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(G*) Protein folding and fold switching of the C-terminal domain of transcription factor RfaH.

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The classical view holds that proteins fold into a three-dimensional structure or native state, which determines the biological function of the protein. According to the energy landscape theory, folding proceeds on a rough funnel-shaped multidimensional free energy surface to the native conformation. However, some proteins have recently been discovered to reversibly switch between two entirely different native states, which are exceptions to this rule. Do these so-called metamorphic proteins exhibit energy landscapes with multiple deep funnels corresponding to the different native states? We used an all-atom hybrid model with a potential energy function formed as a linear mixture of physics-based and structure-based potentials. As a case study, we focus on the C-terminal domain (CTD) of the transcription factor RfaH. The CTD undergoes a large-scale structural transition from an α-helical hairpin fold to a 5-stranded β-barrel fold upon dissociation from the N-terminal domain (NTD), which remains structurally stable. We show that our hybrid model demonstrates the crucial thermodynamic behavior of RfaH CTD, i.e., a switch in the global free energy minimum from one fold to the other upon domain dissociation. Our model suggests that for the isolated CTD, the free energy landscape has a single funnel related to the β-barrel fold and no detectable funnel for the α-helical state. This behavior is consistent with data from NMR on the isolated CTD and shows that a multi-funnel landscape cannot be assumed for metamorphic proteins.

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