Characterizing the impact of traumatic injury on neurodegenerative disease risk using engineered cell and tissue model

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Neurotrauma encompasses a broad category of injuries affecting the central nervous system (CNS), which includes both the traumatic brain injury (TBI) and spinal cord injury (SCI). These injuries can result from various causes, including accidents, falls, sports-related incidents, and other traumatic events, affecting millions of individuals annually. Traumatic injuries are the leading cause of disability, and moreover are associated with elevated risk of developing cognitive impairments and neurodegenerative diseases (ND) such as Alzheimer's Disease (AD) and Parkinson's Disease (PD). The elevated ND risk arising from neurotrauma poses significant burdens on healthcare systems and affect life quality of affected individuals, emphasizing the critical need for research aimed at understanding the underlying mechanisms conferring ND risk from the lesion center to CNS. The goal of my thesis is to understand persistent molecular changes post SCI associated with ND using a combination of a rat animal model and neuronal cultures derived from human induced pluripotent stem cells.

I started with Sprague-Dawley rats with T10 spinal cord contusive injury; and assessed immediate and persistent changes in transcriptomic and epigenetic markers via next generation sequencing (NGS) at primary lesion site and distal spinal cord tissue. Along with global changes in chromatin arrangements and DNA methylation, we observed significant transcriptomic changes enriched for pathways of inflammatory responses, and synaptogenesis. These changes were further verified using immunohistochemistry and super resolution microscopy. To further understand the long-term brain abnormality linked to SCI, we investigated persistent alterations in the composition and molecular profiles of both the male and female motor cortex 30 days after injury. Immunohistochemistry revealed that SCI leads to neuronal loss and changes in synaptic density and morphology; and significant alterations in the neuron-astrocyte ratio and astrocyte morphology, in male motor cortex supporting our hypothesis that SCI may increase the risk of neurodegeneration by affecting the motor cortex. Comparison of transcriptomic data collected at a sub-acute stage in male rats, namely 7 days post injury, with 30 days post injury, identified persistent and de novo changes that occur primarily after recovery of spinal cord injury, which are

enriched for neuronal and synaptic function related pathways. Interestingly, neuroendocrine-related pathways were prominently implicated at the chronic stage of SCI, with Esr1 identified as a major upstream regulator offering protective effects in females that did not exhibit significant alterations in cellular composition or morphology after SCI. Collectively, our study paved the way towards understanding sexual dimorphism in brains after spinal cord injury and provides a plausible connection between spinal cord injury and neurodegeneration later in life that were further investigated using a humanized culture model.

We established the feasibility of using hiPSC derived neurons to examine long term neurotoxic mechanism using lead (Pb) as a model chemical with strong associations with elevated AD risks later in life. A similar culture system was then used to assess persistent neurotoxicity of acrolein, a chemical that is known to emerge in brains post traumatic injury. We found that acrolein induced alterations in neuronal network morphology, synaptic density, and excitability. Furthermore, acrolein exposure negatively impacted mitochondrial function and persistently altered neuronal resilience towards a secondary stressor of mitochondria, namely MPP+. Acrolein exposure also alters the expression of tau and tau phosphorylation which collectively result in increased cellular vulnerability toward paired helical filament (PHF-tau) seeding, a known neurotoxin associated with ND. These findings collectively provide molecular insights as to how acrolein can partake alterations in neural function and resilience to stressors; and relay ND risks in neurotrauma patients alter in life.

In conclusion, our comprehensive investigation employing both rat and hiPSC models uncovers plausible molecular pathways connecting SCI to neurodegenerative diseases, providing insights into the enduring consequences of these injuries on affected patients.