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Molecular and transcriptional regulation of the interleukin-10 gene: Implications of the -1082 G/A promoter polymorphism on the immune response in pulmonary tuberculosis

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ABSTRACT

Background: Host immune responses critically determine tuberculosis outcomes. Although the interleukin-10 (IL-10) -1082 G/A promoter polymorphism alters IL-10 expression and pulmonary tuberculosis susceptibility, global studies report conflicting findings that lack a comprehensive molecular synthesis. Objective: This review critically evaluates IL-10 molecular regulation and the immunological and clinical implications of the -1082 G/A polymorphism in pulmonary tuberculosis. Methods: A narrative literature review utilized PubMed, ScienceDirect, and Google Scholar (2008–2026). Employing a structured literature selection flowchart and the Joanna Briggs Institute (JBI) Critical Appraisal tools for quality assessment, 55 high-quality articles were ultimately selected and synthesized narratively. Results: The G allele exhibits greater affinity for the Sp1 transcription factor, increasing IL-10 expression. This hyper-secretion suppresses macrophage activation and Th1-mediated immunity via the JAK/STAT pathway. Crucially, susceptibility differences among populations are heavily influenced by linkage disequilibrium, ethnic genetic diversity, epigenetic regulation, and gene–environment interactions. Conclusion: This review provides an integrated perspective linking the IL-10 promoter polymorphism with immune regulation, highlighting its potential as a predictive biomarker for precision medicine and risk stratification in vulnerable demographics. Large-scale, multi-ethnic longitudinal studies integrating genetic and epigenetic analyses are recommended.

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INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide from a single infectious agent (Ahmed, 2025). Exposure to Mycobacterium tuberculosis (M.tb) produces a broad clinical spectrum where only about 5-10% of infected individuals develop active TB, while the

majority control the infection in a latent state (Adane et al., 2021; Liu et al., 2025; Montenegro et al., 2024). This phenomenon confirms that environmental factors and pathogen virulence are not the only disease determinants, as immunological status and genetic predisposition play a central role in individual susceptibility (Naranbhai, 2016; Tipparthi et al., 2022).

The immune response to M.tb involves dynamic interactions between the innate and adaptive immune systems, where alveolar macrophages act as the first line of defense by phagocytizing the bacteria (De Martino et al., 2019; Flynn & Chan, 2022; Tobin & Tristram, 2024). Macrophages and dendritic cells respond to the infection by producing pro-inflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF-α) and Interferon-Gamma (IFN- γ), which are essential for bacterial elimination (Cavalcanti et al., 2012; Etna et al., 2014). Simultaneously, immune cells also produce anti-inflammatory cytokines, specifically Interleukin-10 (IL-10), to maintain immune balance and prevent immunopathological damage to lung tissue (Redford et al., 2011; Wong et al., 2020).

Although IL-10 has a protective function for host tissues, M.tb exploits high levels of this cytokine for immune evasion (Bouzeyen et al., 2019; Park et al., 2021). IL-10 production significantly suppresses macrophage activation and inhibits Th1 cell differentiation, creating a microenvironment conducive to bacterial survival (Redford et al., 2011). IL-10 production levels are genetically regulated and influenced by genetic variations, particularly single nucleotide polymorphisms in the IL-10 gene promoter region (Asgharzadeh et al., 2016; Joshi et al., 2015).

Despite the established theoretical understanding of IL-10's immunosuppressive role, current epidemiological findings regarding the -1082 G/A polymorphism remain highly contradictory. For instance, while studies in Indian and Brazilian populations identify the G allele and GG genotype as significant risk factors for active TB progression (Joshi et al., 2018; Montenegro et al., 2024). Research in Ukrainian and certain Iranian cohorts paradoxically suggests a protective effect of the same genotype (Asgharzadeh et al., 2016; Butov et al., 2016). This fundamental controversy highlights a critical research gap previous reviews have largely treated this polymorphism in isolation, failing to critically analyze the underlying factors such as linkage disequilibrium, epigenetic modifications, and distinct gene-environment interactions that drive these cross-population disparities. This study critically evaluates the interplay between the -1082 G/A variant and ethnic-specific clinical outcomes. The comprehensive objective of this narrative review is to dissect the molecular and transcriptional regulation of the IL-10 gene, analyze the root causes of the prevailing genetic controversies, and propose how understanding this polymorphism can advance molecular diagnostics and precision medicine strategies in managing pulmonary TB.

RESEARCH METHOD

This study employed a Narrative Literature Review design to comprehensively synthesize current evidence regarding the molecular regulation of the interleukin-10 (IL-10) gene and the implications of the -1082 G/A promoter polymorphism in pulmonary tuberculosis. A narrative review approach was selected because it enables broad and critical integration of findings from diverse study designs, facilitating the interpretation of complex interactions among genetic polymorphisms, transcriptional regulation, epigenetic mechanisms, and host immune responses. Considering the substantial heterogeneity of available evidence across different ethnic populations and study methodologies, a systematic review or meta-analysis was considered less appropriate for addressing the objectives of this review.

A structured literature search was conducted using three electronic databases PubMed, ScienceDirect, and Google Scholar, covering publications published between 2008 and 2026. The Boolean search strategy consisted of the following keywords: ("Interleukin-10" OR "IL-10") AND ("Polymorphism" OR "Promoter -1082 G/A") AND ("Tuberculosis" OR "Pulmonary TB") AND ("Immune Response" OR "Sp1 Transcription Factor").

Studies were eligible if they were original research articles (case-control, cohort, cross-sectional, or clinical studies) or authoritative review articles investigating the IL-10 -1082 G/A promoter polymorphism, IL-10-mediated signaling pathways, or their relationship with pulmonary tuberculosis susceptibility and immune responses. Articles published in languages other than English, studies lacking clinical relevance, purely in vitro investigations without translational implications, and publications with insufficient methodological information were excluded.

The initial search retrieved a comprehensive pool of literature. Following the removal of duplicates and an initial title/abstract screening, full texts were thoroughly assessed. A literature selection flowchart (Figure 1) was utilized to transparently track the identification, screening, and inclusion of the articles. Ultimately, 55 high-quality articles and supporting literature met all inclusion criteria for the comprehensive narrative synthesis. To ensure high levels of evidence and minimize selection bias within this narrative review, a rigorous quality assessment was conducted using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist appropriate for each study design. While the full set of 55 references was utilized to critically discuss the molecular, epigenetic, and immunological mechanisms, a specific subset of 11 representative epidemiological studies was systematically selected to be summarized in Table 1. The overall evidence was synthesized narratively to identify existing controversies, clinical implications, and future research directions.

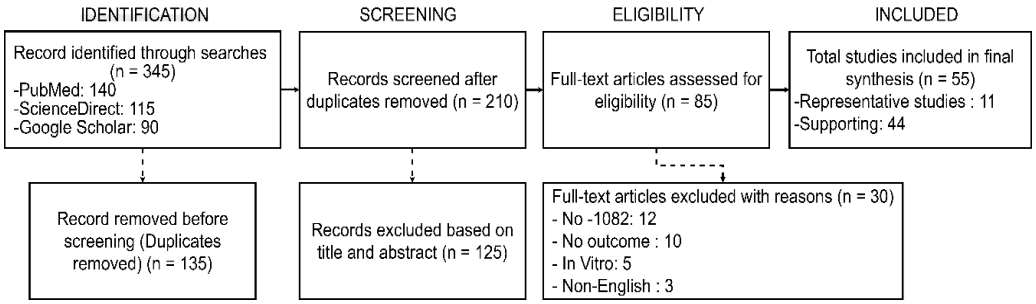

Figure 1. Structured literature selection flowchart detailing the identification, screening, and inclusion of articles for the narrative review

RESULTS AND DISCUSSIONS

The initial database search yielded 345 records. Following the removal of duplicates and rigorous screening based on predefined eligibility criteria, 55 high-quality articles were ultimately included in this narrative synthesis, as detailed in the selection flowchart (Figure 1). Among these, 11 representative epidemiological studies evaluating the clinical association between the IL-10 -1082 G/A polymorphism and tuberculosis susceptibility across various populations are highlighted in Table 1.

Table 1. Representative studies evaluating the association between the IL-10 -1082 G/A promoter polymorphism and pulmonary tuberculosis susceptibility

Author & Year	Population	Study Design	Sample Size Case/Control	Key Findings
Montenegro et al., (2024)	Brazil	Case-Control	101/71	G allele/AG/GG are risk factors for PTB.
Amoras et al., (2023)	Brazil	Case-Control	100/245	GG genotype associated with increased active TB risk.
Abdelraheem et al., (2021)	Egypt	Case-Control	60/30	GG and AG genotypes are risk factors for MDR-TB.
Adane et al., (2021)	Ethiopia	Cross-Sectional	100/100	No significant correlation found for A allele/AA.
Wani et al., (2021)	India	Case-Control	100/102	GG genotype associated with reduced risk of EPTB.
Silva et al., (2020)	Brazil	Case-Control	141/135	No significant effect of -1082 SNP.

Joshi et al., (2018)	India	Case-Control	150/150	GA genotype confers 2.3 fold higher risk for Active PTB.
He et al., (2018)	China	Case-Control	467/503	GG genotype protective against TB
Shahsavar et al., (2016a)	Iran	Case-Control	100/100	AG genotype frequency increased potential risk marker.
Asgharzadeh et al., (2016)	Iran	Case-Control	124/200	AA more frequent in controls (protective).
Butov et al., (2016)	Ukraine	Case-Control	140/30	GG genotype protective against TB.

Immune Response Against *Mycobacterium tuberculosis* Infection

The immune response against *Mycobacterium tuberculosis* (*M.tb*) represents a complex interaction between bacterial survival strategies and host immune regulation, and although exposure to *M.tb* is common worldwide, only a subset of infected individuals develop active tuberculosis, indicating that differences in host immune responses influence disease progression and susceptibility to active infection (Naranbhai, 2016; Tipparthi et al., 2022). Following inhalation, *M.tb* enters the alveolar environment and is initially recognized by innate immune cells, particularly macrophages and dendritic cells, which detect mycobacterial components through pattern recognition receptors, initiating inflammatory signaling pathways that contribute to early bacterial containment (De Martino et al., 2019; Flynn & Chan, 2022).

Activated macrophages produce pro-inflammatory cytokines, including TNF-α and IFN-γ, which are essential for macrophage activation, granuloma formation, and intracellular control of *M.tb* replication (Cavalcanti et al., 2012; Etna et al., 2014). Dendritic cells further promote adaptive immunity through antigen presentation, resulting in activation of CD4+ T cells and differentiation into Th1 cells that produce IFN-γ to enhance macrophage antimicrobial activity (Zhuang et al., 2024). However, effective immune control of *M.tb* requires a balance between inflammatory activation and immune regulation, as excessive inflammatory responses may lead to tissue damage, whereas insufficient immune activation may allow bacterial persistence within host cells (Redford et al., 2011). Therefore, regulatory cytokines such as Interleukin-10 (IL-10) play an important role in maintaining immune balance during tuberculosis infection (Wong et al., 2020).

Role of Interleukin-10 in Tuberculosis Immunopathogenesis

Interleukin-10 (IL-10) is an immunoregulatory cytokine that functions to limit excessive inflammatory responses and prevent immune-mediated tissue injury during infection (Redford et al., 2011). However, in tuberculosis, increased IL-10 activity may suppress protective immune mechanisms and contribute to bacterial persistence (Teixeira et al., 2017). IL-10 inhibits macrophage activation, reduces antigen presentation, and suppresses production of inflammatory mediators required for effective intracellular killing of *M.tb* infection (Redford et al., 2011). These effects may reduce macrophage antimicrobial activity and impair the ability of host cells to eliminate intracellular bacteria (Ferreira et al., 2021).

In addition, IL-10 negatively regulates Th1-mediated immune responses by reducing IFN-γ production and limiting macrophage activation (Teixeira et al., 2017). This immunosuppressive effect may create a favorable environment for *M.tb* survival and contribute to progression from controlled infection toward active pulmonary tuberculosis (Bouzeyen et al., 2019). The dual role of IL-10 as both a regulator of inflammation and a potential mediator of immune escape highlights the importance of understanding its molecular regulation, including genetic variations within the IL-10 promoter region that may influence cytokine production and tuberculosis susceptibility (Zhang & Kuchroo, 2019).

Gene Structure and Expression Regulation of Interleukin-10

Based on the central dogma of molecular biology, the flow of genetic information is precisely controlled to ensure the information forms an efficient immune response (Mercadante et al., 2019). The human IL-10 gene is located on the long arm of chromosome 1 (1q32.1), measuring approximately 4.9 kilobases (kb) in length and consisting of 7 exons (National Library of Medicine, 2025). IL-10 expression is regulated through three main molecular stages: chromatin structural

changes (epigenetics), transcriptional regulation in the promoter region, and post-transcriptional regulation (Rutz & Ouyang, 2016; Zhang & Kuchroo, 2019).

Crucial transcriptional control occurs in the 5' flanking region (promoter), which contains cis-regulatory elements (Caragine et al., 2025). Rather than functioning as a static blueprint, the IL-10 promoter region acts as a highly dynamic rheostat heavily influenced by epigenetic modifications (Zhang & Kuchroo, 2019). For instance, DNA methylation at CpG islands within the promoter directly dictates gene accessibility (Zheng et al., 2020). Hypermethylation physically obstructs the binding of crucial transcription factors, effectively silencing IL-10 expression regardless of the underlying genetic sequence (Zheng et al., 2020). This epigenetic layer is critical for scientific interpretation, a patient may carry the high-producing GG genotype, but if the promoter is heavily methylated due to environmental stressors or severe malnutrition, the expected IL-10 hypersecretion will not manifest (Rutz & Ouyang, 2016). Therefore, genetic screening of the -1082 G/A polymorphism must be interpreted alongside the patient's epigenetic landscape to accurately predict immune responses (Zhang & Kuchroo, 2019).

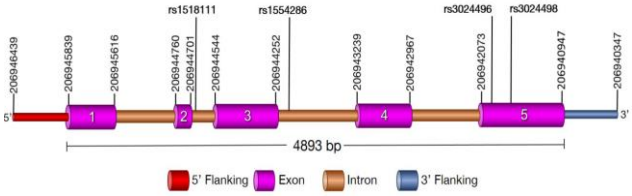

Figure 2. Structure of the human IL-10 gene (Mishra et al., 2015)

Gene components are color-coded as follows: exons (pink), introns (brown), 5' flanking (red), and 3' flanking (blue) (Mishra et al., 2015)

Manipulation of IL-10 Signaling Pathways by Mycobacterium tuberculosis

To maintain intracellular survival, M.tb actively stimulates host cells, primarily targeting macrophages and dendritic cells, to secrete excess IL-10 (Zhai et al., 2019). This cytokine exerts biological effects by binding to a heterotetrameric receptor complex on the cell surface consisting of the IL-10Rα subunit (primary ligand binder) and the IL-10Rß subunit (accessory signaling) (Carlini et al., 2023).

Receptor binding triggers a signaling cascade via the main canonical Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathway (Sun et al., 2021). This process activates JAK1 and Tyk2 kinases, which activate each other through phosphorylation and recruit STAT3 molecules Once phosphorylated, STAT3 forms dimers and translocates to the nucleus where it induces the transcription of anti-inflammatory genes, such as Suppressor of Cytokine Signaling 3 (SOCS3), and suppresses pro-inflammatory activation pathways, such as NF-κB (Antoniv & Ivashkiv, 2011; Ip et al., 2017; Lali et al., 2016). Additionally, IL-10 mediates cellular survival by activating the non-canonical PI3K/Akt pathway (Antoniv & Ivashkiv, 2011; Sun et al., 2021).

As a result of this immunosuppressive cascade, macrophage bactericidal function is paralyzed (Teixeira et al., 2017). IL-10 inhibits phagolysosome maturation, downregulates the expression of Major Histocompatibility Complex (MHC) class II molecules, and reduces the production of essential lethal antimicrobial agents such as reactive nitrogen intermediates (RNI) (Ferreira et al., 2021; Sudarto et al., 2025) Furthermore, IL-10 directly dampens pathogen-specific T cell proliferation and blocks IFN-γ production by Th1 cells, which is essential in controlling tuberculosis (Ferreira et al., 2021; Teixeira et al., 2017).

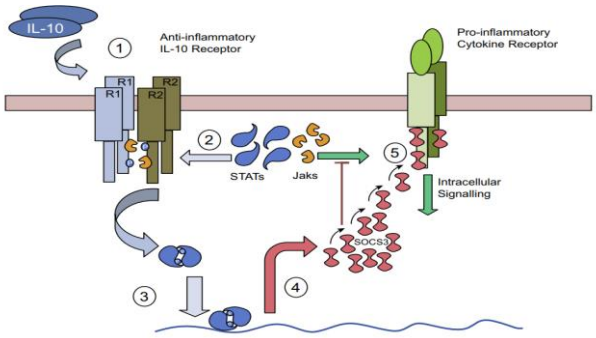

Figure 3. IL-10 signaling through binding to its receptor complex (Lali et al., 2016)

As depicted in Figure 3, the IL-10/JAK/STAT cascade is not merely a physiological feedback loop, but a critical vulnerability actively exploited by *M.tb*. The induction of SOCS3 does more than dampen inflammation, it acts as a definitive brake on pro-inflammatory cytokine receptors, effectively paralyzing the host's bactericidal machinery. Understanding this structural pathway highlights the exact molecular juncture where precision interventions such as targeted JAK1 inhibitors could potentially decouple this *M.tb*-induced immunosuppression in high-risk patients carrying the GG genotype.

The profound immunosuppressive cascade initiated by the IL-10/JAK/STAT axis presents significant clinical implications and novel therapeutic targets. In the era of precision medicine, identifying patients with the high-producing GG genotype opens the door for targeted immunomodulation (Amoras et al., 2023; Montenegro et al., 2024). For patients exhibiting extreme IL-10 hypersecretion and failing standard anti-TB therapy, localized delivery of IL-10 neutralizing antibodies or specific JAK1/STAT3 inhibitors could theoretically release the brake on macrophage bactericidal activity (Redford et al., 2011; Sun et al., 2021). Furthermore, understanding this pathway provides an opportunity for molecular diagnostics, profiling a patient's IL-10 genotype could help clinicians stratify the risk of rapid disease progression or multidrug-resistant tuberculosis (MDR-TB), allowing for the customization of treatment duration and the early introduction of host-directed therapies (Abdelraheem et al., 2021; Sadeghi Shermeh et al., 2020).

Implications of the -1082 G/A Promoter Polymorphism on Host Susceptibility

IL-10 production varies greatly among individuals due to genetic variations in the promoter region (Sadeghi Shermeh et al., 2020). The single nucleotide polymorphism at position -1082 involves the substitution of Guanine (G) with Adenine (A), functionally altering the transcriptional regulation of the gene (Ahmad et al., 2025; Almolakab et al., 2022). Transcriptional-level studies show that the Sp1 transcription factor preferentially binds the G allele at this site with a much higher affinity than the A allele (Larsson et al., 2010).

Strong Sp1 binding to the G allele triggers increased promoter activity and transcription rates, which correlates directly with increased production of mRNA and IL-10 protein (Larsson et al., 2010). Consequently, individuals carrying the homozygous GG genotype are categorized as high IL-10 producers, those with the heterozygous GA genotype are medium producers, and the homozygous AA genotype yields the lowest producers (Surhan et al., 2018).

This genetically driven cytokine production profile directly modifies the host immune response balance against M.tb (Shahsavar et al., 2016; Wani et al., 2021). Pulmonary TB patients with genotypes containing the G allele tend to experience IL-10 hypersecretion, which predominantly suppresses the Th1 immune response and triggers infection progression to active TB(Metanat et al., 2013; Surhan et al., 2018). Cross-population data proves this phenomenon, as studies in India, Iran, and Brazil found a significant association where the presence of the G allele or GA/GG genotype is a risk factor that increases susceptibility to active TB(Amiri et al., 2022; Ates

et al., 2008; Montenegro et al., 2024). However, inconsistent findings exist in other populations, such as a protective effect of the GG genotype reported in Ukraine, confirming that disease susceptibility is heavily determined by interactions between genetic backgrounds and environmental factors in each local population (Butov et al., 2016; Liu et al., 2022) .

While these molecular mechanisms provide a clear biological framework, the translation of these genetically driven cytokine profiles into clinical outcomes is highly complex and not straightforward (Abel et al., 2018; Naranbhai, 2016). A critical comparison of international cohorts reveals stark contradictions in disease susceptibility (Abel et al., 2018). Studies conducted in Northeast Brazil, Egypt, and the Iranian Lur population consistently identified the G allele and the AG/GG genotypes as significant risk factors for PTB and multi-drug resistant tuberculosis (MDR-TB) (Abdelraheem et al., 2021; Montenegro et al., 2024; Shahsavar et al., 2016). Similarly, a comprehensive study in a Tibetan Chinese population correlated multiple IL-10 single nucleotide polymorphisms (SNPs) with an increased risk of PTB (He et al., 2018).

Conversely, findings from other geographic regions present a protective or null effect for the exact same genotype (Trajkov et al., 2009). In the Ukrainian population, the GG genotype was found to exert a protective effect against PTB (Butov et al., 2016). In the Iranian Azeri population, the AA genotype was more frequent in healthy controls, suggesting a protective role against disease progression (Asgharzadeh et al., 2016). Furthermore, studies in Ethiopia and the Brazilian Amazon region found no significant isolated effect of the -1082 SNP on TB susceptibility, while research on Kashmiri Indians demonstrated that the GG genotype was associated with a reduced risk of extrapulmonary tuberculosis (EPTB) (Adane et al., 2021; Silva et al., 2020; Wani et al., 2021).

This fundamental controversy cannot be attributed to mere chance; rather, it is driven by a complex interplay of multiple variables that modulate the clinical impact of the IL-10 polymorphism (Abel et al., 2018; Naranbhai, 2016). First, regarding Ethnic Genetic Background and Population Substructure, human genetic diversity is heavily influenced by environmental selective forces, leading to population-specific allele distributions (Kehdy et al., 2015). In admixed populations, such as those in the Brazilian Amazon, individuals possess varying proportions of African, European, and Amerindian ancestries, which directly influence genetic susceptibility (Silva et al., 2020). The failure to account for genomic ancestry and population substructure can lead to misinterpretations of genetic associations (Hinds et al., 2004; Silva et al., 2020). Furthermore, the genetic distance and historical admixture of populations such as the similarity of the Iranian Azeri IL-10 genotype frequencies to Saudi Arabians rather than East Asians highlight how migration and evolutionary history shape localized disease resistance (Asgharzadeh et al., 2016).

Second, concerning Linkage Disequilibrium (LD) and Haplotype Blocks, the biological impact of a polymorphism is rarely isolated (He et al., 2018; Silva et al., 2020). The -1082 A>G variant is often inherited as part of a larger haplotype block, in strong linkage disequilibrium (LD) with the -819 C>T and -592 A>C SNPs within the IL-10 promoter (Silva et al., 2020). Haplotype analyses, such as those performed in the Tibetan Chinese and Brazilian cohorts, demonstrate that the protective or detrimental effect often stems from the specific haplotype block prevalent in an ethnic group, rather than the isolated locus (He et al., 2018; Silva et al., 2020). For example, the *ATGGATA* haplotype block significantly decreased PTB risk in Tibetan Chinese individuals, proving that regional LD architecture dictates the ultimate immunological outcome (He et al., 2018).

Third, regarding Gene-Gene Interactions (Epistasis), tuberculosis pathogenesis is inherently polygenic, meaning the host immune response relies on complex cytokine networks (Amoras et al., 2023). Single SNP analysis often masks true susceptibility because the effects of IL-10 hypersecretion can be amplified or neutralized by concurrent polymorphisms in pro-inflammatory genes (Joshi et al., 2018). Multifactor dimensionality reduction (MDR) analysis in an Indian cohort revealed that the IL-10 GA genotype only becomes a high-risk factor when interacting synergistically with specific IL-6 and TNF-α genotypes (Joshi et al., 2018). Similarly, an

Amazonian study showed that combined allelic profiles of IFNG (+874 A/T) and IL4 (-590 C/T) drastically alter the risk of developing active TB (Amoras et al., 2023).

Finally, Environmental Factors and Methodological Variance further exacerbate discrepancies across studies, specifically regarding sample sizes, varying clinical definitions (e.g., MDR-TB vs. latent TB), and the logic of association studies (Abdelraheem et al., 2021; Amoras et al., 2023). Moreover, environmental factors interact dynamically with the host's genetic background (Montenegro et al., 2024). Factors such as localized nutritional status, environmental selective pressures, and exposure to different strains of *M. tuberculosis* dictate whether a high IL-10 phenotype results in tissue protection or fatal bacterial persistence (Asgharzadeh et al., 2016).

CONCLUSION

This narrative review elucidated the dualistic and highly complex role of Interleukin-10 in tuberculosis immunopathogenesis. The primary scientific contribution was the critical synthesis of previously conflicting global data, demonstrating that the ultimate clinical impact of the -1082 G/A polymorphism is heavily dictated by a complex interplay involving linkage disequilibrium, ethnic haplotypes, and epigenetic modifications. Clinically, these findings held substantial practical implications for healthcare practice. The identification of the -1082 G/A polymorphism served as a highly promising predictive biomarker for precision medicine, allowing for the early risk stratification of vulnerable demographics, including pregnant women. For future research, it was highly recommended to shift from isolated cross-sectional observations to large-scale, multi-ethnic longitudinal cohorts that integrate genetic profiling with targeted host-directed therapies

Limitations and future works, this review has certain limitations. First, the included studies primarily consist of cross-sectional and population-based research, which provides a snapshot of IL-10 activity rather than a continuous longitudinal assessment. Second, the variability in genetic backgrounds across different global populations may influence the consistency of the observed IL-10 promoter polymorphism effects. Future research should prioritize longitudinal clinical studies to monitor changes in IL-10 expression and activity over time in response to tuberculosis treatment. Future studies should focus on longitudinal clinical investigations integrating IL-10 genetic variants, cytokine expression profiles, and clinical outcomes in pulmonary tuberculosis.

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