Science@CornellVet
A science blog straight from the students and trainees of Cornell Vet

Tuberculosis bacteria love lipids

Cheeseburger, bacon, ice cream...sounds delicious, doesn't it? Many people would love to eat these tasty things even more frequently — if only we had a way to limit the uptake of calories and fat. Interestingly, the bacterium *Mycobacterium tuberculosis* (Mtb) not only exhibits a similar preference for fatty nutrients, it also has a way to regulate the uptake of fat into its system. In fact, controlled acquisition of fatty acids and cholesterol (the scientific term is lipids) are essential for the bacterium to survive within the human host and to fully unfold its infectious potential.

Here we answer some key questions about how research of bacterial nutrition here at Cornell University could help stop tuberculosis.

What is tuberculosis and why do we care about bacterial nutrition?

Mtb is one of the greatest health care threats that we face today. It's the causative agent of tuberculosis and claimed 4,900 lives per day in 2015 According to the CDC, more than 1.5 billion individuals are infected with the bacterium and many of them receive long-term antibiotic treatment. Thus, it is not surprising that resistances to one or multiple antibiotic compounds occur more and more frequently in Mycobacterium tuberculosis – there were 580,000 new cases of drug resistant Mtb in 2015 alone. These multi-drug resistant or extensively drug-resistant tuberculosis bacteria are at least insensitive to isoniazid and rifampin, the two most potent and most commonly used anti-tuberculosis drugs on the market. These numbers illustrate the degree and speed to which current anti-tuberculosis drugs lose functionality an why we need to find new ways of hindering microbial spread. Intervening with bacterial nutrition and starving out the mycobacteria would be a very elegant way to attack the bugs without harming the host. It would also cause less damage for beneficial microbes in our bodies, which we need in order for our organisms to complete many physiological tasks.

How does Mtb acquire fatty acids and cholesterol?

Like every other organism, Mtb needs a way to take up energy from the environment in order to be able to grow and reproduce. Mtb lives predominantly in host cells and shields itself from host's defense through a bacterial cell envelope. This barrier does not allow for large lipid molecules to spontaneously pass, but selectively allows certain lipids to pass through using specialized transporters. This allows the mycobacteria to steal selected lipids from the host environment and to transport them into the cell. There, these nutrients are metabolized anc used as a source of energy and self-renewal.

What is new about this story?

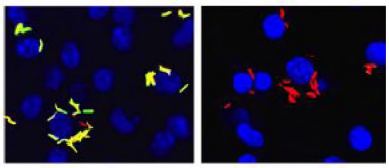
We do know since the 1950s that Mycobacterium tuberculosis preferentially consumes lipids. However, we still have huge gaps in our knowledg when it comes to the regulation and the mechanisms of fatty acid and cholesterol uptake in Mycobacterium tuberculosis. In other words, what is the switch that selectively turns transport of specific lipids across the cell barrier on or off? Brian VanderVen, PhD and his team at Cornell

Members of the VanderVen laboratory inspect their bacterial cultures. Working with the pathogen Mycobacterium tuberculosis requires special safety precautions.

University are currently using a genetic screen of Mtb in a cholesterol and fatty acid rich environment to find new molecules that are responsible for the lipid uptake. This screen has revealed several gene candidates involved in cholesterol metabolism.

They were able to identify a previously uncharacterized protein (Rv3723) which regulates lipid transporters in the mycobacterial cell envelope. The researchers in the VanderVen laboratory named i LucA, being an acronym for lipid uptake coordinator A. LucA binds and stabilizes two lipid transporter called Mce1 and Mce4 in the bacterial cell wall and thus facilitates both fatty acid and cholesterol uptake and transport across the bacterial membranes. This process is required for Mtb to become full infectious and to persist in the host.

How does this help the fight against tuberculosis?



This picture shows Mycobacterium tuberculosis (red) in Macrophages, a type of immune cell. The cell itself is not fully visible, but the cell nucleus is shown in blue by labelling host cell DNA. The bacteria are engineered to illuminate green when they metabolize lipids (left), which turns out yello when combined with the red Mtb label. The VanderVen lab recently discovered a chemical tha blocks Mtb's ability to metabolize lipids. Red cells are not able to metabolize lipids, because they are blocked with the new compound (right).

If we could inhibit preferred food acquisition pathway of the tuberculosis bacteria with a drug, the mycobacterial fitness and pathogenicity could potentially be severely reduced. Due to the unique structure of the mycobacterial cell wall, the lipid uptake pathways are not shared by the host or other commensal bacteria. Thus, targeting key molecules in those pathways would not be harmful for both the human host and the physiological bacterial flora. The combination of novel treatment strategies, such as specific inhibition of microbial nutrient uptake, with a classical antibiotic treatment regimen, could enhance treatment efficacy and delay development of antimicrobial tolerance.

What's next?

VanderVen and his team are hoping to find out how exactly Mce transporters are able to guide fatty acids and cholesterol through both the bacterial cell envelope and the cell membrane. They hope to determine if other transporters may take over and compensate for the loss of the Mce transporters if they are non-functional.

The VanderVen lab could show that LucA directly binds to subunits of the Mce1 and 4 transporters, but they further want to elucidate the exact mechanism of LucA-mediated enhancement of Mce1 and Mce4 stability and function. A more precise knowledge about the physiological processes of mycobacterial nutrition will facilitate specific drug development.

Do we find tuberculosis in other species?

Yes, tuberculosis affects pets, domestic animals and wildlife animals. The human pathogen Mycobacterium tuberculosis mostly causes illness in people and nonhuman primates. However, there are many different types of mammalian tubercle bacilli and most of them are capable of infecting several animal species. What they all have in common is the unique structure of the mycobacterial cell wall. Thus, LucA itself or a similar molecule could potentially be targeted to fight animal tuberculosis.

–by Simon Frueh, Immunology and Infectious Diseases Graduate Student

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