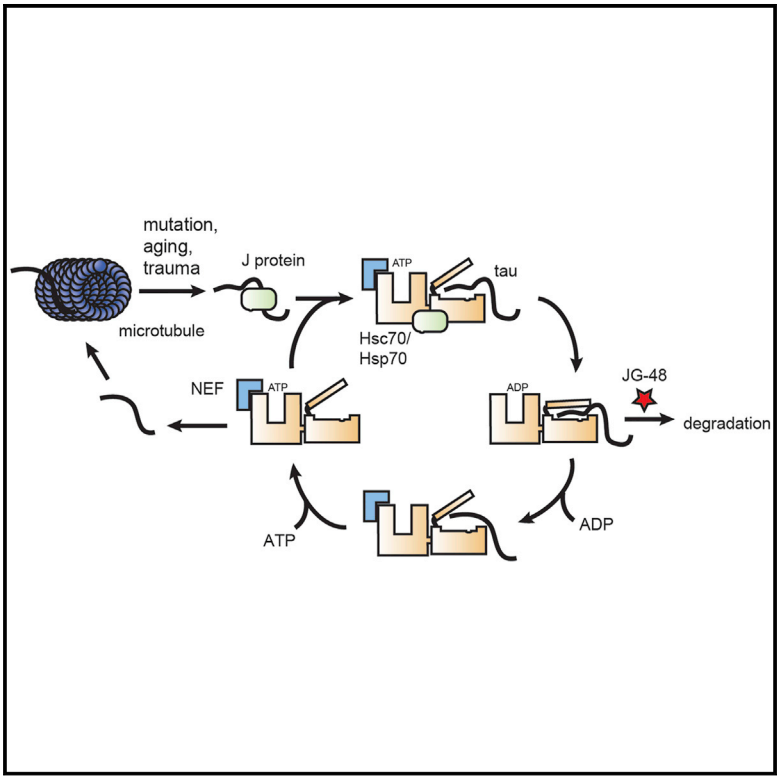
Article

Cell Chemical Biology

Stabilizing the Hsp70-Tau Complex Promotes Turnover in Models of Tauopathy

Graphical Abstract



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In Brief

Tauopathies are characterized by the accumulation and aggregation of tau into neurofibrillary tangles. Young et al. use a chemical biology approach to show that favoring the association of Hsp70-family chaperones with tau leads to its degradation, normalizing tau homeostasis in multiple disease models.

Highlights

- The Hsp70 inhibitor JG-48 reduces tau levels in models of tauopathy
- JG-48 traps tau in an Hsp70-bound complex
- Perturbations that promote binding to tau also trigger its degradation

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Stabilizing the Hsp70-Tau Complex Promotes Turnover in Models of Tauopathy

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SUMMARY

Heat shock protein 70 (Hsp70) is a chaperone that normally scans the proteome and initiates the turnover of some proteins (termed clients) by linking them to the degradation pathways. This activity is critical to normal protein homeostasis, yet it appears to fail in diseases associated with abnormal protein accumulation. It is not clear why Hsp70 promotes client degradation under some conditions, while sparing that protein under others. Here, we used a combination of chemical biology and genetic strategies to systematically perturb the affinity of Hsp70 for the model client, tau. This approach revealed that tight complexes between Hsp70 and tau were associated with enhanced turnover while transient interactions favored tau retention. These results suggest that client affinity is one important parameter governing Hsp70-mediated quality control.

INTRODUCTION

Heat shock protein 70 (Hsp70/HSPA1A) and heat shock cognate 70 (Hsc70/HSPA8) are highly conserved molecular chaperones that are expressed in the cytosol of all eukaryotic cells. These factors are often referred to as "triage" chaperones because they bind to misfolded proteins and somehow choose to shuttle them to the lysosome-autophagy pathway or ubiquitin-proteasome system for degradation (Mayer, 2013). Although they play a complex and important role in proteostasis, members of the Hsp70 family have a relatively simple structure, composed of a 45 kDa nucleotide-binding domain (NBD) and a 25 kDa substrate-binding domain (SBD) (Jiang et al., 2005; Zhuravleva et al., 2012). The NBD has a deep cleft for binding ATP, while client proteins bind in a β-sandwich region of the SBD (Bertelsen et al., 2009). These two domains are allosterically linked, with nucleotide turnover in the NBD controlling the affinity of SBD-client interactions (Bauer et al., 2015; Clerico et al., 2015; Palleros et al., 1993; Zhuravleva and Gierasch, 2015). In the ATP-bound form, clients bind Hsp70s with fast-on, fast-off kinetics, while hydrolysis to the ADP-bound form stabilizes the SBD-client interaction by slowing the off-rate (Ha and McKay, 1995).

Co-chaperones bind members of the Hsp70 family to regulate their nucleotide cycling (Mayer, 2013). These co-chaperones include J proteins, which accelerate ATP hydrolysis, and nucleotide exchange factors (NEFs), which promote the discharge of ADP. Together, J proteins and NEFs coordinate turnover, ultimately regulating the affinity for clients. Then, additional co-chaperone families, including the tetratricopeptide repeat domain proteins, bind Hsp70s and help direct bound clients into specific pathways. For example, CHIP is an E3 ubiquitin ligase that directs Hsp70 clients to the proteasome (Dickey et al., 2006; Shimura et al., 2004). Other co-chaperones, including members of the Bag family of NEFs, link Hsp70 and its clients to the lysosome-autophagy pathway (Demand et al., 2001). Together, Hsp70, Hsc70, and their co-chaperones cooperate to identify misfolded proteins and somehow enact the decision to degrade them. This process is central to health and proteostasis because it limits protein accumulation; however, the molecular mechanisms are not clear.

Microtubule-binding protein tau (MAPT/tau) has served as an important client for understanding chaperone-mediated quality control (Miyata et al., 2011). The accumulation of aggregated tau is a pathological feature of many neurodegenerative disorders, including Alzheimer's disease, frontotemporal dementia, and progressive supranuclear palsy. Tau is an intrinsically disordered protein (Narayanan et al., 2010) that normally stabilizes microtubules. As a result of alternative splicing, tau exists as six major isoforms (Ballatore et al., 2007), which are named based on the inclusion of variable numbers of microtubule-binding repeats (either 3R or 4R) and the number of N-terminal extensions (0N, 1N, or 2N). The aggregation-prone regions of tau are located in the microtubule-binding repeats, such that free tau (i.e., the pool that is not bound to microtubules) is considered to be most likely to aggregate. Indeed, mutations, such as P301L and A152T (Coppola et al., 2012; Hong et al., 1998; Kara et al., 2012; Vogelsberg-Ragaglia et al., 2000), and/or