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Single-Nucleotide Polymorphisms of Interleukin-17 and Susceptibility to Tuberculosis

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ABSTRACT

Interleukin-17 (IL-17) is involved in the immune response to various infectious diseases. Two isoforms, IL-17A and IL-17F, are well studied and may play an important role in host defence towards tuberculosis. Genetic polymorphisms involving genes coding for these IL-17 isoforms may influence the function of this cytokine, hence affecting an individual's susceptibility to tuberculosis infection. This narrative review discusses the role of several single-nucleotide polymorphisms involving IL-17A and IL-17F in tuberculosis susceptibility. Several SNPs, including rs2275913 and rs8193036 of the IL-17A gene and rs763780 of the IL-17F gene influence the immune response mediated by IL-17 to tuberculosis through different ways. The rs2275913 and rs8193036 SNPs are located in the promoter of the IL-17A gene, altering the expression of the gene by regulating the binding of transcription factors. Meanwhile, the rs763780 SNP is located in the coding region of the IL-17F gene, resulting in an amino acid substitution that affects the function of expressed IL-17. Future studies may elaborate the interactions of these SNPs with related polymorphisms in a haplotype-based approach, as well as their roles against infection of different *Mycobacterium tuberculosis* lineages.

1. Introduction

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* (Mtb). TB remains a major burden to health and the world's second leading cause of death from a single infectious agent in 2022. In 2022, TB affected an estimated 10.6 million people, and this number had increased in comparison to previous years. Two-thirds of the global TB burden came from eight countries: India (27%), Indonesia (10%), China (7.1%), the Philippines (7.0%), Pakistan (5.7%), Nigeria (4.5%), Bangladesh (3.6%) and the Democratic Republic of the Congo (3.0%). In addition, Indonesia, Myanmar and the Philippines had been major contributors to the global increase of TB cases between 2020 and 2022 [1,2]

The most common manifestation and transmission mechanism of TB is pulmonary TB. [3] In most cases, Mtb transmission involves the exit from respiratory tract, survival in the outside environment, and inhalation to the lung of a new potential host. Immune evasion is also necessary to cause new infection.[4] Pulmonary TB has divergent outcomes, ranging from complete Mtb clearance through asymptomatic latent infection to active disease. The outcomes of Mtb infection depend on both the pathogen and natural variations in host immune response. The type and extent of immune activation and inflammation are thought to be essential in determining host protection against Mtb.[5]

The immune response to Mtb infection is regulated by both innate and adaptive immune components. Interactions between antigen-presenting cells (APCs), lymphocytes, macrophages, monocytes, and immune mediators, as well as T helper (Th)-dependent immune response, are known to be essential in the response against Mtb.[6] Th1 and Th17 are the main effector T helper populations responsible for both protection against and pathological processes of TB.[5]

Th17 cells are CD4+ T cells named for their production of the IL-17 family cytokines. Th17 are implicated in the induction of neutrophilic inflammation and mediation of tissue damage.[5,7] Th17 cells have pleiotropic activities, including activation and recruitment of neutrophils, stimulation of granulopoiesis lineage of differentiation, and support of inflammation. Th17 cytokines chiefly protect the host from pathogens at

epithelial and mucosal tissues.[8] In infection models, Th17 cells and their main product IL-17 were first implicated in the immune response against rapidly-growing extracellular bacteria in the lung and gut mucosal surfaces. The protection effect occurs via efficient induction of neutrophil recruitment and tissue repair.[9,10]

Studies on genetic components that may determine one's susceptibility to TB had indicated that, instead of a single major type, variations in susceptibility may be contributed by several small predisposing genes.[11] As such, single-nucleotide polymorphisms (SNPs) in genes encoding for IL-17 may cause alterations in the structure and function of IL-17 in the immune response towards TB, hence contributing towards host susceptibility to TB. This narrative review aims to discuss select SNPs in genes encoding for IL-17.

2. Overview of IL-17 in tuberculosis

The role of IL-17 in host defenses against Mtb infection has been supported by studies in mice and humans. In murine models infected with Mtb strain HN878 and H37Rv, it has been suggested that IL-17 is required for early protective immunity following infection with Mtb. However, the infecting strain may elicit different responses, as different levels of pulmonary IL-17 expression were observed between mice infected with Mtb H37Rv and HN878.[12] Furthermore, autocrine IL-17 produced by neutrophils was shown to inhibit Mtb H37Rv growth on early stages of infection by mediating production of reactive oxygen species and migration of neutrophils.[13] Studies in humans also showed that plasma IL-17 levels were increased in patients with positive acid-fast bacilli (AFB) smear and active TB. This increased expression supports the protective role of IL-17 early in the course of Mtb infection by activation, recruitment and mobilization of neutrophils. However, IL-17 plasma levels eventually decreased after smear conversion.[14,15]

The IL-17 family consists of six members, namely IL-17A to IL-17F. IL-17A and IL-17F are two most widely-studied isoforms of IL-17. IL-17A is implied in various pathologies, such as the development of autoimmunity, inflammation, and tumors.[6,8] Studies in IL-17 deficient mice and humans with inborn errors of IL-17 immunity have shown that IL-17A and IL-17F have overlapping, yet distinct, functions in the host defenses against bacterial and fungal infections. At the same time, IL-17A and IL-17F are important in maintaining symbiotic relationships with commensal microbiota.[16–18] IL-17A is chiefly expressed to eliminate primary infection and establish an effective memory response.[19,20] Hence, increased IL-17A expression could be beneficial to halt the progression of Mtb infection by formation of mature granuloma.[21] In the absence of IL-17A, IL-17F expression increases as a compensatory mechanism.[22]

IL-17A and IL-17F have similar biological activities and bind to the same receptor, IL-17 receptor A (IL-17RA) and C (IL-17RC).[5,20] IL-17RA is ubiquitously expressed in the skin and mucosal membranes of different organs, including lung, liver and spleen.[5,9] IL-17A and IL-17F can form either homodimers or heterodimers, and both dimer forms can interact with their receptors. IL-17A and IL-17F's targets include innate immune cells, fibroblasts, endothelial and epithelial cells.[16,20] They induce the production of pro-inflammatory cytokines (IL-6, IL-1, tumor necrosis factor), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokines, and matrix metalloproteinases, which in turn will increase neutrophil production and recruitment. In their role against microbial pathogens, both IL-17A and IL-17F also induce the secretion of antimicrobial factors (defensins, S100 proteins).[10,16]

IL-17A and IL-17F are mainly produced by Th17 cells. However, several innate immune cells also produce these cytokines, such as γδ T cells, invariant natural killer T (iNKT) cells, lymphoid-tissue inducer (LTi)-like cells, natural killer (NK) cells, Paneth cells of the intestines, and neutrophils.[16] IL-17A and IL-17F are encoded separately in the IL17A and IL17F genes. These two genes are located close to each other on the short arm of chromosome 6 (6p12).[6,9] The IL17A and IL17F genes have 55% sequence homology with similar expression profiles.[20]

3. SNPs affecting IL-17A

Two important SNPs in the IL17A gene are located in the promoter region. The rs2275913 SNP is a G>A nucleotide base substitution in the IL-17A gene promoter. It is a functional polymorphism located within a binding motif for the nuclear factor activated T cells (NFAT) to the IL-17A promoter. This polymorphism modifies the binding of the transcriptional factor.[19,23] Another SNP, rs8193036, is a C>T base substitution that influenced gene expression by regulating the binding of transcription factors RORγt and RUNX1 to the promoter.[24]

Several studies explored the role of the rs2275913 SNP in the susceptibility to TB. Ocejo-Vinyals et al. first reported in a Spanish population that rs2275913 influenced susceptibility to pulmonary TB, where individuals carrying the G allele and GG genotype had an increased risk of pulmonary TB.[23] Subsequent studies in Chinese and Southern Brazilian populations also showed an association between the rs2275913 SNP and susceptibility to TB. However, in these studies, the A allele was instead associated with TB.[21,25] Espinosa-Soto et al. conducted a study with both active and latent TB patients in Mexico, and while they did not find a significant association between the rs2275913 SNP with susceptibility to active TB, they found that the A allele did increase IL-17A secretion in active TB

patients.[26] These findings are later confirmed by Rolandelli et al. by stimulating peripheral blood mononuclear cells cultured from Argentinean patients carrying the AA genotype with Mtb antigen. The study found higher levels of IL-17A measured in culture supernatants. In addition, the majority of patients carrying the AA genotype also had the highest bacterial burden in sputum and most severe pulmonary lesions.[19]

A study by Wang et al. in Southern Chinese population found an association of the rs8193036 SNP with susceptibility to TB. There was a significant difference in the frequency of polymorphic allele T between patients with active TB and healthy controls. This study also discovered that peripheral blood mononuclear cells from individuals carrying the TT genotype showed an increased level of IL-17A secretion after CD3/28 stimulation.[24]

4. SNPs affecting IL-17F

While several studies on IL-17F SNPs have been performed, the rs763780 SNP is the most well-studied. The rs763780 SNP is a non-synonymous variant that cause a T>C base substitution, resulting in histidine-to-arginine amino acid substitution (H161R). It is located in the third exon of the IL17F gene. The rs763780 SNP was demonstrated to result in a loss in the ability of IL-17F to induce expression of certain cytokines and chemokines, hence acting as a natural antagonist to the wild-type IL-17F. Peng et al. first reported that patients with the CT/TT genotype of the rs763780 SNP were more susceptible to TB compared to the CC genotype.[27] Subsequent studies in Chinese populations supported that the CC genotype of rs763780 gene polymorphism was associated with an increased risk of TB.[25,28]

Rolandelli et al. identified an association between the C allele of the rs763780 SNP and the susceptibility to tuberculosis disease in Argentina. In addition, the study also reported the association between the rs763780 SNP with TB severity, where patients carrying the C allele presented with highest bacilli burden in sputum and more severe disease.[20]

5. Current limitations

While several studies have demonstrated the possible roles of IL-17 SNPs in TB susceptibility, some limitations remain. A lacking heterogeneity of samples is one such concern, as studies regarding the role of IL-17 SNPs in TB susceptibility were mostly conducted in Chinese populations.[6,29] Therefore, future studies need to be conducted in various other populations to provide a better view on how the SNPs in IL-17 may affect host susceptibility to TB in a more diverse population.

A haplotype-based approach may also be beneficial in determining the roles and interactions of various SNPs in host susceptibility to TB. Previous studies demonstrated linkage disequilibrium (LD) between several SNPs and their combined effect towards the susceptibility to TB. The concept of LD determines the nonrandom association of alleles from two or more loci. LD can be influenced through a variety of processes in a population, such as natural selection, strong genetic drift, admixture, and new mutations. Mutation and recombination in future generations may then disrupt the association between each mutant allele and its ancestral haplotype. Future studies with haplotype approach need to identify the responsible functional SNPs in the LD areas with previously-identified risk alleles.[7,29]

Different Mtb strains may also elicit differences in the host immune response towards Mtb. When applied to the context of Indonesian TB patients, most TB cases are caused by modern lineages. The majority of Mtb strains isolated from western part of Indonesia was of East Asian lineage, being predominated by type W-Beijing family strains. Meanwhile, East-African-Indian and Euro-American (Latin American-Mediterranean) lineages tended to predominate Mtb infections in the eastern Indonesian regions. and family D (type LAM) isolates.[30] In a Madagascan study, decreased production of IL-17 was observed in patients infected with modern lineages (2 to 4) compared with patients infected with ancestral lineages.[31] Therefore, future studies elucidating the interactions between infections of different Mtb strains and genetic host factors are greatly needed.

6. Conclusion

The cytokine IL-17 has been known to play an important role in host defense against infectious agents, including Mtb. Therefore, polymorphisms in genes encoding for the IL-17 family may influence host susceptibility to Mtb infection and the development of active TB.

Several SNPs, including rs2275913 and rs8193036 of the IL-17A gene and rs763780 of the IL-17F gene are thought to influence the immune response mediated by IL-17 to tuberculosis through different ways. The rs2275913 and rs8193036 SNPs are located in the promoter of the IL-17A gene. These SNPs affect the expression of the gene by regulating the binding of transcription factors to the promoter region. Meanwhile, the rs763780 SNP is located in the coding region of the IL-17F gene, resulting in an amino acid substitution that affects the function of expressed IL-17.

Current limitations to the studies about the role of IL-17 SNPs include a concern about population heterogeneity, a need for a haplotype-based approach to account for changes in the population, as well as the diversity of infecting Mtb strains and lineages. Future studies are needed to elaborate the interactions of these SNPs with related polymorphisms in a haplotype-based approach, as well as their roles against infection of different Mtb strains.

7. Acknowledgements

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