PROJECT

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1) Project title

Study of the role of autophagy and dietary habits on pathogenesis of Parkinson's disease

2)Abstract (max 500 words)

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, and it is characterized by the progressive death of dopaminergic neurons in the substantia nigra, as well as intracellular accumulation of aggregates of α-synuclein in neurons of the brainstem, spinal cord, and cortex.

In several experimental models of PD, a selective loss of dopaminergic neurons is associated with chronic neuroinflammation, partly mediated by microglia, the resident immune cells in the brain. In this setting, a pivotal role has covered by NLRP3 inflammasome, which is a multi-protein complex capable of initiating inflammation in response to cellular stress, including PD-associate factors such as reactive oxygen species and pathologically misfolded proteins. Autophagy is conservative process responsible to regulate cell homeostasis by degradation or recovering cytoplasmic contents, abnormal protein aggregates, or damaged organelles, and many evidences established a relationship between defective autophagy and α-synuclein accumulation in PD pathogenesis. Furthermore, growing evidence indicates that the activation of inflammasome can be associated to autophagy. Dietary habits, such as hyperlipidic diet, may have an important role in neurodegenerative disease pathogenesis by NLRP3 inflammasome activation driving a low-grade chronical inflammation condition.

Indeed, some studies reported a decline on dynamism of the autophagic pathway in obese context, once autophagy also regulates lipid metabolism, improves insulin resistance, and reduces oxidative stress. For this reasons, in this project the central hypothesis is that exposure to HFD can develop peripheral inflammation driven by NLRP3 activation and affect the autophagy pathway, contributing to PD-associate alterations at central level, through the gut-brain and anticipate/exacerbate the pathological features of PD. In this research project, we will use a combination of in vivo/in vitro, functional, behavioral, and molecular biology approaches to pursue the following aims: I) to characterize the effects of NLRP3 inhibitor in vitro on neuroinflammation, neuroprotection and autophagic process; II) to test in rotenone-induced PD model the impact of pharmacological modulation of NLRP3, in terms of prevention, reduction of brain alteration and intestinal dysfunction; III) to study the impact of HFD in a A53T transgenic mouse on NLRP3 and autophagy pathways. We expect to find that promoting autophagy can be an important way to control the α-synuclein aggregation and chronic neuroinflammation by NLRP3 inflammasome activation, representing a suitable therapeutic approach, in terms of prevention, cure or maintenance of remission in PD.