The Complex Phosphorylation Patterns That Regulate the Activity of Hsp70 and Its Cochaperones

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Proteins must fold into their native structure and maintain it during their lifespan to display their functions. Cells synthesize a wide variety of molecular chaperones that assist folding of other proteins and avoid their aggregation to ensure proper folding and stability, and avoid generation of misfolded conformations that can be potentially cytotoxic. A protein machinery in metazoa composed of Hsp70, Hsp40 and Hsp110 chaperone families can reactivate protein aggregates. Although Hsp70s are the heart of this system, Hsp40s drive much of the versatility, since depending on which Hsp40 interacts with Hsp70, the machinery will be driven to one function or another. Although the interaction of a specific Hsp40 with the main chaperone must be well regulated, the lack of structural information about this complex severely limits the understanding of its functional mechanism. Post-translational modifications (PTMs) constitute a main route used by cells for simple and reversible regulation of protein functions. Phosphorylation is the most studied PTM and triggers different biologically important effects, such as induction of structural changes, protein labelling for cellular translocation and regulation of protein-protein interactions. In this work, we focused on the phosphorylation sites found in a representative of Hsp40 (DnaJA2) and the functional consequences associated with some of them. Experimental results of different phospho-mimetic forms of DnaJA2 might indicate that phosphorylation of this protein could regulate not only its affinity for Hsc70, but also its Hsc70-independent capacity to bind misfolded substrates to avoid their aggregation. These results suggest that phosphorylation of DnaJA2 co-chaperone, and in general phosphorylation of any component of this versatile and multifunctional system, could be a specific, reversible and fast way to modulate their functions, and thus, to rapidly adapt to different conditions ensuring cell proteostasis and survival.