Cooperation between intrinsically disordered chaperone alpha crystallin and small organic molecules in protection against protein aggregation and inactivation

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Intrinsically disordered proteins are a class of proteins recently recognised, that lack the tertiary structure overall or in some regions, but still have biological functions. Various molecular chaperones have been also included in IDPs. The small heat shock protein alpha crystallin, contains a well conserved alpha crystallin domain, flanked by the N- and C-terminal domains intrinsically disordered, flexible, prone to posttranslational modifications. The tertiary and quaternary structures of this dynamic molecule are not known, it exists as a polydisperse population with a variable number of subunits. In fact, the intrinsically disordered nature confers a large flexibility of the binding sites to accommodate various substrates, giving us an answer to the different molar ratios corresponding to the protective concentration of alpha-crystallin, found in our experiments on enzymes protection against inactivation by various posttranslational modifications. During the ageing, such modifications can alter its chaperone activity.

However, we have demonstrated that small organic molecules like trehalose, a non-reducing disaccharide protect the chaperone against structural and functional changes induced by glycation, oxidation and glucocorticoids binding. Here we show that other effects of protein glycation, AGEs cross-linking, aggregation and amyloid-like fibrils formation was prevented by small organic molecules such as proline, pyruvate and aminoguanidine. Pyruvate also induced a significantly decreased fluorescence associated with amyloid fibrils, suggesting its potential as an inhibitor of amyloid deposits. Aggregated AGEs in various regions of human aged-brain homogenates were also evaluated.