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Bacteria hijack plentiful iron supply source to flourish

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In an era of increasing concern about the prevalence of antibiotic-resistant illness, Case Western Reserve researchers have identified a promising new pathway to disabling disease: blocking bacteria's access to iron in the body.

The scientists showed how bacterial siderophore, a small molecule, captures iron from two abundant supply sources to fan bacterial growth—as well as how the body launches a chemical counterassault against this infection process. Their findings appear in a recent edition of *The Journal of Experimental Medicine*.

"Bacterial siderophore will be an important target for therapeutics one day because it can be modified to prevent bacteria from acquiring iron, but at the same time, it's possible to preserve host access to iron," said senior author Laxminarayana Devireddy, DVM, PhD, assistant professor of pathology, Case Comprehensive Cancer Center.

Investigators knew from the outset that bacterial siderophore captures iron from the host mammal and transforms it so that bacteria can absorb and metabolize the mineral. In this investigation, Devireddy and his colleagues discovered that human mitochondria, which very closely resemble bacteria, possess their own iron-acquisition machinery—mitochondrial siderophore. Mammalian mitochondria are membrane-encased subunits within cells that generate most of the cell's energy, and like their bacteria counterparts, mammalian mitochondria have their own siderophore mechanism that seeks out, captures and

delivers iron for utilization.

At the test tube level, investigators found that bacteria can feed on iron supplied by bacterial siderophore and mitochondrial siderophore. From this glut of iron, bacteria proliferate and make the host mammal very ill with an infection.

"It's like bacteria can use their own iron-capture machinery or the host's. It just doesn't matter," Devireddy said. "They are very good at utilizing siderophore from both bacterial and mammalian siderophore sources. That means that bacteria get the most iron."

Case Western Reserve researchers also demonstrated that the absence of mitochondrial siderophore in a mammal can enhance its ability to resist infection. When investigators exposed mice deficient for mitochondrial siderophore to systemic infection by *E. coli*, the animals resisted infection. The reason? *E. coli* bacteria had less iron to access from mitochondrial siderophore-deficient mice.

Additionally, mammals are not entirely defenseless from a bacteria raid on mitochondrial siderophore iron supplies. In another phase of their investigation, scientists found that normal mice secrete the protein lipocalin 24p3, which isolates bacterial siderophore and suppresses synthesis of mammalian siderophore.

"The action of lipocalin significantly reduced the mortality of the mice from the *E. coli* infection, and some mice actually recovered," Devireddy said. "That kind of delay in bacterial proliferation gave the immune system time to identify and then neutralize the microbe."

These findings highlight the potential of developing effective therapeutics to reverse bacterial infection.

"Any approach that would suppress either bacterial or mitochondrial siderophore and activate lipocalin-2 would likely slow infection, allowing the host's immune system to respond," Devireddy said. "Such novel approaches would also provide a much-needed alternative to treat those infections that have become antibiotics resistant."

Provided by Case Western Reserve University