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# Gut Microbiota in Tuberculosis: Immune Mechanisms and Therapeutic Potential along the Gut-Lung Axis

**Lizhi Wang[1,2], Pu Wang[1,2*]**

[1]Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[2]Respiratory Chronic Diseases and Comorbidities, Key Laboratory of Chongqing Education Commission of China, Chongqing, China
Email: *2802901313@qq.com

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## Abstract

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), remains a major cause of illness and death worldwide. Growing evidence links the gut microbiota to host immunity, and this connection appears to matter in TB—shaping how the disease progresses and how patients respond to treatment. In this review, we first describe how the gut microbial community is altered in TB patients. We then examine whether anti-TB treatment leaves lasting marks on the microbiota, and discuss the possible routes by which gut microbes influence anti-MTB immunity. Finally, we consider adjunctive strategies that target the microbiota. Importantly, current evidence is largely derived from cross-sectional observational studies and animal models. These studies reveal associations between gut dysbiosis and TB and provide mechanistic insights into microbiota-mediated anti-MTB immunity, but they do not establish clinical benefit. Whether microbiota-targeted interventions can improve clinical outcomes in patients with TB remains to be demonstrated in large-scale randomized controlled trials. A clearer understanding of these interactions could help move TB care toward more precise prevention and personalized treatment.

## Keywords

Tuberculosis, Gut-Lung Axis, Immunomodulation, Microbiota-Targeted Therapy

## 1. Introduction

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (MTB) and still im-

*Corresponding author.

poses a heavy global burden. In 2024, the WHO estimated about 10.7 million new active TB cases and 1.23 million deaths from TB, with China among the countries bearing the highest burden [1] [2]. The human gut contains hundreds of trillions of microorganisms. Their combined genomes are roughly 150 times larger than the human genome, which is why this community has been called the "second genome". These microbes contribute to nutrient metabolism, intestinal barrier function, and immune regulation [3] [4]. Disruption of this community, or dysbiosis, has been linked to several infectious diseases. The gut and lungs communicate in both directions along the "gut-lung axis". This crosstalk involves immune cell migration, translocation of microbial metabolites, and systemic inflammatory signals, all of which can shape pulmonary immunity [5]. In active TB, patients often show clear gut microbiota dysbiosis, and standard anti-TB therapy can substantially remodel the gut microecology. Such changes may weaken host clearance of MTB by disturbing immune regulation, with possible consequences for disease progression and treatment response. Yet key questions remain: how the gut-lung axis operates in TB, whether microbiota changes are causal, and how microbiota-targeted interventions can be translated into clinical practice. Notably, a recent review has systematically discussed microbiome alterations and therapeutic potential in mycobacterial infections—including both TB and nontuberculous mycobacterial pulmonary disease—from the perspective of the gut-lung axis [2]. In contrast, this review does not attempt to cover the entire gut-lung axis framework. Instead, it focuses on TB-specific microbiota-immune interactions, with particular emphasis on epigenetic regulation, the bidirectional effects of microbial metabolites (such as short-chain fatty acids, palmitoleic acid, and propionate), and the specific barriers to clinical translation of microbiota-targeted interventions. We examine gut microbiota dysbiosis in TB, the effects of anti-TB treatment, the immune pathways that may link the microbiota to TB progression, and adjunctive strategies that target the microbiota. Our aim is to support precision prevention and treatment of TB.

## 2. Characteristics of Gut Microbiota Dysbiosis in Tuberculosis

### 2.1. Gut Microbiota Characteristics in Patients with Active Tuberculosis

Compared with healthy controls, patients with active tuberculosis (ATB) have been reported to exhibit three major features of gut microbiota alteration: reduced diversity, depleted beneficial bacteria, and enrichment of opportunistic or pro-inflammatory taxa. $\alpha$-Diversity is significantly lower in ATB patients, and $\beta$-diversity clearly separates microbial community structure between the two groups [6]. At the phylum level, several studies have reported reductions in Firmicutes and increases in Bacteroidetes or Proteobacteria, although the direction and magnitude of these changes are not fully consistent across cohorts [7]. Such heterogeneity may reflect differences in treatment exposure, prior antibiotic use, diet, met-

abolic comorbidities, and geographical background rather than TB disease alone. At the genus level, short-chain fatty acid (SCFA)-producing beneficial bacteria are generally depleted, with significant reductions in *Faecalibacterium prausnitzii, Roseburia, and Bifidobacterium* (all $P < 0.05$). Functional and metabolic alterations have also been reported in TB. In patients with active TB, fecal bcoA gene copy number, a functional marker associated with the capacity of the gut microbiota to produce butyrate, was approximately five-fold lower than that observed in healthy controls [8]. Separately, a metabolomic study of patients with latent and active pulmonary TB identified significant alterations in fecal metabolites, including changes in short-chain fatty acids and amino acids [7]. Several genera, including Bacteroides, Enterococcus and Escherichia-Shigella, have been reported to be enriched in patients with pulmonary TB and are associated with potentially opportunistic or pro-inflammatory phenotypes [9]. These genera include both Gram-negative and Gram-positive bacteria; however, increased relative abundance at the genus level alone does not prove pathogenic behavior. Notably, Bifidobacterium changes are regionally heterogeneous—enriched in a Pakistani study but reduced in Chinese and Indian studies—suggesting diet, genetics, or comorbidities may modulate specific genera responses to TB infection [10]. Thus, cross-study differences should be considered when interpreting specific microbial changes as disease-associated features.

### 2.2. Correlation between Gut Microbiota Characteristics and Clinical Indicators

Dysbiosis in patients with ATB is significantly associated with nutritional and immunological indicators. The abundance of SCFA-producing bacteria is positively correlated with serum albumin and total cholesterol; the resulting butyrate deficiency may impair the intestinal barrier, increase energy expenditure, and aggravate malnutrition. However, these associations may also reflect patients' nutritional status and metabolic comorbidities rather than TB disease alone. This consideration is particularly relevant in patients with diabetes, in whom metabolic abnormalities and TB-related immune responses may independently influence the gut microbiota. Bacteroides abundance is positively correlated with IL-17 and negatively correlated with IFN-$\gamma$, whereas *Blautia,* which is enriched in healthy individuals, shows the opposite pattern [10], suggesting that distinct genera may influence anti-TB immunity by modulating the Th17/Th1 balance. In patients with latent tuberculosis infection (LTBI) complicated by diabetes, TNF-$\alpha$ and IL-17F levels were lower in the LTBI group than in the non-LTBI group and were associated with genera such as *Bacteroides and Prevotella_9* [11], suggesting an interaction among diabetes, host immunity, and gut microbiota rather than a microbiota pattern attributable solely to TB infection. Regarding diagnosis, a model based on *Lachnospira, Lachnospiraceae ND3007 group, and Roseburia* effectively distinguished ATB patients from healthy controls [12], providing a rationale for developing auxiliary diagnostic tools for smear-negative patients.

## 3. Impact of Anti-Tuberculosis Treatment on the Gut Microbiota

### 3.1. General Features and Persistence of Gut Microbiota Perturbation Induced by Anti-Tuberculosis Treatment

Anti-tuberculosis treatment (ATT) is the cornerstone of tuberculosis (TB) cure, and its persistent perturbation of the gut microbiota has attracted considerable attention. Both the standard first-line regimen (HRZE/HR; H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol) and multidrug-resistant regimens significantly perturb the gut microbiota, but differ in the aspects of perturbation, temporal dynamics, and associations with host factors. In newly diagnosed pulmonary TB, $\alpha$-diversity (Shannon index) decreased significantly after 2 months of intensive treatment and remained unrecovered at the end of the 6-month course [13]. In rifampicin-resistant patients, second-line therapy did not significantly alter $\alpha$-diversity, but $\beta$-diversity revealed marked structural changes that persisted into the continuation phase [14]. At 9 months after treatment, although diversity partially recovered, several genera, including Lactobacillus, remained significantly different, and alterations in the plasma metabolome and cytokines persisted [15]. Longer follow-up showed that compositional differences were still detectable at a mean of 1.2 years after treatment completion in drug-susceptible TB [16]; in multidrug-resistant tuberculosis (MDR-TB), microbial richness remained lower than normal 3 - 8 years after drug discontinuation [17]. Analyses of multi-regional 16S datasets confirmed the suppressive effects of ATT on SCFA-producing pathways and suggested that geographical factors may influence microbiota structure more strongly than the disease itself [18]. Collectively, these findings indicate that ATT-induced perturbation of the gut microbiota is not only extensive but can persist long after treatment cessation, influenced by both geographical factors and MTB infection itself.

### 3.2. Composition of Anti-Tuberculosis Treatment-Associated Dysbiosis and Host-Microbiota Interactions

A consistent pattern across studies is that ATT causes sustained depletion of butyrate-producing bacteria. Treatment usually reduces Clostridiales, including *Faecalibacterium, Roseburia,* and *Ruminococcus*, while allowing opportunistic pathogens such as Escherichia-Shigella and Enterococcus to expand [19]. In animal models, rifampicin appears to be the main driver of dysbiosis induced by the HRZ regimen, although pyrazinamide and isoniazid also modulate the microbiota [20]. After HRZE treatment, *Veillonella* and Bacteroides increase and *Clostridium* decreases, changes that coincide with altered fecal metabolites [21]. The fungal community is also affected: studies report lower fungal diversity, a reduced *Basidiomycota/Ascomycota* ratio, enrichment of the pathogenic genus Nakaseomyces, and marked disruption of bacterial-fungal cross-kingdom networks [22]. How different ATT regimens shape the microbiota and host immunity remains an important question. In mice, pretreatment with isoniazid/pyrazinamide aggravates microbi-

ota dysbiosis and increases subsequent susceptibility to MTB; fecal microbiota transplantation reverses this effect, which has been attributed to impaired metabolism and bactericidal function of alveolar macrophages [23]. Similarly, dysbiosis caused by broad-spectrum antibiotics impairs isoniazid-mediated clearance of MTB, leading to higher pulmonary bacterial burdens and weaker $CD4^+$ T cell responses [24]. ATT-induced dysbiosis may also contribute to the vulnerability of cured patients to reinfection or relapse [25]. The pretreatment microbiota itself influences drug exposure: in two independent cohorts, pretreatment $\alpha$-diversity correlated positively with plasma concentrations of anti-TB drugs, especially rifampicin, and patients with greater *Faecalibacterium prausnitzii* abundance had higher exposure levels [26]. Rifamycin-based preventive therapy depletes butyrate-producing bacteria, and recovery remains incomplete two months after drug discontinuation [27]. In a controlled intervention trial, nitazoxanide did not reduce bacterial burden but still caused pronounced microbiota alterations and worsened inflammation, whereas standard treatment cleared the pathogen and normalized inflammation; resolution of inflammation tracked closely with reduced MTB burden and restoration of Clostridium clusters IV and XIVa [28]. Overall, ATT—particularly rifampicin-containing regimens—strongly modulates the gut microbiota, reducing diversity, depleting butyrate producers, enriching opportunistic pathogens, and disrupting cross-kingdom networks. These changes are linked to drug metabolism, immune status, and the risk of reinfection. However, the observed microbiota profile likely reflects the combined effects of anti-TB drugs, underlying infection, and host and environmental factors. Longitudinal studies with pretreatment sampling and adjustment for key confounders are needed to distinguish treatment-related effects from disease-associated dysbiosis.

## 4. Potential Mechanisms by Which the Gut Microbiota Modulates Tuberculosis

### 4.1. Immunoregulatory Mechanisms

#### 4.1.1. Innate Immune Regulation

Alveolar macrophages are the central effector cells of early anti-MTB immunity, and their functional status is profoundly regulated by the gut microbiota. Dysbiosis directly compromises the antibacterial function of alveolar macrophages, reducing macrophage phagocytic activity and pattern recognition receptor signaling, weakening their capacity to clear MTB, and exacerbating M1/M2 polarization imbalance [29] [30]. Dysbiosis can block the Mincle-Syk-Card9 signaling pathway, inhibit dendritic cell maturation and antigen presentation, and suppress CD4+ T cell activation and Th1 polarization, thereby attenuating innate and adaptive immune responses against MTB; in contrast, *Lactobacillus plantarum* restores anti-MTB immunity by activating this pathway [31]. Recent studies have further revealed the bridging role of "trained immunity" in the microbiota-lung axis: subcutaneous bacillus Calmette-Guérin (BCG) vaccination induces lung-resident memory alveolar macrophages, a process dependent on gut microbiota-mediated

signaling pathways, and transplantation of gut microbiota from BCG-treated mice confers a memory alveolar macrophage phenotype and anti-MTB protection in recipient mice [32]. Antibiotic-induced dysbiosis attenuates BCG-induced activation and proliferation of $CD4^+$ and $CD8^+$ T cells and memory T cell generation, decreases IFN-$\gamma$ and TNF-$\alpha$ secretion, and ultimately leads to increased pulmonary MTB burden and aggravated pathological injury [33].

#### 4.1.2. Adaptive Immune Regulation

Although early MTB infection depends on innate immunity, eventual clearance of MTB mainly relies on adaptive immunity, in which $CD4^+$ T cells and their subsets Th1, Th2, Th17, and Treg are particularly critical. Studies have shown that intestinal Prevotella abundance is reduced after MTB infection; this bacterium exerts anti-inflammatory effects and regulates Th17 responses. Supplementation with this bacterium upregulates intestinal Th17 cells and IL-17, which recruits neutrophils via granulocyte colony-stimulating factor(G-CSF) and enhances host defense against MTB, suggesting that the microbiota may influence pulmonary TB progression through the Th17 axis [34]. The Th1/Treg balance is also modulated by the microbiota: antibiotic-induced dysbiosis increases Tregs, reduces Th1 cells producing IFN-$\gamma$ and TNF-$\alpha$, impairs immunity, and promotes pathogen dissemination [33], whereas fecal microbiota transplantation increases Th1, reduces Treg, and decreases MTB infection severity. In addition, *Bacteroides fragilis* improves the Th1/Th2 balance and reduces pulmonary pathology and bacterial burden. These studies indicate that the gut microbiota participates in anti-MTB immunity through multiple pathways, including Th17, Th1/Treg, and Th1/Th2. However, current studies mostly focus on changes in microbiota composition, and the specific functions and molecular mechanisms remain unclear; clinical translation still requires further validation.

#### 4.1.3. Epigenetic Pathway Regulation

The microbiota-regulated lncRNA-CGB binds to zeste homolog 2 (EZH2), inhibits H3K27me3 modification in the IFN-$\gamma$ gene promoter region, and promotes IFN-$\gamma$ expression. Antibiotic-induced dysbiosis significantly downregulates lncRNA-CGB; oral administration of *Bacteroides fragilis* restores its expression and enhances anti-MTB immunity. In patients with active TB, the human homolog of this lncRNA is also downregulated and is associated with reduced *Bacteroides fragilis* abundance and decreased IFN-$\gamma$. Intestinal protozoa can also modulate pulmonary immunity through the gut-lung axis. Colonization with rodent trichomonads induces intestinal inflammatory lymphoid cells (ILC2s) to migrate to the lungs in a sphingosine-1-phosphate receptor 4 (S1PR4)-dependent manner, forming an ILC2-T cell-B cell ternary network that limits MTB dissemination to the spleen through early IL-5-dependent eosinophil aggregation [35]. Antibiotic-induced dysbiosis reduces pulmonary mucosal-associated invariant T(MAIT) cell numbers and impairs their IL-17A production, increasing early MTB burden [36]. The interferon alpha/beta receptor 1 (IFNAR1) rs2257167 G allele enhances type

I interferon signaling, inhibits *Akkermansia* colonization, and reduces palmitoleic acid production, leading to excessive TNF-$\alpha$ production and aggravated TB; palmitoleic acid can inhibit TNF-$\alpha$ expression by reducing histone H3 lysine 27 trimethylation (H3K27me3) enrichment in the TNF-$\alpha$ promoter region [37]. This section is one of the important features that distinguish this review from recently published reviews on the gut-lung axis, systematically summarizing the specific pathways through which the microbiota regulates anti-MTB immunity via epigenetic mechanisms.

### 4.2. Intestinal Barrier Function and Metabolic Regulatory Mechanisms

Dysbiosis compromises the intestinal epithelial barrier, causing "leaky gut" and low-grade systemic inflammation. Antibiotics reduce $\alpha$-diversity and Bacteroidetes, expand Firmicutes and Proteobacteria, and disrupt bacterial-fungal networks. In dysbiotic mice, serum intestinal fatty acid-binding protein and lipopolysaccharide rise, indicating barrier impairment, and correlate positively with pulmonary mycobacterial burden. In obese mice with TB, intestinal permeability and serum endotoxin increase, alongside excessive pulmonary IFN-$\gamma$ and worse pathology. In vitro, propionate deficiency causes loss of phthiocerol dimycocerosate (PDIM), a key MTB virulence lipid, while propionate supplementation maintains PDIM and increases drug resistance. This suggests the intestinal metabolic environment may indirectly shape MTB pathogenicity and drug susceptibility [38]. SCFAs are the most studied microbial metabolites. In TB patients, the abundance of butyrate- and propionate-producing genera (Faecalibacterium, Roseburia, Eubacterium) is controversial: some report increases, perhaps compensatory immunoregulation [39], while others report decreases linked to reduced anti-inflammatory capacity [40]. SCFAs have dual effects on anti-TB immunity. Butyrate inhibits histone deacetylases and NF-$\kappa$B, lowers IL-12 and IFN-$\gamma$, and suppresses Th1 responses; it also induces Tregs, negatively regulating anti-TB immunity [41]. Its regulatory direction depends on concentration, local microenvironment, and disease stage. Propionate supplementation increases MTB resistance to vancomycin and PDIM production, suggesting the propionate pathway may be key to MTB virulence. The MTB-secreted protein MPT53 oxidatively modifies host TAK1, activating NF-$\kappa$B and MAPK signaling and proinflammatory cytokines [42]. Metabolomics shows fecal hypoxanthine, xanthine, and dipeptides decrease in latent infection and correlate negatively with Ruminococcus; purine and pyrimidine degradation pathways are upregulated in latent and active TB, suggesting microbiota-mediated nucleotide reprogramming may contribute to early TB pathogenesis [43]. From healthy to latent to active TB, $\alpha$-diversity declines progressively; SCFA-producing genera enrich during latency, while proinflammatory genera increase in active disease [44]. Intestinal Roseburia abundance correlates negatively with BCG-induced trained immunity markers (IL-6, TNF-$\alpha$, IL-1$\beta$); higher abundance is linked to altered plasma phenylalanine metabolites, suggesting microbial me-

tabolites influence vaccine-induced immunity [41]. Overall, the gut microbiota promotes TB through three routes: reshaping pulmonary anti-TB immunity via multi-level immune networks; disrupting the intestinal barrier to drive low-grade systemic inflammation; and altering key metabolites (SCFAs, palmitoleic acid, propionate, purine metabolism) to modulate immune and inflammatory balance.

## 5. Adjunctive Therapeutic Strategies Targeting the Gut Microbiota for Tuberculosis

### 5.1. Probiotics and Prebiotics

Probiotics are among the most extensively studied microbiota-targeted interventions, with potential benefits related to intestinal microbial homeostasis and host immune regulation [45]. Some randomized trials suggest that probiotic supplementation, particularly with Lactobacillus species, may alleviate ATT-related gastrointestinal adverse effects and may have beneficial effects on selected immune and inflammatory indicators [46]. A prospective cohort reached a similar conclusion, although it found no clear improvement in TB treatment success or quality of life [47]. Probiotic efficacy is highly strain-specific and can be affected by immunosuppression or antibiotics. Prebiotics such as inulin and fructooligosaccharides can selectively promote the growth or activity of beneficial microorganisms and may increase the production of microbial metabolites such as SCFAs [48]. Plant fiber-rich diets can reduce intestinal permeability [49]. Nutritional support is a particularly critical component of comprehensive care. Diets rich in fiber, micronutrients, and fermented foods may improve microbial community resilience, enhance immune function, and act synergistically with anti-TB treatment [50]. These dietary interventions are non-invasive and cost-effective. L-arginine is reduced in both the serum of patients with nontuberculous mycobacterial pulmonary disease (NTM-PD) patients and NTM-infected mice; supplementation enhances Th1-mediated pulmonary immunity and M1 macrophage polarization, improving bacterial clearance. Furthermore, fecal microbiota transplantation from L-arginine-treated mice conferred stronger protection against NTM infection, whereas antibiotic pretreatment abolished this protection. These findings illustrate how dietary intervention can reshape the gut microbiota through the gut-lung axis and strengthen pulmonary immune defense [51]. That said, clinical evidence for probiotics and prebiotics in TB remains limited. A recent systematic review of randomized controlled trials identified five RCTs involving 926 patients and suggested that probiotic supplementation, particularly with *Lactobacillus casei*, may reduce the incidence and duration of gastrointestinal adverse effects during anti-TB treatment and may have beneficial effects on selected immune and inflammatory indicators [46]. However, the available trials remain limited in number, sample size, and follow-up duration, and convincing evidence is still lacking for clinically important TB outcomes, including treatment success, microbiological response or sputum conversion, relapse, mortality, and long-term quality of life. In addition, evidence for prebiotics remains particularly limited, with much of the

available evidence derived from animal studies or small observational studies. Therefore, larger, multicenter, well-designed randomized controlled trials with clinically relevant endpoints and adequate long-term follow-up are needed to determine whether microbiota-targeted interventions can improve TB treatment outcomes.

### 5.2. Postbiotics and Fecal Microbiota Transplantation (FMT)

Postbiotics offer another route beyond these interventions. These microbe-derived compounds—including butyrate, propionate, and bacterial peptides—can act directly on host immunity. Because they do not require live bacteria, they may retain anti-inflammatory effects even during severe dysbiosis. FMT aims to restore the microbiota more broadly. It is well established for recurrent *Clostridioides difficile* infection and has been proposed as an adjunct in TB [52]. Preclinical studies have suggested that FMT may restore gut microbiota diversity and modulate host immune responses, including Th1/Treg balance, with potential effects on MTB infection severity [53]. Still, clinical use of FMT in TB remains largely preclinical because of safety concerns, regulatory barriers, and marked donor-to-donor variation [54]. Bringing microbiota-based interventions into clinical practice remains difficult. Animal models and humans differ in microbial ecology, immune environment, disease stage, and long-term multidrug antibiotic exposure, and these differences limit direct extrapolation of experimental findings [55].

## 6. Challenges and Future Perspectives

Although the role of the gut microbiota in TB has attracted widespread attention, the field is still in its early stages. Current evidence comes mainly from cross-sectional studies and animal models, and the causal link between dysbiosis and TB still requires confirmation through prospective cohort studies and Mendelian randomization. Recent Mendelian randomization studies have preliminarily identified specific genera associated with PTB risk, such as Dorea and Parasutterella increasing risk and Lachnoclostridium exerting a protective effect, but these findings still require validation in more populations [56]. Microbial metabolites such as SCFAs show bidirectional effects on anti-TB immunity, and the mechanisms underlying their concentration dependence and disease-stage specificity remain unclear, which limits the precision of targeted interventions. Clinical translation of probiotics, FMT, and other strategies faces obstacles such as donor variability, safety assessment, and antibiotic interference. In addition, microbiota heterogeneity caused by regional diet and genetic background affects the generalizability of biomarkers. Future work should integrate metagenomics, metabolomics, and immunomics, conduct multicenter longitudinal follow-up, and systematically dissect the spatiotemporal dynamic network of the gut-lung axis. It should also focus on specific metabolic pathways (e.g., palmitoleic acid, propionate) or design engineered strains to explore mechanism-driven targets for adjunctive therapy, and stratify patients by microbiota features to provide new strategies for individual-

ized TB treatment.

## Author Contributions

Investigation, Lizhi Wang; data curation, Lizhi Wang; writing—original draft preparation, Lizhi Wang; writing—review and editing, Pu Wang; supervision, Pu Wang. All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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