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“Maresin-1 prevents alpha-synuclein activation of microglia in vitro and in vivo”

Parkinson's Disease (PD) is characterized by the loss of neurons in the Sustantia Nigra pars compacta (SNpc) and the presence of Lewy bodies, an abnormal aggregation of alpha-synuclein (a-Syn) and other proteins. At the time of diagnosis, patients have lost 30-50% of dopaminergic neurons in the SNpc. By this time, some events preceded the dopaminergic loss for over 10 years before the motor symptoms arose. Anosmia/hyposmia, a proposed prodromal symptom, is observed in 50-90% of the PD patients. Recently, it was observed that Maresin-1 (MaR-1), an omega-3 fatty acid derivative, reduces the dopaminergic cell death in 6-hydroxy-dopamine (6HODA) injection model and decreases the activation of microglial cells. We hypothesize that changes in support cells, such as microglia, precede the death of the dopaminergic neurons in SNpc and Maresin-1 prevents these changes.

To determine the symptoms emerging in the early events before diagnosis, we developed a rat model to study the propagation of a-syn aggregates from the nasal epithelium as proposed in Braak et al. theory of the stages of PD. These rats presented with anosmia/hyposmia 24 weeks post-intranasal delivery of a-syn preformed fibrils as of the Buried Food behavioral test. This time was taken as a starting point to screen for changes in microglia phenotypes. Two months after the appearance of the prodromal symptom, an increased content of α-Syn Phosphorylated in Serine 129 was detected along with a reduced number of dopaminergic neurons. Mar-1 administration rescued dopaminergic neurons from death and improved their overall morphology. We found an increase in microglial inflammasome formation 8 weeks after the first indication of olfactory deficiencies arises. Microglial inflammasome formation was determined by immunocytochemistry targeting ASC polymerization speckles in cells depicting IBA1, a marker of microglial cells. Maresin-1 administered intranasally 24 hours and 1 week after a-syn PFF delivery decreased the formation of inflammasome in microglia, suggesting that the bioactive lipid possessed anti-inflammatory properties.

In conclusion, the loss of smell correlated with the formation of protein aggregates in the SNpc in the animal model. Mar-1 reduced olfactory deficits along with the prevention of inflammasome triggered death of microglial cells to protect neurons in the SNpc. This evidence lays the basis to unveil the mechanisms by which the a-syn adducts spread, leading to the phenotype change of supportive cells that drives the SNpc neurodegeneration. In addition, Maresin-1 can be evaluated as a candidate for treatment of PD during prodromal stages.