Pathomechanisms of TDP-43 in Alzheimer's disease

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Mutations in TAR DNA-binding protein 43 (TDP-43) are implicated in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), where its nuclear clearance and cytoplasmic aggregation are key pathological features. Increasing evidence shows that TDP-43 pathology also occurs in Alzheimer's disease (AD), with cytoplasmic TDP-43 inclusions present in a significant subset of cases. However, the mechanistic link between TDP-43 proteinopathy and classical AD features, such as amyloid-β (Aβ) deposition, remains unclear. TDP-43 can undergo liquid–liquid phase separation (LLPS), forming membraneless biomolecular condensates. Disruptions in LLPS have been associated with TDP-43 aggregation, yet its role in AD has not been directly studied. To explore this, we generated mice expressing LLPS-deficient endogenous TDP-43 and crossed them with 5XFAD mice, a model of amyloid pathology. We found that TDP-43 condensates are significantly elevated in AD patients and 5XFAD mice, implicating LLPS in disease progression. Strikingly, suppressing TDP-43 LLPS in 5XFAD mice led to reduced amyloid plaque burden, neuroinflammation, neurodegeneration, and cognitive deficits. These findings provide the first direct evidence that TDP-43 LLPS contributes to amyloid pathology and neurotoxicity in AD. Our study identifies LLPS as a critical mechanism in TDP-43-mediated AD pathogenesis and a potential therapeutic target. Given TDP-43 LLPS is implicated in multiple neurodegenerative diseases, targeting this process may offer broad translational potential.

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