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Researchers identify new strategy for decreasing neonatal mortality

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Researchers have discovered how the bacteria Group B streptococcus (GBS) avoids detection by the immune system during pregnancy. The findings, reported in the journal *mBio*, could lead to the development of new drugs and strategies for treating GBS infection, which is a leading cause of neonatal morbidity and mortality.

"We now know that GBS utilizes the enzyme hyaluronidase to prevent detection from the host during pregnancy. If we can devise ways to block this enzyme from dampening host immune responses, this may enable eradication of GBS," said lead author Lakshmi Rajagopal, PhD, associate professor of pediatrics, and a professor of microbiology and global health, Center for Global Infectious Disease Research, University of Washington, Seattle.

GBS is a leading cause of neonatal pneumonia, sepsis, meningitis, and preterm birth. People are often asymptomatically colonized with GBS, and approximately 30% of healthy women have GBS in their rectum and vagina. Heavy vaginal GBS colonization is the primary risk factor for GBS-associated preterm birth. An estimated 25% to 40% of preterm births are a result of in utero bacterial infection with vaginal bacteria, such as GBS. GBS is known to cause ascending infection, a process by which the bacteria traffics from the vagina into the uterus, leading to fetal damage and preterm birth.

Despite the large number of women at risk for this infection, little is known about the bacterial and host factors involved in GBS colonization

and ascending infection. Recent research has shown that cervical hyaluronic acid protects against ascending infection and that in mice, inappropriate hyaluronidase expression increases the risk of preterm birth. The hyaluronidases are a family of enzymes that are known to degrade hyaluronic acid.

In the new study, Dr. Rajagopal isolated GBS strains from women with preterm labor and from neonates who had invasive disease and showed that both had increased hyaluronidase activity compared to GBS strains isolated from rectovaginal swabs of healthy women. "In healthy women, GBS appear to be residing as commensal bacteria," said Dr. Rajagopal.

Using a mice model to examine the role of the GBS hyaluronidase in preterm birth, the investigators discovered that hyaluronidase production by GBS permits ascending infection by reducing antibacterial inflammation in uterine tissues. Essentially, GBS uses the hyaluronidase it produces to mask itself from the human immune system.

"What we know is that the GBS hyaluronidase breaks down the host's hyaluronic acid into small molecules, disaccharide fragments, which blocks Toll-like receptors 2 and 4 and prevents GBS ligands from activating pro-inflammatory signaling cascades," explained Dr. Rajagopal. "The host's immune system seems to be unable to recognize GBS, and therefore does not mount an effective immune response. The bacteria take advantage of this, ascending into the uterus and infecting the placenta and fetus. It's like a Trojan horse."

The researchers say that developing a way of blocking hyaluronidase could lead to new treatments for GBS, as well as other ascending infections that may work the same way. "Why do we have GBS in the vagina and the rectum? It is not a beneficial organism," said Dr. Rajagopal. "If we can develop reagents or tools to specifically eradicate GBS from the rectovaginal tract, then we don't have to worry about GBS

infecting our neonates and newborns or causing preterm births."

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