Abstract

Chronic sterile inflammation is a pathological feature of Alzheimer’s disease (AD) and other neurodegenerative diseases. The mechanisms that drive neuroinflammation and its impact on AD progression are still incompletely understood. The accumulation of molecular damage in somatic cells can trigger cellular senescence, an irreversible state of cell cycle arrest accompanied by the expression of proinflammatory mediators known collectively as the “senescence-associated secretory phenotype” (SASP). During the pathogenesis of AD and other tauopathies, the microtubule-stabilizing factor tau is phosphorylated, becomes misfolded, and detaches from microtubules, destabilizing the microtubule cytoskeleton. Misfolded tau forms pathogenic soluble aggregates that are released extracellularly and are transmitted trans-neuronally, promoting native tau phosphorylation and aggregation in target cells. We recently showed that, in addition to neurons, pathogenic soluble extracellular tau aggregates propagate to brain microvascular endothelial cells, where microtubule destabilization triggers senescence/SASP. Because astrocytes have a critical role in the regulation of both synaptic function and cerebral blood flow and are directly exposed to tau at its site of release, the tripartite synapse, we conducted studies to define whether soluble aggregated tau propagates to astrocytes, inducing astrocyte senescence/SASP and neuronal dysfunction/damage.

Our studies indicate that, similar to neurons, tau can be propagated transcellularly to astrocytes, triggering cellular senescence/SASP. Our studies suggest that astrocyte senescence is detrimental to dendritic and synaptic structure and density, suggesting that pathogenic soluble tau-induced astrocyte senescence may contribute to synaptic dysfunction and loss in AD. Drugs that eliminate senescent cells are FDA-approved and antibody-based approaches to remove tau from brain are already in clinical trials. Our studies suggest that these interventions could be effective in the treatment of AD.

Results

Background

Pathogenic tau triggers microtubule destabilization and senescence in HBECs

Figure 1. Soluble tau aggregate exposure induces senescence and SASP in human brain microvascular endothelial cells in vitro. (A) Representative images of cultures of primary human brain microvascular endothelial cells (HBECs) treated with soluble tau aggregates (O. Tau) or vehicle. Cells were labeled with Hoechst33342 to highlight the nucleus and were imaged. Quantitative analyses of cell, P416, p21 and p53. (B) Quantitative real-time PCR measurements of mRNAs abundance for cell cycle arrest markers and inflammatory SASP (P416, p21, p53). (C) Representative images of microtubule density (β-tubulin) in control (left) and oligomeric tau-treated (right) HBECs. Cross-sectional microtubule density was decreased in HBEC treated with oligomeric tau. Representative Western blot of p21 and phosphorylated p21 (p21DP) in HBECs. The ratio of tau to phosphorylated tau was increased in oligomeric tau-treated HBECs, indicating increased microtubule destabilization. Data are representative images and means ± SEM.

Figure 2. Proprietary tau aggregates have a wider distribution of aggregate lengths than self-oligomerized tau. Preparatory soluble tau O4, aggregates prepared using an analytical size-exclusion method, self-aggregating tau (tau-2) at 37°C overnight. Replicate image of tau aggregates ranging from micrometers (MM) to 100 micrometers (μm) were measured. The average aggregate width of tau aggregates was 12 μm (±0.8). (B) Representative image of tau aggregates ranging from micrometers (MM) to 100 micrometers (μm) were measured. The average aggregate width of tau aggregates was 12 μm (±0.8).

Figure 3. Increased cellular senescence markers after transmission of soluble tau aggregates to human astrocytes and in brains of human tau transgenic mice. (A) Human astrocyte cells treated with soluble tau oligomers (O. Tau) or vehicle for 48 hours. (B) Representative images of primary human astrocytes expressing increased SASP (P416, p21, p53). (C) Western blots of total and phosphorylated p21 in control and tau-treated astrocytes. (D) Real-time PCR of p21 expression in astrocytes treated with tau oligomers (O. Tau) or vehicle.

Cellular senescence is increased primary human astrocytes

Figure 4. Increased cellular senescence in cortices of human tau transgenic mice and isolation of single cell types for senescence characterization. Mean ± SEM of cell cycle arrest and SASP activity in primary mouse cortical astrocytes from wild-type (O) and human tau transgenic mice (O. Tau). (B) Real-time PCR of p21 expression in wild-type and human tau transgenic mice astrocytes treated with vehicle (O) and tau oligomers (O. Tau).

Figure 5. Primary mouse neurons co-cultured with senescent astrocytes decreases measures of neuronal integrity. (A) Representative images of primary mouse neurons treated with soluble tau aggregates (O. Tau) or vehicle. Cells were labeled with DAPI to highlight the nucleus and were imaged. Quantitative analyses of cell, P416, p21, and p53. (B) Real-time PCR of p21 expression in primary mouse neurons treated with soluble tau aggregates (O. Tau) or vehicle. Mean ± SEM.

Conclusions

(a) Soluble higher molecular weight tau are transmitted to astrocytes
(b) Internalization of HMW tau oligomers triggers cellular senescence in vitro
(c) In vitro, elevated tau expression leads to increased brain cellular senescence.
(d) Co-culture of senescent astrocytes induces negative changes in primary neurons

Future Directions

(a) Develop an in vivo model targeting senescent cell manipulation
(b) Measure synaptic bouton density
(c) Immunodepletion of SASP Tau

Acknowledgments

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Conclusions and Future Directions

Abstract

Tau-induced astrocyte senescence as a driver of neuronal dysfunction in AD

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