The Amazing Versatility of Proteins – Structural Polymorphism and Evolution

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Structures of hydrophobic core residue mutants of the immunoglobulin binding domain B1 of streptococcal protein G (GB1), a universal model protein, were determined. Surprisingly, the oligomeric state and quaternary structure of several of these mutant proteins is drastically changed. A domain-swapped dimer and a symmetric tetramer, with inter-molecular strand-exchange involving all four units were discovered. These findings demonstrate that proteins are able to undergo substantial global rearrangements through the acquisition of very few point mutations. The domain-swapped dimer dissociated into a partially folded, monomeric species at low micromolar protein concentrations and we have characterized this monomeric, partially folded species by NMR. Extensive conformational heterogeneity for a substantial portion of the polypeptide chain exists and exchange between the conformers within the monomer ensemble on the micro- to millisecond timescale renders the majority of backbone amide resonances broadened beyond detection. Despite these extensive temporal and special fluctuations, the overall architecture of the monomeric mutant protein resembles that of wild-type GB1 and not the monomer unit of the domain-swapped dimer. Interestingly, this partially folded monomeric species seems to constitute the critical folding intermediate for amyloid fibril formation.

Our results suggest that destabilization of a monomeric protein can be compensated for by multimerization and that alternative structures (multimers or higher order oligomers) are accessible to proteins from long-lived partially folded intermediates that are capable of large scale conformational fluctuations.

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