

Microbiology

Shining a light on first contact in tuberculosis

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'First contact' with M. tuberculosis bacteria occurs in the deep lung, making early tuberculosis difficult to study. A lung-on-chip model recreates this environment on a platform that allows direct visualization of these early interactions. Together, they reveal that pulmonary surfactant, a substance secreted by non-immune lung cells that facilitates breathing, slows or even halts bacterial growth, which otherwise occurs rapidly in its absence.

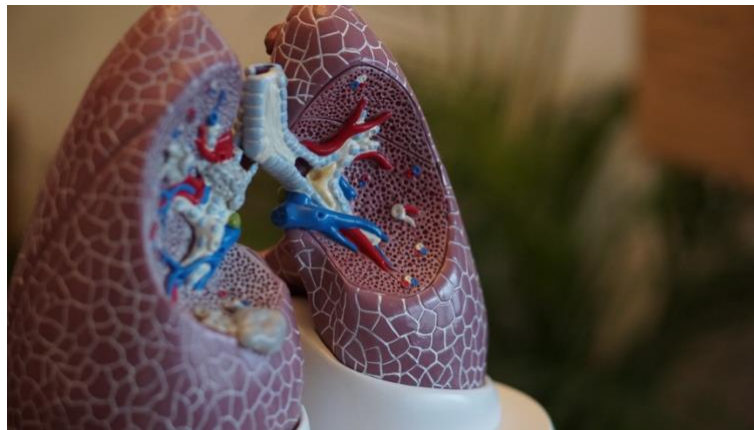


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In the science fiction series Star Trek, first contact between species occurs on a galactic scale; a recurring theme whose consequences are richly developed and explored throughout the series. In infection biology, first contact of a susceptible host with an infectious agent, albeit on a less gargantuan scale, plays no less of a role in determining subsequent outcomes. Nowhere might this be truer than for tuberculosis, an ancient disease and the leading cause of global mortality from any single infectious agent. Caused by the very slow-growing bacterium *M. tuberculosis* (*Mtb*), tuberculosis can be triggered by the infection of the deep areas of the lung by even a single bacterium, yet only 5-10% of individuals exposed to the bacterium go on to develop a full infection. This astonishing diversity in outcomes might in part be a consequence of the

early interactions of *Mtb* bacteria with both non-immune and immune cells at 'first contact' in the lung. However, even in the best animal model, the disease dynamics at this early stage are extremely hard to follow.

What if we could recreate this tissue environment outside of a living host (*in vitro*) and study these early interactions with *Mtb* bacteria in real-time? In recent years, bioengineering advances have led to the development of organs-on-chip, biocompatible platforms the size of a thumb. These platforms recreate key aspects of tissue physiology while retaining the accessibility of more traditional *in vitro* systems. For example, the lung-on-chip platform allows lung cells to be cultured at an air-liquid

interface and exposed to air just as they are in the lungs.

These platforms are only beginning to be used to study infectious diseases. We adapted a lung-on-chip model developed by Prof Ingber at the Wyss Institute to model first contact in tuberculosis. The platform recreates tissue physiology in a modular manner, which we took advantage of in three key respects. First, we populated the chip with immune cells from a mouse line that expressed a fluorescent marker; this allowed us to unambiguously identify this cell type via imaging. Second, the air-liquid interface provided the chance to probe pulmonary surfactant's direct role in early infection, which is not possible in traditional *in vitro* platforms. We were thus able to study how bacteria grew in chips populated with non-immune cells that either did or did not secrete surfactant and directly comparing the rates of bacterial growth in these otherwise identical platforms. Such an intervention would be lethal in an animal. Lastly, the optically transparent material that the platform is made of allowed us to monitor the growth of tens of individual bacteria into small microcolonies in both non-immune and immune cells in real-time with a microscope over a period of a few days, which would be impossible to achieve with an animal model.

These technological advances together revealed several new insights. We observed that non-immune

cells could also be a site of first contact and that bacterial growth rates during these early encounters were highly heterogeneous. On average, non-immune cells offered a more permissive environment for the bacteria to grow when compared to immune cells. Yet, in both cell types, a significant minority of bacteria did not grow at the site of first contact. In contrast, surfactant deficiency led to prolific and rapid bacterial growth in both immune and non-immune cells. This result provides evidence for a direct role for surfactant in suppressing bacterial growth. Furthermore, we could complement the deficiency of surfactant with surfactant replacement formulations prescribed for prematurely born infants, which indicated that a direct interaction between the *Mtb* bacteria and surfactant was necessary to slow bacterial growth.

Both the elderly and smokers are at an increased risk of developing active tuberculosis and often have altered surfactant profiles, consistent with our observations. Going forward, the model provides the ideal platform to investigate if surfactant-based therapeutics can alter the balance of these early interactions further in favour of the host. More broadly, one can also apply these approaches to studying other acute respiratory infections caused by bacteria and viruses, both to elucidate the role of physiology in how these diseases occur and to develop new treatment strategies.