Scientists pioneer new method for watching proteins fold

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(PhysOrg.com) -- A protein's function depends on both the chains of molecules it is made of and the way those chains are folded. And while figuring out the former is relatively easy, the latter represents a huge challenge with serious implications because many diseases are the result of misfolded proteins. Now, a team of chemists at the University of Pennsylvania has devised a way to watch proteins fold in "real-time," which could lead to a better understanding of protein folding and misfolding in general.

The research was conducted by Feng Gai, professor in the Department of Chemistry in the School of Arts and Sciences, along with graduate students Arnaldo Serrano, also of Chemistry, and Robert Culik of the Department of Biochemistry and Molecular Biophysics at Penn's Perelman School of Medicine. They collaborated with Michelle R. Bunagan of the College of New Jersey's Department of Chemistry.

Their research was published in the international edition of the journal Angewandte Chemie, where it was featured on the cover and bestowed VIP (very important paper) status.

"One of the reasons that figuring out what happens when proteins fold is difficult is that we don't have the equivalent of a high-speed camera that can capture the process, " Gai said. "If the process were slow, we could take multiple 'pictures' over time and see the mechanism at work. Unfortunately, no one has this capability; the folding occurs faster than the blink of an eye."

Gai's team uses infrared spectroscopy — a technique that measures how much light different parts of a molecule absorbs — to analyze proteins' structure and how this changes. In this case, the researchers looked at a model protein known as Trp-cage with an infrared laser setup.

In this experiment, Gai's team used two lasers to study structural changes as a function of time. The first laser acts as the starting gun; by heating the molecule, it causes its structure to change. The second laser acts as the camera, following the motions of the protein's constituent amino acids.

"The protein is made of different groups of atoms, and the different groups can be thought of as springs," Gai said. "Each spring has a different frequency with which it moves back and forth, which is based on the mass of the atom on either end. If the mass is bigger, the spring

oscillates slower. Our 'camera' can detect the speed of that motion and we can relate it to the atoms it is made of and how that segment of the protein chain moves."

Even in a simple protein like Trp-cage, however, there are many identical bonds, and the researchers need to be able to distinguish one from another in order to see which of them are moving while the protein folds. One strategy they used to get around this problem was to employ the molecular equivalent of a tracking device.

"We use an amino acid with a carbon isotope marker," Culik said. "If it's incorporated into the protein correctly, we'll know where it is."

With a single carbon atom of the Trp-cage slightly heavier than the others, the research team can use its signature to infer the position of the other atoms as they fold. The researchers could then "tune" the frequency of their laser to match different parts of the protein, allowing them to isolate them in their analyses.

Similar isotopes could be inserted in more complicated molecules, allowing their folds to also be viewed with infrared spectroscopy. "This technique enhances our structural resolution. It allows us to see which part is moving," Gai said. "That would allow us to see exactly how a protein is misfolding in a disease, for example."

Provided by University of Pennsylvania