

Clearance of intracellular tau protein pathology through novel immunotherapy approaches

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Pathological tau aggregates cause cognitive decline in neurodegenerative tauopathies, including Alzheimer's disease (AD). These aggregates are prevalent within intracellular compartments. Current tau immunotherapies have shown limited efficacy in clearing intracellular tau aggregates and improving cognition in clinical trials. In this study, we developed toxic tau conformation-specific monoclonal antibody-2 (TTCM2) that selectively recognized pathological tau aggregates in brain tissues from patients with AD, dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP). TTCM2 potently inhibited tau-seeding activity, an essential mechanism underlying tauopathy progression. To effectively target intracellular tau aggregates and ensure rapid delivery to the brain, TTCM2 was loaded in micelles (TTCM2-ms) and administered through the intranasal route. We found that intranasally administered TTCM2-ms efficiently entered the brain in hTau-tauopathy mice, targeting pathological tau in intracellular compartments. Moreover, a single intranasal dose of TTCM2-ms effectively cleared pathological tau, elevated synaptic proteins levels, and improved cognitive functions in aged tauopathy mice. Mechanistic studies revealed that TTCM2-ms cleared intracellular, synaptic, and seed-competent tau aggregates through tripartite motif-containing 21 (TRIM21), an intracellular antibody receptor and E3 ubiquitin ligase known to facilitate proteasomal degradation of cytosolic antibody-bound proteins. TRIM21 was found to be essential for TTCM2-ms-mediated clearance of tau pathology. Our study collectively provides evidence of the effectiveness of nasal tau immunotherapy in targeting and clearing intracellular tau pathology through TRIM21 and enhancing cognition in aged tauopathy mice. This study could be helpful in designing effective tau immunotherapies for AD and other tauopathies.