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Novel Facets of Diverse Role of miRNA in the Survival and Pathogenesis of *Mycobacterium tuberculosis*

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Abstract

Tuberculosis is becoming a threat to world's population as its proper diagnosis and medication is still quite challenging. Survivals of mycobacteria within host macrophages are strongly connected with various aspects of host innate immune response. MicroRNAs (miRNAs) are small non-coding RNA molecules which shows profound effect on reflected action by host through its immune response. In host several miRNA are found which shows differential expression during mycobacterial infection. These miRNA are found to play significant role in various physiological and pathological purposes, thus providing a way to treat and diagnose the disease in early phase. This review deals with the several aspects of miRNA which gets altered during tuberculosis infection.

Keywords: miRNA; *Mycobacterium tuberculosis*; Epigenesis; Biomarker

Abbreviations

***M.tb*:** *Mycobacterium tuberculosis*; **TB:** Tuberculosis; **miRNAs:** MicroRNAs; **DRAM2:** Damage Regulated Autophagy Modulator 2; **iNOS:** Nitric Oxide Synthase; **TRAF6:** Tumor Necrosis Receptor-Associated Factor; **UVRAG:** UV Radiation Resistance-Associated Gene

Introduction

Tuberculosis (TB) has existed in the world from millennium and still its diagnosis is a global issue. *Mycobacterium tuberculosis* H_{37}Rv (*M.tb*) is known to be the vital causal organism of the disease [1]. According to WHO report, 2017 10 million people each year are subject to ill health due to TB and also its ranked as 9th cause of death worldwide. In 2016 there were 1.3 million deaths reported due to TB in HIV negative patients and an additional of 374,000 deaths among HIV positive cases [2]. Bacilli of TB are obligate aerobes which inhibit in alveolar macrophage of lungs. Long term survival of *M.tb* depends on its ability to escape through various strategy of host immune system [3]. Bacterial infections have effect on host epigenome which provokes disease susceptibility [4]. Epigenetic changes are subject to phenotypic changes rather than any genotypic changes in gene expression. Epigenetic mechanism has critical role in maintaining the gene expression under specific stimulus. Nowadays, MicroRNAs (miRNAs) are becoming a novel target for diverse diseases as they involve in regulating gene expression [5].

miRNAs and Its Significance

miRNAs are the small non-coding RNA molecule (approx. 22 nucleotides) found in almost all organisms. They are regulator of gene expression by RNA silencing and post transcriptional modifications [6]. Their altered appearance in infected patients had showed their involvement in TB. Researchers are presently taking interest to find out the expression profile of various miRNAs during active and latent TB. This elaborates the role of miRNAs in epigenetic alterations survival and pathogenesis of TB.

Role of miRNA in Regulation of TB

Several miRNA are involved in regulating T cell differentiation, and plays critical role in modifying innate immune functions related to macrophages, dendritic cells and Natural Killer Cells (NK cells) [7]. In a study, expression of miR-135b, miR-21, miR155, miR146a, miR146b were seen altered in leukocyte of infected mice and also had validated the inhibition of Pellino1 (involved in regulation of innate and adaptive immunity in individual by ubiquitylation) by miR-135b *in-vitro* [8]. Similarly a study has shown that miR-155 and miR-132 could be used as biomarker for early detection of pulmonary tuberculosis (PTB) [9]. miRNA involved in promoting autophagy in macrophages *via* enhancing the expression of miR144/has-144-5p which binds to the 3' untranslated region of DNA damage regulated autophagy modulator 2 (DRAM2) in human macrophages. Induced expression of miR-144 contrary downregulates the DRAM2 expression as well as arrests the formation of auto-phagosome in monocytes whereas inhibition of miR-144 shows counter effect [10]. miRNA are also important regulators of immune system and they recruit a regulatory network during *M.tb* infection where miR-155 maintains the survival of *M.tb* infected macrophages providing niche preferring bacterial replication. On the other hand miR-155 promotes the persistence and function of *M.tb* specific T cells allowing an adaptive immune response. miR-155 induce cell existence which is mediated by SH2 domain containing inositol-5-phosphate involving AKT pathway. Dual regulation of cell survival in innate and adaptive immune cells leads to enormously different outcomes with respect to bacterial component [11]. Some of the miRNA shows markedly increase after *M.tb* infection in macrophages. Since miR-146a suppresses expression of Nitric Oxide Synthase (iNOS) which in turn stimulates *M.tb* survival in macrophages. Nitric oxide (NO) production and mycobacterial clearance are increased by inhibition of miR-146a. Diminution of miR-146a activates NF-κB and MAPK which suppresses iNOS expression. Chemically miR-146a targets Tumor Necrosis Receptor-Associated Factor 6 (TRAF6) at post transcriptional level. Silencing of TRAF6 had shown to reduce iNOS

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expression. By over expressing of TRAF6, inhibition of NO mediated miR-146a get reversed. So they play role in synergistical way [12]. miR-144 control macrophage function *via* targeting of tumor progression locus 2 (TpL2 which is also named MAP3K8) and Extracellular Signal-Regulated Kinase (ERK) signaling. In macrophage infected with *M.tb*, miR-144 gets downregulated and acts as negative regulator which binds to 3'UTR of TpL2. Inhibition of miR-144 or over expression of TpL2 can activate ERK signaling pathway. Meanwhile TNFα, IL-1B, IL-6 secretion are also enhanced [13]. Autophagy plays critical role in regulating bacterial load while causing infection. During *M.tb* infection downregulation of miR-17 and upregulation of its target myeloid cell leukemia-1 (McL-1) and signal transducer and activator of transcription-3 (STAT-3) regulates the autophagic activation in macrophage. STAT-3 is transcriptional activator of McL-1. Enforced expression of miR-17 declines expression of McL-1 and STAT-3. This directly linked with enhanced autophagy as McL-1 enhanced expression mitigates the effects of miR-17 [14].

Thus miRNAs are showing great evidence involving in host pathogen interaction. In one of the study various mRNAs are profiled by RT-PCR where it was observed that some of them were upregulated and some were downregulated during active TB. It depicts that they get expressed in differential manner. There is one significant miR-29a which discriminate the TB patients with healthy individuals suggesting as a biomarker for medical purpose [15]. miRNA-125a targets the UV radiation resistance-associated gene (UVRAG) to prevent autophagy and antimicrobial response during TB infection as it work on contrary by using inhibitors of miR-125a. TLR2 and MyD88 were required for synthesis of miR-125a in Mtb infected macrophages and also high expression of miR-125a or silencing of UVRAG shows significantly depletion in the antimicrobial effect of macrophages towards *M.tb* [16].

Conclusion

It can be concluded that, there are various important aspects of studying the role of miRNA in diagnosis of TB. Bacterial infection has profound effect on host epigenome as it triggers the susceptibility towards disease. Thus miRNA plays an significant part in epigenetic changes through modulating transcriptional machinery which modifies immune system. miRNA are in relation with host defense against mycobacteria, which need proper tuning of innate immune response. Several researches showed that miRNA plays critical interconnection between *M.tb* survival strategies and host innate immune response. Various miRNAs are involved in autophagy modification during *M.tb* infection. It depicts the prominence of miRNA in the field of TB diagnosis as they may be used as biomarker to resolve the issue of new diagnostic approaches related to TB.

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