SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS LEARN HOW G PROTEINS ACTIVATE THEIR ENZYMES

DALLAS – December 12, 1997 – Researchers have answered a fundamental question about how G proteins, the cell's message relay switch, coordinate and control signals that determine cell activities. By looking at the crystal structure of one type of G protein (Gs-alpha) bound to its target, an enzyme found in heart tissue, UT Southwestern Medical Center at Dallas scientists also uncovered a possible target for cardiac drugs.

The research results were published in today's issue of *Science.* The investigators examined the crystallized molecules using X-rays and saw how Gs-alpha interacts with the enzyme, adenylyl cyclase, to stimulate the production of an intracellular "second messenger." The research team consisted of Dr. Stephen Sprang, senior author of the study, professor of biochemistry and associate investigator in the Howard Hughes Medical Institute (HHMI) at UT Southwestern; Dr. John Tesmer, HHMI associate; Dr. Roger Sunahara, research fellow in pharmacology; and Nobel laureate Dr. Alfred Gilman, chairman of pharmacology and holder of the Raymond Willie and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D. Gilman shared the 1994 Nobel Prize in medicine or physiology for his work with G proteins.

G proteins, named because they bind and are regulated by guanine nucleotides, time and turn on and off biochemical processes of cellular communication. Guanine nucleotide is a basic unit of nucleic acid comprised of an organic base (guanine), a sugar and one or more phosphates.

The investigators believe that a conformational change occurs when Gs-alpha binds to its target, adenylyl cyclase, causing the latter's activation. Adenylyl cyclase triggers a number of biochemical activities that are part of the relay of cellular information. For example, when it is stimulated in the heart muscle, cardiac output increases.

"We found the means by which the G-protein alpha subunit binds to and activates its effector, adenylyl cyclase. This is a first in structural biology," Sprang said.

(MORE)

In a companion study in the same issue, the researchers explained how Gs-alpha is able to activate adenylyl cyclase while another G protein, Gi-alpha, acts as an inhibitor of the same enzyme.

"Researchers had known for years that the GTP-bound form of G-protein is always active," Sprang said. "Now, we see why only the GTP-bound form is an effective activator of cyclase."

There are nine known forms of adenylyl cyclase. They are similar to each other, but each form of the enzyme differs from the others in two ways: the tissues in which they are found and the way they can be regulated.

Scientists know that Gs-alpha regulates and activates all forms of adenylyl cyclase, but they want to understand the other mechanisms by which these enzymes are regulated. For instance, Gi-alpha may bind to another site on the cyclase in a way that inhibits its activation.

Of broader importance is the similarity of adenylyl cyclases to a second family of enzymes that is involved in cellular communication but for different biochemical processes. "So knowing the structure of adenylyl cyclases helps to understand other cyclases as well," Sprang said.

Every type of cyclase is regulated differently, and the pathways that each affects are diverse and depend on the tissues in which they are expressed.

Now that the researchers have crystallized the active Gs-alpha protein-bound form of adenylyl cyclase, they want to determine the structure of the same enzyme when it is inactive.

"It's important to see the conformational differences between the cyclase when it is turned off compared to when it's turned on so that we can understand how Gs takes the enzyme from an inactive state to an active state," Sprang said. In this way the researchers may learn how to target the molecule for drug development.

The final piece of the G-protein signaling puzzle will involve crystallizing one of the receptors that begins the cellular communication process by initially activating a G protein. "This would tell us how the G-protein signaling cycle works," Sprang said.

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