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News Release

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Single-molecule, real-time measurements of a key biological process

Biophysicists manipulate "zipper," reveal protein folding dynamics

Biophysicists at TUM, the Technische Universität München, have published the results of single-molecule experiments that bring a higher-resolution tool to the study of protein folding. How proteins arrive at the three-dimensional shapes that determine their essential functions – or cause grave diseases when folding goes wrong – is considered one of the most important and least understood questions in the biological and medical sciences. Folding itself follows a path determined by its energy landscape, a complex property described in unprecedented detail by the TUM researchers. In this week's issue of the Proceedings of the National Academy of Sciences (USA), they report taking hold of a single, zipper-like protein molecule and mapping changes in its energy landscape during folding and unfolding.

Previous studies, including atomic force microscopy experiments by the same Munich laboratory, have gone a long way toward characterizing energy thresholds or barriers that stand between a protein's unfolded and folded states. Detailed observations of the quick transition from one state to the other have remained elusive. The results published this week open the door to higher-resolution, direct measurements. Better characterization of the folding process is seen as a vital link in understanding the chain of events leading from DNA coding for a protein to that protein's biological function. Another motivation for research in this field is the search for new drugs and therapies, because malfunctions in protein folding are implicated in a number of serious diseases – including diabetes, cancer, cystic fibrosis, prion diseases, and Alzheimer's.

This is the latest in a long series of single-molecule biophysical experiments carried out by Professor Matthias Rief and colleagues in the TUM Department of Physics. Co-authors Christof Gebhardt and Thomas Bornschlögl are members of Rief's lab; Gebhardt also is a member of the Munich Center for Integrated Protein Science.

As a model system for studying real-time protein folding dynamics, the TUM scientists chose a so-called leucine zipper found in yeast. It offers, as proteins go, a relatively simple "coiled coil" structure and zipper-like folding action: Picture two amino acid strings side by side, joined at the bottom, open at the top, and made essentially to zip together.

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The researchers extended this structure so that they could make independent measurements at the top, bottom, and middle parts of the zipper. They took hold of the free ends at the top of the zipper with handles made of double-stranded DNA. These DNA handles in turn were attached to tiny beads that could be directly manipulated by "optical tweezers" – a tool based on the ability of laser beams with a certain kind of profile to pin down nanoscale objects. One end of the protein molecule was held fixed, and the other was held under tension but with some freedom to move, so that folding dynamics could be measured directly, in real time, as the protein zipped and unzipped. This arrangement enabled measurements with high resolution in both space and time.

"What I consider the major improvement is that the new experiments allow the observation of thousands of transitions between the folded and the unfolded state," Rief said. "This enables us to detect not only the folded and unfolded states but also, directly, the excursions of the large energy barriers separating those states. This has previously been impossible, and it now allows direct insight into the precise energy profile of this barrier."

Publication:

Full distance resolved folding energy landscape of one single protein molecule, by J. Christof M. Gebhardt, Thomas Bornschlögl, and Matthias Rief, PNAS Early Edition for the week of Jan. 18, 2010.

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