Researchers Identify Molecular Anchor That Allows Bacterial Invasion Of Central Nervous System

Could be target to block CNS infection

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A single molecular anchor that allows bacteria to invade the nervous system may hold the key to treating many types of bacterial meningitis, a UCSD School of Medicine study has found.

By blocking the molecule's anchoring ability, researchers may be able to find a way to stave off the most common serious infection of the central nervous system and a major cause of childhood death and disability. The researchers' findings appear in the September 2005 issue of the *Journal of Clinical Investigation*.

Kelly Doran, Ph.D, assistant professor of pediatrics, Victor Nizet, M.D., associate professor of pediatrics, and their colleagues have identified a gene that produces a fat-sugar complex, which in turn anchors a molecule called LTA (short for lipoteichoic acid), found on the bacterial cell wall. This anchoring is a necessary first step for bacteria to cross from the bloodstream into the central nervous system through an anatomical obstacle called the blood-brain barrier.

"*Streptococcus*, which can cause meningitis, has to penetrate the normally impermeable blood-brain barrier in order to enter the central nervous system and cause disease," said Doran. "How this happens is not well known for bacteria. We wanted to see how bacteria interact with blood-brain barrier cells to begin the process of crossing over into the nervous system."

The team began by looking for new bacterial genes that allowed them to penetrate the barrier. Through a process that involved generating and screening thousands of *Streptococcus* mutants in a laboratory model of the human blood-brain barrier, the researchers found that a gene called iagA (short for invasion association gene-A) played a central role.

By producing a fat-sugar complex that anchors LTA, iagA establishes a link that allows bacteria to begin making its way into the nervous system. The researchers found that removing the *iag* A gene from the *Streptococcus* inhibited bacterial interactions with the blood-brain barrier, reducing mortality rates up to 90 percent in mice.

"Mice that were infected with the normal, or wild-type, *Streptococcus* bacteria containing *iag* A died within days showing evidence of bacterial meningitis. In contrast, most of the mice survived when infected with bacteria missing the single *iag* A gene," Doran said. "Blocking the anchoring of LTA on the bacterial cell surface could become new a therapeutic target for preventing bacterial meningitis."

Doran and Nizet noted that the study focused on how bacteria can begin the invasion process, and that additional *Streptococcus* toxins and the body's own immune response also contribute to the development of meningitis. In their ongoing efforts, the researchers are looking at all of these factors in order to paint a complete picture of how the bacteria invade the brain and spinal cord to produce this potentially devastating infection.

Bacterial meningitis must be treated quickly and aggressively with antibiotics, since up to 25 percent of affected children may die or suffer permanent cognitive deficits, cerebral palsy, blindness, deafness or seizures. Therefore, an early acting treatment would help reduce the high rates of disability and death.

"Previous studies have found that *Streptococcus* bacteria from infants with serious disease have significantly higher levels of LTA than bacterial strains in infants without symptoms," Nizet said. "This underscores the importance of this anchor-LTA interaction, as well as its potential importance as a drug target."

The researchers' work was supported by the Burroughs Wellcome Fund, the American Heart Association, the Edward J. Mallinckrodt, Jr., Foundation, the United Cerebral Palsy Research Foundation and the National Institutes of Health.

Doran and Nizet's colleagues include Erin Engelson, Arya Khosravi and Heather Maisey of UCSD; Iris Fedtke and Andreas Peschel of the University of Tübingen, Germany, and Ozlem Equils, Kathrin Michelsen, and Moshe Arditi of Cedars-Sinai Medical Center, Los Angeles.

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