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Detection, treatment and prevention of tuberculosis

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ABSTRACT

Mycobacteria tuberculosis (Mtb) infects millions yearly in many countries. Numerous multi-generational genetic factors have been identified that account for high host susceptibility to Mtb. Diagnostic tests based on quantification of interferon-γ generation by Mtb antigen-stimulated blood mononuclear leukocytes detect infection accurately and show far lower false-positive and false-negative results than Mtb antigen skin tests. Antibiotic resistance of Mtb has limited effective treatment. Now new tests for antibiotic resistance of Mtb based on genetic mutations characteristic of resistance to individual antibiotics report more accurately and rapidly than prior assays of resistance of cultured Mtb growth to antibiotics. The Bacillus Calmette-Guerin vaccine given to babies protects them against serious Mtb manifestations, such as Mtb meningitis, but does not prevent childhood or adult Mtb disease. Development of human Mtb vaccines has succeeded recently with antigens composed of mRNAs encoding Mtb polypeptides or recombinant peptides fused to proven adjuvant systems. Two of these vaccines have completed phase IIb or III trials and have prevented > 50% of individuals with inactive pulmonary Mtb from progressing to active disease over three years.

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KEYWORDS: Genetic susceptibility; Evasion of immunity; Intracellular persistence; Antibiotic resistance; Vaccine development

Background

In 2024, 10.8 million patients were infected with *Mycobacterium tuberculosis* which led to 1.25 million deaths. Clinical diagnosis and treatment have been complicated traditionally by the difficulty of laboratory culturing of *Mycobacterium tuberculosis*, high rates of false negative skin testing, mechanisms by which *Mycobacterium tuberculosis* evades host immune defenses and the absence of an effective vaccine. Now increases in susceptible populations and development of drug-resistant strains of *Mycobacterium tuberculosis* have further complicated medical management. In addition to multi-generational adverse genetics and a high rate of exposure, factors that increase susceptibility to tuberculosis are young and old age, excessive use of alcohol and tobacco, and medical conditions including HIV/AIDS, type 1 and 2 diabetes, end-stage kidney diseases, pulmonary silicosis and immunosuppression from any cause.[1] The International Tuberculosis Host Genetic Consortium has studied tens of thousands of patients in nine countries, including fine-mapping of multi-ancestry genetic heritability of susceptibility to *Mycobacterium tuberculosis* infection. Although still in progress, their results implicate three genes involved in susceptibility to *Mycobacterium tuberculosis* infection. Human leukocyte antigen (HLA) variants impair antigen presentation to the immune system. Variants in the tyrosine kinase gene 2, that encodes the TYK2 member of the intracellular Janus kinase family, also disrupt protective immune responses to *Mycobacterium tuberculosis*. Polymorphisms in the vitamin D receptor (VDR) gene also are associated with increased risk of *Mycobacterium tuberculosis* infection.

Immune responses to aerosol *Mycobacterium tuberculosis* infection of the lungs

Knowledge of the phases of development of T cell immunity to *Mycobacterium tuberculosis*, the roles of several

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subtypes of mononuclear phagocytes, mechanisms of *Mycobacterium tuberculosis* subversion of T cell responses and the separate events in lung-draining lymph nodes and parenchymal granulomas permits an understanding of the prolonged persistence of intracellular *Mycobacterium tuberculosis* infections. When aerosol *Mycobacterium tuberculosis* enters the lungs, they are first taken up by alveolar macrophages and allowed to proliferate intracellularly. After alveolar macrophage death, *Mycobacterium tuberculosis* is transferred to monocytes and interstitial monocyte-derived macrophages. Innate immune generation of type I interferon (IFN) is the major first cytokine response, that recruits neutrophils, but is limited by the appearance of a robust type II IFN response. Interstitial macrophages limit *Mycobacterium tuberculosis* proliferation and transfer them to draining lymph nodes. Here lymph node-resident dendritic cells accept *Mycobacterium tuberculosis* antigens from infected macrophages for presentation to naïve T cells. *Mycobacterium tuberculosis*-specific $CD4^+$ and $CD8^+$ effector T cells then develop and return to the lungs to be activated by and kill *Mycobacterium tuberculosis* in infected macrophages and organize granuloma formation.

CLINICAL SIGNIFICANCE

- *Mycobacterium tuberculosis* (Mtb) continues to infect ten million annually worldwide.
- The persistence of Mtb infections are attributable to its many immune evasive mechanisms.
- High production of interferon-γ by Mtb-challenged blood immune cells gives rapid diagnosis.
- Antibiotic resistance of some Mtb seriously complicates effective therapy.
- Anti-Mtb vaccines developed with polypeptide-adjuvant or mRNA antigens show early success.

The early balance between type I IFN-neutrophil response and type II IFN-macrophage/CD4 T cell response determines the course of *Mycobacterium tuberculosis* infections. The infection will be more severe if a type II IFN-macrophage/CD4 T cell response develops too slowly and the type I IFN-neutrophil response progresses.[2] In pulmonary granulomas, *Mycobacterium tuberculosis*-infected macrophages are at the core and *Mycobacterium tuberculosis*-specific T cells are in the periphery. Direct contact of $CD4^+$ and cytotoxic $CD8^+$ effector T cells with infected macrophages is required for control of intracellular *Mycobacterium tuberculosis*, so this spatial segregation may be one barrier to T cell effectiveness in *Mycobacterium tuberculosis* pulmonary infections.

Mycobacterium tuberculosis (Mtb) employs several different mechanisms to reduce T cell-dependent responses and thus evade immune elimination, including interference with antigen presentation, prevention of T cell signaling and activation, and induction of regulatory pathways (Table 1). Much of the immune data were generated in mouse models of Mtb infections in which some immune mechanisms and the time course of disease differ significantly from those of humans. The information in Table 1 is derived specifically from *in vivo* studies of humans. Mtb virulence factors alter trafficking of Mtb antigen-containing vesicles in macrophages or reduce presentation of Mtb antigens by macrophages or decrease levels of secreted IFN-γ (upper columns, Table 1). Abnormal levels of several T cell constituents are attributable to contact with viable Mtb, but without known effects of specific virulence factors. These mechanisms diminish CD4 and CD8 T cell proliferation, decrease immune cytokine generation and increase levels of Treg cells (lower columns, Table 1).

Patient testing for Mycobacterium tuberculosis infection

An Mtb skin test involving intradermal injection of antigen and evaluation of the site 48 hours later has been a standard means of assessing patient prior exposure to Mtb. A positive response consists of a delayed-type immune reaction of

Table 1 *Mycobacterium tuberculosis* suppressive effects on immune responses to infection

Mycobacterium tuberculosis (Mtb) effect	Mtb Virulence factor
Disrupt immune cell/macrophage processing and presentation of Mtb antigens	EsxH
Inhibit autophagy and release of Mtb antigens by macrophages	PE_PGRS47
Facilitate export of Mtb antigens from macrophages to divert them from MHC-II	Mtb facilitates kinesin 2-dependent vesicular trafficking
Inhibit infected immune cell apoptosis and release of Mtb antigens to non-immune cells	NuoG
Decrease IFN-γ secretion by $CD8^+$>$CD4^+$T cells	D-serine
Decreased $CD4^+$and $CD8^+$T cell proliferation, increased $CD4^+$T reg cells through elevated level of indoleamine-2,3-dioxygenase	Viable intact Mtb, but specific virulence factor unknown
Decreased levels of Th1 cells and IFN-γ by effects of elevated TGFβ and IL-10	
Decreased $CD4^+$and $CD8^+$T cell expression of cytokines by elevated T cell level of T cell immunoglobulin and mucin domain 3(Tim-3)	

EsxH = product H of early secretory antigenic target system; NuoG, NADH = ubiquinone oxidoreductase subunit G; PE_PGRS47 = pro-glu_polymorphic glycine-rich domain 47 protein.

lymphocyte infiltration leading to induration of 5 mm diameter or greater. Positive responses indicate very likely active or inactive Mtb infection. False positive skin tests are seen in individuals who have received Bacillus Calmette-Guerin (BCG) vaccine and false negative tests are observed with inadequate immune systems due to HIV/AIDS, diabetes mellitus, end-stage kidney or liver disease, or overwhelming systemic infections including those from Mtb. Further confirmatory testing can include one of two blood tests: T-SPOT®.TB test or QuantiFERON®-TB Gold Plus, which currently are often replacing the skin test.[3] In the SPOT®. TB test, blood mononuclear leukocytes are incubated with Mtb antigens, a mitogen (positive control) or medium alone (negative control). After incubation, interferon (IFN)-γ in T cells of the samples is quantified by an enzyme-linked Spot-test. A higher than threshold number of IFN-γ-positive T cells indicates either active Mtb infection or latent or inactive Mtb without clinical signs of activity. Similarly, the QuantiFERON®-TB test involves incubation of blood T cells with Mtb antigens, but one sample has $CD4^+$ and $CD8^+$ *T* cells and a second sample has only $CD4^+$ *T* cells. IFN-γ in the medium is quantified and positive tests thus identified. Both assays may show false positives in individuals with other mycobacterial infections or who have received BCG vaccine. However, false negative results are less common than with Mtb skin tests.

Mycobacterium tuberculosis drug resistance

More than ten million new cases of Mtb infection have been reported annually in the past several years. Unfortunately, the incidence of Mtb drug resistance, defined as lack of response to one of the most effective usual treatment medications, has remained high over the past decade.[4] Primary drug resistance is caused by person-to-person transmission of drug-resistant Mtb. Secondary drug resistance develops when treatment is delayed, patient did not follow treatment guidelines, medications were not normally absorbed or drug-drug interactions resulted in lower than necessary medication levels. Case numbers of multi-drug resistant Mtb infections, defined as resistance at least to isoniazid and rifampin, also have remained high at 450,000 in 2012 and 410,000 in 2022. Treatment success rate for multi-drug resistant Mtb has only increased from 50% in 2011 to 63% in 2019. If response to treatment is delayed, Mtb growth-based drug susceptibility testing should be performed either in solid medium (results in 18-22 days) or liquid medium (results in 7-14 days). Molecular detection of drug resistance more rapidly identifies mutations of the Mtb genome characteristic of resistance to one or more drugs, allowing earlier initiation of treatment and detection of treatment-ongoing changes in resistance pattern.

New possibilities for vaccine development

The Bacillus Calmette-Guerin (BCG) vaccine is a weakened strain of Mtb injected into babies during the first month of life in countries with a high rate of Mtb infections. It has been used successfully for over 100 years and has only uncommon minimal side-effects of a local blister, adenopathy under the injected arm, and fever or headache lasting a few days. It does not prevent Mtb infection, but does prevent by 70%-80% very serious infections such as Mtb meningitis in children.

The newly developed M72/AS01E vaccine consists of a recombinant fusion protein (M72) derived from two antigens of the *Mycobacterium tuberculosis* bacterium (Mtb32A and Mtb39A) combined with the AS01E adjuvant system of GlaxoSmithKline, that was used in their Herpes zoster vaccine. A successful phase IIb trial for adults with latent Mtb infection, defined by a positive IFN-γ test without clinically active disease, showed 54% protection against pulmonary Mtb over 3 years relative to controls by two doses of M72/AS01E vaccine 1 month apart.[5] A phase III trial for 20,000 patients now is in progress. If successful in phase III, this will be the first vaccine to prevent Mtb infection in adults.

The most hopeful pathway for development of an Mtb vaccine involves mRNAs encoding Mtb antigens known to be highly immunogenic targets of CD4 T cells in humans with latent Mtb.[6] Mice were immunized with mRNA-lipid nanoparticles for each antigen and mouse splenocytes were challenged *in vitro* with these antigens as well as both non-reactive and cross-reactive antigens to determine specific increases in intracellular levels of IL-2, TNF and IFN-γ indicative of protection against Mtb infection. A trivalent vaccine was prepared that contains mRNAs encoding the three most stimulatory antigens: PPE20, EsxG and E18 in lipid nanoparticles. Protection provided by this vaccine against Mtb infection in multiple mouse models was greater than and additive with that from BCG vaccine. Blood mononuclear leukocytes from 95 adolescent individuals with proven latent Mtb were challenged *in vitro* with the antigens of the trivalent vaccine that yielded positive cytokine responses by 84%. Similar testing of the two antigens in M72/AS01E vaccine showed cytokine responses by only 67%. Large clinical trials of this new trivalent vaccine are in progress.

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Declaration of competing interest

The author has no conflicts-of-interest to declare in relation to this manuscript.

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