INTRODUCTION

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (M. tb), most often affects the lungs and it is one of the top 10 causes of death worldwide. World Health Organization (WHO 2019) has reported a total of 10 million incidence rates and 1.5 million deaths worldwide. Individuals exposed to M. tb do not develop active disease. However, about one-third of the world’s population has latent TB, who has been infected by M. tb but are asymptomatic. When a person develops active TB, can infect their household contacts (HHC) who are more prone to develop the disease than the non exposed individuals. This infection mainly depends on immune activation and inflammatory responses. Hence, screening of HHC might help in the early detection of disease or infection for the better control of TB program.

INDUCTION AND DIFFERENTIATION OF Th17

The immune response against M. tb is multifactorial and is mainly depends upon the innate and adaptive immune responses. Tubercle bacilli mainly multiply in the macrophages, which requires a cell-mediated immune response to control the infection by invading the lung phagocytes such as dendritic cells (DCs), macrophages, monocytes and neutrophils. M. tb infected DCs and macrophages interact with T cells, which play an essential role in the development of protective immunity. DCs regulate the immune response through the stimulation of CD4+ T cells, which are differentiated into different types of T helper cells such as Th1, Th2 and Th17 cells. Th1 cells secrete interferon-γ (IFN-γ) and activate the anti-mycobacterial responses in macrophages to
contribute the protection towards the disease.\textsuperscript{9} On the other hand, Th2 cells produce IL-4, IL-5, IL-10 and IL-13 to contribute to the humoral immune response along with eosinophils and B lymphocyte stimulating factors to promote the production of antibodies.\textsuperscript{5} Distinct from Th1 and Th2 lineages, Th17 produces pro-inflammatory cytokines by recruiting leukocytes and neutrophils to create a link between innate and adaptive immunity for killing infected target cells or microbes in early host defence. Production of Th17 is inhibited by IL-4, IL-10 and IFN-γ via downregulation of the IL-23 receptor.\textsuperscript{10,11}

Differentiation of Th17 cells is controlled by retinoic acid-related orphan receptor-γt (ROR-γt), which is a ‘master-regulator’ transcription factor that directs a specific gene expression.\textsuperscript{12,13} It is mediated by the activation of naive T cells in the presence of IL-6, TGF-β, IL-1β, IL-21 and IL-23.\textsuperscript{11} Cytokines IL-6, IL-21 and IL-23 activate another transcription factor STAT3 (signal transducer and activator of transcription3) protein for the expression of ROR-γt and the production of Th17 cytokines such as IL-17A, IL-17F, IL-21 and IL-22.\textsuperscript{3,14} The family of IL-17 consists of six similar members designated from IL-17A (referred to as IL-17) to IL-17F, in which IL-17A and IL-17F are highly homologous and share the IL-17RA receptor.\textsuperscript{2,12} IL-21 is an autocrine cytokine necessary for the continuous production of IL-17, while IL-17A, IL-17F and IL-22 are signature cytokines with similar biological functions and mainly secreted by innate and adaptive lymphocytes that influence the outcome of TB.\textsuperscript{14-16} (Figure 1).

Figure 1 demonstrates the mechanism of Th17 in TB. After interaction with \textit{M. tb} antigen, DCs activate the TCR through the MHC-II complex and regulate the immune response through the naive CD4\textsuperscript{+} T cells. IL-12, IFN-γ and IL-4 inducing differentiation of naive CD4\textsuperscript{+} T cells into Th1 and Th2 lineages, whereas IL-6 along with TGF-β inducing differentiation of Th17 cells via expression of transcription factors (T-bet, ROR-γt or GATA3). Cytokines produced by Th17 inducing the expression of chemokines, which either destruct the pathogen or cause inflammation.\textsuperscript{17,18}
3 | ROLE OF Th17 IN TB PATHOGENESIS

Th17 cytokines play an important role in coordinating the pulmonary immune defence, primarily acting on the lung epithelium and induce several signalling cascades, which mediate neutrophil recruitment to lungs by stimulating the secretion of granulocyte-colony stimulating factor (G-CSF) and CXC chemokines (chemoattractants) to form granuloma by recruiting immune cells to the infected site for killing the bacteria.2,3,15,16,19

In the early stage of infection, neutrophils engulf M. tuberculosis into phagosomes which rapidly fuse with intracellular granules to form phagolysosomes. Th17 cytokines induce the expression of chemokines and promote the recruitment of defensins, monocytes and neutrophilic granulocytes to inflammatory sites to form granuloma to control bacterial growth and mycobacterial destruction.5,14 Neutrophilic granules and their cellular contents such as multiple antimicrobial agents, oxygen-independent lysozyme (peptidoglycan degradation) and lactoferrin (iron chelator) are highly toxic. Through the generation of further reactive oxygen species (ROS), neutrophils release preformed oxidants and proteolytic enzymes from granules to control M. tuberculosis pathogen. During oxidative burst/killing, granule oxidases produce toxic metabolites including superoxide and hydrogen peroxide, which are involved in the assembly of the NOX2-containing NADPH oxidase complex at the phagolysosomal membranes which are essential for bactericides of neutrophils.20,21

In the chronic phase, even if phagocytosis occurs, M. tuberculosis can still escape immune response depending on M. tuberculosis virulence and host immune response. Production of excessive IL-17 levels may prolong the excessive neutrophil recruitment that leads to tissue damage.2,21 The balance between Th1 (macrophages) and Th17 (neutrophils) responses associated with a higher resistance or susceptibility to M. tuberculosis infection.23,24 Th17 cytokines induce the expression of cytokines and chemokines to form granuloma to control bacterial growth and mycobacterial destruction.1

Several genetic variants of Th17 cytokines are essential for bactericides of neutrophils.20,21 Neutrophilic granules and their cellular contents such as multiple antimicrobial agents, oxygen-independent lysozyme (peptidoglycan degradation) and lactoferrin (iron chelator) are highly toxic. Through the generation of further reactive oxygen species (ROS), neutrophils release preformed oxidants and proteolytic enzymes from granules to control M. tuberculosis pathogen. During oxidative burst/killing, granule oxidases produce toxic metabolites including superoxide and hydrogen peroxide, which are involved in the assembly of the NOX2-containing NADPH oxidase complex at the phagolysosomal membranes which are essential for bactericides of neutrophils.20,21

4 | GENETIC VARIANTS OF TH17-RELATED CYTOKINES IN TB

Several association studies have been described in Th17-related cytokine genes such as IL-17A, IL-17F and IL-22 which are involved in the susceptibility, severity and clinical outcome of TB in humans.24,25

The human IL-17A gene is located on chromosome 6p12 and is composed of 3 exons and 2 introns. It is a disulphide-linked homodimeric glycoprotein consisting of 155 amino acids as a homodimer with a molecular weight of around 35 kDa.26,27 Previous studies in IL-17A gene 2KB upstream SNP variants rs2275913 (−197G/A), rs8193036 (−737 C/T), rs3819024 (−444A/G) and 3′ UTR variant rs3748067 (1249 C/T) were reported in TB.3,23,25,28,36 (Table 1).

Earlier studies have shown that IL-17A promoter (rs2275913 −197G/A) polymorphism, where G allele is associated with susceptibility 28,32,33 and A allele with decreased risk of TB.23,29,36

IL-17F gene is composed of 2 exons, the second of which shares significant homology with exon 3 of the IL-17A gene with a similar molecular weight 35 kDa 26,27 IL-17F SNP missense variants, rs763780 (7488T/C), rs2397084 (7383A/G) and rs1889570 (G/A) 2KB upstream genetic variants were reported in TB.9,25,30,35,39 The IL17F rs763780, a non-synonymous variant that causes a His-to-Arg (H161R) substitution was demonstrated to cause a loss in the ability of IL17F to induce expression of certain cytokines and chemokines and shown susceptibility to TB in different populations (Table 1). 30-32,35,39

IL-22 is a member of the IL-10 family, located on chromosome 12q15 composed of 5 coding exons and an additional non-coding exon with a molecular weight of approximately 16.5 kDa.40 Genetic variants in IL-22 promoter rs2227472 (−1851bp), rs2227473 (−1756bp), rs2227478 (−1340bp), rs3819024 (−444A/G) and 3′ UTR variant rs3748067 (1249 C/T) were reported in TB (Table 1).

Among these, the rs2227472 polymorphism is related to the risk of pulmonary TB, in which G allele is the risk factor and it controls IL-22 response upon M. tuberculosis infection by affecting the protein expression.40

5 | DISCUSSION

Several studies have reported that Th17-related gene polymorphisms are associated with inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, asthma, Grave’s disease, ulcerative colitis, cancer and TB.41-50 Th17 cytokine genes are important for host susceptibility and TB progression. Multiple studies have focused on the correlations between IL-17A rs2275913, rs3748067; IL-17F rs763780, rs1889570 & rs9382084 gene polymorphisms with TB but the results were inconsistent.9,23,25,28,36,39

In IL-17A polymorphisms, the combined effect of rs2275913 and rs3748067 has shown risk towards TB in the Chinese population.9 IL-17A rs2275913 SNP AA genotype
### Table 1: Single nucleotide polymorphisms (SNPs) of Th17-related cytokines IL-17A, IL-17F and IL-22 variants in TB patients and healthy controls in different populations

| SNP location | Sample size (N) | Association | Population | References |
|--------------|----------------|-------------|------------|------------|
| IL-17A rs2275913 G/A | 192 | G allele and GG genotype associated with susceptibility to TB (P < .05) | Spanish | 28 |
| IL-17Ars2275913 G/A | 191 | AA genotype and A carrier (AG/AA) associated with protection against TB (P < .05) | Southern Brazilian | 29 |
| IL-17F rs763780 T/C | 596 (PTB), 176 (EPTB) | CT/TT genotypes are associated with susceptibility to TB (P < .05) | Chinese | 30 |
| IL-17A rs2275913 G/A & rs3748067 C/T | 1601 | A combined effect of rs2275913 and rs3748067 together showed the risk of TB (P < .05) | Chinese | 9 |
| IL-17A rs2275913 G/A & rs3748067 C/T | 428 | No significant association (P > .05) | Chinese | 31 |
| IL-17F rs763780 T/C | 336 | AA genotype and the GA + AA genotypes are associated with susceptibility to TB (P < .05) | Chinese | 32 |
| IL-17F rs2397084 A/G | 115 | G allele is associated with susceptibility to TB (P < .05) | Mexican Amerindian | 33 |
| IL-17A rs2275913 G/A | 185 | AA genotype is associated with protection against TB (P < .05) | Argentinian | 23 |
| IL-17A rs3748067 C/T | 244 | CC genotype is associated with susceptibility to TB (P < .05) | Croatian Caucasian | 34 |
| IL-17A rs3748067 C/T | 2161 | No statistically significant association in both (P > .05) | Asian | 35 |
| IL-17A rs3748067 C/T | 3905 | A allele, AG and AA+AG genotypes associated with protection against TB (P < .05) | Asian and four in Caucasians | 36 |
| IL-17F rs763780 T/C | 200 | The C allele is associated with susceptibility to TB (P < .05) | Argentinian | 39 |
| IL-22 rs2227473 | 479 | Associated with susceptibility to TB (P < .05) | Chinese | 40 |

**Abbreviations:** EPTB, Extra pulmonary TB; PTB, pulmonary TB.
is protective against TB in Argentinean and Caucasian populations [23, 36]. In the Brazilian population, it was suggested that A allele of rs2275913 (~197G/A) is associated with TB protection.[29] In contrast, in the Chinese population GA +AA genotypes are associated with susceptibility.[32] In Northern Spain, Mexican Amerindian populations were reported that the G allele and GG genotype were significantly more frequent in TB patients than controls.[28,33] Few reports confirmed an association between the rs2275913 and TB in populations from Sudanese, Spain and China[25,28,32] whereas other studies failed to show the association in Chinese and Croatian population.[30,31,34,35]

In IL-17F, rs763780 (7488T/C) CT &TT genotypes are strongly associated with susceptibility towards TB in the Chinese population.[30] In another Chinese study, it was reported that the CC and TC genotypes were associated with an increased risk of TB when compared with the TT genotype.[32] It was confirmed that C allele and CC genotype were associated with increased risk of TB in Argentinean and Asian population.[35,39]

In the Indian population, the IL-17A rs2275913 and IL17F rs763780 were not associated with the risk of TB and also there was no difference in serum levels between cases and controls.[51]

Further, a meta-analysis did not indicate any association of IL-17A rs2275913 with the risk of TB. However, wild-type "C" allele of IL-17A rs3748067 and the mutant "C" allele of IL-17F rs763780 polymorphisms are involved in susceptibility towards TB in Asian population.[35]

In the IL-22 gene, among the other studied SNPs, rs2227473 polymorphism has shown G allele as the risk factor towards TB in the Chinese population.[40]

The results that are shown in the present review confirmed that there are discrepancies in the outcome of the studies which may be due to differences in genetic backgrounds, study design and sample size. Further studies are needed to assess the associations in a large sample size.

6 CONCLUSION

Indeed, there are several previous studies reported on the role of IL-17 in TB, however, the factors which influence the disease outcome is not clear. The interaction of M. tuberculosis components with innate and adaptive cells produces higher levels of IL-17, which induces tissue damage and the release of other cytokines and chemokines. On the other hand, IL-17 recruits immune cells at the site of infection and restricts the pathogenesis.

Association studies of Th17 cytokines which are related to TB have shown the influence of genes in the susceptibility to infection. With this scenario, the screening of the HHC of patients might help in identifying the susceptible genetic markers, and setting longitudinal studies to investigate further may help in better understanding of the role of Th17 in TB pathogenesis.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

GSL conceived the concept. RBL, PA, SG, PLK and GSL wrote the manuscript. All authors read, edited and agreed to publish the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

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