

Tuberculosis bacteria build 'edible' havens in immune cells

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This photomicrograph reveals *Mycobacterium tuberculosis* bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for *M. tuberculosis*. Credit: public domain

Bacteria that cause tuberculosis trick immune cells meant to destroy them into hiding and feeding them instead. This is the result of a study led by researchers from NYU Langone Medical Center and published

online April 18 in *Nature Immunology*.

The study results revolve around the ancient battle between the human immune system and bacterial invaders, where [immune cells](#) strive to recognize [bacteria](#) as the microbes work to evade them. *Mycobacterium tuberculosis* remains the leading bacterial cause of death globally because, like other successful pathogens (e.g. HIV), it goes beyond evasion to take over functions of immune cells.

The newly published study describes how [tuberculosis bacteria](#) cause mammalian immune cells, called macrophages, to make more of a key snippet of genetic material. Higher levels of this snippet, called microRNA-33 (miRNA-33), change the action of many genes to strip macrophages of their ability to package TB bacteria for destruction. At the same time, these genetic regulatory changes force the cells to build up fat for the TB bacteria to feed on. Although this study was done in mice, the same mechanisms were found in human macrophages infected with TB.

"Our study results describe precise mechanisms that enable tuberculosis bacteria to persist in the body, which is central to the infection's deadliness," says senior study author Kathryn Moore, PhD, the Jean and David Blechman Professor of Cardiology at NYU Langone. "While anti-cholesterol medications like statins are currently under investigation for the treatment of tuberculosis, our study points to other ways in which we might reverse TB-driven fat build-up in immune cells to better clear the disease."

Upon entering macrophages, most bacteria are enfolded into vesicles called phagosomes. These pockets then fuse with lysosomes, a second set of compartments filled with bacteria-destroying chemicals. TB bacteria can evade capture by phagolysosomes, getting free in the cell's cytosol where a back-up mechanism, autophagy, seeks again to deliver them to

lysosomes.

While the first role of autophagy is to enfold aging cell parts into vesicles where they can be broken down and recycled, evolution has also put this mechanism to work in controlling fat (lipid) levels and as a back-up system for removing harmful bacteria. TB bacteria take advantage of this convergence of cell functions to change conditions in their favor.

Specifically, the new study found that TB bacterial proteins trigger an immune signaling pathway inside macrophages, where a protein complex called NFKappaB triggers a key gene to make more of microRNA-33. This dramatically dials down the signal delivered by several autophagy genes that would otherwise keep fat levels down.

Future Treatment Design

With the emergence of the idea that TB might need fat build-up to thrive, there had been excitement around the idea of using statins against TB. Could these inhibitors of cholesterol synthesis counter some lipid build-up in macrophages? In 2010, Moore's team published a paper in *Science* that found miR-33 to be encoded in the same gene that statins turn up, so statins would cause [macrophages](#) to make more miR-33 even as they lowered cholesterol levels.

Given the better understanding of the role of miR-33 and fat build-up in TB infection, the study authors argue that the bacterial lipid effect may be countered using antisense oligonucleotides, another set of molecular chains that are the right shape to grab miR-33 and remove it from action. An example of this kind of medication is mipomersen, an antisense molecule already available for the treatment of inherited conditions that cause high cholesterol levels.

"Like many diseases that are now rare in the United States, but still

common causes of death in developing countries, the economics of engaging industry to help develop new treatments will be challenging," says Moore. Any treatment would have to be very inexpensive to be viable in the developing world, and antisense oligonucleotide injectable drugs are costly.

Moving forward, the team will be looking for other drugs to test in mouse models of TB infection that can lower levels of miR-33 to boost the pathways suppressed by TB through this tiny RNA.

More information: Mycobacterium tuberculosis induces the miR-33 locus to reprogram autophagy and host lipid metabolism, *Nature Immunology*, [DOI: 10.1038/ni.3434](https://doi.org/10.1038/ni.3434)

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