MINIREVIEW

Latent *M. tuberculosis* Infection – Pathogenesis, Diagnosis, Treatment and Prevention Strategies

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Abstract

One third of the earth’s population is infected with *Mycobacterium tuberculosis* (*Mtb*), but only 5–10% of the infected individuals develop active tuberculosis (TB) over their lifetime. The remaining 90–95% stay healthy and are called latently infected individuals. They are the biggest reservoir of the tubercle bacilli and identifying the cases of latent TB is a part of the global plan of TB control. From the clinical point of view detection of latent TB infections (LTBI) in individuals with the highest active TB risk including cases of HIV infection, autoimmune inflammatory diseases or cancer, is a priority. This review summarizes the recent findings in the pathogenesis of latent TB, its diagnosis, treatment and prevention.

Key words: latent TB infection, interferon-gamma release assays, tuberculin skin test

Introduction

Tuberculosis (TB) continues to be one of the major infectious diseases threatening millions of lives worldwide, mainly in developing (TB high-endemic) but also in developed (TB intermediate- and low-endemic) countries. It is estimated that approximately one-third of the world’s population is infected with *Mycobacterium tuberculosis* (WHO, Global Tuberculosis Control, 2010). Most people infected with *M. tuberculosis* (*Mtb*) remain asymptomatic, termed latently infected (LTBI), and the intensive studies have been performed to elucidate the role of bacillary virulence determinants, host genetic and immune background as well as environmental effects in LTBI. The patients with active pulmonary TB are the main source of *Mtb* infections, however, the latently infected people are the biggest reservoir of the tubercle bacilli, because LTBI may develop to active TB disease within a few years or decades after the prime infection with *Mtb*. Defects in cell-mediated immunity resulting from human immunodeficiency virus infection, malnutrition, administration of chemotherapy or steroids and anti-tumor necrosis factor treatment predispose to developing TB disease in people latently infected with *Mtb* (Dyrhol-Riise *et al.*, 2010; Stefan *et al.*, 2010; Launois *et al.*, 2011; Hsia *et al.*, 2012; Minguez *et al.*, 2012). Presently, the diagnosis and treatment of LTBI are recommended, particularly in developed countries, to minimize the risk of TB disease in immunocompromised patients.

1. Pathogenesis of latent TB

The term latent *Mtb* infection was first described by Clemens von Pirquet (Wagner, 1964), who created a tuberculin skin test using a crude mixture of mycobacterial antigens called Koch’s tuberculin. He proposed a definition to describe a child who had a positive skin reaction to tuberculin but had no symptoms of pulmonary or extrapulmonary TB. In contrast to patients with active TB disease, latently infected individuals are not infectious and have chest radiographs that do not present any abnormalities or signs of healed TB disease (Singh *et al.*, 2011).

There is a great variability in the course of *Mtb* infections among humans (Ducati *et al.*, 2006; Lin *et al.*, 2010). Some people remain uninfected, which is evidenced by a negative tuberculin skin test and Interferon-gamma (IFN-γ) Release Assay (IGRA) for...
of mycobacteria without their eradication (Stein et al., 2008). In the majority of people, a prime Mtb infection induces the development of specific acquired cell-mediated immunity inhibiting the growth of mycobacteria without their eradication (Dye et al., 1999). In such individuals tuberculosis bacilli persist in a dormant state. The risk of reactivating latent TB for immunocompetent subjects is in the order of 10% in a lifetime (Bhatt and Salgame, 2007; Lin and Flynn, 2010). Cell-mediated immunity is the major component of host defence against TB. In resistant individuals, the control of Mtb infection relies on the development of a Th1 immune response. This type of response involves the participation of resident alveolar macrophages, dendritic cells, T lymphocytes (TCD4+, TCD8+, Tyδ), and release of proinflammatory cytokines, interferon-γ (IFN-γ), interleukin-2 (IL-2), IL-12, IL-18, tumour necrosis factor-α (TNF-α)) and chemokines (IL-8, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α)). All of them play an important role in the recruitment of additional cells to the infection site for the formation of granuloma that contains and kills tuberculosis bacilli, but also provides a long-time niche needed for LTBI (Co et al., 2004; Day et al., 2010).

Granuloma is a structural organisation of different type immune cells, macrophages, T cells, B cells, dendritic cells, neutrophils, natural killer (NK) cells and a fibroblast which is formed in response to pulmonary inflammation resulting from the stimulation of host cells with mycobacterial antigens (Co et al., 2004; Gideon and Flynn, 2011). Granuloma is initiated by resident macrophages that phagocyte bacilli and release proinflammatory cytokines, such as TNF-α, to recruit additional cells (Flynn et al., 1995). Within the granuloma macrophages differentiate into epithelioid cells or fuse to form multinucleated giant cells (Peyron et al., 2008). The above cells are surrounded by a rim of lymphocytes including CD4 T cells of adaptive immune response which may enhance bactericidal capacity of macrophages by the released IFN-γ (Flynn et al., 1993). At the later stage a tight coat of fibroblasts encloses the granuloma (Peyron et al., 2008). The adapted cell-mediated immune response and proper formation of granuloma determine the outcome of Mtb infection. In about 90% Mtb infected individuals the host response is sufficient to prevent the TB disease (Ducati et al., 2006; Bhatt and Salgame, 2007; Lin and Flynn, 2010). The persistence of tuberculosis bacilli in granuloma is accompanied by changes in bacterial metabolism and in host metabolism that are in part driven by Mtb effector proteins and glycolipids (Harding et al., 2011; Guidry et al., 2007). In granuloma the persistent bacilli are subject to various stress conditions like hypoxia, nutrient deficiency, acidic pH and inhibition of respiration by nitric oxide. All these factors induce the expression of genes that lead to the transformation of Mtb into a dormant stage (Gideon and Flynn, 2011). The dormant bacilli are able to minimize their metabolic and replicative activity as well as inhibit their growth and development. They become resistant to the immune attack and avoid the elimination by the immune cells (Divangahi et al., 2009; Niki and Matsumoto, 2011). In granuloma, macrophages filled with droplets of lipids, so called foamy macrophages, constitute a nutrient-rich reservoir for persistent bacilli (Peyron et al., 2008). After years or decades of dormancy tuberculosis bacilli can again change their own metabolism, reactivate and influence the pressure on granuloma, which leads to necrotic cell death (Harding et al., 2011). It has been suggested that in Mtb infections the formation of correct granuloma is crucial to limiting the mycobacterial growth as well as tissue damage and dissemination, two components of active TB disease (Saunders et al., 2000). An insufficient upregulation of adhesion molecules on circulating lymphocytes may hinder the localization of antigen-specific lymphocytes within lungs. As a result the formation of correct granuloma capable of inhibiting Mtb growth is affected (Turner et al., 2001). The intensity and quality of T cell response within granuloma depends on the mechanisms targeting antigen presentation. Several Mtb components such as 19-kDa lipoprotein, mannose capped lipoarabinomannan (Man-LAM), trehalose dimycolate (cord factor) and others can modulate antigen processing and presentation of mycobacterial protein and glycolipid antigens by MHC class I, MHC class II and CD1 molecules (Baena and Parcelli, 2009). In this way, tuberculosis bacilli may suppress the presentation of antigens to T lymphocytes by macrophages (Chang et al., 2005; Ahmad, 2010). An insufficient activation of effector CD4+, CD8+, and γδ T lymphocytes, CD1 restricted and cytotoxic T cells, results in defective microbicidal functions of macrophages and modified activity of other immune cells including those implicated in inflammatory response leading to tissue damage and dissemination (Saunders and Cooper, 2000; Baena and Parcelli, 2009; Ahmad, 2010; Chang et al., 2005).

The lifetime risk of developing active TB disease after primary infection is often said to be about 10% and it is stated that approximately one half of those who develop the disease will do so within 5 years after infection. However, the factors influencing the pathogen clearance and the progression of the disease from latent infection are poorly understood (Lillebaek et al., 2002; Vynnycky and Fine, 2000). Known risk factors of TB reactivation include: HIV infection, immunosuppressive treatment – glucocorticoids, anti-TNF therapy, anti-cancer therapies, malnutrition, tobacco smoking, alcoholism, malignancy, insulin dependent diabetes,
renal failure (Corbett et al., 2007; Lin and Flynn, 2010; Gideon and Flynn, 2011). However, in the majority of cases, the specific cause of reactivation is unknown (Lillebaek et al., 2002).

2. Detection of latent TB infection

According to the World Health Organization (WHO), more than 2 billion people in the world are latently infected with *M. tuberculosis* (WHO, Global Tuberculosis Control, 2010). Latently infected individuals do not show any clinical signs or symptoms of TB disease and have normal chest radiographs. The detection of such cases relies on the immunological markers of the immune response. Two methods used in the clinical practice have been designed to measure the adaptive cell-mediated immune response of asymptomatic hosts exposed to *Mtb*. The tuberculin skin test (TST) and interferon-gamma release assays (IGRA) are standard immunologic diagnostic tools for LTBI (Table I).

**Tuberculin Skin Test.** Until 2001, the tuberculin skin test (TST) was the only method for diagnosing LTBI (Gideon and Flynn, 2011; Vittor et al., 2011). The test was first described by Robert Koch in 1890 and named after Charles Mantoux and Clemens von Pirquet who put the test into practice in 1907 (Singh et al., 2011). Tuberculin is a glycerol extract of mycobacteria, and PPD (purified protein derivative) is a precipitate of non-species-specific antigens obtained from filtrates of mycobacterial cultures. Presently performed TSTs measure the induration of the skin 48–72 hours after the intradermal administration of PPD (the Mantoux procedure). The test triggers a PPD driven classical T-cell-mediated delayed-type hypersensitivity reaction (DTH) (Ayub et al., 2004). The criteria for a positive TST result vary from region to region and depend on the dose and type of the PPD antigen used in the test. In many countries 2 IU (international units) of the PPD RT23 preparation (Statens Serum Institut, Copenhagen, Denmark) is used and the induration of skin ≥6 mm (e.g. in Norway, a TB low-epidemic country; Dyrrholl-Riise, 2010) or ≥10 mm (e.g. in Poland, a TB intermediary-epidemic country; Druszczyńska et al., 2006); is regarded as positive. A higher dose of 5 IU PPD (Chiron, Siena, Italy) was used to estimate the frequencies of positive TSTs among close contacts of active TB patients and homeless people in Italy (Butera et al., 2009). In this study, skin induration of at least 5 mm was considered as a positive response for the group of close contacts and a reaction of ≥10 mm was considered positive for homeless people and healthy controls unexposed to *Mtb*. The TSTs with 5 IU PPD (RT23) performed in patients with TB disease and healthy controls, all have been vaccinated with *M. bovis* BCG (Bacille Calmette-Guérin), in a TB high-endemic country (China), provoked skin induration ≤5 mm in 42.7 and 37.7%, respectively, 5–10 mm in 18.4 and 28.3%, respectively, and ≥10 mm in 55.3 and 34.0%, respectively (Zhang et al., 2010). The differences between frequency and intensity of PPD driven skin indurations between two groups were not strongly marked with a probable implication of the effects of BCG vaccination. As it is known, the BCG vaccination results in the development of DTH to PPD (Druszczyńska et al., 2006). This fact largely limits the usefulness of TSTs in LTBI detection, particularly in countries where children are routinely vaccinated with BCG. Great variations in the performance of the skin tuberculin tests and interpretation of the results make the estimation of sensitivity difficult.

**Table I**

<table>
<thead>
<tr>
<th>Intended use</th>
<th>TST</th>
<th>QuantiFERON-TB Gold In-Tube</th>
<th>T-SPOT.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>in-vivo</td>
<td>ex-vivo</td>
<td>ex-vivo</td>
</tr>
<tr>
<td>Technique</td>
<td>skin prick test</td>
<td>ELISA</td>
<td>ELISPOT</td>
</tr>
<tr>
<td>Antigen(s) used</td>
<td>PPD</td>
<td>ESAT-6, CFP-10, TB 7.7(p4)</td>
<td>ESAT-6, CFP-10</td>
</tr>
<tr>
<td>Results reported as</td>
<td>skin induration in mm</td>
<td>IFN-gamma concentration</td>
<td>spot-forming number</td>
</tr>
<tr>
<td>Result interpretation</td>
<td>subjective</td>
<td>objective</td>
<td>objective</td>
</tr>
<tr>
<td>Result availability</td>
<td>48–72 hours</td>
<td>24 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Patients visit required</td>
<td>two</td>
<td>one</td>
<td>one</td>
</tr>
<tr>
<td>Influence by prior BCG vaccination</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Cross-reactions with non-TB bacteria</td>
<td>yes</td>
<td>rare (<em>M. fortuitum</em>)</td>
<td>no</td>
</tr>
<tr>
<td>Side effects</td>
<td>yes (rare)</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Booster effect</td>
<td>yes (possible)</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

* Dyrholl-Riise, 2010
and specificity of TSTs in LTBI very difficult. The meta-analysis of the results from 20 studies (Pai et al., 2008) showed that sensitivity of TSTs was heterogeneous, with a pooled estimate of 77% (CI, 71% to 82%). Specificity in non-BCG vaccinated populations was high, with a pooled estimate of 97% (CI, 95–99%). Specificity in BCG-vaccinated population was heterogeneous and lower, 59% (CI, 46–73%) (Pai et al., 2008). Although TST has been widely used for LTBI screening and making decisions about chemoprophylaxis and treatment, its most important drawback is low specificity (Richeldi, 2006). PPD contains over 200 antigens, which are not specific for M. tuberculosis but also present in the M. bovis BCG vaccine and several environmental mycobacterial strains (Gideon and Flynn, 2011). Therefore, the TST does not differentiate between infection with virulent M. tuberculosis, prior immunization with BCG or contact with environmental mycobacteria. Its sensitivity was also found to be low in the case of HIV-infected and other immunocompromised individuals, in whom the risk of progression to active TB is high (Santin et al., 2011; Hsia et al., 2012). In HIV-infected adults TST reactivity declined sharply as the number of CD4+ cells fell (Santin et al., 2011). Moreover, many immunocompetent people with confirmed TB do not respond to PPD at the time of diagnosis due to the anergy. Despite these limitations, TST is still routinely used in the clinical practice to screen for TB infection.

Interferon-Gamma Release Assays (IGRAs). The knowledge of complete genome sequences of mycobacteria has led to the discovery of a region of difference (RD1), that is present in all M. tuberculosis and pathogenic M. bovis strains but absent from BCG strains and most of the atypical mycobacteria (Ahmad, 2010). This region represents one of the most interesting genomic loci of the tubercle bacilli because it appears to be involved in enhancing the mycobacterial virulence by encoding two secretory proteins, ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) (Teutschbein et al., 2009). Both antigens have been found to be strong inducers of IFN-γ production and development of DTH in animals (Richeldi, 2006; Ahmad, 2010). The rESAT-6 obtained from E. coli was successfully used as an antigen for the TB diagnostic skin test in humans (Arend et al., 2008; Wu et al., 2008). The combination of rESAT-6 and CFP-10 was found to be more specific than PPD for both in vitro and in vivo diagnosis of M. tuberculosis infection in the guinea pig model (van Pijnxteren et al., 2000; Weldingh and Andersen, 2008). Thus, the antigenic complex seems to be a very promising candidate for LTBI identification, which could probably replace PPD as a skin test reagent.

The strong antigenicity of ESAT-6 and CFP-10 has been the basis for developing interferon-gamma release assays (IGRAs). They are diagnostic tests that measure the IFN-gamma released by T-lymphocytes in the response to M. tuberculosis-specific antigens. On the market there are three T-cell dependent tests: QuantiFERON-TB Gold (QFT-G) and QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Ltd, Carnegie, Australia) and T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). The tests have been approved by Food and Drug Administration (FDA) for the diagnosis of infection with M. tuberculosis. According to the NICE (UK National Institute for Health and Clinical Excellence) guidelines, all individuals with positive TST results should be considered for IGRA testing (Denkinger et al., 2011). The QuantiFERON-TB Gold (QFT-G), contains two antigens of the Mtb RD1 region, ESAT-6 and CFP-10. 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(Santin et al., 2011). However, false-negative QFT-GIT results connected with the immunosuppression can be easily detected by the positive control included in the test (Singh et al., 2011). Positive QFT-GIT, T-SPOT. TB results were not affected by the immunosuppressive therapies in patients with inflammatory arthritis (Minguez et al., 2012) and sarcoidosis (Milman et al., 2011).

The utility of IGRAs in diagnosing active TB disease was also considered. Thus, the accuracy of two IGRAs, QFT-GIT and T-SPOT.TB, was evaluated for patients with suspected TB in a high-burden setting of South Africa (Ling et al., 2011). The sensitivity and specificity (95% CI) were 76% (68–83%) and 42% (36–49%) for QFT-GIT and 84% (77–90%) and 47% (40–53%) for T-SPOT.TB, respectively. The accuracy was independent of HIV status but even so, the IGRAs alone were found to have low diagnostic value for active TB. In smear-negative patients, chest radiography had better predictive value than IGRAs. On the contrary, the T-SPOT.TB assay was found much more promising for detecting active TB (the positive rate 94.7%) than TST (the positive rate 73.7%), in China (Zhang et al., 2011). Because the T-SPOT.TB rates declined during TB treatment, the author suggested that this assay could serve as a potential predictor of therapeutic efficacy. However, the meta-analysis in 27 studies published in 2001–2009 (Sester et al., 2011) which evaluated the utility of IGRAs for the diagnosis of active TB, showed the pooled sensitivity 80% (95% CI 75–84%) for QFT-GIT and 81% (95% CI 78–84%) for T-SPOT.TB. Thus, the diagnostic sensitivity of both IGRAs was not enough to use as a rule out test for active TB disease in immunocompetent individuals and in HIV-infected patients (Chen et al., 2011; Cattamanchi et al., 2010).

### 3. Treatment of latent TB infection

Treatment of latent TB infection seems to be essential for controlling and eliminating TB all over the world. Successful therapy of latent TB reduces the risk of activation of dormant infection and subsequent progression to active TB disease. Every effort should be made to start appropriate treatment and to ensure that persons at the highest risk of reactivation complete the entire course of therapy. Treatment of LTBI should not begin until active TB disease has been excluded.

The currently recommended treatment of latent TB is based on the monotherapy with isoniazid (INH), however, the period of treatment can vary from 6 to 9 months (Table II). The randomized International Unit Against Tuberculosis (IUAT) (currently International Union against Tuberculosis and Lung Disease – IUATLD) trial conducted in Eastern Europe demonstrated that INH taken for 3 months reduced the risk of TB reactivation by 31%, while individuals who completed 6 or 9 months of INH therapy had 69 or 93% reduction in the TB risk (Menzies et al., 2011).

The time of 6 months treatment is recommended for HIV-seronegative adults (Ahmad, 2010). Under certain circumstances, the frequency of the INH use can be also reduced from once daily to twice weekly with increased dosage of the drug (Blumberg et al., 2005). However, INH treatment of latent TB is problematic for several reasons. Although the drug is well tolerated by the majority of humans, it can lead to liver injury, dermatitis, metabolic acidosis or peripheral neuropathy (Menzies et al., 2011). Laboratory testing should be performed to evaluate possible side effects that may occur during the treatment.

Another alternative treatment of latent TB is the use of rifampicin (RMP) alone for 4 months or in combination with pyrazinamide (PZA) for 2 months (Gao et al., 2006). The RMP monotherapy is recommended for people who do not tolerate INH or were exposed to an INH-resistant M. tuberculosis strain. The therapy with RMP appears to be better tolerated than INH and shows fewer adverse reactions (Page et al., 2006).

The combined therapy with INH and RMP is another option for combating the LTBI. A series of clinical trials have demonstrated that 3- or 4-month INH + RMP treatment is equivalent to that of 6- or 9-month INH usage, although adverse effects are significantly more frequent (Kunst and Khan, 2010). Rifampicin can be replaced by rifapentin (RPE), which has its half life period 5-times longer than RMP and allows the use of drugs twice weekly instead of once daily (Table II).

### 4. Strategies for LTBI prevention in the future

Three approaches can be taken into account to reduce the burden of TB in the future. One strategy is based on the rapid diagnosis of persons with active TB.
and early introduction of effective treatment to stop them from spreading *M. tuberculosis* in the environment. This will reduce the rate of transmission and the number of people latently infected with the bacteria. It is estimated that each person with untreated TB can infect on average between 10 and 15 people every year and remain a reservoir from which active TB can develop. One of the main objectives of the DOTS (Directly Observed Treatment, Short-course) strategy is the search for alternative diagnostic methods based on the detection of microbiological or host cellular and humoral biomarkers (Walzl et al., 2011). These techniques would be particularly important in the diagnosis of such forms of TB, in which it is not possible to detect mycobacteria using traditional diagnostic methods. Besides, they could provide some prognostic information that might help to evaluate the TB development risk and discriminate between latent *M. tuberculosis* infection and active disease (Walls et al., 2010). However, the practical utility of various TB biomarkers is so far poorly defined.

An alternative approach is prophylactic vaccination against TB. The only available and most widely used TB vaccine is BCG. More than 120 million doses of the vaccine are administered every year all over the world (Daniel, 2006). It is considered that the immunization of infants with BCG can protect against TB meningitis and other severe forms of TB in children less than five years old. BCG vaccine is not recommended by the WHO after 12 months of age because the protection provided is variable and less certain (WHO, Immunization surveillance, assessment and monitoring, 2010). BCG should not be given to HIV-infected children because of the increased risk of developing disseminated BCG disease (Hesseling et al., 2010). BCG should not be given to HIV-infected children because of the increased risk of developing disseminated BCG disease (Hesseling et al., 2010; WHO, 2007). Several large human clinical trials revealed a great variation in the protection conferred by BCG vaccination, from 0% efficacy in some endemic areas such as Southern India to 75% protection in the United Kingdom (Colditz et al., 1994; Brewer, 2000; McMurray and Ly, 2009; Mori, 2011). It is stated that the wide variation in vaccine efficacy might be a result of genetically determined immunogenicity of BCG strains, the nature of the host immune response and the exposition to environmental mycobacteria (Mahairas et al., 1996). The need for an improved vaccine against TB has never been more urgent. Several new TB vaccine candidates have been identified and a few have entered phase I or II clinical trials. It remains to be seen if any of them will become a part of an effective TB programme in the future (McShane, 2009).

The third strategy in the fight against TB is the detection and treatment of people with latent TB. This approach is aimed at persons with the highest risk of progression to active TB. Treatment is recommended in HIV-infected individuals, recent contacts of TB cases, patients with organ transplants or otherwise immunosuppressed individuals (Lin and Flynn, 2010; Gideon and Flynn, 2011). The screening of latently infected people has become a part of the global plan of TB control.

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**Literature**


