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Commentary

Dormancy antigens as biomarkers of latent tuberculosis infection

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Mycobacterium tuberculosis (MTB) is a major microbial pathogen that threatens global health. The WHO has estimated about 9 million new tuberculosis (TB) cases and around 1.5 million deaths due to TB in the year 2013 (World Health Organization, 2014). In MTB-infected individuals, bacteria may exist in a dormant state for lengthy periods without causing disease symptoms, or may finally start multiplying and evading immune control, resulting in active TB in 5–10% of infected cases. At present, factors that promote progression from latent tuberculosis infection (LTBI) to disease are not totally understood. Therefore, management of LTBI plays a significant role for TB disease control given that quiescent bacilli are a big reservoir of potential TB cases.

Tuberculin skin test (TST) has been the classical method used for LTBI diagnosis in spite of its compromised specificity due to cross-reaction with *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccine strain and non-tuberculous mycobacteria. Furthermore, it has low sensitivity in immune compromised patients, who are in particular those that mainly need this test because they have a high risk of developing active TB if they are infected. Interferon (IFN)-γ release assays (IGRAs) appeared more than a decade ago as an alternative method to TST for diagnosing LTBI. They detect the IFN-γ released by sensitized T cells after stimulation with specific MTB antigens encoded in the region of difference (RD) 1 and 11 (ESAT-6, CFP-10 and TB7.7) (Andersen et al., 2000). Nowadays, IGRAs implementation has improved LTBI diagnosis because of their higher specificity with respect to TST and good correlation with MTB exposure degree; however, they do not discriminate between LTBI and active TB (Pai et al., 2014). As a consequence, there is a need for studying new biomarkers to explore the biology and the immune response for distinguishing latency from disease.

At present, some new MTB phase-dependent antigens have been studied in LTBI individuals and active TB patients showing promising results. These studies explore the response of T cells producing IFN-γ because they are the major players in the protection against TB. However, variable results regarding these antigens have been obtained since now due to disparities in methodology and population heterogeneity (Serra-Vidal et al., 2014; Goletti et al., 2010; Singh et al., 2014). In *EBioMedicine*, Delfina Peña and colleagues (Peña et al., 2015) have investigated the efficacy of several DosR regulon-encoded latency antigens as potential markers for LTBI. The antigens included and studied in this work were Rv2624c, Rv2626c, and Rv2628; together with ESAT-6 and CFP-10. Interestingly, Rv2626c was found to produce significant IFN-γ levels in BCG LTBI individuals with respect to active TB patients or healthy controls. In a first approach, the response to MTB antigens was investigated stimulating peripheral blood mononuclear cells (PBMCs) from BCG LTBI individuals (QFT-GIT positive) and healthy controls (QFT-GIT negative), finding that IFN-γ response was significantly higher in LTBI individuals with respect to healthy controls upon Rv2626c stimulation. Interestingly, these findings were also confirmed by flow cytometry. Then, in a second approach, the IFN-γ response to Rv2626c was also analyzed in a third group of active TB patients stimulating PBMCs and whole blood with this specific antigen. In contrast to the results obtained with RD1 antigens (ESAT-6 and CFP-10), stimulation with this latency antigen allowed to discriminate between active and latent infection since patients with active TB did not secrete IFN-γ against Rv2626c. Finally, these results were also reinforced by a ROC analysis. Investigators also identified several specific and immunogenic Rv2626c immunodominant peptide pools that improved LTBI diagnosis.

Delfina Peña and colleagues study (Peña et al., 2015) investigates an interesting and promising field; as a consequence, their results are encouraging for several reasons. First, as currently IGRAs are not designed for distinguishing between LTBI and disease; investigations based on new antigens linked to latency are required. In this sense, the novel Rv2626c antigen studied in the present work could be promising and improve LTBI diagnosis. However, further investigations on other latency antigens different from those contemplated in this study are still required. Second, the study of new immune-biomarkers for detecting IFN-γ *in vitro* may open the door to the development of next generation assays based on new antigens. Furthermore, potential host biomarkers are urgently needed to provide risk of LTBI progression as well. In this sense, a recent published study have assessed the utility of measuring IFN-γ/TNF-α ratio against 16 antigens, finding that Rv2626c and Rv3716c improved QFT-GIT diagnostic performance and LTBI diagnosis (Prabhavathi et al., 2015). In addition, the use of flow cytometry is currently being utilized for the study of the immune response and cell surface marker expression (immunophenotyping) in order to find a signature related with infection or disease (Harari et al., 2011; Portevin et al., 2014). Together these findings will help to develop and design novel state-of-the-art techniques for LTBI and active TB diagnosis in not so near distant future.

Conflict of interest

We declare no competing interests.

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