TB antibiotic activity impacted by cell pH
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Researchers at the Francis Crick Institute have shown that an antibiotic used to treat tuberculosis (TB) is affected by pH levels in the environment the bacteria has infected.

In 2020 alone, it is estimated that TB led to the deaths of around 1.3 million people. While it is curable, the treatment involves taking a course of various antibiotics over at least six months and the drugs can have severe side-effects.

On infection with TB, the bacteria enter into a type of immune cell, called macrophages. One of the defense mechanisms these cells use is creating an acidic environment to kill the infecting agent.

In their study, published in mBio on World TB Day (24 March), the researchers developed a fluorescence-based imaging technique to study the effects of this acidic environment on both the bacteria and antibiotics. Using this approach, they were able to monitor, in real-time, the effects of changes in pH levels.

By experimentally changing pH levels in infected cells, they found that TB is able to maintain and regulate its own pH independently of the pH of the macrophage, providing a defense against the immune system.

The researchers then tested whether four front-line TB antibiotic treatments are affected by different acidity levels. They found that one antibiotic often used as part of the TB treatment regime, pyrazinamide, is only effective within an acidic environment.

Pierre Santucci, co-corresponding author and postdoctoral training fellow in the Host-Pathogen Interactions in Tuberculosis Laboratory at the Crick, says: "Understanding that the effectiveness of antibiotics can be impacted by environmental pH levels is really valuable. It underlines the importance of testing new treatments or treatment combinations in conditions which closely mimic what happens inside cells."

The researchers also found that pyrazinamide affects the ability of TB to regulate its own acidity levels. Pyrazinamide is an important part of the TB treatment strategy as it reduces the length of time drugs need to be taken for.

Max Gutierrez, senior author and group leader of the Host-Pathogen Interactions in Tuberculosis Laboratory at the Crick, says: "With rising levels of antibiotic resistance globally, finding new, more effective treatments is crucial. This has been challenging, in part because TB lives inside cells, so any treatment has to be able to enter into the cells and work effectively in this intracellular environment.

"By understanding more about how current antibiotics are impacted by conditions inside of cells, such as acidity, we hope it could help the search for new drugs or better drug combinations."

The researchers will continue this work studying how the environment within TB and macrophages affects antibiotics. And the imaging approach developed to monitor pH levels could be adapted to
study other bacteria and parasites.


Provided by The Francis Crick Institute

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