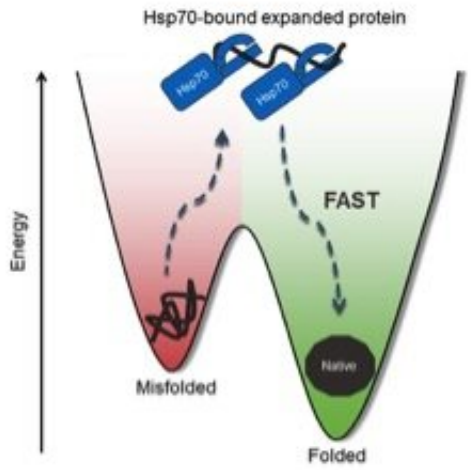
How chaperones promote correct shapes of proteins even under denaturing stress conditions

January 20 2020, by Rahmi Imamoglu



Hsp70 resolves misfolded states and accelerates productive folding of proteins via the expanded conformation. Credit: Rahmi Imamoglu

Proteins are macromolecules synthesized under the control of DNA and perform almost all functions in our cells. However, they must fold into their unique three-dimensional structures to fulfill their biological activities. Protein folding is an error-prone process, and how it is accomplished successfully is a great question in cell biology, given that misfolded proteins are the primary cause of many neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and

Huntington's disease. To ensure correct folding and to prevent misfolding, cells express various classes of proteins called molecular chaperones. Molecular chaperones are a protein class that assist proteins in reaching the correct three-dimensional structures and prevent misfolding. Impairment in molecular chaperones has been found to be relevant to neurodegenerative diseases and cancers. Understanding how molecular chaperones assist other proteins has great biological and medical importance.

Hsp70 is one of the main chaperone classes that play an essential role in protein folding and protein homeostasis, and is therefore involved in neurodegenerative diseases and cancers. Researchers have known that Hsp70 binds to unfolded and misfolded proteins, thereby preventing their aggregation. Aggregation occurs when more than one unfolded or misfolded proteins clump together, which usually results in pathological forms.

It has been long assumed that Hsp70 does not change the folding kinetics of proteins, it could bind unfolded or misfolded proteins and prevent non-native, undesired interactions that cause aggregation. However, interestingly, we found that Hsp70 chaperones accelerate the productive folding of proteins in addition to aggregation prevention. It is surprising because it gives a new insight on the physiological roles of Hsp70 that not only prevent aggregation at stress conditions, but also promote the native state via an accelerated folding mechanism. Under stress conditions such as high temperature, proteins tend to misfold since their native, functional structures are marginally stable. We suggest that Hsp70, even under denaturing conditions, promotes the native state via an accelerated folding mechanism since the Hsp70 assisted folding is faster than the misfolding of proteins under stress conditions.

Additionally, we tested how Hsp70 accelerates the folding of proteins. We found that Hsp70 itself cannot prevent the formation of misfolded

proteins, but rapidly converts it to the native state via a highly expanded mechanism. Hsp70 binds to the compact, misfolded, non-native states of proteins, and leads to the formation of a highly expanded conformation. Hsp70 commits the bound expanded protein to fast folding, and the Hsp70 system promotes folding via the expanded conformation.

Understanding the folding mechanism of Hsp70 offers a new perspective on developing therapies for neurodegenerative diseases and cancers.

More information: Rahmi Imamoglu et al. Bacterial Hsp70 resolves misfolded states and accelerates productive folding of a multi-domain protein, *Nature Communications* (2020). DOI: 10.1038/s41467-019-14245-4

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