

Pathogenic role and therapeutic targets of nuclear factor- κ B signaling pathway in cancer (Review)

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Received March 28, 2025; Accepted August 20, 2025

DOI: 10.3892/ol.2025.15313

Abstract. The nuclear factor- κ B (NF- κ B) signaling pathway not only exerts a notable role in inflammation and immune modulation but is also considered a key driver in the initiation and progression of cancer. NF- κ B is closely associated with tumor cell proliferation, differentiation, apoptosis, invasion and metastasis, indicating its notable role in cancer pathogenesis. Based on research into the NF- κ B pathway, the present article studied the biochemical processes involved in the NF- κ B pathway, analyzed potential drug targets and inhibitors and clarified therapeutic strategies for targeting NF- κ B in cancer treatment. The NF- κ B signaling pathway consists of both classical and non-classical pathways and plays a fundamental role in multiple cancer processes, including cancer cell proliferation, apoptosis, autophagy, inflammation, tumor microenvironment interactions, therapy resistance, ion channel modulation, tumor heterogeneity, and epithelial-mesenchymal transition (EMT)-mediated migration, invasion and metastasis. Current therapeutic development has yielded diverse pharmacological agents targeting this pathway, including phytochemical-derived NF- κ B inhibitors and synthetic molecules for cancer therapy.

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1. Introduction

Nuclear factor- κ B (NF- κ B) was first identified by Sen R and Baltimore D (1) in 1986 as a nuclear transcription factor that binds to the immunoglobulin κ light chain of activated B-cells. The mammalian NF- κ B family consists of five subunits, including p50, p52, transcription factor p65 (RelA), transcription factor RelB and the proto-oncogene c-Rel. These proteins can combine through their Rel homologous domain to form various homo- and heterodimeric complexes with distinct DNA binding, dimerization and nuclear localization (2,3). The NF- κ B signaling cascade represents a notable cellular regulatory system, which governs fundamental processes such as cell survival, proliferation, differentiation and apoptosis. As a master regulator of numerous physiological and pathological processes, the NF- κ B signaling pathway has been implicated in the pathogenesis of various human diseases, particularly malignancies. The NF- κ B signaling pathway consists of both classical and non-classical pathways and plays a fundamental role in multiple cancer processes, including cancer cell proliferation, apoptosis, autophagy, inflammation, tumor microenvironment interactions, therapy resistance, ion channel modulation, tumor heterogeneity and epithelial-mesenchymal transition (EMT)-mediated migration, invasion and metastasis. The present review systematically elaborates on the molecular mechanisms underpinning NF- κ B signal transduction and discusses therapeutic methods for cancer treatment through NF- κ B pathway modulation, which might offer potential directions for clinical translation.

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Key words: biochemical processes, cancer, drugs, inhibitors, nuclear factor- κ B pathway

2. NF- κ B signaling pathways

The NF- κ B signaling pathway comprises both classical and non-classical signaling pathways (Fig. 1).

Classical signaling pathways: The interaction between upstream signaling molecules, such as inflammatory factors, tumor necrosis factor (TNF) α , interleukin 1 (IL-1), thrombin, lipopolysaccharide (LPS), and receptors such as the TNF receptor superfamily, T cell receptor, Toll like receptor (TLR) and B cell receptor, results in the activation of inhibitor of κ kinase (I κ B), which is composed of I κ α , I κ β and I κ γ subunits. Phosphorylated I κ B undergoes ubiquitination and is subsequently recognized and degraded by the 26S proteasome via the ubiquitin-proteasome pathway. Consequently, NF- κ B can be released from the cytoplasmic NF- κ B/I κ B complex, activated and exposed to the nuclear localization domain, forming a p50/RelA dimer, which is then translocated from the cytoplasm into the nucleus. By binding to specific sites of the target gene, it initiates transcription and expression of the target genes (4-7).

The non-classical pathway is triggered by the activation of various receptors, including lymphotoxin β receptor (LT β R), B cell activating factor receptor (BAFFR), receptor activator of NF- κ B (RANK) and CD40R. Upon activation of a receptor, NF- κ B induced kinase (NIK) undergoes phosphorylation-mediated activation, subsequently initiating I κ α activation. The activated I κ α then promotes the phosphorylation and degradation of p100 (the precursor of p52), triggering its proteasomal processing into mature p52. After this processing, p52 binds to RelB in the cytoplasm and the resulting heterodimer translocates to the nucleus, where it modulates transcription of target genes (8,9).

3. NF- κ B pathway-related biochemical processes

The NF- κ B signaling pathway is implicated in multiple biochemical processes, such as cancer cell proliferation, stemness, apoptosis, autophagy, inflammation, microenvironment, drug resistance, ion channel regulation, tumor heterogeneity, and EMT-mediated migration, invasion and metastasis (Figs. 2 and 3).

Cancer cell proliferation. The NF- κ B signaling pathway is critically involved in tumorigenesis and treatment via its regulation of genes controlling cell proliferation, migration and apoptosis (10). The tripartite motif (TRIM) protein family members are widely implicated in tumor cellular processes. TRIM52 is highly expressed in cancer and promotes the invasion, migration and proliferation of ovarian cancer cells. TRIM52 acts as a positive regulator of the NF- κ B pathway, and its overexpression enhances TNF- α and IL-8 levels by activating the NF- κ B signaling pathway (11). The phosphatase and tensin homolog (PTEN) is a notable tumor suppressor gene. Knockout of ubiquitin-specific protease 13 (USP13) down-regulates PTEN, enhancing bladder cancer cell proliferation, invasion and migration. Furthermore, NF- κ B signaling activation suppresses both USP13 and PTEN expression, thereby promoting tumorigenesis (12). Silencing Midkine (MDK) inhibits breast cancer cell proliferation and migration by reducing the expression of nuclear receptor subfamily 3 group C

member 1 (NRS3C1) via inhibition of the NF- κ B pathway and NF- κ B nuclear distribution (13). Meis homeobox 2 (MEIS2), a crucial regulator of organ development and tumorigenesis is significantly downregulated in tumor tissues and cell lines compared with adjacent healthy counterparts. Research has found that MEIS2 inhibits the proliferation of thyroid cancer cells via regulation of the NF- κ B pathway (14).

MicroRNAs (miRNAs/miRs) play a notable role in carcinogenesis, with bioinformatics analysis of cancer samples identifying notable downregulation of miR-139-5p and inhibition of gastric cancer cell proliferation by regulating peripheral myelin protein 22 (PMP22) via the NF- κ B signaling pathway (15). Members of the let-7 family are abnormally expressed in human cancer, and homeobox B1 (HOXB1) is a potential target gene for the miRNA hsa-let-7. Downregulation of HOXB1 gene by hsa-let-7g activates the NF- κ B pathway and promotes the development of osteosarcoma (16). In esophageal cancer cell lines, overexpression of transglutaminase 3 (TGM3) inhibits cell proliferation and induces apoptosis by activating the NF- κ B signaling pathway (17). MiR-let-7a has been identified as an inhibitory factor for human tumor development and a positive regulator of ubiquitin-specific protease 35 (USP35) expression, which is closely associated with cancer development. USP35 regulates cell proliferation both *in vivo* (4-5 weeks of age athymic BALB/c nude mice xenograft model) and *in vitro* (prostate cancer cells, breast cancer cells, cervical cancer cells, lung cancer cells). USP35 promotes its de-ubiquitination to stabilize TNFAIP3-interacting protein 2 (ABIN-2) and inhibits NF- κ B activation, thereby inhibiting cell proliferation (18). CXC chemokine ligand (CXCL) 16 is a membrane protein present in both transmembrane and soluble forms, which is associated with the pathogenesis of tumors. The silencing of CXCL16 not only reduces lung cancer cell proliferation and invasion, but also leads to the inactivation of the NF- κ B pathway in tumor cells; thus, silencing CXCL16 regulates the NF- κ B pathway to treat cancer (19).

Stemness. F-box and WD-repeat-containing protein 2 (FBXW2), as an E3 ligase, is crucial to tumorigenesis regulation. Studies have revealed that NF- κ B-p65 is a novel substrate for FBXW2, and the FBXW2-p65 axis is a key regulatory factor for sex-determining region Y-box 2 (SOX2)-induced cancer-stem cells (CSCs). FBXW2 suppresses SOX2 by degrading p65, thereby promoting the stemness of breast cancer cells (20). Current cancer therapies often show limited efficacy due to chemotherapy-induced enrichment of CSCs. Metallothionein-1G (MT1G) is a cysteine-rich protein that is downregulated in CSCs. Activin A, a downstream target of NF- κ B, is crucial for regulating self-renewal ability and stemness characteristics. Mechanically, MT1G inhibits NF- κ B to limit the secretion of activin A, thereby suppressing pancreatic cancer cell stemness (21). TNF- α is a pro-inflammatory cytokine that is upregulated in cancer cells and is associated with cancer recurrence. Transcriptional co-activator with PDZ-binding motif (TAZ) is a transcription co-activator, and its high expression levels are associated with oncogenesis. A previous study demonstrated that TNF- α upregulates TAZ transcription via the non-classical NF- κ B signaling pathway, thereby increasing breast cancer stemness (22). PTEN is a tumor suppressor gene, and it has been observed in multiple

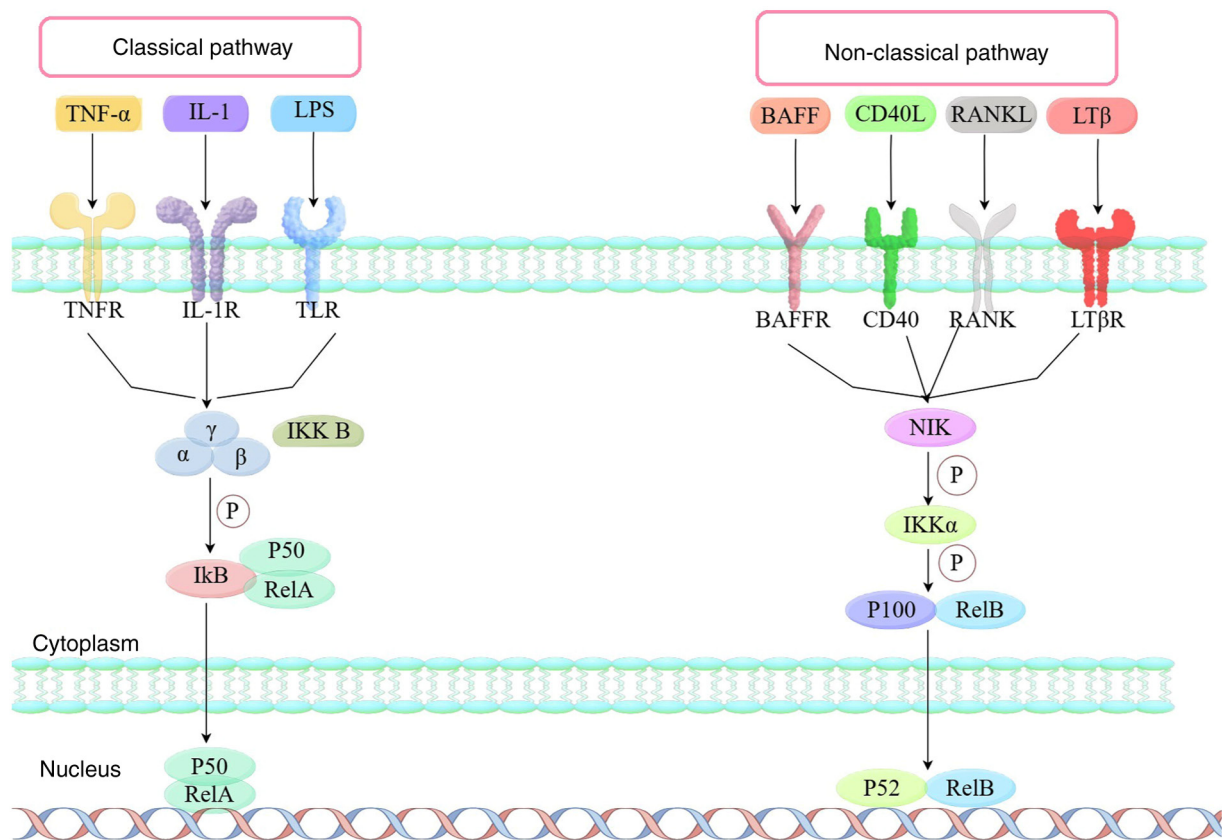


Figure 1. Simplified diagram of classical and non-classical NF- κ B signaling pathway. NF- κ B, nuclear factor- κ B; TNF- α , tumor necrosis factor- α ; TNFR, tumor necrosis factor receptor; IL, interleukin; LPS, lipopolysaccharide; TLR, Toll-like receptor; I κ B, inhibitor of nuclear factor- κ B kinase subunit β ; P, phosphate group; RelA, transcription factor p65; BAFF, B-cell activating factor; BAFFR, B-cell activating factor receptor; CD40L, CD40 ligand; CD40, tumor necrosis factor receptor superfamily member 5; RANKL, receptor activator of nuclear factor- κ B ligand; RANK, receptor activator of NF- κ B; LT β , lymphotoxin β ; LT β R, lymphotoxin β receptor; NIK, NF- κ B induced kinase; IKK α , inhibitor of κ kinase α ; RelB, transcription factor RelB; p52, 52 kDa repressor of the inhibitor of the protein kinase.

diverse types of cancer that the knockout of PTEN is closely related to tumorigenesis. CSCs are not only a renewable source of tumor cells, but also a source of antitumor drug resistance. PTEN deficiency, augmented by NF- κ B signaling, promotes the generation of CSCs, indicating that the NF- κ B signaling pathway has an important role in maintaining stemness in prostate cancer (23). A study has reported a positive correlation between inflammatory cytokines and CSCs. Research has determined that IL-32 γ inhibits stemness and an inflammatory tumor microenvironment (TME) through inhibiting NF- κ B signaling transduction, thus regulating the malignant behavior of skin carcinogenesis (24). MiRNAs have been implicated in a diverse range of biological activities, including CSC activity. Eps15 homologous domain-containing (EHD) 1 is a protein with a c-terminal comprising a member of the EHD family. A previous study has revealed that miR-590 downregulates EHD via the NF- κ B signaling pathway and inhibits non-small cell lung cancer stem-like characteristics both *in vitro* (non-small cell lung cancer cells) and *in vivo* (male BALB/c nude mice xenograft model) (25).

Apoptosis. Aberrant activity of the NF- κ B signaling pathway is implicated in the pathogenesis of multiple human malignant tumors by affecting cellular processes such as apoptosis. NF- κ B collaborates with other transcription

factors in cancer progression via subunit interactions or target gene regulation, with its activity is further modulated by crosstalk with kinases, including glycogen synthase kinase 3 β (GSK3 β) (26). GSK3 β is a phosphorylated glycogen synthase that is central to cell proliferation, cell apoptosis, cell migration and embryonic development. TNF-related apoptosis-inducing ligands (TRIM) can selectively target tumor cells for cell death. Experimental data has demonstrated that GSK3 β exerts anti-apoptotic effects through the NF- κ B signaling pathway, while TRIM21 can inhibit the activation of NF- κ B by GSK3 β to promote apoptosis of non-small cell lung cancer cells (27). Thioredoxin-dependent peroxide reductase (PRDX) 3 is a member of the peroxiredoxins family that is associated with the regulation of intracellular signaling pathways controlling cell apoptosis and proliferation. Silencing of overexpressed PRDX3 in cancer cells leads to ovarian cancer cell apoptosis, possibly by inhibiting the NF- κ B signaling pathway (28). Previous evidence has revealed that maternally expressed gene 3 (MEG3) is a tumor suppressor gene and plays a key role in the development, progression and metastasis of cancer. The experimental data demonstrated that MEG3 is upregulated in cancer cells and promotes cell apoptosis, indicating that MEG3 is a tumor suppressor of cancer. Ectopic overexpression of MEG3 inhibits breast

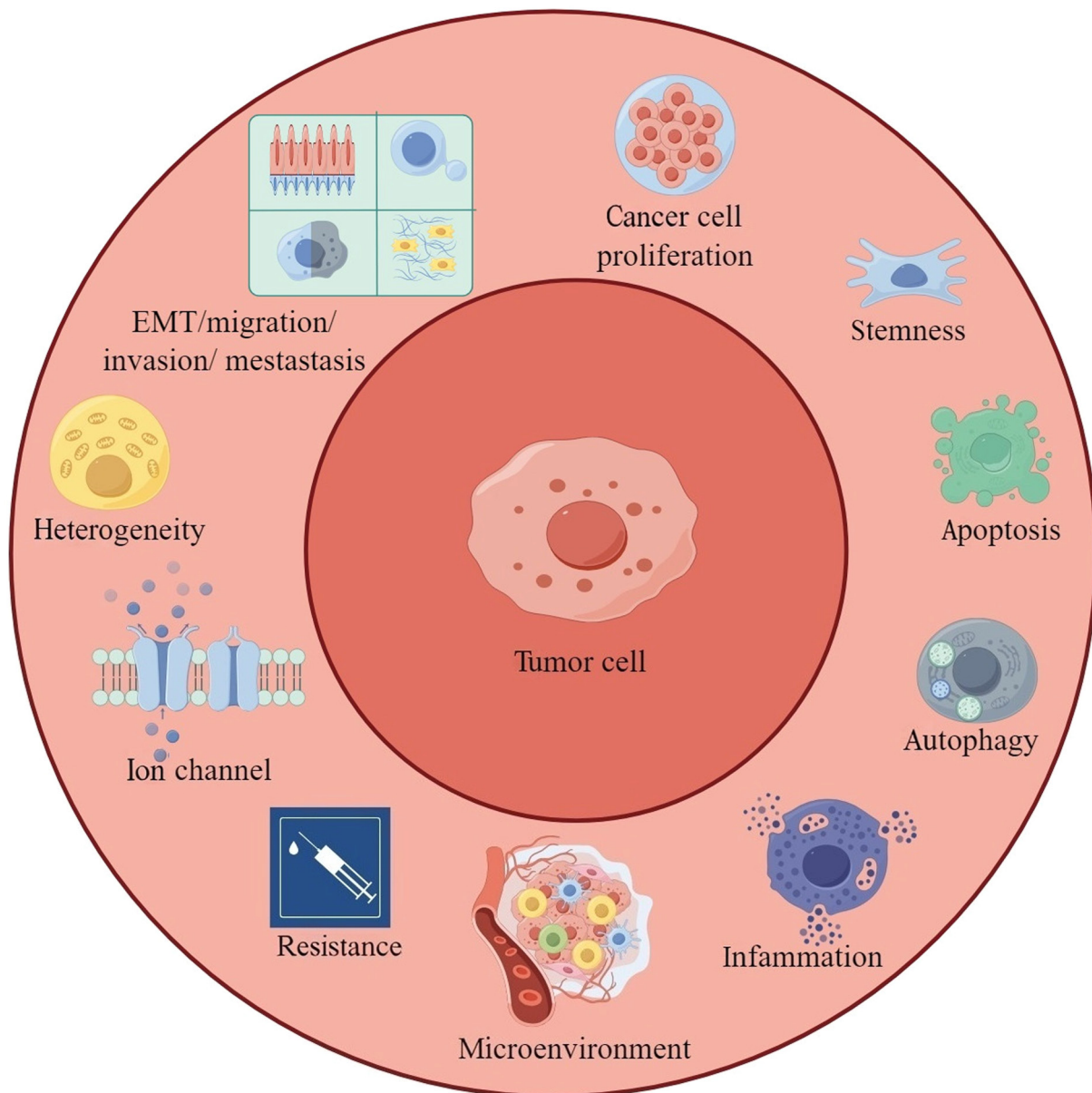


Figure 2. Tumor cells and biochemical processes. EMT, epithelial-mesenchymal transition.

cancer cell growth and induces apoptosis of cancer cells by activating the NF- κ B signal pathway (29).

Autophagy. Autophagy is a metabolic process that captures cellular waste for degradation in lysosomes. Autophagy primarily regulates cytoplasmic quality control by degrading proteins and organelles, while recycling intracellular components to maintain cellular homeostasis. Autophagy is upregulated in a majority of cancers to promote cell survival, proliferation and metastasis (30). During the development of cancer, apoptosis and autophagy can be triggered simultaneously, and in some cases autophagy can be suppressed by inducing apoptosis. Cells undergoing cancerous transformation are prone to utilizing any alterations in the process of apoptosis. Autophagy usually exerts an inhibitory role in the early stages of carcinogenicity and a promoting role in advanced stages of cancer (31). Autophagy is a double-edged sword. In the early stages/pre-cancerous stages, autophagy

can selectively clear damaged organelles, reduce ROS production, maintain genomic stability and cellular homeostasis, thereby preventing normal cells from becoming malignant and inhibiting tumorigenesis. In the late stage/once a tumor has formed, autophagy recycles nutrients for energy, responds to hypoxia and nutrient deprivation, clears damage caused by treatment, and suppresses ROS generated by chemotherapy, thereby supporting tumor growth, enhancing adaptability, and producing treatment resistance (32). Exosomes (Exos) are membranous vesicles that fuse with targets to transfer miRNAs to the receptor cell membrane, thereby regulating cell proliferation, differentiation and apoptosis. Evidence indicates that Exos that transfer miR-1910-3p promote cancer proliferation and migration and induce autophagy. MiR-1910-3p down-regulates myotubularin-related protein 3 and activates the NF- κ B signaling pathway to promote breast cancer progression (33). TLRs activation of the NF- κ B signaling pathway, while β -arrestin maintains the upregulated state by prolonging

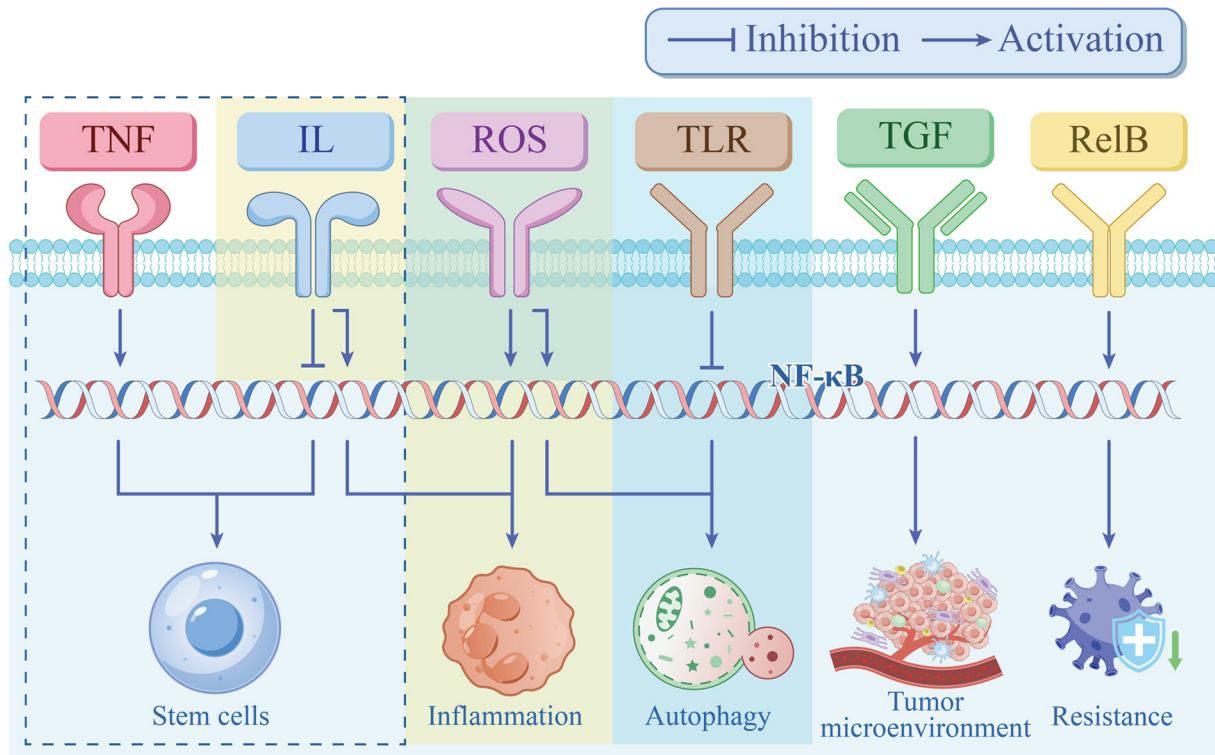


Figure 3. NF- κ B pathway-related biochemical processes. NF- κ B, nuclear factor- κ B; TNF- α , tumor necrosis factor- α ; IL, interleukin; ROS, reactive oxygen species; TLR, Toll like receptor; TGF, transforming growth factor; RelB, transcription factor RelB.

and altering the characteristics of NF- κ B signaling. TLRs and β -arrestin can result in the development and progression of tumors by coordinating cellular signaling pathways, such as NF- κ B signal transduction. β -arrestin 2 (ARRB2) is a multifunctional cellular adapter protein that regulates cellular signaling pathways. In a previous study, ARRB2 was identified to negatively regulate NF- κ B activation and autophagy, thereby alleviating the progression of lung cancer induced by TLR3 and TLR4 (34). Long non-coding RNAs (lncRNAs) are typically upregulated in cancer. Highly upregulated in liver cancer (HULC) is an oncogenic lncRNA, and immunofluorescence staining further confirms that HULC may drive tumor development by promoting autophagy. HULC has been identified to be upregulated in human cancer and it was determined that the lncRNA can, to some extent, activate the NF- κ B signaling pathway to drive malignant progression in an autophagy-dependent manner in liver cancer (35).

Inflammation. Inflammation is considered a hallmark of cancer and plays a notable role in the pathogenesis of multiple cancers (36). Inflammation plays a dual role in cancer progression, where it is capable of promoting or inhibiting tumor development, leading to divergent treatment outcomes. Chronic inflammation has been reported to promote tumor progression, while acute inflammation leads to antitumor immune responses (37). A study has described that dysregulation of the NF- κ B pathway contributes to inflammation-related diseases as well as cancer. The pro-tumor functionality of NF- κ B arises from several mechanisms that regulate diverse features of tumor progression (38). Primarily, ROS drives tumorigenesis through multiple mechanisms. Under physiological conditions,

the high-mobility group box-1 (HMGB1) protein localizes to the nucleus but acts as a pro-inflammatory factor upon cellular damage. Beyond its classical role as an antioxidant enzyme mitigating lipid peroxidation, glutathione peroxidase 4 (GPX4) regulates cytokine signaling. Results of immunoprecipitation show that HMGB1 interacts with GPX4 in cancer cells, which leads to ROS accumulation and inflammation, contributing to the development of colon cancer. HMGB1 knockdown inhibits inflammation and ROS accumulation through the NF- κ B pathway (39). Additionally, pro-inflammatory factors can also affect the proliferation of malignant cells. Spectrin β , non-erythrocytic 1 (SPTBN1) acts as a tumor suppressor, and its loss upregulates pro-inflammatory cytokines, such as IL-1 α , IL-1 β and IL-6, and enhances NF- κ B transcriptional activity, driving hepatocellular carcinoma initiation and progression (40). Finally, the NF- κ B signaling pathway also facilitates tumor invasion (such as VEGF, macrophage inflammatory protein-1 and CXC-chemokine ligand 8) by regulating the expression of pro-angiogenesis genes and inducing chemokines (38).

Microenvironment. The TME refers to the non-cancer cells and components present in tumors, including the molecules they produce and release. The sustained interaction between tumor cells and the TME plays a notable role in the occurrence, development, metastasis and treatment response of tumors (41). The NF- κ B signaling pathway affects oncogenesis by interacting with the TME. As a crucial component of the TME, cancer-associated fibroblasts (CAFs) are a key determinant of cancer progression (42). Transforming growth factor- β (TGF- β) receptors are known tumor suppressors for

cancer. In ovarian cancer cells, TGF- β increases the expression of versican in CAFs present in the TME by activating the NF- κ B signaling pathway, thereby regulating the progression of ovarian cancer (43). A study has identified that the TME plays an important role in the progression of cancer. Activin B is a member of the TGF- β superfamily and is a dimeric structure containing the inhibin β subunit (INHBB). INHBB has been demonstrated to positively regulate the proliferation, migration and invasion of cancer cells *in vitro* (gastric cancer cells). In addition, activin B promotes the occurrence of cancer by reprogramming fibroblasts into CAFs. The overexpression of INHBB in gastric cancer cells results in activin B secretion, which activates the NF- κ B signaling pathway of normal fibroblasts. The activated fibroblasts create a pro-tumor microenvironment, which can increase the tumor growth of gastric cancer through a positive feedback loop (44).

Chitinase-3 like protein 1 (CHI3L1) has been demonstrated to be upregulated in various types of tumors, which contributes to tumor progression. Experimental results indicated that CHI3L1 is upregulated in glioma cells and binds to actin $\alpha 4$ and NF- κ B1, which result from the activation of the NF- κ B signaling pathway within glioma cells and reprograms the TME to influence cancer progression; CHI3L1 was up-regulated in all disease stages of glioma, which was closely related with tumor survival, growth and invasion. Therefore, it serves as a promising therapeutic target for glioma (45). Stomatin-like protein 2 (STOML2) is a notable lipid raft component and a member of the stomatal protein superfamily. STOML2 is essential for the tumor inflammatory microenvironment, which induces angiogenesis and facilitates tumor immune escape simultaneously both *in vitro* and *in vivo*. Mechanistically, STOML2 regulates colorectal cancer proliferation, angiogenesis and immune escape through activated NF- κ B signaling pathway via binding to tumor necrosis factor receptor-associated death domain protein, resulting in upregulation of Cyclin D1, VEGF and PD-L1 (46).

Tumor-associated macrophages, as one of the most important components of TME, play a dual role in promoting tumor growth and antitumor immunity (47). Evidence has revealed that tumor-derived Exos induce an immunosuppressive phenotype to promote tumor metastasis, and upregulate programmed cell death 1 ligand 1 (PD-L1) in macrophages by activating the NF- κ B signaling pathway (48). PD-L1 is a biomarker on various cell surfaces, including tumor cells. The expression of PD-L1 in macrophages is associated with cancer development. Interferon-inducible 16 (IFI16), as a carcinogenic effect of PD-L1, activates a stimulator of interferon genes-(TANK-binding kinase-1) that mediate immune regulation, thereby activating the NF- κ B pathway. In this manner, PD-L1 is reported to promote the progression of cervical cancer (49).

BRCA1 associated protein 1 (BAP1) is a hydrolytic enzyme. BAP1 mutations are shown to inhibit the NF- κ B signaling pathway, and repress macrophage cytokine secretion and antigen presentation, thereby inducing an immunosuppressive TME and enhancing the malignant phenotype of uveal melanoma cells, ultimately promoting cell growth and metastasis (50). D2 dopamine receptor (DRD2) exerts tumor-suppressive effects by inhibiting the NF- κ B signaling pathway. DRD2 also regulates the TME as it promotes M1

polarization of macrophages and triggers pyroptosis in breast cancer cells (51). Mesenchymal stem cells (MSCs) are a key component of TME and play a notable role in the development of tumors. Exos derived from tumor cells affect the biological characteristics of MSCs. For example, Exos derived from the gastric cancer cell line AGS affect the immune regulatory function of MSCs via the NF- κ B signaling pathway, enhancing their ability to activate immune cells, maintaining an inflammatory environment and supporting tumor growth in gastric cancer cells (52). Rho-associated protein kinase (ROCK)-Myosin II activity and NF- κ B establish a positive feedback loop initiated by ROCK regulation of IL-1 α and perpetuated and amplified by IL-1 α /IKK β /NF- κ B supporting amoeboid behavior in return. In addition, elevated activity of myosin II enhances cellular mechanical properties and signal secretion, thereby reshaping innate immune cell function and forming an immunosuppressive microenvironment, ultimately supporting tumor growth (53).

Resistance. Cancer remains the leading global cause of mortality. While chemotherapy is a primary treatment option, drug resistance poses a major challenge in oncology. The NF- κ B signaling pathway has emerged as a key mediator of drug resistance, including chemotherapy, endocrine therapy and immune therapy resistance (54). F-box and WD-repeat-containing protein 2 (FBXW2) critically regulates tumor progression by directly binding to the p65 subunit, leading to its ubiquitination and degradation. Both *in vitro* (breast cancer cells) and *in vivo* (4-week-old female athymic nude mice xenograft model) experiments from a single study have revealed that FBXW2 overexpression eliminates p65-mediated paclitaxel resistance in breast cancer cells (20). Rac1b is an isomer of Rac1 in the Rho family of GTPases and is involved in cancer and oxaliplatin resistance. In one study, upon the upregulation of Rac1b, the NF- κ B signaling pathway was activated, which promoted colorectal cancer cell proliferation and inhibited cell apoptosis. Furthermore, The NF- κ B pathway ‘locks’ cancer cells in a state that is more susceptible to oxaliplatin-induced apoptosis by upregulating Rac1b (a pro-survival and anti-apoptotic protein), thereby increasing sensitivity. The core logic is a ‘pro-survival paradox’: Excessive activation of pro-survival signals paradoxically makes cells more sensitive to specific types of death (55).

TRIM47 is a potential diagnostic biomarker for tamoxifen resistance. NF- κ B signaling pathway activation induces protein kinase C- ϵ and D3 interaction with TRIM47, forming a ternary complex. The formation of the TRIM47-PKC- ϵ -PKD3 complex accelerates division (proliferation) on the one hand and activates alternative pathways on the other, rendering endocrine therapy ineffective and leading to tumor expansion and drug resistance (56). Cancer progression leads to RelB upregulation, which transcriptionally activates Bcl-2, cyclin D1 and matrix metalloproteinase (MMP)1 to promote cancer cell proliferation, EMT and metastasis. A previous study suggested that the RelB-mediated non-classical NF- κ B pathway is a key contributor to late-stage breast cancer progression and estrogen receptor (ER) functional impairment. In the early stages of breast cancer, the ER signaling pathway initiates tumorigenesis and promotes local tumor growth. Ultimately, in the absence of estrogen, activation of the non-canonical NF- κ B

signaling pathway primarily replaces ER function to maintain breast cancer metastasis (57). Research has demonstrated that epidermal growth factor receptor-tyrosine kinase inhibitor resistance develops via the NF- κ B-induced upregulation of PD-L1, enabling immune escape in lung cancer (58).

The NF- κ B pathway promotion of cancer cell survival and matrix fibrosis is driven by IL-1 receptor associated kinase-4 (IRAK4). IRAK4 deficiency eliminates NF- κ B activity, multiple immunosuppressive factors, checkpoint ligands and hyaluronic acid synthase 2, resulting in T cell dysfunction in pancreatic ductal adenocarcinoma (59). CSCs represent promising therapeutic targets in oncology. Actin-related protein (ARP)-2/3 complexes are associated with cancer migration, invasion and differentiation. ARP subunit C1B activates the NF- κ B and signal transducer and activator of transcription-3 signaling pathways by inhibiting the TRIM21-mediated degradation of IFI16 and Hu-antigen R in stem cells, thereby promoting mesenchymal phenotype maintenance and radiation resistance in glioma stem cells (60). δ -like canonical notch ligand 1 (Dll1⁺) cells represent quiescent CSCs. In a study on tumor initiation and progression, Dll1⁺ cells increased the sensitivity of tumor cells to chemotherapy and significantly eliminated tumor growth and metastasis through pharmacological inhibition of the NF- κ B pathway in breast cancer (61). Heat shock protein β -1 (HSPB1) expression is upregulated in breast cancer tissues, which can promote the growth and metastasis of cancer both *in vivo* (4-6 weeks female BALB/c nude mice xenograft model) and *in vitro* (breast cancer cells). Mechanistically speaking, HSPB1 binds I κ B α and promotes its ubiquitination-mediated degradation, resulting in increased nuclear translocation and activation of the NF- κ B signaling pathway. Furthermore, HSPB1 overexpression leads to enhanced secretion of IL-6, which contributes further towards cancer progression. In addition, HSPB1 promotes doxorubicin resistance by protecting cancer cells from drug-induced iron-deprivation disease (62).

Ion channels. Aberrant calcium (Ca²⁺) signaling contributes to tumorigenesis. Mucolipin-2 (MCOLN2), as a Ca²⁺ ion channel, is upregulated in malignant tissues, where it promotes prostate cancer progression via IL-1 β /NF- κ B pathway activation (63). Previously, research has identified that chloride (Cl⁻) channels are pivotal in oncogenic progression. Cl⁻ intracellular channel 1 (CLIC1) is a member of the Cl⁻ ion channel (CLC) protein family, which are mainly expressed in the stomach, pancreas, liver and cervix. Knockout of CLIC1 significantly reduces the proliferation, migration and invasion of cervical cancer cells *in vitro*, as well as suppressing tumorigenesis *in vivo* (mouse xenograft models). At the molecular level, CLIC1 directly interacts with the IKK complex, a key kinase in the NF- κ B pathway, and promotes its activation. Pyrrolidine dithiocarbamate, as an inhibitor of NF- κ B, mitigates the tumor promoting effect of CLIC1 in cervical cancer cells (64). Acid-sensing ion channel 1 (ASIC1) is a non-selective cation channel that upregulates cell proliferation, apoptosis, angiogenesis and metastasis in tumor cells. For the acidic stimulation, pH 6.4 medium was prepared using lactic acid. MDA-MB-231 cells were seeded in 96-well plates and treated with control, pH 6.4, or control medium containing IL-8. Acidic treatment induced IL-8 expression in cancer cells; phosphorylation of NF- κ B was

induced by acidic treatment, and inhibition of NF- κ B activation reduced acid-induced IL-8 expression. Acid stimulation increases the expression of ASIC1 and inhibition of the NF- κ B pathway, and reduces acid-induced IL-8 expression, resulting in breast cancer progression (65).

The RNA of transient receptor potential cation channel subfamily M member 8 (TRPM8), a gene highly expressed in the prostate epithelium, triggers aseptic inflammatory states in healthy and prostate cancer cells via TLR3. Upon extracellular vesicles endocytosis, TRPM8 mRNA binds TLR3 in endosomes, thereby promoting NF- κ B activation and release of pro-inflammatory signals. The NF- κ B signaling pathway induces inflammation and promotes anticancer activity in cancer (66). The intermediate-conductance Ca²⁺-dependent potassium channel (K_{Ca}3.1) is highly expressed in the plasma membrane and in the inner mitochondrial membrane (mitoK_{Ca}3.1) of various cancer cells. By enhancing the production of mitochondrial ROS and activation of the NF- κ B pathway, as well as downregulating Bcl-2 19 kDa-interacting protein, pharmacological targeting of mitoK_{Ca}3.1 significantly reduces cancer cell migration in melanoma, pancreatic ductal adenocarcinoma and breast cancer lines (67). CLC-3 is a member of the voltage-gated CLC family and is involved in the resistance of tumor cells to chemotherapy drugs (e.g., paclitaxel or doxorubicin). The upregulated expression of CLC-3 in cancer cells induces multidrug resistance by upregulating NF- κ B-signal-dependent P-glycoprotein expression in lung adenocarcinoma and breast carcinoma cell lines (68).

Overexpressed voltage gated Ca²⁺ (Ca_v) channel subunit $\alpha_2\delta$ -1 is associated with the development and malignancy of various cancers. The Ca_v channel has been identified to exert a fundamental role in tumor biology. The activation of TLR4 upregulates the transcription and expression of $\alpha_2\delta$ -1 by modulating the NF- κ B signaling pathway, thereby driving the proliferation and migration of human glioblastoma cells (69). The activation of the Ca²⁺ channel permits storage operation, initiation of the downstream NF- κ B signaling pathway and phosphorylation of extracellular signal regulated kinase (ERK) 1/2, all of which promote the expression of the inflammatory gene cyclooxygenase (COX)-2 in gastric cancer cells (70). Ca²⁺ influx serves as a crucial regulator of cellular function and fate across diverse cell types. The transient receptor channel 3 (TRPC3) regulates Ca²⁺ flux through non-selective osmotic channels. In patients with colon cancer, knocking down TRPC3 significantly decreases the activation of the NF- κ B pathway and impairs the ability of mesenchymal stem cell-transformed CAF cells to promote tumor migration and invasion (71). Extracellular pressure drives proliferation by increasing Ca²⁺ through the pressure-sensitive Ca_v3.3 channel. Extracellular pressure increases Ca²⁺ influx through Ca_v3.3, promotes proliferation through protein kinase C- β activation, and ultimately increases cell cycle protein D and proliferation through classic NF- κ B signaling in colon, breast and prostate cancer cells (72).

Heterogeneity. EMT is a hallmark of cancer and is strongly correlated with cancer metastasis. The EMT status is frequently heterogeneous within a single tumor. Mechanistically, cyanidin-3-glucoside (C3G) induces EMT reversal, characterized by changes in epithelial markers and the related transcription

factor Snail1. Research has found that NF- κ B is attenuated by C3G in triple negative breast cancer cells, while Sirt1 is induced by C3G. Later evidence demonstrates that abrogation of Sirt1 with small interfering RNA transfection abolished NF- κ B inhibition and EMT reversion by C3G. Subsequent experiment revealed that miR-138 inhibits Sirt1 through mRNA translation and is suppressed by C3G. Additionally, the inhibition of miR-138 contributes to the reactivation of Sirt1 and migration and invasive inhibition of TNBC by C3G (73). Tumor cells that have undergone EMT exhibit characteristics highly similar to those of CAFs and are capable of performing the tumor-promoting functions of CAFs. EMT has been recognized as a potential source of CAFs in solid tumors and a contributor to the heterogeneity of tumors, making it possible to initiate the invasion-metastasis cascade. EMT is reported to generate a unique phenotype of mesenchymal subpopulations that are resistant to traditional therapies, leading to cellular heterogeneity in head and neck squamous cell carcinoma and the abundance of E-cadherin being affected by NF- κ B and Akt pathway (74). Non-glioblastomatous diffuse gliomas (non-GDGs) are a group of heterogeneous tumors. EMT has been verified as essential for tumor heterogeneity. Retinol binding protein 1 gene (RBP1) has been identified as one of the most upregulated genes in severe subtypes of non-GDGs. Upregulated RBP1 is implicated in the EMT process and participates in the NF- κ B signaling pathway. Research has indicated that RBP1 induces phosphorylation of I κ α and enhances the expression of the NF- κ B signaling pathway, thereby driving the invasion and migration characteristics of EMT, such as phenotype and cell proliferation, in non-GDG cells (75).

Low grade gliomas (LGGs) exhibit significant genetic heterogeneity. Fatty acid binding protein 5 (FABP5) is one of the most upregulated genes in malignant LGGs. EMT, which the NF- κ B signaling pathway is involved in, is associated with the expression of FABP5 in LGGs, EMT. In addition, FABP5 induces I κ α phosphorylation, thereby activating the NF- κ B signaling pathway. Furthermore, FABP5 enhances malignant tumors of LGG through classical activation of the NF- κ B signaling pathway (76). Tumor heterogeneity arises not only from the tumor cells themselves, but also from different TMEs. The presence of nutrient-deficient hypoxic areas in the TME increases tumor occurrence and metastasis. IL-8 is a chemokine mainly produced by macrophages, neutrophils and cancer cells in the TME. TME is the main source of IL-8. The experiment found that IL-8 induces EMT in colorectal cancer cells by upregulating the phosphorylation of p65 (one of the five components of the NF- κ B pathway), which is the core mechanism of TME driven cell metastasis (77). Research has suggested that CSCs exhibit heterogeneity. Annexin A3 (ANXA3) contributes to tumorigenesis across multiple cancer types, with its expression markedly upregulated in malignant tissues. Knockdown of ANXA3 has been shown to inhibit breast cancer cell invasion but promotes cell proliferation in both *in vitro* (breast cancer cells) and *in vivo* (6-8 weeks old female BALB/c nude mice xenograft model) assays and inhibits the NF- κ B pathway by upregulating I κ B α , leading to EMT and decreased heterogeneity of CSCs (78). In addition, cancer recurrence may stem from the chemoresistance of CSCs and their ability to reconstruct heterogeneous tumors,

with the NF- κ B signaling pathway involved in this process. TNF-like weak apoptosis inducer, a multifunctional cytokine important for tissue repair, has exhibited upregulation after chemotherapy to induce the activation of non-classical NF- κ B, enhance the stem-like characteristics of CSCs and thus leading to ovarian cancer recurrence (79).

EMT-mediated migration, invasion and metastasis. MRG domain binding protein (MRGBP) plays a pro-cancer role in human cancers, and abnormally elevated MRGBP is considered to drive the occurrence of cancer. The expression of MRGBP is significantly upregulated in cancer tissues and is associated with EMT mediated by the Wnt/ β -catenin and NF- κ B/p65 pathways, which promotes colorectal cancer progression (80). DNA-damage-inducible transcript 4 (DDIT4) plays an important regulatory role in various cancer cell processes. DDIT4 overexpression has been significantly associated with lymph node metastasis in patients with cervical cancer. Knockout of DDIT4 mitigates the migratory and invasive activity of colorectal cells *in vitro*, and downregulates EMT related proteins and the NF- κ B pathway in cancer cells. DDIT4 has also been demonstrated to promote tumor progression (81). Fermitin family member 1 (FERMT1) is broadly expressed in epithelial tissues and participates in diverse cellular processes. A study has demonstrated that FERMT1 was upregulated in nasopharyngeal carcinoma tissues. Both *in vitro* (cervical cancer cells) and *in vivo* (intraperitoneal injection mouse model) data demonstrated that knocking out FERMT1 significantly reduces cell proliferation, migration and invasion by inhibiting EMT and the NF- κ B signaling pathway (82). Zipper interacting protein kinase (ZIPK) belongs to the death-related protein kinase family and has been identified as a tumor-suppressor factor. The upregulation of ZIPK promotes cell growth, migration, invasion, tumor formation and metastasis in gastric cancer nude mice. ZIPK activates Akt/I κ B α /NF- κ B signaling to promote EMT and metastasis in BGC-823, SGC-7901 and SNU-1 cells (83). Nucleotide-binding oligomerization domain-like receptors (NLRs) are anti-oncogenes in lung adenocarcinoma cells. NLRP2-silencing promotes cell proliferation and migration by promoting NF- κ B signaling in the microenvironment, thereby inducing EMT phenotype and cytoskeletal reorganization (84).

N-myc downstream-regulated gene 1 (NDRG1) has been reported as a notable gene in cancer progression. The overexpression of NDRG1 inhibits migration, invasion and EMT *in vitro* (prostate cancer cells), and inhibits metastasis *in vivo* (5-6 weeks old male BALB/c nude mice xenograft model). In addition, miR-96-5p contributes to NDRG1 deficiency and promotes the migration and invasion of prostate cancer cells. Mechanistically, NDRG1 deficiency activates the NF- κ B pathway, stimulates phosphorylation of p65 and I κ B α , and induces EMT in cancer (85). S100 calcium-binding protein A14 (S100A14), is a functional regulatory factor and the expression of S100A14 in nasopharyngeal carcinoma cells and tissues has been reported to be significantly lower than in adjacent non-cancerous tissues. Overexpression of S100A14 inhibits cancer metastasis by inhibiting the NF- κ B signaling pathway and reversing EMT (86). The absence of ATP-dependent DNA helicase Q4 (RECQL4), which is a member of the RECQ

helicase family in cancer cells, has been shown to affect cell proliferation, invasion, apoptosis and tumorigenesis. Compared with adjacent non-tumor tissues, RECQL4 is highly expressed in esophageal squamous cell carcinoma tissues. RECQL4 activates Akt, ERK, and NF- κ B, which are implicated in the proliferation and migration of esophageal squamous cell carcinoma cells (87). CAFs are key stromal cells that play a dominant role in tumor progression. Asporin, an extracellular matrix protein primarily expressed in CAFs across multiple tumor types, promotes tumor invasion and migration. Notably, it is also highly expressed in a variety of tumors (e.g., pancreatic ductal adenocarcinoma, gastric cancer and colorectal cancer), where it actively results in the invasion and migration of cancer cells. CD44 is a receptor involved in the invasion and migration of refractory cancer induced by asporin. Evidence has found that asporin interacts with CD44, activates the NF- κ B/p65 signaling pathway and promotes pancreatic cancer invasion and migration by regulating EMT (88). Lipocalin2 (LCN2), as an upstream mediator of the NF- κ B/snail signaling pathway, exerts a negative regulatory role in EMT, invasion and metastasis in colorectal cancer. LCN2 blocks cell proliferation, migration and invasion both *in vitro* (colorectal cancer cells) and *in vivo* (4-5 weeks old BALB/c nude mice xenograft model), and inhibits the translocation of NF- κ B to the nucleus. LCN2 significantly inhibits EMT and metastasis induced by the NF- κ B/snail pathway *in vitro* and *in vivo* by weakening the pathways promoter activity (89).

The inhibition of heat shock protein 90 (HSP 90) leads to EMT inhibition, motility and invasiveness by downregulating both HIF-1 α and the NF- κ B pathway in colorectal cancer (90). MiR-210-3p, a small endogenous non-coding RNA, is significantly elevated in prostate cancer tissues compared with the adjacent healthy tissues. Overexpression of miR-210-3p enhances EMT, invasion and migration of prostate cancer cells *in vitro* (prostate cancer cells) by activating the NF- κ B signaling pathway (91). LncRNAs are considered to play a notable role in various cancer cell events. LncRNA MAFG antisense RNA 1 (MAFG-AS1) is significantly increased in ovarian cancer tissues and cells. MAFG-AS1 also upregulates the NF- κ B signaling pathway and affects the EMT, invasion and migration of cancer cells (92).

TLRs play a crucial role in inflammation and innate immune responses by activating the NF- κ B pathway. TLR2 levels are heightened in intrahepatic cholangiocarcinoma tissues and cell lines. TLR2 regulates the inflammatory response mediated by the NF- κ B pathway, induces the expression of EMT markers, and promotes cancer cell migration and invasion (93). Ezrin is an important molecule involved in EMT. The expression of ezrin affects the nuclear translocation of p65 and phosphorylated I κ B α in tumor cells. Ezrin affects the EMT, proliferation and migration of osteosarcoma cells through the NF- κ B signaling pathway (94).

Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a secreted protein induced by endoplasmic reticulum stress, which inhibits inflammation by interacting with a key subunit of p65 in NF- κ B signaling pathway. MANF and albumin in liver cancer tissues are downregulated compared with the adjacent non-cancer tissues. MANF inhibits the migration and invasion of liver cancer cells by regulating the NF- κ B signaling pathway (95).

The NF- κ B interaction lncRNA (NKILA) has been verified to exert tumor suppressive effects in diverse cancer types (e.g., liver cancer, cervical cancer and esophageal squamous cell carcinoma). The expression level of NKILA is reduced in cervical cancer tissues and cell lines. NKILA inhibits the migration and invasion of cervical cancer cells by regulating the EMT process, which is related to NKILA-mediated inhibition of the NF- κ B activation (96).

Double cortin-like kinase 1 (DCLK1), as an effective oncogene, drives malignant EMT features in colorectal cancer cells in an NF- κ B dependent manner. During the EMT process of cancer cells, DCLK1 silencing *in vivo* (6-week-old female nude mice) inhibits the invasion and metastasis of CRC cells by regulating NF- κ B signaling pathway activity (97). Sparc/osteonectin, cwcv and kazal-like domain proteoglycan 1 (SPOCK1) has been reported to act as an oncogene, participating in a cascade of metastasis reactions, including invasion, EMT and the formation of micro-metastasis. SPOCK1 has been demonstrated to be significantly elevated in pancreatic cancer tissues and is related to lymph node metastasis. SPOCK1 activates the NF- κ B signaling pathway through direct interaction with I κ B α , regulates the progress of EMT and promotes the migration and invasion of cancer cells (98).

Amphiregulin is a member of the epidermal growth factor (EGF) family and may play a key role in cell migration, invasion and EMT by activating the NF- κ B signaling pathway in pancreatic cancer cells (99). RPB5-mediating protein (RMP) promotes the migration, invasion and progression of hepatocellular carcinoma and EMT *in vitro* (hepatocellular carcinoma cells), and promotes cancer metastasis *in vivo* (pulmonary metastases mouse model). Further research indicates that RMP activates the NF- κ B pathway to inhibit Snail degradation and induce EMT and metastasis (100). T-cell immunoglobulin domain and mucin domain 4 (TIM-4) are novel growth-promoting factors in the progression of cancer. IL-6 relies on the NF- κ B signaling pathway to promote TIM-4 expression in cancer cells. Both TIM-4 and IL-6 can promote the migration, invasion and EMT of non-small-cell lung cancer cells (101). N-myc downregulated gene-1 (NDRG1) plays an important role in the growth and metastasis of tumors. Knockout of NDRG1 promotes EMT in colorectal cancer cells through the NF- κ B signaling pathway. The depletion of NDRG1 increases the phosphorylation level of NF- κ B. NDRG1 may prevent EMT-induced metastasis via inhibition of the NF- κ B signaling pathway in colorectal cancer (102).

CXCL8 is an autocrine growth factor that promotes tumor growth, invasion, angiogenesis, metastasis and resistance. Elevated CXCL8 expression in colon cancer cells is associated with enhanced metastatic potential and invasiveness. CXCL8 overexpression promotes the proliferation, migration and invasion of colon cancer cells, while promoting tumor growth *in vivo* (6-8 weeks BALB/c nude mice xenograft model). CXCL8 may facilitate these effects by inducing EMT by activating the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt)/NF- κ B signaling pathway (103). The expression of the oncogene Twist1 is associated with the development and metastasis of tumors. An *in vitro* (papillary thyroid carcinoma cells) study has shown that reducing the expression of Twist1 and reversing EMT through the NF- κ B pathway can reduce the invasiveness and metastasis of papillary thyroid carcinoma

cells (104). CD133 (also known as prominin-1) is considered a surface marker of CSCs in various malignant tumors (e.g., colorectal cancer, esophageal squamous cell carcinoma, and head and neck squamous cell carcinomas). CD133 induces EMT and increases *in vitro* (pancreatic cancer cells) invasion in pancreatic cancer cells, which is mediated by the activation of the NF- κ B pathway (105). MiR-129 has been recognized as a tumor inhibitor or oncogene. As compared with normal tissues, the expression of miR-129 is notably reduced in colorectal cancer tissues and cells. Overexpression of miR-129 significantly inhibits cancer cell proliferation, migration, invasion and EMT, while inhibition of miR-129 shows the opposite effect. MiR-129 is reported to inhibit cancer cell proliferation, migration, invasion and EMT by activating the NF- κ B signaling pathway in colorectal cancer cells (106).

Aquaporin 5 (AQP5), a transmembrane protein implicated in cancer progression, demonstrates elevated expression in malignant cell lines while inhibiting cancer cell invasion and metastasis both *in vivo* (4 to 6 weeks old male BALB/c nude mice) and *in vitro* (hepatocellular carcinoma cells). Downregulation of AQP5 attenuates EMT by regulating EMT-related molecules, with mechanistic investigation suggesting that AQP5 depletion partially inhibits hepatocellular carcinoma metastasis and EMT through the inactivation of the NF- κ B signaling pathway (107). The upregulation of miR-940 inhibits IL-8-induced migration and invasion, while the silencing of CXCR2 chemokine receptor type 2 (CXCR2) may mitigate this effect. The miR-940/CXCR2 system inhibits tongue squamous cell carcinoma cell migration and invasion through NF- κ B signaling pathway-induced EMT processes (108). MiRNAs are notable regulators in human carcinogenesis. MiR-145-5p has been observed to be down-regulated in esophageal squamous cell carcinoma tissues, where it exerts tumor suppressive effects by inhibiting cancer cell migration, invasion and EMT via the NF- κ B signaling pathway (109).

4. Drugs and inhibitors

Development of agents/phytochemicals targeting the NF- κ B pathway for cancer treatment. The main directions of NF- κ B pathway therapy for cancer include inhibiting the phosphorylation of the I κ B α protein; inhibiting the nuclear localization and DNA binding activity of NF- κ B; inducing Bcl-2 family activity; downregulating the expression of vascular endothelial growth factor (VEGF); regulating the levels of cytokines that promote tumor growth (TNF, IL-6, IL-8); and inducing the cell cycle through regulation of cell cycle proteins (Table I) (110-139). Agents and phytochemicals targeting the NF- κ B pathway for cancer treatment are shown in Fig. 4.

Phytochemicals can affect the progression of cancer by regulating the NF- κ B signaling pathway. Curcumin is a natural non-toxic phenol isolated from turmeric. Substantial evidence suggests that curcumin has anticancer properties in various tumors. Curcumin and 5-fluorouracil have antiproliferative effects in cells, which are related to inhibiting the NF- κ B pathways (140). Punicalagin is a dietary phytochemical that alters various cellular signaling pathways associated with apoptosis and proliferation. Punicalagin has demonstrated inhibition of the NF- κ B signaling pathway to block cancer cell proliferation

and stimulate cell apoptosis (141). Emodin was found to reduce the viability of cancer cells and induce apoptosis in a concentration-dependent manner. Emodin treatment increased the translocation of NF- κ B from cytoplasm to nucleus, indicating that the NF- κ B pathway is involved in emodin induced apoptosis of lung cancer cells (142). Beyond its application in the food and cosmetics industry due to its pleasant aroma, *Osmanthus fragrans* (OF) possesses well-documented anti-inflammatory and anticancer activities that have been applied in traditional Chinese medicine. Ethanol extract of OF has a significant antiproliferative effect on human colorectal cancer cells, and triterpenoids are important components of the ethanol component. Ethanol extract of OF also results in cell cycle arrest and apoptosis, accompanied by an increase in intracellular ROS and mitochondrial dysfunction. In addition, it inhibits the NF- κ B signaling pathway, leading to a decrease in COX-2 expression (143). As the predominant polyphenol tea, epigallocatechin-3-gallate (EGCG) has demonstrated evident biological activities, functioning as an antioxidant, while offering protective benefits against cardiovascular disease and anticancer effects. Research has demonstrated that EGCG induces cancer cell apoptosis by activating caspase-8, -9, and -3, Bax, and Bcl-2. Additionally, EGCG downregulates the expression of the NF- κ B and MMP-9 at both protein and mRNA levels to inhibit tumor proliferation (144). Quercetin is a flavonoid compound identified in diverse fruits and vegetables, which has demonstrated an ability to inhibit proliferation, induce apoptosis and prevent numerous types of human cancer, demonstrating its potential in cancer prevention and treatment. Quercetin also regulates the NF- κ B signaling pathway and its target genes Bcl-2 and Bax to induce cell apoptosis (145).

Development of inhibiting molecules targeting the NF- κ B pathway for cancer treatment. Certain biologics can regulate NF- κ B signaling pathway (Table II) (146-189). For example, *Hibiscus sabdariffa* leaf extract has been verified to inhibit MMP-9 expression by suppressing the Akt/NF- κ B signaling pathway, thereby decreasing the invasiveness of cancer cells (190). Baicalin promotes apoptosis by altering the Bax/Bcl-2 ratio. Furthermore, it regulates the NF- κ B signaling pathway to induce autophagy and triggers mitotic cell cycle arrest by reducing the concentration of cyclin B1 (191). Alantolactone, an important sesquiterpene lactone derived from the Asteraceae family, enhances the expression of apoptosis regulatory proteins in cancer cells, prolongs the G₂/M phase of the cell cycle and inhibits the expression of various cyclins. Furthermore, alantolactone has displayed a dose-dependent inhibition of the NF- κ B signaling pathway (127). Baohuoside I is a flavonoid isolated from *Epimedium koreanum* Nakai and significantly inhibits the proliferation of cancer cells by inducing apoptosis and downregulating the NF- κ B signaling pathway (192). Sulforaphene, a naturally occurring iso-thiocyanate identified in cruciferous vegetables, enhances the inhibitory effect of radiation on tumor growth within both *in vitro* (hepatocellular carcinoma cells) and *in vivo* (5 weeks old athymic BALB/c nude mice xenograft model) studies. Sulforaphene inhibits cell proliferation and induces apoptosis in cancer cells. It inhibits NF- κ B activity and reduces downstream gene expressions of the NF- κ B pathway to enhance the

Table I. Agents/phytochemicals targeting the NF- κ B pathway.

Agents/ phytochemicals	Origin	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Zerumbone	Southeast Asian ginger	Gastric cancer	Classical	Reduced the expression of VEGF, inhibited angiogenesis	(110)
Icariin	Epimedium	Triple- negative breast cancer	Classical	Induced cell apoptosis via a mitochondria- mediated pathway, as indicated by the up- regulated ratio of Bax/Bcl-2 and ROS induction; regulated the tumor immuno- suppressive microenvironment	(111)
Alpinetin	<i>Alpinia katsumadai</i>	Breast cancer	Classical	Dampened HIF-1 α signaling due to a lack of NF- κ B activation through reduced mitochon- drial ROS production, decreasing HIF-1 α transcription	(112)
Oroxylin A	<i>Scutellaria baicalensis</i>	Breast cancer	Classical	Increased the mRNA and protein expression levels of E-cadherin, decreased N-cadherin and vimentin; suppressed the expression of inflammatory factors and NF- κ B activation	(113)
Hyperoside	Hypericum	Breast cancer	Classical	Decreased levels of Bcl-2 and XIAP, and increased levels of Bax and cleaved caspase-3; reduced ROS production, decreased tumor volume	(114)
Baicalein	<i>Scutellaria baicalensis</i>	Cervical cancer	Both	Activated caspase3 activity, blocked cell cycle in G ₀ /G ₁ phase, reduced at cyclin D1 mRNA and protein levels, inhibited NF- κ B activity by repressing nuclear translocation	(115)
Ginsenoside Rg3	Ginseng	Colorectal cancer	-	Suppressed the DNA binding ability of NF- κ B, decreased NF- κ B-regulated gene transcription, downregulated expression of the NF- κ B-regulated MMP9, COX-2 and c-Myc	(116)
Curcumin	Turmeric	Pancreatic cancer	-	Suppressed the secretion and expression of IL-6, suppressed EMT and the changes in the expression of E-cadherin, vimentin and MMP9	(117)
Methanolic extract of <i>Justicia adhatoda</i> leaves	<i>Justicia adhatoda</i> leaves	Breast cancer	Classical	Increased the production of nitric oxide and reactive oxygen species; decreased the activities of superoxide dismutase and glutathione; increased the expressions of caspase-3, Bax, and cleaved-poly ADP- ribose polymerase; increased the expression of NF- κ B in the cytoplasm	(118)
Ethanollic extract of leaves of <i>Dillenia pentagyna</i>	<i>Dillenia pentagyna</i>	Non-small cell lung cancer, cervical cancer	Classical	Reduced metastasis via the NF- κ B pathway, decreased the expression of vimentin, N-cadherin, and increased the expression of Claudin-1	(119)
Polyphenols extract of <i>Artemisia annua</i> leaves	<i>Artemisia annua</i> leaves	Colorectal cancer	Classical	TGF- β 1 and NGF- β attenuated anticancer effects by inhibiting the downregulation of caspase-8, NF- κ B, p65 and cyclin D1	(120)

Table I. Continued.

Agents/ phytochemicals	Origin	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Triptolidenol	<i>Tripterygium wilfordii</i>	Clear cell renal cell carcinoma	Classical	Suppressed cancer cell proliferation, cell migration, and induced cell cycle arrest at S phase; induced apoptosis by activating the cyt c/caspase cascade signaling pathway; reduced the expression of COX-2 by inhibiting the kinase activity of IKK β via targeting its ATP-binding domain and then attenuating the transactivation of NF- κ B	(121)
Machilin D	Saururus	Breast cancer	Classical	Reduced the proportions of CD44 ⁺ /CD24 ⁻ and ALDH1 ⁺ cells; reduced the nuclear localization of the NF- κ B protein and decreased the IL-6 and IL-8 secretion in mammospheres; induced cancer stem cells death	(122)
Geraniin	<i>Geranium thunbergii</i>	Ovarian cancer	Classical	Increased cyt c release and caspsase-3 activity; downregulated Mcl-1 and impaired NF- κ B p65 binding to the Mcl-1 promoter	(123)
24-acetyliso-dahurinol-3-O- β -D-xylopyranoside	<i>Cimicifuga foetida</i>	Triple negative breast cancer	Classical	Reduced the expression levels of XIAP, Mcl-1, survivin and cyclin B1/D1 proteins; inhibited TNF- α -induced IKK α/β phosphorylation, I κ B α phosphorylation, p65 nuclear translocation and NF- κ B downstream target gene expression, including XIAP, Mcl-1 and survivin, in TNBC cells	(124)
Sesamin	Sesame	Colorectal cancer	Classical	Reduced the expression of VEGFA to inhibit angiogenesis; inhibited the phosphorylation of I κ B α and thus restrained NF- κ B p65 to activate HIF-1 α transcription under hypoxic conditions	(125)
Nobiletin	<i>Citrus depressa</i>	Pancreatic cancer	Classical	Activated G ₀ /G ₁ cell cycle arrest cause cancer cells accretion; accompanied with depletion of cyclin D1 and CDK4 expression; suppressed cancer cells migration; blocked the NF- κ B pathway	(126)
Alantolactone	Asteraceae	Cervical cancer	-	Induced mitochondrial mediated cell apoptosis, enhanced the expression of apoptosis regulatory proteins such as caspase 3 and Bax, promoted the accumulation of cancer cells in the G ₂ /M phase of the cell cycle, and inhibited the expression of various cell cycle proteins	(127)
Salviolone	Salvia	Cervical cancer	-	Triggered autophagic cell death; caused arrest of the cervical cancer cells in the G ₂ /M phase of the cell cycle and suppressed their ability to migrate and invade	(128)
Andrographolide	<i>Andrographis paniculata</i>	Triple negative breast cancer	-	Suppressed CSC properties, delayed tumor growth; reduced the activity of NF- κ B	(129)

Table I. Continued.

Agents/ phytochemicals	Origin	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Ethanol root extract of <i>Saussurea</i> <i>costus</i> (falc.) lipsch	<i>Saussurea</i> <i>costus</i> (falc.) lipsch	Breast cancer	Classical	Reduced of biochemical indices, oxidative stress parameters, histological changes, pro-inflammatory cytokines (NF- κ B and TNF- α), cellular proliferation (Ki-67), metastases (MMP-9) and neovascularization (VEGF) markers	(130)
Resveratrol	Polyphenol compound	Gastric cancer	Classical	Increased SOD activity in a dose-dependent manner; reduced the DNA-binding activity of NF- κ B and the enzymatic activity of heparanase	(131)
Withaferin A	Indian winter cherry	Colorectal cancer	Classical	Inhibited the IL-6- and TNF- α -induced cancer cell invasion and decreased colono-sphere formation; inhibited STAT3 phosphorylation and abolished the STAT3, STAT1 and NF- κ B interactions	(132)
Daucosterol linoleate	Sweet potato	Breast cancer	Classical	Diminished the expression of Bcl-x1, Bcl-2 and XIAP, while increasing Bax, Bad and activated caspase-dependent apoptosis in tumor tissues; suppressed VEGF, MMP 2 and MMP 9 expression in both tumor and lung tissues	(133)
Anthocyanin	<i>Vitis</i> <i>coignetiae</i> <i>Pulliat</i>	Breast cancer	Classical	Suppressed the NF- κ B-regulated proteins involved in cancer cell proliferation (COX-2, c-Myc), invasion, and angiogenesis (MMP-2, MMP9, ICAM-1 and VEGF); increased the expression of E-cadherin	(134)
2,3,5,4'-tetrahy droxystilbene- 2-O- β -D- glucoside (THSG)	<i>Polygonum</i> <i>multiflorum</i> Thunb	Colorectal cancer	Classical	Reduced the levels of MMP-2 and phospho-rylated VE-cadherin, reduced the levels of cell adhesion ability and the E-selectin and ICAM-1 protein, reduced the levels of the cytoplasmic phosphorylation of I κ B, the nuclear p65 level and the DNA-binding activity of NF- κ B	(135)
Berberamine	Berberis	Prostate cancer	-	Induced cell cycle arrest in the S phase; increased ROS as an upstream molecule that inhibited the NF- κ B pathway	(136)
Polyporus polysaccharide	<i>Polyporus</i> <i>umbellatus</i>	Bladder cancer	Classical	Promoted the expression of pro-inflamma-tory factors, such as IL-1 β , TNF- α and iNOS, and surface molecules CD86, CD16, CD23, and CD40 in macrophages and then polarized macrophages to M1 type, inhibited EMT, downregulated JAK2/NF- κ B pathway	(137)
6-methoxy- mellein	<i>Daucus</i> <i>carota</i> L.	Breast cancer	Classical	Decreased the proportion of CD44 ⁺ /CD24 ⁻ cells in breast cancer cells and decreased the expression of stemness-associated proteins c-Myc, SOX2 and Oct4, reduced the nuclear localization of NF- κ B subunit p65 and p50, decreased the mRNA transcription and secretion of IL-6 and IL-8	(138)

Table I. Continued.

Agents/ phytochemicals	Origin	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Hydroxysafflor yellow A	<i>Carthamus Tinctorius</i> L.	Esopha- geal cancer	Classical	Inhibited the expression of ICAM1, MMP9, TNF-α, and VCAM1 and induced the expression of phosphorylated-NF-κB p65 and phosphorylated IκBα, but it did not influence the expression of P65 and IκBα	(139)

VEGF, vascular endothelial growth factor; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; HIF-1α, hypoxia-inducible factor-1α; MMP, matrix metalloproteinase; COX-2, cyclooxygenase 2; c-Myc, MYC proto-oncogene; IL, interleukin; EMT, epithelial-mesenchymal transition; TGF-β1, transforming growth factor-β1; NGF-β, β-nerve growth factor; cyt c, cytochrome c; IKK, inhibitor of kappa kinase; CD44, CD44 antigen; CD24, signal transducer CD24; ALDH1, aldehyde dehydrogenase 1; Mcl-1, mantle cell lymphoma-1; XIAP, E3 ubiquitin-protein ligase XIAP; TNF-α, tumor necrosis factor-α; IκB, inhibitor of kappa kinase B; TNBC, triple negative breast cancer; CDK4, cyclin-dependent kinase 4; CSC, cancer stem cell; Ki-67, proliferation marker protein Ki-67; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; ICAM-1, intercellular cell adhesion molecule-1; iNOS, inducible nitric oxide synthase; JAK2, tyrosine-protein kinase JAK2; SOX2, sex-determining region Y-box 2; Oct4, octamer-binding protein 4; VCAM1, vascular cell adhesion molecule 1.

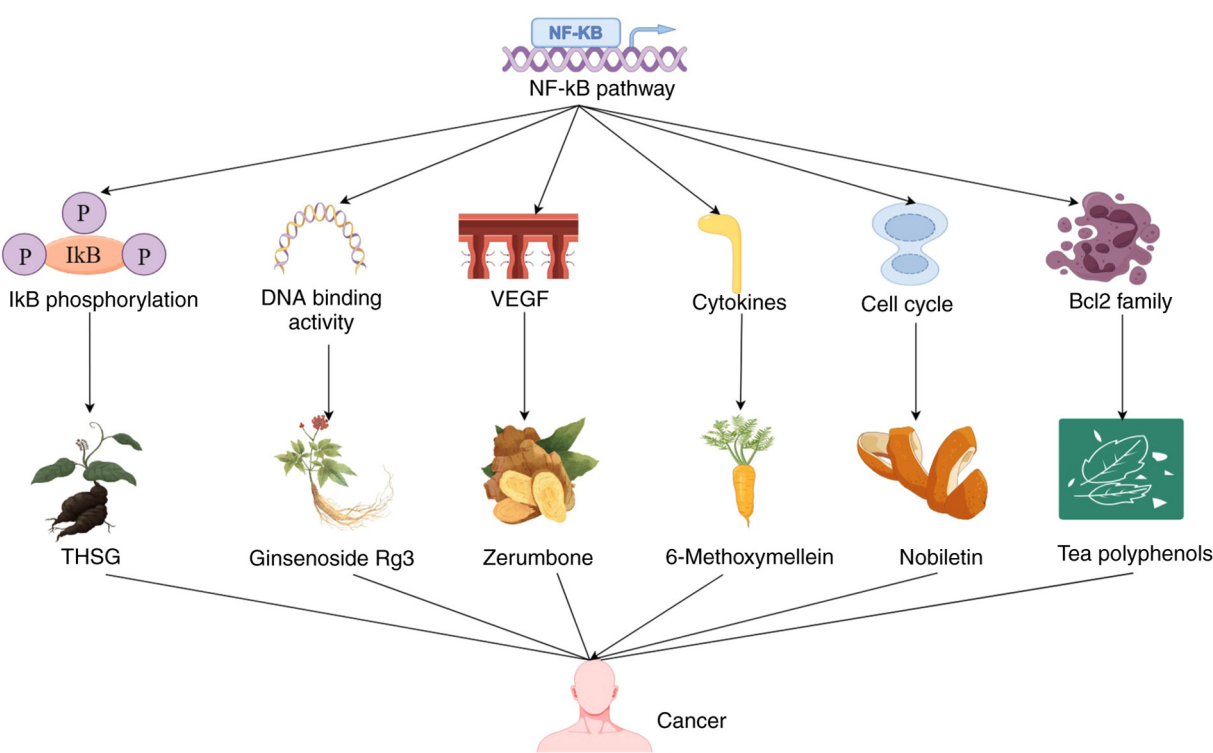


Figure 4. Agents and phytochemicals targeting the NF-κB pathway for cancer treatment. NF-κB, nuclear factor-κB; IκB, inhibitor of nuclear factor-κB kinase subunit β; TSHG, 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside; VEGF, vascular endothelial growth factor.

radiosensitivity (193). A bis-demethoxycurcumin-analog treatment has been shown to downregulate the levels of MMP-9, VEGF, TGF-β, IL-6 and IL-8, while upregulating tissue inhibitor of metalloproteinase 2 levels. By inhibiting the NF-κB pathway, it effectively inhibited key markers of invasion, angiogenesis and metastasis (194). The ethyl acetate extract of *Annona muricata* inhibits cancer cell proliferation, leading to cell cycle arrest and programmed cell death through activation of the mitochondrial-mediated apoptosis signaling pathway, with the involvement of the NF-κB signaling pathway (195).

5. Discussion

Following bone metastasis, tumor cells release various soluble mediators that stimulate osteoblasts to overexpress receptor activator of nuclear factor-κB ligand (RANKL) and inhibit osteoprotegerin (OPG) expression. As a result, the RANKL/OPG ratio is elevated, which leads to excessive osteoclast activation and bone destruction. The subsequent release of growth factors, such as transforming growth factor-β (TGF-β), further promotes tumor progression, forming a ‘vicious cycle’ (196). RANKL is a cytokine belonging to the TNF

Table II. NF- κ B inhibiting molecules for disease.

Name	Classification	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Shikonin	I κ B/NEMO complex inhibitor	Colorectal cancer	Classical	Inhibited the expression of inflammation-related proteins, such as COX-2, iNOS, IL-6 and TNF- α	(146)
NLOC-015A	Small molecule	Non-small cell lung cancer	Classical	Attenuated the oncogenic properties (colony formation, migratory ability, and spheroid formation) with concomitant downregulation of expression levels of EGFR/mammalian target of rapamycin/AKT, NF- κ B signaling pathway	(147)
YM155	Small molecule	Breast cancer	Both	YM155-induced cell death was dependent on autophagy and NF- κ B but independent of p53 and it coincided with DNA damage and a DNA damage response in p53-proficient cells	(148)
Dehydroxy-methylepoxyquinomicin	NF- κ B inhibitor	Nasopharyngeal carcinoma	Classical	Blocked nuclear translocation of activated NF- κ B	(149)
Mollugin	NF- κ B inhibitor	Cervical cancer	Classical	Inhibited the expression of an NF- κ B reporter gene; inhibited phosphorylation and nuclear translocation of p65; inhibited phosphorylation and degradation of inhibitor of I κ B α and I κ B kinase phosphorylation	(150)
NKILA	LncRNA	Breast cancer	-	Inhibited of NF- κ B signaling pathway to abrogate EMT	(151)
miR-148b	miRNA	Non-small cell lung cancer	Classical	Inhibited activated leukocyte cell adhesion molecule	(152)
Ovatodiolide	Macrocyclic diterpenoid	Cervical cancer	-	Triggered apoptotic cell death, increased in Bax and decreased in Bcl-2 expression; caused arrest at the G ₂ /M phase of the cell cycle, suppressed cyclin B1 expression; decreased the NF- κ B expression	(153)
miRNA-506	miRNA	Lung cancer	Classical	Inhibited NF- κ B p65 expression, induced ROS accumulation and then activated p53 to suppress cancer cell viability	(154)
Piperlongumine	Alkaloid/amide	Prostate cancer	Classical	Downregulated NF- κ B DNA-binding activity; decreased nuclear translocation of p50 and p65 subunits; attenuated the expression of IL-6, IL-8, MMP-9, and ICAM-1	(155)
Melatonin	Neurohormone	Cervical cancer	-	Downregulated the expression of pro-inflammatory transcription factor, NF- κ B and the expression of COX-2 protein, downregulated the expression of MMP-9 and Bcl-2, and upregulated the expression of Bax	(156)
Moringin	Isothiocyanate	Breast cancer	Classical	Induced proapoptotic proteins expression such as cytochrome c, p53, and cleaved caspase-7; suppressed cell survival proteins such as survivin, Bcl-2, and Bcl-xL	(157)
Betulinic acid	Pentacyclic triterpenoid	Gastric cancer	-	Downregulated the expression of vasodilator-stimulated phosphoprotein at the protein and mRNA level by inhibiting NF- κ B activity	(158)

Table II. Continued.

Name	Classification	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
3,14,19-tripropionylandrographolide (SRS06)	Andrographolide derivative	Non-small cell lung cancer	Classical	Decreased NF- κ B protein expression, reduced the nuclear p65 DNA binding activity	(159)
LA-EPS-20079	Pentasaccharide	Colorectal cancer	Classical	Upregulated the expression of I κ B α , p53 and TGF genes	(160)
Parthenolide	Small sesquiterpenoid molecule	Hepatocellular carcinoma	Classical	Inhibited the metastatic, invasive and clone formation abilities of cancer cells, reduced the cell proliferative potential, and suppressed the glycolysis; inhibited the HIF-1 α expression	(161)
Cyclopeptide RA-V	Cyclopeptide	Breast cancer	Classical	Reduced the expressions of VCAM, ICAM, focal adhesion kinase and integrins; inhibited the activities and expressions of MMPs, tissue inhibitors of matrix metalloproteinases and urokinase-type of plasminogen activator	(162)
N,N-Dimethyl-D-erythro-sphingosine	Sphingosine	Lung cancer	Classical	Suppressed the activation of sphingosine kinase 1 and NF- κ B p65, increased intracellular Ca ²⁺	(163)
Hapalindole H	NF- κ B inhibitor	Prostate Cancer	Classical	Inhibited NF- κ B p65 activity and induced apoptosis through the intrinsic mitochondrial pathway	(164)
Gallotannin	Polyphenolic hydrolyzable tannin	Colorectal cancer	Classical	Downregulated the expression of NF- κ B-regulated inflammatory cytokines (IL-8, TNF- α , IL-1 α) and caused cell cycle arrest and accumulation of cells in pre-G ₁ phase	(165)
Chamaejasmine	Biflavanone	Breast cancer	Classical	Decreased in cyclins A and cyclins B1, decreased cdk 2 and cdc2; inhibited nuclear translocation and phosphorylation of NF- κ B; activated I κ α and I κ β ; inhibited phosphorylation and degradation of I κ B α	(166)
6-Shogaol	Gingerols	Oral carcinogenesis	Classical	Inhibited constitutive phosphorylation and degradation of I κ B and inhibited phosphorylation of oncogenes c-jun and c-fos to inhibit nuclear translocation of NF- κ B p65 and activator protein-1	(167)
Fucoidan	Sulfated polysaccharides	Pancreatic cancer	Classical	Activated caspase -3, -8 and -9, and cleaved PARP; inhibited NF- κ B DNA-binding activity	(168)
Karyopherin α -2	Karyopherin	Breast cancer	Non-classical	Inhibited the proliferation, migration and invasion of cancer cells, while the cycle arrest was induced, via blocking NF- κ B signaling pathway and c-Myc nuclear translocation	(169)
Xanthatin	Sesquiterpene lactone	Non-small cell lung cancer	Classical	Downregulated Chk1, Chk2, and phosphorylation of cdc2; increased total p53 protein levels; decreased Bcl-2/Bax ratio and expression of the procaspase-9 and procaspase-3; blocked phosphorylation of NF- κ B (p65) and I κ B α ; inhibited NF- κ B (p65) translocation	(170)

Table II. Continued.

Name	Classification	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
Epoxymiche- liolide	Novel guaiane- type sesquiterpene lactone	Renal cell carcinoma	Classical	Increased apoptosis by activating the mito- chondria- and caspase-dependent pathway; suppressed cell invasion and metastasis by inhi- biting EMT; suppressed the expression of COX2 by inhibiting the translocation of p50/p65 and the activity of NF-κB	(171)
B7-H3	Immune checkpoint molecule	Colorectal cancer	Classical	Upregulated VEGFA expression and angio- genesis by activating the NF-κB pathway	(172)
Aquaporin 5	Transmembrane protein	Hepatocellular carcinoma	-	Suppressed the EMT process by modulating EMT-related molecules such as E-cadherin, α-catenin, N-cadherin and vimentin; inhibited cell metastasis and EMT partly via inactivation of the NF-κB signaling pathway	(107)
Asiaticoside	Chemical modulator or chemopreven- tive agent	Breast cancer	Classical	Increased caspase-9 activity; inhibited TNF-α and IL-6 expression via NF-κB pathway	(173)
TNF receptor- related factor 3	Cancer gene	Intrahepatic cholangio- carcinoma	Non- classical	Promoted cancer development through NF-κB- inducing kinase-mediated hepatocyte trans- differentiation	(174)
Fas apoptosis inhibitory molecule 1	Negative regulator of NF-κB pathway	Non-small cell lung cancer	Both	Suppressed the NF-κB pathway, decreased expression of cyclin D1	(175)
Pyruvate kinase M2	Kinase	Head and neck squamous cell carcinoma	Classical	Lactate produced by pyruvate kinase M2 upregulation promoted tumor progression and galectin-9-mediated immunosuppression via NF-κB signaling inhibition	(176)
Novel seleno- aspirinyl compound AS-10	Aspirinyl compound	Pancreatic ductal adeno- carcinoma	Classical	Induced apoptosis through caspase-3/7 cascade and ROS; induced G ₁ cell cycle block; decrea- sed NF-κB nuclear translocation, DNA binding activity and degradation of cytosolic inhibitor of IκB protein	(177)
Serine/ threonine protein kinase-3	Kinase	Ovarian cancer	Classical	Promoted the migration of CD8 ⁺ T-cells by activating NF-κB signaling pathway	(178)
Crebanine	Aporphine alkaloid	Lung adeno- carcinoma	Classical	Sensitized TNF-α-induced apoptosis and suppressed invasion of cancer cells by blocking NF-κB-regulated gene products	(179)
T-LAK cell- originated protein kinase miR-181a	Protein kinase	Cutaneous squamous cell carcinoma	Classical	Promoted the malignant progression by upregu- lating histone deacetylase 1 to activate the NF-κB pathway and promote autophagy	(180)
	miRNA	Colorectal cancer	Classical	Repressed PTEN to promote cancer cell proliferation	(181)
microRNA- 520a-3p	miRNA	Non-small cell lung cancer	Both	Targeted and downregulated the expression of AKT1 to inhibit the invasion and metastasis of cancer cells via suppressing the activation of NF-κB signaling pathway	(182)

Table II. Continued.

Name	Classification	Disease type	Pathway specificity	Intervention mechanism	(Refs.)
MUC13	Transmembrane mucin glycoprotein	Colorectal cancer	Classical	Prevented cancer cell death by promoting NF- κ B pathway activation, consequently upregulating antiapoptotic genes <i>BCL2L1</i> (encodes BCL-X _L)	(183)
Activated protein kinase C 1	Protein kinase	Gastric cancer	Classical	Suppressed gastric tumor progression through the NF- κ B signaling pathway	(184)
Momelotinib /CYT387	Inhibitor of TBK1/IKBKE and JAK	Triple-negative breast cancers	Classical	Inhibited activation of both NF- κ B and STAT and disrupted expression of the pro-tumorigenic cytokines CCL5 and IL-6 in cancer cells	(185)
Imipramine	Antidepressant	Prostate Cancer	Classical	Attenuated cell viability, migration and invasion of cancer cells by suppressing the expression of AKT and NF- κ B-related signaling proteins and secretion of TNF- α , IL-1 β , and monocyte chemoattractant protein-1	(186)
Thymo-quinone	NF- κ B inhibitor	Colorectal cancer	Classical	Suppressed metastasis through NF- κ B inhibition and activation of JNK and p38 in cancer cells	(187)
NIBP	Binding protein	Colorectal cancer	Classical	Impacted on the expression levels of E-cadherin, CD44 and vimentin via the NF- κ B pathway	(188)
S100A4	Calcium-binding protein	Hepatocellular carcinoma	Both	Contributed to cancer metastasis by activation of NF- κ B dependent MMP-9 expression	(189)

IkK β /I κ B, inhibitor of kappa kinase β ; NEMO, nuclear factor- κ B essential modulator; COX-2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; IL, interleukin; TNF- α , tumor necrosis factor- α ; EGFR, epidermal growth factor receptor; AKT, protein kinase B; NF- κ B, nuclear factor- κ B; p53, cellular tumor antigen p53; LncRNA, long non-coding RNA; EMT, epithelial-mesenchymal transition; Bcl-2, apoptosis regulator Bcl-2; miRNA, microRNA; ROS, reactive oxygen species; MMP, matrix metalloproteinase; ICAM, intercellular cell adhesion molecule; c-Myc, MYC proto-oncogene; YM155, survivin inhibitor; TGF, transforming growth factor; HIF-1 α , hypoxia-inducible factor-1 α ; VCAM, vascular cell adhesion molecule; Ca²⁺, calcium; cdk, cyclin-dependent kinase; cdc, cell division cycle kinase; PARP, poly ADP ribose polymerase; Chk, Checkpoint kinase; VEGFA, vascular endothelial growth factor A; CD8⁺, T-cell surface glycoprotein CD8; PTEN, phosphatase and tensin homolog; BCL-X_L, B-cell lymphoma-extra large; TBK1, serine/threonine-protein kinase TBK1; IKBKE, inhibitor of nuclear factor- κ B kinase subunit epsilon; JAK, tyrosine-protein kinase JAK; CCL, chemokine ligand; STAT, signal transducer and activator of transcription; JNK, c-Jun N-terminal kinase.

superfamily, whose main function is to activate the formation and function of osteoclasts. Most tumor cells have sustained activation of RANKL, and inhibiting RANKL can prevent bone destruction caused by tumor growth and metastasis. Therefore, RANKL is closely related to the occurrence and development of tumors. RANKL activates the non-classical NF- κ B signaling pathway by binding to RANK, leading to the activation of NF- κ B and playing a key role in the activation of osteoclasts in multiple myeloma. The RANKL/RANK/NF- κ B pathway is the core signaling pathway regulating bone metabolism (197). P62 protein is a classic autophagy related protein, and its level is related to the degree of autophagy, thereby affecting the occurrence and development of cancer. A study has confirmed that the P62 protein, as a downstream adaptor protein of RANKL/RANK signaling, does not rely on autophagy to regulate the proliferation and invasion of giant cell tumors of bone by activating classical or non-classical

NF- κ B signaling pathways (198). In addition, a study has identified that the RANKL/RANK axis promotes the migration, invasion and metastasis of osteosarcoma by activating the NF- κ B signaling pathway (199).

The NF- κ B signaling pathway exhibits sustained abnormal activation, becoming a key driving factor for tumor occurrence and development. Hence, the NF- κ B signaling pathway is considered a central target for cancer treatment. Despite NF- κ B being an attractive therapeutic target, a number of NF- κ B-targeted inhibitors cannot be widely applied in clinics due to detrimental side effects. A key challenge in targeting NF- κ B depends on its dual role. While NF- κ B activation promotes oncogenesis, its fundamental activity remains essential for normal cellular functions such as tissue homeostasis and immunity (200). Comprehensive inhibition of NF- κ B can lead to side effects such as immune suppression. Furthermore, tumor heterogeneity and compensatory pathway activation

often lead to drug resistance issues. In clinical applications, multiple myeloma drugs such as bortezomib indirectly inhibit NF- κ B, but are subject to dose limiting toxicity and drug resistance.

To overcome the limitations of traditional inhibitors, researchers have developed an innovative method termed Highly Optimized Pol III-based Expression (HOPE), which utilizes the NF- κ B-specific promoter dentin matrix acidic phosphoprotein to selectively activate the exogenous effector gene CRISPR-Cas13a in cancer cells, enabling the targeting of oncogenes such as telomerase reverse transcriptase, polo-like kinase 1 and kirsten rat sarcoma proto-oncogene at the mRNA level. Data have shown that HOPE induces cancer cell-specific death *in vitro* (cervical carcinoma cells, gastric cancer cells, non-small cell lung cancer cells, colorectal adenocarcinoma cells.) without affecting normal cells and significantly inhibits tumor growth without systemic toxicity in a colorectal cancer mouse model delivered by adeno-associated virus (200). Dual inhibition of NF- κ B and programmed cell death protein 1/PD-L1 signaling revealed synergistic potential in overcoming tumor immune tolerance. In terms of targeted drug delivery systems, heparin bisphosphonates use targeted localization technology to reduce drug dosage to 1/50 of traditional therapies, while significantly reducing side effects.

Patient stratification is the core prerequisite for optimizing the efficacy of NF- κ B inhibitors. Emerging biomarker candidates include the ubiquitin-conjugating enzyme E2S (UBE2S)/A-kinase-interacting protein 1 expression profile. In glioblastoma, UBE2S levels are positively correlated with NF- κ B activity and demonstrate strong associations with tumor grading and the Ki67 proliferation index, which can serve as prognostic indicators and therapeutic response monitoring markers (201). Single cell signaling profiles reveal that HOPE treatment not only decreases the proportion of cancer cells but also significantly weakens their stemness characteristics. These phenotypic and molecular shifts might serve as early predictive biomarkers of treatment response (200).

NF- κ B inhibitors retain notable potential in cancer treatment. However, traditional broad-spectrum inhibition strategies are limited by clinical challenges due to inevitable toxicity and drug resistance. Future breakthroughs in NF- κ B-target management will require four key shifts: i) From systemic inhibition to tumor selective intervention; ii) from monotherapy to rational combination strategies; iii) from traditional drug delivery to intelligent delivery systems; and iv) from empirical medication to biomarker stratified precision medicine. However, these strategies demand large-scale clinical validation, particularly focusing on long-term safety profiles and drug resistance evolution issues. With a deeper understanding of the role of the NF- κ B pathway in tumor heterogeneity and microenvironment regulation, and with advances in patient stratification techniques, NF- κ B targeted therapies targeted therapies have potential in developing novel precision oncology treatments and ultimately improving the survival outcomes of patients with cancer.

6. Conclusions

The NF- κ B transcription factor serves as a master regulator of cell survival, with dysregulated NF- κ B signaling having

been implicated in the pathogenesis of multiple human malignancies. The present review focused on the discussion of the pleiotropic roles of NF- κ B in oncogenesis, particularly its involvement in diverse cellular processes, including cell proliferation, apoptosis, autophagy, invasion and metastatic potential. Dysregulated NF- κ B signaling is a well-established driver of tumorigenesis, while pharmacological inhibition of this pathway has emerged as a promising therapeutic strategy. Although basic research and some clinical evidence confirm the target role of NF- κ B in cancer, its safety and efficacy have not been fully confirmed. Therefore, optimal therapeutic effects must be balanced with potential safety factors.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XL, LC and MZ drafted the manuscript. JD, FC, LY and MA reviewed the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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