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REVIEW ARTICLE

Role of miRNAs in Immune Regulation And Bacterial Infections

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ABSTRACT

Micro RNAs (miRNAs) are small noncoding RNAs that regulate gene expression at the post-transcriptional level. The miRNA in the RNA-induced silencing complex acts as a guide strand and binds the target mRNA. Subsequently, the gene is silenced either by cleaving the target mRNA or repressing the translation. Since the discovery of the first miRNA three decades ago, more than 2000 human miRNAs have been discovered. It is known to regulate hundreds of genes in various physiological and pathophysiological processes, including the development and function of immunologically essential cells. miR-155 plays a vital role in the function of T helper 1, 17, and T regulatory cells. miR-24 positively regulates the function of T helper 1, 17, and T regulatory cells, whereas miR-23 and 27 have a negative regulatory effect. miR-223 regulates the differentiation of neutrophils and monocytes. The role of miRNAs in bacterial infections came to light in 2006 after discovering miR-163 as a negative regulator of defense response in *Arabidopsis thaliana* infected with *Pseudomonas syringae*. During bacterial infection in the host, aberrant expression of several miRNAs was discovered. miR-155 was found to be the most commonly dysregulated miRNA in bacterial infections such as *Helicobacter pylori*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Chlamydia trachomatis*. Therefore, miRNAs can be utilized as a diagnostic and prognostic tool for bacterial infections. *J Microbiol Infect Dis 2022; 12(4):1-7.*

Keywords: *Bacterial infections, microRNA, miRNA, monocyte, neutrophil, T-cell*

INTRODUCTION

MicroRNAs (miRNAs) are approximately 22 nucleotides (nt) long noncoding (nc) RNAs encoded endogenously in eukaryotes, including plants and animals [1,2]. miRNA was discovered in the early 1990s. lin-4, a gene known to control the developmental timing in *Caenorhabditis elegans*, does not code for a protein; instead, codes for small RNAs were discovered in 1993. These small RNAs were found to be ~61 nt and ~22 nt in length. Later it was discovered that ~61 nt RNA is a precursor of ~22 nt RNA [3]. miRNAs are widely distributed in mammalian cells and are known to regulate several thousand genes. After the discovery of miRNA, extensive research on miRNA biology in the following years revealed that over 2000 unique human miRNAs regulate the expression of hundreds of genes associated with various physiological processes [4]. The other members of ncRNAs in gene regulation include piwi interacting RNAs and long ncRNAs. miRNA is sequentially generated from stem-loop RNA with several proteins such as Drosha, DGCR8, and Dicer [5–7]. The mature miRNA is loaded into the RNA-induced silencing complex (RISC) to execute the gene silencing post-transcriptionally [8]. Although several ncRNAs are implicated in disease, miRNAs have received the most attention and have been studied thoroughly. Dysregulation of miRNAs has an extensive impact on physiological functions and consequently plays a role in some metabolic disorders. Recent research has shown that miRNAs play a pivotal role in immune cell growth, differentiation, and function. Moreover, several miRNAs are dysregulated in the host during bacterial infection. This review focuses on the role of different miRNAs in immune regulation and dysregulation of miRNAs in bacterial infections such as *Helicobacter pylori*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Pseudomonas*

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aeruginosa, *Escherichia coli*, and *Chlamydia trachomatis*.

miRNA machinery

miRNA biogenesis is a multi-step process in the nucleus and the cytoplasm. miRNA genes are found in both introns and exons. In humans, nearly 25% of miRNA genes are located in the introns, which indicates that they are unlikely to possess their promoters and are processed from the introns [9]. Some miRNA genes are located between two genes that encode protein and have a different direction of transcription to neighboring protein-coding genes. lin-4 and let-7 genes in C. elegans are transcribed as independent units [10]. RNA polymerase II transcribes the miRNA genes resulting in primary miRNA (pri-miRNA) and contains one or more stem-loops. In the nucleus, the proteins responsible for processing the pri-miRNA are Drosha and its essential cofactor protein called DiGeorge syndrome critical region 8 (DGCR8). A complex composed of Drosha and DGCR8 together is called a microprocessor complex. The microprocessor complex cleaves the pri-miRNA into 70 nt long precursor miRNA (pre-miRNA) with a 3' 2 nt overhang [7]. Expotin-5 is involved in the transport of pre-miRNA generated in the nucleus. It is dependent on Ran-GTP for energy sources. It binds pre-miRNAs specifically but in a sequence-dependent manner [11]. After the export of pre-miRNA from the nucleus into the cytoplasm, 2-nt overhangs at the 3' end of pre-miRNA are recognized by the Piwi, Argonaute, and Zwille/Pinhead (PAZ) domain of Dicer and dices the pre-miRNA to generate 21-25 nt long miRNAs [12]. The mature miRNA is loaded into RISC, after which the passenger strand cleaves, leaving the guide strand bound to the RISC. The core and essential component of the RISC is the Argonaute protein. The nucleoprotein complex with the guide miRNA strand seeks and recognizes the target mRNA resulting in mRNA cleavage or repression of protein translation (Figure 1). The destiny of the mRNA to be cleaved or protein translation repression depends on the perfect sequence or partial sequence complementarity, respectively, between miRNA:mRNA interaction [13].

microRNAs in immune regulation

Innate and adaptive immunity plays a fundamental role in combating infections. miRNAs that exert important roles in the human immune system have been discovered. These miRNAs are called immuno-miRs, which regulate both innate and adaptive immunity. Along with other miRNAs, immune miRs are dysregulated in various inflammatory diseases and infections. Repression of T helper cell (Th) 2 immunity by interleukin (IL)-4 cytokine signaling impairment is mediated by miR-23~27~24 clusters [14,15]. miR-24 promotes Th1, Th17 and T regulatory cell (Treg) differentiation, whereas miR-23 and miR-27 restricts the differentiation of Treg/Th17 and function of Th1 cells [14,16] (Figure 2). miR-23~27~24 clusters are known to suppress the T cytotoxic cell effector function by targeting the interferon (IFN)-γ [17]. miR-146a negatively regulates tumor necrosis factor (TNF) α, IL-6 immune pathways, and Th1 cell differentiation [18,19]. miR-155 is known to regulate the functions of both Th1, Th17 and T cytotoxic cell [20,21]. The miR-17~92 cluster, though known to regulate the different subsets of T-cells, additionally plays a crucial role in B-cell development and the negative regulation of macrophage differentiation [22] (Figure 2). miR-223 is known to regulate the differentiation of neutrophils and monocytes/macrophages. Down-regulation of miR-223 levels downregulates the differentiation of monocytes/macrophages, whereas the increased levels of miR-223 upregulate the granulocytes differentiation, specifically the neutrophils [23]. miR-181a plays a crucial role in T cell receptor activation and signaling strength (TCR) [24].

microRNAs in bacterial infections

The first ever evidence of miRNA in bacterial infection became evident from the studies of Lionel Navarro et al., 2006. They showed that miR-163 is a negative regulator of defense response in *Arabidopsis thaliana* infected with *Pseudomonas syringae*. In miR-163 mutants, enhanced resistance against *Pseudomonas syringae* was observed, whereas the results were vice versa with miR163 overexpression [25]. Several studies revealed miRNAs' contribution to defending the bacterial infections encountered by the host.

Helicobacter pylori are the etiological agent for peptic ulcer disease and gastric carcinoma globally. An altered expression of miRNAs, including let-7, miR-30b, miR-210, miR-152/miR-200b, and most importantly, miR-155, was noted with *H. pylori* infection in gastric

epithelial cells [26]. Specifically, an increase in miRNA-146a and miRNA-155 levels were noticed in gastritis but not in gastric cancer. However, these miRNAs were incapable of eliminating *H. pylori*. TNF-α expression was found to be increased in gastritis and decreased in gastric cancer [27]. Since miR-155 is known to regulate the Th1 and Th17 functions, downregulation of miR-155 in *H. pylori* infection failed to control the infection due to alteration of Th response [28] (Figure 2). Other miRNAs, such as miR-20334, miR-20435, miR-37536, and miR-27b37, were dysregulated in *H. pylori* and associated with oncogenesis [26]. *H. pylori* restricts human leukocyte antigen (HLA)-II expression in macrophages by upregulating the expression of let-7f-5p, let-7i-5p, miR-146b-5p, and miR-185-5p miRNAs. These miRNAs down-regulate the expression of the class II major histocompatibility complex transactivator that controls the expression of HLA class II genes. Upregulation of let-7i-5p, miR-146b-5p, and miR-185-5p in gastritis and gastric cancer helps the persistence of *H. pylori* infection [29].

Staphylococcus aureus is commonly associated with pyogenic infections, endocarditis, bacteremia, and pneumonia. An independent study showed that in *S. aureus* infection, elevated levels of miR-15, miR-24, miR-128, miR-223, miR-142, and miR-155 were detected. In neutrophils with knocked out miR-142 gene, the chemotactic and phagocytic activity was impaired due to disruption of GTPase levels and activity. With low levels of miR-142, skin healing is impaired when challenged with *S. aureus*. Therefore, miR-142 protects against *S. aureus* skin infections [30]. In *S. aureus* pneumonia, the underexpression of miR-155 in the lungs increased the expression levels of IL-17 in whole lung tissues and IL-23 in macrophages, thereby increasing the clearance of the bacteria. Chitinase-3-like1 (CHI3L1) gene is a target of miR-24 and inhibits CHI3L1 mRNA expression. CHI3L1 molecules may have antibacterial roles. In *S. aureus* infection, miR-24 overexpression downregulated the expression of CHI3L1, which favors the bacteria's survival [31].

Listeria monocytogenes is an intracellular bacteria that causes listeriosis in immunocompromised individuals and pregnant women. In neonates, it causes early-onset and late-onset meningitis. Although several miRNAs are altered, some miRNAs, such as miR-146a, miR-155, miR-125a-3p/5p, and miR-149, are severely dysregulated [32]. miR-155 is required to mount a proper cytotoxic T-cell response, which is pivotal in killing intracellular pathogens. Therefore, the alteration of miR-155 expression hampers the cytotoxic T-cell response to *Listeria monocytogenes* infection (Figure 2).

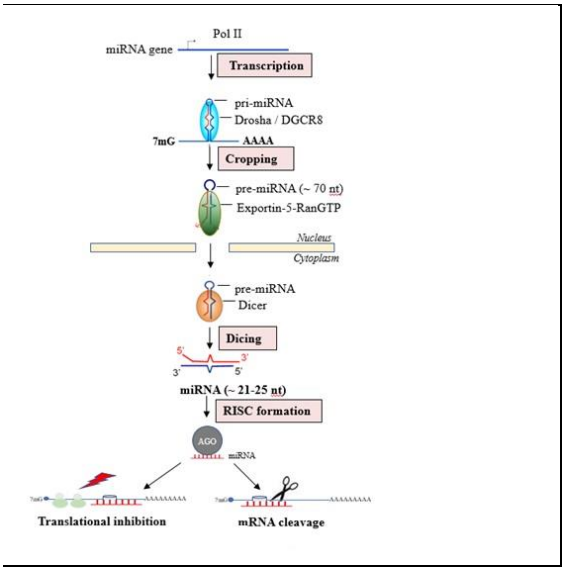

Figure 1. Biogenesis of miRNA.

Mycobacterium tuberculosis causes tuberculosis disease. In developing countries, TB causes significant morbidity and mortality. Under expression of miR-223 it increased the susceptibility to M. tuberculosis infection. miR-223 recruits the neutrophils through chemokine ligand 3, chemoattractant chemokine ligand 2, and IL-6 to control the infection [33]. miR-29 binds to the IFN-γ mRNA and reduces the IFN-γ production. Therefore, the expression levels of miR-29 during M. tuberculosis infection determine the susceptibility or resistance to the bacteria. Overexpression of miR-29 shifts the latent TB to become active TB [34]. miR-125b directly targets the mRNA of TNF-α and reduces its expression. A study reported high levels of miR-155 and lower levels of miR-125 in M. tuberculosis infection [35]. miR-155 upregulation might determine the M. tuberculosis infection by inducing autophagy through the inhibition of Ras homolog enriched in brain (Rheb) negative regulator and mammalian target of rapamycin (mTOR) signaling pathway [36]. In macrophages with M. tuberculosis infection, upregulation of miR-155 favors its survival as the miRNA inhibits IL-6, which plays a vital role in resisting the TB bacteria [35]. Various studies have shown

different results regarding the expression of miR-144 in M. tuberculosis infection. One study showed that miR-144 is overexpressed during M. tuberculosis infection, whereas the others showed no difference in expression or underexpression [37]. miR-144 plays essential roles by inhibiting TNF-α and IFN-γ. In mycobacterial infections, miR-146a was found to be overexpressed in macrophages. miR-146a acts to reduce the cytokines TNF-α, IL-1b, IL-6, and chemokine monocyte chemoattractant protein-1 (MCP-1) by affecting the Toll-like receptors / nuclear factor kappa-light-chain-enhancer of activated B cells (TLR / NF-kB) pathways [38]. miR-33 is induced to overexpress in mycobacterial infection. This miRNA inhibits the autophagy response by regulating the transcription of genes associated with autophagy, aiding the intracellular survival of bacteria [39]. In addition, miR30a, a negative regulator of autophagy, was found to be overexpressed in the macrophages of mycobacterial infection.

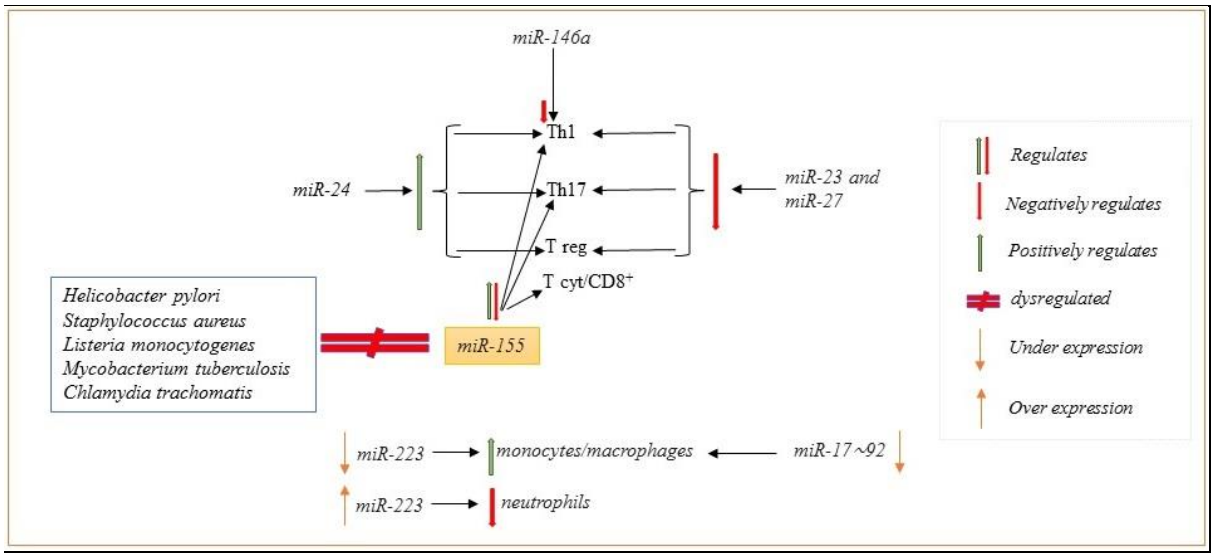

Figure 2. miRNAs in immune regulation and bacterial infections.

Pseudomonas aeruginosa is an opportunistic bacteria that is associated with nosocomial infection. The miR-302 family and miR-301b are activated by TLR2 and TLR4/MyD88/NF-κB pathway during *P. aeruginosa* infection. miR-301b is under-expressed during *P. aeruginosa* infection eventually increases the neutrophil filtration and thus augments the inflammation [40]. Let-7 family miRNAs are well known to play important roles in developmental regulation, pluripotency, aging, and metabolism. Let-7 family miRNAs control pseudomonas infection through an innate immune response. During *P. aeruginosa* infection, the let-7 family miRNAs are under-expressed through p38 mitogen-activated protein kinases (MAPK) signals, thus hindering the host's ability to clear the bacteria [41]. In cystic fibrosis patients, the bronchial epithelial cells, after infection with *P. aeruginosa* bacteria, showed reduced levels of miR-93 and elevated levels of IL-8 [42]. Elevated IL-8 is associated with neutrophil infiltration and non-resolving inflammation.

Escherichia coli causes community-acquired urinary tract infections, traveler's diarrhea, and neonatal meningitis. It also causes nosocomial sepsis. miR-15a/16 regulates the phagocytosis and production of reactive oxygen species. Experimental under-expression of miR-15a/16 reduces the mortality rate of *E. coli* associated with sepsis [43]. In *E. coli* sepsis, the bacteria reduces the expression of miR-15a/16 to escape the innate immune mechanism of macrophages. In Crohn's disease patients, adherent-invasive *E. coli* (AIEC) abnormally colonizes the intestinal mucosa. The levels of miR-30c and miR-130a increased during the multiplication of bacteria. The overexpressed miR-30c and miR-130a inhibited the autophagy response by inhibiting autophagy-related (ATG) 5 and ATG16L1 expression, thus favoring the AIEC replication intracellularly. Additionally, the

intestinal epithelial cells secrete exosomes, transfer the miRNAs to the recipient cells, and inhibit the autophagy response to favor the intracellular multiplication of the AIEC [44].

In neonatal sepsis patients, irrelevant of the causative agent, overexpression of miRNA-15b, and under-expression of miRNA-378a were observed in serum [45]. However, the specific roles of these miRNAs in sepsis still need to be understood. A study by Alma Fatima et al. 2020 showed that in neonatal sepsis, miR23b levels gradually increase in early and late sepsis. Furthermore, the miR23b expression was significantly lowered in neonates who died of sepsis and was consistently high in the survivors, thus confirming its protective role in sepsis. Therefore, miR23b is protective in sepsis and might help diagnose and prognosis as a molecular marker for neonatal sepsis [46].

Chlamydia trachomatis causes trachoma and sexually transmitted infections, including lymphogranuloma venereum. Several miRNAs are aberrantly expressed in trachoma. The two miRNAs that showed remarkable changes in the levels are miR-155 and miR-184. miR-155 was upregulated, and miR-184 was downregulated in trachoma. miR-155 regulates T-cell functions, whereas miR-184 plays an important role in corneal wound healing. These changes in the miRNA levels aid the host immune system in defending against the *Chlamydia trachomatis* infection and healing corneal epithelial wounds [47].

Intracellular bacteria such as *Listeria*, *Rickettsia*, and *Shigella* polymerize actins on their surface to power their motility, called actin-based motility. miRNAs such as miR-3668, miR-4732-5p, and miR-6073 control the Shigella infection by specifically impairing the bacterial actin-based motility by down-regulating the Neural Wiskott-Aldrich syndrome protein (N-WASP). In addition, it was identified that let-7i-3p miRNA specifically inhibits Salmonella infection by targeting the host regulator of G protein signaling 2 (RGS2) protein and modulating the endolysosomal trafficking and the vacuolar environment [48].

Conclusion

miRNAs have crucial roles in immune regulation and bacterial infections. miR-155 plays an important role in T-cell functions and is the most usually dysregulated miRNA in many bacterial infections. miRNAs can be considered biomarkers for the diagnosis and prognosis of bacterial infections.

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