SOUTHWESTERN NEWS

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X-RAY CRYSTALLOGRAPHY DETERMINES STRUCTURE OF ENZYME EFFECTING G-PROTEIN CATALYSIS

DALLAS — April 18, 1997 — The first crystal structure of a molecule that facilitates an enzyme reaction essential to signal transmission in cells may help explain cell proliferation, reported researchers at UT Southwestern Medical Center at Dallas.

The molecule, RGS4, touted as an enzyme for enzymes, regulates how quickly some G proteins push messages along a cellular signaling pathway. Using X-ray crystallography to successfully determine the structure of a member of the Regulators of G-Protein Signaling (RGS) family has enabled scientists to learn more about how and why these proteins help regulate catalysis, the scientists reported in today's issue of the journal *CELL*.

G proteins, so called because they bind and are regulated by guanine nucleotides, are signaling enzymes that collect information from hormones bombarding a cell's exterior, amplify it, then initiate a cascade of biochemical events that send messages to the correct regulatory systems in the cell's interior. This occurs when a molecule of guanosine 5'-diphosphate (GDP) is exchanged for a molecule of guanosine 5'-triphosphate (GTP) on the alpha subunit of the G protein. The cascade turns off when the alpha subunit converts GTP to GDP, a process that may require 10 to 20 seconds.

RGS4 accelerates this conversion by reducing the energy it takes to catalyze this chemical transformation, known as GTP hydrolysis.

"What the RGS4 protein basically does is to turn the G protein alpha subunit into a decent enzyme," said Dr. Stephen Sprang, senior author of the study, a professor of biochemistry and an associate investigator in UT Southwestern's Howard Hughes Medical Institute (HHMI). "RGS4 really acts like an enzyme because as soon as it helps the alpha subunit hydrolyze GTP, RGS4 falls off and then can deactivate another G protein. That's why I call it an enzyme for enzymes."

Dr. John Tesmer, a HHMI associate, said, "This is the first stable crystal structure of any member of the RGS family of proteins. RGS4 times the duration of the signal to the cell and helps shut off the signal by hydrolyzing the GTP bound to the alpha subunit."

This study also allowed scientists to see for the first time how RGS4 or any GTPase

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Activating Protein (GAP), as the enzymes are known, is bound to a G protein alpha subunit.

"This structure is important because you get to see the atomic details of the interaction of the two protein molecules in a physiologically relevant complex," Tesmer said. "We want to explain how RGS4 is acting as a GTP hydrolysis accelerator.

"By looking at the crystallized structure of this complex, we can try to find some conformational changes imposed by the RGS4 protein on the alpha subunit causing it to be a better enzyme, or it might be some other biochemical change, such as contributing amino acid residue to the site where GTP is converted to GDP."

Other UT Southwestern researchers — David Berman, Medical Scientist Training Program student, and Dr. Alfred Gilman, chairman of pharmacology — studied the biochemistry of RGS proteins and determined that they functioned as GAPs. This research was previously reported in *CELL*.

Gilman shared the 1994 Nobel Prize in physiology or medicine for his work on G proteins. He holds the Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology, in Honor of Harold B. Crasilneck, Ph.D.

Gilman's group continues to study RGS proteins in hope of developing useful biochemical tools that might be used to turn on or off various messages to cells. Knowing how to do this could help in finding causes and cures for various diseases.

"So now there is this new molecule, RGS4, that basically regulates the G-protein timer. The timer is usually set by the rate of GTP hydrolysis. Whether RGS4 is functional depends on the tissues in which it is made, when it's made and to which G protein alpha subunits it binds," said Sprang. "Much about where it is and what it does is still a mystery.

"We know that RGS4 is very highly expressed in brain tissue. Its job is presumably to control the strength of signals that arrive at the nerves in the brain and make sure that they get turned off correctly. If RGS proteins are expressed in some tissues but not others or if they're expressed in a specific manner at certain times in the life of the cell, they can modify response of that particular cell to hormones or other chemical stimuli."

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