Role of J-domain proteins in regulation of Hsp70-mediated protein disaggregation

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Cells are at constant risk of stress affecting protein homeostasis. Environmental factors as well as mutations and translational errors could lead to protein misfolding. The inability to attain native conformation by multiple proteins leads to formation of protein aggregates. To fight their detrimental influence cells developed multiple pathways of their clearance. One of them is the Hsp70-Hsp100 chaperone system, which can act on protein aggregates ultimately leading to recovery of proteins in their native state. Main regulators of the Hsp70 system's activity are J-domain proteins (JDPs). Their main objective is to recognize and bind substrates and eventually recruit Hsp70 protein to them.

Considering the fact that the promotion of protein disaggregation through Hsp70 is not limited to a single J-domain protein, I examined what are the functional differences in protein disaggregation imposed by J-domain proteins of different classes. As a model, I used the yeast cytosolic Hsp70 system, which involves Class A Ydj1 or Class B Sis1 JDPs.

Using real-time biochemical methods, I studied how the activity of the Hsp70 system changes due to the employed JDP. I found that Class A Ydj1 is superior in aggregate binding, which then promotes Hsp70 loading onto the substrate. In turn, Sis1 requires simultaneous presence of Hsp70 to interact with an aggregate but yields more abundant loading of Hsp70. High level of Hsp70 on the aggregate potentiates the entropic effect, which can lead to overall relaxation of the aggregate, which uncovers more binding sites for Hsp70. This cycle of events can ultimately lead to aggregate dissolution and recovery of native proteins. In turn, Class A Ydj1, due to its autonomous substrate binding ability, can bind previously released polypeptides, preventing their reaggregation, to allow them to await Hsp70-assisted folding. Taken together, these complementary activities in disaggregation could be the driver of efficient protein recovery.

Since Metazoa, unlike yeast, lack the Hsp100 disaggregase, such diversification of Hsp70 system activity could play a key role in disaggregation and refolding in these organisms. Using human orthologues of Class A and B JDPs, I observed similar trends as for the yeast proteins. Class B JDP, contrary to Class A JDP, can promote higher level of protein recovery during disaggregation and lead to more abundant chaperone complex formation on the substrate. This implicates the evolutionary relevance of the J-domain driven complementing Hsp70 system activities in protein disaggregation and refolding.