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DANCE OF THE PROTEINS: SCIENTISTS PLOT PROTEIN FOLDING TO UNDERSTAND CODING THAT DETERMINES STRUCTURE

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If scientists like Dr. Martha Briggs can learn exactly how and why proteins 'dance' as they form, the information could benefit biotechnologists -- by providing a blueprint for new pharmaceuticals, enzymes that scrub environmental toxins, and consumer products such as detergent.

Briggs, an assistant professor of chemistry at the Georgia Institute of Technology, is charting the movement of a protein called ubiquitin. She recently presented her findings during the AAAS (American Association for the Advancement of Science) conference in New Orleans, La. on February 18.

As proteins form, an amino acid sequence folds -- thus transforming "beads on a string" into a fully developed, three-dimensional structure. Briggs and her mentor, Dr. Heinrich Roder at the University of Pennsylvania, are plotting the choreography of this folding process to understand how amino acid coding determines protein structure and function.

By combining two analysis techniques -- hydrogen-exchange labelling and nuclear magnetic resonance (NMR) spectroscopy -- Briggs was able to 'freeze-frame' the various intermediate stages of folding ubiquitin. She said ubiquitin seems to fold "all at once," without forming any distinct, intermediate structures.

"The surprise was, most of the ubiquitin folds very fast and at the same rate," she explained. "It's hard to imagine how everything would come in so quickly, all at once. You'd think it would have to be sequential."

To study human movement, photographer Harold Edgerton pioneered a technique for rigging a camera and strobe light together. Whenever the subject moved, a strobe light flashed as the camera simultaneously snapped a photo, thus documenting a complex sequence of movements. But how do scientists study the intermediate structures of protein folding, which may change every millisecond?

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Roder said the technique is actually quite similar to Edgerton's photo-flash system, since a rapid pulse of hydrogen solvent exposes a sequence of atoms in the ubiquitin, thereby recording the various stages of protein folding.

First, Briggs explained, ubiquitin is unfolded in a bath of deuterium oxide, also known as "heavy water." In the process, hydrogen atoms in the ubiquitin change places with deuterium atoms in the solvent. (Hydrogen is invisible to the detection method, but a disappearing signal can be spotted when hydrogen and deuterium swap places.) Next, the solution is diluted, prompting the ubiquitin to begin refolding. At specific points in time, Roder said, the deuterium solvent is rapidly replaced by hydrogen. Now, accessible portions of the protein chain that are still on the outside or "backbone" of the structure will quickly pick up hydrogen. Inaccessible portions of the chain inside the structure will retain their deuterium label. Through NMR spectroscopy, scientists then chart the movement of individual protons.

Why ubiquitin? Although Briggs used samples from bovine red blood cells, ubiquitin is found in all higher organisms. The function of this protein is still unclear, but it is known to bond with DNA, Briggs said, and it apparently plays a key role in scavenging dysfunctional or improperly folded proteins. Further, Roder said, ubiquitin is probably a good, representative protein, since its structure is fairly regular, lacking any eccentricities.

"Many proteins are known to have a very cooperative folding transition, where the structure seems to be formed all at once," he said. "It appears that all the information needed to define protein characteristics is contained in amino acids. One would like to predict the three-dimensional structure -- based on a protein's amino acid sequence only."

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