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MIR-33 ALTERS CHOLESTEROL TRANSPORT BETWEEN ASTROCYTES AND NEURONS IN AGING.

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The brain is the most cholesterol-rich organ in the human body, containing about 25% of the body's total cholesterol. In neurons, cholesterol has been shown to play a critical role in neurite growth, synaptogenesis, and the proper function of pre and post-synaptic compartments. Thus, the cholesterol homeostasis has to be tightly regulated in the brain in order to avoid potential imbalances which will have severe consequences to brain performance.
Previous reports from our laboratory indicate that the decrease in neuronal cholesterol levels in aging would be related to the development of cognitive problems. Due to the incapacity of cholesterol to cross the blood-brain barrier, the brain cholesterol homeostasis is strictly controlled through synthesis *de novo*, mainly carried out by glial cells. Mature neurons depend mainly of cholesterol synthesized by astrocytes, which is imported in the form of ApoE-Cholesterol complexes. Once endocytosed, the cholesterol is released from the endolysosomal system by the cooperative action of the Niemann-Pick Type C proteins 1 and 2 (NPC1 and NPC2), which allow the incorporation of this lipid into the intracellular pool.
In this work we show that aging results in increased miR33 which triggers a Niemann Pick phenotype in senescent astrocytes which accumulate cholesterol in lysosomal compartments. Furthermore using astrocyte-neuron cocultures we found that the cholesterol delivery from astrocytes to neurons is also impaired in astrocytes aged in vitro. Interestingly, cholesterol accumulation in aged astrocytes could be alleviated by endocannabinoid treatment. We believe that understanding these mechanisms will allow the identification of new targets for therapies or prevention of central nervous system pathologies associated with aging.

LI-09

OXIDATIVE STRESS AND LIPOLYSIS: NEW INSIGHTS IN FAT METABOLISM

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Prolonged oxidative stress (OS) directly affects fat metabolism, with implications in the onset of obesity, insulin resistance, and type 2 diabetes. Particularly in adipocytes, it is well known that OS participates in several mechanisms related with proliferation and differentiation. Our aim was to study the signaling events underlying lipolysis triggered by OS. For this purpose, we worked with different adipocyte in vitro cultures (differentiated 3T3L1 and mesenchymal stem cells) and with an in vivo model, all subjected to iron-induced OS.
3T3L1 adipocytes challenged with ferric ammonium citrate (FAC, 500-1000 µM) displayed augmented lipid peroxides and membrane permeability when compared with non-treated cells. The increase in OS markers observed in 3T3L1 adipocytes was coincident with a rise in glycerol release to the medium. These results were also corroborated in the in vivo model, where a decreased neutral lipid content in gonadal adipose tissue of iron-treated mice was observed. In addition, iron-treated animals presented a different architecture of gonadal fat characterized by cell shrinkage, decreased volume tissue, and fibrosis.
Lipolysis in the white adipose tissue of humans and rodents is a step-wise process regulated by adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase. Exacerbated lipolysis was accompanied by the upregulation of β-catenin expression in 3T3L1 and in gonadal adipocytes. To ascertain the role of this signaling pathway in OS-induced lipolysis, we worked with adipocytes differentiated from primary mesenchymal stem cells with wild type expression or deletion of β-catenin gene. To this end, stem cells were isolated from outer ears of β-catenin fl/fl mice and after differentiation to adipocytes, gene deletion was induced with adenoviral Cre recombinase. The expression of the lipolytic enzymes, *ATGL* and *HSL*, was evaluated by qRT-PCR in wild type and β-catenin knock out (β-catenin KO) adipocytes exposed to vehicle or FAC. In wild type adipocytes, iron exposure increased *ATGL* and *HSL* mRNA levels, whereas lipolytic enzyme expression remained unchanged in β-catenin KO cells. Our results demonstrate that iron-induced OS is able to activate lipolysis through a mechanism involving the β-catenin pathway in fat cells.