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Editorial: Immunology of tuberculosis

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Editorial on the Research Topic
Immunology of tuberculosis

The causing agent of tuberculosis (TB), *Mycobacterium tuberculosis* (*Mtb*), is a respiratory pathogen that is estimated to infect one-quarter of the population globally, *Mtb* has killed more people than any other microorganisms during the history of human beings. With the improvement of people's living standards and the regulated use of anti-TB chemotherapy, the number of TB-related death kept declining during the past decades. However, this trend was reversed in the last three years, especially as a result of resource limitation due to the COVID-19 pandemic. As a result, an estimated 10.6 million people fell ill and 1.6 million was dead with TB in 2021 (1). Till now, TB is still the leading cause of death from a single infectious agent besides COVID-19.

Bacille Calmette-Gueérin (BCG) vaccine and anti-TB chemotherapy were regarded as two of the most powerful weapons combating TB. However, BCG is only effective in offering protection against aggressive childhood forms of the disease: meningeal and miliary TB. Its protection against pulmonary TB prevention ranges from 0% to 80% in different populations (2). In addition, human immunodeficiency virus coinfection and the emergency and dissemination of multidrug- and extensively drug-resistant TB pose challenges to TB control due to insufficient treatment success rates (3). Knowledge gaps still exist for the successful development of novel therapies, vaccines, and diagnostics for this old pathogen (4, 5). In this Research Topic, we summarize a number of studies addressing TB diagnosis, treatment, and pathogenic mechanisms.

One of the fundamental pillars to reduce the spread of TB disease is rapid and accurate diagnostics. The current TB diagnosis methods include culture, smear, real-time polymerase chain reaction-based (GeneXpert MTB/RIF, Xpert), interferon-γ release assays (IGRAs), imaging examination, etc. However, no diagnostic method fits the bill perfectly (6–8): 1) The traditional bacterial culture method is time-consuming. 2) The stained smear method is low in sensitivity. 3) Although Xpert assay is rapid, sensitive, and has high accuracy, it is expensive and impractical for widespread clinical use in developing countries. 4) IGRA is a T-cell-based assay that is used to measure *Mtb*-specific IFN-γ immune response to determine whether the individuals are infected or historically infected with *Mtb*, it cannot distinguish between latent TB infection and active TB diseases. 5) The imaging examination could be only used as an auxiliary diagnosis in TB due to its low specificity. Thus, the diagnosis of TB remains a huge challenge.

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The loop-mediated isothermal amplification (LAMP) for TB, which is much cheaper than Xpert (50–70% less cost in China), is a nucleic acid amplification assay approved by WHO for TB diagnosis. Lin et al. conducted a multi-center study with a relatively large sample size to determine the performance of LAMP in diagnosing pulmonary TB in China. It was found that the sensitivity of LAMP was slightly lower than Xpert (209/304 *vs* 250/304), however, its specificity was slightly higher (439/495 *vs* 426/495). Thus, the authors concluded that the LAMP assay performed as well as Xpert assay. Considering that the LAMP assay requires less infrastructure, has a shorter turnover time, and is cheaper than Xpert, it could facilitate the early diagnosis of TB in resource-limiting countries. Yao et al. retrospectively analyzed the diagnostic performance of CapitalBio *Mycobacterium* real-time polymerase chain reaction assay (CapitalBio test) by using samples from suspected spinal TB. Their data showed that the sensitivity and specificity of the CapitalBio test were 75.2% and 98.0%, respectively, compared with composite reference standard. The combination of histopathology and CapitalBio test showed an enhanced sensitivity (81.0%) without reducing specificity (98.0%). These two studies provide us new information on TB diagnosis.

As the most fatal type of TB, central nervous system TB (CNSTB) includes TB meningitis, tuberculoma without meningitis, and spinal TB (9). Although early treatment with glucocorticoids could improve the prognosis of CNSTB patients and reduce mortality (10), a few CNSTB patients do not respond well to glucocorticoids and anti-TB chemotherapy. It was shown that an immunomodulatory drug, thalidomide, could be used in CNSTB patients if glucocorticoids are ineffective (11). Liu et al. retrospectively reviewed the clinical efficacy and safety of thalidomide in treating four complicated CNSTB patients in a case reports article, supporting that thalidomide is an effective and well-tolerated drug for the treatment of CNSTB.

Besides chemotherapy, therapy targeting the host factors is an alternative approach to developing new treatment strategies against TB (12). As an intracellular pathogen, *Mtb* colonized into the cell, thus, the host cellular immune and inflammatory responses as well as basic cellular physiologic mechanisms play critical roles in TB disease establishment and progression (13). Host-directed therapies (HDTs) usually aim at optimizing the host immune responses by interfering with host cellular processes required for *Mtb* survival/replication, or improving the microbicidal activity of macrophages and other infected cells, or by alleviating exacerbated inflammation that may cause damage to host tissues (14, 15). In a perspective article, Baindara et al. focused on the Notch signaling pathway, which is one of the highly conserved pathways that transmit signals through direct contact with adjacent cells in a very short range of cellular communications. The authors summarized studies illustrating the role of the Notch signaling pathway during *Mtb* infection, which suggested that the Notch signaling might be a potential host factor target for the development of clinical therapeutics against TB.

Epidemiological studies showed that type 2 diabetes mellitus (T2DM) increased the risk of latent TB infection and active TB diseases, and worsened the TB treatment outcomes (16, 17). However, the mechanisms underlying this observation are not well elucidated. Ssekamatte et al. reviewed studies that focused on the effect of T2DM on the innate/adaptive immune responses against TB infection, and on the immunometabolic, gene-transcriptional mechanisms of TB susceptibility. The authors summarized the current challenges and future perspectives that might facilitate novel modulators to lessen the combined burden of the diseases.

Overall, the manuscripts published within this Research Topic provided new information on TB research. With more advanced knowledge, we are hopeful that more effective therapies, vaccines, and diagnostics will be achieved in the near future.

Author contributions

ZH, TB and X-YF conceived, designed, and wrote the manuscript. All the authors contributed to the article and approved the submitted version.

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Conflict of interest

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