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NF-κB addiction and its role in cancer: 'one size does not fit all'

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Abstract

Activation of nuclear factor (NF)-κB, one of the most investigated transcription factors, has been found to control multiple cellular processes in cancer including inflammation, transformation, proliferation, angiogenesis, invasion, metastasis, chemoresistance and radioresistance. NF-κB is constitutively active in most tumor cells, and its suppression inhibits the growth of tumor cells, leading to the concept of 'NF-κB addiction' in cancer cells. Why NF-κB is constitutively and persistently active in cancer cells is not fully understood, but multiple mechanisms have been delineated including agents that activate NF-κB (such as viruses, viral proteins, bacteria and cytokines), signaling intermediates (such as mutant receptors, overexpression of kinases, mutant oncoproteins, degradation of IκBα, histone deacetylase, overexpression of transglutaminase and iNOS) and cross talk between NF-κB and other transcription factors (such as STAT3, HIF-1α, AP1, SP, p53, PPARγ, β-catenin, AR, GR and ER). As NF-κB is 'preactive' in cancer cells through unrelated mechanisms, classic inhibitors of NF-κB (for example, bortezomib) are unlikely to mediate their anticancer effects through suppression of NF-κB. This review discusses multiple mechanisms of NF-κB activation and their regulation by multitargeted agents in contrast to monotargeted agents, thus 'one size does not fit all' cancers.

Keywords

NF-κB; constitutive activation; cancer; inflammation; multitargeted therapy

Introduction

In the previous century, many research initiatives were focused on understanding the genetic etiology of human tumorigenesis. However, cancer remains a major health problem and is responsible for one in eight deaths worldwide (Garcia *et al.*, 2007). Also, an estimated 55% increase in cancer incidence is expected by the year 2020 (Warren *et al.*, 2008).

Cancer is an extremely complex disease (Roukos, 2010). Large-scale analysis of genes has shown that the types of mutations that occur in various cancers are highly heterogeneous (Hudson *et al.*, 2010). Only a minority of cancers are caused by germline mutations, whereas the vast majority (~90%) are linked to somatic mutations and environmental factors

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Conflict of interest
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(Aggarwal *et al.*, 2009). The mutations found in the cancer cell genome accumulate over the lifetime of the cancer patient. Mutation rate increases in the presence of substantial exogenous mutagenic exposures, such as tobacco smoke carcinogens, naturally occurring toxic chemicals present in some foods or various forms of radiation including ultraviolet light. These exposures are associated with increased rates of lung, liver and skin cancer, respectively (Grivennikov *et al.*, 2010). Moreover, these agents induce inflammatory responses, suggesting a strong association between inflammation, nuclear factor (NF)-κB and cancer (Mantovani *et al.*, 2008; Aggarwal and Gehlot, 2009; Grivennikov *et al.*, 2010).

Currently, 18 485 genes and 464 139 tumors have been sequenced, resulting in a cataloge of 20 090 unique mutations, which have been curated in the Catalogue of Somatic Mutations in Cancer (http://www.sanger.ac.uk/cosmic, v47 release, 24 May, 2010). Studies of the genetic complexities of breast, colorectal, pancreatic and brain cancers have revealed that cancer genomes are highly complex (Bignell *et al.*, 2010; Ding *et al.*, 2010; Pleasance *et al.*, 2010a), with a range of 48–101 somatic alterations in each tumor, depending on the cancer type (Jones *et al.*, 2008; Parsons *et al.*, 2008; Bell, 2010). Within a given cancer type, there is considerable intertumor heterogeneity, resulting in large number of altered genes. However, this complexity is reduced significantly by considering the biological pathways, rather than the altered gene themselves (Wood *et al.*, 2007; Verhaak *et al.*, 2010). For example, 12 core biological processes or pathways appear to be deregulated in most pancreatic tumors, although precisely how this deregulation is achieved varies from tumor to tumor (Jones *et al.*, 2008). This suggests alterations in the complex network of signaling pathways (Ledford, 2010), and has very clear practical implications for the development of targeted therapeutics, as it is less likely that a drug targeting just one mutated gene or one particular pathway alone could be effective for treating any type of cancer.

The area of research involving NF-κB has grown tremendously in the past decade. This is evident from the fact that although NF-κB was discovered only 25 years ago (Sen and Baltimore, 1986) and is one of ~2000 estimated transcription factors in humans (Lander *et al.*, 2001; GuhaThakurta, 2006), ~10% of research articles listed in PubMed on the subject of transcription factors are associated with NF-κB. Furthermore, of the more than 39 000 articles published about NF-κB, about 19 000 are associated with tumors and cancers underscoring the importance of this transcription factor in cancer studies.

As NF-κB is the key transcription factor involved in the inflammatory pathway, NF-κB is constitutively active in most cancers (Table 1), and many of the signaling pathways implicated in cancer are likely to be networked to the activation of NF-κB (Figure 1) (Karin, 2009; Grivennikov *et al.*, 2010; Grivennikov and Karin, 2010). Mammalian NF-κB is a family of transcription factors that includes five members: RelA/p65, c-Rel, RelB, NF-κB1 (p50) and NF-κB2 (p52) (Ghosh and Karin, 2002; Vallabhapurapu and Karin, 2009). The primary regulation of the NF-κB pathway is through the association of NF-κB complexes with their inhibitor, IκB proteins. There are multiple human IκB proteins, including IκBα, IκBβ, IκBε and IκBζ. In addition, the precursors p50 and p52 and the full-length proteins p105 and p100 also function as IκB proteins. The principle inactive form of the NF-κB complex is a p50–p65 (RelA)–IκBα trimer, primarily located in the cytoplasm. In the classic or canonical pathway, in response to various external stimuli, IκBα is phosphorylated at Ser 32 and Ser 36 by the IκBα kinase (IKK). This promotes K-48 ubiquitination of IκBα by the SCF–βTrCP complex and its degradation by the proteasome. The released NF-κB dimer (p50–p65, which is also phosphorylated by IKK) is translocated in the nucleus, where it binds to its cognate response elements in promoters to activate the transcription of responsive genes (Vallabhapurapu and Karin, 2009). At the NF-κB responsive promoters, the p65 subunit of NF-κB is further modified by acetylation and methylation, and it interacts with additional coactivators (Werner *et al.*, 2005). A second, non-canonical or alternative

pathway involves activation of the p100–RelB complex to p52–RelB in response to specific extracellular signals (Senftleben *et al.*, 2001). Unlike its response to IκBα, p100, after phosphorylation at Ser 866 and Ser 870, undergoes limited processing to generate p52, also regulated by SUMOylation (Vatsyayan *et al.*, 2008).

For activation of NF-κB by canonical and non-canonical pathways, the regulatory kinase is IKK, which is a complex of three proteins, two catalytic (IKKα and IKKβ) and one regulatory (IKKγ, also known as the NF-κB essential modulator (NEMO)). The IKK complex is believed to be activated by a wide variety of stimuli that finally modify IKKγ by K-63 ubiquitinylation (Bhoj and Chen, 2009; Chen and Sun, 2009) and by phosphorylation (Perkins, 2006; Scheidereit, 2006). However, pathways that do not involve IKK have been described for NF-κB activation (Kato *et al.*, 2003; O'Dea *et al.*, 2008; Ge *et al.*, 2009). Even the IKK family, the key kinases that phosphorylate IκBα, is known to phosphorylate proteins other than IκBα (Chariot, 2009; Hutti *et al.*, 2009). The p65 transactivator subunit has been shown to be phosphorylated by IKK (Figure 2). In addition to phosphorylation, it is also acetylated and methylated that are catalyzed by different set of enzymes (discussed later). Moreover, the activated NF-κB interacts and cooperates with other transcription factors such as STAT3, HIF-1α and AP1 to up- or down-modulate gene expression (Figure 3).

In the present review, we will discuss the ramifications and networking of these diverse pathways in the etiology and treatment of cancer in an attempt to show that targeting just one step or one pathway would not be a successful strategy for the prevention or treatment of cancer.

NF-κB mutation and cancer

The p65 transactivator subunit of NF-κB, RelA, was recognized earlier as the potential oncogene (Gilmore, 2003). However, the mutations that confer Rel-A, c-Rel, or other NF-κB proteins with oncogenic potentialities are not abundant and are mainly limited to lymphoid malignancies. *REL* gene amplifications have been detected frequently in many types of human B-cell, and to a lesser extent T cell, lymphoma (reviewed in (Gilmore *et al.*, 2004; Courtois and Gilmore, 2006)). Chronic lymphocytic leukemia, the most common adult leukemia, is currently incurable with conventional chemotherapeutic agents. Rel-A is a prognostic marker and a therapeutic target in this disease (Pepper *et al.*, 2009; Lopez-Guerra and Colomer, 2010).

Similarly, the *NFKB2* gene undergoes structural alterations in certain T-cell lymphomas, chronic lymphocytic leukemias, myelomas and B-cell lymphomas (Courtois and Gilmore, 2006). In Hodgkin's lymphoma, mutations or deletions in the *IκBα* gene have been described (Cabannes *et al.*, 1999). The *Bcl-3* gene, another family member of IκBα, is overexpressed and translocated in B-cell leukemia (Martin-Subero *et al.*, 2007; Chapiro *et al.*, 2008). Similarly, amplification of the *c-Rel* gene is reported in several types of B-cell lymphoma (Pileri *et al.*, 2003). Mutations in other *NF-κB* genes, such as *NEMO*, result more frequently in immunological disorders (Courtois and Gilmore, 2006).

In lymphoid malignancies, the dysregulation of NF-κB activation results in aberrant expression of target gene proteins such as cyclin D1, cyclin D2, c-myc, c-myb, BCL2 and BCL-XL that regulate cell proliferation or survival, as well as cytokines such as interleukin (IL)-2, IL-6 and CD40-L that regulate growth and proliferation of lymphocytes. Thus, constitutively active NF-κB has been implicated in various lymphoid malignancies (Aggarwal and Gehlot, 2009). Acute myeloid leukemia involves the activation of RTK Flt3, N-Ras and K-Ras, which activate NF-κB through the Akt pathway (Stirewalt and Radich, 2003; Tenen, 2003). As can be seen in Table 1, although *NF-κB* genes are not directly

mutated in most cases, mutations in key genes such as *RAS*, *phosphatidylinositol 3-kinase (PI3K)/Akt1*, *TP53* and *EGFR* affect the cellular processes that are known to involve the activation of NF-κB in some capacity (Grivennikov *et al.*, 2010).

NF-κB as a tumor promoter and tumor suppressor

In recent years, *in vitro* studies have established strong support for the critical role of NF-κB in cancer. Abnormally high NF-κB activity is a clinical hallmark of chronic inflammation and has been found in many types of cancer cells. Therefore, drugs that inhibit NF-κB activity have been found to be useful additions to the chemotherapy regimens of a variety of cancers (Hoffmann *et al.*, 2007). However, some recent findings have suggested that this generalization should be viewed with caution (Luedde *et al.*, 2007; Bettermann *et al.*, 2010). The role of the NF-κB signaling pathway in the development of hepatocellular carcinoma, for example, continues to remain controversial (Greten *et al.*, 2004; Pikarsky *et al.*, 2004; Vainer *et al.*, 2008). Using a conditional knockout approach for IKKγ (NEMO), Luedde *et al.* (2007) showed that elimination of NF-κB activity in hepatocytes surprisingly resulted in elevated inflammatory cytokine expression and spontaneous carcinogenesis in every animal within a year, suggesting a tumor suppressor role for NF-κB (Luedde *et al.*, 2007). They further showed that the conditional knockout of TAK1, the kinase that phosphorylates IKK, gives a similar phenotype. In an earlier study, deletion of IKKβ was also shown to induce hepatocellular carcinoma (Maeda *et al.*, 2005). However, the pathway through which hepatocellular carcinoma is generated does not involve NF-κB (Bettermann *et al.*, 2010).

Recent experimental data from several laboratories have revealed that IKKα also functions as a tumor suppressor in human squamous cell carcinomas of the skin, lungs, and head and neck (Maeda *et al.*, 2007; Van Waes *et al.*, 2007). Chemical carcinogenesis studies in mice have shown that reduction in IKKα expression increased the number and size of Ras-initiated skin tumors and promoted their progression, indicating that reduced IKKα expression provides a selective growth advantage that cooperates with Ras activity to promote skin carcinogenesis (Zhu *et al.*, 2009). Of interest, IKKα kinase activity is not required for the development of mouse embryonic skin. Further mechanistic study revealed that IKKα interacts with histone H3 in nucleosomes and blocks the access of histone methyl transferase SUV39h1 to H3 (Zhu *et al.*, 2007).

Two other tumor suppressor genes that regulate NF-κB activation, *CYLD* and *A20*, belong to the deubiquitinase family. Mutations in the *CYLD* gene that encodes for a tumor suppressor protein negatively regulate NF-κB activation. *CYLD* codes for a deubiquitinase (Brummelkamp *et al.*, 2003; Kovalenko *et al.*, 2003; Trompouki *et al.*, 2003) that catalyses removal of K-63 polyubiquitin groups required for the activation of TAK1 and NEMO (Bhoj and Chen, 2009; Chen and Sun, 2009). A20 (Vereecke *et al.*, 2009; Hymowitz and Wertz, 2010) also acts as a tumor suppressor gene (Shembade *et al.*, 2010; Sriskantharajah and Ley, 2010).

In contrast to these findings, however, a recent study showed that conditional ablation of IKKβ inhibited melanoma tumor development in mice (Yang *et al.*, 2010a). In addition, the non-canonical IKK family member IKKε, a recently discovered breast cancer oncoprotein, was shown to be essential for regulating antiviral signaling pathways. Phosphorylation of the tumor suppressor CYLD by the breast cancer oncogene IKKε promoted cell transformation (Hutti *et al.*, 2009). Using integrative genomic approaches, Boehm *et al.* identified IKKε as a breast cancer oncogene (Boehm *et al.*, 2007).

The above discussion clearly indicates that the IKK complex that was once believed to be responsible only for activating the canonical pathway of NF-κB may have many diverse

functions. The roles of IKKs and their regulators vary with tissue types and with the context in which they act. Some of these points will be further elaborated in the following sections.

Constitutive activation of NF-κB in cancers (NF-κB addiction)

It has become increasingly clear that besides having a role in regulating adaptive immune response, NF-κB signaling also has a critical role in cancer development and progression (Aggarwal, 2004; Basseres and Baldwin, 2006; Karin, 2006; Mantovani *et al.*, 2008; Prasad *et al.*, 2010). The major tumor-promoting mechanism is the production of tumor-promoting cytokines by immune/inflammatory cells that activate transcription factors such as NF-κB, STAT3 and AP1, which induce genes responsible for cell proliferation, survival, angiogenesis and metastasis (Grivennikov *et al.*, 2010). Constitutive activation of NF-κB has been reported in a wide variety of malignancies such as hematological, gastrointestinal, genitourinary, gynecological, thoracic, head and neck, and breast tumors and in melanoma and fibrosarcoma (Table 1) (reviewed in (Prasad *et al.*, 2010)). Though the activated NF-κB was initially described in lymphoid cancers, it is also detected in most solid tumors as well (Karin *et al.*, 2002). Recently, activated NF-κB was shown to be a prognostic factor in metastatic serous ovarian carcinoma. Immunoblotting showed NF-κB p65 phosphorylation in 72 (96%) of 75 effusions (Kleinberg *et al.*, 2009).

Diverse mechanisms have been ascribed to the constitutive activation of NF-κB in cancers. Autocrine secretion of inflammatory mediators (chemokines and cytokines such as tumor necrosis factor α (TNF-α) and IL-1β) have been shown to activate NF-κB constitutively in head and neck cancer cells, acute myeloid leukemia, T-cell lymphoma, breast cancer (Giri and Aggarwal, 1998; Wolf *et al.*, 2001; Estrov *et al.*, 2003; Jackson-Bernitsas *et al.*, 2007; Braunstein *et al.*, 2008) and acute myeloid leukemia. Another mechanism that is implicated in the constitutive activation of NF-κB is mutations and/or overexpression of ligands and receptors such as epidermal growth factor (Sethi *et al.*, 2007), HER-2/Neu (Pianetti *et al.*, 2001; Le Page *et al.*, 2005), hepatocyte growth factors (Fan *et al.*, 2005) and integrins (Guo and Giancotti, 2004; Nikolopoulos *et al.*, 2004). Constitutive activation of NF-κB is also due to aberrant expression/activation of kinases such as IKK in brain cancer (Politi *et al.*, 2008) and in liver cancer (Jiang *et al.*, 2010), NIK in melanoma (Dhawan *et al.*, 2008), GSK-3β in pancreatic cancer (Wilson and Baldwin, 2008), Akt in breast cancer (Pianetti *et al.*, 2001), Raf in multiple myeloma (Keats *et al.*, 2007), and Bcr–abl in acute lymphoblastic leukemia and chronic myeloid leukemia (Reuther *et al.*, 1998). Mutations in signaling intermediates such as MUC1-C (Ahmad *et al.*, 2007, 2009) and CARD11 (Lenz *et al.*, 2008) are also reported to activate NF-κB in an IKK-independent and IKK-dependent manner, respectively. In addition, in many types of cancer, chemotherapy and radiotherapy induce constitutive activation of NF-κB, thereby making the tumor non-responsive to the treatment. Additional mechanisms for activation of NF-κB in cancers have been discussed in the following sections.

NF-κB network

There are essentially three sites at which NF-κB signaling has been shown to be networked: IKK, IκBα and NF-κB heterodimer. As the IKK complex is the most extensively investigated site in canonical pathway of activation by TNF-α and Toll-like receptors, it is the major site wherein most of the diverse stimuli converge for activation of NF-κB. IκBα is also activated by many stimuli in an IKK-independent manner. Finally, the p50–p65 heterodimer interacts with many other transcription factors that are regulated by epigenetic modifications at the promoters of responsive genes, as summarized in Figures 2 and 3. The other pathways that interact and network with NF-κB pathways mainly in cancer are

epidermal growth factor receptor (EGFR), RAS, TP53, PI3K–AKt and mTOR. These will be discussed in detail in the following section.

Signaling interactions

In the canonical pathway, IKKβ is the kinase that phosphorylates IκBα, and IKKγ is the regulator that is activated by upstream signaling emanating from ligand–receptor interaction. Although IKKα is the part of the complex, it is dispensable. TNF-α interacts with TNFR1-TRADD-TRAF2-RIP-TAK1-TAB1, which activates the IKK complex. The formation of this complex requires K-63 polyubiquitination as an important step, wherein the RING domain of TRAF acts as K-63 ubiquitin ligase. All TRAFs except TRAF1 have a RING domain; however, the RING domain of TRAF2 does not have active ligase activity. Recently, sphingosine-1-phosphate was shown to act as a cofactor for TRAF2 ubiquitin ligase activity (Alvarez *et al.*, 2010). Whether the kinase that phosphorylates IKKβ is TAK1 has not been unequivocally established because MEKK3 is another potential kinase that has been shown to have a role in activating IKKβ. NIK is another kinase that may have a role in this pathway. TAK1/TAB1 is an established kinase in Toll-like receptor and IL-1-mediated activation of NF-κB, in which TRAF6 was the first ubiquitin ligase shown to activate TAK1/TAB1 by K-63 polyubiquitinylation (Deng *et al.*, 2000). In contrast, the non-canonical NF-κB pathway proceeds primarily through activation of IKKα. The non-canonical pathway is activated mainly through members of the TNF receptor superfamily, such as the lymphotoxin-β receptor (Hacker and Karin, 2006; Scheidereit, 2006).

The cell signaling intermediates that are frequently mutated in human cancers have been directly/indirectly networked with NF-κB pathway. Several G-protein-coupled receptors were also recently identified and shown to contribute to the malignant phenotype in head and neck squamous cell carcinoma, including overexpression of H- and K-RAS (Vitale-Cross *et al.*, 2004; Hunter *et al.*, 2005; Lu *et al.*, 2006; Thomas *et al.*, 2006; Patel *et al.*, 2007). Aberrant function of the PI3K, phosphatase and tensin homolog (PTEN), AKT and mTOR signaling networks is a frequent event in head and neck squamous cell carcinoma (Molinolo *et al.*, 2009). G-protein-coupled receptor-coupled protein kinase A (PKA) phosphorylates p65 at Ser 276 and is responsible for constitutive activation of NF-κB and for modulation of its responsive genes implicated in the pathogenesis of head and neck squamous cell carcinoma (Arun *et al.*, 2009). In lung cancer, activating mutations of the protein kinases *EGFR*, *ERBB2* and *BRAF* and inactivating mutations of *STK11* have been reported (Brose *et al.*, 2002; Naoki *et al.*, 2002; Sanchez-Cespedes *et al.*, 2002; Paez *et al.*, 2004; Stephens *et al.*, 2004; Davies *et al.*, 2005). In small cell lung cancer, several tumor suppressor genes are inactivated, including *TP53* (80–90% of cases), *RB1* (60–90% of cases) and *PTEN* (13% of cases). Infrequent activating mutations have been found in *PIK3CA*, *EGFR* and *KRAS* (all 10% or lower), and *MYC* is amplified in 20% of cases (Sher *et al.*, 2008) (http://www.sanger.ac.uk/genetics/CGP/cosmic/).

Recent sequencing of a small cell lung cancer genome (Pleasance *et al.*, 2010b) has shown a complex signature of tobacco exposure, a potent NF-κB activator (Shishodia and Aggarwal, 2004; Ahn and Aggarwal, 2005) (Tang *et al.*, 2006). Epidermal growth factor and EGFR pathways (Ras–Raf–MEK) (Duffy and Kummar, 2009) have been shown to activate NF-κB through Akt activation as well as through direct tyrosine phosphorylation of IκBα (Sethi *et al.*, 2007). The PI3K–Akt signaling pathway, induced by EGFR and Her-2, is involved in the constitutive activation of NF-κB in prostate cancer cell lines (Koumakpayi *et al.*, 2010). GSK3β is another kinase shown to regulate activation of NF-κB because genetic disruption of GSK3β abrogates TNF-α- or IL-1β-induced NF-κB activation (Hoeflich *et al.*, 2000). GSK3β activates a subset of NF-κB responsive genes by phosphorylating p65 at Ser 468 (Steinbrecher *et al.*, 2005).

With use of lung cell lines expressing oncogenic *K-Ras*, NF-κB has been shown to be activated in these cells in a K-Ras-dependent manner, and this activation by K-Ras has been shown to require IKKβ kinase activity. Together, these results reveal the importance of the NF-κB subunit p65–RelA in K-Ras-induced lung transformation and identify IKKβ as a potential therapeutic target for K-Ras-induced lung cancer (Basseres *et al.*, 2010). Interaction between K-Ras, TP53 and NF-κB signaling was demonstrated by Meylan *et al.* in mouse model of lung adenocarcinoma (Meylan *et al.*, 2009). TGF-β also activates NF-κB by acetylation of p65 by activating PKA (Ishinaga *et al.*, 2009). Furthermore, TGF-β downregulates PTEN by activating NF-κB in pancreatic cancer cells (Chow *et al.*, 2010), suggesting a linkage between NF-κB and PTEN in TGF-β signaling.

Altered TAB1–IKK interaction promotes TGF-β-mediated NF-κB activation during breast cancer progression (Neil and Schiemann, 2008). Another pathway that has been linked with many pathophysiological conditions is the Akt–mTOR pathway. The mTOR downstream from Akt controls NF-κB activity in *PTEN*-null/inactive prostate cancer cells by interaction with and stimulation of IKK. Akt requires the mTOR-associated protein Raptor to induce NF-κB activity. Correspondingly, the mTOR inhibitor rapamycin has been shown to suppress IKK activity in PTEN-deficient prostate cancer cells through a mechanism that may involve dissociation of Raptor from mTOR (Dan *et al.*, 2008).

IKK complexes and their regulators

Initially, IKKα and IKKβ were characterized as part of a large complex of molecular weights ranging from 700 to 900 kDa (Chen *et al.*, 1996; DiDonato *et al.*, 1997). The IKKγ (NEMO) has subsequently been identified through genetic complementation of an NF-κB activation-defective cell line (Yamaoka *et al.*, 1998). Not every component of the high-molecular weight IKK complex has been characterized, and the exact stoichiometry of the IKK complex has not been unambiguously determined. As IKK activation is involved in diverse modes of activating NF-κB, it is not surprising that the complex is dynamic and that there may be many as yet uncharacterized transient components associated with it. A recent review by Israel, 2010 contains a detailed discussion about the properties and characteristics of these subunits.

It now seems clear that TAK1 functions as an IKK kinase, at least in response to certain signals (Wang *et al.*, 2001; Bhoj and Chen, 2009). TAK1 complexes with TAB1 and TAB2 (or TAB3) and phosphorylates IKKβ. Another kinase, MEKK3, has also been suggested to act upstream of the IKK complex, as cells lacking MEKK3 are partially defective in NF-κB activation in response to certain stimuli (Huang *et al.*, 2004). NIK is the upstream kinase for activation of the IKKα subunit, and it requires neither IKKβ nor NEMO (Park *et al.*, 2005). In another study, the oncoprotein MUC1 interacted with the highmolecular weight IKK complex (IKKβ and γ) and was associated with constitutive activation of NF-κB p65 in many human cancer cell lines (Ahmad *et al.*, 2007, 2009).

The role of IKKs has not been restricted to the NF-κB activation pathway (Chariot, 2009). The kinase activity of IKKβ is also required in TNF-α-induced mTOR pathway. The IKKβ physically interacts with and phosphorylates TSC1, resulting in its suppression, which activates the mTOR pathway, enhances angiogenesis and results in tumor development. Furthermore, expression of activated IKKβ is associated with TSC1 Ser 511 phosphorylation and VEGF production in multiple tumor types, and correlates with poor clinical outcome in breast cancer patients (Lee *et al.*, 2007). IKKβ has also been shown to phosphorylate and induce the degradation of transcription factor FOXO3a, which has an important role in controlling cell proliferation and survival, therefore, promoting tumorigenesis (Hu *et al.*, 2004). IKKα, free from IKKβ and γ, can also be found in the nucleus, where it phosphorylates histone H3 on Ser 10, triggering its subsequent

CREBbinding protein-mediated acetylation on K14, a crucial step in modulating chromatin accessibility (Gloire *et al.*, 2006). IKKα also phosphorylates the SMRT repressor, which is recruited by p50 and p52 homodimers, and induces its nuclear export (together with histone deacetylase 3) and degradation. Then it phosphorylates chromatin-bound p65 on Ser 536, leading to the displacement of SMRT-histone deacetylase 3 repressor activity and allowing p300 to acetylate p65 at K310, an event necessary for full transcription (Hoberg *et al.*, 2006).

The role of IKKγ (NEMO) has also been reported in pathways other than NF-κB. In interferon regulatory factor signaling pathways, the interferon regulatory factor 3/interferon regulatory factor 7 pathway and two IKK-related kinases (TANK-binding kinase-1 and IKKε) are activated by NEMO through its interaction with TANK (Zhao *et al.*, 2007). In the DNA damage-induced ATM activation pathway, SUMOylation of NEMO and IKKε is essential for NF-κB activation (Wu and Miyamoto, 2007; Renner *et al.*, 2010). Chaperones such as hsp90 and hsp70 have also been described as components of the IKK complex. Hsp70 seems to behave as a NEMO-interacting inhibitor of NF-κB signaling, whereas hsp90 has been associated with its cochaperone cdc37 and behaves as a stabilizing factor of IKK through its interaction with cdc37 and the IKKα and IKKβ kinase domains (Salminen *et al.*, 2008).

Modification of p65

The NF-κB transactivator subunit has been shown to undergo extensive and diverse post-translational modifications, such as phosphorylation, acetylation and methylation (Figure 2). These modifications regulate the DNA-binding and oligomerization properties of p65, a principle target for phosphorylation by various kinases. These kinases function both in the cytoplasm and in the nucleus, and are differentially induced by various stimuli. Six different serine phosphoacceptor sites have been identified in Rel-A (p65): serines (S) 236, S276, S311, S468, S529 and S536. Phosphorylation of S276 is mediated by the catalytic subunit of protein kinase A (PKAc) (Mosialos and Gilmore, 1993) and mitogen- and stress-activated kinase-1 (Vermeulen *et al.*, 2003; Jamaluddin *et al.*, 2009; Reber *et al.*, 2009). S311 is phosphorylated by protein kinase C-ζ (Duran *et al.*, 2003; Kai *et al.*, 2009). Activated casein kinase II catalyzes the phosphorylation of p65 at S529 (Wang *et al.*, 2000). S536 is targeted for phosphorylation either by the IKKs (Sakurai *et al.*, 2003) or by ribosomalsubunit kinase-1 (Bohuslav *et al.*, 2004). Of interest, PKA phosphorylates p65 in the cytoplasm, whereas MASK-1 phosphorylates p65 in the nucleus. However, PKA-interacting protein 1 (AKIP1) facilitates the nuclear translocation of PKA and retention of phosphorylated p65 in the nucleus (Gao *et al.*, 2008). Another kinase, PKCζ, phosphorylates p65 at Ser 311. p65 is also subject to phosphorylation by a number of other kinases including GSK3β at S468 (Gong *et al.*, 2008), AKT/PI3K and NF-κB-activating kinase (also known as TANK-binding kinase-1 and TRAF2-associated kinase (reviewed in (Chen and Greene, 2004)). NIK and Cot have been shown to cooperate to trigger p65 phosphorylation (Wittwer and Schmitz, 2008).

Ubiquitination of p65 is required for its degradation. As part of the negative regulation of NF-κB, the p65 in cytoplasm is phosphorylated at Ser 236 by IKKα (Lawrence *et al.*, 2005), which accelerates its proteasomal degradation in the nucleus. Ubiquitinylation of p65 at lysine 195 (Fan *et al.*, 2009) is mediated by COMMD1 (Maine *et al.*, 2007) and GCN5 (Mao *et al.*, 2009). Another altogether different mode of processing of p65 has been reported that requires copine-1-dependent endoproteloysis of the N-terminus of p65 (Ramsey *et al.*, 2008).

Phosphorylation of p65 is primarily reported at serine residues. However, there is a report of tyrosine phosphorylation of p65 by Syk that is activated by PKCδ and is responsible for

thrombin-induced ICAM-1 expression in endothelial cells (Bijli *et al.*, 2008). Thrombin and collagen also induce a feedback inhibitory signaling pathway in platelets involving dissociation of the catalytic subunit of PKA from an NF-κB–IκBα complex (Gambaryan *et al.*, 2010). Recently, WIP1 phosphatase has been shown to dephosphorylate p65 at Ser 536, which is required for p300 interaction and transactivation. Thus, WIP1 negatively regulates NF-κB signaling (Chew *et al.*, 2009).

There are three main sites of acetylation within RELA (p65): lysines 218, 221 and 310 (Chen *et al.*, 2002), and these modifications have different consequences on the function of NF-κB (Chen and Greene, 2004). Recently, it was shown that the acetylation of lysine 310 of p65 impairs the Set9-mediated methylation of lysines 314 and 315, which is important for the ubiquitinylation and degradation of chromatin-associated p65 (Yang *et al.*, 2010b). Reversible lysine methylation of the p65 subunit is carried out by a lysine methylase, the nuclear receptorbinding SET domain-containing protein 1, and a lysine demethylase, F-box and leucine-rich repeat protein 11. Overexpression of F-box and leucine-rich repeat protein 11 inhibits NF-κB activity, and a high level of nuclear receptor-binding SET domain-containing protein 1 activates NF-κB and reverses the inhibitory effect of F-box and leucine-rich repeat protein 11, whereas reduced expression of nuclear receptor-binding SET domain-containing protein 1 decreases NF-κB activation. The targets are K218 and K221 of p65, which are methylated in cells with activated NF-κB. This shows that reversible lysine methylation of p65 is also an important element in the complex regulation of NF-κB (Lu *et al.*, 2010).

Multiple post-translational modifications of NF-κB can, therefore, affect DNA binding, interactions with coactivators and corepressors, and the termination of the NF-κB response. These modifications might regulate each other and/or might create specific marks for the recruitment/docking of different effectors to control the temporal and spatial activation of NF-κB (Chen and Greene, 2004; Perkins, 2006).

Multiple pathways of activation of NF-κB and targeting NF-κB for cancer prevention and therapy

As alluded to in previous sections, although the NF-κB pathway constitutes the central pathway regulating inflammation and cancer, multiple signaling pathways are operating at any given time in any given cancer (for an elaborate review, refer to Staudt (2010)). First, the NF-κB pathway is activated by diverse stimuli that are networked and regulated by many other pathways (for example, EGFR/HER2-PI3K-Akt-IKKα, TP53, PTEN, Akt-mTOR, G-protein-coupled receptor-RAS-RAF-Akt and Wnt–β-catenin), including canonical and non-canonical pathways (Figure 1). Another altogether different mechanism was shown for the activation of IκBα involving tyrosine phosphorylation (Imbert *et al.*, 1996; Singh *et al.*, 1996), brought about by syk kinase induced by H_2O_2 (Takada *et al.*, 2003). In another study, EGFR tyrosine kinase activity induced Tyr 42 phosphorylation of IκBα (Sethi *et al.*, 2007). H_2O_2-induced Tyr phosphorylation does not require degradation of IκBα for activation of NF-κB (Imbert *et al.*, 1996; Tang *et al.*, 2006); however, pervanadate-induced Tyr-phosphorylated IκBα does undergo degradation (Mukhopadhyay *et al.*, 2000). Of interest, hypoxiainduced activation of NF-κB in fetal lung fibroblasts also involved phosphorylation of IκBα at Tyr 42 residues (Wright *et al.*, 2009). Therefore, it is likely that a hypoxic tumor environment may activate NF-κB through such a mechanism.

Second, the activated NF-κB (p50–p65) cooperates and interacts with many other transcription factors to form on and off promoter complexes, such as STAT3 (Grivennikov and Karin, 2010), SP1(Perkins *et al.*, 1993) HIF-1α (Scortegagna *et al.*, 2008) and so on (Figure 1). Because of the networking of the pathways inhibiting one step or one the

pathway, activates the alternative route of activation. This can be exemplified by the fact that as IκBα is degraded by proteasomal pathway, the proteasomal inhibitors are developed to inhibit the NF-κB pathway. Velcade (bortezomib) is such a drug already approved by Food and Drug Administration for the treatment of multiple myeloma. However, recent reports indicate that velcade now induces NF-κB, instead of inhibiting as was thought by inducing calpane (Li *et al.*, 2010) and caspasedependent (Hideshima *et al.*, 2009b) mechanisms. In a similar way, IKKβ inhibitor MLN120B blocks the canonical pathway and growth of MM cell lines but does not inhibit the non-canonical NF-κB pathway (Hideshima *et al.*, 2009a). Therefore, inhibitors that block more than one step in the pathway or inhibit multiple pathways would be more effective for the treatment of cancer. Figure 4 shows cancer drugs approved by Food and Drug Administration, although not conceived as NF-κB inhibitors, these drugs can suppress NF-κB activation. For instance, EGFR kinase inhibitors have been shown to suppress NF-κB activation induced by epidermal growth factor (Sethi *et al*, 2007).

Almost 15 years ago, we showed that nutraceuticals such as curcumin effectively inhibits TNF-α-induced activation of NF-κB through inhibition of IκBα phosphorylation (Singh and Aggarwal, 1995). Subsequently, curcumin was shown to inhibit not only IKK kinase activity but also p65 phosphorylation at serine 536, and p65 acetylation (Aggarwal *et al.*, 2006); and p300–HAT (Balasubramanyam *et al.*, 2004). Like curcumin, anacardic acid was found to suppress NF-κB activation by inhibition of HAT (Sung *et al.*, 2008). Interestingly, several nutraceuticals such as berberine, butein, piceatannol, xanthohumol and wedelolactone, have been shown to directly bind to IKKβ through cysteine 179 (Kobori *et al.*, 2004; Pandey *et al.*, 2007, 2008; Harikumar *et al.*, 2009; Son *et al.*, 2010). Other nutraceuticals such as picroliv, thymoquinone, xanthohumol and plumbagin were found to inhibit NF-κB activity through directly binding to Cys 38 in p65 (Anand *et al.*, 2008; Sethi *et al.*, 2008; Harikumar *et al.*, 2009). Sesquiterpene lactones were also found to suppress NF-κB through direct interaction with Cys 38 in p65 (Garcia-Pineres *et al.*, 2001). Recently, we showed that crotepoxide inhibits the NF-κB pathway by inhibiting TAK1 directly, thus chemosensitizing tumor cells through inhibition of the proinflammatory pathway (Prasad *et al.*, 2010). Thus, it is clear that various nutraceuticals can suppress NF-κB-mediated inflammatory pathways and this may be linked to their chemopreventive potential.

Conclusions

Extensive sequence-based analysis of the genome of various cancers has revealed that the driver mutations in a wide variety of genes fall into pathways of multiple signal transduction networks. Therefore, it is less likely that targeting just one mutated gene or one particular pathway could be effective alone for treating any type of cancer. Of interest, the inflammatory linkage and constitutive activation of NF-κB has emerged as one of the attractive targets for intervention and treatment of cancer. However, NF-κB itself is activated by diverse stimuli and by highly networked pathways, suggesting the need for a multitargeted approach. Nutraceuticals derived from fruits, vegetables and spices that target multiple steps in the NF-κB pathways are emerging as promising agents for the prevention and treatment of cancers.

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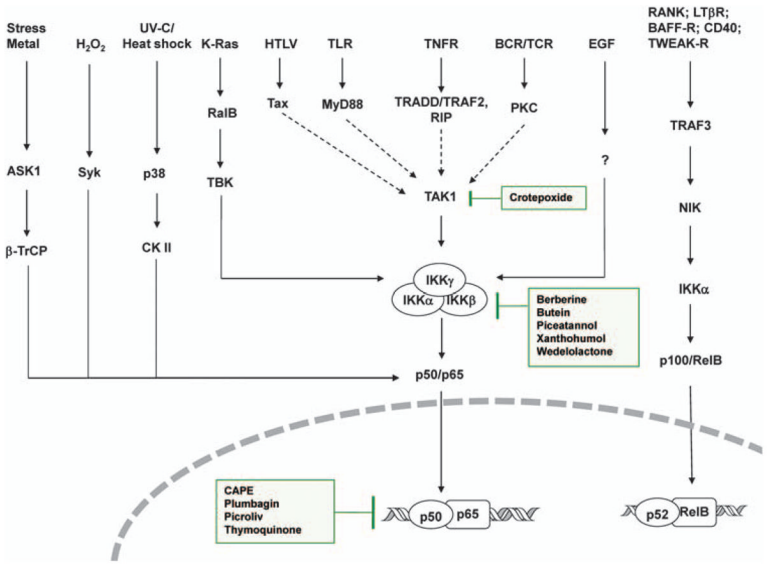

Figure 1.

Signaling network of NF-κB activation in cancer. Various pathways of NF-κB activation in cancers are shown. The sites of action of some phytochemicals are also indicated in the boxes. The network converges at three major sites (IKK kinase such as TAK1, IKK itself and the p50–p65 heterodimer). ASK1, apoptosis signal-regulating kinase 1; BAFF-R, TNF family member B cell-activating factor-receptor; CK II, casein kinase II; HTLV, human T-lymphotropic virus; LTβR, lymphotoxin-β receptor; MyD88, myeloid differentiation primary response gene 88; RalB, RAS-like protein B; RANK, receptor activator for nuclear factor κB; RIP, receptor interacting protein; Syk, spleen tyrosine kinase; TAK1, transforming growth factor (TGF)-β activating kinase 1; TBK, TRAF family member-associated NF-κB activator (TANK)-binding kinase; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; TRADD, TNFR1-associated death domain; TRAF, TNF-receptor-associated factor; β-TrCP, β-transducin repeat-containing protein; TWEAK-R, TNF-related weak inducer of apoptosis-receptor; UV, ultra violet.

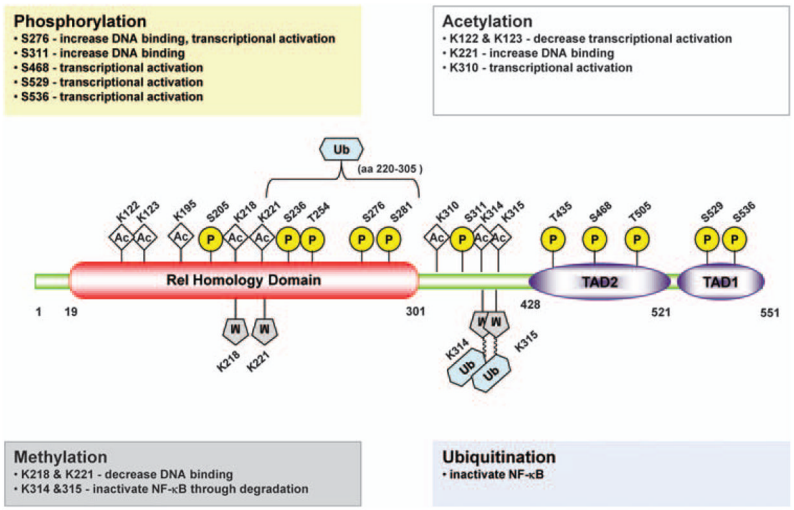

Figure 2.

Sites of modification in p65 (RelA) subunit of NF-κB in cancer. Locations of various modification sites in the Rel homology domain and transactivation domains (TAD1 and 2) of p65 are shown. The possible effects are shown in the boxes. Ac, actylation; K, lysine residues; M, methylation; P, phosphorylation; S, serine residues; Ub, ubiquitination.

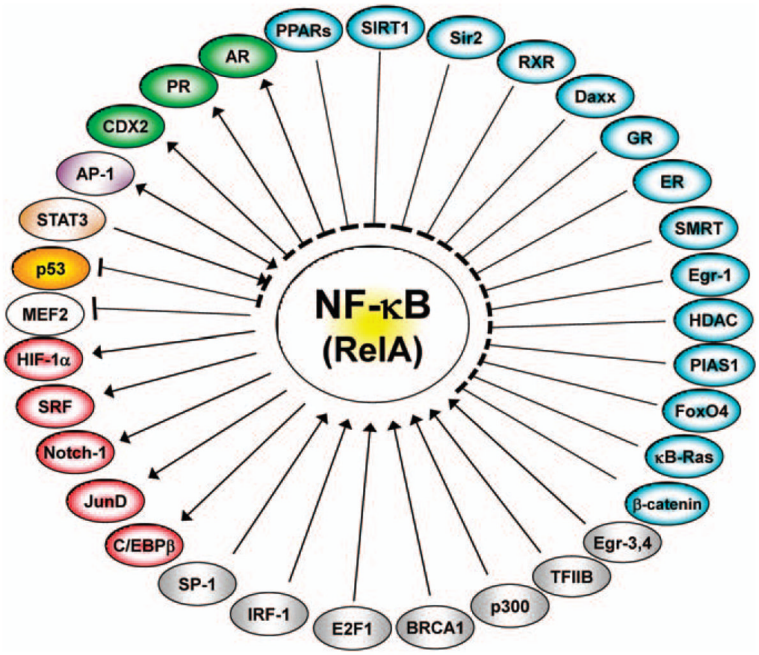

Figure 3.

NF-κB interactions in cancer. NF-κB interacts with many transcription factors and transcriptional regulators. The interactions could be direct at the promoter, such as in AP1, HIF-1α, Notch1, JunD, CREB, SP1 or off the promoter, such as STAT3, p53 or both. The single-head arrow indicates activation, whereas the double-head arrow indicates direct and indirect activation. The blunt-end arrow indicates inhibition and negative regulation. For PPARs, see (Delerive *et al.*, 1999; Chung *et al.*, 2000; Planavila *et al.*, 2005); for SIRT1 (Yeung *et al.*, 2004); for Sir2 (Yang *et al.*, 2007); for RXR (Na *et al.*, 1999); for Daxx (Park *et al.*, 2007); for GR (Ray and Prefontaine, 1994); for ER (Galien and Garcia, 1997); for SMRT (Lee *et al.*, 2000); for Egr-1 (Chapman and Perkins, 2000); for HDACs (Ashburner *et al.*, 2001; Liu *et al.*, 2005); for PIAS (Chen *et al.*, 2001); for FoxO4 (Zhou *et al.*, 2009); for κB-ras (Tago *et al.*, 2010); for β-catenin (Deng *et al.*, 2002); for Egr-3 & 4 (Wieland *et al.*, 2005); for TFIIB (Schmitz *et al.*, 1995); for p300 (Morimoto *et al.*, 2008); for BRCA1 (Benezra *et al.*, 2003); for E2F1 (Lim *et al.*, 2007); for IRF-1 (Sgarbanti *et al.*, 2008); for SP-1 (Perkins *et al.*, 1993); for C/EBPβ (Zwergal *et al.*, 2006); for JunD (Toualbi-Abed *et al.*, 2008); for Notch-1 (Cheng *et al.*, 2001); for SRF (Franzoso *et al.*, 1996); for HIF-1α (Scortegagna *et al.*, 2008); for MEF2 (Kumar *et al.*, 2005); for p53 (Jeong *et al.*, 2004); for STAT3 (Yoshida *et al.*, 2004; Yu and Kone, 2004); for AP-1 (Stein *et al.*, 1993); for CDX2 (Kim *et al.*, 2004); for PR (Kovalenko *et al.*, 2003); and for AR (Palvimo *et al.*, 1996).

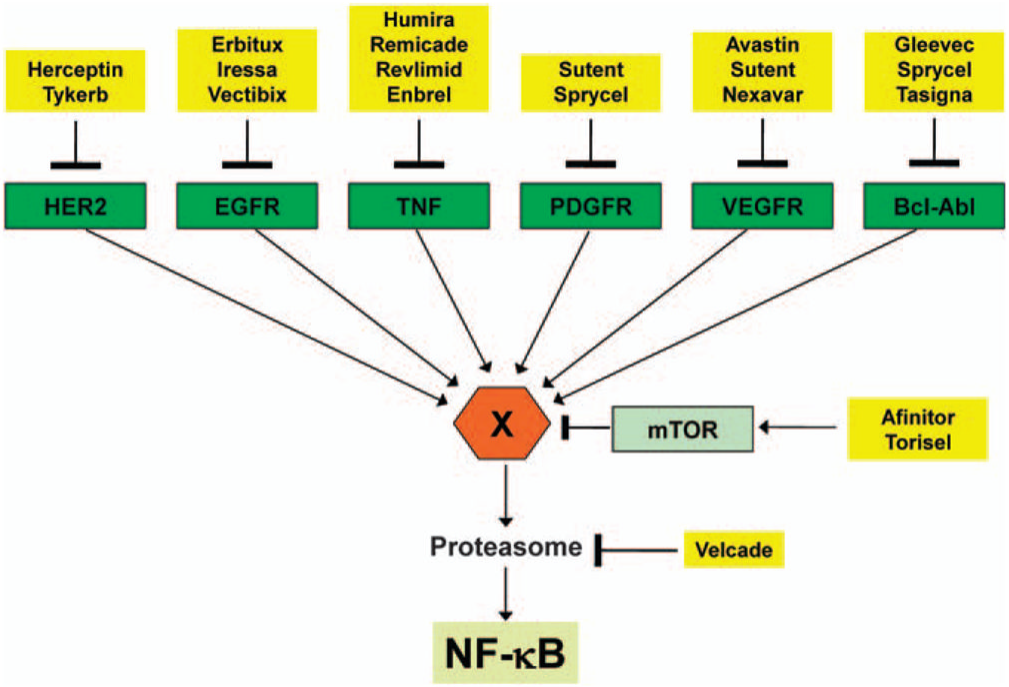

Figure 4.

Suppression of NF-kB activation by the Food and Drug Administration-approved drugs for cancer therapy. Molecular targets for many Food and Drug Administration-approved drugs for treatment of cancer are shown. Although these drugs act through their defined molecular targets, they inhibit NF-κB via pathway(s) that are not well defined. The X indicates an intermediate that could be either IKK or its upstream activators, which may be different for different pathways. EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor receptor; TNF, tumor necrosis factor; VEGFR, vascular endothelial cell growth factor receptor.

Table 1

Different mechanisms of constitutive activation of NF-κB in cancers

Cancer type	Mutated gene	Pathway	Reference
Cancers			
Acute myeloid leukemia			
	c-KIT	PI3K–Akt	(Lennartsson *et al.*, 2005; Linnekin, 1999)
	FLT3	PI3K–Akt	(Choudhary *et al.*, 2005; Grosjean-Raillard *et al.*, 2008)
		ERK–MAPK	(Takahashi *et al.*, 2005)
	Ras	PI3K-PKB–Akt-IKK	(Birkenkamp *et al.*, 2004)
Chronic myeloid leukemia			
	Bcr–Abl	MEKK1	(Nawata *et al.*, 2003)
Pancreatic cancer			
	K-Ras	PI3K-RacEGF-Rac	(Almoguera *et al.*, 1988)
		PI3K–Akt-IKK	(Liptay *et al.*, 2003)
Prostate cancer			
	AR	PI3K–Akt	(Newmark *et al.*, 1992; Sun *et al.*, 2010)
Small cell lung cancer			
	K-Ras	TBK1–IKKβ	(Basseres *et al.*, 2010)
Head and neck cancer			
	EGFR	CK2–IKK	(Molinolo *et al.*, 2009)
Glioma			
	EGFR/PTEN	PI3K–Akt-IKK	(Wang *et al.*, 2004)
	PDGF	PI3K–Akt-IKK	(Smith *et al.*, 2008)
Non-small cell lung cancer			
	K-Ras/EGFR	PI3K–Akt-IKK	(Tang *et al.*, 2006)
Breast cancer			
	HER2	PI3K–Akt-IKK	(Cao *et al.*, 2007)
	TAB1	TAK1–IKKβ	(Neil and Schiemann, 2008)
Multiple myeloma			
	NFKB2	Alternative	(Demchenko *et al.*, 2010)
	CYLD, NFKB1, and TACI	Classical	(Demchenko *et al.*, 2010)
	NIK, TRAF2, TRAF3, cIAP1 and 2, and CD40	Both alternative	(Demchenko *et al.*, 2010)
Others			
B-cell line		Enhanced IκBα degradation	(Miyamoto *et al.*, 1994)

Abbreviations: AR, androgen receptor; cIAP, cellular inhibitor of apoptosis; CK2, casein kinase 2; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FLT3, FMS-like tyrosine kinase 3; IKK, IκB kinase; MAPK, mitogen-activated protein kinase; MEKK, MAPK kinase; NIK, NF-κB inducing kinase; PKB, protein kinase B; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; TAB1, TAK1 binding protein 1; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; TAK1, transforming growth factor (TGF)-β activated kinase 1; TBK1, TNF receptor-associated NF-κB kinase (TANK)-binding kinase 1; TRAF, TNF receptor-associated factor.