Computational Modeling of Unfolding and Translocation of Substrate Proteins by Ring-Shaped Biological Machines

by
Prof. George Stan

University of Cincinnati, Department of Chemistry

Abstract:

Specialized AAA+ nanomachines assist protein degradation by unfolding and translocating substrate proteins (SPs) through repetitive ATP-driven cycles. We use coarse-grained and implicit solvent models to study the protein remodeling actions of two hexameric AAA+ nanomachines, the single-ring ClpY and the double-ring p97. We find that conserved central channel loops of ClpY initiate SP unravelling near the tagged C-terminus on timescales dependent on the protein fold. Translocation of the SP through the narrow central pore of ClpY involves sharp stepped transitions. An ordered sequential allosteric mechanism of ClpY is more effective than random or concerted allostery. In contrast to these ATP-driven remodeling actions , SP unfolding by mechanical pulling proceeds via multiple unfolding pathways, while SP threading through a non-allosteric ClpY nanopore involves simultaneous unfolding and translocation effected by strong pulling forces.

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Contact: Prof. Matthias Rief, mrief@ph.tum.de , phone: 089 289-12471