UT SOUTHWESTERN MEDICAL CENTER NEWS

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Friendly gut bacteria lend a hand to fight infection, UT Southwestern study suggests

DALLAS – Aug. 19, 2009 – Immunology researchers at UT Southwestern Medical Center have found that bacteria present in the human gut help initiate the body's defense mechanisms against *Toxoplasma gondii*, the parasite responsible for toxoplasmosis.

Toxoplasmosis is generally a mild infection, but it can have serious and potentially fatal effects in pregnant women, their fetuses and others with weakened immune systems.

In mice, *T gondii* directly activates a specific immune protein in the host, called toll-like receptor 11 (TLR-11), which helps control the animals' immune response to the parasite. Humans, however, don't have an active form of this receptor. Exactly how the body senses *T gondii* has remained unclear because the parasite doesn't activate any of the functioning toll-like receptors that humans do possess.

In a new study appearing online and in the Aug. 20 issue of *Cell Host & Microbe,* researchers at UT Southwestern suggest that instead of activating toll-like receptors directly, *T gondii's* first interaction in the human gut is with the helpful bacteria that live inside us. Those bacteria then release signaling molecules, alerting the human host to the invader.

"While this is very early data, our results suggest that looking at the bacteria present in each patient's gut could help physicians understand their susceptibility to infectious diseases," said Dr. Felix Yarovinsky, assistant professor of immunology at UT Southwestern and senior author of the paper. "It also suggests the possibility of developing novel probiotic strategies for treating parasitic infections such as toxoplasmosis and cryptosporidiosis, a related disease caused by the parasite *Cryptosporidium.*"

T gondii affects more than 1 billion people worldwide. The protozoan parasite can infect most warm-blooded animals, but the primary host is the house cat. Animals are generally infected with *T gondii* by ingesting contaminated meat, water or the feces of a cat that has recently been infected; however, the parasite also can be passed from mother to fetus.

Because toxoplasmosis is passed to humans through contaminated cat feces, pregnant women are encouraged to keep all house cats indoors and recruit someone who is not pregnant to clean the litter box daily. Once a person is infected, the parasite penetrates the intestine and spreads throughout all organs.

The researchers studied mice in which TLR-11 had been genetically eliminated. This mimics the human immune response to *T gondii*. They then infected the TRL-11-deficient mice with *T gondii* both

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orally and systemically by injection.

Even though the mice lacked their normal mechanism for fighting infection, they nonetheless mounted an attack against *T gondii*. The researchers found that the commensal – or good – bacteria in the gut activated their immune system, thereby inducing various inflammatory responses against the invading pathogen. In humans, he said, it is those helpful bacteria that send activating signals to the three toll-like receptors that are functional, inducing various inflammatory responses against invading pathogens like *T gondii*.

"This seems to be the first example of indirect pathogen recognition in vivo where activation of the immune system depends on indirect rather than direct sensing of a pathogen," Dr. Yarovinsky said.

The problem, Dr. Yarovinsky said, is that TLR-11 appears to cause more harm than good. Though the mice lacking the receptor – but with commensal bacteria – were able to mount enough signaling proteins to defeat the parasite, those with the receptor activated too many signaling proteins and developed severe inflammation in their small intestines. When infected with higher doses of *T gondii*, the mice with TLR-11 also died in much greater numbers because of the increased inflammatory response.

"We speculate that because commensal bacteria co-evolved with the host, they must have found this fine balance to induce the sufficient stimulatory effects of the immune system without causing illness or death," Dr. Yarovinsky said. "The fact that commensal bacteria vary dramatically from person to person might explain why therapeutic outcomes vary so much."

The next step, Dr. Yarovinsky said, is to determine whether particular species of commensal bacteria are more beneficial than others.

Other UT Southwestern researchers involved in the study were Alicia Benson, lead author and research assistant in immunology; Reed Pifer, research assistant in immunology; Cassie Behrendt, research technician for the Howard Hughes Medical Institute; and Dr. Lora Hooper, assistant professor of immunology and microbiology and an investigator for the Howard Hughes Medical Institute at UT Southwestern.

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