



# The Roles of Host Noncoding RNAs in *Mycobacterium tuberculosis* Infection

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Tuberculosis remains a major health problem. *Mycobacterium tuberculosis*, the causative agent of tuberculosis, can replicate and persist in host cells. Noncoding RNAs (ncRNAs) widely participate in various biological processes, including *Mycobacterium tuberculosis* infection, and play critical roles in gene regulation. In this review, we summarize the latest reports on ncRNAs (microRNAs, piRNAs, circRNAs and lncRNAs) that regulate the host response against *Mycobacterium tuberculosis* infection. In the context of host-*Mycobacterium tuberculosis* interactions, a broad and in-depth understanding of host ncRNA regulatory mechanisms may lead to potential clinical prospects for tuberculosis diagnosis and the development of new anti-tuberculosis therapies.

**Keywords:** *Mycobacterium tuberculosis* (*M. tuberculosis*), miRNA, piRNA, circRNA, lncRNA, immune response

## INTRODUCTION

Tuberculosis (TB), which is caused by the intracellular pathogen *Mycobacterium tuberculosis* (*M. tuberculosis*), remains the leading cause of death from a single infectious agent (ranking higher than HIV/AIDS). According to the WHO global TB report, there were 10 million new cases of infection and 1.5 million TB-related deaths in 2018 (1). Drug-resistant TB has become a challenge for treating TB infection. In 2018, there were approximately 5 million new rifampicin-resistant TB cases (78% of which were multidrug-resistant (MDR)-TB) (1). The prevalence of TB is far more extensive than previously estimated.

The development of modern antibiotics and vaccines has helped humans overcome many infectious diseases, but TB has still not been eradicated. The main reasons are that *M. tuberculosis* rapidly exhibits drug-resistant mutations under the pressure of antibiotics and that the development of new TB vaccines and effective anti-tuberculosis drugs is prolonged (2, 3). Another reason is that during the evolutionary processes involved in coexisting with the host for thousands of years, *M. tuberculosis* has evolved with a set of almost perfect immune escape mechanisms that enable *M. tuberculosis* to skillfully avoid the elimination and killing of the host immune system and ensure its survival in macrophages for a long time (4, 5). These problems have made *M. tuberculosis* infection a severe health concern in recent years.

The immune system initiates effective defense mechanisms, including cellular and humoral factors, when the host is attacked by pathogens such as bacteria, fungi and viruses (6). While proteins and their immunomodulatory properties have been extensively studied, the roles of noncoding RNAs (ncRNAs) in controlling host defense have not been completely elucidated (especially for *M. tuberculosis*

infection). With the development of sequencing technology, a large number of ncRNA species have been discovered (7). ncRNAs are classified into small ncRNAs less than 200 nt in length (including microRNAs (miRNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), PIWI-interacting RNAs (piRNAs), long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) greater than 200 nt in size (7).

In addition, ncRNA plays a role in controlling host gene expression at the transcriptional and posttranscriptional levels. Preliminary studies on the function of ncRNA in infection have focused on pathogen infections such as viruses, parasites and bacteria (8–10). Furthermore, ncRNAs are involved in the host immune response against infection and play important roles in the complex interactions between the host and *M. tuberculosis*. In the past decade, various reports on ncRNA-mediated regulation of *M. tuberculosis* in hosts have been reviewed (11). Here, we focus on the regulation of host ncRNAs involved in host-*M. tuberculosis* interactions.

## HOST CELL MICRORNA INVOLVED IN *M. TUBERCULOSIS* INFECTION

### Background of miRNA

As key players in multiple biological processes, microRNAs (miRNAs) play crucial roles in shaping cell differentiation and biological development (12). Dysregulation of miRNA expression will cause diseases, including infection, cancer and immune disorders (9, 13, 14). Navarro and colleagues first found that miRNAs participate in regulating bacterial infection and showed that *Arabidopsis thaliana* recognition of *Pseudomonas syringa* flagellin-derived peptides induces miR-393a transcription and subsequently inhibits the expression of three F-box auxin receptors (15). Taganov et al. showed that miR-146 regulates the immune response by controlling Toll-like receptor 4 (TLR4) and cytokine signaling in monocyte ThP-1 cells induced by lipopolysaccharide (LPS) to protect host cells from excessive inflammation in an NF- $\kappa$ B dependent manner (16). Because each miRNA can regulate hundreds of genes, the dysregulated expression of host miRNAs can affect its vast target gene regulatory network. Subsequent studies established miRNA regulation upon bacterial infection (including *M. tuberculosis*) as a common phenomenon, with implications for multiple host cell functions ranging from autophagy and modulation of immune responses involved in signaling pathways, cell cycle and cell apoptosis. Therefore, a review of the roles of host miRNAs in *M. tuberculosis* infection is particularly important for revealing the pathogenesis of TB and finding anti-tuberculosis drug targets. Next, we summarize host miRNA regulation in the context of *M. tuberculosis* infection.

### The miRNA-Mediated Regulation of Signaling Pathways During *M. tuberculosis* Infection

The miRNAs regulate NF- $\kappa$ B activation induced by TLRs by targeting adaptor proteins in the pathway (17) (Table 1). TLR4 is

essential for the survival of *M. tuberculosis* infection, while this pathway needs to be controlled to preventing a strong damaging response. Several lines of reports have revealed miRNAs have emerged as important controllers of TLRs signaling (17). For instance, overexpression of miR-708-5p and miR-1178 negatively regulates the level of TLR4, reducing the secretion of proinflammatory factors including interleukin-6 (IL-6), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), thus protecting the host and allowing *M. tuberculosis* contained (18, 19). In RAW264.7 and THP-1 cells infected by *M. tuberculosis*, miR-125a was significantly upregulated in a TLR4 signaling-dependent manner, and then the upregulated miR-125a negatively regulates the NF- $\kappa$ B pathway by directly targeting TRAF6, thereby inhibiting cytokines, attenuating the immune response and promoting *M. tuberculosis* survival in macrophages (20). In infected macrophages, the elimination of *M. tuberculosis* requires a proper immune response; however, an abnormal inflammatory response may lead to the spread of the pathogen (31). MiR-27b is a good example of an ncRNA preventing excessive inflammation and maintaining proinflammatory mediator levels. The TLR2/MyD88/NF- $\kappa$ B pathway triggered by *M. tuberculosis* induces the expression of miR-27b, which inhibits the activity of NF- $\kappa$ B and proinflammatory genes and increases p53 by directly targeting the Bag2 activity of the ROS signaling pathway to positively regulate cell apoptosis (21). *M. tuberculosis* secretes an effector antigen, the early secreted antigenic target 6 (ESAT-6), which downregulates miR-Let-7f in macrophages that targets A20, a feedback inhibitor of the NF- $\kappa$ B pathway. The experiment proved that in A20-deficient macrophages, the production of proinflammatory factors (TNF- $\alpha$ , IL-1 $\beta$ ) was increased and *M. tuberculosis* survival was attenuated (22). In infected macrophages, experiments confirmed that Rv2346c, an ESAT-6-like protein, which augmented the phosphorylation of P38, simultaneously upregulates miR-155 and miR-99b, which reduced the production of TNF- $\alpha$  and IL-6 by inhibiting the activation of NF- $\kappa$ B, thereby facilitates intracellular *M. tuberculosis* survival (23).

It is well known that IFN- $\gamma$  is the predominant activator of macrophage microbicidal activity and IFN- $\gamma$ -activated macrophages play a key role in fighting intracellular pathogens (24). MiR-132 and miR-26a are upregulated in macrophages upon *M. tuberculosis* infection, which downregulate the transcriptional coactivator p300, a molecule involved in IFN- $\gamma$  signaling, limiting macrophage response to IFN- $\gamma$  (24). For efficient clearance of *M. tuberculosis*, macrophages tilt toward M1 polarization, at the same time, the regression of inflammation is related to M2 polarization. MiR-20b is downregulated in *M. tuberculosis*-infected macrophages and directly regulates NLRP3. Further experiments proved that miR-20b induces M1 to M2 macrophage polarization via targeting the NLRP3/caspase-1/IL-1 $\beta$  axis (25). In addition, *M. tuberculosis* infection decreases miR-26a-5p, accompanied by upregulation of transcription factor KLF4, and targets CREB-C/EBP $\beta$  signaling transduction, which favors M2 macrophage polarization (26). Another study demonstrated that the

**TABLE 1** | miRNA-mediated regulation of signaling pathways during *M. tuberculosis* infection.

MiRNA	Regulation (Express)	MiRNA-target predictions and validation platform/assay	Predicted targets	Cell types	Outcome	Reference
miR-1178	↑(High)	Bioinformatics analysis and luciferase reporter assay	TLR-4	THP-1 and U937 cells	Inhibit the expression of IFN- $\gamma$ , IL-6, IL-1 $\beta$ and TNF- $\alpha$	(18)
miR-708-5p	↑(High)	TargetScan bioinformatics software	TLR-4	THP-1 and U937 cells	Inhibit the expression of IFN- $\gamma$ , IL-6, IL-1 $\beta$ and TNF- $\alpha$	(19)
miR-125a	↑(High)	TargetScan bioinformatics software and luciferase reporter assay	TRAF6	RAW264.7 and THP-1 cells	Inhibit the expression of TNF- $\alpha$ , IL-6, IFN- $\gamma$ and IL-1 $\beta$	(20)
miR-27b	↑(High)	miRanda, TargetScan, PicTar bioinformatics software and luciferase reporter assay	TLR2	HEK293T and RAW264.7 cells	Inhibit the expression IL-1 $\beta$ , TNF- $\alpha$ , iNOS, NF- $\kappa$ B and IL-6	(21)
miR-let-7f	↓(High)	MAGIA bioinformatics software and luciferase reporter assay	A20	RAW264.7, HEK293T, BMDMs, and human MDMs	Reduced production of IL-1 $\beta$ , TNF- $\alpha$ , and NO	(22)
miR-99b	↑(High)	Western blotting, qRT-PCR analyses and Dual-luciferase reporter assay	P38	U937 and RAW264.7 cells	Promote the expression TNF- $\alpha$ and IL-6	(23)
miR-132	↑(High)	miRWalk bioinformatics software	p300	MDM	Inhibition of IFN- $\gamma$ signaling cascade	(24)
miR-26a	↑(High)	miRWalk bioinformatics software	p300	MDM	Inhibition of IFN- $\gamma$ signaling cascade	(24)
miR-20b	↓(High)	Plasmid transfection and luciferase reporter assay	NLRP3	HEK-293T cells	Promote the expression of IL-1 $\beta$ and IL-18, aggravate inflammation	(25)
miR-26a-5p	↓(High)	TargetScan and PicTar bioinformatics software and luciferase reporter assay	CREB-C/EBP $\beta$	RAW264.7 cells	Increased arginase and decreased iNOS activity	(26)
miR-146a	↑(High)	TargetScan bioinformatics software and Plasmid constructs	TRAF6	RAW264.7 cells, Murine BMDMs	Inhibit the expression of iNOS and NO	(27)
miR-21	↑(High)	TargetScan and PicTar bioinformatics software and luciferase reporter assay	IL-12p35	RAW264.7, HEK293T and THP-1 cells	Inhibits IL-12 production and attenuate T cell response	(28)
miR-155	↑(High)	Western blotting analyses and luciferase reporter assay	Bach1, Cox-2 and IL-6	RAW264.7 cells and Murine BMDMs	Promote the activation of Mtb dormancy regulon and attenuate host immune response	(29)
miR-155	↑(High)	cMonkey biclustering algorithm and western blotting analyses	SHIP1	RAW264.7 cells and Murine BMDMs	Promote the activation of Mtb dormancy regulon and attenuate host immune response	(30)

BMDM, bone marrow-derived macrophages; MDM, monocyte derived macrophages; ↑, upregulation; ↓, Downregulation.

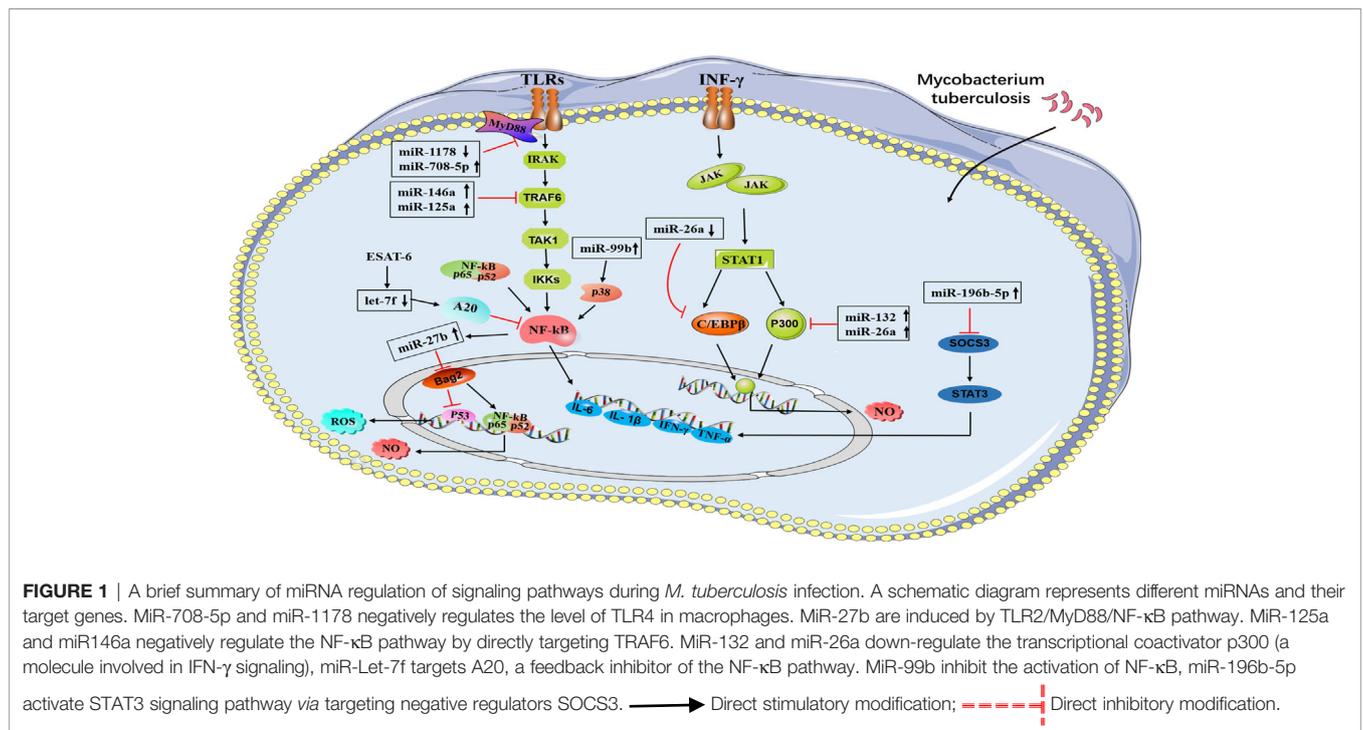
upregulation of miR-196b-5p could activate the STAT3 signaling pathway *via* targeting negative regulators SOCS3, whereas STAT3 directly affects M2 macrophage polarization, which in turn leads to inhibition of *Bacillus Calmette-Guérin* (BCG) uptake by macrophages due to attenuated proinflammatory responses (32). Furthermore, miR-146a attenuates the activation of NF- $\kappa$ B and mitogen-activated protein kinase signaling pathways during BCG infection, which in turn represses iNOS expression. Moreover, miR-146a modulates the host defense against *M. tuberculosis* infection by repressing NO production by targeting TRAF6 (27) (**Figure 1**).

The role of miRNA in regulating the immune response of dendritic cells (DCs) against *M. tuberculosis* infection has also been gradually discovered. In DCs with *M. tuberculosis* infection, miR-381-3p is thought to mediate the reduction of CD1c expression, thereby inhibiting T-cell immune responses to *M. tuberculosis* (33). In addition, miR-99b was highly expressed in DCs infected with *M. tuberculosis* strain H37Rv and upregulated the expression of inflammatory factors such as IL-6, IL-12, and IL-1 $\beta$ . More importantly, it regulates the production of TNF- $\alpha$  and TNF-4, thereby activating DCs to clear the phagocytic *M. tuberculosis* (34). After BCG vaccination injection, miR-21 (induced by activated NF- $\kappa$ B) promotes the apoptosis of DCs by targeting Bcl-2 and inhibits IL-12 production by targeting IL-12p35, which weakens the T-cell response to *M. tuberculosis* (28) (**Figure 2A**).

## The miRNA-Mediated Regulation of Apoptosis During *M. tuberculosis* Infection

Evidence have indicated apoptosis of infected macrophages leads to innate control of early bacterial growth in pulmonary *M. tuberculosis* infection (35) (**Figure 2A**). Study also showed apoptotic vesicles from mycobacteria-infected macrophages stimulate CD8 T cells and enhance host control of infection (36).

The involvement of several miRNAs in apoptosis after *M. tuberculosis* infection has also surfaced (**Table 2**). Down regulation of miR-20a-5p was demonstrated to negatively modulate Bim expression in a JNK2-dependent manner and to promote mycobacterial clearance and reduce survival in macrophages, while JNK2 was shown to be a novel direct target of miR-20a-5p (37). In addition, a study found that miR-125b-5p was upregulated in patients with TB and in macrophages infected with *M. tuberculosis* (38). Inhibition of miR-125b-5p can improve the apoptosis rate of macrophages and the expression of apoptosis-related genes Bax and Bim and reduce the secretion of proinflammatory cytokines IL-6 and TNF- $\alpha$  to protect macrophages from injury induced by *M. tuberculosis*. In addition, downregulation of miR-125b-5p also attenuated *M. tuberculosis* infection in human macrophages *in vitro* by targeting DNA damage-regulated autophagy modulator 2 (DRAM2), promoting apoptosis and inhibiting



inflammatory response (38). Not surprisingly, *M. tuberculosis* can regulate the host's miRNAs to inhibit apoptosis, thereby replicating in the cell, conducive to their own survival. Several miRNAs that were differentially expressed were investigated to suppress the apoptosis of *M. tuberculosis*-infected macrophages. In particular, miR-223 in macrophages infected with *M. tuberculosis* inhibits apoptosis by reducing the expression of the transcription factor FOXO3 (39). Similarly, miR-1281 can protect human macrophages from programmed necrosis and apoptosis induced by *M. tuberculosis* by targeting cyclophilin-d (43). Studies have suggested that miRNA-143 and miRNA-365 differentially target c-Maf, Bach-1, and Elmo-1 by promoting the intracellular growth of *M. tuberculosis* in macrophages activated by IL-4/IL-13 (40). The downregulation of miR-20b-5p enhanced *M. tuberculosis* survival in macrophages via attenuating the cell apoptosis by Mcl-1 upregulation (44). Recent reports have suggested that miR-325-3p is upregulated after *M. tuberculosis* infection and directly targets LNX1 (the E3 ubiquitin ligase of NEK6), leading to abnormal accumulation of NEK6, which in turn activates the STAT3 signaling pathway, thereby inhibiting apoptosis and promoting the intracellular survival of *M. tuberculosis* (45). Furthermore, miRNAs can also be used in new strategies to regulate host cell phagocytosis; in particular, miR-142-3p, which is induced in *M. tuberculosis*-infected macrophages, can target N-WASP (an actin-binding protein essential for phagocytosis) to regulate the production of phagosomes and reduce the uptake of *M. tuberculosis* (46). Overall, these studies highlight the host cellular miRNA regulation of apoptosis during *M. tuberculosis* infection (Figure 2B).

## The miRNA-Mediated Regulation of Autophagy During *M. tuberculosis* Infection

Autophagy plays a critical role in maintaining homeostasis within cells. A study in 2004 revealed that autophagy exhibited strong antimicrobial activity against invading pathogens (47). Since the role of autophagy against *M. tuberculosis* was first reported, the literature has further confirmed and enriched the findings (47, 48). One study proved that toxic *M. tuberculosis* in macrophages of infected mice and humans could be effectively eliminated by autophagy (47). The downregulation of miR-26a facilitates upregulation of the KLF4 (transcription factors of macrophage polarization) during *M. tuberculosis* infection, which favors the increased expression of Mcl-1 which in turn inhibits autophagosome formation and consequently lysosomal trafficking of *M. tuberculosis* (26). Moreover, miRNA-17-5p prevents *M. tuberculosis* from being eliminated by regulating autophagy in two ways. A study suggested that reducing miRNA-17-5p inhibits autophagy in *M. tuberculosis*-infected macrophages by inhibiting Mcl-1 and binds to Beclin-1 to target Mcl-1 and STAT3 (transcriptional activator of Mcl-1) (49). Another study showed the increased expression of miR-17-5p inhibits autophagosome formation in BCG-infected cells by inhibiting autophagy activating kinase 1 (ULK1) and the autophagosome-related protein LC3I/II, subsequently reducing the ability of the host cells to kill intracellular BCG (50). Ouimet et al. revealed that miR-33 and miR-33\* inhibit autophagic flux by targeting lysosomal pathway transcription factors (FOXO3 and TFEB), activators



**TABLE 2** | miRNA-mediated regulation of apoptosis during *M. tuberculosis* infection.

MiRNA	Regulation (Express)	MiRNA-target predictions and validation platform/ assay	Predicted targets	Cell types	Outcome	Reference
miR-27b	↑(High)	miRanda, TargetScan, PicTar bioinformatics software and luciferase reporter assay	Bag2	RAW264.7 and HEK293T cells	Promote the expression of p53 and ROS	(21)
miR-21	↑(High)	TargetScan and PicTar bioinformatics software and luciferase reporter assay	Bcl-2	RAW264.7, HEK293T and THP-1 cells	Promote apoptosis	(28)
miR-20a-5p	↓(High)	RT-PCR analyse and Cells transfection and dual luciferase reporter assay	JNK2	Human macrophages, THP-1 cells and RAW 264.7 cells	Promote Bim expression	(37)
miR-125b-5p	↑(High)	TargetScan bioinformatics software and dual luciferase reporter assay	DRAM2	RAW264.7 and BMDMs	promote apoptosis	(38)
miR-223	↑(High)	Systematic bioinformatics and and Western blot analysis	FOXO3	MDMs and THP-1 cells	Inhibit apoptosis	(39)
miR-143	↑(High)	IRNdb, TargetScan bioinformatics software and luciferase reporter assay	c-Maf, Bach-1 Elmo-1	BMDMs MDMs	Inhibit apoptosis	(40)
miR-365	↑(High)	RNdb, TargetScan bioinformatics software and luciferase reporter assay	c-Maf, Bach-1	BMDMs MDMs	Inhibit apoptosis	(40)
miR-155	↑(High)	Lentivirus-mediated miR-155 sponge and SOCS1 overexpression, Western blotting, qRT-PCR analyse	SOCS1	RAW264.7 cells	Promote caspase-3 activity	(41)
miR-155	↑(High)	Western blot analysis and luciferase assay	FOXO3	THP-1 cells	Inhibit apoptosis	(42)

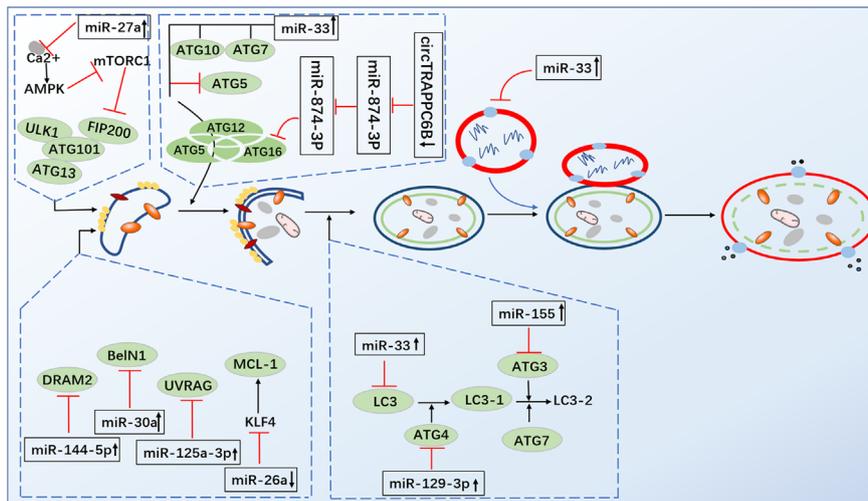
BMDM, bone marrow-derived macrophages; MDM, monocyte-derived macrophages; ↑, upregulation; ↓, Downregulation.

posttranscriptionally inhibiting the expression of TWEAK (an activator of AMP-activated protein kinase AMPK) to maintain mycobacterial survival in granulomas (55). Furthermore, miR-129-3p expression was triggered by *M. tuberculosis* infection, which was found to be related to autophagy, inhibiting phagosome formation by targeting Atg4b, which was shown to promote *M. tuberculosis* survival in macrophages (56). Additionally, miR-27a inhibited autophagy to promote the intracellular survival of *M. tuberculosis* by directly targeting the Ca<sup>2+</sup> transporter Cacna2d3 and downregulating ER Ca<sup>2+</sup> signaling (57). *M. tuberculosis* survival is modulated by miR-23a-5p through the TLR2/MyD88/NF-κB pathway and mediated autophagy by targeting TLR2 during *M. tuberculosis* infection (58) (**Figure 3** and **Table 3**).

Each miRNA can regulate hundreds of genes; thus, the same miRNA can perform different functions in host defenses. As an important regulator of adaptive and innate immune responses, miR-155 is encoded by the noncoding gene BIC (42). Under different experimental conditions with different mycobacterial strains, the role of miR-155 in regulating *M. tuberculosis* infection remains controversial. Early research revealed that miR-155 (the most highly upregulated miRNA in the macrophages of *M. tuberculosis* infection) induction depends on the ESAT-6 and attenuates SH2-containing inositol 5'-phosphatase (SHIP1) and the transcriptional repressor BTB and CNC homology 1 (Bach1). Bach1 inhibits the transcription of heme oxygenase-1 (HO-1) (the activator of dormant *M. tuberculosis*), while SHIP1 inhibits serine/threonine kinase Akt activation, which reduces the apoptosis rate of infected macrophages and promotes the survival of *M. tuberculosis* in macrophages (29). Rothchild et al. demonstrated that miR-155 regulates SHIP1-Akt signaling pathways in both macrophages and T cells, which have opposite effects on controlling *M. tuberculosis* infection. In addition, miR-155

maintains the survival and proliferation of bacteria in the early stage of infection in macrophages, whereas miR-155 promotes the long-term maintenance of *M. tuberculosis*-specific T cells capable of secreting the effector cytokines required to control infection in the late stage in T cells (30).

This study revealed a critical and dual role for miR-155 in *M. tuberculosis* infection. Previous studies showed that ESAT-6 stimulation induced miR-155 depending on the activation of TLR2/NF-κB, and miR-155 promoted apoptosis of macrophages by targeting the miR-155/SOCS1 pathway, which was conducive to the clearance of *M. tuberculosis* (29, 41). Ghorpade et al. found that upregulated miR-155 activated caspase-3 and induced the expression of Bid, Bim and Bak1 through TLR2-PI3K-PKC-MAPK signal transduction to induce apoptosis of macrophages after BCG infection (60). Further studies showed that miR-155 in monocytes infected with *M. tuberculosis* inhibited apoptosis by reducing the expression of the transcription factor FOXO3 (42). As a negative regulator of intracellular Rheb expression, miR-155 binds to the Ras homolog (Rheb) in the 3'-untranslated region, which accelerates the process of autophagy and eliminates *M. tuberculosis* in macrophages (59). In DCs, miR-155 induced by *M. tuberculosis* negatively regulates ATG3 and impairs LC3 conversion into its lipidated form (LC3-II), thereby affecting the formation of autophagosomes and inhibiting autophagy to maintain survival of *M. tuberculosis* in cells (61). Compared with that in the lungs of wild-type mice, *M. tuberculosis* infection in miR-155 (-/-) mice was significantly increased, which further demonstrated that miR-155 plays a protective role in the host immune response to *M. tuberculosis* infection (62). Taken together, these studies show that autophagy and *M. tuberculosis* are involved in a compensatory relationship. Understanding how miRNAs regulate autophagy provides a new way to control *M. tuberculosis* infection; that is, a TB



**FIGURE 3** | Infection by *M. tuberculosis* leads to alterations of miRNA expression in host cells, which regulate multiple steps of autophagy. MiR-26a facilitates upregulation of the KLF4, that favor the increased expression of Mcl-1 which in turn inhibits autophagosome formation miRNA-17-5p inhibits autophagy by inhibiting Mcl-1 and by binding to Beclin-1 to target Mcl-1. MiR-33 inhibit autophagic flux by targeting lysosomal pathway transcription factors (FOXO3 and TFEB), activators (AMPK) and multiple effectors (ATG5, ATG12, LC3B and LAMP1). MiR-30a, miR-125a-3p and miR-144-5p respectively targeting Beclin-1, UVRAG and DRAM2. MiR-129-3p inhibit phagosome formation by targeting Atg4b. MiR-27a directly targets the Ca<sup>2+</sup> transporter Cacna2d3 to inhibit autophagy. CircTRAPPC6B antagonized the ability of miR-874-3p to inhibit ATG16L1 expression, thereby activating and increasing autophagy. —> Direct stimulatory modification; —| Direct inhibitory modification; - - - -> Tentative stimulatory modification; - - - -| Tentative inhibitory modification.

**TABLE 3** | MiRNA-mediated regulation of autophagy during *M. tuberculosis* infection.

MiRNA	Regulation (Express)	MiRNA-target predictions and validation platform/assay	Predicted targets	Cell types	Outcome	Reference
miR-21	↑(High)	TargetScan and PicTar bioinformatics software and luciferase reporter assay	Bcl-2	RAW264.7 cell	Inhibit autophagy	(28)
miR-17-5p	↓(High)	luciferase assay	Mcl-1	RAW264.7, HEK293 cells and murine BMDMs	Inhibit autophagosome formation	(49)
miR-17-5p	↓(High)	luciferase assay	STAT3	RAW264.7, HEK293 cells and murine BMDMs	Inhibit autophagosome formation	(49)
miR-17-5p	↑(High)	miRanda, PicTar and TargetScan bioinformatics software and luciferase reporter assay	ULK1	RAW264.7 and HEK293T cells	Limitation of phagosomes maturation	(50)
miR-33	↑(High)	PCR and 3' UTR luciferase reporter assays	FOXO3, TFEB	HEK293 and THP-1 cells	Inhibited autophagic flux	(51)
miR-125a-3p	↑(High)	Targetscan, miRanda bioinformatics software and luciferase reporter assay	UVRAG	RAW264.7 and J774A.1 cell, BMDMs	Inhibit phagosomal maturation	(52)
miR-144-5p	↑(High)	DIANA-microT, Targetscan, miRanda bioinformatics software and luciferase reporter assay	DRAM2	HEK293T and THP-1 cells	Inhibit phagosomal maturation	(54)
miR-889	↑(High)	miRanda bioinformatics software and luciferase reporter assay	TWEAK	THP-1 cells, PBMCs from LTBI patients	Inhibit mycobacterial autophagosome maturation	(55)
miR-129-3p	↑(High)	miRDB, miRanda, Targetscan bioinformatics software and luciferase reporter assay	ATG4b	RAW264.7 and HEK-293 T cells	Inhibit autophagic flux	(56)
miR-27a	↑(High)	Base alignment approach and luciferase reporter assay	CACNA2D3	HEK293T cells and Raw264.7 cells, Mouse macrophage	Limit autophagosome formation	(57)
miR-155	↑(High)	TargetScan bioinformatics software and luciferase reporter assay	Rheb	RAW264.7 cells	Promote the maturation of phagosomes	(59)

BMDM, bone marrow-derived macrophages; MDM, monocyte-derived macrophages; PBMC: PBMC, peripheral blood mononuclear cells. ↑, upregulation; ↓, Downregulation.

immunotherapy method can be based on the optimization of the host cell immune function.

## THE ROLE OF CIRC RNAs IN ANTI-TB IMMUNITY

First identified in RNA viruses by electron microscopy in 1976, circRNAs, were later identified as transcripts in the early 1990s (63). As a special class of endogenous ncRNAs, circRNAs have continued to be reported in viruses, plants, and mammals (63–65). Due to the special mechanism of “back-splicing”, circRNA undergoes a cyclization process, resulting in the lack of a typical terminal structure (5' cap or 3' polyadenylation), which makes them resistant to exonucleases (66). On the other hand, circRNAs enriched miRNA-binding sites, therefore serving as miRNA sponges (67). Recent studies have reported circRNAs bind with RNA-related proteins and forming RNA protein complexes that act as RNA-binding protein (RBP) sponges (68), and nuclear localized circRNAs function as potent regulators of transcription at the transcription level (69). Continuous studies have shown that circRNAs play crucial roles in various cellular processes such as proliferation, differentiation, apoptosis, and metastasis (66, 70). Simultaneously, a wide range of circRNAs are highly stable and specific to cells and tissues, and circRNAs are highly expressed in the blood and in bodily fluids secreted by various tissues (such as saliva) (71, 72). Thus, the above studies have demonstrated it is reasonable that circular RNA is implicated with multiple types of diseases (73, 74).

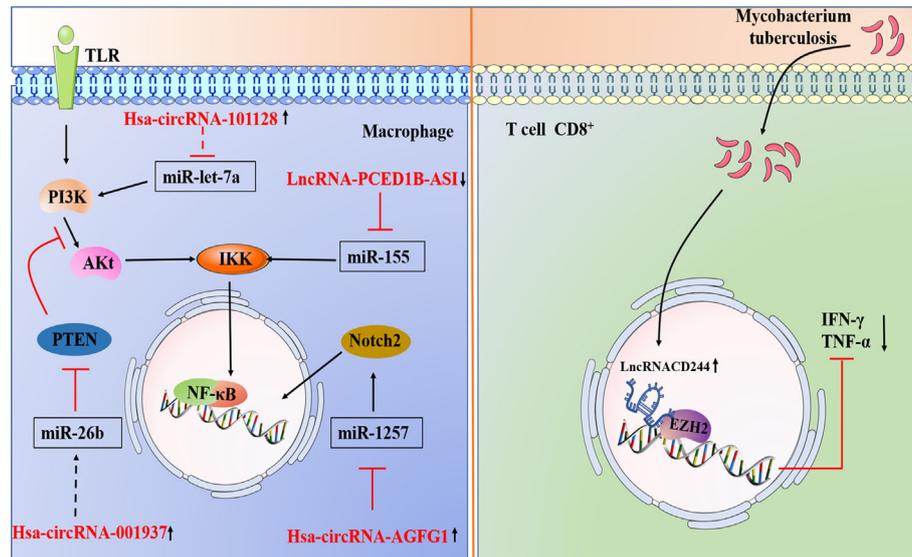
A link of circRNAs to infectious disease has also been established. For instance, Wang et al. confirmed that circ-chr19 enhances the expression of CLDN18 (which affects cell permeability) by targeting miR-30b-3p in Ebola virus infection (75). During the host response against viral infection, the immune factor NF90/NF110 exits the nucleus and reduces the expression of circRNA; at the same time, more NF90/NF110 is released through circRNPs and binds to viral mRNAs, exerting an antiviral effect (76). Liu et al. found that circRNA\_051239 was significantly upregulated in drug-resistant TB patients, and circRNA\_051239 may act as sponges of miR-320a and play a crucial role in the development of TB drug resistance (77, 78). Moreover, circAGFG1 can enhance autophagy and reduce the rate of apoptosis, which is achieved by targeting miRNA1257 to regulate Notch signaling in the macrophages infected by *M. tuberculosis* (79). Another study indicated that in the macrophages infected by *M. tuberculosis*, the overexpression circRNA-0003528 upregulates CTLA4 by downregulating miR-224-5p, miR-324-5p, and miR-488-5p to promote macrophage polarization (80). Recent studies have demonstrated that circTRAPPC6B, as a novel ceRNA, antagonized the ability of miR-874-3p to inhibit ATG16L1 expression, thereby activating and increasing autophagy to limit *M. tuberculosis* growth in macrophages (Figure 3) (81). Numerous studies have identified circRNAs that are differentially expressed in *M. tuberculosis* infection and predicted their target miRNAs (Figure 4 and

Table 4). Due to the biological characteristics of circRNAs, they have become potential biomarkers of *M. tuberculosis* infection stages (89). Zhuang et al. found that hsa\_circ\_0005836 and hsa\_circ\_0009128 in PBMCs of patients with active TB were significantly downregulated and indicated hsa\_circ\_0005836 might serve as a novel potential diagnostic biomarker for *M. tuberculosis* infection (82). Gene Ontology and KEGG enrichment analyses showed that differential expression of circular RNA was related to immune system activation, which indicated that there is a correlation between *M. tuberculosis* infection and immune system activity (82). Huang et al. discovered that the expression of hsa\_circ\_0043497 and hsa\_circ\_0001204 in monocyte-derived macrophages (MDMs) was significantly increased, and they found that the potential target miRNAs may be miR-377-3p and miR-186-5p (83). Subsequently, the team found that hsa\_circ\_001937 was significantly increased in the PBMCs of TB patients and was associated with TB severity, suggesting that its levels may be related to the clinical grade and stage of TB, and its potential miRNA target is miR-26b (84). Furthermore, miR-26b has been shown to participate in the inflammatory response by modulating the NF- $\kappa$ B pathway by targeting PTEN (90). Fu et al. found that circRNA\_103017, circRNA\_101128 and circRNA\_059914 were increased in TB patients. Bioinformatics analysis indicated that hsa\_circ\_101128 may be involved in the pathogenesis of active TB by negatively regulating let-7a and may be involved in the MAPK and PI3K-AKT pathways, which are thought to be associated with active TB (85). Zhang et al. found that STAT1 and its related molecules, including hsa-miR-223-3p, hsa-miR-448, SAMD8\_hsa\_circWF1\_hsa\_circRNA9897, are potential biomolecules for the host's defense response to *M. tuberculosis* infection (86). Another study showed that hsa\_circ\_103571 was significantly reduced in active TB patients and showed potential interactions with TB-associated miRNAs such as miR-29a and miR-16 (87, 88).

All the above studies have elucidated the presence of differentially expressed circRNAs in *M. tuberculosis*-infected host cells. However, it remains unknown how these circRNAs are involved in the regulation of miRNAs in *M. tuberculosis* infection. To investigate this question, different research groups focused on downstream signaling pathways to analyze differentially expressed circRNAs to identify potential miRNAs with potential binding sites, and further identify potential target genes for these miRNAs. This approach has been used in an attempt to identify candidate circRNAs as novel diagnostic markers, which could provide reliable targets for the treatment of TB. However, more research is still needed to elucidate the biological role of circRNAs in *M. tuberculosis*-host interactions and their true potential as clinical indicators.

## THE ROLE OF LncRNAs IN ANTI-TB IMMUNITY

Over the last decade, tens of thousands of lncRNAs have been discovered in mammalian genomes (91). While lncRNAs constitute a class of RNAs that are longer than 200



**FIGURE 4** | 1. A brief summary of circRNA and LncRNA regulation of signaling pathways during *M. tuberculosis* infection. Hsa\_circ\_101128 may be involved in the pathogenesis of active TB by negatively regulating let-7a and may be involved in the MAPK and PI3K-AKT pathways. Hsa\_circ\_001937 potential miRNA target is miR-26b, which participate in the inflammatory response by modulating the NF- $\kappa$ B pathway by targeting PTEN. CircAGFG1 can enhance autophagy is achieved by targeting miRNA1257 to regulate Notch signal in the macrophages infected by *M. tuberculosis*. 2. Models involving lncRNAs that target the host immune system of *M. tuberculosis*. *M. tuberculosis* infection leads to upregulation of lncRNA-CD244 in CD8<sup>+</sup> T cells, which interacts with chromatin modifying enzyme EZH2, and lncRNA-CD244 acts as an epigenetic regulator of IFN- $\gamma$  and TNF- $\alpha$  in CD8<sup>+</sup> T cells and suppresses their expression to modulate the TB immune response of CD8<sup>+</sup> T cells. —————> Direct stimulatory modification; ———| Direct inhibitory modification; - - - - -> Tentative stimulatory modification; - - - - -| Tentative inhibitory modification.

nucleotides, they are not translated into a protein product and instead function as an RNA molecule (92). Similar to most mRNAs, lncRNAs have a special cap structure at 5' and a polyadenylate at 3', and it was previously thought that there was no open reading frame in their sequence (91, 93). Moreover, lncRNAs can localize to target sites within the nucleus or cytoplasm of the cell and are widely expressed in eukaryotes (94, 95). They vary among different species but have high cell-type specificity (91). However, a few recent studies have confirmed that some lncRNAs show small open reading frames that encode short peptides with key biological functions. The existence of small functional peptides encoded by these lncRNAs indicates that these lncRNAs can play dual roles in RNA and peptides at the same time (96). In addition, lncRNAs are classified according to the relative position of the protein-coding gene, namely, forward lncRNAs, reverse lncRNAs, bidirectional lncRNAs, intragenic lncRNAs, and intergenic lncRNAs (97).

Emerging as an important regulator in many aspects of biology, lncRNAs have been proven to play an important role in various biological processes from development to immune response (98). For example, lncRNA-EPS, an inhibitor of the inflammatory response, is precisely regulated in macrophages to control the expression of immune response genes (IRGs) (99), and lncRNA-cox2 regulates activation and represses immune response genes induced by TLRs (100).

Fortunately, lncRNAs offer a new direction in exploring human host immunity to *M. tuberculosis* infection. A larger number of studies have shown abnormally expressed lncRNAs in macrophages of TB patients by different experimental methods (101–104) (Figure 2B and Table 5). For instance, the lncRNA HOTAIR facilitates the survival of virulent *M. tuberculosis* in SATB1- and DUSP4-dependent manners (101). Kamlesh Pawar et al. reported that IFN- $\gamma$ -mediated autophagy in infected macrophages leads to the downregulation of lncRNA MEG3 expression, which contributes to the elimination of intracellular mycobacterium in BCG infection (103). In addition, lncRNAs play a role in transcriptional and posttranscriptional gene regulation (110). lncRNAs enriched miRNA-binding sites, therefore serving as miRNA sponges and competing with the target mRNAs for binding miRNA in the cytoplasm. This indicates that lncRNA regulate gene expression at the posttranscriptional level and participate in RNA networks, acting as competing endogenous RNAs (ceRNAs) (111). The ceRNA regulation hypothesis was proposed by Salmena et al. (112). Recent studies have shown that lncRNA MEG3 can also control miR-145-5p expression and regulate macrophage proliferation to control *M. tuberculosis* infection (105). Ke et al. found that lncRNA-EPS expression was downregulated in monocytes from patients with active pulmonary tuberculosis (PTB) compared with those in healthy individuals. Further

**TABLE 4** | The regulatory role of CircRNAs in anti-TB immunity.

Circular RNA	Regulation (Express)	Samples	Technology of CircRNAs expression	Predicted miRNAs targets	Potential value	Reference
circRNA_051239	↑(High)	Serum	Microarray analysis, RT-qPCR	miR-320a	Be related to drug resistance	(77, 78)
circAGFG1	↑(High)	Bronchoalveolar lavage	Western blotting, Cell transfection, CCK-8 assay, flow cytometry, RT-qPCR, luciferase reporter assay	miRNA-1257	Decreased monocyte apoptosis and enhanced autophagy	(79)
circRNA-0003528	↑(High)	Plasma	RT-qPCR, luciferase reporter assay	miR-224-5p, miR-324-5p, miR-488-5p	Promote macrophage polarization	(80)
circTRAPPC6B	↓(High)	PBMCs	Plasmid transfection, RT-qPCR, Western blot, Bioinformatics prediction, luciferase assay, FISH	miR-874-3p	Enhanced autophagy	(81)
hsa_circ_0005836	↓(High)	PBMCs	High-throughput sequencing, RT-qPCR	hsa-miR-93-3p, hsa-miR-367-5p, hsa-miR-629-3p	Potential biomarker for TB	(82)
has_circ_0009128	↓(High)	PBMCs	High-throughput sequencing, RT-qPCR	hsa-miR-93-3p, hsa-miR-367-5p, hsa-miR-629-3p	Belated to immune system activation	(82)
hsa_circ_0043497	↑(High)	PBMCs	Microarray analysis, RT-qPCR	miR-335-3p, miR-186-5p, miR-380-5p, miR-296-3p, miR-522-3p	Potential biomarker for TB	(83)
hsa_circ_0001204	↓(High)	Plasma specimens	Microarray analysis, RT-qPCR	miR-612, miR-657, miR-362-3p, miR-377-3p, miR-136-5p	Potential biomarker for TB	(83)
hsa_circ_001937	↑(High)	PBMCs	Microarray analysis, RT-qPCR	miR-22-5p, miR-26b-3p, miR-10b-3p	Effective diagnostic biomarkers for TB	(84)
hsa_circ_101128	↑(High)	PBMCs	Microarray analysis, RT-qPCR	let-7a	Be related to autophagy	(85)
SAMD8_hsa_circRNA994	NA	whole blood	GEO database, GSEA, RT-qPCR	hsa-miR-223-3p	Be related to autophagy	(86)
TWF1_hsa_circRNA9897	NA	whole blood	GEO database, GSEA, RT-qPCR	hsa-miR-448	Be related to autophagy	(86)
has_circ_103571	↑(High)	Plasma specimens	Microarray analysis, RT-qPCR	miR-29a, miR-16	Be related to autophagy	(87, 88)

PBMC, peripheral blood mononuclear cells. ↑, upregulation; ↓, Downregulation; NA, not available.

research shows that knocking down lncRNA-EPS inhibited apoptosis and enhanced autophagy by activating the JNK/MAPK signaling pathway in BCG-infected RAW264.7 macrophages, allowing *M. tuberculosis* to survive in macrophages (104). Li et al. found that the expression of PCED1B-AS1 was downregulated in patients with active TB, and PCED1B-AS1 acted as an endogenous sponge to block the expression of miR-155 in macrophages by directly binding to miR-155, thereby reducing the apoptosis rate and promoting autophagy (Figures 2B and 4) (106). Bai et al. found that the expression levels of lnc-AC145676.2.1-6 and lnc-TGS1-1 were significantly downregulated in PTB (107). The previous studies and bioinformatics predictions suggest that lnc-TGS1-1 and lnc-AC145676.2.1-6 may be able to act as miRNA sponges to interact with miR-143 and miR-29a to participate in the occurrence and development of TB (107). One study investigated the effect of lncRNA NEAT1 (nuclear-rich transcript1) on *M. tuberculosis* infection. Moreover, NEAT1 promoted the increase of inflammatory factors in *M. tuberculosis*-infected macrophages, reduced the phagocytosis of macrophages and inhibited cell apoptosis through regulating miR-377-3p, leading to the occurrence of TB (108). Moreover, ceRNA analysis of ENST00000570366, NR\_003142, NR\_038221, and ENST00000422183 predicted the potential relationships with

ncRNAs. The results indicated that NR\_038221 was the most considerably associated with TB (113). A previous study verified hsa-miR-378a-3p as a potential biomarker for pulmonary TB, and hsa-miR-378a-3p was associated with NR\_038221, which indicated NR\_038221 and hsa-miR-378a-3p might play a similar function during the pathological process of pulmonary TB (113, 114).

In the immune response to *M. tuberculosis* infection, CD4<sup>+</sup> T cell immunity is dominant. CD4<sup>+</sup> T cells can produce cytokines, which in turn activate macrophages to inhibit the growth of intracellular *M. tuberculosis* (115). Although the role of CD8<sup>+</sup> T cells in the immune response to *M. tuberculosis* infection is controversial, recent studies have confirmed that CD8<sup>+</sup> T cells, similar to CD4<sup>+</sup> T cells, produce the critical functions of IL-2, IFN- $\gamma$  and TNF, thereby providing a protective immune response after infection with *M. tuberculosis* (115, 116). Zeng's research group found that lncRNA-CD244 acts as an epigenetic regulator of IFN- $\gamma$  and TNF- $\alpha$  in CD8<sup>+</sup> T cells and inhibits their expression to regulate the TB immune response of CD8<sup>+</sup> T cells (109). Fu et al. found that lncRNA was differentially expressed in CD8<sup>+</sup> T cells, and heme oxygenase 1 (HMOX1) was downregulated in CD8<sup>+</sup> T cells of PTB patients, while its related lncRNA (XLOC-014219) was upregulated, suggesting that lncRNA may be related to the dysfunction of CD8<sup>+</sup> T cells and

**TABLE 5** | The regulatory role of lncRNAs in anti-TB immunity.

LncRNAs	Regulation (Express)	Technology of LncRNAs expression	Predicted targets	Validated targets	Samples	Function	Reference
LncRNA HOTAIR	↓(High)	Chromatin Immunoprecipitation, western blot, RT-qPCR, gene silencing by siRNA		EZH2	THP-1 cells	Favors the transcription of SATB1 and DUSP4 and inhibit the production of ROS	(101)
LincRNA-EPS	↓(High)	Flow cytometry, RT-qPCR, Immunofluorescence, western blot		JNK/ MAPK	RAW264.7 cells	Attenuate apoptosis and enhance autophagy	(104)
LncRNA MEG3	↓(High)	Dual-luciferase reporter assay, Flow cytometry, RT-qPCR	miR-145-5p		THP-1, U937, HeLa, HT-29 cells	Attenuate the ability of inhibiting autophagy	(105)
LncRNA PCED1B-AS1	↓(High)	Microarray analysis, western blot, CCK-8 assay, immunofluorescence and TEM, flow cytometry	miR-155		PBMCs, THP-1 cells	Attenuate in monocyte apoptosis and enhance in autophagy	(106)
Lnc-AC145676.2.1-6	↓(High)	RT-qPCR	miR-29a		Whole blood	Interference with the toll-like receptor signaling pathway and other immune-response interactions	(107)
Lnc-TGS1-1	↓(High)	RT-qPCR	miR-143		Whole blood	Leads to presence of thrombocytopenia during anti-TB treatment/interference with the toll-like receptor signaling pathway and other immune-response interactions	(107)
LncRNA NEAT1	↑(High)	RT-qPCR, gene silencing by siRNA	miR-377-3p		PBMCs	Decrease inIL-6/enhances in duration of infection/ related with outcome of TB	(108)
LncRNA-CD244	↑(High)	Flow cytometry, intracellular cytokine staining (ICS), immune analyses of MTB-infected mice		EZH2	CD8 <sup>+</sup> T cells	Inhibit the expression of IFN- $\gamma$ and TNF- $\alpha$	(109)

↑, upregulation; ↓, Downregulation.

may participate in the pathophysiological process of active PTB (117); in the same year, they also found that SOCS3 (a key negative regulator of the response to *M. tuberculosis* infection) and its adjacent lncRNA (XLOC-012582) were highly expressed in *M. tuberculosis*-infected B cells (118).

In recent years, with the development of modern biotechnology such as gene chips, a larger number of lncRNAs have been continuously discovered, and the functions of lncRNAs and their regulatory mechanisms upon *M. tuberculosis* infection have been studied from many perspectives, particularly their differential expression in host cells. Thus, lncRNAs will help us understand the pathogenesis of TB and provide new clues for the prevention and treatment of TB.

## CONCLUSIONS AND PERSPECTIVES

Overall, the advancement of RNA-sequencing technology has contributed to the discovery of host ncRNAs. Host ncRNA is now considered to be the main participant in the infection process of *M. tuberculosis*. Many studies have revealed differentially expressed ncRNAs in TB patients and healthy individuals, but whether differentially expressed ncRNAs can be used as ideal biomarkers for the diagnosis of TB or as targets for the treatment of TB remains to be determined, and many questions still need to be answered, such as are there sex and race

differences for the ncRNAs that are differentially expressed? In addition, understanding whether ncRNA regulates *M. tuberculosis* infection as a common phenomenon or whether specific phenomena exist under certain conditions remains unclear. Additionally, most of the research about ncRNA mainly focuses on miRNA. More research focused on circRNA and lncRNA studies regarding *M. tuberculosis* infection would be of benefit in attracting people's attention to these areas. Despite the problems and questions, ncRNAs are highly promising as biomarkers of TB. Due to the complexity of the ncRNAs themselves, there are many host ncRNAs that have not been discovered, and their functions and regulatory networks are thus unknowable. In addition, the lack of accurate databases for the host ncRNAs that are being discovered is restricting research to the analysis of differences in gene expression. The corresponding gene regulatory function, the identification of downstream targets and the potential mechanisms involved in regulation still need to be further studied.

In this article, we summarized the role and mechanism of dysregulated expression of ncRNA in regulating host immune response in *M. tuberculosis* infection. Understanding this could promote the development of therapeutic strategies against *M. tuberculosis* infection that are used as therapeutic targets, that is, by reducing or increasing the expression of key ncRNAs and then inhibiting or activating the genes influenced by these ncRNAs. In fact, this ncRNA-based therapeutic approach is currently under development.

Finally, these data will not only provide basic knowledge about the function of ncRNAs in host-*M. tuberculosis* interactions but will also be critical for the development of new anti-TB diagnostic and therapeutic approaches.

## AUTHOR CONTRIBUTIONS

LW drafted the manuscript. QJ drew the figures. HZ and KL contributed equally to plot the table. BZ and QB revised the review. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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