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Ironing Out New Details of Tuberculosis Infection

Scientists in India, led by a Howard Hughes Medical Institute (HHMI) international research scholar, have identified five key genes that enable *Mycobacterium tuberculosis* to acquire the iron it needs to sustain growth and promote infection.

Targeting genes within this cluster represents a good strategy for preventing tuberculosis and other mycobacterial infections, said Rajesh S. Gokhale, an HHMI international research scholar at the National Institute of Immunology in New Delhi, India, and lead investigator on the study. Because some of these genes are conserved across a number of related bacterial families, they are promising targets for drugs to treat TB and other bacterial diseases.

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The *tuberculosis* bacterium, which infects more than one third of the world's inhabitants, is a leading cause of death and disease worldwide.

Gokhale and colleagues report their findings in early online publication January 30, 2006, in the *Proceedings of the National Academy of Sciences*.

When *M. tuberculosis* infects humans, it takes up residence in immune cells called macrophages. To survive in this harsh environment, mycobacteria, like many other types of bacteria, need iron to carry out life-sustaining functions, such as creating proteins and synthesizing nucleotides to form DNA. However, free iron is not easily found in an intracellular environment. To obtain this rare element, most bacteria manufacture and secrete chemical compounds called siderophores that scavenge iron from the environment.

Researchers discovered siderophores—chemical compounds used by bacteria to scavenge iron from their cellular environment—well over 50 years ago, but the genes involved in adding the long-chain lipid anchor that enables *M. tuberculosis* to do so more efficiently, remained a mystery until now.

Mycobacteria have evolved siderophores with lipid-chain tails that enable them to exploit the macrophage's lipid-trafficking system to capture iron more efficiently. Instead of using siderophores that diffuse freely, mycobacteria anchor their siderophores to lipid membranes by means of a long fatty acid tail. After these siderophores bind to iron within the macrophage, the lipid tail makes the iron sticky enough to permit delivery to the very compartment in macrophages where the mycobacteria are lurking.

Using microarray data, the available literature, and intuition, Gokhale's group identified the location of the four genes that produce the lipid tail after observing that the expression of the genes significantly increased in response to low iron concentrations. The gene required for the synthesis of the siderophore core, called *mbt-1*, functions the same way, so Gokhale's team named the new locus *mbt-2* and the new genes *mbtK*, *mbtL*, *mbtM*, and *mbtN*.

Now that the major siderophore genes and their functions have been defined, understanding the biosynthetic pathway provides an opportunity to develop small-molecule inhibitors with the potential for developing anti-tuberculosis drugs, said Gokhale. His team has already determined that some of genes from the *mbt-2* cluster is conserved across several other bacterial species that cause various pulmonary, skin, and organ diseases. Since the *mbt-1* genes are also conserved across many bacterial families, the *mbt* genes appear to be ideal antibacterial targets for treating tuberculosis and other bacterial infections, he said.