UT SOUTHWESTERN MEDICAL CENTER NEWS

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Researchers identify antibiotic protein that defends the intestine against microbial invaders

DALLAS – Aug. 25, 2006 – Researchers at UT Southwestern Medical Center have identified a protein that is made in the intestinal lining and targets microbial invaders, offering novel insights into how the intestine fends off pathogens and maintains friendly relations with symbiotic microbes.

The study, published today in the journal *Science*, might lead to new medications aimed at helping patients with inflammatory bowel disease. The findings might also aid in understanding the effectiveness of probiotics – mixtures of beneficial bacteria that are added to food products – in boosting the immune system, said Dr. Lora Hooper, assistant professor of immunology and the paper's senior author.

Scientists have known for decades that microbial cells in the human gut outnumber the body's own cells by about 10 to 1. Humans offer a safe haven to these microbes because they help us to break down food that we can't digest by ourselves. But it hasn't been clear how we keep these microscopic gut dwellers from invading our tissues and causing infections.

To help answer this question, Dr. Hooper's research team used mice raised inside sterile plastic bubbles. Because they are never in contact with the outer, microbe-filled world, these mice do not have the bacteria that normally colonize the gut. By exposing these "germ-free" mice to different types of gut bacteria, the researchers were able to observe how the epithelial cells lining the intestine react to microbial invaders.

"We found that when the gut lining comes into contact with bacteria, it produces a protein that binds to sugars that are part of the bacterial outer surfaces," Dr. Hooper said. "Once bound, these proteins quickly destroy their bacterial targets. They're killer proteins with a sweet tooth."

The protein, called RegIIIgamma in mice and HIP/PAP in humans, belongs to a protein class called lectins, which bind to sugar molecules. These particular lectins' seek-and-destroy

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mission may help to create an "electric fence" that shields the intestinal surface from invading bacteria, Dr. Hooper said.

The findings of this study may offer researchers new clues about the causes of inflammatory bowel disease. Most healthy people have a friendly relationship with their gut microbes, but in patients with inflammatory bowel disease this tolerant relationship turns sour and the immune system mounts an attack on the gut's microbial inhabitants that can lead to painful ulcers and bloody diarrhea. What triggers this attack is not clear, but the fact that these patients have elevated HIP/PAP production suggests that they are coping with increased numbers of invading intestinal bacteria.

The study may also help scientists devise more effective treatments for intestinal infections. "We are now working to understand the mechanism by which the intestinal lining senses bacterial threats. What turns this protein antibiotic on?" Dr. Hooper asked. "We want to explore whether this is something we can stimulate artificially to stave off pathogenic infections."

Other contributors to the study, all from UT Southwestern's Center for Immunology, are co-lead authors Heather Cash, a former graduate student; and Cecilia Whitham, research assistant, and Cassie Behrendt, research associate.

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