SESSION IV
PERIPHERAL SYSTEM AND GUT

A PRECLINICAL STUDY ON THE MODULATION OF THE MICROBIOTA–GUT–BRAIN AXIS BY A FUNCTIONAL SNACK PROMOTING HEALTHY AGING

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Clinical and preclinical studies increasingly report alterations in gut microbial composition and reduced microbial diversity in patients with Alzheimer's disease (AD), suggesting the gut ecosystem may influence disease onset and progression. Preclinical studies in transgenic AD mouse models indicate that gut dysbiosis could be correlated with impaired intestinal barrier function, local deposition of amyloid-β (Aβ) in the gastrointestinal tract, and regional and systemic inflammatory changes. These alterations have been proposed to accelerate central Aβ accumulation and neuroinflammation through immune and metabolic pathways. Together, these findings support a model in which gut microbiota and mucosal barrier modulation contribute to reinforce the cascade that may promote neuropathology in AD. However, although causal links in humans remain to be fully established. A novel engineered health-promoting cookie formulated with red lentil prebiotics and coated in multi-strain probiotic (SLAB51®)-fortified chocolate was tested in 3xTg-AD mice. At eight weeks of age, mice were divided into experimental groups and subjected to a four-month supplementation protocol. The groups received a functional cookie containing the prebiotic and probiotic formulation, a prebiotic cookie without SLAB51®, a standard recipe cookie, or SLAB51® administered in drinking water. The possible effects on intestinal mucosa morphology, secretion and integrity, neuroplasticity in the enteric and central nervous system, and neuroinflammation were evaluated with biochemical and immunohistochemical approaches. Experimental groups receiving the functional snack exhibited well-preserved intestinal wall architecture and a restoration of epithelial homeostasis. These effects were associated with enhanced mucus layer stability and improved barrier integrity, linked by attenuated pro-inflammatory microenvironment consequent to the decrease in enteric glial cells activation. Furthermore, the intake of this symbiotic formulation preserved cognitive function and was associated with decreased amyloid load, oxidative stress, gliosis, and neuroinflammation in brain areas including the hippocampal region. This symbiotic formulation represents a novel dietary vehicle that may provide a nutritional approach to mitigate AD–related microbiota–gut–brain axis disturbances and promote healthy aging.

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SENSORY NEURON TOXICITY TRIGGERED BY ANTICANCER DRUGS IS COUNTERACTED BY EXTRACELLULAR VESICLES DERIVED FROM ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

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Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent and disabling adverse effect of several anticancer drugs, characterized by paraesthesia, numbness, and dysesthesia, often leading to dose reduction or therapy discontinuation. Despite extensive research, no neuroprotective strategy has yet demonstrated definitive clinical efficacy. However, *in vitro* evidence suggests the therapeutic potential of Adipose-derived mesenchymal Stem Cell Extracellular Vesicles (ASC-EVs). EVs function as key mediators of intercellular communication, transporting proteins, RNAs, and lipids, and ASC-EVs in particular have been implicated in cellular repair mechanisms. In this study, we employed primary cultures of dorsal root ganglion (DRG) neurons isolated from rat embryos, a well-established model for investigating neurotoxicity, neuroprotection, and post-mitotic neuronal development. We specifically investigated the effects of two clinically relevant chemotherapeutic agents – cisplatin (CDDP, 6 μM) and bortezomib (BTZ, 20 nM) – administered either alone or in combination with a single dose of extracellular vesicles (EVs) for 24 and 48 h. Neuronal viability was assessed by a cellular count at bright-field microscopy, quantifying live cells based on the presence of a birefringent outline. Treatment with CDDP resulted in a pronounced and time-dependent decline in neuronal viability at both 24 and 48 h. Co-administration with ASC-EVs significantly mitigated this effect, indicating a strong neuroprotective action. In contrast, BTZ induced a distinct neurotoxic profile, characterized by milder alterations at earlier time points – likely reflecting differences in its mechanisms of action compared with CDDP. Despite these differences, ASC-EVs were also able to counteract BTZ-induced toxicity, further reinforcing their neuroprotective potential. Collectively, these results indicate that the neuroprotective efficacy of ASC-EVs is influenced by both the pharmacological properties of the chemotherapeutic agent and the duration of exposure, suggesting a dynamic, time-dependent interplay between EV- mediated mechanisms and drug-induced neuronal stress. The observed protection is plausibly linked to the modulation of oxidative stress and apoptotic pathways, which are currently being explored. Future investigations will aim to identify the specific molecular mechanism within ASC-EVs responsible for mediating these neuroprotective effects.