

Trapping a functional folding intermediate via onboard chaperone-like activity

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Anfisen proposed that the folded and functional state of nearly all proteins is the most thermodynamically stable conformation. Exceptions to this hypothesis include the inhibitory serpins, which adopt a native state that is metastable. It is unknown, however, how serpins avoid folding to their most thermodynamically preferred conformation, the functionally inactive latent state. Here we investigate this problem by characterizing the structure and folding of a unique prokaryote serpin that contains a 56 amino acid region N-terminal to the serpin domain. Our data reveal that three critical residues in the N-terminal region function to trap the native metastable conformation of tengpin by protecting an exposed hydrophobic patch. Deletion of the N-terminus allows the serpin domain to fold past the native state and adopt the latent conformation. Interestingly, the function of the N-terminus resembles closely the role of protein co-factors that prevent mammalian serpins from spontaneously adopting the latent conformation. It is suggested that genetic separation of a stabilizing N-terminal region from the serpin domain may represent an important mechanism for the evolution of serpin co-factors.