SIV-3

Protein unfolding by ATP-dependent proteases

Cheolju Lee[1,2], Michael Schwartz[1], Sumit Prakash[1], Masahiro Iwakura[1], and Andreas Matouschek[1]

[1]Department of Biochemistry, Molecular Biology, and Cell Biology, Northwestern University, Evanston, Illinois 60208, USA
[2]Life Sciences Division, Korea Institute of Science and Technology, Seoul, Korea

Protein unfolding is a key step in several cellular processes, including protein translocation across some membranes and protein degradation by ATP-dependent proteases. ClpAP protease and the proteasome can actively unfold proteins in a process that hydrolyzes ATP. These proteases catalyze unfolding by processively unraveling their substrates from the attachment point of the degradation signal. As a consequence, the ability of a protein to be degraded depends on its structure as well as its stability. An α-helix is easier to unravel than a β-strand. In multidomain proteins, independently stable domains are unfolded sequentially. The steric constraints imposed on substrate proteins during their degradation by the proteasome were investigated by constructing a model protein in which specific parts of the polypeptide chain were covalently connected through disulfide bridges. The cross-linked model proteins were fully degraded by the proteasome, but two or more cross-links retarded the degradation slightly. Our results suggest that the pore of the proteasome allows the concurrent passage of at least three stretches of a polypeptide chain, and also explain the limited degradation by the proteasome that occurs in the processing of the transcription factor NF-ĸB, and also implicate difficulty in degradation of amyloidal aggregates by the proteasome