UT SOUTHWESTERN MEDICAL CENTER NEWS

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EMBARGOED UNTIL 4 P.M. CDT, MONDAY, JUNE 26

Bacteria, beware: New finding about *E coli* could block infections, lead to better treatments

DALLAS – June 26, 2006 – A newly discovered receptor in a strain of *Escherichia coli* can be blocked to avert infection, a finding that might aid in developing better therapies to treat bacterial infections resulting in food poisoning, diarrhea or plague.

Researchers at UT Southwestern Medical Center are the first to identify the receptor, known as QseC, used by a diarrhea-causing strain of *E coli* to receive signals from human flora and hormones in the intestine and express virulence genes to initiate infection.

In a study made available online this week and in an upcoming issue of the *Proceedings of the National Academy of Sciences,* researchers describe how they used phentolamine, an alpha blocker drug used to treat hypertension, to successfully impede signaling to the receptor. Without such signals, bacteria then pass blindly through the digestive tract without infecting cells.

"This receptor is found in many pathogens, so we can use this knowledge to design specific antagonists to block bacterial infections," said Dr. Vanessa Sperandio, senior author of the study and assistant professor of microbiology at UT Southwestern.

Prior research by Dr. Sperandio found that when a person ingests the more virulent enterohemorrhagic *E coli*, or EHEC – which is usually transmitted through contaminated food such as raw meat – it travels peacefully through the digestive tract until reaching the intestine. There, however, chemicals produced by the friendly gastrointestinal microbial flora and the human hormones epinephrine and norepinephrine alert the bacteria to its location.

This cellular cross talk triggers a cascade of genetic activations prompting EHEC to colonize and translocate toxins into cells, altering the makeup of the cells and robbing the body of nutrients. An infected person may develop bloody diarrhea or even hemolytic uremic syndrome, which can cause death in immune-weakened people, the elderly and young children.

The new study identifies QseC as the specific receptor by which EHEC senses the signals. When the receptor binds to signaling molecules, the bacterium can infect cells.

Researchers tested the capacity of adrenergic antagonists, drugs such as alpha and beta

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blockers, to disrupt the receptor's sensing ability. They found that phentolamine binds to the QseC receptor and occupies the pocket that the receptor would use to recognize the host epinephrine and norepinephrine signals – thus blocking the QseC receptor from sensing the signals and preventing it from being able to express its virulence genes in cells.

This knowledge opens the door to further understanding of the signaling processes between microbes and humans and to the development of novel treatments of bacterial infections with antagonists to these signals, Dr. Sperandio said.

New therapies are important because treating some bacterial infections with conventional antibiotics can cause the release of more toxins and may worsen disease outcome.

That importance is magnified because of the QseC receptor's existence in other types of bacteria, including, *Shigella*, which causes dysentery; *Salmonella*, which causes food poisoning and gastroenteritis; and *Yersinia*, which causes bubonic plague. Those are all emerging infectious diseases that afflict thousands of people each year in the United States and worldwide, according to the Centers for Disease Control and Prevention.

"Overuse of antibiotics has led bacteria to develop resistance to antibiotics, so a novel type of therapy is needed," Dr. Sperandio said.

Other UT Southwestern researchers involved in the study were first author Dr. Marcie B. Clarke, a graduate of the molecular microbiology program who now works in a Boston patent law firm, and David T. Hughes, a molecular microbiology graduate student. Researchers from the University of Maryland School of Medicine also were involved.

The work was supported by the National Institutes of Health and the Ellison Foundation.

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