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Identifying a Neurotoxic Mechanism Present in West Nile Neuroinvasive Disease

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More than half of patients who survive West Nile neuroinvasive Disease exhibit chronic cognitive impairments, such as spatial learning deficits. With various studies implicating interferon gamma (IFNg) in a mechanism responsible for cognitive deficits following viral infection, the lab studied WNV-infected interferon gamma receptor knockout ($IFNgR^{-/-}$) mice to determine if signaling through this receptor contributed to spatial learning deficits. All $IFNgR^{-/-}$ mice were protected from spatial learning defects. I used this global gene deletion model to determine gene expression downstream of IFNg that confers poor learning. Brain tissue was harvested from these mice at 7, 25 and 52 days post-infection. Virus is present in the brain at day 7 but cleared by day 25 and 52. I used this tissue to determine the changes in gene expression for an array of genes suspected to underlie memory dysfunction. I also studied Cx3Cr1-Cre^{ER}-$IFNgR^{fl/fl}$ mice, which have IFNgR conditionally deleted from microglia and are also protected against spatial learning deficits. This allowed me to evaluate how interferon gamma signaling, specifically to microglia, plays a role in the cognitive deficits observed in WNV infected mice. I assessed changes in microglia activating gene expression in these microglia-specific knockout mice. The global knockout mice exhibited decreased expression of complement regulatory and microglia activating genes during early recovery. These results suggest that elevated expression of complement regulatory and microglia activation genes during early recovery may contribute to the spatial learning deficits present in wild type (WT) mice following WNV infection. Elucidating this neurotoxic mechanism is vital to the development of therapies for people experiencing cognitive deficits following WNV infection.