Chaperone Titration as a Mechanism of Prion Appearance

Prion proteins confer new phenotypes to cells by adopting an alternative fold that changes their function and by templating the conversion of normally folded protein to the same state. While we understand how prions in yeast maintain themselves in cells and colonies once they arise, the mechanism by which prions first appear is poorly understood. Our studies suggest that one prion, called \([PIN^+]\), encourages the induction of another prion, called \([PSI^+]\), by titrating away chaperones that would otherwise resolve the alternative protein folds as they initially arise and thereby inhibit \([PSI^+]\) induction. My studies reveal additional evidence of chaperone titration by demonstrating that \([PIN^+]\) interferes with the accumulation of \([PSI^+]\) in cells already propagating the two prions when chaperone levels are reduced. Thus, \([PIN^+]\) acts as a decoy for chaperones and thereby promotes the persistence of nascent \([PSI^+]\) particles.

During \([PSI^+]\) prion formation a nucleation event must occur to form the initial prion aggregate, followed by amplification of the aggregate. Fragmentation by chaperones actively prevents the initial nucleation event. The \([PIN^+]\) prion helps overcome this barrier to nucleation by titrating chaperones away from newly forming aggregates, allowing them to nucleate and amplify before destruction by chaperones.