New TB treatment limits infection while reducing drug resistance

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It's estimated that nearly one-third of the world's population -- more than two billion people -- are infected with Mycobacterium tuberculosis. According to the World Health Organization, 5 to 10 percent of infected people eventually develop active tuberculosis and can transmit the bacterium to others. Almost two million die from the disease each year. But the current treatment regimen for the disease is long and arduous, making patient compliance difficult. As a result, some strains of the bacteria have become resistant to many or all of the available antibiotics.

A team of researchers has shown that M. tuberculosis and several of its close relatives, including M. marinum, exploit a family of host enzymes known as ABL-family tyrosine kinases to gain entry into host cells and to survive once inside. The researchers also showed that imatinib, an Abl-family inhibitor, limits infection, and works just as well against antibiotic resistant strains. Also, when given alongside traditional front-line antibiotics, the drugs worked synergistically to enhance their effectiveness.

The bottom line: by targeting the host-not the mycobacteria itself-researchers were able to reduce the host's mycobacteria load, and even target antibiotic-resistant strains, all while enhancing the effectiveness of front-line antibiotics.

"This study implicates host tyrosine kinases in entry and intracellular survival of M. tuberculosis and M. marinum and suggests that imatinib may have therapeutic efficacy against tuberculosis," says Daniel Kalman, PhD, lead investigator of the study. Kalman is associate professor of pathology in Emory University School of Medicine. Imatinib is known commercially as Gleevec and is already FDA approved.

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Specifically, the researchers found that M. tuberculosis and its relatives exploit ABL within the host cell to gain entry, and then again once inside the cell, to prevent the formation of phagolysosomes. Phagolysosomes normally fuse with lysosomes, which contain enzymes that can break down their contents.

"Once inside the cell, tuberculosis hangs out in phagocytic cells in a compartment called the phagosome," says Kalman. "But what the Mycobacterium does once inside the phagosome is very crafty. It stops the phagosome from fusing with the lysosome, where the bacteria could be killed, and instead replicates and isolates itself. Inhibiting ABL with Gleevec disrupts this carefully orchestrated bacterial survival mechanism, and tips the balance back in our favor."

Because Gleevac targets the host rather than the pathogen it is less likely to engender resistance compared with conventional antibiotics," says Kalman. "And by reducing bacterial load, imatinib will likely reduce the possibility of M. tuberculosis developing resistance against co-administered conventional antibiotics, which could extend the lifespan of these drugs."

Provided by Emory University