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Short Communication

miRNA-mediated Immune Response to *Mycobacterium tuberculosis* Infection

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Abstract

Mycobacterium tuberculosis, the causative agent of human Tuberculosis (TB), kills nearly two million people annually and has been a major health threat for centuries. Despite its importance as a global health threat, *M. bovis* Bacille Calmette-Guerin (BCG) introduced in 1921 is currently the only tuberculosis vaccine approved for human use with almost no protective effect in adults. Further, the emergence of Multi Drug Resistant (MDR) and extremely Drug Resistant (XDR)-TB also poses a vital challenge to the control of the disease. Although the interaction between *M. tuberculosis* and its environment have been extensively studied but our knowledge about potential *M. tuberculosis*-host interaction at the RNA level is still very limited. Recently, miRNAs has been emerged as a potential candidate controlling the host immune response during tuberculosis; however, this area is yet to be explored. Therefore, in this review, we discuss to elucidate the role of miRNAs during *M. tuberculosis* infection and speculate possible roles of miRNAs in regulating the disease.

Introduction

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is the leading cause of death. Approximately 5,000 deaths per day were reported throughout the world and the World Health Organisation (WHO) reported 1.8 million deaths per year due to TB in 2008 [1]. *M. bovis* Bacille Calmette-Guerin (BCG) is currently the only tuberculosis vaccine approved for human use. However, the protective immunity generated by BCG wanes off with age and its efficacy against the disease has been less than satisfactory in adults and older individuals. Besides, the inability of BCG to provide sterilizing immunity at the time of primary infection leads to an enormous reservoir of asymptomatically infected individuals worldwide (~2 billion) [2]. Further, the emergence of Multi Drug Resistant (MDR) and extremely Drug Resistant (XDR)-TB also poses a vital challenge to the control of the disease. The investigation for a new drug target involving modern drug delivery systems and immune modulators is essential to continue the battle against MDR and XDR-TB.

The lethality of *M. tuberculosis* infection is considered to be related to bacterial expansion, excessive inflammation and subsequent tissue damage [3,4]. The host immunity to tuberculosis relies mainly on Th1 cells producing IL-12, IFN-γ and TNF-α [5-8] and patients with defective receptors for IFN-γ or IL-12 have markedly increased susceptibility to severe infection [9]. IFN-γ and TNF-α establish protective immunity in the host by promoting macrophage function thus helping in bacterial clearance from the host [4,10]. Recent study on Mycobacterium infected individuals showed that the proliferation of Th1 cells and the expression of IFN-γ and TNF-α was downregulated by certain microRNAs such as miRNA-144 thus increasing the severity of the disease [11].

MicroRNAs (miRNAs) are 21-24 nucleotide long non-coding RNAs which play a critical role in the regulation of gene expression [12-14]. They are believed to either repress mRNA translation or reduce mRNA stability by binding with the miRNA-Recognition Elements (MRE) within the 3′ Untranslated Region (UTR) of target genes. These regulatory RNAs provide a unique level of post-transcriptional gene regulation that modulates a range of fundamental cellular processes. Several studies showed that miRNAs can effectively modulate host immune response thus helps in maintaining the survival of the pathogen within the host. The field of host gene regulation through miRNA has tremendous potential suggesting that they can be optimal candidate for the control of immune response [15]. Activation of the T cell-mediated immune response has been associated with changes in the expression of specific miRNAs. However, the role of miRNAs in the development of an effective immune response is just beginning to be explored. The identification of specific miRNA expression patterns during tuberculosis and their comprehensive understanding in disease pathogenesis can be used as molecular diagnostic markers and also in the development of effective therapeutic strategies against disease. Therefore, the present review discusses to identify the miRNAs in resistant Mycobacterium strains and tuberculosis and their potential use in the treatment of the disease.

Challenges

Since the first description of *M. tuberculosis* as the causative agent of human tuberculosis by Robert Koch on 1882, it continues to ravage mankind throughout the world till date. According to the WHO an estimated 1.7 million deaths occurred in 2009 due to TB. Failure to eliminate tuberculosis that is 100% preventable and 100% curable is man kind's worst ongoing blunder [16]. The key to successful elimination of TB is optimum treatment of cases. Erratic drug supplies and failure of patients to complete treatment lead to even more dangerous forms of TB i.e. drug-resistant disease. Multidrug-resistance (MDR-TB) is defined as resistance to the main first-line drugs isoniazid (H) and rifampicin (R). Extensive drug-resistance (XDR-TB) is defined as MDR-TB plus resistance to a fluoroquinolone and anyone of the second-line injectable drugs (capreomycin,

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amikacin or kanamycin).

Immune Response during Mycobacterium Infection

M. tuberculosis recognition by macrophages results in the induction of a large number of cytokines, some of which have been demonstrated to be essential for the proper control of TB. The host immunity to tuberculosis relies mainly on Th1 cytokines such as IL-12, IFN- γ and TNF-α [5-8] and patients with defective receptors for IFN-γ or IL-12 have markedly increased susceptibility to severe infection [9]. IFN-γ and TNF-α establish protective immunity in the host by promoting macrophage activation to produce nitric oxide synthase 2 (NOS_2), allowing infected macrophages to eliminate intracellular bacteria [4,10]. Recent study on Mycobacterium infected individuals showed that the proliferation of Th1 cells and the expression of IFN-γ and TNF-α was downregulated by certain microRNAs such as miRNA-144 and thus increasing the severity of the disease [11]. MicroRNAs are endogenous short RNAs (19-23 nucleotides) molecules involved in post-transcriptional gene repression via degradation or translational repression of their targeted mRNAs. When poorly regulated, miRNAs are critically involved in a range of human diseases [17,18] and potentially serve as good diagnostic markers [19], prognostic markers [20] or therapeutic targets [18]. Similar to miRNA, in bacteria small (50-250 nucleotide) non-coding RNA molecules (sRNAs) are reported [21]. They function by base pairing with the 5' ends of target genes to promote their degradation or repress their translation. Although the functions of many of them remain to be elucidated, an emerging view is that these sRNAs act as important players in regulatory cascades consisting of diverse physiological processes in bacteria [22]. Few studies in bacteria showed that these sRNA also regulate virulence genes. In *Staphylococcus aureus* sRNA known as RNAIII functions by base-pairing with several mRNA targets related to related to toxin and enzyme production [23,24]. In some bacteria, sRNAs regulate virulence genes. Similarly, in Salmonella the InvR and SgrS sRNA regulate the expression of major outer membrane protein and secretory proteins responsible for the disease [25]. In Streptococcus pyogenes the FasX and Pel sRNAs are encoded in loci associated with virulence [26]. Induction of sRNAs depends on stress or environmental conditions. It is quite possible that the emergence of drug resistance in M. *tuberculsosis* is in part due to sRNAs and further these sRNAs may impart the role in the generated host immune response during Mycobacterium infection.

The first indication that miRNAs might regulate the immune responses was a report in 2004 showing selective expression of miR-142a, miR-181a and miR-223 in immune cells [27]. Gene regulation by miRNAs has recently emerged to be critical for both development and proper function of the immune system. Thus, various miRNAs such as miR-155, miR-223, miR-146, miR-150, miR-181a or the miR-17~92 cluster have been implicated in hematopoietic lineage decisions or in controlling different developmental checkpoints [28] and have a liberal role in the maturation, proliferation and differentiation of myeloid and lymphoid cells. Another study has reported that miR-29 participated in the regulation of NK cell function and Th1 responses to intracellular pathogens by directly targeting IFN-γ mRNA, which indicates a previously unknown mechanism for post-transcriptional regulation of IFN-γ production and IFN-γ-mediated immune responses Ma et al.

Scope of the Future Research

sRNA identified in drug resistant and susceptible strains of *M. tuberculosis* can be used as therapeutic target using anti-sRNA strategies. Anti-sRNA strategy can be further developed to replace antibiotic therapy. This also helps us to cope up with the problem of emerging drug resistance strains in Mycobacterium. Similarly, miRNAs which will be upregulated in the host against Mycobacterium infection can be also targeted as therapeutic agent. Understanding miRNA targets that orchestrate T-cell immune response during the infection also will allow us to understand immune homeostasis and also to identify targets for development of gene therapy. It helps us in the identification of sRNA and/or miRNA that leads to the disease development through regulation of specific genes and facilitate our understanding of the mechanism of Mycobacterium-host cell interaction.

Conclusions

Despite all this accumulating knowledge about host immunity against *M. tuberculosis* infection, a person is dying every 20 seconds of TB. It limits our understanding for this devastating disease. Therefore, better innovative treatment options will be only possible if we get to know more about the basic biology of this devastating disease. miRNAs research now seems a emerging field in the area of basic and translational research, and represents an innovative therapeutic options. According to primary evidences, the future research on identification and regulation of miRNAs-mediated immune response in Mycobacterial infection may be of exquisite importance of novel biomarkers and therapeutic agents that may open up a new area in both miRNA and *M. tuberculosis* research, and may determine the therapeutic strategies for the treatment of the disease.

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