To Be Soluble, or Not to Be, That is the Question

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Abstract

A number of human diseases such as Alzheimer’s, Parkinson’s, and type II diabetes are associated with the formation of toxic protein aggregates. Protein aggregation also represents a major bottleneck in the biotechnological production of polypeptide-based drugs and antibody-based reagents. Understanding the molecular determinants of the relative propensity for proteins to aggregate in a cellular environment has therefore been a central issue in attacking protein-aggregation diseases and in the development of human therapeutics. Despite the prevailing expectation that the protein aggregation can largely be attributed to the direct protein-protein interactions within an aggregate or in solution, we here unveil a crucial role of water in ruling the aggregation propensity of proteins both in vitro and in vivo. The protein overall hydrophobicity, defined solely by the hydration free energy of a protein in its monomeric state sampling its equilibrium structures, was shown to predominantly dictate the protein aggregation propensity in aqueous solutions. This is demonstrated for in total 61 protein systems of largely varying aggregation propensity, ranging from intrinsically disordered to natively folded forms. We also find striking and unexpected discrimination of positively and negatively charged residues by surrounding layered water in regulating the solubility of a protein. Guided by such observations, we provide novel protein design principles to control protein solubility, which impacts strategies for the biotechnological generation of aggregation-resistant proteins as biotherapeutics.

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