Haghighi Lab

Peripheral inflammatory signals, brain aging and the progression of AD

My research program investigates molecular mechanisms that underlie the regulation of synaptic function and neuronal survival. We are interested in understanding how signals that arise from non-neuronal origin such as glia, muscle, intestine, fat tissue or immune cells, influence the set point for presynaptic neurotransmitter release. This is of particular importance in the field of aging biology, as changes in the setpoint of neurotransmitter release and synaptic homeostasis have been implicated in various developmental and age-dependent brain diseases from Autism and schizophrenia to Parkinson's and Alzheimer's disease (AD). Our preliminary and published data indicate that many signals that are acutely needed for synaptic compensation can become detrimental if they are exerted chronically, ultimately compromising neuronal survival. The current project builds on these findings to interrogate how signaling mechanisms arise from peripheral tissues can converge on the nervous system and affect brain aging. Recently in a collaborative work, we have demonstrated that pathogenic infections in the gut can acutely induce the expression of inflammatory cues (cytokines) in the gut epithelium, which then signals to the brain via cytokine receptors expressed in glia. Binding of gut secreted cytokines with their receptor activates an inflammatory signaling cascade in the glia, which is conserved from flies to humans. This activation, we show, is critical for the olfactory avoidance behavior in flies; however, as the flies age, this chronic inflammatory signaling becomes deleterious and negatively affects olfactory sensitivity in older flies (Cai et al., *Nature*, 2021). We plan to build on this work to investigate the role of gut and muscle cytokines during normal aging on brain health and function. We hypothesize that limiting peripheral inflammatory signals will benefit brain function and improve health and life span. We propose to take advantage of the powerful genetic tools in *Drosophila* in combination with electrophysiology, biochemistry and mass spectroscopy to build a mechanistic picture of the details of this link between peripheral stress and brain health. Importantly, we plan to use this knowledge to assess how the chronic inflammatory stress signals from the periphery influence the progression of disease in a fly (AD) model. One of the ways in which peripheral stress appears to exacerbate the progression of AD is by interfering with the integrity of the blood brain barrier (BBB). BBB is a protective barrier that controls the flow of ions and nutrient and prevents the access of toxins to the nervous system; multiple signaling cascades (including inflammatory pathways) are involved in the regulation of BBB (Calderon et al., *PNAS*, 2022). We believe this project will generate foundational knowledge in the field and help pave the way for novel future therapeutic strategies for tackling AD.