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Cytoplasmic accumulation of the Alzheimer's disease- and ALS-linked RNA-binding protein SFPQ by zinc-induced polymerisation

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SFPQ is an abundant nuclear protein implicated in many aspects of RNA biogenesis. Importantly, nuclear depletion and cytoplasmic accumulation of SFPQ has been linked to neuropathological conditions such as Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Here we report the structural basis of cytoplasmic relocation of SFPQ induced by zinc. The crystal structure in complex with zinc reveals the intermolecular interactions of SFPQ mediated by zinc, resulting in infinite polymerisation of SFPQ. As anticipated, the application of zinc to neuronal cells induced cytoplasmic relocation and aggregation of SFPQ. Mutagenesis on the three histidine residues ligating zinc resulted in a significant reduction in zinc-binding affinity *in vitro* and the zinc-induced cytoplasmic aggregation of SFPQ in neuronal cells. Taken together, we propose that dysregulation of zinc in neuronal cells may represent one potential mechanism that leads to an imbalance in the nucleocytoplasmic distribution of SFPQ, which is emerging as a hallmark of neurodegenerative diseases including AD and ALS.

Speakers Gender

Female

Travel Funding

No

Level of Expertise

Experienced Researcher

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No

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