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Exploration of the tumorigenic, metabolic, and cognitive consequences of tau protein removal

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Theme

Basic Science and Pathogenesis

Abstract

Background: Tau accumulation causes tauopathies and drives cellular senescence, which can lead to inflammation, neurodegeneration, and cognitive impairment. The association between intracellular tau deposition and pathogenesis has prompted therapeutic strategies that reduce tau expression. However, tau is also critical in microtubule stabilization, synaptic plasticity, and maintaining DNA integrity. We investigated the impact of tau removal on brain cell senescence and associated neurocognitive behaviors in aged tau knockout (*Mapt*$^{0/0}$) and wild type control (*Mapt*$^{+/+}$) mice. We also assessed physical, metabolic, histological, and biochemical outcomes in *Mapt*$^{0/0}$ and *Mapt*$^{+/+}$ mice and in response to high fat diet (HFD), a stressor that drives DNA damage.

Method: 20-month-old female *Mapt*$^{0/0}$ and *Mapt*$^{+/+}$ mice were subjected to the Elevated Plus Maze to assess anxiety-like behavior. Mice were then fed control (CTL) or HFD (60% kcal fat) for 9 weeks. Behavioral and physical measures were then assessed, and brain tissue was further analyzed via gene expression, biochemistry, and histological assays.

Result: Tau knockout and HFD, separately and additively, caused weight gain and insulin resistance. Removing tau primed cells to proliferate, as *Mapt*$^{0/0}$ mice had increased body size, organ size, and tumor burden compared to *Mapt*$^{+/+}$. We observed no difference in senescence between genotypes on CTL diet. The HFD increased senescence only in *Mapt*$^{+/+}$ mice, whereas *Mapt*$^{0/0}$ mice displayed increased tumor burden. *Mapt*$^{0/0}$ mice displayed anxiety- and depressive-like behaviors on both diets. Transcriptomic and protein expression data revealed that several molecules responded similarly to tau removal and HFD exposure, but *Mapt*$^{+/+}$ and *Mapt*$^{0/0}$ mice responded differently to HFD. Genotype differences in DNA damage and cell cycle dysregulation were also observed.

Conclusion: *Mapt*$^{0/0}$ mice did not accumulate senescent cells but demonstrated anxiety-like behaviors in the presence of elevated DNA damage; thus tau knockout may drive neuropsychiatric phenotypes which can be dissociated from obesity and senescence. *Mapt*$^{0/0}$ mice also developed tumors, suggesting that tau plays a critical role in cell fate decisions, including senescence versus cancer. Overall, we found that tau removal prevents senescent cell accumulation with the tradeoff of tumorigenic, metabolic, and cognitive consequences. We caution against removing tau until a better understanding of its physiological roles are defined.

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