Report

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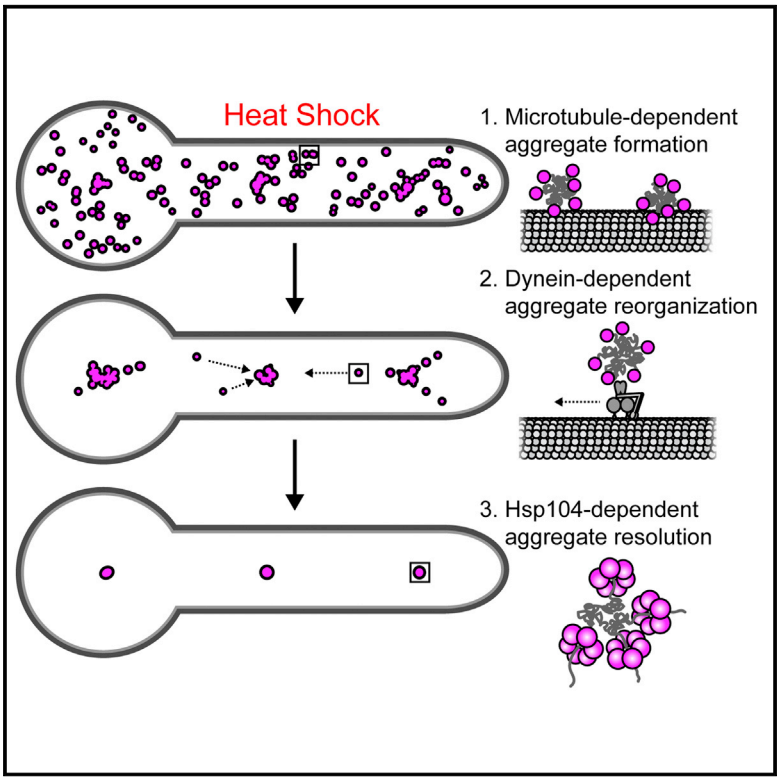
Cytoplasmic Dynein Is Required for the Spatial Organization of Protein Aggregates in Filamentous Fungi

Graphical Abstract



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In Brief

Spatial organization and clearance of damaged proteins is important for cell viability and aging. Egan et al. investigate this process in *Aspergillus nidulans*, finding that the microtubule-based motor cytoplasmic dynein promotes clearance through coalescence of protein aggregates. This has implications for understanding transport processes in disease.

Highlights

- *Aspergillus nidulans* protein aggregates coalesce into discrete structures
- Microtubules facilitate the formation of Hsp104-positive inclusions
- Cytoplasmic dynein promotes aggregate clearance through their coalescence
- Impaired aggregate clearance impedes trafficking of conventional dynein cargo

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Cytoplasmic Dynein Is Required for the Spatial Organization of Protein Aggregates in Filamentous Fungi

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SUMMARY

Eukaryotes have evolved multiple strategies for maintaining cellular protein homeostasis. One such mechanism involves neutralization of deleterious protein aggregates via their defined spatial segregation. Here, using the molecular disaggregase Hsp104 as a marker for protein aggregation, we describe the spatial and temporal dynamics of protein aggregates in the filamentous fungus *Aspergillus nidulans*. Filamentous fungi, such as *A. nidulans*, are a diverse group of species of major health and economic importance and also serve as model systems for studying highly polarized eukaryotic cells. We find that microtubules promote the formation of Hsp104-positive aggregates, which coalesce into discrete subcellular structures in a process dependent on the microtubule-based motor cytoplasmic dynein. Finally, we find that impaired clearance of these inclusions negatively impacts retrograde trafficking of endosomes, a conventional dynein cargo, indicating that microtubule-based transport can be overwhelmed by chronic cellular stress.

INTRODUCTION

Maintaining the integrity of the cellular proteome is a universal biological challenge that is addressed with a variety of proteostatic mechanisms, including the ubiquitin-proteasome system, autophagy pathways, and molecular disaggregases and chaperones (Tyedmers et al., 2010). Failure of these quality control mechanisms carries severe penalties for the cell, ranging from the cytotoxic accumulation of misfolded and damaged proteins to accelerated cellular aging (Coelho et al., 2013, 2014; Erjavec et al., 2007; Moseley, 2013; Nyström and Liu, 2014; Vendruscolo et al., 2011). Defects in maintaining protein homeostasis are also pervasive in human pathology, particularly in neurodegenerative disorders such as Alzheimer's disease and amyotrophic lateral sclerosis (Vendruscolo et al., 2011). Despite such broad consequences, an understanding of the mechanistic relationship between aberrant protein aggregation and cytotoxicity is still incomplete.

Recent studies have focused on how spatial organization of protein aggregates promotes cellular fitness (Moseley, 2013; Sontag et al., 2014; Tyedmers et al., 2010). Coalescence and asymmetric inheritance of proteinaceous inclusions have been described in mammalian cells, budding yeast, fission yeast, and bacteria, and represent a conserved mechanism of cellular aging in which damaged proteins accumulate in mother cells, allowing daughter cells to maximize their replicative potential (Moseley, 2013; Ogrodnik et al., 2014; Sontag et al., 2014; Tyedmers et al., 2010). While the advantages conferred by such spatial quality control are evident across the evolutionary scale, mechanistic details of these defined pathways are still emerging.

The role of the cytoskeleton in spatial quality control is an area of active investigation. In fission yeast and bacteria, coalescence and asymmetric inheritance of damaged proteins are independent of cytoskeletal elements (Coelho et al., 2014; Lindner et al., 2008; Winkler et al., 2010). Although there are conflicting reports regarding the dispensability of actin for the coalescence of aggregates into defined inclusions in budding yeast (Escusa-Toret et al., 2013; Specht et al., 2011; Spokoini et al., 2012), an intact actin cytoskeleton is required for the selective retention of these inclusions in mother cells during cytokinesis (Erjavec et al., 2007; Ganusova et al., 2006; Liu et al., 2010; Tessarz et al., 2009). However, alternative models have been proposed and include the possibility of retention through tethering to organelles (Liu et al., 2010; Spokoini et al., 2012; Zhou et al., 2011, 2014).

Microtubules are also involved in spatial quality control. The best studied example is the mammalian aggresome-autophagy pathway, which uses microtubule-based transport to compartmentalize protein aggregates at the microtubule-organizing center (MTOC) during interphase (Chin et al., 2010). Additionally, this association of damaged cellular proteins with the MTOC facilitates their asymmetric inheritance during cytokinesis (Ogrodnik et al., 2014). The contribution of microtubules in other eukaryotes is less clear. Microtubule-dependent inclusions have been reported in yeast, particularly in disease models in which aggregation-prone human proteins localize to aggresome-like structures (Kaganovich et al., 2008; Muchowski et al., 2002; Wang et al., 2009). However, because yeast cells use actin rather