Biochemistry

Hardy synthetic patterned after nature

Taking a cue from microorganisms that thrive in near-boiling water on the ocean floor, chemists are learning how to build tough synthetic proteins that may pave the way for lab-made molecules with potentially far-reaching applications.

"These organisms have proteins in them that make them very stable," says Ramy S. Farid, a chemist at Rutgers University in Newark, N.J. "I wanted to understand what is so special about these proteins."

One clue to their properties is hydrophobic interaction, the same phenomenon that keeps gasoline and water from mixing. In the string of molecular units that makes up any protein, hydrophilic segments attract water molecules, while hydrophobic segments repel them. Robust ocean floor microorganisms—called archaeons—have proteins with long hydrophobic segments, which twist away from water until the protein becomes a ball with a tightly packed core. This packaging leaves open a small surface area of hydrophilic elements (SN: 3/11/95, p. 150).

Because these proteins are dense, high energy—for example, high heat—is required to unravel the string, Farid says. So he and his colleagues wrote a computer program to design an even more tightly packed protein. They then devised a procedure to synthesize this protein. Rather than re-create the archaeon protein exactly, Farid and his colleagues Xin Jiang and Edmund J. Bishop used a chemical backbone not found in the microorganisms, they report in the Jan. 29 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. The computer program simulates evolution by first designing a simple protein based on that backbone and then adding onto it to model a larger, more complicated protein.

The results would have been interesting, but not groundbreaking, if the scientists had stopped at the design stage, says biochemist Mike Adams of the University of Georgia in Athens. However, they made the protein based on their design, tested it, and found that it remained tightly coiled at temperatures approaching 80°C. "There is no natural example of a protein like this," Adams says.

Taking the next step—creating industrial catalysts, medicines that remain stable in heat, and enzymes based on robust synthetic proteins—could be tricky: Natural proteins may not work when reengineered to maximize hydrophobic stabilization. Also, Adams cautions, other, undiscovered forces could help stabilize the archaeon protein. "Nature has been at this business a lot longer than we have." —*P.S.*

Toying with a modular enzyme

Instead of searching for existing enzymes with desirable properties or designing new ones from scratch, a team of scientists has taken an in-between approach. Using a method akin to making a model with a toy construction set, the scientists have created a working hybrid enzyme by connecting individual pieces of other enzymes.

Stephen J. Benkovic and his colleagues at Pennsylvania State University in State College stitched together the genes for sections of two bacterial enzymes involved in the synthesis of adenine and guanine, components of DNA. The resulting hybrid enzyme successfully combines functions of the original enzymes.

The group's work, which appears in the Feb. 18 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, shows that enzymes may have evolved by mixing and matching distinct working parts. Benkovic suggests that "when Nature found a solution to this complicated problem of catalysis, she used it over and over again," assembling enzymes in a modular fashion. The scientists' next step is to see if they can substitute sections from a third enzyme and retain the hybrid's function. —*C.W.*

Biology

From a meeting in Seattle of the American Association for the Advancement of Science

Cells can stop HIV once it gets inside

One of the more puzzling mysteries in AIDS research is why some people exposed frequently to HIV remain uninfected by the virus. A few answers have begun to emerge. Some of these individuals have mutations in a gene that encodes a cell surface protein commonly used by HIV to infect human immune cells (SN: 8/17/96, p. 103). The mutations apparently alter this receptor protein in a manner that prevents the virus from using it to sneak into cells. In essence, people with these mutations lock the virus out of their immune cells.

What protects other exposed, yet uninfected, people? "The majority remain uninfected for unknown reasons," says Miles W. Cloyd of the University of Texas Medical Branch in Galveston. To address this mystery, Cloyd and his colleagues have been drawing blood from volunteers and testing how easily various HIV strains infect the immune cells in these blood samples. In 1991, the researchers reported findings from a study of a dozen people, some of whose immune cells resist infection by certain strains of the AIDS virus.

While Cloyd acknowledges that the relevance of this observation to real-life HIV resistance remains unclear, his group has since extended the study to 50 randomly chosen people. The investigators found that for some strains of HIV, up to 15 percent of the group has immune cells that are resistant to infection. The protection isn't complete, however. If the cells are exposed to enough virus, they'll succumb. Still, they seem to fend off HIV by a different mechanism than the receptor mutations described last year. The resistance develops after the virus has infected a cell, Cloyd asserts.

HIV carries its genetic material in the form of the nucleic acid RNA. Once inside a cell, the virus copies its RNA into DNA and inserts this DNA into the chromosomes of its host. The virus then takes over the cell and forces it to produce copies of HIV. Yet despite evidence that the virus has copied its RNA into DNA, the resistant cells studied by Cloyd do not churn out new viruses.

Cloyd suggests that the resistant cells somehow prevent HIV from integrating its DNA into host chromosomes. Another possibility, he says, is that the virus does insert its genes but that the cells do not turn those genes on, thus preventing HIV from copying itself. —*J.T.*

Aging gene linked to heart attacks

Scientists have made an intriguing connection between a gene linked to aging, discovered last year, and a person's risk of having a heart attack. Last May, George M. Martin of the University of Washington in Seattle and his colleagues announced that they had found the mutant gene responsible for Werner syndrome (SN: 5/11/96, p. 301). People with this rare condition seem to undergo premature aging. Their hair turns gray in their twenties, and they begin to suffer age-related diseases—atherosclerosis, cataracts, osteoporosis, and cancer. Most people with Werner syndrome die of a heart attack by age 50.

Martin and a Japanese research group headed by Toshio Ogihara of the Osaka University Medical School have recently started to study two known normal versions of the Werner syndrome gene. They have compared the distribution of these versions in Japanese people who have had a heart attack and those who have not. The scientists found that having one of the versions may significantly increase an individual's risk of suffering a heart attack.

Martin cautions that the new research involves only a few hundred individuals and that the conclusions are preliminary. "We're very conservative about our interpretation," he says. "It's urgent that this be looked at in other Japanese populations and other populations worldwide. No geneticist would believe this finding unless it was reproduced." —*J.T.*