MicroRNA in innate immunity and autophagy during mycobacterial infection

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Abstract
The fine-tuning of innate immune responses is an important aspect of host defenses against mycobacteria. MicroRNAs (miRNAs), small non-coding RNAs, play essential roles in regulating multiple biological pathways including innate host defenses against various infections. Accumulating evidence shows that many miRNAs regulate the complex interplay between mycobacterial survival strategies and host innate immune pathways. Recent studies have contributed to understanding the role of miRNAs, the levels of which can be modulated by mycobacterial infection, in tuning host autophagy to control bacterial survival and innate effector function. Despite considerable efforts devoted to miRNA profiling over the past decade, further work is needed to improve the selection of appropriate biomarkers for tuberculosis. Understanding the roles and mechanisms of miRNAs in regulating innate immune signaling and autophagy may provide insights into new therapeutic modalities for host-directed anti-mycobacterial therapies. Here, we present a comprehensive review of the recent literature regarding miRNA profiling in tuberculosis and the roles of miRNAs in modulating innate immune responses and autophagy defenses against mycobacterial infections.

KEYWORDS
autophagy, innate immunity, macrophages, MicroRNA, mycobacteria, tuberculosis

1 INTRODUCTION

Tuberculosis (TB) remains a frequent and important infectious disease with a very high burden of morbidity and mortality (WHO, 2016). Mycobacterium tuberculosis (Mtb) is the major causative agent of human TB and has adapted to replicate within the phagosomal compartment of innate immune cells via manipulation of host defense mechanisms (Stanley & Cox, 2013). Intrinsic/innate host defenses consist of early and natural defenses against mycobacterial infection. Appropriate mounting of innate immune responses to intracellular mycobacteria is crucial for controlling the outcome of infection. Autophagy is an intracellular physiological process that plays an important role in host defense mechanisms against intracellular pathogenic infections, including mycobacterial infection (Jo, Yuk, Shin, & Sasakawa, 2013). There is increasing evidence of a link between innate immune signaling and autophagy to eliminate intracellular mycobacteria through enhancement of phagosomal maturation (Deretic & Levine, 2009).

MicroRNAs (miRNAs) are endogenous, small non-coding RNAs that regulate the expression of target mRNAs post-transcriptionally (Kim, Han, & Siomi, 2009). They are important regulators involved in modulating diverse biological and pathological processes through inhibition of translation or induction of mRNA degradation (Mehta & Baltimore, 2016). Over the last decade, data have accumulated regarding their roles and mechanisms, indicating that particular miRNAs can regulate autophagy and modulate host innate immune responses during infections (Gantier, Sadler, & Williams, 2007; Xiao & Rajewsky, 2009; Eulalio, Schulte, & Vogel, 2012; Forster, Tate, & Hertzog, 2015; Wei & Schober, 2016; Das, Ganic, & Dhandayuthapani, 2016). However, studies on the role of miRNAs in the regulation of innate defenses during mycobacterial infection are in their infancy. miRNAs themselves can be up- or downregulated during mycobacterial infections, suggesting a potential role for miRNAs as biomarkers of TB (Liu et al., 2011). This review will highlight our current understanding, based on the growing body of research, on the role of miRNAs in regulating innate host defenses and the autophagy pathway in mycobacterial infections. Understanding the complexity of the miRNA network in host-pathogen interactions may open up new avenues for identifying biomarkers and improving the efficacy of therapies against TB in humans.
OVERVIEW OF MIRNA BIOGENESIS

miRNAs are epigenetic modulators that regulate the expression of protein-coding genes post-transcriptionally (Figure 1). They have emerged as novel regulators involved in various biological processes and pathogenic conditions, such as inflammation, cancer, and infectious diseases. miRNAs are small RNA molecules, typically ~18–25 nucleotides in length. They are initially transcribed as primary-miRNA (pri-miRNA) transcripts containing at least one hairpin loop. These pri-miRNA transcripts are cleaved by the RNase III enzyme Drosha into precursor miRNAs (pre-miRNA) and are transported from the nucleus into the cytoplasm by exportin 5. In the cytoplasm, the RNase III enzyme Dicer cleaves the pre-miRNA into an imperfect intermediate RNA duplex of 20–25 nucleotides, comprising the functional mature miRNA and its complementary miRNA* strand. Although one strand of the duplex is degraded, mature miRNAs can be produced under certain conditions from both strands, designated as miR-X/miR-X* (the asterisk indicates the less predominantly expressed transcript). The functional mature miRNA strand is preferentially stabilized by the RNA-induced silencing complex, the molecular effector of miRNA function, whereas the other strand is degraded (Bartel, 2004). As an important gene regulatory factor in multicellular genomes, more than 50% of cellular mRNAs are thought to be regulated by miRNAs. Additionally, one miRNA can target multiple mRNAs, and in turn, one mRNA can be targeted by multiple miRNAs (Hobert, 2008).

OVERVIEW OF miRNA FUNCTION IN REGULATION OF INNATE IMMUNITY

MiRNAs play a critical role in numerous biological processes including regulation of the host innate immune responses. Accumulating evidence has revealed the roles of miRNAs in controlling magnitude of host inflammatory responses in response to innate signal activation. Among them, miR-146a, miR-155, miR-21, and miR-132 are the important miRNAs that negatively regulate the host inflammatory pathways triggered by Toll-like receptor (TLR) signaling in myeloid cells (Hou et al., 2009; Ruggiero et al., 2009; Sheedy et al., 2010; Nahid et al., 2013). miR-146a is one of the best characterized miRNAs that negatively regulate host inflammatory signaling through target genes, IRAK1 and TRAF6 (Saba, Sorensen, & Booth, 2014). Both miR-146a and miR-155 are upregulated in myeloid cells by activation of TLR signaling. Both are involved in the regulation of inflammatory responses through modulation of target

**FIGURE 1** Biogenesis of miRNAs. Diverse miRNA genes are synthesized in the nucleus as precursor pri-miRNAs containing stem-loop structures, by RNA polymerase II/III. The stem-loop structures are cleaved by Drosha and DGCRI6 complex, and the resultant pre-miRNAs are transported into the cytoplasm through Exportin-5. Pre-miRNA is processed by Dicer, RNase III, and its cofactor TRBP. The resulting miRNA duplex contains mature miRNA and passenger strand miRNA. The mature miRNA is loaded on to the RISC complex, while the passenger miRNA is degraded. Finally, mature miRNA regulates target mRNA.
gene expression (Taganov, Boldin, Chang, & Baltimore, 2006; Tili et al., 2007). MiR-155 is particularly important in fine-tuning of innate immune responses through down-regulating multiple mRNAs including SOCS1, DC-specific intercellular adhesion molecule-3 grabbing non-integrin, and a TLR signaling adaptor TAB2 (Ceppi et al., 2009; Martinez-Nunez, Louafi, Friedmann, & Sanchez-Elsner, 2009; Lu et al., 2011; Jia, Zhai, & Zhao, 2014). Earlier studies reported a negative regulatory role of miR-21 in TLR4 signaling by inhibition of NF-kappa B activity and promotion of IL-10 production through targeting the proinflammatory tumor suppressor PDCD4 (Sheedy et al., 2010). In addition, during hepatitis C virus (HCV) infection, miR-21 modulates TLR signaling by targeting MyD88 and IRAK1 leading to the suppression of type I interferon production (Chen et al., 2013). miR-132, which targets IRAK4, was rapidly induced in THP-1 monocytes, PBMCs, and primary macrophages by stimulation with peptidoglycan/TLR2. It is required for induction of tolerance to subsequent peptidoglycan challenge (Nahid et al., 2013; Figure 2). Overall, numerous miRNAs are induced by innate immune signaling to modulate the inflammatory responses and host defense to infections. In this review, we specifically focus on the miRNAs that control innate and inflammatory responses during mycobacterial infection.

Mycobacterial infection in host cells is one of the best-known examples of host–pathogen interactions. Mtb is a unique facultative intracellular pathogen that resides and multiplies within phagocytes (Ehrt & Schnappinger, 2009). Macrophages play key roles in innate immune responses to Mtb through the induction of antimicrobial proteins and inflammatory mediators after recognition of mycobacteria and their components via innate immune receptors (Ehrt & Schnappinger, 2009; Rajaram, Ni, Dodd, & Schlesinger, 2014). Indeed, macrophages play a role as sentinels that tailor specific immune responses against the invasion of various pathogenic mycobacteria through dynamic intracellular signaling networks (Schorey & Cooper, 2003; Bhatt & Salgame, 2007; Jo, Yang, Choi, & Harding, 2007; Korbel, Schneider, & Schaible, 2008; Cooper, Mayer-Barber, & Sher, 2011; A et al., 2012; Rajaram et al., 2014). Over the last several decades, the research field of innate immunity in TB and related mycobacterial infectious diseases has advanced greatly, and the innate immune mechanisms of host protection and immune pathology in humans and animal models have been elucidated (Ottenhoff, 2012). Innate immune receptors, including membrane-bound TLRs and cytosolic receptors,
play important roles in sensing and initiating host defense responses in macrophages after mycobacterial infection (Schorey & Cooper, 2003; Jo et al., 2007; Korbel et al., 2008; Cooper et al., 2011). The rapid growth in research has included elucidating mycobacterium-mediated induction of specific host miRNAs and their biological functions in innate host defenses and autophagy during infection. Indeed, it is now clear that specific host miRNAs induced by mycobacterial infection can target crucial factors and pathways in host innate immune signaling.

4.1 MiRNAs as modulators of host innate responses during mycobacterial infection

Diverse functions of miRNAs have been recognized in their roles as pivotal players in modulating innate immune responses, cytokine responses, and immune development and in transducing signals via TLRs (Gantier et al., 2007; Lodish, Zhou, Liu, & Chen, 2008). However, studies on the role of miRNAs in regulating host defenses against mycobacterial infection remain in their infancy. To date, most studies have suggested a novel role for miRNAs in dictating the mycobacterial capacity to inhibit host innate immune responses in infected macrophages for eluding immune surveillance (Figure 3a; Harapan et al., 2013). Earlier reports showed that infection of mice with M. bovis Bacillus Calmette-Guérin (BCG) or Listeria monocytogenes downregulated the expression of miR-29, to enhance the expression of its target interferon (IFN)-γ in NK cells, CD4+ T cells and CD8+ T cells (Ma et al., 2011). miR-21 is upregulated in macrophages after infection with M. bovis BCG. It inhibits IL-12 production by targeting IL-12 p35, thus inhibiting anti-mycobacterial T cell immunity. Additionally, miR-21 upregulates dendritic cell apoptosis by targeting Bcl-2, thus participating in the fine-tuning of Th1 immune responses (Wu, Lu, Sheng, & Li, 2012). Considering that Bcl-2 inhibits autophagy, it is plausible that miR-21 tunes Mtb-induced autophagy.

A recent study by Kumar et al. showed that Mtb infection in macrophages downregulates the expression of miR-let-7f, which targets A20, a negative regulator of the NF-κB pathway involved in controlling bacterial burden and enhancing host innate immune responses in macrophages (Kumar et al., 2015). Overexpression of let-7f inhibits, but A20 increases, Mtb survival in macrophages by modulating the immune responses to Mtb (Kumar et al., 2015). Many bacterial infections, including BCG infection, induce Hedgehog signaling, promoting innate immune responses against intracellular bacteria (Ghorpade et al., 2013). Another study showed that both miR-132 and miR-26a

![FIGURE 3](link) Roles of miRNAs in regulating innate and inflammatory responses in mycobacterial infections (a) BCG infection upregulates miR-21, which inhibits IL-12 production by targeting IL-12p35, thus modulating anti-mycobacterial T cell immunity. miR-21 also activates dendritic cell (DC) apoptosis by targeting Bcl-2. BCG suppresses the production of miR-29 in NK cells, CD4+ T cells, and CD8+ T cells to augment IFN-γ production. Mtb infection inhibits the expression of miR-let-7f, which blocks NF-κB signaling by targeting A20, in murine macrophages. Mtb-induced miR-132 and miR-26a inhibit IFN-γ signaling by targeting p300 in human macrophages. (b) Mtb infection induces upregulation of miR-155, which targets both Bach1 and SHIP1, promoting intracellular mycobacterial survival in macrophages. Additionally, miR-155 targets forkhead box O3 to inhibit apoptosis of CD14+ monocytes during Mtb infection. Furthermore, M. marinum infection upregulates the levels of miR-155 to inhibit inducible nitric oxide synthase 2 through targeting C/EBP-β. Another study has shown that miR-155 targets Ras homolog enriched in brain, a negative regulator of autophagy, to enhance host antimicrobial responses. (C) Hedgehog signaling in macrophages activates both miR-31 and miR-15, which target the TLR adaptor MyD88, to attenuate TLR2 responses during BCG infection. In addition, BCG infection induces the expression of miR-142-3p, which targets IRAK1 and regulates inflammation. BCG infection leads to induction of miR-146a which inhibits host innate responses and the production of iNOS and NO through targeting TRAF6.)
are upregulated in primary human macrophages upon Mtb infection and act as negative regulators of transcriptional coactivator p300, a molecule involved in IFN-γ signaling (Ni, Rajaram, Lafuse, Landes, & Schlesinger, 2014). Knocking down miR-132 and miR-26a upregulated p300 protein levels and improved IFN-γ responsiveness in human macrophages, suggesting a role for these miRNAs by which Mtb inhibits macrophage responses to IFN-γ (Ni et al., 2014).

4.2 | MiR-155-regulated network in host innate defenses against various mycobacterial infections

Mtb infection in macrophages induces miR-155 expression, which modulates host innate responses by attenuating the expression of BTB and CNC homology 1 (Bach1) and SH2-containing inositol 5′-phosphatase (SHIP1; Figure 3b). The target gene Bach1 is a transcriptional repressor of heme oxygenase-1, an activator of the Mtb dormancy regulon. The target gene SHIP1 inhibits Akt activation, inhibits macrophage responses to IFN-γ in macrophages, suggesting a role for these miRNAs by which Mtb infection (Iwai et al., 2015). In human macrophages, miR-155 targets forkhead box O3 (FOXO3), thereby inhibiting apoptosis in CD14+ monocytes (Huang et al., 2015). Another recent study showed that M. marinum infection resulted in increased miR-155, which binds to the 3′-UTR of ccaAT/enhancer binding protein β, a transcriptional activator of nitric oxide synthase, thereby inhibiting the production of nitric oxide synthase and enhancing mycobacterium survival (Qin, Wang, Zhou, Duan, & Gao, 2016). miR-155 directly targets the autophagy pathway players Ras homolog enriched in brain, RICTOR and RPS6KB2 (Wan et al., 2014). During mycobacterial infection, miR-155 augments autophagy by targeting Ras homolog enriched in brain (Wang et al., 2013), decreasing the survival rate of intracellular mycobacteria. Its effect on its other two targets mentioned above has not been determined. Thus, even the same miRNA can exhibit different functions in host defenses, depending on the specific mycobacterial strain involved.

### 4.3 | MiRNAs that regulate host inflammatory responses during mycobacterial infection

Previous studies showed that sonic hedgehog signaling induces expression of miR-31 and miR-15, which target MyD88, an important adaptor in TLR2 signaling, to attenuate TLR2 responses during infection (Figure 3c; Ghorpade et al., 2013). Additionally, BCG infection-induced miR-142-3p negatively regulated the generation of pro-inflammatory mediators, including NF-κB (NF-κB1), tumor necrosis factor (TNF-α), and IL-6, by targeting IRAK-1 expression (Xu et al., 2013). Another study comparing miRNA profiles in human THP-1 cells between Mtb H37Rv and H37Ra strains showed that nine miRNA genes (miR-30a, miR-30c, miR-155, miR-1275, miR-3665, miR-3178, miR-4484, miR-4668-5p, and miR-4497) were differentially expressed in cells infected

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### TABLE 1 Overview of the candidate microRNA biomarkers in TB

| Analysis          | Candidate of microRNA biomarkers                                                                 | References          |
|-------------------|--------------------------------------------------------------------------------------------------|---------------------|
| **Cellular miRNAs** | Active TB versus latent TB<br>7 miRNAs (hsa-miR-130b*, hsa-miR-21*, hsa-miR-223, hsa-miR-302a, hsa-miR-424, hsa-miR-451, hsa-miR-486-5p)<br>Active TB versus healthy controls<br>7 miRNAs (hsa-miR-144, hsa-miR-133a, hsa-miR-365, hsa-miR-424, hsa-miR-500, hsa-miR-661, and hsa-miR-892b)<br>Active TB versus healthy controls<br>Upregulated 28 miRNAs (hsa-miR-500*, hsa-miR-450b-5p, hsa-miR-144*, hsa-miR-452, hsa-miR-302c*, hsa-miR-582-5p, hsa-let-7c*<br>hsa-miR-138-2*, hsa-miR-597, hsa-miR-671-5p, hsa-miR-296-5p, hsa-miR-545, hsa-miR-125a-3p, hsa-miR-660, hsa-miR-365<br>hsa-miR-23a*, hsa-miR-675, hsa-miR-362-3p, hsa-miR-362-5p, hsa-miR-627, hsa-miR-532-5p, hsa-miR-943, hsa-miR-500<br>hsa-miR-421, hsa-miR-301b, hsa-miR-326, hsa-miR-1304, hsa-miR-24-2*)<br>Downregulated 2 miRNAs (hsa-miR-335, hsa-miR-199a-5p)<br>Active TB versus latent TB<br>4 miRNAs (hsa-miR-21, hsa-miR-26a, hsa-miR-29a, hsa-miR-142-3p)<br> | Wang et al., (2011) |
| **Circulating miRNAs** | Childhood TB versus healthy controls<br>Upregulated 15 miRNAs (hsa-miR-1, hsa-miR-10a, hsa-miR-181a-2* hsa-miR-125b, hsa-miR-1275, hsa-miR-1305, hsa-miR-874, hsa-miR-146a<br>hsa-miR-155, hsa-miR-150, hsa-miR-342-5p, hsa-miR-31, hsa-miR-342-3p, hsa-miR-95, hsa-miR-564)<br>Downregulated 14 miRNAs ( hsa-miR-142-5p, hsa-miR-21*, hsa-miR-144, hsa-miR-141, hsa-miR-142-3p, hsa-miR-29b, hsa-miR-193a-3p, hsa-miR-33a<br>hsa-miR-136, hsa-miR-17*, hsa-miR-136, hsa-miR-17*, hsa-miR-32, hsa-miR-324-5p, hsa-miR-503, hsa-miR-542-5p)<br>Active TB versus healthy controls<br>Upregulated 33 miRNAs (including hsa-miR-125b, hsa-miR-146a, hsa-miR-29a, and so on)<br>Downregulated 59 miRNAs (including hsa-miR-518d-5p, hsa-miR-520c-5p, and so on)<br> | Zhou et al., (2016) |
| **Sputum miRNAs** | Active TB versus healthy controls<br>Overexpressed 43 miRNAs (including hsa-miR-3179, hsa-miR-147, and so on)<br>Unexpressed 52 miRNAs (including hsa-19b-2* and so on)<br> | Yi, Fu, Li, and Guan (2012) |
with either virulent or avirulent Mtb strains (Das, Saikolappan, & Dhandayuthapani, 2013). A recent study showed that miR-146a, which is increased during mycobacterial infection, inhibits iNOS expression and NO generation through targeting TNF receptor-associated factor 6, suppressing mycobacterial clearance (Li et al., 2016). Thus, several studies have revealed that mycobacterial infection leads to miRNA activation, which contributes to modulating the host innate immune response to Mtb for its own benefit.

5 | miRNA PROFILING IN HUMAN TB

Many miRNAs are altered in peripheral blood cells during active TB (Table 1). Global miRNA profiling of peripheral blood cells have indicated numerous candidate miRNA biomarkers in human TB (Ueberberg, Kohns, Mayatepek, & Jacobsen, 2014). Previous studies identified a cluster of 17 miRNAs, among 451 detectable miRNAs, differentially expressed in PBMCs from patients with TB, patients with latent TB infection, and contacts without TB (Wang et al., 2011). Another study showed that miRNA signatures differed between PBMCs and pleural fluid mononuclear cells (PFMCs) in patients, with strongly downregulated expression of several miRNAs, including miR-223, miR-144*, and miR-421, in PFMCs (Spinelli et al., 2013). Dorhoi et al. showed that miR-223 levels were upregulated in the blood and lung parenchyma of TB patients, compared with healthy controls (Dorhoi et al., 2013). MiR-223 plays an important role in regulating the recruitment of myeloid cells to the lungs by targeting the chemokines CXCL2 and CCL3, as well as IL-6 (Dorhoi et al., 2013). Deletion of miR-223 in mice increased susceptibility to TB infection, via defective control of neutrophil-driven lethal inflammatory responses (Dorhoi et al., 2013). More recent studies also showed that miR-223 levels were upregulated in peripheral blood macrophages from active TB patients and that miR-223 targets FOXO3, a mediator of macrophage apoptosis associated with host defenses in mycobacterial infections (Haoues et al., 2014; Xi et al., 2015). MiR-223 expression was elevated significantly in monocytes/macrophages from TB patients, compared with healthy controls, and miR-223 inhibited NF-kB activation and proinflammatory cytokine production (Liu et al., 2015).

Studies investigating the putative regulatory network of miRNAs showed that seven miRNAs (hsa-miR-130b*, hsa-miR-21*, hsa-miR-223, hsa-miR-302a, hsa-miR-424, hsa-miR-451, and hsa-miR-486-5p) were differentially expressed in PBMCs between active TB and latent TB patients (Wang et al., 2011). Additionally, seven miRNAs (hsa-miR-144, hsa-miR-133a, hsa-miR-365, hsa-miR-424, hsa-miR-500, hsa-miR-661, and hsa-miR-892b) showed differential expression between active TB patients and healthy controls. Only hsa-miR-424 was upregulated in active TB patients in both comparisons (i.e., versus latent TB patients and versus healthy controls; Wang et al., 2011). A global miRNA array and qPCR analysis showed that miR-29 levels were increased in CD4+ T cells from TB patients, compared with healthy controls and latent TB patients, with an inverse correlation between miR-29 and IFN-γ miRNA expression (Fu et al., 2014). In addition to IFN-γ, miR-29a targets phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a lipid phosphatase that affects phosphoinositide 3-kinase signaling, to negatively regulate antigen-activation in T cells (Buckler, Walsh, Porrett, Choi, & Turka, 2006). PTEN deficiency also leads to hypersusceptibility to BCG infection, suggesting a role for PTEN in inhibiting mycobacterial infection (Huang, Redelman-Sidi, Rosen, Glickman, & Jiang, 2012).

Earlier studies of miRNA profiling showed upregulation of 28 miRNAs in active pulmonary TB, among which miR-144* was found to play a role in inhibiting TNF-α and IFN-γ production and T cell proliferation (Liu et al., 2011). As mentioned above, miR-144* levels were downregulated in PBMCs from TB patients (Spinelli et al., 2013). Another study comparing miRNAs associated with TB immunity showed that miR-21, miR-26a, miR-29a, and miR-142-3p were differentially expressed between patients with TB and those with latent TB infection (Kleinsteuber et al., 2013). However, there was no difference in miR-144* levels between TB patients and healthy controls in that study (Kleinsteuber et al., 2013). Our recent studies showed that MiR144* levels were upregulated in PBMCs and disease sites from active TB patients, compared with healthy controls (Kim et al., 2016). Further biological analyses showed that MiR144* targeting DRAM2, an autophagy and lysosomal protein, contributed to the pathogenesis of TB by autophagic inhibition controls (Kim et al., 2016). Thus, unique miRNA expression patterns can be observed depending on the cell type, cell compartment, and cellular heterogeneity.

Circulating miRNA profiling studies on childhood TB have shown that 14 miRNAs, including miR-150, miR-146a, and miR-125b, provide key diagnostic value and that a combination of differentially expressed miRNAs increases this diagnostic value in childhood TB (Zhou et al., 2016). Additionally, some miRNAs (33 of 92) were upregulated in TB patients compared with healthy controls (Fu et al., 2011). Among them, miR-29a received attention for its potential as a biomarker of active pulmonary TB (Fu et al., 2011). A study of sputum miRNA identified 95 differentially expressed miRNAs in sputum samples between TB patients and controls (Yi et al., 2012). Moreover, the miRNA expression patterns differed between sputum and serum samples (Yi et al., 2012). Hsa-miR-3179 and hsa-miR-19b-2* were the most increased and decreased miRNAs, respectively, in sputum samples from TB patients compared with those from controls (Yi et al., 2012). Another miRNA profiling study showed unique signatures of miRNAs differentially expressed in macrophages upon infection with Beijing/W versus non-Beijing/W Mtb clinical strains (Zheng et al., 2015). Despite efforts to detect differentially expressed miRNAs in TB, miRNA candidate datasets available for clinical use are still limited (Xu et al., 2015).

Additionally, there are still many challenges in the accurate normalization of miRNA levels among different cohorts. Recent trials that normalized miRNA levels between cohorts from Australia and China identified only miR-93 as the most suitable reference miRNA in both cohorts, with large variations in several miRNAs between the cohorts (Barry et al., 2015). Currently, several miRNAs, including miR-223, miR-144*, and miR-29, may be associated with host responses against TB, but the value of these miRNAs as biomarkers for diagnostics has not been demonstrated.

6 | AUTOPHAGY AND miRNAs IN MYCOBACTERIAL INFECTION

Autophagy is a lysosomal degradation process, targeting long-lived cytosolic protein aggregates and damaged organelles. Beyond its...
essential role in regulating intracellular quality, autophagy activation contributes to innate immune effector functions during various intracellular infections, especially mycobacterial infection. The molecular processes of autophagy activation have already been reviewed extensively. Here, we will briefly review the overall process of autophagy and its principal function with regard to innate immune responses to mycobacterial infection.

The ability of Mtb to arrest phagosomal maturation and to exploit host defense pathways involved in autophagy and lysosomal function is key to Mtb pathogenesis (Figure 4; Vergne, Chua, Singh, & Deretic, 2004; Rohde, Yates, Purdy, & Russell, 2007). Recent studies have shown that miR-33 and its passenger strand miR-33* inhibit autophagy flux through repression of key autophagy effectors (such as ATG5, ATG12, LC3B, and lysosomal-associated membrane protein 1) and the transcription factors FOXO3 and transcription factor EB (TFEB; Ouimet et al., 2016). TFEB, a member of the basic-helix-loop-helix leucine-zipper transcription factor MITF/TFE family, has been reported to be a master regulator of autophagic and lysosomal biogenesis (Sardiello et al., 2009; Settembre et al., 2011). In mycobacterial infection, nuclear receptor subfamily 1, group D, member 1, an adopted orphan nuclear receptor, is involved in enhancing antimicrobial responses via autophagy activation and lysosomal biogenesis by inducing lysosomal-associated membrane protein 1 and TFEB in human macrophages (Pastore et al., 2016). TFEB is an important regulatory factor in the transcriptional regulation of autophagy-related gene expression, lysosomal biogenesis, and proinflammatory cytokine induction involved in activating innate immune responses (Pastore et al., 2016). A negative correlation has been demonstrated between miR-30a expression and Beclin-1 and ATG5 levels in Mtb infected THP-1 cells, and miR-30a has been suggested to repress Mtb-induced autophagy (Chen et al., 2015).

Certain miRNAs are downregulated by Mtb infection in macrophages and are involved in modulating autophagy. For example, Mtb inhibits miR-17-5p but upregulates its targets Mcl-1 and STAT3, a transcriptional activator of Mcl-1 (Kumar et al., 2016). Overexpression of miR-17-5p reduces the expression of Mcl-1 and STAT3 and the phosphorylation of protein kinase C δ (an activator of STAT3), thereby regulating autophagy during Mtb infection (Kumar et al., 2016). Another recent study demonstrated a role for miR-17-5p in targeting ULK1, an initial autophagy-related gene, resulting in the inhibition of autophagosome formation and host defenses against BCG (Duan et al., 2015). In a previous study, we showed that Mtb infection increased miR-125a-3p (miR-125a), which targets UVRAG, resulting in inhibition of autophagy activation and antimicrobial responses in macrophages in response to Mtb infection (Kim et al., 2015). Additionally, an earlier study proposed mechanisms by which mycobacteria inhibit IFNG-induced autophagy in macrophages via MTOR-responsive epigenetic modifications in the induction of Mir155 and Mir31, both of which are involved in autophagy fine-tuning (Holla, Kurowska-Stolarska, Bayry, & Balaji, 2014). Recently, we have shown that Mtb infection increased MIR144*/hsa-miR-144*, which targets the 3′-untranslated region of DRAM2/DNA damage-regulated

![Image](https://example.com/image.png)

**FIGURE 4** miRNA-mediated regulation of autophagy in host cells during mycobacterial infection. Mtb-induced mTOR signaling leads to upregulation of both miR-155 and miR-31, which target the phosphatase PP2A to inhibit GSK3B signaling and IFN-γ-induced autophagy. Additionally, Mtb infection induces upregulation of miR-125a, modulating the induction and maturation of autophagy by targeting the UVRAG protein in macrophages. In addition, hsa-miR144* levels are increased in pulmonary and extrapulmonary TB patients. In human macrophages, Mtb infection upregulates MIR144*, which targets DRAM2, an essential autophagy and lysosomal protein. Mtb infection enhances the levels of miR-33 and its passenger strand miR-33*, both of which modulate autophagy activation in macrophages by targeting a set of autophagy-related genes (LC3B, ATG5, ATG12, and lysosomal-associated membrane protein 1). However, Mtb infection inhibits the expression of miR-17, thus enhancing the expression of its targets Mcl-1 and STAT3, as well as the interaction between Mcl-1 and Beclin-1. BCG infection also upregulates the expression of miR-17, regulating autophagy by targeting ULK1.
autophagy modulator, in human monocytes/macrophages (Kim et al., 2016). Notably, autophagy protein DRAM2 physically interacts with BECN1 and UVRAG, leading to displacement of Rubicon, an inhibitor of autophagy maturation, from the BECN1 complex and enhancing PtdIns3K/Vps34 activity (Kim et al., 2016). A previous study showed that TLR/MyD88/IA-kB pathway activation by mycobacterial infection induced the expression of DNA damage-regulated autophagy modulator (DRAM1; van der Vaart et al., 2014). Additionally, DRAM1‐mediated selective autophagy against mycobacteria requires STING and p62 expression in human macrophages and zebrafish models (van der Vaart et al., 2014). Thus, both DRAM1 and DRAM2 apparently have partially redundant functions in autophagic defenses against mycobacterial infections and the enhancement of antimicrobial responses (van der Vaart et al., 2014; Kim et al., 2016). However, the mechanism(s) regulating autophagy activation may differ between DRAM1 and DRAM2.

To date, the impact of miRNAs in autophagy regulation during mycobacterial infection has not been evaluated in detail. Because manipulation of autophagy activation in host cells is essential for promoting innate host defenses, accumulating data on miRNAs as autophagy regulators is likely to stimulate new developments in host-directed therapies in the near future. Despite the major barriers to pulmonary small RNA delivery, future studies are warranted to develop novel and effective RNA interference therapeutics and/or vaccines via host‐directed interventions against TB (Bettencourt, Pires, & Anes, 2016; Man, Chow, Casettari, Gonzalez‐Juarrero, & Lam, 2016).

7 | CONCLUDING REMARKS

The emerging relationships between the innate signaling pathway autophagy and its regulation by miRNAs are beginning to show great importance in mycobacterial infection. Accumulating studies have begun to illustrate miRNA regulatory features that may be key mechanisms in the control of microbial replication and homeostasis of the host innate response, thus suggesting that small RNAs could be exploited for therapeutic strategies. Determining the roles and mechanisms of miRNAs affecting host immune responses during mycobacterial infection will help clarify and lead to a better understanding of the immunopathogenesis of TB. Although the current review focused on the effects of individual miRNAs in vitro, future studies are needed to clarify how multiple miRNAs with diverse targets may affect overall host responses during infection. Currently, there are no putative biomarkers to diagnose TB; however, trials seeking to identify systemic/tissue biomarkers could potentially lead to development of tool for improved diagnosis and management of TB. Future studies revealing the functions of host miRNAs that regulate autophagy and immune responses could contribute to the development of miRNA‐based approaches for host‐directed therapeutics/vaccines against mycobacterial infections.

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