Neuroprotection in preterm birth by modification of astrocyte polarization

Project Overview

Between the 26th and 32nd week of gestation, the major axon tracts of the developing human brain are exquisitely vulnerable to injury. For reasons that are incompletely understood, repeated inflammatory and ischemic insults during this period irreversibly damage the myelinating cells of these axon tracts, leading to defects in subcortical myelination (white matter injury, WMI) and long-term neurological disability. Most cases of WMI occur in infants born preterm as a result of prenatal, intrapartum, and/or postnatal insults during this window of white matter vulnerability. Treatments to rescue or inhibit this brain damage are extremely limited due to poor understanding of underlying disease pathophysiology. Given the rising rate of preterm birth worldwide, more effective neuroprotective therapies are desperately needed.

While reactive astrocytes have long been recognized as hallmarks of WMI, whether reactive astrocytes are beneficial or detrimental to disease outcomes has remained unclear. One reason for this controversy is likely heterogeneity of the astrocyte response to injury. So far, two different types of reactive astrocytes are recognized in Central Nervous System injury. A1 astrocytes are induced by inflammation and form in response to factors released by reactive microglia. A1s kill neurons, delay the maturation of myelinating cells, and are increasingly recognized to play a role in neurodegenerative disease. In contrast, A2 astrocytes form predominately in response to ischemia and appear to be supportive of neuronal survival and tissue repair. The specific nature of astrocyte reactivity after WMI (A1s, A2s, or other) is unclear.

The proposed research focuses on neurodegenerative (A1) reactive astrocytes as putative key early mediators of WMI and a novel therapeutic target in infants born preterm. In the experiments described, we set out to define the precise timing of A1 formation relative to brain insults in WMI, to test the ability of *in utero* versus postnatal blockade of A1 astrocyte formation to improve disease outcomes, and to design a therapeutic approach to WMI targeting these cells in the preterm fetus.