ABSTRACT
UNDERSTANDING HOW CHAPERONES INFLUENCE PROTEIN AGGREGATION

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Cells depend on properly folded proteins to function and remain healthy. If proteins adopt a nonnative conformation, they may have an increased propensity to clump together or aggregate, which can compromise cell viability. Unwanted aggregates are linked to a class of diseases called proteinopathies, which include fatal disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS). Fortunately, cellular factors, known as molecular chaperones, help maintain protein homeostasis by limiting and disassembling protein aggregates. However, the mechanisms that underlie how chaperones modify protein aggregation are poorly understood. The goal of this dissertation is to explore the molecular mechanisms used by chaperones to limit aggregate formation, and how chaperones facilitate aggregate disassembly. I use *Saccharomyces cerevisiae* as a model system to study two different aggregate types: amorphous and amyloid. Stress granules (SGs) are a type of amorphous aggregate that form in response to environmental insults and are disassembled by chaperones once stress subsides. Amyloids are much less dynamic than SGs but can be fragmented by chaperone intervention. First, I find that the Hsp70 chaperone members Ssa1 and Ssa2 limit SG protein aggregation under non-stress conditions and help properly disassemble SGs following heat shock. The next chapter addresses how amorphous and amyloid aggregates coexist. I find that the presence of amyloid delays the disassembly of SGs following heat shock, and this delay is overcome by chaperone overexpression. My data suggest that amyloid limits the availability or accessibility of chaperones to SGs, which may lead to SG solidification and disease progression. Lastly, I explore Hsp104, a disaggregase chaperone specific to fungi that is required for SG and amyloid disassembly. Using engineered point mutations, I find that the middle domain of Hsp104 controls the partial threading of substrates to ensure they are functional following disaggregation. Taken together, this dissertation has advanced our knowledge of how chaperones manage and disassemble protein aggregates and may offer important insights for understanding proteinopathy progression and potential therapeutics.