Title: Nuclear-import receptors as gatekeepers of pathological phase transitions

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Cytoplasmic mislocalization and aggregation of TAR DNA-binding protein-43 (TDP-43) is a hallmark of the amyotrophic lateral sclerosis and frontotemporal dementia (ALS/FTD) disease spectrum, causing both nuclear loss-of-function and cytoplasmic toxic gain-of-function phenotypes. While TDP-43 proteinopathy has been associated with defects in nucleocytoplasmic transport, how this process is linked to TDP-43 pathophysiology is still poorly understood. Recent advances suggest that beyond their canonical function in the nuclear import of protein cargoes, nuclear-import receptors (NIRs) of the karyopherin-β protein family can prevent and reverse aberrant phase transitions of TDP-43, FUS, and related RNA-binding proteins with prion-like domains and restore their nuclear localization and function. Here we present new evidence for the role of NIRs and other components of the nucleocytoplasmic transport machinery in regulating pathological phase transitions of TDP-43 and other aggregation-prone proteins in neurodegenerative proteinopathies.

Sponsored By: NIH grants RF1AG076122, R21AG085314, R01AG077771, and Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Award #23A04 to WR.

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