Title:	Substoichiometric Hsp104 regulates the genesis and persistence of self-replicable amyloid seeds of Sup35 prion domain
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Abstract:	Prion-like self-perpetuating conformational conversion of proteins is involved in both transmissible neurodegenerative diseases in mammals and non-Mendelian inheritance in yeast. The transmissibility of amyloid-like aggregates is dependent on the stoichiometry of chaperones such as heat shock proteins (Hsps), including disaggregases. To provide the mechanistic underpinnings of the formation and persistence of prefibrillar amyloid seeds, we investigated the role of substoichiometric Hsp104 on the in vitro amyloid aggregation of the prion domain (NM-domain) of Saccharomyces cerevisiae Sup35. At low substoichiometric concentrations, we show Hsp104 exhibits a dual role: it considerably accelerates the formation of prefibrillar species by shortening the lag phase but also prolongs their persistence by introducing unusual kinetic halts and delaying their conversion into mature amyloid fibers. Additionally, Hsp104-modulated amyloid species displayed a better seeding capability compared to NM-only amyloids. Using biochemical and biophysical tools coupled with site-specific dynamic readouts, we characterized the distinct structural and dynamical signatures of these amyloids. We reveal that Hsp104-remodeled amyloidogenic species are compositionally diverse in prefibrillar aggregates and are packed in a more ordered fashion compared to NM-only amyloids. Finally, we show these Hsp104-remodeled, conformationally distinct NM aggregates display an enhanced autocatalytic self-templating ability that might be crucial for phenotypic outcomes. Taken together, our results demonstrate that substoichiometric Hsp104 promotes compositional diversity and conformational modulations during amyloid formation, yielding effective prefibrillar seeds that are capable of driving prion-like Sup35 propagation. Our findings underscore the key functional and pathological roles of substoichiometric chaperones in prion-like propagation.
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