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Renal function declines progressively with age, and EMT -a process in which cells lose their epithelial phenotype and acquire the characteristics of the mesenchymal cells- has been suggested as a mechanism that drives renal fibrosis, with the consequent loss of tissue functions. In previous works, we demonstrated that the inhibition of sphingomyelin (SM) synthase 1, induces an EMT process in collecting duct (CD) cells from renal papilla of young rats (70 days-old). We also demonstrated that the EMT occurs spontaneously in renal papillary CD cells of middle-aged (8 months) and aged-rats (15 months), denoted by an impairment of cell-cell adhesion, a higher number of CD cells expressing the mesenchymal protein vimentin, and the *de novo* synthesis of α-smooth muscle actin (α-SMA), another mesenchymal biomarker. These results motivated us to study the implication of SM metabolism in the occurrence of EMT in renal papilla CD cells during aging. To analyze the SM content, CD were isolated from renal papilla and dried lipid extracts were separated by TLC. Different concentrations of a SM standard (C12-SM) were used to calculate the SM amount. The quantitative analysis showed a decrease in SM content in CD cells isolated from renal papilla of middle- and aged-rats. Taking into account that cells in culture behave as in intact tissue, primary cultures of CD cells isolated from renal papilla of young, middle-aged and aged-rats were performed. We evaluated the expression of SMS1 mRNA by qRT-PCR in cultured CD cells. Contrary to what we expected, significant increase in SMS1 mRNA was found in aged-rats. So, the decrease in the amount of SM in CD from older rats was not due to a decrease in SMS1 expression. To evaluate the activity of the enzymes responsible for the SM synthesis, CD cells were incubated in the presence of C6-NBD-ceramide at 37ºC for 1 h to determine total SMS activity, quantifying the amount of NBD-SM converted from NBD-ceramide. The SM fluorescence intensity of the sample extracted from middle-age rats was lower than that extracted from young rats denoting a decrease in SMS activity in older rats. In order to analyze whether the decrease in the amount of SM was due to an increase in its degradation, we evaluated the activity of sphingomyelinases (SMase), which catalyzes the hydrolysis of SM to ceramide. We used as inhibitor of acid SMase (aSMase) amitriptyline and, as inhibitor of neutral SMase (nSMase) GW4869, and we evaluated the percentage of CD cells that expressed α-SMA. We observed that the treatment with the nSMase inhibitor, but not with the aSMase inhibitor, significantly reduced α-SMA expression in CD cells in older rats. So, the decrease in SM content observed in CD cells during aging may be due to a combination of a decreased SMS activity and an increase in SM degradation mediated by nSMase. Altogether, we propose that the sphingolipid metabolism play a central role as a modulator of the fate of renal papilla CD cells during aging.

LI-C02-23

EFFECT OF PHOSPHATIDYLCHOLINE ON NEURONAL PLASTICITY OF NEURAL STEM CELLS UNDER INFLAMMATORY CONDITIONS

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The balances between neural stem cells (NSCs) growth and differentiation, and between glial and neuronal differentiation play a key role for brain regeneration after any pathological conditions. It is well known that the nervous tissue shows a poor recovery after injury due to the factors present in the wounded microenvironment, particularly inflammatory factors, that prevent neuronal differentiation. Thus, it is essential to generate a favourable condition for NSCs and conduct them to differentiate towards functional neurons. We have previously demonstrated that phosphatidylcholine (PtdCho) regulates the fate of NSCs by inducing neurogenesis. Therefore, we hypothesized that the supply of PtdCho would improve the neuronal plasticity of NSCs under inflammatory stress. We utilized the Raw 264.7 mouse macrophages cell line activated with lipopolysaccharide (LPS) to generate an activated media containing interleukins (ILs) and tumor Necrosis Factor (TNF-α) (activated media) or cells without activation as a control. NSCs were incubated with these media in the presence or in the absence of PtdCho. Here, we show that neuroinflammation induces an aberrant neuronal differentiation that gives rise to dystrophic, non-functional neurons. This is perhaps the initial step of brain failure associate to many neurological disorders. Interestingly, we demonstrate that PtdCho-enriched media enhances neuronal differentiation even under inflammatory stress by modifying the commitment of post-mitotic cells. A detailed morphometric analysis showed that the size of the soma was restored in the presence of PtdCho, in turn increased the phenotypically normal neurons and restored synaptic defect caused by neuroinflammation. In addition, we provide evidences that this phospholipid ameliorates the damage of neurons and, in consequence, modulates neuronal plasticity. These results contribute to our understanding of NSCs behaviour under inflammatory conditions, opening up new venues to improve neurogenic capacity in the brain.

LI-C03-45

EX VIVO PROGRESSION OF SPERMATOGENESIS ENTAILS ACCRETION OF LIPIDS WITH LONG AND VERY-LONG-CHAIN POLYENOIC FATTY ACIDS

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Spermatogenesis can proceed *ex vivo* in neonatal mouse testes using a gas-liquid interphase culture system. Previously we observed both *in vivo* and *ex vivo*, a relationship between the progression of spermatogenesis (at cytological and histological

level) and the gene expression of some of the enzymes involved in fatty acid and lipid biosynthesis. The aim of this study was to survey whether the same developmental changes that occur *in vivo* in the testicular lipids that contain long-chain (C18-C22) and very-long-chain (C24-C32) polyunsaturated fatty acids (PUFA) are present in neonatal testis explants kept in culture. Testis explants from 6-day old mice cultured for 22 days evidenced a progress in spermatogenesis beyond the meiotic phase in some of the tubules. The appearance of haploid germ cells concurred with an increase in the expression of *Fabp9*, *Dgat2* and *Fa2h*. Notably, genes involved in PUFA biosynthesis (*Elovl2, Elovl4, Fads2*) were up-regulated in the testicular explants in comparison with the *in vivo* situation. Interestingly, during the period in culture the tissue accumulated triacylglycerides (TAG), triglycerides with an ether bond (TEB) and cholesterol esters (CE) and, like *in vivo*, this was associated with *perilipin 2* (*Plin*2) up-regulation. Concomitantly, although to a lesser extent than *in vivo*, the proportion of major C_{22} PUFAs (22:5n-6, 22:5n-3 and 22:6n-3) increased in the glycerophospholipids (GPL) of explants. Like *in vivo*, the 22:5n-6/20:4n-6 ratio increased with *ex vivo* development, and 22:5n-6 was the major PUFA of total testicular lipid after 22 days of culture. Interestingly, the explants accumulated n-9 PUFAs in GPL, CE and TEB (*e.g.*, 20:3n-9, 22:3n-9 and 22:4n-9), while *in vivo* these PUFAs were negligible at all postnatal ages. Finally, we observed that the biosynthesis of ceramides (Cer) was activated in the explants in culture. Notoriously, traces of germ cells-specific molecular species of Cer with 28:4n-6 and 30:5n-6 were detected. The data are consistent with specific PUFA elongation and desaturation being activated during *ex vivo* germ cell differentiation, and highlight that influences that promote the biosynthesis of PUFA-containing lipids should be considered to optimize *ex vivo* spermatogenesis. *Supported by SGCyT UNS-PGI-UNS [24/B272 to GMO], FONCyT, [PICT2017-2535 to GMO]*.

LI-C04-59

CYCLOOXYGENASES AND LIPOXYGENASES: KEY PLAYERS IN THE NEURONAL RESPONSE TO MANEB TOXICITY

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Maneb (MB) is a widely used fungicide for plague control in a variety of crops. The prolonged use causes human toxicity, especially in the Central Nervous System, and it is considered an environmental risk factor for Parkinson's disease. However, the mechanisms underlying pesticide neurotoxicity are not completely elucidated. Based on this, we studied the effect of MB toxicity on lipid mediators' pathways in dopaminergic neurons (N27 cell line) as well as in glial cells (C6 astrocytes cell line). MB treatment affected neuronal and glial viability in a time- and concentration-dependent manner. To characterize the cellular response to MB, we analyzed the expression and subcellular localization of the transcription factor NF-κB and its downstream gene cyclooxygenase-2 (COX-2). The increased expression and nuclear translocation of NF-κB p50 subunit was associated with a rise in COX-2 levels in MB-exposed neurons. Astrocytes treated with MB showed increased GFAP, NF-κB p50 and COX-2 expression, indicative markers of glial activation. Interestingly, MB only triggered the nuclear translocation of COX-2 in neurons. To further elucidate the role of COX-2 in MB toxicity, cells were treated with pharmacological and suicidal enzymatic inhibitors, celecoxib and acetylsalicylic acid (ASA), respectively. Neurons incubated with celecoxib were more sensitive than astrocytes to MB exposure. Surprisingly, COX-2 acetylation by ASA turned neurons and astrocytes more vulnerable to MB toxicity. Given that COX-2 acetylation not only inhibits prostaglandin synthesis but also enhances the production of specialized pro-resolving lipid mediators (SPMs), these findings indicate that, probably, prostaglandins derived from arachidonic acid are protective against MB toxicity and ASA-triggered lipid mediator pathways might be involved as promoters of pesticide-induced neuronal injury. To shed light on the interplay between prostaglandins and SPMs producing pathways, the effect of cytochrome P450 and lipoxygenase-15 (LOX-15) inhibition was also evaluated. The inhibition of both pathways separately enhanced MB toxicity and this effect was potentiated by ASA treatment. To investigate neuron-glia crosstalk during MB toxicity, N27 cells were incubated with C6 secretome and *vice versa*. Astrocytes secretome showed to be protective for neurons challenged with MB. In addition, neurons secreted glial proliferative factors after MB exposure. Our results demonstrate the interplay among COX-2, LOX-15 and cytochrome P450 in SPMs production during MB exposure. Moreover, cell type-specific responses are indicative of particular roles of neurons and glia in the protective mechanisms against pesticide toxicity.

LI-C05-85

NUCLEAR CARBOXYLESTERASE IS A LIPASE INVOLVED IN LIPID-DROPLETS HOMEOSTASIS

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In eukaryotic cells under normal conditions, hydrophobic lipids (triacylglycerol: TAG; cholesterol-ester: CE; cholesterol: C) are stored and organized as Lipid Droplets (LD). LD are mainly located in the cytosol (cLD), and within the nucleus we have already identified a small LD population (nLD). nLD consists of a hydrophobic TAG-CE-C core enriched in oleic acid surrounded by a monolayer of polar lipids, cholesterol, and proteins. nLD are probably involved in nuclear-lipid homeostasis