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NF-κB and cancer: how intimate is this relationship

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Abstract

NF-κB, a transcription factor first discovered in 1986, is now known to be closely connected to the process of tumorogenesis based on a multiplicity of evidence. (1) NF-κB is activated in response to tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli that account for as much as 95% of all cancers. (2) The transcription factor has been linked with transformation of cells. (3) It is constitutively active in most tumor cells. (4) It has also been linked with the survival of cancer stem cells, an early progenitor cell that has acquired self-renewal potential. (5) NF-κB regulates the expression of most anti-apoptotic gene products associated with the survival of the tumor. (6) It also regulates the gene products linked with proliferation of tumors. (7) The transcription factor controls the expression of gene products linked with invasion, angiogenesis, and metastasis of cancer. (8) While most carcinogens activate NF-κB, most chemopreventive agents suppress its activation. These observations suggest that NF-κB is intimately intertwined with cancer growth and metastasis. The mechanism that leads to constitutive activation of NF-κB in hematological, gastrointestinal, genitourinary, gynecological, thoracic head and neck, breast, and skin cancers, and the ways NF-κB is activated are the topics of discussion in this review.

Keywords

NF-κB; Cancer; Constitutive expression

Introduction

Nuclear factor of κB (NF-κB) is a sequence-specific transcription factor that is known to be involved in the inflammatory and innate immune responses. It was so named because it was found in the nucleus bound to an enhancer element of the immunoglobulin kappa light chain gene in B cells [1]. It was initially considered to be a B-cell-specific transcription factor but was later shown to be present in every cell type. The molecular identification of its p50 subunit as a member of the reticuloendotheliosis (REL) family provided the first evidence that linked NF-κB to cancer, as v-REL is an oncoprotein of the REL retrovirus (REV-T) [2].

The REL proteins belong to two classes, which are distinguishable by their mode of synthesis and transactivation properties. One class consists of RELA (also known as p65), RELB, and c-REL, proteins that are synthesized in their mature forms. These proteins contain an amino-terminal REL homology domain (RHD) that is required for dimerization and DNA binding and transcription-modulating domains at their carboxy terminus. The

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second class consists of NF-κB1 (also known as p105) and NF-κB2 (also known as p100), which are synthesized as large precursors (p105 and p100) with an N-terminal RHD and a C-terminal series of ankyrin repeats. Ubiquitin-dependent proteolytic processing removes this C-terminal domain, resulting in production of the mature DNA-binding proteins (p50 and p52). The final products contain the RHD, but lack transcription-modulating domains [3].

These proteins form various NF-κB homo- and heterodimers, and their activity is regulated by two main pathways. The first regulatory pathway—the canonical NF-κB activation pathway—applies to dimers that are composed of RELA, c-REL, and p50, which are held captive in the cytoplasm by specific inhibitors that are known as the inhibitor of κB (IκB) proteins. IκB proteins consist of an N-terminal regulatory domain followed by a series of ankyrin repeats, similar to those present within the C-terminal portions of p100 and p105. The canonical pathway is normally triggered in response to microbial and viral infections and exposure to proinflammatory cytokines, all of which activate the IκB kinase (IKK) complex. IKK phosphorylates NF-κB-bound IκBs at two conserved serines within the IκB N-terminal regulatory domain. This targets IκB for ubiquitin-dependent degradation and allows the liberated NF-κB dimers to translocate to the nucleus [4]. IκB phosphorylation depends mainly on the IKKβ catalytic subunit of the IKK complex [5]. In the non-canonical pathway, inducible proteolytic processing of the NF-κB2 gene product, p100 are involved. Different members of the TNF-receptor superfamily, such as B-cell activating factor (BAFF) and CD40, selectively activate the NF-κB-inducing kinase (NIK), and IKK1, leading to the phosphorylation of p100, followed by its ubiquitination, and partial proteolytic processing of the 26S proteasome, yielding p52. NIK regulation is also through its dynamic interaction with the tumor necrosis factor receptor-associated factor 3 (TRAF3). TRAF3 physically associated with NIK via a specific sequence motif located in the N-terminal region of NIK; this molecular interaction appears to target NIK for degradation by the proteasome. This pathway principally generates p52–RELB heterodimers as opposed to the p50–RELA heterodimers produced by the canonical pathway [6–9].

Activation of NF-κB is a tightly regulated event. In normal cells, NF-κB becomes activated only after the appropriate stimulation, and then it upregulates the transcription of its target genes. NF-κB is activated by many divergent stimuli, including proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), epidermal growth factor (EGF), T- and B-cell mitogens, bacteria and lipopolysaccharides (LPS), viruses, viral proteins, double-stranded RNA, and physical and chemical stresses [10]. Cellular stresses such as ionizing radiation and chemotherapeutic agents also activate NF-κB [11]. One of the first genes that NF-κB activates is IκBα itself, which transports activated NF-κB from the nucleus to the cytoplasm. NF-κB activation is therefore an inducible, but transient event in normal cells. In tumor cells, different types of molecular alterations may result in an impaired regulation of NF-κB activation. In such cases, NF-κB becomes constitutively activated. This leads to deregulated expression of NF-κB controlled genes. According to Hanahan and Weinberg [12], tumorigenesis requires six essential alterations to normal cell physiology: self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, immortalization sustained angiogenesis, and tissue invasion and metastasis. NF-κB is able to induce several of these cellular alterations by producing inflammation, and has been shown to be associated with development of cancer (Fig. 1).

Constitutive expression of NF-κB in cancer cells

Although cancer is the second most frequent cause of death in the United States, the molecular mechanisms involved in its initiation and progression, and the ultimate development of metastatic disease are largely unknown. These processes undoubtedly

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involve multiple genetic events, including activation of oncogenes and tumor suppressor genes alteration of mutant phenotypic leading to neoplastic changes. However, the diversity of its clinical presentation, aggressiveness, and current treatment strategies imply an equally diverse number of potential targets in the molecular pathways leading to its formation. NF-*κ*B activation participates at multiple steps in these pathways, and its suppression may lead to the suppression of cancer development. The activation of NF-*κ*B occurs as it is transported from the cytoplasm to the nucleus upon degradation of the inhibitory subunit. In the nucleus, it binds to specific *κ*B sites on the DNA and mediates the expression of a number of genes involved in the cellular response to various stresses. The persistence of NF-*κ*B in the nucleus is referred to as constitutive activation. Constitutive activation NF-*κ*B is shown in a wide variety of tumor types (Table 1), including those tumors induced in animal models. The precise role of constitutive activation in tumors is not known, but it has been linked to resistance to apoptosis in human cutaneous T-cell lymphoma cells [57]. It is tempting to believe that a similar mechanism accounts for the progression of all tumors that constitutively express NF-*κ*B, but such a link has yet to be clearly identified.

Mechanisms of constitutive NF-*κ*B activation

The mechanism of expression of constitutively active NF-*κ*B is not fully understood; however, several mechanisms have been proposed, as described in Table 2. Some explained reasons for constitutive expression of NF-*κ*B include infected virus proteins expression, activation of kinases, overproduction of cytokines, dysregulation of cell surface receptors, activation of oncoproteins etc.

The possible explanatory mechanisms include aberrant IKK activity and a shorter I*κ*B*α* half-life (as seen in B-cell lymphoma), I*κ*B*α* mutation (as seen in Hodgkin lymphoma), IL-1b production (as seen in AML), and TNF-*α* production (as seen in cutaneous T-cell lymphoma and Burkitt's lymphoma). There have been reports of autocrine or paracrine activation of NF-*κ*B resulting from overexpression of ligands and receptors of EGF [84], HER-2/neu [64, 69], TNF-*α* [57, 73], IL-1 [74, 85], hepatocyte growth factor [86], and integrins [87]. Epidermal growth factor receptor and HER-2/neu signaling involving phosphoinositide 3-kinases (PI3K), IKK, and casein kinase-2 (CK2) has been demonstrated in breast cancer [88]; hepatocyte growth factor/PI3K/p21-activated kinase (Pak)/IKK signaling in prostate carcinoma [86]; kinase inhibitor of NF-*κ*B1 in melanoma [89], receptor tyrosine kinase Flt3 in AML [90], and NF-*κ*B activation via persistent IKK activation in colon carcinomas, mantle cell lymphoma, melanomas, and brain [1, 54, 63, 91]. Recently, both glycogen synthase kinase (GSK)-3 isoforms (GSK-3*α* and GSK-3*β*) were reported to be involved in regulating NF-*κ*B activation and cell proliferation in pancreatic cancer cell lines [29]. Wilson and Baldwin showed that GSK-3 isoforms are differentially required to maintain basal NF-*κ*B DNA-binding activity, transcriptional activity, and cell proliferation in Panc-1 and MiaPaCa-2 cells.

The BCR–ABL fusion oncogene has also been implicated in NF-*κ*B activation, cell survival, and tumorigenesis in human leukemias [67]. Activation by a translocation that produces a MALT-1 fusion protein has been reported in diffuse large B-cell lymphomas [92]. Constitutive activation of NF-*κ*Bp52:p52 due to overexpression and association with the transactivating family member Bcl-3 has been detected in breast carcinomas and lymphomas [17, 93]. Overexpression of MUC1 in human carcinoma cells is also associated with constitutive activation of NF-*κ*B p65. MUC1 interacts with the high-molecular-weight IKK complex. The MUC1 cytoplasmic domain binds directly to IKK*β* and IKK*γ* [71]. Direct mutation or altered expression of NF-*κ*B molecules has been only rarely found in human cancers and in Hodgkin lymphomas, where mutations of I*κ*B*α* that favor activation have been identified [94]. Oncogene CARD11 contributes to tumorigenesis by inducing NF-*κ*B

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activation. Experimental introduction of CARD11 coiled-coil domain mutants into lymphoma cell lines resulted in constitutive NF-κB activation and enhanced NF-κB activity upon antigen receptor stimulation [22]. Mutations in the coil-zipper (CoZi) domain of IKKγ also cause constitutive NF-κB activity. Mann et al. [28] reported an association between transglutaminase (TG2, a family of Ca^{2+}-dependent enzymes that catalyze acyl-transfer reactions between peptide-bond glutamine residues and the E-amino group of lysine residues of other peptides) overexpression and constitutive activation of NF-κB in various types of cancer cells. They found that inhibition of TG2 activity by synthetic inhibitors or small interfering RNA (siRNA) inhibits the constitutive activation of NF-κB. Moreover, they observed a direct association between TG2 and the IκBα/p65:p50 complex and cross-linked forms of IκBα in TG2-expressing cells. Immunohistochemical analysis of pancreatic ductal carcinoma samples obtained from patients further support a strong correlation between TG2 expression and NF-κB activation [28]. The TGase family is composed of several members, including plasma factor XIII, TG1 (keratinocyte TGase), TG2 (tissue TGase), TG3 (epidermal TGase), and TG4 (prostate TGase). Among them, TG2 has been most widely identified in many cell types and implicated in diverse physiological functions. All mammalian TGs are known to be activated by an increase in the cytosolic Ca^{2+} concentration and various tumor promoters.

Many viruses achieve their oncogenic effects via the NF-κB signaling cascade. A notable example relevant to human cancer is the oncoprotein human T-cell leukemia virus-1 (HTLV-1) implicated in acute T-cell leukemia (ATL). Persistent activation of NF-κB by HTLV-1 Tax causes nuclear accumulation of NF-κB dimers, helps to overcome their inhibition by the p105/NF-κB1 subunit, and is an essential step in the transformation of T cells [95]. The Tax oncoprotein HTLV-1 has been shown to directly interact with and constitutively activate the IKK complex, which results in the activation of both the canonical and non-canonical NF-κB signaling pathways [6]. Other viral oncoproteins have also been shown to activate NF-κB by means of different mechanisms [96]. Another virus that contributes to human cancer via NF-κB is the Epstein-Barr virus (EBV), implicated in Burkitt's and Hodgkin's lymphomas. The EBV nuclear antigen (EBNA)-2 and latent membrane protein (LMP)-1 enhance NF-κB activity, thereby preventing apoptosis in EBV-transformed B cells [97]. The avian REV-T oncovirus produces the constitutively active v-REL oncoprotein, which causes rapidly progressing lymphomas and leukemias [2].

Cancer-associated chromosomal translocations, deletions, and mutations might also disrupt genes that encode NF-κB and IκB proteins, uncoupling NF-κB factors from their regulators and causing constitutive NF-κB activation. Constitutively activated NF-κB transcription factors have been associated with several aspects of tumorigenesis, including promoting cancer-cell proliferation, preventing apoptosis, and increasing a tumor's angiogenic and metastatic potential. We have also shown that a TNF-TNFR1-TRADD-TRAF2-RIP-TAK1-IKK pathway mediates constitutive NF-κB activation and proliferation in human head and neck squamous-cell carcinoma [47]. In head and neck squamous cell cancer (HNSCC) cells, constitutive NF-κB activation has been seen in association with autocrine expression of TNF, TNF receptors, and receptor-activators of NF-κB and its ligand but not with autocrine expression of IL-1β. Furthermore, treatment of HNSCC cells with anti-TNF antibody downregulated the expression of constitutively active NF-κB, and was associated with inhibition of IL-6 expression and cell proliferation.

Constitutive expression of NF-κB-regulated gene products in cancer cells

Nuclear factor of κB (NF-κB) regulates many genes involved in the promotion of cancer (e.g., clonal expansion, growth, diversification, angiogenesis, adhesion, extravasation, and degradation of extracellular matrix; Fig. 2).

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Metastatic genes

The metastasis of cancer requires the migration of cancerous cells both into and out of the vessel walls that transport them to other parts of the body. The ability to cross vessel walls is mediated by specific molecules that are expressed in response to a number of signals from inflammatory cells, tumor cells, and others. Among those special molecules are ICAM-1, ELAM-1, and VCAM-1, all of which have been shown to be regulated by NF-*κ*B activation [98–100]. The gene encoding granulocyte macrophage-colony stimulating factor (GM-CSF), as a key target of NF-*κ*B, mediates osteolytic bone metastasis of breast cancer by stimulating osteoclast development [101].

Angiogenic genes

Tumor cells, just like normal cells, need oxygen to survive, and so poor access to oxygen can limit progression of tumors. Vascularization of tumors requires the release of angiogenic growth factors (e.g., VEGF, MCP-1) from tumor cells and/or inflammatory cells such as macrophages and neutrophils or in response to pro-inflammatory cytokines (e.g., TNF) [102–104]. NF-*κ*B regulates the expression of the growth factors and cytokines (VEGF, TNF, and MCP-1) necessary for angiogenesis [105–108].

Tumor promoting genes

NF-*κ*B regulates many genes involved in the promotion of cancer (e.g., clonal expansion, growth, diversification, angiogenesis, adhesion, extravasation, and degradation of extracellular matrix). For example, NF-*κ*B may regulate the production of prostaglandins via the proinflammatory gene COX2, which has been shown to be overexpressed in a variety of cancers including colorectal cancer and mesothelioma [109, 110]. Similar studies have reported many other proinflammatory genes regulated by NF-*κ*B including TNF [111], IL-1 [112], iNOS [113], matrix metalloproteinase (MMP-9) [114], urokinase-type plasminogen activator (uPA) [115], and many other chemokines [116–118].

Apoptotic/survival genes

Nuclear factor of *κ*B (NF-*κ*B) has been shown to play a pro-apoptotic role in addition to its more common anti-apoptotic role. Examples of its pro-apoptotic effects in cells include those found in B cells [119], T cells [120, 121], neuronal cells [122, 123], and endothelial cells [124]. The opposing effects of NF-*κ*B are thought to be cell-type specific and/or dependent on the inducing signal (e.g., IL-1, TNF-*α*, and UV radiation). Different activation pathways of NF-*κ*B may cause the expression of proteins that promote apoptosis (e.g., Fas, c-myc, p53, and I*κ*B*α*) or inhibit apoptosis (e.g., TRAF2, IAP proteins, and Bcl-2 like proteins) [123, 125, 126]. In addition, NF-*κ*B activation variably controls the regulation of cell cycle proteins (e.g., cyclin D1 and CDK2 kinase) [127–129] and the interaction with various cellular components (e.g., p300 and p53) that promote or induce apoptosis [130, 131].

Induction of NF-*κ*B by carcinogens

Several studies revealed that NF-*κ*B is activated by various carcinogens, such as 7,12-dimethylbenz(a)anthracene (DMBA) and cigarette smoke and tumor promoters, such as phorbol 12-myristate 13-acetate (PMA) and benzoapyrene diol-epoxide (BaPDE) [132, 133]. The mechanisms of NF-*κ*B activation by these carcinogens are not clear. However, some carcinogens, e.g., DMBA and 12-*O*-tetra-decanoylphorbol-13-acetate (TPA), degrade I*κ*B*α* by its phosphorylation. PMA also activates NF-*κ*B by phosphorylating I*κ*B*α* as observed in BEAS-2B human lung epithelial cells [134]. It has been observed that topical treatment of DMBA–TPA on mouse skin activates the NF-*κ*B and its nuclear translocation through an increase in the phosphorylation of I*κ*B*α* [135]. TPA also induces activation of

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IKK, NF-κB transcriptional, and DNA-binding activity [136]. Hepatic tumor-promoting agent phenobarbital activates NF-κB in the rat liver and promotes DNA-binding activity of NF-κB [137]. Numerous studies indicate that TNF, which can also mediate carcinogenesis through induction of proliferation, invasion and metastasis of tumor cells [138, 139], is perhaps the most potent activator of NF-κB.

Ultraviolet (UV) radiation can cause inflammatory changes and may further contribute to carcinogenesis. UVB caused NF-κB (p65) translocation from the cytosol to the nucleus, and it induced phosphorylation of IκBα, an inhibitor of NF-κB activity, which results in the degradation of IκB and subsequent release of NF-κB, which translocates to the nucleus where it is active in regulation of gene transcription [140]. Other than UV, gamma-radiation also activates NF-κB. Treatment of Ramos cells with gamma-irradiation leads to marked phosphorylation of IκB and translocation of p65/NF-κB to the nucleus [141].

Suppression of NF-κB by chemopreventive agents

Chemoprevention was described as the use of natural or synthetic chemicals allowing suppression, retardation, or reversal of carcinogenesis [142]. Chemopreventive products produce low side effects and toxicity and neutralize carcinogens as well as their effects on cells. Several phytochemicals from different plants have been identified that can suppress NF-κB activation effectively (Table 3). These include curcumin (turmeric), resveratrol (red grapes), guggulsterone (guggul), ursolic acid (from holy basil), betulinic acid (birch trees), eugenol (cloves), gingerol (ginger), oleandrin (oleander), silymarin (artichoke), emodin (aloe), capsaicin (red chili), anethole (anise), and others. How these agents suppress NF-κB activation is becoming increasingly apparent. For example, curcumin blocks IKK activation [14], resveratrol suppresses p65 phosphorylation [161], ferulic acid inhibits p65 translocation to the nucleus [162], asiatic acid inhibits IκBα degradation [163], and lupeol inhibits binding of NF-κB to the DNA [164]. All these blockers of NF-κB have potential in the treatment of a wide variety of diseases. Pharmacological safety, bioavailability, and efficacy in vivo will determine their therapeutic potential in particular diseases. Since NF-κB regulates the expression of numerous genes that are involved in carcinogenesis, the suppression of expression of these genes through inhibition of NF-κB activation may be one of the mechanisms by which chemopreventive and chemotherapeutic agents mediate their effects. Recently, in a phase II clinical trial, curcumin was found to beneficial for patient with advanced pancreatic cancer [165]. Characterization of NF-κB pathway in zebra fish [166] opens up a significant opportunity to screen for various inhibitors and look for toxicity and other preclinical issue using this whole vertebrate organism.

Conclusion

Constitutive activation of NF-κB is an emerging hallmark of various types of tumors. NF-κB is activated in response to oncogenes, viral proteins, carcinogens, tumor promoters, and inflammatory stimuli. Its activation controls the expression of genes that mediate transformation, proliferation, invasion, angiogenesis, and metastasis (Fig. 3). While NF-κB is required for the normal function of the immune system and for hematopoiesis; its deregulation has been implicated in a variety of cancers in which NF-κB is constitutively expressed. Suppression of constitutive NF-κB activation by various agents including bioactive components of natural compounds inhibits the oncogenic potential of transformed cells and thus makes NF-κB an interesting new therapeutic target in cancer. Overall, this review describes our current understanding of the mechanism of the constitutive expression of NF-κB in tumor cells, its suppression by natural compounds, and the future direction of the research.

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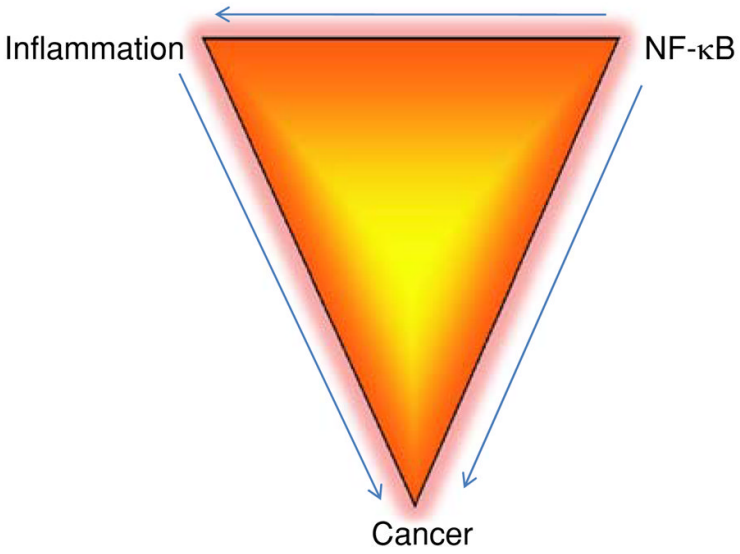

Fig. 1.
Link between NF-*κ*B, inflammation, and cancer

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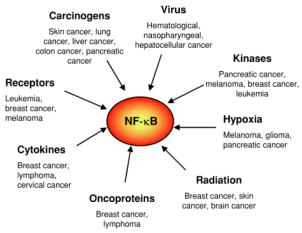

Fig. 2.
Role of NF-κB and NF-κB-regulated gene products in cancer development

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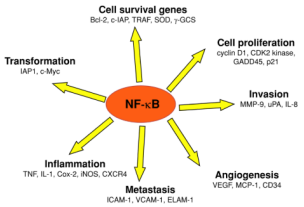

Fig. 3.
Various targeted therapies discovered within last 10 years for the treatment of cancer

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Table 1

A list of human cancer cell line and tumor that express constitutive nuclear factor-κB activation

Cell/Tumor	References
Hematological cancer	
Burkitt lymphoma	Rath [13], Hussain et al. [14]
Acute lymphoblastic leukemia	Kordes et al. [15], Munzert et al. [16]
Anaplastic large-cell lymphoma	Mathas et al. [17]
Hodgkin's lymphoma	Bargou et al. [18]
Mantle cell lymphoma	Shishodia et al. [1], Yang et al. [19], Rudelius et al. [20]
Diffuse large B-cell lymphoma	Davis et al. [21], Lenz et al. [22]
Acute myelogenous leukemia	Brauns et al. [23], Jenkins et al. [24]
Multiple myeloma	Bharti et al. [25], Markovina et al. [26]
Gastrointestinal cancer	
Pancreatic cancer	Wang et al. [27], Mann et al. [28], Wilson and Baldwin [29]
Colorectal cancer	Yu et al. [30], Hochwald et al. [31]
Gastric cancer	Lee et al. [32], Wu et al. [33]
Esophageal carcinoma	Izzo et al. [34]
Laryngeal cancer	Du et al. [35]
Liver cancer	Qiao et al. [36], Tai et al. [37]
Genitourinary cancer	
Prostate cancer	Shukla et al. [38], Rettig et al. [39]
Bladder cancer	Warren et al. [40]
Renal cell carcinoma	Oya et al. [41]
Gynecologic cancer	
Ovarian cancer	Lu et al. [42], Chu et al. [43]
Cervical cancer	Kato et al. [44]
Vulvar carcinoma	Seppanen et al. [45]
Thoracic and head and neck cancer	
Lung cancer	Baby et al. [46]
Head and neck cancer	Jackson-Bernitsas et al. [47]
Thyroid cancer	Ludwig et al. [48], Pacifico et al. [49]
Oral cancer	Nakayama et al. [50]
Other	
Breast cancer	Buchholz et al. [28], Mann et al. [51]
Fibrosarcoma	Higgins et al. [52], Kohno et al. [53]
Melanoma	Yang and Richmond [54], Uffort et al. [55]
Squamous-cell carcinoma	Tamatani et al. [56]

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Table 2

A list of mechanisms for constitutive activation of NF-κB in tumor cells

Mechanism	Tumor	References
Viruses		
HTLV-1 Tax protein induction	T-cell leukemia	Azran-Shaish et al. [58]
Human herpesvirus infection	T-lymphoma cells	Chugh et al. [59]
Hepatitis B virus infection	Hepatocellular carcinoma	Tai et al. [37]
Expression of LMP1 of EBV	Nasopharyngeal carcinoma	Shair et al. [60]
Expression of vFLIP from KSHV	Dendritic cells	Rowe et al. [61]
Kinases		
Overexpression of GSK-3β	Pancreatic cancer	Wilson and Baldwin [29]
Overexpression of NIK	Melanoma	Dhawan et al. [62]
Aberrant IKK activation	Brain	Politi et al. [63]
Overexpression of Akt	Breast cancer	Pianetti et al. [64]
Overexpression of TEL–Jak2	Acute leukemia	Santos et al. [65]
Overexpression of Raf	Multiple myeloma	Keats et al. [66]
Overexpression of Bcr–Abl	ALL and CML	Reuther et al. [67]
Receptors		
Activation of Flt3	Acute myeloid leukemia	Grosjean-Raillard et al. [68]
Overexpression of EGFR and Her-2	Breast cancer	Le Page et al. [69]
Overexpression of TEL-PDGFR	Hematopoietic Ba/F3 cells	Besancon et al. [70]
Overexpression of LT-βR	Melanoma	Dhawan et al. [62]
Overexpression of BAFF or BAFF-R	African monkey kidney cells	Kohno et al. [53]
Oncoproteins		
Aberrant overexpression of MUC1	Breast cancer	Ahmad et al. [71]
Mutation of CARD11	B-cell lymphoma	Lenz et al. [22]
Overexpression of oncogenic Ras	Mouse embryo fibroblast	Joneson and Bar-Sagi [72]
Cytokines		
TNF production	Breast cancer	Braunstein et al. [73]
IL-1β production	AML	Estrov et al. [74]
Miscellaneous		
IκBα degradation	Gastric carcinoma	Wu et al. [75]
TRAF1 production	Cervical cancer	Kato et al. [44]
p53 mutations	Head and neck, lung tumors	Weisz et al. [76]
DNA histone deacetylase	AML	Fabre et al. [77]
Transglutaminase production	Pancreatic cancer	Mann et al. [28]
Mutations CoZi domain	Somatic cells	Bloor et al. [78]
Helicobacter pylori infection	Gastric epithelial cells	Kim et al. [79]
IRF-2 production	African monkey kidney cells	Chae et al. [80]
Nitric oxide synthase activation	Osteoarthritic chondrocytes	Rosa et al. [81]
Tyrosine nitration of IκBα	CHO cells	Yakovlev et al. [82]
Dbl/Dbs transformation	Mouse embryo fibroblast	Whitehead et al. [83]

ALL acute lymphoblastic, *CML* chronic myelogenous leukemia, *AML* acute myeloid leukemia, *HTLV-1* human T-cell leukemia virus type 1, *LMP1* latent membrane protein 1, *EBV* epstein bar virus, *GSK-3β* glycogen synthase kinase-3beta, *NIK* NF-κB-inducing kinase, *LTβ-R* lymphotoxin-beta receptor, *KINK-1* kinase inhibitor of nuclear factor-κB-1, *KSHV* Kaposi's sarcoma-associated herpesvirus, *IRF-2* Interferon regulatory factor-2

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Table 3

A list of mechanism of inhibition of NF-κB activation by different natural products in different cancers

Mechanisms	Cancer type/cells	Natural compounds (Source)	References
Inhibition of activity of IKK:			
	Human prostate cancer PC-3 cells	Apigenin (Peppermint parsley, thyme)	Shukla and Gupta [143]
	Human prostate cancer PC-3 cells	Boswellin (*Boswellia serrata*)	Syrovets et al. [144]
	Malignant meanoma cells	Capsaicin (Chili peppers)	Patel et al. [145]
	Human CF bronchial gland cells	Genistein (Soy)	Tabary et al. [146]
	Multiple myeloma U266 cells	Xanthohumol (hops)	Harikumar et al. [147]
Inhibition of p65 phosphorylation:			
	Human prostate cancer Du145 cells	Pomegranate (Pomegranate fruit)	Rettig et al. [39]
	Multiple myeloma U266 cells	Resveratrol (Grape, red wine)	Bhardwaj et al. [148]
Inhibition of activity of IKKK:			
	Multiple myeloma U266 cells	AKBA (*Boswellia serrata*)	Takada et al. [10]
	Multiple myeloma U266 cells	ACA (*Languas galangal*)	Ichikawa et al. [149]
	Human prostate cancer Du145 cells	Anacardic acid (Cashew nuts)	Sung et al. [150]
	Human prostate cancer PC-3 cells	Betulinic Acid (Bark of white birch)	Rabi et al. [151]
	Multiple myeloma U266 cells	Coronarin D (*Hedychium coronarium*)	Kunnumakkara et al. [152]
	Burkitt's lymphoma cell lines	Curcumin (Turmeric)	Hussain et al. [14]
	SCC-4 cells	Deguelin (*Mundulea sericea*)	Nair et al. [153]
	Multiple myeloma U266 cells	Embelin (*Embelia ribes*)	Ahn et al. [154]
	Pancreatic cancer BxPC3 cells	Gossypin (*Hibiscus vitifolius*)	Kunnumakkara et al. [155]
	Multiple myeloma U266 cells	Guggulsterone (*Commiphora mukul*)	Shishodia et al. [156]
	Multiple myeloma MM.1	Indole-3-carbinol (Cabbage)	Takada et al. [157]
	Multiple myeloma MM.1	Isodeoxyelephantopin (*Elephantous scaber*)	Ichikawa et al. [158]
	Multiple myeloma U266 cells	Plumbagin (*Plumbago rosea*)	Sandur et al. [159]
	SCC-4 cells	Simvastatin (*Aspergillus terreus*)	Ahn et al. [154]
	Multiple myeloma U266 cells	Withanolide (*Withania somnifera*)	Ichikawa et al. [158]
Inhibition of p65 translocation:			
	HNSCC cells	(−)-Epicatechin (Green tea)	Kim et al. [160]
Inhibition of DNA binding of NF-κB:			
	Multiple myeloma U266 cells	Celastrol (Celastrus species)	Sethi et al. [84]

ACA 1′-acetoxychavicol acetate, *AKBA* acetyl 11-keto-b-boswellic acid, *SCC* squamous cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *CF* cystic fibrosis, *IKKK* IKK kinase