One secret to how TB sticks with you

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Mycobacterium tuberculosis is arguably the world's most successful infectious agent because it knows how to avoid elimination by slowing its own growth to a crawl. Now, a report in the July 10 issue of the journal *Cell*, a Cell Press publication, offers new insight into the bugs' talent for meager living.

"Tuberculosis can resist the host immune system and remain latent for decades," said Michael Glickman of the Memorial Sloan-Kettering Cancer Center. To do so, the mycobacterium responsible must resist an arsenal of DNA-damaging mutagens produced within the macrophage, the immune cell in which it lives. "It's incompletely understood how it can do that. We've identified one such mechanism."

The discovery could lead to new drugs that might eliminate strains of TB that have grown resistant to those that are currently available.

A whopping 30% of the world's population is infected with latent TB, the researchers said. In some people, the Tuberculosis bacterium will reactivate, causing an estimated 1.3 million deaths a year, according to the World Health Organization.

One secret to TB's success is a protein that the researchers call CarD, the new study shows. That protein ratchets down transcription of the genes encoding ribosomal RNA (rRNA) by directly binding RNA polymerase, the cellular machinery that transcribes DNA into RNA. rRNA is the central component of the ribosomes that serve as the cell's protein factories, and, Glickman explained, its production accounts for some 90

percent of all transcription.

"The mycobacterium tailors its translational machinery in response to stress within the host and we have identified CarD as a critical mediator of this response" he said.

Loss of CarD is fatal to *M. tuberculosis* living in cell culture, Glickman and his colleague Christina Stallings show. CarD depletion leaves the pathogen sensitive to killing by oxidative stress, starvation, and DNA damage as it fails to cut its transcription of rRNA.

Importantly, Glickman said, they were able to show in infected mice that the mycobacterium depends on CarD not just when it is in its early, most active phase of growth, but also later in the course of infection. Drugs that target CarD's interaction with RNA polymerase could therefore lead to sorely needed, new TB drugs, the researchers said.

"The TB health crisis is exacerbated by the alarming emergence of multidrug- and extensively drug-resistant strains," Glickman said. "The development of new chemotherapeutic strategies is imperative, which requires insight into the pathways involved in *M. tuberculosis* infection, persistence, and drug resistance. CarD is one such pathway that we plan on targeting for therapeutic development. "

The findings might also prove to be clinically important for other disease-causing microbes.

Scientists knew before how some bacteria adapted to stress by limiting rRNA transcription, Glickman said. But the new study is the first to show how this is done in a mycobacterium, which lack a key gene responsible in other bugs like E. coli.

CarD is widely distributed in the bacterial world, he said, for instance it

is found in Bacillus anthracis, the bacterium that causes anthrax. "This finding may have broader application to other important pathogens," he said.

Source: Cell Press (news : web)