Abstract

Interleukin-1 (IL-1) as a potential contributor to the pathophysiology of Alzheimer's Disease

By

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Elevations of the pro-inflammatory cytokine interleukin-1 (IL-1) have been reported as part of the inflammatory response to injury and neurodegenerative disorders. The observation of increased IL-1 levels in the brains of patients with Alzheimer’s disease (AD) triggered over two decades of research implicating IL-1 in the disease pathogenesis. IL-1 has been suggested to modulate a variety of actions related to AD pathology, including the processing of the Aβ precursor protein and deposition of amyloid plaques. IL-1 also activates glial cells and induces recruitment of leukocytes and peripheral macrophages to the CNS across the blood-brain barrier (BBB). When exposed to IL-1, microglia and macrophages take on a classical activation phenotype resulting in the release of more inflammatory cytokines and reactive oxygen species that can cause cell degeneration. In addition, IL-1 expression has been shown to impair hippocampally-mediated memory processes. In fact, imaging studies with AD patients have demonstrated closer correlations between cognitive function and activated microglia than between cognitive function and amyloid plaque burden. Epidemiological studies reveal a reduced risk of developing AD for chronic users of anti-inflammatory drugs, but clinical trials have not shown a consistent benefit of NSAID treatment. In this study, we attempted a more targeted approach to anti-inflammation treatment through chronic, systemic administration of the mIL-1 Trap, which specifically inhibits IL-1 signaling, to transgenic swAPP/PS1 mice. After 5 months of treatment, animals that were treated with the mIL-1 Trap performed significantly
better on water maze acquisition, a measure of learning, than transgenic animals treated with mFc (placebo). However, the hippocampal plaque burden (number of plaques, average plaque size, and proportion of hippocampus covered with plaques) was unchanged by the treatment. We also found an effect of the mIL-1 Trap treatment on microglial morphology in the hippocampus. Animals treated with mIL-1 Trap had larger somas for microglia adjacent to amyloid plaques but smaller somas for microglia that were distant from plaques. Finally, correlations between the plaque measurements, cognitive performances, and microglial measurements revealed differences between the two treatment groups. These findings may shed more light on the relationship between interleukin-1, neuroinflammation, and plaque pathology in Alzheimer’s disease.