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Molecular Behavior of Disordered Translation Factor Eif4b: From Monomers to Oligomers and Condensates

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Disordered translation initiation factor eIF4B is essential for efficient cap-dependent translation, particularly for mRNAs with structured 5' untranslated regions. Despite the significant functional importance, this factor is rarely observed in cryo-EM structures of translation complexes due to high intrinsic disorder. As a result, its molecular details and especially those of the long intrinsically disordered region (IDR) remain largely unknown.

By integrating experiments with molecular simulations, we demonstrate that the IDR eIF4B orchestrates an intricate transition from monomers to a condensed phase. Across this transition dynamic oligomeric clusters form that favor mesoscopic phase separation. Our single-molecule FRET assays allow following the conformation and dynamics of the protein across all these molecular states. The observed complex self-association landscape displays strong sensitivity to even marginal changes of ionic strength and molecular crowding. This translates into sensitive regulation of eIF4B nanoscopic and mesoscopic behaviors driven by protein post-translational modifications, binding partners or changes to the cellular environment. Unsurprisingly, the molecular driving forces that govern the in vitro self-association of eIF4B play a pivotal role in determining its condensation behavior during cellular stress and the assembly into stress granules.