

Discovery alters longstanding concept of fixed protein structure

The thousands of proteins found in nature are simply strings of amino acids, assembled by genes, and scientists have long believed that they automatically fold themselves into uniquely fixed, 3-dimensional shapes to fire the engine of life. In the era of genetic research, identifying those shapes and their functions has become a worldwide focus of biomedical science.

Now, researchers at the Medical College of Wisconsin in Milwaukee have found that a protein, lymphotactin, which plays a vital role in the body's immune response, can rapidly shift its shape --up to ten times a second-- between two totally unrelated structures, each with a unique role in defending the body.

Their discovery, published in the *Proceedings of the National Academy of Science*, March 17, alters a fundamental concept of biochemistry established in the 1960s. It may also inspire the search for other proteins with the ability to change form, and help address diseases of misfolded proteins such as Alzheimer's, Parkinson's, ALS, mad cow disease and many cancers.

"While our discovery raises more questions on the protein folding enigma, we hope it generates intensified research to learn the complex processes of these devastating diseases," says team leader Brian Volkman, Ph.D., associate professor of biochemistry.

Dr. Volkman's team is using highly sensitive nuclear magnetic resonance (NMR) spectroscopy to solve three-dimensional protein structures. NMR provides information on the number and type of chemical entities in a molecule, and can measure distances between pairs of atoms within the molecule to produce a computer-generated 3-D model of its structure.

They discovered that human lymphotactin, a regulatory protein released by the immune system to attract and activate white blood cells, exists naturally in two distinct structures, and that the newly-identified form has no similarity to any other known protein. They also learned that each form has a unique role, one attaching to the interior wall of the blood vessel, and the other reaching out to grab white blood cells. This means that converting from one lymphotactin structure to the other is likely essential for its activation, according to Dr. Volkman.

"Proteins often have multiple functional states that are closely related to a single structure" he says. "In its natural state however, we found that lymphotactin adopts two equally-populated but unrelated structures that rapidly change from one to the other."

Source: Medical College of Wisconsin

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