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Dynamics of knotted and entangled neurotoxic polypeptides

Marek Cieplak

Institute of Physics, Poland

We review the physics of processes involving large conformational transformations in knotted proteins in bulk water and then consider folding in ribosomes and unfolding in proteasomes. Formation of a knot is demonstrated to be facilitated by the nascent conditions at the ribosome. Knots in proteins have been proposed to resist proteasomal degradation. Ample evidence associates proteasomal degradation with neurodegeneration. One interesting possibility is that indeed knotted conformers stall this machinery leading to toxicity. However, although the proteasome is known to unfold mechanically its substrates, at present there are no experimental methods to emulate this particular traction geometry. Here, we consider several dynamical models of the proteasome in which the complex is represented by an effective potential with an added pulling force. This force is meant to induce translocation of a protein or a polypeptide into the catalytic chamber. The force is either constant or applied periodically. The translocated proteins are modelled in a coarse-grained fashion. We do comparative analysis of several knotted globular proteins and the transiently knotted polyglutamine tracts of length 60 alone and fused in exon 1 of the huntingtin protein. Huntingtin is associated with Huntington disease, a well-known genetically-determined neurodegenerative disease. We show that the presence of a knot hinders and sometimes even jams translocation. We demonstrate that the probability to do so depends on the protein, the model of the proteasome, the magnitude of the pulling force, and the choice of the pulled terminus. In any case, the net effect would be a hindrance in the proteasomal degradation process in the cell. This would then yield toxicity *via* two different mechanisms: one through toxic monomers compromising degradation and another by the formation of toxic oligomers.

Biography

Marek Cieplak is the Head of Laboratory of Biological Physics, Institute of Physics, Polish Academy of Sciences in Warsaw, Poland. He completed MS, Department of Physics, University of Warsaw, 1973; PhD, Department of Physics, University of Pittsburgh, 1977; DSc, Department of Physics, University of Warsaw, 1984. His fields of interest are: condensed matter theory (spin waves, spin glasses, porous media, growth processes, atomic friction, river networks, nanofluidics, self-organized nanostructures) and biological physics (large conformational changes of biomolecules within coarse-grained models, especially as induced by stretching, proteins with knots and slipknots, protein folding, dynamics of virus capsids and other multi-proteinic structures such as a cellulosome, interaction of proteins with solids, proteins at air-water interface, modeling of proteasomes, inference of genetic networks from the microarray data). He is the Co-author of textbook "Theory of Quanta", Oxford University Press 1992 and has published 250 research papers.

mc@ifpan.edu.pl

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