Battling bacteria: Research shows iron's importance in infection, suggests new therapies

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(Phys.org)—A Kansas State University research team has resolved a 40-year-old debate on the role of iron acquisition in bacterial invasion of animal tissues.

The collaborative research—led by Phillip Klebba, professor and head of the department of biochemistry—clarifies how microorganisms colonize animal hosts and how scientists may block them from doing so. The findings suggest new approaches against bacterial disease and new strategies for antibiotic development.

The study—in collaboration with Tyrrell Conway, director of the Microarray and Bioinformatics Core Facilities at the University of Oklahoma, and Salete M. Newton, Kansas State University research professor of biochemistry—recently appeared in *PLOS ONE*. It shows how iron acquisition affects the ability of bacteria to colonize animals, which is the first stage of microbial disease.

"This paper establishes that iron uptake in the host is a crucial parameter in bacterial infection of animals," said Klebba, the senior author on the publication. "The paper explains why discrepancies exist about the role of iron, and it resolves them."

Iron plays a key role in metabolism, leading bacteria and animals to battle each other to obtain it. Klebba's team found that E. coli must

acquire iron from the host to establish a foothold and colonize the gut—a concept that was often debated by scientists.

"For years it was theorized that iron is a focal point of bacterial pathogenesis and infectious disease because animals constantly defend the iron in their bodies," Klebba said. "Animal proteins bind iron and prevent microorganisms from obtaining it. This is called nutritional immunity, and it's a strategy of the host defense system to minimize bacterial growth. But successful pathogens overcome nutritional immunity and get the iron."

Little was known about what forms of iron enteric bacteria—which are bacteria of the intestines—use when growing in the host, but this study shows that the native Gram-negative bacterial iron uptake systems are highly effective. Scientists questioned whether prevention of iron uptake could block bacterial pathogenesis. This article leaves no doubt about the importance of iron when E. coli colonizes animals because bacteria that were systematically deprived of iron became 10,000-fold less able to grow in host tissues, Klebba said.

"This is the first time our experiments unambiguously verified the indispensability of iron in infection, because here we created the correct combination of mutations to study the problem," Klebba said.

Enteric bacteria have so many iron transport systems that it's difficult to eliminate them all. For example, E. coli has at least eight iron acquisition systems.

"These transporters are redundant because iron is essential," Klebba said. "Bacteria are resilient. If one system is blocked, then another one takes over."

These findings suggest strategies to block microorganisms from creating

diseases in animals and humans, including the potential for antibiotic development and for therapeutic antibodies.

"It gives us insight," Klebba said. "Now we know that iron deprivation protects against disease, but we must be comprehensive and inhibit multiple systems to completely shut down the microorganisms' ability to obtain the metal."

The researchers are using their findings to isolate antibodies that block bacterial iron uptake. This may help animals and humans defend themselves against microbial diseases.

"We would like to apply this research and protect people from bacterial infection," Klebba said. "That's one of the focal points of our laboratory."

Klebba's research was supported by a $1.25 million grant from the National Institutes of Health.

The study was led by Hualiang Pi, Klebba's student at his former institution, the University of Oklahoma. Another Kansas State University collaborator on the project was Lorne Jordan, doctoral student in biochemistry, Toledo, Ohio.

More information: The *PLOS ONE* article, by Hualiang Pi et al.,—titled "Role of Catecholate Siderophpores in Gram-negative Bacterial Colonization of the Mouse Gut"—is available at dx.plos.org/10.1371/journal.pone.0050020

Provided by Kansas State University

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