SOUTHWESTERN NEWS

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GENE DISCOVERY PAVES WAY FOR PREVENTING DEADLY BACTERIAL SHOCK

DALLAS – December 11, 1998 – Identification of a gene that normally prevents endotoxic shock – which causes at least 20,000 deaths a year in the United States and possibly one million worldwide – was reported by UT Southwestern Medical Center at Dallas researchers in today's issue of *Science.*

Mutations of the "toll-like receptor-4" *(Tlr4)* gene in mice, and presumably in humans, create susceptibility to overwhelming infections caused by bacteria such as *Salmonella.* Endotoxic shock can occur when bacterial invasions become severe and systemic. Discovery of the gene may enable creation of a test to screen for people with *Tlr4* genetic defects. Doctors could then use antibiotics to prevent the acceleration of infection.

"The knowledge that these mutations make mice highly susceptible to certain bacterial infections puts us in a position to identify comparable mutations in people to determine if they also are predisposed to these diseases," said Dr. Bruce Beutler, professor of internal medicine, Howard Hughes Medical Institute (HHMI) investigator and lead researcher on the study. "If so, we could protect susceptible individuals with antibiotics, eliminating some and perhaps most cases of endotoxic shock before they begin."

Tlr4 is necessary for cells to respond to endotoxin, a substance made by bacteria that is among the most potent activators of the body's defense against infections. Its cloning culminated a five-year effort in which the scientists mapped a minute region of the mouse genome, identified every gene in the region, and then pinpointed *Tlr4.* The project was intensely competitive with several groups of scientists from industry and academia racing to find this important gene.

(MORE)

"Endotoxin does not directly harm most cells of the body, but it triggers release of chemical weapons against infection," Beutler said. "At an early stage of an infection, these weapons, including tumor necrosis factor (TNF) and interleukin-1 (IL-1), alert the immune system, mobilizing a defensive response.

"If the early-warning system fails, the infection continues to spread throughout the body. This can result in massive overproduction of TNF and IL-1," Beutler said. "This deluge of chemical weapons can cause shock."

Discovery of the gene which is vital in activating the early-warning system is especially significant because it advances researchers' understanding of how the immune system detects endotoxin.

"We have proven that a single gene is essential for sensing endotoxin, and we have identified the protein this gene encodes," he said. "This knowledge might lead to effective methods to block the endotoxin signal, thereby preventing the worst complications of certain infections."

The other researchers involved in the study were: Dr. Alexander Poltorak, internal medicine postdoctoral fellow; Drs. Irina Smirnova, Xiaolong He and Chrisophe Van Huffel, HHMI postdoctoral fellows; Dr. Mu-Ya Liu, a postdoctoral fellow in pharmacology; Dale Birdwell, Erica Alejos and Maria Silva, HHMI research technicians; and researchers at the Max-Planck Institute fur Immunobiologie, Freiburg, Germany, and the Cellular and Molecular Pharmacology Center, Milan, Italy.

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