INNOVATIVE TECHNOLOGIES TO STUDY MECHANISMS OF CNS AXONAL DEGENERATION

by

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Abstract

Central nervous system (CNS) axons often span substantial distances and are sit- uated in compositionally distinct microenvironments as compared to their cell bodies. Under conditions that result in injury or inflammation to the CNS, axonal degener- ation and subsequent recruitment of microglia are often seen. However, the exact role(s) of microglia in the setting of axonal degeneration are poorly understood. The overall aim of the research was two-fold. First, in vitro micro-technologies would be developed to compartmentalize CNS axons from their cell bodies to allow exploration of chemically- and physically-mediated events implicated in axonal degeneration. Sec- ond, these platforms would be used to establish novel axon-microglia co-cultures to investigate molecular mechanisms that govern microglial activation in the setting of axonal degeneration. My hypothesis was that Toll-like receptor signaling could assist microglia in identifying broad classes of degenerative products to effectively modulate their phenotype. In addition, axonal degeneration, whether through cell body death or direct physical insult to the axon, triggers a series of events that uniquely involve microglia in vivo, a feature I aimed to reproduce in vitro.

In this research, I have developed a number of innovative microfluidic platforms that have enabled the investigation of unique neurobiological questions. My research advanced microfluidic technologies to study inflammation- and compression-induced axonal degeneration and subsequent microglial responses. Using the circular neural open system (cNOS) and axonal injury microsystem (AIM), I have contributed to two major bodies of biological work. The first was the development of a novel microglia- axon co-culture assay. Using this method, I showed that microglia in the presence of degenerating

axons perform migratory and phagocytic activities. Specifically, mi- croglial interaction with axonal debris promotes priming of a type-1 Interferon (IFN) state through a TRIF-dependent pathway. Secondly, I quantitatively assessed the cellular response of CNS axons to focal compressive injury. My investigations re- vealed a critical threshold (> 95 kPa) at which axons spontaneously regrow in the absence of exogenous factors. These biological findings coupled to the microfluidic platforms built in the course of this research have significantly added to the field of basic neurobiology and biomedical engineering.