Jasmine B. Matsuda
Undergraduate
University of California, Los Angeles (UCLA), Los Angeles, CA

Mentor: Jorgelina Calandria, PhD.
LSUHSC School of Medicine: Neuroscience Center of Excellence, New Orleans, LA

"Characterization of astrocytes phenotype in models of alpha-synuclein toxicity"

Although Parkinson's disease (PD) is clinically recognized by its motor symptoms, pathological changes begin years before diagnosis with the accumulation of alpha-synuclein (α-syn)-containing Lewy bodies and progressive loss of dopaminergic neurons causing neurodegeneration. Increasing evidence suggests that dysfunction of non-neuronal support cells contributes to these early disease processes. Astrocytes are essential for maintaining neuronal homeostasis, and their loss of protective function has emerged as a potential driver of PD progression.

It has recently been shown that Maresin-1 (Mar1), an omega 3-derived specialized pro-resolving lipid mediator, reduced dopaminergic neuron loss in a 6-hydroxydopamine (6-OHDA) model of PD and preserves the homeostatic phenotype of astrocytes in vitro. We hypothesize that astrocyte senescence precedes dopaminergic neuron degeneration in the SNpc and that Mar1 prevents these pathological changes, thereby preserving astrocyte homeostasis during PD progression.

To investigate early astrocyte dysfunction during PD progression, we employed a rat model based on Braak's hypothesis in which α-syn preformed fibrils (PFFs) were administered intranasally to initiate pathology through the olfactory (OF) pathway. Buried Food behavioral test supported the idea of development of OF deficits prior to substantial dopaminergic neuron loss. Brain sections from the OF bulb, substantia nigra (SN), and prefrontal cortex (PFC) were analyzed using immunohistochemistry and confocal microscopy to evaluate astrocyte phenotype, senescence, and α-syn pathology. Astrocyte senescence was assessed by β-galactosidase activity colocalized with GFAP-positive cells. Because senescent astrocytes lose their homeostatic and phagocytic functions, we evaluated changes in astrocyte morphology and α-syn clearance. Mar1 treatment reduced astrocyte senescence and preserved a more homeostatic astrocyte phenotype.

In conclusion, OF dysfunction correlated with α-syn pathology and astrocyte senescence during the early stages of PD in this animal model. Mar1 reduced OF deficits and preserved a homeostatic astrocyte phenotype, suggesting that astrocyte dysfunction is an early contributor to PD progression. These findings support the growing recognition of astrocytes as key mediators of neurodegeneration rather than passive support cells. Targeting astrocyte senescence may therefore represent a promising therapeutic strategy for slowing PD progression during its prodromal stages.