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Tyrosine kinase in ulcerative colitis associated compromised microglial functions.

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Microglia plays an essential role in the maintenance of brain homeostasis and compromise in microglia functions are well documented to trigger neurodegenerative disorders including Alzheimer's disease. However, the role of gut immunity and intestinal inflammation in microglia function and neurodegeneration remains unclear. Previously, we have established that the loss of Jak3 induces predisposition of compromised intestinal barrier function mediated colitis. In the present study, we demonstrate that loss of Jak3 induces chronic inflammation associated with increased circulating pro-inflammatory cytokines that led to increased neuroinflammation and microglia dysfunction. Our data showed that DSS induced mucosal inflammation was more severe in Jak3 global knockout (KO) and intestinal epithelial-specific knockout (Int-KO) mouse compared to corresponding wild type mouse. Further, loss of Jak3 increased TLR signaling and associated pro-inflammatory cytokines expression and together, exacerbated neuroinflammation in the brain. The increase in neuro-inflammation triggered dysfunctional microglia (Iba1) and reduced TREM2 expression in brain further increased the β-Amyloid and pTau accumulation in DSS treated KO and Int-KO mice compared to corresponding control wild type group. Taken together these results demonstrate the essential role of intestinal-Jak3 in mucosal homeostasis and microglial dysfunction associated Alzheimer's disease.