Researchers create functioning artificial proteins using nature's rules

September 21 2005

By examining how proteins have evolved, UT Southwestern Medical Center researchers have discovered a set of simple "rules" that nature appears to use to design proteins, rules the scientists have now employed to create artificial proteins that look and function just like their natural counterparts.

In two papers appearing in the Sept. 22 issue of the journal *Nature*, Dr. Rama Ranganathan, associate professor of pharmacology, and his colleagues detail a new method for creating artificial proteins based only on information they derived from analyzing certain characteristics that individual natural proteins have in common with each other.

"The goal of our research was not to find another way to make artificial proteins in the lab, but to discover the rules that nature and evolution have used to design proteins," Dr. Ranganathan said. "The rules we have extracted from the evolutionary record of proteins contain a substantial fraction of the information required to rebuild modern-day proteins. We're building solutions so close that, at least in a test tube, we can't tell them apart from natural proteins."

Dr. Ranganathan said there could still be many small differences between the artificial proteins and the natural ones, and further testing would need to be done to determine whether they work within an actual organism.

"Our work suggests that modern-day proteins have likely inherited much

of the information specifying their structure and basic aspects of function from their ancestors, but it is also possible that they have been fine-tuned over time to have their own idiosyncratic features in specific cells," said Dr. Ranganathan, who also is a Howard Hughes Medical Institute (HHMI) investigator. "We are suggesting that the functions proteins have today are the result of fine-tuning a basic ancestral template that we have now figured out."

Proteins, which carry out the body's life functions, are composed of molecules called amino acids, which are strung together in long chains. These chains loop about each other, or fold, in a variety of ways. Their specific three-dimensional shapes help proteins to perform their biological functions.

For decades, scientists have known that the sequence of amino acids that make up a protein determines the protein's structure and its function. What has not been known is what information contained within that sequence produces the proper structure.

All proteins are made up of 20 specific amino acids. Even for a small protein made up of 100 amino acids, the number of possible combinations of amino acids is staggering, many times more than the number of atoms in the known universe.

"How did nature devise the right sequences that resulted in functioning proteins? Somehow, it found a way," Dr. Ranganathan said. "One implication of our work is that the evolutionary protein-design process may not be as complex as was previously thought."

Earlier research has shown that for a given group of related proteins, or protein family, all family members share common structures and functions. By examining more than 100 members of one protein family, the UT Southwestern group found that the proteins share a specific

pattern of amino acid selection rules that are unique to that family.

"What we have found is the body of information that is fundamentally ancient within each protein family, and that information is enough to specify the structure of modern-day proteins," Dr. Ranganathan said.

He and his team tested their newly discovered "rules" gleaned from the evolutionary record by feeding them into a computer program they developed. The program generated sequences of amino acids, which the researchers then "back-translated" to create artificial genes. Once inserted into laboratory bacteria, the genes produced artificial proteins as predicted.

"We found that when isolated, our artificial proteins exhibit the same range of structure and function that is exhibited by the starting set of natural proteins," Dr. Ranganathan said. "The real test will be to put them back into a living organism such as yeast or fruit flies and see how they compete with natural proteins in an evolutionary sense."

Other UT Southwestern researchers involved in the work are lead authors Michael Socolich, HHMI research specialist, and Dr. William Russ, assistant instructor of pharmacology; Steve Lockless, medical student; Prashant Mishra, Medical Scientist Training Program student; Heather Lee, HHMI technician; and Dr. Kevin Gardner, associate professor of biochemistry and pharmacology. Researchers from the Massachusetts Institute of Technology also participated.

Source: UT Southwestern Medical Center

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