New chemical can kill latent tuberculosis bacteria

March 14 2008

Success in the laboratory suggests that a new compound can point the way to preventing active tuberculosis in people infected with the latent form of the bacterium, says a team led by researchers at Weill Cornell Medical College in New York City. A drug with such properties could also be useful in treating people who already have tuberculosis by shortening the lengthy treatment period. The discovery also points to new ways of thinking about fighting bacterial infection, which is becoming increasingly resistant to traditional antibiotics.

"With each new case of antibiotic resistance, doctors are losing ground against Mycobacterium tuberculosis and other infectious diseases," explains the study's senior author Dr. Carl Nathan, chairman of Microbiology and Immunology and the R.A. Rees Pritchett Professor of Microbiology at Weill Cornell Medical College. "This new approach fights the pathogen in a way that's different from conventional antibiotics. For what may be the first time, we have found compounds that only kill M. tuberculosis when they are not dividing. This lack of replication is a characteristic of latent bacteria, which are tough to eradicate with existing antibiotics and ultimately play a huge role in the epidemic's spread."

The new findings are published in the March 12 online issue of the journal *Cell Host & Microbe*.

It's tough to overestimate TB's impact on public health. According to the World Health Organization, the lung infection kills over 1.6 million

people worldwide each year.

About a third of the world's people are also thought to be infected with latent or non-replicating M. tuberculosis. In about 5 to 10 percent of these individuals, the latent bacteria eventually begin to replicate, causing active disease. On average, each person with active TB is thought to spread the infection to between 9 and 20 other people, experts say.

"That means that killing latent M. tuberculosis is one of the keys to curtailing or eliminating TB as a disease," Dr. Nathan says. "Antibiotic research has typically focused on killing rapidly dividing bacteria. But with antibiotic resistance rising, that no longer seems like a winning strategy. The long duration of treatment required for curing TB may reflect the fact that some of the bacteria remain non-dividing even during clinically active disease."

With current drugs, it can take six months to eradicate most non-dividing bacteria, and adherence to that long a regimen is difficult for many patients. But if they stop treatment prematurely, drug-resistant bacteria can emerge. Those bacteria are even harder to eradicate if treatment is resumed, and in the meantime, the resistant strain may have also been passed on to others.

In their experiments, the Weill Cornell researchers focused on a bacterial enzyme called dihydrolipoamide acetyltransferase (DlaT). "DlaT's main job is to help M. tuberculosis get energy from nutrients. But when the bacterium is under stress, it also uses the enzyme to defend itself against oxidative damage from human immune cells, such as macrophages," explains study lead author Dr. Ruslana Bryk, assistant research professor in the Department of Microbiology and Immunology at Weill Cornell Medical College.

The team's work in guinea pigs revealed that DlaT is crucial to triggering active TB disease. "So we screened 15,000 compounds to find chemicals that might inhibit DlaT," Dr. Bryk says. The researchers discovered one such compound from a class of chemicals called rhodanines. Their collaborators at deCODE Chemistry then synthesized over 1,000 different variants until the Weill Cornell team found several that can enter and selectively kill non-dividing M. tuberculosis.

"We believe that these DlaT inhibitors probably target additional mechanisms that non-dividing M. tuberculosis needs to survive, and we are currently investigating that possibility," Dr. Nathan says. "We also believe that these compounds work in synergy with human immune responses and the chemical environment inside the host to kill latent bacteria."

The inhibitors described in the paper are surely not the only ones with the ability to kill non-dividing M. tuberculosis selectively. "This was really a proof-of-principle effort to show that targeting non-dividing bacteria was feasible," Dr. Nathan explains. "In recent work supported by the Bill and Melinda Gates Foundation, we have since found additional compounds that appear to kill non-dividing M. tuberculosis selectively."

"As a parent, a citizen and an occasional patient, I worry about losing the hard-fought gains we've made against infectious disease," Dr. Nathan says. "When traditional antibiotics work, treating TB, pneumonia and other bacterial diseases seems routine. When they don't work -- as is happening now with growing frequency -- these infections become emergencies. The growing crisis of microbial resistance demands innovative new approaches. We hope this work will encourage more scientists that such innovations are worth seeking."

Source: New York- Presbyterian Hospital/Columbia University Medical

Center

Citation: New chemical can kill latent tuberculosis bacteria (2008, March 14) retrieved 26 April 2024 from https://phys.org/news/2008-03-chemical-latent-tuberculosis-bacteria.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.