Protein Quality Control Mechanisms: Protein Unfolding and Translocation by Biological Nanomachines

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Defects in intracellular regulatory mechanisms for protein degradation and disassembly of protein aggregates result in pathologies such as cardiac dysfunction, Alzheimer's disease, and cancer. Clp macromolecular machines, found in all domains of life from prokaryotes to multi-cellular eukaryotes, perform such protein quality control using powerful ATPase components that effect protein unfolding and translocation through narrow pores. We study the action of Clp ATPases using computer simulations, which provide microscopic details of biomolecular motions over biological timescales. Structurally, Clp ATPases are hexameric assemblies with identical subunits. Substrate proteins targeted for degradation are threaded through the narrow central channels of the ATPase and delivered to the peptidase component. Protein unfolding and translocation are proposed to result from cyclical mechanical pulling mediated by flexible loops located within the central channel. Our simulations of Clp-mediated remodeling of a four helix bundle protein reveal sequential unraveling starting at the tagged C-terminus. We show that protein unfolding occurs prior to translocation and that unfolding pathways contrast those resulting from mechanical pulling of the protein ends.