Mycobacterial Diseases
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Perspective

New Options for Diagnosis of Latent Tuberculosis Infection

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DESCRIPTION

The term "Latent Tuberculosis Infection" (LTBI) refers to a subclinical mycobacterial infection defined by cellular immune responses to mycobacterial antigens. Latent Tuberculosis Infection (LTB) is currently diagnosed using the Tuberculin Skin Test (TST) and the Interferon Gamma Release Assay (IGRA). However, neither TST nor IGRA can distinguish between active and latent tuberculosis. Furthermore, these tests cannot predict whether a person with LTBI will develop active Tuberculosis (TB) or whether LTBI therapy could be effective in lowering the risk of developing active TB. As a result, current approaches and efforts to identify an immunological marker that could be useful in distinguishing LTBI from TB and evaluating the efficacy of LTB treatment on the risk of progression to active TB.

Diagnosis of LTBI

For LTBI, there is no gold standard test. Indeed, the low tissue bacterial burden associated with LTBI excludes any diagnostic strategy based on identifying the bacteria or its components. LTBI is diagnosed in a difficult way, based on evidence of a cellular immune response to mycobacterial antigens. The Intradermal Tuberculin Test (TST) and IGRA are the most commonly used tests for LTBI diagnosis. The TST, also known as "Old Tuberculin" or the Mantoux test after Charles Mantoux established the diagnosis criteria for reading a TST, was developed more than a century ago by Robert Koch. TST is widely used around the world, particularly in developing countries, because it is less expensive and easier to implement than IGRAs. TST has also been used in epidemiology to assess the prevalence of LTBI. TST is performed by injecting intradermal Purified Protein Derivate (PPD) into an individual's forearm. Induced induration of 15 mm or greater after 48 or 72 hours is considered indicative of past or current mycobacterial infection. Trained personnel are required to administer, read, and interpret the TST.

TST is based on skin reactivation to tuberculin PPD caused by Delayed-Type Hypersensitivity (DTH). Tuberculin PPD is a protein precipitated from mycobacterial culture filtrates that has been modified. There are various manufacturers of PPD referred to as international standard (PPD-SI) and commercial brands under the US FDA standard PPD-S2, such as Aplisol (JHP Pharmaceuticals, Inc, Rochester, MI, USA) or Tubersol (JHP Pharmaceuticals, Inc, Rochester, MI, USA) (Sanofi Pasteur Limited, Swiftwater, PA, USA). Aside from PPD-S2, there are several other formulations available, such as PPD RT23 from Statens Serum Institut, which is the most widely used PPD in the world, and potency variability among PPD may affect the TST result.

Latency antigens and its potential to distinguish LTBI from active TB

Because LTBI is defined by immune reactivity to mycobacterial antigens, selecting the right antigens to evaluate is critical in the diagnosis of LTBI and the development of assays capable of distinguishing between different states of infection and the risk of progression to active TB. Numerous studies have been conducted to identify mycobacterial antigens that are naturally expressed during LTBI.

In vitro latency models, in conjunction with genome-wide transcriptome profiling, have identified genes that remain up regulated during LTBI and code for proteins known as "Latency Antigens." It should be noted that the term "Latency" refers to the host's state, whereas the term "Dormancy" refers to the bacteria's state during the latency state. Dormancy is a reversible metabolic shutdown, a state of low bacterial metabolism associated with a transition from replicating to non-replicating *bacilli*, in which cells can survive for long periods of time without replication while employing immune-evading strategies. Oxygen deprivation and nitric oxide levels are two factors that favour a low metabolic state.

Antibodies' potential role in LTBI diagnosis

A widely held paradigm regards the role of the human antibody response against *Mycobacterium tuberculosis* in TB protection as marginal, at least when compared to cell-mediated immunity. This paradigm is supported by two types of observations: the presence of high levels of antibodies in the active form of the disease, implying that antibodies do not confer protection, and

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the apparently unaffected risk of TB reactivation in patients receiving rituximab, a human/mouse chimeric anti-CD20 antibody that causes a rapid depletion of normal CD20-expressing B cells.

CONCLUSION

Despite the fact that the presence of antibodies in the serum of patients with active tuberculosis has led to the development of commercial diagnostic tests, the World Health Organization (WHO) has not recommended their use as diagnostic tools due to suboptimal sensitivity and specificity. LTBI is an occult manifestation of the larger global health problem of tuberculosis. A reliable diagnosis and successful treatment of individuals with LTBI is critical in the control of TB because they may progress to the active form of the disease. Because of its simplicity and the *in vivo* evidence it provides for an antimycobacterial cellular immune response, the diagnosis of LTBI has been found to be useful in identifying individuals with LTBI or active TB.