PROJECT

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1) Project title

Role of multiproteic complex NLRP3 inflammosome and dietary habits in central and peripheral inflammatory processes in Parkinson disease

2)Abstract (max 500 words)

Parkinson disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer disease and it is a chronic and progressive disorder. It is estimated that 10 million people worldwide and about 1% of the population over 60 years of age are living with PD. PD is characterized by the 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. The underlying mechanisms of the neuronal degeneration are not well understood, but mitochondrial dysfunction, chronic inflammation and oxidative stress have been implicated in different animal models of PD. In various 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 inflammosome, 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. Several studies indicated that among factors associated with risk of developing PD, dietary habits have an important role. In particular, hyperlipidic diet is associated with an increase risk of PD, and this effect seems to be related to obesity-induced inflammation. Indeed, metabolic inflammation arising from exposure to high fat diet (HFD) could cause at central level a condition of chronic neuroinflammation which in turn increases nigral dopaminergic neurons damage and neurodegeneration. NLRP3 inflammosome activation is associated with obese condition, but still the role of peripheral NLRP3 inflammosome in CNS pathology has to be defined.

For this reason, in this project the central hypothesis is that peripheral inflammation driven by NLRP3 activation could contribute to PD-associate alterations at central level, through the gut-brain axis and HFD could anticipate/exacerbate the pathological features of PD. To test this hypothesis, experiments will be carried on rotenone-induced PD in mice, which is currently one of the most used preclinical model of PD, based on induction of PD-like pathological alterations by systemic administration of rotenone, a neurotoxin which causes degeneration of dopaminergic neurons of the *substantia nigra* along with an up-regulation of a-synuclein in surviving neurons. In this research project, we will use a combination of *in vivo/in vitro*, functional, behavioural and molecular biology approaches to pursue the following aims: i) to characterize the expression of NLRP3 inflammosome components (NLRP3, ASC, caspase-1, IL-1b) in rotenone-induced model at central, circulating and intestinal level ii) to study the impact of HFD on intestinal and central alterations induced by rotenone treatment

iii) to verify in rotenone-treated NLRP3 KO mice the role of NLRP3 iiii) to test in PD-mice the impact of pharmacological modulation of NLRP3, in terms of prevention, reduction of brain alteration and intestinal dysfunction, with an antioxidant food derived product such as blueberry extract and with a specific non adsorbable NLRP3 inhibitor acrylate derivate. We expect to find that modulation of NLRP3 represents a suitable therapeutic approach, in terms of prevention, cure or maintenance of remission in PD.