SOUTHWESTERN NEWS

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Feedback loop found that could forestall liver disease

DALLAS – Oct. 11, 2005 – Researchers at UT Southwestern Medical Center have discovered that the small intestine communicates with the liver to control the production of bile acids – a finding that has great medical implications in treating people at risk for certain types of liver disease.

"We've discovered a new hormone, and new hormones are always exciting," said Dr. Steven Kliewer, professor of molecular biology and pharmacology and senior author of a study available online and appearing in the October issue of *Cell Metabolism.*

The findings may eventually play a role in understanding and preventing liver damage that can occur in biliary cirrhosis, viral hepatitis, alcoholic liver disease and pregnancy.

The central elements in the research are the body's bile acids – powerful and essential detergents that help digest fatty foods and fat-soluble vitamins in the small intestine.

The liver makes bile acids out of cholesterol and sends them to the gall bladder, where they're stored until food is digested. The presence of food stimulates the gall bladder into releasing the bile acids to the small intestine, where they do their work. Finally, they're absorbed into the bloodstream and returned to the liver.

Because they're so powerful, bile acids can damage the body if not controlled properly.

"These bile acids are really nasty in terms of being strong detergents," said Dr. Kliewer.

Scientists have previously known about a mechanism within the liver that prevents too much bile acid from being produced. Normally, a protein called CYP7A1 stimulates production of the acids. When enough bile acids are made, they trigger a series of reactions that blocks the gene for CYP7A1, and production stops.

For this study, UT Southwestern researchers looked at a protein in mice called fibroblast growth factor 15 (FGF15), which is part of a cascade of chemical reactions that also dialed down production of CYP7A1 and reduced the production of bile acids in the liver.

Surprisingly, they found that FGF15 was made in the small intestine, not in the liver, suggesting a new role for the small intestine in regulating bile acid levels.

When the researchers injected FGF15 into the bloodstream, CYP7A1 production in the liver was

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again shut down. Conversely, mutant mice lacking FGF15 made too much CYP7A1, and thus had abnormally high levels of bile acids.

"We can inject FGF15 in the jugular vein, and see the effects in the liver," Dr. Kliewer said.

These discoveries pointed to FGF15 acting as a hormone, which is defined as a substance that's secreted into the bloodstream to work on distant targets.

The findings may be relevant to diseases that involve a condition called cholestatis, in which the bile ducts are blocked. When that happens bile acids accumulate in the liver and severe liver disease may follow. Cholestatis can also occur in patients who are getting all their nutrition through intravenous feeding, because the gall bladder never receives the signal from the small intestine to release bile acids.

Dr. Kliewer said perhaps giving cholestatis patients FGF19 – the human equivalent of FGF15 – may turn off the overproduction of harmful bile acids in these cases.

"So now we have a hormone that's not going to damage the liver, that we could perhaps administer and turn off the production of bile acids, and that could alleviate one of the important causes of cholestatis," he said. "I think that's one of the exciting implications of this."

Future research is needed to determine whether the fibroblast growth factor protein family prevents liver disease in animals, Dr. Kliewer said.

Other UT Southwestern researchers involved in the study were Drs. Takeshi Inagaki and Mihwa Choi, postdoctoral research fellows in molecular biology; Dr. Antonio Moschetta, postdoctoral research fellow in pharmacology and a research associate in the Howard Hughes Medical Institute; Li Peng, senior research assistant in molecular biology; Dr. Carolyn Cummins, postdoctoral research fellow in pharmacology and HHMI research associate; Dr. Jeffrey McDonald, assistant professor of molecular genetics; Dr. James Richardson, professor of pathology; Dr. Robert Gerard, associate professor of internal medicine and of molecular biology; Dr. Joyce Repa, assistant professor of physiology; and Dr. David Mangelsdorf, professor of pharmacology and an HHMI investigator. Researchers from GlaxoSmithKline Research and Development also participated.

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