University of Rochester School of Medicine and Dentistry

The Neuroscience Graduate Program

Presents:

Mariah Marrero

In a Thesis Proposal

Advisor: Harris Gelbard, PhD

Investigating the role of High mobility group box 1 (HMGB1) in postoperative delirium

Postoperative delirium (POD) is the most prevalent surgical complication in geriatric patients – with a global incidence rate of 20% and a three-fold likelihood among individuals over the age of 65. POD is strongly associated with neurocognitive decline (NCD), leading to faster rates of cognitive decline with memory deficits. Despite its socioeconomic burden and high incidence rate, the lack of preventative or therapeutic strategies is a pressing issue, largely due to research gaps in molecular signatures of pathology. Clinical evidence shows that increased CSF and High mobility group box 1 (HMGB1) protein plasma are strong predictors for POD and neurocognitive decline. HMGB1 is a DNA chaperone-binding protein localized to the nucleus, and when extracellularly released, binds to toll-like receptor-2/4 (TLR2/TLR4) and receptor for advanced glycation end products (RAGE), becoming immunologically active. Exogenous HMGB1 in the bloodstream has been shown to breach the blood-brain barrier (BBB) and enter the brain, increasing protein levels in areas such as the hippocampus. Previous literature shows that increased exogenous HMGB1 in the hippocampus can bind to RAGE receptors on microglia and increase secretion of complement protein C1q, leading to a feedforward loop of activation and synapse-elimination. This relationship has not been explored with POD. Therefore, I propose to investigate the role of HMGB1 signaling in the BBB and neuroinflammation in the context of sterile surgery, with the potential to advance our understanding significantly and potentially lead to developing new preventative or therapeutic strategies for POD. I hypothesize that exogenous HMGB1 from innate immune cells will inflame and disrupt the BBB, causing soluble HMGB1 to enter the hippocampus and activate microglia. Specifically, HMGB1-induced microglia activation will increase complement secretion of C1q, thereby dysregulating microglia-dependent synaptic elimination. I will use a Transwell system to model the blood murine brain microvascular endothelial cells (BMECs) and pericytes (PCs) to address these unknown mechanisms to