Title:	Mechanistic insights into the role of molecular and small chemical chaperones in the prion-like transmission via yeast prison amyloids
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Abstract:	Mechanistic insights into the role of molecular and small chemical chaperones in the prion-like transmission via yeast prion amyloids Sayanta Mahapatra Supervisor: Dr. Samrat Mukhopadhyay Abstract: The prion-like self-perpetuating conformational conversion is involved in transmissible neurodegenerative diseases and the non-Mendelian inheritance traits of yeasts. The transmissibility of amyloids depends on several factors that regulate their number and seeding potential during autocatalytic amplification cycles. Toward that aim, we studied the prion determinant of Saccharomyces cerevisiae Sup35 (NM domain) to investigate the role of two such critical molecular regulators via in vitro recapitulation. For our study, we used the disaggregase Hsp104 as the molecular chaperone and ATP as the small chemical chaperone. Sub-stoichiometric Hsp104, reminiscent of chaperone under-expression during aging, accelerates the formation of prefibrillar species but also prolongs their persistence by introducing unusual kinetic halts and delaying their conversion into less transmissible matured fibrils. Biochemical studies and site- specific dynamic readouts reveal that Hsp104-created amyloids possess an altered, more ordered packing than the NM-only amyloids and also display an enhanced seeding ability that may promote prion-like amyloid propagation. On the other hand, our aggregation kinetics reveal that physiologically high concentrations of ATP molecules accelerate NM aggregation. Nevertheless, ATP also dose-independently disaggregates existing NM fibrils. However, the stable, compact, ATP-bound amyloids polymerized in the presence of high concentrations of ATP show nominal fragmentation by additional ATP or by Hsp104, which may restrict the prion-like transmission by limiting the number of seeds. Also, circular dichroism and Raman spectroscopic data suggest that trace amounts of ATP give rise to seeding-inefficient amyloids for their reduced β-sheet content, showing another anti-prion attribute of ATP. We also carry out seeding with the amyloids generated from seeded aggregation reactions of NM. In subsequent seeding cycles, we observe a variation in the seeding efficiency of the amyloids generated in seeded aggregations with different seed sizes.
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