Tuberculosis bacterium's outer cell wall disarms the body's defense to remain infectious

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The bacterium that causes tuberculosis has a unique molecule on its outer cell surface that blocks a key part of the body's defense. New research suggests this represents a novel mechanism in the microbe's evolving efforts to remain hidden from the human immune system.

Researchers found that the TB bacterium has a molecule on its outer surface called lipomannan that can stop production of an important protein in the body's immune cells that helps contain TB infection and maintain it in a latent state. This protein is called tumor necrosis factor (TNF). When TNF is not produced in sufficient quantities, the TB bacterium can grow unchecked and cause an uncontrolled active infection inside and outside of the lungs.

"There are several unique components on the Mycobacterium tuberculosis outer cell wall that help it sneak into the lung relatively unnoticed," said Larry Schlesinger, professor and chair of the Department of Microbial Infection and Immunity at Ohio State University and senior author of the study. "The more we can learn about how these cell wall structures influence the human immune response, the closer we can get to developing a more effective strategy to treat or even prevent an active tuberculosis infection."

Lipomannan resembles a tree branch sprinkled with smaller sugar molecules protruding from the outer cell wall of the bacterium. The

findings show that lipomannan can block TNF production at the microRNA level. MicroRNAs are small segments of RNA that regulate -- or fine-tune -- a gene's protein-building function.

To date, microRNAs have been implicated most frequently in the development of cancer. Schlesinger said this research is among the first studies to show that pathogenic bacteria can influence microRNA activation in immune cells and is the first to explore how microRNAs regulate the macrophage inflammatory response to Mycobacterium tuberculosis.

Macrophages are first-responder cells in the immune response. They eat TB bacteria at the point of infection in the lung and then normally activate molecules that make pieces of the bacteria visible to infection-fighting warriors, triggering an eventual T-cell response to come to the macrophages' aid.

The research is published this week in the online early edition of the *Proceedings of the National Academy of Sciences*.

About 2 billion people worldwide are thought to be infected with TB bacteria. People who are infected can harbor the bacterium without symptoms for decades, but an estimated one in 10 will develop active disease characterized by a chronic cough and chest pain. Both active and latent infections are treated with a combination of antibiotics that patients take for at least six months, and such treatment is becoming less effective with more drug-resistant bacterial strains.

Schlesinger and colleagues conducted the study comparing lipomannans from two types of bacteria -- a virulent strain of Mycobacterium tuberculosis and a harmless strain called Mycobacterium smegmatis, which is often used as a control bacterium in TB research.

Many of these same researchers, led by Schlesinger, had previously isolated the lipomannans from each type of bacterial cell's surface and used powerful biochemical analyses to characterize the significance of the lipomannans' structural differences. In a study published recently in the *Journal of Biological Chemistry*, the group reported on how the surface structures on virulent TB bacteria lowered the response of a specific T-cell that typically gets recruited to fight tuberculosis.

In this newer study, the scientists compared how the structures affected the production of TNF in primary human macrophage culture experiments.

They first established that human macrophages respond differently to the two different types of bacteria lipomannans after 24 hours of exposure. Lipomannan from the virulent TB bacterium produced significantly less TNF than lipomannan from the M. smegmatis bacterium.

Though the study showed that the harmless cells increase production of TNF through a well-known receptor pathway as expected, the virulent TB bacteria did not make use of that receptor pathway. This supported the concept that the pathogenic TB bacterium has figured out another way to block the TNF protein in its quest to keep the immune system guessing, said Schlesinger, also the director of Ohio State's Center for Microbial Interface Biology.

A single microRNA can affect the production of hundreds of proteins, and the process of identifying those relationships is ongoing. However, two microRNAs in this study were known to be relevant for their connections to genes and proteins already established as players in the immune response to TB infection: miR-125b and miR-155.

Biochemical and genetic experiments showed that macrophages

stimulated with lipomannan from TB bacteria had enhanced expression of miR-125b, effectively inhibiting the production of TNF. In contrast, the lipomannan from the harmless bacteria had enhanced expression of miR-155, which regulates other compounds in a way that stimulates TNF production.

Researchers' experimental manipulation to lower the expression of miR-125b in macrophages increased production of TNF in response to the TB bacteria lipomannan, further confirming that this regulation of TNF occurred at the microRNA level, Schlesinger said.

"This really speaks to the power of the tuberculosis bacterium to adapt to the human host," he said. "It has had centuries to develop a sophisticated way to deal with its encounter with the human. Fortunately, genomic technology is allowing us to identify microRNAs more and more rapidly, which might allow us to catch up with the TB bacterium and figure out a way to outsmart it."

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