

Role of the NFκB-signaling pathway in cancer

Longzheng Xia^{1,*}Shiming Tan^{1,*}Yujuan Zhou¹Jingguan Lin¹Heran Wang¹Linda Oyang¹Yutong Tian¹Lu Liu¹Min Su¹Hui Wang¹Deliang Cao^{1,2}Qianjin Liao¹

¹Hunan Key Laboratory of Translational Radiation Oncology, Hunan Cancer Hospital and Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, Hunan, China;
²Department of Medical Microbiology, Immunology, and Cell Biology, Simmons Cancer Institute, Southern Illinois University School of Medicine, Springfield, IL, USA

*These authors contributed equally to this work

Correspondence: Qianjin Liao;

Deliang Cao

Hunan Key Laboratory of Translational Radiation Oncology, Hunan Cancer Hospital and Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, 283 Tongzipo Road, Changsha, Hunan 410013, China
 Tel +86 731 8865 1681
 Fax +86 731 8865 1999
 Email march-on@126.com;
 dcao@siu.edu

Abstract: Cancer is a group of cells that malignantly grow and proliferate uncontrollably. At present, treatment modes for cancer mainly comprise surgery, chemotherapy, radiotherapy, molecularly targeted therapy, gene therapy, and immunotherapy. However, the curative effects of these treatments have been limited thus far by specific characteristics of tumors. Abnormal activation of signaling pathways is involved in tumor pathogenesis and plays critical roles in growth, progression, and relapse of cancers. Targeted therapies against effectors in oncogenic signaling have improved the outcomes of cancer patients. NFκB is an important signaling pathway involved in pathogenesis and treatment of cancers. Excessive activation of the NFκB-signaling pathway has been documented in various tumor tissues, and studies on this signaling pathway for targeted cancer therapy have become a hot topic. In this review, we update current understanding of the NFκB-signaling pathway in cancer.

Keywords: nuclear factor kappa-B, p65, signaling pathway, cancer, inflammation

Introduction

Malignant tumors have become one of the most deadly diseases and a prominent public health problem threatening human lives around the world.¹ In recent years, with social and economic development, as well as aging of the population, the incidence and mortality of cancer are increasing.² The overall incidence of common malignant tumors will rise from 14 million in 2012 to a predicted 19 million in 2025 and 24 million in 2035, according to the World Health Organization.^{3,4} Cancer occurs due to oncogene activation, tumor-suppressor gene inactivation, loss of control of the cell cycle, genomic instability, telomerase loss, and resistance of apoptosis.⁵ However, the specific pathogenesis of cancer varies with types of cancers.

The cell-signaling pathway is the process by which cell responds to stimuli of extracellular signaling molecules that bind to receptors located on the cell membrane or in the cytoplasm of cells. This binding to receptors transfers signals to the nucleus and induces corresponding gene expression, thus producing biological effects and cellular responses.⁶ In tumorigenesis, signaling pathways are less controlled.^{7,8} Abnormal regulation and cross-talk of cell-signal-transduction pathways play a key role in cancer, and obstruction of or anomalies in signaling pathways may lead to excessive cell proliferation, apoptotic resistance, angiogenesis, invasion, and metastasis, leading to development and progression of cancer.⁵ NFκB is an important signaling pathway that is involved extensively in cancer development and progression. Through controlling the expression of target genes, such as *TNFA*, *IL6*, *BCLXL*, *BCL2*, *BCLXS*, *XIAP*, and *VEGF*, NFκB mediates tumor-cell proliferation, survival, and angiogenesis.⁹ This review focuses on this NFκB-signaling pathway in tumors.

Overview of NFκB-signaling pathways

Proteins and structure of NFκB family

NFκB is an important transcription-factor family of five subunits: Rel (cRel), p65 (RelA, NFκB3), RelB, p105/p50 (NFκB1), and p100/p52 (NFκB2).^{10–12} Among these, p65, cRel, and RelB contain an N-terminal Rel-homologous domain (RHD; about 300 amino acids) and a C-terminal transactivation domain (TAD; Figure 1),^{13,14} while p50 and p52 have only an RHD, but not a TAD.^{15,16} The C-terminal of p100 and p105 contains ankyrin repeats that function as a p52 and p50 inhibitor. The RHD is responsible for DNA binding and dimerization between different or identical family members, including the nuclear localization sequence and IκB-binding region, leading to homomeric or heteromeric binding of the subunits.¹⁷ The TAD is associated only with transcriptional activation.¹⁸ Therefore, the p50–p52 homologous dimer does not activate gene transcription, but acts as an inhibitory molecule. Both p50 and p52 are usually

present in cells in the form of their precursors.¹⁹ In these members, RelB can form dimers only with p50 or p52, but others can form either homologous or heterologous dimers. However, the most common NFκB dimer is the heterodimer of p65–p50. These homologous and/or heterologous dimers can bind to a specific sequence (ie, NFκB sites) of the target gene to regulate gene transcription. Therefore, NFκB regulates the activity of cells through the slight difference in binding of these NFκB dimers to targeted sequences.

IκBs and IKKs

IκBs and IKKs are upstream regulators of the NFκB-signaling pathway. In cells that are not stimulated, NFκB dimers are present in an inactive state by binding to three inhibitory factors (IκBα, IκBβ, and IκBε) of the NFκB in the cytoplasm, which blocks the nuclear localization sequence and prevents the NFκB from transition into the nucleus.^{20,21} In addition, there are also two precursor IκBs: p105/IκBγ and p100/IκBδ.²² IκBα specifically inhibits the p50/RelA

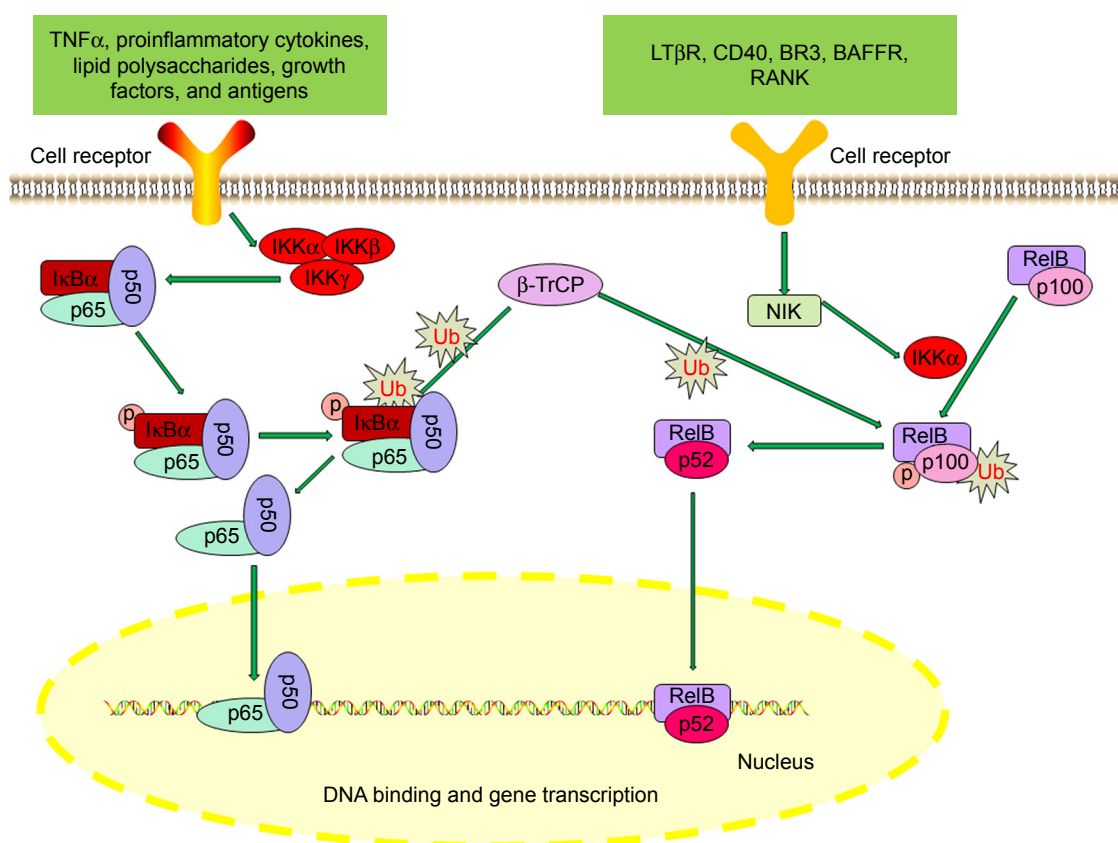


Figure 1 Structure of NFκB members.

Notes: The NFκB family consists of three proteins with a transactivation domain (RelA [p65], cRel, and RelB) and two proteins lacking a transactivation domain (p105/p50 and p100/p52). Similarly, only p105/p50 and p100/p52 have ankyrin repeats that function as p52 and p50 inhibitors. However, all these proteins share an Rel-homology domain, associated with DNA binding, dimerization, nuclear localization and IκB binding, and nuclear localization signal exposure, which is vital to the translocation of the dimer into the nucleus.

Abbreviation: NIK, NFκB-inducing kinase.

heterodimer, IκBβ targets the RelA/cRel heterodimer,²³ and IκBε inhibits the RelA and cRel dimers.²⁴ Although different external stimuli cause differential activation of NFκB through different IκBs,²⁵ almost all known NFκB agonists can rapidly and transiently activate NFκB by degradation of IκBs.²⁶ The IκB proteins p105/IκBγ and p100/IκBδ play a dual role, ie, precursors of the NFκB proteins p50 and p52 and inhibitors of NFκB signaling.²⁷ Different external stimuli have differential effects on the different subunits of IκBs, leading to differential activation of the NFκB pathway.

The IKK (IκB kinase) complex consists of the catalytic subunits IKKα and IKKβ and the regulatory subunit NFκB essential modifier (NEMO; also called IKKγ).²⁰ The IKKs are upstream regulators of IκBs.²⁸ Both IKKα and IKKβ subunits have about 52% of the sequence identity, but play a key but divergent role in regulation of global NFκB-signaling activity.²⁹ NEMO contains several domains that are crucial for its function as a regulatory subunit of the canonical IKK complex. The N-terminal coiled-coil domain of NEMO interacts with IKKα and IKKβ.³⁰ Different IKKs demonstrate differential strength and speed for different substrates. IKKα is mainly the specific upstream kinase of IκBβ and can strongly phosphorylate the Ser23 of IκBβ, but not the Ser19. This inequivalent phosphorylation of Ser23 and Ser19 in IκBβ leads to degradation of IκBβ.³¹ IKKβ can specifically phosphorylate the Ser sites of IκBα and IκBβ, and the intensity is 20 times that of IKKα. In addition, the

phosphorylation speed of the same IKK for IκBα and IκBβ are different. IKKβ has stronger affinity for IκBα than IκBβ. Also, the IκB-kinase complex can phosphorylate the NFκB-bound IκB protein and contribute to proteasomal degradation of the IκB protein faster.³²

Activation of NFκB-signaling pathway

In a resting status of cells, complexes formed from NFκB and IκB (NFκB–IκBα or NFκB–IκBε) shuttle between the cytoplasm and nucleus in a dynamic equilibrium.³³ When cells are stimulated by extracellular signals, such as TNFα, IL1, lipopolysaccharide, viral double-stranded RNA, and ionizing radiation, NFκB is activated and enters the nucleus to bind to target genes.^{34–39} Upon activation, NFκB-signaling pathways are classified as canonical or noncanonical (Figure 2).⁴⁰ The common regulatory step in both pathways is activation of the IKK complex. The IKK complex is phosphorylated, and in turn induces phosphorylation of IκB proteins IκBα or IκBβ, leading to ubiquitination and degradation by proteasomes. Similarly, p100 and p105 are phosphorylated and cleaved into matured p52 and p50 upon IKK activation. Therefore, NFκB dimers are released from their inhibitors and free to translocate into the nucleus to regulate expression of their target genes.

The canonical NFκB-transcription factor is an inactive dimer composed of a p50 and RelA/p65 subunit, which largely resides in the cytoplasm as part of a latent complex

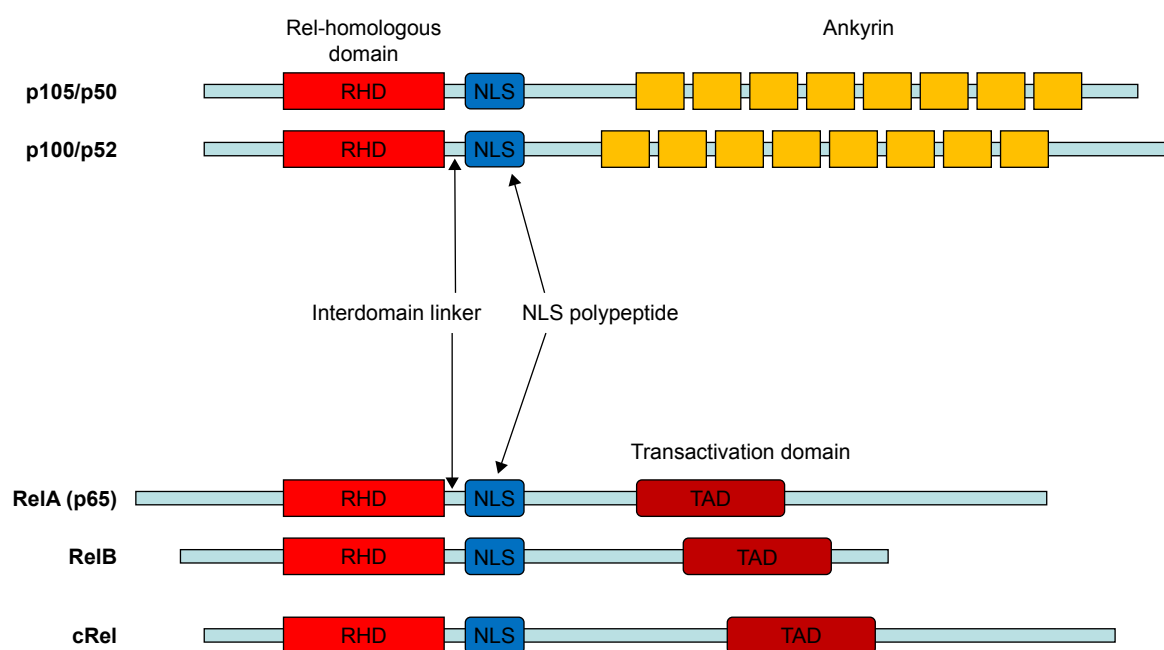


Figure 2 Activation of NFκB cascade by the classical/canonical signaling pathway (right) and alternative/noncanonical signaling pathway (left).

Abbreviations: NLS, nuclear localization sequence; RHD, Rel-homologous domain; TAD, transactivation domain.

with I κ B α under basal conditions.^{41,42} The formation of p65 (RelA)–p50 or p65–cRel heterodimers is a key to activation.⁴³ Stimulation by proinflammatory cytokines, such as TNF α , IL1 β , TLR ligands, and T-cell-receptor activators, results in activation of the IKK β complex, and then I κ B α is phosphorylated at Ser32 and Ser36 by the IKK complex,^{44,45} polyubiquitinated at K63, and degraded by proteasomes.^{46–49} Degradation of I κ B α consequently releases the canonical NF κ B dimer p50-RelA/p65 to translocate into the nucleus and activate gene transcription.⁵⁰

Although the canonical NF κ B pathway has been more extensively studied, it is not to be ignored that the noncanonical pathway (or alternative NF κ B pathway) is vital in some aspects.⁵¹ This alternative pathway is activated by TNF-receptor (TNFR) family members, such as LT β R, BAFFR, RANK, and CD40.^{52–56} Once the receptor is activated, TRAF proteins are able to mediate the activity of NF κ B-inducing kinase and activate an IKK α homodimer at the same time,^{57,58} ultimately leading to heterodimerization of the p100 precursor with RelB and processing into the active p52 subunit.⁵⁹ This processing of p100 induces the generation of the noncanonical transcription factor, a p52-RelB dimer, which then binds to κ B DNA-binding sites and controls expression of targeted genes.⁵⁹ Therefore, activation of these two pathways is achieved by phosphorylation of I κ B proteins, which relieve the inhibition of I κ B proteins to NF κ B dimers.⁶⁰

Posttranslational modifications of NF κ B proteins

NF κ B has hundreds of validated transcriptional targets,⁶¹ and thus NF κ B-signaling activity is under stringent spatial and temporal control at the levels of nuclear translocation and posttranslational modifications (PTMs) of signaling components.^{61,62} There is a wide range of PTMs of NF κ B subunits,⁶³ and PTMs provide essential mechanisms differentially to regulate NF κ B-signaling activity in response to the various stimuli that activate this pathway in many cancer cells.^{64,65} Although these modifications have a critical role in the normal and pathological functions of NF κ B *in vivo*, the physiological significance of PTMs remains unclear in cancer cells.⁶⁶ PTMs not only can contribute to the control of nuclear translocation but also have an important influence in functions of NF κ B subunits, including protein degradation, DNA binding, and transcriptional activity.^{67–69} PTMs of NF κ B include phosphorylation, ubiquitination, acetylation, and methylation.⁷⁰ Herein, we focus on the ubiquitination, phosphorylation, and methylation of the functional subunits of NF κ B.

Ubiquitination, a PTM of addition of ubiquitin (Ub) moieties to a protein, is the primary mechanism of protein turnover in the cell, and is recognized as the “traditional” function of Ub tagging.⁷¹ Ub moieties on NF κ B-signaling proteins can serve as a docking platform for other proteins with specific Ub-binding domains.⁷² First, the Ub moiety is activated by the E1 Ub-activating enzyme. Following activation, one of several E2 Ub-conjugating enzymes transfers Ub from E1 to several E3 enzymes (Ub ligases), to which the substrate protein is specifically bound. The Ub moiety includes seven lysine (K) residues (K6, K11, K27, K29, K33, K48, and K63) and a methionine at the N-terminus (M1), which can link another Ub to form a polyUb chain.⁷³

Ub signaling controls activation of NF κ B and innate immunoresponses downstream of pattern-recognition receptors, such as Toll-like receptors, nucleotide-oligomerization domain-like receptors, and cytokine receptors, eg, TNFR1, in normal intestinal epithelial cells and colon cancer cells.^{74–76} K48-linked polyubiquitination is a key step in releasing NF κ B from I κ Bs in the canonical pathway and processing of p100/102 into p52/50 in the noncanonical pathway to activate the NF κ B pathway in inflammatory diseases, autoimmune diseases, and cancers.^{70,77,78} The Skp1–Cullin–F-box (SCF)– β TrCP complex catalyzes the K48-linked polyubiquitination of I κ B α at two N-terminal lysine residues (K21 and K22), inducing 26S proteasome-dependent degradation of I κ B α and nuclear translocation of canonical NF κ B. In addition, the phosphorylation of I κ B α induced by NF κ B-inducing kinase could cause the phosphorylation of p100 on the C-terminal region (Ser866 and Ser870) and polyubiquitination of p100 by the SCF– β TrCP–E3 ligase complex to regulate the activity of the noncanonical NF κ B.⁷⁰ The IKK β subunit is also polyubiquitinated by a K63-linked chain in human cervical HeLa cells.⁷⁹ Importantly, activation of IKK is essential to productive signaling and NF κ B-mediated transcription, and its activation depends on the binding of Met1–Ub by the IKK subunit NEMO.⁸⁰

Phosphorylation is critical for NF κ B activity, including binding to and transcription of genes that contain a consensus sequence.⁸¹ Phosphorylation of key NF κ B-signaling molecules often positively mediates signal transduction by inducing protein conformational changes in breast cancer cell lines.^{82,83} Activation of NF κ B signaling is involved in a series of phosphorylation events of upstream NF κ B regulators and NF κ B family members. In fact, the activity of NF κ B is controlled to a great extent by phosphorylation of RelA or upstream regulators in esophageal squamous-cell carcinoma, gastric cancer, and oral cancer.^{81,84} The main subunit RelA of

NFκB is targeted for phosphorylation at many phosphoacceptor sites within both the RHD (Ser205, Ser276, Ser281, Ser311, and Thr254) and TAD (Ser468, Ser529, Ser535, Ser536, Thr435, and Thr505).⁸¹ For example, the phosphorylation of Ser536 induced in the cytoplasm can increase NFκB transcriptional activity, while phosphorylation of Ser529 increases DNA binding and oligomerization in laryngeal cancer cells. The phosphorylation of Ser536 results in nuclear accumulation of RelA through disruption of the cytoplasmic/nuclear shuttling of NFκB–IκBα complexes. In addition, phosphorylation of Ser276 can promote RelA interaction with the transcriptional coactivator CBP/p300.⁸⁵ Meanwhile, p-Ser276 RelA facilitates recruitment of DNMT1/DNA (cytosine 5)–methyltransferase 1 to chromatin and subsequent BRMS1-promoter methylation and transcriptional repression in human NSCLC cells.⁸⁶ In addition, phosphorylation of IκBs is a key step of their proteasomal degradation and the release of NFκB for nuclear translocation and activation of gene transcription. Cytokines in the tumor microenvironment, such as TNFα, could bind to the cell-surface TNF receptor, causing TNF-receptor multimerization and interacting with TRADD in the cytoplasm.^{87,88} TRADD recruits TRAF⁸⁹ and kinase RIP.⁹⁰ Then, the stimulated signals are transmitted to IKK by RIP, which can make the Ser32 and Ser36 residues in α-subunits of IκB and Ser19 and Ser23 residues in β-subunits of IκB phosphorylated.^{91,92} Then, IκB protein is dissociated from the p50-p65-IκB trimer and subsequently degraded by proteasomes, activating the NFκB pathway.⁷⁷

In recent years, accumulated evidence has suggested that histone-modifying enzymes not only modify histone proteins but also play a role in the modification of nonhistone proteins, such as NFκB.⁹³ NFκB can be methylated reversibly on lysine or arginine residues by histone-modifying enzymes, including lysine and arginine methyl transferases and demethylases. The methylations of both lysine and arginine occur mainly on the p65 subunit of NFκB.^{94,95} The methylated K sites include K37, K218, K221, K310, K314, and K315 that are modified by different histone-modifying enzymes.⁹⁶ Among the histone methyl transferases, SET9, SETD6, and NSD1 are capable of activating NFκB by methylating K218 and K221 of p65, which provides a potential mechanism for how NSD1 might contribute to tumor formation, as constitutive activation of NFκB is a hallmark of many cancers. Methylation of NFκB can profoundly affect the functions of NFκB by altering its stability, transactivation potency, and affinity to DNA, and thus affect the strength and duration of inducible gene expression. Meanwhile, the differential methylation

of K37 and K218/221 on NFκB is able to constitute “bar codes” that guide differential activation of NFκB, binding to specific promoters.⁹⁶

Roles of NFκB in cancer

At present, the role of the NFκB-signaling pathway in cell biogenic activities is the hot spot of cancer research. NFκB signaling is involved in cellular immunity, inflammation, and stress, as well as regulation of cell differentiation, proliferation, and apoptosis.^{97–101} The NFκB pathway is often altered in both solid and hematopoietic malignancies, promoting tumor-cell proliferation and survival.^{52,102,103} However, recent evidence indicates that NFκB plays a tumor-suppressive role in certain cancers through transcriptional activation of the Fas ligand.¹⁰⁴

Pro- and anti-inflammatory effects of NFκB

The pathogenic role of inflammation in cancer has drawn intensive research and highlighted the context-dependent modulation of inflammation-associated cancer by the transcription factor NFκB.¹⁰⁵ Through control of inflammatory responses, NFκB has influence in tumor development and progression by excessive innate immunity activation and abnormal cell growth.¹⁰⁶ Inflammation-associated cancer can secrete various cytokines and chemokines through NFκB binding to the promoters of genes, such as *IL1B*, *TNF*, and *IL6*.¹⁰⁷ At the same time, activation of NFκB can be regulated by the TNFα-receptor family, including RANKL.^{108,109}

It is well known that inflammatory gene signatures are altered in various tumor-cell lines and specimens of different histological and molecular subtypes. Researchers have found that the inflammatory genes, such as *IL1*, *IL6*, *IL8*, and *CCL2*, are also actively expressed in glioma-cell lines, playing differential and cooperative roles in promoting proliferation, invasion, angiogenesis, and macrophage polarization in vitro.¹¹⁰ Interestingly, the NFκB signaling activated by TNF can also induce proinflammatory chemokines, such as CCL20, CXCL13, and CXCL8, that are specific ligands for the chemokine receptor CXCR2 in ovarian cancer cells.^{111,112} It is a positive-feedback loop that high expression of proinflammatory genes in the tumor microenvironment can be increased through activation of canonical and noncanonical NFκB pathways to accelerate the development of tumors and also promote the expression of proinflammatory proteins through binding of specific dimers of activated NFκB to promoters of proinflammatory genes. For example, IL1 can induce the phosphorylation of MKK4, which is indispensable

in the processing of NF κ B p100 to the p52-active form and translocation of p52 from the cytoplasm to the nucleus.^{10,113} Besides the proinflammatory function, NF κ B has a direct anti-inflammatory effect. NF κ B can inhibit the formation of inflammasomes through inhibition of inflammasome-dependent caspase 1 activation, but the mechanism is not entirely clear and is probably related to NF κ B-induced expression of antiapoptotic proteins, such as PAI2 and Bcl-xL.¹¹⁴

Protumorigenic roles of NF κ B

The potential role of NF κ B in oncogenesis was confirmed in the discovery of the retroviral oncogene *v-Rel*, the homologue of the gene encoding cRel, one of the NF κ B subunits.¹¹⁵ The genes encoding NF κ B subunits or I κ B proteins are mutated in a variety of malignancies. Mutations and gene fusions of *IKKA*, which leads to the activation of IKK α , were detected in breast cancer, where the activation of IKK α can maintain the self-renewal of breast cancer progenitors and has been shown to be responsible for the tumor-promoting effects of progesterone in breast cancer.¹¹⁶ However, the number of tumors with persistently activated nuclear NF κ B is much larger than the subfraction of malignancies with confirmed mutations in NF κ B or I κ B-encoding genes.¹⁰⁵ In breast cancer, colon cancer, and lymphatic cancer, the persistent activation of the NF κ B-signaling pathway leads to abnormal cell proliferation and differentiation, enhanced metastasis, and treatment resistance.^{102,117,118} In colitis-associated colon cancer, positive effects of NF κ B have been shown by conditional silencing of IKK β , which persistently activates NF κ B in intestinal epithelial cells.¹¹⁹ Recent studies have found that the Epstein–Barr virus (EBV) in several T- and NK-cell neoplasms can persistently activate NF κ B via the viral protein LMP1, resembling the proteins in the TNF-receptor superfamily that induce NF κ B activation through interaction with TRAF and TRADD,^{120,121} and contribute to development of EBV-positive T- and NK-cell neoplasms.¹²²

Mutations in upstream NF κ B effectors in tumor cells will also result in the activation of the NF κ B pathway, and then the persistent activation of NF κ B can specifically target the promoters of oncogenes to form a positive-feedback loop. For instance, BRCA1 silencing in breast cancer cell lines induces phosphorylation of the Ser536 site of p65 and processing of p100/p52, causing constitutive activation of the canonical NF κ B pathway (p65/p50) and noncanonical NF κ B pathway (p100/p52) and promoting the nuclear translocation and accumulation of p52/RelB, which can enhance proliferation of MCF1 cells.¹⁰² In glioma stem cells, MLK4 binds to and phosphorylates the NF κ B regulator IKK α , leading

to enhancement of the ability of NF κ B binding to DNA and activation of NF κ B, which can induce mesenchymal *trans*-differentiation and radioresistance.¹²³ Similarly, the activation of mTORC1 induced by LMP1 is a key regulator of the NF κ B pathway in NPC cells.¹²⁴ With knockdown of the *MTORC1* gene, activation of NF κ B induced by LMP1 and the transcription of Glut1 are markedly inhibited, negatively affecting the aerobic glycolysis in nasopharyngeal carcinoma cell HONE1. Therefore, the activation of NF κ B pathway plays an important role in regulating the energy metabolism of nasopharyngeal carcinoma cells.

Antitumorigenic roles of NF κ B

The role of NF κ B in cancer is not always positive. Researchers have found that blockade of NF κ B via overexpression of I κ B α promoted oncogenic Ras-induced invasive epidermal growth, resembling squamous-cell carcinoma.¹²⁵ The overexpression of I κ B α induced by ablation of IKK β can enhance the stability of I κ B by inhibition of the phosphorylated I κ B α protein, resulting in inactivation of canonical NF κ B. In addition, the high expression of IKK β that activates classical and nonclassical NF κ B can suppress the progression of hepatocellular carcinoma by preventing DEN-induced cell death.¹²⁶ Meanwhile, ablation of IKK β can enhance the activation of JNK family members, including JNK1, which contributes to hepatocellular carcinoma development.¹²⁷ Functional cross-talk between Nrf2 and NF κ B/RelA protects the liver from necrosis, inflammation, and fibrosis, and thus prevents development of hepatocellular adenoma.¹²⁸ Transcription factors Nrf2 and NF κ B regulate the cellular antioxidant defense system, which is important in cell survival.¹²⁹ Recently, researchers found that *LCN2* is an upstream regulatory gene of the NF κ B–Snail pathway and can inhibit the phosphorylation of p65 (p-p65) and the nuclear accumulation of p-p65 and Snail to inhibit activation of the NF κ B pathway, thereby inhibiting colorectal cancer cell epithelial–mesenchymal transition and metastasis induced by the NF κ B–Snail pathway.¹³⁰ However, a number of studies have suggested that the NF κ B pathway may upregulate the expression of *LCN2* to promote the development of many cancers.^{131,132} Therefore, the NF κ B pathway is diversified in different tumor cells,^{133,134} and the complex anticancer mechanism of the NF κ B pathway is still not clear. Further study is warranted.

Prospects of NF κ B inhibitors

It is unquestionable that NF κ B inhibition as a means of cancer treatment has to be prioritized. Hundreds of NF κ B inhibitors have been developed.¹³⁵ These inhibitors are mainly designed

to target one of four key points in the NFκB pathway: IKKs, NFκB-subunit dimers, proteasome 26S in the case of proteasome inhibitors, and the Ub-ligase complex in the case of ubiquitination blockers.¹³⁵ These four elements are essential to activation of the NFκB pathway. Moreover, natural products, antioxidants, nonsteroidal anti-inflammatory drugs, and glucocorticoids are capable of interfering with the NFκB-signaling cascade.¹³⁶ As the phosphorylation step of IκBα is a common reaction for the NFκB signaling induced by diverse stimuli, IKK inhibitors are considered an interesting approach for NFκB modulation.¹³⁷ After phosphorylation of IκBα, the polyubiquitination and proteasomal degradation of the IκBα protein will result in NFκB release for translocation to the nucleus. Therefore, ubiquitination blockers and proteasome inhibitors could also be considered as interesting modulators of the NFκB cascade.¹³⁸

Many NFκB inhibitors have demonstrated appreciable anticancer activity in preclinical approaches. For example, BAY11-7082 can specifically abolish the binding of p65 to targeted DNA and downregulate the expression of TNFα.¹³⁹ As an IKKβ inhibitor, EF24 can block the NFκB-signaling pathway by inhibiting IKKβ phosphorylation, leading to cell-cycle arrest at the G₂/M phase and apoptosis.¹⁴⁰ The proteasome inhibitor MG132 inhibits tumor growth through downregulation of the NFκB-signaling pathway.^{141,142} In addition, T901 is a novel selective NFκB inhibitor functioning through binding to the NFκB complex in the cytosol, thus blocking its nuclear translocation and target-gene expression.¹⁴³ Although many NFκB inhibitors have been developed to exert antitumor effects in a variety of experimental cancer models, ranging from lymphoma to solid tumors, no such drug has been clinically approved.^{144–146} Because the mechanism of the antitumor effect of NFκB inhibitors is not totally understood, many NFκB inhibitors are not effective as a single antitumor agent.¹⁴⁷ The alterations of cellular signaling induced by NFκB inhibitors are generally involved in the establishment, evolution, and spread of malignant tumors. Therefore, considering the positive role of NFκB in the vast majority of cancer pathogenesis, NFκB inhibitors that are able to modulate more than one therapeutic target related to this disease are currently considered the most promising alternatives to single anticancer drugs.¹⁴⁸ Due to the wide range of possibilities to regulate the NFκB-signaling pathway, targeting different key points along the cascade offers a major opportunity. The challenge of NFκB inhibitors being applied in clinical intervention as novel anticancer-drug candidates lies in whether or not these NFκB inhibitors have better pharmacotherapeutic and safety profiles. Therefore, this approach still requires some improvements and more

extensive studies to ensure and optimize the expected therapeutic benefit in the future.¹⁴⁹

Conclusion

As a molecular hub linking inflammation and cancer, NFκB has been established as a crucial contributor in the development of malignant tumors. Although inhibition of NFκB activity is incapable of fully suppressing the growth of cancer, expression of NFκB components and activated NFκB signaling still reflect a potentially serious risk of malignancies.¹⁵⁰ Despite great progress in targeting NFκB signaling for cancer therapy, NFκB inhibitors have not been put into clinical application. Exploration of more effective and specific NFκB-targeted anticancer strategies is needed. With the development of technology, the inhibition of NFκB by a variety of inhibitors may pave the way for future personalized treatment strategies.

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Author contributions

LZS and SMT contributed to drafting and editing of the manuscript. DLC and QJL designed, revised, and finalized the manuscript. HRW and LDO participated in drafting and editing of the manuscript. YJZ participated in revision and coordination. JGL, YTT, and LL contributed to the literature search. MS and HW participated in conception and coordination. All authors contributed toward data analysis and drafting and revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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