PROTEIN FOLDING

Technique reveals never-before-seen states as protein unfolds

An improved version of single-molecule force spectroscopy (SMFS) has enabled researchers to study the unfolding of a membrane protein with much higher time resolution and force precision than ever before, revealing a multitude of new details. Proteins must adopt specific three-dimensional shapes to work properly. If they don’t, they can malfunction or cause protein-misfolding conditions such as Alzheimer’s disease. Scientists would therefore like to better understand how proteins fold and unfold, including all the intermediate states they adopt along the way.

One type of SMFS technique probes protein-folding intermediates by using an atomic force microscopy (AFM) cantilever to pull on a single protein molecule, unraveling it a little at a time. Most unfolding steps are reversible, so studying unfolding reveals a protein’s folding behavior as well.

In the past, SMFS studies found two intermediate states in the unfolding of two helices in the membrane protein bacteriorhodopsin. But molecular dynamics simulations predicted that this process is much more complex, with 10 unfolding intermediates.

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The flow system is 10 to 100 times as fast as batch-based solid-phase peptide synthesis methods currently used, Pentelute says. If the Amidator worked nonstop for a year, it could create tens of thousands of peptides 30 amino acids long. “This really removes one of the bottlenecks to pushing chemical research forward,” Pentelute points out, “which is just the time it takes to get your hands on molecules.”

SYNTHESIS

Flow process speeds up peptide synthesis

Nature makes amide bonds—the key linkages that string together amino acids in a polypeptide—like a knitting whiz. The ribosome in Escherichia coli bacteria, for example, can make eight amino acids in one second. Chemists are novices by comparison, taking minutes to hours to form an amide bond in a flask.

These scientists are stepping it up, though; a group led by Bradley L. Pentelute of MIT has developed a fully automated flow approach to solid-phase peptide synthesis that can make an amide bond in seven seconds and assemble a peptide at a rate of 40 seconds per amino acid (Nat. Chem. Biol. 2017, DOI: 10.1038/nchembio.2318).

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—BETHANY HALFORD