



Getting TB off Steroids

For over 40 years, tuberculosis has been treated using a cocktail of antibiotics that must be taken for six months to a year. The long course of treatment is necessary to ensure that all of the *Mycobacterium tuberculosis* (*Mtb*), the bacteria that causes TB, is killed off.

Abandoned courses of treatment not only lead to relapses and further risk of spreading the disease, but also to the evolution of multidrug-resistant (MDR) and extensively drug resistant (XDR) strains, which now make up 20 and 2 percent of all TB cases, respectively. A discovery recently reported in the *Journal of Biological Chemistry* by researchers from the Canadian Light Source and the University of British Columbia sheds light both on the source of the TB bug's resilience and a new way to treat the infection.

"We found a biochemical pathway that appears to play a role in the bacteria's ability to survive inside the host by using the cholesterol inside white blood cells for food," explains Igor D'Angelo, research associate at the CLS and a lead author on the paper. "By developing drugs that can block a step in that pathway we have a new way to treat TB that can be added to the treatments that already exist."

The secret to *Mtb*'s tenacity is its ability to harvest energy from the cholesterol (a steroid) stored inside macrophages, the type of white blood cell the body uses to combat bacterial infections. Rather than being digested by the macrophage, the bacteria instead is able to set up housekeeping and live off the cholesterol stored in the cell, using enzymes to break the cholesterol down into smaller molecules that can then be used as an energy source.

Working with Professors Lindsay Eltis and Natalie Strynadka at the University of British Columbia, D'Angelo determined the structure of one of these enzymes, dubbed KshAB and performed computer simulations to predict how different molecules could bind to it. Graduate student Jenna Capyk isolated the enzyme and performed biochemical analyses. The detailed structural information can now be used to develop drug molecules that stop the enzyme from functioning and disrupt the secret to the bug's success.

"This work addresses some unanswered questions about how bacteria like *Mtb* can survive, and that steroids may play an essential role in this kind of persistence," says D'Angelo. "With that knowledge, we now have a scaffold on which to develop treatments that can slow the *Mtb* down so that the immune system can take it out."

On average, someone dies from tuberculosis every 15 seconds and over 2 billion people carry strains of *M. tuberculosis*. TB most often infects people in the developing world, particularly in patients whose immune systems are weakened by HIV. In Canada, approximately 1600 new cases of TB are diagnosed annually, many from First Nations and northern communities.



Molecular model of the KshA enzyme from *Mycobacterium tuberculosis*, a new target for treating TB.

From Capyk, et al. 2009, *J. Biol. Chem* 284: 9937-9946.

Fast facts:

- On average, someone worldwide dies from tuberculosis every 15 seconds, and over 2 billion people carry strains of the bacteria that cause the disease.
- Current treatment involves lengthy courses of antibiotics, with discontinued treatments contributing to the rise in drug-resistant forms.
- A key to tuberculosis' resilience the bacteria's ability to use the cholesterol within the white blood cells sent to kill the infection as an energy source.
- Using the CLS, researchers have identified the enzyme used by the tuberculosis bacterium to harvest that energy. The discovery could lead to new drug therapies to treat TB.

Reference: Capyk et al. 2009, *Journal of Biological Chemistry* 284, pp. 9937-9946.
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