mADAM10), mainly expressed in platelets and neuronal cells, and the soluble form (sADAM10), detectable in plasma, serum, and CSF. Previous studies have shown alterations in platelet and plasma ADAM10 levels in Alzheimer's disease (AD) compared to cognitively healthy controls. However, few investigations have explored whether these alterations also occur in non-AD dementias. This study aimed to investigate the blood forms of ADAM10 in AD, frontotemporal dementia (FTD), Parkinson's disease dementia (PD), and Lewy body dementia (LBD). It was a multicenter, cross-sectional, and analytical study carried out among community-dwelling older adults aged ≥ 60 in the interior of the State of São Paulo, Brazil. Analyses were performed using one-way ANOVA with Kruskal-Wallis, two-tailed Mann-Whitney tests, Receiver Operating Curves, GraphPad Prism, and MedCalc. It included 38 participants, 10 AD, 13 FTD, 8 PD, and 7 LBD. The highest mADAM10 levels were observed in the PD group, with significantly elevated values compared to all other dementia types. The AD group exhibited the lowest sADAM10, with statistically significant differences observed between this group and all other dementia types. Additionally, the FTD group showed a significant difference compared to the PD group. The association of isoforms did not demonstrate improvements in differentiating between dementias. Only the AD group showed a marked distinction between the isoforms, underscoring the greater diagnostic relevance of sADAM10 particularly for AD.

SESSION: 1
POSTER#35

INTRODUCED BY: Francisco José Fernández Acosta.

PRINCIPAL INVESTIGATOR: Carlos Vicario.

RESEARCH AREA: CIBERNED.

TITLE: IMPACT OF APOE POLYMORPHISM AND G206D-PSEN1 MUTATION ON HIPPOCAMPAL NEURONS AND BRAIN ORGANOIDS FROM ALZHEIMER´S DISEASE PATIENTS .

AUTHORS: Rebeca Vecino, Francisco José Fernández Acosta, Eva Díaz-Guerra, Esther Arribas-González, Samuel Alberquilla, Lucía Vicario del Río, Miriam Sánchez Calvo, Adela Orellana, Leire Boveda, Elena Patricia Moreno-Jiménez, Eduardo Soriano, José María García Verdugo, Adolfo Ruiz, Rosario Moratalla, Carlos Vicario.

ABSTRACT: The human APOE polymorphism, specifically the presence of the ε4 allele (encoding the APOE4 protein isoform), represents a genetic form of late-onset AD, whereas mutations in the PSEN1 gene are responsible for many cases of early-onset familial AD. There is evidence implicating APOE4 in multiple facets of AD pathogenesis; however, the full extent of its impact remains to be fully elucidated. Also, the effect of the G206D-PSEN1 mutation remains to be thoroughly investigated. To address this, we have generated human hippocampal neurons and brain organoids by adding small molecules and growth factors to induced pluripotent stem cells (iPSCs). These iPSCs were derived in our laboratory from fibroblasts of AD patients carrying the ε3 or ε4 alleles (in homozygosis) or the G206D-PSEN1 mutation, and healthy individuals. The iPSC-derived neurons expressed hippocampal markers and displayed a functional profile as evidenced by glutamate release, electrical activity and synapse formation (determined by electron microscopy and synaptic bouton analysis). The role of APOE4 in neurodegeneration was confirmed by detecting amyloid-beta 42/40, total tau and phosphorylated tau in the culture medium, and by the presence of an increased number of extracellular amyloid-beta-like plaques and intracellular p-tau181 aggregates. Finally, APOE polymorphism also affected neuronal morphology and synaptic bouton number. Collectively, these findings underscore the distinct impact of APOE polymorphism and G206D-PSEN1 mutation on neuronal maturation, dysfunction, and neurodegeneration in AD. Subsequent analyses on brain organoids will provide a more physiological framework, enhancing our understanding of the impact and potential interplay between APOE4 and PSEN1 in neurodegeneration.

SESSION: 1
POSTER#36

INTRODUCED BY: Blanca Alfonso López.

PRINCIPAL INVESTIGATOR: Leocadio Rodriguez Mañas.

RESEARCH AREA: CIBERFES.

TITLE: EFFECTIVENESS OF DIGITALLY-SUPPORTED INTERVENTIONS IN OLDER ADULTS WITH COGNITIVE IMPAIRMENT: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL. DECI PROJECT.

AUTHORS: Blanca Alfonso López, Alejandro Álvarez Bustos, Ignacio Peinado Martínez, María Isabel Tornero López, Rodrigo Pérez Rodríguez, Leocadio Rodríguez Mañas, DECI Consortium.

ABSTRACT: INTRODUCTION

The effect of technology-based home interventions on older adults with cognitive decline has been barely explored. The objective of the present study is to evaluate the impact of the use of DECI platform interventions on the cognitive and functional status of older adults with Mild Cognitive Impairment (MCI) or Mild Dementia (MD).

MATERIALS AND METHODS

A multicenter, prospective, randomized clinical trial was conducted. Participants were community-dwelling older adults (60+ years) diagnosed with MCI or MD. Participants were randomized into three distinct groups: control (usual care), IT-based organizational intervention (IG1) and organizational plus cognitive and physical training with activity monitoring (IG2). Participants were followed up 6 months.

RESULTS

A total of 115 (mean age 77.3 ± 6.1 years, 52.2% women) were included. Of those, 98 participants completed the study.

No between-groups significant differences were observed in any of the variables studied (i.e., quality of life [EuroQOL], cognitive function [semantic fluency, phonemic fluency, Mini-Mental State Examination score, Clinical Dementia Rating Scale]; physical function, [Short Physical Performance Battery and 6-meter walking speed test], frailty [Frailty Phenotype] nor disability [Barthel Index and Lawton and Brody Scale]).

CONCLUSIONS

The DECI platform combined IT-based organizational strategies and cognitive and physical training. After 6 months of use, it did not result in significant improvements in quality of life, cognitive function, physical function, frailty or disability in older adults with MCI or MD.

SESSION: 1
POSTER#37

INTRODUCED BY: Virginia García-Calvo.

PRINCIPAL INVESTIGATOR: Ana Martínez.

RESEARCH AREA: CIBERNED.

TITLE: Evaluation of TDP-43 levels and propagation in human SOD-1 ALS immortalized lymphocytes treated with IGS2.7, a CK-1 inhibitor candidate for ALS therapy.

AUTHORS: Virginia García-Calvo, Loreto Martínez-González, Eva Pérez Cuevas, Carmen Gil, Ana Martínez Gil.

ABSTRACT: Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterized by the progressive deterioration of motor neurons in the brain and spinal cord. While the majority of cases are sporadic ALS, 5-10 % of cases are familial. Among the genes associated familial ALS, SOD1 (superoxide dismutase 1) is responsible for approximately 15% cases. The overexpressed mutant SOD1 protein, which normally functions as a primary antioxidant enzyme, causes numerous toxic effects through its pathological misfolding and aggregation.

A pathological hallmark of ALS is the nuclear protein TDP-43 whose post-translational modifications result in a loss of nuclear function and a gain of toxic properties in the cytoplasm. In this study, we aimed to investigate in depth the propagation mechanisms of disease related to this specific protein in familial ALS patients carrying SOD1 mutations.

We used lymphoblastoid cell lines derived from SOD1-ALS patients as a source of pathogenic forms of TDP-43, and healthy lymphoblastoid cells as recipient cells to study the initial seeding and spread of TDP-43 proteinopathy. In addition, we isolated extracellular vesicles (EVs) from these cells to evaluated the extracellular role and transmission potential of TDP-43 in disease propagation.

Furthermore, we assessed the therapeutic potential of targeting TDP-43 phosphorylation by inhibiting casein kinase 1 (CK1), using IGS2.7, a small heterocyclic molecule with CK1-inhibitory activity. This approach aims to prevent the pathological spread of TDP-43 and mitigate its toxic effects.

Our preliminary findings suggest that IGS2.7 may reduce the spread of TDP-43 pathology, supporting its development as a potential therapeutic strategy for ALS. .

SESSION: 1
POSTER#38

INTRODUCED BY: Gemma Navarro Brugal.

PRINCIPAL INVESTIGATOR: Rafael Franco.

RESEARCH AREA: CIBERNED.

TITLE: Cannabidiol as a Multifaceted Therapeutic Agent: Mitigating Alzheimer's Disease Pathology and Enhancing Cognitive Function .

AUTHORS: Iu Raïch, Jaume Lillo, Joan Biel Rebassa, Christian Griñán-Ferré, Aina Bellver-Sanchis, Irene Reyes-Resina, Rafael Franco, Mercè Pallàs, Gemma Navarro.

ABSTRACT: Cannabidiol (CBD), the second most abundant phytocannabinoid in Cannabis sativa, has garnered significant interest due to its non-psychoactive nature and diverse receptor interactions. This study employs in vitro and in vivo methodologies to validate CBD's potential as a treatment for Alzheimer's disease (AD) by addressing key hallmarks of the condition and promoting neuroprotective effects on spatial memory. Our findings demonstrate CBD's ability to decrease ptau and Aβ aggregation and to mitigate their axonal transport between cortical and hippocampal neurons. Moreover, CBD treatment was shown to reduce neuroinflammation, as CBD was able to skew microglia towards a neuroprotective M2 phenotype while attenuating proinflammatory cytokine release in the 5xFAD AD mouse model. Notably, daily CBD injections (10 mg/Kg) for 28 days in 5xFAD mice resulted in significant improvements in both short- and long-term spatial memory. The study also reveals CBD's capacity to partially revert neurite formation loss induced by Aβ, Tau, and pTau proteins, suggesting a potential role in promoting neuronal plasticity. Additionally, CBD treatment led to a reduction in reactive oxygen species (ROS) formation and increased neuronal viability in the presence of AD-associated protein aggregates. These multifaceted effects of CBD, ranging from molecular-level modulation to behavioral improvements, underscore its potential as a comprehensive therapeutic approach for AD. The findings not only support CBD's neuroprotective properties but also highlight its ability to target multiple pathological processes simultaneously, offering a promising avenue for future AD treatment strategies.

SESSION: 1
POSTER#39

INTRODUCED BY: Molina, Nora.

PRINCIPAL INVESTIGATOR: Rosario Osta.

RESEARCH AREA: CIBERNED.

TITLE: CAN MICRORNAS PREDICT THE PROGRESSION OF MILD COGNITIVE IMPAIRMENT TO DEMENTIA IN THE OLDEST OLD?.

AUTHORS: Molina, Nora, Platero C, Moreno-García L, López-Royo T, Moreno-Martínez L, Perez O, Mesa P, Lobo A, Calvo AC, de La Cámara C , Osta R.

ABSTRACT: Introduction: Mild cognitive impairment (MCI) represents an intermediate stage between healthy aging and dementia. While some individuals with MCI progress to dementia, others remain stable. This study aimed to compare the prognostic value of non-coding RNAs with traditional cognitive, functional, and frailty scales in elderly patients.

Methods: A longitudinal, prospective nested case-control study was conducted with 59 patients aged 70 years and older (median age 82.5 ± 5.1 years; 68% women) who met the MCI International Working Group criteria. Patients underwent evaluations and blood sampling at baseline, 12 months, and 24 months. Assessments included the ZARADEMP interview (MMSE, clock test, verbal fluency, Barthel Index, Lawton Index, EURO-D, VIG-FRAIL). Additionally, plasma levels of microRNAs were measured. From the obtained variables, a Disease Progression Model (DPM) was developed to predict survival and cognitive decline.

Results: Of the 59 patients, 27(46%) were classified as progressive MCI (pMCI), while 32 (54%) were stable MCI (sMCI). miRNA-128 was significative in a Cox Model (p=0.008). However, its trajectory overlapped as time progressed. Only miR-155 was consistently higher in the pMCI group, albeit not statistically significant (rmANOVA, p=0.078). The DPM identified the Lawton Index, MMSE, and clock test as the most robust predictors of progression. miR-155 was the biomarker that best adapted to the proposed DPM.

Conclusions: The trajectories of miRNAs varied through the progression of MCI to dementia in a cohort of elderly patients. Only miR-155 had a stable trajectory, being higher in the pMCI group.

SESSION: 1
POSTER#40

INTRODUCED BY: Darío García-Rodríguez.

PRINCIPAL INVESTIGATOR: Juan Pedro Bolaños.

RESEARCH AREA: CIBERFES.

TITLE: Impact of the mitochondrial pyruvate carrier on astrocytic metabolism and mouse physiology.

AUTHORS: Darío García-Rodríguez, Daniel Jiménez-Blasco, Leticia Sancha-Ortega, Sara Yunta-Sánchez, Luisa Hidalgo-López, Marta Antequera, Jesús Agulla, Mélanie Planque, David Nittner, Pedro Ramos-Cabrer, Simon Pope, Simon Eaton, Simon Heales, Blanca I Aldana, Ángeles Almeida, Juan P Bolaños.

ABSTRACT: In physiological conditions, the brain primarily uses glucose as a metabolic fuel, and it does it in a highly compartmentalized manner between different cell types. Astrocytes are potent glycolytic cells, producing substantial amounts of pyruvate that is converted to lactate. Lactate is then transferred to neurons, where it is transformed back to pyruvate to fuel the tricarboxylic acid cycle. Since the inner mitochondrial membrane is impermeable to pyruvate, it enters to the mitochondrial matrix through the mitochondrial pyruvate carrier (MPC). Recent findings suggest that MPC modulation drives the metabolic reprogramming of different tissues, impacting pathways like fatty acid and glutamine metabolism. Given the central role of glucose and pyruvate in brain bioenergetics, our main objective is to understand MPC role in astrocytic metabolism, and how MPC modulation can impact on neuronal physiology and mouse cognitive performance. Our results show that MPC ablation in astrocytes does not have a dramatic effect on their survivability at a resting state, since these cells were able to shunt pyruvate entry to the mitochondria through alanine transamination. However, in energy demanding conditions, mitochondrial pyruvate uptake resulted to be necessary to maintain cellular respiration. Deleting MPC in astrocytes compromised mouse survival, impaired higher-order brain functions, and altered neuronal activity. Additionally, the levels of key metabolites and neurotransmitters were disrupted when astrocytic mitochondria lack the ability to uptake pyruvate.

SESSION: 1
POSTER#41

INTRODUCED BY: Rafael Villino-Rodríguez.

PRINCIPAL INVESTIGATOR: María Cruz Rodríguez Oroz.

RESEARCH AREA: CIBERNED.

TITLE: Olfactory Dysfunction Reflects Neuroinflammatory-Driven Cognitive Impairment in Parkinson's Disease.

AUTHORS: Rafael Villino-Rodríguez, Adolfo Jiménez-Huete, Miguel Germán Borda, Genoveva Montoya-Murillo, Antonio Martin-Bastida, Eduardo Salinas, Graciela Díaz, Jimmy Ulloa, Iñaki Garcia-Gurtubay, Juan Jose Lasarte, Noelia Casares, Secundino Fernández, María Cruz Rodríguez-Oroz.

ABSTRACT:

Background and Objectives: Neuroinflammation may contribute to the development and progression of Parkinson's disease (PD). This study aimed to investigate the relationship between peripheral immune activation and clinical manifestations in PD patients.

Methods: We analyzed 81 PD patients prospectively evaluated at Clínica Universidad de Navarra between 2021 and 2023. Clinical assessments included motor evaluation (MDS-UPDRS-III), neuropsychological testing, olfactory function (Sniffin' Sticks test), and blood analysis of lymphocyte proliferation and inflammatory cytokines. Associations between immune markers and clinical variables were examined using unadjusted and adjusted models (robust linear regression controlling for age, sex, and disease duration). Based on initial results, the sample was stratified according to the presence of dysosmia. Group differences were explored using non-parametric tests and further evaluated with adjusted analyses.

Results: Dysosmia was associated with increased lymphocyte proliferation and elevated levels of IL-1β, IFN-γ, GM-CSF, and TNF-α. IL-4 levels correlated with disease duration, and IL-8 was linked to visuospatial performance (VOSP). In the dysosmia group, patients performed worse on global cognition (MoCA), delayed memory (FCSRT-30min), and processing speed (SDMT). The sample was stratified by the diagnosis of dysosmia. Group differences were first analyzed using non-parametric tests and then further explored through adjusted analyses using the same covariates.

Conclusion: Our findings suggest that peripheral immune activation measurements may be markers of a neuroinflammatory process leading to cognitive impairment in Parkinson's disease. Dysosmia could represent an early manifestation of these changes, also an underlying cognitive disturbance. These results support the role of olfactory impairment as a marker of broader neurodegenerative processes.

SESSION: 1
POSTER#42

INTRODUCED BY: Tomás Sobrino.

PRINCIPAL INVESTIGATOR: Tomas Sobrino.

RESEARCH AREA: CIBERNED.

TITLE: FROM MOLECULES TO BEHAVIOR: COMPREHENSIVE CHARACTERIZATION OF THE PS19 TAUOPATHY MOUSE MODEL AND ITS PRECLINICAL UTILITY FOR ALZHEIMER'S DISEASE.

AUTHORS: Antía Custodia, Marta Aramburu-Nuñez, Noemí Gómez-Lado, Mariña Rodríguez-Arrizabalaga, Mónica Castro-Mosquera, Manuel Debasa-Mouce, Juan Manuel Pías-Peleteiro, Javier Camino-Castiñeiras, José Manuel Aldrey, Daniel Romaus-Sanjurjo, Pablo Aguiar, Alberto Ouro, Tomás Sobrino.

ABSTRACT:

INTRODUCTION & AIM This study aimed to characterize the PS19 tauopathy model (B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J) to investigate tau's role in AD.

METHODS: A total of 36 PS19 and 24 non-carrier mice were monitored from 12 to 50 weeks, evaluating neurodegeneration, neuroinflammation, BBB integrity, cerebral glucose metabolism, retinal thickness, neurodegenerative biomarkers, as well as behavioral, motor, and memory function.

RESULTS: Neuroimaging revealed reduced cortical ($p=0.0023$) and hippocampal ($p=0.0128$) volumes. Additionally, decreased Fe2+ levels (cortex: $p=0.0184$; hippocampus: $p=0.0023$) and gadolinium extravasation suggested vascular changes and BBB disruption. PS19 mice also showed reduced glucose metabolism and retinal thinning. Biomarker analysis highlighted elevated circulating CD34+ cells ($p=0.0122$). Plasma biomarkers analysis, assessing using Olink® Target96 Mouse Exploratory, indicated that upregulated proteins are related to signal transduction, cell death, and cytokines pathways, and downregulated proteins with morphogenesis, axonogenesis, neuronal projection, and synapses pathways. Motor deficits were evident, with diminished maximum speed in the open field test ($p<0.0001$), and reduced rotarod maximum latency time in the continuous speed ($p=0.0003$) and acceleration ($p=0.0378$) tests. Behavioral assessments showed hyperactivity, reduced anxiety-like behavior, memory impairment, and altered exploration. Increased neurodegeneration in hind-limb clasping test, and weight loss (both $p<0.0001$) were observed. Immunofluorescence confirmed increased pTau (hippocampus, $p=0.0013$), neuroinflammation (hippocampus $p=0.0002$), microglial activation (hippocampus $p=0.0008$), synapse and pTau phagocytosis by microglia (cortex $p=0.0009$, hippocampus $p=0.0102$ and <0.0001, respectively), and synapse loss (hippocampus $p=0.035$).

CONCLUSIONS: PS19 model serves as a valuable preclinical tool for investigating therapeutic and diagnostic strategies in tau-related AD pathology.

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SESSION: 1
POSTER#43

INTRODUCED BY: Javier Ojalvo Pacheco.

PRINCIPAL INVESTIGATOR: Jose Manuel Fuentes.

RESEARCH AREA: CIBERNED.

TITLE: Modulation of mitochondrial activity following autophagy induction in cellular models of Huntington's disease.

AUTHORS: Javier Ojalvo Pacheco, Marta Paredes Barquero, Eva Alegre Cortés, Alberto Giménez Bejarano, Mercedes Blanco Benítez, Nerea Domínguez Rojo, Enrique Carretero Morán, Patricia Gómez Suaga, Rosa Ana González Polo, Sokhna M.S Yakhine-Diop, José Manuel Fuentes Rodríguez, Mireia Niso Santano.

ABSTRACT: Introduction: Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by the accumulation of mutant huntingtin (HTTm), causing motor, cognitive and psychiatric symptoms. HTTm accumulation promotes, among other processes, mitochondrial dysfunction which in turn can induce neuronal death. One of the key mechanisms in the cell to eliminate toxic proteins is autophagy, responsible for degrading misfolded proteins such as HTTm and eliminating damaged organelles.

Objective: The aim of our work is to analyze whether the activation of autophagy mediated by a fatty acid unique to royal jelly can reduce the accumulation of mutant huntingtin protein and improve impaired mitochondrial function in Huntington's disease.

Material and Methods: For this purpose, we used cellular models of HD and analyzed the levels of aggregates by Dot-blot and immunofluorescence. In addition, we evaluated their impact on mitochondrial function using techniques such as Western-blot, fluorescence microscopy and flow cytometry.

Results: The results showed that autophagy activation reduced mHTT accumulation and improved mitochondrial function, evidenced by higher energy production and lower oxidative stress.

Conclusions: These findings support the therapeutic potential of royal jelly fatty acid for HD, suggesting new possibilities in the development of treatments based on natural compounds with neuroprotective effects.

Key Words: Huntington’s Disease; Autophagy; Aggregates; QBA; Mitochondria

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SESSION: 1
POSTER#44

INTRODUCED BY: Carlos Matute.

PRINCIPAL INVESTIGATOR: Carlos Matute.

RESEARCH AREA: CIBERNED.

TITLE: Reversible reduction in brain myelin content upon marathon running causes transient mild cognitive deficits.

AUTHORS: Iñigo López, Julen Zabalo, Soraya Pozueta, Gixane González García, Carlos Matute.

ABSTRACT: We recently demonstrated that myelin may provide energy substrates to brain cells during endurance exercise (https://doi.org/10.1038/s42255-025-01244-7). Specifically, we found a reversible reduction in myelin content in white matter tracts related to locomotion, motor coordination, somatosensory perception and emotional processing. Here, we have studied if myelin changes impact on motor and sensory control fidelity as well as cognitive processing speed. To that end, we carried out a panel of neurophysiological assays to evaluate nerve conduction velocity in central and peripheral pathways. We found that the latency of the motor, somatosensory, acoustic and visual evoked potential was not increased at 24-48 h after completion of the race, indicating that myelin content reduction in related pathways does not change axon potential traveling speed. In addition, we used six neuropsychological tests commonly use in clinical practice to evaluate cognitive reaction time. Runners performed worse in single digit modality and the Stroop colour and word tests, while scored equally in less complex trials including the trailing making test. All subjects, control and runners matched in score a month later. These findings indicate that marathon runners show transient subtle cognitive deficits that revert by a month after the race. Together, our data support the notion that myelin is an energy source for neural cells under metabolic stress, while sustain physiological brain function and cognition. This integrated approach shows a holistic picture of brain adaptation beyond gross structural changes that preserves functional and cognitive performance unharmed in endurance exercise.

Supported by CIBERNED, MCINN, Gobierno Vasco and EITB-Maratoia.

SESSION: 1
POSTER#45

INTRODUCED BY: Juan José Garrido.

PRINCIPAL INVESTIGATOR: Francisco Wandosell Jurado.

RESEARCH AREA: CIBERNED.

TITLE: Early postnatal Axon Initial Segment alterations in APP/PS1 mice: Role of astrocytes transcriptomic changes.

AUTHORS: María José Benitez, Lara Ordoñez, Diana Retana, Inés Colmena, María José Gómez, Rebeca Alvarez, María Ciorraga, Ana Dopazo, Francisco Wandosell, Juan José Garrido.

ABSTRACT: Alzheimer´s disease (AD) is characterized by neuronal function loss and degeneration. The integrity of the axon initial segment (AIS) is essential to maintain neuronal function and output. AIS alterations are detected in human post-mortem AD brains and mice models, as well as, neurodevelopmental and mental disorders. However, the mechanisms leading to AIS deregulation in AD and the extrinsic glial origin are elusive. We studied early postnatal differences in AIS cellular/molecular mechanisms in wild-type or APP/PS1 mice and combined neuron-astrocyte co-cultures. We observed AIS integrity alterations, reduced ankyrinG expression and shortening, in APP/PS1 mice from P21 and loss of AIS integrity at 21 DIV in wild-type and APP/PS1 neurons in the presence of APP/PS1 astrocytes. AnkyrinG decrease is due to mRNAs and protein reduction of retinoic acid synthesis enzymes Rdh1 and Aldh1b1, as well as ADNP (Activity-dependent neuroprotective protein) in APP/PS1 astrocytes. This effect was mimicked by wild-type astrocytes expressing ADNP shRNA. In the presence of APP/PS1 astrocytes, wild-type neurons AIS is recovered by inhibition of retinoic acid degradation, and Adnp-derived NAP peptide (NAPVSIPQ) addition or P2X7 receptor inhibition, both regulated by retinoic acid levels. Moreover, P2X7 inhibitor treatment for 2 months impaired AIS disruption in APP/PS1 mice. Our findings extend current knowledge on AIS regulation, providing data to support the role of astrocytes in early postnatal AIS modulation. In conclusion, AD onset may be related to very early glial cell alterations that induce AIS and neuronal function changes, opening new therapeutic approaches to detect and avoid neuronal function loss.

SESSION: 1
POSTER#46

INTRODUCED BY: Miriam Martínez Huélamo.

PRINCIPAL INVESTIGATOR: Cristina Andres Lacueva.

RESEARCH AREA: CIBERFES.

TITLE: Metabolic Signatures of Nutrition and Prostate Cancer Risk: Insights from a Nested Case-Control Study in EPIC.

AUTHORS: Miriam Martínez Huélamo, Enrique Almanza-Aguilera, Meryl Cruz, Anna Guadall, Daniel Guiñón-Fort, Yamilé López-Hernández, David S. Wishart, Raul Zamora-Ros, Cristina Andres-Lacueva.

ABSTRACT: Background: Previous studies using a metabolomics approach in relation to prostate cancer (PCa) risk assessment have focused on endogenous metabolism. As far as we know, the associations between circulating metabolites derived from exogenous sources, such as diet or lifestyle, and PCa risk have not been widely studied.

Objective: We aimed to prospectively investigate the associations between plasma metabolite concentrations and PCa risk, including clinically relevant tumor subtypes.

Methods: We used a targeted metabolomics approach to analyze plasma samples of 851 matched PCa case–control pairs from the EPIC cohort. Associations between metabolite concentrations and PCa risk were estimated by multivariate conditional logistic regression analysis. False discovery rate (FDR) was used to control for multiple testing correction.

Results: Thirty-one metabolites (predominately derivatives of food intake and microbial metabolism) were associated with overall PCa risk and its clinical subtypes ($p < 0.05$. The strongest positive and negative associations were for dimethylglycine (OR = 2.13; 95% CI 1.16–3.91) with advanced PCa risk (n = 157) and indole-3-lactic acid (OR = 0.28; 95% CI 0.09–0.87) with fatal PCa risk (n = 57), respectively; however, these associations did not survive correction for multiple testing.

Conclusions: The results from the current nutrimetabolomics study suggest that apart from early metabolic deregulations, some biomarkers of food intake might be related to PCa risk, especially advanced and fatal PCa. Our results reinforce the use of nutritional metabolomics to deepen the understanding of the complex role of diet and its potential mechanisms of action in prostate carcinogenesis.

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SESSION: 1
POSTER#47

INTRODUCED BY: José Ramón Naranjo Orovio.

PRINCIPAL INVESTIGATOR: Jose Ramón Naranjo.

RESEARCH AREA: CIBERNED.

TITLE: DREAM ligands normalize REST nuclear translocation in pathologically aging brain.

AUTHORS: Rafael Gonzalo-Gobernado, Paz González, Xosé M. Dopazo, Iván Burgueño-García, Laura Sainz, Marta Gutiérrez-Rodríguez, Irene Santos, Javier Fernández-Ruiz, Alberto Rábano, Britt Mellström, José R. Naranjo.

ABSTRACT: It has been proposed that the repressor element-1 silencing transcription/neuron-restrictive silencer factor (REST/NRSF), hereafter REST, coordinates a neuroprotective stress response that is induced during aging preventing cognitive decline. Notably, this protective response is missing in the frontal cortex and hippocampus in mild cognitive impairment (MCI), Alzheimer (AD) and fronto-temporal dementia (FTD) patients. Moreover, an endogenous neuroprotective response that delays motor and cognitive decline associated with Huntington's disease has been related to reduced brain levels of the transcriptional repressor DRE-antagonist modulator (DREAM).

Here we show that nuclear levels of REST and DREAM are significantly reduced in the cerebral cortex and the hippocampus in transgenic mouse models of AD (J20) and FTLD (hTauP301S & hTDP-43), even in young mice well before disease symptoms are noticeable. Notably, DREAM and REST levels are also decreased in human cortical samples from AD and FTLD patients.

Pull-down and co-immunoprecipitation assays identified the DREAM-REST interaction which is enhanced in the presence of DREAM ligands (repaglinide and PC330) and regulates the nuclear translocation of REST. Chronic administration of repaglinide in J20, P301S-tau and TDP-43 transgenic mice restored nuclear levels of REST, modified the expression of specific REST target genes and ameliorated disease symptoms. Thus, DREAM ligands activate REST-dependent neuroprotection in pathologically aging brain.

Research funded by Collaborative project (CIBERNED 2022_02) & Asahi Kasei Pharma.

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SESSION: 1
POSTER#48

INTRODUCED BY: Ana Simón-García.

PRINCIPAL INVESTIGATOR: Teresa Iglesias.

RESEARCH AREA: CIBERNED.

TITLE: Downregulation of neuroprotective Protein Kinase D in Huntington´s Disease.

AUTHORS: Ana Simón-García, Álvaro Sebastián-Serrano, María Santos-Galindo, Marina Prudencio Sánchez-Carralero, Alberto H.-Alcántara, Cristina Clemente, Julia Pose-Utrilla, Miguel R. Campanero, Eva Porlan, José J. Lucas, Teresa Iglesias.

ABSTRACT: Huntington's Disease (HD) is an inherited neurodegenerative disorder characterized by motor, cognitive and psychiatric symptoms. The cause is a cytosine-adenine-guanine (CAG) repeat expansion within the coding region of the huntingtin (Htt) gene that generates aberrant proteins containing extended polyglutamine (polyQ) stretches affecting particularly the striatum and cerebral cortex. GABAergic medium-sized spiny neurons (MSNs) in the striatum have been observed to be particularly sensitive to excitotoxicity. However, the molecular mechanisms underlying MSNs death in HD remain poorly understood. In our lab, we have demonstrated that Protein Kinase D1 (PKD1) activity is neuroprotective, as it decreases excitotoxic neuronal death and oxidative stress damage in cortical glutamatergic neurons. Therefore, we wondered whether PKD1 activity could be disrupted in HD, compromising a hypothetical neuroprotective effect on inhibitory MSNs. We found a reduction in PKD1 protein levels in striatal neurons from HD patients. Similarly, R6/1 mouse model exhibited a progressive loss of PKD1 protein accompanied by a decrease in Prkd1 transcript levels. Functionally, pharmacological inhibition of PKD1 in striatal neurons enhances their vulnersability to excitotoxic insults, whereas the expression of constitutively active PKD1 conferred neuroprotection. Furthermore, PKD1 is also able to hamper polyQ-induced apoptosis in a mouse neuroblastoma cell model of HD. In a translational approach, intrastriatal lentiviral delivery of PKD1 in symptomatic R6/1 mice prevented the loss of DARPP32, a molecular marker of MSNs. Collectively, our findings suggest that the loss of PKD1 function contributes to HD pathogenesis and the selective vulnerability of MSNs, positioning PKD1 as a promising therapeutic target for mitigating the death of these neurons in HD.

SESSION: 2
POSTER#1

INTRODUCED BY: Mercè Pallàs.

PRINCIPAL INVESTIGATOR: Rafael Franco.

RESEARCH AREA: CIBERNED.

TITLE: 2-BFI and Idazoxan: friends or foes in neuroprotective role of imidazoline I2 receptors.

AUTHORS: Marta Riblata-Vilella, Teresa Taboada-Jara, Beste Ozaydin, Jordi Juarez-Jimenez, Carles Curutchet, Carmen Escolano, Christian Girñán-Ferré, Rafael Franco, Gemma Navarro, Mercè Pallàs.

ABSTRACT: Neuroinflammation is established as a pivotal process in addition to the classical Alzheimer's disease (AD) hallmarks of amyloid and tau pathologies. In this way, glial cells and neuroinflammation. Imidazoline I2 receptor (I2-IR) is recognized as a promising biological target. Gold standard ligands are 2-BFI and Idazoxan. We have two objectives: identify the nature of I2-IR and to characterize the neuroprotective role of I2-IR ligands. First, to identify putative proteins (candidates) as a target of I2-IR, we performed Thermal shift assays (TSA) experiments in mice brain tissue challenged with 2-BFI (5mg/kg). We identified 17 proteins of interest, that were further narrowed to 7 putative targets following a molecular dynamics-based screening. Up to now, Inhibition of the MAO-B enzymatic activity was 9% for 2-BFI hydrochloride and 1% for Idazoxan and nor agonists or antagonist profile on α2A adrenergic receptor was determined.

For the second objective, mice glia primary cultures (microglia and astroglia) were treated with by 2-BFI and Idazoxan. Results showed both neuroprotection in microglia and astroglia primary cultures , cytokine expression was evaluated, 2-BFI (30 μM) increased the expression of cytokines (IL6, IL1, IL10 and TNF α), whereas Idazoxan (3 0 μM) had different effects on pro-or anti-inflammatory cytokines. In whole, results demonstrated that 2-BFI and Idazoxan deliver similar neuroprotective effects in the proinflammatory landscape (in vitro and in vivo) and I2-IR modulation has potential to stop or delay the progression of AD; for this reason, it is necessary and timely to fully identify I2-IR as a new target for AD to sum up efforts to find a treatment for AD patients, increasing their life quality and reducing health cost, and family suffering. This study was supported by the Ministerio de Ciencia e Innovación and Fondo Europeo de Desarrollo Regional (PID2021-138079OB-I00 and PIDsupported by MICIU/AEI/10.13039/501100011033 and ERDF, UE to M.P.) .

SESSION: 2
POSTER#2

INTRODUCED BY: Ana I. Rodríguez-Pérez.

PRINCIPAL INVESTIGATOR: Jose Luis Labandeira.

RESEARCH AREA: CIBERNED.

TITLE: Serum angiotensin type-1 receptor autoantibodies and neurofilament light chain as markers of neuroaxonal damage in post-COVID patients.

AUTHORS: Ana I. Rodríguez-Pérez, Gemma Serrano-Heras, Carmen M. Labandeira, Laura Camacho-Meño, Beatriz Castro-Robles, Juan A. Suarez-Quintanilla, Mónica Muñoz-López, Pepa Piqueras-Landete, Maria J. Guerra, Tomás Segura, José L. Labandeira-García.

ABSTRACT: Introduction: Dysregulation of autoimmune responses and the presence of autoantibodies (AA), particularly those related to the renin-angiotensin system (RAS), have been implicated in the acute phase of COVID-19, and persistent dysregulation of brain RAS by RAS-related AA may also contribute to neurological symptoms of post-COVID.

Methods: We analyzed levels of serum and CSF RAS AA in post-COVID patients with neurological symptoms, individuals who have fully recovered from COVID-19 (after-COVID controls), and uninfected individuals, and their possible correlations with the serum marker of neuroaxonal damage neurofilament light chain (NfL) and the degrees of cognitive deficit.

Results: In neurological post-COVID patients, serum and CSF levels of agonistic AA against the pro-inflammatory angiotensin II type 1 receptor (AT1-AA) were significantly elevated compared to uninfected and after-COVID controls and correlated with NfL serum levels. A compensatory upregulation of the anti-inflammatory RAS axis was also observed in CSF, with increased agonist AA for AT2 (AT2-AA) and Mas receptors (MasR-AA) and downregulation of the antagonist AA of ACE2 (ACE2-AA). Patients with more pronounced cognitive impairment showed significantly higher CSF levels of MasR-AA and a trend toward elevated AT2-AA. Persistent brain RAS dysregulation, particularly sustained elevation of AT1-AA, may contribute to neuroaxonal damage and cognitive symptoms after COVID-19. Serum AT1-AA and NfL levels may serve as promising biomarkers for early detection of CNS involvement in patients with post-COVID neurological symptoms.

Conclusion: These findings highlight the potential of targeting AT1 receptors as a therapeutic strategy for mitigating cognitive deficits in post-COVID patients showing upregulated AT1-AA levels.

.**SESSION**: 2

POSTER#3

INTRODUCED BY: Mª Salomé Sirerol Piquer.

PRINCIPAL INVESTIGATOR: Isabel Fariñas.

RESEARCH AREA: CIBERNED.

TITLE: Age-dependent progression from clearance to vulnerability of microglia to αSyn toxic species .

AUTHORS: Mª Salomé Sirerol-Piquer, Ana Pérez-Villalba, Pere Duart-Abadia, Germán Belenguer, Ulises Gómez-Pinedo, Pau Carrillo-Barberà, Laura Blasco-Chamarro, Azucena Pérez-Cañamás, Victoria Navarro, Benhamin Dehay, Javier Vitorica, Francisco Pérez-Sánchez, Miquel Vila, Isabel Fariñas.

ABSTRACT: Microglia represent a specialized population of macrophage-like cells in the central nervous system (CNS) considered immune sentinels, constantly scanning and surveying the environment through their ramified processes. Microglial phagocytosis is important for the clearance of pathogens and abnormal proteins from the CNS and provides the first host defence. However, aging has a detrimental impact on microglial morphology (reduced ramification and fragmented processes) and function. Compelling evidence suggests that these age-related changes might have an impact in the progression of neurodegenerative disorders. Cytoplasmic alpha-synuclein (αSyn) aggregates are a typical feature of Parkinson's disease (PD). Extracellular insoluble αSyn can induce pathology in healthy neurons suggesting that PD neurodegeneration may spread through cell-to-cell transfer of αSyn proteopathic seeds. Early pro-homeostatic reaction of microglia to toxic forms of αSyn remains elusive. Here, we show that periventricular microglia of the subependymal neurogenic niche monitor the cerebrospinal fluid (CSF) and can rapidly phagocytize and degrade different aggregated forms of αSyn delivered into the lateral ventricle CSF. With age, functional impairment in this capacity results in the abnormal aggregation of endogenous αSyn in aged treated mice, an accumulation also observed in human PD samples. We also show that exposure of aged microglia to aggregated αSyn isolated from human PD samples results in the phosphorylation of the endogenous protein and the generation of αSyn seeds that can transmit the pathology to healthy neurons. Our data indicate that while microglial phagocytosis rapidly clears toxic αSyn in young animals, aged microglia can contribute to synucleinopathy spreading.

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SESSION: 2
POSTER#4

INTRODUCED BY: Tomas Meroño.

PRINCIPAL INVESTIGATOR: Cristina Andres Lacueva.

RESEARCH AREA: CIBERFES.

TITLE: Gender differences in the associations between lifestyle, intestinal permeability and brain health in middle-aged adults. .

AUTHORS: Tomás Meroño, Rafael Tume, Gabriele Cattaneo, Francisco Carmona-Pontaque, Javier Solana-Sánchez, Andrea Unión-Caballero, Marta Cubedo, Anna Guadall, Montse Rabassa, Miriam Martínez-Huelamo, David Bartrés-Faz, Cristina Andrés-Lacueva.

ABSTRACT: Background: Many brain disorders are associated with alterations in intestinal function. Intestinal permeability (IP) as a risk factor for brain health in middle-aged adults has not been studied.

Aim: To evaluate the association between IP and brain health (cognitive, psychiatric, serum neurofilament light-chain (NfL) levels and MRI measurements) in a middle-aged cohort of healthy men and women.

Methods: 827 participants from the Barcelona Brain Health Innitiative (BBHI) study were analyzed (median age 52y, 427 males). IP was evaluated by levels of lipopolysaccharide-binding protein (LBP), zonulin and sCD-14. Brain health included a cognitive and psychometric (DASS) evaluation, NfL levels and hippocampus, white matter and cortex volume (MRI). Covariates were clinical variables, physical exercise, sleep, nutrition, social interactions, and life purpose. Integrative analyses included multiple factor analysis. Diagnosis of neurodegenerative, psychiatric and a 17-diseases composite-endpoint during a 4-year follow-up were also analyzed.

Results: An inverse association between zonulin and some cognitive tests, and between LBP and DASS scores were observed mainly in females. In males, LBP was inversely associated with cognitive tests and with right hippocampus volume. Integrative analyses revealed that IP combined with lifestyle factors were associated with MRI-signatures of brain aging and NfL levels. Last, only in women dimensions integrating IP were associated with both higher and lower odds for the diagnosis of neurodegenerative diseases (OR, 95%CI: 2.0, 1.4-3.1; and 0.6, 0.4-0.9, respectively).

Conclusion: In middle-aged adults, IP was differently associated with brain health markers in women and men. IP influence in brain health depends on gender and lifestyle factors.

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SESSION: 2
POSTER#5

INTRODUCED BY: Eneritz López Muguruza.

PRINCIPAL INVESTIGATOR: Carlos Matute.

RESEARCH AREA: CIBERNED.

TITLE: Myelin-derived fatty acids fuel brain neurons and glia in health and disease.

AUTHORS: Eneritz López Muguruza, Carla Peiró Moreno, Alicia Pellitero, Iñigo López, Juan Carlos Chara-Ventura, Andrea Sainz, Rocío Rojas Martín, Fernando Pérez-Cerdá, Alberto Pérez-Samartín, Asier Ruiz, Carlos Matute.

ABSTRACT: We recently demonstrated that myelin may serve as a source of energy substrates for brain cells during endurance exercise. In parallel, neuropsychological testing in marathon runners showed transient subtle cognitive changes, but not neurophysiological deficits. To dig into the molecular and cellular mechanisms underlying myelin use and replenishment, we employed a multidisciplinary approach in murine and human brain cells and tissues. We observed that labelled myelin, and myelin-derived fatty acids, enhanced viability and accelerated differentiation of cultured oligodendrocytes. Fatty acids were efficiently taken up by oligodendrocytes in vitro and by neurons and glia in vivo. Using Seahorse analysis, we found that astrocytes under metabolic stress utilize fatty acids for ATP production. Moreover, fatty acids improved mitochondrial membrane potential in aglycemic neurons. In turn, we observed, using electrophysiological recordings of glucose-deprived optic nerves ex vivo, that myelin-derived fatty acids support the recovery of compound action potentials. Furthermore, we carried out initial experiments in running mice and detected a local reduction in myelin content in motor and sensory areas of white matter tracts. On the translational side, we also found that treating cortical organoids, originating from iPSCs from a female with sporadic Alzheimer disease, with myelin-derived fatty acids attenuates oxidative stress and p-Tau phosphorylation. Together, our findings support the notion that myelin is an energy source for neural cells under metabolic stress, and that myelin fatty acids may alleviate Alzheimer disease pathology pointing to myelin deterioration in aging as a contributor to this illness.

Supported by CIBERNED, MCINN, Gobierno Vasco and EITB-Maratoia.

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SESSION: 2
POSTER#6

INTRODUCED BY: Jose Luis Cantero.

PRINCIPAL INVESTIGATOR: Jose Luis Cantero.

RESEARCH AREA: CIBERNED.

TITLE: Salivary mitochondrial DNA is associated with biomarkers of Alzheimer's disease in cognitively normal older adults.

AUTHORS: Jose Luis Cantero, Mercedes Atienza, Petar Podlesniy, Margalida Puigros, Ramon Trullas.

ABSTRACT: Introduction. There is growing evidence that mitochondrial dysfunction plays a key role in the development and progression of Alzheimer's disease (AD). However, the lack of reliable biomarkers for mitochondrial dysfunction limits its clinical use. Mitochondrial DNA (mtDNA) copy number, a proxy of mitochondrial function, has shown promise in detecting early stages of AD and predicting the risk of developing AD in cerebrospinal fluid and blood, respectively. Interestingly, recent studies have found mtDNA molecules in human saliva, but its relationship with AD biomarkers remains unexplored.

Materials and Methods. Here, we investigated potential associations between salivary mtDNA copy number, a proxy of mitochondrial function, and amyloid-β (Aβ) PET and blood AD markers in cognitively normal older adults.

Results. Salivary mtDNA copy number was positively associated with cortical Aβ accumulation and plasma pTau-181 levels, and negatively correlated with general cognitive ability. Additionally, we found that plasma pTau-181 levels influenced the relationship between cortical Aβ load and salivary mtDNA, while cortical Aβ load mediated the association between plasma pTau-181 and salivary mtDNA.

Conclusions. These findings represent the first evidence linking salivary mtDNA with well-established AD biomarkers in normal aging, suggesting that salivary mtDNA could be a promising non-invasive biomarker to identify individuals at risk of developing AD in the general population.

SESSION: 2
POSTER#7

INTRODUCED BY: Aina Comas-Albertí.

PRINCIPAL INVESTIGATOR: Raquel Sánchez del Valle.

RESEARCH AREA: CIBERNED.

TITLE: Differential Brain DNA Methylation in Primary Tauopathies: CBD vs Pick FTLD Subtypes.

AUTHORS: Aina Comas-Albertí, Sergi Borrego-Écija, Laura Molina-Porcel, Julien Bauer, Roger Puey, Mircea Balasa, Albert Lladó, Anna Antonell, Raquel Sánchez-Valle.

ABSTRACT: Introduction: Frontotemporal lobar degeneration (FTLD) spectrum disorders are neuropathologically heterogeneous, with a balanced distribution of TDP-43 proteinopathies and tauopathies among sporadic cases. FTLD-tauopathies are primarily classified based on the presence of 3-repeat (3R) or 4-repeat (4R) tau isoforms, with FTLD-CBD representing a 4R tauopathy and FTLD-Pick a 3R subtype. We focused on these two subtypes to explore DNA methylation differences and identify potential epigenetic markers that distinguish each one.

Materials and methods: In this study, we analyzed frozen prefrontal cortex brain tissue from neuropathologically confirmed FTLD-CBD (N=19) and FTLD-Pick (N=13) cases using the Inf MethylationEPIC V2.0 Kit from Illumina. Differentially methylated positions (DMPs) were identified using the dmpFinder method from the R package Minfi with an F-test. Differentially methylated regions (DMRs) were identified using the dmrCate method from the R package dmrcate. Biological pathway and functional analyses were then performed with DMRs genes using Enrich-KG.

Results: The dmpFinder analysis identified 3,328 DMPs. A trend of global hypermethylation in FTLD-Pick compared to FTLD-CBD was observed. The dmrCate method identified 282 DMRs. Notable genes included in the most significant regions were RMDN2, ATP11A, CAMKK1, SEL1L, and IFT122. Gene Ontology analysis revealed functions such as synapse organization, chromatin silencing at telomeres, and neuronal ion channel clustering. The most significant pathway identified by Reactome analysis was phospholipid metabolism.

Conclusions: Several pathways were differentially methylated in FTLD-CBD compared to FTLD-Pick. Further research is needed to confirm specific molecular mechanisms driving each FTLD subtype and to reveal potential distinct diagnostic biomarkers for these disease subtypes.

SESSION: 2
POSTER#8

INTRODUCED BY: Mikel Muñoz-Oreja.

PRINCIPAL INVESTIGATOR: Adolfo Lopez de Munain.

RESEARCH AREA: CIBERNED.

TITLE: Elevated cholesterol in ATAD3 mutants is a compensatory mechanism that leads to membrane cholesterol aggregation.

AUTHORS: Mikel Muñoz-Oreja, Abigail Sandoval, Diego Rodriguez-Perez, Uxoa Fernandez-Pelayo, Amaia Lopez de Arbina-Labandibar, Marina Villar-Fernandez, Haizea Hernandez-Eguiazu, Ixiar Hernandez, Leire Goicoechea, Jose Fernandez-Checa, Itxaso Martí-Carrera, Gorka Gereñu-Lopetegui, Antonella Spinazzola, Wan Hee Yoon, Ian J. Holt.

ABSTRACT: Dysregulation of cholesterol metabolism and mitochondrial dysfunction have been linked in Harel-Yoon syndrome, a broad neurological disorder caused by various mutations in the ATAD3 gene cluster. In this study, we identify a novel missense mutation in ATAD3 in a family exhibiting progressive neurodegenerative symptoms and corroborate the previously reported connection between cholesterol and mitochondrial dysfunction seen in other ATAD3 variants. Additionally, cells harboring different ATAD3 mutations show an expansion of the lysosomal pool, including structures resembling membrane whorls—characteristic features of lysosomal storage disorders.

Using Drosophila melanogaster models with the corresponding Atad3 point mutation, we further confirm the pathogenicity of this variant. Neural progenitor cells in these models also display an increased lysosomal population. A newly developed in vivo probe for labeling membrane-associated cholesterol reveals that cells expressing mutant Atad3 accumulate membrane-cholesterol aggregates, many of which co-localize with lysosomes. Similarly, patient-derived cells stained with PFO-GST—a probe for membrane-bound cholesterol in vitro—exhibit increased cholesterol signal and partial lysosomal overlap.

Moreover, subjecting mutant dAtad3 flies to nutrient restriction followed by cholesterol supplementation improves viability, suggesting that cholesterol has a protective effect in this context. Overall, our findings reinforce the link between mitochondrial function and cholesterol homeostasis, indicating that while elevated cholesterol levels may confer some resilience to ATAD3 dysfunction, they also contribute to detrimental cellular effects such as cholesterol aggregation in membranes and the subsequent impaired lysosomal degradation, a clear hallmark of lysosomal storage disorders.

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SESSION: 2
POSTER#9

INTRODUCED BY: Almudena Avendaño Céspedes.

PRINCIPAL INVESTIGATOR: Pedro Abizanda.

RESEARCH AREA: CIBERFES.

TITLE: Multicenter cluster randomized clinical trial to analyze the efficacy of the Spanish National Health System Prevention Strategy-based intervention to improve frailty or physical function in prefrail or frail older adults: THE FRAILMERIT STUDY.

AUTHORS: Almudena Avendaño Céspedes, Adriana Abizanda Saro, Rafael García Molina, Rubén Alcantud Córcoles, Manuel Maestre Moreno, Maximiliano Martínez Ramírez, Pilar Montero Alía, Ignacio Morón Merchante, Antonio Aragonés Jiménez, María Dolores González Céspedes, Marta Simarro Rueda, Beatriz Rodríguez Sánchez, Marta Sáez Blesa, Elisa Belén Cortés Zamora, FRAILMERIT Study Group, Pedro Abizanda Soler.

ABSTRACT: Objective: To evaluate the effectiveness of an intervention based on an algorithm proposed by the Spanish Ministry of Health for Primary Care (PC) to reduce frailty and improve physical function in community-dwelling older adults. Methods: A multicenter randomized clinical trial was conducted across 12 PC teams. The intervention adhered to the 2022 updated Consensus Document on Frailty Prevention in Older Adults and included a multicomponent exercise program, nutritional intervention, and PC training. Interventions were delivered in two 12-week blocks separated by an 8-week rest period. Participants aged ≥70 years with pre-frailty/frailty or gait speed <0.8 m/s were included. The primary outcome was improvement in frailty phenotype or a one-point increase in the Short Physical Performance Battery (SPPB), analyzed via intention-to-treat. A total of 237 participants were enrolled (132 intervention, 105 control; mean age 78.1 years, 68.4% women). After the first block, 190 participants completed the protocol (96 intervention, 94 control), and 128 completed the second block (69 control, 59 intervention). The intervention group showed significant improvements compared to controls after the first block (70.4% vs. 49.5%; RR: 1.55; CI: 1.16–2.06; p<0.01; NNT: 4.8), at the start of the second block (75.3% vs. 46.9%; RR: 1.73; CI: 1.29–2.31; p<0.001; NNT: 3.5), and at its conclusion (81.7% vs. 51.9%; CI: 1.46–3.24; p<0.001; NNT: 3.4). SPPB scores improved by 1 and 1.6 points after the first and second blocks, respectively (p<0.001). Conclusion: This multicomponent intervention effectively reversed frailty and improved physical function in older adults within PC settings.

SESSION: 2
POSTER#10

INTRODUCED BY: María Martín-Estebané.

PRINCIPAL INVESTIGATOR: Germaine Escames.

RESEARCH AREA: CIBERFES.

TITLE: Molecular mechanisms of sarcopenia: protective effect of exercise and melatonin in a Bmal1 knockout mouse model.

AUTHORS: Yolanda Ramírez-Casas, José Fernández-Martínez, María Martín-Estebané, Paula Aranda-Martínez, Germaine Escames, Darío Acuña-Castroviejo.

ABSTRACT: Sarcopenia is characterized by the loss of muscle mass, strength, and function during aging. Current treatments are limited due to an incomplete understanding of the underlying mechanisms leading to the onset of this disease. Studies using an inducible, skeletal muscle-specific Bmal1 knockout mouse model (iMS-Bmal1−/−) demonstrated that the absence of this gene causes sarcopenia, resulting in structural muscle alterations, disruption of activity rhythms, reduced oxidative capacity, and mitochondrial damage. These changes were reversed by exercise and/or melatonin treatments, regardless of the absence of Bmal1.

Molecular analysis revealed myogenesis impairment, indicating dysfunction in muscle proliferation and differentiation, which was restored by the treatments. Although iMS-Bmal1−/− mice did not show changes in OCR, it was affected by exercise and improved by melatonin through complex I. Additionally, changes were identified in mitochondrial dynamics, including biogenesis, fusion, fission, and mitophagy processes, which were also restored by the treatments. Finally, the loss of Bmal1 compromised antioxidant defenses, triggered inflammatory changes, and affected muscle metabolism.

These results highlight the importance of Bmal1 in muscle homeostasis and position exercise and melatonin as promising strategies to prevent or treat sarcopenia.

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SESSION: 2
POSTER#11

INTRODUCED BY: Luisa Hidalgo-López.

PRINCIPAL INVESTIGATOR: Juan Pedro Bolaños.

RESEARCH AREA: CIBERFES.

TITLE: Phenotypical alterations in mice deficient in astrocytic mitochondrial complex I.

AUTHORS: Luisa Hidalgo-López, Juan Pedro Bolaños.

ABSTRACT: Energy metabolism is tightly regulated by the availability of oxygen and substrates and may be altered by other factors, such as reactive oxygen species (ROS). One of the ROS production main sites is the mitochondrial complex I (MCI). Changes in endogenous levels of ROS in astrocytes lead to metabolic and functional alterations of the central nervous system. Given the relevant role of MCI in ROS production, we set out to investigate a knock-out of Ndufs2, a central subunit of MCI, to cause the loss of this mitochondrial complex. We present data related with the characterization of mice harboring such a lack of mitochondria complex I specifically in astrocytes. To induce Ndufs2 gene deletion, mice were injected with an adeno-associated virus (AAV) expressing Cre recombinase governed under GAFP promoter. Mice weight and food intake were continuously monitoring. One month after Ndufs2 deletion, animals display a marked arrest in weight gain. Finally, three months later, mice die. Mice death is accompanied by a very quick and severe loss of weight. Previously to death, animals show cognitive and motor alterations without signs of pain or suffer. In parallel with mice behavior, the metabolism of astrocytes from Knock-out mice is also disrupted. In this sense, we observe a decline in basal respiration, maximal respiration, and spare respiratory capacity in these cells.

SESSION: 2
POSTER#12

INTRODUCED BY: Rebeca Vecino.

PRINCIPAL INVESTIGATOR: Carlos Vicario.

RESEARCH AREA: CIBERNED.

TITLE: Modulation of the inflammatory response by APOE polymorphism in human iPSC-derived astrocytes .

AUTHORS: Rebeca Vecino, Eva Díaz-Guerra, Esther Arribas-González, David Sanz Gil, Irene Serra-Hueto, Alexander Rodero, Elena P Moreno-Jiménez, Marta González, Maria José Román, Marta Navarrete, Carlos Vicario.

ABSTRACT: Alzheimer's disease (AD) is the leading cause of dementia in the aging population, with the ε4 allele of apolipoprotein E (APOE) being the strongest genetic risk factor. Astrocytes are pivotal in mediating key processes during the progression of AD, including the clearance of amyloid-beta aggregates and the inflammatory response. Nevertheless, the impact of different APOE alleles on astrocyte differentiation, functional maturation, and/or dysfunction remains to be fully elucidated. To this aim, we obtained induced pluripotent stem cells (iPSCs) from fibroblasts of AD patients carrying ε3 and ε4 alleles (in homozygosis) and from healthy individuals. We also used gene-edited iPSC lines homozygous for the main APOE variants and an APOE knock-out line. Human astrocytes were generated by establishing a differentiation protocol by adding small molecules and growth factors. The expression of typical markers and APOE were then analysed to confirm the astrocytic phenotype. In addition, human astrocytes exhibited calcium wave production and glutamate uptake capacity. They also responded to an inflammatory stimulus by changing their morphology and increasing the expression levels of IL-1α, IL-1β, TNF-α, IL-6, C3, and CXCL3, among others, and the release of pro-inflammatory cytokines such as IL-6, suggesting that APOE polymorphism may influence the basal and inflammatory state of astrocytes. Furthermore, the ε4 allele may modify Aβ uptake/degradation capacity by astrocytes and its distribution within the cell. The present findings underscore the significance of APOE polymorphism in the morphological and functional profile of astrocytes and its potential implication in the context of neuroinflammation in Alzheimer's disease.

SESSION: 2
POSTER#13

INTRODUCED BY: Rita Valenzuela Limiñana.

PRINCIPAL INVESTIGATOR: Jose Luis Labandeira.

RESEARCH AREA: CIBERNED.

TITLE: Mitochondrial Dynamics modulation by the Angiotensin System in Dopaminergic Neurons and Microglia.

AUTHORS: Rita Valenzuela , Aloia Quijano, Ana Isabel Rodríguez, María Alicia Costa-Besada, Andrea Lopez-Lopez, María J. Guerra, Jose Luis Labandeira-García.

ABSTRACT: Renin-angiotensin system (RAS) dysfunctions have been associated to neurodegenerative diseases, such as Parkinson's disease (PD), and the neuroinflammatory associated processes. Mitochondrial dysfunctions play a major role in dopaminergic neurodegeneration and neuroinflammation. However, the mechanisms of RAS/mitochondria interactions remain to be clarified. In the present work, we studied the role of major RAS components in the mitochondrial dynamics in dopaminergic neurons and microglia using in vitro and in vivo models. In dopaminergic neurons, we observed that activation of the RAS pro-oxidative/pro-inflammatory axis (Angiotensin II/Angiotensin type-1 receptor, AT1/ NADPH oxidase complex) produces a dysregulation of mitochondrial dynamics towards mitochondrial fission, via Drp1 phosphorylation at Ser616 and translocation to mitochondria. However, activation of the RAS antioxidative/anti-inflammatory axis, using Angiotensin 1-7 (Ang 1-7), counteracts this effect. RAS components also modulated the microglial inflammatory response through mitochondrial dynamic changes. INF-γ-induced activation of human microglial cells produced increased mitochondrial fission, superoxide production and metabolic changes that were inhibited by Ang 1-7 treatment. The role of RAS in mitochondrial dynamic was confirmed in vivo using the LPS induced inflammation model in wild-type, AT1KO, and AT2KO mice. The effect of Ang 1-7 is mediated by IL-10, specifically by decreasing the posttranscriptional phosphorylated Drp1 form, and translocation of STAT3 to mitochondria. Ang 1-7, acting on mitochondrial Ang 1-7 receptors (Mas/Mas related receptors), increased the phosphorylated form of STAT3 at Ser727 by mitochondrial PKA activation. In conclusion, the present findings show the role of RAS components in modulation of mitochondrial dynamics and mitochondrial function, revealing the associated signaling pathways. .

SESSION: 2
POSTER#14

INTRODUCED BY: Lucia Baselga Bellosillo.

PRINCIPAL INVESTIGATOR: Ana Martínez.

RESEARCH AREA: CIBERNED.

TITLE: New cellular models and novel drugs for Dementia with Lewy Bodies.

AUTHORS: Lucia Baselga, Gracia Porras, Loreto Martinez-Gonzalez, Carmen Gil, Ana Martinez.

ABSTRACT: Introduction: Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative disease that causes dementia following Alzheimer disease (AD). DLB is an α-synucleinopathy, characterized by α-synuclein aggregates forming Lewy bodies and dystrophic neurites [1]. Moreover, other protein aggregates such as TDP-43 are also observed in DLB [2]. Currently, no cure or disease-modifying therapies are available for DLB. Lymphoblastoid cell lines (LCLs) derived from patients have been widely used to study several neurodegenerative diseases, as they recapitulate several pathogenic features commonly associated with neurodegeneration [3].

Materials and methods: We have characterized LCLs from DLB patients by evaluating α-synuclein and TDP-43 pathology, cholesterol uptake, proinflammatory cytokines profile and maximal oxidative phosphorylation capacity (OXPHOS). Furthermore, we have evaluated the effect of IGS2.7 and neflamapimod. IGS2.7 is an inhibitor of CK1 synthesized by our group, that has demonstrated the ability to modulate TDP-43 pathology in vivo [4] and neflamapimod is currently under investigation in clinical trials for this disease [5].

Results: We have found significantly increased levels of α-synuclein together with mislocalization and phosphorylation of TDP-43 by immunofluorescence analysis. Additionally, we have observed a lower OXPHOS rate, higher cholesterol uptake and a dysregulated pro-inflammatory cytokine profile. We have obtained promising results of IGS2.7 particularly in recovering TDP-43 homeostasis and OXPHOS.

Conclusions: Based on our findings, we propose that LCLs derived from DLB patients provide an effective model for the study and drug discovery of DLB. Moreover, IGS2.7 could be a promising therapeutic candidate for treating this disease and requires further investigation.

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SESSION: 2
POSTER#15

INTRODUCED BY: Christian Griñan-Ferré.

PRINCIPAL INVESTIGATOR: Rafael Franco.

RESEARCH AREA: CIBERNED.

TITLE: Epigenetic Reprogramming in Alzheimer's Disease: FLAV-27 G9a Inhibition Restores Synaptic Function and Validates Novel Biomarkers Across Models.

AUTHORS: Aina Bellver-Sanchis, David Valle-García, Júlia Jarne-Ferrer, Foteini Vasilopoulou, Carmen Martínez-Fernández, Núria Pérez-Salvador, Juan A. Fafián-Labora, María C. Arufe, Carolin Wüst, Aida Castellanos, David Soto, Núria Casals, Rut Fadó, Jennifer M Pocock, Gemma Navarro, Albert Lleó, Juan Fortea, Daniel Alcolea, Laura Herrero, Ana Guerrero, Santiago Vázquez, Carmen Escolano, Rafael Franco, Mercè Pallàs, Christian Griñán-Ferré.

ABSTRACT: FLAV-27, a novel brain-penetrant G9a inhibitor, demonstrates multi-target therapeutic potential in Alzheimer's disease (AD) models by reversing epigenetic dysregulation linked to neurodegeneration. In primary neuronal cultures, it reduced Aβ, Tau, and p-Tau aggregation while restoring neurite architecture. SAMP8 and 5xFAD mice treated with FLAV-27 showed improved short- and long-term memory, enhanced dendritic spine density, and normalized AMPAR-mediated synaptic transmission. Epigenomic profiling revealed genome-wide H3K9me2 reduction and reversal of aberrant H3K18 methylation, with transcriptomic data indicating upregulated synaptic/neurodevelopmental genes and suppressed microglial activation. Our lead compound mitigated neuroinflammation (reduced pro-inflammatory cytokines) and ferroptosis (increased Gpx4/Fsp1, decreased oxidative stress) in C. elegans and mice models. Proteomic analyses in 5xFAD mice highlighted restored synaptic, metabolic, and proteostatic pathways. Crucially, FLAV-27 normalized plasma H3K9me2, SMOC1, p-Tau, and neuroinflammatory markers, correlating with biomarker changes in human AD plasma/CSF. H3K9me2 and SMOC1 emerged as epigenetically linked biomarkers with translational relevance. These findings position G9a inhibition as a promising disease-modifying strategy. It addresses synaptic dysfunction, protein aggregation, neuroinflammation, and ferroptosis while providing a biomarker framework for precision AD therapeutics.

Fundings: This work was supported by grants PID2022-139016OA-I00, PDC2022-133441-I00, PID2022-138829OA-I00 funded by MICIU/AEI/ 10.13039/501100011033 and FEDER, UE awarded to CGF, MP, and AG; Generalitat de Catalunya (2021 SGR 00357) to CGF and MP; and by grants RYC2021-034046-I and CNS2023-144676 funded by MICIU/AEI/ 10.13039/501100011033 and European Union NextGenerationEU/PRTR awarded to AG. AG is the recipient of an Alzheimer Association Research Fellowship (AARF-21-848511). CW receives a predoctoral fellowship PREP20.

SESSION: 2
POSTER#16

INTRODUCED BY: Miren Ettcheto Arriola .

PRINCIPAL INVESTIGATOR: Antoni Camins.

RESEARCH AREA: CIBERNED.

TITLE: Targeting the Liver-Brain Axis: Licochalcone-A as a Therapeutic Agent Against Metabolic Syndrome-Induced Neurodegeneration.

AUTHORS: Marina Carrasco, Laura Guzman, Leila Driouech, Mireia Millet, Carme Auladell , Jordi Olloquequi, Ester Verdaguer , Jesus Ureña, Antoni Camins, Miren Ettcheto.

ABSTRACT: The understanding of neurodegenerative diseases is evolving toward a systemic view, highlighting the connection between liver dysfunction and brain impairment, where metabolism and inflammation play central role. Licochalcone-A (LCA), has demonstrated antidiabetic and anti-inflammatory effect. Therefore, the aim of this study is to evaluate the neuroprotective potential of LCA under metabolic syndrome conditions.

C57BL/6J male mice were fed either with control (CT) or high-fat diet (HFD) from weaning. At eight months, animals received intraperitoneal LCA (15 mg/kg/day) or saline three times weekly for four weeks. The resulting groups were CT-Saline, HFD-Saline, and HFD-LCA. Behavioral assessments and glucose/insulin tolerance tests were performed to evaluate cognitive and metabolic alterations, respectively. Molecular analysis included synaptic and neuroinflammatory markers in the hippocampus and histological evaluation of liver damage.

LCA administration improved metabolic parameters, including reductions in body and liver weight, enhanced glucose tolerance, and improved liver histology. These changes were linked to the inhibition of PTP1B and activation of AKT in both, liver and hippocampus. As a result of this restored metabolic balance, LCA treatment effectively mitigated HFD-induced neural impairments, exhibiting improved memory performance, preservation of dendritic spine density, and increased levels of synaptic proteins such as BDNF, PSD95, and DBN1. Additionally, LCA reduced glial activation and amyloid beta accumulation, indicating a broader neuroprotective effect.

In conclusion, these findings support LCA as a promising candidate for treating neurodegenerative conditions, acting through modulation of metabolic and inflammatory pathways in both central and peripheral systems.

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SESSION: 2
POSTER#17

INTRODUCED BY: Avetik A. Khachatryan-Boyajyan.

PRINCIPAL INVESTIGATOR: Externo.

RESEARCH AREA: EXT.

TITLE: CPEB4 mis-splicing in murine models of idiopathic ASD.

AUTHORS: Avetik A. Khachatryan-Boyajyan, Miriam Lucas-Santamaría, Sara Picó, Alberto Parras, José J. Lucas, Julia Pose-Utrilla.

ABSTRACT: Autism spectrum disorder (ASD) is a neurodevelopmental condition affecting ~1% of the population(1). Core symptoms consist of deficits in social interaction, impaired communication and restricted, repetitive behaviors. ASD is classified as syndromic or non-syndromic. Syndromic forms (~25% of cases) are caused by single-gene mutations, whereas non-syndromic or idiopathic ASD involves a complex interplay of genetic and environmental risk factors(2).

Murine models are commonly used to investigate the pathology of idiopathic ASD. One such model is the inbred BTBR strain, which presents ASD-related genetic, neuroanatomical and behavioral traits(3,4). Environmental models are also employed, such as maternal immune activation (MIA), linking prenatal infection with ASD susceptibility in offspring(5).

CPEB1-4 are RNA-binding proteins that regulate target mRNA translation by modulating poly(A)-tail length(6). In idiopathic ASD brains, inclusion of a neurospecific 24-nt microexon (exon 4) in CPEB4 is reduced, resulting in elevated levels of the CPEB4Δ4 isoforms and downregulation of ASD risk genes(7). We have recently shown that the 8 amino acids encoded by this microexon alter the biophysical state of CPEB48, which transitions between soluble and condensate forms. Loss of exon 4 favors the latter, favoring the formation of stable aggregates where CPEB4 is believed to be translationally inactive(8).

Although the pathological relevance of microexon is established, the pathophysiological relevance of the preceding exon 3 –also alternatively spliced– remains unknown. Surprisingly, we found increased levels of the CPEB4Δ3 isoform in both BTBR and MIA models. This finding led us to hypothesize that exon 3 skipping may affect CPEB4's biophysical states in a similar manner to exon 4 loss and that, through distinct upstream phenomena, both splicing alterations may converge on a shared neuropathological mechanism.

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SESSION: 2
POSTER#18

INTRODUCED BY: José Jiménez-Villegas.

PRINCIPAL INVESTIGATOR: Antonio Cuadrado Pastor.

RESEARCH AREA: CIBERNED.

TITLE: NRF2 Deficiency Exacerbates Stress Granule Persistence and Protein Aggregation in ALS.

AUTHORS: José Jiménez-Villegas, Daniel Carnicero-Senabre, Adrià Sicart, Antonio Cuadrado, Ludo Van Den Bosch, Ana I Rojo.

ABSTRACT: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the loss of upper and lower motor neurons and remains without effective therapeutic interventions. A major pathological hallmark of ALS is the cytoplasmic aggregation of TDP-43, associated with the aberrant persistence of stress granules: ribonucleoprotein condensates that form in response to cellular stress. Altered redox homeostasis and oxidative stress have been implicated in stress granule formation in ALS, suggesting a potential role for NRF2, a key transcription factor involved in redox control, whose response we have previously found to be compromised in ALS models. This study investigates the impact of NRF2 deficiency on stress granule dynamics. We observed that NRF2-deficient neurons exhibited increased sensitivity to stress granule formation. Mechanistic studies in NRF2-deficient mouse embryonic fibroblasts revealed that this increased sensitivity was not due to enhanced phosphorylation of eIF2α, a principal upstream regulator of stress granule formation. Furthermore, NRF2 deficiency resulted in delayed stress granule clearance, due to diminished p62 recruitment to stress granules. Additionally, the accumulation in stress granules of disease-associated proteins such as FUS and a constitutive cytosolic TDP-43 mutant was promoted by NRF2 deficiency. Importantly, NRF2 activation with the natural compound sulforaphane normalized the elevated stress granule formation in iPSC-derived motor neurons from a C9orf72-ALS patient. In conclusion, our findings highlight the role of NRF2 in modulating the formation and clearance of stress granules, suggesting that NRF2-targeted therapeutic strategies may mitigate persistent stress granules and TDP-43 aggregation in ALS.

SESSION: 2
POSTER#19

INTRODUCED BY: Rebeca Acin Perez.

PRINCIPAL INVESTIGATOR: Jose Antonio Enríquez.

RESEARCH AREA: CIBERFES.

TITLE: ATP synthase reverse activity emerges as a new metabolic indicator of aging.

AUTHORS: Rebeca Acin Perez, Orian S Shirihai, Jose Antonio Enriquez.

ABSTRACT: Complex V can function in both forward and reserve modes, either generating or consuming ATP through ATP synthesis or hydrolysis, respectively. ATP hydrolysis is essential for maintaining the mitochondrial membrane potential and preventing the activation of pro-apoptotic signals that could lead to cell death. Thus, the balance between ATP synthesis and hydrolysis is crucial for maintaining healthy cellular metabolism. On the other hand, excessive ATP synthesis could lead to a sudden collapse of the membrane potential, triggering cell death under unexpected stress. As we age, the efficiency of ATP production declines, resulting in diminished cellular function and accumulated damage. This depletion of ATP is thought to contribute to aging, as cells become less capable of maintaining homeostasis and repairing themselves. We propose that an increase in ATP degradation—particularly its chronic maintenance, as seen in aging—could shift mitochondria into a net consumer of ATP, creating metabolic stress that threatens cell viability. To investigate this further, we are studying genetic models where some aging-related hallmarks appear either delayed or accelerated, allowing us to explore the role of ATP hydrolysis in this process. Our prior work has shown that selective inhibition of ATP hydrolysis improves disease models with compromised mitochondrial function, and we plan to apply these findings to aging research.

SESSION: 2
POSTER#20

INTRODUCED BY: Maria Cabañas-Cotillas.

PRINCIPAL INVESTIGATOR: Diego Clemente.

RESEARCH AREA: CIBERNED.

TITLE: Peripheral myeloid-derived suppressor cells predict the extent of optic nerve myelin damage in a murine model of multiple sclerosis.

AUTHORS: Maria Cabañas-Cotillas, Isabel Machín-Diaz, MªCristina Ortega, Cristina Martos-Polo, Diego Clemente .

ABSTRACT: Multiple sclerosis (MS) is a heterogeneous neurodegenerative disease, demanding reliable remyelination biomarkers. The optic nerve (ON) has been proposed as a pathway for remyelination monitoring through visual evoked potentials, though its relationship with clinical severity remains elusive. Our group has characterized monocytic myeloid-derived suppressor cells (M-MDSCs) as biomarkers of relapse recovery and disease severity in MS and its model experimental autoimmune encephalomyelitis (EAE). In this study, we investigate the correlation between EAE severity and ON myelin impairment and evaluate M-MDSCs as predictive biomarkers of ON pathology.

A longitudinal, individualized study of EAE was monitored for 35 days post-immunization (dpi), once recovery had been achieved. Peripheral blood M-MDSCs/lymphocytes were quantified at disease onset and peak. Mice were classified as severe/mild and poor/good-recoverers based on severity and recovery indices. ONs were dissected out for Ranvier's node density analysis through CASPR immunostaining. Age/sex matched non-immunized mice were used as controls (CT). Node density was significantly reduced in EAE peak compared to CT, regardless of disease severity. At 35 dpi, good-recoverers showed higher ON node density than poor-recoverers, although neither reached CT levels. Higher M-MDSCs levels at onset/peak correlated with enriched node density at peak/recovery, respectively. ROC analysis revealed that M-MDSCs cut-offs of 3.16% (onset) and 5.24% (peak) predicted high node density, and a CD3/M-MDSC ratio of 7.27% at onset predicted low node density at peak.

These findings highlight a connection between reduced EAE severity, enhanced recovery, and preserved ON myelin, supporting the role of M-MDSCs as potential biomarkers to predict ON myelin integrity.

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SESSION: 2
POSTER#21

INTRODUCED BY: Rafael Villino-Rodríguez.

PRINCIPAL INVESTIGATOR: María Cruz Rodríguez Oroz.

RESEARCH AREA: CIBERNED.

TITLE: Study of Peripheral Immunity in patients with Hyposmia and REM Sleep Behavior Disorder, Parkinson's Disease and Alzheimer's Disease.

AUTHORS: Rafael Villino-Rodríguez, Adolfo Jiminez-Huete, Miguel Germán Borda, Genoveva Montoya-Murillo, Antonio Martin-Bastida, Eduardo Salinas, Graciela Díaz, Jimmy Ulloa, Iñaki Garcia-Gurtubay, Juan Jose Lasarte, Noelia Casares, Secundino Fernández, María Cruz Rodríguez-Oroz.

ABSTRACT:

Introduction: Abnormal immunity is a factor contributing to neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). This process may trigger an inflammatory cascade that contributes to disease progression. Prodromal stages of these diseases may also have altered immunity.

Population and Methods: An observational study was conducted in 156 patients with AD, PD, and prodromal stages (hyposmia and REM sleep behavior disorder [RBD]), and in 42 healthy controls. Blood samples were collected to measure cytokines and lymphocyte activity, including lymphocyte proliferation index, IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17A, IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1) levels. Clinical groups were compared using linear models adjusted for age and sex, with post hoc comparisons performed using Tukey's HSD test.

Results: GM-CSF was the only variable showing significant differences between groups ($p = 0.03$). Post hoc tests revealed that patients with REM sleep behavior disorder (mean ± standard deviation: 702.14 ± 1332.10) had significantly higher GM-CSF levels compared to individuals with AD (174.45 ± 452.52; $p = 0.044$) and PD (228.25 ± 412.88; $p = 0.047$).

Conclusion: Peripheral inflammation is altered in RBD, which is a prodromal stage of PD. In particular, GM-CSF is increased indicating a proinflammatory microglial state, which might contribute to microglial activation and blood-brain barrier dysfunction (Stanley et al., 2023). These mechanisms could underlie the initial neuroinflammatory processes driving disease progression.

SESSION: 2
POSTER#22

INTRODUCED BY: Pablo Aguiar.

PRINCIPAL INVESTIGATOR: Tomas Sobrino.

RESEARCH AREA: CIBERNED.

TITLE: PET imaging using radiolabelled anti-tau antibodies: comparison between DFO and DFO* chelators.

AUTHORS: Maria Muñoz-Gonzalez, Noemi Gomez-Lado, Alberto Ouro, Marta Aramburu, Jessica Codesido, Lara Garcia-Varela, Tomas Sobrino, Pablo Aguiar.

ABSTRACT: Introduction: The use of radiolabelled antibodies (mAbs) in PET offers a powerful strategy for early and accurate diagnosis of Alzheimer's disease, as well as for monitoring disease. Desferrioxamine (DFO) is widely used for 89Zr radiolabelling of mAbs, but the commonly used p-NCS-Bz-DFO form can partially dissociate in vivo, releasing 89Zr4+, which accumulates in bones and interferes with quantitative imaging, which is particularly problematic for the current bispecific mAbs designed to cross the blood-brain barrier (BBB). DFO*, featuring an additional hydroxamate group, may offer improved chelation stability. Our study compares the in vivo performance of 89Zr-labelled anti-Tau and BBB-penetrating bispecific anti-Tau-TfRscFv using either DFO or DFO*, assessing their impact on PET brain quantification.

Methods: regular and bispecific mAbs were conjugated to DFO or DFO* and radiolabelled with 89Zr. Radiochemical purity (RCP > 95%) and antigen-binding functionality were confirmed. Mice (n=3 per group) received approximately 4.5 MBq of the radiolabelled mAbs. PET/CT scans were acquired at 6, 24, and 74 hours post-injection (p.i.), with blood samples taken at multiple time points. Ex vivo biodistribution was assessed after the final scan. Time-activity curves (TACs) were derived using standardized uptake values (SUVs).

Results: DFO*-conjugated regular mAbs exhibited higher blood/plasma stability and liver uptake, but also higher bone accumulation. In contrast, bispecific mAbs labelled with DFO* showed lower bone uptake, suggesting better in vivo stability, despite reduced plasma stability. Notably, only [89Zr]-DFO*-Tau-TfRscFv demonstrated detectable brain uptake at 6 h p.i., confirmed by ex vivo analysis.

Conclusion: DFO* improves brain PET imaging of BBB-penetrating bispecific mAbs, reducing bone uptake and enhancing early brain signal. These findings support its use in theranostic applications in Alzheimer disease.

SESSION: 2
POSTER#23

INTRODUCED BY: Rocío Pérez-González.

PRINCIPAL INVESTIGATOR: Javiez Saez Valero.

RESEARCH AREA: CIBERNED.

TITLE: Proteomic Profiling of Circulating Extracellular Vesicles in Carriers of the Alzheimer's-Linked Presenilin-1 E280A Mutation.

AUTHORS: Rocío Pérez-González, Alba M. Lucart-Sanchez, Gema Sevila-González, Guillermo Pérez-Lacarcel, Gloria Patricia Cardona-Gomez, Rafael Andrés Posada-Duque, Javier Sáez-Valero, Inmaculada Cuchillo Ibáñez.

ABSTRACT: Introduction: Circulating extracellular vesicles (EVs) are emerging as promising sources of biomarkers for neurodegenerative diseases. In this study, we characterized EVs derived from plasma of both non-symptomatic and symptomatic carriers of the familial Alzheimer's disease (AD)-associated "Paisa" E280A mutation in the presenilin-1 gene, recognized as the largest and most genetically homogeneous AD family cohort described to date.

Materials and Methods: EVs were isolated from EDTA-plasma using Size-Exclusion Chromatography (SEC) followed by ultrafiltration in three groups: non-symptomatic mutation carriers (N=20), symptomatic carriers (N=10), and healthy controls (N=10). For proteomic analysis, 200 ng of FASP-digested proteins were analyzed on a timsTOF Pro mass spectrometer with PASEF, coupled to an Evosep ONE liquid chromatography system. Data-independent acquisition (DIA) data were processed using DIA-NN software with default settings.

Results: SEC fractions 1–4, enriched in the EV marker CD9, were pooled for proteomic profiling. Mass-spectrometry analysis confirmed enrichment of canonical EV markers, blood microparticles, and lipoproteins, with 474 proteins consistently detected across all samples. Comparative analysis revealed 78 proteins differentially expressed between non-symptomatic and symptomatic carriers, including markers linked to EVs, immune and defense responses, and complement/coagulation pathways. In addition, 39 proteins, including proteins related to cholesterol metabolism, were differentially expressed between non-symptomatic carriers and controls.

Conclusions: Proteomic profiling of EVs from presenilin-1 E280A mutation carriers identified candidate protein biomarkers potentially indicative of disease onset and progression. Further research is necessary to test the utility of circulating EVs in the early detection and monitoring of familial AD that can be extrapolated to sporadic AD.

SESSION: 2
POSTER#24

INTRODUCED BY: Marta Turegano Lopez.

PRINCIPAL INVESTIGATOR: Javier DeFelipe.

RESEARCH AREA: CIBERNED.

TITLE: Application of Volume Electron Microscopy to the Study of Alzheimer's Disease.

AUTHORS: Marta Turegano Lopez, Sveva Dallere, Lidia Blázquez Llorca, Angel Merchán Pérez, Javier DeFelipe.

ABSTRACT: A central aim in neuroscience is to unravel the microorganization of the human brain to better understand both healthy and diseased states. In Alzheimer's disease (AD), a key question is what synaptic alterations drive early cognitive decline, as synaptic loss is the strongest structural correlate of cognitive impairment and often precedes neuronal loss. To address this issue, we utilize volume electron microscopy (vEM) for detailed 3D ultrastructural analysis of human brain tissue (postmortem and biopsy), animal models, and in vitro AD models such as cell cultures and cerebral organoids. We use dedicated software (EspINA) to quantify synaptic parameters—including density, size, type, morphology, and spatial distribution—across brain regions. We have also developed the Nanoconnectivity Skeleton Tool, which enables us to efficiently trace, reconstruct and measure axonal and dendritic fibers and their synaptic connections within brain tissue volumes. Additionally, we perform quantitative analyses of key organelles, including mitochondria, endosomes, and autophagosomes, which are essential for energy supply, molecular trafficking, and autophagy. This comprehensive methodological approach allows us to accurately identify and quantify synaptic and other subcellular changes directly implicated in neurodegeneration. Ultimately, our work contributes to the understanding of early synaptic and structural alterations in AD, providing critical insights into the mechanisms underlying cognitive decline and informing the development of targeted therapeutic strategies.

SESSION: 2
POSTER#25

INTRODUCED BY: Assumpcio Bosch.

PRINCIPAL INVESTIGATOR: Xavier Navarro.

RESEARCH AREA: CIBERNED.

TITLE: Mice overexpressing mutated profilin 1 (PFN1 G118V) recapitulate motor, neuromuscular and cognitive ALS/FTD phenotype.

AUTHORS: Judith Sauleda-Sauleda, Sergi Verdés, Núria Gaja-Capdevila, P Hande Ozdinler, Miguel Chillón, Mahmoud Kiaei, Xavier Navarro, Assumpció Bosch.

ABSTRACT: Introduction: Impaired axonal transport is one of the pathophysiological mechanisms involved in ALS, which contributes to neuromuscular impairment, synaptic detachment and muscle atrophy. By binding to monomeric actin, profilin 1 (PFN1) promotes its polymerization. Mutations in the PFN1 gene were described in familial ALS, reinforcing the role of the cytoskeleton and defective axonal transport in this disease.

Materials and Methods: Here, we characterized a heterozygous mouse model overexpressing the human mutant PFN1G118V gene under the control of the mouse prion promoter (PrP). Neuromuscular impairment was assessed throughout disease progression by nerve conduction studies and rotarod, while novel object recognition test was used to evaulate cognitive impairment.

Results: Distinct patterns of degeneration were found for different muscles: the tibialis anterior (TA) showed a progressive decline in the amplitude of the compound muscle action potential starting by 24 weeks of age, before overt symptoms onset. In contrast, the more distal plantar interossei muscles were more resistant to denervation. Notably, a reduction in Motor Evoked Potential (MEP) amplitudes occurred from 20 weeks, suggesting that, in this model, corticospinal tract and cortical motoneuron involvement precede spinal motoneuron degeneration. Consistent with MEP decline, cognitive impairment was detected at 27 weeks of age, while locomotor onset did not start until 28 weeks. Moreover, PFN1G118V mice showed a decreased proportion of occupied muscular endplates in the TA muscle, indicating neuromuscular junction denervation due to axonal retraction.

Conclusions: PFN1G118V mouse exhibits ALS and FTD-like pathogenic phenotypes, including upper and lower motoneuron degeneration, locomotor decline and cognitive dysfunction. .

SESSION: 2
POSTER#26

INTRODUCED BY: Álvaro Moreno Rupérez.

PRINCIPAL INVESTIGATOR: Teresa Iglesias.

RESEARCH AREA: CIBERNED.

TITLE: PKD1 Downregulation in Aging Excitatory Neurons: A Potential Mechanism Driving Neurodegeneration and Cognitive Decline.

AUTHORS: Julia Pose Utrilla, Santiago López Begines, Claudia Rodríguez López, Celia López Menéndez, Álvaro Sebastián Serrano, Marina Prudencio Sánchez-Carralero, Miguel Ángel Pozo García, José Luis Izquierdo García, Lucía García Guerra, José Javier Lucas , Miguel Campanero, Rafael Fernández Chacón, Teresa Iglesias.

ABSTRACT: The brain is one of the organs most affected by aging, strongly linked to cognitive decline and an increased risk of neurodegenerative diseases. This process is marked by pathological features such as mitochondrial dysfunction, oxidative stress damage, dysregulated metabolism, abnormal neuronal activity, and inflammation. The complex molecular events driving brain aging remain unclear, and identifying pivotal proteins that orchestrate these changes is crucial for understanding the mechanisms behind neuronal degeneration.

A potential candidate is the essential kinase Protein Kinase D1 (PRKD1 or PKD1), which has emerged as a regulator due to its roles in oxidative stress, synaptic signaling, and neuronal differentiation. Additionally, PKD1 contributes to several CNS diseases, including spinal cord injury, ischemic stroke, Huntington's and Parkinson's disease. Interestingly, a recent study showed that mutations in the homolog dkf-1 in C. elegans accelerate age-related locomotor impairment and are linked to synaptic dysfunction, although its contribution in mammals remains unknown.

In this study, we show that PKD1 decreases with age in excitatory neurons of the human brain. To investigate the impact of this reduction, we used a PKD1 knockout mouse model in excitatory neurons (PKD1 KO). This model emulates key aspects of aging brain, including increased ROS, microstructural and metabolic changes and synaptic disruption. Behaviorally, the mice show early cognitive impairments, with progressive learning and memory deficits, along with an anxiety-like phenotype.

Taken together, our findings highlight PKD1 as a potential critical modulator in brain aging, suggesting that its decline may contribute to age-related neuronal dysfunction.

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SESSION: 2
POSTER#27

INTRODUCED BY: Deborah Romualdi.

PRINCIPAL INVESTIGATOR: Eva Carro.

RESEARCH AREA: CIBERNED.

TITLE: Microglial lactoferrin expression in the APP/PS1 model of Alzheimer's Disease.

AUTHORS: Deborah Romualdi, Laura Carrero, Desiree Antequera, Andrés Fernández, Lara Ordóñez-Gutiérrez , Francisco Wandosell, Eva Cano, Cristina Municio, Eva Carro.

ABSTRACT: Lactoferrin has been detected in brain cells where it protects from injuries through anti-inflammatory and immunomodulatory processes. However, lactoferrin was also associated with amyloid plaques in Alzheimer's disease (AD), therefore, the presence of lactoferrin in the AD brain was classically associated with a negative outcome. Nevertheless, it is still not sufficiently clear which cells produce or express lactoferrin in the brain, and how that expression is altered in AD.

We investigated the expression and localization of lactoferrin in the brain of male and female APP/PS1 mice at 3 and 12 months of age. Using BV2 cells we further explored the interaction with β-amyloid (Aβ) and its effect on microglial lactoferrin expression.

We demonstrated that lactoferrin is specifically synthesized by microglia, and its expression depends on the age and sex of mice. Our results also confirmed that Aβ-stained area was significantly increased in the female brain compared with male APP/PS1 mice. However, microglial lactoferrin from female APP/PS1 mice was inversely associated with increased amyloidosis, enhancing Lf expression in an early disease age (3-month-old), whereas Lf expression was found significantly reduced at 12-month-old. This trend was also found at the protein level in vivo. We propose that sex-related differences in microglial lactoferrin could be, at least partially, contributory to sexual dimorphism observed in AD.

SESSION: 2
POSTER#28

INTRODUCED BY: Ana Guerrero.

PRINCIPAL INVESTIGATOR: Eduardo Soriano.

RESEARCH AREA: CIBERNED.

TITLE: Cellular senescence: the missing link between aging and Alzheimer's Disease?.

AUTHORS: Iker Bengoetxea de Tena, Carolin Wüst, Lutz Matthies, Mercè Pallàs, Eduardo Soriano, Yasmina Manso, Ana Guerrero.

ABSTRACT: Senescence is a cellular response to stress or damage that leads to irreversible growth arrest. With age, senescent cells accumulate and contribute to age-related diseases, including neurodegeneration. This has fueled growing interest in senotherapies - either eliminating senescent cells (senolytics) or modulating their pro-inflammatory secretome. We have previously contributed to this field by successfully applying senotherapies in models of age-related decline. However, although senescent cell accumulation is a hallmark of ageing - and ageing remains the greatest risk factor for Alzheimer´s Disease (AD) - the extent and role of senescence in the AD brain remain poorly understood. Thus, senescence emerges as a promising yet underexplored therapeutic target in AD.

Strikingly, some individuals exhibit cognitive resilience despite significant accumulation of amyloid-β and tau, the pathological hallmarks of AD. Understanding the molecular basis of this resilience may reveal novel therapeutic avenues. A recent discovery showed that a rare variant of Reelin (RELN-COLBOS) delays AD symptoms by up to 30 years in familial cases, highlighting Reelin's neuroprotective potential. Here, in a collaborative effort with Prof. Soriano and Dr. Manso, we hypothesize that Reelin's neuroprotective effects are mediated, at least in part, by alleviating cellular senescence and its associated inflammation. To test this, we are combining in vitro and in vivo models of AD to investigate how Reelin modulates senescence and its therapeutic potential. Unveiling a crosstalk between Reelin and cellular senescence could open the door to new pharmacological strategies, including the development of agents that enhance the Reelin pathway.

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SESSION: 2
POSTER#29

INTRODUCED BY: Silvana Javiera Soto Rodríguez.

PRINCIPAL INVESTIGATOR: María Carmen Gómez Cabrera.

RESEARCH AREA: CIBERFES.

TITLE: Effects of Resistance Training on Frailty and Physical Performance in Community-Dwelling Older Women.

AUTHORS: Abril Gorgori González, Aitor Carretero Martínez, Remus Iulian Lupu, Esther García Dominguez, Abdelrahman Khaled Salah, Blanca Alabadí Pardiñez, Juan Ignacio Cervera Miguel, Miguel Civera Andrés, José Tomas Real Collado, Eva Tamayo Torres, Kristine Stromsnes , Juan Gambini, Gloria Olaso González, Maria Carmen Gómez Cabrera.

ABSTRACT: Introduction: Frailty in older adults entails significant healthcare costs due to its association with disability and mortality. Since skeletal muscle is essential for preserving physical function and autonomy, this study aimed to implement a short-term strength training program to promote functional improvements and delay frailty1,2,3.

Methods: This ongoing experimental study involves 16 women over 65 years old (mean age: 72.8 ± 4.3 y). Participants followed a six-week training program, twice per week, focused on leg press and knee extension exercises. Baseline (n=16) and post-intervention (n=8) assessments were conducted, including body composition, muscle strength, functionality, frailty, and molecular analyses through vastus lateralis biopsies and blood samples. Paired t-tests or non-parametric tests were used to compare pre- and post-intervention means.

Results: Post-intervention results showed significant improvements in: lean mass (20.23±2.01 vs 20.71±1.78 kg, $p=0.03$), quadriceps thickness (1.90±0.38 vs 2.17±0.37 cm, $p<0.01$), leg press strength (200.80±100.50% vs 295.90±117.30 % body weight, $p<0.01$), and knee extension strength (55.38±15.85% vs 75.98±18.57% body weight, $p<0.01$). Frailty also improved: SHARE-FI scores decreased (0.77±1.87 vs 0.05±1.38, $p=0.01$) and Fried's phenotype shifted toward robustness. Functional tests such as FallSkip indicated reduced fall risk.

Conclusion: The results are consistent with existing literature on the positive effects of strength training in aging populations. This study highlights the potential of targeted resistance exercise as a specific and effective strategy to reverse frailty in older women.

References:

(1) Nascimento CM, et al.2019. DOI: 10.1016/j.freeradbiomed.2018.08.035.

(2) Viña J, et al. 2016. DOI: 10.1016/j.freeradbiomed.2016.03.024.

(3) Viña J, etal. 2016. DOI: 10.1113/JP270536.

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SESSION: 2
POSTER#30

INTRODUCED BY: José Miguel Brito Armas.

PRINCIPAL INVESTIGATOR: Jordi Alberch.

RESEARCH AREA: CIBERNED.

TITLE: Comparative Characterization of Novel TDP-43 Mouse Models for ALS and FTLD Research.

AUTHORS: José Miguel Brito Armas, Ramón Alejo Muñoz de Bustillo Alfaro, Davinia Domínguez González, Lucas Taoro González, Beatriz Rodríguez Villa, Arianna Vastola Mascolo, Francesca De Giorgio, Elizabeth M C Fisher, Thomas J Cunningham, Abraham Acevedo Arozena.

ABSTRACT: INTRODUCTION: TAR DNA-binding protein 43 (TDP-43) is a nuclear RNA-binding protein that is centrally involved in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). In most cases of ALS, TDP-43 is abnormally phosphorylated, ubiquitinated and mislocalised to the cytoplasm, forming pathological aggregates. Despite its clear involvement, the mechanisms by which TDP-43 drives neurodegeneration remain unclear. As with other major neurodegenerative diseases, TDP-43 proteinopathies are complex and no single model recapitulates all the pathological features. In ALS, the clinical and pathological heterogeneity suggests multiple disease pathways. To address this, we have characterised several complementary TDP-43 mouse models - each reflecting different aspects of TDP-43 dysfunction - using phenotypic, biochemical and molecular approaches.

MATERIALS AND METHODS: We studied four TDP-43 mouse models: 1) a genomically humanised TARDBP model in which the endogenous Tardbp gene was replaced by the full human TARDBP ortholog (including all exons and introns); 2) the same allele carrying the ALS-associated M337V mutation; 3) a humanised variant with a disrupted nuclear localisation signal (ΔNLS); and 4) a model lacking the TDP-43 3'UTR binding region (ΔBR). The mice were evaluated at different ages using behavioural, histological, biochemical and molecular analyses.

RESULTS AND CONCLUSIONS: Each model showed distinct phenotypic and molecular characteristics. Together, they provide a versatile platform to study different mechanisms of TDP-43-related neurodegeneration and to support future therapeutic strategies.

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SESSION: 2
POSTER#31

INTRODUCED BY: Rubén Alcantud Córcoles.

PRINCIPAL INVESTIGATOR: Pedro Abizanda.

RESEARCH AREA: CIBERFES.

TITLE: Muscle Ultrasound Normative Values and Malnutrition in Community-Dwelling Older Adults.

AUTHORS: Rubén Alcantud Córcoles, Ester López Jiménez, Marta Neira Álvarez, Adriana Abizanda Saro , Marisa Fernández González de la Riba, Juan Rodríguez Solís, Alfonso González Ramírez, María Auxiliadora Castillo Delgado, Almudena Avendaño Céspedes, Rafael García Molina, Marta Sáez Blesa, Pedro Abizanda Soler.

ABSTRACT: Objective: This study aimed to establish normative values for muscle ultrasound in community-dwelling older adults and assess its association with physical function, muscle strength, frailty, and activities of daily living. It also evaluated muscle ultrasound measurements in relation to nutritional status as assessed by GLIM criteria. Methods: The cross-sectional study involved 423 participants aged ≥70 years from ten centres, including seven geriatric services and three primary care teams. Mid-thigh ultrasound measurements were taken using the Clarius L7 HD3 device, including rectus femoris thickness, area, pennation angle, subcutaneous tissue thickness, and total thigh thickness. Results: Participants had a mean age of 81.5 years, with 66.5% being women. Average BMI was 27.3, Charlson Index 1.3, Barthel Index 92.5, SPPB score 8.7, and Fried criteria score 1.8. Grip strength averaged 20.7 kg. Sixty-seven participants (16.6%) met GLIM criteria for malnutrition. Normative ultrasound values were presented by sex. Associations between ultrasound parameters and functional variables were found in men but not women. The lower tertile of total thigh thickness was the best parameter for identifying normonutrition and ruling out malnutrition. Participants above this cutoff had a 90% probability of being well-nourished, while those below required specific nutritional evaluation. Conclusion: This study provides normative muscle ultrasound values for ambulatory older adults. The association with functional variables was observed only in men. The lower tertile of total thigh thickness is a valuable tool for nutritional assessment, indicating a high probability of being well-nourished above this threshold. .

SESSION: 2
POSTER#32

INTRODUCED BY: Agnès Pérez-Millan.

PRINCIPAL INVESTIGATOR: Raquel Sánchez del Valle.

RESEARCH AREA: CIBERNED.

TITLE: Cortical asymmetry index over time in Autosomal Dominant Alzheimer's Disease: findings from the Clínic Barcelona and DIAN cohorts.

AUTHORS: Agnès Pérez-Millan, Beatriz Bosch, Sergi Borrego-Écija, Anna Antonell, Núria Guillén, Guadalupe Fernández-Villullas, Diana Esteller-Gauxax, Adrià Tort-Merino, Mircea Balasa, Albert Lladó, Neus Falgàs, Raquel Sánchez-Valle, The Dominantly Inherited Alzheimer Network (DIAN).

ABSTRACT: Introduction: The Cortical Asymmetry Index (CAI) evaluates brain asymmetry, showing increased asymmetry in sporadic Alzheimer's Disease (AD). We investigate CAI in asymptomatic (AMC) and symptomatic (SMC) mutation carriers of Autosomal Dominant Alzheimer's Disease (ADAD).

Materials and Methods: Baseline T1-weighted MRI were collected from the ADAD cohort at Clínic Barcelona (Clinic Barcelona cohort) (SMC: N=19, AMC: N=22, CTR: N=19) and the DIAN-OBS study (DIAN cohort) (SMC: N=115, AMC: N=234, CTR: N=215). SMC in DIAN was further classified as SMC-MCI (CDR=0.5) and SMC-AD (CDR≥1). Available CSF and plasma NfL levels were included. Cortical thickness was analyzed with Freesurfer, and CAI was calculated using an open-source pipeline. Cross-sectional analyses assessed diagnosis and APOE differences, adjusting for age, sex, and EYO. Longitudinal progression was examined using GAM models in DIAN, incorporating age, sex, and group-by-EYO interactions as fixed effects.

Results: CAI distinguished AMC and SMC from CTR in the Clinic Barcelona cohort and SMC-AD from CTR and AMC in DIAN. Higher CAI in carriers and SMC in Clinic Barcelona cohort correlated with elevated plasma-NfL, advanced EYO, and lower MMSE. DIAN carriers showed increased CAI linked to plasma/CSF NfL, reduced MMSE, and advanced EYO (also SMC-AD). DIAN APOE3/3 individuals differed from other APOE genotypes in carriers and distinctions between AMC and SMC. In DIAN, SMC and SMC-AD presented significant CAI increases over time.

Conclusions: ADAD individuals show increased brain asymmetry with disease progression, correlating with key biomarkers. APOE3/3 showed higher asymmetry. CAI increases over time in SMC and SMC-AD, suggesting its potential for disease monitoring.

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SESSION: 2
POSTER#33

INTRODUCED BY: Elia Ivars.

PRINCIPAL INVESTIGATOR: Ramón Trullas.

RESEARCH AREA: CIBERNED.

TITLE: Circulating mitochondrial DNA in serum as a biomarker of Lewy Body Diseases.

AUTHORS: Elia Ivars, Margalida Puigròs, Burcu Şekerzade, David Adamuz, Alex Menéndez, Anna Colell, Katrin Beyer, Pau Pastor, Ramon Trullas.

ABSTRACT: Background: Idiopathic REM sleep behavior disorder (IRBD) is a prodromal stage of Lewy Body Diseases (LBD). In previous work, we observed a significant increase in circulating mtDNA (c-mtDNA) copies in serum and CD9-Evs from serum in patients with IRBD who later converted to a LBD. Here, we assessed whether the increased release of cf-mtDNA in serum is also observed in LBD patients and if it is contained in CD9+, CD81+, and CD63+ extracellular vesicles (EVs).

Methods: We used multiplex digital PCR to quantify cf-mtDNA copies and deletion ratio in CSF and serum in a cohort of 114 subjects from the Hospital Germans Trias i Pujol, including 1) 28 patients with prodromal dementia with Lewy Bodies (pDLB), 2) 38 patients diagnosed with LBD, and 3) 48 age-matched controls without clinical neurological symptoms. In addition, we investigated whether CD9-, CD81- and CD63-EVs serum samples contained c-mtDNA.

Findings: Patients with pDLB and LBD exhibited a higher c-mtDNA copy number and a higher c-mtDNA deletion ratio in serum than controls. In addition, we found the presence of c-mtDNA in CD9-, CD81- and CD63-Evs in serum. Subjects with pDLB and LBD also presented an elevated c-mtDNA copy number and c-mtDNA deletion ratio in serum-derived CD63-EVs but not in CD9-EVs, compared to controls.

Interpretation: These results suggest that mtDNA dysfunction is a biomarker of a primary molecular mechanism of the pathophysiological cascade that precedes the complete clinical motor and cognitive manifestation of LBD. Supported by MJFox Foundation, MJFF-000011; ISCIII “EU NextGenerationEU/PRTR”, grant PMP22/00100PMP22/00100; and MICIU/AEI/10.13039/-501100011033, PID2023-153168OB-I00.

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SESSION: 2
POSTER#34

INTRODUCED BY: Jordi Duran.

PRINCIPAL INVESTIGATOR: Jose Antonio del Río.

RESEARCH AREA: CIBERNED.

TITLE: Glycogen-Induced Neurodegeneration and Epilepsy: Insights from Lafora Disease.

AUTHORS: Núria Moral Blazquez, José Antonio del Río , Jordi Duran.

ABSTRACT: Lafora disease (LD) is a fatal neurodegenerative disorder caused by the accumulation of insoluble glycogen aggregates (the so-called Lafora bodies) in the brain. Patients typically develop a severe, progressive form of myoclonic epilepsy during adolescence, marked by progressively worsening seizures, cognitive decline, and ultimately death. No effective treatments exist, highlighting the importance of understanding the underlying mechanisms of the disease. Our previous studies showed that glycogen accumulation underlies the pathology of LD, and that Lafora bodies are present in both neurons and astrocytes. Furthermore, we demonstrated that glycogen accumulation in astrocytes drives the pathophysiology of neurodegeneration in LD, but not epilepsy. Building on this, our objective is now to investigate the relationship between abnormal glycogen accumulation in GABAergic interneurons, critical cells for maintaining the brain's excitatory/inhibitory balance, and seizure development. Using genetically modified mouse models, we have found that glycogen accumulation in these inhibitory neurons impairs their function, leading to increased network excitability and heightened seizure activity. These findings establish a direct link between metabolic disturbances in GABAergic neurons and epileptic symptoms in LD. Furthermore, our results suggest that similar metabolic dysfunction in inhibitory circuits could be relevant to other forms of epilepsy, offering broader implications for treatment development.

SESSION: 2
POSTER#35

INTRODUCED BY: Rucsanda Pinteac.

PRINCIPAL INVESTIGATOR: Manuel Comabella.

RESEARCH AREA: CIBERNED.

TITLE: Vesicular microRNAs as Astrocytic Messengers of Neuroinflammation.

AUTHORS: Rucsanda Pinteac, Clara Matute-Blanch, Gloria López Comellas, Susan Goelz, Xavier Montalban, Manuel Comabella.

ABSTRACT: Astrocytes are increasingly recognized as central regulators of neuroinflammation in multiple sclerosis (MS), not only by releasing cytokines but also via extracellular vesicles (EVs) enriched in regulatory microRNAs (miRNAs). These vesicles can shape immune responses and may serve as biomarkers of glial activation. Here, we investigated the miRNA cargo of astrocyte-derived EVs (ADEVs) to identify inflammation-induced signatures relevant to MS.

Human induced pluripotent stem cells (iPSCs) from a healthy donor and a relapsing-remitting MS (RRMS) patient were differentiated into astrocytes. Their identity and functionality were confirmed by expression of canonical markers, glutamate uptake, and NF-κB nuclear translocation upon stimulation with a cytokine cocktail (TNFα, IL-1α, C1q). EVs were isolated from astrocyte-conditioned medium by size-exclusion chromatography and characterized by flow cytometry for CD63, GLAST, AQP4, and CD49f. Vesicular RNA was extracted, quality-checked, and subjected to small RNA sequencing.

Bioinformatic analysis revealed 24 significantly regulated miRNAs in the RRMS line and 9 in the control line (adjusted $p < 0.05$). Only miR-146a-5p and miR-27a-3p were upregulated in both lines, with no shared downregulated miRNAs. RT-qPCR validation confirmed a robust and significant upregulation of miR-146a-5p in EVs from inflamed RRMS astrocytes ($p < 0.001$).

These findings suggest that ADEVs reflect the inflammatory status of astrocytes and carry conserved miRNA signatures. The consistent upregulation of miR-146a-5p supports its potential as a biomarker of astrocytic activation and a relevant target for future studies in MS pathophysiology.

SESSION: 2
POSTER#36

INTRODUCED BY: Yaiza López Sampere.

PRINCIPAL INVESTIGATOR: Mónica Povedano.

RESEARCH AREA: CIBERNED.

TITLE: Characterization of Hippocampal Nrf2 Deficit: Implications in Aging and Tau Seeding and Spreading in an Induced Tauopathy Mouse Model.

AUTHORS: Yaiza López Sampere, Pol Mengod Soler, Sergio Roca Pereira , Antonia Vinyals Rioseco, Farida Dakterzada , Leila Romero, Enrique Santamaría , Joaquín Fernández-Irigoyen , Isidro Ferrer, Mónica Povedano , José Antonio del Río, Gabriel Santpere, Manuel Portero Otín, Gerard Piñol Ripoll, Pol Andrés Benito.

ABSTRACT: Introduction: Aging impairs physiological functions and increases susceptibility to neurodegenerative diseases like Alzheimer's Disease (AD). Central to this process are oxidative stress, proteostasis failure, and neuroinflammation—all linked to declining NRF2 activity, a key regulator of oxidative stress responses and cellular homeostasis.

Materials and methods: This study used Nrf2-knockout (Nrf2-KO) mice to explore how Nrf2 deficiency impacts hippocampal physiology. Through transcriptomic (RNA-seq) and proteomic (SWATH-MS) analyses, we identified age-related molecular changes relevant to AD and aging. Additionally, we examined how Nrf2 deficiency influences tau protein seeding and spreading in a paired helical filaments (PHFs)-tau inoculated model.

Results: RNA-seq revealed 745 differentially expressed genes, with upregulated immune pathways and downregulated redox and glutathione-related genes—primarily in astrocytes. RT-qPCR partially validated gene expression changes, including those involved in lipid transport and astrocyte metabolism. Proteomics identified 157 altered proteins: synaptic and mitochondrial proteins were downregulated, while those related to neurotransmission and immune activation were upregulated. Western blotting confirmed changes in astrocytic markers. To assess Nrf2's role in tau pathology, 3-month-old mice were injected with PHF-tau from AD brain. After 3 months, Nrf2-KO mice showed reduced tau spreading, with aggregates largely confined to the injection site, unlike in wild-type controls.

Conclusions: These findings highlight that Nrf2 deficiency disrupts hippocampal homeostasis at multiple levels, especially affecting astrocyte function, neuroinflammation and redox balance. Furthermore, impaired tau propagation in Nrf2-KO mice suggests NRF2 influences the brain's vulnerability to tau pathology. Overall, Nrf2 emerges as a key modulator of brain aging and tauopathy progression, providing potential therapeutic avenues.

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SESSION: 2
POSTER#37

INTRODUCED BY: Eva Alegre Cortés.

PRINCIPAL INVESTIGATOR: Jose Manuel Fuentes.

RESEARCH AREA: CIBERNED.

TITLE: Disrupted EGFR Trafficking and Enhanced Autophagy in Myotonic Dystrophy Type 1.

AUTHORS: Eva Alegre Cortés, Alberto Giménez Bejarano, Marta Paredes Barquero, Mercedes Blanco Benítez, Nerea Domínguez Rojo, Javier Ojalvo Pacheco, Enrique Carretero Morán, Mireia Niso Santano, Rosa Ana González Polo, Patricia Gómez Suaga, José Manuel Fuentes Rodríguez, Sokhna M.S Yakhine Diop.

ABSTRACT: Myotonic dystrophy type 1 (DM1) is an autosomal dominant genetic disorder caused by a CTG trinucleotide repeat expansion in the DMPK gene. This mutation is associated with multiple cellular dysfunctions, particularly affecting key processes like autophagy and endocytosis. One notable example is the epidermal growth factor receptor (EGFR), which plays a crucial role in cell signaling through the AKT pathway and shows abnormal trafficking in DM1 cells.

In our study, using primary fibroblasts from both DM1 patients and healthy individuals, we observed a significant increase in autophagic flux, along with enlarged endosomes and lysosomes in DM1 cells. When fibroblasts were stimulated with EGF, these cells showed distinct early endocytic defects, such as reduced EGF-EGFR binding and slower internalization of EGFR. Interestingly, despite these issues, DM1 cells exhibited increased phosphorylation of AKT and ERK1/2 following EGF treatment.

These findings suggest that EGF-induced EGFR endocytosis is delayed in DM1, likely due to impaired ligand-receptor interactions rather than reduced AKT pathway signaling. This research highlights the complex molecular relationship between autophagy, endocytosis, and cell signaling in DM1, offering potential paths for targeted therapies.

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SESSION: 2
POSTER#38

INTRODUCED BY: Andrea Iribarren-López.

PRINCIPAL INVESTIGATOR: David Otaegui.

RESEARCH AREA: CIBERNED.

TITLE: Age-related changes in the immune system of people with multiple sclerosis .

AUTHORS: Andrea Iribarren-López, Laura Martins-Almeida , Jadon K Wells, Tamara Castillo-Triviño , Alvaro Prada, Hilda A Pickett , Ainhoa Alberro , David Otaegui .

ABSTRACT: Introduction: Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease driven by immune dysregulation. With increasing life expectancy in people with MS (pwMS), understanding the impact of aging on the immune system (immunosenescence) is crucial.

Objectives/Aims: We characterized immunosenescence in pwMS by analyzing age-related changes in immune cell populations, thymic involution, inflammatory mediators, neurodegeneration markers, and telomere attrition.

Methods: Blood samples were collected from pwMS and healthy controls (HCs). PBMCs (n=110) were used to assess immune populations by flow cytometry. DNA (n=150) was used for thymic involution study by sjTREC quantification and telomere length measurement using terminal restriction fragment analysis. Plasma (n=142) was used for inflammation and neurodegeneration analysis using automated ELISAs.

Results: Age-related analysis of immune populations revealed distinct correlations between pwMS and HCs in key populations, such as B or NK cells. In pwMS, we observed an age-associated increase CD28-CD57+ and CD28+CD57+ cells within both CD4 and CD8 subsets. Thymic involution occurred earlier in younger pwMS. Regarding inflammaging in pwMS, positive correlations between age and IL-6, TNF-α, and CRP was found. While IL-6, IL-10, and TNF-α were higher in pwMS, CRP elevation in pwMS occurs only in individuals over 50. NFL levels were elevated in pwMS and correlated positively with age in both groups. Only in pwMS, NFL correlates with IL-6 and TNF-α. Telomere attrition occurred with age in both groups, without significant inter-group differences.

Conclusion: Our findings reveal age-related immune changes in pwMS that underscore the importance of considering age in MS management and therapeutic strategies.

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SESSION: 2
POSTER#39

INTRODUCED BY: Eva de Lago.

PRINCIPAL INVESTIGATOR: Javier Fernandez Ruiz.

RESEARCH AREA: CIBERNED.

TITLE: Unraveling neuroprotective pathways: Targeting enzymes that inactivate endocannabinoids for ALS therapeutic management.

AUTHORS: Marta Gómez-Almería, Raquel Martín-Baquero, Carmen Rodríguez-Cueto, Julián Romero, Uwe Grether, Benjamin F Cravatt, Javier Fernández-Ruiz, Eva de Lago.

ABSTRACT: The endocannabinoid system is involved in the pathophysiology of amyotrophic lateral sclerosis (ALS), so targeting some of its components has emerged as a promising therapeutic option. An endocannabinoid-based therapeutic approach currently in progress is the use of inhibitors of those enzymes, fatty acid hydrolase (FAAH) and monoacylglycerol lipase (MAGL), that inactivate endocannabinoids. Previous studies showed beneficial effects using the classic SOD-1 transgenic mouse model of ALS. We are now interested in investigating the benefits of modulating FAAH or MAGL in an alternative model as PrP-TDP43A315T mice through: (i) crossing these mice with FAAH-deficient mice; (ii) chronically inhibiting FAAH with URB597; and (iii) chronically inhibiting MAGL with RO727 (irreversible inhibitor) and RO723 (reversible inhibitor). The progression of the pathological phenotype was recorded weekly using behavioral tests, whereas their spinal cords were used to assess neuronal survival and glial reactivity. TDP43A315T/FAAH-/- mice showed a delay in motor decline and increased survival compared with TDP-43A315T/FAAH+/+ mice. These improvements were associated with a higher preservation of spinal motor neurons and a significant decrease in Iba-1 immunoreactivity. The treatment with URB597, RO723, or RO727 also reduced neuronal death in the spinal cord and, in some cases, also attenuated glial reactivity, although these benefits did not result in an improvement in behavioral responses. In summary, our results strongly suggest the neuroprotective potential of modulating endocannabinoid inactivation in ALS using genetic or pharmacological tools. This inactivation increased neuronal survival and attenuated glial reactivity, providing a promising avenue for further development toward the clinical scenario of pharmacological agents inhibiting FAAH and/or MAGL enzymes.

Supported by MICINN (RTI-2018-098885-B-100 and PID2021-128906OB-I00).

SESSION: 2
POSTER#40

INTRODUCED BY: Veronica Brito.

PRINCIPAL INVESTIGATOR: Jordi Alberch.

RESEARCH AREA: CIBERNED.

TITLE: Quantifying DNA Repair Synthesis in HTT Exon 1: A Novel Readout for Somatic Instability in Huntington's Disease.

AUTHORS: Judith Praena Fernandez, Jesus Perez Perez, María Berge, Carla Castells Esteve, Anna Vazquez Olive, Jia Feng, Katherine van Belois, Petar Podlesniy, Huu Phuc Nguyen, Jaime Kulisevsky, Mahmoud A. Pouladi, Paolo Beuzer, Veronica Brito.

ABSTRACT: Huntington's disease (HD) is a neurodegenerative disorder caused by CAG repeat expansions in the Huntingtin gene. Currently, no disease-modifying treatments exist, highlighting the need for therapeutic advancements. Like other polyglutamine disorders, HD is characterized by somatic instability (SI), where CAG repeats expand further in neurons, exacerbating neurodegeneration. DNA mismatch repair (MMR) has been implicated in somatic triplet repeat expansion, making it a potential therapeutic target. However, challenges remain in measuring somatic expansions in accessible tissues, detecting subtle changes during clinical trials, and understanding the therapeutic benefits of limiting expansions beyond certain thresholds.

To address these gaps, we developed the Unscheduled DNA Repair Synthesis Assay (URSA), hypothesizing that DNA repair events near repeats occur more frequently than expansion/contraction events. Using the thymidine analogue EdU, incorporated DNA repair sites are tagged, enriched via click chemistry, and analyzed. We applied URSA to fibroblasts, PBMCs, and hPSC-derived neurons with varying CAG sizes (27–81 repeats) in HTT exon 1. ddPCR revealed higher DNA repair synthesis in HD cells, correlating with CAG size but not age, onset, or disease stage in PBMCs. The whole genome sequencing of newly synthesized DNA in neurons and PBMCs identified a DNA repair hotspots in the HTT gene. Ongoing studies aim to link this repair activity to MMR pathways, validating URSA as an SI readout.

These findings suggest that measuring DNA synthesis reflects MMR activity at HTT exon 1, offering a novel and sensitive indicator of somatic instability, potentially enabling earlier detection and therapeutic targeting in HD.

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SESSION: 2
POSTER#41

INTRODUCED BY: Rodrigo Barderas.

PRINCIPAL INVESTIGATOR: Teresa Moreno Casbas.

RESEARCH AREA: CIBERFES.

TITLE: Determining and characterizing circulating nucleosomes with electrochemical biosensors assisted by magnetic supports and proteomic technologies.

AUTHORS: Sandra Tejerina-Miranda, Elisa Carral-Ibarra, Maria Gamella, Ana Montero-Calle, María Pedrero, José M. Pingarrón, Rodrigo Barderas, Susana Campuzano.

ABSTRACT: Nucleosomes are the fundamental chromatin units released during cell death and detectable in the bloodstream. They are now considered both as potential biomarkers for diagnosis, staging, prognosis and minimally invasive therapeutic monitoring of relevant diseases and as promising therapeutic targets.

This study reports the first multilevel approach combining results from labeled electroanalytical technologies with label-free quantitative proteomics to selectively capture, quantify, and characterize circulating nucleosomes, identifying characteristic nucleosome-associated proteins.

The electroanalytical immunotechnology developed, the first described for the determination of these biotargets, allowed the simple, sensitive and rapid detection of standards, efficiently discriminated against the metastatic potential of colorectal cancer (CRC) cell lines and evaluated the expression levels of the H3.1 nucleosome in plasma samples from healthy individuals and patients with advanced CRC, requiring small sample quantities and minimal treatment.

Furthermore, the analysis of isolated plasmatic nucleosomes using advanced proteomic techniques proved their specific isolation, clear differences in their circulating levels between healthy individuals and advanced CRC patients and allowed to identify ten extracellular proteins, four of them described in databases as prognostic factors in other cancers different from CRC.

These breakthrough findings, highlighting the potential of H3.1 nucleosomes and associated proteins as promising markers for CRC monitoring and prognosis in a minimally invasive way, invite further exploitation of the combination of bioelectroanalytical and proteomic technologies to advance in the determination and characterization of these biotargets also in other relevant scenarios including neuroinflammation, aging and neurodegeneration.

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SESSION: 2
POSTER#42

INTRODUCED BY: Marta Paredes-Barquero.

PRINCIPAL INVESTIGATOR: Jose Manuel Fuentes.

RESEARCH AREA: CIBERNED.

TITLE: Role of Autophagy in Mitochondrial Function.

AUTHORS: Javier Ojalvo-Pacheco, Eva Alegre-Cortés, Alberto Giménez-Bejarano, Mercedes Blanco-Benítez, Nerea Domínguez-Rojo, Enrique Carretero-Morán, Patricia Gómez-Suaga, Sokhna M.S. Yakhine-Diop, Rosa Ana González-Polo, José Manuel Fuentes, Mireia Niso-Santano.

ABSTRACT: Age-related diseases, such as neurodegenerative diseases, are a major health problem for an aging world population. Among the risk factors that can lead to neurodegeneration, aging has the greatest effect.

One of the hallmarks of such diseases is mitochondrial dysfunction. For this reason, cells possess multiple quality control mechanisms for the maintenance of cellular homeostasis, including autophagy and mitophagy, a specific type of autophagy responsible for eliminating damaged mitochondria.

One of the key challenges in the study of age-related diseases is the search for compounds whose activity promotes longevity and/or slows ageing and the onset of age-related diseases. Among those compounds we could find QBA, the major fatty acid from royal jelly, with diverse physiological and pharmacological properties and the ability to induce autophagy and increase longevity in various species.

We used different neuronal cell models and primary culture from an aging mouse model and analyzed the autophagy-induction by QBA using techniques such as Western-blot and fluorescence microscopy. In addition, we evaluated their impact on mitochondrial function by flow cytometry and Seahorse analysis.

Our results showed that QBA induced autophagy, had an impact on senescent cells and improved mitochondrial function in a mouse model of age-related disease.

These findings support the therapeutic potential of royal jelly fatty acid, making it a potential treatment for a wide range of diseases.

Age-related diseases; Autophagy; Mitochondria; QBA

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SESSION: 2
POSTER#43

INTRODUCED BY: José Luis Cantero.

PRINCIPAL INVESTIGATOR: Jose Luis Cantero.

RESEARCH AREA: CIBERNED.

TITLE: Characterization of age-related changes in human salivary extracellular vesicles.

AUTHORS: Lucia Reseco, Angela Molina-Crespo, Mercedes Atienza, Esperanza Gonzalez, Juan Manuel Falcon-Perez, Jose Luis Cantero.

ABSTRACT: Introduction. Salivary extracellular vesicles (EVs) represent an attractive source of biomarkers due to the accessibility of saliva and its non-invasive sampling methods. However, the lack of comparative studies assessing the efficacy of different EV isolation techniques hampers the use of salivary EVs in clinical settings. Moreover, the effects of age on salivary EVs are largely unknown, hindering the identification of salivary EV-associated biomarkers across the lifespan.

Materials and Methods. We compared salivary EV concentration, size mode, protein concentration, and purity using eight EV isolation techniques, before and after magnetic bead immunocapture using antibodies against CD9, CD63, and CD81. The effects of age on salivary EVs obtained with each isolation technique were further investigated.

Results. We showed higher expression of CD63 on isolated salivary EVs compared to the expression of CD81 and flotillin-1. Overall, magnetic bead immunocapture was more efficient in recovering salivary EVs with Norgen's Saliva Exosome Purification Kit and ExoQuick-TC ULTRA at the cost of EV yield. Regardless of age, Invitrogen Total Exosome Isolation Solution showed the highest level of protein concentration, whereas Izon qEVOriginal-70nm columns revealed the highest purity.

Conclusions. This study provides the first comprehensive comparison of salivary EVs in younger and older adults using different EV isolation techniques, which represent a step forward for assessing salivary EVs as a source of potential biomarkers of tissue-specific diseases throughout the life cycle.

SESSION: 2
POSTER#44

INTRODUCED BY: Anna Vázquez-Oliver.

PRINCIPAL INVESTIGATOR: Jaime Kulisevsky.

RESEARCH AREA: CIBERNED.

TITLE: Alix as a potential biomarker for disease progression in Huntington's disease.

AUTHORS: Anna Vázquez-Oliver, Nil Salvat-Rovira, Elisa Rivas-Asensio, Saül Martínez-Horta, Jesús Pérez-Pérez, Rocío Pérez-González, Jaime Kulisevsky.

ABSTRACT: Background: Impairment of the endosomal/lysosomal system is present in HD. Indeed, we previously described reduced levels of Alix, a protein associated with this system and neuronal death, in postmortem HD brains.

Aims: Here, we investigated whether alterations in Alix protein levels could be detected in cerebrospinal fluid (CSF) of HD mutation carriers, potentially serving as a novel disease biomarker.

Methods: In a cross-sectional study, we analyzed CSF from HD mutation carriers and controls. Alix was measured by ELISA, displaying linearity (37–530 pg/mL) and low intra- and interplate coefficients of variation (5%).

Results: Our data show reduced Alix expression in CSF from presymptomatic HD mutation carriers, with increased levels in symptomatic individuals. Given that our data in the brain mirrored the decrease of Alix seen in premanifest individuals, correlations were firstly performed considering only this subgroup of HD carriers. Notably, Alix positively correlated with striatal volume ($r=0.45$, $p<0.05$). Subsequently, we examined the entire cohort collectively. Alix expression inversely correlated with CAG age product ($r=0.43$, $p<0.01$), indicating a close association with disease progression. Furthermore, Alix expression correlated with standardized clinical scales for HD, including the composite Unified Huntington's Disease Rating Scale ($r=-0.38$, $p<0.05$). Correlations were also observed between Alix and CSF biomarkers of neuronal cell damage, including tau ($r=0.62$, $p<0.001$) and neurofilament light chain ($r=0.40$, $p<0.01$).

Conclusions: Our findings suggest Alix as a potential peripheral biomarker for HD progression, warranting further exploration into its roles in HD pathogenesis.

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SESSION: 2
POSTER#45

INTRODUCED BY: María Isabel Orts-Cortés.

PRINCIPAL INVESTIGATOR: Teresa Moreno Casbas.

RESEARCH AREA: CIBERFES.

TITLE: Risk, Diagnosis, and Clinical Management of Dysphagia in Hospitalized Older Patients.

AUTHORS : María Isabel Orts Cortés , Cristina Carretero -Randez , Rafaela Camacho - Bejarano , Joan Blanco - Blanco , Marco Aldonza -Torres , Felipe Rodríguez de Castro , Ángel Luis Abad -González , Laura Meseguer -Galiana , Paloma Portillo -Ortega , Mª José Morano-Torrescusa, on behalf of the NUTRIFAG Study Group .

ABSTRACT:

Introduction: Dysphagia is common among hospitalised older adults and is associated with complications such as malnutrition, pneumonia, and prolonged hospital stays. Early identification through screening and clinical evaluation, along with interdisciplinary interventions, is essential for effective management.

Aim: To describe the prevalence of dysphagia in hospitalised older adults and analyse the association between early identification —via screening and clinical diagnosis—and the implementation of healthcare interventions during admission.

Materials and Methods: A multicentre, observational, cross-sectional study was conducted between 2022 and 2024 as part of the NUTRIFAG Project, across nine public hospitals in Spain. Patients aged ≥65 years admitted to medical or surgical units were included. Dysphagia risk was assessed using EAT-10 at admission. Clinical diagnosis was made using the MECV-V protocol in patients who screened positive. Sociodemographic, functional, and clinical data and interventions applied during admission were collected.

Results: A total of 3,139 patients were included (51.5% male), with a mean age of 79.3 years. Risk of dysphagia was detected in 16.0% of patients. Among those evaluated with MECV-V, 69.7% were clinically diagnosed. Risk or confirmed diagnosis was associated with significantly higher implementation of interventions ($p < 0.001$), particularly speech therapy referral, dietary adjustments, nursing actions, thickened fluids, postural strategies, and oral hygiene adaptations.

Conclusions: Dysphagia is highly prevalent among hospitalised older adults. Screening and clinical diagnosis both contribute to the greater implementation of essential interventions. Integrating both approaches may optimise care and improve patient safety and outcomes.

SESSION: 2
POSTER#46

INTRODUCED BY: Javier Sáez-Valero.

PRINCIPAL INVESTIGATOR: Javiez Saez Valero.

RESEARCH AREA: CIBERNED.

TITLE: Plasma ADAM17, ADAM10 and TMPRSS2 resulted increased during SARS-CoV-2 infection.

AUTHORS: Jorge Sáez-Leyva, Juan García-Arriaza, María-Salud García-Ayllón, Javier Sáez-Valero.

ABSTRACT: The SARS-CoV-2 coronavirus infects human cells through the cellular receptor angiotensin-converting enzyme 2 (ACE2), and the serine protease TMPRSS2 for the priming of viral spike (S) protein. ACE2 acts as a transmembrane receptor and results also cleaved during viral penetration. The main proteases that cleave ACE2 in non-infected subjects are the members of the membrane-bound disintegrin metalloproteinase family, ADAM17 and ADAM10 whereas TMPRSS2 can compete with the metalloprotease ADAM17 for ACE2 processing. It has been proposed that ACE2 cleavage augments viral infectivity. However, the relevance of protease activation during acute COVID-19 has not yet been determined. In this study, we have addressed whether ADAM17, ADAM10 and TMPRSS2 plasma levels are altered in severe and moderate COVID-19 cases from the first wave of the pandemic. We used electrophoresis and western blotting for the individual quantification of active species of the proteases that co-exist in circulation with non-active species. We further examined their levels in the serum of a transgenic K18-hACE2 mice challenged with a lethal dose of SARS-CoV-2. In both, COVID-19 patients and K18-hACE2 infected mice, we observed an increase in the levels of ACE2 fragments, as well of the overall levels of the three examined proteases. However, when we consider the levels of the active species of the proteases, ADAM17 and ADAM10 resulted increased, while TMPRSS2 protease fragment not paralleled the increase in the zymogen form. These findings highlight the role of ADAM17 during SARS-CoV-2 infection, which can be of relevance for development of therapy strategies to attenuate disease progression.

SESSION: 2
POSTER#47

INTRODUCED BY: Blanca Salgado .

PRINCIPAL INVESTIGATOR: María Jesús Bullido Gómez-Heras.

RESEARCH AREA: CIBERNED.

TITLE: Two- and three-dimensional neuronal models to assess the mechanisms linking HSV-1 infection with Alzheimer's disease pathogenesis. .

AUTHORS: Blanca Salgado , María Martín, Isabel Sastre, Isabel Olmedo, María J. Bullido, Jesús Aldudo.

ABSTRACT: Introduction. Neurotropic viral infections, such as the one induced by herpes simplex virus type I (HSV-1), have been proposed to contribute to neurodegeneration and neuroinflammation, thus playing a role as environmental risk factors for Alzheimer's disease (AD). However, the molecular mechanisms underlying this likely connection between viral infection and neurodegeneration are not completely understood. Considering the drawbacks of current disease models and the limited transferability of experimental results, developing new study platforms that better resemble the complexity of the human brain is a pressing concern.

Materials and methods. We have been working with different lines of human neural stem cells, ReNcells VM and LUHMES, to establish two- and three-dimensional neuronal models of HSV-1 infection and keep exploring the links between viral infection and AD-like neurodegeneration. These cells are able to differentiate into neurons and, in the case of ReN cells, astrocytes.

Results. We have been able to develop Matrigel with embedded cells cultures as well as spheroid-like structures that are susceptible to HSV-1 and reproduce certain features observed in neuroblastoma cultures upon infection, which include beta-amyloid and tau pathology, as well as lysosomal alterations. By increasing the complexity of our in vitro models, we aim to develop more physiologically relevant tools that could serve to explore alternative pathways, e.g. cholesterol homeostasis, that might participate in the crossroad between viral infection and neurodegeneration.

Conclusions. These platforms could contribute to better understand AD pathogenesis as well as to identify potential targets to prevent or delay the onset of such a devastating disease.

SESSION: 2
POSTER#48

INTRODUCED BY: Gerard Roch Alba.

PRINCIPAL INVESTIGATOR: Miquel Vila.

RESEARCH AREA: CIBERNED.

TITLE: MODULATION OF MICROGLIAL PHENOTYPE WITH IVERMECTIN ATTENUATES NEUROMELANIN-LINKED PARKINSON PATHOLOGY.

AUTHORS: Joan Compte Barron, Marta Gonzalez Sepulveda, Thais Cuadros, Joana M Cladera-Sastre, Annabelle Parent, Carlos Matute, Jordi Bove Badell, Miquel Vila Bover.

ABSTRACT: Introduction: Activation of both innate and adaptive immune responses occurs in Parkinson's disease (PD) postmortem brains. PD-linked inflammatory changes are highly localized within neuromelanin (NM)-containing brain areas, in which extracellular NM released from dying neurons is surrounded by or in contact with activated microglia. However, whether the NM-linked immune response contributes to the neurodegenerative process remains unknown, partly because in contrast to humans NM is absent in common experimental animals such as rodents. To address this, our group developed a novel NM-producing PD rodent model based on the overexpression of melanin-producing enzyme tyrosinase (TYR). On the other hand, treatment with Ivermectin (IVM), an allosteric activator of the P2X4 receptor, which has crucial functions in inflammatory modulation, has been shown to have an ameliorating effect on an autoimmune encephalitis model.

Materials & Methods: In this project, we injected IVM to our NM-accumulating rats and assessed both nigrostriatal dopaminergic loss and the inflammatory response in the substantia nigra (SN). Using immunohistochemical markers such as Tyrosine Hydroxylase (TH), IBA1 and CD68, we were able to demonstrate not only that a strong innate response occurs in the presence of NM, but also that IVM treatment reduced inflammatory markers and ameliorated dopaminergic loss. Additionally, AI-powered algorithms allowed us to observe a morphological change in the microglial population of IVM-treated animals suggestive of a switch from a pro-inflammatory to an anti-inflammatory profile.

Conclusions: overall, our results shed light on the NM-linked immune response and highlights the therapeutic potential of inflammatory modulators in the context of PD.