University of Rochester School of Medicine and Dentistry

The Neuroscience Graduate Program

Presents:

MaKenna Cealie

In a Thesis Proposal

Advisor: Ania Majewska, PhD

Effects of Developmental Ethanol Exposure on Cerebellar Microglia and Purkinje Cells

Fetal alcohol spectrum disorders (FASD) are the most common cause of non-heritable, preventable mental disability. It occurs in almost 5% of births in the U.S., leading to a wide range of cognitive, behavioral, and physical impairments. There is no known cure for FASD, and its mechanisms remain unclear.

I will be investigating the cerebellum, as this unique structure is affected in FASD. Deficits in behaviors related to the cerebellum, such as impaired motor coordination and learning, have been discovered after developmental ethanol exposure (Servais et al., 2007; Topper et al., 2015). The changes in behavior may arise from ethanol's effects on the cellular level. Studies in rodents have found reductions in the number of the neurons that are the sole output of the cerebellum, Purkinje cells, as well as microglia, the immune cells of the Central Nervous System, after developmental ethanol exposure (Goodlett et al., 1990; Kane et al., 2011; Topper et al., 2015). Additionally, ethanol has been shown to alter Purkinje cell excitability and firing (Servais et al., 2007; Zamudio-Bulcock et al., 2014). Microglia, on the other hand, display a phenotype associated with immune activation and release pro-inflammatory factors after developmental ethanol exposure (Topper et al., 2015). Blocking this immune activation with peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists has been shown to attenuate some of the inflammatory responses in microglia and reduce Purkinje cell loss in rodents (Drew et al., 2015; Kane et al., 2011), suggesting that microglia may be a therapeutic target in FASD.

While it is clear that ethanol affects both cerebellar neurons and microglia, it is not yet known when these changes occur and how they are maintained or progressively altered into adulthood. Additionally, while each cell type has been studied individually, how microglia and Purkinje cells interact is also unclear. Microglia are known to shape neuronal circuit development and connectivity in the cerebellum through phagocytosis, synaptic refinement, and modulation of neuronal activity. Elucidating how ethanol-induced changes in microglia mediate some of the pathological changes in cerebellar Purkinje cells may be critical for understanding the onset of FASD pathology. Furthermore, modulating microglial survival and activity during ethanol exposure through PPAR-γ agonists may provide some answers and potential therapies for this disease.

I hypothesize that ethanol induces neuroimmune changes in cerebellar microglia that alter their interactions with Purkinje cells, and reducing microglia-mediated inflammation through PPAR-γ agonists mitigate the pathological effects of ethanol. To test this hypothesis, I will pursue two aims using a mouse model of FASD. The first will investigate how developmental ethanol and a PPAR-γ agonist affects microglial phenotype over time using immunohistochemistry, quantitative real time PCR, and in vivo two-photon imaging of microglial dynamics. This will further our knowledge of the role of microglia and microglia-mediated neuro-immune responses in the onset and propagation of FASD pathology. The second will determine if Purkinje cell and microglia interactions are affected throughout life by developmental ethanol exposure and PPAR-γ agonist administration with immunohistochemistry, electron microscopy, and two-photon imaging. These experiments will elucidate the effects of cerebellar microglia on Purkinje cells in the cerebellum after developmental ethanol exposure and assess microglia as a potential target to mitigate disease pathology in a mouse model of FASD.

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https://urmc.zoom.us/j/96981714936?pwd=Y29mWUl2a0c4dVV6OXRjbWZENjQvZz09; Passcode: 540151