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"Exploring the Effects of TBI and Alcohol in Inducing TDP-43 Proteinopathy in the Lumbar Spinal Cords of Rats"

Although considered as a rare neurodegenerative disorder, veterans who have served in the military are at a nearly 60% greater risk of being diagnosed with Amyotrophic Lateral Sclerosis (ALS) than those with no history of military service. Traumatic brain injury (TBI) has been identified as one of the major risk factors for ALS development in veterans. Alcohol and TBI are a deadly pair; while alcohol increases one's risk for TBI, TBI also increases one's likelihood of alcohol abuse. Currently, the knowledge of the mechanism(s) underlying TBI-mediated neurodegeneration and whether alcohol modulates these mechanism(s) is not known.

Approximately 97% of ALS cases exhibit a common neuropathology known as TDP-43 (TAR DNA binding protein 43) proteinopathy, which is characterized by the accumulation of non-degraded TDP-43 proteins in nerve cells, potentially due to impaired ubiquitin-mediated protein degradation. Interferon stimulated gene 15 (ISG15), a ubiquitin-like protein, has previously been shown in our lab to antagonize ubiquitin-mediated protein degradation. Notably, we have demonstrated that the ISG15 pathway (free ISG15 and its protein conjugates (ISGylation)) is elevated in the lumbar spinal cords (LSCs) of ALS veterans, a region of the spinal cord that is commonly affected in ALS patients. We have also found that levels of ISGylation are significantly increased in the LSCs from female *vs* male ALS veterans. TBI induces ISG15 expression in other experimental model(s). Based on these results, we hypothesize that TBI-induced activation of the IFNβ/ISG15 axis impairs the ubiquitin-mediated turnover of neuronal proteins (*e.g.,* TDP-43) in the spinal cord. Toxic accumulation of non-degraded proteins leads to neurodegeneration, and alcohol exacerbates this mechanism.

To test this hypothesis, we gave Wistar rats a single mild-moderate TBI using a lateral fluid percussion injury model. The rats received alcohol by a two-lever operant self-administration alcohol model, where one lever delivered water and the other delivered 10% ethanol. We collected the LSC from the rats 2- and 12-weeks post-TBI. To determine the presence of neurodegeneration, Fluoro Jade C was used to stain 12-week LSC tissue sections. We found that there was increased neurodegeneration in female LSCs as compared to sham groups with no effect of alcohol. To begin exploring the molecular mechanisms underlying this neurodegeneration, we examined the relative gene expression levels of IFNβ and ISG15 using qPCR, ISGylation using Wes, and TDP-43 proteinopathy using Western, in LSCs collected from TBI (2- and 12-weeks post-TBI)/alcohol administered rats. These same assays were conducted with the motor cortices of the same rats; as similar to LSCs, this part the brain is also affected in ALS patients. Although data is still being collected, so far, data indicate that TBI may be inducing neurodegeneration, an interferon response, and TDP-43 proteinopathy in the spinal cord of female rats, particularly at later time-points (12 weeks post TBI), while moderate alcohol use has little effect. Completion of this project, will reveal if elevated ISGylation contributes to motor neuronal pathology in ALS veterans and civilians exposed to TBI.