MicroRNA Roles in the NF-κB Signaling Pathway during Viral Infections

Zeqian Gao, Yongxi Dou, Yixia Chen, and Yadong Zheng

1 State Key Laboratory of Veterinary Etiological Biology, Key Laboratory of Veterinary Parasitology of Gansu Province, Lanzhou Veterinary Research Institute, CAAS, Lanzhou, Gansu 730046, China
2 College of Life Science and Engineering, Northwest University for Nationalities, Lanzhou 730030, China

Correspondence should be addressed to Yongxi Dou; douyongxi@caas.cn and Yadong Zheng; zhengyadong@caas.cn

Received 31 December 2013; Accepted 8 March 2014; Published 2 April 2014

Academic Editor: Zhisheng Dang

Copyright © 2014 Zeqian Gao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

NF-κB signaling network is a crucial component of innate immunity. miRNAs are a subtype of small noncoding RNAs, involved in regulation of gene expression at the posttranscriptional level. Increasing evidence has emerged that miRNAs play an important role in regulation of NF-κB signaling pathway during viral infections. Both host and viral miRNAs are attributed to modulation of NF-κB activity, thus affecting viral infection and clearance. Understandings of the mechanisms of these miRNAs will open a direction for development of novel antiviruses.

1. Introduction

Innate immune system constitutes a first line of defense against inherent and environmental threats and therefore plays a vital role in the early recognition of invading organisms. The NF-κB signaling network, an ancient signaling pathway initially found in unicellular organisms, is a central regulator in innate immunity. Activation of NF-κB signaling cascade relies on germ line-encoded pattern recognition receptors (PRRs) to recognize pathogen derived substances—pathogen associated molecular patterns (PAMPs) [1]. The recognition subsequently triggers a series of proinflammatory responses that alter inflammatory cytokines profiles, thus regulating the host-virus interactions [2].

miRNAs (miRNAs) represent a subclass of small noncoding, regulatory, and single-stranded RNAs and mainly bind to the 3′ untranslated region of mRNAs to posttranscriptionally regulate gene expression. miRNAs were first discovered in Caenorhabditis elegans [3, 4] and then found to be present in many viruses, animals, and plants, such as Epstein-Barr virus, humans, and Arabidopsis [5–7]. However, the miRNA-mediated silencing pathway may be absent in yeast and some unicellular organisms [8, 9]. miRNAs are mediators of gene silencing via small RNA induced silencing complex (RISC) to induce translational repression or degradation of targeted mRNAs. miRNAs-mediated silencing machinery executes important regulatory functions in multiple cellular processes, including immune responses, cellular proliferation, differentiation, apoptosis, and oncogenic transformation [10–12]. Increasing evidences support the notion that miRNAs also play important roles in modulating NF-κB signaling pathway during viral infections [13–15].

2. Biogenesis of Animal miRNAs

In the canonical pathway, the transcription of miRNA genes is performed mostly by RNA polymerase II (Pol II) with a minor proportion of miRNAs that are associated with Alu repeats by RNA polymerase III (Pol III) (Figure 1) [16, 17]. The long primary transcripts (pri-miRNAs) process a 5′ cap and 3′ polyA tail and form the stem-loop structure which contains a mature miRNA as a part of the double stranded stem connected by a terminal loop [18]. Then, pri-miRNAs are recognized and spliced by Drosha and its cofactor, DiGeorge syndrome critical region gene 8 (DGCR8) in human or Pasha in Drosophila and C. elegans [16, 19–21]. The cleavage generates a hairpin-structured precursor of miRNAs (pre-miRNAs) with a size of approximately 70
Figure 1: Biogenesis of canonical and mirtron miRNAs in animal cells. In canonical pathway, miRNA genes are transcribed by RNA polymerase II (Pol II) or RNA polymerase III (Pol III) to produce the primary miRNA (pri-miRNA) transcripts. The cropping of pri-miRNAs is mediated by the Drosha-DGCR8 complex (viz. microprocessor) that generates 60–70 nt precursor miRNAs (pre-miRNAs). After being exported by exportin-5 from the nucleus, pre-miRNAs are processed into ~22 nt miRNA/miRNA* duplexes by Dicer-TRBP complex. Finally, mature miRNAs are loaded onto Argonaute proteins, leading to cleavage or degradation of the targeted genes. In the mirtron pathway, the miRNA-containing introns, termed as mirtrons, are spliced and debranched into pre-miRNAs that bypass Drosha processing. Afterwards, the intron-derived pre-miRNAs access the canonical miRNA pathway during nuclear export and then are spliced by Dicer and loaded onto Argonaute proteins.

nucleotides. With the help of a nuclear transport receptor (exportin-5) and Ran-GTP, pre-miRNAs are transported from nucleus to cytoplasm [22, 23]. In the cytoplasm, pre-miRNAs are recognized by Dicer, which works in cooperation with human immunodeficiency virus (HIV-1) transactivating response (TAR) RNA binding protein (TRBP or Loquacious in Drosophila) to cleave pre-miRNAs into miRNA duplexes [24–28]. Together with Argonaute and other proteins, a miRNA duplex is then loaded to generate RISC [29–31]. The mature miRNA retains, whereas the accompany passenger
stand, named miRNA*, is degraded in most cases. Recently, studies have revealed that miRNAs* are also present at a relative level and have the ability to targets [32]. Once loaded into the miRNAs-containing RISC, miRNAs serve as a guide to target mRNAs through imperfect sequences complementarities with sites located in the 5′ UTR [33, 34], coding regions [35, 36], or 3′-UTR [37], leading to mRNA cleavage or translational repression [38].

In addition to canonical miRNAs, approximately 40% of animal miRNAs, termed as mirtrons, are derived from introns of protein-coding genes [18, 39]. Compared to the canonical pathway, the mirtron production is Drosha-independent to generate pre-miRNAs. The short intron-derived pri-miRNAs are spliced by Spliceosome [40]. The initial splicing products are not linear but are instead of a lariat in which the 3′ branchpoint is ligated to the 5′ terminus of the intron. With the help of a debranching enzyme, the intron lariats are folded directly to form pre-miRNAs [41, 42]. Afterwards, the intron-derived pre-miRNAs are processed as mentioned in the canonical biogenesis.

Furthermore, there are also several alternative miRNAs biogenesis pathways, such as tRNA-derived miRNAs in mammals, snoRNA-derived miRNAs in Giardia lamblia, and AGO-dependent pathway in zebrafish and mammals [43–45].

3. Conventional NF-κB Signaling Pathway

NF-κB is a dimeric transcriptional factor, which plays a crucial role in the immediate early pathogen responses and regulates varieties of cellular processes such as inflammation, cellular proliferation, and differentiation [46–48]. NF-κB contains five members NF-κB1 or p50, NF-κB2 or p52, c-Rel, RelA or p65, and RelB, all of which belong to Rel family. These five members can be classified into two groups: one consists of c-Rel, p65, and RelB, which are synthesized as an active form, and the other includes p50 and p52, which are proteolytically processed from precursor subunits, p100 and p105, respectively [49]. The five Rel proteins share a Rel homology domain (RHD), which is essential for binding to cognate DNA elements and nuclear translocation as well as dimerization to the other members of NF-κB proteins [50]. All NF-κB proteins can form homodimers or heterodimers with an exception of RelB that can only form heterodimers [51]. In most quiescent cells, a p50–p65 heterodimer is the predominant form and bound to IκBα, of which the ankyrin repeats interact with the DNA-binding region. Moreover, binding of p50–p65 to IκBα also masks the nuclear localization signals (NLs) of p50–p65 and then sequesters the p50–p65-IκBα complex in the cytoplasm, making NF-κB inactive [52].

Activation of NF-κB signaling pathway is initiated in response to extracellular stimuli, including viral and bacterial infection, exposure to proinflammatory cytokines, and stress-inducing agents. These stimuli are recognized by different kinds of pattern recognition receptors (PRRs) and transmitted into the cell. The altered conformation of PRRs caused by extracellular stimuli triggers the recruitment of myeloid differentiation primary response gene 88 (MyD88) [53]. This adaptor protein recruits a variety of downstream components and initiates the signaling cascade. The signaling cascade culminates in the activation of IkB kinases (IKKs). IKKs are a multisubunit complex, consisting of two catalytic subunits (IKKα and IKKβ) and the NF-κB Essential Modulator (NEMO or also termed IKKγ) noncatalytic accessory subunit [54]. The NF-κB-IκB complex is activated by IKKs through the phosphorylation of IκB [55]. This phosphorylation facilitates ubiquitin-dependent degradation of IκB by 26S proteasome, releasing NF-κB from the inhibitory complex and allowing translocation of NF-κB dimers to the nucleus and activation of target gene transcription [56].

4. Regulation of NF-κB Signaling Pathway by miRNAs during Viral Infections

Increasing evidences have emerged that viral infections can alter expression of cellular miRNAs that are involved in regulation of NF-κB [57]. At the same time, viral miRNAs are also active in modulation of immune responses via direct targeting of NF-κB (Figure 2 and Table 1). The interaction between viruses and host cells needs to initially recognize viruses by PRRs. Thus, exact control of PRRs expression by miRNAs is one of the approaches to modulate the NF-κB signaling pathway. After HIV and Kaposi’s sarcoma-associated herpesvirus (KSHV) stimulation, all the members of Let-7 family and miR-223 were downregulated. Reduced Let-7 and miR-223 gave rise to an increase of TLR3 and TLR4 expression, resulting in excessive inflammation and tissue damage [58]. Recent studies have revealed that miR-146 is also involved in regulation of TLR4 [59]. miR-146 was first functionally identified as an immune response regulator that had impacts on mammalian responses to microbial infections. miR-146 was found to be involved in regulation of Interleukin-1 receptor-associated kinase 1 ( IRAK1) and TNF receptor-associated factor 6 (TRAF6), downstream molecules of MyD88, and to be expressed under the control of NF-κB signaling pathway [60]. These suggest the presence of a negative regulatory network, in which HIV and hepatitis C virus (HCV) infections upregulate miR-146 and miR-21 that in turn downregulate IRAK1 and TRAF6 to reduce the activity of NF-κB [61, 62].

Accumulating evidence has demonstrated that miR-155 can negatively regulate NF-κB signaling pathway by targeting different key signaling protein genes. The adaptor protein MyD88 has been identified as one of the targets, and overexpression of miR-155 results in significantly reduced IL-8 synthesis induced by Helicobacter pylori infection [63]. It was also documented that MyD88 was targeted by other miRNAs, including miR-200b/c and miR-21 [61, 64]. In the HCV or HIV infected cells, the expression of miR155 and miR-21 was upregulated, leading to repression of NF-κB signaling pathway [65–67]. However, miR-200b/c were downregulated in the HCV or HIV infected cells [68, 69]. So far, it is not fully clear what makes the difference of those miRNA genes’ expressions.

TGF-β-activating kinase 1 (TAK1) forms a complex with TAK1-binding protein 1 (TAB1) and TAK1-binding protein 2 (TAB2), which modulates the activity of IKKβ. Evolutionarily
conserved miR-10a binding sites were identified in TAK1. miR-10a is able to target TAK1 transcripts, increasing the total expression of IkB and impairing NF-κB activation [70]. Expression of TAB2, a signal molecule downstream of TRAF6, was also regulated by the same miRNAs as ones involved in regulation of MyD88. For instance, miR-155 is able to bind to the 3'UTR of TAB2 transcripts, resulting in activation of mitogen-activated protein kinases (MAPK) kinases [71]. IKKs, downstream signal molecules of TAK1, are predominantly present in the form of which consists an IKKα-IKKβ heterodimer and NEMO subunit. IKKα was recently shown to be targeted by miR-16 and -223 and IKKβ targeted by miR-199, leading to negative regulation of NF-κB signaling pathway [72, 73].

In addition to the direct targeting of the components of NF-κB signaling pathway, miRNAs can also target regulatory molecules, such as Cylindromatosis (CYLD) [74], mothers against decapentaplegic homolog 7 (SMAD7) [75], and NF-κB repressing factor (NFR) [75, 76], to modulate the NF-κB signaling pathway indirectly. The tumor suppressor, programmed cell death protein 4 (PDCD4), is a proinflammatory protein that promotes activation of NF-κB through an

Figure 2: Canonical NF-κB signaling network regulated by miRNAs. PRRs are activated by different types of pathogens and initiate signaling transduction to induce the production of inflammatory cytokines. Host- or virus-derived miRNAs are involved in delicate regulation of the pathway at multiple levels. PRRs: pattern recognition receptors; MyD88: myeloid differentiation primary response gene 88; IRAK: Interleukin-1 receptor-associated kinase; TRAF: TNF receptor-associated factor; CYLD: Cylindromatosis; TAB: TAK1-binding protein; TAK: TGF-β-activating kinase; NEMO: NF-κB Essential Modulator or IKKγ; PENT: phosphatase and tensin homologue; SMAD7: mothers against decapentaplegic homolog 7; PDCD4: programmed cell death protein 4; NFR: NF-κB repressing factor.
Table 1: miRNAs involved in viral infections via regulation of NF-κB.

| miRNA genes | Origin | Expression | Targets | Reference |
|-------------|--------|------------|---------|-----------|
| miR-21      | Host   | Up         | MyD88, IRAK1, PTEN, SMAD7, PDCD4, and IL-12p35 | [61, 66, 77, 78, 82–84] |
| miR-155     | Host   | Up         | MyD88, TAB2, and IKKα | [63, 85, 86] |
| miR-199a    | Host   | ND         | IKKβ    | [87, 88] |
| miR-146     | Host   | Up         | IRAK1, IRAK2, and TRAF6 | [60, 83, 84, 89] |
| miR-200b/c  | Host   | Down       | MyD88   | [64] |
| miR-301a    | Host   | Down       | NKFR    | [90, 91] |
| miR-181     | Host   | Up         | CYLD    | [74, 92] |
| miR-16      | Host   | Down       | IKKα and TNF-α | [73, 93] |
| miR-223     | Host   | Down       | TLR3, TLR4, STAT3, and IKKα | [73, 94–97] |
| miR-125b    | Host   | Down       | TNF-α   | [85, 98] |
| miR-210     | Host   | Up         | NF-κB1  | [70, 99] |
| miR-10a     | Host   | Up         | TAK1    | [70, 99] |
| Let-7       | Host   | Down       | IL-6 and TLR-4 | [100, 101] |
| miR-K5      | Virus  | Up         | MyD88   | [79] |
| miR-K9      | Virus  | Up         | IRAK1   | [79] |
| miR-K12-1   | Virus  | Up         | IκBα    | [80] |

Note: “Up”: upregulated; “Down”: downregulated; “ND”: not determined.

unknown mechanism. miR-21 has been shown to inhibit both NF-κB activities via targeting PDCD4 and expression of other proinflammatory factors [77].

The major consequence of NF-κB activation is the production of inflammatory cytokines, which are crucial in virus clearance and inflammatory cell recruitment to infectious sites. Cytokine genes can be targeted directly by miRNAs (Figure 2). For instance, IL-12p35 can be targeted by miR-21 in macrophages and dendritic cells, resulting in restricted adaptive Th1 responses [78]. In addition to host miRNAs, virus-encoded miRNAs have also found ways to modulate NF-κB signaling cascade (Table 1). For instance, KSHV encodes miRNAs, miR-K1, miR-K5, and miR-K9 that directly target IκBα, MyD88, and IRAK1, thus regulating the NF-κB signaling pathway [79, 80].

5. Perspectives

During viral infections, miRNAs serve as posttranscriptional regulators of gene expression in virus replication and host’s immune responses. A number of miRNAs are known to be involved in regulation of the NF-κB signaling pathway through multiple steps, thus affecting viral infection outcomes. Some miRNAs have been shown to play bilateral roles in viral clearance and replication. For instance, during HIV infection downregulation of miR-16 results in the promotion of NF-κB signaling pathway, thus enhancing the level of immune responses [73]. However, downregulation of miR-16 also increases the HIV-1 replication via indirectly promoting the translation of its target gene, Pur-α [81]. The precise mechanisms whereby the host regulates the expression of miR-16 to balance the viral clearance and replication are not fully understood. Further studies will be required to investigate the regulatory network for regulation of miR-16, which increases our understanding of molecular mechanisms of viral infections.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was sponsored by National Natural Science Foundation (31260609 and 31201900), the Gansu Natural Science Foundation (1308RJZA105), and the Science Fund for Creative Research Groups of Gansu Province (Grant no. I210RJIA006).

References

[1] C. A. Janeway Jr., “Approaching the asymptote? Evolution and revolution in immunology,” Cold Spring Harbor Symposia on Quantitative Biology, vol. 54, no. 1, pp. 1–13, 1989.
[2] T. S. Blackwell and J. W. Christman, “The role of nuclear factor-κB in cytokine gene regulation,” American Journal of Respiratory Cell and Molecular Biology, vol. 17, no. 1, pp. 3–9, 1997.
[3] R. C. Lee, R. L. Feinbaum, and V. Ambros, “The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14,” Cell, vol. 75, no. 5, pp. 843–854, 1993.
[4] N. C. Lau, L. P. Lim, E. G. Weinstein, and D. P. Bartel, “An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans,” Science, vol. 294, no. 5543, pp. 858–862, 2001.
[5] S. Pfeffer, M. Zavolan, F. A. Grässer et al., “Identification of virus-encoded microRNAs,” Science, vol. 304, no. 5671, pp. 734–736, 2004.
[6] M. Lagos-Quintana, R. Rauhut, W. Lendeckel, and T. Tuschl, “Identification of novel genes coding for small expressed RNAs,” Science, vol. 294, no. 5543, pp. 853–858, 2001.
[7] B. J. Reinhart, E. G. Weinstein, M. W. Rhoades, B. Bartel, and D. P. Bartel, “MicroRNAs in plants,” Genes & Development, vol. 16, no. 13, pp. 1616–1626, 2002.
[8] A. Grimson, M. Srivastava, B. Fahey et al., “Early origins and evolution of microRNAs and Piwi-interacting RNAs in animals,” *Nature*, vol. 455, no. 7217, pp. 1193–1197, 2008.

[9] Y. Zheng, X. Cai, and J. E. Bradley, ”MicroRNAs in parasites and parasite infection,” *RNA Biology*, vol. 10, no. 3, pp. 371–379, 2013.

[10] D. P. Bartel, ”MicroRNAs: genomics, biogenesis, mechanism, and function,” *Cell*, vol. 116, no. 2, pp. 281–297, 2004.

[11] V. Ambros, ”The functions of animal microRNAs,” *Nature*, vol. 431, no. 7006, pp. 350–355, 2004.

[12] D. P. Bartel, ”MicroRNAs: target recognition and regulatory functions,” *Cell*, vol. 136, no. 2, pp. 215–233, 2009.

[13] C.-H. Lecellier, P. Dunoyer, K. Arare et al., ”A celluar microRNA mediates antiviral defense in human cells,” *Science*, vol. 308, no. 5721, pp. 557–560, 2005.

[14] L. Song, H. Liu, S. Gao, W. Jiang, and W. Huang, ”Cellular microRNAs inhibit replication of the H1N1 influenza A virus in infected cells,” *Journal of Virology*, vol. 84, no. 17, pp. 8849–8860, 2010.

[15] C. L. Jopling, M. Yi, A. M. Lancaster, S. M. Lemon, and P. Sarnow, ”Modulation of hepatitis C virus RNA abundance by a liver-specific microRNA,” *Science*, vol. 309, no. 5740, pp. 1577–1581, 2005.

[16] Y. Lee, M. Kim, J. Han et al., ”MicroRNA genes are transcribed by RNA polymerase II,” *The EMBO Journal*, vol. 23, no. 20, pp. 4051–4060, 2004.

[17] G. M. Borchert, W. Lanier, and B. L. Davidson, ”RNA polymerase III transcribes human microRNAs,” *Nature Structural & Molecular Biology*, vol. 13, no. 12, pp. 1097–1101, 2006.

[18] X. Z. Cai, C. H. Hagedorn, and B. R. Cullen, ”Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs,” *RNA*, vol. 10, no. 12, pp. 1957–1966, 2004.

[19] A. M. Denli, B. B. J. Tops, R. H. A. Plasterk, and G. J. Hannon, ”Processing of primary microRNAs by the microprocessor complex,” *Nature*, vol. 432, no. 7014, pp. 231–235, 2004.

[20] R. I. Gregory, K.-P. Yan, G. Amuthan et al., ”The microprocessor complex mediates the genesis of microRNAs,” *Nature*, vol. 432, no. 7014, pp. 235–240, 2004.

[21] M. Landthaler, A. Yalcin, and T. Tuschl, ”The human DiGeorge syndrome critical region gene 8 and its role in germ-line stem cell maintenance requires loguous, a double-stranded RNA-binding domain protein,” *PLoS Biology*, vol. 3, no. 7, pp. 1187–1201, 2005.

[22] K. Förstemann, Y. Tomari, T. Du et al., ”Normal microRNA maturation and germ-line stem cell maintenance requires loguous, a double-stranded RNA-binding domain protein,” *PLoS Biology*, vol. 3, no. 7, pp. 1187–1201, 2005.
C. Ender, A. Krek, M. R. Friedländer et al., “A human snoRNA with microRNA-like functions,” *Molecular Cell*, vol. 32, no. 4, pp. 519–528, 2008.

D. Cifuentes, H. Xue, D. W. Taylor et al., “A novel miRNA processing pathway independent of Dicer requires Argonaute2 catalytic activity,” *Science*, vol. 328, no. 5986, pp. 1694–1698, 2010.

D. Z. Li, Q. X. Zhang, X. X. Dong, H. D. Li, and X. Ma, “Treatment with hydrogen molecules prevents RANKL-induced osteoclast differentiation associated with inhibition of ROS formation and inactivation of MAPK, AKT and NF-kB pathways in murine RAW264.7 cells,” *Journal of Bone and Mineral Metabolism*, 2013.

M. A. Lindsay, “MicroRNAs and the immune response,” *Trends in Immunology*, vol. 29, no. 7, pp. 343–351, 2008.

T. Yoshida, M. Hashimura, T. Mastumoto et al., “Transcriptional upregulation of HIIF-1α by NF-kB/p65 and its associations with β-catenin/p300 complexes in endometrial carcinoma cells,” *Laboratory Investigation*, vol. 93, no. 11, pp. 1184–1193, 2013.

J. Caamaño and C. A. Hunter, “NF-kB family of transcription factors: central regulators of innate and adaptive immune functions,” *Clinical Microbiology Reviews*, vol. 15, no. 3, pp. 414–429, 2002.

M. J. May and S. Ghosh, “Rel/NF-kB and IκB proteins: an overview,” *Seminars in Cancer Biology*, vol. 8, no. 2, pp. 63–73, 1997.

D.-B. Huang, D. Vu, and G. Ghosh, “NF-kB RelB forms an intertwined homodimer,” *Structure*, vol. 13, no. 9, pp. 1365–1373, 2005.

A. A. Beg and A. S. Baldwin Jr., “The IκB proteins: multifunctional regulators of Rel/NF-kB transcription factors,” *Genes & Development*, vol. 7, no. 11, pp. 2064–2070, 1993.

P. G. Motshwene, M. C. Moncrieffe, J. G. Grossmann et al., “An oligomeric signaling platform formed by the toll-like receptor signal transducers MyD88 and IRAK-4,” *The Journal of Biological Chemistry*, vol. 284, no. 37, pp. 25404–25411, 2009.

M. Karin, “How NF-kB is activated: the role of the IκB kinase (IKK) complex,” *Oncogene*, vol. 18, no. 49, pp. 6867–6874, 1999.

M. Karin, “The beginning of the end: IκB kinase (IKK) and NF-kB activation,” *The Journal of Biological Chemistry*, vol. 274, no. 39, pp. 27339–27342, 1999.

M. Karin and Y. Ben-Neriah, “Phosphorylation meets ubiquitination: the control of NF-kB activity,” *Annual Review of Immunology*, vol. 18, pp. 621–663, 2000.

X. Ma, L. E. B. Buscaglia, J. R. Barker, and Y. Li, “MicroRNAs in NF-kB signaling,” *Journal of Molecular Cell Biology*, vol. 3, no. 3, pp. 159–166, 2011.

A. Androulidaki, D. Iliopoulos, A. Arranz et al., “The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs,” *Immunity*, vol. 31, no. 2, pp. 220–231, 2009.

K. Yang, Y. S. He, X. Q. Wang et al., “miR-146a inhibits oxidized low-density lipoprotein-induced lipid accumulation and inflammatory response via targeting toll-like receptor 4,” *FEBS Letters*, vol. 585, no. 6, pp. 854–860, 2011.

K. D. Taganov, M. P. Boldin, K.-J. Chang, and D. Baltimore, “NF-kB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 33, pp. 12481–12486, 2006.

W. Cao, R. Fan, L. Wang et al., “Expression and regulatory function of miRNA-34a in targeting survivin in gastric cancer cells,” *Tumor Biology*, vol. 34, no. 2, pp. 963–971, 2013.

D. Bhaumik, G. K. Scott, S. Schokrpur, C. K. Patil, J. Campisi, and C. C. Benz, “Expression of microRNA-146 suppresses NF-kB activity with reduction of metastatic potential in breast cancer cells,” *Oncogene*, vol. 27, no. 42, pp. 5643–5647, 2008.

B. Tang, B. Xiao, Z. Liu et al., “Identification of MyD88 as a novel target of miR-155, involved in negative regulation of Helicobacter pylori-induced inflammation,” *FEBS Letters*, vol. 584, no. 8, pp. 1481–1486, 2010.

E. B. Wendlandt, J. W. Graff, T. L. Gioannini, A. P. McCaffrey, and M. E. Wilson, “The role of microRNAs miR-200b and miR-200c in TLR4 signaling and NF-kB activation,” *Innate Immunology*, vol. 18, no. 6, pp. 846–855, 2012.

L. Houzet, M. L. Yeung, V. de Lame, D. Desai, S. M. Smith, and K.-T. Jeang, “MicroRNA profile changes in human immunodeficiency virus type 1 (HIV-1) seropositive individuals,” *Retrovirology*, vol. 5, article 118, 2008.

R. T. Marquez, S. Bandypadhyay, E. B. Wendlandt et al., “Correlation between microRNA expression levels and clinical parameters associated with chronic hepatitis C viral infection in humans,” *Laboratory Investigation*, vol. 90, no. 12, pp. 1727–1736, 2010.

Y. Zhang, W. Wei, N. Cheng et al., “Hepatitis C virus-induced up-regulation of microRNA-155 promotes hepatocarcinogenesis by activating Wnt signaling,” *Hepatology*, vol. 56, no. 5, pp. 1631–1640, 2012.

S. Ramachandran, H. Ilias Basha, N. J. Sarma et al., “Hepatitis C virus induced miR200c down modulates FAP-1, a negative regulator of Src signaling and promotes hepatic fibrosis,” *PLoS ONE*, vol. 8, no. 8, Article ID e70744, 2013.

K. Cheng, P. Rai, A. Plagov et al., “MicroRNAs in HIV-associated nephropathy (HIVAN),” *Experimental and Molecular Pathology*, vol. 94, no. 1, pp. 65–72, 2013.

Y. Fang, C. Shi, E. Manduchi, M. Civelek, and P. F. Davies, “MicroRNA-10a regulation of proinflammatory phenotype in athero-susceptible endothelium in vivo and in vitro,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 30, pp. 13450–13455, 2010.

M. Ceppi, A. M. Pereira, I. Dunand-Sauthier et al., “MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 27, pp. 2735–2740, 2009.

R. Chen, A. B. Alvero, D. A. Silasi et al., “Regulation of IKKβ by miR-199a affects NF-kB activity in ovarian cancer cells,” *Oncogene*, vol. 27, no. 34, pp. 4712–4723, 2008.

T. Li, M. J. Morgan, S. Choksi, Y. Zhang, Y.-S. Kim, and Z.-G. Liu, “MicroRNAs modulate the noncanonical transcription factor NF-kB pathway by regulating expression of the kinase IKKα during macrophage differentiation,” *Nature Immunology*, vol. 11, no. 9, pp. 799–805, 2010.

D. Iliopoulos, S. A. Jaeger, H. A. Hirsch, M. L. Bulyk, and K. Struhl, “STAT3 activation of miR-21 and miR-181b-1 via PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer,” *Molecular Cell*, vol. 39, no. 4, pp. 493–506, 2010.

F. Lallemand, A. Mazars, C. Prunier et al., “Smad7 inhibits the survival nuclear factor kB and potentiates apoptosis in epithelial cells,” *Oncogene*, vol. 20, no. 7, pp. 879–884, 2001.
[76] X. Feng, Z. Guo, M. Nourbakhsh et al., “Identification of a negative response element in the human inducible nitric-oxide synthase (hiNOS) promoter: the role of NF-κB-repressing factor (NRF) in basal repression of the hiNOS gene,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 22, pp. 14212–14217, 2002.

[77] F. J. Sheedy, E. Palsson-Mcdermott, E. J. Hennessy et al., “Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21,” *Nature Immunology*, vol. 11, no. 2, pp. 141–147, 2010.

[78] T. X. Lu, A. Munitz, and M. E. Rothenberg, “MicroRNA-21 is up-regulated in allergic airway inflammation and regulates IL-12p35 expression,” *The Journal of Immunology*, vol. 182, no. 8, pp. 4994–5002, 2009.

[79] J. R. Abend, D. Ramalingam, P. Kieffer-Kwon et al., “Kaposi’s sarcoma-associated herpesvirus microRNAs target IRAK1 and MYD88, two components of the Toll-like receptor/interleukin-1R signaling cascade, to reduce inflammatory-cytokine expression,” *Journal of Virology*, vol. 86, no. 21, pp. 11663–11674, 2012.

[80] X. Lei, Z. Bai, F. Ye et al., “Regulation of NF-κB inhibitor IκBα and viral replication by a KSHV microRNA,” *Nature Cell Biology*, vol. 12, no. 2, pp. 193–199, 2010.

[81] Z. Klase, L. Houzet, and K. T. Jeang, “MicroRNAs and HIV-1: complex interactions,” *The Journal of Biological Chemistry*, vol. 287, no. 49, pp. 40884–40890, 2012.

[82] B. H. Xiong, Y. Cheng, L. Ma, and C. Q. Zhang, “MiR-21 regulates biological behavior through the PTEN/PI-3 K/Akt signaling pathway in human colorectal cancer cells,” *International Journal of Oncology*, vol. 42, no. 1, pp. 219–228, 2013.

[83] T. W. Hoffmann, G. Duverlie, and A. Bengrine, “MicroRNAs and hepatitis C virus: toward the end of miR-122 supremacy 2012,” *Virology Journal*, vol. 9, article 109, 2012.

[84] T. W. Hoffmann, G. Duverlie, and A. Bengrine, “MicroRNAs and hepatitis C virus: toward the end of miR-122 supremacy 2012,” *Virology Journal*, vol. 10, article 59, 2013.

[85] E. Tili, J.-J. Michaille, A. Cimino et al., “Modulation of miR-155 and miR-125B levels following lipopolysaccharide/TNF-α stimulation and their possible roles in regulating the response to endotoxin shock,” *The Journal of Immunology*, vol. 179, no. 8, pp. 5082–5089, 2007.

[86] M. Ceppi, A. M. Pereira, I. Dunand-Sauthier et al., “MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 8, pp. 2735–2740, 2009.

[87] R. Chen, A. B. Alvero, D. A. Silasi et al., “Regulation of IKKβ by miR-199a affects NF-κB activity in ovarian cancer cells,” *Oncogene*, vol. 27, no. 34, pp. 4712–4723, 2008.

[88] G.-L. Zhang, Y.-X. Li, S.-Q. Zheng, M. Liu, X. Li, and H. Tang, “Suppression of hepatitis B virus replication by microRNA-199a-3p and microRNA-210,” *Antiviral Research*, vol. 88, no. 2, pp. 169–175, 2010.

[89] J. Hou, P. Wang, L. Lin et al., “MicroRNA-146a feedback inhibits RIG-I-dependent type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2,” *The Journal of Immunology*, vol. 183, no. 3, pp. 2150–2158, 2009.

[90] Z. Lu, Y. Li, A. Takwi et al., “miR-30a as an NF-κB activator in pancreatic cancer cells,” *The EMBO Journal*, vol. 30, no. 1, pp. 57–67, 2011.

[91] X. Zhang, M. Daucher, D. Armitstead, R. Russell, and S. Kottilil, “MicroRNA expression profiling in HCV-infected human hepatoma cells identifies potential anti-viral targets induced by interferon-α,” *PLoS ONE*, vol. 8, no. 2, Article ID e55733, 2013.

[92] J. Ji, T. Yamashita, A. Budhu et al., “Identification of microRNA-181 by genome-wide screening as a critical player in EpCAM—positive hepatic cancer stem cells,” *Hepatology*, vol. 50, no. 2, pp. 472–480, 2009.

[93] Q. Jing, S. Huang, S. Guth et al., “Involvement of microRNA in AU-rich element-mediated mRNA instability,” *Cell*, vol. 120, no. 5, pp. 623–634, 2005.

[94] R. Heikham and R. Shankar, “Flanking region sequence information to refine microRNA target predictions,” *Journal of Biosciences*, vol. 35, no. 1, pp. 105–118, 2010.

[95] Q. W.-L. Wong, R. W.-M. Lung, P. T.-Y. Law et al., “MicroRNA-223 is commonly repressed in hepatocellular carcinoma and potentiates expression of Stat3,” *Gastroenterology*, vol. 135, no. 1, pp. 257–269, 2008.

[96] Q. Y. Chen, H. Wang, Y. Liu et al., “Inducible microRNA-223 down-regulation promotes TLR-activated IL-6 and IL-1β production in macrophages by targeting STAT3,” *PLoS ONE*, vol. 7, no. 8, Article ID e42971, 2012.

[97] X. Wang, L. Ye, W. Hou et al., “Cellular microRNA expression correlates with susceptibility of monocytes/macrophages to HIV-1 infection,” *Blood*, vol. 113, no. 3, pp. 671–674, 2009.

[98] L. Fowler and N. K. Saksena, “Micro-RNA: new players in HIV-pathogenesis, diagnosis, prognosis and antiviral therapy,” *AIDS Reviews*, vol. 15, no. 1, pp. 3–14, 2013.

[99] J. Qi, Y. Qiao, P. Wang, S. Li, W. Zhao, and C. Gao, “MicroRNA-210 negatively regulates LPS-induced production of proinflammatory cytokines by targeting NF-κB1 in murine macrophages,” *FEBS Letters*, vol. 586, no. 8, pp. 1201–1207, 2012.

[100] D. Iliopoulos, H. A. Hirsch, and K. Struhl, “An epigenetic switch involving NF-κB, Lin28, Let-7 microRNA, and IL6 links inflammation to cell transformation,” *Cell*, vol. 139, no. 4, pp. 693–706, 2009.

[101] X.-M. Chen, P. L. Splinter, S. P. O’Hara, and N. F. LaRusso, “A cellular micro-RNA, let-7i, regulates toll-like receptor 4 expression and contributes to cholangiocyte immune responses against *Cryptosporidium parvum* infection,” *The Journal of Biological Chemistry*, vol. 282, no. 39, pp. 28929–28938, 2007.