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Mycobacterium tuberculosis, macrophages, and the innate immune response: does common variation matter?

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Summary

Despite the discovery of the tuberculosis (TB) bacillus over 100 years ago and the availability of effective drugs for over 50 years, there remain a number of formidable challenges for controlling *Mycobacterium tuberculosis* (MTb). Understanding the genetic and immunologic factors that influence human susceptibility could lead to novel insights for vaccine development as well as diagnostic advances to target treatment to those who are at risk for developing active disease. Although a series of studies over the past 50 years suggests that host genetics influences resistance to TB, a comprehensive understanding of which genes and variants are associated with susceptibility is only partially understood. In this article, we review recent advances in our understanding of human variation of the immune system and its effects on macrophage function and influence on MTb susceptibility. We emphasize recent discoveries in human genetic studies and correlate these findings with efforts to understand how these variants alter the molecular and cellular functions that regulate the macrophage response to MTb.

Keywords

innate immunity; tuberculosis; macrophage; human genetics

Introduction

Mycobacterium tuberculosis (MTb) latently infects approximately one-third of humanity and is currently only comparable to human immunodeficiency virus (HIV) as a leading infectious cause of mortality in the world. Despite the discovery of the tuberculosis (TB) bacillus over 100 years ago and the availability of effective drugs for over 50 years, there remain a number of formidable challenges for controlling MTb infection (1). These obstacles include lengthy treatment regimens of 6 to 9-month duration, drug resistance, the lack of a highly efficacious vaccine, and incomplete understanding of what controls infectivity and progression of disease. Although vaccination with *Mycobacterium bovis* bacille Calmette–Guérin (BCG) does offer some protection against MTb, its efficacy is suboptimal and not adequate for disease control (2–4). Development of a more effective vaccine is a high priority worldwide and depends on a thorough understanding of the host response to infection.

There are a number of critical questions about the host immune response to MTb that are not well understood. Although only 10% of individuals who are infected with MTb develop

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active disease, it is not known which immune responses are associated with susceptibility or resistance. In addition, it is not known why some individuals have disseminated TB that spreads to the meninges and central nervous system, while most people have localized disease in the lungs. Finally, we do not understand the wide variation in efficacy of the BCG vaccine that has been observed in many studies (2–4). The central topic of this review is to understand how common genetic variation in the innate immune response influences host susceptibility to MTb. The emphasis is twofold: first, to understand which variants have been identified through human genetic studies to be associated with TB susceptibility; and second, to understand how these polymorphisms alter the function of the encoded protein and the ensuing cellular immune response.

Of mice and men

Murine studies of TB have contributed significant advances to our understanding of the host immune response. Despite these insights, there remain important differences between mice and humans, and the relevance of murine infection studies needs to be interpreted with caution (5). Murine studies generally use high doses of MTb, often with strains that are attenuated by laboratory passage, and sometimes with artificial routes of inoculation. The mouse is usually inbred, and often only one strain is studied. Furthermore, experimental mice have a standardized age, are rarely vaccinated, and have a short life span. In addition, most mouse studies are performed on a C57Bl/6 background that models primary progressive TB rather than reactivation disease, which is the most common form of human TB. The mice develop chronic persistent TB, while 90% of humans contain their primary infection in a latent state without active symptoms. Furthermore, mouse granulomas do not caseate, a pathologic feature that is a hallmark of human granulomas. Rabbits form caseating granulomas, but studies in rabbits lack the powerful immunologic tools of the mouse (6). At the cellular level, nitric oxide killing mechanisms may differ between murine and human macrophages, although this point is controversial (7,8). All of these factors influence the interpretation of murine results and their relevance for human disease. In this review, we emphasize findings from studies of human infection, including genetic studies of the role of the innate immune response in human MTb infection.

TB risk factors

In addition to genetic risk factors, there are other host factors as well as environmental influences associated with susceptibility to TB. A recent case–control study from West Africa investigated these potential risk factors in smear-positive individuals with TB that were matched with household or community controls (687 matched pairs). In a multivariate analysis, a number of risk factors were associated with TB susceptibility including male sex [odds ratio (OR) 1.43], HIV infection (OR 2.07), smoking (past, OR 1.53; current, OR 2.03), asthma (OR 0.28), single/widowed/divorced marital state (OR 1.48–1.67), family history of TB (OR 3.24), number of adults in the household (OR 1.37 for 6–10 adults; 2.80 for >10 adults), and house ownership (OR 1.42) (9). In a household contact study in Uganda (302 index cases and 1206 household contacts), risk factors associated with active TB in contacts were HIV infection (OR 4.03), age ≤5 years (OR 6.88), BCG vaccination (OR 0.51),≥18 h contact per day with index case (OR 2.39), house type (OR 2.80 for Muzigo style, a multifamily house that often has shared rooms and limited air ventilation), and cavitary lung disease in the index patient (OR 1.97) (10). Despite evidence of these host and environmental influences, many individuals have TB without any identifiable risk factors, suggesting that host genetic variation may influence susceptibility.

Human genetics and TB susceptibility

A series of studies over the past 50 years suggest that host genetic factors influence susceptibility to TB (11,12). Although previous studies have uncovered some of the genes involved in human predisposition to mycobacterial infections, a comprehensive understanding of genetic susceptibility factors remains an elusive and important goal (11). There are four major lines of evidence to support a role for genetics in TB. First, twin studies indicate that TB rates among monozygotic twins are more than twice the rate of dizygotic twins (31.4 versus 14.9 TB cases per 100 twins for monozygotic versus dizygotic twins, $P < 0.05$, binary variable multiple regression analysis) (13). Second, several primary immunodeficiency disorders are associated with susceptibility to mycobacteria in a Mendelian fashion attributable to rare single gene mutations with high penetrance. These disorders include severe combined immunodeficiency, hyper-immunoglobulin (Ig) E syndrome, chronic granulomatous disease, anhidrotic ectodermal dysplasia with immunodeficiency, hyper-IgM syndrome, and Mendelian susceptibility to mycobacterial disease (MSMD) (11). This latter group of disorders is more selectively associated with mycobacterial infection and sometimes also with *Salmonella* but not with excessive susceptibility to other pathogens. In a series of elegant studies over the past 10 years, a number of single gene defects have been identified that center around the interleukin-12 (IL-12)/interferon-γ (IFN-γ) axis that culminates in macrophage activation by T cells and subsequent killing of organisms. The genes with identified mutations include IL-12Rβ1, IL-12p40, IFN-γR1, IFN-γR2, and signal transducer and activator of transcription-1 (STAT-1). Most of the infections associated with these Mendelian disorders have been from BCG or environmental bacteria. However, some of disorders are also associated with MTb susceptibility (IFN-γR2 and IL-12p40 among the MSMD). These disorders have been extensively reviewed elsewhere and are not the topic of the current review (11,14).

The third line of evidence for host genetics and TB susceptibility comes from the study of complex inheritance patterns, where the assumption is that genetic influence is polygenic and attributable to alleles that are common in the population with low penetrance for any single allele. Several genome-wide studies of susceptibility to TB have been performed with family-based linkage studies. These studies have identified several loci that include 2q35 in a Canadian population (15), 8q12–13 in a study from Morocco (16), 17q11.2 in Brazil (17), and 15q and Xq in populations from The Gambia and South Africa (18). Fine mapping of the 15q locus in families from Africa (The Gambia, Guinea, South Africa) suggests that Ube3a or a closely linked gene may contain the causative locus (19). Efforts to identify the genes underlying each of these associations are ongoing.

The fourth line of evidence comes from candidate gene association studies. These studies evaluate whether common polymorphisms in candidate genes are associated with susceptibility to disease. The most common study design is a case–control format with comparison of polymorphism (single nucleotide, insertions, deletions, or microsatellite markers) frequencies between cases and controls. The strength of this study design is the capacity to enroll large cohort sizes. One disadvantage is the problem of population heterogeneity or admixture, where differences in ethnic composition of the cases and controls can lead to false associations that are not attributable to differences in disease susceptibility. Methods to control for population admixture include matching cases and controls for ethnicity and adjusting for ethnicity as a possible confounder in a multivariate logistic regression model. In addition, the population can be examined for subtle evidence of admixture by genotyping a set of ‘genomic controls’, which are unlinked single nucleotide polymorphisms (SNPs) that are chosen for their variation across ethnicities. This approach has recently been used for several case–control studies of TB (20,21). An alternative study design that is not vulnerable to population admixture is the transmission disequilibrium test

(TDT). This strategy is family based and looks for evidence of non-random transmission of the candidate allele from a heterozygous parent to an affected child. In addition to the problem of population admixture, candidate gene association studies are vulnerable to false-positive results from multiple comparisons. This is a particularly poignant problem in the current era of high throughput genotyping strategies. In light of this, replication and validation of findings with independent cohorts is an essential part of a careful study design. In addition to genetic evidence of association of a particular allele with susceptibility, the candidate gene approach can be linked to functional studies of the polymorphisms to determine whether there is biologic plausibility and mechanistic insight into disease pathogenesis.

Advances in genomic technology and immunology have accelerated the number of candidate gene association studies in infectious diseases. Table 1 summarizes the genes and variants that have been examined, whether there have been replication studies, and whether a functional defect is associated with the polymorphism. This review prioritizes discussion of the innate immune genes that have been most thoroughly examined with consistent and validated genetic findings and/or associated with well-defined functional defects. Studies of the human leukocyte antigen (HLA) locus are not discussed because they have been reviewed elsewhere (12,22,23). Together, these studies are providing insight into human susceptibility to TB and the underlying mechanisms of pathogenesis from genetically regulated variation of macrophage function and the innate immune response.

Initial detection of MTb

A number of receptors are critical for MTb detection by phagocytes, including the complement receptors, the mannose receptor (MR), dendritic cell-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing non-integrin (DC-SIGN) (CD209), surfactant protein A (Sp-A) receptor, the class A scavenger receptor, mannose-binding lectin (MBL), and possibly also dectin-1 (24–26). In human macrophages, the primary receptors for MTb are the MR and complement receptor 3 (CR3) (27,28)(Fig. 1). In contrast, human dendritic cells primarily use DC-SIGN with no significant role for CR3 or MR (29). Dectin-1 is a C-type lectin that recognizes β-glucans and has previously been shown to cooperate with Toll-like receptor 2 (TLR2) to recognize fungi (30–32). A recent study suggests that dectin-1 cooperates with TLR2 to recognize MTb and other mycobacteria (33). The significance of these findings is unclear at present because mycobacteria are not known to contain β-glucans. Among these receptors, studies of polymorphisms and TB susceptibility in MBL, surfactant protein, and DC-SIGN have been undertaken and are discussed in more detail.

Mannose-binding lectin

MBL is an innate immune molecule that recognizes microbial surface carbohydrates and regulates opsonization, phagocytosis, and activation of the complement pathway (34). MBL is a 32-kDa protein with a collagen-like domain as well as a carbohydrate recognition domain (CRD) that binds to high mannose and *N*-acetylglucosamine oligosaccharides present on a range of pathogens, including MTb (35,36). MBL activates the complement pathway in an antibody-independent manner in conjunction with the MBL-associated serine protease and leads to phagocytosis through the complement receptors or collectin receptor (37).

Common variant alleles of MBL exist and have been characterized with numerous functional and human genetic studies. Three polymorphisms are correlated with low levels of functional MBL. The wildtype allele is referred to as allele A, and the variant alleles are in codons 54 (allele B), 57 (allele C), and 52 (allele D). These variants disrupt the collagen domain and lower the levels of functional protein by 5 to 10-fold in heterozygotes and to

nearly undetectable levels in homozygotes. There are also promoter region variants that influence MBL levels, including a variant G-221C, that is termed allele Y or X. In general, MBL deficiency leads to increased susceptibility to various infections. A small number of studies have examined whether MBL deficiency is associated with susceptibility to TB. The results have ranged from showing that MBL deficiency is associated with an increased risk [Indian cohort, frequency in controls (n = 109) 0.018 versus cases (n = 202) 0.109, OR 6.5, P = 0.008] (38), a decreased risk in South Africa [frequency in controls (n = 79) 0.278 versus cases (n = 155) 0.109, P = 0.001] (39) and Tanzania (36), mixed results in Denmark (depending on level of deficiency) (40), and a mild protective effect of the codon 57 mutation, but not other alleles, in The Gambia [allele frequency in controls (n = 794) 0.33 versus cases (n = 844) 0.28, P = 0.037]. The heterogeneity of these results could be attributable to several factors, including population admixture, incomplete genotyping (most of the studies did not genotype the promoter alleles), different clinical phenotypes, and variable allele penetrance in different ethnic backgrounds. Overall, the current data do not support a consistent or major effect from MBL deficiency on susceptibility to TB.

Dendritic cell-specific ICAM-3-grabbing non-integrin

DC-SIGN is a C-type lectin that recognizes a number of microbes, including HIV and MTb. MTb ligands for DC-SIGN include lipoarabinomannan (LAM), lipomannan, arabinomannan, and the 19-kDa antigen (29,41,42). Initial studies indicated that DC-SIGN was primarily a receptor on dendritic cells rather than macrophages. However, a more recent study showed that DC-SIGN expression is induced on alveolar macrophages and was found on macrophages from bronchoalveolar lavage fluid from TB patients but not from healthy adults, asthmatic patients, or sarcoid patients (43). These results present a model whereby infection of alveolar macrophages from naive hosts occurs through the complement and MRs. Then, further spread of infection may occur through DC-SIGN-expressing alveolar macrophages.

Genetic studies of human DC-SIGN in South Africa have identified two promoter variants, −871G and −336A, that are associated with TB susceptibility [SNP A-336G, AG/AA genotype frequency in cases (n = 351) 0.293 versus controls (n = 360) 0.381, P < 0.001; SNP A-871G, AG/GG genotype frequency in cases (n = 351) 0.168 versus controls (n = 360) 0.272, P = 0.01] (20). The study design used genomic controls to adjust for population admixture. The −336 SNP has also been found to be associated with Dengue fever and alters transcriptional activity at an Sp1-binding site, where the SNP resides (44). Several other polymorphisms were not associated with TB susceptibility, including variants that regulate the length of the neck region that separates the CRD from the transmembrane domain (45). In a study from Colombia, there was no association of the −336 SNP with TB susceptibility (46). Together, these results suggest a possible role for DC-SIGN variation and susceptibility to human TB, although the magnitude of the effect is small and has not been validated in a second TB population.

Surfactant proteins

Pulmonary surfactant is a complex structure with lipids and proteins that reduces surface tension of alveoli and promotes lung expansion (25). There are four surfactant proteins that are C-type lectins and members of the collectin family. Similar to MBL, collectins form multimeric structures with a collagenous N-terminal domain and a carbohydrate C-terminal domain. These proteins bind to pathogens, mediate uptake into phagocytes, and modulate effector mechanisms such as oxidant production, lung inflammation, and bacterial killing (47). Of the four surfactant proteins (Sp-A, Sp-B, Sp-C, Sp-D), two have been shown to modulate host interactions with MTb. Sp-A increases phagocytosis of MTb, probably through a direct action on the macrophage as well as through opsonic activity (48). SP-D

binds to MTb and appears to reduce phagocytosis, possibly through a LAM–mannose interaction (49). In a study from Mexico, several variants of Sp-A and Sp-D were associated with susceptibility to TB (50). These results have not been verified in an independent cohort, and the functional significance of the variants has not been reported.

TLR pathway

TLRs and *in vitro* recognition of MTb

TLRs constitute a family of transmembrane proteins that are known as pattern recognition receptors for their detection of microbial ligands and subsequent initiation of inflammatory signaling pathways (51–54). The bacterial molecules that are recognized by TLRs include lipopeptides by TLR2 (as a heterodimer with TLR1 or TLR6), lipopolysaccharide by TLR4, flagellin by TLR5, and bacterial CpG DNA by TLR9. Several *in vitro* and *in vivo* studies suggest that TLRs are critical regulators of the immune response to TB. *In vitro* studies indicate that TB is recognized by several TLRs, including TLR2/1/6, TLR9, and possibly also TLR4 (55,56). Initial studies documented a central role for TLR2 in TB recognition by macrophages (57–59). The mycobacterial cell wall contains a number of proinflammatory TLR2 ligands, including lipoproteins, mycolylarabinogalactan–peptidoglycan complex (the cell wall core structure), lipids, and LAM (57–61). LAM contains a mannose-rich core carbohydrate with highly branched arabinofuranosyl side chains, which are linked to acyl groups. LAM from MTb has mannose-capped ends and is non-stimulatory (Man-LAM). In contrast, rapidly growing mycobacterial species lack mannose end capping (ara-LAM) and are strong inducers of cytokine production. ara-LAM but not Man-LAM has been shown to be a TLR2 ligand (58,59).

TLR2 works as a heterodimer with TLR1 or TLR6 in a complex with CD36 to recognize lipopeptides with different structures. TLR1 exhibits preferential recognition of triacylated lipopeptides, while TLR6 is activated by diacylated structures. The stimulatory activity is also affected by the terminal peptide composition, chirality of the diacylglycerol carbon, and the fatty acid composition (62–67). The 19-kDa lipoprotein of MTb is recognized by TLR1 (68). In addition, *Mycobacterium leprae* is recognized by TLR1 with an additional contribution by TLR6 (69). One study suggests that an extract of MTb (called soluble TB factor) is recognized by TLR6 (70). Together, these results suggest that both TLR1 and TLR6 cooperate with TLR2 to recognize mycobacteria.

Recent data indicate that TLR9 cooperates with TLR2 to recognize MTb in macrophages as well as splenic dendritic cells. When murine *Tlr9*$^{-/-}$ splenic dendritic cells were stimulated with live MTb, there was a partial reduction in IL-12p40. However, in *Tlr2/9*$^{-/-}$ cells, there was further inhibition of cytokine to background levels, suggesting that the majority of TLR-mediated mycobacterial signaling is through these two receptors (along with the heterodimerization with TLR1 or 6). Finally, there is one report of TLR4-mediated signaling in response to stimulation with a heat-labile cell-associated factor from viable mycobacteria (58). The identity of this ligand remains unknown and is predicted to be a non-canonical TLR4 ligand because mycobacteria do not contain endotoxin. There is also a substantial degree of macrophage activation by MTb that is myeloid differentiation factor 88 (MyD88) and TLR independent (71,72).

TLRs and *in vivo* recognition of MTb

Although TLRs and the innate immune system are essential for defending the host against microbes, the degree of redundancy and specificity manifested *in vivo* among different TLR family members is only partially understood. Despite the overwhelming evidence showing a critical role for TLR mediation of MTb recognition *in vitro*, the *in vivo* significance of individual TLRs has been more difficult to show consistently. Three different studies have

shown that MyD88 regulates a protective immune response to MTb in mice. In all three studies, *Myd88*$^{-/-}$ mice had increased numbers of bacteria in the lung in comparison with wildtype controls (100 to 1000-fold) (73–75). There were also important differences in these studies. One study, which used the Kurono strain, found no major differences in survival or lung histopathology (75). In contrast, the other two studies, which both used the H37Rv strain, showed increased mortality and lung pathology in the *Myd88*$^{-/-}$ strains (73,74). The explanation for these differences is not currently known, although one possibility is the strain of MTb that was used. A critical role for individual TLRs during murine MTb or BCG infection has been more difficult to show consistently. Although some studies have shown a critical role for TLR2, others have not (76–79). In one study, increased susceptibility was only observed in high-dose infections (78). The preponderance of evidence suggests no significant *in vivo* role for TLR4 in mediating protective immunity to murine MTb (77,78,80), although there is one study that did find a difference (81). *Tlr9*$^{-/-}$ mice have increased mortality and increased lung bacterial burdens compared with wildtype mice, effects that were magnified in *Tlr2/9*$^{-/-}$ mice (82). Interestingly, TLR9 but not TLR2 was found to control production of IFN-γ from CD4^{+} T cells in infected mice. Together, these *in vivo* studies suggest an important though not absolute role for the TLR pathway in mediating host protection to murine MTb infection. Furthermore, the effects appear to be strongest when multiple TLRs are impaired.

Human genetics, TLRs, and MTb

Human genetic studies of TLR pathway variants indicate that there are several common variants that may influence disease susceptibility. A polymorphism in TLR2 in the Toll-IL-1 receptor (TIR) domain (G2258A), which changes an arginine to glutamine (R753Q), was originally described in 2000 and later found to influence signaling to diacylated and triacylated lipopeptides as measured by nuclear factor kappa B (NF-κB) luciferase assays (83,84). Furthermore, in human whole-blood studies, there was a slight decrease in cytokine production to stimulation with *Borrelia burgdorferi* lysates in heterozygous individuals (753RQ) as compared with homozygous individuals (753RR). Heterozygosity was associated with protection from Lyme disease with a modest OR and marginal statistical significance (84). In a small study from Turkey (129 TB cases, 116 controls), the homozygous (753QQ) and heterozygous (753RQ) genotypes were associated with an increased risk of TB (753QQ: OR 6.4, $P = 0.022$; 753QR: OR 1.60, $P = 0.019$) (85). Although the statistical significance was marginal and this association has not yet been replicated, the findings are suggestive of a real and possible causal association, in light of the functional defect associated with this SNP. A second polymorphism in the TLR2 TIR domain (C2029T, R677W) was described originally in the context of an association with susceptibility to lepromatous leprosy (86). This SNP was later found to be an artifact that resulted from a variant in a duplicated region of TLR2 that is present several kilobases upstream of the true gene (87). In a study from Korea (176 TB cases original cohort, 82 TB cases validation cohort, 191 controls), a microsatellite GT dinucleotide repeat polymorphism in intron II was found to be associated with TB. Shorter GT repeats were associated with increased susceptibility to TB (OR 1.6–2.0, $P = 0.009$–0.02) as well as slightly altered TLR2 promoter activity measured in a luciferase assay (88,89). We recently found a synonymous polymorphism (T597C, N199N) that was associated with susceptibility to TB meningitis in Vietnam [183 pulmonary TB, 175 TB meningitis, 392 controls; 597C allele frequency of 0.252 in controls versus 0.330 in cases (OR 1.47, $P = 0.007$); 597CC genotype frequency 0.048 in controls versus 0.14 in TBM cases (OR 3.26, $P = 0.0002$)] (T.T. Nguyen, T.R. Hawn, S.J. Dunstan, A. Aderem, unpublished observations). We also recently found that this SNP is associated with reversal reaction in leprosy (P.Y. Bochud, T.R. Hawn, G. Kaplan, A. Aderem, unpublished observations). There are no known functional defects associated with this polymorphism.

Recent studies of the adapter protein, TIR domain containing adapter protein/Myd88-adapter like (TIRAP/MAL) suggest an association with susceptibility to TB. TIRAP has two isoforms (221 and 235 amino acids), and both have a C-terminal TIR domain that mediates signals from TLR2 and TLR4. A polymorphism was recently described that changes a serine to a leucine at amino acid 180 (S180L, C539T) and impairs TLR2-mediated NF-κB signaling in reconstitution experiments (90). In addition, the 180L variant was less able to bind TLR2 in comparison with the 180S variant. The heterozygous state is associated with protection from several diseases, including malaria, invasive pneumococcal disease, bacteremia, and one study of TB from Guinea-Bissau. In the latter study (675 cases, 605 controls), the heterozygous frequency was 0.6% in cases versus 2.0% in controls (OR 0.23, $P = 0.041$). This association was confirmed in a family-based study with a TDT. Although the protective effect of this SNP for TB was marginal and the polymorphism was of low frequency in this population, this SNP appears to be important with its functional defect and number of replicated studies.

We recently examined TIRAP variants in a study from Vietnam (91) that included studies of overall susceptibility to TB as well as susceptibility to TB meningitis. Although we did not find an association of S180L with susceptibility to TB, the frequency of this SNP was too low for a proper statistical evaluation (2.3% in cases versus 1.7% in controls, $P = 0.61$). We did find that a synonymous SNP (C558T, A186A) was associated with increased susceptibility to TB with a 558T allele frequency of 0.035 in controls versus 0.074 in cases (OR 2.25, $P < 0.001$). Subgroup analysis showed that SNP 558T was more strongly associated with susceptibility to meningeal TB (OR 3.02, $P < 0.001$) than pulmonary TB (OR of 1.55, $P = 0.22$). In comparison with the 558CC genotype, the 558TT genotype was associated with decreased whole-blood IL-6 production, which suggested that TIRAP influences disease susceptibility by modulating the inflammatory response. We do not currently understand how this SNP alters cytokine protection, but possibilities include that it is in linkage disequilibrium with a coding region SNP or one that alters expression levels. These results suggest that the TLR pathway influences susceptibility to meningeal and pulmonary TB by different immune mechanisms.

Cytoplasmic sensors: NOD2 and NLRP12

The human nucleotide oligomerization domain (NOD)-like receptor (NLR) or NACHT [domain present in NAIP (neuronal apoptosis inhibitor protein), CIITA (class II transactivator), HET-E (plant het product involved in vegetative incompatibility) and TP-1 (telomerase-associated protein 1)-LRR (leucine-rich repeat)] family contains over 20 proteins. NLRs are cytoplasmic proteins that contain a leucine-rich region at the C-terminus and a central nucleotide-binding (NOD) domain (92–94). The N-terminus contains a protein interaction domain and varies within different family members. N-terminal motifs include caspase activation and recruitment domain (CARD), pyrin, or baculovirus inhibitor of apoptosis repeat domains. Two of these proteins have been shown to have effects when signaling with mycobacterial products: NOD2 and NLR family, pyrin domain containing 12 (NLRP12).

NOD2

NOD2 [also known as CARD15 (caspase recruitment domain family, member 15) or NLR family, CARD domain-containing 2)] contains a leucine-rich region, a central NACHT nucleotide-binding domain, and two CARD domains. Frameshift mutations in the N-terminal leucine-rich region have been associated with Crohn's disease in adults (95). Controversy exists as to whether Crohn's disease has an environmental or infectious trigger. Crohn's disease itself resembles a chronic intestinal granulomatous infection seen in animals called Johne's disease, which appears to be caused by *Mycobacteria avium* spp.

paratuberculosis (96). Rare missense mutations in the NACHT domain of the CARD12 protein have also been linked to Blau's syndrome, which is an uncommon autosomal dominant granulomatous arthritis with uveitis seen in children (97). NOD2 detects intracellular muramyl dipeptide, a component of the peptidoglycan molecule that is found on mycobacteria and Gram-positive bacteria (98). After stimulation, NOD2 mediates production of α-4 defensins or cryptdins, which have bactericidal activity against mycobacteria and may play a role in host immune defense to MTb infection (99). Despite support that NOD2 plays a non-redundant role in the recognition of MTb (100), there is no evidence that variation in NOD2 plays a role in susceptibility to human mycobacterial disease. Two studies, one in The Gambia and the other in South Africa, have failed to link known Crohn's disease mutations with MTb susceptibility, but the frequency of the mutations in both studies were rather low in the study populations (no homozygous patients were noted) (101,102). Furthermore, no differences were seen in the Gambian cohort when they examined a number of promoter region SNPs. Although studies to date suggest that there is no correlation with human SNPs and susceptibility to TB, further analysis needs to be carried out before definitive conclusions can be made.

NLRP12

NLRP12 (also known as NALP12, Monarch-1, or PYPAF7) is an NLR that mediates inflammatory responses to MTb *in vitro*. NLRP12 regulates expression of major histocompatibility complex class I genes and is thought to inhibit proinflammatory cytokine production to a number of stimuli, including MTb, by interacting with IL-1 receptor-associated kinase-2 (103,104). Although it has been shown that NLRP12 can impair the immune response in cells stimulated with heat-killed MTb, there are no studies of the role of genetic variation in NLRP12 and susceptibility to MTb.

Other receptors: P2X7

The purinergic P2X7 receptor is highly expressed on macrophages and mediates adenosine triphosphate (ATP)-induced killing of mycobacteria. Stimulation of P2X7 causes opening of a divalent cation channel, influx of calcium, induction of caspases, and eventual apoptosis. Phospholipase D is activated, which promotes phagolysosomal fusion and killing of mycobacteria. Several polymorphisms exist in P2X7, including those in the promoter region, an ATP-binding domain, a trafficking domain, and an ankyrin-like repeat domain (A1513C, E496A). Studies of several of the coding region polymorphisms have shown functional defects with decreased ATP-induced uptake of ethidium as well as ATP-induced apoptosis (105,106). Two case–control studies have found associations of P2X7 SNPs with TB susceptibility. A promoter region polymorphism (−762) with unknown functional significance was associated with pulmonary TB in The Gambia (allele frequency 0.254 in cases versus 0.329 in controls, OR 0.70, $P = 0.003$) (107). A recent study of the A1513C SNP showed an association with extrapulmonary TB but not pulmonary TB in Sydney, Australia (OR approximately 3.1–4.0 for extrapulmonary TB, $P < 0.01$) (108). One strength of this study is replication of the findings in two separate cohorts. Possible weaknesses include the small sample size and the level of population heterogeneity with subjects from a number of different countries. The A1513C polymorphism is also associated with impaired killing of MTb and BCG in ATP-stimulated macrophages (108,109). This is the only SNP that is currently known to be associated with impaired effector function that alters the ability of the macrophage to kill MTb.

Cytokines, chemokines, and effector molecules

Innate immune recognition of MTb by phagocytic cells leads to cellular activation and rapid production of pro- and anti-inflammatory cytokines (Fig. 2). These cytokines and

chemokines recruit inflammatory cells [T cells, neutrophils, and natural killer (NK) cells] to areas of infection, activate transmigrated cells, and coordinate the inflammatory and adaptive immune response to MTb. Successful outcome of mycobacterial infections depends upon cytokine networks established and maintained by macrophages. We review cytokines and chemokines important for the host to control MTb and then discuss genetic variations seen in these molecules that lead to enhanced susceptibility to active disease.

Tumor necrosis factor-α

Tumor necrosis factor-α (TNF-α) is a prototypic proinflammatory cytokine that is produced by monocytes and macrophages when exposed to microbial products derived from MTb. TNF-α is produced as a trimeric surface molecule and is then cleaved by TNF-α-converting enzyme to release the trimeric molecule from the cell. In synergy with IFN-γ, TNF-α activates macrophages to produce nitric oxide synthase 2 (NOS2), allowing the macrophage to kill intracellularly replicating MTb (110,111). Mice deficient in TNF-α and TNF-α receptor (TNFR) show increased susceptibility to MTb and impaired granuloma formation following infection with MTb (112,113). Expression of TNF-α, which is unable to be cleaved from the cells, restores partial protection to mycobacterial infections and allows for normal granuloma formation (114). In humans, there is evidence that TNF-α plays an important role in host defense to MTb because patients receiving TNF-α inhibitors are more susceptible to TB (115). In humans, genetic control of TNF-α expression ma2y be associated with the development of TB, as suggested by work from Uganda, which showed that in MTb, smear-positive patients and their household contacts, TNF-α production from MTb-stimulated whole-blood assays had significant heritability (116). Variation in both the TNF-α gene and TNFR were associated in linkage and association studies with *in vitro* TNF-α production as well as the development of active TB disease (117). Further support that TNF-α plays a critical role in controlling human disease comes from increased rates of reactivation disease seen in patients receiving TNF-α inhibitors (115). There is also evidence that polymorphisms in the TNF-α reporter gene at the −308 position are associated with increased susceptibility to lepromatous leprosy (118), as well as other diseases such as malaria and septic shock (119,120). However, the evidence for association of these polymorphisms with TB has been less consistent. The main polymorphisms that have been identified are found in the promoter region at −238 and −308. In a Colombian study, both the −238G (OR 1.8, $P = 0.02$) and −308G (OR 2.2, $P < 0.0001$) polymorphisms were associated with pulmonary TB. Interestingly, these polymorphisms were also associated with protection against autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome (121). An association with increased TB susceptibility was also seen in an Iranian cohort for −238GG homozygous but not for −238AG heterozygous carriers (122). Lack of association with pulmonary TB with either the −238 or −308 polymorphisms has also been documented in Turkish, Chinese, and Thai populations (123–125). In Chinese miners, an association for TB acquisition was identified in the −308GG persons only if a concurrent solute carrier family 11 member a1 (Slc11a1) [natural-resistance-associated macrophage protein (NRAMP)] mutation was noticed (OR 2.38, 95% CI 1.14–4.98). Functional studies of the SNP −308 have shown mixed results regarding its association with altered TNF-α levels (126,127). Although the majority of evidence suggests that the TNFα promoter polymorphisms are not consistently associated with TB susceptibility, many of the studies have been insufficient in size to show minor differences. Further studies are needed before these common polymorphisms can be discredited.

Interleukin-1β

IL-1β is a proinflammatory cytokine that is produced by a myriad of infections and proinflammatory conditions (128). IL-1β is produced in the cell in an inactive precursor

form (pro-IL-1β) and then is cleaved by Caspase-1 to an active form, which is secreted from the cell through an unknown mechanism. Conversion of pro-IL-1β to IL-1β can occur with numerous bacterial stimuli, including MTb, and can also occur when bacterial products are sensed within the cytoplasm by NLR proteins (i.e. NOD2), which contain a CARD domain important for Caspase-1 activation and inflammasome function. Once secreted, IL-1β acts primarily through IL-1R type I receptor, which further activates the expression of other proinflammatory cytokines. In some cases, however, IL-1β function is blocked by either binding to a membrane-bound decoy receptor (IL-1R type II) or by a soluble receptor antagonist (IL-1RA) that blocks the proinflammatory effects of IL-1β. Evidence that IL-1β plays an important role in the pathogenesis of MTb comes from knockout animal studies. Animals that have both IL-1β and IL-1α deleted form larger granulomas after infection and are unable to clear the mycobacteria as efficiently as wildtype mice (129). Furthermore, animals that lack the IL-1R type I have impaired survival and are unable to contain growth of the organism *in vivo* (130). This response may be because of impaired cell-mediated immunity, as measured by IFN-γ production. There is also evidence that susceptibility to clinical disease in an African cohort with MTb is associated with IL-1 gene cluster, specifically variation in the IL-1RA gene (131). In this study, other polymorphisms in the IL-1β and IL-1α gene did not show significant difference in TB susceptibility. Polymorphisms in non-coding regions of IL-1β have been linked to human variation in cytokine production and a −511 C allele in the promoter region of the gene is associated with protection from acquiring pulmonary TB (OR 0.63, 95% CI 0.44–0.90, $P = 0.029$) (132). Furthermore, studies carried out on emigrated Indians in London showed a relationship between polymorphisms in both IL-1β and IL-1RA and the functional ratio of expression and the acquisition of tuberculous pleurisy ($P = 0.028$), although multiple polymorphisms in either IL-1β or IL-1RA gene when analyzed individually were not associated with differences in TB resistance (123). Whether variation in genes of the IL-1 cluster confer risk to TB clinical disease continues to be preliminary, and further studies are needed before substantial conclusions can be made.

Interleukin-10

IL-10 is a cytokine produced by alternatively activated macrophages, dendritic cells, B cells, and regulatory T-cell subsets, and IL-10 is known to suppress proinflammatory cytokine response by the innate immune and adaptive immune systems. IL-10 is also thought to play an important regulatory role in many bacterial and viral infections (124). Studies carried out on mice have identified that IL-10 may not be important for susceptibility to initial infection with MTb but may play a role in reactivation of latent disease (125,133). The contribution of IL-10 to the pathogenesis of mycobacterial disease in humans has focused on identification of polymorphisms in the promoter region, which are associated with increased production of IL-10 by monocytic cells in blood and enhanced susceptibility to MTb in certain populations (134). Evidence suggests that these polymorphisms are associated with disease severity in leprosy (135,136). There is discrepant data regarding the effect of these polymorphisms on human TB susceptibility. Some have identified that those with the A-1082G have significant predisposition to TB in Sicilian and Cambodian patients and significant predisposition of the A-592C SNP in a Korean population, but the first two associations have been questioned because the control population were not in Hardy–Weinberg equilibrium (137–139). Others have shown no association with variation from these promoter SNPs in Spanish and African populations (131,140). In the Ugandan study mentioned previously, there was also evidence of an association of a set of tagged haplotype IL-10 SNPs (that included the A-592C SNP) with acquisition of active disease from MTb (117). Some studies suggest that A-592C is associated with altered levels of IL-10 (141,142) and impaired Sp-1 enhancer binding (139). The A-1082G variation has also been associated with altered levels of IL-10 (134). Whether

IL-10 promoter polymorphisms play a role in susceptibility to TB continues to be controversial.

IL-12/IL-12Rβ1

IL-12 is a heterodimeric, covalently linked cytokine comprised of two subunits (p40 and p35). The p40 subunit is present in both IL-12 and IL-23, while the p35 subunit is specific for IL-12. IL-12 is mainly secreted by hematopoietic phagocytic cells (monocytes, macrophages, and neutrophils) and dendritic cells, and promotes T-cell differentiation into T-helper 1 (Th1) cells and production of IFN-γ by signaling through IL-12Rβ1 and IL-12Rβ2 (143). IL-12 plays an important role in stimulating IFN-γ production and establishing a potent Th1 response to intracellular pathogens such as MTb and *Salmonella*. Early studies showed that mice, when given exogenous IL-12, had increased resistance to MTb (144). Furthermore, mice deficient in IL-12p40 and IL-12p35 show enhanced susceptibility to MTb infection (145). The role of IL-12 in mycobacterial disease has been firmly established by the presence of patients with uncommon polymorphisms or mutations that predispose to severe disseminated mycobacterial infection in a Mendelian fashion (11). In addition to these Mendelian phenotypes, there is conflicting evidence that common variations in the IL-12Rβ1 gene confer susceptibility to MTb. In a Japanese cohort, there has been shown an increase in susceptibility [OR 2.45 (1.20–4.99), $P = 0.013$] to MTb when three missense non-synonymous polymorphisms (M365T, G378R, and Q214R) are present (146). These identical missense polymorphisms were present in a Moroccan cohort at high frequency, but no susceptibility was associated with these SNPs (147). The authors did identify additional non-coding region SNPs that were associated with increased susceptibility to TB acquisition. Lack of association with clinical TB was seen in a Korean population with these Q214R, G378R, and M365T polymorphisms (148). Studies suggesting an association of IL-12Rβ1 polymorphisms with impaired signaling are mixed. Some have shown impaired signaling through a STAT-4 pathway (146), while others have shown no effect on IFN-γ production (147). Because of the inconsistencies in the above data, the role of common polymorphisms of IL-12Rβ1 in TB susceptibility remains incompletely understood.

Similar discrepancies have been seen among various populations when attempting to identify clinically relevant variation in IL-12B, the gene encoding IL-12p40. In a Hong Kong patient population of 1030 people, four non-coding region polymorphisms were identified, and two haplotypes showed significant differences between those affected with disease versus healthy controls (149). The 3′ non-coding region SNP identified in this cohort has been associated with insulin-dependant diabetes as well as decreased production of IL-12 mRNA transcript and protein levels but not with TB in an African American cohort from Houston (150–153). All of this evidence points to an important role for IL-12 in the pathogenesis of TB. However, functional correlates are still being analyzed, and the overall consistency of the genetic data is still being resolved.

IFN-γ/IFN-γR

IFN-γ, the prototypic cytokine of the Th1 cell response, is a cytokine essential for the effective control of MTb in the host. IFN-γ is made of $CD4^+$ T cells, $CD8^+$ T cells, and NK cells, and it stimulates a mycobactericidal response in macrophages characterized by the induction of NOS (154,155). Mice that fail to produce IFN-γ have disseminated mycobacterial infection whether challenged by aerosolized route or intravenously (156,157). Furthermore, increased resistance to MTb by mice given IL-12 intravenously was abrogated when repeated in IFN-γ gene-disrupted mice (158). In humans, a series of uncommon genetic mutations in IFN-γR1 and R2 lead to MSMD in humans and have been extensively reviewed elsewhere (11,159). There have been inconsistent findings using IFN-γR1

microsatellite markers and association studies with TB susceptibility. Only one small study reported a significant change in frequency in occurrence of a microsatellite marker, but this change was at low frequency and marginally significant ($P = 0.02$) (160). This finding was not replicated in a Gambian population (161). In a separate study from The Gambia, a T-56C polymorphism was marginally associated with susceptibility to TB (CC genotype: OR 0.75, $P = 0.02$) (162). A recent study in Uganda replicated this association of SNP T-56C with active TB as well as *in vitro* TNF-α production (see above) (117). Studies looking at IFN-γR2 have not shown any associations (162).

Studies of IFN-γ suggest that common polymorphisms in the IFN-γ gene play a role in TB susceptibility. There have been three polymorphisms in the IFN-γ gene that have been studied in various populations (A-1616G, T+874A, C+3234T) (160,162–165). Variation in the promoter region of the IFN-γ gene disrupts an NF-κB binding site (T+874A) and is associated with an increased frequency of MTb in a study comparing 314 South Africans with pulmonary and meningeal TB versus 235 healthy controls (T allele, OR 1.64, 95% CI 1.16–2.30, $P = 0.0055$) (164). Susceptibility was confirmed in a Sicilian study, where there was a significantly lower frequency of +874TT in cases versus controls (163). Furthermore, a Spanish study also confirmed that the +874AA allele was associated with TB susceptibility and significantly decreased levels of IFN-γ in peripheral blood monocytic cells stimulated with TB antigens (140). These findings, however, were not repeated in another West African population from Guinea-Bissau, The Gambia, and Republic of Guinea for the T+874A variation, but significance was seen in two other promoter polymorphisms located in the IFN-γ gene A-1616G (OR 1.49 95% CI 1.11–2.00; $P = 0.008$) and C+3234T (OR 1.40, 95% CI 1.09–1.80, $P = 0.009$) (162). The T874A polymorphism was also not associated with susceptibility in a small south Indian study (165). Overall, the evidence that IFN-γ promoter variation is significantly associated with susceptibility to develop active TB disease is strong, while evidence that IFN-γR1 common variation is less convincing.

Chemokines: CCL2 and IL-8

CCL2, also called monocyte chemoattractant protein 1, is a β chemokine that is induced by monocytes infected with MTb (166). CCL2 causes chemotaxis of memory T lymphocytes, NK cells, and macrophages to sites of inflammation. In animal models, there is evidence that CCL2 may modulate disease severity. Mice that overexpress CCL2 showed high levels of CCL2 in all tissues, and these animals were susceptible to intracellular pathogens (167). Mice with targeted gene deletion of CCL2 failed to show increased susceptibility to MTb (168). CCL2 may act in mice to cause decreased IL-12p40 production and skew the T-cell response away from a Th1 response (169). In humans, variation in the promoter region of CCL2 causes significant changes in chemokine expression to IL-1β (170). Furthermore, genetic analysis in Brazilian patients has indicated that susceptibility to intracellular pathogens (*Leishmania*, MTb) are linked to 17q11–12 chromosome, which contains the CCL2 protein, along with many other chemokines and NOS2A (17). These authors, however, failed to show significant association of CCL2 promoter polymorphisms and increased TB susceptibility. In contrast, another study with both Mexican and Korean cohorts found increased susceptibility to TB in those with the A-2518G CCL2 promoter polymorphism [Mexican: OR 5.4, 95% CI 3.4–8.6, $P = 0.00001$; Korean: OR 2.63, 95% CI 1.9–3.7, $P = 0.0001$] (21). Patients with the affected GG genotype have increased amounts of CCL2 in their plasma and lower amounts of IL-12, and they make less CCL2 when their monocytes are stimulated with MTb antigens. These findings agree with the mouse studies and are consistent with the thought that elevated levels of CCL2 may favor Th2 cytokine response and decreased IL-12 production.

Another chemokine produced by phagocytic cells and tissue cells after simulation with MTb or its products is IL-8 (171–173). Increased levels of IL-8 are seen in the bronchoalveolar lavage fluid of humans with TB infection, and proportionately higher levels of IL-8 may be associated with increased mortality (174,175). A polymorphism in the promoter region of IL-8, T-251A, is seen in high frequency in both Caucasian and African American populations. This polymorphism not only is associated with enhanced severity to bronchiolitis in infants with respiratory syncytial virus (176) but is also significantly more prevalent in two separate Caucasian and African American populations from Houston with MTb infection (177). Both A allele homozygotes and heterozygotes showed a higher frequency of MTb in these two populations [Caucasian: TA allele, OR 2.01 95% CI 1.06–3.80, $P = 0.07$, AA allele, OR 3.41 95% CI 1.52–7.64, $P < 0.01$; African American TA allele, OR 3.39, 95% CI 1.40–8.25, $P < 0.01$, AA allele, OR 3.46, 95% CI 1.48–8.08, $P < 0.01$] (177). In an African study, however, the T-251A was not associated with significant risk for pulmonary TB (178). A mechanism associated with this SNP is currently unknown but may involve increased IL-8 production. Further studies need to be carried out to identify the role IL-8 plays in MTb infection.

Other genes

Slc11a1

Slc11a1, better known by its former name NRAMP1, was originally identified in mice, where it regulates resistance to intracellular pathogens such as *Salmonella typhimurium*, BCG, and *Leishmania donovani* (179,180). The murine susceptibility locus is associated with a single polymorphism in a non-conserved region, which encodes for a glycine to aspartic acid substitution at position 169. Slc11a1 has been extensively studied over the years and has complex functional phenotypes (181). Although the precise function of Slc11a1 continues to be actively pursued, it is thought to encode a protein which functions in transportation of divalent cations across phagosomal membranes and sequester essential cofactors (Mn^{2+}, Fe^{2+}, Cu^{2+}, orMg^{2+}) from bacteria and enhancing phagosomal killing (182). Other possible functions include regulation of chemokine and cytokine production, nitric oxide release, oxidative burst, and anti-microbial activity. A series of mouse studies have shown an influence of Slc11a1 on susceptibility to MTb infection (179,180).

Many Slc11a1 polymorphisms have been associated with a number of diseases including TB, autoimmune disease, meningococcal meningitis, and leishmaniasis (181). Because of the known association in mouse models of TB susceptibility, many studies have attempted to associate genetic variation in the human Slc11a1 homolog with TB susceptibility in humans. Four polymorphisms [3′UTR, D543N, INT4, and 5′(GT)n] were examined in many of these studies, and the data have been summarized in recent reviews as well as a meta-analysis of the 15 known studies (22,23,137,183–195). In the meta-analysis, subgroup analysis of the four separate polymorphisms indicates that three of the polymorphisms are associated with susceptibility to TB in Asian populations: 3′UTR (OR 1.46, 95% CI 1.1–1.9, $P = 0.009$), D543N (OR 1.65, 95% CI 1.29–2.12, $P = 0.001$), and 5′(GT)n (OR 1.86, 95% CI 1.33–2.62, $P < 0.01$). No significance was seen when European studies were grouped. African populations showed significance in all studies, except the D543N (OR 1.69, 95% CI 1.14–2.50, $P = 0.01$), INT4 (OR 1.50, 95% CI 1.17–1.91, $P = 0.001$), and 5′(GT)n (OR 1.31, 95% CI 1.05–1.64, $P = 0.02$). When all of the studies were pooled, significant associations were seen with the 3′UTR (OR 1.33, 95% CI 1.08–1.63; $P = 0.008$), D543N(OR 1.67, 95%CI 1.36–2.05, $P < 0.001$), and 5′ (GT)n (OR 1.32, 95% CI 1.03–1.68; $P = 0.026$). Only one of these variations, the promoter 5′(GT)n polymorphic z-DNA repeat, has been associated with changes in levels of mRNA transcription and possibly altered protein levels with various alleles (196). In aggregate, these studies indicate that Slc11a1 variants are

consistently associated with TB susceptibility in Asian and African populations, but the role of Scl11a1 variation to TB susceptibility in European populations is questionable.

Vitamin D receptor

The possible role of vitamin D in TB pathogenesis has a long history, including hypotheses regarding the benefits of cod liver in the 1800s, effects of hypocalcemia, and the benefits of sunlight exposure in sanatoriums (197,198). A large number of studies indicate that vitamin D influences the immune response, including effects on lymphocytes and macrophages (199). Furthermore, several studies have shown that vitamin D suppresses the growth of MTb in macrophages (200–202). Recent work has further elucidated the mechanism of this anti-tuberculous property of vitamin D and linked it to TLR signaling (203). Activation of human macrophages with the 19 kDa MTb lipopeptide (TLR2/TLR1 ligand) induced expression of the vitamin D receptor (VDR) as well as Cyp27B1, a vitamin D-1-hydroxylase that converts inactive provitamin D [$25(OH)D_3$] into the active $1,25(OH)_2D_3$. Treatment of macrophages with $1,25(OH)_2D_3$ induced expression of the anti-microbial peptide cathelicidin, which was sufficient for killing of MTb.

These mechanistic studies broaden our current understanding of genetic studies of vitamin D and TB susceptibility. Previous work has shown an association of vitamin D deficiency with susceptibility to TB [OR for undetectable $25(OH)D_3$ was 9.9 ($P = 0.009$) and for relative $25(OH)D_3$ deficiency was 2.9 ($P = 0.008$)] (196). There have also been a number of studies of VDR polymorphisms and susceptibility to TB. There are several VDR polymorphisms with nomenclature derived from their restriction enzyme cleavage sites. The FokI (alleles F and f) polymorphism creates an alternative initiation codon in the f allele, which results in a protein that is 3 amino acids longer and is associated with less efficient transcription and decreased bone mineral density (204,205). The *Taq*I polymorphism (alleles T and t) is associated with altered bone mineral density and may influence transcription levels (206). There are two additional SNPs, *Bsm*I and *Apa*I, which are non-functional and in linkage disequilibrium with *Fok*I and *Taq*I (207). A number of studies have been performed on VDR polymorphisms and susceptibility to MTb. Overall, there is substantial heterogeneity of the results that makes it difficult to make definitive conclusions (137,208–212). The heterogeneity of these results could be attributable to several factors including population admixture, different case and control definitions, small sample sizes for some of the studies, different ethnic backgrounds, and incomplete genotyping of the VDR locus, as the various studies examined different numbers of the known VDR SNPs. This latter possibility was further examined in a case–control and family study in West Africa, which examined *Fok*I–*Bsm*I–*Apa*I–*Taq*I haplotypes. The family study (using a TDT) found stronger associations of haplotypes with TB susceptibility in comparison with individual polymorphisms. Together, these results suggest a possible role for VDR polymorphisms and TB susceptibility, although further examination is still warranted, preferably with complete analyses with large sample sizes and family-based designs with haplotype analysis.

SP110

The *sst1* locus controls resistance to MTb in mice and was found in fine mapping studies to be attributable to the gene *Ipr1* (intracellular pathogen resistance 1) (213). Two polymorphisms in *SP110*, the nearest human homologue to *Ipr*, were found to be associated with susceptibility to TB in a family-based study in The Gambia and were also replicated in cohorts from Guinea-Bissau and the Republic of Guinea. The function of SP110 is not well understood, but it may be involved with myeloid cell differentiation or transcriptional regulation (214).

Conclusions and future trends

Recent advances in immunology and genetics are rapidly expanding our understanding of the role of common variation on susceptibility to TB. A number of candidate genes have been identified in case–control studies for their possible role in TB susceptibility. The most promising candidates that have shown consistent effects in their association with TB susceptibility in multiple studies include HLA and Slc11a1. Other genes with strongly suggestive associations include IFN-γ, TIRAP/MAL, and CCL2. In the genetics field, technologic advances are redefining the scope of studies that are feasible. Current efforts are using large-scale genome-wide association studies with hundreds of thousands of polymorphisms and case–control study designs. With rigorous study designs that address problems of population admixture, multiple comparisons, and adequate sample sizes, the ensuing years will provide an extraordinary wealth of information. In parallel, advances in our understanding of innate immunity and macrophage function are equally rapid and leading to detailed molecular and cellular pathogenesis models of MTb infection. Furthermore, a number of variants in candidate genes that are associated with disease susceptibility have been shown to alter the molecular and cellular function of the gene, either through effects on expression level or direct alteration of protein function through non-synonymous variants in the coding region. For several genes, there is evidence that allelic variants are associated with altered expression at the mRNA or protein level (DC-SIGN, IFN-γ, IL-1β, IL-12Rβ1, IL-10, CCL2, and TNF-α). However, for most of these genes, the effects are modest, inconsistent, or not replicated in multiple studies. Further work is needed to clarify the functional role of the effect of these polymorphisms on expression levels or signaling pathways. The evidence is compelling that several genes contain variants that directly alter the functional properties of the encoded protein. These examples include MBL (alleles B, C, and D), P2XA7_A1513C (E469A), TLR2_G2258A (R753Q), and MAL/TIRAP_C539T (S180L). Overall, there is a small and growing list of genetic variants that appear to regulate function. The combined analysis of the association of genetic variants with susceptibility to TB *in vivo* and altered functional effects *in vitro* suggests that common variation in macrophage genes does influence host susceptibility to TB. Future discoveries in genetics and immunology should further clarify these mechanisms and substantially illuminate our understanding of genetic regulation of host susceptibility to TB.

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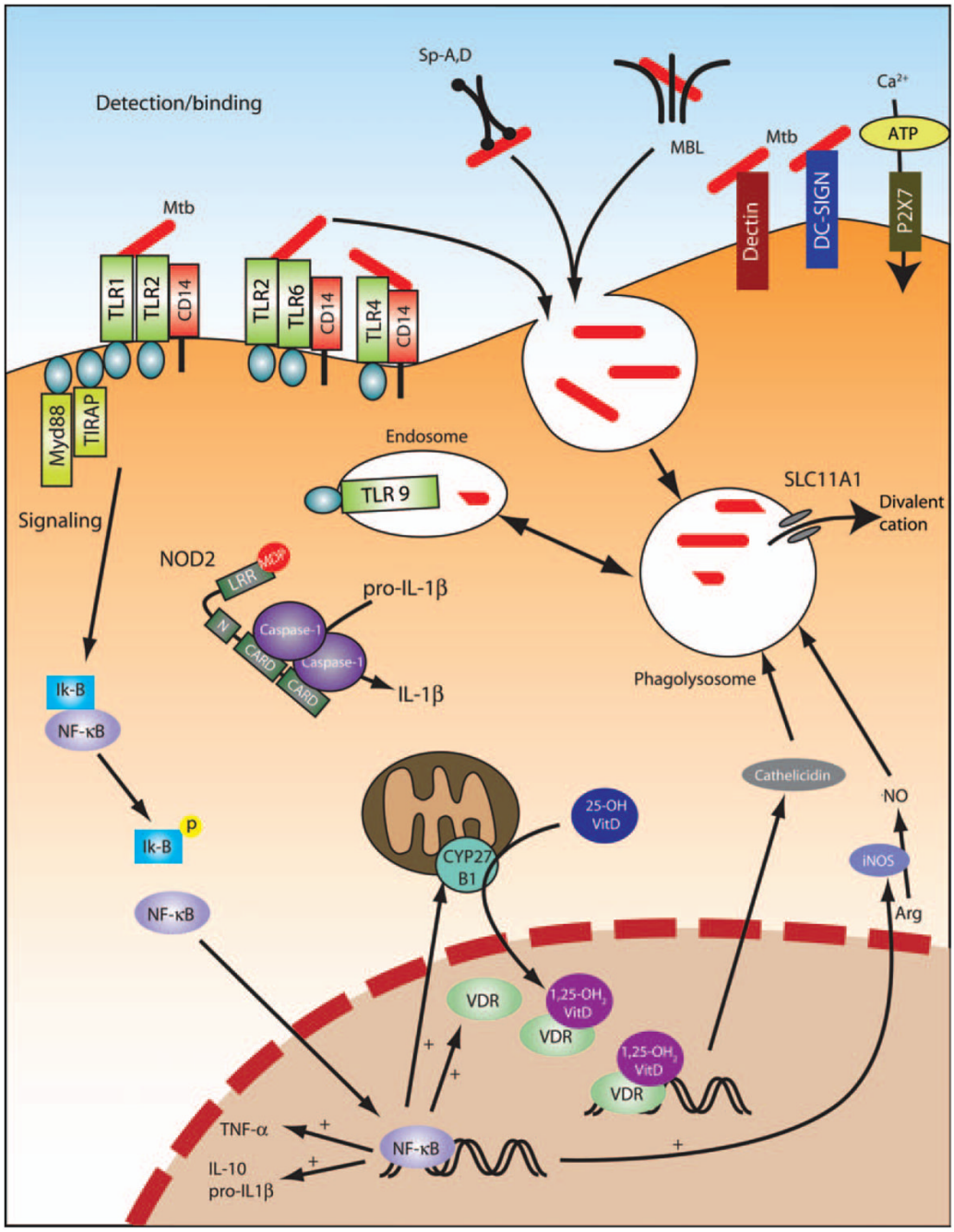

Fig. 1. Macrophage response to MTb

Depicted are the molecules that have been identified as important mediators of the macrophage response to MTb. iNOS, inducible nitric oxide synthase; LRR, leucine-rich region. MTb is recognized by several receptors and ingested by the alveolar macrophage. For example, MTb expresses several ligands that activate TLRs, in turn leading to signaling downstream of the MyD88 adapter protein. See text for more detail.

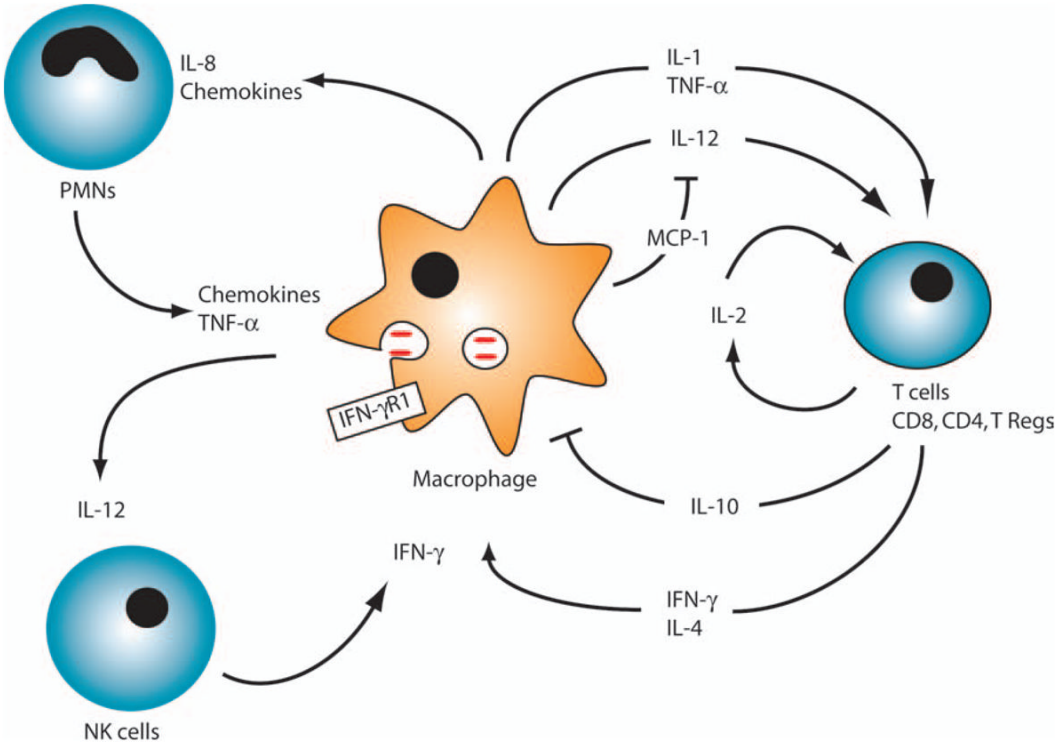

Fig. 2. Cellular immune response to MTb

After infection, activated macrophages secrete cytokines and chemokines that activate macrophages, T cells, neutrophils, or NK cells. T cells and NK cells produce IFN-γ that acts with other cytokines to activate macrophages to produce NO, which contributes to clearance of MTb. See text for more detail.

Table 1

Candidate gene association studies and susceptibility to tuberculosis

Gene	Variants	Validate*		Function of varianty	Comments
		TB	Other diseases		
Binding, receptors, and signaling					
MBL	Alleles B, C, and D and promoter	Variable	Variable	Y	Heterogeneous results from various studies
Surfactant protein	Multiple in Sp-A and Sp-D	N	N	N	
DC-SIGN	−871G, −336A	N	Y, dengue	P, expression	
P2XA7	−762	N	N	N	
	A1513C (E469A)	Y	N	Y	Alters ATP-induced macrophage functions, including MTb killing
TLR2	G2258A (R753Q)	N	Y, lyme	Y, signaling	
	Intron 2 GT microsatellite	N	N	P, expression	
	C597T (N199N)	N	Y, leprosy	N	
TIRAP/MAL	C539T (S180L)	Y	Y, malaria, bacteremia, pneumococcal empyema or baceremia	Y, signaling	
	C558T (A186A)	N	N	P, signaling	Associated with TB meningitis
Cytokines/chemokine					
IFN-γ	þ874A, −1616T, þ3234T	874, likely. Others: N	N	Y, 874 and IFN-γ expression	874 variant affects function and has the most promising association with Tb, but not replicated in all studies
IFN-γR1	Microsatellite	N	N	N	
	T-56C	Y	N	N	
IL-1β/IL-1RA	Multiple	N	Y, *H pylori*, HBV	P, for some alleles	
IL-12-Rβ1	Q214R, G378R, and M365T	Variable	N	P, signaling	
IL-12B	Multiple	N	N	P	
IL-10	A-1082G, A-592C	Variable	Y, leprosy	P, expression	
CCL2 (MCP1)	A-2518G	Y	N	Y, expression	Variant may inhibit IL-12 production
TNF-α	G-308A, G-238A	Variable	Y, malaria, leprosy	P	
TNFR1	Multiple	Y	N	P, signaling	
IL-8	T-251A	N	Y, RSV	N	
Other					

Gene	Variants	Validate*		Function of varianty	Comments
		TB	Other diseases		
HLA					Multiple studies demonstrate an association. Reviewed elsewhere
VDR	*Fok*1, *Bsm*I, *Apa*I, *Taq*I	Variable	Y, bone mineral density	P	Heterogeneous results from various studies
Slc11a1 (NRAMP1)	3′UTR, D543N, INT4, and 5′(GT)n	Y	Y, Neisseria, leishmania	P, transcription	Best documented association with 15 studies. Functional data are not clear
Ube3a	Multiple	Y	N	N	
SP110	Two variants	Y	N	N	Identified from mouse *sst1* locus

See text for references and more detail.

N, no; Y, yes; P, possible effect.

*Validation refers to whether the genetic findings were replicated in another MTb cohort or with a separate study design (family-based or case–control).

Validation is also noted if it occurred with another disease (other diseases).

†Function refers to whether the variant is associated with altered function of the gene, either through regulation of expression levels or through a non-synonymous coding region polymorphism that alters the function of the gene.