Early test for a killer of the sickest

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An early test for fungal infections that measures how a patient's genes are responding could save the lives of some very sick patients. Researchers at Duke University's Institute for Genome Sciences & Policy have devised an early gene-expression test for the fungal pathogen Candida that worked in mice.

It is an entirely new and more rapid way to reveal an infection which occurs in very sick or immunocompromised patients, particularly critical care patients. Candidemia can kill 10-15 percent of critically ill patients within the first 24 hours of infection. If the disease goes undetected for up to three days, the mortality rate rises to 30 percent.

Now that the gene-based test has worked well in mice, the Duke scientists are gathering human specimens to devise a similar test to be used in people.

"This study provides the basis for development a blood-gene expression test in humans to detect a life-threatening infection earlier than can be done using currently available methods," said Geoffrey Ginsburg, M.D., Ph.D., director of Duke University's Center for Genomic Medicine in the Institute for Genome Sciences & Policy, professor of medicine, and the senior author of the study. "Earlier detection will lead to earlier treatment and save lives. This work is also part of a portfolio of blood gene-expression-based tests we are developing to detect viral, bacterial and now fungal infections that will lead to more precise diagnosis and more appropriate therapies for infectious disease. This is personalized medicine."

The findings, which appear in the journal *Science Translational Medicine,* mark the beginning of an entirely new way of diagnosing infectious disease, said co-lead author Aimee Zaas, M.D., assistant professor of medicine in the Duke Division of Infectious Diseases and International Health, and the Duke Institute for Genome Sciences & Policy. "We are redefining the way that physicians identify infectious disease using a combination of host-based blood RNA tests with traditional microbiology methods."

One of the challenges in diagnosing candidemia is that it often appears to be similar in symptoms to other serious bloodstream infections. To discriminate whether a patient has a bloodstream fungal infection versus a bacterial infection often can take 48 to 72 hours until blood culture tests are completed and even then the results may only be positive 50 percent of the time. People most at risk for candidemia include patients hospitalized in intensive care units, those who've had abdominal surgery, those receiving antibacterial therapies, those with central line catheters, and those who are immunosuppressed.

"Our results show that this new gene-signature test works well to find candidemia in mice that had the infection versus mice without infection," said Zaas, who is also an assistant professor in the Department of Molecular Genetics and Microbiology at Duke. "We were very pleased to learn that we could further distinguish the fungal infection from a staph infection, another bloodstream disease that shares the same set of symptoms."

The team of scientists sees the findings as a jumping off point for producing gene-expression signatures to detect a number of infections. They pursued the candidemia test first because of the high mortality rate in hospitalized patients with that hard-to-treat infection.

The scientists performed an analysis of gene expression - which genes

are turned on and active - in the blood samples of mice that were exposed to *Candida albicans* (*C. albicans*) and a group of healthy control mice. They looked at genes that are associated with immune response and found there were 20 sets of 60 to 80 genes being expressed together. One group of genes in particular distinguished the infected samples from the control samples.

Likewise, they were able to combine data from the *C. albicans* group with data from a group of mice infected with Staphylococcus aureus, which is sometimes found in hospitalized patients. The team identified two groups of genes that could discriminate among the three groups of mice (healthy, those with candidemia and those with a staph infection).

They also developed distinct groups of genes that correlated with samples at different time points during the course of Candida infection. Using these groups of genes, the researchers could differentiate between an early and a late infection.

Provided by Duke University Medical Center

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