FUS Phase Separation is Modulated by Chaperones and by Interdomain Cation-pi Interactions

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Physiological and Pathological Phase Separation of FUS is Regulated by Methylation of Cooperative Cross-Domain Cation-Pi Interactions and interaction with TNPO1

Reversible phase separation underpins the role of FUS in ribonucleoprotein granules and other membraneless organelles. This process is driven in part by the intrinsically disordered low complexity (LC) domain. However, we have recently shown that cooperative cation-pi interactions between tyrosines in the LC domain and arginines in structured C-terminal domains also contribute. These interactions are likely to be authentic cation-π interactions, rather than planar-π interactions because replacement of arginines by lysine preserves phase separation. Crucially, FUS phase separation is modulated by the post-translational state of arginine residues. Arginine methylation (especially asymmetric dimethylation) and citrulllination reduce phase separation, whereas arginine hypomethylation promotes phase separation and gelation. Indeed, significant hypomethylation, which occurs in FUS-associated frontotemporal lobar degeneration, induces FUS condensation into stable β-sheet-rich hydrogels that disrupt RNP granule function and impair new protein synthesis in neuron terminals. We have also shown that transportin 1 (TNPO1) acts as a physiological molecular chaperone of FUS in neuron terminals, reducing FUS phase separation and gelation, and rescuing protein synthesis. These results demonstrate how FUS condensation is physiologically regulated, and how perturbations in these mechanisms either by missense mutations associated with fALS-FUS, or by altered post-translational modification and interactome states can lead to disease.