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-kB 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-κB 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-γ (IFN-γ), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α), 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-κB 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-κB pathway triggered by M. tuberculosis induces the expression of miR-27b, which inhibits the activity of NF-κB 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-κB pathway. The experiment proved that in A20-deficient macrophages, the production of proinflammatory factors (TNF-α, IL-1β) is 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-α and IL-6 by inhibiting the activation of NF-κB, thereby facilitates intracellular M. tuberculosis survival (23).

It is well known that IFN-γ is the predominant activator of macrophage microbicidal activity and IFN-γ-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-γ signaling, limiting macrophage response to IFN-γ (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-1β axis (25). In addition, M. tuberculosis infection decreases miR-26a-5p, accompanied by upregulation of transcription factor KLF4, and targets CREB-C/EBPβ signaling transduction, which favors M2 macrophage polarization (26). Another study demonstrated that the
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-κB and mitogen-activated protein kinase signaling pathways during BCG infection, which in turn represses iNOS expression. Moreover, miR-146a modulates the host defense of NF-κB and mitogen-activated protein kinase signaling cascade (24) and reduces the secretion of proinflammatory factors such as IL-6, IL-12, and IL-1β (21).

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 (27). 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 inhibition of TRAF6 RAW264.7 and THP-1 cells (28) (Figure 2A).
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* (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

![Diagram of miRNA regulation of signaling pathways during M. tuberculosis infection](image)

**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.
(AMPK) and multiple effectors (ATG5, ATG12, LC3B and LAMP1) during mycobacterial infection to promote *M. tuberculosis* survival and persistence in cells (51). Upregulation of miR-30a, miR-125a-3p and miR-144-5p levels in *M. tuberculosis*-infected macrophages inhibited autophagy by targeting Beclin-1, UVRAG and DRAM2, respectively, thus suppressing the elimination of intracellular *M. tuberculosis* (52–54). Recent studies have found that miR-889 prevents autophagy by

**FIGURE 2** | Strategy of non-coding RNA regulating apoptosis pathway in *M. tuberculosis* infected cells. (A) MiR-155 and miR223 inhibit apoptosis by targeting FOXO3, miR-1281 inhibited apoptosis by targeting cyclophilin-d, miRNA-143 and miRNA-365 inhibit apoptosis by differentially targeting c-Maf, Bach-1, and Elmo-1. MiR-20a-5p negatively modulating Bim expression in a JNK2-dependent manner. MiR-125b-5p targets DRAM2 to promote apoptosis, miR-325-3p targets LNX1 (the E3 ubiquitin ligase of NEK6), leading to abnormal accumulation of NEK6, which in turn activates the STAT3 signaling pathway. At the same time, potential ceRNAs are also flagged here. lincRNA-EPS inhibited apoptosis and enhanced autophagy by activating the JNK/MAPK signaling pathway. PCED1B-AS1 can directly bind to miR-155 to reduce the rate of apoptosis. LncRNA MEG3 can control miR-145-5p expression and regulate macrophage proliferation. The mechanism of action of ceRNA needs to be further studied and verified. (B) The apoptotic cells present antigen to DCs to trigger T-cell immunity. MiR-381-3p mediate the reduction of CD1c expression, thereby inhibiting T cell immune responses to *M. tuberculosis*. MiR-21 promotes the apoptosis of DCs by targeting Bcl-2, and inhibits IL-12 production by targeting IL-12p35, weakening the T-cell response to *M. tuberculosis*.
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$^{2+}$ transporter Cacna2d3 and downregulating ER Ca$^{2+}$ signaling (57). M. tuberculosis survival is modulated by miR-23a-5p through the TLR2/MyD88/B pathway and mediated autophagy by targeting TLR2 during M. tuberculosis 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-AMPK 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

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 analysis 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 | MDMs | Inhibit apoptosis | (40) |
| miR-385 | †(High) | IRNdb, TargetScan bioinformatics software and luciferase reporter assay | c-Maf, Bach-1 | SOCS1 | Inhibit apoptosis | (40) |
| miR-155 | †(High) | Lentivirus-mediated miR-155 sponge and SOCS1 overexpression, Western blotting, qRT-PCR assay | 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.
# 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 | ULRK1             | RAW264.7 and HEK293T cells | Limitation of phagosomes maturation | (50)      |
| miR-30a | ↑(High)              | miRanda, PicTar and TargetScan bioinformatics software and luciferase reporter assay | FOXO3, TFE3       | HEK293 and THP-1 cells | Inhibited autophagic flux | (51)      |
| miR-33  | ↑(High)              | miRanda bioinformatics software and luciferase reporter assay | UVRAG             | RAW264.7 and J774A.1 cell, BMDMs | Inhibit phagosomal maturation | (52)      |
| miR-125a-3p | ↑(High)         | DIANA-microT, Targetscan, miRanda bioinformatics software and luciferase reporter assay | DRAM2             | HEK293T and THP-1 cells | Inhibit phagosomal maturation | (54)      |
| miR-125a-3p | ↑(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-27a | ↑(High)              | TargetScan bioinformatics software and luciferase reporter assay | Rheb              | RAW264.7 cells | Promote the maturation of phagosomes | (58)      |

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

**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 autophagophic 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 Ca²⁺ transporter Cacna2d3 to inhibit autophagy. CricTRAPP60B antagonized the ability of miR-874-3p to inhibit ATG16L1 expression, thereby activating and increasing autophagy.
immunotherapy method can be based on the optimization of the host cell immune function.

THE ROLE OF CIRCRNAS 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 hasa_circ_0005836 and hsa_circ_0009128 in PBMCs of patients with active TB were significantly downregulated and indicated hasa_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 hasa_circ_0043497 and hasa_circ_001204 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 hasa_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-κB 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 hasa_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 hasa-miR-223-3p, hasa-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 hasa_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
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).

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-γ-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, OCK-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, miR-874-3p | Promote macrophage polarization | (80) |
| circTRAPPO6B | ↑(High) | PBMCs | Plasmid transfection, RT-qPCR, Western blot, Bioinformatics prediction, luciferase assay, FISH | hsa-miR-93-3p, hsa-miR-367-5p, hsa-miR-629-3p | Potential biomarker for TB | (82) |
| hsa_circ_0005836 | ↑(High) | PBMCs | High-throughput sequencing, RT-qPCR | hsa-miR-93-3p, hsa-miR-367-5p, hsa-miR-629-3p, miR-335-3p, miR-188-5p, miR-380-5p, miR-296-3p, miR-522-3p, miR-612, miR-657, miR-362-3p, miR-377-3p, miR-136-5p | Potential biomarker for TB | (83) |
| hsa_circ_0009128 | ↑(High) | PBMCs | High-throughput sequencing, RT-qPCR | miR-22-5p, miR-26b-3p, miR-10b-3p, let-7a | Effective diagnostic biomarkers for TB | (84) |
| hsa_circ_0043497 | ↑(High) | PBMCs | Microarray analysis, RT-qPCR | hsa-miR-223-3p | Be related to autophagy | (85) |
| hsa_circ_0001204 | ↑(High) | Plasma specimens | Microarray analysis, RT-qPCR | hsa-miR-448 | Be related to autophagy | (86) |
| hsa_circ_001937 | ↑(High) | PBMCs | Microarray analysis, RT-qPCR | miR-29a-3p, miR-16 | Be related to autophagy | (87, 88) |
| hsa_circ_101128 | ↑(High) | PBMCs | Microarray analysis, RT-qPCR | | | |
| SAMD8_hsa_circRNA994 | NA | whole blood | GEO database, GSEA, RT-qPCR | hsa-miR-223-3p | | |
| TWF1_hsa_circRNA9897 | NA | whole blood | GEO database, GSEA, RT-qPCR | hsa-miR-448 | | |
| has_circ_103571 | ↑(High) | Plasma specimens | Microarray analysis, RT-qPCR | hsa-miR-223-3p | | |

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 Inc-AC145676.2.1-6 and Inc-TGS1-1 were significantly downregulated in PTB (107). The previous studies and bioinformatics predictions suggest that Inc-TGS1-1 and Inc-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+ T cell immunity is dominant. CD4+ T cells can produce cytokines, which in turn activate macrophages to inhibit the growth of intracellular M. tuberculosis (115). Although the role of CD8+ T cells in the immune response to M. tuberculosis infection is controversial, recent studies have confirmed that CD8+ T cells, similar to CD4+ T cells, produce the critical functions of IL-2, IFN-γ, 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-γ and TNF-a in CD8+ T cells and inhibits their expression to regulate the TB immune response of CD8+ T cells (109). Fu et al. found that lncRNA was differentially expressed in CD8+ T cells, and heme oxygenase 1 (HMOX1) was downregulated in CD8+ T cells of PTB patients, while its related lincRNA (XLOC-014219) was upregulated, suggesting that lncRNA may be related to the dysfunction of CD8+ T cells and
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 and regulatory networks of lncRNAs themselves have not been fully understood. In addition, the lack of accurate databases for the discovery and regulation of lncRNAs, in nature, 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 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.

**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.

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**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)     |
| LncRNA-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)     |
| LncRNA-AC145676.2-6 | ↑[High]       | RT-qPCR                          | miR-29a           | Whole blood       | Interference with the toll-like receptor signaling pathway and other immune-response interactions | (107)     |
| LncRNA-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 NEAT  | ↑[High]             | RT-qPCR, gene silencing by siRNA | miR-377-5p        | PBMCs             | Decrease in IL-6/enhanced 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+ T cells      | Inhibit the expression of IFN-γ and TNF-α                                | (109)     |

↑, upregulation; ↓, downregulation.
Finally, these data will not only provide basic knowledge about the function of ncRNAs in host- \textit{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 article and approved the submitted version.

**REFERENCES**

1. World Health Organization. Global Tuberculosis Report. Geneva, Switzerland: World Health Organization (2019).
2. Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, et al. Epidemiology of Antituberculosis Drug Resistance 2002-07: An Updated Analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. \textit{Lancet} (2009) 373(9678):1861-73. doi: 10.1016/s0140-6736(09)60331-7
3. MacDonald EM, Lizzo AA. Tuberculosis Vaccine Development — Its History and Future Directions. In: \textit{Tuberculosis - Expanding Knowledge, IntechOpen} (2015) doi: 10.5772/95658
4. Stanley SA, Cox JS. Host-Pathogen Interactions During Mycobacterium Tuberculosis Infections. \textit{Curr Top Microbiol Immunol} (2015) doi: 10.5772/59658
5. Arnvig K, Young D. Non-Coding RNA and its Potential Role in Tuberculosis. \textit{Nat Rev Immunol} (2011) 11(3):163–75. doi: 10.1038/nri2957
6. Shi G, Mao G, Xie K, Wu D, Wang W. MiR-1178 Regulates Mycobacterial Survival and Inflammatory Responses in Mycobacterium Tuberculosis-Infected Macrophages Partly Via TLRA. \textit{J Cell Biochem} (2018) 119(9):7449–57. doi: 10.1002/jcb.27054
7. Li WT, Zhang Q. MicroRNA-708-Sp Regulates Mycobacterial Virulence and the Secretion of Inflammatory Factors in Mycobacterium Tuberculosis-Infected Macrophages by Targeting TLRA. \textit{Eur Rev Med Pharmacol Sci} (2019) 23(18):8028–38. doi: 10.26355/eurev_201909_19019
8. Niu W, Sun B, Li M, Cui J, Huang J, Zhang L. TLRA-MicroRNA-125a/NF-κB Signaling Modulates the Immune Response to Mycobacterium Tuberculosis Infection. \textit{Cell Cycle} (2018) 17(15):1931–45. doi: 10.1080/15384101.2018.1509636
9. Liang S, Song Z, Wu Y, Gao Y, Gao M, Liu F, et al. MicroRNA-27b Modulates Inflammatory Response and Apoptosis During Mycobacterium Tuberculosis Infection. \textit{J Immunol} (2018) 200(10):3506–18. doi: 10.4049/jimmunol.1701448
10. Kumar M, Sahu SK, Kumar R, Subuddhi A, Maji RK, Jana K, et al. MicroRNA Let-7 Modulates the Immune Response to Mycobacterium Tuberculosis Infection Via Control of A20, an Inhibitor of the NF-κB Pathway. \textit{Cell Host Microbe} (2015) 17(3):345–56. doi: 10.1016/j.chom.2015.01.007
11. Yao J, Du X, Chen S, Shao Y, Deng K, Jiang M, et al. Rv2346c Enhances Mycobacterial Survival Within Macrophages by Inhibiting TNF-α and IL-6 Production Via the P38/MicroRNA/NF-κB Pathway. \textit{Emerg Microbes Infect} (2018) 7(1):158. doi: 10.1038/s41426-018-0162-6
12. Ni B, Rajaram MV, Lafuse WP, Landes MB, Schlesinger LS. Mycobacterium Tuberculosis Decreases Human Macrophage IFN-γ Responsiveness Through miR-132 and mir-26a. \textit{J Immunol} (2014) 193(9):4537–47. doi: 10.4049/jimmunol.1400124
13. Lou J, Wang Y, Zhang Z, Qiu W. MiR-20b Inhibits Mycobacterium Tuberculosis Induced Inflammation in the Lung of Mice Through Targeting NLRP3. \textit{Exp Cell Res} (2017) 358(2):120–8. doi: 10.1016/j.yexcr.2017.06.007
14. Sahu SK, Kumar M, Chakraborty S, Banerjee SK, Kumar R, Gupta P, et al. MicroRNA 26a (miR-26a)/KLF4 and CREB-C/EBPβ Regulate Innate Immune Signaling, the Polarization of Macrophages and the Trafficking of Mycobacterium Tuberculosis to Lysosomes During Infection. \textit{PloS Pathog} (2017) 13(5):e1006410. doi: 10.1371/journal.ppat.1006410
15. Li M, Wang J, Fang Y, Gong S, Li M, Wu M, et al. MicroRNA-146a Promotes Mycobacterial Survival in Macrophages Through Suppressing Nitric Oxide Production. \textit{Sci Rep} (2016) 6:23351. doi: 10.1038/srep23351
16. Xu Z, Lu H, Sheng J, Li L. Inducive microRNA-21 Impairs Anti-Mycobacterial Responses by Targeting IL-12 and Bcl-2. \textit{FEBS Lett} (2012) 586(16):2459–67. doi: 10.1016/j.febslet.2012.06.004

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29. Kumar R, Halder P, Sahu SK, Kumar M, Kumari M, Jana K, et al. Identification of a Novel Role of ESAT-6-dependent miR-155 Induction During Infection of Macrophages With Mycobacterium Tuberculosis. Cell Microbiol (2012) 14(10):1620–31. doi: 10.1111/j.1462-5822.2012.01827.x

30. Rothchild AC, Sissons JR, Shafiani S, Plaisier C, Min D, Mai D, et al. MiR-155-regulated Molecular Network Orchestrates Cell Fate in the Innate and Adaptive Immune Response to Mycobacterium Tuberculosis. Proc Natl Acad Sci U S A (2016) 113(41):E6172–e6181. doi: 10.1073/pnas.1608255113

31. Sibria TJ, Coussens AK, Fletcher HA. Human Immunology of Tuberculosis. Microbiol Spectr (2017) 5(1):23–37. doi: 10.1128/microbiolspec.TTB2-0016-2016

32. Yuan Y, Lin D, Feng L, Huang M, Yan H, Li Y, et al. Upregulation of miR-20a-5p Triggers Cell Apoptosis to Facilitate Mycobacterial Clearance. Front Immunol (2019) 10:421. doi: 10.3389/immunol.2019.00421

33. Wei et al. Host NcRNAs and M. tuberculosis Infection. Targeting LNX1 Via NEK6 Accumulation to Promote Anti-Apoptotic STAT3 Signaling. mBio (2020) 11(3). doi: 10.1128/mBio.00557-20

34. Bettencourt P, Marion S, Pires D, Santos LF, Lastrucci C, Carmona N, et al. Actin-Binding Protein Regulation by microRNAs as a Novel Microbial Strategy to Modulate Phagocytosis by Host Cells: The Case of N-Wasp and miR-142-3p. Front Cell Infect Microbiol (2013) 3:19. doi: 10.3389/fcimb.2013.00019

35. Gutierrez MG, Master SS, Singh SB, Taylor GA, Colombo MI, Deretic V. Autophagy is a Defense Mechanism Inhibiting BCG and Mycobacterium Tuberculosis Survival in Inolated Macrophages. Cell (2004) 119(6):753–66. doi: 10.1016/j.cell.2004.11.038

36. Singh SB, Davis AS, Taylor GA, Deretic V. Human IRGM Induces Autophagy to Eliminate Intracellular Mycobacteria. Science (2006) 313(5792):1438–41. doi: 10.1126/science.1129577

37. Scible TJ, Coussens AK, Fletcher HA. Human Immunology of Tuberculosis. Microbiol Spectr (2017) 5(1):23–37. doi: 10.1128/microbiolspec.TTB2-0016-2016
63. Capel B, Swain A, Nicolas S, Hacker A, Walter M, Koopman P, et al. Circular Transcripts of the Testis-Determining Gene Sry in Adult Mouse Testis. Cell (1993) 73(3):1909–30. doi: 10.1016/0092-8674(93)90279-y

64. Ye CY, Chen L, Liu C, Zha QH, Fan L. Widespread Noncoding Circular RNAs in Plants. New Phytol (2015) 208(1):88–95. doi: 10.1111/nph.13585

65. Rybak-Wolf A, Stottmeister C, Glazar P, Jens M, Pino N, Giusti S, et al. Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. Mol Cell (2015) 58(5):870–85. doi: 10.1016/j.molcel.2015.03.027

66. Kristensen LS, Andersen MS, Stagsted LWV, Ebbesen KK, Hansen TB, Kjems J. The Biogenesis, Biology and Characterization of Circular RNAs. Nat Rev Genet (2019) 20(11):675–91. doi: 10.1038/s41576-019-0158-7

67. Hansen TB, Jensen TI, Clausen BH, Bransem JB, Finsen B, Damgaard CK, et al. Natural RNA Circles Function as Efficient microRNA Sponges. Nature (2013) 495(7441):384–8. doi: 10.1038/nature12033

68. Conn SJ, Pillman KA, Toubia J, Conn VM, Salamandis M, Phillips CA, et al. The RNA Binding Protein Quaking Regulates Formation of CircRNAs. Cell (2015) 160(6):1125–34. doi: 10.1016/j.cell.2015.02.014

69. Li Z, Huang C, Bao C, Chen L, Wang X, et al. Exon-Intron Circular RNAs Regulate Transcription in the Nucleus. Front Mol Biol (2015) 2(3):256–64. doi: 10.3389/fmolb.2015.00295

70. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P, Yang BB. Foxo3 Circular RNAs Regulate Transcription in the Nucleus. Mol Cell (2015) 22(4):256–65. doi: 10.1016/j.molcel.2015.03.002

71. Vea A, Llorente-Cortes V, de Gonzalo-Calvo D. Circular RNAs in Blood. Exp Med Biol (2018) 1087:119–30. doi: 10.1007/978-981-13-1426-1_10

72. Jafari Ghods F. Circular RNA in Saliva. Adv Exp Med Biol (2018) 1087:131–9. doi: 10.1007/978-981-13-1426-1_11

73. Li HM, Ma XL, Li HG. Intriguing Circles: Conflicts and Controversies in Circular RNA Research. Wiley Interdiscip Rev RNA (2019) 10(5):e1538. doi: 10.1002/wrrn.1538

74. Haddad G, Lorenzen JM. Biogenesis and Function of Circular RNAs in Health and in Disease. Front Pharmacol (2019) 10:428. doi: 10.3389/fphar.2019.00428

75. Wang ZY, Guo ZD, Li JM, Zhao ZW, Fu YY, Zhang CM, et al. Genome-Wide Search for Competing Endogenous RNAs Responsible for the Effects Induced by Ebola Virus Replication and Transcription Using a trVLP System. Front Cell Infect Microbiol (2017) 7:479. doi: 10.3389/fcimb.2017.00479

76. Li X, Liu CX, Xue W, Zhang Y, Jiang S, Yin QF, et al. Coordinated CircRNA Biogenesis and Function With NF90/NF110 in Viral Infection. Mol Cell (2017) 67(2):24–172.217. doi: 10.1038/molcell.2017.05.023

77. Liu H, Lu G, Wang W, Jiang X, Gu S, Wang J, et al. A Panel of CircRNAs in the Serum Serves as Biomarkers for Mycobacterium Tuberculosis Infection. Front Microbiol (2020) 11:1215. doi: 10.3389/fmicb.2020.01215

78. Cui JY, Liang HW, Pan XL, Jiao N, Liu YH, et al. Characterization of a Panel of CircRNAs in Mononuclear Cells From Patients With Active Tuberculosis. Cell Physiol Biochem (2018) 45(5):780–9. doi: 10.1007/s00595-018-13885-0

79. Huang ZK, Yao FY, Xu IQ, Deng Z, Su RG, Peng YP, et al. Microarray Expression Profile of Circular RNas in Peripheral Blood Mononuclear Cells From Active Tuberculosis Patients. Cell Physiol Biochem (2018) 45(3):1230–40. doi: 10.1007/s00595-018-4754-5

80. Fu Y, Wang J, Qiao J, Yi Z. Signature of Circular RNAs in Peripheral Blood Mononuclear Cells From Patients With Active Tuberculosis. J Cell Mol Med (2019) 23(3):1917–25. doi: 10.1111/jcmm.14093

81. Yi XH, Zhang B, Fu YR, Yi ZJ. STAT1 and its Related Molecules as Potential Biomarkers in Mycobacterium Tuberculosis Infection. J Cell Mol Med (2020) 24(5):2866–78. doi: 10.1111/jcmm.14856

82. Yi Z, Gao K, Li R, Fu Y. Dysregulated circRNAs in Plasma From Active Tuberculosis Patients. J Cell Mol Med (2018) 22(9):4076–84. doi: 10.1111/jcmm.13684

83. Wang Y, Urhekar A, Modi D. Levels of microRNA miR-16 and miR-155 are Altered in Serum of Patients With Tuberculosis and Associate With Responses to Therapy. Tuberculosis (Edinb) (2017) 102:24–30. doi: 10.1016/j.tube.2016.10.007

84. Ojha R, Pandani R, Chatterjee S, Prapsajat VK. Emerging Role of Circular RNAs as Potential Biomarkers for the Diagnosis of Human Diseases. Adv Exp Med Biol (2018) 1087:131–41. doi: 10.1007/978-981-13-1426-1_12

85. Zhang L, Huang C, Guo Y, Hinsdale M, Lloyd P, et al. MicroRNA-26b Modulates the NF-κB Pathway in Alveolar Macrophages by Regulating PTEN. J Immunol (2015) 195(11):5404–14. doi: 10.4049/jimmunol.1402933

86. Wu Y, Shirokova TA, Reid N, Gao W, et al. Natural RNA Circles Function as Effectors in Mycobacterium Tuberculosis Infection and Healthy Individuals. PLoS One (2017) 12(9):e0184113. doi: 10.1371/journal.pone.0184113

87. Chen J, Shishkin AA, Zhu X, Kadi S, Maza I, Guttman M, et al. Evolutionary Analysis Across Mammals Reveals Distinct Classes of Long Non-Coding RNAs. Genome Biol (2016) 17:19. doi: 10.1186/s13059-016-0880-9

88. Engetz JM, Ollikainen N, Guttman M. Long Non-Coding RNAs: Spatial Amplifiers That Control Nuclear Structure and Gene Expression. Nat Rev Mol Cell Biol (2016) 17(12):736–70. doi: 10.1038/nrm.2016.126

89. Ransohoff JD, Khavari PA. The Functions and Unique Features of Long Intergenic Non-Coding RNA. Cold Spring Harb Perspect Biol (2019) 11(12). doi: 10.1101/cshperspect.a032151

90. Atianand MK, Hu W, Satpathy AT, Shen Y, Ricci EP, Alvarez-Domínguez JR, et al. A Long Noncoding RNA LincRNA-EPS Acts as a Transcriptional Brake to Restrain Inflammation. Cell (2016) 165(7):1672–85. doi: 10.1016/j.cell.2016.05.075

91. McDoneal P, Guttman M. Approaches for Understanding the Mechanisms of Long Noncoding RNA Regulation of Gene Expression. Cold Spring Harb Perspect Biol (2019) 11(12). doi: 10.1101/chsperspect.a023151

92. Subudhi A, Kumar M, Majumder D, Sarkar A, Ghosh Z, Vasudevan M, et al. Unraveling the Role of H3K4 Trimethylation and LncRNA HOTAIR in SATB1 and DUSP4-dependent Survival of Virulent Mycobacterium Tuberculosis Infection in Macrophages. Tuberculosis (Edinb) (2020) 120:101897. doi: 10.1016/j.tube.2019.101897

93. Fan H, Xu R, Zhang X, Wang P, Jiang X, et al. Identifying Differentially Expressed Long Non-Coding RNAs in PBCs in Response to the Infection of Multidrug-Resistant Tuberculosis. Infect Drug Resist (2018) 11:945–59. doi: 10.2147/IDR.S154255
103. Pawar K, Hanisch C, Palma Vera SE, Einspanier R, Sharbati S. Down Regulated LncRNA MEG3 Eliminates Mycobacteria in Macrophages Via Autophagy. *Sci Rep* (2016) 6:19416. doi: 10.1038/srep19416

104. Ke Z, Lu J, Zhu J, Yang Z, Jin Z, Yuan L. Down-Regulation of lincRNA-EPS Regulates Apoptosis and Autophagy in BCG-infected RAW264.7 Macrophages Via JNK/MAPK Signaling Pathway. *Infect Genet Evol* (2020) 77:104077. doi: 10.1016/j.meegid.2019.104077

105. Sun W, Lou H, Cao J, Wang P, Sha W, Sun Q. LncRNA MEG3 Control Mycobacterium Tuberculosis Infection Via Controlled MiR-145-5p Expression and Modulation of Macrophages Proliferation. *Microb Pathog* (2020) 149:104550. doi: 10.1016/j.micpath.2020.104550

106. Li M, Cui J, Niu W, Huang J, Feng T, Sun B, et al. Long Non-Coding PCED1B-AS1 Regulates Macrophage Autophagy and Apoptosis by Sponging miR-155 in Active Tuberculosis. *Biochem Biophys Res Commun* (2019) 509(3):803–9. doi: 10.1016/j.bbrc.2019.01.005

107. Bai H, Wu Q, Hu X, Wu T, Song J, Liu T, et al. Clinical Significance of Inc-AC145676.2.1-6 and Inc-TGS1-1 and Their Variants in Western Chinese Tuberculosis Patients. *Int J Infect Dis* (2019) 84:8–14. doi: 10.1016/j.ijid.2019.04.018

108. Sun Q, Shen X, Ma J, Lou H, Sha W. LncRNA NEAT1 Participates in Inflammatory Response in Macrophages Infected by Mycobacterium Tuberculosis Through Targeted Regulation of miR-377-5p. *Microb Pathog* (2021) 130:104674. doi: 10.1016/j.micpath.2020.104674

109. Wang Y, Zhong H, Xie X, Chen CY, Huang D, Shen L, et al. Long Noncoding RNA Derived From CD244 Signaling Epigenetically Controls CD8+ T-Cell Immune Responses in Tuberculosis Infection. *Proc Natl Acad Sci U S A* (2015) 112(29):E3883–92. doi: 10.1073/pnas.1501662112

110. Munschauer M, Nguyen CT, Siroman K, Hartigan CR, Hogstrom L, Engreit JM, et al. The NORAD lncRNA Assembles a Topoisomerase Complex Critical for Genome Stability. *Nature* (2018) 561(7721):132–6. doi: 10.1038/s41586-018-0453-z

111. Tay Y, Rinn J, Pandolfo P. The Multilayered Complexity of ceRNA Crosstalk and Competition. *Nature* (2014) 505(7483):344–52. doi: 10.1038/nature12986

112. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfo P. A ceRNA Hypothesis: The Rosetta Stone of a Hidden RNA Language? *Cell* (2011) 146(3):553–8. doi: 10.1016/j.cell.2011.07.014

113. Chen ZL, Wei LL, Shi LY, Li M, Jiang TT, Chen J, et al. Screening and Identification of IncRNAs as Potential Biomarkers for Pulmonary Tuberculosis. *Sci Rep* (2017) 7(1):16751. doi: 10.1038/s41598-017-17146-y

114. Zhang X, Guo J, Fan S, Li Y, Wei L, Yang X, et al. Screening and Identification of Six Serum microRNAs as Novel Potential Combination Biomarkers for Pulmonary Tuberculosis Diagnosis. *PloS One* (2013) 8(12):e81076. doi: 10.1371/journal.pone.0081076

115. Jasenkosky LD, Scriba TJ, Hanekom WA, Goldfeld AE. T Cells and Adaptive Immunity to Mycobacterium Tuberculosis in Humans. *Immunol Rev* (2015) 264(1):74–87. doi: 10.1111/imr.12274

116. Lin PL, Flynn JL. CD8 T Cells and Mycobacterium Tuberculosis Infection. *Semin Immunopathol* (2015) 37(3):239–49. doi: 10.1007/s00281-015-0490-8

117. Fu Y, Gao K, Tao E, Li R, Yi Z. Aberrantly Expressed Long Non-Coding Rnas In CD8(+) T Cells Response to Active Tuberculosis. *J Cell Biochem* (2017) 118(12):4275–84. doi: 10.1002/jcb.26078

118. Fu Y, Xu X, Xue J, Duan W, Yi Z. Deregulated IncRNAs in B Cells From Patients With Active Tuberculosis. *PloS One* (2017) 12(1):e0170712. doi: 10.1371/journal.pone.0170712

**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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