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New study helps explain why some ear and respiratory infections become chronic

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Scientists have figured out how a bacterium that causes ear and respiratory illnesses is able to elude immune detection in the middle ear, likely contributing to chronic or recurrent infections in adults and children. A team from the Research Institute at Nationwide Children's Hospital published the findings in a recent issue of *PLOS Pathogens* and has now received a $1.6 million grant from the National Institutes of Health to further the work.

Led by Kevin M. Mason, PhD, and Sheryl S. Justice, PhD, principal investigators in the Center for Microbial Pathogenesis, the effort is offering new information about nontypeable *Haemophilus influenzae* (NTHI). Contrary to what its name suggests, NTHI does not cause the flu. It is, however, the culprit behind most childhood cases of otitis media, or chronic ear infections. NTHI also can cause sinusitis, pneumonia and a range of other upper and lower respiratory illnesses.

"Infections caused by NTHI are chronic and recurrent similar to other bacterial infections that are difficult to treat," Dr. Justice says. "Findings from our studies help to explain reasons for that."

Humans are the only known hosts for *Haemophilus influenzae* bacteria, a family comprised of many different strains, the most well-known of which is type b, or Hib. Once the leading cause of bacterial meningitis in children under age 5, Hib is largely under control today, thanks to a Hib vaccine that was introduced in 1985. Now, NTHI is responsible for the majority of invasive *H. influenzae* infections in all age groups.

At any given time, NTHI is present in the nose and mouth in about 50 percent of young children, an environment rich in nutrients such as heme-iron, which all bacteria need to survive. Still, the bacterium leads to few if any serious symptoms when confined to this nasopharynx region. It isn't until NTHI moves into the lungs and middle ear—where heme-iron is sequestered as part of the body's immune response—that the bacterium causes the most problems. Therein lay the mystery that Drs. Mason and Justice were trying to solve: Why, they wanted to know, did NTHI have better success in a part of the body that was more hostile to its existence?

"Our data support a paradox, wherein mechanisms that are thought to clear the bacteria at these sites actually may be promoting increased survival of bacteria and contributing to disease severity," says Dr. Mason, who also is an assistant professor of pediatrics at The Ohio State University College of Medicine.

Specifically, the scientists figured out how NTHI uses the body's own immune response to its advantage. At the first sign of bacterial attack in the lungs, middle ear and certain other parts of the body, the immune system blocks access to nutrients bacteria need to survive—including heme-iron—a process called nutritional immunity. This initial immune response gives way to a series of other defensive maneuvers to fight the infection, including inflammation, which involves the release of chemicals that are supposed to isolate the invading bacterium and direct white blood cells to the site of infection to kill the invader.

By devising a lab experiment that mimicked the body's immune response to NTHI infection in the middle ear, the scientists were able to observe how the bacterium responds to this onslaught. They found that the serum that carries disease-fighting chemicals and white blood cells to the site of infection also includes heme-iron. When NTHI was re-exposed to heme-iron, it underwent structural changes that allowed it to divide much more

slowly and become elongated and spaghetti-like in appearance. Because white blood cells typically target the rapidly dividing shorter cells, they ignored NTHI, leaving the bacterium to grow and thrive.

"This clearly suggests that NTHI is changing to become more fit in the host," says Dr. Justice, who also is an assistant professor of pediatrics and urology at the Ohio State University College of Medicine.

This sort of bacterial adaptation has contributed to the rising problem of antibiotic resistance, which has prompted scientists to look for new ways to treat infection. One possibility is to cut off bacteria's nutrient supply by blocking essential metabolic pathways with a small molecule inhibitor, essentially starving the bacteria to death.

"If we could design a small molecule inhibitor that would look like heme-iron but would actually clog up a key metabolic pathway in bacteria, we may be able to get around the problem of antibiotic resistance," suggests Dr. Mason, who adds that he and Dr. Justice plan to use the new five-year NIH grant to further studies of just such an inhibitor. They also plan to investigate whether other bacteria undergo similar changes in response to immune defenses.

"We would predict that the effects we observe with nutritional modulation of pathogenic behaviors in the NTHI strains would resemble behaviors in other mucosal pathogens," Dr. Mason says.

More information: Szelestey BR, Heimlich DR, Raffel FK, Justice SS, Mason KM. Haemophilus responses to nutritional immunity: epigenetic and morphological contribution to biofilm architecture, invasion, persistence and disease severity. *PLoS Pathogens*. 2013 Oct, 9(10):e1003709.

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