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Review Article

Host Immune Factors Related to Susceptibility to Tuberculosis in Animal Models

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Abstract

Tuberculosis (TB) along with AIDS and malaria constitute the three most deadly infectious diseases faced by all human kinds. Recent advances in diagnosis, drugs and vaccines as well as other TB related researches have shed light on the development of new strategies for prevention, treatment and control of the disease. Among those studies, improved understanding of the interplay between the bacterium and host is critical. The final outcome of bacterial infection is determined by multiple factors such as bacterial virulence factors, host susceptibility factors, the interplay between pathogen and host immunity. The importance of host genetic factors to the susceptibility of TB has long been realized and extensively studied in both human and animal models over the past decade. This review is intended to summarize the recent progress in studies of host immune factors related to TB susceptibility identified from animal models.

Keywords: Immune; Mycobacterium; Tuberculosis; Susceptibility

Abbreviations

TB: Tuberculosis; AIDS: Acquired Immuno Deficiency Syndrome; IL: InterLeukin; IFN: Interferon; MHC: Major Histocompatibility Complex; TAP: Transporter Associated with antigen Processing; ER: Endoplasmic Reticulum; NOS: Nitric Oxide Synthase; NRAMP1: Natural Resistance Associated Macrophage Protein 1; RNI: Reactive Nitrogen Intermediates; ROI: Reactive Oxygen Intermediates; SP: Surfactant Protein; STAT: Signal Transducer and Activator of Transcription; IRF: Interferon Regulatory Factor; TPL-2-ERK1/2: Tumor Progression Locus 2- Extracellular signal-Regulated Kinase1/2; TNF: Tumor Necrosis Factor; TNFR: Tumor Necrosis Factor Receptor; MCP-1: Monocyte Chemo attractant Protein-1; CCR: C-C Chemokine Receptor type 2; CXCR: Chemokine (C-X-C motif) Receptor; ICAM-1: Intra Cellular Adhesion Molecule-1; TLR: Toll-Like Receptor; QTL: Quantitative Trait Locus; GM-CSFR: Granulocyte/Macrophage Colony-Stimulating Factor; Gab2: Growth factor receptor bound protein-2 Associated binding protein -2

Introduction

About one-third of the world's population has been infected with *Mycobacterium tuberculosis*, the major causative pathogen of tuberculosis (TB). However, only about 10% of *M. tuberculosis* infected people develop into active TB [1]. It remains elusive why *M. tuberculosis* can stay in the host without causing clinical symptoms. Though the final outcome of *M. tuberculosis* infection is determined by many factors such as environmental, bacterial and genetic components, many studies have confirmed that host genetic factors played important roles in TB disease.

In 1926, the same dose of virulent *M. tuberculosis* strain was accidentally injected into 251 babies in Lubeck, Germany. Among them, 174 finally survived, including 47 who did not develop clinical disease and 127 who had radiological signs of TB [2, 3]. It has also been observed for over 100 years that people of different races have different susceptibility to TB. When TB was introduced to Qu'appelle Indians in 1890, it caused a 10% death rate initially and then dropped to 0.2%. This phenomena might be due to about 40 years of strong selection pressure against TB-resistance genes [4].

Currently, there are still remarkable racial differences in prevalence of the disease, which was often shown by a higher resistance to TB among White population than among Black population. It has been reasoned that those racial differences might due to social factors instead of genetic ones. However, a study done in Arkansas nursing home residents showed that Blacks with African ancestry were twice as likely to have TB as Whites with European ancestry, which could not be explained by any social or environmental factors [5]. A few other studies on twins have found that monozygotic twins have higher concordance for TB than dizygotic twins [6, 7]. All these evidences prompt us to ask: what kind of roles do host genetic factors play in the pathogenesis of TB?

Along with those studies mentioned above, other investigations such as adoption studies [8], genome wide linkage analyses [9] and population based association studies [10, 11], all indicated that host genetics play important roles in the susceptibility or resistance to TB. Additional evidence that corroborated the involvement of human genome in TB susceptibility was from the discovery of individuals with the rare human syndrome of Mendelian susceptible to mycobacterial disease. Those individuals were found to have mutations in genes of interleukin 12 beta (IL-12β), IL-12 receptor β-1, and interferon-gamma (IFN-γ) receptor 1 & 2, which caused them more susceptible to even non-pathogenic mycobacteria [12]. The repertoire of genetic factors involved in the susceptibility to TB is now continuing to grow.

Studies of animal models of *M. tuberculosis* infections have also suggested that genetic factors are important determinants of susceptibility to TB disease. For example, inbred strains of rabbits

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Table 1: Animal models used in studies of TB susceptibility.

Host Gene or Loci	Mouse strain used	Reference
Bcg (Nramp1)	C57BL/6J, BALB/C, DBA1/J, A/J, C3H/Hecr, DBA/2J, CBA/J, C57Br, AKR	(67)
CCR-2	CCR-2(-/-) C57BL/6, CCR2(+/+) C57BL/6	(54)
CD44	CD44(-/-) C57BL/6	(58)
CR3	CR3(-/-) (129Sv/J x C57BL/6), CR3(-/-)(C57BL/6 x BALB/C)	(57)
CXCR3	CXCR3(-/-) C57BL/6, WT C57BL/6	(55)
Gab2	Gab2 (-/-), WT	(85)
H2	B10, BALB.B, BALB.K, BALB/C	(17, 19, 20)
ICAM-1	ICAM-1(-/-) C57BL/6, WT C57BL/6	(56)
IFNG	IFN-γ disrupted mice (C57BL/6J)	(33, 42)
IL-4	IL-4Rα(-/-) C57BL/6, IL-4/IL-13(-/-) C57BL/6, WT and Stat6(-/-) BALB/C	(45)
IL-12	IL-12p35(-/-), IL-12p40(-/-), (129Sv/Ev, C57BL/6)	(34)
IL-18	IL-18(-/-) C57BL/6	(36)
IRF8	C57BL/6J (B6) and C3H/HeJ (C3H) mice, BXH-2 (with a defective IRF-8(R294C) allele)	(37)
Ipr1	C3HeB/FeJ (sst1R allele from C57BL/6J)	(81)
Ltα	C57Bl/6 (Ly5.2), C57Bl/6.Ly5.1, and C57Bl/6.RAG- 12/2 mice	(47)
MAL(MyD88)	C57BL/6, MyD88-/- deleted mice	(61-63)
MCP-1	MCP-1 (-/-)(129Sv/J x C57BL/6) ; MCP-1 overexpressing mice (129Sv/J x C57BL/6)	(52, 53)
NOS2	NOS2(-/-), F2 or F3 (129/SvEv x C57BL/6)	(29)
Nramp1(Slc11a1)	DBA/2J (Bcgr), BALB/C(Bcgs), C.D2-N20 Bcgr; 129/Sv mice	(69, 70)
Nramp1(Slc11a1)	Top of Form CBA, DBA/2, C3H, 129/SvJ; BALB/C, C57BL/6Bottom of Form	(69, 70)
SST1	C57BL/6J, C3HeB/FeJ, F2 progeny	(80)
STAT4	STAT4(-/-) BALB/C, WT BALB/C	(35)
TAP-1	(129/Sv,C57BL/6) TAP1(-/-); (C57BL/6 × 129/Sv) F1 or F2 mice	(24)
TCR(γδ)	TcR-beta(-/-), TcR-delta(-/-) mice, C57BL/6	(28)
TLR 2, 4, 6	C57BL/6, BALB/C, C3H/HeJ, C3HHeN	(59, 60)
TNF	TNF-α(-/-) C57BL/6, TNFR (-/-) C57BL/6, Ltα(-/-) C57BL/6	(45, 46)
TNFRp55, TNFRp75	TNFRp55(-/-), TNFRp75(-/-), TNFRp55/75(-/-), WT(C57BL/6)	(49-51)
Trl-1, 2, 3, 4	DBA/2J , C57BL/6, F2 progeny	(14, 77, 78)
Usp18	Usp18lty9 mice , Usp18lty9 mice lacking Isg15	(44)

exhibited both resistant and susceptible patterns of disease after infection with virulent *M. bovis* [13]. Inbred strains of mice also demonstrated different patterns of disease after infection of virulent *M. tuberculosis* [14]. The availability of inbred, congenic, recombinant and mutant mouse strains, along with the complete information on mouse genome and the immunity similar to human have made the mouse a popular model for screening genetic factors involved in TB disease. In this review, we will discuss the host genetic factors involved in TB identified to date using animal models.

TB Susceptible Genes Identified from Animal Models

Animal models with *M. tuberculosis* infection confirmed host genetic factors play vital roles in the susceptibility to TB. Mice of the I/St strain are extremely susceptible to *M. tuberculosis* infection but resistant to *M. avium* infection, whereas C57BL/6 mice have a reversed pattern of susceptibility [15]. Further study indicated that characteristics of pathology are largely determined by the level of susceptibility of the host to distinct mycobacterial species, underscoring the importance of host genetics in pathogenesis of TB [15]. Galina Shepelkova et al. profiled the gene expression files in the lungs of TB resistant A/Sn and TB-susceptible I/St mice and found that resistant A/Sn mice have stronger expression of genes involved in activation of host defense pathways compared to their susceptible counterparts, while the susceptible strain upregulated specific genes encoding cysteine protease inhibitors [16]. The TB susceptibility loci found through studies of animal models, particularly inbred genetically modified mice are listed in **Table 1**.

Lymphocyte immunity

H-2 is a complex of genetic loci on mouse chromosome 17 that define the major histocompatibility complex (MHC). In 1993, A. S. APT et al. studied the impact of distinct haplotypes and of different alleles at mouse H-2 loci on the susceptibility to lethal *M. tuberculosis* strains and found that susceptibility to TB was associated with I-A^b and D^b alleles. Host resistance to TB was associated with I-A^k and D^d alleles. These findings demonstrated the importance of MHC genes in controlling the susceptibility to TB [17], though another gene *Tbc-1*

was found to have stronger effects on susceptibility to TB than H-2 loci [18]. Besides, carriers of the H-2^K haplotype displayed a greater degree of susceptibility to TB compared to strains bearing H-2^b or H-2^d haplotype [19, 20]. All those studies suggested the important role of H2 gene in the susceptibility to TB.

MHC-I presents peptides to $CD8^+$ T cells. During the antigen presentation, protein antigens need to be cleaved and processed by the proteasome and transported by the transporter associated with antigen processing (TAP) complex from the cytosol into the endoplasmic reticulum (ER). The processed peptides associate with the MHC-I and β2 microglobulin (β2m) proteins to form a trimeric complex [21]. Mice genetically deficient in β2m are lack of $CD8^+$ T cells and are unable to control infection in the lungs [22]. In *tap1*-deficient mice, the MHC-I antigen-processing pathway is deficient, which results in reduced numbers of $CD8^+$ T cells in all lymphoid organs [23]. After infection, *tap1*-deficient mice died rapidly and had a higher bacterial burden and more severe tissue pathology than the wild type mice, underscoring the importance of CD8 T cell mediated immunity against *M. tuberculosis* infection [24]. Further studies indicated that the effects of these T cells on TB may be mediated by other mechanisms including the synthesis of the gamma interferon (IFN-γ) cytokine [25].

In a recent study, mice lacking B cells were found to have slightly higher *M. tuberculosis* burdens and recruited few leukocytes to the lungs after infection [26, 27]. Another study of mice with a disruption in the γδ T cell receptor showed that mice could survive a low dose challenge with *M. tuberculosis*, but succumbed rapidly to a high inoculum [28].

ROI and RNI

In 1997, John D. Macmicking et al. reported that nitric oxide synthase (NOS) had a protective role against TB [29]. They also indicated that susceptibility to TB due to NOS mutation appeared to be independent of the only known inherited antimicrobial gene by then, natural resistance associated macrophage protein 1 (*Nramp-1*), which we will discuss in detail later in this review. IFN-γ stimulates the expression of inducible nitric oxide synthase (iNOS) in macrophage, thus increases the production of reactive nitrogen intermediates (RNI). Studies using mice with deletion of the *Nos2* gene confirmed the role of iNOS in TB susceptibility [29]. However, *Nos2* knockout mice have less degree of TB susceptibility than mice deficient in IFN-γ, in the IFN-γ receptor 1, or in the signal transducer and activator of transcription 1 (STAT1) [30]. Surfactant protein A (SP-A) has been found to suppress reactive nitrogen intermediates in alveolar macrophages in *M. tuberculosis* infection [31], while another study showed that surfactant protein D (SP-D) can inhibit the phagocytosis of *M. tuberculosis* [32].

Cytokines, chemokines, and effector modules

Cellular immunity plays a pivotal role in control of *M. tuberculosis* infection. To access the function of different cell types in response to TB, mice with deletion of genes encoding different cytokines have been studied.

Interferons regulate immunity against *M. tuberculosis* infection. However, type I and type II Interferons have different roles in this battle. The type II Interferon, IFN-γ, promotes protection against TB. Mice with a disruption of *Ifng* gene had the utmost susceptibility to TB, and succumb to a rampant and disseminated form of the disease [33]. IL-12 and 18, two IFN-γ stimulating factors, are critically involved in the immunity against TB. Mice lacking both IL-12a and IL-12b genes showed an inferior resistance to TB when they were compared to mice with a deletion IL-12a or IL-12b alone [34]. IL-12 signals through the STAT4 protein. Mice with a disrupted STAT4 gene were more susceptible to TB and exhibited early death after *M. tuberculosis* infection [35]. IL-18 deficient mice showed a slight increase in TB susceptibility and it was associated with a reduced level of IFN-γ [36]. Interferon regulatory factor 8 (IRF-8) can positively regulates IFN-γ production. Using BXH-2 mice bearing a defective IRF-$8R^{294C}$, J.F. Marquis et al. found that *M. tuberculosis* infection led to severely reduced IFN-γ productions, complete shutdown of IL-12p40 expression and impaired T cell priming in BXH-2 mice, highlighting a critical regulatory role of IRF-8 in host defense against TB [37].

Other cytokines or related components such as IL-6, IL-1 receptor and IL-27, were also found to contribute to a decreased level of IFN-γ production, however, they seem to have complicated roles in TB susceptibility, not necessarily resulting in increased susceptibility to TB infections [38-41].

Different from the role of type II interferon in controlling TB, type I interferons were found promote susceptibility to TB. Finlay W. McNab et al. found that TPL-2-ERK1/2 pathway mediates host resistance to TB through negative regulation of type I interferons production [42]. A gene in type I IFN signaling pathway, named ubiquitin-specific peptidase 18 ($Usp18^{ity9}$), can negatively regulate type I interferons signaling [43]. Mutation of this gene increased mouse susceptibility to *Salmonella Typhimurium* and *M. tuberculosis* [44].

Other than cytokines involved in Th1 cell mediated immunity discussed above, the role of Th2 response characterized by production of IL-4 and IL-10 in the host against TB has been defined clearly. Deficiency in the alpha chain of IL-4 receptor (IL4-Rα) and IL-4 responsive STAT6 molecules only showed a slightly increased susceptibility to TB [45].

TNF is also one of the most important cytokines involved in the cellular adaptive immune responses against *M. tuberculosis* infection. Mice deficient in tumor necrosis factor-alpha (TNF-α) showed a defective granulomatous response, exhibited poorly organized granulomas and caused a fatal and disseminated TB infection [45, 46]. Mice with defective LTα, another member of TNF family, also exhibited an increased susceptibility to TB, manifested by less survival time and abnormal granuloma formation [47]. However, excessive TNF may aid in degradation of lung tissue and help bacterial replication in alveolar macrophage [48]. TNF mediate cellular signaling through TNFRs (TNFRp55 and TNFRp75, respectively),the role of TNFRp55 signaling in host immune response to *M. tuberculosis* infection has been studied in various animal models. G. Senaldi et al. found that the granuloma formation in *M. bovis* BCG strain infected TNFRp55 knockout mice was abnormal, indicating the protective role of TNFRp55 [49]. Another study also found that TNFRp55 is required in the protective immune response against TB in mice [50]. However, little is known about the exact

role of TNFRp75 in the protective immunity against *M. tuberculosis* infection until a recent work by R. Keeton et al.. They investigated the possible role of TNFRp75 and found that TNFRp75 deficient mice exhibited greater control of *M. tuberculosis* infections compared with the wild type mice, suggesting TNFRp75 negatively regulates protective immunity against *M. tuberculosis* infection [51].

Other host factors of susceptibility to TB such as chemokines and adhesion molecules are also important for controlling the recruitment of immune cells into the inflammatory site. However, their roles in controlling *M. tuberculosis* infection remain elusive. For instance, Lu, B et al. studied the role of monocyte chemo attractant protein-1 (MCP-1) in recruiting mononuclear cells *in vivo* using MCP-1 deficient mice, and found MCP-1 (-/-) mice were indistinguishable from the wild type mice in their ability of clearing *M. tuberculosis* [52]. However, over-expressing MCP-1 in transgenic mice was correlated to increased susceptibility to TB [53]. Mice deficient in CCR2, MCP-1's receptor, exhibited an exacerbation of *M. tuberculosis* growth and rapid mortality after high dose of *M. tuberculosis* infection [54]. Mice deficient in other CXC chemokine receptor (CXCR) members such as CXCR3 have no effect on mycobacterial growth, but *Cxcr3* mutant mice showed poor granuloma formation [55]. Mice with truncated intracellular adhesion molecule-1 (ICAM-1) succumbed within four months of infection, though no sign of alternation in the initial course of *M. tuberculosis* infection [56]. ICAM-1 can interact with complement receptor type 3 (CR3). However, mice with deletion of complement receptor type 3 (CR3) didn't show any change of the outcome of *M. tuberculosis* infection, suggesting other ligand may compensate for the role of CR3 in terms of interacting with ICAM-1 [57]. In addition, CD44 deficient mice showed increased bacterial growth, impaired granuloma formation, rapid mortality after *M. tuberculosis* infection [58].

Innate immunity components

Macrophage phagocytosis of mycobacteria involves a number of cell-surface receptors including Toll-like receptors (TLRs). Studies using TLR4 and TLR6 knockout mice revealed that neither receptor is involved in clearance of *M. tuberculosis* [59, 60]. Since TLR-dependent activity is mediated by intracellular adaptor molecule MyD88, its role in TB immunity has been studied in a knockout mouse model. However, different groups generated inconsistent results in terms of the impact of MyD88 on mycobacterial proliferation and survival times [61-63]. For more information about the innate immunity against TB, please refer to other review papers [64-66].

Earlier seminal studies starting in the 1980s identified a single autosomal gene on Chromosome 1 to be responsible for the innate resistance to *M. bovis* BCG vaccine strain, thus the gene was designated as Bcg. Gros P. et al. found that two different alleles of Bcg genes contributed to two completely different phenotypes in initial phase of *M. tuberculosis* infection in mice, TB susceptible (Bcg^s) and resistant (Bcg^r), respectively [67]. Later on, *Bcg* gene was renamed as *Nramp1* (natural resistance associated macrophage protein 1), also known as *Slc11a1* (solute carrier family 11A), which encodes a macrophage-specific, integral membrane transporter protein. Nramp1 gene was found to affect intracellular mycobacterial replication by modulating phagosomal pH [68]. However, the creation of *Nramp1* congenic strains and *Nramp1* deletion strains has further demonstrated *Nramp1* may not be as important as we thought in medicating resistance to TB in mice [69, 70]. Quite surprisingly, human *Nramp1* gene appeared to be strongly associated with TB susceptibility in a number of populations [71-73]. Another member of *Nramp* gene family named *Nramp2* was found to increase phagosome acidification, possibly by transporting divalent cations such as Fe^{2+} out of the phagosome and into the cytoplasm [74].

Other factors

Quantitative trait locus (QTL) analysis has been widely used in genetic identification of candidate locus related to TB susceptibility due to the complex factors affecting the progression of this disease [75, 76]. In the QTL approach, mouse strains of different susceptibility spectra are selected and crossed for linkage studies. Polymorphic genetic markers tightly correlated with a phenotype of infection are segregated to define the TB susceptibility loci. The mouse DBA/2 (D2) strain is very susceptible to *M. tuberculosis* infection and C57BL/6 (B6) is more resistant. By using B6 X D2 mice and QTL, four loci have been identified related to TB resistance, designated as tuberculosis resistance loci (Trl-1, 2, 3, and 4) [14, 77, 78]. *Trl-1* to *4* are on chromosome 1, 3, 7 and 19, respectively. *Trl-3* and *Trl-2* are possible components contributing the distinct patterns of susceptibility to *M. tuberculosis* H37Rv infections between DBA/2J (D2) and C57BI/6J (B6) strains [14]. Trl-4 was found to closely interact with Trl-3 to control *M. tuberculosis* replication in the lungs [77]. Later on, J.F. Marquis further characterized the protective roles of *Trl-3* and *Trl-4* loci against TB using B6 × D2 F2 mice and found that F2 mice homozygous for B6 alleles at both *Trl-3* and *Trl-4* were resistant to TB, whereas mice homozygous for D2 alleles were more susceptible [78].

Several interesting genes are identified in the *Trl-1* region, including those encoding the chemokine receptor CXCR4, IL-10, Fas ligand (FasL), the neutrophil cytosolic factor 2 (Ncf2), and three selectins (Sele, Sell, Selp) [14, 79]. Other few genes including IL-2, IL-2a, and IL-6 receptor alpha (IL-6Rα) were found in the *Trl-2* region [14, 79]. In the *Trl-4* region, genes encoding nuclear factor-Kappa B (NFκB), inhibitor of NFκB kinase alpha subunit (IKKα) and the alpha-chain of the cell surface receptor for granulocyte/ macrophage colony-stimulating factor (GM-CSFRα) were found to regulate the pulmonary bacterial replication, when animals were aerosol infected with low doses of *M. tuberculosis* [77, 79].

In another study of genome-wide mapping in a F-2 population derived from resistant C57BL/6J and susceptible C3HeB/FeJ progenitor strains, Kramnik et al. identified a major genetic locus, the super susceptibility to tuberculosis 1 (*sst1*) locus, which controlled the progression of lung disease caused by virulent *M. tuberculosis* infection [80]. Later, Pan, Hui et al. found a candidate gene, intracellular pathogen resistance 1 (*Ipr1*) within the *sst1* locus [81]. The *Ipr1* expression was induced in TB resistant macrophages, but was absent in TB susceptible phagocytes. Moreover, transgenic mice with the *Ipr1*gene were found to restrict pulmonary *M. tuberculosis* growth *in vivo* [81]. Ipr1 functions by limiting replication of *M. tuberculosis* and switched the cell death pathway of infected macrophages from necrosis to apoptosis, underscoring an important role of mediating innate immunity, cell death pathway and pathogenesis [81].

Growth factor receptor bound protein-2 associated binding

protein -2 (Gab2), a wide expressed protein in the central nervous system, has been involved in many signaling pathways. Gab2 has been found to play multiple roles: such as an ovarian cancer oncogene [82] and genetic susceptibility factor to sporadic Alzheimer's disease [83, 84]. Recently it has been reported that GAB2 plays a negative regulatory role in the host protective immune response against TB. After infected with *M. tuberculosis,* Gab2 knockout mice has less bacterial load and milder lung damage compared with wide type mice [85].

Conclusions

TB disease is a result of complex interactions between environmental, microbial and host factors. Studies of host genetic factors contributing to the susceptibility to TB using either forward or reverse genetic methods have provided us an ever-growing repertoire of genetics components responsible for regulating the TB susceptibility in animal models to various degrees. The availability of high throughput oligo nucleotide arrays as well as new genome scanning methods are combined with specific phenotypes of TB in animal models to identify new TB susceptibility loci.

Another aspect of host factors of TB susceptibility lies in the specific immune mechanisms against *M. tuberculosis* infection. Identification of immunological markers associated with specific phenotypes of *M. tuberculosis* infection will advance our understanding of TB immunity.

The host susceptibility factors to TB from animal model studies demonstrated the important roles of genetic components in susceptibility to TB, but the extent and specifics of the involvement of many genes are not elucidated yet. Technical innovation in genetics and newly emerging fields, such as metabolomics and interactomics, will help us gain more insight on the genetic susceptibility loci to this ancient disease.

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