Tuberculosis protects itself against toxic agents sent to destroy it

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(PhysOrg.com) -- Tuberculosis fights off the toxic agents, acidity and oxidants, that our immune system sends to destroy it, which is why the maddeningly drug-resistant bacterium can survive in harsh conditions in our bodies for essentially as long as its human host lives, new research shows.

This environment inside a human cell called the macrophage is the body's equivalent to the jungles of Congo or the sands of Niger, and researchers believe they're closer to understanding how TB survives in this harshest of environments as long as it does, said Tapan Biswas, research scientist in the University of Michigan College of Pharmacy. Biswas is the lead author on a paper that describes the structure of the protective protein that allows TB to live inside the macrophage.

Understanding how this protein works could lead to new drugs against TB, said Oleg Tsodikov, assistant professor in the College of Pharmacy and a principal investigator on this study. Nearly one-third of the world's population is infected with Mycobacterium tuberculosis, an extremely drug resistant bacterium that can live for decades. Of people infected, 5-10 percent will develop symptoms and if left untreated, TB is fatal. There is no vaccine.

The macrophage is a cell that normally destroys bacteria by engulfing them and subjecting them to an extremely acidic environment rich in oxidants and other very reactive chemicals, said Tsodikov. Researchers in the Tsodikov laboratory at U-M and in the Sabine Ehrt laboratory at

Weill Medical College of Cornell University were able to unravel the protein, called Rv3671c, which is encoded by the TB gene.

This protein turns out to be a novel type of a protease, meaning a class of proteins that are designed to cleave other proteins. By using this cleavage function, Rv3671c may destroy other proteins that build up in the destructive environment of the macrophage and are toxic to TB, and in this way protect the bacterium, Tsodikov said.

"That's just one possibility," said Tsodikov. "But what is clear is that if one inhibits this protein by developing a drug, this bacterium should not be able to survive inside of a human and it's likely that latent tuberculosis would be cleared by our immune system."

Said Biswas, "If we know how this protein functions we can actually try to find an inhibitor against this protein, that can be further developed into a drug."

Currently, there are multiple drugs used to treat TB, and the bacterium has developed a resistance to all of them, said Biswas. TB is extremely difficult to treat, and takes months of antibiotics to cure.

Other authors of this study include Sabine Ehrt, professor of microbiology and immunology, as well as Jennifer Small, Omar Vandal and Toshiko Odaira from the Sabine Ehrt's research group at Cornell.

The paper appears in the Oct. 13 issue of the journal *Structure*.

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