Another Way That TB Subverts the Immune System

New findings could open the way to better vaccines.

Sometimes it really does pay to kill the messenger—especially when it comes bearing tuberculosis. That is the message of a study published in the January 2012 issue of *Cell Host and Microbe* by Joel Ernst, MD, the Jeffrey Bergstein Professor of Medicine and professor of pathology and microbiology.

An electron microscope captures clusters of the rod-shaped tuberculosis bacterium.

In a series of experiments, Dr. Ernst and his colleagues demonstrated that *Mycobacterium tuberculosis* subverts the immune system by prolonging the lives of cellular couriers called neutrophils.

One-third of the world's population is infected with the bacterium that causes tuberculosis, and an estimated 1.7 million people die from the disease each year. Current tuberculosis vaccines are only partially effective, and Dr. Ernst's discovery of a novel mechanism by which the bacterium thwarts the immune system could lead to better vaccines.

Dr. Ernst and his collaborators had previously discovered that neutrophils, white blood cells known as the immune system's first responders, contribute to activating T cells, specialized white blood cells that play a leading role in combating tuberculosis. Their most recent work reveals precisely how neutrophils act as cellular messengers to trigger the body's adaptive immune response to tuberculosis and how *M. tuberculosis* works to stop them.

Usually, neutrophils in the lungs engulf foreign bacteria and then self-destruct through a precisely orchestrated process called apoptosis, or programmed cell death. Once they have expired, other immune cells called dendritic cells convey the dead neutrophils and their bacterial cargo to lymph nodes. There, the T cells recognize unique proteins in the bacteria and target them for destruction.

This process works properly, however, only if the neutrophils actually die on schedule. And that is where *M. tuberculosis* gums up the works.

Researchers already knew that the bacterium uses a gene called *nuoG* to inhibit the suicide of macrophages, larger immune cells that also swallow pathogens. Now Dr. Ernst, Ludovic Desvignes, PhD, assistant professor of medicine, and postdoctoral fellow Robert Blomgran, PhD, now at Linköping University, Sweden, and their collaborator Volker Briken, PhD, at the University of Maryland, discovered that *M. tuberculosis* uses the same gene to inhibit the death of neutrophils as well. By postponing the suicide of these cellular messengers, the bacteria stop the neutrophils from delivering their cargo to dendritic cells and short-circuit the body's immune response.

"Evolutionarily, that's probably the reason that mycobacteria adapted this capability," Dr. Ernst says. He and his colleagues show that mice infected with a mutant strain of *M. tuberculosis* that lacks the *nuoG* gene have higher rates of T cell activation because their neutrophils die more promptly, get handed off to dendritic cells more rapidly, and activate T cells earlier.

Dr. Ernst's work could promote development of more effective tuberculosis vaccines that counteract the ability of the bacterium to keep immune cells alive longer than nature intended. "Discovering how this mycobacterium perturbs the immune system helps the whole field as we work together to try to beat back tuberculosis," Dr. Ernst says. ●

—ALEXANDER GELFAND

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