MAR06-2005-001082

Abstract for an Invited Paper
for the MAR06 Meeting of
the American Physical Society

The energy landscape for folding and function[1]

JOSE ONUCHIC, Center for Theoretical Biological Physics, UCSD

Globally the energy landscape of a folding protein resembles a partially rough funnel. The local roughness of the funnel reflects transient trapping of the protein configurations in local free energy minima. The kinetics of folding is best considered as a progressive organization of an ensemble of partially folded structures through which the protein passes through on its way to the folded structure. The folding mechanisms for several fast-folding proteins can be described using an energy landscape theory to set up the correspondence with simulations of protein minimalist models. Using these simulations together with analytical theory, we can learn about good (minimally frustrated) folding sequences and non-folding (frustrated) sequences. An important idea that emerges from this theory is that subtle features of the protein landscape can profoundly affect the apparent mechanism of folding. Experiments on the dependence of the folding/unfolding times, and the stability of these proteins to denaturant concentration and site-directed mutagenesis, and on the early events of folding allow to infer the global characteristics of the landscape. In addition to need to minimize energetic frustration, the topology of the native fold also plays a major role in the folding mechanism. Some folding motifs are easier to design than others suggesting the possibility that evolution not only selected sequences with sufficiently small energetic frustration but also selected more easily designable native structures. Several proteins (such as CI2 and SH3) have sufficiently reduced energetic frustration) that much of the heterogeneity observed in their transition state ensemble (TSE) is determined by topology. Topological effects go beyond the structure of the TSE. The overall structure of the on-route and off-route (traps) intermediates for the folding of more complex proteins is also influenced by topology. Utilizing this theoretical framework, simulations of minimalist models and computationally-expensive all-atom simulations, we are now obtaining a quantitative understanding of the folding problem, which allows for a direct comparison to a new generation of folding experiments. Connections between the folding landscape and protein function will also be discussed.

[1]Supported by the NSF