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ABSTRACTS

# Abstracts for the Latin American Glia Club Workshop: Paving the Way for Glial Cells Function

## SYMPOSIA

## OLIGODENDROCYTES SYMPOSIUM

### Intranasal Administration of Transferrin-Loaded Extracellular Vesicles Enhances Remyelination

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Extracellular vesicles (EVs) are key mediators of intercellular communication with advantages such as low immunogenicity and efficient cellular uptake. Oligodendrocytes (OLs), the myelinating glial cells of the central nervous system (CNS), are impaired in demyelinating diseases like multiple sclerosis. Transferrin (Tf), a glycoprotein involved in iron homeostasis, promotes OL differentiation and remyelination. Here, we evaluated EVs as carriers of Tf to the CNS via the intranasal (IN) route, a non-invasive strategy for brain delivery. EVs were isolated from plasma (human, rat, mouse), cell lines (N2a, OLN-93), and primary astrocyte cultures using size-exclusion chromatography or ultracentrifugation. Characterization confirmed EV identity (CD63, Alix) and exclusion of contaminants. Tf loading was achieved by passive incubation with plasma-derived EVs, demonstrating a specific interaction mediated by the Tf receptor (TfR1). In vitro, Tf-loaded EVs (EVTf) were efficiently internalized by oligodendroglial precursor cells, promoting their differentiation. EVTf uptake was primarily clathrin- and lipid raft-dependent, with Tf trafficking to recycling endosomes while EVs accumulated in lysosomes. In vivo, intranasal administration of EVTf enhanced oligodendroglial maturation during developmental myelination and significantly promoted remyelination in a cuprizone-induced demyelination model, as confirmed by immunohistochemistry and electron microscopy. Notably, free Tf administration did not replicate these effects, highlighting the advantage of EV-mediated delivery. Furthermore, EVTf reached the brain parenchyma and were internalized by microglia and astrocytes. These findings support EVs as a promising Tf delivery system via the intranasal route, offering a potential therapeutic approach for demyelinating diseases.

### Circulating Platelets During Myelin Repair in Multiple Sclerosis—Friend or Foe?

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Multiple sclerosis (MS) is an autoimmune neuroinflammatory demyelinating disease of the central nervous system (CNS) that affects more than 2.5 million people worldwide. Remyelination represents a robust regenerative response to myelin damage; however, during the later stages of MS, this process largely fails. Upon demyelination, oligodendrocyte progenitor cells (OPCs) proliferate, migrate, and differentiate into mature remyelinating oligodendrocytes. Why does remyelination fail in MS? Platelets, also known as thrombocytes, are small, oval, anucleate cells that circulate in the bloodstream and form a haemostatic plug to stop blood leakage upon endothelial damage. Platelet function is not restricted to haemostasis; they also display tissue-regenerative activities. Indeed, platelets contain large quantities of growth factors that promote OPC survival, proliferation, and recruitment. These observations suggest that circulating platelets may directly and/or indirectly modulate OPC function and contribute to remyelination. However, different studies suggest a detrimental role of platelets during MS. For example, circulating platelets in MS patients are in a hyper-reactive state, displaying increased adhesiveness and correlating with clinical severity. MS patients show increased numbers of blood-resident platelet microparticles, which further increase after clinical exacerbations. Moreover, platelets and platelet-contained molecules have been found in human chronic non-remyelinated MS lesions. In this talk, I will present data demonstrating the complex role of platelets in remyelination and discuss its consequences for MS.

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## Astrocytes Preserve the Inflammation/Resolution balance in a Cellular Neurotoxicity Paradigm

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The inflammation/resolution balance is a key factor for preventing neuroinflammation associated with Central Nervous System degenerative disorders. After neuronal injury, glial cells act as key regulators of inflammatory/anti-inflammatory homeostasis. We have recently reported that environmental neurotoxicants, such as the pesticide maneb, trigger dopaminergic neuronal death by ferroptosis. However, how glial cells respond to the pesticide has not been deeply investigated. In this work, our goal was to study biochemical signals associated with inflammation/resolution balance in glial cells. To this end, astrocytic cell lines, glial primary cultures, and secretomes from neuronal cells exposed to the neurotoxicant were used to untangle biochemical events associated with glial resolution. Astrocytes and primary glial cultures exposed to the pesticide showed increased glial fibrillary acidic protein (GFAP) expression, Nuclear Factor Kappa B (NFkB) nuclear translocation, and ciclooxigenase-2 (COX-2) expression. In the case of mixed cultures, microglia with increased Ionized calcium-binding adapter molecule 1 (IBA-1) and decreased Arginase-1 (Arg-1) expression were also detected. In this pro-inflammatory scenario, glial viability was slightly affected by the pesticide, and astrocytes were able to rescue neurons from pesticide-induced death. Regarding resolution pathways, the production of specialized pro-resolving lipid mediators is catalyzed by the concatenated metabolization of polyunsaturated fatty acids by phospholipases A2 (PLA2), lipoxygenases (ALOX), and cytochrome oxidases (CYP). When key components of lipid-mediated resolution pathways such as sPLA2, ALOX-15, and CYP450 were blocked, we found a detrimental effect on astrocyte survival. In addition, the secretome of maned-exposed neurons was able to upregulate ALOX-15 expression and promote a proliferative phenotype in astrocytes. The neuronal proliferative effect on astrocytes was also found to be dependent on ALOX-15 and CYP450 activity. Altogether, our results suggest that the inflammation/resolution balance operates under mild injury conditions, attenuating astrocyte injury and promoting a neuroprotective phenotype.

## GABAergic Communication and Ammonia Metabolism Are Altered in the Streptozotocin-Induced Sporadic Alzheimer's Disease Model

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In the sporadic model of Alzheimer's disease (AD), induced by intracerebroventricular streptozotocin (STZ) administration, cognitive impairment is accompanied by specific astrocytic changes in the hippocampus prior to amyloid deposition. Hypothesizing that the synthesis of GABA, via MAO-B, contributes to ammonia elevation, thereby compromising antioxidant defense and ATP synthesis, and possibly contributing to cognitive damage, we determined the hippocampal levels of glutamine synthetase (GS), monoamine oxidase B (MAO-B) and other enzymes related to GABA metabolism (immunoblotting and RT-qPCR assays), at 4 and 16 weeks post-STZ, in the sporadic STZ-induced AD model (forty-eight male Wistar rats, 90 days old, Ethics Committee for the Use of Animals approval 37872), corresponding to the pre-amyloid and amyloid phases, respectively. Data were statistically analyzed using Student's *t*-test ($p < 0.05$ was considered significant). We observed a reduction in GS activity and increased MAO-B content, even from the pre-amyloid phase, which was maintained during the amyloid phase, reinforcing the idea that astroglial dysfunction precedes the amyloid phase. These alterations were accompanied by an increase in the content of ornithine decarboxylase 1 (ODC1), which catalyzes the synthesis of putrescine (substrate for GABA synthesis, via MAO-B), and a reduction in the gene expression of arginine-glycine amidinotransferase (AGAT), an enzyme involved in the synthesis of creatine, and in the generation of GABA agonists. These changes were only seen in the amyloid phase of the AD model. Our findings contribute to explain the greater damage that occurs in energy metabolism at this stage, in addition to the greater GABAergic loss. The changes observed reinforce the importance of the intracerebroventricular STZ-administration model of AD and further our understanding of the changes in AD during both phases of the disease.

## Aging-Related Morphological and Molecular Changes in Astrocyte-Blood Vessel Interactions

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Astrocytes cover about 99% of the cerebrovascular surface through highly specialized perivascular endfeet. This interaction is crucial for maintaining blood-brain barrier integrity and the homeostatic functions of astrocytes. Although disruptions of this unit are observed in various age-related neurodegenerative diseases, little is known about their role in the physiological aging. Here, we investigated morphological and molecular changes in the interactions between astrocytes and brain endothelial cells during aging. To do this, we used hippocampal tissue from young (2–3 months) and aged (18–24 months) C57BL/6 mice and post-mortem human hippocampal tissue from middle-aged and elderly donors. We also employed an in vitro model of astrocyte senescence long-term cultures (30–35 DIV) or control cultures (7–10 DIV). We found a decrease in the expression of agrin, laminin α2, and dystrophin in the aged hippocampus, genes associated with the dystrophin-glycan complex, which anchors the astrocytic cytoskeleton to the blood vessels extracellular matrix. Supporting this, we observed an aberrant



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