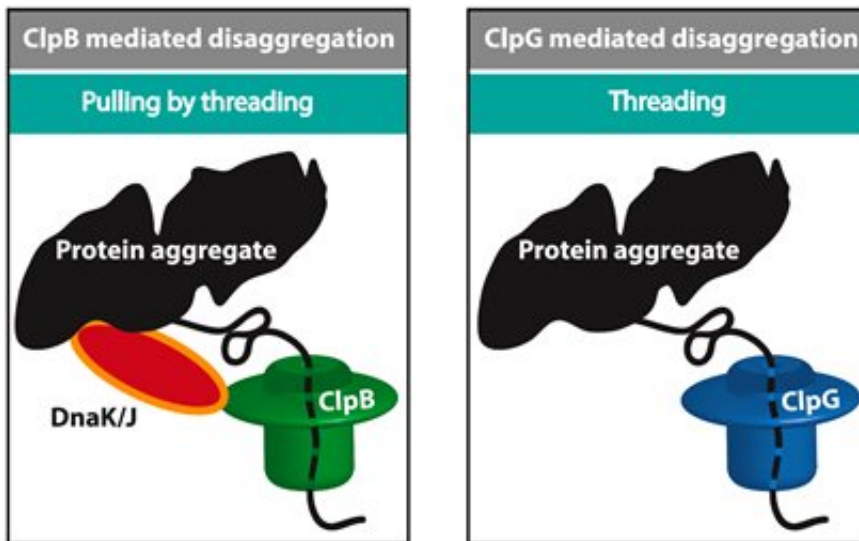


How do cellular machines unfold misfolded proteins?

December 14 2018



Credit: Leiden University

Protein chains typically fold to function. Folding is a complex process and if done correctly leads to a unique functional fold topology for a given protein chain. Other topologies are also possible but are often non-functional or toxic. These misfolded proteins are then unfolded and subsequently refolded to the correct fold topology; otherwise, they undergo degradation.

Several machines including ClpB and ClpG are responsible for unfolding a folded protein. ClpB works closely with HSP70 (DnaK) and HSP40

(DnaJ) and uses energy to unfold a chain while ClpG does not depend on HSP70. A major question is that why cells are equipped with different types of [machines](#) and what determines the efficiency of unfolding. Alireza Mashaghi and his team at LACDR/Leiden University solved this puzzle by monitoring unfolding of misfolded chain models at the single-molecule level. Three unfolding approaches were compared, namely, threading through a pore, pulling from the ends, and pulling by threading.

The results of this analysis, which are published on October 25th in the *Journal of Physical Chemistry B*, reveal that circuit topology of the folded chain critically determines the number of pathways and the efficiency of unfolding in a manner that depends on the employed mechanical approach. The study provides insights into cellular [protein](#) unfolding mechanisms. These findings may help in selecting optimal chaperone targets for pharmacotherapy of misfolding diseases.

More information: Narges Nikoofard et al. Implications of Molecular Topology for Nanoscale Mechanical Unfolding, *The Journal of Physical Chemistry B* (2018). [DOI: 10.1021/acs.jpcc.8b09454](https://doi.org/10.1021/acs.jpcc.8b09454)

Provided by Leiden University

Citation: How do cellular machines unfold misfolded proteins? (2018, December 14) retrieved 26 April 2024 from <https://phys.org/news/2018-12-cellular-machines-unfold-misfolded-proteins.html>

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