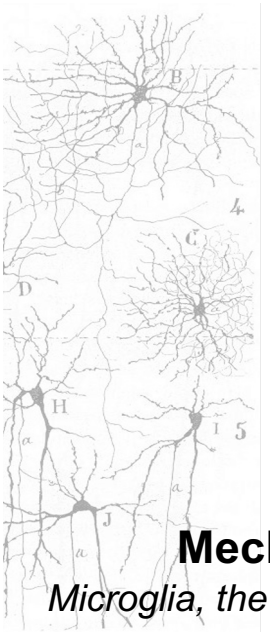
CUNY Neuroscience Collaborative Seminar Series
SPRING 2024

Friday, March 1st, 3:00 - 4:30 PM
The CUNY Graduate Center, Rm. 6495



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Mechanisms of Microglia-Mediated Neurodegeneration

Microglia, the brain's primary resident immune cells, are a heterogeneous population and can assume phenotypes with diverse functional outcomes on brain homeostasis. In Alzheimer's disease (AD), where microglia are a leading causal cell type, microglia subsets with protective functions have been well characterized. Yet, the identity of microglia subsets that drive neurodegeneration remains unresolved. Here, we identify a neurodegenerative microglia phenotype that is characterized by a conserved stress signaling pathway, the integrated stress response (ISR). Using mouse models to activate or inhibit ISR in microglia, we show that ISR underlies the ultrastructurally distinct "dark" microglia subset linked to pathological synapse loss. Inducing microglial ISR in murine AD models exacerbates neurodegenerative pathologies, such as Tau pathology and synapse loss. Conversely, inhibiting microglial ISR in AD models ameliorates these pathologies. Mechanistically, we present evidence that ISR promotes the secretion of toxic long-chain lipids that impact neuron and oligodendrocyte homeostasis in vitro. Accordingly, small molecule-based inhibition of lipid synthesis in AD models ameliorates synaptic protein loss. Our results demonstrate that activation of ISR within microglia represents a novel pathway contributing to neurodegeneration and suggest that this may be sustained, at least in part, by the secretion of long-chain lipids from ISR-activated microglia.

In-person

Hosts: **Dr. Nesha Burghardt (nb844@hunter.cuny.edu) and Dr. Asohan Amarasingham (aamarasingham@ccny.cuny.edu)**

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