Monocyte and Macrophage miRNA: Potent Biomarker and Target for Host-Directed Therapy for Tuberculosis

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The end TB strategy reinforces the essentiality of readily accessible biomarkers for early tuberculosis diagnosis. Exploration of microRNA (miRNA) and pathway analysis opens an avenue for the discovery of possible therapeutic targets. miRNA is a small, non-coding oligonucleotide characterized by the mechanism of gene regulation, transcription, and immunomodulation. Studies on miRNA define their importance as an immune marker for active disease progression and as an immunomodulator for innate mechanisms, such as apoptosis and autophagy. Monocyte research is highly advancing toward TB pathogenesis and biomarker efficiency because of its innate and adaptive response connectivity. The combination of monocytes/macrophages and their relative miRNA expression furnish newer insight on the unresolved mechanism for Mycobacterium survival, exploitation of host defense, latent infection, and disease resistance. This review deals with miRNA from monocytes, their relative expression in different disease stages of TB, multiple gene regulating mechanisms in shaping immunity against tuberculosis, and their functionality as biomarker and host-mediated therapeutics. Future collaborative efforts involving multidisciplinary approach in various ethnic population with multiple factors (age, gender, mycobacterial strain, disease stage, other chronic lung infections, and inflammatory disease criteria) on these short miRNAs from body fluids and cells could predict the valuable miRNA biosignature network as a potent tool for biomarkers and host-directed therapy.

Keywords: monocyte and macrophage miRNAs, tuberculosis, differential expression, immune regulation, autophagy and biomarkers

INTRODUCTION

Tuberculosis being the life-threatening disease caused by *Mycobacterium tuberculosis* (MTB) is intricate to understand their mycobacterial-mediated host immune subversion. The intracellular nature and delayed cell division of MTB added access to dodge the host microbicidal effect for its survival. The host’s innate defense ability and the pathogen’s strategy in evading the host’s immunity determine the sequel of TB infection (1). MTB establishes infection through multiple modalities, such as i) circumvent phagolysosome fusion and phagocytosis destruction; ii) neutralize the acidic environment (2, 3); iii) blocks the formation of the apoptotic envelope (4); iv) inhibits the plasma membrane repair,
leading to the spread of infection through macrophage necrosis (5); v) suppresses activation of immune cells and antigen presentation; vi) limits the proinflammatory response by restricting proinflammatory cytokines; and vii) modulates the disease responsive genes and miRNAs through their targeted pathways. The disease becomes complex as the stages of infection are varied from latency to drug resistance because of the evolution of MTB strains. One third of the population exhibit latent infection, in which MTB remains dormant for a long period and becomes susceptible to the active disease under immune compromised condition. This latency is a menace to mankind as the diagnosis and its effective treatment toward breakdown of the disease in future need unbridled enthusiastic investigations. However, the management of the latent condition can be made possible with public awareness by improving the incidence of TB determinants, such as malnutrition, poverty, smoking, and diabetes, or through the development of new treatment or vaccines (6). The emergence of drug-resistant Mycobacterium due to poor treatment adherence (acquired resistance) and the transmission of drug-resistant strains (primary resistance) is another peril in TB research toward the end TB strategy (7). The multi-drug resistance and its treatment pose multiple challenges as it requires prolonged treatment duration, complex drugs (second-line fluoroquinolones) that may affect adherence along with lower treatment success rate (6). Other co-morbidities, like AIDS and diabetes, intensify TB disease pathogenesis.

Mononuclear cells (monocytes/macrophages) are professional phagocytic defenders against TB infection (8). The disputed behavior of monocytes as a defender against antimycobacterial activity exhibited by CD16<sup>neg</sup> subset and habitat for MTB promoted by CD16<sup>pos</sup> subset is well accepted for TB disease (9, 10). The disease-specific perturbation in the mononuclear cell subsets and their immune phenotypes contributed to underlying pathophysiology and as biomarkers for MTB infection. However, the unresolved mechanisms and the pathways affected can be studied through the molecular impression of these subsets from omics platforms in a quest for differentially expressed miRNAs and miRNAs. miRNAs are short, biologically conserved noncoding RNAs that participate in the regulation of inflammatory response, tumorigenesis, and other biological processes. Several studies focused on miRNAs revealed altered miRNA levels during infection and their impact in modulating immune functions within macrophages from TB patients (11–13). Thus, miRNA studies open up new avenues and fascinate the researchers for constructing miRNA-based vaccines, biomarkers, and host-directed therapies. This review is focused on monocyte/macrophage miRNAs, their differential expression, regulatory function, and biomarker utility in tuberculosis disease.

miRNAs

Micro RNAs are discovered as biologically conserved, short noncoding RNAs (14–16) that constitute 18 to 25 nucleotides in length. This groundbreaking innovation by Ambros and Ruvkun prompted the researchers to investigate their functional behavior toward host immune regulation and disease pathogenesis, which resulted in the exponential growth of published studies on miRNA reported by Almeida et al. (17).

miRNAs work as mRNA repressors inhibiting protein synthesis (18), translational activators (19), and molecular decoys for RNA-binding proteins (20), depending on the environment and cell type. The processing, maturation, expression, and action of miRNAs are regulated through multiple mechanisms: a) single-nucleotide polymorphism interfere with the processing and maturation of miRNAs that affect their expression profile (21); b) modulation of epigenetic mechanisms, such as histone acetylation and DNA methylation, influence the transcriptional rate of miRNAs (22); c) impairment in the mRNA-miRNA interactions by the competition of miRNAs with cellular factors and miRNAs with other competitive RNAs (pseudogenes, long non-coding RNAs, and circular RNAs) (23, 24); and d) occurrence of miRNA editing through nucleotide modification by adenosine or cytidine deaminases (21, 25). miRNA research and transcriptomic platform enabled the disease-mediated deregulation of miRNAs and their targeted pathways in multiple diseases, including cancer (26, 27), cardiovascular diseases (28, 29), autoimmune diseases (30, 31), and infectious diseases (32, 33).

MONOCYTE AND MACROPHAGE miRNAs

The disease-oriented modification for any microbial infection is visualized primarily on mononuclear cell lineage as being the first-line defenders of innate immunity. Immunological aspect-derived alterations in the subset composition of monocytes/macrophages decipher the role of a pathogen in the peripheral compartment. However, the stimulus for the alteration is better studied through their responsive mRNA and miRNAs. miRNA research for TB is advancing toward a proper understanding of disease mechanism for better prognosis and early prevention. The immune efficiency and other cellular processes of monocyte/macrophages are governed by various miRNAs in both healthy and disease states (34).

Many reports available for the miRNAs mediated monocytic biological functions, such as tissue homeostasis, signaling, cell differentiation, apoptosis, cell motility, cytokine production, inflammatory responses, resolution of inflammation, and other immune responses (35–40). A trio of miRNAs constituting miR-146a, miR-21, and miR-155 are the principal regulators of inflammatory pathways in myeloid cells (41). miR-511 was identified as the putative positive regulator of Toll-like receptor 4 during monocyte differentiation by Tserel et al. (42). miR-214, as suggested by Li et al., targets the phosphatase and tensin homolog in monocyte survival induction during advanced glycation (43). miR-20a, miR-106a, and miR-17 of miR-17/92 and miR-106a/363 clusters are involved in tuning the proinflammatory cytokine production, infiltration of macrophages, and phagocytosis through targeting the expression of signal-regulatory protein alpha (44). Upon Notch activation, miR-148a-3p promotes M1 polarization by hindering M2 activation (45). Myeloid cell differentiation to granulocytes or monocytes is governed by miR-223 with negative control on NLRP3 inflammasome activity (46).
The intense research on miRNA profiling of monocyte subsets delivered their unique profile and regulated functions. Dang et al. deciphered the role of miR-432 in apoptotic potential and miR-19a in cell motility. They also observed that miR-345 was involved in the inflammatory responses by targeting RelA. Besides, upregulated miR-34 in CD16+ monocytes are suggestive of their differentiation ability to dendritic cells by altering the expression of Wingless-Type MMTV Integration Site Family, Member 1 (WNT1), and Jagged 1 (JAG1) (34, 47). Richard et al. focused on the sequencing of miRNAs among monocyte subsets in humans and mice to identify their role in monocyte heterogeneity. From their work, they suggested three miRNAs—miR-21, miR-150, and miR-146a—as immune regulators that mediate resolution of inflammation in the myeloid cells (48). MicroRNA profiling of intermediate monocytes (CD14++ CD16+) yielded a unique miRNA profile, and their connected pathways are involved in gene regulation, TLR, and cytokine-mediated signaling, phagocytosis, antigen processing, and presentation, as well as lipid and triglyceride metabolism (49).

### MicroRNA AS A PROMINENT IMMUNE REGULATOR OF MACROPHAGE MECHANISMS DURING TB

miRNAs regulate about 60% of mammalian genes through its effective binding to 3′ UTR on mRNA and leads to translational repression and mRNA degradation (50, 51). Most of the cellular functions in humans are governed by single or multiple miRNAs. The emergence of miRNA research uncovered the possibility of pathogen (specially their cell wall components) induced alteration of miRNA levels (52). The altered miRNA profile could enhance the disease progression by modulation of the innate and adaptive responses through the hindrance of cell differentiation (53). The distinctive role of miRNA in the maintenance of immune homeostasis and activation of immune defense is largely studied (54). Upon MTB infection, several miRNAs modulate the host mechanism, either favoring the host or the pathogen. In most cases, the underlying causes for host immune evasion by the Mycobacterium are associated with miRNAs. The host signaling pathways, cytokine production, and killing machinery are adversely affected by miRNAs as represented in Figure 1.

### miRNAs IN SIGNALING PATHWAYS AND CYTOKINE PRODUCTION

The prime innate defense recognition starts with the Toll-like receptors (TLRs) upon induction with pathogen-associated molecular patterns (PAMPs). However, this initial priming is affected by multiple miRNAs during MTB infection. TLR/MyD88 activation and cytokine response are inhibited by miR-30a in MTB-infected THP-1 cells (55). TLR3 signaling is attenuated by miR-27a through targeting TICAM1 and c-Abl-BMP signaling (56). Survival of Mycobacterium is favored through the upregulation of miR-26a.
and miR-132 induced by live and attenuated MTB that negatively controls p300 mRNA in human monocyte-derived macrophages (human MDMs). miR-132 and miR-26a dampen the host responsiveness toward IFN-gamma genes, phagocytosis process, and decreases the HLA-DR and FCgammaR1 levels (57). Inhibition of NF-kB pathway with the hindered downstream secretion of cytokines, chemokines, and NO is achieved through the increased expression of A20 (TNFAIP3) by downregulated let-7f induction mediated by ESAT-6 in both in vitro and in vivo conditions (58). miR-223 and miR-146a also negatively control the NF-kB pathway in MTB-infected macrophages and suppress the proinflammatory response and the clearance of pathogen (59–62). Infection with BCG induces elevation of miR-21 via NF-kB and ERK pathways that target IL-12p35 mRNA through which it inhibits IL-12 production and T-cell priming function by APCs (63).

The activity of miR-155 is focused on various cell types, such as macrophages, dendritic cells, and T cells. ESAT-6 induces miR-155 in a time- and dose-dependent manner, which downregulates SHIP1, leading to an ultimate increase of the AKT phosphorylation and, thus, exerts pro-survival of MTB on macrophages. Host IL-6 production and Cox-2 activity are limited by upregulated miR-155, as the Cox-2 is essential to prevent necrosis by generating PGE2 and production and Cox-2 activity are limited by upregulated miR-155, as SHIP1, leading to an ultimate increase of the AKT phosphorylation in a time- and dose-dependent manner, which downregulates ERK pathways that target IL-12p35 mRNA through which it inhibits IL-12 production and T-cell priming function by APCs (63).

The downstream killing machinery of phagocytosed pathogen actively occurred through apoptosis of infected macrophages. Macrophages infected with Beijing strain demonstrate its virulence by escaping from host apoptosis and macrophage lysis through miR-485-3p (71). Upon infection with MTB, RAW264.7 macrophages establish attenuated apoptosis through the reduction of miR-20b-5p and elevation of its target Mcl-1 (72). Increased miR-223 expression in macrophages of active TB patients negatively suppresses forkhead box O3 (FOXO3) to inhibit apoptosis (62). The secreted protein MPT64 inhibits apoptosis of RAW264.7 macrophages via NF-kB/miR-21/Bcl-2 pathway (73). Inhibition of apoptosis through the downregulation of Fas protein is demonstrated in TPH-1 macrophages mediated by upregulated let-7b-5p (74). The decrease in the apoptotic monocytes of active TB patients and decreased apoptosis in THP-1 cells are mediated through the downregulation of FOXO-1 by miR-582-5p (75). Some of the miRNAs positively promote apoptosis for enhanced mycobacterial clearance. For example, reduction of miR-20a-5p is observed in TPH-1 macrophages and CD14+ monocytes of active TB patients. Reduced miR-20a-5p inversely increases Bim expression through its target JNK2, which could promote apoptosis (76). Infection of macrophages with M. bovis BCG results in elevated miR-155 expression, which could induce apoptosis through PKA signaling by inhibiting PKI-α (77). Sp110-mediated suppression of miR-125a in RAW264.7 macrophages enhances the expression of Bmf, which could induce apoptosis (78). Upregulated miR-27b enhances p53 signaling, thus favoring apoptosis and bacterial killing by downregulating Bag2 (79).

Autophagy is a highly regulated eukaryotic cellular pathway in which intracellular pathogens are trapped in autophagosomes and degraded in lysosomes. Induction of xenophagy (a selective form of autophagy against microbes) in monocyte-derived macrophages is one of the innate immune mechanisms to intracellular pathogens, such as MTB (80). However, MTB is a successful intracellular pathogen and can escape from host responses by expression of some of the miRNAs and affects autophagy machinery (81). Certain miRNAs control both mycobacterial survival and autophagy pathways by targeting their proteins within macrophages through its altered expression (82, 83). miRNA-33 and miRNA-33b inhibit the fusion of lysosome with bacterial endosome by targeting ATG5, ATG12, LC3B, and LAMP proteins and lipid metabolism by targeting transcription factors FOXO3 and TFEB (84). The occurrence of active TB is suggested because of the suppression of autophagosome-lysosome fusion in macrophages by miR-423-5p.

miRNAs IN HOST KILLING MACHINERY

The human host has an enormous killing machinery, like phagocytosis, apoptosis, and autophagy, and so on, for the invading pathogen. The intracellular MTB, however, exploits the host defense through various strategies. The recent transcriptomic approach sheds light on miRNA-based modulatory responses by Mycobacterium. The phagocytic function of macrophages is attenuated in the different stages by the Mycobacterium-induced miRNAs. The bacterial encounter and imbibe are affected through N-wasp by miR-142-3p. N-wasp is an actin-binding protein essential for actin dynamics in the phagocytosis process that was negatively regulated by upregulated miR-142-3p in J774A.1 cell line and primary human macrophages during MTB infection (68). Mononuclear cell function and phagocytosis are inhibited in active TB patients, where miR 23a-3p is downregulated. miR-23a-3p targets IRF1/SP1 through TLR4/TNF-α/TGF-B1/IL-10 signaling (69). The principal lysosomal enzyme of phagocytosis process for MTB clearance is cathepsin proteases. miR-106-5p targets the 3' UTR cathepsin and suppresses the lysosomal activity in MTB-infected macrophages (70).
through post-transcriptional regulation of VPS33A (85). Active TB patients and MTB-infected mice abundantly express miR-27a, which blocks the Ca\(^{2+}\) signaling through ER-located Ca\(^{2+}\) transporter protein CACN2D. Blockade of Ca\(^{2+}\) signaling inhibits the formation of autophagosome (86). The autophagy protein, DRAM2, promotes PtdInt3K, which initiates the nucleation of auto phagophore formation. In human and murine monocytes or macrophages, MIR144/hsa-miR-144 and miR-125a help in mycobacterial survival by forming a complex with the 3’ UTR of DRAM2 mRNA (87, 88).

TB infection triggered the expression of a new type of miRNA, i.e., miR-1958, which silences the ATG5 in RAW264.7 cells (89). miR-129-3p favors MTB survival by inhibiting ATG4B (90). miR-20a promotes BCG survival by affecting the expression of both ATG7 and ATG16L1 (91). miR-17-5p blocks autophagy by blocking ULK1 in BCG-infected RAW264.7 cells (92). Chen et al. showed that miR-30a inhibits the autophagy pathway and negative correlation between Beclin and miR-30a (93). miR-889d affects the tumor necrosis factor-like weak inducer of apoptosis (TWEAK), which maintains the granuloma formation and promotes the maturation of AMPK (94). miR-125a-5p overexpression was observed in M. avium–infected THP1-derived macrophages and targets STAT3, which activates the autophagy (95). At the same time, miR-26a targets the KLF4, by which it inhibits MTB survival, and miR-17/PKC\(\beta\)/STAT3 pathways also attenuate MTB by activating autophagy (96).

According to Wang et al., miR-155 targets Rheb (autophagy blocker) and promotes autophagy (97). PCED1BAS1 is downregulated in TB patients, which directly binds with miR-155, and subsequently inhibits the activity of miR-155 (98). miR-155 expression helps in the survival of MTB by regulating ATG3 protein in dendritic cells (99). Yang et al. found that the expression of miR-155 was diminished in patients with spinal tuberculosis (100). This approach will help to understand the underlying pathogenesis and for identifying TB-specific biomarkers. The differential expression of miRNAs from MTB infection studies on macrophages and the monocye-derived macrophages are depicted in Table 1 and Figure 2.

Although many studies are available on the macrophage infection-derived miRNAs, the actual in vivo scenario of a patient is minimal. The limitations of these biomarker candidates are variable between the studies, and each was performed on identifying the miRNA targets for understanding the disease pathology. In the future, the biomarker efficiency of these candidates should be largely examined as multi-centric studies with diverse ethnicities.

miRNAs IN HOST-DIRECTED THERAPY (HDT)

Host-directed therapy is one of the emerging strategies to improve the host immunity and eliminate pathogens in which vitamins, repurposed drugs, cytokines, miRNAs, and, monoclonal antibodies are used as an adjunct with chemotherapy. It helps to control challenges of TB treatments, such as drug resistance, the toxicity of chemotherapy, and immune reconstitute inflammatory syndrome, and so on (116). Induction of autophagy is one of the host-mediated therapy for tuberculosis (117) and is induced by mTOR kinase inhibitors and certain immunomodulators, such as rapamycin and vitamin D\(_3\), respectively (118, 119). The PubMed search on miRNAs in HDT for tuberculosis yielded no results. However, many HDT strategies using miRNAs have been proposed by Sabir et al. (96). They suggested direct administration of miRNAs or the use of siRNAs to modulate the host responses. The downregulated antimycobacterial miRNAs can be induced by synthetic oligos, and the overexpressed pro-mycobacterial miRNAs can be repressed using anti-miRNA complementary to mature miRNA (120–122). This approach will benefit the host in achieving the proper signaling and their downstream pro-inflammatory responses. Synthetic delivery of miRNAs to macrophages is possible with nanoparticles or liposomes (123, 124). Novel HDT approaches on miRNA-mediated induction of host killing machinery (phagocytosis, apoptosis, and autophagy) could be a beneficial therapy to evade the pathogen strategies and for efficient pathogen clearance.

FUTURE PERSPECTIVES

The research of miRNA-mediated regulation of TB is enormous; however, the pro diagnosis and effective therapy for TB are
As miRNAs are regulators and modulators of the immune response, the avenue for potential biomarkers and therapeutic possibilities are much promising. Some of the key factors to be considered for future research on miRNA are as follows:

1. Various circulating miRNAs are available from many studies as biomarkers but research on identifying cell-oriented miRNAs, particularly monocytes and macrophages will help better to understand the evasion of initial defense.

**TABLE 1 | Monocyte/macrophage-based miRNAs as biomarker candidates for TB.**

| Cells | Differentially Expressed miRNAs | Analysis Platform | Reference |
|-------|---------------------------------|-------------------|-----------|
| Human |                                |                   |           |
| MDMs infected with MTB or BCG | miR-155, miR-146a, miR-145, miR-222, miR-27a, and miR-27b | Taqman low-density array | (110) |
| MDMs from TB patients, LTB, and Healthy individuals | Upregulated (hsa-miR-16, hsa-miR-137, hsa-miR-140-3p, hsa-miR-193a-3p, hsa-miR-399-5p, and hsa-miR-598) | Taqman microarray quantitative PCR | (71) |
| MDM infected with TB LM | miR-125b | qPCR | (50) |
| MDM infected with M. smeg LM | miR-155 | qPCR | (63) |
| MDM infected with MTB H37Rv | Upregulated (miR-155, miR-21, miR-146a, miR-29a, miR-26a, let-7b, miR-34, miR-26a, miR-26a, and miR-29a) | Nanostring nCounter miRNA assay | (65) |
| MDM infected with MTB | Downregulated (hsa-miR-155, miR-21, miR-146a, miR-29a, miR-26a, let-7b, miR-34, miR-26a, miR-26a, and miR-29a) | Nanostring nCounter miRNA assay | (57) |
| Primary monocytes and MDMs from active TB patients and controls | Upregulated-miR-582-5p | qPCR | (79) |
| Primary macrophages from TB patients vs controls | Upregulated miR-223 | qPCR | (62) |
| Macrophages from TB patients and controls | Downregulated miR-365 | qPCR | (67) |
| MDM infected with MTB | Upregulated miR-106b-5p | qPCR | (70) |
| Mouse |                                |                   |           |
| BMDMs infected with MTB | 6 upregulated (miR-21, miR-21*, miR-146a, miR-146 b, miR-210, and miR-155), 1 downregulated (miR-223) | Microarray and qPCR | (111) |
| BMDMs infected with Mtb | 4 upregulated (miR-24, miR-142, miR-155, and miR-212) and 3 downregulated (miR-19a, miR-202, and miR-376a) | Gene expression microarray | (112) |
| BMDMs infected with BCG | miR-21 | Taqman quantitative real-time PCR | (63) |
| BMDMs infected with MTB | Upregulated miR-27b | qPCR | (79) |
| BMDMs infected with MTB | 3 upregulated (miR-155, miR-146a & miR-21) | Taqman low-density arrays | (1) |
| Mouse peritoneal macrophages & BMDMs | Upregulated miR-146a | qPCR | (63) |
| Cell Line |                                |                   |           |
| U937 macrophages | 149 DE (miR-424–5p, miR-493-5p, miR-27 b-3p, miR-296-5p, miR-377–5p, and miR-3680–5p) | Microarray | (113) |
| THP-1 cells infected with Beijing/W or non-Beijing/W strains | 13 downregulated (let-7e, let-7i, miR-10a, miR-21, miR-26a, miR-99a, miR-140–3p, miR-150, miR-181a, miR-320, miR-339–5p, miR-425, and miR-582–5p) | Taqman microarray quantitative PCR | (71) |
| THP-1 cells infected with virulent or avirulent Mtb strains | 9 DE (miR-30a, miR-30e, miR-155, miR-1275, miR-3665, miR-3178, miR-4484, miR-4668-5p, and miR-4497) | Microarray | (114) |
| THP-1 cells infected with MTB HN878 | 12 upregulated (miR-339*, miR-146a, miR-155, miR-132, miR-146b-5p, miR-720, miR-30e, miR-661, miR-140–3p, miR-3651, miR-328, and miR-378 | Microarray | (115) |
| THP-1 cells and U937 cells | Upregulated miR-32-5p | qPCR | (66) |
| THP-1 cells | Upregulated miR-30a | qPCR | (55) |
| RAW264.7 cells and infected with MTB | 3 upregulated (miR-155, miR-146a, and miR-21) | Taqman low-density arrays | (1) |
| RAW264.7 cells infected with MTB | Upregulated miR-27b | qPCR | (79) |
| RAW264.7 cells infected with MTB | Downregulated let-7i | SYBR Green-based miRNA profiling array | (58) |
| RAW264.7 cells | Downregulated miR-20b-5p | Semi quantitative PCR | (72) |
2. Research on identified miRNAs to investigate their diagnostic efficacy and therapeutic value is highly needed. This will help address whether this differential expression is really specific for TB or overlaps with a disease of similar pathology.

3. The mycobacterial strain-specific miRNA expression is another concern since there is diversity in TB strains, and the distribution is different in different geographical locations.

4. Deep single-cell sequencing approach may enable the complete miRNA profile for better understanding their biosignatures.

5. Patient samples from all disease stages of TB at diagnosis and during treatment may give the disease-based profile during the entire course of infection for understanding their pathophysiology.

6. Novel HDT approaches using nanoparticle and siRNAs for direct modulation of these expression signatures to induce the host-mediated defense responses against Mycobacterium will open up a better therapy adjunct with minimal chemotherapy.

7. More animal studies with miRNA/long non-coding RNA intervention for TB therapeutics should be carried out and explored.

Future collaborative efforts involving multidisciplinary approach in various ethnic population with multiple factors (age, gender, mycobacterial strain, disease stage, other chronic lung infections, and inflammatory disease criteria) on these short miRNAs from body fluids and cells could predict the valuable miRNA biosignature network for biomarker discovery and host-directed therapy.

**AUTHOR CONTRIBUTIONS**

PS and KP contributed to the literature collection, writing, drafting, and revision of the manuscript. PS, UR, and RB participated in the conception of the idea, design, drafting, revision, and approval of the manuscript. All authors contributed to the article and approved the submitted version.

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**REFERENCES**

1. Kumar R, Halder P, Sahu SK, Kumar M, Kumar 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

2. Flannagan RS, Cosio G, Grinstein S. Antimicrobial Mechanisms of Phagocytes and Bacterial Evasion Strategies. *Nat Rev Microbiol* (2009) 7:355–66. doi: 10.1038/nrmicro2128

3. Meena LS, Rajni. Survival Mechanisms of Pathogenic *Mycobacterium Tuberculosis* H37Rv. *FEBS J* (2010) 277:2416–27. doi: 10.1111/j.1742-4658.2010.07666.x
25. Blanc V, Davidson NO. APOBEC-1-Mediated RNA Editing.

19. Vasudevan S, Tong Y, Steitz JA. Switching From Repression to Activation:

21. Correia de Sousa M, Gjorgjieva M, Dolicka D, Sobolewski C, Foti M, et al. Altered Expression of MicroRNA in Synovial Fibroblasts and Synovial Tissue in Rheumatoid Arthritis. Arthritis Rheumatism (2008) 58 (4):1001–9. doi: 10.1002/art.23386

26. Li C, Feng Y, Coukos G, Zhang L. Therapeutic microRNA Strategies in Human Cancer.

27. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA Genes Are Frequently Located at Fragile Sites and Genomic Regions Involved in Cancers. Proc Natl Acad Sci USA (2004) 101(9):2999–3004. doi: 10.1073/pnas.0307323101

10. Phillips JA, Ernst JD. Tuberculosis Pathogenesis and Immunity.

11. Yi Z, Fu Y, Ji R, Li R, Guan Z. Altered microRNA Signatures in Sputum of Patients With Active Pulmonary Tuberculosis. Chin J Cell Mol Immunol (2009) 11(4):747–57. doi: 10.1208/s12248-009-9145-9

28. van Rooij E, Sutherland LB, Liu N, Williams AH, McAnally J, Gerard RD, et al. A Signature Pattern of Stress-Responsive microRNAs That Can Evoke Cardiac Hypertrophy and Heart Failure. Proc Natl Acad Sci USA (2006) 103 (48):18255–60. doi: 10.1073/pnas.0608791103

29. Tserell L, Runnel T, Kisand K, Pihlaj M, Bakhoff L, Kolde R, et al. MicroRNA Expression Profiles of Human Blood Monocyte Subsets Highlights Functional Differences. Immunology (2015) 145(3):404–16. doi: 10.1111/imm.12456

30. Stanczyk J, Pedrioli DM, Brentano F, Sanchez-Pernaute O, Kolling C, Gay RE, et al. Altered Expression of MicroRNA in Synovial Fibroblasts and Synovial Tissue in Rheumatoid Arthritis. Arthritis Rheumatism (2008) 58 (4):1001–9. doi: 10.1002/art.23386

31. Dai Y, Huang YS, Tang M, Lv TY, Hu CX, Tan YH, et al. Microarray Analysis of microRNA Expression in Peripheral Blood Cells of Systemic Lupus Erythematosus Patients. Lupus (2007) 16(12):939–46. doi: 10.1177/096123307084158

32. Bala S, Tilahun Y, Taha O, Alao H, Kodys K, Catalano D, et al. Increased miR-146a and miR-155 Expression in the Synovial Fluid of Patients With Active Rheumatoid Arthritis. J Cell Mol Immunol (2015) 31(2):163–7.

33. Yang T, Ce R. microRNAs in Immune Responses to Mycobacterium Tuberculosis. Proc Natl Acad Sci USA (2012) 109(35):14285–90. doi: 10.1073/pnas.1207917109

34. Bazzoni F, Rossato M, Fabbri M, Gaudiosi D, Mirolo M, Mori L, et al. Induction and Regulatory Function of miR-9 in Human Monocytes and Neutrophils Exposed to Proinflammatory Signals. Proc Natl Acad Sci USA (2009) 106:5282–7. doi: 10.1073/pnas.0810990106

35. Self-Fordham JB, Naqvi AR, Uttamani JR, Kulkarni V, Nares S. MicroRNA, Dynamic Regulators of Macrophage Polarization and Plasticity. Front Immunol (2017) 8:1106. doi: 10.3389/fimmu.2017.01106

36. O’Connell RM, Rao DS, Baltimore D. microRNA Regulation of Inflammatory Responses. Annu Rev Immunol (2012) 30:295–312. doi: 10.1146/annurev-immunol-021110-170513

37. Nahid MA, Pauley KM, Satoh M, Chan EKL. microRNA-146a Is Critical for Endotoxin-Induced Tolerance: Implication in Innate Immunity. J Biol Chem (2009) 284:34590–9. doi: 10.1074/jbc.M109.056317

38. Bieganowski M, Faccenda A, Kolde R, Lambrecht BN, Heremans BP. Altered Expression of microRNA in Synovial Fibroblasts and Synovial Tissue in Rheumatoid Arthritis. Arthritis Rheumatism (2008) 58 (4):1001–9. doi: 10.1002/art.23386

39. Bala S, Tilahun Y, Taha O, Alao H, Kodys K, Catalano D, et al. Increased microRNA Expression in the Serum and Peripheral Monocytes in Patients With Active Tuberculosis. PLoS One (2012) 7(8):e43184. doi: 10.1371/journal.pone.0043184

40. Huang HC, Yu HR, Huang LT, Huang HC, Chen RF, Lin IC, et al. miRNA-214-Targeting Phosphatase and Tensin Homolog in Advanced Non-Small Cell Lung Cancer and Cardiovascular Diseases. Cells (2020) 9(1):113. doi: 10.3390/cells9010113

41. Quinn SR, O’Neill LA. A Trio of microRNAs That Control Toll-Like Receptor Signaling. Int Immunol (2011) 23:421–5. doi: 10.1038/intimm.dox034

42. Tserell L, Runnel T, Kisand K, Pihlaj M, Bakhoff L, Kolde R, et al. MicroRNA Expression Profiles of Human Blood Monocyte-Derived Dendritic Cells and Macrophages Reveal miR-511 as Putative Positive Regulator of Toll-Like Receptor 4. J Biol Chem (2011) 286:26487–95. doi: 10.1074/jbc.M111.235561

43. Li M-I, Hou DX, Guo YL, Yang JW, Liu Y, Zhang CY, et al. Role of microRNA-214-Targeting Phosphatase and Tensin Homolog in Advanced Glioblastoma and Fibroblasts. Int J Mol Sci (2012) 13:4126–36. doi: 10.3390/ijms13020412

44. Huang F, Zhao JL, Wang L, Gao CC, Liang SQ, An DJ, et al. miR-148a-3p Mediates Notch Signaling to Promote the Differentiation and M1 Activation of Monocyte and Macrophage MiRNA for Tuberculosis

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8 June 2021 | Volume 12 | Article 667206

Sampath et al.
62. Xi X, Zhang C, Han W, Zhao H, Zhang H, Jiao J. MicroRNA-223 Is
51. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-
58. Kumar M, Sahu SK, Kumar R, Subuddhi A, Maji RK, Jana K, et al.
49. Zawada AM, Zhang L, Emrich IE, Rogacev KS, Krezdorn N, Rotter B, et al.
54. O
55. Wu Y, Sun Q, Dai L. Immune Regulation of miR-30 on the
56. Mahadik K, Prakhar P, Rajmani RS, Singh A, Balaji KN. c-Abl-TWIST1 Epi-
47. Hashimi ST, Fulcher JA, Chang MH, Gov L, Wang S, Lee B, et al. MicroRNA
38. doi: 10.1080/15384101.2016.1215386
39. Wu Y, Guo Z, Yao K, Miao Y, Liang S, Liu F, et al. Dicer-1 Regulator of the Innate Immune Response, Front.
45. doi: 10.1128/MB.06597-11
42. Wang Q, Liu S, Tang Y, Liu Q, Yao Y. MPT64 Protein From Mycobacterium
71. Zheng L, Leung E, Lee N, Lui G, To KF, Chan RC, et al. Differential
50. Liu, Wang R, Wang J, Xiang Y, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 73(3):345–56. doi: 10.1016/j.molimm.2015.01.007
59. Saba R, Sorensen DL, Booth SA. MicroRNA-146a: A Dominant, Negative Regulator of the Innate Immune Response, Front. Immunol (2014) 5:578. doi: 10.3389/fimmu.2014.00578
50. Liu, Wang R, Wang J, Xiang Y, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 73(3):345–56. doi: 10.1016/j.molimm.2015.08.006
52. Li S, Yue Y, Xu W, Xiong S. MicroRNA-146a Represses Mycobacteria-Induced Inflammatory Response and Facilitates Bacterial Replication Via Targeting IRAK-1 and TRAF-6. PloS One (2013) 8:e81438. doi: 10.1371/journal.pone.0081438
53. Liu, Wang R, Liang J, Yang G, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 67:475–81. doi: 10.1016/j.molimm.2015.08.006
54. Xi X, Zhang C, Han W, Zhao H, Zhang H, Jiao L. MicroRNA-223 Is Upregulated in Activated and Tuberculosis Patients and Inhibits Apoptosis of Macrophages by Targeting FOXO3. Genet. Test Mol Biomarkers (2015) 19:650–6. doi: 10.1089/gtmb.2015.0090
65. Wu Z, Lu H, Sheng J, Li L. Inductive microRNA-21 Impairs Anti-
57. Ni B, Rajaram MV, Laffse WP, Landes MB, Schlesinger LS. Mycobacterium Tuberculosis Decreases Human Macrophage IFN-γ Responsiveness Through miR-132 and miR-26a. J Immunol (2014) 193(9):4537–47. doi: 10.4049/jimmunol.1401024
58. 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. Cell Host Microbe (2015) 17(3):345–56. doi: 10.1016/j.chom.2015.01.007
59. Saba R, Sorensen DL, Booth SA. MicroRNA-146a: A Dominant, Negative Regulator of the Innate Immune Response, Front. Immunol (2014) 5:578. doi: 10.3389/fimmu.2014.00578
60. Li S, Yue Y, Xu W, Xiong S. MicroRNA-146a Represses Mycobacteria-Induced Inflammatory Response and Facilitates Bacterial Replication Via Targeting IRAK-1 and TRAF-6. PloS One (2013) 8:e81438. doi: 10.1371/journal.pone.0081438
61. Liu, Wang R, Liang J, Yang G, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 67:475–81. doi: 10.1016/j.molimm.2015.08.006
62. Xi X, Zhang C, Han W, Zhao H, Zhang H, Jiao J. MicroRNA-223 Is
51. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-
58. Kumar M, Sahu SK, Kumar R, Subuddhi A, Maji RK, Jana K, et al.
49. Zawada AM, Zhang L, Emrich IE, Rogacev KS, Krezdorn N, Rotter B, et al.
54. O
55. Wu Y, Sun Q, Dai L. Immune Regulation of miR-30 on the
56. Mahadik K, Prakhar P, Rajmani RS, Singh A, Balaji KN. c-Abl-TWIST1 Epi-
47. Hashimi ST, Fulcher JA, Chang MH, Gov L, Wang S, Lee B, et al. MicroRNA
38. doi: 10.1080/15384101.2016.1215386
39. Wu Y, Guo Z, Yao K, Miao Y, Liang S, Liu F, et al. Dicer-1 Regulator of the Innate Immune Response, Front.
45. doi: 10.1128/MB.06597-11
42. Wang Q, Liu S, Tang Y, Liu Q, Yao Y. MPT64 Protein From Mycobacterium
71. Zheng L, Leung E, Lee N, Lui G, To KF, Chan RC, et al. Differential
50. Liu, Wang R, Wang J, Xiang Y, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 73(3):345–56. doi: 10.1016/j.molimm.2015.08.006
52. Li S, Yue Y, Xu W, Xiong S. MicroRNA-146a Represses Mycobacteria-Induced Inflammatory Response and Facilitates Bacterial Replication Via Targeting IRAK-1 and TRAF-6. PloS One (2013) 8:e81438. doi: 10.1371/journal.pone.0081438
53. Liu, Wang R, Liang J, Yang G, Bao C, Zeng X, Cheng X. miR-223 Is Upregulated in Monocytes From Patients With Tuberculosis and Regulates Function of Monocyte-Derived Macrophages. Mol Immunol (2015) 67:475–81. doi: 10.1016/j.molimm.2015.08.006
54. Xi X, Zhang C, Han W, Zhao H, Zhang H, Jiao L. MicroRNA-223 Is Upregulated in Activated and Tuberculosis Patients and Inhibits Apoptosis of Macrophages by Targeting FOXO3. Genet. Test Mol Biomarkers (2015) 19:650–6. doi: 10.1089/gtmb.2015.0090
65. Wu Z, Lu H, Sheng J, Li L. Inductive microRNA-21 Impairs Anti-

80. Siqindel MDS, Ribeiro RDM, Travassos LH. Autophagy and Its Interaction With Intracellular Bacterial Pathogens. Front Immunol (2018) 9:935. doi: 10.3389/fimmu.2018.00935

81. Abadalla AE, Duan X, Deng W, Zeng I, Xie J. MicroRNAs Play Big Roles in Modulating Macrophages Response Toward Mycobacteria Infection. Infect Genet Evol (2016) 45:378–82. doi: 10.1016/j.meegid.2016.09.023

82. Kim JK, Kim TS, Basu J, Jo JK. MicroRNA in Innate Immunity and Autophagy During Mycobacterial Infection. Cell Microbiol (2017) 19(1): e12687. doi: 10.1111/cmi.12687

83. Zhao Y, Wang Z, Zhang W, Zhang L. MicroRNAs Play an Essential Role in Autophagy Regulation in Various Disease Phenotypes. BioFactors (2019) 45(6):344–56. doi: 10.1002/biof.1555

84. Ouimet M, Koster S, Sakowski E, Ramkhelawon B, Van Solingen C, Oldebeek S, et al. Mycobacterium Tuberculosis Induces the miR-33 Locus to Reprogram Autophagy and Host Lipid Metabolism. Nat Immunol (2016) 17(6):677–86. doi: 10.1038/nii.2014.434

85. Tu H, Yang S, Jiang T, Wei L, Shi L, Liu C, et al. Elevated Pulmonary Tuberculosis Biomarker miR-423-5p Plays Critical Role in the Occurrence of Active TB by Inhibiting Autophagosome-Lysosome Fusion. Emerg Microbes Infect (2019) 8(1):448–60. doi: 10.1002/emm2.20175.191590129

86. Liu F, Chen J, Wang P, Li H, Zhou Y, Liu H, et al. MicroRNA-27a Controls the Intracellular Survival of Mycobacterium Tuberculosis by Regulating Calcium-Associated Autophagy. Nat Commun (2018) 9(1):1–14. doi: 10.1038/s41467-018-06683-4

87. Kim JK, Yim JK, Kim SY, Kim TS, Jin HS, Yang CS, et al. MicroRNA-125a-5p Are Altered in Mycobacterium Avium-Infected Macrophages and Associated With the Triggering of an Autophagic Response. Microbes Infect (2018) 22(1):31–9. doi: 10.1016/j.micinf.2017.07.002

88. Sabir N, Hussain T, Shah SZA, Peramo A, Zhao D, Zhou X. microRNAs in Tuberculosis: New Avenues for Diagnosis and Host-Directed Therapy. Front Microbiol (2018) 9:602. doi: 10.3389/fmicb.2018.00602

89. Wang J, Yang K, Zhou L, Wu Y, Zhu M, Lai X, et al. MicroRNA-155 Promotes Autophagy to Eliminate Intracellular Mycobacteria by Targeting RhoB. PLoS Pathog (2013) 9(10):e1003697. doi: 10.1371/journal.ppat.1003697

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

91. Ema MP, Sinigaglia A, Grassi G, Agiornomi E, Romagnoli A, Pardini M, et al. Mycobacterium Tuberculosis-Induced miR-155 Subverts Autophagy by Targeting ATG3 in Human Dendritic Cells. PLoS Pathog (2018) 14(1): e1006790. doi: 10.1371/journal.ppat.1006790

92. Yang C, Shi Z, Hu J, Wei R, Yue G, Zhou D. miRNA-155 Expression and Role in Pathogenesis in Spinal Tuberculosis—Induced Intervertebral Disc Destruction. Exp Ther Med (2019) 17(4):3239–46. doi: 10.3892/etm.2019.7313

93. Rodriguez A, Vigorito E, Clare S, Warren MV, Couttet P, Soond DR, et al. Requirement of bci/microRNA-155 for Normal Immune Function. Science (2007) 316:608–11. doi: 10.1126/science.1139253

94. Jackson AL, Levin AA. Developing microRNA Therapeutics: Approaching the Unique Complexities. Nuclear Acid Ther (2012) 22:213–25. doi: 10.1089/fc.2012.0356/PfMID:22913594

95. Liu Y, Wang X, Jiang J, Cao Z, Yang B, Cheng X. Modulation of T Cell Cytokine Production by miR-144* With Elevated Expression in Patients With Pulmonary Tuberculosis. Mol Immunol (2011) 48:1084–90. doi: 10.1016/j.molimm.2011.02.001

96. Wu J, Lu C, Diao N, Zhang S, Wang S, Wang F, et al. Analysis of microRNA Expression Profile Identifying miR-155 and miR-153* as Potential Diagnostic Markers for Active Tuberculosis: A Preliminary Study. Hum Immunol (2012) 73(1):31–7. doi: 10.1016/j.jhimmun.2011.10.003

97. Fu Y, Yi Z, Wu X, Li X, Fu C. Circulating microRNAs in Patients With Active Pulmonary Tuberculosis. J Clin Microbiol (2011) 49:4246–51. doi: 10.1128/jcm.05459-11

98. Qi Y, Cui L, Ge Y, Shi Z, Zhao K, Guo X, et al. Altered Serum microRNAs as Biomarkers for the Early Diagnosis of Pulmonary Tuberculosis Infection. BMC Infect Dis (2012) 12:384. doi: 10.1186/1471-2334-12-384

99. Spinelli SV, Díaz A, D’Attilio L, Marchesini MM, Bogue C, Bay ML, et al. Altered microRNA Expression Levels in Mononuclear Cells of Patients With Pulmonary and Pleural Tuberculosis and Their Relation With Components of the Immune Response. Mol Immunol (2013) 55:265–9. doi: 10.1016/j.molimm.2012.08.008

100. Wang J, Zhu X, Xiong X, Ge P, Liu H, Ren N, et al. Identification of Potential Urine Proteins and microRNA Biomarkers for the Diagnosis of Pulmonary Tuberculosis Patients. Emerg Microbes Infect (2018) 7(1):63. doi: 10.1038/s41426-018-0066-5

101. Pedersen JL, Bokil NJ, Saunders BM. Developing New TB Biomarkers, Are microRNAs the Answer? Tuberculosis (Edinb) (2019) 118:101860. doi: 10.1016/j.tube.2019.101860

102. Fuaj JS, Schena E, Mutio P, Cirillo DM. Alteration of Human Macrophages microRNA Expression Profile Upon Infection With Mycobacterium Tuberculosis. Int J Mycobacteriol (2013) 2(3):128–34. doi: 10.1016/j.ijmyco.2013.04.006

103. Iwai H, Funatogawa K, Matsumura K, Kato-Miyazawa M, Kikae K, et al. MicroRNA-155 Knockout Mice Are Susceptible to Mycobacterium Tuberculosis Infection. Tuberculosis (Edinb) (2015) 95(3):246–50. doi: 10.1016/j.tube.2015.03.006

104. Rothchild AC, Sissons JR, Sha MC. The Molecular Basis of Tuberculosis. Pak J Biol Sci (2008) 11(4):617–21. doi: 10.3973/pjas.160225513

105. Meng QL, Liu F, Yang XY, Liu XM, Zhang X, Zhang C, et al. Identification of Potential Serum miRNAs as Biomarkers for Active Tuberculosis. Am J Respir Crit Care Med (2015) 191(9):935. doi: 10.1164/rccm.201403-0545OR

106. Qi Y, Cui L, Ge Y, Shi Z, Zhao K, Guo X, et al. Altered Serum microRNAs as Biomarkers for the Early Diagnosis of Pulmonary Tuberculosis Infection. BMC Infect Dis (2012) 12:384. doi: 10.1186/1471-2334-12-384

107. Spinelli SV, Díaz A, D’Attilio L, Marchesini MM, Bogue C, Bay ML, et al. Altered microRNA Expression Levels in Mononuclear Cells of Patients With Pulmonary and Pleural Tuberculosis and Their Relation With Components of the Immune Response. Mol Immunol (2013) 55:265–9. doi: 10.1016/j.molimm.2012.08.008

108. Wang J, Zhu X, Xiong X, Ge P, Liu H, Ren N, et al. Identification of Potential Urine Proteins and microRNA Biomarkers for the Diagnosis of Pulmonary Tuberculosis Patients. Emerg Microbes Infect (2018) 7(1):63. doi: 10.1038/s41426-018-0066-5
116. Palucci I, Delogu G. Host Directed Therapies for Tuberculosis: Futures Strategies for an Ancient Disease. *Chemotherapy* (2018) 63(3):172–80. doi: 10.1159/000490478

117. Paik S, Kim JK, Chung C, Jo EK. Autophagy: A New Strategy for Host-Directed Therapy of Tuberculosis. *Virulence* (2019) 10(1):448–59. doi: 10.1080/21505594.2018.1536598

118. Bento CF, Empadinhas N, Mendes V. Autophagy in the Fight Against Tuberculosis. *DNA Cell Biol* (2015) 34(4):228–42. doi: 10.1089/dna.2014.2745

119. Periyasamy KM, Ranganathan UD, Tripathy SP, Bethunaickan R. Vitamin D–A Host Directed Autophagy Mediated Therapy for Tuberculosis. *Mol Immunol* (2020) 127:238–44. doi: 10.1016/j.molimm.2020.08.007

120. Meister G, Landthaler M, Dorsett Y, Tuschi T. Sequence-Specific Inhibition of microRNA- and SiRNA-Induced RNA Silencing. *RNA* (2004) 10:544–50. doi: 10.1261/rna.5235104

121. Grimm D, Streetz KL, Jopling CL, Storm TA, Pandey K, Davis CR, et al. Fatality in Mice Due to Oversaturation of Cellular microRNA/Short Hairpin RNA Pathways. *Nature* (2006) 7092:537–41. doi: 10.1038/nature04791

122. Baumann V, Winkler J. MiRNA-based Therapies: Strategies and Delivery Platforms for Oligonucleotide and Non-Oligonucleotide Agents. *Future Med Chem* (2014) 17:1967–84. doi: 10.4155/fmc.14.116

123. Duan W, Yang T, Zhou SF, Wang ZL, Zhou ZW, He ZX. Novel Targeting of PEGylated Liposomes for Codelivery of TGF-Beta1 siRNA and Four Antitubercular Drugs to Human Macrophages for the Treatment of Mycobacterial Infection: A Quantitative Proteomic Study. *Drug Des Dev Ther* (2015) 9:4441–70. doi: 10.2147/DDDT.S79369

124. Moore LB, Sawyer AJ, Saucier-Sawyer J, Saltzman WM, Kyriakides TR. Nanoparticle Delivery of miR-223 to Attenuate Macrophage Fusion. *Biomaterials* (2016) 89:127–35. doi: 10.1016/j.biomaterials.2016.02.036

**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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