Antithetical Effects of MicroRNA Molecules in Tuberculosis Pathogenesis

Sir,

Tuberculosis (TB) has been remained as a major cause of human death around the world. The disease is caused by *Mycobacterium tuberculosis* (MTB) complex (MTBC). Approximately 10.4 million new TB cases and 1.4 million deaths were reported by the World Health Organization (WHO) in 2016.[1] Unfortunately, coinfection of TB with HIV and also emerging drug-resistant MTB strains such as multidrug-resistant TB and extensively drug-resistant TB eliminating the disease has become a health problem. Following a weak cellular immunity of current TB vaccine, Bacillus Calmette–Guerin (BCG) against TB adults can lead to serious problems in TB control programs.[2] Furthermore, based on the current reports, approximately 2 billion people carry MTB in latent form that 10% of these people develop to active TB form and they are considered as TB sources which can transmit MTB to other healthy individuals.[1,2]

On the other hand, recent studies have revealed that infectious disease can induce microRNA (miRNA) molecule responses, for example, MiR-155 in *Helicobacter pylori* infection, let-7 family in *Salmonella* infection, and particularly, MiR-29 in mice infected with BCG vaccine.[3,4] Moreover, continuously miRNAs are presented in body fluids (e.g. sputum) as unique diagnostic markers in various diseases, such as lung cancer or chronic obstructive pulmonary disease.[3-5] Nowadays, it has been proven that miRNAs are involved in different forms of TB, but it is necessary to establish numerous clinical studies for more understanding about the roles of miRNAs in TB pathogenesis.[6]

The miRNAs are small noncoding single strands (~22 nt) and conserved types of molecular RNA which are known as regulatory elements of gene expression process. In eukaryotic system at the posttranscriptional level, specific miRNAs are able to bind 3′ untranslated region (UTR) of messenger RNAs (mRNAs). These genetic elements are coded by only 1% of the human genome but influence on >60% of all protein-coding genes. Overall, they impress various cell functions including cell proliferation and differentiation, DNA repair system, DNA modification (e.g. DNA methylation), apoptosis, and particularly, anti-inflammatory signaling pathways.[4-6] Today, clinical experiments demonstrate that miRNAs can influence the proliferation, differentiation, and function of T-cells. Furthermore, miRNAs also can effect on innate immune system responses, such as macrophages, natural killer cells, and dendritic cells (DCs).[3-6]

MTB and other members of MTBC are aerobic and intracellular microorganisms which are transmitted throughout inhalation of contaminated aerosols produced by patients' coughs and sneezes. Following infection by MTB, cell-mediated immunity (CMI) response is more important compared with humoral immune response. Bacteria in the lung are enclosed by antigen-presenting cells such as alveolar macrophages, DCs, and also epithelioid and polymorphonuclear cells. Surface antigens such as lipoarabinomannan and phosphatidylinositol mannoside are recognized by Toll-like receptors (TLRs). Inside of the infected cells, fusion of MTB with phagolysosome leads to the production of nuclear factor-kappa B (NF-κB) pathway proteins. However, in the active phase of infection, microorganism using some antigens such as antigen 85 complex (Ag85 complex) for prevention of phagolysosome fusion. In the CMI response, body employs of the major histocompatibility complex (MHC) as the most important member. Processing antigens are presented by MHC I and MHC II and consequently recognized by TCD4+ and TCD8+ cells, respectively. Activated TCD4+ (Th1) cells recognize presented antigens by MHC II and produce immune cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2), but TCD8+ cells as cytotoxic T-lymphocytes recognize presented antigens by MHC I and consequently kill the infected cells. IFN-γ and tumor necrosis factor-α (TNF-α) are the main pro-inflammatory cytokines and play pivotal roles in protection against MTB infection. In addition, studies have demonstrated protective roles of IL-6 and IL-1β against MTB and also IL-10 and Treg cells in suppression of Th1 cell responses.[1,6]

There are numerous studies that have shown critical roles of miRNAs in both protection and progression pathways of TB. Given that reports, in patients with active form of TB, miRNA-29 is overexpressed following infection and suppresses the immune response by decreasing of IFN-γ expression through Argonaute 2 protein. The miRNA-29 also can active apoptotic pathway through binding to anti-apoptotic B-cell lymphoma-2 (Bcl-2) and myeloid cell leukemia-1 proteins and leads to the prevention of TB progression through destroying bacteria in macrophages.[7] According to clinical studies, BCG vaccine can increase IFN-γ level and also decreases miRNA-29 level; therefore, decreasing of miRNA-29 can helpful in defense against MTB.[8]

The miRNA-21 is another miRNA which can suppress immune response against TB throughout downregulating of immune cytokines and upregulating of anti-inflammatory cytokines (e.g. IL-10). Furthermore, miRNA-21 binds to 3′ UTR of IL-12 mRNA and inhibits expression of IL-12 and eventually stopping

of Th1 responses.[6,9] Rajaram *et al*. demonstrated that miRNA-125b can impair innate immune response by blocking TNF-α mRNA. Furthermore, miRNA-99b is similar to miRNA-125b can downregulate TNF-α expression by targeting TNF receptor superfamily member 4.[10] In recent years, Shi *et al*. have found that *Mtb* during phagocytosis can induce expression of miR-1178 in both HTP-1 and U937 macrophages cell line. On the other hand, the miRNA-1178 promotes replication and intercellular growth of tubercle bacilli during phagocytosis through downregulating expression of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1 β, and IL-6.[11] According to Liang *et al*. experiments, TLR-2/MyD88/NF-kB signaling pathway in MTB-infected macrophages causes to the expression of miR-27b which leads to suppress pro-inflammatory cytokines. In addition, miR-27b modulates immune response through blocking the Bcl-2/Bag2 pathway in macrophages. Furthermore, miR-27b can induce the production of oxygen radicals in macrophages through interaction with p53 protein which leads to decrease in bacterial proliferation.[12]

The miR-155 binds to 3′ UTR region of inositol phosphatase SHIP1 and causes longer stability of TNF-α mRNA. Furthermore, miR-155 also can inhibit the protein kinase inhibitor-alpha, as an inhibitor of protein kinase A (PKA). PKA has pivotal roles on the cellular immune system, for example, activation of mitogen-activated protein kinase and induction of apoptotic pathway in MTB-infected macrophages.[6,13] Based on Wang *et al*. researches, high-level amounts of miR-424 in peripheral blood mononuclear cells of patients with active TB encourage monocyte differentiation and should be considered as efficient miRNAs.[14]

In summary, miRNAs are considered as one of the most important strategies that involve in TB pathogenesis [Figure 1]. These small ribonucleic acid molecules target several immune-depended mRNAs and regulate various immune pathways in T-cells, DCs, and other immune cells. However, our knowledge about the impact of miRNA on TB is limited, and there is a contrary hypothesis about molecular mechanisms of some miRNAs [Tables 1 and 2]. Recently, it has been approved that both of healthy and patient groups with different forms of TB have their own specific miRNA profiles. Nowadays, it is accepted that miRNAs are the best candidates which can be as new strategies of TB treatment.

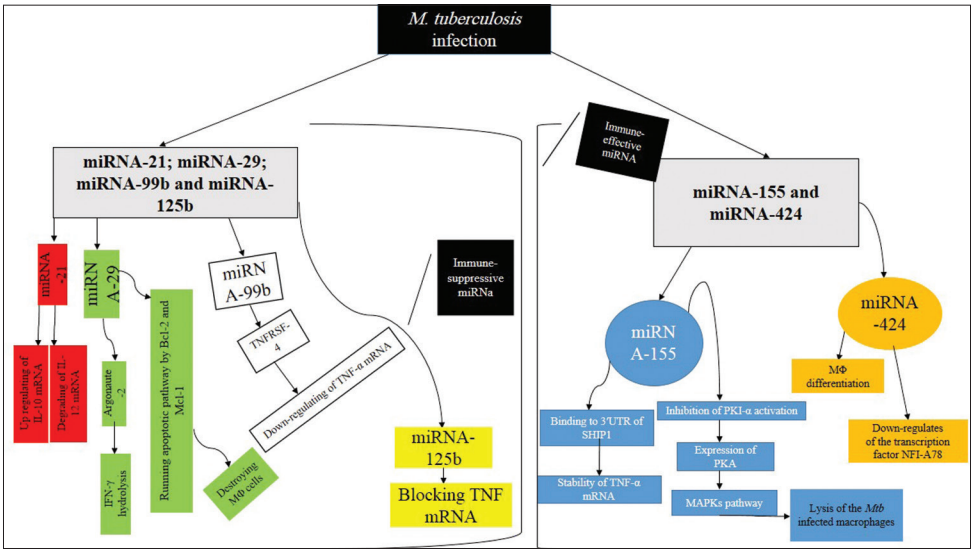

Figure 1: The roles of several microRNAs that suggested in the text on tuberculosis pathogenesis

Table 1: List of immune-suppressive miRNAs in TB patients

MirRNA	Mechanism of action	Final effect
miR-21	Overexpression of IL-10 mRNA and Down-regulation of IL-12 mRNA	Suppression of immune-response against TB
miR-29	Degradation of IFN-ϒ	Intercellular growth of tubercle bacillus within macrophages
miR-99b	Decline expression of TNF-α	Suppression of immune-response against TB
miR-125b	Blockade TNF-α mRNA	Suppression of immune-response against TB
miR-27b	Suppression of NF_kB signaling pathway	Suppression of immune-response against TB and intercellular growth of MTB
miR-1178	Attenuation of TLR-4 expression and inhibition of pro-inflammatory cytokines	Suppression of immune-response against TB

Table 2: List of immune-effective miRNAs in TB patients

MirRNA	Mechanism of action	Final effect
miR-155	Stability of TNF-α mRNA and activation of MAPKs signaling pathway	Efficient immune-response against MTB, provoke phagocytosis and elimination of MTB
miR-424	Dysregulation of NFI-A78	Macrophage maturation and differentiation
miR-223	Targeted Mef2c	Granulocytes production and stimulation pro-inflammatory response
miR27a	Blocking IRAK4 signaling pathway	Increase of pro-inflammatory cytokines such as IL-β, IL-6 and IFN-γ
miR-20b	targeting the NLRP3/caspase-1/IL-1β pathways	Induce inflammation process
miR-582-5p	Decline monocytes apoptosis via down-regulating FOXO1	Promotion of anti-tuberculosis immune response

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Conflicts of interest

There are no conflicts of interest.

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References

1. Karbalaei Zadeh Babaki M, Soleimanpour S, Rezaee SA. Antigen 85 complex as a powerful *Mycobacterium tuberculosis* immunogene: Biology, immune-pathogenicity, applications in diagnosis, and vaccine design. Microb Pathog 2017;112:20-9.
2. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, *et al.* WHO's new end TB strategy. Lancet 2015;385:1799-801.
3. Yi Z, Fu Y, Ji R, Li R, Guan Z. Altered microRNA signatures in sputum of patients with active pulmonary tuberculosis. PLoS One 2012;7:e43184.
4. Fu Y, Yi Z, Wu X, Li J, Xu F. Circulating microRNAs in patients with active pulmonary tuberculosis. J Clin Microbiol 2011;49:4246-51.
5. Oglesby IK, McElvaney NG, Greene CM. MicroRNAs in inflammatory lung disease – Master regulators or target practice? Respir Res 2010;11:148.
6. Harapan H, Fitra F, Ichsan I, Mulyadi M, Miotto P, Hasan NA, *et al.* The roles of microRNAs on tuberculosis infection: Meaning or myth? Tuberculosis (Edinb) 2013;93:596-605.
7. Xiong Y, Fang JH, Yun JP, Yang J, Zhang Y, Jia WH, *et al.* Effects of microRNA-29 on apoptosis, tumorigenicity, and prognosis of hepatocellular carcinoma. Hepatology 2010;51:836-45.
8. Ma F, Xu S, Liu X, Zhang Q, Xu X, Liu M, *et al.* The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ. Nat Immunol 2011;12:861-9.
9. 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;14:1620-31.
10. Rajaram MV, Ni B, Morris JD, Brooks MN, Carlson TK, Bakthavachalu B, *et al. Mycobacterium tuberculosis* lipomannan blocks TNF biosynthesis by regulating macrophage MAPK-activated protein kinase 2 (MK2) and microRNA miR-125b. Proc Natl Acad Sci U S A 2011;108:17408-13.
11. 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 TLR4. J Cell Biochem 2018;119:7449-57.
12. 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. J Immunol 2018;200:3506-18.
13. O'Connell RM, Chaudhuri AA, Rao DS, Baltimore D. Inositol phosphatase SHIP1 is a primary target of miR-155. Proc Natl Acad Sci U S A 2009;106:7113-8.
14. Wang C, Yang S, Sun G, Tang X, Lu S, Neyrolles O, *et al.* Comparative miRNA expression profiles in individuals with latent and active tuberculosis. PLoS One 2011;6:e25832.

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