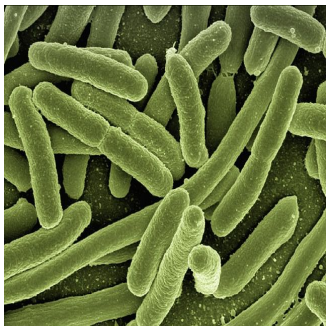
ICU
MANAGEMENT & PRACTICE

Research Targets Bacteria Behind Hospital-associated Infections



Kansas State University researchers are defeating persistent bacteria known for causing infections in hospitals.

The bacteria, Enterococcus faecalis, are the second-leading cause of hospital-associated infections in the U.S., said Lynn Hancock, associate professor of biology and leader of the research. His team has discovered how a regulatory system helps this bacteria resist a host's innate immune defense -- a finding that may help develop novel drug compounds to fight the bacteria.

"Right now, we have very limited therapeutic interventions because the bacteria is highly resistant to not only antibiotics but a variety of other environmental stresses," Hancock said. "With the diminishing number of antibiotics that are effective at treating these types of infections, we need to come up with new strategies."

Enterococcus faecalis, or E. faecalis, is naturally found in the gastrointestinal tract of humans and other mammals. But outside the intestinal walls, the bacteria can cause bacteremia, urinary tract infections and endocarditis.

An added obstacle is that the bacteria are 100 to 1,000 times more resistant to lysozyme than other bacteria, Hancock said. Lysozyme is an infection-fighting substance that humans produce and is found in numerous body tissues, such as tear film, the urinary tract and saliva. The regulatory system of E. faecalis also makes it very resistant to other cellular stresses -- such as elevated temperature, low pH and oxidative stress -- that are part of a person's innate immune defense and help fight infection.

"Enterococcus has evolved sensing systems to find out the kind of environment it is in," said Sriram Varahan, doctoral student in microbiology and member of Hancock's research team. "It is a really rugged bacteria that is known to persist and survive in environments where other pathogens are unable to do so. Many infectious disease specialists have given it the moniker of being the cockroach of the microbial world."

By understanding the bacteria's regulatory network, the researchers hope to develop novel drug compounds that can block the bacterium's ability to sense and respond to the presence of lysozyme and other stresses during infection. To find the bacteria's weakness, the scientists focused on a protein called Eep. While studies have shown that Eep is important during infection, the Kansas State University researchers discovered how Eep contributes to an important stress response that the bacteria use to survive the host defense.

It is an important finding because now researchers can develop compounds that inhibit the Eep protein, which makes the bacteria susceptible to lysozyme and stops infection. When humans produce lysozyme to fight the bacteria, the bacteria will be unable to fight back.

"It's kind of like hitting it in the Achilles' heel," Hancock said. "Then it is very much compromised to establish infection."

While the bacteria are still able to live without the Eep protein, the bacteria need it to cause infection, Hancock said. Studies have shown that when the Eep is inactivated, bacteria are compromised nearly 10,000-fold in their ability to cause infection.

"The ability to interfere with a bacteria's ability to establish infection is going to become a more popular theme for treating infections rather than simply killing the bacteria," Hancock said. "When you put selective pressure on bacterial populations to live or die, they are really good at circumventing the drugs and getting around the killing mechanism."

For future research, Hancock and his team want to find what compounds are most effective at interfering with Eep to make the bacteria susceptible to lysozyme. They also want to study the SigV protein, which coordinates expression of target genes that are controlled by the Eep protein. Similar to Eep, if SigV is inactivated, then the target genes are not expressed and the bacteria do not become resistant to lysozyme. These target genes and proteins may also lead to new drug development possibilities.

"In the dawn of the post-antibiotic era, I think it is essential for us to have more options, rather than depending on a few silver bullets that are seemingly failing a lot in hospitals nowadays," Varahan said. "We have come up with new targets and hopefully they will work."

The scientists recently published their research in the Journal of Bacteriology. The research was part of a $1.5 million five-year grant from the National Institutes of Health.

Other researchers involved include Vijayalakshmi Iyer, research associate in biology, and William Moore, a former doctoral student in microbiology.

View the Journal of Bacteriology publication at http://www.ncbi.nlm.nih.gov/pubmed/23645601.

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