Researchers suggest novel prevention of recurrent ear infections

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Eliminating bacteria's DNA and boosting antimicrobial proteins that already exist may help prevent middle ear infections from reoccurring. These are the findings from a Nationwide Children's Hospital study that examined how an immune defense protein common in the middle ear interacts with a structure meant to protect a colony of bacteria.

The bacterium nontypeable Haemophilus influenzae (NTHI) causes a wide range of diseases of both the lower and upper airways, including middle ear infection. NTHI, like most other bacteria, can form a biofilm , a robust community of bacteria that allows the bacteria to evade the host's immune system and protects the bacteria from antibiotics and other therapies designed to kill them.

Human beta-defensin-3 is an antimicrobial defense protein expressed in the middle ear of humans and other mammals that kills both Gram-positive and Gram-negative bacteria. Previous research has shown that if expression of beta-defensin is disrupted, the host's ability to control the bacteria in the upper airway is altered and infection worsens.

Investigators in The Research Institute at Nationwide Children's Hospital hypothesized that human beta-defensin-3 might lose its power to kill NTHI if it got caught up within the extracellular DNA that makes up a biofilm's outer layer, thus preventing its contact with bacteria within the biofilm.

"Antimicrobial host defense proteins, like human beta-defensin-3, have

been shown to bind to non-host DNA," says Lauren O. Bakaletz, PhD director of the Center for Microbial Pathogenesis "This interaction has an impact on the defense protein's ability to function."

Upon examining their animal model of middle ear infection, Dr. Bakaletz' team found that bacterial DNA and the animal's defense peptides were detected together in biofilms that developed during infection. Also, the defense peptide was predominantly co-localized with the biofilm's extracellular DNA.

When the team exposed the bacteria that cause ear infections to a concentration of human-beta defensin-3 that is typically detected in the a middle ear of a child with active infection, the peptide was able to kill 100 percent of the NTHI, but the killing stopped when extracellular DNA was introduced to the reaction.

"These data support the conclusion that the killing activity of the antimicrobial defense protein was decreased in an NTHI-induced biofilm due to its interaction with eDNA," says Dr. Bakaletz, who is the lead study author and professor of Pediatrics and Otolaryngology at The Ohio State University College of Medicine.

When they removed extracellular DNA from the biofilm, the killing activity of the defense peptide was rescued.

"The ability to restore antimicrobial defense protein activity is encouraging, since biofilms are resistant to most treatments, including traditional antibiotics," says Dr. Bakaletz.

Dr. Bakaletz says this study provides evidence for a new treatment regimen to target biofilms formed by NTHI during middle ear infection. One approach would be to deliver a therapeutic agent that can disrupt bacterial DNA, in conjunction with human beta-defensin-3 to the middle

ear of a child with chronic, recurrent infection. Physicians could follow the same pathway used to target the middle ear during ear tube surgery, a common treatment for chronic ear infections.

"This approach would likely bolster the ability of the innate immune system to manage NTHI-induced biofilms, avoiding the need for antibiotics or empowering the use of antibiotics we already have in our arsenal," says Dr. Bakaletz. "Doing so could help diminish the recurrent nature of middle ear infection."

More information: Jones EA, McGillivary G, Bakaletz LO. Extracellular DNA within a Nontypeable Haemophilus influenzae -Induced Biofilm Binds Human Beta Defensin-3 and Reduces Its Antimicrobial Activity. *J Innate Immun*. 2012 Aug 22.

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