

# Host–Pathogen Specificity in Tuberculosis

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**Abstract** The host response to mycobacterial infection including tuberculosis depends on genetically controlled host and bacterial factors and their interaction. A largely unknown aspect of this interaction is whether disease results from an additive and independent effect of host and pathogen or from specific host–pathogen combinations. The preferential association of specific mycobacterial strains with specific ethnic groups provided tentative evidence in favor of host–pathogen specificity in tuberculosis and is consistent with the hypothesis of host–mycobacterial co-adaptation. Substantial evidence for specificity has now been provided by animal models and human case–control association studies. These studies indicate that differences in the host response to infection are at least in part due to specific combinations of host genetic factors and genetic and phenotypic characteristics of the infecting mycobacterial strain.

**Keywords** *Mycobacterium tuberculosis* • Host–pathogen specificity • BCG infection • ANOVA • RC strains • Chemokine and chemokine-related genes • Toll-like receptors • Pathogen-associated molecular patterns • Meningeal tuberculosis • Phagosome maturation • Autophagy • Mannose-binding lectin (MBL)

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## 1 Introduction

The host response to *Mycobacterium tuberculosis* is highly variable. Among individuals exposed to *M. tuberculosis*, approximately 30–50 % become infected during an outbreak and only about 10 % of those infected progress to clinical disease [1]. Several lines of evidence support the importance of host genetic factors in tuberculosis susceptibility. These include the geographic and ethnic clustering of tuberculosis cases [2, 3], increased concordance rates of tuberculosis in monozygotic compared to dizygotic twins [4, 5], and documented cases of Mendelian predisposition to disease [6, 7]. Genetic variants have been identified as risk factors for tuberculosis through genome-wide linkage [8–14] and association studies [15, 16] as well as candidate gene studies [17]. Although these studies have greatly increased our insight into the genetic basis of tuberculosis susceptibility, the results have been somewhat inconsistent. With candidate gene studies, the identified effects have generally been weak and poorly reproducible. Similarly, there is minimum overlap between susceptibility regions identified through genome-wide studies. Non-reproducibility has been attributed primarily to population genetic factors, differences in phenotype definition, and genetic diversity among *M. tuberculosis* strains [17, 18].

Increasing evidence suggests genetic differences among *M. tuberculosis* strains may have important phenotypic consequences. For example, *M. tuberculosis* strains differ in their virulence and immunogenicity in animal models [19–22]. In humans, *M. tuberculosis* isolates have been associated with specific clinical phenotypes [23]. An increasing number of studies also indicate that specific strains of *M. tuberculosis* are more prevalent in certain geographical areas [24]. Six geographically constrained lineages have been identified using isolates from San Francisco [25] and replicated independently using a Montreal cohort [26]. These include the East-Asian, Euro-American, Indo-Oceanic, East-African-Indian, and West-African-1 and -2 lineages. East-Asian strains include, but are not confined to, the Beijing family of strains [25]. Strains of the Euro-American lineage predominate in Europe and the Americas but are also found in regions of Africa and the Middle East [25]. The East-Asian, Euro-American, Indo-Oceanic, and East-African-Indian groups are sub-lineages of *M. tuberculosis sensu stricto*, whereas the West African lineages 1 and 2 are traditionally referred to as *M. africanum* [27]. These geographical associations are highly stable [28] and were shaped by human migration and demography [29], suggesting *M. tuberculosis* strains are preferentially transmitting and causing disease among specific ethnic groups. They may also reflect co-adaptation of *M. tuberculosis* with its human host.

Together, these observations raise the biological question if host and mycobacterial factors are acting additively and independently to cause disease or if specific combinations of host and pathogen are associated with increased risk of tuberculosis. If host and pathogen factors contribute independently to disease, hosts would display a range of phenotypes from highly resistant to highly susceptible regardless of the infecting strain and mycobacteria would vary from

highly to mildly virulent across all hosts. Only hosts that are intrinsically susceptible to *M. tuberculosis* or those exposed to highly virulent strains of *M. tuberculosis* would present with disease. Alternatively, if disease results from specific combinations of host and pathogen, specific strains of *M. tuberculosis* would only cause disease in certain hosts while hosts would only be susceptible to particular strains of *M. tuberculosis*. In the latter instance, the concepts of “virulence” or “susceptibility” would only hold true when jointly considering host and *M. tuberculosis* strain. Understanding the dynamics and specificity of host–pathogen associations in tuberculosis pathogenesis is imperative for the development of effective tuberculosis control tools. This chapter reviews the current evidence supporting host–pathogen specificity in increased tuberculosis risk.

## 2 Mycobacterial Strain Specificity in Host Response Phenotypes

Inbred mice display a switch in host susceptibility/resistance to virulent *M. tuberculosis* and attenuated *M. bovis* Bacille Calmette–Guérin (BCG). Mouse strains, which are classically considered resistant to BCG infection, are susceptible to infection with *M. tuberculosis* and vice versa [30, 31]. Susceptibility of the mouse to tuberculosis is defined as early death caused by progressive lung disease and/or uncontrolled bacterial replication. Unlike *M. tuberculosis*, BCG produces a non-lethal, self-limiting infection. Susceptibility to BCG is assessed by the extent of bacterial replication in the organs of the mononuclear phagocyte system within the first 3 weeks of infection. The A/J and C57BL/6J mouse strains represent polar ends of this operationally defined susceptibility/resistance spectrum. Death following infection with *M. tuberculosis* in the susceptible A/J strain results from a progressive interstitial pneumonitis characterized by diffuse cellular infiltration, widespread tissue necrosis, and bacterial dissemination. *M. tuberculosis* infection is also lethal in the resistant C57BL/6J strain, although these mice survive for prolonged periods due to the development of functional lung granulomas and corresponding bacterial containment [Di Pietrantonio et al., unpublished data, [32–34]. Host susceptibility is reversed in response to infection with either the Montreal or Pasteur substrains of BCG: *M. tuberculosis*-resistant C57BL/6J mice are permissive to BCG replication within the reticuloendothelial organs, whereas the *M. tuberculosis*-susceptible A/J strain is resistant [35, 36]. The shift in host susceptibility in response to attenuated and virulent mycobacteria provides strong support for pathogen-specific susceptibility in infections caused by closely related mycobacterial species.

To provide formal and direct evidence for specificity in the host–pathogen crosstalk, biological and mechanistic phenotypes were investigated in A/J and C57BL/6 J mice following intravenous infection with *M. tuberculosis* or the Russia, Japan, and Pasteur substrains of BCG [37]. Biological phenotypes are markers of host susceptibility and resistance, whereas mechanistic phenotypes

describe the mechanisms underlying susceptibility and resistance traits. Host phenotypes also provide a measure of bacterial virulence, a property that is investigated in terms of changes induced by a panel of bacterial strains in genetically identical hosts. The individual and joint contribution of the host and mycobacteria on phenotype expression can be assessed using three-way analysis of variance (ANOVA). With ANOVA, the significance of each variable (here host, bacteria, and time) and the interaction between each pair of variables is determined by independent F tests. Evidence for host–pathogen specificity is provided by the host  $\times$  bacteria interaction term [38].

In a proof-of-principle study, pulmonary bacterial counts (CFU) and transcript levels of three cytokines (*Ifng*, *Il12b*, and *Il4*) were measured at 1, 3, and 6 weeks post-infection as biological and mechanistic phenotypes, respectively. The bacterial load is an important biomarker of host resistance and susceptibility to infection and is a useful parameter to assess differences in virulence among mycobacterial strains. In the lung, *M. tuberculosis* had the highest bacillary counts in both A/J and C57BL/6J mice when compared to the three BCG strains. Among the BCG strains, the pulmonary counts of BCG Russia increased progressively over time while BCG Pasteur remained consistently low and BCG Japan was unrecoverable in both mouse strains. When the impact of the mycobacterial strain on the pulmonary counts was assessed using three-way ANOVA, significant bacterial-related effects were detected independent of the host and time [ $F(2, 30.9) = 118.3$ ;  $P < 0.001$ ]. For the host component, a significant contribution of the mouse strain was observed independent of the bacteria and time [ $F(1, 34.3) = 18.6$ ;  $P < 0.001$ ]. The effect of time was also significant [ $F(2, 23) = 49.2$ ;  $P < 0.001$ ]. Importantly, significant interaction effects were observed between the bacteria and mouse strain [ $F(2, 30.9) = 5.5$ ;  $P < 0.01$ ], providing significant evidence of host–pathogen specificity in pulmonary bacterial replication. For the mechanistic phenotypes, host–pathogen specificity was detected in the transcriptional induction of *Ifng* and *Il12b* but not *Il4*. A significant contribution of host genetic background on phenotype expression was observed for *Il12b* transcription only, whereas an effect of the mycobacterial strain was observed across all mechanistic phenotypes. Pulmonary expression profiles of chemokine and chemokine-related genes further indicated that variation across mycobacterial strains had a larger impact than host genetic variation. While differences in the transcriptional response between A/J and C57BL/6J mice were modest, a large subset of immune genes was differentially regulated across mycobacteria. Importantly, mycobacterial-related effects were more prominent in the A/J mouse strain, indicating that the host genetic background modulated the impact of the mycobacterial strain on these responses. These results suggested that the mycobacterial strain had a greater effect on the studied phenotypes compared to the host genetic background in this experimental setting. However, it is important to realize that the genetic similarity among the host strains was comparatively higher relative to the mycobacteria, which included two different species. In situations involving outbred hosts, both the impact of the host and the significance of host–pathogen effects are expected to be substantially stronger [37].

### 3 Mycobacterial Strain Specificity in the Genetic Control of Infection and Disease

Mouse genetic studies have generally focused on one mycobacterial strain to map and identify the host genetic factors that control infection and the progression of infection. Using this approach, differential susceptibility of inbred mouse strains to BCG infection was shown to be largely under the control of the natural resistance-associated macrophage protein 1 (*Nramp1*, alias solute carrier family 11 member 1, *Slc11a1*) gene [35], whereas the host genetic control of *M. tuberculosis* infection was found to be multigenic [39–43]. The shift in genetic control from simple to complex across mycobacteria of varying virulence strongly suggested that pathogen genome variability impacted on the host genetic response to infection. This raised the question of if and to what extent different strains of the same mycobacterial species were under different host genetic control, a necessary consequence of specificity in host–pathogen interactions. To test for strain-specific genetic control of susceptibility, a comparative genetic analysis was performed in the A/J- and C57BL/6J-derived recombinant congenic mouse (RC) strains following infection with BCG Russia or BCG Pasteur. A unique feature of RC strains is that host response phenotypes are estimated with greater accuracy due to repeat measurements in genetically identical animals. Linkage genome scans can then be conducted with high resolution using the relatively limited number of RC strains within the panel. Employing eight parallel genome scans, bacillary counts in the lung and spleen were shown to be under the control of shared as well as tissue- and BCG-specific susceptibility loci. A locus indistinguishable from *Nramp1* on chromosome 1 impacted on both BCG Pasteur and BCG Russia infection in a spleen-specific manner. Loci influencing the counts of BCG Russia but not BCG Pasteur were identified on chromosome 13 for the spleen and on chromosome 11 for the lung and spleen [44]. The observation that only a minority of genetic control elements was shared among closely related strains of BCG and across tissues in the mouse indicated that the genetic control of BCG infection was sensitive to the infecting strain and to phenotype definition (here, bacillary counts in the lung versus the spleen). Another important aspect of phenotype definition is the stage of the infectious process. Clearly, more advanced stages are under different genetic control as compared to the initial stages of infection [44]. It is likely that the same disease stage specificity of the genetic control also applies to tuberculosis and contributes to the difficulty in identifying strong genetic risk factors of susceptibility.

At present, five human genetic studies have incorporated the *M. tuberculosis* genotypes of their sample population into the analysis of genetically controlled tuberculosis susceptibility. All five studies found an interaction between a human genetic variant and the mycobacterial lineage known to be associated with the corresponding geographic region and human population.

### 3.1 *Toll-Like Receptor 2 (TLR2)*

Toll-like receptors (TLRs) are signaling molecules involved in innate immunity. TLRs detect pathogen-associated molecular patterns (PAMPs) on bacterial molecules. Binding of the PAMP ligand to the extracellular domain of the TLR initiates a signaling cascade through the Toll/IL-1 receptor domain, resulting in the expression of pro-inflammatory molecules including cytokines and chemokines. Among the TLRs, TLR2 recognizes lipoprotein/lipopeptides which are expressed by all bacteria including mycobacteria [45].

In a population-based study from Vietnam, the *TLR2* T597C polymorphism was shown to be associated with increased risk of developing tuberculosis. The association was strongest in cases caused by the East Asian/Beijing isolates [ $P = 0.004$ , odds ratio (OR) 1.57 (95 % confidence interval (CI) 1.45–2.15)], but not significant in cases caused by the Indo-Oceanic and Euro-American isolates, although heterogeneity testing was not reported. This suggests that the *TLR2* T597C polymorphism or a polymorphism in linkage disequilibrium with T597C specifically affects the interaction of the East Asian/Beijing strains with TLR2. The association between disease caused by the East Asian/Beijing genotype and *TLR2* T597C increased when the clinical phenotype was considered: the OR for meningeal tuberculosis caused by East Asian/Beijing isolates was 1.91 [ $P = 0.001$ , 95 % CI 1.28–2.86]. By contrast, the Euro-American lineage was associated with pulmonary rather than meningeal tuberculosis: the OR for meningeal tuberculosis caused by Euro-American strains was 0.395 [ $P = 0.009$ , 95 % CI 0.193–0.806] [23]. The increased propensity of East Asian/Beijing strains to cause meningeal tuberculosis may be linked to production of a phenolic glycolipid (PGL-tb) molecule. Experiments involving animal models have shown that PGL-tb specifically inhibits the immune response and promotes dissemination from the lungs [22, 46]. Euro-American strains lack expression of PGL-tb due to a seven-base pair deletion in the polyketide synthase (*pks1/15*) gene [25, 47] and may conversely cause less extra-pulmonary disease.

### 3.2 *Solute Carrier Family 11 Member 1 (SLC11A1) Natural Resistance-Associated Macrophage Protein 1 (NRAMP1)*

In inbred mice, allelic variation in *Nramp1* (also known as *Slc11a1*) is strictly correlated with susceptibility to low dose BCG infection [48]. During BCG infection, *Nramp1* recruitment to the membrane of BCG-containing phagosomes abrogates the ability of BCG to block phagosome-lysosome fusion, causing increased vacuolar acidification and decreased intracellular replication [49]. In humans, NRAMP1 (SLC11A1) was shown to promote phagosome maturation in a monocytic cell line [50].

The contribution of *SLC11A1* variants to *M. tuberculosis* genotype-specific susceptibility was studied in an Indonesian population sample. The GG genotype of the non-synonymous exonic variant D543 N (G1703A) was significantly associated with increased risk of tuberculosis caused by Beijing strains [ $P = 0.05$ , OR 2.15 (95 % CI 1.25–3.70)]. The homozygous insertion genotype for the TGTG insertion/deletion polymorphism in the 3' untranslated region (3' UTR) (1729 + 55 ins/del4) was also associated with tuberculosis caused by strains of the Beijing genotype [ $P < 0.001$ , OR 2.40 (95 % CI 1.19–4.83)] [51]. The increased risk of disease caused by Beijing strains in carriers of these *SLC11A1* variants suggests strains of this lineage may be more resistant to SLC11A1-mediated protection.

### 3.3 Immunity-Related GTPase Protein Family, *M* Gene (*IRGM*)

The immunity-related GTPase M (*IRGM*) participates in the host defense against *M. tuberculosis* by inducing autophagy. During autophagy, cytosolic components such as organelles are sequestered in an autophagosome and become degraded following fusion with a lysosome [52]. *M. tuberculosis* is accessible to autophagy either through the phagosome or directly from the cytoplasm following translocation from the phagosome [53]. Formation of the autophagosome involves light chain 3 (LC3), which is activated by *IRGM* [54].

The *IRGM* -261TT genotype was associated with increased protection to tuberculosis in a population-based study from Ghana. The protective effect applied to tuberculosis caused by *M. tuberculosis* sensu stricto [ $P_{\text{corrected}} = 0.0045$ , OR 0.66 (95 % CI 0.52–0.84)] but not to *M. africanum* or *M. bovis*. Stratification by *M. tuberculosis* lineage further revealed that protection was exclusive to the Euro-American subgroup [ $P_{\text{corrected}} = 0.0019$ , OR 0.63 (95 % CI 0.49–0.81)] and did not apply to the East-African-Indian, East-Asian/Beijing, or Indo-Oceanic/Delhi genotypes [55]. The increased vulnerability of the Euro-American strains to *IRGM*-triggered innate immune mechanisms including autophagy may be related to absence of PGL-tb.

### 3.4 Arachidonate 5-Lipoxygenase (*ALOX5*)

Arachidonate 5-lipoxygenase (also known as 5-lipoxygenase or 5-LO) is an enzyme involved in the biosynthesis of leukotrienes (LT) and lipoxins (LX) from arachidonic acid. Among the different classes of LTs, LTB<sub>4</sub> is a pro-inflammatory mediator which attracts and stimulates leukocytes, resulting in increased production of IFN- $\gamma$  and IL-12 [56, 57]. LXs antagonize LTB<sub>4</sub> activity by suppressing

leukocyte effector functions, downregulating IL-12 production [56] and enhancing IL-4 secretion [58].

The non-synonymous exonic variant g.760G/A (Glu254Lys) of *ALOX5* was shown to be associated with increased risk of developing tuberculosis in a case-control sample from Ghana, West Africa. Stratification by phylogenetic mycobacterial clades revealed that the association was strongest for tuberculosis caused by the *M. africanum* West African-2 genotype [ $P_{\text{corrected}} = 0.024$ , OR 1.70; (95 % CI 1.2–2.6)] or for the West African-2 and *M. bovis* strains combined [ $P_{\text{c12}} = 0.006$ , OR 1.85 (95 % CI 1.27–2.65)] [59]. The implications of these findings are two-fold. First, they suggest that *M. africanum* and *M. bovis* may differentially activate 5-lipoxygenase compared to *M. tuberculosis*. Secondly, the association between the West African-2 lineage which is virtually unique to Africa and the g.760G/A polymorphism which has a higher frequency in African relative to European and Euro-American populations is consistent with the hypothesis of co-evolution.

### 3.5 Mannose Binding Lectin 2 (MBL2)

Mannose-binding lectin (MBL) is an innate immune effector. It binds carbohydrate structures on the surface of a wide variety of pathogens and promotes phagocytosis either directly by acting as an opsonin or indirectly by activation of classical complement pathway [60].

The impact of genetic *MBL2* variants on susceptibility to pulmonary tuberculosis was investigated in a Ghanaian study population. Among the three structural variants tested in exon 1, the G57E polymorphism at position 57 was protective against tuberculosis caused by *M. africanum* or *M. bovis* [ $P_{\text{nominal}} = 0.008$ , OR 0.60 (95 % CI 0.4–0.9)] but not by *M. tuberculosis* sensu stricto. A haplotype of three polymorphisms of the *MBL2* promoter at positions –550 (alleles H and L), –221 (alleles Y and X) and +4 (alleles P and Q) together with the variant at position 57 of exon 1 (alleles A and C) revealed that the LYQC combination was protective against *M. africanum*/*M. bovis* [ $P_{\text{corrected}} = 0.007$ ] but not *M. tuberculosis* [61]. The LYQC haplotype is almost exclusive to sub-Saharan Africa and occurs there at a high relative frequency, suggesting it may have been selected for because of its protective effect against *M. africanum* and *M. bovis*.

Given the presumed function of MBL, it is tempting to speculate that *M. tuberculosis* differs from *M. africanum* and *M. bovis* in the expression of cell surface structures which may be relevant to MBL binding. For example, the TBd1 region is absent in all *M. tuberculosis* sensu stricto strains but not in *M. africanum*/*M. bovis*. This region contains genes encoding membrane proteins which may be involved in lipid transport and may impact on cell wall composition [61].



## 4 Conclusion

There is now clear evidence from experiments in both animal models and human case–control samples for pathogen specificity in the genetic control of tuberculosis susceptibility. These findings are not unexpected since the mechanisms of pathogenesis in animal models and cell explants differ among closely related strains and species of mycobacteria. Differences in pathogenesis open entry points for variable host genetic control of mycobacterial infection and disease. While the presence of host–mycobacteria specificity is indisputable, the genetic effects detected are of moderate size. Whether this reflects a true minor contribution to disease risk of such host–mycobacteria specific interactions or the lack of high-resolution genetic characterization of host and pathogen will be the object of further investigation.

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