UT SOUTHWESTERN MEDICAL CENTER NEWS

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

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Plague agent helps UT Southwestern researchers find novel signaling system in cells

DALLAS – May 25, 2006 – The bacterium that causes bubonic plague would seem unlikely to help medical scientists, but researchers at UT Southwestern Medical Center have harnessed it to uncover a new regulatory mechanism that inhibits the immune system.

Three species of the *Yersinia* bacteria, known to cause plague and gastroenteritis, contain a small molecule, called a virulence factor, that the researchers have found modifies host enzymes critical to normal functioning.

"This type of modification has never been seen in cells and presents a new paradigm for how cells may regulate signaling," said Dr. Kim Orth, assistant professor of molecular biology and senior author of the study appearing in the May 26 edition of *Science.*

"*Yersinia* is a nasty pathogen that uses an arsenal of virulence factors to cause disease," she said.

When a cell is infected with a bacterial pathogen, it activates a chain of reactions involving enzymes. One enzyme adds a group of atoms containing phosphorus – called a phosphate group – to another enzyme, a process called phosphorylation, which spurs that enzyme to add a phosphate group to yet another enzyme, and so on. These "cascading" events trigger an appropriate immune response.

Yersinia, however, has the ability to prevent its host from mounting the response, enabling the bacteria to survive and multiply.

The researchers found that one of the *Yersinia* outer proteins, called YopJ, cripples these cascades by adding a small molecule called an acetyl group to two key sites on a host enzyme where the phosphate groups are usually added.

Because the host's enzymes are modified by acetyl groups, they can no longer be activated by phosphate groups, and the enzymatic cascade critical for triggering an innate immune response is not activated.

The internal signaling that YopJ affects is common to many species, from yeast to mammals. In

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addition, other pathogens that attack animals and plants use proteins that are similar to YopJ.

The research is not geared toward finding a cure for plague, which affects about a dozen people in the United States a year and is treatable with antibiotics. Instead, the scientists are working to find out how the pathogen disrupts the immune system and to understand the machinery critical for stimulating an immune response.

"There are many virulence factors used by bacterial pathogens to co-opt the host signaling molecules," Dr. Orth said. "These virulence factors affect central signaling machinery, and we want to understand how they are doing it."

Understanding the relationship between the pathogens and the hosts will help researchers uncover critical steps in how host cells normally operate, Dr. Orth said.

"The next step is to see whether the addition of acetyl groups to key sites on enzymes during cellular signaling is normal for animal and plant cells, and if so, under what circumstances," said Dr. Orth.

Other UT Southwestern researchers involved in the study were first author Sohini Mukherjee, student research assistant in molecular biology; Gladys Keitany, research assistant in molecular biology; Dr. Yan Li, instructor of biochemistry; Yong Wang, research assistant in molecular biology; Dr. Haydn Ball, assistant professor of biochemistry; and Dr. Elizabeth Goldsmith, professor of biochemistry.

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