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Tau protein aggregation induces cellular senescence in the brain

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Statement of the Problem: Tau protein accumulation is the most common pathology among degenerative brain diseases, including Alzheimer's disease, progressive supranuclear palsy, chronic traumatic encephalopathy and over twenty others1. Mechanisms mediating tau toxicity are not well understood resulting in few treatment options and poor patient prognosis. Tau-containing neurofibrillary tangle (NFT) accumulation is the closest correlate with cognitive decline and cell loss. NFT-containing neurons do not die, which suggests secondary mechanisms are driving toxicity.

Methodology & Theoretical Orientation: We evaluated gene expression patterns of NFT-containing neurons microdissected from Alzheimer's disease patient brains, brain tissue from patients with supranuclear palsy and four independent Alzheimer's disease mouse models. The tau transgenic Alzheimer's disease mouse models were treated with a well-characterized pharmacological approach to remove senescent cells. The effects of drug treatment on tau pathology, brain structure and function were determined with careful histology and brain MRI analyses.

Findings: Neurons with NFTs from human Alzheimer's disease brain develop an expression profile consistent with cellular senescence. This complex stress response induces a near permanent cell cycle arrest, adaptations to maintain survival, cellular remodeling, and metabolic dysfunction. Moreover, senescent cells induce chronic degeneration of surrounding tissue through the secretion of pro-inflammatory, pro-apoptotic molecules termed the senescence-associated secretory phenotype (SASP). Using transgenic mouse models of tau-associated pathogenesis we found that NFTs induced a senescence-like phenotype including DNA damage, karyomegaly, mitochondrial dysfunction and SASP. Cdkn2a transcript level, a hallmark measure of senescence, directly correlated with brain atrophy and NFT load. We found this relationship extended to postmortem brain tissue from humans with progressive supranuclear palsy to indicate a phenomenon common to tau toxicity. Treatment of tau transgenic mice with drugs to remove senescent cells had decreased NFT burden, preserved neuronal and glial brain cells and improved brain structure and function.

Conclusion & Significance: Collectively, these findings indicate that NFTs induce cellular senescence in the brain, which contributes to neurodegeneration and brain dysfunction. Moreover, removing senescent cells offers a new therapeutic approach for the dozens of neurodegenerative diseases arising from pathogenic tau accumulation. Given the prevalence of tau protein deposition among neurodegenerative diseases, these findings have broad implications for understanding, and potentially treating, dozens of brain diseases.

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