Published in final edited form as:

Int Rev Immunol. 2017 September 03; 36(5): 287–299. doi:10.1080/08830185.2017.1347649.

MicroRNA Mediated Regulation of Immunity against Gram-Negative Bacteria

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Abstract

Evidence over the last couple decades has comprehensively established that short, highly conserved, non-coding RNA species called microRNA (miRNA) exhibit the ability to regulate expression and function of host genes at the messenger RNA (mRNA) level. MicroRNAs play key regulatory roles in immune cell development, differentiation, and protective function. Intrinsic host immune response to invading pathogens rely on intricate orchestrated events in the development of innate and adaptive arms of immunity.

We discuss the involvement of miRNAs in regulating these processes against gram negative pathogens in this review.

Keywords

bacteria; gram negative; microRNAs; host immunity

INTRODUCTION

MicroRNA

Historically, Lin-4 was the first miRNA to be discovered and in *Caenorhabditis elegans* attributed to control of larval development [1]. Interestingly, this small RNA had the ability to regulate another mRNA (*lin-14*) and reduce the amount of lin-14 protein [2]. Discovery of lin-4 demonstrated a unique pairing with the 3' untranslated region (3'UTR) of the gene and repressing lin-14 translation during larval stage cell division [1, 2]. Following lin-4, multiple such mRNA regulators have been found conserved across multiple organisms [3]. These small RNA single stranded ~22 nucleotide species were named microRNA (miRNA) [4]. Additionally, post-transcriptional regulation by miRNA was soon discovered on 5'UTR and

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DISCLOSURE

The authors declare that they have no competing interests.

coding sequences of target genes [5–7]. MiRNA binds target transcripts, which lead to either degradation or enhancement of mRNA allowing for additional control to environmental conditions [8–10].

The biogenesis of miRNA is a highly regulated process, miRNA are transcribed by RNA polymerase II into a long primary RNA (pri-miRNA) (Figure 1). These pri-miRNA can be longer than 1kb and contain a stem-loop structure [11]. Nuclear cleavage follows transcription of pri-miR, cleaving the stem-loop structure one helical turn (approximately 11 bp away from the basal junction, and 22 bps from the apical junction) into the stem leaving approximately 60 nucleotides [12]. Cleavage of the pri-miR is achieved by RNase III endonucleases Drosha along with RNA binding protein DGCR8 collectively called the Microprocessor complex [13–15]. Microprocessor cleavage leaves a staggered end 5' phosphate and a small 2 nucleotide 3' overhang called pre-miRNA. The pre-miRNA is exported out of the nucleus by the protein Exportin5 (EXP5) binding RAN-GTP and the pre-miRNA trans-locates outside of the nucleus. Once GTP is hydrolyzed it releases the pre-miRNA into the cytoplasm [11, 16].

In the cytoplasm, another RNase III type enzyme (Dicer) binds the 5' end of the pre-miRNA and cleaves the double stranded RNA approximately two helical turns from the base of the hairpin [17]. After cleavage of the pre-miRNA by Dicer, the ~22 nucleotides double-stranded miRNA is identified by Argonaute (AGO2) protein and one strand is preferentially loaded into a microRNA-induced silencing complex (miRISC) [16, 18]. MiRISC targets conserved Watson-Crick pairing at the 5' end of the miRNA centered on nucleotides 2-7 called the seed sequence and either blocks translation or increases mRNA degradation [4, 19, 20].

Disruption of Dicer1 in mouse embryonic stem (ES) cell lines display defects in differentiation showing the role of miRNA in development [21]. Complete loss of Dicer1 leads to early embryonic lethality which required researchers to develop conditional deletion of Dicer in order to further evaluate its role in immune signaling pathways [22]. Conditional deletion of Dicer in T cells impaired development and disrupts normal cytokine production [23]. These previous studies were key components of the miRNA biogenesis pathway and have implicated miRNA as an important regulator of immune response to gram-negative pathogens [23]. The ability of miRNA to coordinate precise protein expression in response to differentiation, apoptosis, inflammation and cell proliferation following stimulation has demonstrated their critical role in the immune system [10, 24, 25].

Innate Immunity

The immune system can be broadly characterized into two general components, the innate and adaptive immune systems. The innate immune system relies on dendritic cells, macrophages, monocytes, neutrophils, and NK cells. Both neutrophils and macrophages respond to microbial infection while other granulocytes such as basophils, mast cells, and eosinophils respond to parasites. More specifically, in response to the local environmental conditionals, macrophages are activated differently to respond to invading pathogens. Classically activated macrophages (M1) following microbial infection and alternatively activated macrophages (M2) to fungi and parasites further demonstrate the ability of the

immune system to fine-tune a correct immune response to invading pathogens [26]. While this classification of macrophages does not exhibit the full spectrum of activated macrophages and can be thought of as oversimplification it shows how environmental conditions mediate pathogen resistance through differential activation. It has been shown that both monocytes and macrophages induce epigenetic changes, which leads to enhanced cytokine production and changes in cellular activation [27, 28]. Innate immunity is thought to be a nonspecific response to pathogens but has recently shown a great deal of specificity through epigenetic reprogramming [29]. These observations led to the hypothesis that certain infections or vaccines are able to induce reprogramming of the innate immune response, leading to nonspecific protection [30]. Different cell lineages with distinct chromatin signatures and transcriptional regulation help regulate innate cell function. Therefore, how cell lineage and the specific signaling pathways trigger activation in response to a particular pathogen needs to be considered [31].

Recognition of Lipopolysaccharide (LPS), an essential part of the outer membrane surface of most gram-negative bacterium, is a key detection target by host immune cells [32–34]. Modifications of its lipid-A portion of LPS allows gram-negative bacterium to evade host immune identification, enabling bacterium to survive in specific niches inside the host [35]. Host mucosal environment contains a high abundance of gram-negative commensal bacteria and it is essential that the host establish tolerance to these commensal bacterium [36]. Conserved targets, known as a pathogen-associated molecular pattern (PAMPs), are recognized by pattern-recognition receptors (PRR), which aid in further identification of gram-negative pathogens [37, 38]. Generalized recognition is the underlying premise for the innate immune system to be the first/ primary line of defense against invading organisms. Signaling through Toll-like receptors (TLRs), antigen presenting cells (APCs) elicit cytokine production among other early warning systems [39]. The TLR families are trans-membrane proteins that respond differently to surface markers on gram-negative bacteria [40]. Given that cytoplasmic domain of TLR proteins are homologous to IL-1R, these regions are referred to as Toll/IL-1R (TIR) domain. TLRs recruit adaptor molecule(s) containing TIR domain to its cytoplasmic TIR domain. One such adaptor, myeloid differentiation factor 88 (MyD88), associates with IL-1R-associated kinases (IRAKs) to mediate signaling to TNF-receptor-associated factor 6 (TRAF6), and stimulates IKKs and MAPKs. Ultimately, TLR signaling leads to activation of transcription factors such as NF- κ B and AP-1, increasing clearance of a specific pathogen (Figure 2a) [37].

TLR4 recognizes LPS and signals through MyD88 and TRIF pathway to downstream TRAF6 [38]. Multiple miRNA have been implicated in regulating TLR4 signaling following LPS stimulation (Figure 2b). Relative miRNA expression in chronic obstructive pulmonary disease (COPD) patients showed increased levels of miR-203 [41]. Bronchial epithelial cells from COPD patients stimulated with LPS have increased miR-203 and decreased Tak1 expression [41]. Immune suppression of Tak1 by miR-203 reduces NF- κ B activity and may contribute to increased susceptibility to bacterial infection [41]. Treatment of A549 cells with LPS enhanced miR-381 in a dose dependent manner and identified I κ B α as one of its targets [42]. Expression of miR-322 was suppressed in LPS treated macrophages, and regulated NF- κ B p50s ability to fine-tune inflammatory responses following stimulation [43]. LPS-induced acute lung injury in vivo and in LPS-treated mouse cells in vitro

demonstrated regulation of VEGFA by miR-126-5p [44]. Overexpression of miR-126-5p attenuated LPS-induced regulation of alveolar fluid clearance [44]. LPS-induced acute lung inflammation apoptosis is mechanistically controlled by miR-181a regulating anti-apoptotic gene BCL-2 [45]. Induction of miR-375 and miR-106b following LPS stimulation in *Helicobacter pylori* infection has been identified as putative regulators of JAK2/STAT3 pathway in gastric epithelial cells [46, 47].

TLR2 recognizes lipoproteins signaling by MyD88, similar to TLR4 MyD88 pathway signaling, and enables the translocation of NF- κ B to the nucleus which activates target immune response genes [35]. THP-1 macrophage-derived foam cells infected with *Chlamydia pneumoniae* suppress ABCA1 and ABCA1-dependent cholesterol efflux, which is mediated by TLR2- NF- κ B and miR-33 pathways [48]. MiR-146 expression following NF- κ B translocation negatively regulates bacterial activated TLRs and cytokine receptor signaling [49]. TRAF6 and IRAK1 are direct targets for miR-146, which up-regulate following NF- κ B activation [50]. Control of IRAK1 expression by miR-718 has also been identified [51]. The overlap of miR-718 with the 5' UTR of IRAK1 suggests a role for miR-718 in controlling TLR signaling through a negative feedback loop [51]. MiR-155 is known to be a key role player in immunity [52, 53] and has also been identified as a regulator of LPS/TLR stimulation [48, 54]. While miR-146a acts as a negative regulator, miR-155 establishes a pro-inflammatory condition through direct targeting TAB2, IKK ϵ , and NIK [55]. Indirect regulation of RelA (p65) by miR-7 through targeting IKK ϵ was observed in gastric cancer and shows feedback loops between miR-7 and NF- κ B signaling [56]. Endosome located TLR9 identifies oligonucleotides containing unmethylated cytosine-phosphate-guanine (CPG) dinucleotides, and induces expression of IFN- α through transcription factor IRF7 [57]. NF- κ B activation following TLR9 stimulation induces pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α), IL-1 β , and IL-6. TLR9 activation by CPG leads to up-regulation of miR-146 targeting *Notch1* and repression of IL-12p70 within dendritic cells [58].

Aside from TLRs, other PRR such as the cytosolic NOD-like receptor (NLRs), the cell-surface C-type lectin receptors (CLRs) show the diversity of PRRs. Nucleotide-binding oligomerization domain-containing protein 1 (NOD1), a member of the NOD-like receptor protein family, regulates miR-155 in macrophages following recognition of *H. pylori* T4SS translocation [59]. In the absence of miR-155, bone marrow derived macrophages are less resistant to DNA damage induced apoptosis [60]. *H. pylori* regulation of apoptosis through miR-155 targets *Trp53inp1*, *Bach1*, *Lpin1*, *Pmaip1*, and *Tspan14* allowing stabilization of macrophages in a hyper inflamed environment [59]. The variety of PRR ultimately delineate to a common intracellular signaling cascade involving NF- κ B, mitogen-activated protein kinases (MAPKs), or interferon-regulatory factors (IRFs) [61]. A highly virulent type A strain of *Francisella tularensis* strain (Schu S4) has the ability to subvert host immune detection by regulating specific immune response pathways [62]. Upon engulfment, Schu S4 can escape from the phagosome [63] and when compared to less virulent stain *F. tularensis novicida* (F.n.) the regulation of miR-155 was substantial [64]. Increased NF- κ B activity is seen in monocytes and macrophages following infection with the less virulent strain compared with Sshu S4[65]. SH-2 containing inositol 5' polyphosphatase 1 (SHIP1), a negative regulator of PI3K/Akt pathway was down regulated following F.n. infection but did

not change significantly following Sshu S4 [65]. MiR-155 is a direct target of SHIP1 and following miRNA regulation leads to increased activation of Akt [66]. Recruitment of neutrophils to lower genital tract following *Chlamydia trachomatis* genital infection in mice is mediated by intracellular adhesion molecule 1 (*ICAM1*) [67]. Recent evidence has shown that miR-214 mediates *ICAM1* and up regulates miR-214, which in turn decreases neutrophil recruitment leading to greater pathology in mice [67, 68]. In the absence of IL-17A, miR-214 was increased and *ICAM1* levels decreased with the subsequent abrogation of genital pathology in IL-17A^{-/-} mice. IL-17A has been linked to neutrophil recruitment, hyper inflammation, and tissue damage eluding to a potential role for miR-214 mediated control of *ICAM1* in neutrophils with the contribution of IL17A [67, 69, 70].

The innate immune system is very effective in recognizing PAMPs, but an uncontrolled immune response could lead to hyper inflammation or sepsis followed by multiple organ dysfunction and potentially death [57]. *Klebsiella pneumoniae* is one of the most prevalent gram-negative bacteria found in intensive care units [71]. A common cause of surgical sepsis, patients with peritonitis lack the ability to mount an effective immune response, which leads to a persistent infection, and an overactive immune response [72]. It is vital that the host counteracts hyper inflammation, and through the development of tolerance it's able to prevent endotoxin shock. Mice can be desensitized with a non-lethal amount of LPS prior to a lethal dose and leads to a reduction in LPS related immune response [73]. Following tolerance, monocytes increase their ability to phagocytose pathogens by up-regulation of CD64 while down regulating major histocompatibility complex class II (MHCII) gene *CIITA* [73]. Early expression of miR-132 with LPS-pretreatment down-regulated IL-1 β [72]. A confirmed target of miR-21, PDCD4 shows lower mortality rates by LPS and lower IL-6 while increasing IL-10 production [72]. Selective and transient silencing of inflammatory genes at the level of chromatin plays a critical role in LPS tolerant macrophages [74]. During *H. pylori* infections of ASG cell lines, decreased miR-218 expression elevates ECOP inducing NF- κ B activation [75]. TLR4 signaling can be reduced by direct targeting of IKK ϵ or MyD88 by miR-155, and allows a decrease in rapid response to pathogens without inducing hyper inflammation. *Salmonella* sp. infection prevents septic shock and apoptosis through macrophage mediation of let-7 [76]. A common regulator in gram-negative immune response, let-7 decreases following TLR-4 signaling by LPS and correlates to an increase in IL-6, IL-8, and IL-10 [76, 77]. Multiple binding sites on IL-10 by let-7 suggest an important role for let-7 mediation of IL-10 [76].

Macrophages deficient in miR-146 show higher levels of phagocytic activity and reduced levels of bacteria burden [78]. IL-10 or TGF- β up-regulation suppress MHC Class II presentation albeit through different pathways and reduces pro-inflammatory immune responses. IL-10 down regulates miR-155 while up-regulating miR-146 further eluding to the fact that miR-146 is an anti-inflammatory gene while miR-155 favors a pro-inflammatory phenotype. Inhibition of miR-21 reduced severe steroid-insensitive allergic airway disease induced by gram-negative bacteria through regulation of PTEN, PI3K, and HDAC2 potentially identifying a novel treatment for asthma [79]. During wound healing (efferocytosis), engulfment of apoptotic cells by macrophages induces an anti-inflammatory condition by up-regulating both miRNA and interleukins. IL-10 up regulation and PTEN down-regulation is seen following efferocytosis and has been identified as targets for miR-21

[80]. PTEN repression and enhanced PI3K/Akt signaling by miR-718 in macrophages infection with LPS demonstrates multiple miRNA involvement in PTEN regulation [51]. Furthermore, Anti-miR-718 macrophages exhibited control over *N. gonorrhoeae* replication by reducing the number of bacteria recovered compared to miR-718 macrophages [51]. Silencing of key tight junction proteins Zona occludens-1,2 (ZO-1, ZO-2) by both miR-106b and miR-146a has been shown to lead to compromised wound closure following infiltration by *Acinetobacter sp.* [81].

Adaptive Immunity

The recognition of conserved regions by the innate immune system allows for a rapid response to pathogens and their antigens. The ensuing adaptive immune response provides a more robust and antigen specific immune defense against invading pathogens. Immune effector cells called antigen presenting cells (APC) such as dendritic cells or macrophages present antigens to the adaptive immune arm of lymphocytes via MHC on the APC along with other co-stimulating signals [82]. Antigen recognition by T cells through T Cell Receptors (TCR) or B cells through B Cell Receptors (BCR) allow antigens to be recognized by the adaptive immune system. Hematopoiesis in the bone marrow and later in respective organs; thymus for T cells and spleen by B cells on surface receptors are generated [83]. Following MHC Class I binding by TCRs a commitment to Cytotoxic CD8⁺ T cell (CD8⁺) lineage is established. Conversely, when TCR binds to MHC Class II it promotes T cell differentiation into T regulatory, Th₁, Th₂, Th₉, or Th₁₇ lineages [84–86]. The identification of self and non-self is an important step that leads to accurate pathogen identification while reducing the amount of damage to the host [82, 83]. During development in the thymus, T cells that recognize self-proteins are destroyed and a similar mechanism is put into place in the periphery to eliminate mature T cells that develop a propensity toward self. Importantly, immune response to pathogens by miRNA ultimately leads to fate-determining steps within T cells (Figure 3). Following activation, T cells produce IL-2 through the binding of IL-2/IL-2R cascade. Conditional deletion of Dicer in CD4⁺ cells disrupts the ability of mTOR to discriminate between activation and anergy, allowing CD4⁺ cells to escape inactive states [87–89]. *H. pylori* regulation of SOX4 through decreased miR-204 expression aids in T cell differentiation [90]. Induced by TGF- β , SOX4 inhibits *GATA-3* function leading to a decrease in Th₂ differentiation [91–93]. MiR-155 deficient mice exhibit an inability to initiate an adaptive immune response to *S. typhimurium* or *H. pylori* through impaired Ag-specific Th₁ or Th₁₇ [94, 95]. T cell proliferation experiments with miR-155 showed little change in Th1 production of IFN- γ while elevated Th2 producing cytokines IL-4, IL-5, and IL-10 demonstrate an intrinsic bias toward Th2 differentiation [94]. A transactivator of IL-4 promoter, c-MAF was identified as a match for miR-155 further supporting increased Th2 cytokine production seen in knockdown mice [94]. Additionally, mice produced significantly reduced amounts of immunoglobulin M (IgM), indicative of impaired B cell response [94]. B cells that lack miR-155 fail to produce high affinity IgG₁ antibodies due to decreased regulation of miR-155 direct binding of PU.1 [96]. Th₁ mediated protection *via* miRs-182 and miR-183, expressed in the same operon [97], have been reported in genital tract infection with *C. trachomatis* intravaginally infected mice [98]. Importantly, IFN- γ secretion in infected mice was synergistically regulated by miR-155 and miR-182 [98]. Similar to this study, a report published simultaneously demonstrated a role for miR-182/

183 cluster in regulation in Th₁₇ lineage specific cells [99, 100]. Regulation of IFN- γ mRNA has also been shown to be controlled by miR-29, miR-29 downregulation in Th₁, Th₂, Th₁₇, CD8⁺, along with NK cells facilitated IFN- γ production [101].

CONCLUSION

Overall, accumulating evidence has demonstrated that miRNA play important roles in several host processes [102–105] including the innate and adaptive immune signaling network following bacterial infections [106–108]. It may however be misleading to consider individual cell pathways or populations as having a predominant effect during a gram-negative infection. Immune cell activation may be individually customized by single or cohorts of miRNAs in response to specific gram-negative pathogens [109–111]. Compromised immune systems from severe steroid-insensitive allergic airway disease [112], septic shock induced tolerance [76], or wound healing [80] has the potential to controlled miRNA regulation and restore the balance between key regulators of the immune system. Harnessing the intrinsic functionality of miRNA has led to the appreciation of the previously untapped therapeutic potential [113, 114] and resulted in patents [115–118], and advancements in various areas including cervical cancers [119, 120], tissue transplantation [121–123], and infections such as influenza [118, 124, 125], HCV [126, 127], HBV [128], Salmonella [129], *Mycobacterium sp.* [106, 130] and *Helicobacter sp.* [131]. The role of miRNA in vaccination has also been reported [113, 132, 133]. For example, co-involvement of miR-462/731 in IFN-mediated protection was conferred by TLR-3 agonist (poly I:C; polyinosinic: polycytidylic acid) in vaccinated fish challenged with viral hemorrhagic septicemia [134]. The immune augmenting capability of miRNA was demonstrated *in vivo* by overexpression of miR-155 in hepatotropic adeno-associated virus (AAV)-8 vectors thereby enhancing the protective capacity of genetically attenuated malarial parasites in mice prime-booster vaccination regime with a prime only regime [135]. Similarly, AAV-based miR-26a replacement therapy was used for a liver cancer mouse model [136], *in vivo* targeted delivery of a let7g-aptamer led to reduction in lung adenocarcinomas [137]. MiR-22 impaired the anti-tumor ability of dendritic cells by targeting p38 in a B16 melanoma murine model [138], while miR-182 reduced *in vivo* glioblastoma multiforme xenografts growth [139]. The exosome-associated miR-150 has been found as a sensor for vaccination against 2009 pandemic flu (H1N1) in cohorts of adults and children [140]. Importantly, the success of MRX-34 [141, 142], a liposome formulation of miR-34 mimic for hepatic carcinomas and miravirsen [126, 143], a locked nucleic acid (LNA)-anti-miR-122 alone or in combinatorial regimes with telaprevir and ribavirin controls HCV [144, 145] and has led to phase I / II trials showing promise in miR mediated therapy [113, 146, 147]. Additionally, miRNA-based RNA interference [148] or combination miRNA-based strategies, have been reported to control *influenza* [149] and non-small cell lung cancers [150], respectively. To this end, specific miRNA that may affect critical host functions and directly or indirectly contribute to antigen specific immunity hold further promise (Table 1) [50, 151–182]. Hence as our current understanding of miRNA in gram-negative pathogens continues to grow, the possibility that miRNA could be used as new therapeutics [183–185] to regulate dysfunctional immune networks would allow medical professionals additional approaches for identification and treatment for gram-negative bacteria.

ACKNOWLEDGEMENTS

This work was supported by National Institutes of Health Grant (1RO3AI11771401A1), Army Research Office, Department of Defense Contract No. W911NF-11-1-0136 to BPA and National Institute of Child Health and Human Development Grant (HD061580) to LKC.

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Figure 1. A generic model for post-transcriptional miRNA expression.

Full length pri-microRNA (pri-miRNA) containing a stem-loop structure initially transcribed by RNA polymerase II is cleaved by the microprocessor complex. Pre-miRNA transported out of the nucleus by Exportin 5 (Exp5) and identified by Dicer. Cleavage of pre-miRNA hairpin loop structure by Dicer leaves a mature double-stranded miRNA approximately 22 nucleotide in length. Argonaute (AGO2) preferentially loads one strand into microRNA-induced silencing complex (miRISC) which blocks translation or increases mRNA degradation.

Figure 2. Role of microRNA (miR) in regulating Toll-like receptor (TLR) signaling.
a. TLR signaling pathway. TLR families share similar signaling components, including MyD88, IRAK (IL-1R associated kinase), TRAF6 (TNF receptor-associated factor 6), and TAK1 (TGF- β -activated kinase). Activation leads to MAPK (mitogen-activated protein kinase) and nuclear factor- κ B (NF- κ B) translocation into the nucleus, targeting gene expression. **b.** Working model for miR mediated control of LPS-TLR4 signaling network.

Figure 3. CD4⁺ T cell differentiation mediated by microRNA.

MiRNA regulates lineage determination and differentiation by fine-tuning signal strength, duration, and cytokine expression following gram-negative bacterial infection.

Figure 4. Gram-negative host miRNA immune regulation working model.

Representation of miRNA regulation following commitment of cell lineage in response to gram-negative bacteria infection. Hematopoietic stem cells (HSC); common myeloid progenitor (CMP); and common lymphoid progenitor (CLP).

Table 1.**Regulation of MicroRNAs and Gram Negative Bacteria**

MicroRNA	Pathogen	Source
Let-7	<i>Salmonella</i>	Voinnet, O. [2011].
Let-7c	<i>Helicobacter</i>	Kiga, K., et al. [2014].
Mir-101	<i>Helicobacter</i>	Zhou, X., et al. [2015].
Mir-106a	<i>Klebsiella</i>	Kanaan, Z., et al. [2013].
MiR-106b	<i>Acinetobacter</i>	Roy, S., et al. [2014].
Mir-106b	<i>Helicobacter</i>	Ye, F., et al. [2015].
MiR-122	<i>Bordetella</i>	Qi, Y., et al. [2012].
Mir-125	<i>Chlamydia</i>	Gupta, R., et al. [2015].
Mir-132	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].
	<i>Treponema</i>	Nayar, G., et al. [2016].
Mir-137	<i>Helicobacter</i>	Steponaitiene, R., et al.[2016].
Mir-141	<i>Helicobacter</i>	Zhou, X., et al. [2014].
Mir-142-3p	<i>Klebsiella</i>	Kanaan, Z., et al. [2013].
Mir-142-5p	<i>Helicobacter</i>	Saito, Y., et al. [2012].
Mir-143	<i>Salmonella</i>	Yao, M., et al.[2016].
Mir-146	<i>Salmonella</i>	Vigorito, E., et al. [2007]., Schulte, L. N., et al. [2013]., Ordas, A., et al. [2013].
	<i>Acinetobacter</i>	Roy, S., et al.[2014].
	<i>Borrelia</i>	Lochhead, R. B., et al.[2014].
	<i>Campylobacter</i>	Kaakoush, N. O., et al.[2015].
	<i>Chlamydia</i>	Wang, W., et al. [2009], Derrick, T., et al.[2016].
	<i>Helicobacter</i>	Wu, K., et al.[2014]., Xiao, B., et al.[2012]., Hishida, A., et al. [2011]., Liu, Z., et al. [2010].
	<i>Klebsiella</i>	Barnett, R. E., et al.[2013]., Kanaan, Z., et al.[2013].
	<i>Neisseria</i>	Liu, M., et al.[2014].
	<i>Treponema</i>	Nayar, G., et al.[2016]., Nahid, M. A., et al.[2011].
Mir-147b	<i>Chlamydia</i>	Derrick, T., et al.[2013].
Mir-15	<i>Salmonella</i>	Maudet, C., et al.[2014].
Mir-155	<i>Borrelia</i>	Lochhead, R. B., et al.[2015].
	<i>Chlamydia</i>	Gupta, R., et al.[2016].
	<i>Helicobacter</i>	Cheng, S. F., et al. [2015]., Koch, M., et al.[2012]., Xiao, B., et al.[2009]., Tang, B., et al.[2010]., Wu, K., et al.[2016]., Lv, X., et al.[2014]., Lv, X., et al.[2014]., Fassi Fehri, L., et al.[2010].
	<i>Salmonella</i>	Vigorito, E., et al. [2007]., Schulte, L. N., et al.[2013]., Ordas, A., et al.[2013].

MicroRNA	Pathogen	Source
	<i>Treponema</i>	Nayar, G., et al.[2016].
	<i>Klebsiella</i>	Barnett, R. E., et al. [2013]., Kanaan, Z., et al.[2013].
Mir-17-5p	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
Mir-182	<i>Chlamydia</i>	Gupta, R., et al. [2016].
miR-182	<i>Pseudomonas</i>	Muraleedharan, C. K., et al.[2016].
Mir-183	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
	<i>Pseudomonas</i>	Muraleedharan, C. K., et al.[2016].
Mir-184	<i>Chlamydia</i>	Derrick, T., et al.[2016].
Mir-185	<i>Helicobacter</i>	Yoon, J. H., et al.[2013].
MiR-197	<i>Bordetella</i>	Qi, Y., et al.[2014]
Mir-200	<i>Helicobacter</i>	Huang, W. T., et al.[2014].
	<i>Klebsiella</i>	Kanaan, Z., et al.[2013].
Mir-203	<i>Helicobacter</i>	Zhou, X., et al.[2014].
	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].
Mir-204	<i>Helicobacter</i>	Craig, V. J., et al. [2011]., Zhou, X., et al.[2014].
Mir-20a	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
Mir-21	<i>Fusobacteria</i>	Nosho, K., et al.[2014].
	<i>Klebsiella</i>	Kanaan, Z., et al.[2013].
	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
	<i>Salmonella</i>	Voinnet, O. [2011].
Mir-210	<i>Helicobacter</i>	Kiga, K., et al. [2014].
Mir-214	<i>Chlamydia</i>	Arkatkar, T., et al. [2015].
Mir-218	<i>Helicobacter</i>	Gao, C., et al.[2010].
Mir-221	<i>Campylobacter</i>	Kaakoush, N. O., et al.[2015].
	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
	<i>Vibrio</i>	Yan, H., et al.[2016].
Mir-222	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
	<i>Vibrio</i>	Yan, H., et al.[2016].
Mr-233	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
Mr-26	<i>Salmonella</i>	Yao, M., et al.[2016].
Mr-2687	<i>Campylobacter</i>	Kaakoush, N. O., et al.[2015].
Mr-29	<i>Vibrio</i>	Peng, W., et al.[2016]., Ma, F., et al.[2011].

MicroRNA	Pathogen	Source
Mr-299	<i>Klebsiella</i>	Kanaan, Z., et al.[2013].
Mr-29b1	<i>Campylobacter</i>	Kaakoush, N. O., et al.[2015].
Mr-301a	<i>Klebsiella</i>	Barnett, R. E., et al.[2013].
Mr-307	<i>Helicobacter</i>	Feng, Y., et al.[2013].
Mr-30c	<i>Chlamydia</i>	Roy Chowdhury, S., et al.[2017].
Mr-31	<i>Fusobacteria</i>	Nosho, K., et al.[2014].
Mr-328	<i>Helicobacter</i>	Ishimoto, T., et al.[2015]., Kiga, K., et al.[2014].
Mr-33	<i>Chlamydia</i>	Zhao, G. J., et al. [2014].
Mr-34	<i>Helicobacter</i>	Suzuki, R., et al.[2014].
Mr-34a	<i>Helicobacter</i>	He, M., et al.[2014].
Mr-3648	<i>Campylobacter</i>	Kaakoush, N. O., et al.[2015].
Mr-375	<i>Chlamydia</i>	Derrick, T., et al.[2016].
	<i>Helicobacter</i>	Miao, L., et al. [2014]., Kiga, K., et al. [2014].
	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].
Mir-3916	<i>Campylobacter</i>	Kaakoush, N. O., et al. [2015].
Mir-411	<i>Helicobacter</i>	Kiga, K., et al. [2014].
Mir-4477b	<i>Campylobacter</i>	Kaakoush, N. O., et al. [2015].
Mir-451	<i>Salmonella</i>	Uribe, J. H., et al. [2016].
Mir-490	<i>Helicobacter</i>	Shen, J., et al. [2015].
Mir-6080	<i>Campylobacter</i>	Kaakoush, N. O., et al. [2015].
Mir-621	<i>Campylobacter</i>	Kaakoush, N. O., et al. [2015].
MiR-629	<i>Bordetella</i>	Qi, Y., et al. [2014]
Mir-652	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].
Mir-672	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].
Mir-7	<i>Helicobacter</i>	Zhao, X. D., et al. [2015].
Mir-7162	<i>Campylobacter</i>	Kaakoush, N. O., et al. [2015].
MiR-899	<i>Bordetella</i>	Qi, Y., et al. [2012].
miR-96	<i>Pseudomonas</i>	Muraleedharan, C. K., et al. [2016].
Mir-99	<i>Helicobacter</i>	Kiga, K., et al. [2014].
Mir-99b	<i>Klebsiella</i>	Barnett, R. E., et al. [2013].

MicroRNA	Pathogen	Source
Mir-718	<i>Neisseria</i>	Kalantari, P. et al. [2017]

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