SOUTHWESTERN NEWS

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RESEARCHERS FIND WAY TO CONTROL CHOLESTEROL ABSORPTION IN MICE

DALLAS - Sept. 1, 2000 – Researchers at UT Southwestern Medical Center at Dallas have found a way to control intestinal absorption of cholesterol in mice and potentially prevent the production of plaque in arteries.

Researchers used rexinoids -- compounds developed for their unique ability to activate a protein receptor and thus alter metabolic pathways -- to determine how the cholesterol pathway would be affected.

The results of their study, published today in *Science,* show that rexinoids block cholesterol absorption and increase the elimination of cholesterol from the body, said Dr. David Mangelsdorf, a Howard Hughes Medical Institute (HHMI) investigator and associate professor of pharmacology and biochemistry at UT Southwestern.

"We were interested in knowing if we gave rexinoids to an animal, would it alter this pathway at all," he said. "We found something very surprising. This compound completely blocked all absorption of cholesterol. So this is a compound that shut down all absorption of cholesterol in [a mouse model]. Whether it works in humans is still a question that's open, but it probably will because of its mechanism of action."

Mangelsdorf said the rexinoid "clearly blocks dietary cholesterol." The drug also repressed bile-acid synthesis, thus altering one of the usual ways to regulate cholesterol. In the study, when the mice were fed bile acids to recoup the amount that was lost, 50 percent of the cholesterol level was regained.

Cholesterol can either be made from biosynthesis or obtained from the diet. There are two major ways the body controls its level of cholesterol: It can inhibit the process by turning off the pathway to cholesterol production, or it can get rid of the excess by converting it to bile acids. Bile acids help the body absorb certain fats and cholesterol and are a major route for eliminating excess cholesterol.

The nuclear receptors that regulate these pathways of cholesterol control are LXR (liver

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orphan receptor) and FXR (farnesoid orphan receptor). When LXR was eliminated from the mice used in the study, the mice could no longer regulate their cholesterol levels. The liver of such an animal builds up a toxic level of cholesterol. Binding to bile acids activates FXR, repressing further bile acid production and hence cholesterol absorption. Neither of these proteins works independently. Both work together with another protein called RXR, the receptor affected by rexinoids.

In the study, the researchers also found that rexinoids increase the ABC1 protein, which prevents cholesterol absorption and the development of macrophages -- scavengers that take up large amounts of low-density lipoprotein cholesterol. When macrophages become engorged, they develop into foam cells, attach themselves to the walls of arteries and form plaque, which causes atherosclerosis, or hardening of the arteries.

The researchers believe that drugs could be used to increase the expression of ABC1, thus decreasing the accumulation of cholesterol.

"Rexinoids potentially are important not just in lowering cholesterol, but in getting rid of foam cells. This suggests that it would be a good drug for preventing atherosclerosis," Mangelsdorf said. "The idea is that, therapeutically, this would lower cholesterol.

"The bottom line is, we've discovered a mechanism by which cholesterol is absorbed, and found a regulator and potential drug therapy, something that will have to be evaluated, of course. We start with the animal models and work toward the human models. The therapeutic benefits are lowering cholesterol and preventing atherosclerosis."

Other UT Southwestern researchers participating in this study were lead author Dr. Joyce Repa, Howard Hughes Medical Institute associate in pharmacology; Dr. Stephen Dean Turley, professor of internal medicine; Dr. Jean Marc Lobaccaro, HHMI associate in pharmacology; and Dr. John Dietschy, chief of gastroenterology. Collaborators included scientists from Tularik and Ligand Pharmaceuticals.

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