

TB bacteria mask their identity to intrude into deeper regions of lungs

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Flying under the radar: tuberculosis-causing mycobacteria initiate infection in the lower lung to evade pathogen-killing cells. Credit: Ramakrishnan Lab/University of Washington

TB-causing bacteria appear to mask their identity to avoid recognition by infection-killing cells in the upper airways. The bacteria call up more permissive white blood cells in the deeper regions of the lungs and hitch

a ride inside them to get into the host's body.

Details on this finding are reported Dec. 16 in the advanced online edition of the journal *Nature*. The research was a collaboration between the University of Washington and the Seattle Biomedical Research Institute.

Dr. Lalita Ramakrishnan, who studies how TB evades the body's immune system and manipulates the body's defenses for its own ends, is the senior author. She is a UW professor of microbiology, medicine and immunology. The lead author is C.J. Cambier of the UW Department of Immunology.

Ramakrishnan noted that the recent study also suggests an explanation for the longstanding observation that tuberculosis infections begin in the comparatively sterile lower lungs. In the upper respiratory tract, resident microbes and inhaled microbes of a variety of species signal their presence.

These tip-offs alert and attract many infection-fighting cells to the upper airways. The presence of other microbes in the upper airway may thereby help to keep TB infections at bay by creating a hostile environment.

Their presence may explain why TB is a less contagious disease than those caused by several other respiratory pathogens.

To cause disease, TB bacteria must sneak through this well-patrolled area and head for parts of the lungs where fewer microbiocidal cells are policing.

Almost like intruders wearing a stocking over their faces to keep surveillance cameras from clearly recording their features, the TB

pathogens produce particular types of fatty substances, or lipids, on their cell surfaces.

These lipids, abbreviated as PDIM, are already known to be associated with bacterial virulence. The researchers showed that PDIM lipids function by masking the underlying molecular patterns that would reveal their dangerous nature to macrophages, a first-line defense of infection-fighting cells.

At the same time, a related lipid - called PGL - on the bacterium's cell surface promotes the recruitment of cells described as permissive macrophages. These clean-up cells engulf but don't kill the TB pathogens. Instead, they take them across the lung lining, deep into the lung tissue where the bacteria can establish an infection.

According to the researchers on this study, these mechanisms appear to allow certain TB pathogens to avoid detection by the pattern recognition receptors that enable some infection-fighting cells to spot a variety of different disease microbes through the pathogen-associated molecular patterns on or near their cell surface.

Like most other bacteria, TB pathogens have many of these telltale molecular patterns that should activate an immune response. However, TB pathogens have evolved mechanisms to circumvent tripping the alarm, in this case by physically masking the otherwise detectable pattern. This cover-up allows them to infect the airway initially by avoiding the infection-fighting cell populations that are detrimental to their survival, the researchers noted.

The TB pathogens then use the other lipid molecule, PGL, to co-opt a host chemical pathway that triggers the recruitment of the permissive macrophages.

The present study expands on earlier work in the Ramakrishnan and collaborative labs, which helped describe the strategies by which TB pathogens manipulate host pathways for their own purposes after they enter certain host cells.

These include the secretion of proteins that help expand the niche for TB by recruiting macrophages to the early lung tubercles characteristic of the disease. The present study describes earlier stages in infection, when the pathogens first come in contact with their potential host at the surface of the lining of the lung.

"The current study suggests the manner in which the TB pathogens manipulate recruitment of the first responding macrophages to gain access to their preferred niche," the researchers noted.

"The choreographed entry involves two related TB cell lipids acting in concert to avoid one host pathway while inducing another," they wrote. The findings link the previously known, absolutely essential virulence factor on the surface of TB cells, PDIM, to the evasion of immune cell detection. They also might explain why a certain pathogen molecular pattern recognition system is dispensable in protecting against TB. On the other hand, PGL is not required on the surface of TB cells for them to infect the body.

Ramakrishnan noted that globally, a lot of samples of TB taken from infected patients do not have PGL. "However," she and her research team noted, "the importance of PGL in mediating TB virulence or transmission is underscored by its presence in many of the W-Beijing strains" of TB which are starting to rapidly appear in more patient samples, and which have predominated in outbreaks in North America.

Ramakrishnan explains that their findings suggest how PGL may play an important role in increasing TB's infectivity.

"The presence of PGL in ancestral strains of TB suggest it played an integral role in the evolution of TB infectivity," the researchers noted. "TB is an ancient disease and the enhanced infectivity conferred by PGL may have been essential for most of its history before human crowding, with its increased opportunity for transmission, made it dispensable."

The study findings, and previous work on TB, might also explain why smaller droplets of TB are more infectious than larger ones. Only the smaller droplets can make their way down into the lower airways. On the flip side, all it takes is 3 or fewer TB mycobacteria with PGL-producing ability to enter the lower lungs and start an infection.

Provided by University of Washington

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