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New Whole Blood Assay May Help Overcome Roadblocks to TB Eradication
Assay Accurately Differentiates Patients with Latent TB from those with Active Disease,
According to Report in The Journal of Molecular Diagnostics

Philadelphia, PA, January 6, 2015 – One of the roadblocks to the eradication of tuberculosis (TB) is the difficulty in identifying patients with latent TB infections (LTBI). Neither the tuberculin skin test (TST) nor interferon-gamma release assays (IGRAs) are capable of distinguishing active from latent infection or predicting the chance of reactivation. A new multiple-target, real-time reverse transcription-PCR (real-time RT-PCR) TaqMan assay targeting eight human immune markers can differentiate active pulmonary TB from LTBI, according to a study in The Journal of Molecular Diagnostics.

“The World Health Organization reports that one third of the world’s population is latently infected with Mycobacterium tuberculosis (MTB). It has been estimated that in 5% to 10% of LTBI individuals, the infection progresses to an active disease state, and the conversion rate is greater in immunosuppressed individuals such as those with HIV,” explains Hyeyoung Lee, PhD, of the Department of Biomedical Laboratory Science, College of Health Sciences, Yonsei University (Republic of Korea). “Therefore, rapid diagnostic tests and effective treatment of LTBI are important to reduce and control the TB burden.”

In previous work, the researchers quantified interferon-γ (IFN-γ) mRNA expression levels as an indicator of IFN-γ levels in an IGRA test. However, the results of IFN-γ RT-PCR showed poor specificity and sensitivity, and the test could not be used to distinguish between active and latent TB.

With these results in mind, the investigators developed a multiple-target RT-PCR TaqMan assay that could target eight human immune markers: Th1-type factors (IFN-γ, TNF-α, and IL-2R), Th2-type cytokines (IL-4 and IL-10), and IFN-γ-induced chemokines [CXCL9 (MIG), CXCL10 (IP-10), and CXCL11 (I-TAC)]. MTB-specific, antigen-dependent mRNA expression levels were measured in blood samples from 28 patients with active pulmonary TB, 22 with LTBI, and 29 non-TB controls.
When five of the human immune markers were evaluated individually, three were found to be suitable for detecting active pulmonary TB: TNF-α, IL-2R, and CXCL10, with sensitivities ranging from 96.43% to 100%. Two individual markers, IL-2R and CXCL10, were able to detect LTBI, with sensitivities of 86.36% and 81.82%, respectively.

To optimize sensitivity, Dr. Lee and her colleagues used the assay to simultaneously detect multiple targets. They found that the combination of TNF-α, IL-2R, CSCL9, and CSCL10 could differentiate active pulmonary TB from healthy controls (P <0.001) and LTBI from healthy controls (P <0.01). More importantly, the combination could differentiate those with active pulmonary TB from those with latent infection (P <0.01). The combination had a sensitivity of 100% for active disease and 81.82% for LTBI. “These results imply that a combination of suitable single markers is very useful for the efficient diagnosis and differentiation of MTB infection,” says Dr. Lee.

In a commentary published in the same issue of The Journal of Molecular Diagnostics, David H. Persing, MD, PhD, Executive Vice President and Chief Medical and Technology Officer of Cepheid, Inc., Sunnyvale, CA, notes that the work by Dr. Lee and colleagues presents an interesting and potentially promising alternative approach to measure immune responses to MTB.

Dr. Persing underscores the healthcare threat resulting from the burden of future TB cases emerging from within the latent pool. He highlights some of the shortfalls of TST, mainly the risk of false-positive results in patients who have received the bacille Calmette-Guérin vaccine and the need for skilled interpretation of the results in a follow-up visit. He cautions that IGRAs are also limited by their potential for false-positive and false-negative results, are technically challenging to perform reproducibly, and have less than ideal sensitivity, especially in those who are immunologically compromised.

“It is possible that one day a combination of selected antigen stimulation with multiplexed cytokine, chemokine, and interferon mRNA detection will lead to new ways of evaluating suspected TB patients for current and future disease risk,” comments Dr. Persing. “With one third of the world’s population at risk for recurrence, the investment in such technology is recommended.”

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NOTES FOR EDITORS


“Latent Tuberculosis: Interferon and Beyond?,” by David H. Persing, MD, PhD, DOI: http://dx.doi.org/10.1016/j.jmoldx.2014.08.0094.


Full text of this study and commentary is available to credentialed journalists upon request; contact Eileen Leahy at 732-238-3628 or jmdmedia@elsevier.com. Journalists wishing to interview the authors of the study should contact Sang-Nae Cho, DVM, PhD, at raycho@yuhs.ac or Hyeyoung Lee, PhD, at +82-33-760-2740 or hyelee@yonsei.ac.kr. David H. Persing, MD, PhD, may be contacted at 408-400-8207 or david.persing@cepheid.com.
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ABOUT THE JOURNAL OF MOLECULAR DIAGNOSTICS

The Journal of Molecular Diagnostics, (http://jmd.amjpathol.org), the official publication of the Association for Molecular Pathology, co-owned by the American Society for Investigative Pathology, and published by Elsevier, Inc., seeks to publish high quality original papers on scientific advances in the translation and validation of molecular discoveries in medicine into the clinical diagnostic setting, and the description and application of technological advances in the field of molecular diagnostic medicine. The editors welcome for review articles that contain: novel discoveries or clinicopathologic correlations including studies in oncology, infectious diseases, inherited diseases, predisposition to disease, or the description of polymorphisms linked to disease states or normal variations; the application of diagnostic methodologies in clinical trials; or the development of new or improved molecular methods for diagnosis or monitoring of disease or disease predisposition.

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