SOUTHWESTERN NEWS

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Researchers identify the pattern of gene-expression changes for tuberculosis in a living host

DALLAS – March 22, 2004 – Researchers at the Center for Biomedical Inventions at UT Southwestern Medical Center at Dallas have identified the genetic changes that *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis, undergoes during infection of a living host.

For the first time, researchers have adapted gene-chip technology to carry out genomic analysis of gene expression during the course of infection not only for *M. tuberculosis,* but for any pathogen. The findings will appear in an upcoming issue of the *Proceedings of the National Academy of Sciences* and are currently available online.

To analyze multiple questions about the pathogenesis of tuberculosis, the researchers used gene chips, which allowed them to assess the pattern in which bacterial genes are expressed during the course of infection. This work demanded two years of technology development to establish a protocol that allowed high-throughput analysis of genes that were expressed in a pathogen that was extracted from an infected animal, rather than simply grown in culture.

"This is an example of how the high-throughput system is a new avenue to study a variety of pathogens and how they affect living hosts," said Dr. Stephen Albert Johnston, director of the CBI and one of the senior authors of the study. "We see it as a tool for vaccine and drug development against disease and the threat of biological weapons."

In the *PNAS* paper, researchers discuss how the tuberculosis bacterium had previously undergone genetic analysis based only on lab tests outside of a living organism. Once the entire genome of *M. tuberculosis* was sequenced, Drs. Johnston and Adel Talaat, then a postdoctoral researcher at UT Southwestern, began using high-speed microarray techniques, or gene-chip technology, to analyze the bacterium's gene expression at different stages of infection in mice.

Since other pathogens have been sequenced, Dr. Johnston and coworkers are now genetically analyzing anthrax and plague infection in *in vivo* animal models, gaining more insight into how the potential bioweapons might behave in humans. The genetic analysis also could be applied to previously unknown diseases, like SARS.

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"By identifying the genes that cause disease progression *in vivo*, we can begin to piece together the knowledge that will allow us to discover better targets for drug therapies," said Dr. Johnston.

To study tuberculosis – it annually kills about 2 million people around the world – researchers analyzed the bacterium's gene activity in healthy mice, in mice with compromised immune systems, and in lab cultures. They looked at which genes were active and at what stages of the infection, from the first day to several weeks after exposure.

They discovered that a specific set of tuberculosis genes was activated only in healthy mice 21 days after the initial infection, a critical time in the progression of the disease in humans and other animals. This indicates that these genes are activated to help the pathogen survive within the host.

"We found that some genes are turned down so they stay below the immune system's radar," said Dr. Johnston, professor of microbiology. "The bug (tuberculosis) acts in a stealthy way, hoping not to become a target of the host's immune system but needing to stay just active enough to continue surviving."

Some genes were expressed only if the pathogen was active in an animal model. Infection in lab cultures – previously the only way that tuberculosis has been studied at the genetic level – did not express the same genetic responses in the tuberculosis pathogen. The new findings indicate that infectious diseases need to be studied in live animals models if meaningful results are to be attained.

"Understanding bacterial gene expression *in vivo* is central to our understanding of how bacteria colonize, invade and interact with or disrupt the normal host-cell functions and eventually produce disease," the researchers write.

The study was funded by the National Institutes of Health and Defense Advanced Research Projects Agency. This work was carried out in collaboration with the Animal Model Development Center at the University of New Mexico Health Science Center.

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