UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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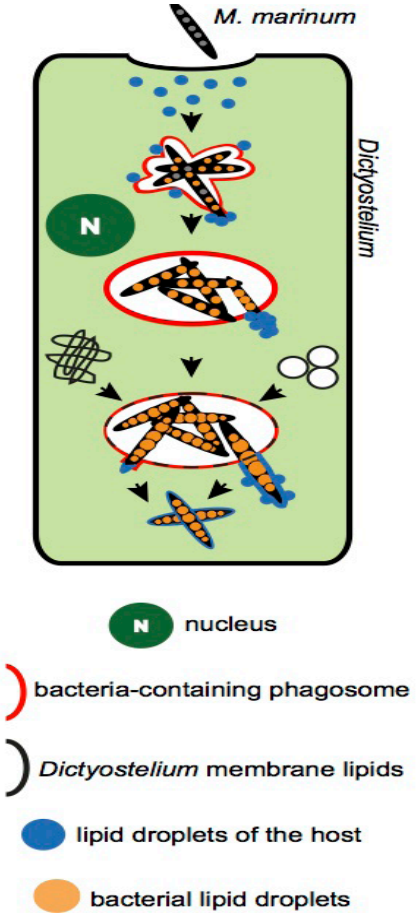
Time to put TB on a diet!

Global Tuberculosis Report, the disease kills over 1.5 million people a year. Although the mortality rate has dropped by 47% since 1990 due to advances in preventive and treatment options, the tuberculosis bacillus is growing increasingly resistant to antibiotics. For this reason, biochemists at the University of Geneva (UNIGE), Switzerland, are attempting to identify the mechanisms that enable the bacterium to reproduce, spread and survive in latent form in our macrophages. The scientists have discovered that the bacterium has the ability to "reprogramm" the cell it infects so that it can feed on its lipids. The UNIGE research results, which will be published in the *PLOS Pathogens journal*, will pave the way for new treatment opportunities based on starving and weakening the bacterium.

Tuberculosis is a highly contagious disease that spreads through the air via droplets of saliva. Although treatments exist for tuberculosis, new antibiotic-resistant strains are preventing TB from being eradicated. The goal is to find new ways to tackle the disease, which requires a thorough understanding of how the bacterium, known as *Mycobacterium tuberculosis*, behaves once it takes hold of the macrophages in our lungs. The team headed by Thierry Soldati, Professor at the Biochemistry department in UNIGE's Science faculty, has been working on a model system that acts like the macrophages in our immune system: the social amoeba *Dictyostelium*, a unicellular microorganism.

«We infected the amoebae with the *Mycobacterium marinum* bacterium, which induces tuberculosis in fish,» explains Caroline Barisch, a researcher at UNIGE and the study's first author. «The pathogen behaves in the same manner as the TB bacillus, which means that we were able to use our simple and ethically responsible system to undertake experiments that could not be carried out directly on humans.» Scientists had previously recognised that for the bacterium to survive, replicate and spread, it needed to consume the lipids that exist in the form of droplets in macrophages. Without this source of food, the bacillus cannot survive latently and wait for a weakness in the immune system in order to develop. It is well worth remembering that 30% of the world's population is infected by a dormant form of the TB bacillus.



Lipid droplets (blue) and membrane lipids (black) during the infection of Dictyostelium with mycobacteria. In wild-type cells, the host lipid droplets are recruited and used by mycobacteria. Alternatively, in a mutant Dictyostelium that cannot form lipid droplets, the bacillus exploits membrane lipids.

The UNIGE biochemists observed the infection *in vitro*, analysing each stage of the process whereby the bacterium feeds on the lipids of its host. As Thierry Soldati explains: «We subsequently discovered that the mycobacterium can "reprogramm" the infected cell so that it diverts and attracts all the amoeba's fat reserves —not just the lipid droplets but also the membranes— so that it can feed on them.» The researchers suppressed the lipid droplets of the host cells, the bacterium's preferred food source, and found that the bacterium has a back-up plan that allows it to compensate for this shortage by drawing on the lipids within the host's membranes. This shows that this lipid diet is most likely crucial for the survival of the bacterium.

«We now know that the bacillus is extremely 'addicted' to this high-fat food,» continues Caroline Barisch. «Our current aim is to find a way to starve the bacillus by depriving it of access to the fat stores in our macrophages. The goal will be to target the enzymes of the bacillus and render them incapable of absorbing lipids.» It is a discovery that opens the door to the prospect of new forms of treatment for neutralising the strains that are resistant to antibiotics.

The article will publish at the following link: <http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006095>

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