Innate immunity in Neurodegenerative disease

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The accumulation of neurotoxic amyloid beta peptides along with neurofibrillary tangle formation are key pathological hallmarks of Alzheimer's disease. The brain has been considered as an immune-privileged organ, however, increasing evidence from translational, genetic, and pathological studies suggests that activation of distinct innate immune pathways are a third important disease hallmark which actively contributes to disease progression and chronicity.

Microglia play a pivotal role in this immune response and are activated by binding of aggregated proteins or aberrant nucleic acids to pattern recognition receptors. This immune activation leads to the release of inflammatory mediators, but also distracts microglia cells from their physiological functions and tasks, including debris clearance and trophic factor support. NLRP3 inflammasome activation microglial clearance capacities and such contributes to the increase amyloid beta burden of the brain. Additionally, NLRP3 is a negative regulator of hippocampal long-term potentiation and spatial navigation memory. Chronic activation of the NLRP3 inflammasome causes microglial pyroptosis and thereby the release of ASC specks. The latter contribute to spreading of pathology by enhancing the propensity of beta-amyloid peptides to aggregate. Importantly, sustained NLRP3 activation can increase tau pathology and the formation of neurofibrillary tangles in vitro and in vivo, through a bidirectional regulation of tau kinases CAMKII-apha and GSK3-beta on one hand and phosphatase PP2A on the other.

In keeping with this immune hypothesis of neurodegeneration, inhibition of NLRP3-related immune pathways protect from neurodegeneration in cellular and murine models of Alzheimer's disease and primary tauopathies, collectively suggesting that this pathway could be exploited for future therapeutic interventions.