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Targeting IκappaB kinases for cancer therapy

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Abstract

The inhibitory kappa B kinases (IKKs) and IKK related kinases are crucial regulators of the pro-inflammatory transcription factor, nuclear factor kappa B (NF-κB). The dysregulation in the activities of these kinases has been reported in several cancer types. These kinases are known to regulate survival, proliferation, invasion, angiogenesis, and metastasis of cancer cells. Thus, IKK and IKK related kinases have emerged as an attractive target for the development of cancer therapeutics. Several IKK inhibitors have been developed, few of which have advanced to the clinic. These inhibitors target IKK either directly or indirectly by modulating the activities of other signaling molecules. Some inhibitors suppress IKK activity by disrupting the protein-protein interaction in the IKK complex. The inhibition of IKK has also been shown to enhance the efficacy of conventional chemotherapeutic agents. Because IKK and NF-κB are the key components of innate immunity, suppressing IKK is associated with the risk of immune suppression. Furthermore, IKK inhibitors may hit other signaling molecules and thus may produce off-target effects. Recent studies suggest that multiple cytoplasmic and nuclear proteins distinct from NF-κB and inhibitory κB are also substrates of IKK. In this review, we discuss the utility of IKK inhibitors for cancer therapy. The limitations associated with the intervention of IKK are also discussed.

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Conflict of interest

None.

Keywords

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1. Introduction

The nuclear factor-κB (NF-κB) is an evolutionarily conserved proinflammatory transcription factor that was first identified by Sen and Baltimore in response to pathogens and viruses [1]. It plays a crucial role during development, differentiation, and various pathological conditions. Accumulating evidence suggests that NF-κB is a link between inflammation and cancer [1–10]. NF-κB is known to regulate inflammatory molecules such as adhesion molecules, chemokines, cyclooxygenase (COX)-2, interleukin (IL)-1, IL-6, 5-lipooxygenase (5-LOX), matrix metalloproteinases (MMPs), tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF), all of which are involved in tumor development. This has provided a molecular basis for the role of inflammation in cancer. In mammals, NF-κB is comprised of five subunits: NF-κB1 (p105/p50), NF-κB2 (p100/p52), c-Rel, RelA (p65), and RelB [11]. These subunits associate to form heterodimers or homodimers and regulate the expression of NF-κB dependent target genes [8,9]. Under normal conditions, NF-κB subunits reside in the cytoplasm in association with inhibitory κB (IκB) proteins (IκBα, IκBβ, IκBε, IκBNS) that control NF-κB activation [11–14].

Although more than 15 pathways have been reported for NF-κB activation, two most common pathways are canonical (classical) and noncanonical (alternative) pathways (Fig. 1) [15]. The canonical pathway is initiated by p105/p50, while the noncanonical pathway is initiated by p100/p52. The canonical pathway depends on IKKβ and the inhibitory subunit IκBs, whereas the alternative pathway depends on IKKα homodimers and NF-κB inducing kinase (NIK) [16–18]. In the canonical pathway, IKKβ specifically phosphorylates IκBα on two conserved N-terminal serine residues ($Ser^{32/36}$). IκBα phosphorylation triggers the polyubiquitination (by E2- and E3-ligases) and subsequent degradation (by 26S proteasome) of IκBα [19]. IκBα degradation releases NF-κB dimers (p65/p50) in the cytoplasm. Subsequently, the dimer is translocated to the nucleus where it regulates the expression of NF-κB dependent target genes. The p65 subunit of NF-κB undergoes a series of posttranslational modifications including phosphorylation at Ser^{536} by IKK that is required for NF-κB's full activity [20]. Conversely, p65 phosphorylation at Ser^{536} can also suppress NF-κB signaling leading to harmful inflammation as observed in mice model [21]. The activation of the alternative pathway, which is commonly associated with RelB, results in regulated processing of the p100 precursor protein to p52 and subsequent translocation of p52-RelB heterodimers to the nucleus [17]. Because of its central role in the NF-κB signaling pathway, IKK has been targeted by various means for cancer therapy. In the following sections, we discuss the IKK signaling pathway and the potential strategies for its intervention in cancer cells.

2. IKK signaling

IKK is a trimeric complex consisting of IKKα, IKKβ, and NF-κB essential modulator (NEMO) or IKKγ [22–24]. Whereas IKKα and IKKβ subunits possess kinase activities, IKKγ is the regulatory subunit. An additional substrate-targeting subunit called ELKS may also be present in the IKK complex [25]. IKKβ is required for rapid degradation of NF-κB-bound IκBs. IKKα controls the processing of p100, leading to activation of p52: RelB dimers [26]. Both IKKα and IKKβ were identified as constituents of a 700- to 900-kD protein complex that exhibits TNFα-induced IKK activity [22,27]. In general, IKK can be activated through (i) direct phosphorylation of one of its catalytic subunits, (ii) *trans*-autophosphorylation; and (iii) conformational change induced by post-translational modification of its subunits [28]. IKKα and IKKβ were purified and cloned by their ability to phosphorylate IκB proteins in response to tumor necrosis factor-α (TNF-α) [27,29]. Although both IKKα and IKKβ possess considerable similarities, they have largely nonoverlapping functions because of the difference in their substrate specificity. The IKKβ-dependent pathway is essential for activation of innate immunity, whereas IKKα is important for regulation of adaptive immunity and lymphoid organogenesis [26].

Two other IKK-related kinases called IKKε (IKK-i) [30,31] and TBK1 [NF-κB-activated kinase (NAK) or TRAF2-associated kinase (T2 K)] have been identified [32–34]. Although both IKKε and TBK1 possess sequence similarity to IKKα and IKKβ, none of these kinases are part of the classical IKKγ-containing IKK complex [30,31,35]. IKK related kinases are known to play a crucial role in promoting transformation, survival, and proliferation of cancer cells [36–42]. IKKε is also a potential target for cancer immunotherapy [43]

The role of IKK in regulating cancer pathogenesis is reported from several lines of evidence. First, IKK is a regulator of NF-κB that controls various aspects of tumor development such as transformation, survival, proliferation, invasion, angiogenesis and metastasis [44,45] [46]. Second, the activation of the IKKs has been observed in both solid tumors and hematological malignancies such as breast cancer, prostate cancer, colorectal cancer, leukemia, lymphoma and multiple myeloma [47–50]. Third, epidemiological studies employing gene expression analyzes has revealed that IKK is a mediator of clear cell renal cell carcinoma overall survival [51]. Fourth, gene silencing of IKK subunits by siRNA or by pharmacological inhibitors is known to promote cell death and sensitize cancer cells to chemotherapeutic agents [47,52]. Fifth, IKKs may also regulate cell cycle progression independent of NF-κB [52]. Sixth, IKK is known to regulate cancer stem cell growth through TAK1 mediated TGF-β signaling [53]. Seventh, a mouse model of prostate cancer expressing an inactive form of IKKα showed delayed cancer onset, decreased distant-site metastases and an increase in the survival of mice [54]. The implication of all these suggests that IKK could be a potential target for cancer therapy [55,56]. We discuss the strategies used for IKK inhibition in the following section. The potential of IKK inhibitors for cancer therapy as evident from in vitro, *in vivo* and human studies, are discussed.

3. IKK inhibitors

Because IKK and IKK related kinases play a crucial role in the NF-κB activation pathway, several inhibitors have been developed against these kinases for cancer therapy. Since IKKβ is the primary regulator of NF-κB, most inhibitors are based on the modulation of the activity of this kinase. The efficacy of IKK inhibitors has been examined mostly in preclinical studies; a few have advanced to the clinic (Table 1). Although various IKK inhibitors have been developed, we discuss only important inhibitors in this review. These inhibitors are of varying nature such as natural products, proteasome inhibitors, viral components, peptides, synthetic agents, and many others (Fig. 2). Furthermore, IKK inhibitors are structurally diverse (Fig. 3).

3.1. Pre-clinical studies

3.1.1. Specific IKK inhibitors—Some specific inhibitors of IKK include BMS-345541, PS-1145, Bay 11-7085, IMD-0354, AS602868, and ACHP. BMS-345541 inhibits IKK activity selectively by targeting an allosteric site of IKKα (IC_{50}: 4 μmol/L) and IKKβ (IC_{50}: 0.3 μmol/L) [57]. Furthermore, this agent produces no inhibitory effects on a panel of 15 other kinases [57]. Interestingly, the agent was found to be safe in mice [58]. BMS-345541 can also suppress breast tumorigenesis and metastases by targeting GD2+ cancer stem cells [59]. In another study, BMS-345541 was found to reduce proliferation and induce apoptosis in PC-3 cells [60]. Furthermore, the level of phospho-IκBα and nuclear p65 was also suppressed by BMS-345541. This inhibitor also down-regulated mesenchymal markers, such as N-cadherin, Snail, Slug, and Twist, while up-regulating epithelial markers such as E-cadherin and phospho-NDRG1. The changes in molecular markers were associated with reduced invasion and metastasis of PC-3 cells. The authors of this study concluded that IKK plays a key role in inducing epithelial-to-mesenchymal transition (EMT) and apoptosis in prostate cancer cells. Moreover, BMS-345541 can reverse EMT phenotype in prostate cancer cells. BMS-345541 is also known to inhibit constitutive IKK activity and melanoma cell survival both by in vitro and *in vivo* studies [61]. Furthermore, BMS-345541 induced mitochondria-mediated apoptosis in melanoma cells [61].

PS-1145 is a derivative of β-carboline alkaloid with the potential of inhibiting IKKβ activity (IC_{50}: 150 nM) without any effect on PKA, PKC and CKII activity. It can also suppress TNFα-induced IκBα phosphorylation and degradation and thereby inhibit NF-κB activation [62]. PS-1145 also induces multiple myeloma cell toxicity in the presence of TNFα [63]. The agent was selectively toxic to activated B-cell-like subgroup of diffuse large B-cell lymphoma [64]. BAY 11-7085, a specific IKK inhibitor was found to inhibit EMT and invasiveness in pancreatic cancer mice model [65]. This inhibitor can also significantly reduce the proliferation of ovarian cancer cells [66]. IMD-0354, a selective inhibitor of IKKβ is known to suppress neoplastic proliferation of human mast cells with constitutively active c-kit receptors [67]. It also induces G0/G1 cell cycle arrest and apoptosis in breast cancer cells [68].

Visfatin is a 52-kDa adipokine originally found in the visceral fat [69,70]. An increase in visfatin expression is positively correlated with tumorigenesis and/or metastasis of many cancer types [71]. This adi-pokine can discriminate between post-menopausal breast cancer

patients at an early cancer stage and those at a late stage [72]. ACHP is a selective inhibitor of IKKα (IC_{50}: 8.5 nM) and IKKβ (IC_{50}: 250 nM). It inhibits NF-κB DNA binding activity, and induces cell growth arrest and apoptosis in multiple myeloma cell lines [73]. It was also found to block visfatin-induced NF-κB activation and up-regulation of matrix metalloproteinase (MMP)-2 and MMP-9 in non-small cell lung cancer (NSCLC) [74]. Amlexanox is a selective inhibitor of TANK-binding ki-nase 1 (TBK1) and IKKε (IC_{50}: ~1–2 μM) [75]. Amlexanox interacts with human S100A4 protein [76], reduces proliferation, and induces G1-phase cell cycle arrest of melanoma cells [77]. Amlexanox is also known to selectively inhibit the viability of NSCLC cells with EGFR mutations [78]. In addition, some other specific IKK inhibitors include GSK 319347A for IKKε, and BI 605906 (IC_{50}: 380 nM) [79], PF 184 (IC_{50}: 37 nM) [80] and SC 514 (IC_{50}: 3–12 μM) [81] for IKKβ.

It is clear from the above that the different subunits of IKK can be targeted in a specific manner. The specific IKK inhibitors exhibit activities at nanomolar to micromolar range. However, the evidence for the activities of these inhibitors is based on preclinical studies in animals and cell lines. Future studies should be focused to examine the clinical efficacy of these inhibitors.

3.1.2. Potential of natural products as IKK inhibitors—Because of their safety, affordability and being used since ancient time, agents derived from mother nature are preferred. These agents are called ‘nutraceutical’ (nutrition + pharmaceutical) and possess potential to inhibit IKK activity. Curcumin, a polyphenol derived from the golden spice (turmeric) is one of the most widely studied nutraceuticals. This polyphenol is known to exhibit activities against several cancer types [82]. Curcumin’s anti-inflammatory activity through modulation of NF-κB activation pathway was first reported in 1995 [83]. Furthermore, the polyphenol inhibits IKKβ activity by inducing its S-nitrosylation [84]. Artemisinin is a sesquiterpene lactone derived from a medicinal plant Artemisia annua. For its discovery, Dr. Tu Youyou shared Nobel Prize in Medicine in 2015. Artemisinin and its derivatives are now considered standard therapy for malaria. One study was aimed to explore the anti-inflammatory activity of artemisinin [85]. The sesquiterpene exhibited anti-inflammatory activities in 12-O-tetra-decanoylphorbol-13-acetate (TPA)-induced skin inflammation in mice. Mechanistically, artemisinin inhibited TNFα induced NF-κB reporter gene expression, phosphorylation and degradation of IκBα, and p65 nuclear translocation. Artemisinin treatment also inhibited the kinases upstream to IKK such as TNF receptor-associated factor 2 (TRAF2) and receptor interacting protein 1 (RIP1). Furthermore, artemisinin suppressed TNFα-induced NF-κB target genes involved in cell survival (c-IAP1, Bcl-2, FLIP), proliferation (COX-2 and cyclinD1), invasion (MMP-9), and angiogenesis (VEGF). Additionally, major inflammatory cyto-kines (TNF-α, iNOS, MCP1) were also suppressed by artemisinin treatment. Sesquiterpene also potentiated TNF-α-induced apoptosis. Moreover, reactive oxygen species (ROS) production and phosphorylation of p38 and ERK were significantly suppressed by artemisinin. However, the phosphorylation of JNK was unaffected. Collectively, these results suggest that artemisinin may be a potential therapeutic agent against inflammation, that is associated with cancer [85].

Mangiferin is a naturally occurring glucosyl xanthone derived from several folk medicines and foods including mango [72]. One study was aimed to evaluate the efficacy of mangiferin against tumor growth and metastasis in a mouse model of melanoma [86]. Mangiferin inhibited spontaneous metastasis and tumor growth, p65 nuclear translocation, and activation of the NF-κB-inducing kinase (NIK) and IKK. Additionally, mangiferin inhibited the expression of matrix metalloproteinases (MMPs) and very late antigens (VLAs) in vivo. Mangiferin also induced the cleavage of caspase-3 and poly ADP ribose polymerase (PARP). Furthermore, an up-regulation in p53 up-regulated modulator of apoptosis (PUMA), p53, and phosphorylated p53 proteins, along with down-regulation of survivin and Bcl-xL was observed after mangiferin treatment. The authors of this study concluded that mangiferin could be a potential therapeutic agent against NIK for the treatment of metastatic melanoma [86]. Betulinic acid, a triterpenoid was found to induce apoptosis in prostate cancer cells that was mediated through decreased phosphorylation of IKKα and IκBα, and inhibition of NF-κB p65 nuclear translocation [87]. In another study, betulinic acid inhibited lipopoly-saccharide (LPS)-triggered phosphorylation of IKK in CRC cells that contributed to its anti-cancer activities [88]. In addition to purified components, crude extract and powder from natural sources have also been shown to inhibit IKK activation pathways. For example, colorant powder from a perennial vine, *Basella alba* was found to suppress IKK activation induced by LPS in macrophages [89].

3.1.3. IKK inhibition by non-cancer agents—A potential strategy for cancer drug development is to evaluate the effectiveness of drugs approved for diseases other than cancer. This process called ‘drug repurposing’ is based on the fact that most human diseases share common pathways and thus one drug can be useful for more than one disease [90]. Doxycycline is an antibiotic used for the treatment of bacterial and protozoan infections. Originally used as an antibiotic, doxycycline can also inhibit LPS-induced IKKβ and NF-κB activation, and the expression of NF-κB dependent tumorigenic proteins in PC3 human prostate cancer cells [91]. Aspirin (acetylsalicylic acid) is one of the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs). Originally used as an analgesic and as an anti-pyretic, aspirin has now been found to possess anti-cancer activities, particularly for colorectal cancer [90]. In a recent study, aspirin was found to directly inhibit IKK activity in cancer cells [92]. Aspirin can also suppress prostate cancer cell invasion by decreasing IKK-β-induced NF-κB activation that leads to a reduction in MMP-9 activity and uPA expression [93]. Arsenic has been used for more than 2400 years for some human ailments including ulcers, plague, and malaria [94]. It is now used for the treatment of acute promyelocytic leukemia [95]. In one study, arsenic was found to rapidly down-regulate constitutive IKK/NF-κB activity in Hodgkin/Reed-Sternberg (HRS) cell lines with functional IκB proteins [96]. This was concomitant with an increased apoptosis in HRS cell lines. Additionally, administration of arsenic trioxide dramatically reduced tumor formation in NOD/SCID mice xenotransplanted with L540Cy Hodgkin tumors.

3.1.4. IKK inhibition by peptides/bio-molecules—Another approach for suppressing IKK activity is by disrupting protein-protein interactions in the IKK complex. IKKγ (NEMO) interacts at the carboxyl-terminal of IKKα and IKKβ through NEMO-binding domain (NBD) that contains a conserved hexapeptide sequence (LDWSWL) [97]. Cell

permeable peptides have been shown to disrupt protein-protein interactions in the IKK complex. For example, the cell permeable NBD peptide inhibited the association of NEMO with the IKK complex [97], and suppressed cytokine-induced NF-κB activation and its target gene expression. Furthermore, in mouse models of acute inflammation, NBD blocked TNFα- and PMA-induced NF-κB activation without inhibiting the constitutive NF-κB activity. NBD peptide can also inhibit osteoclastogenesis, which is a pathological hallmark of several chronic diseases including cancer [98].

Apart from peptides, other bio-molecules have also been used to inhibit protein-protein interaction in the IKK complex. For example, the protein pVHL is a product of the von Hippel-Lindau (VHL) tumor suppressor and functions as an adaptor of E3-ligase [99]. In one study, pVHL was found to inhibit NF-κB activation through K63-ubiquitination of IKKβ [74]. This lead to an inhibition of TAK1 binding and inhibition of IKKβ phosphorylation. Furthermore, prolyl hydroxylase activities were essential for pVHL-mediated K63-linked ubiquitination of IKKβ. Overall, these results suggest a function for pVHL in which it regulates IKK/NF-κB signaling by mediating IKKβ K63-ubiquitination. MC159 protein of Molluscum contagiosum virus (MCV) interacts with the NEMO [100]. This prevented the interaction of NEMO with the cIAP1 E3 ubiquitin ligase and thus inhibition of NEMO polyubiquitination and NF-κB activation. The inhibition of cIAP1-NEMO interactions could be used as a strategy to minimize IKK activation and to maximize anticancer activity.

The adenovirus E1A, a tumor suppressor, was found to inhibit TNFα-induced IKKβ activity that in turn leads to inhibition of IκBα degradation and NF-κB activation in cancer cells [101]. E1A has also been shown to inhibit radiation-induced NF-κB activation and to sensitize multiple cancer types to TNFα [102]. Viral IL-10 (vIL-10) is an Epstein-Barr virus homolog of human IL-10 (hIL-10). One study examined whether vIL-10 inhibits components of antigen processing machinery (HLA-I, LMP-2, LMP-7, TAP-1, and TAP-2) through the NF-κB signaling pathway in nasopharyngeal carcinoma cells [103]. An inhibition of NF-κB activation was observed by vIL-10 that was mediated through suppression of IKK phosphorylation. While TNF-α treatment led to a substantial translocation of NF-κB p65, pretreatment with vIL-10 blocked this translocation. vIL-10 also inhibited TNF-α-induced DNA-binding of NF-κB p65 in the nucleus. Chromatin immunoprecipitation (ChIP) assay demonstrated that NF-κB p65 could bind to the TAP-1, TAP-2, LMP-2, LMP-7 and HLA-I gene promoters. Furthermore, vIL-10 was found to induce NF-κB-mediated down-regulation of TAP-1, TAP-2, LMP-2, LMP-7 and HLA-I transcription in nasopharyngeal carcinoma cells. It was concluded that the inhibition of NF-κB activity might be an important mechanism for vIL-10 suppression of transcription of the antigen processing machinery (HLA-I, LMP-2, LMP-7, TAP-1, and TAP-2) in nasopharyngeal carcinoma cells.

TNF receptor-associated factor 6 (TRAF6) is implicated in poly-ubiquitin-mediated IL1R/TLR signaling through activation of IKK to regulate NF-κB and JNK signaling pathways. In one study, higher expression of TRAF6 was observed in bone marrow mononuclear cells from patients with multiple myeloma [104]. TRAF6 was significantly elevated in BMMCs from patients with progressive disease. Furthermore, a reduction in the

activation of IKK and cellular growth, and an increase in the apoptosis of multiple myeloma tumor cells was observed by the use of TRAF6 dominant-negative (TRAF6dn) peptides. Finally, TRAF6dn peptide dose-dependently inhibited RANKL- and mCSF-induced osteoclast formation from $CD14^+$ monocytes and markedly reduced bone resorption in dentin pits. Collectively, these data demonstrate that blocking TRAF6 signaling is associated with anti-multiple myeloma effects and reduces bone loss. Thus, targeting TRAF6 signaling and associated pathways could be a promising approach for multiple myeloma therapy.

One study assessed the role of IKKα in melanoma patients [105]. The expression of IKKα and overall activation of NF-κB were heterogeneous. Furthermore, IKKα-specific p100/p52 processing was detected in a small subset of melanoma patients as well as in melanoma cell lines. Down-regulation of IKKα by siRNA was associated with a reduction in doxorubicin-induced NF-κB activation. Furthermore, constitutive and TNFα-stimulated expression of CXCL8 and ICAM-1, and cell migration was also reduced by IKKα gene silencing. In contrast, overexpression of IKKα in melanoma cell lines did not significantly affect progression-related functions. The authors of this study concluded that IKKα may be a potential target only in some individuals but not for general melanoma therapy.

3.1.5. Direct inhibitors of IKK—A cysteine residue at position 179 in the activation loop is critical for IKKβ activity. Some agents are known to inhibit IKK activity by directly targeting this residue. Epoxyquinone A monomer (EqM) is a synthetic derivative of epoxyquinol A. EqM is a potent inhibitor of TNF-α-induced NF-κB activation. EqM targets Cys^{179} of IKKβ to inhibit IκBα phosphorylation and degradation. Furthermore, inhibition of NF-κB activity by EqM is associated with its anti-growth effects on colon, kidney, and leukemia cancer cells [106]. Cys^{179} of IKKβ is targeted by several other agents, such as arsenite [107], prostaglandins [108], nimbolide [15], nitric oxide [109], butein [110], and cobrotoxin [111].

3.1.6. Utility of IKK inhibition in combination therapy—A major obstacle in the cancer therapy is that although in the beginning cancer cells respond to drugs, over time, these cells develop resistance to therapy partly owing to the development of resistance mechanism. For example, 5-fluorouracil (5-FU) is a pyrimidine analog that can induce apoptosis in salivary gland cancer cells through inhibition of IKK activity [112]. Conversely, 5-FU was found to induce IKK-mediated NF-κB activity in colorectal cancer (CRC) cells [70]. The inhibition of IKK can enhance the efficacy of conventional chemotherapeutic agents. For example, AS602868 is a specific inhibitor of IKKβ that can induce apoptosis in human primary AML cells [113]. AS602868 also enhanced the apoptotic effects of chemotherapeutic agents, such as doxorubicin, cytarabine, and etoposide [113]. Similarly, a combination of TRAF6 dominant-negative (TRAF6dn) peptide with bortezomib or carfilzomib is associated with an enhanced anti-multiple myeloma effects [104]. Bay 11-7085, in combination with vorinostat significantly reduced tumor growth in ovarian cancer mice model [114]. Because HDAC inhibitors can activate NF-κB activation pathway [115], use of IKK inhibitors can reverse the effects of HDAC inhibitors. Thus, a combination of IKK and HDAC inhibitors could be an ideal strategy to fight ovarian cancer. However, further animal studies are required to support these conclusions.

TPCA-1 is a potent and selective inhibitor of IKKβ (IC_{50}: 17.9 nM). It exhibits more than 22- and 550-fold selectivity over IKKα and other kinases, respectively [116]. Vesicular stomatitis virus (VSV) based recombinant viruses such as VSV-ΔM51, are effective oncolytic viruses (OVs) against a majority of pancreatic ductal adenocarcinoma (PDAC) cell lines. However, some PDAC cell lines are highly resistant to VSV-ΔM51. TPCA-1 can break the resistance of PDAC cells to VSV-ΔM51 [117,118]. In combination with tyrosine kinase inhibitors (TKI), TPCA-1 produces synergistic effects on non-small cell lung cancer (NSCLC) [119]. IKK-related kinases promote KRAS-driven tumorigenesis. CYT387, a potent JAK/TBK1/IKKε inhibitor is known to impair KRAS-driven murine lung cancer growth [120]. CYT387 in combination with mitogen-activated protein kinase (MAPK) inhibition regresses aggressive KRAS mutant and p53 null lung adenocarcinomas in mice. These observations suggest that simultaneous inhibition of TBK1/IKKε, JAK, and MEK signaling could be an effective treatment in oncogenic KRAS-driven lung adenocarcinoma [120]. Mucoepidermoid carcinoma (MEC) is the most common type of salivary gland cancer [121,122]. MEC is associated with low survival rates and high morbidity. Although ionizing radiation (IR) is the first line option for MEC, patients frequently develop resistance to IR over time. In one study, pharmacological inhibition of IKK-β/IκBα/NFκB axis, using a single dose of emetine was found to sensitize MEC cells to IR [123]. Similarly, combining amlexanox with MEK inhibitor AZD6244 was found to significantly inhibit the xenograft tumor growth of NSCLC cells harboring EGFR mutations [78]. Thus, inhibition of IKK could be a novel approach to overcome radioresistance in MEC cells.

Overall, studies mentioned above suggest that the inhibition of IKK can be helpful to combat chemoresistance. However, comprehensive pre-clinical studies are warranted before this strategy can proceed for human clinical trials.

3.2. Clinical studies

Although several agents have shown efficacy against IKK by preclinical studies, the efficacy of IKK inhibitors in human is unclear. Only few IKK inhibitors have been tested in clinical trials for human diseases. Bortezomib (Velcade/PS-341) is one of the most successful inhibitor approved by United States Food and Drug Administration (FDA) for the treatment of relapsed and newly diagnosed multiple myeloma (MM) patients [124–129]. An inhibitor of 20S proteasome, bortezomib is known to suppress NF-κB activation in an indirect manner. Bortezomib is also useful in patients with mantle cell lymphoma [130], acting at least in part by inhibiting NF-κB activation [131,132]. Because IκBα subunit of NF-κB is a substrate of the proteasome, the initial rationale for the use of bortezomib in MM patients was through its inhibition of IκBα degradation. Indeed, bortezomib has been reported to inhibit inducible NF-κB activation [133,134]. However, in MM cell lines and primary tumor cells from MM patients, bortezomib significantly down-regulated IκBα expression and induced NF-κB activation [135]. Furthermore, bortezomib was found to trigger phosphorylation of IKKβ and its upstream receptor-interacting protein 2. The use of MLN120B, an IKKβ inhibitor, was found to abrogate IκBα down-regulation and NF-κB activation induced by bortezomib [135]. Moreover, IKKβ inhibitor enhanced bortezomib-induced cytotoxicity [135]. A phase II clinical trial was designed to examine the effectiveness of bortezomib in treating patients with metastatic or recurrent colorectal cancer

(www.clinicaltrials.gov). A total of 21–41 patients within 2–4 months were recruited in the study. As of 18th Feb 2018, the study was completed. However, the results are yet to be published, to our knowledge. Overall, these studies suggest that depending on the cellular context, bortezomib can inhibit as well as induce NF-κB activation in MM cells.

Denosumab is a monoclonal antibody against RANKL. It is the first RANKL inhibitor to be approved by FDA for use in postmenopausal women with risk of osteoporosis [136]. Denosumab has also been approved for the prevention of skeleton-related events in patients with bone metastases from solid tumors. It has been shown to indirectly inhibit IKK pathway through modulation of RANKL/RANK pathway [137,138]. Brentuximab vedotin is an antibody-drug conjugate (ADC) with a potential to target CD30, which is one of the surface antigens expressed in lymphoma cells. Brentuximab vedotin is approved for the treatment of relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL). A member of the TNFR superfamily, CD30 is involved in the activation of the NF-κB pathway [139]. Thus, Brentuximab vedotin could also indirectly inhibit the IKK/NF-κB activation pathway. However, whether these agents modulate IKK activity in cancer patients remains unexplored.

3.3. Miscellaneous studies

BX-795 is a pharmacological inhibitor identified against IKKε/TBK1 [140]. BX-795 can also target Aurora B and phosphoinositide-dependent kinase-1 (PDK1). To our knowledge, the anti-tumor activity of BX-795 has not been explored. A derivative of 6-Aminopyrazolopyrimidine was identified as an inhibitor of TBK1 kinase activity from a library of 250,000 compounds [141]. This pharmacological inhibitor is reported toxic to TBK1-dependent cancer cell lines. However, the efficacy of this inhibitor has not yet been explored in vivo. Overall, these studies suggest that non-canonical IKKs could be targeted for cancer therapy. However, non-canonical IKKs are known to regulate the production of Type 1 interferons during bacterial and viral infection [140] Thus, systemic inhibition of IKKε/TBK1 may lead to compromised anti-bacterial and anti-viral responses.

IKKα shuttles between the cytoplasm and the nucleus. The nuclear IKKα is known to regulate the expression of several genes including Maspin (mammary serine protease inhibitor or SerpinB5), a tumor suppressor whose expression is negatively regulated by nuclear IKKα [54]. One study explored the ability of a glucosamine derivative, 2-(N-carbobenzyloxy)l-phenylalanylamido-2-deoxy-β-D-glucose (NCPA) to stimulate the production of Maspin in osteosarcoma cells [142]. NCPA inhibited IKKα nuclear translocation and stimulated Maspin production. Furthermore, Maspin production was accompanied by down-regulation in the expression of β1 integrin, MMP-9, MMP-13, and reduced cell migration. In summary, these results suggest that inhibition of IKKα by NCPA contribute to its activities against osteosarcoma.

(*E*)-3-(3,5-dimethoxyphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one [DPP23], the derivative of a synthetic polyphenol induces apoptosis in cancer cells through the unfolded protein response in a selective manner. One study evaluated the potential of DPP23 on tumor invasion and metastasis [143]. This polyphenol inhibited TNF-α-induced motility, F-actin formation, and the invasive capability of MDA-MB-231 cells. The polyphenol also inhibited

NF-κB-dependent MMP-9 expression at the transcriptional level. Furthermore, DPP23 inhibited IKK and AKT activation; the gene silencing of AKT2 significantly suppressed TNF-α-induced IKK phosphorylation. Collectively, these results suggested that DPP23 can prevent TNF-α-induced invasiveness of MDA-MB-231 breast cancer cells by inhibiting AKT-IKK-NF-κB-mediated MMP-9 expression. In addition, DPP23 attenuated liver metastasis in syngeneic mice model bearing 4T1 mammary carcinoma cells. The authors of this study concluded that DPP23 possess the potential for the prevention of invasion and metastasis or as an adjuvant for breast cancer chemo/radiotherapy. However, further studies are required to support these claims.

An analysis performed in 288 human colorectal cancer (CRC) samples revealed a significant association between nuclear IKK and malignancy [144]. Importantly, tumor cells were characterized by the presence of an active truncated nuclear IKKα with a predicted molecular weight of 45 kDa (p45-IKKα). The active nuclear p45-IKKα was found to possess kinase domain but lacked several regulatory regions. Furthermore, nuclear p45-IKKα formed a complex with nonactive IKKα and NEMO that mediates phosphorylation of SMRT and histone H3. Interestingly, proteolytic cleavage of full-length IKKα into p45-IKKα was associated with suppressed apoptosis of CRC cells in vitro and sustained tumor growth in vivo. Overall, these results identified a potential drug target for treating patients with advanced refractory CRC. In a subsequent study, activation of p45-IKKα was observed downstream of mutant KRAS and BRAF proteins [145]. Interestingly, activation of p45-IKKα was independent of the NF-κB pathway but was dependent on the endosomal compartment. Accordingly, chloroquine or bafilomycin A1 (inhibitors of endosomal acidification) completely suppressed p45-IKKα phosphorylation without affecting the activity of the NF-κB pathway. Using orthotopic xenografts of CRC, an enhancement in the anti-tumor effects of conventional chemotherapy (irinotecan, 5-azacytidine) was observed by bafilomycin A1 and chloroquine treatment. Most notably, the metastatic capacity of CRC cells was completely suppressed by the combined treatment. Overall, these results suggest that NF-κB-independent functions of IKK can be targeted for therapeutic intervention. Moreover, other endosomal-dependent pathways such as Notch [146] and Wnt [147] can also be inhibited by blocking the endosomal functions.

CHS 828 is a pyridyl cyanoguanidine known to exert antitumor activities both by *in vitro* and *in vivo* studies [148]. This cyanoguanidine is in phase I/II clinical trials [148,149]. CHS 828 was found to inhibit LPS-induced nuclear localization as well as the transcriptional activity of NF-κB in human THP-1 leukemia cells [50]. Furthermore, CHS 828 inhibited IKK activity (IC_{50}: 8 nM) that correlated with its anti-proliferative effect in lung cancer cells.

In general, agents with the potential to inhibit IKK possess anticancer activities. However, some anti-cancer agents are known to activate IKK. For example, UV and ionizing radiation, used commonly in cancer therapy can activate the NF-κB pathway in an IKKβ-dependent manner [150]. This relies on the nuclear translocation, sumoylation and ataxia telangiectasia mutated (ATM) mediated phosphorylation of NEMO scaffolding protein [151]. The de-sumoylation and ubiquitylation of NEMO can facilitate the nuclear export of an NEMO-ATM complex and activation of the IKK complex, chiefly IKKβ [151]. However, it is

unknown if IKK is activated in response to all forms of radiation in all cancer types. It is also not known if IKKβ is the predominant kinase activated in response to UV and ionizing radiation. However, the non-canonical NF-κB activation pathway has been implicated in mediating survival of endometrial carcinoma cells in response to ionizing radiation [152]. Curdlan is a 1,3-β-D-glucan produced by the bacterium Alcaligenes faecalis. Curdlan is approved by United States FDA for use in foods as a formulation aid, processing aid, stabilizer, thickener, or texturizer. Despite having antitumor activities [153], curdlan is also known to induce phosphorylation of IKK in dendritic cells [154].

4. Conclusions

IKK plays a crucial role in NF-κB activation pathway and cancer pathogenesis and thus represents a potential target for therapeutic intervention. Several inhibitors have been developed based on the IKK-NF-κB pathway, few of which have advanced to the clinic. These inhibitors target IKK directly or indirectly. Some inhibitors suppress IKK activity by disrupting protein-protein interaction in the IKK complex. IKK inhibitors have also been shown to enhance the efficacy of conventional chemotherapeutic agents. Although IKK inhibitors have shown promise for cancer therapy, there are certain limitations associated with the intervention of IKK that deserve attention.

First, although several inhibitors have been developed, only a few have been tested in the clinic. Future studies should be focused on evaluating the clinical efficacy of more IKK inhibitors. Second, cancer cells are intelligent and can compensate for the loss of IKK by adapting to alternate survival signaling pathways. This may lead to the attenuation of the efficacy of kinase inhibition. For example, loss of TBK1, an IKK related kinase leads to compensatory activation of receptor tyrosine kinases in lung cancer cells [155]. Thus, a co-targeting strategy could be helpful in these situations. Geldanomycin is an antibiotic with ability to block both IKKα/β and EGFR pathways [156]. This antibiotic is reported to be more active than IKKβ-specific inhibitors in suppressing NF-κB activation and proliferation and inducing cell death in head and neck cancer [156]. Similarly, targeting IKKα and the proteasome can increase efficacy of bortezomib in androgen-independent prostate cancer cells [157]. Third, IKK and NF-κB are the key components of innate immunity; the inhibition of these pathways may lead to compromised immune response. For example, systemic inhibition of IKKε/TBK1 may lead to compromised anti-viral responses. Future efforts should be focused on targeting IKK in a cancer-specific manner. Fourth, although much is known about IKK signaling, more and more IKK-associated signaling molecules continue to emerge that leads to a challenge in targeting this pathway. Fifth, several NF-κB independent substrates of IKK such as p53, TSC1, and FOXO3a, have been identified. In fact, IKK is also known to limit tumor progression and inflammation by targeting proteins other than IκBα [158]. IKKα/β can control biliary homeostasis and hepatocarcinogenesis in mice by phosphorylating the cell-death mediator receptor-interacting protein kinase 1 (RIPK1) [159].

In conclusion, several inhibitors have demonstrated potential against IKK by preclinical studies. However, none has been reported to directly inhibit IKK in humans. Several factors such as dual nature of IKK, lack of reliable pharmacokinetics/pharmacodynamics data for

inhibitors, and redundancy in the kinase pathways may contribute to the failure of IKK inhibitors in humans. It is our hope that ongoing studies across the world will help to produce novel IKK inhibitors for human use in the coming years.

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Abbreviations

ACHP	(2-amino-6-[2(cyclopropylmethoxy)-6-hydroxyphenyl]4-piperidin-4-yl nicotinonitrile
Bay11-7085	*N*-(6-Chloro-9H-pyrido[3,4-b]indol-8-yl)-3-pyridinecarbox-amide
BMS-345541	*N*′-(1,8-dimethylimidazo[1,2-a]quinoxalin-4-yl)ethane-1,2-diamine
BX-795	*N*-(3-(5-Iodo-4-(3-(thiophene-2-carboxamido)propylamino)pyrimidin-2-ylamino) phenyl)pyrrolidine-1-carboxamide
CHS828	N-(6-(4-chlorophenoxy)hexyl)-*N*′-cyano-*N*″-4-pyridyl guanidine)
CYT387	*N*-(cyanomethyl)-4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl] benzamide
CKII	casein kinase II
CRC	colorectal cancer
CXCL8	C-X-C motif chemokine ligand 8
DPP23	(E)-3-(3,5-dimethoxyphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one
EGFR	epidermal growth factor receptor
EMT	epithelial-to-mesenchymal transition
EqM	epoxyquinone A monomer (EqM)
HDAC	histone deacetylase
HLA	human leukocyte antigen

ICAM-1	intercellular adhesion molecule-1
IKK	IκB kinase
IMD-0354	N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide
IκB	inhibitor of kappa B
IR	infrared
LMP	latent membrane protein
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MCV	*Molluscum contagiosum* virus
MMP	matrix metalloproteinase
NBD	NEMO-binding domain
NCPA	2-(*N*-Carbobenzyloxy)l-phenylalanylamido-2-deoxy-β-D-glucose
NF-κB	nuclear factor kappa B
NOD/SCID	non-obese diabetic/severe combined immunodeficiency
NSCLC	non-small-cell lung carcinoma
PKA	protein kinase A
PKC	protein kinase C
PS-1145	*N*-(6-chloro-9H-pyrido[3,4-b]indol-8-yl)pyridine-3-carboxamide
pVHL	product of the von Hippel-Lindau
RANKL	receptor activator of nuclear factor kappa B ligand
RIP1	receptor-interacting protein 1
TAP	transporter associated with antigen processing
TBK1	TANK binding kinase 1
TPCA-1	2-[(Aminocarbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide
TNFα	tumor necrosis factor alpha
TRAF	TNF receptor-associated factor

vIL-10	viral IL-10
uPA	urokinase type plasminogen activator
VSV	vesicular stomatitis virus

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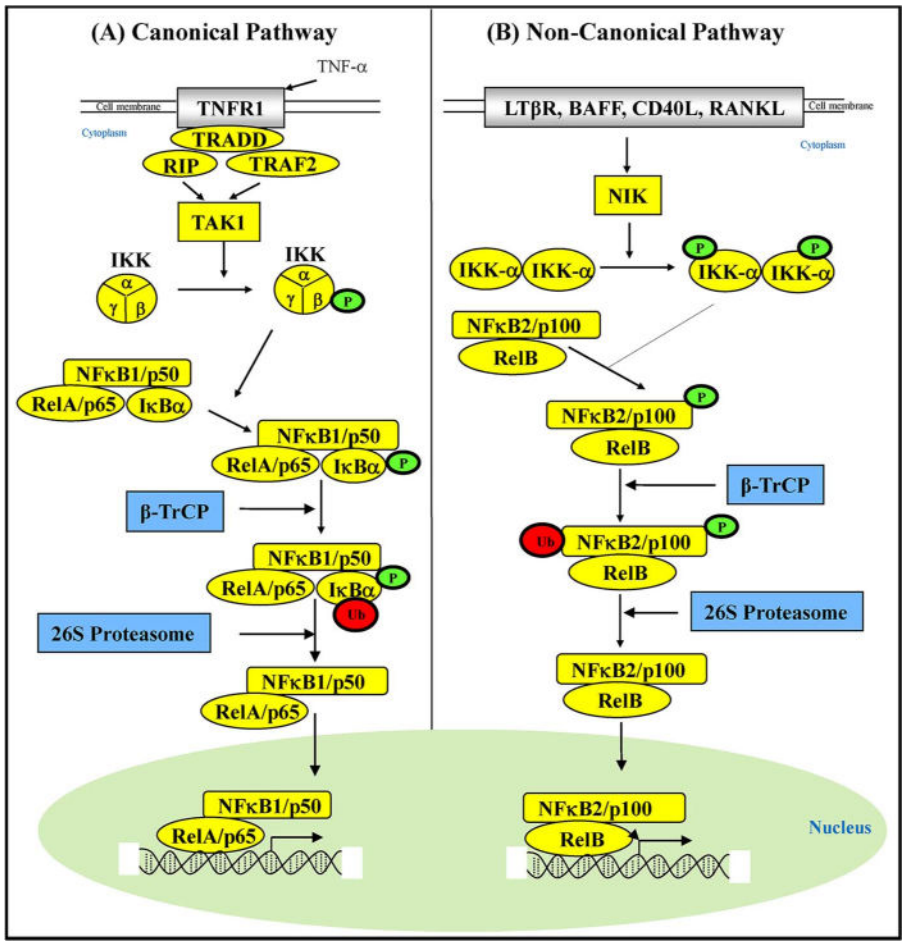


Fig. 1.
Common pathways of NF-κB activation.

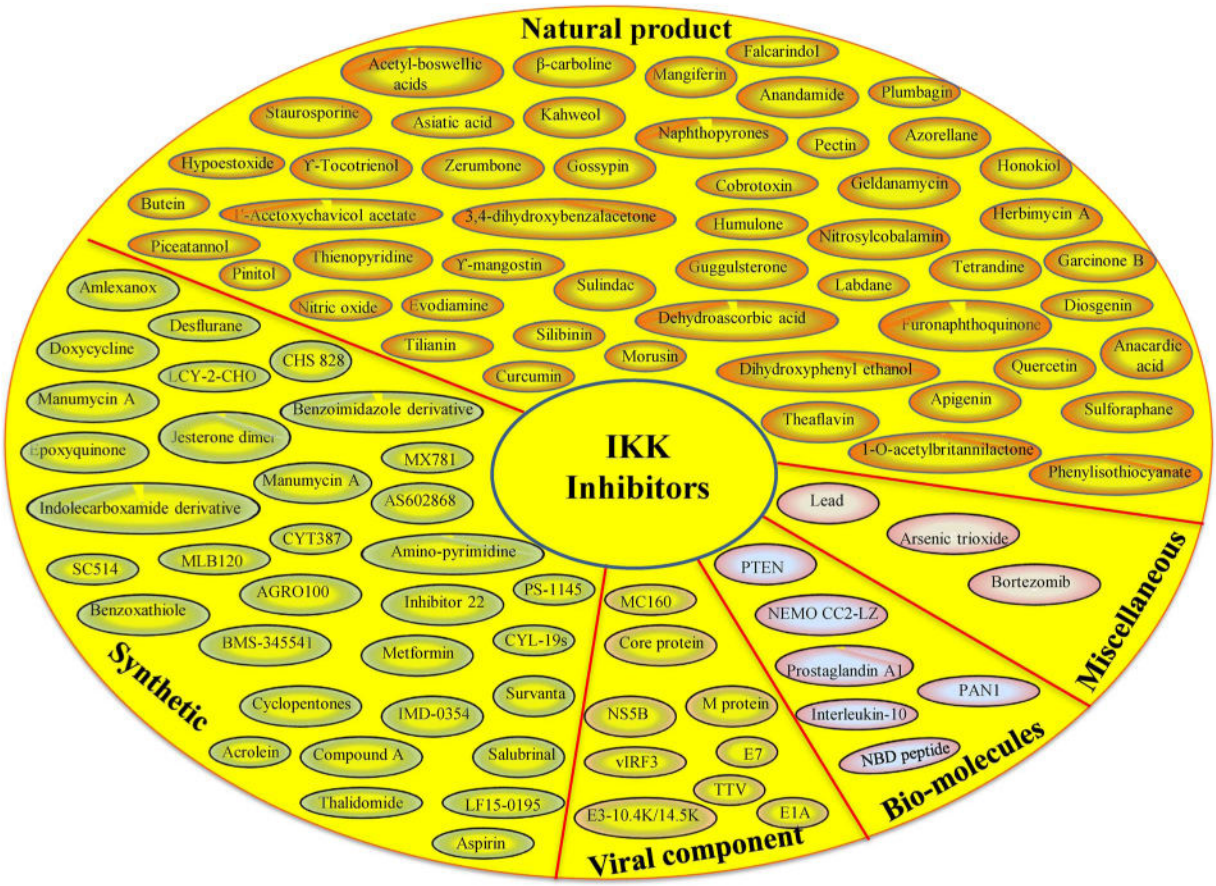
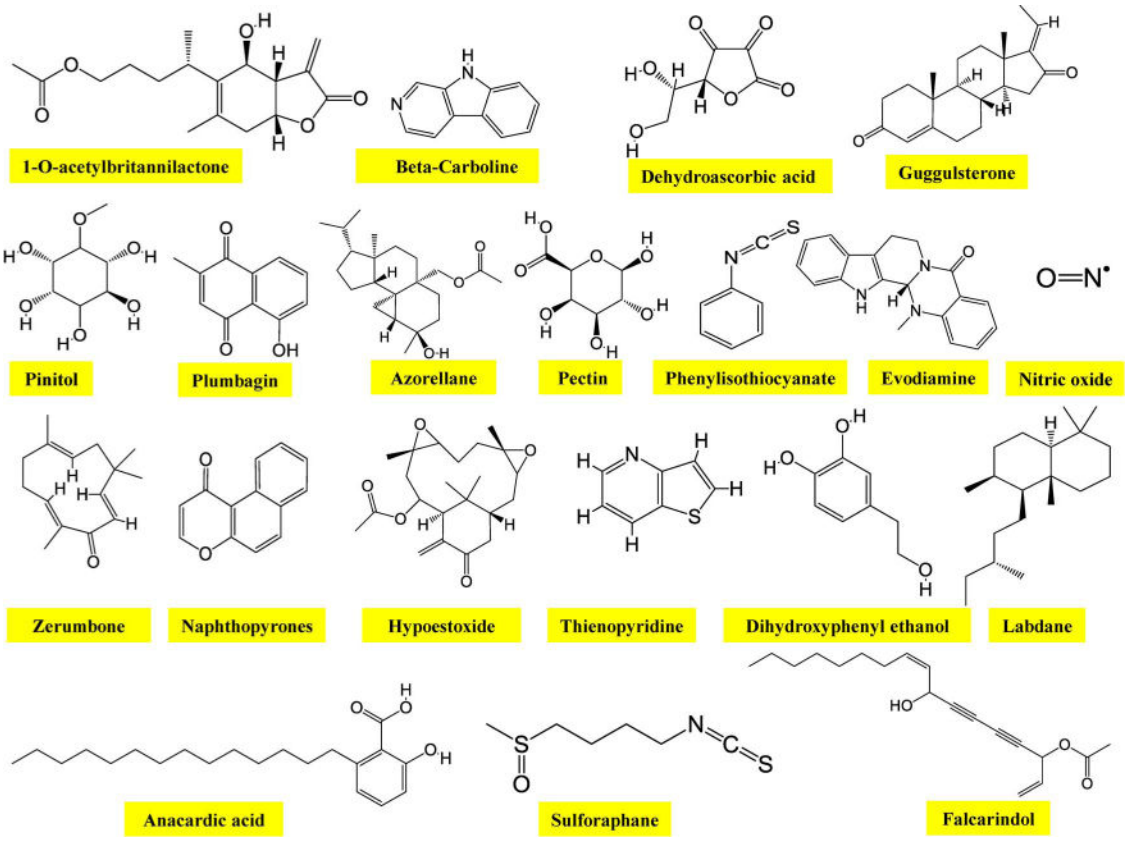
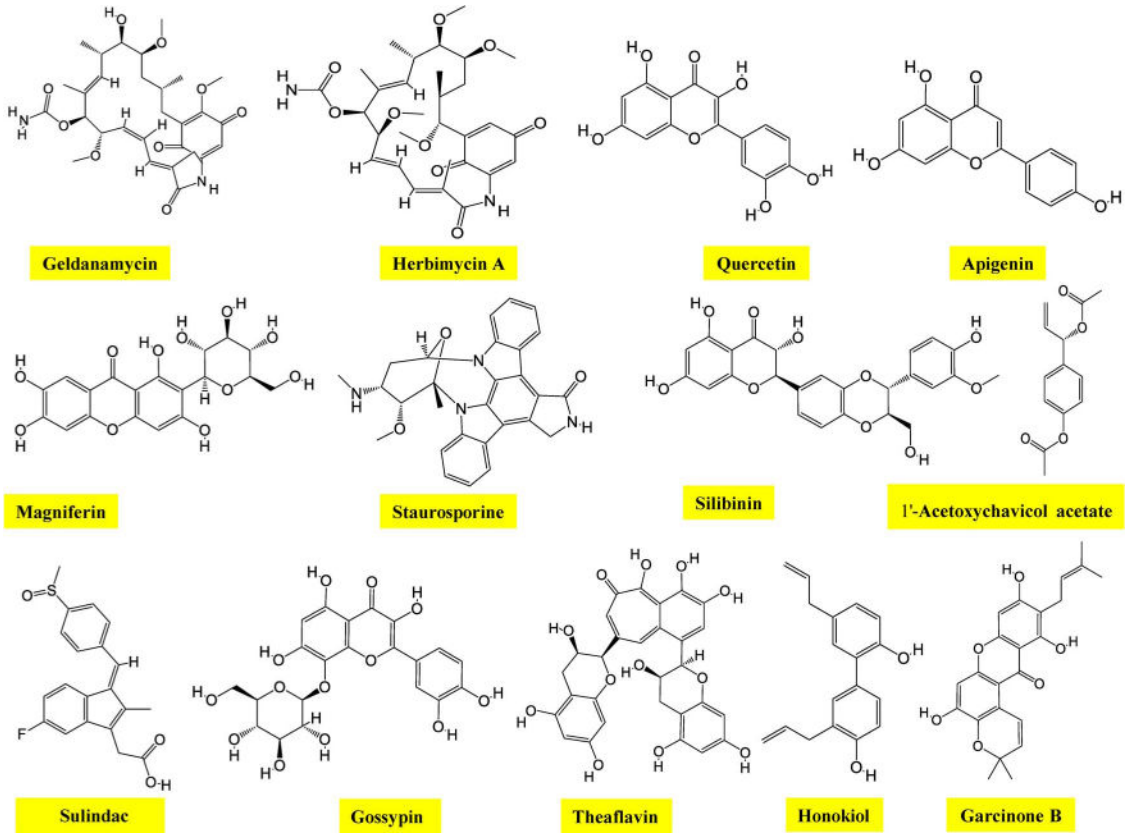
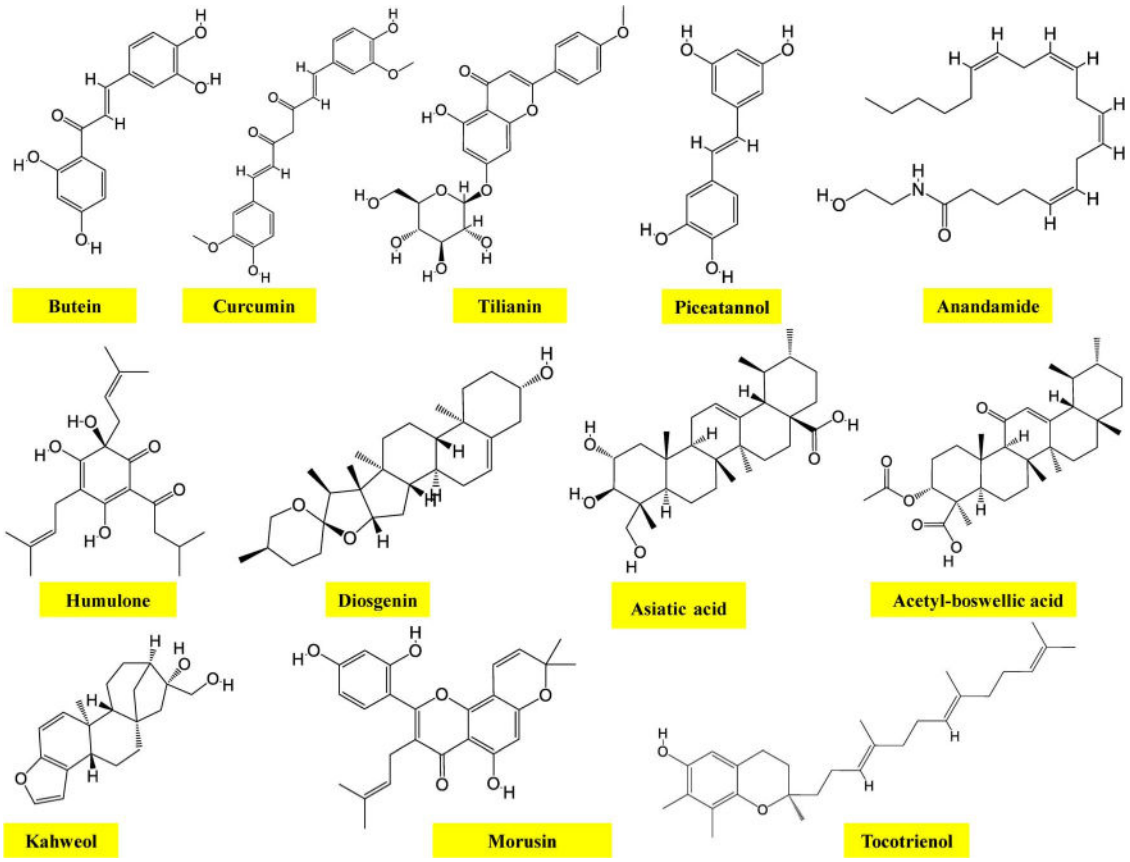


Fig. 2.

Common IKK inhibitors studied in cancer models. *Abbreviations:* AGRO100: G-quadruplexoligodeoxynucleotide; BMS-345541: N-(1,8-Dimethylimidazo[1,2-*a*]quinoxalin-4-yl)-1,2-ethanediamine; Compound A: fluoromethyl-2,2-difluoro-1-[trifluoromethyl]vinylether; CHS828: 2-[6-(4-chlorophenoxy)hexyl]-1-cyano-3-pyridin-4-ylguanidine; CYL-19s: α-methylenegamma-butyrolactone derivatives; CYT387: N-(cyanomethyl)-4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl] benzamide; E7: human papillomavirus; IMD-0354: N-[3,5-bis(trifluoromethyl)phenyl]-5-chloro-2-hydroxybenzamide; LCY-2-CHO: 9-(2-chlorobenzyl)-9H-carbazole-3-carbaldehyde; LF15-0195: 2-[6-(diaminomethylideneamino)hexylamino]-2-oxoethyl] N-[4-[[(3*R*)-3-aminobutyl]amino]butyl]carbamate; MC160: *Molluscum contagiosum* 160; ML120B: N-(6-chloro-7-methoxy-9H-pyrido[3,4-*b*]indol-8-yl)-2-methylpyridine-3-carboxamide; NBD peptide: NEMO-binding domain peptide; NS5B: nonstructural protein 5B; PS-1145: N-(6-Chloro-9H-pyrido[3,4-*b*]indol-8-yl)-3-pyridinecarboxamide; PTEN: phosphatase and tensin homolog; SC-514: 3-Amino-5-thiophen-3-ylthiophene-2-carboxamide; TTV: torque teno virus; vIRF3: viral interferon regulatory factor 3.







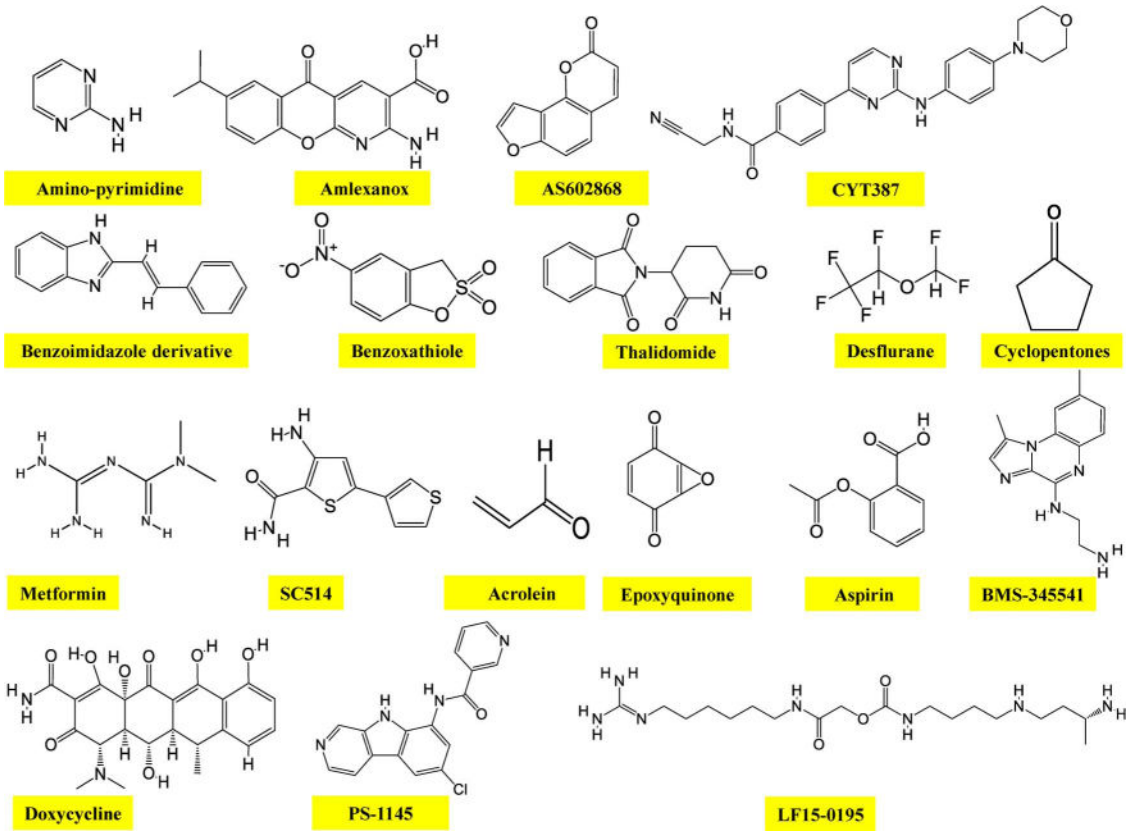


Fig. 3.
Chemical structure of common IKK inhibitors.

Table 1

IKK inhibitors and their potential in cancer therapy.

Specific IKK inhibitors

- BMS-345541: Selectively targets an allosteric site of IKKα (IC_{50}: 4 μM) and of IKKβ (IC_{50}: 0.3μM) [57]; suppressed breast tumorigenesis and metastases by targeting GD2+ cancer stem cells [59]; inhibited EMT, induced apoptosis and suppressed proliferation of prostate cancer cells in a dose-dependent manner [60]; inhibited constitutive IKK activity and melanoma cell survival both *in vitro* and *in vivo* [61]; induced mitochondria-mediated apoptosis in melanoma cells [61].
- PS-1145: Inhibited IKKβ activity (IC50: 150 nM) without affecting PKA, PKC and CKII activity [62]; suppresses TNFα-induced IκBα phosphorylation, IκBa degradation and subsequently inhibits NF-κB activation [62]; induced toxicity in the multiple myeloma cells in combination with TNFα [63]; selectively toxic to activated B-cell-like subgroup of diffuse large B-cell lymphoma [64].
- Bay 11-7085: Inhibited epithelial-to-mesenchymal transition and invasiveness in pancreatic cancer mice model [65]; significantly reduced the proliferation of ovarian cancer cells[66].
- IMD-0354: Suppressed neoplastic proliferation of human mast cells with constitutively activated c-kit receptors [67]; arrested breast cancer cells in G0/G1 phase and induced apoptosis [68].
- ACHP: Inhibited NF-κB DNA binding activity; induced cell growth arrest and apoptosis in multiple myeloma cell lines [73]; blocked visfatin-induced NF-κB activation and up-regulation of MMP-2 and MMP-9 in NSCLC [74].
- Amlexanox: Reduced proliferation and induced G1-phase arrest of melanoma cells [77]; selectively inhibited the viability of NSCLC cells with EGFR mutations [78].

Natural products

- Curcumin: Inhibited IKKβ activity by inducing its S-nitrosylation [84].
- Artemisinin: Exhibited anti-inflammatorv activities in a TPA-induced skin inflammation in mice; inhibited the expression of TRAF2 and RIP1; inhibited TNFα induced NF-κB reporter gene expression, phosphorylation and degradation of IκBα, and p65 nuclear translocation [85].
- Mangiferin: Inhibited spontaneous metastasis and tumor growth, p65 nuclear translocation, and activation of NIK and IKK in mice model [86].
- Betulinic acid: Suppressed phosphorylation of IKKα and IκBα and induced apoptosis in prostate cancer cells [87]; inhibited LPS-triggered phosphorylation of IKK in CRC cells that contributed to its anti-cancer activities [88].
- Colorant powder from *Basella alba*: Inhibited LPS-induced IKK activation in macrophages [89].

Non-cancer agents

- Doxycycline: Inhibited LPS-induced IKKβ and NF-κB activation, and the expression of NF-κB dependent tumorigenic proteins in prostate cancer cells [91].
- Aspirin: Inhibited IKK activity in cancer cells in a direct manner [92]; suppressed prostate cancer cell invasion by decreasing IKK-β-induced NF-κB activation that leads to a reduction in MMP-9 activity and uPA expression [93].
- Arsenic trioxide: Down-regulated constitutive IKK/NF-κB activity and induced apoptosis in HRS cell line containing functional IκB proteins; reduced tumor burden in NOD/SCID mice xenotransplanted with L540Cy Hodgkin tumors [96].

Peptides/Bio-molecules

- NBD: Inhibited association of NEMO with the IKK complex [97]; suppressed cytokine-induced NF-κB activation and its target gene expression [97]; inhibited RANKL-induced NF-κB activation and osteoclastogenesis both *in vitro* and *in vivo* [98].
- pVHL: Inhibited NF-κB activation through K63-ubiquitination of IKKβ; prevented TAK1 binding [74].
- MCV: MC159 protein of MCV inhibited the interaction of NEMO with the cIAP1 E3 ubiquitin ligase; inhibited NF-κB activation [100].
- Adenovirus E1A: Inhibited TNFa-induced IKKβ activity that in turn leads to inhibition of IκBα degradation and NF-κB activation in cancer cells [101]; inhibited radiation-induced NF-κB activation and sensitized cancer cells to TNFα [102].
- vIL-10: Suppressed components of antigen processing machinery (HLA-I, LMP-2, LMP-7, TAP-1, TAP-2) in nasopharyngeal carcinoma cells by blocking IKK phosphorylation [103].
- TRAF6dn peptides: Inhibited IKK activation; exhibited activities against multiple myeloma and reduced bone loss [104].
- IKKα siRNA: Reduced doxorubicin-induced NF-κB activation, constitutive and TNFα-stimulated expression of CXCL8 and ICAM-1, and cell migration in melanoma cells [105].

Direct inhibitors

- EqM: Inhibited TNFα-induced NF-κB activation by targeting Cys^{179} of IKKβ and inhibiting IKBα phosphorylation and degradation; exhibited anti-growth effects on leukemia, colon, and kidney cancer cells [106].

Combination therapy

- AS602868: Induced apoptosis in human primary AML cells: enhanced the apoptotic effects of doxorubicin, cytarabine, and etoposide [113].
- TRAF6dn peptides: Enhanced the anti-multiple myeloma effects of bortezomib [104].
- Bay 11-7085: Significantly reduced tumor growth in ovarian cancer mice model when combined with vorinostat, an HDAC inhibitor [114].
- TPCA-1: Reduced resistance of PDAC cells to VSV-ΔM51 [117.118]: oroduced synergistic effects on NSCLC in combination with TKIs [119].
- CYT387: Inhibited KRAS-driven lung cancer formation in mice model in combination with MAPK inhibition [120].
- Emetine: Sensitized MEC cells to IR and reduced cancer stem cells [123].
- Amlexanox: Inhibited the tumor growth in a mice model of NSCLC harboring EGFR mutations in combination with MEK inhibitor [78].

Clinical studies

- Bortezomib: Down-regulated IκBα expression and induced NF-κB activation in multiple myeloma cells that was mediated through IKKβ phosphorylation [135].

Miscellaneous

- BX-795: Inhibited IKKε/TBK1 *in vitro* [140].
- 6-Aminopyrazolopyrimidine derivative: Inhibited TBK1 kinase activity and induced toxicity in TBK1-dependent cancer cell lines at < 1 μM range [141].
- NCPA: Inhibited IKKα nuclear translocation; stimulated Maspin production; down-regulated the expression of β1 integrin. MMP-9, MMP-13, and reduced migration of osteosarcoma cells [142].
- DPP23: Suppressed TNFα-induced invasion of MDA-MB-231 breast cancer cells by inhibiting AKT-IKK-NF-κB axis [143].
- Chloroauine or bafilomycin A1: Blocked p45-IKKα phosphorylation without affecting activity of the NF-κB pathway: enhanced the anti-tumoral effects of irinotecan and 5-azacytidine in an orthotopic xenograft model of CRC [145].
- CHS 828: Inhibited IKK activity (IC_{50}: 8 nM) that was associated with its anti-proliferative activities in leukemia and lung cancer cells [50].