SOUTHWESTERN NEWS

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: susan.steeves@email.swmed.edu

DISCOVERY OF A MOLECULE THAT CONTROLS BILE ACIDS MAY LEAD TO NEW CHOLESTEROL DRUGS

DALLAS — May 21, 1999 — The discovery that a nuclear receptor controls the production of bile acids and works within a pathway that speeds up destruction of cholesterol may lead to new cholesterol drugs, UT Southwestern researchers reported in today's issue of *Science.*

Their finding -- that the receptor FXR (farnesoid orphan receptor) is integral to maintaining the balance of cholesterol and bile acids -- has important implications for developing drugs to control dietary cholesterol in humans, said corresponding author of the study Dr. David Mangelsdorf, associate professor of pharmacology and Howard Hughes Medical Institute (HHMI) investigator.

"Our finding that FXR functions as a bile-acid receptor suggests an expanded model for the regulation of cholesterol homeostasis by nuclear receptors," Mangelsdorf said. He and other researchers previously had shown that accumulation of dietary cholesterol in the liver triggers production of biochemicals called oxysterols. These substances activate liver orphan receptor (LXR) to speed up the breakdown of cholesterol for conversion to bile acids and steroid hormones.

"If we find an antagonist to FXR, then it might increase bile-acid production to control cholesterol," Mangelsdorf said. Both LXR and FXR are members of a family of protein molecules located in the nucleus of cells found in the liver, intestine, kidneys and adrenal glands. Their role in removing cholesterol from the body is important because it prevents arteriosclerosis, which leads to heart attacks.

This study showed that elevated bile acids regulated further production and transport through FXR. This leads Mangelsdorf to believe that FXR is one of the key regulators that controls repression and further synthesis in the liver and increases the production of other proteins that transport bile acids in the intestine.

(MORE)

"People can't live without bile acids as a way to rid the body of cholesterol, so our work characterizing these orphan receptors is becoming very significant in understanding cholesterol synthesis and metabolism," he said.

Orphan receptors are molecules believed to be the locks that control biochemical processes but whose function and ligand, or key, to activate the cellular changes, is unknown. FXR acts as the lock that binds with bile acids. When this happens, the receptor represses the gene to regulate the enzyme cholesterol 7 alpha-hydroxylase, which limits bile-acid synthesis. At the same time, it activates a gene that encodes I-BABP (intestinal bile-acid- binding protein). Mangelsdorf and his group of researchers believe that I-BABP transports the bile acid through the intestine wall.

Other UT Southwestern researchers involved in the study were Dr. Makoto "Mac" Makishima and Joyce Repa, HHMI associates. This was a collaborative effort with scientists from Tularik Inc. in San Francisco.

A grant from the Robert A. Welch Foundation funded the work.

###