Tau-induced astrocyte senescence and dysfunction in AD tauopathy

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Aging, cellular stress, and DNA damage are known inducers of cellular senescence. Cellular senescence is an irreversible state of cell cycle arrest, accompanied by the expression of proinflammatory mediators collectively known as the senescence-associated secretory phenotype (SASP). In Alzheimer's disease (AD), tau protein in neurons undergoes hyperphosphorylation and misfolding, forming pathogenic soluble aggregates (pathogenic tau). Pathogenic tau is then released from neurons during neuronal activation and is transmitted to postsynaptic cells in a prion-like manner. In addition to neurons, tau is expressed in various brain cell types, including astrocytes. In the present study, we tested the central hypothesis that soluble pathogenic tau can be transmitted to astrocytes and that tau transmission to astrocytes induces cytoskeleton destabilization and cellular dysfunction, contributing to AD progression. We found that pathogenic soluble tau is readily transmitted to primary human astrocytes in vitro and in vivo. Pathogenic tau transmission triggers phosphorylation of endogenous astrocyte tau, leading to the destabilization of the microtubule cytoskeleton. Furthermore, pathogenic tau transmission to astrocytes potently upregulated multiple markers of cellular senescence, demonstrating for the first time tau-induced astrocyte senescence. We also found that the density of dendritic spines and the dendritic area was pronouncedly decreased in neurons co-cultured with astrocytes undergoing tau-induced senescence. Our studies confirm that pathogenic tau is transmitted to cultured human astrocytes and triggers astrocyte senescence in a mouse model of AD tauopathy. Our data suggest that senescent astrocytes may be critical mediators of neuronal dysfunction in AD tauopathy.