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Enteroviral infection leads to cytoplasmic mislocalization of TDP-43 in mouse brain

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that targets the motor neurons in the brain and spinal cord, which control the motor movements of the body. The disease is present in similar proportions in the majority of ethnic groups around the world, with the male being the more likely gender to contract the disease. Currently, without any effective therapies, the destruction of the motor neurons will first lead to paralysis, and eventually death. Even though 5% of all ALS cases have been associated with inherited genetic mutations that have been categorized as familial ALS, the majority of all ALS cases are actually sporadic (95%). In other words, these cases occur in the absence of prior ALS history in the family. Enterovirus (EV), a family of positive-stranded RNA viruses including poliovirus and coxsackievirus, is suspected to influence ALS pathogenesis due to the viruses' ability to target motor neurons. In addition, it has also been shown that patients with prior poliomyelitis, paralysis caused by poliovirus, are at a higher risk of ALS than those without. Our lab recently found that *in vitro* EV infection results in protein aggregation, RNA-processing defects and disruption of autophagy via EV-encoded proteases. Of particular interest was the finding that EV infection is able to impair nucleocytoplasmic trafficking, and initiate cytoplasmic aggregation and cleavage of transactive response DNA binding protein-43 (TDP-43), one of the hallmarks of ALS. Together with these findings, we hypothesize that EV infection is a causative and/or risk factor in the development of sporadic amyotrophic lateral sclerosis.

Methods & Results: Neonatal BALB/C mice were infected


intracranially with eGFP-coxsackievirus or mock (DMEM) infected. Brain tissues were then collected at 2, 5, 10, 30 and 90 days post-infection for performing H&E and immunohistochemical staining. Based on our preliminary data, we were able to show brain lesions and inflammation, identified using IBA1 (microglia), pSTAT3 (astroglia) and GFAP (reactive astrocytes) in the cortical and hippocampus regions in parallel with viral protein detection through GFP staining as early as 2 days post-infection. Even though the viral protein was significantly decreased to only 10% of the original intensity at 90 days post-infection, there was sustained inflammatory and immune responses at the later time points. Most notably, our pilot data demonstrated clear ALS-like pathologies, such as cytoplasmic mislocalization and nuclear down-regulation of TDP43 at the areas of infection/tissue damages starting at 5 days post-infection and maintained until 90 days post-infection. Moreover, localization of markers such as p62 and ubiquitin has also been strongly detected within the infected regions.

Conclusion: Our preliminary results reveal that enterovirus infection, such as coxsackievirus, is able to cause ALS-like pathology, especially in the case of localization in abnormal TDP-43, p62 and ubiquitin within the virus infected regions of the mouse brains.

Speaker Biography

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