Protein quality control:
From mechanisms to disease

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ABSTRACT BOOK

Investigation of differential interactions of molecular chaperones with amyloid fibrils of yeast prions

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Baker's yeast Saccharomyces cerevisiae is a convenient model to study various cellular processes. Yeast self-perpetuating protein aggregates (yeast prions) provide a framework to investigate the interaction of misfolded proteins with the protein quality control (PQC) machinery, including molecular chaperones and protein-sorting factors. In our work, we took an efforst to systematically characterize the effects of different PQC components on the two most studied yeast prions, [PSI+] and [URE3]. The major molecular chaperone that facilitates propagation of all known yeast amyloid prions is the hexameric AAA+ ATPase Hsp104 that catalyzes fibril fragmentation thus generating new prion seeds. We show that, despite frequent statements in the literature, overproduction of Hsp104 cures both [PSI+] and [URE3]. On the other hand, we demonstrate that major cytosolic chaperones of the Hsp40 group, Sis1 and Ydj1, as well as protein sorting factors that control their intracellular localization, oppositely affect propagation of [PSI+] and [URE3]. Elevated expression of YDJ1 or decrease in the cytosolic levels of Sis1, caused by its relocalization, efficiently eliminates [URE3], but enhances [PSI+]. We suggest that changes in the cytosolic balance of different Hsp40, i.e. Ydj1 and Sis1, oppositely affect propagation of [PSI+] and [URE3] due to different dependencies of these prions on two distinct activities of the Hsp104 machinery, i.e. fibril fragmentation and aggregate malpartition. These dependencies may in turn result from different affinities of Hsp40 to amyloid fibrils formed by different prion proteins. Preliminary data suggest that Hsp40s indeed differ in their binding capabilities with respect to amyloid fibrils, supporting this hypothesis. Our results provide new insights into the differential interplay between yeast prion fibrils and protein quality control system.

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