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"Microglia conversion M1 to M2 by DHA derivatives in Models of Parkinson's Disease"

Parkinson's disease (PD) is a neurodegenerative disorder that affects the dopaminergic neurons in the substantia nigra. Due to the function of several genes which mutations are cause of genetic inherited PD, inflammation and phagocytosis are key processes to understand its pathology and progression. Microglia, the resident macrophage-like cells located in the central nervous system, mediates synaptic pruning, perform phagocytosis of cellular depositions and waste, and release pro and anti-inflammatory responses contributing to neurodegeneration or neuroprotection. Microglia polarizes into different M1 and M2. These phenotypes modulate defensive or neuroprotective efforts to modulate neuroinflammation. The M1 phenotype exhibits pro-inflammatory cytokine responses, while the M2 phenotype demonstrates anti-inflammatory responses with high LC3-associated phagocytosis (LAP) that scavenges debris and unfolded fibrillar subproducts like alpha-synuclein fibrils. Here we propose that DHA derivatives Maresin 1 and ELV34 induce the second step in the polarization from M1 to M2, leading to a decrease in the inflammatory signals and increasing the LAP activity of microglial cells. This hypothesis was tested "*in vivo*" in a 6- hydroxydopamine (6-HODA) toxicity rat model and "*in vitro*", in adult rat brain cultures of microglial cells treated with TNF-alpha, C1q and IL-alpha or alpha-synuclein fibrils to induce M1 polarization. We used immunocytochemistry to detect p65 nuclear translocation and LC3 decorated vesicles, and immunohistochemistry using IBA1 to detect microglial cells in different areas of the rat brain. The confocal capture z-stacks were processed using Imaris 9.7 and the data was statistically analyzed. In the 6HODA toxicity model, microglia were more abundant, and the shape resembles more to M2 in the rats treated with Maresin 1 than in the saline control. In culture, ELV34 and Maresin 1 induced a decreased in p65 translocation, however Maresin was more effective in eliciting LC3-phagocytosis. Both DHA derivatives were induced significant positive effects in the polarization from M1, inflammatory to M2, pro-survival phenotype laying the road for a future therapeutical development.