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THE ROLE OF TOLL-LIKE RECEPTOR-2 IN THE PATHOGENESIS OF PULMONARY TUBERCULOSIS

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ABSTRACT

Pulmonary tuberculosis (PTB), primarily caused by Mycobacterium tuberculosis (M.tb), remains a major global health burden. Toll-like receptor 2 (TLR-2), a critical component of the innate immune system, plays a key role in the host-pathogen interaction by recognizing specific components of the mycobacterial cell wall and initiating downstream inflammatory pathways. However, the dual role of TLR-2 in both protective immunity and immune evasion by M.tb contributes to the complexity of TB pathogenesis. This study aims to investigate the role of Toll-Like Receptor-2 (TLR-2) in the pathogenesis of pulmonary tuberculosis, including its immunological mechanisms, relationships with disease severity, and the potential of TLR-2 as a diagnostic and therapeutic target. This literature review systematically analyzed molecular mechanisms involving TLR-2 signaling in pulmonary TB using peer-reviewed primary and secondary sources from experimental and clinical studies. Emphasis was placed on signal transduction (NF-κB and MAPK), cytokine profiles, antigen presentation, and the impact of TLR-2 gene polymorphisms on TB susceptibility. Activation of TLR-2 through ligands such as lipoproteins, lipoarabinomannan (LAM), and PE/PPE proteins initiates immune responses via MyD88-dependent pathways, leading to the release of proinflammatory cytokines (TNF-α, IL-6, IL-12). TLR-2 also enhances the function of macrophages and dendritic cells, promoting Th1-mediated immunity. However, chronic or excessive stimulation of TLR-2 can suppress antigen processing, promote IL-10 expression, inhibit phagolysosome fusion, and facilitate M. tb survival within host macrophages. Polymorphisms in the TLR-2 gene (e.g., rs3804099) have been associated with increased susceptibility and variable clinical outcomes in PTB. TLR-2 plays a paradoxical role in pulmonary tuberculosis by mediating both protective immunity and facilitating immune evasion by M.tb. Understanding the balance of TLR-2 signaling and genetic variation is crucial for developing immunomodulatory therapies and personalized interventions in TB management.

Keywords: cytokines; gene polymorphism; innate immunity; mycobacterium tuberculosis; nf-κb; pulmonary tuberculosis

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INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis (M.tb), remains a leading global infectious disease. The World Health Organization (WHO) estimates that each year there are 8.6 million new TB cases and 1.3 million deaths, including substantial numbers among children and individuals with HIV co-infection (Organization, 2022). Most cases are

concentrated in Southeast Asia, Africa, and the Western Pacific, with India and Indonesia together contributing over a third of the global burden. In 2017, Indonesia reported over 420,000 new TB cases, with a male-to-female ratio of 1.4:1, likely linked to higher exposure to risk factors such as smoking (Kemenkes, 2023). M.tb is an airborne, aerobic bacillus that primarily targets the lungs (Isbaniah et al., 2021). The innate immune system plays a crucial role in the early recognition and control of M. tuberculosis (M.tb) infection. Toll-like receptors (TLRs), particularly TLR2, are pattern recognition receptors (PRRs) that detect microbial components and initiate inflammatory responses (Kawai & Akira, 2011; Takeuchi & Akira, 2010). The innate immune system is the body's first line of defense against pathogen invasion, including M.tb. TLRs function as molecular sensors that recognize pathogen-associated molecular patterns (PAMPs) and trigger cellular immune responses(Takeuchi & Akira, 2010). TLR-2 plays a central role in recognizing various components of the M.tb cell wall, such as lipoproteins, lipoarabinomannan (LAM), and PE/PPE family proteins (Kawai & Akira, 2011). Activation of TLR-2 triggers intracellular signaling pathways through the Myeloid Differentiation Primary Response 88 (MyD88) adaptor protein, which subsequently activates Nuclear Factor kappa B (NF-κB) and Mitogen-Activated Protein Kinase (MAPK).

Although TLR-2 activation plays a crucial role in combating M. tuberculosis (M.tb) infection, recent studies have demonstrated that M.tb can also utilize TLR-2 to evade the host immune response. This mechanism is known as immune evasion. Several studies have demonstrated that chronic stimulation of TLR-2 increases the expression of anti-inflammatory cytokines, such as Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β), which play a crucial role in suppressing immune cell activity. In addition, M.tb can also interfere with the fusion process of phagosomes and lysosomes through modulation of TLR-2 signals, allowing bacteria to survive and replicate in macrophages [8]. Imbalance or imbalance in the immune response caused by TLR-2 overactivation can lead to more severe pulmonary TB disease progression This pathway then stimulates the production of various pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and Interleukin-12 (IL-12), which are critical for macrophage activation and induction of T-helper 1 (Th1) cell-mediated immunity. (Takeuchi & Akira, 2010). TLR2 recognizes M.tb cell wall ligands such as lipoproteins and lipoarabinomannan, forming heterodimers with TLR1 or TLR6 to activate downstream MyD88-dependent signaling 6. This leads to the activation of NF-κB and the production of pro-inflammatory cytokines, such as TNF-α and IL-6. Genetic polymorphisms in the TLR2 gene may alter its immune function and influence individual susceptibility to TB4.

Along with the development of molecular biology technology, the understanding of the role of TLR-2 in the pathogenesis of pulmonary TB is growing. In vitro and in vivo studies using animal models, as well as clinical analysis in TB patients, provide a more detailed picture of the dynamics of TLR-2 in the context of M.tb infection. The literature suggests that manipulation of TLR-2 signals may be a potential target in the development of future TB immunomodulatory therapies. On the other hand, studies on TLR-2 polymorphisms also open up opportunities for the application of genetic-based TB treatment strategies. The purpose of this research is to review the role of TLR2 in pulmonary TB pathogenesis, focusing on its molecular interactions with M. tuberculosis, downstream signaling, and genetic variations that may affect host immune responses.

METHOD

This study is a literature review study with a systematic narrative review approach that aims to identify, analyze, and synthesize data related to the role of Toll-like receptor 2 (TLR-2) in the pathogenesis of Pulmonary Tuberculosis, focusing on its molecular interactions with M.tb, downstream signals, and genetic variations that can affect the host immune response. The data

sources used in this study are primary articles and reviews obtained from various international electronic databases, including: PubMed, ScienceDirect, SpringerLink, Google Scholar, NCBI (National Center for Biotechnology Information). The search was conducted for publications from 2015 to 2025, to ensure that the information obtained is still relevant and up-to-date in accordance with the latest scientific developments related to TLR-2 and the pathogenesis of Tuberculosis. Articles included in this review must meet the following criteria: 1) Original research, review articles, or meta-analyses; 2) Have a main topic related to TLR-2 and its role in the pathogenesis of Pulmonary TB, both in terms of protective immunity and immune evasion; 3) Use research subjects in the form of humans, animal models, or in vitro models related to Mycobacterium tuberculosis infection; 4) Publication in the period 2010–2025; 5) Full-text available. Meanwhile, articles that were excluded from the analysis were: 1) Articles that only discussed other TLRs without including TLR-2; 2) Research with populations other than Pulmonary TB (eg, bone TB, systemic TB without TLR-2 data); 3) Abstracts without full-text; 4) Non-peer-reviewed articles or unverified preprints.

The selection process was conducted in three stages: 1) Title and Abstract Screening, where two independent researchers screened articles based on title and abstract to identify suitable articles; 2) Full-Text Assessment (articles that passed the initial stage were then read in full-text to ensure topic suitability and methodological quality); 3) Study Quality Assessment (study quality was assessed using methodological quality evaluation tools appropriate to the study type, namely STROBE for observational studies, CONSORT for clinical trials and PRISMA for reviews and meta-analyses. Articles that did not meet the minimum quality were excluded. Data analysis was conducted descriptively and narratively (narrative synthesis). The selected articles were mapped based on: 1) Study characteristics (year, country, study design, experimental model); 2) Study focus (protective immunity vs immune evasion); 3) Molecular pathways involved (MyD88, NF-κB, MAPK, IL-10, etc.); 4) Effect of TLR-2 polymorphisms on TB susceptibility; 5) Effects of specific TLR-2 ligands of M.tb on host immune responses. Each article was analyzed for general patterns, consistency between studies, and differences in findings. There are 84 articles found with specific keywords sourced from several publication databases such as: PubMed, ScienceDirect, SpringerLink, and Google Scholar. This data was then analyzed based on the fulfillment of inclusion and exclusion criteria, resulting in 42 articles that met the criteria, and then After assessing the quality of the methodology and relevance of the content, 25 articles were finally selected

RESULT

Based on a literature search from PubMed, ScienceDirect, SpringerLink, and Google Scholar databases, 84 relevant articles were found based on the specified keywords. After the title and abstract selection process, 42 articles met the inclusion criteria for a full-text review. After assessing the quality of the methodology and relevance of the content, 25 articles were finally selected for further analysis in this study. Some points that can be found include: 1) The Biological Role of TLR2 in Pathogen Recognition; 2) TLR2-Mediated Recognition of M.tb Components; 3) Genetic Polymorphisms in TLR2 and TB Susceptibility; 4) Therapeutic Implications and Future Directions. Table 1 summarizes the central findings of activation ligands of Mycobacterium tuberculosis (Hu & Spaink, 2022).

Table 1.
Activation Ligands of Mycobacterium tuberculosis

Ligand	Abbreviation	(PRR)	Accessory Molecule	Activation Effect
Lipoproteins				
19-kDa lipoprotein (Rv3763)	LpqH	TLR2/1	CD14	Inhibits MHC expression and antigen processing; IFN-γ–induced genes suppressed by prolonged LpqH stimulation
24-kDa lipoprotein (Rv1270c)	LprA	TLR2/1	CD14 / CD36	Induces cytokine response and regulates antigen-presenting cell function
24-kDa lipoprotein (Rv1411c)	LprG	TLR2/1; TLR2	CD14	Long-term exposure to LprG inhibits MHC-II antigen processing
24-kDa lipoprotein (Rv1016c)	LpqT	TLR2	Unknown	Short-term exposure to LprG induces TNF-α production
38-kDa glycolipoprotein	PhoS1	TLR2/1, TLR4	Unknown	Induces TLR2-dependent apoptosis in macrophages and inhibits MHC expression and antigen processing
Lipoylated and glycosylated Mtb lipoprotein (Rv2873)	MPT83	TLR2	Unknown	MPT83-induced cytokine production is reduced in TLR2-deficient mice
Lipo-/Glycolipids				
Lipoarabinomannan	LAM	TLR2/1; TLR2	CD14	Induces pro- and anti-inflammatory cytokine production by neutrophils
Arabinosylated lipoarabinomannan	AraLAM	TLR2	Unknown	Induces proinflammatory response
Lipomannans	LM	TLR2/1; TLR2	CD40 / CD86	Induces TNF-α and NO secretion to activate macrophages
Phosphatidylinositol dimannoside	PIM2/6	TLR2	Unknown	Induces TNF-α expression to activate macrophages
Trehalose dimycolate	TDM	TLR2	CD14 / MARCO	Induces NF-κB signaling
Others				
Heat shock protein 70	HSP70	TLR2	Unknown	Inhibits IL-6 secretion in TLR2-deficient macrophages; increases TLR2 and co-stimulatory molecule expression
55-kDa flavin-containing monooxygenase (Rv3083)	MymA	TLR2	CD40 / CD80 / CD86 / HLA-DR	Activates macrophages by inducing TNF-α and IL-12
PE_PGRS protein (Rv1818c)	PE_PGRS33	TLR2	CD14	Facilitates Mtb entry into macrophages via interaction with TLR2
ESAT-6 family protein (Rv1198)	EsxL	TLR2	Unknown	Induces TNF-α and IL-6 via TLR2-dependent NF-κB and MAPK signaling
PE/PPE protein (Rv1196)	PPE18	TLR2	Unknown	Interacts with TLR2 to induce IL-10 and SOCS3, inhibiting TLR2 signaling
PE/PPE protein (Rv1789)	PPE26	TLR2	CD80 / CD86	Activates macrophages by inducing proinflammatory cytokines TNF-α, IL-6, and IL-12
PE/PPE protein (Rv1808)	PPE32	TLR2	Unknown	Induces anti-inflammatory IL-10 and proinflammatory TNF-α and IL-6
PE/PPE protein (Rv3425)	PPE57	TLR2	CD40 / CD80 / CD86	Activates macrophages by inducing TNF-α, IL-6, and IL-12
Leucine-responsive regulatory protein	Lrp	TLR2	Unknown	Inhibits LPS-induced production of proinflammatory cytokines IL-12 and TNF-α

Table 2 summarizes significant findings from individual case–control studies examining TLR2 variants about TB susceptibility.

Table 1.
TLR2 Polymorphisms and Tuberculosis Susceptibility

No.	TLR2 SNP(s)	Method	Author (Year)	Population	Sample Size (Cases/Controls)	Association
1	rs5743708 (Arg753Gln)	PCR-RFLP	Ma et al.,	Chinese Han	543 / 544	Positive
2	rs5743708	PCR-RFLP	Selvaraj et al.	South Indian	206 / 212	Not significant
3	-196 to -174 del, rs3804099	PCR/PCR-RFLP	Che Chen et al.	Taiwanese	184 / 184	Positive
4	rs3804099 (T597C)	PCR-RFLP	Arji et al.	Moroccan	343 / 203	Protective (CT genotype)
5	-196 to -174 del	PCR	Khan et al.	Pakistani	87 / 100	Positive
6	rs5743708	PCR-RFLP	Wu et al.	Chinese	109 / 422	Positive
7	rs3804099 (T597C)	PCR-RFLP	Zhao et al.	Chinese	230 / 386	Positive
8	Arg677Trp, Arg753Gln	ARMS-PCR	Jafari et al.	Iranian	96 / 122	Not significant
9	rs1816702, rs3804099, rs7656411	PCR-RFLP	Zaki et al.	Sudanese	207 / 395	Positive
10	rs5743708	PCR-RFLP	Saleh et al.	Egyptian	52 / 50	Positive
11	rs3804099	PCR-RFLP	Wu et al.	Chinese Han	200 / 194	Positive
12	C2029T, G2258T	PCR-RFLP, ARMS-PCR	Mandala et al.	South Indian	102 / 132	Positive

Table 3 presents key results from the meta-analysis, which evaluated pooled data from multiple populations and SNPs, providing further insight into the strength and direction of these associations.

Table 3.
Meta-Analysis of TLR2 SNPs and Tuberculosis Risk (Ruifeng et al., 2023)

TLR2 SNP	Population	Cases / Controls	OR (95% CI)	*p*-value	Interpretation
rs3804099	Overall	3585 / 4308	1.16 (1.06–1.28)	0.002	Significant increased risk
	Caucasian	555 / 449	1.39 (0.84–2.29)	0.20	Not significant
	East Asian	1196 / 1865	1.14 (0.98–1.32)	0.08	Borderline
rs3804100	Overall	2217 / 2037	1.07 (0.82–1.40)	0.60	Not significant
rs5743704	Overall	1479 / 1168	0.49 (0.29–0.84)	0.01	Protective effect
	South Asian	472 / 472	0.14 (0.03–0.61)	0.009	Strong protective effect
rs5743708	Overall	3062 / 2811	0.37 (0.24–0.55)	<0.0001	Highly protective
	Caucasian	301 / 305	0.27 (0.14–0.49)	<0.0001	Strong protective effect
	South Asian	1189 / 992	0.80 (0.34–1.88)	0.61	Not significant

DISCUSSION

The Biological Role of TLR2 in Pathogen Recognition

Toll-like receptors (TLRs) are a central component of the human innate immune system, functioning as the first line of defense against microbial invasion. There are 13 known mammalian TLRs (TLR1 to TLR13), each recognizing distinct sets of pathogen-associated molecular patterns (PAMPs). Together, the TLR family can detect a wide variety of pathogens, including bacteria, viruses, fungi, and parasites (Beutler, 2004; Fitzgerald & Kagan, 2020). TLRs act not only as pathogen detectors but also as signal modulators, recruiting adaptor proteins such as MyD88, TRIF, TIRAP, and TRAM to activate immune cells like macrophages and dendritic cells (Duan et al., 2022; Kawai & Akira, 2011).TLR signaling begins with ligand recognition at the extracellular domain, followed by

conformational changes that facilitate the recruitment of adaptor proteins to the cytoplasmic Toll/IL-1 receptor (TIR) domain (Snyder & Sundberg, 2014; Watters et al., 2007). These adaptors then initiate downstream signaling cascades involving NF-κB and interferon regulatory factors (IRFs), leading to the production of proinflammatory cytokines and type I interferons. This mechanism enables rapid immune activation in response to a wide array of microbial threats (Kusiak & Brady, 2022; Salauddin et al., 2025).

Among the TLR family, TLR2 is unique in its ability to form functional heterodimers with more than two other TLRs, particularly TLR1 and TLR6. This dimerization allows TLR2 to recognize a broader spectrum of microbial molecules. TLR2 also interacts with numerous non-TLR molecules, expanding its recognition capabilities even further. TLR2 expression has been detected in immune cells as well as in endothelial and epithelial cells, enabling it to detect conserved microbial components from nearly all phyla of pathogens (Colleselli et al., 2023).On a molecular level, TLR2 is a type I integral transmembrane glycoprotein consisting of three main domains: a conserved intracellular Toll/IL-1 receptor (TIR) domain, a single-pass transmembrane helix, and an extracellular leucine-rich repeat (LRR) ectodomain responsible for ligand binding. The ectodomain contains approximately 16–28 LRR modules that form a solenoid-like structure tailored for microbial recognition (Durai & Choi, 2016; Oliveira-Nascimento et al., 2012). Genetically, the human TLR2 gene is located on chromosome 4q32 and comprises four exons and three introns. Numerous studies have documented that TLR2 exhibits various polymorphisms in both in vitro and in vivo contexts (Ruifeng et al., 2023). These genetic variations have been implicated in differential host responses to infectious agents, including *Mycobacterium tuberculosis*, highlighting TLR2's vital role in TB pathogenesis.

TLR2-Mediated Recognition of M.tb Components

A wide range of genes contribute to the transition from *M. tuberculosis* infection to active tuberculosis, among which the Toll-like receptor (TLR) family plays a central role. TLRs are involved at every stage of the innate immune response, including initial pathogen recognition, inflammation, and the activation of adaptive immunity. They initiate protective immune mechanisms such as Th1 cytokine production and microbicidal activity, but can also be exploited by *M. tuberculosis* to evade host defenses. Primary immune responses to *M. tuberculosis* are triggered by the interaction between pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs), including TLRs, C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs) (Mortaz et al., 2015; Zihad et al., 2023).Among PRRs, TLR2 is particularly significant due to its ability to form heterodimers with TLR1 or TLR6, enabling recognition of various mycobacterial components such as triacylated/diacylated lipopeptides and peptidoglycan. Genetic defects in the TLR2 gene can disrupt ligand recognition and alter susceptibility to TB (Colleselli et al., 2023; Durai & Choi, 2016). Upon stimulation by *M. tuberculosis*, TLR2 initiates distinct transcriptional programs by activating transcription factors, resulting in the expression of cytokines and regulatory molecules. These TLR2-induced molecules coordinate immune protection, regulatory balance, and, paradoxically, immune evasion—allowing *M. tuberculosis* to persist in host cells with minimal immunopathology (Durai & Choi, 2016).

The recognition of *M. tuberculosis* ligands—such as lipoproteins and lipoarabinomannan—by TLR2 activates intracellular adaptor proteins like MyD88 and TIRAP. These adaptor complexes recruit signaling proteins including IRAK and TRAF6, leading to the activation of the TAK1–TAB2/3 complex, which propagates downstream signals through two major pathways: NF-κB and MAPK. NF-κB is essential for regulating genes involved in inflammation and immunity. Its activation results in the transcription of cytokines such as TNF-α, IL-1β, IL-6, and IL-12, which facilitate macrophage recruitment, granuloma

formation, and the polarization of T helper cells toward the Th1 phenotype—critical for controlling intracellular pathogens (Hu & Spaink, 2022; Jani et al., 2023).Simultaneously, the MAPK pathway (involving p38, ERK1/2, and JNK) contributes to cytokine production and macrophage modulation. For example, p38 MAPK supports IL-10 production, a key anti-inflammatory cytokine. While IL-10 may limit tissue damage, it is also exploited by *M. tuberculosis* to suppress macrophage activation and inhibit phagosome–lysosome fusion, enabling the pathogen to survive intracellularly. Additionally, *M. tuberculosis* can induce negative regulators such as A20 and SOCS1, which dampen NF-κB activity, reducing cytokine output and immune cell activation. (Hu & Spaink, 2022; Jani et al., 2023).

The role of TLR2 extends to dendritic cell maturation and activation of naive CD4+ T cells through MHC-II and costimulatory molecules (CD80/CD86), promoting Th1 differentiation and IFN-γ production. IFN-γ enhances macrophage microbicidal function (Gopalakrishnan & Salgame, 2016; Ruifeng et al., 2023). Thus, TLR2 not only triggers early innate responses but also bridges the transition to adaptive immunity. Nevertheless, persistent or dysregulated TLR2 activation can lead to chronic inflammation and pulmonary tissue damage. *M. tuberculosis* leverages this by promoting an immune environment favoring bacterial persistence, granuloma breakdown, and transmission (Arora et al., 2019; Wang et al., 2025).

Genetic Polymorphisms in TLR2 and TB Susceptibility

Polymorphisms in TLR1, TLR2, TLR4, TLR6, and TLR9 have been widely investigated for their potential role in altering susceptibility to Tuberculosis. TLR2, which forms functional heterodimers with TLR1 or TLR6, has the capacity to detect a broad range of microbial ligands, including lipoproteins, lipoarabinomannan, and peptidoglycan. Mutations in TLR2 may impair receptor function, disrupting immune signaling cascades such as NF-κB and MAPK, and resulting in an altered immune response to *M. tuberculosis* (Arora et al., 2019; Hu & Spaink, 2022; Zihad et al., 2023).Given the complex relationship between TLRs and tuberculosis, it is essential to recognize that while TLRs play a key role in host defense against *M. tuberculosis* infection, the presence of other PRRs and gene–gene interactions must also be considered in future research. The immune system possesses a degree of redundancy, wherein a single PAMP can be recognized by multiple PRRs, triggering overlapping immune pathways. This implies that although certain polymorphisms may contribute to increased susceptibility to TB, other factors—such as genetic interactions, environmental conditions, nutritional status, and additional immunological factors—also play critical roles in determining disease outcomes (Hu & Spaink, 2022; Mishra et al., 2017).

In a study by Schurz et al., most single nucleotide polymorphisms (SNPs) in TLR genes showed no significant association with TB, either in general or within specific ethnic subgroups. However, three SNPs—rs3804099, rs5743704, and rs5743708—did demonstrate statistically significant association 17,20. These findings suggest that specific genetic variants may either increase or reduce an individual's risk of TB depending on broader genetic and environmental contexts. Multiple studies have evaluated the relationship between TLR2 T597C (rs3804099) polymorphism and the risk of various forms of TB in different populations, with results indicating that particular SNPs in TLR genes may influence TB susceptibility, although these outcomes vary by population and study design 20,26. Research by Tong further indicates that TLR genetic polymorphisms may not only influence disease phenotype but also affect the therapeutic response to anti-TB treatment. The interaction between host gene polymorphisms and bacterial genotypes implies that variations such as TLR2 rs3804099T/C (T597C) could be associated with infection by different *M. tuberculosis* strains. Moreover, this SNP has been found to be more strongly associated with tuberculous meningitis than with pulmonary tuberculosis in a cohort-based case–control study conducted

in China, which included 230 patients with pulmonary tuberculosis, 111 patients with tuberculous meningitis, and 386 healthy controls (Varshney et al., 2022).

The evidence from these studies demonstrates both inter-study and inter-ethnic variability in the role of TLR2 polymorphisms in TB. Variants such as rs5743708 (Arg753Gln) and rs3804099 (T597C) have been extensively studied, with numerous reports of a positive association with TB susceptibility. However, other studies have found no significant relationship, highlighting the complexity of genetic interactions and the influence of host population background. Some polymorphisms may even confer a protective effect, such as rs3804099 in Moroccan cohorts, suggesting a gene–environment or gene–pathogen interaction that modulates immune outcomesThe pooled findings (Table 3) reinforce the significance of TLR2 in host defense against *M. tuberculosis* and highlight how specific variants can serve as genetic markers of risk or protection. The variability in associations across ethnic groups and geographical regions suggests a strong influence of host-pathogen interaction, genetic background, and environmental exposure. Moreover, the potential influence of these polymorphisms on cytokine production, immune cell activation, and treatment responsiveness points to the value of exploring TLR2 as both a biomarker and a therapeutic target in personalized medicine for tuberculosis (Ruifeng et al., 2023; Varshney et al., 2022).

A study from Soeroto et.al on 2018 revealed that SNPs in TLR-1 (rs5743572), TLR-2 (rs3804100), and TLR-6 (rs5743808) were significantly associated with an increased risk of multidrug-resistant TB, highlighting a potential genetic predisposition to more severe forms of the disease. Meanwhile, research conducted in Bandung by Soedarsono et al. demonstrated that the TLR-2 Arg753Gln polymorphism markedly increased the likelihood of progression from latent to active TB, with an odds ratio of 28.07, despite no significant differences in cytokine levels. These findings from Indonesia emphasize the importance of host genetic factors in shaping the innate immune response and determining TB outcomes, particularly in high-burden settings (Soedarsono et al., 2020; Soeroto et al., 2018).

Therapeutic Implications and Future Directions

The identification of functional polymorphisms in TLR2 has opened new perspectives on the individual variability in immune responses to *Mycobacterium tuberculosis*, providing a foundation for therapeutic stratification. Variants such as rs5743708 and rs3804099, which modulate the production of cytokines like TNF-α, IL-6, and IL-12, could be instrumental in predicting treatment outcomes and the host's ability to form effective granulomatous responses. Consequently, incorporating TLR2 genotyping into clinical practice may allow for the early identification of individuals at higher risk of disease progression, relapse, or treatment failure (Hu & Spaink, 2022; Ruifeng et al., 2023; Varshney et al., 2022).In light of the growing understanding of host genetics, the integration of pharmacogenomics into TB management could significantly enhance therapeutic efficacy. Patients carrying risk-associated TLR2 alleles may benefit from tailored immunomodulatory strategies, including adjuvant therapies that enhance innate immune responses (Mandala et al., 2020; Saraav et al., 2017). For example, agonists of the TLR2 signaling pathway could be explored as adjunctive treatments to conventional anti-TB regimens, potentially accelerating pathogen clearance and improving long-term outcomes in genetically susceptible individuals (Liu et al., 2011).

Furthermore, the role of TLR2 polymorphisms in influencing vaccine responses warrants attention. Genetic variations that impair TLR2-mediated antigen recognition may diminish the efficacy of BCG and other TB vaccine candidates. Future vaccine design may benefit from stratification based on TLR genotypes, enabling the development of formulations that specifically address innate immune deficits. This approach aligns with the principles of

precision vaccinology, where genetic and immunological profiling guide vaccine strategies at the population or individual level (Hwanga et al., 2017; Khan et al., 2019).Beyond vaccine and drug response, TLR2 may also represent a direct therapeutic target. The dual role of TLR2 in initiating protective immunity and mediating immune evasion by *M. tuberculosis* presents opportunities to modulate this receptor therapeutically. Inhibiting specific downstream molecules that are hijacked by the pathogen, such as SOCS1 or A20, or modulating anti-inflammatory responses (e.g., IL-10), could rebalance the immune environment in favor of bacterial clearance. The challenge remains in selectively targeting these pathways without exacerbating tissue damage or inducing systemic inflammation (Chen et al., 2023).Looking ahead, more extensive multi-ethnic cohort studies and functional validation of TLR2 variants are needed to fully realize their clinical utility. Longitudinal studies that integrate genetic, transcriptomic, and proteomic data may provide deeper insight into host-pathogen interactions and identify biomarkers predictive of disease trajectory and treatment response. Ultimately, the convergence of immunogenetics, molecular diagnostics, and personalized medicine holds the potential to transform TB management, shifting from a uniform approach to one that is adaptive, precise, and patient-centered.

CONCLUSION

Pulmonary tuberculosis (pulmonary TB) remains a global public health challenge with high morbidity and mortality. From the results of this literature review, it can be concluded that Toll-like receptor 2 (TLR-2) plays a complex and dualistic role in the pathogenesis of pulmonary TB. On the one hand, activation of TLR-2 by Mycobacterium tuberculosis cell wall components (such as lipoproteins, LAM, and PE/PPE proteins) is able to trigger a protective immune response through the MyD88-dependent pathway, resulting in NF-κB activation, production of proinflammatory cytokines (TNF-α, IL-6, IL-12), activation of macrophages and dendritic cells, and induction of T helper 1 (Th1) cell responses that are essential in controlling infection.

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