

Bacteria spill their guts to aid researchers in quest for new antibiotics

DALLAS – June 28, 2004 – New findings about a protein that keeps cells alive by opening and closing pores within a cell’s membrane may open the door to the development of new antibiotics.

Researchers at UT Southwestern Medical Center at Dallas are studying a protein, called MscL, found in the membrane of the single-cell bacterium *Escherichia coli*. The protein is essentially an emergency-response valve that changes shape to let salts and other solutes in and out of the cell through a process called “gating” in order to keep tension on the membrane steady. This gating process allows some of the cell’s innards to spill out or liquid from the surrounding environment to rush in.

If this protein – a type of which is found in nearly all microbes – doesn’t function properly, the cell may die. The researchers have refined previous descriptions of MscL, which may have implications for potential drug therapies designed to kill microorganisms. They also developed a novel way to manipulate the protein’s gating, thus killing the bacteria.

The findings will appear in an upcoming issue of the *Proceedings of the National Academy of Sciences* and are available online.

“If you’re looking for targets for drug therapy – and this protein could possibly be one – you need to know what the target looks like and how it functions normally,” said Dr. Paul Blount, assistant professor of physiology at UT Southwestern and senior author of the study. “This information may help you predict drug interactions that lead to the desired effect, like killing the organism.”

Previous studies on the MscL protein from the bacterium that causes tuberculosis provided the model for what scientists believed was MscL’s structure in its “closed” state. But UT Southwestern researchers led by Dr. Blount found that structure may actually have represented the nearly closed, rather than fully closed, state.

Knowing the difference between what the protein's structure looks like when it is in different conformational states can have important implications if, for example, a scientist is trying to develop a drug that will kill bacteria by interfering with gating.

Dr. Blount and his colleagues developed a new technique to gather information about MscL's structure and function by monitoring and controlling the channel as it opened and closed. They engineered a mutant *E. coli* bacterium to contain a substituted amino acid at different sites in the MscL channel protein. When they added a chemical to the environment, the chemical bound to the amino acid, causing, in some instances, the channel protein to change shape, opening the pore inappropriately and killing the cell.

“Not only were we able to examine this protein as it changes shape in a living bacterium, but we also found several sites within the protein that, when modified genetically and chemically, can cause the channel to open inappropriately, thus killing the organism,” Dr. Blount said. “If these regions of the protein could be modified pharmacologically, one may have the makings of an antimicrobial agent.”

The membrane protein MscL is a mechanosensitive channel protein, a class of proteins that detects mechanical force created by changes in tension in a cell's membrane. Changes in membrane tension are brought about when the concentration of the fluid surrounding the cell differs from conditions within the cell. In response to changing membrane tension, MscL alters its shape, opening and closing pores in the membrane.

“Mechanosensitive channels such as this change their structure and act as an ‘emergency release valve,’ equalizing the conditions on both sides of the cell membrane,” Dr. Blount said. “Of course, the ability to detect mechanical forces, whether it is touch, blood pressure or osmotic forces in the kidney, is crucial for essentially all life.”

Little is known of how mechanosensors function. Although MscL is the best-studied of these proteins, scientists aren't in agreement on how the molecule changes its structure as it gates. But,

because molecular mechanisms are often conserved, studying the gating mechanism in bacteria may help scientists better understand the process of mechanosensation in humans, Dr. Blount said.

Other UT Southwestern researchers who participated in the study are lead author Jessica L. Bartlett, a graduate student, and Gal Levin, a physiology postdoctoral researcher.

The research was funded by the National Institutes of Health, the Welch Foundation, and the Air Force Office of Scientific Review.

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