Novel approach by UCSD scientists links protein to inflammatory disease

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NOVEL APPROACH BY UCSD SCIENTISTS LINKS PROTEIN TO INFLAMMATORY DISEASE

An important protein linked to everything from asthma to the onset of labor, from headaches to the pain of arthritis has been identified and inhibited by biochemists at the University of California, San Diego.

The protein is a member of a class of enzymes called phospholipase A2 (PLA2) that's found in virtually every cell, tissue and organ in the body.

In recent years, scientists have described in general how PLA2sets in motion a cascade of chemical events leading to the production of prostaglandins, powerful substances that regulate the swelling, fever and pain associated with inflammatory diseases.

Aspirin and ibuprofen, two common household remedies used to combat most of these symptoms, are believed to work by interfering with the PLA2-initiated pathway. Steroid drugs, including cortisols, are sometimes called upon to treat some of the more chronic conditions.

However, long-term use can create serious side effects including kidney failure, ulcers, brittle bones and liver problems.

"A lot of pharmaceutical companies are targeting phospholipase A2 to come up with new ideas for effective drugs with few side effects," said Edward A. Dennis, professor of chemistry and biochemistry at UCSD. "Can we find inhibitors to this enzyme, and can we find ways to control its activity and enhance control of the production of those harmful products? These are the questions that are being asked."

With Suzanne Barbour, a UCSD postdoctoral fellow, Dennis used a genetic technique to inhibit the production of a specific type of PLA2 that appears to play a major role in prostaglandin formation. Their work is reported in the October 15 issue of the Journal of Biological Chemistry.

In their paper, Dennis and Barbour report synthesizing an antisense molecule built from 20 bases; it represents the first use of antisense technology to "knock out" in a cell culture the production of one particular type of PLA2 called sPLA2. The cells used are macrophages-- white blood cells that are immunologically activated to fight infection.

When this specific enzyme was blocked, the resulting production of prostaglandin was reduced by about 80 percent.

"The pharmaceutical industry needs to know which phospholipase A2 to kill to make a drug," said Dennis. "As a result of this experiment, a great deal of evidence points to the enzyme we studied."

Added Barbour: "This is an important enzyme that is a major contributor to prostaglandin production in these cells."

In future experiments, the scientists say they will use antisense technology to inhibit the production of other forms of PLA2 in cells, to pinpoint their precise roles. In this manner, they hope to gain a better understanding of how prostaglandins are manufactured and released by cells.

Such work not only may shed light on inflammatory diseases such as arthritis, pancreatitis and inflammatory bowel disease, it also may help unravel clues into the causes of premature labor, since prostaglandins are known to play a key role in labor and childbirth.

"There's some thought in the pharmaceutical industry that this enzyme might be one of the absolutely critical controlling steps in all of these processes," said Dennis.

Both Dennis and Barbour caution that their findings represent only one step toward the production of more effective drugs to treat these disorders. Nevertheless, they say, it's a necessary step.

"It is basic research, but it is crucial to the design of a drug or making a pragmatic pill," said Dennis.

Research in Dennis' lab is supported from grants from the National Institute of General Medical Sciences and the National Institute of Child Health. The work was supported because of the central role prostaglandins play in pregnancy and preterm labor.

BACKGROUND

"Antisense" technology interferes with the way genes encode and pass on messages.

Here's how it works:

Four bases--adenine, thymine, guanine, and cytosine-- make up each molecule of DNA, the basic unit of heredity. The arrangement of these bases along the backbone of the DNA molecule constitutes a template that's used to create specific proteins needed for cellular activity.

A molecule of DNA, found in the cell's nucleus, takes the form of a helix consisting of two strands bonded to each other according to their base sequence--the genetic code.

One strand of the DNA serves as a template for the production of an intermediary molecule called messenger RNA, which then leaves the cell's nucleus carrying the code for a protein. The single-stranded messenger RNA subsequently travels through the cell's cytoplasm to a cellular structure called a ribosome--the place where proteins are built.

Researchers artificially flood cells with synthetic molecules tailored to bind to specific strands of messenger RNA. These "antisense" molecules then bind to their complementary sense messenger RNAs before they reach their destination in the ribosomes. Once bound by this piece of genetic material, messenger RNA cannot carry out its protein-making mission.

"The sequence is absolutely specific for whatever protein you are interested in," said Barbour, whose antisense work was funded by the University of California President's Fellowship for Postdoctoral Studies and a National Institutes of Health Postdoctoral Fellowship.

"This means that it will not block the expression of other proteins, and that it will target only those that you are really interested in," she added.

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