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| Title: | Decoding the Interaction of Chaperones with a Yeast Prion Domain |
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| Keywords: | Biology<br>Molecular & Cellular Biophysics |
| Issue Date: | 29-Aug-2023 |
| Publisher: | IISER Mohali |
| Abstract: | Protein misfolding and aggregation are key pathological features of several neurodegener- ative diseases, including Alzheimer's, Parkinson's, and prion diseases. 12 The prion protein Sup35, in particular, serves as a model system for studying the mechanisms underlying pro- tein aggregation and propagation. 3 This in vitro research investigates the complex interplay between molecular chaperones Ydj1, and Hsp104, focusing on their roles in chaperon- ing processes of Sup35 aggregates, in the phase-separated droplets of Ydj1. Employing a comprehensive array of biochemical, biophysical, and cell biology techniques, this study sheds light on the multifaceted interactions between these chaperones and Sup35. Initial investigations focus on the phase separation propensity of Ydj1 at physiological pH and its susceptibility to forming distinct liquid-like compartments. Through co-localization studies using advanced microscopy techniques, the spatial relationships between Sup35 aggregates and the chaperones are explored, shedding light on their potential influence on aggrega- tion behavior. Furthermore, the chaperoning activities of Ydj1 and Hsp104 are thoroughly characterized in the context of Sup35 aggregation. Biochemical assays are employed to as- sess their effects on the solubility, morphology, and size distribution of Sup35 aggregates. The study also investigates the potential of these chaperones to modulate the templated conversion of soluble Sup35 to its aggregated fibril conformation. Our investigation re- veals Ydj1's unique ability to drive Sup35 phase separation in conjunction with Hsp104 at physiological pH. The significance of environmental factors such as pH, temperature, and salt concentration on the propensity of phase separation is highlighted, underscoring the intricate regulation of this process. Furthermore, domain-specific analyses elucidate the variations in phase separation propensity within distinct regions of Ydj1. Ydj1, along with Hsp104, are found to exhibit distinct roles in preventing the early stages of aggrega- tion and maintaining the solubility of Sup35, where Hsp104 demonstrates its unique ability to remodel Sup35 aggregates into a more amorphous and less toxic conformation. 4 This study advances our comprehension of the roles played by chaperones in governing phase separation and protein aggregation, offering insights into potential therapeutic strategies for protein misfolding diseases. Ultimately, this research deepens our understanding of cellu- lar proteostasis mechanisms and their perturbations in disease states, paving the way for innovative approaches to tackle protein misfolding-associated neurodegenerative disorders. The results reveal intricate and dynamic interactions between Sup35 aggregates and the chaperones, influencing aggregation's kinetics and thermodynamics. By deciphering the IXmolecular mechanisms that influence these processes, avenues for targeted interventions emerge, holding promise for the development of future treatments. The findings of this study have broader implications for understanding the fundamental mechanisms underly- ing protein misfolding diseases. By elucidating the roles of chaperones in modulating phase separation and aggregation, this research provides crucial insights into potential therapeutic strategies targeting protein aggregation disorders. Ultimately, this master's thesis advances our understanding of the cellular machinery governing protein homeostasis and offers new perspectives for developing novel therapeutic interventions for protein misfolding diseases. |
| Description: | under embargo period |
| URI: | http://hdl.handle.net/123456789/5716 |
| Appears in Collections: | MS-18 |

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