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Dynamics and chaperone function in the small heat-shock protein αb-crystallin

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Abstract

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Dynamics And Chaperone Function In The Small Heat-Shock Protein αB-Crystallin

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Mammalian small heat-shock proteins (sHSPs) are molecular chaperones that form polydisperse and dynamic complexes with target proteins, preventing their aggregation into either amorphous deposits or amyloid fibrils. How sHSPs carry out their important function is unknown, but it is generally believed to depend on their complex quaternary dynamics, including the formation of large and heterogeneous oligomers, their inter-conversion via subunit exchange, and the presence of disordered terminal domains. Although these dynamics can now be accurately measured using native mass spectrometry and nuclear magnetic resonance (1), the heterogeneity inherent in this system makes it difficult to test conclusively

which aspects of sHSP assemblies are required for chaperone function. To overcome these challenges, we engineered truncated constructs of the two most abundant sHSPs in human tissue, αB-crystallin and HSP27 in a manner allowing us to carefully control their quaternary dynamics and solve their structures by X-ray crystallography (2). We quantified the quaternary dynamics of these domains using native mass spectrometry, and used engineered cysteines to drive their equilibrium stoichiometries from rapidly interconverting monomers and dimers to conformationally restricted dimers that cannot exchange subunits. Remarkably, we find that the αB-crystallin core domain alone has chaperone activity comparable to that of the full-length protein, despite its inability to form large oligomers and lack of disordered terminal domains and regardless of whether the αB-crystallin core domain is locked into a dimer or predominantly monomeric. Furthermore, it is a potent inhibitor of amyloid fibril formation and, by slowing the rate of its aggregation, effectively reduces the toxicity of amyloid-β peptide to cells. Our experiments therefore identify a novel, small and highly structured 'functional unit' of the heterogeneous sHSP oligomeric ensemble, potentially enabling more rational design of amyloid inhibitors. 1. Hochberg G & Benesch J (2014) Dynamical structure of αB-crystallin. *Prog. Biophys. Mol. Biol.* doi: 10.1016/j.pbiomolbio.2014.03.003. 2. Hochberg G*, et al.* (2014) The structured core domain of αB-crystallin can prevent amyloid fibrillation and associated toxicity. *Proc. Natl. Acad. Sci. USA* 111(16):E1562-E1570.