J-domain proteins differently mediate the assembly of disaggregation complex

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Protein aggregates are detrimental for the functioning of a cell. A dramatic example is neurodegeneration in diseases such as Parkinson's and Alzheimer's, in which aggregated proteins accumulate in neurons in a form of insoluble amyloid fibrils. In order to fight aggregation, cells employ a chaperone system consisting of a disaggregase and Hsp70 with co-chaperones: J-domain proteins (JDP) and nucleotide exchange factors (NEF). These proteins are able to recover unfolded polypeptides trapped in aggregates in a process called disaggregation and further allow them to refold. The described chaperones are typical for all organisms but not metazoans. In animals, the chaperone system lacks disaggregases. Despite that fact, disaggregation is still carried out effectively even though the whole process is dependent solely on the Hsp70 system. Recent data suggests that productivity of the human Hsp70 system is largely enhanced by cooperation of JDPs of different classes, which eliminated the need for the disaggregase. JDPs involved in disaggregation belong to Class A and B, the members of which have different structure. Our aim was to identify the functional distinctions of the individual JDPs to describe possible mechanism governing their synergistic action, which might ultimately help to learn about factors affecting Hsp70 activity against aggregated proteins. To investigate the function of Class A and B JDP proteins, we developed a bio-layer interferometry based assay with which we are able to observe the formation of the disaggregation complex in real-time. We found that Class A and B JDP proteins promote different modes of Hsp70 binding to the aggregate. Similarly, in disaggregation activity assays, the presence of different JDPs determines the effectiveness of the whole process. Conducted research will allow to propose a model of Class A/B JDPs-Hsp70-substrate interplay in substrate targeting and disaggregation.

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