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"Exploring the Effects of TBI and Alcohol in Inducing Proteinopathy in the Lumbar Spinal Cords of Rodents: Potential Role of ISGylation"

Traumatic brain injury (TBI) is a prominent cause of death and disability worldwide, as well as a risk factor for a variety of neurodegenerative disorders including amyotrophic lateral sclerosis (ALS). Military veterans and contact sport players are more susceptible to TBI and neurodegenerative disorders. In addition, alcohol use raises the risk of TBI and neuronal damage, while TBI increases the likelihood for alcohol abuse. Currently, the knowledge on the mechanism(s) underlying TBI-mediated neurodegeneration and whether alcohol modulates these mechanism(s) is not known. There is currently no cure for TBI-induced neurodegeneration, stressing the need to better understand the mechanisms by which TBI triggers neurodegeneration.

Interferon stimulated gene 15 (ISG15), a ubiquitin-like protein, has previously been shown in our lab to antagonize ubiquitin-mediated protein degradation. Studies from our lab have also demonstrated ISG15 is elevated in neurodegenerative diseases, namely in human ALS spinal cords. Therefore, we tested to see if TBI-induced activation of the IFNβ/ISG15 axis impairs the ubiquitin-mediated turnover of neuronal proteins in the spinal cord. Toxic accumulation of non-degraded proteins leads to neurodegeneration, and alcohol exacerbates this mechanism.

We used cell culture and rodent models of injury to test our hypothesis. In the cell culture model, we found that TBI induces ISGylation. In rodent models we found that ISGylation of cellular proteins is increased in the lumbar spinal cords (SCLs) of rodents collected 12 weeks post TBI- and TBI-alcohol administered male rats. Interestingly, in the SCLs of 12-week female rats, TBI has no effect on ISGylation induction. To test ISGylation of specific proteins, we chose TDP-43 as a model protein, as its ubiquitin-mediated targeted degradation is affected consequently, non-degraded TDP-43 is accumulated in inclusion bodies. We immunoprecipitated (IP) TDP-43 and analyzed IPs on the Wes assay using anti-ISG15-specific antibody. We found that TBI induced TDP-43 ISGylation in 12-week male rats, yet alcohol reduced it. In the 12 week females, TBI did not induce TDP-43 ISGylation; however, alcohol induced ISGylation of TDP-43 in TBI-exposed female rats. At this point, we conclude that alcohol induces TBI-mediated ISGylation of TDP-43 in females but not in males, suggesting that females may be more vulnerable to TBI.