

Advances in Targeting IKK and IKK-Related Kinases for Cancer Therapy

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Abstract I κ B kinases (IKK) and IKK-related kinases play critical roles in regulating the immune response through nuclear factor- κ B and IFN regulatory factor – dependent signaling transduction cascades. Recently, these kinases have been implicated in the pathogenesis of many human diseases, including cancer. In fact, dysregulation of IKK activities promotes tumor survival, proliferation, migration, metastasis, and angiogenesis—common characteristics of many types of human cancers. Because of their oncogenic effects in human cancer development, targeting IKK and IKK-related kinases is becoming an increasingly popular avenue for the development of novel therapeutic interventions for cancer. This review will briefly cover the recent discovery of the downstream substrates of IKK and IKK-related kinases, and outline the strategies used for targeting IKK as a therapeutic intervention for cancer.

Nuclear factor- κ B (NF- κ B) transcriptional factors are initially characterized central regulators and transcriptional factors in response to pathogens and viruses. Subsequently, NF- κ B have been found to regulate a variety of genes involved in cell proliferation, migration, and survival, many of them have a role in tumor development and progression. In mammals, there are five members of the NF- κ B family, including RELA (p65), RELB, c-REL, NF- κ B1 (p105/p50), and NF- κ B2 (p100/p52), which associate with each other to form different homodimers and heterodimers to regulate the expressions of their downstream targets (1, 2).

Several distinct NF- κ B activation pathways have been identified. The two most frequently studied are the canonical (classic) and noncanonical (alternative) I κ B kinase (IKK)/NF- κ B pathways (Fig. 1). The canonical pathway is induced by various inflammatory stimuli, such as tumor necrosis factor- α (TNF α), interleukin-1 (IL-1), and bacterial products (e.g., lipopolysaccharide) through the IKK α /IKK β /IKK γ complex. This pathway is classified by rapid phosphorylation of I κ B α , an inhibitory protein retaining the NF- κ B complex in the cytoplasm, at Ser³² and Ser³⁶ by IKK β , and subsequent degrada-

tion through the E3 ligase β -transducing repeat-containing protein (β -TrCP)-mediated ubiquitin proteasome proteolysis. The consequence of activation of the canonical pathway is p50/RELA activation, which regulates cell proliferation, survival migration, angiogenesis, and innate immune response. In contrast, the noncanonical pathway is activated by other types of inflammatory stimuli, including B cell-activating factor of the TNF family, lipopolysaccharide, and latent membrane protein 1, through IKK α homodimers which function independently of the IKK α /IKK β /IKK γ complex. This pathway is typified by phosphorylation of p100 and subsequent processes to p52 through ubiquitin-dependent processing. The consequence of activation of the noncanonical pathway is p52/RELB activation, which modulates B-cell development and adaptive immune response (1, 2).

Activation of the IKK Complex

The IKK family contains five members, including IKK α , IKK β , IKK γ , IKK ϵ , and TANK-binding kinase 1 (TBK1). In contrast with IKK α , IKK β , IKK ϵ , and TBK1, which function as kinases, IKK γ lacks any kinase activities and functions as the regulatory subunit in the classic IKK complex, which contains IKK α and IKK β (3). In response to proinflammatory stimuli, such as TNF α , IL-1, and toll-like receptor agonists (such as lipopolysaccharide), two kinases, TGF β -activated kinase 1 (TAK1) and mitogen-activated protein/ERK kinase kinase 3, are recruited into the proximity of the IKK complex by interacting with several receptor-associated proteins, such as receptor-interacting serine-threonine kinase 1, thereby phosphorylating and activating both IKK α and IKK β in the cytoplasm. A major consequence of IKK α /IKK β activation is the initiation of NF- κ B-mediated transcriptional activation. Although these two kinases have a high degree of structural similarity and are both present in the classic IKK complex, their downstream substrates and physiologic functions can be quite different. In fact, both IKK α and IKK β have recently been shown to function independently of each other and to have nonoverlapping

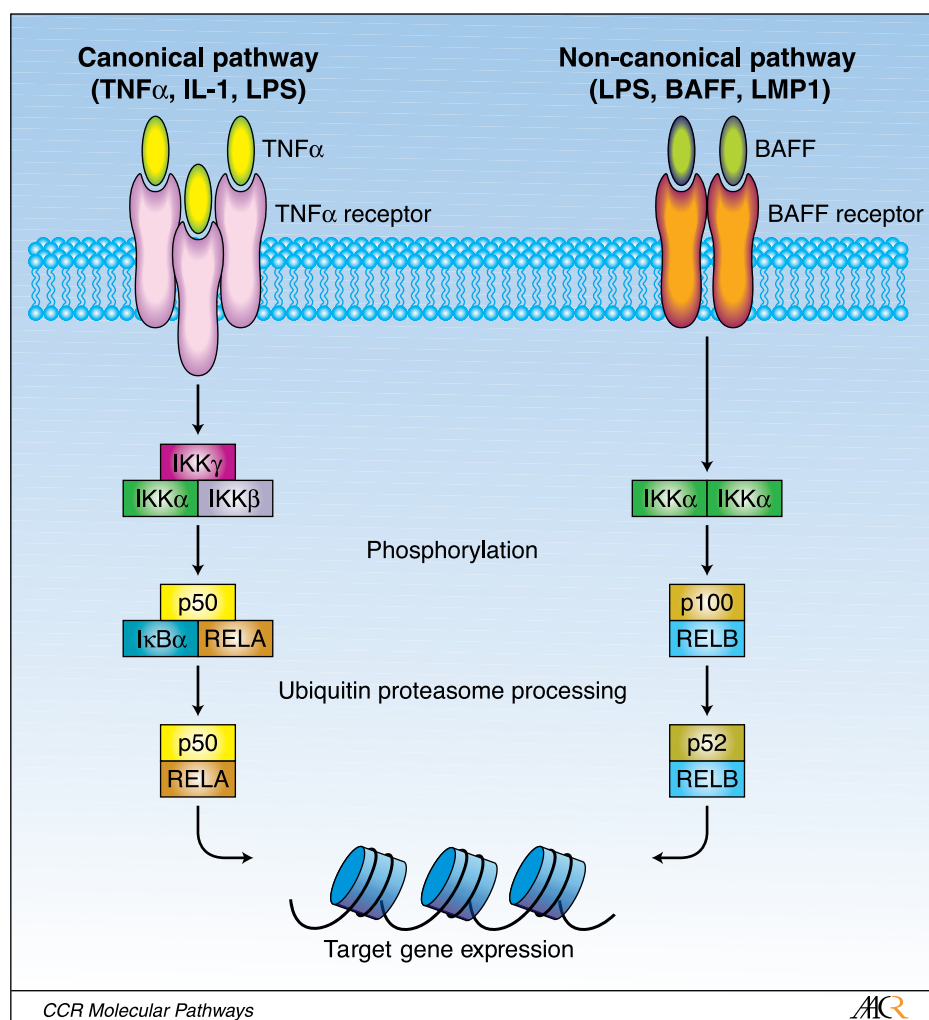
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Fig. 1. The canonical and noncanonical NF- κ B signaling pathways. The canonical pathway is critical for the activation of innate immunity and inflammation (*left*). It is activated by TNF α , IL-1, and lipopolysaccharide. Activation of this pathway depends on the IKK α /IKK β /IKK γ complex, which phosphorylates I κ B proteins to trigger their degradation through β -TrCP ubiquitin proteasome. The noncanonical pathway is crucial for the activation of adaptive immunity (*right*). It is activated by lipopolysaccharide, B cell – activating factor of the TNF family, and latent membrane protein 1. Activation of this pathway depends on IKK α homodimers which phosphorylate p100 to induce p100/RELB heterodimers processing into p52/RELB heterodimers.



functions. This functional difference will be discussed further in this review (see below). Unlike IKK α and IKK β , which are major catalysts of the NF- κ B pathway, IKK ϵ and TBK1 have restricted functions in the NF- κ B activation pathway. They are activated by toll-like receptor agonists and viral ssRNA in the cytoplasm and mainly function as mediators of type I IFN gene expression, which contributes to the antiviral response by their activation of the IFN regulatory transcription factors 3 and 7 (IRF3 and IRF7), which are transcriptional factors with diverse roles in immunity and cellular response to viral infections. Thus, IKK ϵ and TBK1 are important mediators of antiviral response and, together with IKK α and IKK β , coordinate and organize the host immune defense.

Consequences of IKK activation in human cancer. Because of their importance in regulating the expression of proinflammatory cytokines and chemokines, angiogenic factors, antiapoptotic proteins, cell adhesion molecules, and enzymes, IKK and IKK-related kinases are believed to function as oncogenic kinases (4, 5). For instance, IKK β functions as an oncoprotein in breast cancer by promoting the degradation of forkhead box O3a (FOXO3a; ref. 6), which is a forkhead transcriptional factor that functions in both the inhibition of the cell cycle and the promotion of cell apoptosis, and IKK α serves as a tumor metastasis promoter by down-regulating the tumor

suppressor Maspin (7), which is a serpin peptidase inhibitor that blocks tumor metastasis. Also, IKK ϵ and TBK1 prevent cancer cell apoptosis through the NF- κ B and RalB/Sec5 pathways, respectively (8, 9). Before the targeting of IKK and IKK-related kinases becomes a viable therapeutic intervention for cancer, a better understanding of their respective functions in broad-spectrum signaling transduction and gene expression is necessary (Fig. 2).

Consequences of IKK β activation. IKK β is one component of the classic IKK complex, which is composed of three subunits, two catalytic kinases (IKK α and IKK β), and a regulatory scaffold component IKK γ . Upon stimulation by either TNF α or IL-1 β , activated IKK β phosphorylates the NF- κ B inhibitor I κ B α and subsequently triggers its rapid degradation through the β -TrCP–derived ubiquitin-proteasome pathway, which liberates the NF- κ B heterodimer from I κ B α . No longer inhibited by I κ B α , the NF- κ B heterodimer translocates to the nucleus from the cytoplasm, binds to its target DNA sequence, and induces the expression of a myriad of genes involved in immune response (TNF α , IL-1, MCP-1, and COX2), cell proliferation (cyclin D1, cyclin D2, c-MYC, and JUNB), angiogenesis (vascular endothelial growth factor, IL-6, and IL-8), cell survival (XIAP, BCL-xL, c-IAP2, and GADD45 β), invasion and metastasis (matrix metalloproteinase-9 and urokinase-type

plasminogen activator), and epithelial-mesenchymal transition (TWIST and SNAIL; ref. 10). Because a variety of NF- κ B target genes function as hallmarks that are required for cancer development, the biological consequence of IKK β activation is tumor progression.

Although its function as an IKK is scientific dogma, IKK β does more than simply induce I κ B degradation and, consequently, NF- κ B activation. Recently, many of the non-I κ B targets of IKK β have been identified, suggesting that IKK β programs the widespread cellular response to extracellular stimulation and effects on cell signaling that were previously unsought. In addition to phosphorylating I κ B proteins to activate the NF- κ B signaling axis, IKK β can directly phosphorylate RELA, a transcriptional factor binding to p50 NF- κ B1 to form a heterodimer which is the most abundant form of NF- κ B. IKK β -mediated RELA phosphorylation not only induces RELA nuclear translocation but also promotes its interaction with a transcriptional coactivator to enhance its transactivation (11). Additionally, p105 NF- κ B has been found to form a

complex with mitogen-activated protein kinase kinase kinase 8 (MAP3K8, also known as Tpl2 and Cot). IKK β -induced phosphorylation of p105 NF- κ B leads to its degradation, which activates MAP3K8, and the activated MAP3K8 then activates the MAPK pathway, which increases cell proliferation (12, 13). IKK β might also affect the MAPK pathway by phosphorylation-mediated suppression of the ras-GTPase-activating protein-associated tyrosine kinase substrate DOK1 (14), which is a docking protein involved in the inhibition of the MAPK pathway, cell migration, and cell proliferation (15–17). IKK β -mediated DOK1 phosphorylation relieves DOK1-mediated repression of cell migration and spreading, which may contribute to TNF α -induced cell metastasis.

As mentioned above, IKK β -mediated FOXO3a phosphorylation induces its nuclear exclusion and ubiquitination, and the expression of IKK β is correlated with cytoplasmic FOXO3a in multiple human cancers (6), indicating that the regulation of FOXO3a phosphorylation by IKK β is significant in cancer development. Consistent with its role in NF- κ B-mediated

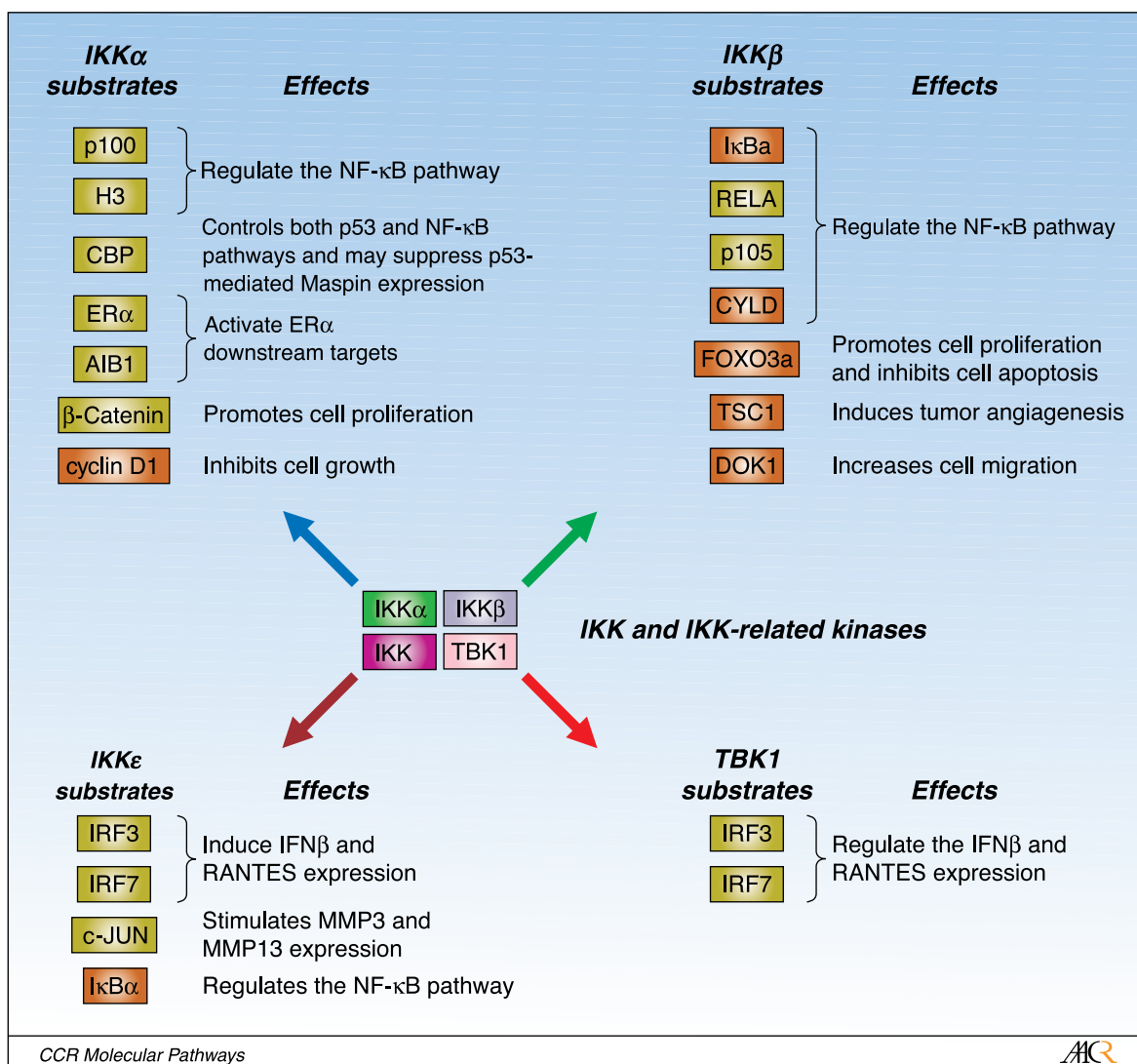


Fig. 2. IKK and IKK-related kinases induce the phosphorylation of their downstream substrates, leading to their activation (yellow) or inhibition (orange). Regulation of these substrates by IKK α , IKK β , IKK ϵ , and TBK1 has been shown to contribute to tumor development by increasing tumor angiogenesis and metastasis, promoting cell proliferation, and generating resistance to cell apoptosis. See text for a detailed description of downstream inhibitory or activation substrates of IKK and IKK-related kinases.

vascular formation via vascular endothelial growth factors (VEGF-A and VEGF-C), IKK β has been shown to phosphorylate tuberous sclerosis 1 (TSC1), a peripheral membrane protein known to be associated with the development of tuberous sclerosis, and inhibit its tumor suppressor function, which increases tumor angiogenesis (18, 19). IKK β -induced TSC1 phosphorylation inhibits its association with GTPase-activating protein (TSC2), alters TSC2 membrane localization, increases mTOR activity, enhances vascular endothelial growth factor-A expression, and culminates in tumorigenesis. The regulation of TSC1 phosphorylation by IKK β has been observed in breast cancer, in which it was found to be correlated with a poor clinical outcome (18, 19). IKK β has been found to regulate TNF α -mediated TRAF2 ubiquitination and activation of downstream signaling events via phosphorylation of the tumor suppressor cylindromatosis (20), which is a deubiquitinating enzyme mutated in familial cylindromatosis (21). Phosphorylation of cylindromatosis by IKK β relieves cylindromatosis-mediated suppression of TRAF2 ubiquitination and induces NF- κ B activation (20).

Consequences of IKK α activation. IKK α (also known as a conserved helix-loop-helix ubiquitous kinase) is the other catalytic kinase of the classic IKK complex. In contrast to IKK β 's effect on I κ B phosphorylation in the canonical pathway, IKK α might have a crucial function to facilitate NF- κ B-dependent gene transcription instead of I κ B phosphorylation due to its lower ability to induce I κ B phosphorylation. In addition, the B cell-activating factor of the TNF family has been found to induce BAFF receptor engagement and NF- κ B p52 precursor p100 processing through activation of the IKK α homodimer, thus mediating the so-called noncanonical IKK pathway. Activated IKK α -mediated p100 phosphorylation gradually causes partial proteolytic degradation of the COOH-terminal ankyrin repeat region of p100 by β -TrCP ubiquitin-proteasome processing, which leads to the activation and nuclear translocation of the p52/RELB heterodimer, and consequently, the induction of cyclin D1 expression. IKK α also regulates cyclin D1 expression via a number of p52/RELB-independent mechanisms. For instance, IKK α phosphorylates β -Catenin, which is an oncogenic transcriptional factor responsible for the development of several types of cancers. IKK α -mediated β -Catenin phosphorylation inhibits β -Catenin ubiquitination and degradation, and stimulates β -Catenin/T-cell factor-dependent cyclin D1 expression, which enhances tumor proliferation (22–25).

In addition to β -Catenin, IKK α phosphorylates both the estrogen receptor- α transcriptional factor and the estrogen receptor- α coactivator protein AIB1/SRC3 and activates estrogen receptor- α downstream targets such as cyclin D1 and c-MYC, thereby promoting cell proliferation in breast cancer (26, 27). The suggestion that IKK α directly phosphorylates cyclin D1 and promotes cyclin D1 degradation remains controversial (28). Based on these findings, the current model implicated that IKK α -mediated cyclin D1 down-regulation may serve as a feedback regulator in the suppression of IKK α -induced cell growth. Recently, several studies have discovered and examined the novel function of nuclear IKK α and have implicated it in tumor progression. IKK α has been found to mediate NF- κ B downstream gene expression by modulating the chromatin structure. Upon activation by TNF α stimulation, IKK α shuttles from the cytoplasm to the nucleus, where it

interacts with the cyclic AMP-responsive element binding protein (CREB)-binding protein (CBP), and phosphorylates histone H3 at serine 10. The regulation of histone H3 phosphorylation by IKK α is critical for the activation of a subset of NF- κ B-dependent genes induced by inflammatory cytokines (29, 30). In addition to binding with CBP to regulate histone function, IKK α directly phosphorylates CBP and switches its binding preference from p53 to NF- κ B. IKK α -mediated CBP phosphorylation not only facilitates NF- κ B-dependent gene expression but also suppresses p53-induced gene transcription (31). Interestingly, the nuclear function of IKK α has also been implicated in prostate cancer metastasis by inhibiting the expression of the tumor suppressor Maspin (7). It would be interesting to know if along with its function as a switch controlling both NF- κ B and p53 signaling events (31), IKK α also functions as a suppressor of p53-mediated Maspin expression via its regulation of CBP phosphorylation (32).

Consequences of TBK1 activation. TBK1, also called the TNF receptor-associated factor 2 (TRAF2)-associated kinase (33) or NF- κ B-activating kinase (34), is one of two noncanonical IKKs implicated in regulating the activation of IRF3 and NF- κ B signaling pathways (35). Although TBK1 is structurally similar to IKK α and IKK β , it is not part of the classic IKK α /IKK β /IKK γ complex, hence, it fails to induce I κ B degradation. TBK1-null cells have been shown to have normal I κ B degradation and NF- κ B DNA binding but a dramatic reduction in NF- κ B-dependent gene transcription, suggesting that, unlike IKK β participating in I κ B degradation, TBK1 has a unique role in NF- κ B activation (33). However, other studies with TBK1 and IKK ϵ single-null and double-null mice did not confirm a deficiency in NF- κ B activation (36, 37). Therefore, the actual role of TBK1 in NF- κ B activation needs more investigation.

Although the role of TBK1 in the NF- κ B pathway remains controversial, its role in regulating the function of IRF3 in response to viral infection has been well recognized. TBK1 coordinates with IKK ϵ to phosphorylate IRF3 and IRF7, and therefore induces their activation and nuclear translocation to drive IFN- β and chemokine RANTES expression (35–37). Using a genome-wide phenotype screen, Korherr et al. identified TBK1 as a “trigger” of the proangiogenic TBK1/IRF3 pathway and found that it was overexpressed in breast and colon cancers (38). Thus, TBK1-mediated tumor angiogenesis may occur through the IRF3-driven expression of several angiogenic factors, which results in tumor progression. Using a chemical proteomic approach, Godl et al. characterized TBK1 as a novel target of the angiogenesis inhibitor SU6668 (39), which further emphasizes the proangiogenic role of the TBK1/IRF3 signaling axis in cancer development. TBK1 has also been shown to be involved in the monomeric RalB GTPase-mediated innate immune signaling response and in tumor cell survival (9). TBK1 is activated by the RalB/Sec5 effector complex, and activation of the RalB/Sec5/TBK1 pathway restricts tumor cell apoptosis induced by oncogenic stress (9). In contrast to its oncogenic role in a variety of human malignancies, TBK1 has been shown to be responsible for the antitumor activity of the chemotherapeutic agent 5,6-dimethylxanthene-4-acetic acid, which is a small molecule in the flavanoid class functioning as a vascular disrupting agent currently under investigation in phase II clinical trials. 5,6-Dimethylxanthene-4-acetic acid has been shown to robustly induce TBK1/IRF3-mediated IFN- β expression in

primary murine macrophages, which is indicative of its antitumor activity (40, 41).

Consequences of IKKε activation. IKKε (also called IKK-i) is the other noncanonical IKK involved in regulating the activation of the IRF3 and NF-κB signaling pathways (35). Upon activation in response to toll-like receptor agonists and viral infection, IKKε phosphorylates IRF3 and IRF7 and triggers IRF3/IRF7 nuclear translocation, which results in the up-regulation of type I IFN expressions. It has been suggested that IKKε is involved in TNFα-induced and lipopolysaccharide-induced matrix metalloproteinase-3 and matrix metalloproteinase-13 gene expressions via phosphorylation and activation of the *c-JUN* transcriptional factor (42). IKKε-mediated *c-JUN* phosphorylation might be responsible for synovial inflammation and extracellular matrix destruction in rheumatoid arthritis as well as being involved in tumor invasion and metastasis. Like IKKβ, IKKε phosphorylates IκBα at Ser³² and Ser³⁶ (preferentially at Ser³⁶) and stimulates NF-κB activation (43). Using three integrative genetic approaches, Boehm et al. identified IKKε as an oncogene in human breast cancer. Abnormal up-regulation of NF-κB activity by IKKε is an essential step for cell transformation induced by AKT, indicating that IKKε acts downstream of AKT and links the phosphoinositide-3-kinase and NF-κB pathways (8). Whole genome structural analyses disclosed that IKKε is amplified and overexpressed in human breast cancers and that knockdown of IKKε promotes apoptosis in breast cancer cells (8), suggesting that a mechanism for NF-κB activation is involved in IKKε-mediated breast cancer development.

Clinical-Translational Advances

Many pharmaceutical companies are developing increasingly smaller molecular protease inhibitors that target IKK and IKK-related kinases. Most of these small-molecule inhibitors target IKKβ because it is the major player in the NF-κB pathway. Although most IKK inhibitors being developed are still in the preclinical stage of testing, some have been well characterized and have shown promising inhibitory effects in either *in vitro* or *in vivo* studies. In addition to using specific small-molecule inhibitors to target IKK and IKK-related kinases, researchers are also investigating other targeting strategies via the use of macromolecules, including genes, oligonucleotides, and peptides. We briefly describe these advances in targeting IKK and IKK-related kinases here and summarize them in Table 1.

PS-1145 (Aventis Research and Technologies/Millennium Pharmaceuticals, Inc.). A β-carboline natural product derivative that has been shown to be an IKKβ inhibitor (IC₅₀ = 150 nmol/L). It suppresses TNFα-mediated IκB phosphorylation and degradation, inhibits NF-κB activation (44), and induces multiple myeloma cell toxicity in the presence of TNFα (45).

BMS-345541. A small-molecule drug that targets an allosteric site of IKKβ (IC₅₀ = 0.3 μmol/L) and of IKKα (IC₅₀ = 4 μmol/L) but has little effect on 15 other cellular kinases. It blocks lipopolysaccharide-stimulated TNFα, IL-1β, IL-6, and IL-8 production with IC₅₀ in the range of 1 to 5 μmol/L *in vitro* (46). No toxicologic changes were observed in mice treated with BMS-345541 (at a daily dose of 100 mg/kg for 6 weeks; ref. 47).

SPC-839 (Celgene Corporation). A quinazoline analogue that has been developed to target IKKβ (IC₅₀ = 67 nmol/L).

Compared with its inhibitory effect on IKKβ, SPC-839 only weakly inhibits IKKα (IC₅₀ = 13 μmol/L). It suppresses NF-κB-mediated IL-6 and IL-8 production in Jurkat T cells (48).

ML120B (Millennium Pharmaceuticals, Inc.). A β-carboline compound reported to be a selective, reversible, and ATP-competitive inhibitor of IKKβ (IC₅₀ = 50 nmol/L). It has little effect on other cellular kinases, including IKKα (IC₅₀ > 100 μmol/L) and IKKε (IC₅₀ > 100 μmol/L). ML120B blocks TNFα-derived IκBα phosphorylation and NF-κB transcriptional activity. It also interferes with TNFα- and IL-1β-induced IL-6, RANTES, and MCP-1 expression (49).

SC-514. An aminothiophenecarboxamide derivative that has been identified as a selective, reversible, and ATP-competitive inhibitor of IKKβ (IC₅₀ = 6.5-15.9 μmol/L). However, it does not inhibit other IKK family members [IKKα (IC₅₀ > 200 μmol/L), IKKε (IC₅₀ > 200 μmol/L), and TBK1 (IC₅₀ > 200 μmol/L)] and has little effect on other cellular protein kinases. It blocks IL-1β-induced IL-6 and IL-8 production via the inhibition of IKKβ-mediated IκBα phosphorylation and degradation, and the partial interference of NF-κB nuclear translocation (50). However, its short half-life (*t*_{1/2} = 12 minutes) and limited bioavailability (2%) may restrict its clinical application.

CHS828. A pyridyl cyanoguanidine derivative that has shown a significant antitumor effect in *in vivo* and *in vitro* studies and is currently being evaluated in phase I/II clinical trials (51). It impairs lipopolysaccharide-mediated NF-κB nuclear translocation and transcriptional activation via the inhibition of IKK activities (IC₅₀ = 8.0 nmol/L). In addition, one of its analogues, CHS850, exhibits a similar ability to inhibit IKK-mediated NF-κB activation (IC₅₀ = 6.5 nmol/L; ref. 52).

SU6668 (Sugen, Inc.). An antiangiogenic small-molecule drug (which has completed phase I clinical trials) that is a receptor tyrosine kinase inhibitor. It is an indolinone compound that has been characterized as an ATP-competitive inhibitor of vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, and fibroblast growth factor receptor (53). Recently, it was found to block TBK1 activity (IC₅₀ = 5.2 μmol/L) and to inhibit TBK1-mediated IRF3 activation and IFN-β production (39).

RNA interference and small interfering RNAs. A promising therapeutic approach for cancer treatment that uses antisense oligonucleotides to directly target the nucleic acid sequence of IKKα, IKKβ, IKKε, and TBK1 (54). These antisense oligonucleotides can be delivered to tumors via liposomes or nanoparticles.

Gene therapy. An attractive therapeutic intervention for cancer that uses DNA vectors encoding therapeutic genes to target cancer cells. Ideally, it can be systemically delivered to any type of tumor, including solid tumors, micrometastatic tumors, and cancer cells in the bloodstream. Adenovirus type 5 E1A has been found to inhibit TNFα-induced IκBα degradation and NF-κB activation via suppression of IKKβ activity (55). It has also been shown to inhibit radiation-induced NF-κB activation and to sensitize cells to TNFα-induced apoptosis in multiple types of cancer (56). Multiple clinical trials have been completed and a phase I/II trial of E1A-paclitaxel combination therapy in patients with ovarian cancer is currently under way at the University of Texas M. D. Anderson Cancer Center (57-60).

Cell-permeable peptides. The NH₂-terminal α-helical region of IKKγ has been found to be associated with the COOH-

Table 1. Summary of targeting strategies to inhibit IKK activity

Strategies	Potential targets	Therapeutic agents	References
Small molecule inhibitors	IKK α / β	PS-1145	Castro et al. (44), Hideshima et al. (45)
		BMS-345541	Burke et al. (46), McIntyre et al. (47)
		SPC-839	Palanki et al. (48)
	IKK β	CHS828	Hiarnaa et al. (51), Olsen et al. (52)
		ML120B	Wen et al. (49)
RNA interference and small interfering RNAs	TBK1	SC-514	Kishore et al. (50)
		SU6668	Godt et al. (39)
	IKK α / β / ϵ and TBK1		Takaes et al. (54)
	IKK β	E1A	Shao et al. (55, 56)
	IKK α / β / γ complex	IKK β [644-756] peptide	May et al. (61)
Gene therapy			
Cell-permeable peptides			

terminal region of IKK β . Based on the concept of competition, the use of cell-permeable peptides that block the IKK γ -binding domain (IKK β [644-756]) to interfere with IKK complex function has been suggested. In two experimental mouse models of acute inflammation, this peptide blocked TNF α -mediated and phorbol 12-myristate 13-acetate-mediated NF- κ B activation but did not inhibit the basal NF- κ B activity (61).

Conclusion

Recent experimental data on the role of IKK and IKK-related kinases suggest that they have critical roles in inflammation-mediated human diseases, including many different types of cancer. IKK and IKK-related kinases promote cancer development in humans not only through the up-regulation of the expression of NF- κ B and IRF downstream targets but also through the interruption of multiple cellular protein functions.

Several small-molecule IKK inhibitors and other strategies targeting IKK and IKK-related kinases have shown significant results in preclinical studies and some are generating promising preliminary results in clinical trials. The hope is that several of these small-molecule drugs and/or targeted gene therapies will enter future clinical trial tests to help provide a complete evaluation of the potential for targeting IKK and IKK-related kinases as a therapeutic intervention for cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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