Conformational selection in protein binding and binding-induced folding

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Abstract: The function of proteins is affected by their conformational dynamics, i.e. by transitions between lower-energy ground-state conformations and higher-energy excited-state confirmations of the proteins. Advanced NMR and single-molecule experiments indicate that higher-energy conformations in the unbound state of proteins can be similar to ground-state conformations in the bound state, and vice versa. These experiments illustrate that the conformational change of a protein during binding may occur before a binding event ('conformational selection'), rather than being induced by this binding event ('induced fit'). However, determining the temporal order of conformational transitions and binding events and, thus, distinguishing conformational-selection and induced-fit processes typically requires additional information on the binding kinetics.

In my talk, I will discuss (1) that a temporal ordering of conformational changes and binding events needs transition times for ligand binding and unbinding that are small compared to the dwell times of proteins in different conformations, and (2) that the temporal order then can be inferred from the dominant, 'observed' rate of binding relaxation experiments with comparable concentrations of proteins and ligands ('non-pseudo-first-order conditions'). (3) For the binding-induced folding of peptides, atomistic simulations and Markov state modelling of the peptide PMI and the protein MDM2 indicate an absence of the timescale separation needed for a clear temporal ordering of binding and folding. Instead, the binding-induced folding of PMI proceeds along multiple routes with different time evolution in the degrees of folding and binding.

[1] TR Weikl and F Paul, "Conformational selection in protein binding and function", Protein Sci 23,1508 (2014)

[2] F Paul and TR Weikl, "How to distinguish conformational selection and induced fit based on chemical relaxation rates", PLoS Comput Biol 16, e1005067 (2016)