UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

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Gut protein found to protect against infection and intestinal breakdown

DALLAS – Feb. 6, 2006 – A protein that binds to bile in the small intestine may hold the key to preventing infection and intestinal breakdown in people with conditions such as obstructive jaundice or irritable bowel syndrome, researchers at UT Southwestern Medical Center have discovered.

"What we've identified is one of the mechanisms for how the body keeps the number of bacteria low in the small intestine, and how it prevents them from getting into other organs," said Dr. Steven Kliewer, professor of molecular biology and the study's senior author. The study is available this week online and in an upcoming issue of the *Proceedings of the National Academy of Sciences.*

Bile, which is generated by the liver and flows into the small intestine via a duct, contains harsh acids that help the body absorb nutrients, kill certain bacteria and help keep intact the lining of the intestine, a major barrier against the infiltration of infectious microorganisms. That's no small task; if the innermost lining of the small intestine alone were unfolded, it would be the size of a tennis court.

When there's no bile in the intestine, as happens in people with obstructive jaundice or in those who rely on feeding tubes for nourishment, the lining breaks down and bacteria pass through it into the body, sometimes causing the massive blood infection known as sepsis. Simply giving bile acids orally as a substitute isn't a good solution because they can cause liver damage, Dr. Kliewer said.

The researchers focused on a molecule – FXR – in the wall of the lining, which binds to bile acids. When FXR was activated by a synthetic binding chemical called GW4064, it was found to activate several genes that are known to protect the intestinal lining or attack bacteria.

The research team also found that FXR molecules heavily lined the inside folds of the intestine in adult mice.

"It's perfectly positioned," Dr. Kliewer said. "It's expressed in just the right place to protect

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us from the environment."

When the bile ducts of mice were tied off, preventing bile from reaching the intestine, adding GW4064 prevented damage to the intestines, showing that it can replace bile in protecting the small intestine.

Genetically engineered mice that lacked FXR showed overall damage to the intestines, "strong evidence that this protein is crucial," Dr. Kliewer said. Drugs that bind to FXR, he said, could eventually become useful in treating various conditions of the small intestine.

Other UT Southwestern researchers involved in the study were Drs. Takeshi Inagaki and Guixiang Zhao, postdoctoral research fellows in molecular biology; Dr. Antonio Moschetta, postdoctoral research fellow in pharmacology and a research associate in the Howard Hughes Medical Institute; Youn-Kyoung Lee, student research assistant in molecular biology; Li Peng, senior research associate in molecular biology; John Shelton, senior research scientist in internal medicine; Dr. James Richardson, professor of pathology; Dr. Joyce Repa, assistant professor of physiology; and Dr. David Mangelsdorf, professor of pharmacology and biochemistry and an HHMI investigator. Drs. Ruth Yu and Michael Downes of the Salk Institute for Biological Studies in La Jolla, Calif., also participated in the study.

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