How Meningitis Bacteria Attack the Brain

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A specific protein on the surface of a common bacterial pathogen allows the bacteria to leave the bloodstream and enter the brain, initiating the deadly infection known as meningitis. The new finding, which may guide development of improved vaccines to protect those most vulnerable, including young infants and the elderly, is now available online in the *Journal of Experimental Medicine*.

"*Streptococcus pneumoniae*, commonly known as pneumococcus, is responsible for half the cases of bacterial meningitis in humans," said the study's senior author, Victor Nizet, MD, professor of pediatrics and pharmacy at the University of California, San Diego's School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. "As many as 30 percent of patients can die from this rapidly progressing infection, while half of survivors may be left with permanent neurological problems including deafness, seizures, intellectual deficits or motor disabilities."

Meningitis develops when bacteria penetrate the "blood-brain barrier." Comprised of a single layer of highly specialized microvascular endothelial cells, the blood-brain barrier prevents most large molecules from entering into the cerebrospinal fluid, preserving an optimal biochemical environment for brain function.

The UC San Diego team investigated the functions of a protein known as NanA in order to discover how an entire bacterium can breech the blood-brain barrier and gain access to the central nervous system. NanA is produced by all strains of pneumococcus and displayed prominently on the bacteria's outer surface.

Through genetic manipulations, the researchers were able to remove the entire NanA protein, or just specific sections of the molecule, from the pathogen. They found that while normal pneumococci were able to bind, enter and penetrate through human brain microvascular endothelial cells, mutant bacteria lacking the NanA protein –or those expressing only a truncated version of the protein – largely lost these abilities. Conversely, when the full-length pneumococcal NanA protein was cloned and expressed on the surface of a nonpathogenic laboratory strain, the transformed bacteria gained the ability to bind and enter the same endothelial cells.

"Our tissue culture studies showed that the NanA protein was both necessary and sufficient for bacterial penetration of the blood brain barrier endothelial cells," said Satoshi Uchiyama, MD, a postdoctoral fellow in the Nizet Laboratory and lead author on the study. "After infecting mice intravenously, we also found that far fewer NanA-deficient bacteria left the bloodstream and entered the brain, in comparison to mice infected with the normal pneumococcus."

NanA is best known as an enzyme that cleaves and releases the sugar molecule known as sialic acid, which is present in abundance on the surface of all human cells. While this enzymatic activity played a small part in promoting NanA-mediated blood-brain barrier interactions, a much stronger role was identified for the outer tip of the protein. This tip seems to directly attach to the brain microvascular endothelial cells and then stimulate them to take in the pneumococcus.

"Antibodies directed against the NanA protein also strongly inhibited the ability of pneumococcus to attach to and invade the blood-brain barrier cells," said Kelly Doran, PhD, an assistant professor at both UC San Diego School of Medicine and San Diego State University, who jointly supervised the project with Nizet.

Because NanA is expressed on the surface of all pneumococcal strains, it is an attractive candidate to include in a universal protein-based vaccine against pneumococcal infection according to Nizet, who is also on the medical staff of Rady Children's Hospital, San Diego. Currently, infants and the elderly are immunized with vaccines comprised of surface capsule sugars from 7 to 23 of the most common strains of pneumococcus.

"Our immune system generates antibodies more readily against protein rather than sugar vaccine antigens," said Nizet. "Since at least 80 different pneumococcal capsule types exist, not all strains can be represented in the capsule sugar-based vaccines. An added benefit of an effective NanA vaccine would be to reduce the risk of pneumococcus spreading into the brain to cause meningitis."

Ongoing research in the Nizet and Doran labs will seek to characterize the receptor on the blood-brain barrier cells to which NanA binds, and to explore whether similar processes contribute to the ability of other meningitis pathogens – such as group B streptococcus – to pass through the blood-brain barrier.

Additional contributors to the project were co-lead author Aaron Carlin, MD, PhD, Arya Khosravi, Shannon Weiman, Darin Quach, and George Hightower of the Department of Pediatrics at UC San Diego School of Medicine; Timothy Mitchell, PhD, of the University of Glasgow; and Anirban Banerjee, PhD, of the Department of Biology at San Diego State University. The research was supported by the National Institutes of Health, the American Heart Association, the Burroughs-Wellcome Fund and the Taylor Thomas Foundation.

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Media Contact: Debra Kain, 619-543-6163, ddkain@kain

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