MECHANISMS OF PROTEIN ASSEMBLY AND FOLDING: LESSONS FROM MINIMALIST MODELS

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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 overall funnel shape of the landscape, superimposed on this roughness, arises because the interactions present in the native structure of natural proteins conflict with each other much less than expected if there were no constraints of evolutionary design to achieve reliable and relatively fast folding (minimal energetic frustration). A consequence of minimizing energetic frustration is that 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. 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 strongly influenced by topology. Many cellular functions rely on interactions among proteins and between proteins and nucleic acids. Going beyond folding, the power of reduced models to study the physics of protein assembly will be discussed. Since energetic frustration is sufficiently small, native topology-based models, which correspond to perfectly unfrustrated energy landscapes, have shown that binding mechanisms are robust and governed primarily by the protein's native topology. These models impressively capture many of the binding characteristics found in experiments and highlight the fundamental role of flexibility in binding.

Key words: protein folding funnel, protein recognition, minimal frustration