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Human Genomics of *Mycobacterium tuberculosis* Infection and Disease

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Abstract

Purpose of review—The study of the genetic basis of tuberculosis pathogenesis has benefited from powerful technological innovations, a more structured definition of latent and clinical manifestations of the disease, and the application of functional genomics approaches. This short review aims to summarize recent advances and to provide a link with results of previous human genetic studies of tuberculosis susceptibility.

Recent findings—Transcriptomics has been shown to be a useful tool to predict progression from latency to clinical disease while functional genomics has traced the molecular events that link pathogen-triggered gene expression and host genetics. Resistance to infection with *Mycobacterium tuberculosis* has been revealed to be strongly impacted by host genetics. Host genomics of clinical disease has been shown to be most powerful when focusing on carefully selected clinical entities and possibly by considering host pathogen combinations.

Summary—Future studies need to build on the latest molecular findings to define disease subtypes to successfully elucidate the human genetic component in tuberculosis pathogenesis.

Keywords

tuberculosis; host genomics of tuberculosis; functional genomics of tuberculosis; transcript biomarkers; human genetics of infection

Introduction

Tuberculosis (TB), caused by the human pathogenic bacterium *Mycobacterium tuberculosis (Mtb)*, is a global health problem that claimed over 1.8 million lives in 2016 (1). Spread of

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Conflict of Interest

Both authors declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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the tubercle bacillus is via the aerosol route by human to human transmission. Not all persons exposed to *Mtb* will become infected and depending on the exposure intensity a sizeable fraction will remain free of the bacillus. Of those who do become infected with *Mtb*, only a small proportion, perhaps as few as 10%, will develop clinical forms of the disease while the majority will control the infection and realize a state that is termed latent TB infection (LTBI). LTBI is inferred from measures of acquired anti-mycobacterial immunity such as the *in-vivo* tuberculin skin test (TST) and *ex-vivo* interferon-γ release assays (IGRAs). Until recently, the approaches used for the genetic investigation of TB were centered on clinical genetics and genetic epidemiology, i.e. linkage and association studies of the binary trait of TB disease vs subjects with immune signs of infection with *Mtb* but no overt clinical symptoms (2). These classical approaches have been expanded to include methods of population genetics and functional genomics. While population genetic approaches focus on the elucidation of how past demography and natural selection have given rise to common genetic variants that underlie resistance to infectious diseases such TB, functional genetic studies evaluate the genetic basis of intermediate phenotypes such as gene expression levels and epigenetic changes (3). The expansion of methodological approaches for the study of TB susceptibility has been paralleled by the realization that TB is a highly dynamic disease displaying a multitude of changing and interconnected pathologies that are poorly reflected by the use of a single binary disease phenotype (4–6).

Transcription and epigenetics

Population genetic studies have unambiguously shown that host defense against infectious diseases is under strong natural selection (7, 8) and natural selection explains a large part of population differences in immune responses (9). While it is challenging to link the ecological driver of selection to specific pathogens such as *Mtb*, innate immunity genes, which play a key role in TB pathogenesis, are under stronger purifying selection than the rest of the genome (10). A fascinating aspect of these population genetic studies is the demonstration that adaptive introgression of Neandertal genes shaped modern innate immune responses (11, 12). Arguably, these population genetic results provide a broad framework in which genetic interactions of humans and *Mtb* occur.

Consistent with the strong purifying selection acting on innate immunity genes, recent work has identified early events in the host-*Mtb* interaction as critical for TB pathogenesis (13). Consequently, a number of studies have probed the host response to infection by *Mtb* on the innate effector cell level and elucidated the genetic control of the provoked transcriptomics response. Infection of monocyte-derived dendritic cells with *Mtb* showed a pronounced upregulation of genes belonging to immune response pathways and a down-regulation of genes belonging to GO terms reflecting metabolic activity (14). Expression levels of over 700 genes were shown to be significantly impacted by single nucleotide polymorphisms (SNPs) located in the 5'-region of target genes in both infected and uninfected cells. Genetic variants that significantly correlate with gene expression levels are termed expression quantitative trait loci (eQTL). A subset of eQTL was observed only in stimulated or non-stimulated cells, i.e. these eQTL were dependent on the interaction of dendritic cells with *Mtb* and were termed response-eQTL (reQTL). The detection of reQTL provided direct proof that *Mtb* can modulate the genetic control of host responsiveness and pointed to the

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importance of epigenetic effects in TB pathogenesis (15). To what extent reQTL are involved in susceptibility to TB is not clear but an enrichment of reQTL among formally significant GWAS SNPs was detected (14). In a subsequent study employing monocyte-derived macrophages and infection with eight different bacterial strains there was very limited specificity of reQTL for *Mtb*. While there was a strong mycobacteria -specific transcriptomic response pattern , the genetic control of the cellular response at 18 hrs post-infection was strain independent. Indeed, except for a single reQTL for the *CAMS* gene, all reQTL were shared among all bacterial strains (16). Since reQTL during the early response are generic for bacterial infection this suggests that later time points are more likely to reveal strain specific effects of the host genetic control of gene expression.

Given a strong mycobacterial specific transcriptomic response it is possible that, even in the absence of specific genetic control, the transcriptome may be useful as a biomarker to identify distinct stages of TB pathogenesis. In addition, the very low predictive accuracy of TST and IGRAs for development of clinical TB disease, it might be more useful to focus on the subset of LTBI patients at increased risk of developing disease. A number of studies used peripheral blood transcriptomics to derive signatures that distinguish TB patients from either healthy controls, LTBI subjects, or successfully treated TB patients [eg (17–20)]. A meta-analysis of 16 published studies identified a set of 380 genes that were differentially expressed in TB in a majority of studies, of which only five genes were differentially expressed in all datasets (21). Employing a prospective approach in a South African adolescent sample, a 16 gene signature for risk of advancement from LTBI to clinical disease was discovered that was successfully replicated in three validation samples (22). Overall, the sensitivity of the signature was approx. 60% with a specificity for progression of approx. 80%. Importantly, predictive accuracy of the signature increased for patients with shorter time intervals to onset of TB disease. This implies substantial phenotypic heterogeneity among pre-clinical LTBI patients, a conclusion that was also reached for clinical TB itself (23). The results also suggest that blood transcriptomics did not capture those destined for progression but rather discerned different stages of pathogenesis for those already committed to progression. Hence, the search for the cause of progression from LTBI to clinical TB is still ongoing.

Infection with *Mtb*

Transcriptomics has proven less powerful in differentiating healthy controls from LTBI patients although recent transcriptomics studies identified histone deacetylation as a key event in *Mtb* infection resistance in monocytes (24). Unfortunately, there is no gold-standard for identifying LTBI patients who are truly infected with *Mtb* since we cannot distinguish a possible anamnestic response to *Mtb* antigens from persistent infection. However, if we accept LTBI as revealed by TST and IGRAs as good proxy for infection with *Mtb* there is compelling evidence for host heterogeneity in resistance to *Mtb* infection (25). While age in high transmission settings is a strong predictor of LTBI, heterogeneity at each age group is not associated with an epidemiologically defined risk score (26). In line with these epidemiological findings it has been shown that TST and IGRA responses display significant heritability. A twin study in the Gambia reported substantial heritability for TST (71%) and IGRA reactivity (39%) (27). In South Africa, heritability of IGRA responses was

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estimated at 43% to 74% depending on the specific read-out and stimulating antigen (28), while heritability of TST responsiveness was estimated at 65% in Colombia (29). A study in Uganda, carefully adjusted for shared environmental factors, estimated heritabilities of IGRA responses above the LTBI threshold at 30–48% depending on the stimulating antigen (30).

A number of linkage and candidate studies have implicated a small number of genetic regions in the control of TST and IGRA responses. In Ghana, an IL10 promoter haplotype, associated with low circulating levels of IL10, was significantly enriched in TST-positive vs TST-negative persons (31). A genome-wide association study (GWAS) reported association of HLA class variants with TST positivity in an Icelandic population (32). A genome-wide linkage analysis using persistent low TST reactivity as the phenotype, detected linkage signals on the long arm of chromosome 2 and chromosome 5 (33). By defining a stringent threshold of TST-negativity (0 mm vs > 0 mm) a major locus termed *TST1* was mapped to chromosome region 11p13. In the same study, a major locus impacting on the intensity of TST reactivity, termed *TST2*, was mapped to chromosome region 5p15 (34). *TST1* was inferred to represent an *Mtb* infection resistance locus while *TST2* was thought to reflect the genetic control of T-cell-mediated anti- mycobacterial immunity (34). The *TST1* locus was replicated in a household contact study of ethnically mixed families (35). Interestingly, a locus (*TNF1*) that strongly impacts the production of TNF by blood cells in response to BCG (+/− IFNγ) was indistinguishable by linkage analysis from *TST1* raising the possibility that TNF was involved in the mediation of *Mtb* infection resistance (36). It appears that TST reactivity and INFγ responses are under distinct genetic control. Two loci that control BCG and ESAT-6 triggered IFNγ production were mapped to chromosomes 8q and 3q, respectively (37). Different genetic control of TST and IFNγ release are consistent with the low correlation between both read-outs of anti- mycobacterial immunity.

Clinical TB disease

Like other complex diseases, the host genetic contribution to TB can be subdivided into common genetic variants (minor allele frequency [MAF] > 2–5%) and rare variants (MAF < 2%). Common variants mainly modulate gene expression levels while rare variants generally impact protein function. It is possible that rare variants more strongly impact early pediatric forms of severe TB while common variants are more prominent later in life (38). The most common monogenetic defect identified in severe childhood disease to date are mutations in *IL12RB1* resulting in IL12Rb1 deficiency (39, 40). Initial estimates suggested that nearly half of severe childhood TB might be caused by single gene defects (41). The contribution of single gene disorders to severe pediatric TB susceptibility defines the extreme pole of the general observation that a stronger contribution of host genetic effects can be detected among early-onset patients (42). This was also shown by the positional cloning of the *TOX* gene as a major TB susceptibility factor only in patients with age-at-onset of less than 25 years old in two independent populations (43).

Employing sputum culture-confirmed pulmonary TB (PTB) as the phenotype, there are ten GWAS studies published to date (44). Two studies from Ghana and the Gambia identified two variants. Both variants, rs4331426, located in a gene desert on chromosome region

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18q11.2 (31), and rs2057178, located 45kb downstream of the *WT1* gene on chromosome region 11p13 (45), displayed modest effect sizes ($p = 6.8 \times 10^{-9}$, OR = 1.19 and $p = 2.63 \times 10^{-9}$; OR=0.77, respectively). Interestingly, the chromosome 11 signal was replicated in a South African study with similar effect size as seen in West Africa [OR=0.62; (46)]. In contrast, replication cohorts of non-African origin (45), detected smaller effect sizes with borderline significance: Indonesia ($p = 9.9 \times 10^{-2}$; OR = 0.84, 95% CI = 0.68–1.03) and Russia ($p = 2.0 \times 10^{-2}$; OR = 0.91, 95% CI = 0.82–0.99). A GWAS in Thai and Japanese populations focused on TB cases less than 45 years of age and identified an independent TB risk locus in chromosomal region 20q12 [OR = 1.73 (1.42–2.11), (47)]. When a very large sample from Russia (comprising over 15,000 active TB cases and controls) was analysed, a protective variant (rs4733781; $p = 2.6 \times 10^{-11}$, OR=0.84) was identified in the intronic region of the *ASAP1* gene on chromosome region 8q24. The same variant displayed only borderline significance for a protective effect in the combined Ghanaian and Gambian samples ($p = 0.052$). Interestingly, one of the variants associated with TB in the Russian sample (rs10956514-G, p=1.0×10^{-10}, OR=0.85) was also associated with a significant reduction of dendritic cell-specific high *ASAP1* expression after *in vitro M. tuberculosis* infection that affected cell mobility function (48). A rather small Indonesian sample of 125 active TB cases and 134 controls was used as a GWAS discovery cohort with two larger replication cohorts from Indonesia (independent 1189 cases and controls) and Russia (4016 cases and controls). This approach revealed suggestive associations for SNPs within 6 genes related to the pro-inflammatory Th1 response of the IFNγ pathway (49). In a sample from Northern Morocco with 556 PTB subjects and 650 controls, four variants located in the *FOXP1* and *AGMO* genes displayed suggestive evidence for association ($2 \times 10^{-6} < p < 4 \times 10^{-5}$) (50). Both genes are critical for proper macrophage function, variation in which may be reflected in characteristics of latency and reactivation of *Mtb* (51, 52). The most significant association was shown for the *AGMO* SNP, rs916943, ($p = 2 \times 10^{-6}$) but only in an early age-at-onset (<25 year old) subset, again indicating the importance of considering age-at-onset for a more accurate definition of PTB in genetic analysis.

The latest GWAS was performed using the Icelandic population (3,686 PTB cases and 287,427 controls) to identify variants associated with TB and LTBI (14,724 subjects including TB cases) (32). New variants associated with TB and LTBI were identified in the *HLA-DQA1* gene and the intergenic region between the *HLA-DQA1* and *HLA-DRB1* genes. The rs9272785 SNP, representing the HLA-DQA1*03 superallele conferred risk to TB (3.5×10^{-7}; OR=1.22) while the two SNPs located between *HLA-DQA1* and *HLA-DRB1* were either indicators of risk (rs557011/T; $p = 5.8 \times 10^{-12}$; OR = 1.25) or protection (rs9271378; ($p = 2.5 \times 10^{-12}$, OR = 0.78). The confirmation samples from Russia and Croatia replicated the identified associations although with smaller effect sizes (32). The Iceland study failed to replicate any of the previously reported associations from West Africa and *ASAP1* observed in the Russian sample. Overall, these results highlight strong sample specific effects in the genetic control of TB susceptibility. The cause of the genetic heterogeneity remains unknown.

One possible reason for the low success rate in detecting PTB susceptibility loci by GWAS may be the fact that TB is a highly dynamic disease that is caused by genetically distinct forms of *Mtb*. For example, it is a reasonable assumption that due to the co-evolution of *Mtb*

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with distinct human populations, co-adaptation of *Mtb* and select human hosts may have occurred. There is a large body of experimental evidence showing that bacteria of different *Mtb* lineages interact in a lineage-specific fashion with effector cells of both the innate and acquired immune system, resulting in different epidemiological transmission scenarios and clinical presentations of TB [reviewed in (53)]. An implication of these observations is that host genetic susceptibility factors may be acting on an *Mtb* lineage-specific level. This conclusion is supported by the results of modelling studies in the mouse that revealed significant differences in the genetic control of growth of BCG Pasteur and BCG Russia, two closely related strains of BCG (54). In human studies the action of host-pathogen "fits" of susceptibility and or resistance is particularly difficult to address. Exploratory studies addressing the question in candidate gene approaches reported encouraging results and this is an area that deserves more careful consideration [reviewed in (55)].

Extreme phenotype heterogeneity, if derived from locus heterogeneity, would not be an obstacle for mapping of susceptibility loci by association. However, in practical terms this may require sample sizes that cannot be collected due to logistical and financial limitations A more attractive solution is to focus on careful selected sub-phenotypes of TB disease. For example, HIV- infected persons are at highly increased risk of becoming infected and progressing to clinical TB when exposed to *Mtb*. Nevertheless, a small group of HIV-positive patients do not develop TB despite continued exposure to *Mtb* and represent a clearly defined phenotype of TB resistance. A recent study analyzed the genetic control of TB resistance in this well-defined group of TB resistors. In a prospective study with 581 HIV-positive Ugandans and Tanzanians, 267 subjects developed active TB and 314 remained disease-free within 8 years of follow-up. In a GWAS approach, a significant association was shown between the common variant rs4951437 and protection from TB disease: OR=0.37 ($p = 2.1 \times 10^{-8}$) (56). The SNP is located in an intron of the *UBLCP1* gene, 51kb downstream of the 3'UTR of *IL12B*, and falls within an H3K27Ac histone mark, indicating its potential role as a regulatory element. The genomic region spanning the *UBLCP1* and *IL12B* genes revealed a block of strong linkage disequilibrium in both studied populations. A 3-variant haplotype within this region demonstrated an even stronger association with TB ($p=4.56 \times 10^{-15}$) and further supports the possible involvement of IL12 in mediating TB resistance. Perhaps equally important, on the conceptual level the study demonstrated that for carefully selected phenotypes strong genetic effects can be detected with samples of modest size.

Host genetics and treatment of meningeal TB

An interesting example for the importance of host genetics in TB susceptibility with possibly strong clinical implications concerns the *LTA4H* gene which encodes the leukotriene A4 hydrolase enzyme. The gene was initially identified in a forward genetic screen for genes affecting the replication of *M. marinum* in zebra fish embryos where loss of enzyme activity resulted in the accumulation of lipoxin A4 (LX4; (57)). LX4 is a strong anti-inflammatory effector molecule and a key mediator of mycobacterial induced necrosis of infected macrophages. On the other hand, LTA4H enzymatic activity leads to the production of Leukotriene B4 (LTB4), a potent pro-inflammatory mediator. Heterozygosity at a promoter region SNP of the *LTA4H* gene was protective for meningeal TB (TBM) suggesting the action of balancing selection. Experiments in the zebra fish supported the

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concept of heterozygote advantage since excess of both LX4 and LTB4 promoted bacterial growth in zebra fish via dysregulation of the key inflammatory mediator TNF These observations led to the concept that homozygosity at the promoter SNP resulted either in a hyper- or in its alternative configuration, a hypo-inflammatory phenotype of TBM patients (57). Clinically, excessive inflammation is a major cause of death among TBM patients while insufficient inflammation may be equally detrimental due to the lack of host response to the infection. Importantly, the promoter SNP was shown to be an eQTL for *LTA4H* where the high expresser genotype correlated with hyper- inflammation. Moreover, when provided with corticoid adjunctive therapy, homozygous carrier of the hyper-inflammatory genotype displayed a significant survival advantage (57). These observations together with the functional studies in zebra fish raised the possibility that corticoid therapy for carriers of the hypo-inflammatory genotype was counter-indicated. In such an event, treatment of TBM patients would need to be personalized based on their *LTA4H* genotype. This question was addressed in two recent large studies in Vietnam and Indonesia with inconsistent results (58, 59). A possible reconciliation of the divergent observation regarding the role of the *LTA4H* genotype on survival may be that the impact of the *LTA4H* gene is most noticeable in a subset of TBM patients (60). Given their high mortality and the difficulties in the clinical management of TBM patients the possible benefits of adapting therapy to the patient *LTA4H* genotype needs to be evaluated in greater detail.

Conclusion

Multiple lines of experimental evidence support the presence of a strong human genetic component in susceptibility to infection with *Mtb* and the subsequent development of clinical TB disease. Impressive advances have been achieved in the study of transcriptomic biomarkers for different forms of clinical forms of TB, while population genetic and functional genomics approaches provide a new framework for the host-*Mtb* interplay. Yet, there remains a paucity of identified TB susceptibility genes. Indeed, the most convincing results were obtained when focusing on specific, highly selected phenotypes. These results suggest as a possible new avenue of research a refined phenotype definition based on a molecular description of the disease state. Such an approach may help us to define genes that impact on different stages of the disease process and lead to a phenotype-based dissection of the genetic control of TB pathogenesis.

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