Modeling and manipulating the phagocyte-mycobacteria interface (HostPathX)

Finding new ways of fighting tuberculosis

The battle against tuberculosis has arrived at a dead end. The pathogen causing the disease is becoming resistant to more and more classical antibiotics. The search for new ones is laborious and does not promise long-term success. As an alternative, the researchers from the SystemsX.ch project HostPathX are currently investigating the effects of 'anti-infectives', agents which directly target the infection. Amoebae are proving to be very helpful in this endeavor.

Thierry Soldati researches the effects of new agents on tuberculosis.

"Tuberculosis is THE major killer," says Thierry Soldati, professor in the Biochemistry Department at the University of Geneva and project leader of the RTD Project HostPathX. "About 30 percent of the world's population are infected, and around 1.7 million people die of it every year." At the moment, antibiotics are the only option in treating the disease. At the same time, many multi- and totally-resistant strains exist. Even when the strain in question is not resistant, it still takes half a year to treat an infection.

One reason that tuberculosis (TB) bacteria are so resilient and successful is their survival strategy in the human body. Once the airborne bacteria reach the lungs, they are taken up by macrophages. These scavenger cells, which make up part of the immune system, roam the body and eliminate intruders by phagocytosis, that is, by engulfing and killing them.

However, the TB bacteria are not simply digested like other intruders. They manipulate the macrophages to block the function of the phagolysosomes – the macrophages' digestive organelles – whose dedicated function is to kill and degrade bacterial intruders. The bacteria are then able to lodge themselves inside these manipulated compartments. So ensconced in their niches, they survive, reorganizing their metabolism.

Learning to understand the interaction between host and pathogen

With this picture in mind, it is not surprising that new antibiotic candidates selected against the bare bacteria are often unsuccessful when it comes to combating the disease in the host. Either they completely fail to reach the bacteria in their intracellular niches, or they target metabolic pathways specific to the bacteria in their environment outside the host and are therefore ineffective against the intracellular bacteria during infection.

"In order to find effective substances to combat tuberculosis, we really need to understand exactly what goes on between macrophage and bacteria," explains Soldati.

Amoeba versus fish pathogen

To find out more about the interplay between the macrophages and tuberculosis bacteria, the researchers from HostPathX make use of a very simple, but no less clever, model system. Instead of macrophages and *Mycobacterium tuberculosis,* the researchers pitch the amoeba *Dictyostelium discoideum* against *Mycobacterium marinum,* a relative of *M. tuberculosis* that is not threatening to humans.

M. marinum is a disease pathogen which primarily affects cold-blooded animals such as frogs and fish. Both human macrophages and the amoeba *Dictyostelium discoideum,* commonly found in soil, share the same ancestors and therefore function similarly. Both react in the same way to mycobacteria by using phagocytosis in an attempt to disarm them.

"The model system *Dictyostelium – M. marinum* allows us to research the host-pathogen interaction simply, economically and in an ethically unproblematic way," explains Soldati. "We are able to study their battle without having to observe the strict safety precautions that would be necessary if we were to work with the highly dangerous TB bacteria, and we also don't need to work with laboratory animals."

The researchers are now probing this model system. "For example, we are interested in how the mycobacteria manipulate the amoebae by turning their usually hostile lysosomes into a bacteria-friendly environment, and how the host and pathogen recognize each other," says Soldati. "We also want to find out what happens when we use agents to directly intervene in the action."

Employing anti-infectives instead of antibiotics

The scientists are addressing this last point using about 20 agents, called anti-infectives, which were identified in a preceding project. These substances, which are distinct from antibiotics, act either as defense

Maja Schaffner

boosters in the host, strengthening resistance against the pathogen, or as anti-virulence agents, directly targeting infectious pathogens by blocking mechanisms or metabolic pathways used by the bacteria only in the course of infection. Due to the fact that these anti-infectives act so specifically during an infection, their application does not lead to the selection of resistant bacteria. Contrastingly, antibiotics attack metabolic pathways that are crucial for the survival of pathogenic mycobacteria as well as many other bacteria. The resulting pressure for selection stimulates the development of resistance.

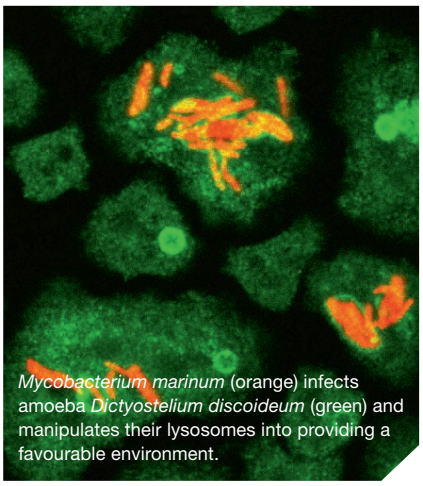
Dual profiling

One of the main goals of HostPathX is to find out exactly how and where such anti-infectives act. To investigate this, the researchers are relying on transcriptomics. "The method is high-throughput, genome-wide and cheap," says Soldati. Using this technique, the researchers are able to simultaneously profile the total RNA produced by the host and the pathogen at a particular time during infection. From the resulting transcriptomes they can infer which genes in each organism are active at a specific point in time, and which are influenced by the anti-infectives.

Genome-wide model

The researchers are integrating all of the data generated from this analysis into a newly developed genome-wide host-pathogen model. "A first!" emphasizes Soldati. In future, this model should be able to simulate the events occurring during infection, for example interactions and defensive responses.

"The goal is to use this model to make *in silico* predictions and therefore discover the best targets for preventing infection or strengthening the macrophages' defenses," explains Soldati. It should also be possible to feed virtual drugs into the model and to observe their effects on the system.



Mycobacterium marinum (orange) infects amoeba *Dictyostelium discoideum* (green) and manipulates their lysosomes into providing a favourable environment.

"Our focus at the moment is to show that it's possible to find and investigate agents that target the infection by using the model system *Dictyostelium – M. marinum*," says Soldati. "We hope that our work will contribute to long-term success in the battle against tuberculosis."

HostPathX at a glance

Principal investigator: Prof. Thierry Soldati

Research groups:

- Prof. Thierry Soldati, Biochemistry Department, University of Geneva – Molecular & cellular microbiology, host-pathogen interactions
- Prof. Hubert Hilbi, Institute of Medical Microbiology, University of Zurich – Genetic manipulation and functional phenotyping of mycobacteria
- Prof. Heinz Koeppl, Department of Electrical Engineering and Information Technology, Technische Universität Darmstadt – Design of algorithms for statistical transcriptome-based network reconstruction
- Prof. Pierre Cosson, Department of Cell Physiology and Metabolism, University of Geneva – Mechanisms of pathogen recognition and elimination by phagocytic cells
- Dr. Marco Pagni, Vital-IT group, SIB Swiss Institute of Bioinformatics – Data analysis, computational experiments and exploratory modeling

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Project type: Research, Technology and Development (RTD) Project

HostPathX
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