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Review

Immune response gene polymorphisms in tuberculosis

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Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis* (*M.tb*), remains a leading public health problem in most parts of the world. Despite the discovery of the bacilli over 100 years ago, there are still many unanswered questions about the host resistance to TB. Although one third of the world's population is infected with virulent *M.tb*, no more than 5–10% develop active disease within their lifetime. A lot of studies suggest that host genetic factors determine the outcome of *M.tb*-host interactions, however, specific genes and polymorphisms that govern the development of TB are not completely understood. Strong evidence exists for genes encoding pattern recognition receptors (TLR, CD14), C-type lectins, cytokines/chemokines and their receptors (IFN-γ, TNF-α, IL-12, IL-10, MCP-1, MMP-1), major histocompatibility complex (MHC) molecules, vitamin D receptor (VDR), and proton-coupled divalent metal ion transporters (SLC11A1). Polymorphisms in these genes have a diverse influence on the susceptibility to or protection against TB among particular families, ethnicities and races. In this paper, we review recent discoveries in genetic studies and correlate these findings with their influence on TB susceptibility.

Key words: tuberculosis, susceptibility/resistance genes

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INTRODUCTION

Tuberculosis (TB) remains an effective killer in spite of a 50-year application of antimycobacterial therapy and BCG (Bacille Calmette Guérin) vaccine. In 2012, 8.6 million people developed TB disease and 1.3 million died from it. As many as 450 000 new TB cases were caused by multi-drug resistant *Mycobacterium tuberculosis* (*M.tb*) strains and some by total drug resistant *M.tb* (WHO, Global Tuberculosis Report, 2014). In this way, TB begins to return to the list of incurable diseases. The World Health Organization has estimated that up to 2 billion individuals are currently infected with *M.tb*. These are latent tuberculosis infections (LTBI), which means that individuals are infected with *M.tb*, although they do not have TB symptoms. In approximately 5% of LTBI individuals, active TB disease will arise within their lifetime. The remaining 95% LTBI people will remain infected but without progression to active TB. The mechanisms that restrict the infection or lead to active TB remain poorly understood. For many years a genetic component has been suspected to play a role in the susceptibility to TB. Genetic studies have revealed higher TB rates in monozygotic twins than in dizygotic twins or siblings, and racial differences in TB resistance (Cooke *et al.*, 2001). Susceptibility to TB might be determined by inherited host factors, such as polymorphisms in key genes that influence the outcome of the mycobacteria-host interactions (Thuong *et al.*, 2008). The immune response to *M.tb*, both in humans and in experimental mouse models, is a complex event involving a variety of immune cells and cytokines. The innate immune system is responsible for the initial sensing of pathogens and stimulates the first line of defense against infectious agents. The recognition of pathogens is mediated by PRR (pattern recognition receptors) on phagocytic and dendritic cells that detect specific PAMPs (pathogen associated molecular patterns) of microorganisms and lead to the development of adaptive immune responses. This review aims to summarize the existing data about functional polymorphisms in specific molecules of the immune and inflammatory responses and correlate this knowledge with the likelihood of developing pulmonary or extra-pulmonary TB disease.

PATTERN RECOGNITION RECEPTORS (PRR)

The interactions between host phagocytes and *M.tb* are crucial to both TB immunity and pathogenesis. A number of PRR are involved in mycobacteria detection by phagocytic cells, including Toll-like receptors, CD14 molecules or C-type lectins. Recognition of ligands by PRR leads to signaling events enabling the induction of cytokines, that initiatiate acute or chronic inflammatory reactions of the host.

Toll-like receptors

Toll-like receptors constitute a family of type I transmembrane evolutionarily conserved proteins. They are expressed on various immune and non-immune cells including macrophages and dendritic cells and play a key role in the innate immune system. Single nucleotide polymorphisms (SNP) in TLR encoding genes were found to influence ligand-receptor interactions and determine susceptibility or resistance to many infectious diseases, including TB. Mycobacterial antigens can bind to TLR2, TLR4, TLR9 and TLR1/TLR6 that heterodimerize with TLR2. A crucial receptor in the immunity to mycobacteria — TLR2, initiates a signaling cascade that involves

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Abbreviations: HLA, human leukocyte antigen; IL, interleukin; LTBI, latent tuberculosis infections; *M.tb, Mycobacterium tuberculosis;* PAMPs, pathogen associated molecular patterns; PRR, pattern recognition receptors; SNP, Single nucleotide polymorphisms; TB, tuberculosis; TNF-α, tumour necrosis factor α

a number of proteins, such as adaptor molecule MyD88 and TIR domain-containing adaptor protein (TIRAP) (Ariji *et al.*, 2014; Schäfer *et al.*, 2009). This cascade leads to the activation of NF-κB, which induces the secretion of proinflammatory cytokines (TNF-α and IL-12). Studies on TLR2-deficient mice revealed that blocking this receptor abolished the ability of macrophages to recognize and respond to mycobacterial antigens (Reiling *et al.*, 2002). Many studies demonstrated associations between TLR polymorphisms and susceptibility to TB (Wu *et al.,* 2015; Salie *et al.,* 2015). In a diversified study evaluating 71 SNPs in five TLRs (TLR1, TLR2, TLR4, TLR6, TLR9) among groups of Caucasians, African-Americans and West Africans, correlations were observed with two TLR2 polymorphisms (an insertion/deletion at –196 to –174) and one TLR9 variant (Velez *et al.*, 2010). Two other TLR2 mutations — *R753Q* and *R677W* were found to be associated with an increased risk of TB development in Korea, Tunisia and Turkey (Ogus *et al.*, 2004; Yim *et al.,* 2006; Ben-Ali *et al.,* 2004). Another SNP of TLR2 (597T/C) was correlated with miliary TB and TB meningitis in Vietnam (Thuong *et al.,* 2007). Recent studies from Spain and Tanzania showed that the TLR4 *Asp229Gly* polymorphism could be a risk factor for TB in HIV-infected patients, whereas previous studies from West Africa and Mexico showed no such association. The missense variant *S180L* in the adaptor molecule TIRAP was reported to contribute to TB susceptibility in West African and Algerian populations, however in Russian, Ghanaian, and Indonesian populations the correlation was not found (Miao *et al.*, 2011). All these results support TLR polymorphisms as one of TB suceptibility factors, however the molecular functions of candidate mutations have remained unknown (Wu *et al.,* 2015).

CD14 molecule

The efficient microbial recognition by TLR2 and TLR4 requires the activity of a co-receptor, CD14 (LeBouder *et al.,* 2003). It is a 55-kDa glycosyl phosphatidylinositol anchored glycoprotein expressed on monocytes, macrophages, and polymorphonuclear leukocytes (Rosas-Taraco *et al.,* 2007). A soluble form of CD14 (sCD14) produced during the enzymatic cleavage of membrane-bound CD14 is one of important acute-phase proteins. CD14 can bind Gram-negative bacteria lipopolysaccharides (LPS) and mycobacterial lipoarabinomannan (LAM) contributing to the ingestion of nonopsonized bacteria by macrophages. The study by Lee et al. has demonstrated that CD14 can also bind double-stranded RNA intracellularly and interact with TLR3 (Lee *et al.,* 2006).

In view of the role of CD14 activation in host defense against mycobacteria, some studies were conducted to examine whether CD14 polymorphisms could account for the increased prevalence of TB. A common single-nucleotide polymorphism (SNP) was found at position –159 in the CD14 gene promoter, where a C→T change occurs. The polymorphism was attributed to higher promoter activity of the variant allele, increased soluble CD14 production, and decreased secretion of IFN-γ (Kang *et al.,* 2009). It was demonstrated that the CD14-159TT genotype diminishes the affinity of specific proteins binding to the CD14 promoter, thereby enhancing the transcriptional activity of CD14 (LeVan *et al.,* 2001). In a study from Mexico, a homozygous CD14-159TT genotype was considered to be a risk factor for development of pulmonary TB. In contrast, no association was found between CD14 polymorphism and different forms of TB disease in white and Mestizos ethnic groups from Colombia (Pacheco *et al.,* 2004). A meta-analysis by Yuan et al suggested that C-159T polymorphism in CD14 gene was associated with an increased risk of TB, especially in Asians, but not in Caucasians (Yuan *et al.,* 2014). The explanation for these differences has not been found. To clarify the biological effect of the C→T SNP and its possible relationship to the development of TB, it seems reasonable to compare the polymorphism frequencies between cases and controls in different populations.

C-TYPE LECTINS

Carbohydrate-binding C-type lectins play an important role in the mycobacterial binding and recognition. They constitute a large family of molecules divided into 17 groups containing similar C-type lectin domains. Among soluble C-type lectins, the main modulators of inflammation are mannose binding lectin (MBL) and lung surfactant proteins A and D (SP-A and SP-D). In the group of transmembrane C-type lectins, DC-SIGN (CD209; dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin) and MR (mannose receptor, CD207) are the most crucial for the initiation of immune response against *M.tb*.

Mannose-binding lectin (MBL)

Mannose-binding lectin is an acute phase protein of the innate immune system. With multiple carbohydrate-recognition domains, MBL acts as an opsonin and binds to sugar groups, especially mannose- and N-acetylglucosamine-terminated glycoproteins, present on the surface of various pathogens including mycobacteria (Kasperkiewicz *et al.,* 2015; Scorza *et al.*, 2015). It is an important part of innate immunity and acts in concert with the complement system to opsonize and facilitate the phagocytosis of microorganisms. Polymorphisms in exon 1 of the MBL gene (*MBL2*) in codons 54 (allele B), 57 (allele C) and 52 (allele D), leading to amino acid changes that disrupt the collagenous backbone of the MBL, result in low serum MBL levels, which increases the risk of infections (Singla *et al.,* 2012). The MBL concentrations are also influenced by nucleotide substitutions in the promoter region of the *MBL2* gene (H/L, X/Y and P/Q at codons –550, –221 and +4, respectively) (Soborg *et al.,* 2003). All the polymorphisms exist in different frequencies in various populations, and the results of studies investigating the influence of MBL mutations on the susceptibility to TB are controversial (Soborg *et al.,* 2003; El-Sahly *et al.,* 2004; Druszczyńska *et al.,* 2006; Singla *et al.,* 2012). A recent meta-analysis of 17 human studies performed by Denholm et al showed no significant association between *mbl2* genotypes and pulmonary TB. However, the authors stipulated that the analysis was limited by a large degree of heterogeneity in the designs of the studies analyzed, and conclusions drawn might be less applicable to specific subpopulations (Denholm *et al.,* 2012). From this point of view, more work is needed to establish a relationship between MBL polymorphisms and TB.

Surfactant proteins (SP)

A lung surfactant is a complex structure of lipids (90–95%) and proteins (5–10%) that reduces surface tension of alveoli and promotes lung expansion (Ferguson *et al.,*

2000). Of the four surfactant proteins (SP-A, SP-B, SP-C, SP-D), two molecules — SP-A and SP-D, expressed by alveolar epithelial type-II cells, recognise mycobacteria by binding to surface mannose, fucose and *N*-acetylglucosamine residues (Sorensen *et al.,* 2007). They have been found to mediate the uptake of pathogens into phagocytes and modulate the oxidative burst and intracellular bacterial killing. Studies on surfactant protein polymorphisms and the levels of proteins in bronchoalveolar lavage and in the circulation have indicated associations with several pulmonary inflammatory diseases, including TB (Sorensen *et al.,* 2007). In a study from Mexico, several allelic variants of genes encoding SP-A and SP-D were shown to influence host susceptibility to TB (Floros *et al.,* 2000). The association of intronic and exonic polymorphisms in the human SP-A1 and SP-A2 genes with pulmonary TB were also found in the Indian and Ethiopian populations (Madan *et al.,* 2002; Malik *et al.,* 2006).

Dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN, CD209)

A dendritic cell-specific ICAM-3-grabbing non-integrin is a calcium dependent carbohydrate-binding molecule with the specificity for mannose-containing glycoconjugates, including those present in the mycobacterial cell wall (Ehlers *et al.,* 2010). The receptor is expressed mainly on dendritic cells, however its presence has also been observed on the surface of alveolar macrophages upon *M.tb* infection (Tailleux *et al.,* 2005). The interaction between CD209 and its ligand, impaired dendritic cell maturation, modulated cytokine secretion by phagocytes and dendritic cells, and has been postulated to cause suppression of protective immunity to TB (Ehlers *et al.,* 2010). The suppression of the pro-inflammatory immune reponse by *M.tb* binding to DC-SIGN was confirmed in the study by Vannberg et al., who demonstrated a downregulation of mRNA expression by a single nucleotide polymorphism at position — 336 in the promoter region of *DC-SIGN* (Vannberg *et al.,* 2008). Two promoter mutations (–871A/G and –336A/G) were associated with TB susceptibility in South African population, whereas in the studies from Tunisia, China and Colombia no such associations were found (Barreiro *et al.,* 2006; Gomez *et al.,* 2006; Ben-Ali *et al.,* 2007; Zheng *et al.,* 2011). The polymorphisms within the 5'- and 3'-untranslated regions of both DC-SIGN and DC-SIGNR, a homologue expressed in endothelial cells, showed possible associations with TB among Caucasian Canadians and indigenous African populations, however, greater genetic diversity was observed among Africans compared to non-Africans (Boily-Larouche *et al.,* 2007).

Mannose receptor (MR, CD206)

A mannose receptor is a type I transmembrane glycoprotein expressed on dendritic cells and macrophages. The carbohydrate recognition domain of CD206 recognizes a broad spectrum of ligands, including mycobacterial mannose-*N*-acetylglucosamine- and fucose-terminated glycoconjugates, i. e. lipoglycan and mannose-capped lipoarabinomannan (ManLAM). The phagocytosis of *M.tb* occurs via the MR, however it depends on the length and abundance of surface-exposed ManLAMs (Schäfer *et al.,* 2009]. The binding of *M.tb* or ManLAM to MR leads to the upregulation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ), which triggers anti-inflammatory immune response (Rajaram *et al.,* 2010). A study by Zhang and coworkers investigated potential associations of six single nucleotide polymorphisms (G1186A, G1195A, T1212C, C1221G, C1303T, C1323T) in exon 7 of the MRC1 gene, encoding the mannose receptor, with pulmonary TB in the Chinese population (Zhang *et al.,* 2013). The frequency of the G allele and the AA genotype for G1186A was significantly lower in pulmonary TB patients than in healthy controls, and a likage disequilibrium analysis showed a significant correlation between GGTCCT or GGTCCC haplotypes and TB susceptibility. In a previous study, the G1186A polymorphism was found to be significantly associated with another mycobacterial disease — leprosy in the Vietnamese and Brazilian populations (Alter *et al.,* 2010).

EFFECTOR PROTEINS REQUIRED FOR THE ACTIVATION OF DEFENSE RESPONSE TO MYCOBACTERIA

The mechanisms that underlie the initiation and then the maintenance of adaptive immune responses generated against *M.tb* involve many different cell types, ranging from dendritic cells, macrophages and natural killer cells (NK) to T cells, B cells and neutrophils. These cells cooperate by direct cell-cell contacts and released cytokines/chemokines and various mediators of cellular immunity (Bedford *et al.,* 2008). CD4(+) T helper cells recognise *M.tb* antigens that are presented *via* MHC (major histocompatibility complex) class II molecules on the surface of phagocytes such as dendritic cells and macrophages. CD8(+) T cells recognise mycobacterial antigens in the context of MHC class I molecules, which are loaded with antigenic peptides that originate from cytosolic antigens in infected cells. Antigen-specific T cells undergo extensive proliferation and are recruited to the lung or other sites of *M.tb* infection. Here, they attract activated monocytes and additional T cells to form a solid granuloma where the mycobacteria are contained. This process contributes to the protection against TB at early stages of infection and it is carried out to establish LTBI, which can last for years or decades, as long as *M.tb* bacteria are constrained in a solid granuloma (Kaufmann, 2013). The granuloma's organization facilitates the interactions between T and B lymphocytes, macrophages and dendritic cells which are necessary to maintain the balance between *M.tb* and the host immunity. Genetic mutations that affect proteins, which are essential to the antigen presentation processes, induction and function of cytokines/chemokines as well as their receptors, can generate the imbalance between *M.tb* and the host immunity, resulting in caseous granuloma, where *M.tb* grow unrestrictedly. The transition of a solid granuloma to caseous development is consistent with TB disease progression. The knowledge of genetic predictors of the devastating consequence of active TB versus asymptomatic chronic LTBI may lead to a novel molecular insight into the protective immunity against *M.tb* and TB pathogenesis.

CYTOKINES AND THEIR RECEPTORS

The outcome of *M.tb* infections depends on the production of various cytokines that recruit inflammatory cells to the areas of infection and coordinate the adaptive immune response. Although cytokine genes have a low frequency of genetic polymorphisms, an increasing number of studies have demonstrated mutations located on promoter regions or coding regions of the genes as host factors influencing susceptibility to TB (Mao *et al.*, 2015). Polymorphisms in these genes may modify tran-

scription factor recognition sites, affect transcriptional activation and alter the levels of cytokine production.

It is known that interferon (IFN)-γ is one of the most crucial cytokines in the control of *M.tb* infection, and therefore, polymorphisms in the IFN-γ gene may play a critical role in anti-TB immune response. It was demonstrated that IFN-γ gene-disrupted mice were not able to restrict intracellular growth of mycobacteria (Cooper *et al.,* 1993). Three single nucleotide polymorphisms in the human IFN-γ gene (A1616G, T874A, C3234T) were found to influence TB susceptibility in different ethnic populations (Cooke *et al.,* 2006). The mutation T+874A in the promoter region of the IFN-γ gene disrupts an NF-κB binding site and leads to a low production of the cytokine (Rossouw *et al.,* 2003). Individuals carrying low IFN-γ-producing genotypes had a higher risk of developing active TB (Lio *et al.,* 2002; Rossouw *et al.,* 2003). These findings were not reproduced in Gambia and the Republic of Guinea, where association with TB was noticed in two other promoter polymorphisms, A-1616G and C+3234T (Cooke *et al.,* 2006). There is also some evidence that different alleles of the gene encoding IFN-γ receptor (IFN-γR) can influence TB susceptibility (Cooke *et al.,* 2006; Fraser *et al.,* 2003). Humans with complete IFN-γ receptor deficiencies develop life threatening disseminated atypical mycobacterial infections (Casanova *et al.,* 2004). Some allelic variations in the gene encoding IFN-γR1 might change the risk of TB as a part of the multigenic predisposition to the disease. An association of TB susceptibility with polymorphisms in the IFN-γR1 gene was observed in studies from Croatia and West Africa but the relevance of these mutations to various forms of TB still remains unclear (Cooke *et al.,* 2006; Fraser *et al.,* 2003).

A tumour necrosis factor (TNF)-α is involved in strong protective immune response against *M.tb*. It acts in synergy with IFN-γ and activates macrophages allowing them to kill intracellularly replicating pathogens. Studies on mice deficient in TNF-α and its receptor (TNFR) showed a decreased resistance to TB and impaired granuloma formation (Berrington *et al.,* 2007). Several polymorphisms in both TNF-α and TNFR genes have been extensively studied. Two mutations in the promoter region of the TNF-α gene at positions –238 (G/A) and –308 (G/A) were associated with pulmonary TB in the Colombian population, however no association was observed in the studies from Turkey, India or Cambodia (Sharma *et al*., 2010; Delgado *et al.,* 2002; Correa *et al.,* 2005). The correlations between TB and polymorphism in the genes encoding TNFR1 or TNFR2 were found in Uganda, South Africa and Ghana (Stein *et al.,* 2007; Moller *et al.,* 2010).

Convincing data indicating the essential role of interleukin (IL)-12 in anti-mycobacterial immunity came from both clinical and experimental studies. IL-12 by signaling through its receptors (IL-12Rβ1 and IL-12Rβ2) stimulates IFN-γ production and promotes naive T lymphocyte differentiation into T-helper (Th) type 1 cells. Experimental studies have shown that mice with deficiencies in both IL-12 subunits (p40 and p35) were more susceptible to *M.tb* and developed severe disseminated mycobacterial infections (Cooper *et al.,* 1997). Polymorphisms of *IL-12B,* the gene encoding the IL-12p40 subunit, were reported at the promoter, intron 2, intron 4, exon 5 and 3'UTR regions (Freidin *et al.,* 2006; Morahan *et al.,* 2007; Noguchi *et al.,* 2001). Two of them, located in the promoter and intron 2, have been found to be strongly associated with pulmonary TB in the Moroccan and Chinese populations, whereas the others did not provide protection against TB (Tso *et al.,* 2004; Remus *et al.,* 2004; Selvaraj *et al.,* 2008). Three missense nonsynonymous polymorphisms (M365T, G378R, Q214R) in the IL-12Rβ1 gene have been shown to increase the susceptibility to *M.tb* in Japan, but no such association was found in studies from Morocco or Korea (Akahoshi *et al.,* 2003; Remus *et al.,* 2004; Lee *et al.,* 2005).

With anti-inflammatory properties, IL-10 is known to downregulate the production of many cytokines and suppress cell-mediated immunity against *M.tb*. Experimental studies showed that enhanced IL-10 production promoted the reactivation of latent *M.tb* infection in mice (Turner *et al.,* 2002). The influence of IL-10 on TB pathogenesis is focused on the studies of IL-10 gene promoter polymorphisms, which determine increased production of the cytokine by monocytes. Studies carried out in Cambodia, Italy and Turkey suggested that A-1082G polymorphism is correlated with increased susceptibility to TB (Delgado *et al.,* 2002; Scola *et al.,* 2003, Oral *et al.,* 2006). Another mutation in the IL-10 gene (A-592C) was identified in African and Asian populations as predisposing to TB (Shin *et al.,* 2005; Lopez-Maderuelo *et al.,* 2003).

A functional promoter polymorphism located at position -2518 of the enhancing promoter region of the macrophage chemoattractant protein (*MCP)-1* gene (the genotype GG) was shown to be associated with increased susceptibility to TB in unmatched case-control studies conducted in Mexico and Korea (Flores-Villanueva *et al.,* 2005). The increased MCP-1 production in response to *M.tb* was accompanied by TB progression in carriers of the susceptible genotype. MCP-1 is a potent chemoattractant of macrophages, that in excess downregulates the IL-12p40 production and upregulates the matrix metalloproteinase (MMP)-1 production by these cells in response to mycobacterial antigens (Ganachari *et al.,* 2010). Human MMP-1 is a collagenase, which may contribute to the liquefaction of a mature granuloma and may promote the spread of *M.tb* bacteria and non-resolving inflammation. Peruvians, whose genetic composition consists mainly of an admixture of Amerindians and Spaniards, carrying the two-locus genotype –2518 *MCP-1 GG* — 1607 *MMP-1 2G/2G* were at a significant risk of progression from LTBI to active TB. Also, it has been demonstrated that excessive MMP-1 may potentiate the MCP-1 and *M.tb*-driven inflammatory responses through the activation of the protease-activated receptor-1, and thereby increase the likelihood of developing severe pulmonary TB disease and delay the response to treatment (Ganachari *et al.,* 2012).

All these data suggest that mutations in genes encoding cytokines may be critical for TB susceptibility. It is interesting to note that the identified cytokine mutations are population-specific, associated with resistance to mycobacterial infection in some but not all studied populations. It suggests that certain polymorphisms may serve as markers of TB susceptibility only in some ethnic groups.

HLA ALLELES

The human leukocyte antigen (HLA) region has the highest level of gene polymorphism compared with other regions in the human genome. This region encodes several proteins involved in the immune response, including HLA molecules, the complement and the tumour necrosis factor (TNF)-α. The HLA complex consists of class I (HLA-A, -B, -C) and class II (HLA-DM,

-DO, -DR, -DQ, -DP) molecules, which present foreign antigens to $CD4^+$ and $CD8^+$ T lymphocytes, respectively. Several HLA alleles, particularly of class II, have been implicated in susceptibility to TB, however, the results of conducted studies have been contradictory. A recent meta-analysis by Tong et al showed that HLA-DRB1*04, *09, *10, *15, and *16 gene polymorphisms might contribute to the risk of TB, especially in East Asia (Tong *et al.,* 2015). The association of the HLA-DQB1*0503 allele with increased susceptibility to TB was noticed in Cambodia (Goldfield *et al.,* 2004). The mutation resulted in less effective production of IFN-γ by CD4+ T cells and impaired immune response against *M.tb* (Lee *et al.,* 2001). TB susceptibility was found to be also associated with other DQB1 alleles — *0301, *0303, *0401, *0402, *0503, *0601, *0602, *0603 (Goldfield *et al.,* 1998). Several studies have identified a positive correlation between TB and the DR2 allele (Kettaneh *et al.,* 2006). Case-control studies in India and Indonesia have demonstrated higher frequency of HLA-DR2 allele (DRB1*1501) in TB patients, on the contrary no association was found in Egypt, Cambodia, Hong Kong or Brazil (Bothamley *et al.,* 1989; Brahmajothi *et al.,* 1991; Goldfield *et al.,* 1998).

VITAMIN D RECEPTOR (VDR)

Vitamin D represents an important link between the activation of TLRs and antibacterial responses in innate immunity. It modulates cytokine responses by T cells through binding to the vitamin D receptor (VDR), which is present on monocytes and activated T and B lymphocytes (Salahuddin *et al.,* 2013). Lui and coworkers showed that activation of TLR1 and TLR2 on human monocytes increased the expression of the VDR and vitamin D1-hydroxylase genes, leading to the induction of cathelicidin and consequent killing of intracellular *M.tb* (Liu *et al.,* 2006). The authors showed that African-American individuals with high susceptibility to TB had low serum 25-hydroxyvitamin D levels, leading to inefficient cathelicidin mRNA expression (Liu *et al.,* 2006). Several *VDR* polymorphisms (FokI, TaqI, BsmI, ApaI) have been found to be associated with TB resistance (Uitterlinden *et al.,* 2004; Sun *et al.,* 2015). A Gambian study has demonstrated that the homozygous T/T TaqI genotype, correlated with higher circulating levels of $1,25(OH)_2D_3$, might be protective against TB (Bellamy *et al.,* 1999). In contrast, studies in Cambodia, West and South Africa found no association of any individual VDR polymorphism with TB susceptibility (Delgado *et al.,* 2002; Soborg *et al.* 2007). The heterogeneity of the results could come from several factors including different ethnic backgrounds, population admixture, different case and control definitions or too small sample sizes (Berrington *et al.,* 2007). A family-based study conducted in a West African population suggested that VDR haplotypes rather than individual alleles or genotypes might be responsible for increased susceptibility to TB (Bornman *et al.,* 2004).

SOLUTE CARRIER PROTEIN 11A1 (SLC11A1)

Solute carrier family 11A member 1 (SLC11A1), formerly known as natural resistance associated macrophage protein 1 (NRAMP1), is a human homologue of the mouse NRAMP1 molecule, which is a potent regulator of the resistance to intracellular pathogens (Yim *et al.,* 2010). It is an integral membrane protein expressed in the lysosomal compartment of macrophages. As a member of the family of metal ion transporters, SLC11A1 pumps up divalent cations (Zn^{2+}, Mn^{2+}, Fe^{2+}) across the phagosome membrane. Experimental studies indicated that SLC11A1 was involved in the activation of microbicidal responses of *M.tb* infected macrophages (Yim *et al.,* 2010). Four *SLC11A1* polymorphisms have been identified (D543N, 3'UTR, 5'(GT)n, INT4) and analyzed separately in African, Asian and European studies. The D543N polymorphism has been indicated as a TB susceptibility factor in Japan, Korea and Gambia (Bellamy *et al.,* 1998; Gao *et al.,* 2000; Ryu *et al.,* 2000). Other SLC11A1 mutations have been reported to be associated with TB among Asian and African populations but no significant association has been seen in Europe (Gao *et al.,* 2000; Ryu *et al.,* 2000; Ma *et al.,* 2002). Although the association of SLC11A1 with TB is not found in all studies, there seems to be enough evidence to suggest that some of the polymorphisms may influence TB resistance. However it is important to realize that SLC11A1 is not a single major gene determining the outcome of *M.tb* infection but accounts for only a small proportion of the total genetic contribution to TB susceptibility.

CONCLUDING REMARKS

TB is a multi-factorial disease that results from an interaction between a potent immune response and a chronically persistent pathogen. It is accepted that the spectra of innate and adaptive immune responses and environmental factors may contribute to the clinical manifestation of TB. The variations in the prevalence and incidence of the disease in individuals from different ethnic groups or families show that host genetic factors have a potential to influence the susceptibility to *M.tb* infection and progression to active TB. Despite identification of many genetic markers of *M. tuberculosis* infection, the practical utility is still doubtful. Currently, it is not possible to identify the subset of latently infected people who will develop active TB, less or more devastating. The practice in selecting well-characterized genes or candidate genes typed on the basis of the studies in mice, limits the possibility of obtaining accurate prognostic information. Presumably, a combination of gene polymorphism studies with microarray techniques and latest gas chromatography-mass spectrometry metabolomic studies can provide clinical monitoring and prognostic diagnosis of the TB disease.

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