SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS DISCOVER ROLE OF TWO GENES INVOLVED IN CHOLESTEROL EXCRETION

DALLAS – Nov. 18, 2002 – Two specific genes involved in cholesterol transport are required for the most common way excess cholesterol is expelled from our bodies, according to scientists at UT Southwestern Medical Center at Dallas.

The genes, the researchers report, are essential for efficient secretion of cholesterol into the bile, which is the major route that cholesterol exits the body. The discovery sheds new light on potential therapies that could play an important role in reducing high cholesterol, a major risk factor of atherosclerotic diseases, such as coronary heart disease and stroke.

The new findings are reported in this week's issue of the *Proceedings of the National Academy of Sciences*.

"The disruption of the two genes, *Abcg5* and *Abcg8*, reveals their crucial role in biliary cholesterol secretion," said Dr. Liqing Yu, an instructor in the Eugene McDermott Center for Human Growth and Development and in molecular genetics and lead author of the study. "In humans and mice, the secretion of cholesterol into the bile is essential for maintaining cholesterol homeostasis and constitutes a major defense against the accumulation of dietary cholesterol in blood and tissues."

Dr. Helen Hobbs, senior author of the study, said, "By activating or upregulating *Abcg5* and *Abcg8* you could theoretically reduce cholesterol in the body by increasing cholesterol transport into the bile and limiting cholesterol absorption. This may also reduce cholesterol in the blood." Hobbs directs the Eugene McDermott Center for Human Growth and Development and the Donald W. Reynolds Cardiovascular Clinical Research Center. She also is an investigator in UT Southwestern's Howard Hughes Medical Institute.

The researchers uncovered this critical pathway by studying mice that lacked the genes.

(MORE)

When researchers fed the mice high cholesterol diets, "We discovered that the fatty liver was developed due to a massive accumulation of cholesterol," Yu said. "We think this happens because the dietary cholesterol cannot be efficiently secreted into the bile, but it is accumulated in the liver and plasma when *Abcg5* and *Abcg8* are disrupted."

Liver and plasma cholesterol levels were increased by as much as 18-fold and 2.4-fold, respectively, in the mice after they ate a cholesterol-rich diet. Disruption of the two genes also resulted in a 30-fold increase in plasma levels of sitosterol, the major plant sterol, and a two- to threefold increase in fractional absorption of dietary plant sterols.

"Plant sterols are similar to cholesterol, structurally, and in the absence of *Abcg5* and *Abcg8* the compounds accumulate in the body, which leads to a rare inherited disease called sitosterolemia," Yu said. "Individuals with this disease have dramatically increased plasma plant sterol levels, which is associated with premature atherosclerotic coronary heart disease."

UT Southwestern researchers, in conjunction with researchers at Tularik Inc., discovered the two genes in 2000.

Before scientists identified the genes, the molecular mechanism by which dietary cholesterol is absorbed and the mechanisms by which cholesterol and other sterols are secreted into the bile were not known, Hobbs said.

"The actual discovery of the two genes in 2000 led to a better understanding of two important pathways of cholesterol metabolism," she said.

Other UT Southwestern researchers involved in the study were Dr. Jonathan Cohen, associate professor of internal medicine; Dr. Robert Hammer, professor of biochemistry; and Dr. Jia Li-Hawkins, now with Pfizer. Researchers from the University of Bonn in Germany also contributed.

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