Parkinson's disease (PD) is a neurodegenerative disease featured by the characteristic loss of dopaminergic (DA) neurons in the substantia nigra. The classical immunopathological feature of PD patient's brain is the occurrence of Lewy bodies (LB), majorly composed of α-synuclein and ubiquitin. Although the normal functions of α-synuclein are still being defined, several studies have shown that this protein has a key role to play in DA neurons primarily for formation & maintenance of synaptic vesicle pools, regulation of lipid metabolism and Ca^{2+} homeostasis. In normal physiological conditions, α-synuclein exists in monomeric form and is recognized and cleared via the ubiquitin-proteasome system and chaperone-mediated autophagy pathways. In the pathological state, misfolding or mutations of α-synuclein (A30P/A53T) lead to the formation of modified species that bind with several cytoplasmic proteins and ultimately aggregate into LBs in the DA neuronal cells. This aberrant level of α-synuclein is cited in familial as well as idiopathic PD subjects. In our earlier study, we have reported α-synuclein modification & accumulation in an *in vitro* model under oxidative stress.

Recent findings suggest that this α-synuclein aggregation is not limited to DA neuronal cell bodies, but has also been observed in the astrocytes of midbrain region. α-synuclein has also been reported in the cerebrospinal fluid of PD patients. Recently it has been suggested that the increased occurrence of extracellular α-synuclein in the CNS may not only derive from the rupture of dysfunctional DA neurons but also be translocated from the gut to the CNS through the vagus nerve. These studies clearly establish the presence of α-synuclein in the CNS microenvironment during disease progression.

In recent years evidences have accumulated to suggest that DA neuronal death is the end result of the disease pathology whereas α-synuclein transfers through the gut-brain axis and from the olfactory route are early events in PD. Thus it is highly likely that the niche cells of the midbrain get affected prior to the death of DA neurons. Given the importance of a compatible niche for the survival and function of remaining live DA neurons and for transplanted graft DA neuronal cells, a thorough evaluation of these niche cells (in this case, the midbrain astrocytes) with respect to the extracellular α-synuclein engulfment, survival and function need to be made.

Despite the clear physical association between astrocytes and α-synuclein aggregates, the importance of astrocytes and their therapeutic potential in PD remain elusive. Ineffective degradation of α-synuclein is of great concern when it comes to the development and progression of PD. Therefore, **we propose to evaluate the role of astrocytes in the clearance of extracellular**

α-synuclein and in turn its effect on the neuroprotective functions of the astrocytes. We first aim to assess the differential effect of various forms of α-synuclein on the protein degradation machinery of astrocytes and consequent effect on survival and oxidative stress. Incomplete degradation of α-synuclein can lead to high intracellular load of toxic phosphorylated and nitrated forms of α-synuclein and/or extracellular release of α-synuclein, which we also aim to assess. This evaluation is crucial because alterations of this protein might alter key regulatory proteins crucial for key neuroprotective function of astrocytes such as gliotransmitter release, glutathione secretion and cell-cell coupling between astrocytes. The trigger of this engulfment for activated astrocytes and inflammatory state will also be evaluated. A dynamic neuron-glia crosstalk is known to be maintained by astrocytes through the release of gliotransmitters, in turn modulating the function of neuronal cells.

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