Microglia and the NLRP3 inflammasome pathway contribute to Tau-mediated pathology *in vivo*

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Aggregation of hyperphosphorylated Tau and neuroinflammation are features of Alzheimer's disease (AD) and frontotemporal dementia (FTD). Together, these two biological phenomena may work in concert to progress neurodegeneration and cognitive impairment. To further understand the contribution of local inflammatory processes to AD and FTD, we explored the activation of glial cells and the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome using a mouse model of Tau-mediated pathology, Tg4510 mice. These transgenic animals express a repressible form of human Tau containing the P301L mutation that has been linked with familial FTD. In Tg4510 mice aged from 2-7 months, a time-course analysis was performed of Tau pathology, neurodegeneration, gliosis and inflammatory markers in the frontal cortex and hippocampus. First, an age-dependent increase in Tau pathology was observed paralleled by cortical and hippocampal atrophy, as assessed using immunohistochemistry (IHC) to evaluate hyperphosphorylated Tau (with antibody, AT8) and neurofilament tangles (amyloid dye Thioflavin S), and biochemistry to assess insoluble hyperphosphorylated Tau levels. Secondly, investigating the state and biological consequences of activated microglia (i.e., Iba1, CD68, C1q) as well as the astrocytosis (by GFAP) confirmed a progressive increase in gliosis in the affected regions. Finally, gene expression and pathway analyses found significant upregulation in neuroinflammatory signatures including involvement of NLRP3 inflammasomes. At the protein level, the pathogenic role of the NLRP3 pathway was illustrated by an increased expression of the NLRP3-activation markers, Apoptosis-associated speck-like protein containing a CARD (ASC) and IL-1β, as these two proteins serve as pro-inflammatory mediators. To confirm the pathogenic role of the NLRP3 pathway to Tau-mediated pathology, the NLRP3 inhibitor, MCC950, was administered for 3 months to the Tg4510 mice. Post treatment, a significant decrease occurred in the levels of pathological Tau, neuroinflammation and microgliosis in the affected brain regions. Taken together, our data demonstrate the interplay of Tau pathology and neuroinflammation, and more specifically, show that pharmacological inhibition of the NLRP3 pathway *in vivo* leads to disease modification and could be of benefit in the clinical setting.