Cornell researcher seeks clues to how tuberculosis infects cells

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Cornell researchers are using advanced genetic techniques to better understand the relationship between the bacteria that cause tuberculosis and the human immune system defense cells that engulf them.

The researchers have discovered that unlike many bacterial pathogens, Mycobacterium tuberculosis does not react when immune system cells called macrophages initially make contact; but the bacterium's genes become activated minutes after the pathogen is enveloped by a macrophage and contained in one of its membrane-bound compartments called vacuoles.

David Russell, professor of molecular microbiology at Cornell's College of Veterinary Medicine, and colleagues reported in a November issue of the journal Cell Host and Microbe, that increased acidity inside the vacuoles containing the bacteria serves as the trigger for M. tuberculosis genes to express proteins.

The study also compared the responses of M. tuberculosis to a live bacterial vaccine against tuberculosis known as Bacillus Calmette-Guerin (BCG). It found that the two bacteria may each respond differently to the same stimuli and that BCG appears less capable of protecting itself once inside a macrophage. The findings are consistent with the reduced virulence of BCG, which is key to its safety as a vaccine.

The study is a small part of a larger plan to understand the processes that allow the bacteria to survive within macrophages and then to use that

knowledge to develop more effective drugs to fight tuberculosis, which currently kills 2 million people worldwide each year. Existing drugs require six to nine months to treat the active disease that invades and replicates within the lungs.

"What we propose is the exploitation of the data obtained from these basic science studies to develop a comprehensive program of drug development that targets bacterial processes critical to survival inside the human host," said Russell.

Russell's lab used gene chips, or microarrays, to identify genes activated under specific environmental conditions. This allowed them to generate real-time readouts of bacterial health and their response to stress. The researchers have also created real-time readouts that measure conditions within the tuberculosis-containing vacuole at any time during the immune system's process.

"Our goal is to develop these bacterial fitness readouts to screen small molecule libraries for compounds that will kill M. tuberculosis inside the macrophage," said Russell. "Unfortunately, Cornell does not have either the instrumentation or the chemical libraries necessary to do this work, so I am trying different, private funding agencies to get the support to purchase equipment and libraries."

Source: Cornell University Communications