Deficiency in interleukin-1 receptor accessory protein (IL-1RAP) alleviates tau pathology

Neuroinflammation is associated with hyperphosphorylation and aggregation of tau, which results in the formation of neurofibrillary tangles in tauopathy brains. However, the precise mechanisms of how brain inflammation drives this process remains unclear. Previously, we have reported that tau pathology is induced in neurons through microglia-derived IL-1. It is unclear how IL-1 signaling is regulated in a cell-specific manner and at the receptor level. An important factor in IL-1/IL-1R1 signaling is IL-1 receptor accessory protein (IL-1RAP). In response to IL-1β, IL-1R1 engages IL-1RAP and activates NF-kB or p38 MAPK leading to downstream effects. In this study, we aimed to determine if IL-1RAP deficiency has any effect on tau pathology and neurodegeneration. We assessed tau pathology in hippocampi of LPS-injected mice with global IL-1RAP knockout and PS19 mice with myeloid/microglial IL-1RAP knockout by western blot, immunofluorescence, and immunohistochemistry, and Gallyas silver staining. Both LPS-injected IL-1RAP global knockout mice and PS19 mice with myeloid conditional knockout showed a significant decrease in their ptau levels compared to their controls. Our data suggests that global deletion of IL-1RAP decreases tau pathology in an LPS model of systemic inflammation. IL-1RAP deficiency in myeloid/microglial cells in PS19 mice also results in reduction of ptau levels which suggests that the myeloid/microglial knock out of IL-1RAP is sufficient to bring down the ptau levels in the brain. This might be due to how the IL-1 signaling is regulated in different cells and at the receptor level which needs further investigation.