Nuclear Factor κB Signaling and Its Related Non-coding RNAs in Cancer Therapy

Xiaomin Liu,1,2,3 Yang Shao,2,3 Jinbao Zhou,2 Guangren Qian,1 and Zhongliang Ma2

1School of Environmental and Chemical Engineering, Shanghai University, Shanghai 200444, China; 2Lab for Noncoding RNA & Cancer, School of Life Sciences, Shanghai University, Shanghai 200444, China

Nuclear factor κB (NF-κB) acts as a nuclear factor that is composed of five main subunits. It is a pluripotent and crucial dimer transcription factor that has a close relationship with many serious illnesses, especially its influences on cell proliferation, inflammation, and cancer initiation and progression. NF-κB acts as part of the signaling pathway and determines its effect on the expression of several other genes, such as epidermal growth factor receptor (EGFR), p53, signal transducer and activator of transcription 3 (STAT3), and non-coding RNA (ncRNA). Continuous activation of the NF-κB signaling pathway has been seen in many cancer types. While the NF-κB signaling pathway is tightly regulated in physiological settings, quite frequently it is constitutively activated in cancer, and the molecular biology mechanism underlying the deregulated activation of NF-κB signaling remains unclear. In this review, we discuss the regulatory role and possible clinical significance of ncRNA (microRNA [miRNA] and long non-coding RNA [lncRNA]) in NF-κB signaling in cancer, including in the conversion of inflammation to carcinogenesis. Non-coding RNA plays an essential and complex role in the NF-κB signaling pathway. NF-κB activation can also induce the ncRNA status. Targeting NF-κB signaling by ncRNA is becoming a promising strategy of drug development and cancer treatment.

INTRODUCTION

Cancer is a malignancy disease, which results in aberrant and amplification function of several oncogenes.1 Many studies have shown that the occurrence and development process of tumors are related to inflammation, and activation of the inflammation-related signaling pathway plays vital roles in the tumor microenvironment. It is worth noting that the tumor cells also have abnormal activation of the inflammatory signaling pathway independent of external stimuli. Nuclear factor κB (NF-κB) signaling pathway activation promotes the transcription of inflammatory factors, chemokines, adhesion molecules, growth factors, and other related genes, which in turn leads to tumor development.2

The transcription factor NF-κB, a nuclear factor that binds to the enhancer of the immunoglobulin kappa light-chain of activated B cell tumors, was discovered in 1986.3,4 NF-κB has also been presented as being closely connected with cancer development and progression. It induces the expression of many genes involved in the developmental process, the inflammatory response, immunoreaction, as well as cellular proliferation apoptosis and angiogenesis.5–7

At present, non-coding RNA (ncRNA) and NF-κB act as crucial factors in the development of cancer, both of which can be applied as tumor markers and drug targets in clinical therapeutics.8 ncRNAs mainly contain microRNA (miRNA) and long non-coding RNA (lncRNA). In addition, there are other ncRNAs, including such circular RNA (circRNA) and piwi-interacting RNA (piRNA), among others.

miRNAs are a class of endogenous regulatory ncRNAs involved in cell carcinogenesis that are about 20–25 nt in length.9 They can bind to the 3' UTR of protein-coding mRNAs, typically leading to mRNA degradation. Alternatively, they can also cause repression of target mRNA translation.10 miRNA cleavage is related to cancer progression and clinical features. Thus, as an important regulator of life processes, miRNAs have a close relationship with tumors.11

lncRNA is a type of ncRNA with a length >200 nt. It has been shown that lncRNAs participate in a variety of biological processes, such as regulation of gene, epigenetic, cell cycle and cell differentiation.12 Therefore, a more in-depth study of the functions and mechanisms of lncRNA will help reveal their role in tumorigenesis as a primary tool for diagnosis and cancer treatment.

In this review, we provide a highlighted overview of the impact of miRNAs and lncRNAs on the inflammatory regulation of the NF-κB signaling pathway in cancer.

NF-κB Signaling Pathway and Its Activation

The NF-κB transcription factor family is composed of five main subunits, including Rel (c-Rel), RelB, p65 (RelA, NF-κB3), p50 (NF-κB1), and p52 (NF-κB2), all of which have an N-terminal segment containing about 300 aa residues called Rel homology domain (RHD)
target genes, making a difference in gene expression. The non-canonical NF-κB signaling pathway is split into the canonical and the non-canonical (CARMA1, BCL10, and MALT1) complex. In general, the NF-κB activation involves several protein kinases and the downstream proteins as important adaptors. The signal passes through the CBM (CARMA1, BCL10, and MALT1) complex. In general, the NF-κB signaling pathway is split into the canonical and the non-canonical NF-κB pathway (Figure 2).

Canonical NF-κB Pathway

1. In the cytoplasm, NF-κB will bind to IκB as a trimer when in the inert state. 2. Upon recognition of external stimulation such as bacteria, viruses, parasites, inflammatory cytokines, and fibroblast growth factors, the tumor necrosis factor receptor (TNFR), Toll-like receptor (TLR), and interleukin-1 receptor (IL-1R) will be activated, which myeloid differentiation factor 88 (MyD88) and IL-1R-associated kinase (IRAK) will bind and pass the activated signal to downstream proteins as important adaptors. The signal passes through the downstream proteins TNFR-associated factor (TRAF2), NF-κB inducing kinase (NIK), and receptor interacting protein (RIP) and consequently activates IKK, leading to ubiquitination and phosphorylation of IκB, which further causes the release of NF-κB dimers, and the dissociated IκB molecules are degraded by proteasomes. 3. The NF-κB dimers enter the nucleus and bind to the κB domain of the target genes, making a difference in gene expression.

Non-canonical NF-κB Pathway

The non-canonical NF-κB pathway is composed of IκB family members, the main parts of which are p100 and p105. Upon stimulation, the B cell-activating factor receptor (BAFR), lymphotixin β receptor (LTβR), receptor activator of NF-κB (RANK), and CD40 will be activated, a consequence of which is that p100 will be phosphorylated by the downstream NIK, eventually leading to the ubiquitination of p100 and its degradation into p52. The free p52-RelB dimers will enter the nucleus and bind to the target genes of the κB domain.

NF-κB Signaling and miRNA in Cancer

In tumorogenesis, abnormal expression of miRNA is usually accompanied by activation of the NF-κB signaling pathway. miRNAs can regulate the NF-κB pathway through translocating themselves to some upstream signal molecules or NF-κB members. Meanwhile, the NF-κB pathway can also regulate the expression level of miRNAs by synthesis of proteins. 

p50/p65 and miRNAs

Studies have shown that the synthesis of miR-9 is under the control of pro-inflammatory cytokine TNF-α and IL-1β regulation, whereas the precursor of p50, p105, is actually a target protein of miR-9. They also suggest that miR-9 will function as a trimming agent in the anti-inflammatory responses to hinder the negative control by p50 homodimers in some monocytes. In addition, miR-9 can inhibit the development of ovarian cancer and gastric cancer through regulation of the NF-κB pathway. Moreover, researchers have discovered that miR-143 can function as the transcription target of NF-κB and promote metastasis in lung cancer. Meanwhile, overexpression of miR-143 will decrease the viability of the cells and have an effect on the expression of p50 in the NF-κB pathway. Besides, there are plenty of miRNAs found to have a direct or indirect regulatory function on p50/p65. This can explain that NF-κB does not work alone, but rather that it forms part of a network with a variety of miRNAs.

One study testified that miR-145-5p is a tumor inhibitor during regulation of the NF-κB/YY1 pathway, whose aberrant expression will lead to the synthesis of rhabdomyosarcoma. In addition, a study by Mott et al. also verified that the inhibitory effect NF-κB has on miR-29b exists in the biliary duct and cholangiocarcinoma. Certainly, a series of miRNAs such as miR-125b-1, miR-125a-5p, miR-494, and miR-130b are under the regulation of NF-κB. (Table 1), which determines the mode of its effects on the expression of several other genes and thus its function (Figure 3).
TNF-α induced through the upregulation of NELL-1 in patients with heart valve disease. Overexpression of miR-27a protected human mitral valve interstitial cells (hMVICs) from TNF-α-induced cellular injury, indicating that miR-27a has as a vital role in the regulation of TNF-α release. To date, miR-27a is considered as an important negative regulatory factor in human inflammations, which has a close connection with TNF-α.

Additionally, studies have shown that miR-146a has a connection with TNF-α in gastric diseases and psoriasis patients. miR-146a can increase the secretion of TNF-α, which is confirmed by experiments. Compared with the control group, the overexpression of miR-146a significantly upregulated the expression level of TNF-α in a gastritis group, while that of the gastric cancer group was significantly reduced.

Thus, TNF-α and NF-κB have a close interaction in which miRNAs have an essential role. Some miRNAs reacted with TNF-α in inflammation, while TNF-α has a vital joint role in NF-κB pathway regulation. p50 and p65 regulate the expression and secretion of TNF-α indirectly through interacting with important members of NF-κB pathway. miR-16 decrease rapidly, which directly leads to the increase of IKKα expression and causes an elevated expression level of p52.

Overexpression of p52 will remarkably inhibit the foundation level of target genes in the NF-κB pathway. When miRNA expression decreases, the activation of macrophages is apparently inhibited. In tumors with NF-κB activity, miR-199a targets IKKβ and inhibits its expression in endometrial stromal cells (ESCs). As the IKKβ expression decreases, miR-199a suppresses activation of the NF-κB pathway and the synthesis of IL-8, which means that miR-199a can reduce the invasiveness of ESCs through inhibiting the NF-κB pathway. IKKε also had a contradictory role in activation of the NF-κB pathway. Studies have verified that miR-155 is involved in the negative-feedback loop through down-regulation of IKKe, IKKβ and other transcription factor of NF-κB.[41] Additionally, building the regulatory feedback loop of IKKe/YAP1/miR-Let-7b/I, IKKe promotes glioblastoma progression.

MyD88 and miRNAs
d’Adhemar et al. found that miR-146a and miR-21 bind to the mRNA of MyD88 in ovarian cancer, influencing the regulatory function of MyD88 in the TLR4 pathway, whose activation does not directly promote the activation of downstream NF-κB. Meanwhile, they found that the regulatory function of miR-146a and miR-21 on MyD88 is not only limited in activating the TLR4 and NF-κB pathways, but also in regulating the expression level of MyD88 to directly influence the sensitivity of ovarian cancer cells to pharmacotherapy. miR-200b and miR-200c also play a significant role in activation of the TLR4 and NF-κB pathway, which is to bind with MyD88. They observed that after transfecting miR-200b and miR-200c into HEK293-TLR4 cells, the expression of MyD88 clearly decrease, while other target genes such as IRAK-1 and TRAF6 have no effect. This shows that miR-200b and miR-200c can influence the TLR4 pathway through regulation of MyD88, which has vital physiological significance in the defense of microbial pathogens.

In short, miRNAs can adjust NF-κB efficiently through MyD88, which has a crucial role in the biogenesis and development of inflammations and tumors.
CBM Complex and miRNAs

The CBM complex plays an essential role mainly by modulating nuclear transcription factor activation, such as NF-κB, which is initiated by antigen receptor activation. CARMA1 is a cytoskeletal protein that changes its conformation after antigen receptor activation and recruits downstream signaling pathway components BCL10 and MALT1. The mutual recognition of CARMA1 and the linker protein BCL10 is mediated by the CARD domain, whereas BCL10 and MALT1 are cytoplasmic. The constitutive complex forms a complex, and the interaction between these three proteins stabilizes the CBM complex. The CBM complex also has a regulatory effect on miRNA. Recent studies have shown that miR-181d acts as a tumor suppressor by targeting MALT1 to suppress glioblastoma through NF-κB pathways.46 Additionally, miR-26 restrains TNF-α/NF-κB signaling and IL-6 expression by silencing MALT1.47 Gu and Sun48 found that miR-539 can regulate migration and invasion through targeting CARMA1 in human thyroid cancer.

TAK1 and miRNAs

Zhao et al.49 found that miR-26b can inhibit activation of the NF-κB pathway by targeting transforming growth factor B (TGF-β)-activated kinase-1 (TAK1) and TAK1 binding protein (TAB). They observed that in the hepatocellular carcinoma (HCC) cell lines QGY-7703 and MHCC-97H, miR-26b can bind directly to the 3′ UTR of TAK1 and TAB3 to suppress their expression, inhibiting the TNF-α-induced NF-κB pathway and eventually enhancing the sensitivity of lung cancer cells to pharmacotherapy. TAK1 has a special and important position in the NF-κB pathway, which can bind to TAB1 to activate NF-κB-induced kinase and IκB kinase.50

Other NF-κB-Associated Components and miRNAs Involved

There is increasing evidence that miRNAs play a crucial part in the regulation of NF-κB signaling pathways in a variety of cancer types. In addition to the genes mentioned above, other NF-κB-associated genes and miRNAs are involved in the regulation of NF-κB signaling pathways in cancer. For example, EGFR can indirectly or directly activate signal transducer and activator of transcription (STAT) members.53 NF-κB mediated extracellular signal-regulated kinase (ERK) reactivation through gefitinib resistance in EGFR mutant non-small cell lung cancer (NSCLC) cells.54 Studies have elucidated that NF-κB is activated by EGFR activation.55–57 In addition, environmental factors can also affect EGFR expression through regulating NF-κB.58 Our laboratory has proved that miR-34a

| miRNA          | Target Gene | Disease/Cancer                          | Function                      | Reference |
|----------------|-------------|-----------------------------------------|--------------------------------|-----------|
| miR-302e       | RelA        | allergic inflammation                    | anti-inflammatory             | 106       |
| miR-194, miR-195| TRAF6, IKKα | intervertebral disc degeneration, Wilms tumor | anti-inflammatory proliferation, apoptosis | 107,108 |
| miR-199a-3p    | IKKβ        | cystic fibrosis                          | chronic pulmonary inflammation | 109       |
| miR-23a        | IKKβ        | articular chondrocytes                   | anti-inflammatory             | 109       |
| miR-429        | IKKβ        | cervical cancer                          | proliferation, apoptosis      | 110       |
| miR-7          | Myd88       | Eriocheir sinensis                       | enhance white spot syndrome   | 111       |
| let-7b         | IKKe        | human gloma                              | invasion, migration           | 112       |
| miR-342-3p     | IKKγ        | hepatocellular carcinoma                 | proliferation                 | 113       |
| miR-503        | IKKβ        | NSCLC                                   | metastasis                    | 114       |
| miR-451        | IKKβ        | hepatocellular carcinoma                 | proliferation                 | 115       |
| miR-199a       | IKKβ        | endometrial stromal cell                 | cell adhesion, migration, invasion | 116       |
| miR-194, miR-502-5p | TRAF6, TRAF2 | nucleus pulposus cells of the intervertebral disc, chondrocyte injury | anti-inflammatory proliferation, apoptosis | 107,116 |
| miR-18a-5p     | IRF2        | NSCLC                                   | proliferation, metastasis, apoptosis | 61       |
| miR-708-3p     | STAT3       | idiopathic pulmonary fibrosis            | inhibit fibrosis              | 62       |
| miR-411        | STAT3       | cervical cancer                          | cell proliferation and invasion | 117       |
| miR-29a        | STAT3       | human retinoblastoma                     | cell proliferation, migration, invasion, apoptosis | 118       |
| miR-124        | STAT3       | NSCLC                                   | proliferation, apoptosis      | 119       |
| miR-181b       | STAT3       | atherosclerosis                         | proliferation, apoptosis, cell cycle | 120       |
| miR-26b        | TAK1        | hepatocellular carcinoma                 | apoptosis                     | 121       |
| miR-20a        | TAK1        | osteosarcoma                             | proliferation                 | 122       |
| miR-23b        | TRAF1       | sepsis                                  | proliferation, immunosuppression | 123       |

NSCLC, non-small cell lung cancer.

**Table 1. miRNAs and the NF-κB Signaling Pathway**

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and miR-107-5p could directly target EGFR to reduce cell proliferation, metastasis, cell cycle, and promote apoptosis in vitro and vivo. Moreover, our laboratory has also verified that miR-18a-5p can downregulate the expression of interferon regulatory factor 2 (IRF2), which is related to the NF-κB signaling pathway.

There is a mutual inhibitory relationship between NF-κB and p53. Studies have shown that p65 can inhibit p53-related transcriptional activity, and p53 can also inhibit NF-κB transcriptional activity. Mutant p53 can increase p52 expression through acetylation by regulating the amount of histone acetyltransferase CBP. In addition, the interaction of NF-κB, such as TNF-α, p53, and NF-κB, with certain specific stimuli also plays a vital role. The miR-34 family is the first miRNA associated with p53. It was shown that upregulated expression of the p53-binding region will increase all members of the miR-34 family, which also implies an important function of the miR-34 family in the p53 signaling pathway. It was shown that miR-124 is the first miRNA associated with p53. It was shown that upregulated expression of the p53-binding region will increase all members of the miR-34 family, which also implies an important function of the miR-34 family in the p53 signaling pathway.

**STAT3**

STAT3 activation is responsible for a variety of genes that promote diagnostic markers and therapeutic targets for many diseases. A study has shown that miR-124 inhibits the growth of colon cancer through targeting STAT3. This shows that the tumor-suppressing effect of miR-124 is based on the combination with STAT3. Additionally, through suppressing the STAT3 signaling pathway activation, miR-125a-5p heightens the sensitivity of cisplatin in esophageal squamous carcinoma. Meanwhile, miR-26a-5p regulates ITGβ8-JAK2/STAT3 to potentiate metastasis of lung cancer. STAT3 and NF-κB co-regulate a series of target genes, including cell cycle and anti-apoptotic genes. Research has shown that STAT3 regulates post-transcriptional translation of p65 by regulating the expression of acetyltransferase p300, thereby promoting pro-inflammatory cytokines in tumor microenvironments.

**Other ncRNAs and NF-κB Signal Transduction**

IncRNA has been found to play a vital part in pathological and physiological processes, containing tumor formation and metastasis. Different IncRNAs have different molecular mechanisms that play different biological functions. The activation of NF-κB is also related with IncRNA.

Tumor-associated NF-κB activation and IncRNA overexpression are most directly related to the inhibition of IκB, which acts as a negative regulator of NF-κB signaling. Liu et al. found that NKILA (NF-κB interacting IncRNA) binds to NF-κB, which is upregulated by inflammatory factors in breast cancer. NKILA inhibits activation of the NF-κB signaling pathway by masking the location of phosphorylation of IκB for IKK phosphorylation suppression. Further studies revealed that there are two hairpin structures, A and B, at 300–500 nt of NKILA. Hairpin A binds to the DNA-binding region of NF-κB, and hairpin B binds to S51-R73 of p65, preventing IκBβ detachment that forming a stable NKILA/NF-κB/IκBβ complex. Yang et al. found that FTH1P3 (long non-protein coding RNA ferritin heavy chain 1 pseudogene 3) regulated metastasis and invasion through SP1 (specificity protein 1)/NF-κB (p65) in esophageal squamous cell carcinoma (ESCC). The mechanism of IncRNAs has been studied. A deeper understanding of the molecular mechanisms and biological functions of IncRNA will help to find new effective anticancer strategies in tumorigenesis.
miR-7 binding sites, which can effectively sponge miR-7 and suppress the inhibition of miR-7 target genes, promoting the correlation of gene expression and activating NF-κB signaling pathways. There are few reports on piRNA in cancer. Leng et al. found that piR-DQ590027, miR-377, and miR-153 in glioma-conditioned endothelial cells (GECs) had lower expression. piR-DQ590027 bound to MIR17HG. FOXXR2 was a downstream target of miR-377 and miR-153. This study proved that the piR-DQ590027/MIR17HG/miR-153(miR-377)/FOXXR2 pathway plays a crucial role in regulating the permeability of glioma-conditioned normal blood-brain barrier (BBB). Another study has shown that piR-021285 can induce the methylation of genes in breast cancer. The roles of these ncRNAs in tumors remain to be further explored.

NF-κB Signaling in Chronic Inflammation to Cancer

Since the discovery of NF-κB more than 30 years ago, researchers have demonstrated that NF-κB is the “master switch” of gene expression in various pro-inflammatory mediators. It is expressed in many cancers, including HCC, colon cancer, breast cancer, prostate cancer, cervical cancer, and chronic lymphocytic leukemia. NF-κB has an important function in inflammation by regulating the expression of pro-inflammatory cytokines such as TNF, IL-1, and monocoyte chemoattractant protein 1 (MCP-1). Drugs such as aminosaliclyates and lipopolysaccharide, which are used clinically to combat inflammation work by inhibiting NF-κB. At the same time, many studies have verified that these drugs can inhibit the activation of some cancers. Although NF-κB activation can prevent self-activated apoptosis, it acts as a transcription factor that regulates the production of cytotoxic drugs such as nitric oxide, which in turn may indirectly lead to apoptosis in other cells. Environmental factors affect NF-κB activation and inflammation secretion, which induce to promote lung tumor growth cancer. Particularly, in glioblastoma, it produces neurotoxic reactive oxygen species, which induces by cytokines through NF-κB activation. Moreover, NF-κB and STAT3 synergistically regulate a number of target genes affecting growth, angiogenesis, and immunosuppression. In addition, they also collaboratively control a common set of genes encoding for cytokines. This means the mechanism of NF-κB activity regulated by STAT3 influences and plays a significant role in cancer.

Studies have shown that the occurrence and development of cancers are closely related to inflammation, and activation of the inflammation-related signaling pathway plays a crucial role in formation of the tumor microenvironment. It is worth noting that cancers also have abnormal activation of the inflammatory signaling pathway independent of external stimuli. Activation of the NF-κB signaling pathway promotes the transcription of inflammatory factors, cytokines, adhesion molecules, growth factors, and other related genes, which in turn leads to tumor development.

Abnormal activation of inflammatory signaling pathways in tumors can promote the expression of cellular inflammatory factors or activate genes associated with tumor progression. At the same time, inflammatory factors can accelerate the development of malignant cells through paracrine effects. For instance, low expression of miR-892b leads to aberrant activation of the NF-κB signaling pathway, increasing tumor cell proliferation, metastasis, and angiogenesis in breast cancer. In addition, IncRNA-SRLR binds to the IL-6 promoter region, activating the STAT3 signaling pathway in tumor cells by autocrine or paracrine secretion. Tumor cell inflammation is similar to a series of phenotypes in traditional inflammatory cells that participate in immune responses. It has the characteristics of rapid proliferation, anti-apoptosis, invasion and migration, and secretion of inflammatory factors. At present, most of the evidence indicates that inflammation in tumors is one of the vital causes of tumor deterioration.

Conclusion and Future Perspectives

In cancer, activation of the NF-κB signaling pathway is ubiquitous. Its activation is not caused by stimulation of external pathogens; instead, it is caused by the abnormal regulation of cells. Previous studies have found that ncRNA may be involved in this regulation process. Compared with protein, the production of RNA products in cells is faster. When cells are stimulated by some factors, DNA rapidly transcribes RNA and undergoes splice processing, without the need for protein modification to function. Different RNA products appear in different splicing modes and perform different functions. Meanwhile, RNA has more modifications than proteins, which have an effect on the subcellular localization, activity, and structure of RNA that makes RNA more diverse in functioning. These properties of RNA determine their status in regulating the signaling pathway. RNA participates in regulation of the NF-κB signaling pathway, which requires more in-depth research and is of great significance for finding new cancer therapies.

Activation of NF-κB signaling can cause cells to be resistant to chemotherapeutic drugs and inhibit cell apoptosis. Combined with the effects of NF-κB signaling on tumor formation and drug resistance, targeting NF-κB can effectively inhibit the development of tumors and alleviate the tolerance to chemotherapeutic drugs caused by the activation of NF-κB signaling.

As a vital transcriptional regulator, miRNA, a non-coding protein single-chain small molecule RNA, has been widely demonstrated to be closely related to the development of various tumors and potential therapeutic approach. miRNA has great clinical significance for research in tumors. Among those pathways in which miRNAs are involved, the NF-κB pathway is one of the most important ones. It is found to perform an important regulatory function in immune reactions, inflammations, and carcinogenesis. The main connection of miRNAs and NF-κB lies in miRNAs directly or indirectly regulating the expression level of target genes in the NF-κB pathway. Currently, the most commonly used method for inhibiting the function of miRNA is using anti-miR oligonucleotides. After the endogenous mature miRNA is inhibited by the anti-miR oligonucleotide, the downstream gene that is inhibited by the miRNA is released. Therefore, anti-miR oligonucleotides are effective in inhibiting miRNAs that promote the NF-κB signaling pathway in cancer. In general,
the clinical application of miRNA-related products requires more in-depth experiments. In addition, lncRNA is a potential therapeutic target, and it is essential to find an effective way to inhibit it. With the study of lncRNA in the NF-κB signaling pathway, it is thought that there will be drugs or treatments designed for lncRNA.

Furthermore, research is increasing on the relationship between non-coding RNA and the NF-κB signaling pathways in tumors. Undoubtedly, the study of this relationship has extremely important clinical significance related to the mechanism of tumor development and for the provision of new drug target sites for tumor treatment. Accordingly, further research is needed to elucidate whether members of the pathway are clinically significant as biomarkers or therapeutic targets.

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CONFLICTS OF INTEREST
The authors declare no competing interests.

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