Scientists discover how some bacteria may steal iron from their human hosts

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Like their human hosts, bacteria need iron to survive and they must obtain that iron from the environment. While humans obtain iron primarily through the food they eat, bacteria have evolved complex and diverse mechanisms to allow them access to iron. A Syracuse University research team led by Robert Doyle, assistant professor of chemistry in The College of Arts and Sciences, discovered that some bacteria are equipped with a gene that enables them to harvest iron from their environment or human host in a unique and energy efficient manner. Doyle's discovery could provide researchers with new ways to target such diseases as tuberculosis. The research will be published in the August issue (volume 190, issue 16) of the prestigious *Journal of Bacteriology*, published by the American Society for Microbiology.

"Iron is the single most important micronutrient bacteria need to survive," Doyle says. "Understanding how these bacteria thrive within us is a critical element of learning how to defeat them."

Doyle's research group studied *Streptomyces coelicolor*, a Gram-positive bacteria that is closely related to the bacteria that causes tuberculosis. *Streptomyces* is abundant in soil and in decaying vegetation, but does not affect humans. The TB bacteria and *Streptomyces* are both part of a family of bacteria called *Actinomycetes*. These bacteria have a unique defense mechanism that enables them to produce chemicals to destroy their enemies. Some of these chemicals are used to make antibiotics and other drugs.

Actinomycetes need lots of iron to wage chemical warfare on its enemies; however, iron is not easily accessible in the environments in which the bacteria live— e.g. human or soil. Some iron available in the soil is bonded to citrate, making a compound called iron-citrate. Citrate is a substance that cells can use as a source of energy. Doyle and his research team wondered if the compound iron-citrate could be a source of iron for the bacteria. In a series of experiments that took place over more than two years, the researchers observed that *Streptomyces* could ingest iron-citrate, metabolize the iron, and use the citrate as a free source of energy. Other experiments demonstrated that the bacteria ignored citrate when it was not bonded to iron; likewise, the bacteria ignored citrate when it was bonded to other metals, such as magnesium, nickel, and cobalt.

The next task was to uncover the mechanism that triggered the bacteria to ingest iron-citrate. Computer modeling predicted that a single *Streptomyces* gene enabled the bacteria to identify and ingest iron-citrate. The researchers isolated the gene and added it to *E. coli* bacteria (which is not an *Actinomycete* bacteria). They found that the mutant *E. coli* bacteria could also ingest iron-citrate. Without the gene, *E. coli* could not gain access to the iron.

"It's amazing that the bacteria could learn to extract iron from their environment in this way," Doyle says. "We went into these experiments with no idea that this mechanism existed. But then, bacteria have to be creative to survive in some very hostile environments; and they've had maybe 3.5 billion years to figure it out."

The *Streptomyces* gene enables the bacteria to passively diffuse iron-citrate across the cell membrane, which means that the bacteria do not expend additional energy to ingest the iron. Once in the cell, the bacteria metabolize the iron and, as an added bonus, use the citrate as an energy source. Doyle's team is the first to identify this mechanism in a bacteria

belonging to the *Actinomycete* family. The team plans further experiments to confirm that the gene performs the same signaling function in tuberculosis bacteria. If so, the mechanism could potentially be exploited in the fight against tuberculosis.

"TB bacteria have access to an abundant supply of iron-citrate flowing through the lungs in the blood," Doyle says. "Finding a way to sneak iron from humans at no energy cost to the bacteria is as good as it gets. Our discovery may enable others to figure out a way to limit TB's access to iron-citrate, making the bacteria more vulnerable to drug treatment."

Source: Syracuse University