Mechanistic basis for the recognition of a misfolded protein by the molecular chaperone Hsp90

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The critical toxic species in over 40 human diseases are misfolded proteins. Their interaction with molecular chaperones is essential for blocking disease progression, because chaperones select misfolded proteins for refolding or elimination. A key element of the proteostasis network is Hsp90, which preferentially interacts with metastable proteins. Here we determined by NMR spectroscopy the three-dimensional structure of the misfolded cytotoxic monomer of the amyloidogenic protein transthyretin, which is characterized by the release of the C-terminal β-strand and perturbations of the A-B loop. Using a combination of NMR methods optimized for macromolecular machines and small-angle X-ray scattering we show that the transthyretin monomer but not the wild-type protein binds to Hsp90. In the bound state, the Hsp90 dimer predominantly populates an open conformation and transthyretin retains its globular structure. The interaction surface for the transthyretin monomer comprises the N-terminal and the middle domain of Hsp90 and overlaps with that of Alzheimer-related protein Tau. In contrast, Hsp90-clients, whose function depends on the interaction with Hsp90, bind to other Hsp90 regions and cause structural consequences in Hsp90 that are different from those induced by amyloidogenic proteins, indicating that Hsp90 can employ distinct mechanisms for regulating protein misfolding and physiological function.

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