Mechanically hot spots correlate with cooperativity and function in human transferrin

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ABSTRACT

We explore 20 ns dynamics within selected microstates of human transferrin (hTf) to identify the extent to which functional knowledge relevant to long term dynamics may be obtained from partial information. We employ perturbation-response scanning (PRS) method to extract essential components from variance-covariance matrices contributing to a pre-selected conformational change. In particular, since large-scale motions may require key residues to mediate correlated motions between different regions of the protein, we use PRS to predict those involved in the conformational transitions between the iron bound and free hTf. Under physiological and endosomal conditions, critical residues responsible for holo→apo and apo→holo transitions are identified. Examination of the local dynamics of hTf in complex with its receptor reveals cooperativity in the quaternary structure, explaining resistance to iron release in the complex. Analysis of hTf complex with a bacterial protein, TbpA, identifies a set of residues that mechanically manipulate dissociation from the pathogen. Point mutations on residues right next to these on-off switches are utilized to achieve mechanical coupling in the structure, revealing an evolutionary strategy to open-close pathways to nearby conformations.