

MicroRNAs in tuberculosis: do they have a functional role in TB?

Abstract

Tuberculosis (TB) is major health problem threatening many people worldwide. It is caused by *Mycobacterium tuberculosis*. *M. tuberculosis* changes its cellular environment with the mechanisms that have been evolved since prehistoric times. The interactions between the bacteria and the host environment have been studied well. But the studies at RNA level began to emerge recently. MicroRNAs (miRNAs) became a target for different diseases depending on their regulatory role on gene expression. As the data about the new class of small non-coding RNA called microRNAs accumulate researchers find more information about their regulatory role in biological processes including immune response to infectious agents like mycobacteria. Several studies detected the alterations in the expression levels of miRNAs in the individuals that are infected. Researchers are trying to find miRNA expression profiles for the infection either in latent or active state which can also be used as biomarkers for diagnosis or miRNA based therapy options. Here we try to summarize some of the studies that include *M. tuberculosis* and the possible functions of miRNAs during TB infection.

Keywords: tuberculosis, miRNA, host-pathogen interactions, infection, host factors

Volume 2 Issue 1 - 2015

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Received: December 22, 2014 | **Published:** January 05, 2015

Abbreviations: *M. tuberculosis*, *mycobacterium tuberculosis*; TB, tuberculosis; miRNA, microRNAs; DC, dendritic cells; PMNs, polymorphonuclear neutrophils

Introduction

Tuberculosis caused by *Mycobacterium tuberculosis*, is a global health problem causing significant morbidity and mortality worldwide.¹ Although one third of the world population is infected, only 5-10% develops the active state of the disease.² Almost more than 8million cases have *M. tuberculosis* infection³ and 1,3million people died in 2012.⁴ Tuberculosis is an ancient disease and it was evolved with hominids and the modern strains of *M. tuberculosis* arose at the same time when humans started to migrate from Africa about 40,000years ago.⁵ After emerging from Africa, it was spread to other regions of the world such as Middle East, Europe and Asia.

When *M. tuberculosis* infection occurs, the intracellular pathogen confronts a certain host cell environment such as reduced oxygen tension and restricted nutrients. Although the genetic mechanisms behind these are unknown, *M. tuberculosis* can overcome different stress conditions that are encountered within phagosomes.⁶ The bacteria manipulate the cellular environment with the mechanisms it evolved for its own sake. The gene expression profiles of *M. tuberculosis* have been extensively studied under various environmental stresses, such as hypoxia, nitric oxide release, nutrient starvation, low pH and drug exposure, and during infection of the lungs and macrophages.⁷ On the other hand the information about host-pathogen interaction at the RNA level is very limited and studies related with regulatory RNA molecules and *M. tuberculosis* speculate possible regulatory roles for miRNAs in the interaction between macrophages and the bacteria.⁸

MicroRNAs (miRNAs) are a large family of post-transcriptional regulators of gene expression. They are small non-coding RNAs that are approximately 21 nucleotides in length and control many developmental and cellular processes in eukaryotic organisms.^{4,9} miRNAs are very important since they are involved in developmental

and pathological processes. Several thousand miRNAs have been identified in eukaryotic cells in animals and plants, and viruses.¹⁰ Regulation of gene and protein expression can be accomplished by targeting RNA transcripts and determining degradation and/or repression of translation by mi RNAs. Studies about roles of miRNAs in complex host responses, such as immunity to chronic bacterial infections, was accelerated by getting more insights about the multifactorial features of miRNAs. The role of miRNAs during viral and parasitic infections was reported in previous studies, but critical role of miRNAs in the interactions between host and bacteria has been shown by others recently.¹¹

In a PubMed search made by using keywords “miRNAs and tuberculosis” gives 63 papers in literature between the years of 2002 and 2014. The main studies start to come about the subject in 2010. Here we try to focus on the studies that were performed mainly after 2010.

In 2010 Guo et al.,⁸ reported their preliminary findings on the possible interactions between human miRNAs and *M. tuberculosis* mRNAs. They used miRNA target prediction software, miRanda, and predicted 26 candidate *M. tuberculosis* genes that may be targeted by human miRNAs expressed in the lung or macrophages.⁸ Alveolar resident macrophages are the first encounter of mycobacteria when it is inhaled into the lungs of the host. If mycobacteria canescape from the initial intracellular destruction it can multiply and disrupt the macrophages. Innate immunological responses to Mycobacterium are explained elsewhere.¹² On the other hand there are reports about the miRNA signature characteristic of active *M. tuberculosis* infection.¹³⁻¹⁷

Fu et al.,¹⁴ worked on the circulating miRNAs in patients with active pulmonary tuberculosis. Their results showed that there are miRNAs that are expressed differentially during active pulmonary tuberculosis infection. In their study 59 miRNAs were over expressed and 33 were under expressed compared to controls.miR-93 was the most upregulated miRNA in active tuberculosis infection according to this group. miR-518d-5p, miR-520c-5p and miR-526a were the

most decreased miRNAs comparing to the levels of the controls. Until their study the functions of miR-518d-5p and miR-520c-5p were largely unknown and in their paper they suggested that these play important roles in tuberculosis infection.¹⁴ Furci et al.,¹⁸ try to identify differentially express miRNAs in *M. tuberculosis* infected macrophages and they compared the virulent strain with the non-virulent vaccine strain. They reported that 358 distinct miRNAs were expressed in monocyte derived macrophages and 52 out of 358 miRNAs were found expressed significantly different in the infected cells comparing to the normals.

There are studies about the main TB protective cytokines including TNF- α and INF- γ and their regulation by miR-125b and miR-29.¹⁹ In a study performed by human macrophages infected with *M. tuberculosis*, high has-miR-125b and low has-miR-155 expression were detected comparing to the infection with non-virulent *M. smegmatis*.^{20,21} According to the study the expression of miRNA influences TNF- α induction in a way that while miR-125b binds and destabilize TNF- α , miR-155 enhances TNF- α production. Another study by Kumar et al showed the decreased *M. tuberculosis* intracellular survival when mouse macrophages were transfected with miR-155.²² Not only macrophages involved and influenced by miRNAs during infection but also dendritic cells (DC) do. Singh et al.,¹⁷ reported that TNF- α production was inhibited by the induction of mir-99b by infection of DCs with *M. tuberculosis* and bacterial burden was decreased when miR-99b was knocked down.

On the other hand it was reported that miR-29 overexpression increased the susceptibility to tuberculosis. It was shown that it inhibits INF- γ expression of T-cells.²³ In another study it was concluded that mycobacteria induce expression of miR-21 and this cause impaired macrophage activation and TH-1 immunity.²⁴

One of the miRNAs that was found to be upregulated in the blood and lungs of TB patients was miR-223. In order to understand its functional role during active TB, Dorhoi et al.,¹⁹ worked with the miR-223 knockout mice and they observed miR-223-/- mice failed to control pulmonary TB and they also found C-X-C motif ligand 2 (CXCL2) and C-C motif ligand 3 (CCL3) as the direct targets of miR-223. They suggested that polymorphonuclear neutrophils (PMNs) negatively control leukocyte chemotaxis at late stages of inflammation by accumulated miR-223.

As supported by the literature the regulatory role of miRNAs in immunity to infection is important. In the light of the published work is it also possible to use them as a diagnostic tool? In the beginning we told that tuberculosis is a global health problem. Every year new people are affected but some individuals are capable of controlling the pathogen. So the diagnosis of the disease and discriminate it from the latent state is very crucial. But according to Ueberberg et al.,²⁵ common biomarker candidates have not been identified yet because of several reasons explained elsewhere.

Here we try to summarize some of the latest work related with microRNAs and their relation with Mycobacterium infection. The studies show us the specific miRNAs are present during infection and influence the disease state. The identification of miRNA signature of tuberculosis will lead us to find biomarkers and to find new immune response search strategies about tuberculosis.

Conclusion

Tuberculosis is global health problem threatening millions every year. Its exact molecular pathogenesis mechanisms have not been

solved yet. Even though the bacterium was one of the firsts to have its genome sequenced, there is still much to learn about the interactions at cellular level. Protein-protein interactions, DNA-protein interactions between host and pathogen should be understood well in order to find better ways to diagnose the disease at an early stage or find new treatment tools in order to fight with *M. tuberculosis*. miRNAs open a new research area. They may be used as biomarkers or may be thought as treatment options after a profile of them are dissected in detail in the disease state. The profiling studies of healthy and normal individuals will give us more insightful knowledge about miRNAs and with the data accumulated from the studies new prediction analysis software should be developed to use the data. Still there is a long way ahead of us...

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

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