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Research Overview:

The coordinated symphony of interactions that take place between cells in the CNS are crucial for its development, function, and ability to adapt and respond to injury and disease. Research in my laboratory focuses on understanding the molecular mechanisms governing these interactions, with particular interest in the role of the Sonic hedgehog (Shh) signaling pathway. While our past work has contributed to a better understanding of the role of the Shh pathway in CNS development, we have recently shifted our focus to examine its role in the adult CNS. The overall goal of this work is to elucidate the molecular and signaling mechanisms employed by cells within the CNS to maintain homeostasis and responds to injury or disease. Our current studies employ cutting edge molecular genetic, surgical, pharmacological, histological and transcriptomic approaches in mice to address the following 2 topics:

1) The role of Shh signaling in regulating the Blood-brain barrier (BBB)

The BBB is a critical diffusion barrier that normally inhibits the infiltration of circulating plasma proteins and compounds into the CNS and in doing so maintains its unique “privileged” immune status. In humans, disruption of the BBB commonly occurs in both injury and disease conditions and can lead to numerous secondary consequences. BBB disruption is recognized as a critical early event in the etiology of many diseases affecting the CNS, including Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and Alzheimer’s Disease (AD). For example, in MS, disruption of the BBB allows immune cell infiltration into the CNS that triggers an autoimmune response to myelin proteins. Thus, understanding the mechanisms that regulate the BBB under normal and pathological conditions is an important step toward preventing or treating such diseases. Despite this, our current knowledge of the specific roles that different CNS cell types and signaling pathways play in maintaining BBB integrity is incomplete.

We have discovered that the Sonic Hedgehog (Shh) signaling pathway plays a previously unappreciated but critical role in maintaining BBB integrity. We have found that the Hh pathway is selectively active in a sub-population of astrocytes and that signaling in these cells is required to maintain BBB integrity in specific regions of the CNS. We have also discovered that Hh signaling within astrocytes is critical for repairing the BBB at experimentally-induced lesions like those that occur in MS.

2) The role of Shh signaling in reactive gliosis and CNS homeostasis

Reactive gliosis is an important process that helps protect the CNS from damage and disease by restoring tissue homeostasis. Chronic reactive gliosis is associated with the development of various neurological disorders including AD, MS and ALS. Thus, understanding the mechanisms that trigger this process in the CNS has direct clinical significance. Despite this, our current knowledge of the specific roles that different glial cell types and signaling pathways play in reactive gliosis is incomplete.

The two primary cell types in the CNS that mediate reactive gliosis are astrocytes and microglia. Astrocytes in particular are known to play various and important roles in response to CNS inflammation and insult, including helping to repair tissue damage by forming a "glial scar" and restoring the BBB. Notably, recent molecular genetic evidence indicates that astrocytes respond in a specific way to different inducing stimuli. However, one major outstanding question that remains is whether distinct subsets of astrocytes exist in the CNS that play specific roles in response to different inducements.

It has previously been shown that a subset of protoplasmic astrocytes in the CNS maintain responsiveness to Sonic Hedgehog (Shh) signaling into adulthood. These cells can be identified by their unique expression of *Gli1*, a target gene of the Shh pathway that is only turned on in cells when the pathway is turned on by ligand binding to the Ptch1 receptor, or by de-repression. Gli1+ cells populate the gray matter regions of the deep cortical layers, parts of the striatum, the hypothalamus, thalamus, brainstem and spinal cord, among other regions. Notably, we have found that Gli1+ astrocytes mount a novel response to demyelinating white matter lesions in the spinal cord. Together, our observations indicate that Gli1+ cells possess a unique molecular and functional identity that distinguishes them from all other glial cell types in the CNS.

Background: I received a Ph.D. in Neuroscience in 1994 from the University of Pittsburgh under Dr. Cynthia Lance-Jones, and postdoctoral training in Developmental Genetics at the Skirball Institute/NYU Medical School with Dr. Alexandra Joyner. I established my own lab in the Dept. of Neuroscience & Cell Biology at RWJMS in 2000.

Publications: PubMed