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4. Physiological expression of mutated TAU impaired astrocyte activity and exacerbates β-amyloid pathology in 5xFAD mice

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ABSTRACT:
Background Alzheimer's disease (AD) is the leading cause of dementia in the world. The pathology of AD is affiliated with the elevation of both tau (τ) and β-amyloid (Aβ) pathologies. Yet, the direct link between natural τ expression on glia cell activity and Aβ remains unclear. While experiments in mouse models suggest that an increase in Aβ exacerbates τ pathology when expressed under a neuronal promoter, brain pathology from AD patients suggests an appearance of τ pathology in regions without Aβ.
Methods Here, we aimed to assess the link between τ and Aβ using a new mouse model that was generated by crossing a mouse model that expresses two human mutations of the human MAPT under a mouse Tau natural promoter with 5xFAD mice that express human mutated APP and PS1 in neurons.
Results The new mouse model, called 5xFAD TAU, shows accelerated cognitive impairment at 2 months of age, increased number of Aβ depositions at 4 months and neuritic plaques at 6 months of age. An expression of human mutated TAU in astrocytes leads to a dystrophic appearance and reduces their ability to engulf Aβ, which leads to an increased brain Aβ load. Astrocytes expressing mutated human TAU showed an impairment in the expression of vascular endothelial growth factor (VEGF) that has previously been suggested to play an important role in supporting neurons.
Conclusions Our results suggest the role of τ in exacerbating Aβ pathology in addition to pointing out the potential role of astrocytes in disease progression. Further research of the crosstalk between τ and Aβ in astrocytes may increase our understanding of the role glia cells have in the pathology of AD with the aim of identifying novel therapeutic interventions to an otherwise currently incurable disease.
Keywords Tau, Beta-amyloid, 5xFAD, Mouse model, Astrocytes, Alzheimer's disease, Tauopathy