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The functional analysis of MicroRNAs involved in NF-κB signaling

Y. YANG, J.-K. WANG

The State Key Laboratory of Bioelectronics, Southeast University, Nanjing, People's Republic of China

Abstract. – Nuclear factor κB (NF-κB) is a transcriptional factor that regulates a large number of genes that controls diverse biological functions, ranging from inflammation, cell proliferation and tumor development to learning and memory. MicroRNAs (miRNAs) are small non-coding RNA molecules involved in most aspects of physiological and pathological processes, including cancer, viral infections, inflammation and autoimmune diseases. miRNAs also play an important role in the regulation of NF-κB signaling pathway, some being inhibitory and others activating. Here, we analyzed the convergence of miRNAs involved in NF-κB signaling regulation and dysregulation of miRNAs and NF-κB activation in human diseases, particularly in cancer. The function of miR-146, miR-125b, miR-21, miR-301a, miR-30b, and miR-199 and their impacts on tumorigenesis are analyzed in this work. miRNAs as one of the most abundant classes of regulatory molecules, deciphering their biological function and pathological contribution in NF-κB dysregulation is essential to understand the complexity of immune systems and to develop therapeutics against cancer.

Key Words:
NF-κB, MicroRNAs, Cancer, Inflammation.

Introduction

NF-κB is a dimeric transcriptional factor first defined by Ranjan, which was latently present in cells and could be induced into its DNA-binding state, known as κB site[1]. All NF-κB proteins share a reticuloendotheliosis (Rel) homology domain (RHD), which is essential for binding to cognate DNA sequence motifs and dimerization to the members of NF-κB proteins as well as nuclear translocation[2]. The Rel protein family consists of five members, including p50, p52, p65, RelB and c-Rel[3]. Except for RelB that can only form heterodimers, all Rel proteins can form homodimers or heterodimers[4]. Among these proteins, p50-p65 heterodimer is the most abundant form of NF-κB in most unstimulated cells, which we discussed in this work unless indicated otherwise. NF-κB activation is mainly regulated by two pathways in response to extracellular stimuli[5]. The classical pathway is usually induced by microbial, viral infections and proinflammatory cytokines, such as tumor necrosis factor (TNFα), which all can activate the β-subunit of IκB kinase (IKKβ) complex through the toll-like receptor (TLR). IκB kinases (IKKs) phosphorylate IκBs (inhibitors of κB) binded to NF-κB, resulting in ubiquitin-dependent degradation of IκBs and translocation of NF-κB dimers to the nucleus[6]. The non-classical pathway is induced by certain members of the TNF cytokine family that selectively activate the α-subunit of IKK (IKKα) through the TNF receptor, BAFFR, RANK (receptor activator for nuclear factor kappaB), TNFR2, Fn14 and CD40R, along with NF-κB inducing kinase (NIK), to phosphorylate p100. This phosphorylation leads to polyubiquitination-dependent degradation of p100 to generate p52, forming p52-RelB heterodimers, which then translocate to the nucleus and activate target genes[7].

NF-κB plays an important role in regulating a large number of genes as well as the regulation of innate and adaptive immunity[8,9], cell proliferation[10,11], inflammation[12,13], tumorigenesis and tumor progression[14,15]. Therefore, NF-κB is a pluripotent and vital transcription factor for physiological and pathological processes. Besides, its transcriptional regulation system is complex, especially considering the fact that different NF-κB dimers have different affinities for different DNA-binding sequences[16] and various target genes are differentially regulated by distinct NF-κB dimers in various cell contexts[17]. In addition, for activation and crosstalk with other signaling pathways, NF-κB subunits contain sites available for phosphorylations and other post-translational modifications[18].

Corresponding Author: Jinke Wang; e-mail: wangjinke@seu.edu.cn

MicroRNAs (miRNAs) are a subclass of short (20-23 nucleotides in length), endogenous, non-coding, single-stranded RNAs that regulate gene expression post-transcriptionally by binding mainly to the 3' untranslated region (UTR) of target mRNAs. miRNAs are transcribed mostly by RNA polymerase II, as a long primary miRNA transcript (pri-miRNA)[19] with a stem-loop structure[20]. It is, then, recognized and cleaved in the nucleus by the microprocessor complex, Drosha-DGCR8 (DiGeorge syndrome critical region gene 8), resulting in a hairpin-structured precursor of miRNAs (pre-miRNA) ranging from 60 to 110 nucleotides in length. The pre-miRNA is exported from the nucleus to the cytoplasm by a nuclear transport receptor (exportin-5) and Ran-GTP[21,22]. In the cytoplasm, Dicer cleaves the pre-miRNA hairpin into a ~22 bp miRNA duplex[23,24]. The mature miRNA is incorporated with Argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC)[25-27], where miRNA guides the complex to partial complementary binding sites located in the 3' untranslated region (UTR)[28], 5' untranslated region (UTR)[29,30], or coding regions[31,32] of target mRNAs to induce translational repression or degradation of targeted mRNAs. Moreover, a small part of miRNAs are derived from introns of protein-coding genes, termed as mirtrons[20,33]; the mirtron production is Drosha-independent to generate pre-miRNAs and is spliced by Spliceosome[34].

miRNAs-mediated gene silencing was via RISC to induce translational repression or degradation of targeted mRNAs. Numerous investigations have confirmed the important roles of miRNAs in the regulation of human cancer, as well as in physiological function including immune responses, cellular proliferation, differentiation, and apoptosis[35-37]. These processes are also known to be regulated by NF-κB[11] and miRNAs play an important role in modulating NF-κB signaling pathway[38,39]. Thus, NF-κB and miRNAs play important roles in the gene expression regulatory network of the organism. Here we analyzed some key miRNAs involved in NF-κB signal pathway regulation (Figure 1).

miR-146

miR-146 is a vital modulator of differentiation and biology function of cells for the innate and adaptive immunity. In addition, it plays an important role in regulating different types of diseases and cancers[40]. Induction of miR-146 is NF-κB dependent through the toll-like receptor (TLR) and its expression is upregulated in human monocytic THP-1 cells treated by lipopolysaccharides (LPS)[41]. As to the NF-κB signal pathway regulation, TRAF6 and IRAK1 were identified as direct targets of miR-146. Generally, NF-κB activation upregulates miR-146 gene expression and, then, miR-146 down-regulates IRAK1 and TRAF6 to suppress the activity of NF-κB. Thus, this is a negative regulatory loop. According to previous literatures, miR-146 was demonstrated as an NF-κB negative regulator[42] and it exhibited an important role in suppressing tumor genesis and progression by inhibiting tumor cell migration and invasion[42,43].

In the stressed human brain primary neural cells, the close connection between NF-κB and miR-146a was confirmed by experiments which had tremendous potential to modulate neurotrophic support, neuroinflammation, synaptogenesis, innate immune signaling and amyloidogenesis[44]. Moreover, miR-146a was highly complementary to the 3'-untranslated region of complement factor H (CFH), an important repressor of the inflammatory response of the brain. Up-regulation of miR-146a accompanied with down-regulation of CFH was discovered in Alzheimer disease (AD) brain and as well as interleukin-1β, Aβ42, and/or oxidatively stressed human neural (HN) cells in primary culture. It indicated that miR-146a-mediated modulation of CFH gene expression could affect the inflammatory response in AD brain and stressed HN cells. In summary, miRNAs could be an effective therapeutic target for treatment of AD disease and inflammation[45]. Besides, the NF-κB-miR-146a complex, as a novel regulatory mechanism, was approved to attenuate inflammation in response to respiratory toxicants through suppressing the expression of cyclooxygenase-2 (COX-2) in mouse lung fibroblasts[46]. It was reported that IL-1β could induce upregulation of miR-146a, which in turn negatively regulates the expression of proinflammatory chemokines IL-8 and CCL5 in human lung alveolar epithelial tumor A549 cells. Besides, IL-8 and CCL5 are regulated by NF-κB activation, which provided additional evidence for the negative feedback regulation of inflammation response by miRNAs and NF-κB[47]. However, IRAK1 and TRAF6 were not involved in the pathway in A549 cell, which indicated that the regulatory effects of miR-146a may be cell type-specific[40]. All in all, miR-146 is a target gene of NF-κB and it could negatively modulate IRAK1

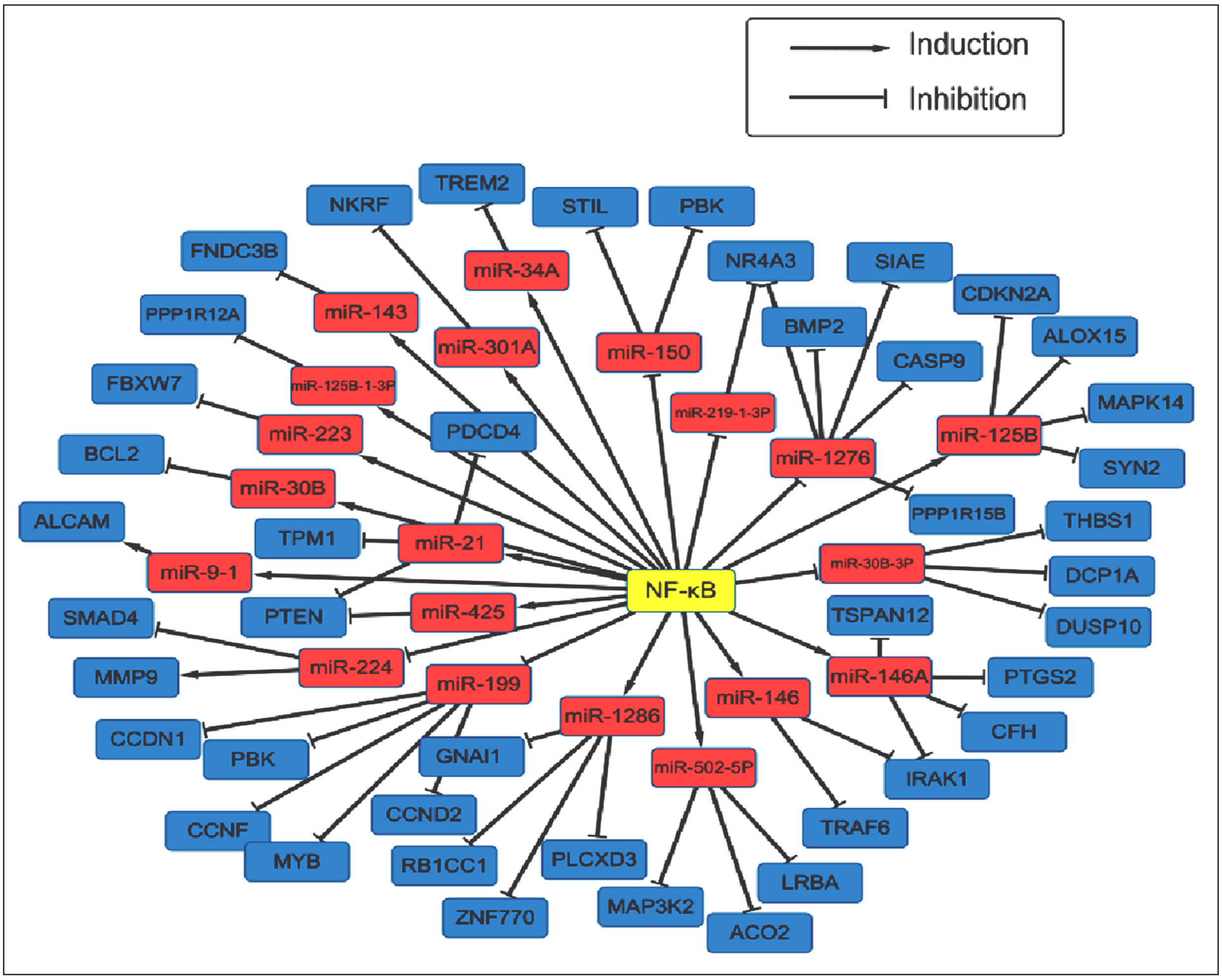

Figure 1. Panoramic view of the NF-κB miRNA target genes and target genes of miRNAs.

and TRAF6, constituting a negative feedback loop. miR-146 is involved in the regulation of the adaptive and innate immune response and tumor progression. Further studies were needed to fully understand the relationship between miR-146 and NF-κB.

miR-125b

Previous literature showed that up-regulation of miR-125b is associated with the suppression of the 15-lipoxygenase (ALOX15) and the synaptic vesicle-associated phosphoprotein synapsin-2 (SYN-2) in the brain. This indicated that miR-125b was involved in the regulation of innate and adaptive immune signaling, inflammation response, synaptogenesis, amyloidogenesis and neurotrophic support[44]. As one of the most human brain abundant miRNAs[48], miR-125b was shown to be up-regulated by neurotoxic metal sulfates and was also up-regulated in brain cancers to suppress the expression of cyclin-dependent kinase inhibitor 2A (CDKN2A), which is a negative regulator of cell growth. These effects of miRNA-125b were related to regulation of astrogliosis and cell cycle[49,50].

A previous study[52] indicated that miR-125a and miR-125b constitutively activate NF-κB by repressing TNFα-induced protein 3 (TNFAIP3)[51]. TNFAIP3 is a critical inhibitor of NF-κB signaling. Thus, miR-25b-1 plays a vital role in the NF-κB signal pathway through forming a positive feedback regulation loop[55]. Meanwhile, up-regulation of miR-125b by ultraviolet can promote cell survival in human embryonic kidney cell line HEK293 and keratinocyte cell line HaCaT through preventing prolonged p38α activation[56]. PPP1R12A, a gene regulating cell survival, is the target gene of miR-125b-1[55]. All these researches suggest that miR-125b plays a role in the regulation of cell survival.

miR-21

The overexpression of miR-21 was identified in most types of human carcinomas[57], and NF-κB activation is also reported in all of these cancers[11], indicating the interplay of miR-21 and NF-κB in cancer. In human breast cancer cells, NF-κB-dependent miR-21 up-regulation following genotoxic treatment contributes to both therapeutic resistance and metastasis through repressing expression of PTEN and PDCD4[58]. Knockdown of miR-21 using peptide nucleic acids (PNAs) inhibits proliferation and migration of MCF-7 and MDA-MB-231 cells[59]. The up-regulation of miR-21 promotes growth, migration, invasion and chemo/radio-resistance of non-small cell lung cancer cells through suppressing its target's expression of PTEN, a tumor suppressor gene[60]. The up-regulation of miR-21 by STAT3 under the treatment of IL-6 induces enhanced proliferation and suppressed apoptosis in human nasopharyngeal carcinoma (NPC) through PTEN-AKT pathway[61]. In human skin and head and neck squamous cell carcinoma (SCC), up-regulation of miR-21 also suppresses the development related transcription factor GRHL3 and PTEN, a direct GRHL3 target, through PI3K/AKT/mTOR signaling pathway, promoting tumorigenesis[62]. In human glioblastoma tissue and glioblastoma-derived cell lines, either downregulation of mir-21 or up-regulation of its target, programmed cell death 4 (Pdcd4), leads to decreased proliferation, colony formation, and increased apoptosis[63]. The up-regulation of mir-21 possesses the important significances as the indicators of prognostic and tumor stage in human hepatocellular carcinoma (HCC)[64]. Furthermore, Ma et al. confirmed that knocking out the miR-21 allele in mice could promote cell apoptosis and suppress cell proliferation, which showed that miR-21 plays its oncogenic function through downregulating its target genes such as Spry1, Pten, and PDCD4[65]. In all, mir-21 may act as a potential diagnostic and prognostic biomarker[66,67] and a novel therapeutic target for cancers.

In human glioblastoma (GBM) cell lines, downregulation of miR-21 could suppress cell proliferation and induced cell apoptosis through inhibiting EGFR pathway with the manner of PTEN-independent[68]. miR-21 induced by LPS attenuates pro-inflammatory effects of TLR4 signaling through suppressing NF-κB activity[69]. Mice deficient in PDCD4, a confirmed miR-21 target, exhibit the lower LPS-induced mortality rates, lower IL-6 production and increased IL-10 protein levels compared to the WT mice. Meanwhile, reduction of PDCD4 by increased miR-21 expression can account for the increased neoplastic transformation in mice JB6 cell lines[70]. As depletion of the NF-kB subunit p65 abolished LPS-induced miR-21 expression, the authors then show that miR-21 is an NF-kB transactivational gene[71]. Moreover, during earlier stages of liver regeneration, the up-regulation of miR-21 leads to down-regulation of pellino1, an activator of NF-κB, indicating that miR-21 may act as an NF-κB inhibitor[72]. Thus, cell-type specificity may determine the various functions of miR-21 in NF-κB signal pathway. Generally, in epithelial cells, miR-21 acts to down-regulate PTEN, activate AKT, and induce NF-κB activation. On the other hand, miR-21 can act as an NF-κB inhibitor to suppress PDCD4, a proinflammatory protein that promotes activation of NF-κB in LPS-stimulated macrophages. It needs more research to dissect the correlation of miR-21 overexpression and NF-κB activation in cancer, as well as the role of miR-21 in NF-κB signaling, inflammation and immune diseases.

miR-301a

miR-301a was identified as an activator of NF-κB by negatively regulating its target gene of NF-κB repressing factor (NKRF)[73]; NKRF broadly suppressed the expression of NF-κB transactivational targets. Besides, the promoter of miR-301a contained a bona fide κB site. Thus, it forms a positive feedback loop as a mechanism for persistent NF-κB activation in which miR-301a suppresses NKRF to activate NF-κB activity, which in turn, promote the expression of miR-301a.

miR-301a, which is the most potent NF-κB activator is over expressed in pancreatic adenocarcinoma and other tumor cell lines[73]. Over expression of miR-301a promoted pancreatic cancer (PC) cell proliferation, and repressed the expression of Bim gene *in vitro* and *in vivo*. Meanwhile, Bim re-expression could suppress PC cell proliferation induced by miR-301a[74]. In human pancreatic ductal adenocarcinoma (PDAC), miR-301a over expression promotes cancer growth through suppressing manganese superoxide dismutase (MnSOD) expression, a tumor suppressor gene. On the other hand, decreased miR-301a levels are associated with increased MnSOD expression and inhibition of PDAC growth[75]. In human colorectal cancer, the up-regulation of miR-301a represses the expression of suppressor of cytokine signaling 6 (SOCS6)[76] and Smad4 through TGF-β/Smad pathway[77], which in turn, promotes cell proliferation, migration and invasion and tumor growth. Meanwhile, miR-301a is an activator of both NF-κB and Stat3, generating a pro-inflammatory microenvironment that promotes colorectal cancer as well as lung cancer tumorigenesis[78]. Suppression of miR-301a can repress tumor cells proliferation, migration and invasion. It indicates that miR-301a acts as an oncogene miRNAs facilitating tumorigenesis. The significant up-regulation of miR-301a both in cells and tissues of gastric cancer can promote cell proliferation, soft agar clonogenicity, cell migration and invasion through downregulating RUNX3 expression[79], which plays a key role in the clinical progression and prognosis of gastric cancer[80]. The significant up-regulation of miR-301a and downregulation of Gax in human hepatocellular carcinoma (HCC) promote cell proliferation, migration and invasion, while inhibiting miR-301a expression induces the up-regulation of Gax and repression of NF-κB expression[81]. Moreover, miR-301a plays an important role in prostate cancer through regulating the miR-301a/androgen receptor (AR)/TGF-β1/Smad/MMP9 signals pathway[82] and in autoimmune demyelination through regulating immune response[83]. Intriguingly, over expression of miR-301a promotes breast cancer cell migration, invasion and metastasis with the hyper-activation of Wnt/β-catenin signaling through suppression of PTEN expression[84]. Meanwhile, the up-regulation of miR-301a and down-regulation of PTEN, a target of miR-301a, reduces the effect of IL-6-induced insulin resistance and hepatic glycogenesis through the AKT/GSK pathway[85]. It shows that PTEN is a vital component in miR-301a target genes. Altogether, miR-301a exerts important roles in many physiological processes and is an important therapeutic target for cancers.

miR-30b

In HER2-positive breast cancer cells, the up-regulation of miR-30b induced by trastuzumab can inhibit cell growth through repressing CCNE2[86]. Up-regulation of miR-30b can promote the apoptosis of gastric cancer cells and significantly inhibit tumorigenicity of gastric cancer through negatively regulating its target of plasminogen activator inhibitor-1 (PAI-1)[87]. miR-30b expression in human colorectal cancer (CRC) is significantly lower than that in normal tissues. The literature showed that over expression of miR-30b could suppress cell proliferation in vitro and tumor growth *in vivo* through regulating its target genes of KRAS, PIK3CD and BCL2. These researches indicated that miR-30b could act as a potential prognostic marker and therapeutic target for CRC[88]. In laryngeal carcinoma cells, the up-regulation of miR-30b can promote p53-mediated tumor cell apoptosis[89]. However, the up-regulation of miR-30b in glioma cells impairs tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-dependent apoptosis by inhibiting the expression of caspase-3[90]. And the up-regulation of miR-30b in human melanoma promotes the metastatic behavior of melanoma cells by repressing the GalNAc transferase GALNT7, which may lead to increased synthesis of the immunosuppressive cytokine IL-10, and decreased immune cell activation and recruitment[91]. Thus, the opposite function of miR-30b in cancers can be explained by its cell type-specific function.

Moreover, miR-30b is a negative regulator of cell death induced by loss of attachment (anoikis) through regulating the expression of caspase 3[92]. miR-30b regulates cell death in cardiomyocytes by repressing Bcl-2[93]. miR-30b also plays an important role in schizophrenia[94], angiogenesis[95] and phagocytosis[96].

miR-199

The down-regulation of miR-199a/b is found in non-small cell lung cancer (NSCLC), which promotes cell proliferation, migration and invasion through negatively regulating Axl expression[97]. The up-regulation of miR-199a can increase survival in aggressive diffuse large B-cell lymphoma patients by modifying drug sensitivity to immunochemotherapy[98]. The up-regulation of miR-199a suppresses renal cancer cell growth and expression ofGSK-3β, which indicates that miR-199a can act as a potential therapeutic target of renal cancer[99]. The down-regulation of miR-199a induced by reactive oxygen species (ROS) in ovarian cancer cells can elevate the expression of ERBB2 and ERBB3, which in turn promote cancer progression[100]. On the other hand, miR-199a-3p is significantly up-regulated in gastric cancer (GC) cell lines and tissues which promote cell proliferation, suppresses cell apoptosis through suppressing the expression of zinc fingers and homeoboxes 1 (ZHX1)[101]. The up-regulation of miR-199a-3p in colorectal cancer suppresses the expression of its target gene NLK, which in turn to promote the lymph node metastasis, venous invasion, liver metastasis of colorectal cancer[102]. Thus, the members of miR-199 have diverse functions in different cancers.

In primary hepatocellular carcinomas (HCCs) and HCC cell lines, miR-199 can modulate Ad-199T virus replication, which is an oncolytic adenovirus. This indicated that miR-199 can be used as a therapeutic potential against liver cancer[103]. The up-regulation of miR-199a is positively and significantly correlated to the progression of liver fibrosis, while the expression levels of fibrosis-related genes in hepatic stellate cells (HSC) are significantly increased by over-expression of miR-199a[104]. Generally, chronic hepatitis can develop into liver cirrhosis (LC) and hepatocellular carcinoma (HCC) consequently. Thus, miR-199 plays important roles in the physiological progression of liver diseases. Interestingly, miR-199 also plays an important role in somatic cell reprogramming through the p53 signal pathway[105]. In summary, the members of miR-199 possess the vital functions in many physiological processes and more researches are needed to uncover its full functions and mechanisms.

Other miRNAs Target Genes Related to NF-κB

There are many other miRNAs that are related to NF-κB signal pathway. In human biliary epithelial cells, miR-125b-1, miR-21, miR-30b and miR-23b-27b-24-1 genes involve in the immune responses following *C. parvum* infection being relevant to the regulation of epithelial anti-microbial defense[106]. In Alzheimer's disease, up-regulation of miR-34a represses TREM2 expression and may shape innate immune and phagocytic responses that contribute to inflammatory neurodegeneration through an epigenetic mechanism[107]. In human esophageal squamous cancer EC109 cell, up-regulation of miR-34a transcribed by NF-κB and p53 plays an important role in tumor progression[108]. NF-κB and p53 also repress miR-224 expression and induce Smad4 expression to influence the proliferation of mouse ovarian granulosa cells[109]. Celastrol can inhibit the migration and invasion of HepG2 cells by efficiently decreasing the expression of miR-224 and MMP-2 and MMP-9[110]. The up-regulation of miR-223 expression represses the tumor suppressor FBXW7 in T-cell acute lymphoblastic leukemia (T-ALL), which in turn to promote cancer progression through Notch signal pathway[111]. Up-regulation of miR-143 expression promotes HCC invasion/migration and tumor metastasis by repression of fibronectin type III domain containing 3B (FNDC3B) expression[112]. Up-regulation of miR-425 expression increases gastric cancer cell survival by repressing PTEN expression[113]. In human hepatoma cell lines, HepG2, GQY-7701 and Bel-7402, up-regulation of miR-9 represses CD166 expression and promotes cells migration[114]. The up-regulation of miR-145 inhibits glucose uptake and induces insulin resistance through repressing IRS-1 expression in HepG2 cells[115]. In summary, miR-155, miR-193b, miR-34a, miR-451, miR-150 and miR-199 involve in the transformation of human B-cells and diffuse large B cell lymphoma (DLBCL) through NF-κB pathway[116].

Conclusions

miRNAs act as posttranscriptional regulators of gene expression and regulate many target genes including NF-κB, IκB, IKK and regulators in the NF-κB signaling pathway forming positive or negative sophisticated feedback loops. miRNAs constitute an important layer of regulation of gene expression with profound impacts on biological organisms. miRNAs have the unique expression profile in cells of the innate and adaptive immune system and have vital roles in the regulation of cell development, function and epigenetic inheritance. Dysregulation of miRNAs often associates with tumor development and progression. miRNAs can function as both oncogenes or tumor suppressors in different tumors and cell types, which is cell type specific. Therefore, miRNAs can act as a therapeutic target of cancers. However, it needs more work to fully understand the role and mechanism of miRNAs in normal and pathologic conditions as well as to identify target genes of miRNAs involved in NF-κB signaling pathway.

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Conflict of Interests

The Authors declare that they have no conflict of interests

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