Wolf in sheep's clothing: Uncovering how deadly bacteria trick immune system

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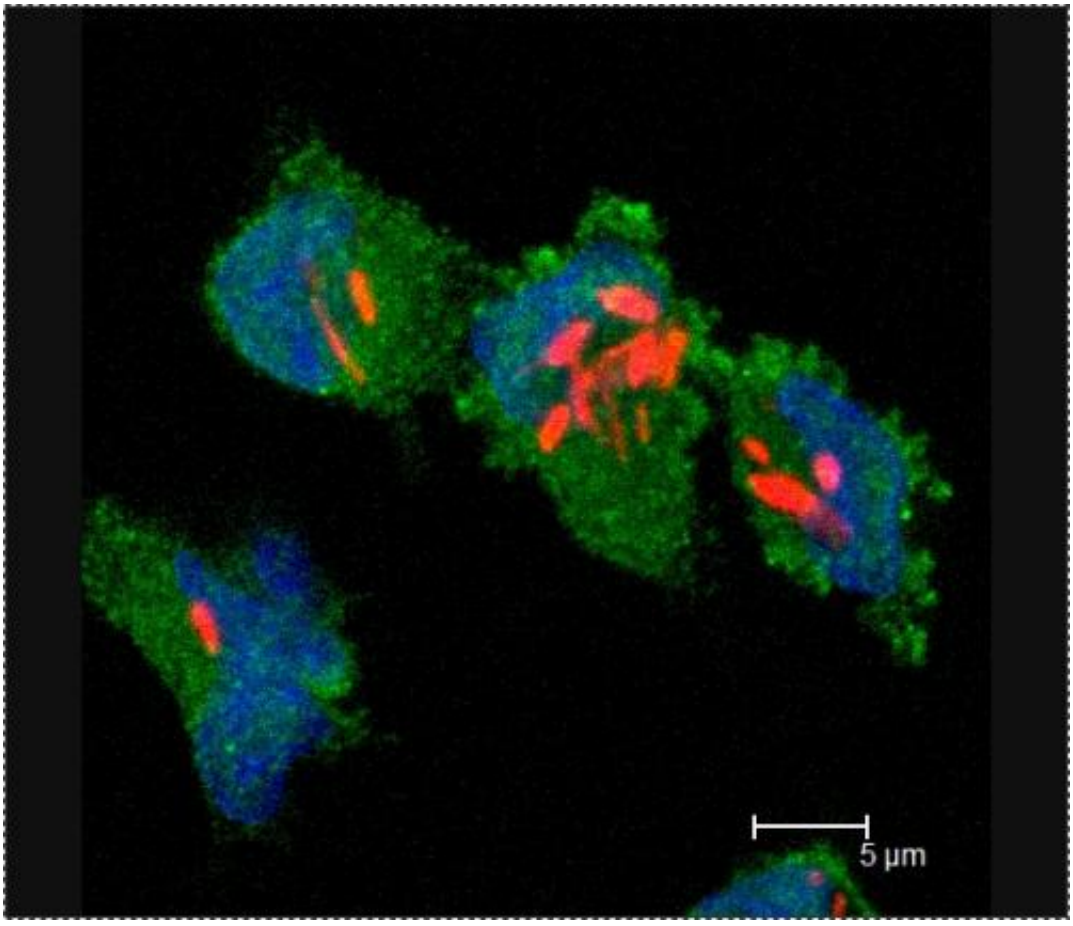


This shows macrophages infected with the leprosy bacterium, *M. leprae*, in vitro. The nucleus is blue. Credit: University of California - Los Angeles

An outbreak of tuberculosis in the skid row area of downtown Los Angeles may have exposed up to 4,500 individuals to the bacterium that

causes the deadly disease and has left federal officials scrambling to intervene.

The outbreak is occurring during winter, when homeless individuals are driven to crowded shelters, when influenza is peaking and when people's vitamin D levels, typically boosted by sunlight exposure, are low. A new UCLA study offers critical insight into how various bacteria may manipulate such factors to their advantage.

In a study published online Feb. 28 in the journal *Science*, UCLA researchers demonstrate that certain cunning bacteria—including the type that causes tuberculosis—can pretend to be viruses when infecting humans, allowing them to hijack the body's immune response so that they can hide out, unhindered, inside our cells. The findings may also help explain how viral infections like the flu make us more susceptible to subsequent bacterial infections such as pneumonia.

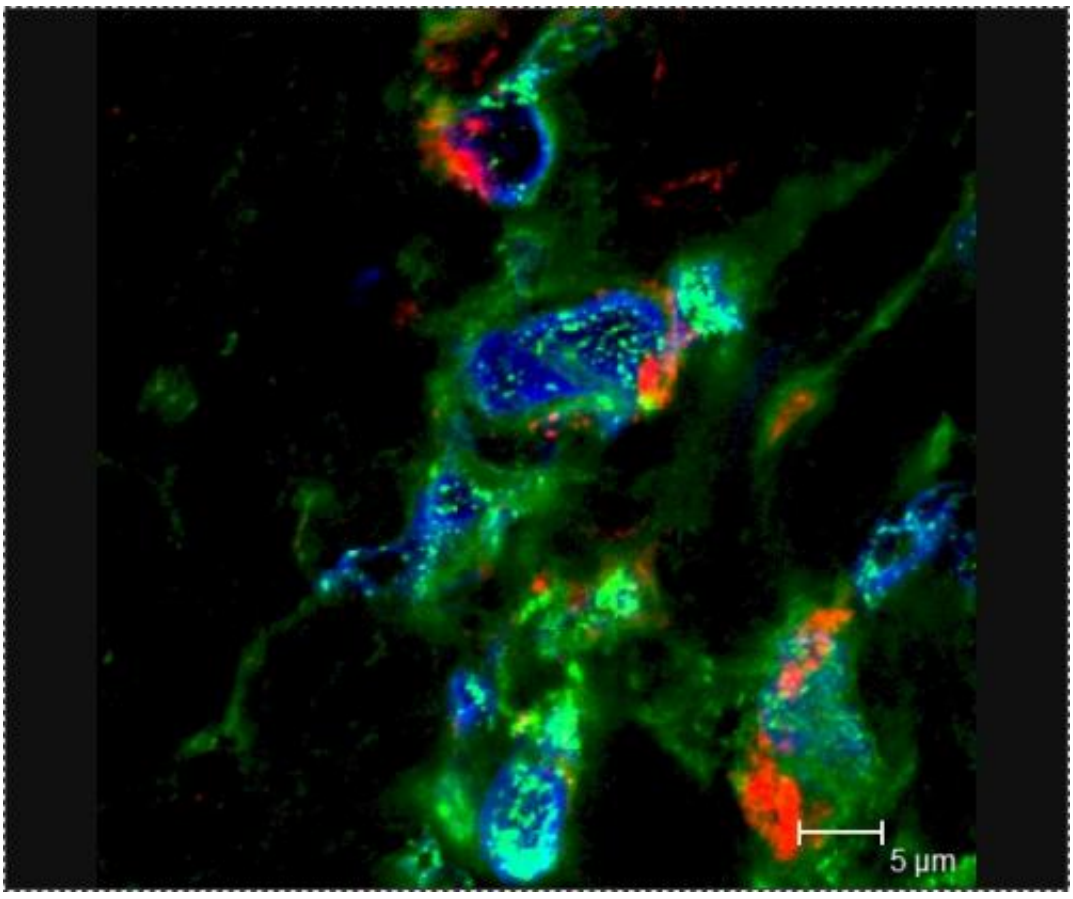
The study is particularly relevant to tuberculosis, which kills 1.4 million people worldwide each year. In the case of the recent Los Angeles outbreak, the findings could provide clues as to how the flu and a lack of vitamin D may have given the tuberculosis bacterium an edge.

"With 8.7 million in the world falling ill with tuberculosis each year, a better understanding of how these bacteria avoid our immune system could lead to new ways to fight them and to better, more targeted treatments," said senior author Dr. Robert L. Modlin, chief of dermatology at the David Geffen School of Medicine at UCLA and a professor of microbiology, immunology and molecular genetics in the UCLA Division of Life Sciences.

The protection our immune system provides against bacteria-based diseases and infections depends on the critical response of T cells—white blood cells that play a central role in fighting infections—and in

particular on the release of a protein called interferon-gamma. Interferon-gamma utilizes the vitamin D hormone to alert and activate cells to destroy invading bacteria.

The research team found that bacteria can pretend to be viruses, triggering the immune system to launch an attack with a different protein, called interferon-beta, which is designed to fight viruses, not bacteria. Not only is interferon-beta ineffective against bacteria, but it can also block the action of interferon-gamma, to the advantage of bacteria. Further, if a real virus were to infect the body, triggering interferon-beta, it would divert the attention of the immune response, preventing an attack on the bacterial invader. The researchers say this may explain why the flu can lead to a more serious bacterial-based infection like pneumonia.



This shows *M. leprae* (red) and IFN-beta (green) in cells in a leprosy lesion. The nucleus is blue. Credit: University of California - Los Angeles Health Sciences

"Like a wolf in sheep's clothing, the bacteria can fool the immune system into launching an attack against the wrong type of infection, thus weakening the response against the bacteria," said first author Rosane M. B. Teles, a researcher in the dermatology division at the Geffen School of Medicine.

For the study, the team examined the mechanisms by which the virus-fighting interferon-beta protein suppresses the interferon-gamma defense response to bacterial infections, tricking the immune system into making the wrong defense choices.

The researchers studied leprosy as a model and then applied what they learned to understand tuberculosis, given that leprosy and tuberculosis are caused by related bacteria. Modlin noted that leprosy is an outstanding model for studying immune mechanisms in host defense since it presents as a clinical spectrum that correlates with the level and type of immune response of the pathogen.

The scientists first compared the genetic expression of the virus-fighting interferon-beta protein and the bacteria-fighting interferon-gamma protein in skin lesions from leprosy patients. They found that interferon-gamma was expressed in patients with the milder form of the disease and that interferon-beta was significantly increased in those with the more serious, progressive form of leprosy.

The researchers then compared the genes triggered by interferon-beta in these leprosy skin lesions with those found by two other groups of

investigators in the blood of tuberculosis patients. Remarkably, there was a significant overlap. The interferon-beta genes were more frequent in both the skin lesions of leprosy patients with extensive disease and the blood of tuberculosis patients with more severe disease.

"We found this common interferon-beta gene pattern correlated with the greater extent of disease in both leprosy and tuberculosis, which are two very distinct diseases," Teles said.

Previous work by the UCLA team demonstrated that the interferon-gamma defense pathway relies on a specific mechanism involving vitamin D, a natural hormone that plays an essential role in the body's fight against infections. The current study found that interferon-beta suppressed elements involved in the interferon-gamma–triggered vitamin D pathway, preventing the immune system from killing the bacteria.

"The study raises the possibility that a decrease or increase of one of these two interferon proteins could shift the balance from mild to more serious disease," Modlin said. "We may find that therapeutic interventions to block or enhance specific interferon responses may be an effective strategy to alter the balance in favor of protection against bacterial diseases."

The new findings may indicate why, in winter, Los Angeles skid row residents are at an added disadvantage in dealing with tuberculosis—for at least three reasons. First, because of colder weather at night, indigent homeless people tend to stay in shelters, where they live in close proximity with others, facilitating the spread of the infection. Second, due to the seasonal rise in influenza, the body's immune system could be diverted by the flu virus to produce interferon-beta, blocking an effective immune response to the tuberculosis bacteria. And finally, the drop in vitamin D levels associated with a decrease in exposure to sunlight during the winter months could diminish the ability of

individuals' immune systems to kill the tuberculosis bacteria.

"With TB on the rise, this scenario could play out not only in cities in the United States but all over the world," Modlin said. "We hope that our findings may provide insight into harnessing new methods to combat TB and other bacterial infections as well."

Modlin noted that 8.7 million become ill with tuberculosis each year, and 1.4 million die from the disease. He added that an increase or decrease in one of the two interferon proteins could help explain why some people may be more resilient against or susceptible to the infection or have a more serious course of the disease.

The next step, according to Teles, is to further understand the mechanisms that bacterial pathogens use to activate interferon-beta and how bacteria can manipulate the immune system to block the potent interferon-gamma host antimicrobial responses in human infections.

Provided by University of California, Los Angeles