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REVIEW ARTICLE

NF-κB in cancer therapy

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Abstract The transcription factor nuclear factor kappa B (NF-κB) has attracted increasing attention in the field of cancer research from last few decades. Aberrant activation of this transcription factor is frequently encountered in a variety of solid tumors and hematological malignancies. NF-κB family members and their regulated genes have been linked to malignant transformation, tumor cell proliferation, survival, angiogenesis, invasion/metastasis, and therapeutic resistance. In this review, we highlight the diverse molecular mechanism(s) by which the NF-κB pathway is constitutively activated in different types of human cancers, and the potential role of various oncogenic genes regulated by this transcription factor in cancer development and progression. Additionally, various pharmacological approaches employed to target the deregulated NF-κB signaling pathway, and their possible therapeutic potential in cancer therapy is also discussed briefly.

Keywords Cancer · NF-κB · Apoptosis · Proliferation · Angiogenesis

Abbreviations

NF-κB	Nuclear factor kappa B
IκBα	Inhibitor of kappa B-α
IKK	IκB kinase
NIK	NF-κB-inducing kinase
TNF	Tumor necrosis factor
LPS	Lipopolysaccharide
TNFR	TNF receptor
TLR	Toll-like receptor
IL-1	Interleukin-1
TCR	T-cell receptor
TRAF	TNFR-associated factor
RIP	Receptor-interacting protein
TAK1	TGF-β-activated kinase 1
BAFF	B-cell-activating factor
HCC	Hepatocellular carcinoma
PI3K	PI3-kinase
HGF	Hepatocyte growth factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
NS5A	Non-structural 5A
IκBα-SR	IκBα super-repressor
DEN	Diethylnitrosamine
CAC	Colitis-associated colon cancer
PRR	Pattern recognition receptors

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CK2	Casein kinase 2
siRNA	Small interfering RNA
ER	Estrogen receptor
EGFR	Epidermal growth factor receptor
RANK	Receptor activator of NF-κB
IκBαM	IκBα mutant
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
DLBCL	Diffuse large B-cell lymphoma
CLL	Chronic lymphocytic leukemia
HL	Hodgkin's lymphoma
ATL	Adult T-cell leukemia
HTLV-1	Human T-cell leukemia virus type 1
EBV	Epstein–Barr virus
CML	Chronic myelogenous leukemia
ALL	Acute lymphoblastic leukemia
ABC	Activated B-cell-like
VEGF	Vascular endothelial growth factor
PGHS	Prostaglandin endoperoxide H synthases
COX	Cyclooxygenase
AP-1	Activator protein-1
PKC	Protein kinase C
Rb	Retinoblastoma
IAP	Inhibitors of apoptosis
PMA	Phorbol myristol acetate
MMP	Matrix metalloproteinase
ECM	Extracellular matrix
ELAM-1	Endothelial-leukocyte adhesion molecule-1
VCAM-1	Vascular cell adhesion molecule-1
ICAM-1	Intercellular adhesion molecule-1
EMT	Epithelial–mesenchymal transition
CXCR4	CXC-chemokine receptor 4
MEKK1	Mitogen-activated protein kinase/ERK kinase kinase
GSK-3β	Glycogen synthase kinase-3 beta
PDK1	Phosphoinositide-dependent protein kinase-1
MAP3K	Mitogen-activated protein kinase kinase kinase
TBK1	TANK-binding kinase 1
JNK	c-Jun NH_2-terminal kinase
MnSOD	Manganese superoxide dismutase
FHC	Ferritin heavy chain
ROS	Reactive oxygen species
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
STAT3	Signal transducer and activator of transcription 3
C/EBPβ	CCAAT/enhancer-binding protein beta
HIF-1α	Hypoxia-inducible transcription factor-1 alpha
NSAID	Nonsteroidal anti-inflammatory drug
UPS	Ubiquitin proteasome system
EGCG	Epigallocatechin-3-gallate
ATO	Arsenic trioxide

NF-κB signaling pathway

Nuclear factor kappa B (NF-κB) was first identified as a DNA-binding protein that specifically bound to the immunoglobulin κ light-chain enhancer, which is restricted in B cells, by David Baltimore in 1986 (Sen and Baltimore 1986). NF-κB is a Rel family transcription factor that consists of five members in mammalian cells, namely RelA (p65), RelB, Rel (c-Rel), NF-κB1 (p50/p105), and NF-κB2 (p52/p100) (Baldwin 1996). Both classical and alternate pathways can activate NF-κB signaling through an IκB kinase (IKK)-dependent manner (Tergaonkar 2006). In the canonical pathway, the activated β-subunit of IKK (IKKβ) phosphorylates the negative regulator of NF-κB [inhibitor of kappa B-α (IκBα) protein] upon the activation of the IKK complex, and thereafter leads to the ubiquitination and proteasome-mediated degradation of IκBα. This releases the p65/p50 heterodimer and allows the translocation of the NF-κB complex into the nucleus (Hayden and Ghosh 2004).

Activation of the non-canonical pathway involves the NF-κB-inducing kinase (NIK)-mediated activation of the IKKα homodimer, which then activates p100/RelB by proteasomal degradation of its inhibitory C-terminal half for processing into the p52/RelB heterodimer (Senftleben et al. 2001). Various pro-inflammatory cytokines; tumor necrosis factor (TNF); lipopolysaccharide (LPS); and other stimuli such as DNA-damaging agents and viral proteins, working through the TNF receptor (TNFR), Toll-like receptor/interleukin-1 (TLR/IL-1R), and T-cell receptor (TCR), activate the classical NF-κB pathway (Hayden and Ghosh 2004). Following the ligand receptor binding, signaling proceeds through TNFR-associated factor/receptor-interacting protein (TRAF/RIP) complexes, usually with the engagement of TGF-β-activated kinase 1 (TAK1), leading to canonical signaling (Hayden and Ghosh 2008). On the other hand, the alternative pathway is stimulated by a more restricted set of cytokines that belong to the TNF superfamily, such as B-cell-activating factor (BAFF), LTβ, and CD40 (Chen and Greene 2004). It is well established that the canonical NF-κB pathway is essential for inflammation and innate immunity, while the non-canonical pathway plays a central role in the lymphoid organ development and adaptive immunity (Bonizzi and Karin 2004). In general, NF-κB family proteins are evolutionarily conserved mediators that integrate multiple stress stimuli to regulate innate and adaptive immune responses; they act broadly to influence gene expression events that impact cell survival, differentiation, proliferation, adhesion, immunity, and inflammation (Ghosh et al. 1998; Perkins 2007; Shen and Tergaonkar 2009).

Role of NF-κB in cancer initiation and progression

Aberrant NF-κB activation has been implicated in the pathogenesis of various human diseases such as inflammatory diseases; metabolic disorders; cancers that are related to inflammation, oxidative stress, and enhanced cell proliferation; viral infection; and genetic disorders (Kumar et al. 2004; Sarkar et al. 2008; Wong and Tergaonkar 2009). The first evidence implicating the oncogenic potential of NF-κB was the identification of retroviral oncoprotein v-rel, which shares a Rel transactivation domain with the mammalian homologs (Carrasco et al. 1996; Gilmore 1999). Numerous evidences have shown that constitutive activation of NF-κB is prevalent in most major human cancers mainly due to the aberrant activation of upstream signaling molecules, or through the autocrine or paracrine activation by cytokines and growth factors, and sometimes by the genetic alteration of genes encoding NF-κB and IκB proteins (Karin et al. 2002; Van Waes 2007; Table 1). The constitutive activation of NF-κB in specific human malignancies is discussed below.

Molecular mechanism(s) of constitutive NF-κB activation in major solid tumors

Hepatocellular carcinoma (HCC)

Several studies have reported the persistent activation of NF-κB in hepatocellular carcinoma cell lines and tissue samples derived from liver cancer patients (Arsura and Cavin 2005; Qiao et al. 2006; Tai et al. 2000). Experimental mouse models have suggested that the growth factor-mediated NF-κB activation in hepatocytes involving the PI3-kinase (PI3K)/Akt axis (Cavin et al. 2005), hepatocyte growth factor (HGF)/Met signaling (Muller et al. 2002), and TAK1/IKK pathway (Arsura et al. 2003) promotes liver tumor development and progression. Viral proteins of oncovirus have been identified to activate the NF-κB signaling pathway (Block et al. 2003), including hepatitis B virus (HBV) X protein (Diao et al. 2001), as well as hepatitis C virus (HCV) non-structural 5A (NS5A) (Waris et al. 2003), and core proteins (Sato et al. 2006; Shrivastava et al. 1998), which are implicated in hepatocellular transformation (Bouchard and Schneider 2004; McGivern and Lemon 2011). Tight connections between inflammation and cancer have long been established, and tumor-promoting inflammation has been described as one of the hallmarks of cancer by Hanahan and Weinberg (Hanahan and Weinberg 2011; Sethi et al. 2012). As a key player in inflammation and cancer, it is no surprise that NF-κB has been identified to be linked to inflammation-associated liver cancer in an *Mdr2*-knockout mouse model, from which the animal spontaneously develops cholestatic hepatitis-induced HCC (Pikarsky et al. 2004). The study demonstrated that IκBα super-repressor (IκBα-SR) or anti-TNFα antibodies inhibited the TNFα-induced NF-κB activation in $Mdr2^{-/-}$ mice, resulted in apoptosis of transformed hepatocytes, and retarded progression to malignancy (Pikarsky et al. 2004). It is correlated with the observation of enhanced carcinogen-mediated hepatocyte death in mice with hepatocyte-specific deletion of IKKβ (Maeda et al. 2005); surprisingly, *IKKβ*-knockout mice presented a significant increase in diethylnitrosamine (DEN)-induced hepatocarcinogenesis owing to the increased compensatory proliferation of surviving hepatocytes. Additional ablation of IKKβ in adjacent myeloid cells (Kupffer cells) markedly reduced hepatocarcinogenesis, which was attributed to the suppression of NF-κB-dependent production of potent hepatomitogens (TNFα, IL-6, and HGF) that stimulate proliferation of hepatocytes (Maeda et al. 2005).

Colorectal cancer

Further evidence linking NF-κB with inflammation-associated tumor development comes from a mouse model of colitis-associated colon cancer (CAC) (Greten et al. 2004). Specific deletion of IKKβ in intestinal epithelial cells (enterocytes) or myeloid cells led to reduction in tumor formation, or a decrease in both tumor incidence and tumor size, respectively, indicating that enterocytes' IKKβ contributes to early tumor promotion by inhibiting apoptosis, while it promotes tumor growth by inducing the expression of pro-inflammatory cytokines in myeloid cells (Greten et al. 2004). The study not only revealed the importance of the IKK/NF-κB pathway in the tumor microenvironment for tumorigenesis, but also highlighted its cell type-dependent functions. In fact, in addition to colon cancer cell lines and colorectal carcinoma tissue samples (Kojima et al. 2004; Lind et al. 2001; Yu et al. 2003), NF-κB has been found to be highly expressed and active in the stroma of human colonic adenomatous polyps (Hardwick et al. 2001). Various factors such as pattern recognition receptors (PRRs) (Karin 2006), tumor-promoting cytokines (Terzic et al. 2010), or casein kinase 2 (CK2) (Farah et al. 2003) have been implicated in the constitutive activation of NF-κB in colorectal cancer; however, the molecular mechanisms underlying this response require further investigation. It has been demonstrated, using a mouse colon cancer metastasis model, that inhibition of NF-κB by IκBα-SR could convert LPS-induced tumor growth to tumor regression (Luo et al. 2004). In addition, knockdown of the NF-κB p65 subunit by small interfering RNA (siRNA) has been shown to enhance in vitro and in vivo sensitivity of colon carcinoma to the chemotherapeutic agent CPT-11 (irinotecan) (Guo et al. 2004).

Table 1 Key molecular mechanism(s) of constitutive NF-κB activation in major human cancers

Mechanism(s)	Cancer type(s)	References
Aberrant signaling pathways		
Tumor-promoting cytokines/growth factors	Colorectal cancer	Terzicet al. (2010)
	HNSCC	Wang et al. (2009)
	Multiple myeloma	Anderson and Carrasco (2011), Hideshima et al. (2004)
HER2 (ErbB-2) overexpression	Breast cancer	Biswas et al. (2004), Pianetti et al. (2001), Singh et al. (2007)
	Prostate cancer	Le Page et al. (2005)
EGFR overexpression	Prostate cancer	Le Page et al. (2005)
	Non-small-cell lung cancer	Sethi et al. (2007)
	HNSCC	Bancroft et al. (2002), Wang et al. (2009)
Bcr-Abl expression	Leukemias (CML, ALL)	Kirchner et al. (2003), Reuther et al. (1998)
PI3K/Akt axis	HCC	Cavin et al. (2005)
	Breast cancer	Pianetti et al. (2001)
	Prostate cancer	Dan et al. (2008), Shukla et al. (2005)
	Pancreatic cancer	Asano et al. (2004)
	HNSCC	Bancroft et al. (2002)
Protein kinase CK2	Colorectal cancer	Farah et al. (2003)
	HNSCC	Yu et al. (2006)
	Breast cancer	Romieu-Mourez et al. (2001)
Overexpression of viral proteins		
HBV X protein	HCC	Diao et al. (2001)
HCV NS5A protein	HCC	Waris et al. (2003)
HCV core protein	HCC	Sato et al. (2006), Shrivastava et al. (1998)
HTLV-1 Tax protein	Adult T-cell leukemia	Matsuoka and Jeang (2007), Yamaoka et al. (1996)
EBV LMP1 protein	Hodgkin's lymphoma	Young and Rickinson (2004)
Genetic alterations		
c-*Rel* gene amplification	Lymphomas (Hodgkin's lymphoma, DLBCL, follicular lymphoma)	Courtois and Gilmore (2006), Rayet and Gelinas (1999)
c-*Rel* gene alterations (chromosomal rearrangements)	Lymphomas (DLBCL, follicular lymphoma, Hodgkin's lymphoma)	Courtois and Gilmore (2006), Rayet and Gelinas (1999)
NFκB1 gene amplification	Multiple myeloma	Annunziata et al. (2007), Demchenko et al. (2010), Keats et al. (2007)
NFκB1 gene alterations (chromosomal rearrangements)	Acute lymphoblastic leukemia	Rayet and Gelinas (1999)
NFκB2 gene alterations (mutations, chromosomal rearrangements)	B- and T-cell leukemias/lymphomas	Courtois and Gilmore (2006), Karin et al. (2002), Rayet and Gelinas (1999)
	Multiple myeloma	Annunziata et al. (2007), Demchenko et al. (2010), Keats et al. (2007)
IκB gene mutations	Hodgkin's lymphoma	Courtois and Gilmore (2006)
Bcl-3 gene alterations (chromosomal rearrangements)	B-cell lymphocytic leukemia	Courtois and Gilmore (2006), Rayet and Gelinas (1999)

Breast cancer

Several studies have documented the aberrant nuclear expression of different NF-κB family members (c-Rel, p50, and RelA) and constitutive NF-κB DNA-binding activity in many human breast tumor cell lines, human breast cancer specimens, and the majority of carcinogen-induced primary rat mammary tumors (Cogswell et al. 2000; Nakshatri et al. 1997; Sovak et al. 1997). In the transgenic mouse model, 31.6 % of mice that overexpressed c-Rel in the mammary gland developed mammary tumors, in which significant increases in the expression of the cancer-related NF-κB target genes were observed (Romieu-Mourez et al. 2003). These findings reveal the important involvement of constitutive NF-κB activation in the early development of breast cancer. It is suggested that the activation of RelA

is associated more with distinct subtypes, as the classic form of NF-κB (RelA/p50 heterodimer) has been detected predominantly in HER2-overexpressing estrogen receptor (ER)-negative breast tumors, which were responsive to treatment with specific NF-κB inhibitors (Biswas et al. 2004; Singh et al. 2007). Another study has shown that an accumulation of nuclear c-Rel, p50, and p52, rather than p65, is differentially activated in breast tumors regardless of ER status (Cogswell et al. 2000). One mechanism, which underlies the elevated activation of NF-κB in breast cancer cells, has been proposed to be regulated by oncogenic signaling. For example, HER2/neu overexpression induces NF-κB through calpain-mediated IκBα degradation by activating the PI3K/Akt pathway (Pianetti et al. 2001; Zhou et al. 2000). Aberrant activation of protein kinase CK2 in breast cancer has also been found to promote the degradation of IκBα by phosphorylating this NF-κB inhibitor, resulting in increased nuclear translocation of NF-κB (Landesman-Bollag et al. 2001; Romieu-Mourez et al. 2001). The essential requirement of IKKα and NF-κB in mammary gland development provides the hint for the importance of increased NF-κB activation in breast cancers (Cao et al. 2001). Evidence has shown that the deletion of IKKα delayed the onset of progesterone-driven mammary cancer with decreased NF-κB activation (Schramek et al. 2010). Besides the substantial role of IKKα in breast carcinogenesis, it has also been found to be important for the self-renewal of HER2-transformed mammary tumor-initiating cells, as well as the metastatic spread of breast cancer (Cao et al. 2007; Tan et al. 2011).

Prostate cancer

NF-κB levels have been found to be constitutively activated in hormone-independent human prostate cell lines that do no response to anti-androgen therapy (Palayoor et al. 1999), while androgen could produce sustained elevation of NF-κB activity in androgen-responsive prostate cancer cells (Ripple et al. 1999). Many studies have also provided evidence of overexpression and activation of NF-κB in human prostate tumors, which correlates with disease progression (Ross et al. 2004; Shukla et al. 2004). Deregulated NF-κB signaling has been implicated in mediating cellular transformation, prostate cancer growth, lymph node metastases, and disease outcome (Fradet et al. 2004; Ismail et al. 2004; Kim et al. 2002; Zhang et al. 2009). The most well-characterized mechanism underlying the constitutive NF-κB activation in prostate cancer has been attributed to Akt activation, which interacts with and stimulates IKK (Dan et al. 2008; Shukla et al. 2005), but other tyrosine kinases such as epidermal growth factor receptor (EGFR), HER2, and NIK are also suggested to be involved in the activation of the pathway (Le Page et al. 2005; Suh et al. 2002). Silencing of IKKα has been found to delay the progression of castration-resistant prostate cancer, whereas IKKβ ablation presents no effect on the development of the tumor (Ammirante et al. 2010). The involvement of IKK in cancer metastasis has been established in the model of prostate cancer, in which IKKα activation mediated through the induction of receptor activator of NF-κB (RANK) promotes metastatic progression by inhibiting the metastasis suppressor Maspin (Luo et al. 2007). Inhibition of NF-κB by the signal-unresponsive IκBα mutant (IκBαM) or peptide antagonist of NF-κB nuclear translocation led to the suppression of prostate cancer cell proliferation, induction of apoptosis, or sensitization to TNFα treatment (Asano et al. 2004; Gasparian et al. 2002; Herrmann et al. 1997). Most importantly, blockade of NF-κB activity decreased angiogenesis, invasion, and metastasis of xeno-transplanted human prostate tumors in nude mice (Huang et al. 2001).

Head and neck squamous cell carcinoma (HNSCC)

Many studies have previously documented the prevalence of constitutively activated NF-κB in diverse HNSCC cell lines and tumor tissue specimens (Bancroft et al. 2001; Mishra et al. 2006; Nakayama et al. 2001; Ondrey et al. 1999). The deregulated NF-κB signaling modulates the expression of programs of functional genes that contributes to different stages of HNSCC development and progression (Allen et al. 2007; Bancroft et al. 2001; Loercher et al. 2004; Molinolo et al. 2009; Ondrey et al. 1999). Global gene profiling analysis has also clearly indicated that NF-κB signaling is a major contributor to metastatic progression of HNSCC (Dong et al. 2001) and a prognostic biomarker of a high-risk disease (Chung et al. 2006). An elevated phosphorylation level of NF-κB in patient samples is associated with poor prognosis in terms of high recurrence and poor survival (Zhang et al. 2005). Autocrine or paracrine secretion of various cytokines or growth factors has been linked to NF-κB activation in HNSCC (Van Waes 2007; Wang et al. 2009). For example, interleukin-1 alpha (IL-1α) has been shown to be overexpressed autonomously by HNSCC and contributes to the activation of NF-κB, thereby promoting cell survival and growth (Wolf et al. 2001).

Major risk factors for head and neck cancer, such as cigarette smoking or human papillomavirus (HPV) infection, have been implicated in NF-κB activation. Cigarette smoke condensate is capable of activating NF-κB via phosphorylation and degradation of IκBα that is mediated through induction of IKK in HNSCC cell lines (Anto et al. 2002). Also, a positive correlation between the nuclear localization of NF-κB and HPV16-encoded E7 protein level has been reported in laryngeal cancer (Du et al. 2003). In HNSCC, several upstream signaling pathways have been

indicated to mediate the constitutive activation of NF-κB, namely PI3K/Akt cascade (Bancroft et al. 2002), CK2 (Yu et al. 2006), and the TNF–TNFR1–TRADD–TRAF2–RIP–TAK1–IKK pathway (Jackson-Bernitsas et al. 2007). Different experimental approaches have been designed to block the deregulated NF-κB activation, such as dominant negative IκBαM (Duffey et al. 1999), IKKα, and IKKβ kinase dead mutants (Yu et al. 2006), or pharmacological inhibitors (Bancroft et al. 2002). The inhibition of NF-κB activation in HNSCC significantly suppresses the expression of NF-κB-modulated genes, such as pro-inflammatory cytokines (IL-6, IL-8, and YAP1), and results in the induction of cell death and tumor growth inhibition (Allen et al. 2007; Wang et al. 2009).

Constitutive NF-κB activation in hematological malignancies

Leukemias and lymphomas

Various genetic abnormalities of the NF-κB pathway have been found in human leukemia and lymphoid malignancies. Amplifications of c-*Rel* are frequently seen in Hodgkin's lymphomas and diffuse large B-cell lymphomas (DLBCLs), while fewer cases of *c-Rel* gene rearrangements are found in certain types of B-cell lymphomas (Courtois and Gilmore 2006; Rayet and Gelinas 1999). In contrast to *c-Rel*, amplifications or chromosomal rearrangements of *RelA and RelB* have not been consistently reported in human leukemias and lymphomas (Gilmore et al. 2004). In addition, constitutive activation of NF-κB by *NFκB2* gene alterations, but not the *NFKB1* gene, and inactivating mutations of the *IκB* gene have been associated with several B- and T-cell lymphomas and chronic lymphocytic leukemia (CLL), as well as Hodgkin's lymphoma (HL) (Courtois and Gilmore 2006; Karin et al. 2002). Aberrant activation of receptors and key upstream mediators also leads to the persistent NF-κB signaling observed in leukemias and lymphomas (Jost and Ruland 2007). NF-κB activation has been found to be associated with virus-induced leukemias and lymphomas. A study of adult T-cell leukemia (ATL) led to the discovery of the first human retrovirus, human T-cell leukemia virus type 1 (HTLV-1), which was then identified as causal agent of ATL (Matsuoka and Jeang 2007). The HTLV-1 Tax oncoprotein stably associates with IKKγ to form Tax/IKK complexes that persistently activate NF-κB through both canonical and non-canonical pathways (Matsuoka and Jeang 2007). Constitutive activation of NF-κB has been found to be essential for Tax-mediated transformation (Yamaoka et al. 1996).

Infection with Epstein–Barr virus (EBV) is associated with a high risk of Hodgkin's lymphoma, Burkitt's lymphoma, and B-cell lymphomas (Young and Rickinson 2004). The EBV-encoded membrane protein LMP1 acts as the member of the TNFR superfamily and constitutively activates the NF-κB pathway in a ligand-independent manner (Young and Rickinson 2004). Another oncogenic protein, Bcr-Abl, which is strongly associated with chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL), is also capable of activating NF-κB (Reuther et al. 1998). The resulting nuclear translocation of NF-κB and enhanced transactivation function has been found to be dependent on the tyrosine kinase activity of Abl (Kirchner et al. 2003; Reuther et al. 1998). Moreover, *Bcr-Abl*-induced transformation of primary bone marrow cells and tumor growth can be blocked by IκBα-SR-mediated NF-κB inhibition (Reuther et al. 1998). Aberrant NF-κB activation has been demonstrated to be required for the proliferation and survival of Hodgkin's disease tumor cells and activated B-cell-like (ABC) DLBCL, and contributes to the poor clinical outcome (Bargou et al. 1997; Davis et al. 2001; Jost and Ruland 2007). Introducing IκBα-SR by retroviral transduction caused reduction in cell proliferation rate, blocked cell-cycle progression, and induced apoptosis in HL and ABC DLBCL cells (Bargou et al. 1997; Davis et al. 2001). It was shown in the same study that HL cells depleted of constitutive nuclear NF-κB revealed strongly impaired tumor growth after being xenografted into SCID mice (Bargou et al. 1997).

Multiple myeloma

Diverse genetic or epigenetic alterations that trigger both the canonical and non-canonical NF-κB pathways have been described in multiple myeloma cell lines and patient samples (Annunziata et al. 2007; , Keats et al. (2007) et al. 2007; Demchenko et al. 2010). The alterations include overexpression or activating mutations of positive regulators of NF-κB signaling such as *TACI, CD40, LTβR, NIK, NFKB1,* and *NFKB2* and inactivating abnormalities of negative regulators such as *BIRC2*/*BIRC3, cIAP1*/*cIAP2, CYLD, TRAF2*, and *TRAF3* (Annunziata et al. 2007; Keats et al. 2007; Demchenko et al. 2010). Constitutive activation of the NF-κB signaling pathway stimulates cell growth, promotes cell survival, inhibits programmed cell death, and induces drug resistance in myeloma cells (Hideshima et al. 2002, 2004; Richardson et al. 2003). Moreover, production of various cytokines and growth factors such as interleukin-6 (IL-6), TNFα, and vascular endothelial growth factor (VEGF) by the NF-κB pathway facilitates the development of autocrine or paracrine signaling loops involving the interaction of myeloma cells and bone marrow stromal cells, resulting in further progression of the disease (Anderson and Carrasco 2011; Hideshima et al. 2004).

Role of major NF-κB-regulated genes in cancer development

Activated NF-κB binds to specific DNA sequences in target genes, designated as κB elements, and regulates transcription of over five hundred genes (Li and Sethi 2010). A number of important NF-κB-regulated genes involved in tumor cell proliferation, survival, angiogenesis, invasion/metastasis, and therapeutic resistance are listed below, and their roles are discussed.

Cyclooxygenase-2 (COX-2)

Aberrant arachidonic acid metabolism is involved in inflammation and carcinogenesis, owing to the tumor-promoting activities of the metabolic products prostaglandins (PGs) and leukotrienes (Wang and DuBois 2006). Pharmacological intervention in the biosynthesis of these metabolites by inhibiting the relevant enzymes has been considered an effective approach for cancer chemoprevention and treatment (Zha et al. 2004). The PG endoperoxide H synthases (PGHS), also known as cyclooxygenases (COX), catalyze the rate-limiting step in PG synthesis (Smith et al. 2000). There are two isoforms of the enzyme, namely COX-1 and COX-2. COX-1 universally exists in most mammalian tissues, while COX-2 is expressed rapidly in response to pro-inflammatory mediators and mitogenic stimuli (Surh et al. 2001). The expression of COX-2 but not COX-1 has been always observed to be upregulated in a wide variety of human cancers (Fosslien 2000; Surh et al. 2001; Zha et al. 2004). The promoter region of the *COX-2* gene contains putative binding sites for NF-κB, which acts as a transcription factor to regulate the induction of COX-2 (Yamamoto et al. 1995).

Activation of NF-κB is required for COX-2 production, as evidenced by the observations of impaired COX-2 expression after specific inhibition of NF-κB (Smith et al. 2000). Moreover, evidence indicates that COX-2 expression is able to promote the activity NF-κB, indicating a positive feedback control mechanism (Poligone and Baldwin 2001). COX-2 can be activated by various chemotherapeutic agents and radiation, and thus contributes to therapeutic resistance (Li and Sethi 2010). Widely used therapeutic microtubule-interfering agents such as taxol, colchicines, and vinblastine have been found to induce activator protein-1 (AP-1) to mediate *COX-2* expression via the cyclic AMP response element site in the *COX-2* promoter (Subbaramaiah et al. 2000). Taxanes including paclitaxel and docetaxel are able to stabilize COX-2 mRNA through protein kinase C (PKC) and p38 MAPK signaling (Subbaramaiah et al. 2003). Also, levels of COX-2 expression have been reported to be correlated inversely with increased tumor radiation sensitivity in oral squamous cell carcinoma (Terakado et al. 2004). It has been reported that specific COX-2 inhibition by celecoxib synergistically enhances the anti-tumor activity of chemotherapeutic drugs such as CPT-11 (Trifan et al. 2002), COL-3, and docetaxel (Dandekar et al. 2005). In addition to the chemosentization effect, celecoxib augmented the response of A431 human tumor xenografts in nude mice to radiation (Nakata et al. 2004). Another COX-2 inhibitor, SC-236, has been shown to potentiate the effects of radiation therapy in different cancer models including sarcoma (Kishi et al. 2000) and glioma (Petersen et al. 2000). COX-2 has been also found to promote colon carcinoma-induced angiogenesis by producing important angiogenic factors (Tsujii et al. 1998). Jung and his colleagues confirmed, using human lung cancer cells, that the induction of VEGF through COX-2 upregulation is NF-κB-dependent (Jung et al. 2003). Furthermore, COX-2-mediated endothelial cell migration and tube formation could be inhibited by the selective COX-2 inhibitor NS-398 and the non-selective inhibitor aspirin (Tsujii et al. 1998).

Cyclin D1

Cyclin Dl, which is encoded by the CCNDl gene, controls the transition from G1 to S phase in the cell cycle (Sherr 1996). Overexpression of cyclin D1 and amplification or translocation of 11q13 (where *CCND1* locates) are found frequently in many human cancers (Donnellan and Chetty 1998; Hunter and Pines 1994; Sherr 1996). NF-κB promotes cell proliferation through transcriptional activation of cyclin D1 by binding to the cyclin D1 promoter (Guttridge et al. 1999; Hinz et al. 1999). The inhibition of NF-κB reduces the cyclin D1 activity, which is associated with delayed phosphorylation of the retinoblastoma (Rb) protein, resulting in impaired cell-cycle progression that can be rescued by ectopic expression of cyclin D1 (Guttridge et al. 1999; Hinz et al. 1999). IKKα has been found to be required for NF-κB-induced cyclin D1 expression, which is proposed as a key element in mammary gland development and mammary carcinogenesis (Cao et al. 2001, 2007). Consistently, transcriptional activation of cyclin D1 by IKKα has been reported in other cell types, but mediated by distinct factors such as β-catenin (Albanese et al. 2003) and ER α (Park et al. 2005). In human breast epithelial cells, IκB homology Bcl-3 in association with p52 homodimers has been demonstrated to stimulate the transcription of the cyclin D1 gene via directly interacting with the NF-κB binding site in the cyclin D1 promoter (Westerheide et al. 2001). This finding is in accordance with the observations of increased nuclear accumulation of p50, p52, and Bcl-3 with elevated expression of cyclin D1 in tumorigenic breast tissues (Cogswell et al. 2000). Inhibition of cyclin D1 expression by using a cyclin D1 antisense

construct in a variety of cancers not only resulted in attenuated cancer cell proliferation and loss of tumorigenicity, but also led to an increased growth-inhibitory effect of chemotherapeutic agents. These findings suggest that cyclin D1 may exert a protective effect against drug-induced cytotoxicity and further implies a requirement for cyclin D1 in the maintenance of chemoresistance in these cells (Arber et al. 1997; Kornmann et al. 1998, 1999; Nakashima and Clayman 2000; Schrump et al. 1996; Zhou et al. 1995).

Anti-apoptotic genes

The Bcl-2 family of proto-oncogenes is a critical negative regulator of apoptosis and is frequently dysregulated in wide variety of cancers. The promoter of human Bfl-1/A1, Bcl-xL, and Bcl-2 has been identified to present an NF-κB binding site, which is responsible for its c-Rel/RelA-, c-Rel-, or p50/p65-dependent induction, respectively (Catz and Johnson 2001; Chen et al. 2000; Zong et al. 1999). In IκBα-SR-expressing cells, overexpression of either Bfl-1/A1 or Bcl-xL has been found to confer resistance to apoptosis induced by TNFα (Chen et al. 2000; Karin and Lin 2002; Zong et al. 1999). Furthermore, NF-κB-induced expression of Bfl-1/A1 potently suppressed chemotherapy-induced apoptosis by inhibiting the release of cytochrome *c* and by blocking caspase-3 activation (Wang et al. 1999). Indeed, most chemotherapeutic drugs and ionizing radiation that activate NF-κB can also activate Bcl-2 family proteins in various cancer cell lines (Li and Sethi 2010). We have previously summarized several studies demonstrating the downregulation of different Bcl-2 family members by antisense oligonucleotides, small-molecule inhibitors, or siRNAs leading to enhanced chemo- or radiosensitization of multiple human cancers (Li and Sethi 2010).

Another important group of survival proteins regulated by NF-κB is the inhibitors of apoptosis (IAPs), which directly bind and inhibit caspase activity (Deveraux and Reed 1999; Tamm et al. 1998). Expression of IAPs is induced in response to several NF-κB-activating stimuli, including TNFα, phorbol myristol acetate (PMA), LPS, and IL-1β, and the induction was blocked by IκBα-SR, suggesting the involvement of IAPs in the anti-apoptotic activity of NF-κB (Chu et al. 1997; Stehlik et al. 1998; Wang et al. 1998). Moreover, cIAP1, cIAP2, and XIAP can further enhance cell survival by their ability to promote NF-κB activation in a positive feedback loop (Chu et al. 1997; Gyrd-Hansen and Meier 2010; Hofer-Warbinek et al. 2000). Survivin, a key regulator of mitosis and programmed cell death, has provided strong evidence for IAP involvement in cancer. RelB and p50 are bound to the NF-κB binding site in the *survivin* promoter between −354 and −345 (Kawakami et al. 2005). Survivin has been found to be selectively expressed in transformed cells and in most human cancers (LaCasse et al. 1998; Mita et al. 2008). The level of survivin correlates with a decreased tumor cell apoptotic index in gastric cancer (Lu et al. 1998) as well as colorectal cancer (Kawasaki et al. 1998); more importantly, patients with a low apoptotic index or with survivin-negative tumors had shortened 5-year disease survival than the group with high apoptosis or those with survivin-positive tumors (Kawasaki et al. 1998; Sarela et al. 2000). Cancer patients with lymph node invasion, metastases, and recurrent disease displayed significantly higher expression of survivin (Mita et al. 2008). Finally, overexpression of survivin can be useful as a predictive factor to determine response to chemotherapy in patients with bladder cancer, breast cancer multiple myeloma, lymphoma, and ovarian carcinoma (Li and Sethi 2010). Consistent with the findings for survivin, alterations in other IAP members found in many types of human cancer are also associated with chemoresistance, disease progression, and poor prognosis (Gyrd-Hansen and Meier 2010; Hunter et al. 2007; LaCasse et al. 2008). Strategies such as antisense oligonucleotides, siRNA, and small-molecule antagonists have been developed to block IAPs, and have resulted in induction of apoptosis, inhibition of tumor growth, and increased sensitivity to chemo- or radiotherapy in a broad spectrum of human cancer models (Gyrd-Hansen and Meier 2010; Hunter et al. 2007; LaCasse et al. 2008).

Angiogenic factors

Tumor-associated neovasculature, generated by angiogenesis, develops during tumorigenesis to facilitate the tumor acquiring nutrients and oxygen and disposing of metabolic wastes (Hanahan and Weinberg 2011). This process is initiated by an "angiogenic switch" in which the balance between pro-angiogenic and anti-angiogenic factors is tipped toward angiogenesis (Carmeliet and Jain 2000). The deregulated NF-κB signaling also contributes to angiogenesis through modulation of major pro-angiogenic factors such as VEGF and pro-inflammatory cytokines (e.g., IL-8) (Aggarwal 2004; Karin 2006). In highly malignant human prostate cancer cells PC-3M, expression of VEGF and IL-8 is upregulated and correlates with the constitutive NF-κB/relA activity (Huang et al. 2001). Furthermore, bombesin-stimulated expression and secretion of VEGF and IL-8 has been found to be dependent on NF-κB activation (Levine et al. 2003). Administration of a NF-κB antisense oligonucleotide abrogated the TNFα-induced IL-8 and VEGF production, along with inhibition of tubular morphogenesis in vascular endothelial cells (Yoshida et al. 1997). In human melanoma, ovarian, and prostate cancer models, blockade of NF-κB signaling by IκBαM suppressed the in vitro and in vivo expression of VEGF and IL-8, which directly correlated with the reduced neovascularization as well as decreased tumorigenicity (Huang et al. 2000a, b; 2001).

Regulators of invasion/metastasis

The transcription targets of NF-κB also include variety of molecules involved in tumor invasion, migration, and metastasis. NF-κB binding sites were identified in the promoters of genes that encode several matrix metalloproteinases (MMPs) that degrade the extracellular matrix (ECM) to facilitate tumor cell invasion in tissues (Karin et al. 2002). NF-κB activation is also required for the transcription of a group of adhesion molecules [endothelial-leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1)] (Collins et al. 1995), which facilitate the extravasation of cancer cells (Kobayashi et al. 2007). Interestingly, VEGF is capable of stimulating the expression of ICAM-1, VCAM-1, and E-selectin, which is mediated through NF-κB activation (Kim et al. 2001). Together with other regulators, MMPs and adhesion molecules cooperate in the induction of epithelial–mesenchymal transition (EMT) for the progression of cancer metastasis (Lopez-Novoa and Nieto 2009). A breast cancer model has exemplified the essential role of NF-κB signaling in the induction and maintenance of EMT, and showed that the reversal of EMT could be achieved by inhibition of NF-κB activity (Huber et al. 2004). Moreover, NF-κB has been implicated in the migration and organ-specific homing of metastatic cancer cells, as demonstrated by Helbig and his co-workers, who showed that NF-κB regulated the motility of breast cancer cells, and promoted tumor migration and metastasis by directly upregulating the expression of CXC-chemokine receptor 4 (CXCR4) (Helbig et al. 2003). Overall, the above studies indicate that it is important to suppress NF-κB activation in order to reduce cancer metastasis.

Potential cross talk between NF-κB and other signal transduction cascades

The full transcriptional activation of NF-κB may involve cross talk with other signal pathways such as EGFR, PI3K/Akt and signal transducer, and activator of transcription 3 (STAT3), and blocking the activity of these signaling pathways can also provide an alternative strategy to regulate NF-κB activity in cancer therapy (Li and Sethi 2010; Fig. 1). The EGFR family acts as a central signal transducer of multiple important signaling pathways that contribute to tumor growth, survival, angiogenesis, invasion, and metastasis (Normanno et al. 2006; Yarden 2001). In many tumors, overexpression of EGFR family members (EGFR or ErbB-2) or their ligand overexpression activates NF-κB, stimulating various intracellular signaling cascades. For example, our group has reported that overexpression of EGFR led to constitutive activation of NF-κB through EGF receptor-kinase-dependent tyrosine 42 phosphorylation of IκBα (Sethi et al. 2007). While Pianetti et al. (2001) found that HER2/neu overexpression also activates NF-κB in an IKK-independent manner, but via the PI3K/Akt pathway in breast cancer.

The kinetics and spectrum of NF-κB activation differs widely in response to various stimuli that require different intermediates to transmit the signal. Several kinases, such as Akt, mitogen-activated protein kinase/ERK kinase kinase (MEKK1), PKC, glycogen synthase kinase-3 beta (GSK-3β), phosphoinositide-dependent protein kinase-1 (PDK1), and TAK1, have been reported to function upstream of NF-κB signaling (Vallabhapurapu and Karin 2009; Viatour et al. 2005). Apart from the canonical and non-canonical NF-κB signaling, PI3K/Akt has been identified as an important mediator to activate NF-κB. Different modes of functional interaction between PI3K/Akt and NF-κB have been discovered in tumors. The most common mechanism has been attributed to direct phosphorylation of IKKα by Akt, thereby leading to the activation of the kinase upstream of NF-κB (Ozes et al. 1999; Romashkova and Makarov 1999). Akt can also indirectly stimulate IKK activity through its downstream effector mammalian target of rapamycin (mTOR) (Dan et al. 2008) or mitogen-activated protein kinase kinase kinase (MAP3K) Cot (Kane et al. 2002). Finally, Akt targets and phosphorylates RelA through a p38- or IKK-dependent mechanism to stimulate NF-κB-dependent transcription by stimulating the transactivation domain of the p65 subunit, rather than inducing NF-κB nuclear translocation via IκBα degradation (Madrid et al. 2000, 2001).

It is possible that oncoproteins that are known to be activated in cancer cells, such as H-Ras, trigger signaling cascades that lead to constitutive NF-κB activation, which is required for efficient Ras-induced cellular transformation (Arsura et al. 2000; Finco et al. 1997; Hanson et al. 2004; Mayo et al. 1997) as well as EMT in Ras-transformed epithelial cells (Huber et al. 2004). The NF-κB activation induced by Ras engages several downstream effector pathways, such as PI3K/Akt signaling or Raf coupling with MEKK1, all of which lead to the activation of the IKK complex (Arsura et al. 2000; Chang et al. 2003; Madrid et al. 2000, 2001). In addition, the IKK-related kinase TANK-binding kinase 1 (TBK1), functioning downstream of Ras, has been shown to trigger the classical NF-κB pathway activation, as judged by the accumulation of nuclear NF-κB (Baldwin 2012; Staudt 2010). Furthermore, Ras is able to stimulate the transcriptional activation function of NF-κB via the targeting of the RelA/p65 subunit, instead of inducing the nuclear translocation of NF-κB (Finco et al. 1997).

In various tumors, the pro-apoptotic c-Jun NH_2-terminal kinase (JNK) signaling and NF-κB appear to have opposing

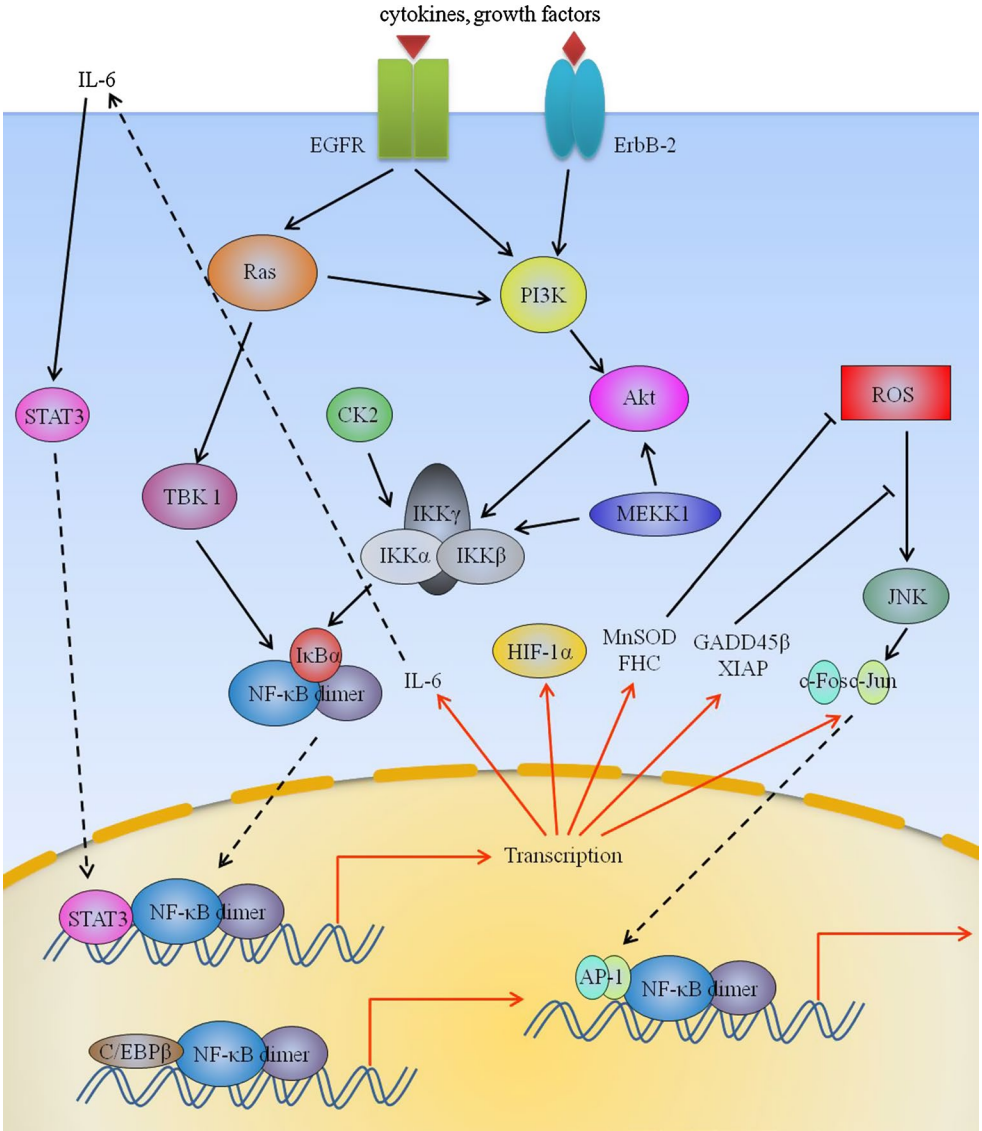

Fig. 1 Schematic diagram of cross talk between NF-κB and other signaling pathways. NF-κB interacts directly or indirectly with multiple signaling pathways or transcription factors in cancer. Abbreviations: *IL-6* interleukin-6, *STAT3* signal transducer and activator of transcription 3, *EGFR* epidermal growth factor receptor, *PI3K* PI3-kinase, *CK2* casein kinase 2, *TBK1* TANK-binding kinase 1, *MEKK1* mitogen-activated protein kinase/ERK kinase kinase, *IκBα* inhibitor of kappa B-α, *IKK* IκB kinase, *NF-κB* nuclear factor kappa B, *C/EBPβ* CCAAT/enhancer-binding protein beta, *HIF-1α* hypoxia-inducible transcription factor-1 alpha, *MnSOD* manganese superoxide dismutase, *FHC* ferritin heavy chain, *XIAP* X-linked inhibitor of apoptosis protein, *ROS* reactive oxygen species, *JNK* c-Jun NH_2-terminal kinase, *AP-1* activator protein-1

biological effects. The activation of JNK results in diverse outcomes of cellular response ranging from the induction of apoptosis to increased survival and altered proliferation, which has been implicated in different stages of cancer development (Herr and Debatin 2001; Wagner and Nebreda 2009). NF-κB activation in response to TNFR1 engagement promotes termination of JNK activation through a mechanism that depends on the induction of antioxidant enzymes such as manganese superoxide dismutase (MnSOD) and ferritin heavy chain (FHC), as reactive oxygen species (ROS) help to sustain JNK activity (Kamata et al. 2005; Pham et al. 2004). In addition, interference with JNK activity can be achieved through NF-κB-dependent upregulation of genes encoding inhibitors of JNK signaling such as *GADD45β*, *XIAP*, and *A20* (De Smaele et al. 2001; Papa et al. 2004; Tang et al. 2001). In many cell types, suppression of JNK-induced apoptosis can contribute to the tumor-promoting activities of NF-κB (Nakano et al. 2006; Papa et al. 2006). Moreover, NF-κB inhibition has been reported to sensitize cells to TNFα-induced or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through the sustained activation of JNK (Liu et al. 2002; Nakshatri et al. 2004).

As STAT3 supports tumor cell survival and proliferation, and plays important roles in tumor inflammation and immunity, it is not surprising that the activities of STAT3 and NF-κB are closely intertwined. Several NF-κB family members, in particular RelA/p65 and p50, have been found to physically interact with STAT3, resulting in either specific transcriptional synergy or repression of target genes, depending on the cellular context (Grivennikov and Karin 2010). One interesting study showed that STAT3 could prolong NF-κB nuclear retention through acetyltransferase p300-mediated RelA acetylation, thereby interfering with

NF-κB nuclear export (Lee et al. 2009). Furthermore, the constitutive activation of NF-κB leads to the production and secretion of cytokines such as IL-6 in an autocrine/paracrine manner, which causes the consequent activation of STAT3 signaling in various human cancers (Grivennikov and Karin 2010; Hodge et al. 2005; Yu et al. 2009). Importantly, STAT3 and NF-κB control both distinct and overlapping groups of genes involved in cell proliferation, survival, angiogenesis, and invasion (Bollrath and Greten 2009; Grivennikov and Karin 2010).

NF-κB is also able to function in concert with other transcription factors, such as CCAAT/enhancer-binding protein beta (C/EBPβ), AP-1, and specificity protein 1 (Sp1) (Perkins 1997, 2007). NF-κB and C/EBPβ either form a complex by direct interaction or cooperatively bind to the same promoter site to transactivate several genes including *serum amyloid A2*, *IL-6*, and *IL-8* (Stein and Baldwin 1993; Xia et al. 1997). Similarly, the Rel homology domain of p65 is capable of physically interacting with bZIP regions of the AP-1 subunits c-Fos and c-Jun, to mutually stimulate DNA binding and transactivation via both κB and AP-1 response elements in a synergistic manner (Stein et al. 1993). Cellular stress or cytokine stimulation leads to the activation of parallel kinase cascades regulating NF-κB and AP-1, and coordinate the induction of many genes encoding inflammatory mediators, pro-apoptotic and anti-apoptotic proteins, cell-cycle regulators, and enzymes that regulate matrix remodeling (Guha and Mackman 2001; Herr and Debatin 2001; Karin et al. 2002; Tak and Firestein 2001). Moreover, NF-κB regulates the induction of AP-1 activity by promoting the expression of several AP-1 family members, which in turn augments a second wave of NF-κB-dependent gene expression (Fujioka et al. 2004; Krappmann et al. 2004). NF-κB is also a critical transcriptional activator of hypoxia-inducible transcription factor-1 alpha (HIF-1α), and IKKβ-mediated NF-κB activity is required for HIF-1α protein accumulation under hypoxia and induction of HIF-1α target genes (Rius et al. 2008). Figure 1 depicts the potential cross talk of NF-κB signaling pathway with other important oncogenic signal transduction cascades.

Pharmacological strategies to block NF-κB activation

Given the pivotal role of activated NF-κB in the development and progression of human cancer, intensive efforts have been made to explore strategies that block NF-κB signaling in aid of cancer prevention and treatment. A number of compounds with NF-κB inhibitory effects are being developed and tested in translational/clinical studies (Sethi and Tergaonkar 2009). Below, we describe few important classes of major NF-κB blockers and briefly discuss the evidence of their therapeutic promise in cancer therapy.

IKK inhibitors

The idea of specifically blocking IκBα phosphorylation has so far attracted much interest and substantial effort to develop selective inhibitors of IKK kinases via high-throughput screening of candidate compound libraries, or design and synthesis of small-molecule antagonists to IKK (Karin et al. 2004). PS-1145, a small-molecule IKK inhibitor, which was developed from natural β-carboline, has been shown to block TNFα-induced NF-κB activation by blocking the IKK complex and subsequently inhibiting IκBα degradation (Castro et al. 2003; Hideshima et al. 2002). PS-1145 suppresses the proliferation of multiple myeloma cells and exhibits selective toxicity against subtypes of DLBCLs (Hideshima et al. 2002; Lam et al. 2005). BMS-345541 binds to both IKKα and IKKβ at similar allosteric sites, and thus presents as a highly selective inhibitor of IKK (Burke et al. 2003). This compound inhibits the expression of NF-κB-regulated cytokines including TNFα, IL-1β, IL-8, and IL-6 in monocytic cells and the production of TNFα in mice (Burke et al. 2003). In a later study, it was reported that BMS-345541 induced apoptosis of melanoma cell lines and attenuated the growth of melanoma tumors in vivo (Yang et al. 2006). A pyridyl cyanoguanidine, CHS-828, was identified as a potent IKK inhibitor (Olsen et al. 2004) and showed remarkable anticancer effects in several tumor cell lines and different mouse xenograft models (Hjarnaa et al. 1999). However, when the compound was tested in phase I clinical trials, no objective tumor responses were observed on patients with solid tumors (Hovstadius et al. 2002; Ravaud et al. 2005). On the contrary, no specific IKKα inhibitors have been developed, probably because the role of IKKα in NF-κB signaling is not yet fully understood; however, many of the IKKβ inhibitors show considerable high inhibition effects on IKKα as well, with an IC_{50} value in the low micromolar range (Karin et al. 2004).

Nonsteroidal anti-inflammatory drugs

The NF-κB proteins are evolutionarily conserved mediators that integrate multiple stress stimuli to regulate inflammatory processes by controlling the gene expression of multiple pro-inflammatory molecules (Ghosh et al. 1998; Li and Verma 2002). Thus, conventional anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) have been re-evaluated to explore their effects on the NF-κB pathway in the context of cancer treatment. Experimental data, clinical trials, and epidemiologic studies have well documented the preventive role of NSAIDs, including the beneficial effect of aspirin against colorectal adenoma as well as many other cancers (Baron et al. 2003; Schreinemachers and Everson 1994; Smith et al. 2000). While the

major targets of NSAIDs are recognized as COX that lead to the inhibition of synthesis of PGs, it has been also found that several NSAIDs inhibit NF-κB activation (Smith et al. 2000).

Aspirin and salicylate drugs exert their anti-inflammatory properties at least partly by their specific inhibition of IKKβ and competing with ATP binding to the molecule, thereby abrogating the subsequent activation of NF-κB (Yin et al. 1998). Similarly, the same group have identified IKKβ kinase as the target of sulindac and its metabolites, and demonstrated that the growth-inhibitory ability of sulindac on a colon cancer cell line is regulated in part by modulating the NF-κB pathway (Yamamoto et al. 1999). A number of commonly used NSAIDs, namely aspirin, ibuprofen, sulindac, phenylbutazone, naproxen, indomethacin, diclofenac, and celecoxib, have been investigated with regard to NF-κB activation (Takada et al. 2004). All these compounds have been shown to inhibit NF-κB activation through suppression of IκBα degradation, but they exhibited a variable inhibitory capacity (Takada et al. 2004). Although the detailed molecular mechanisms of how NSAIDs inhibit the NF-κB pathway still remain unknown, the above-mentioned studies provide evidence that NSAIDs might prevent cancer development through the inhibition of NF-κB signaling.

Immunomodulatory agents

Thalidomide and its analogs are a group of immunomodulatory drugs that have shown therapeutic significance in treating multiple myeloma (Singhal et al. 1999). When thalidomide is used together with dexamethasone (another immunosuppressant), response rates in multiple myeloma patients increased significantly (Kyle and Rajkumar 2004). Currently, thalidomide alone or in combination with other chemotherapeutic agents is used as a standard therapy for treating relapsed and refractory multiple myeloma; however, the mechanisms that underlie the anti-angiogenic and anti-tumor properties of thalidomide are still unclear. Modulation of NF-κB has been proposed as one of the important mechanisms of action by thalidomide. Evidence has shown that thalidomide and its analogs induce apoptosis of multiple myeloma cells, which correlates with the downregulation of constitutive NF-κB activity (Mitsiades et al. 2002b). In addition, thalidomide has also been demonstrated to suppress cytokine-induced NF-κB activation in other cell types such as leukemia, lymphoma, and cervical cell lines (Majumdar et al. 2002). The NF-κB inhibitory effect of thalidomide has been identified as it blocks IKK activity (Keifer et al. 2001). Corticosteroids such as glucocorticoids have been found to inhibit NF-κB activity in studies of their anti-inflammatory and immunosuppressive properties. Two major mechanisms have been described: glucocorticoids increase the transcription of the *IκBα* gene, which in turn elevates the protein level of this NF-κB inhibitor that retains NF-κB in the cytoplasm (Auphan et al. 1995; Scheinman et al. 1995); also, the ligand-activated glucocorticoid receptor can directly interact with the p65 subunit, resulting in the suppression of NF-κB activation (Ray and Prefontaine 1994).

Proteasome inhibitors

The activation of NF-κB is tightly regulated by the turnover of IκBα protein through ubiquitination and proteasome-mediated degradation. Thus, several proteasome inhibitors have been developed and studied as possible cancer therapy. Bortezomib (former name was PS-341, marketed as Velcade by Millennium Pharmaceuticals) is the first proteasome inhibitor approved by the FDA for the treatment for multiple myeloma and mantle cell lymphoma (Kane et al. 2003). Bortezomib, a boronic acid dipeptide, selectively binds to and inhibits the 26S proteasome, which in turn prevents IκBα degradation, leading to the blockade of NF-κB activation (Richardson et al. 2003). The anti-tumor activities of bortezomib have been well documented as it exhibits cytotoxicity in a variety of cancer cell lines and reduces tumor growth in different in vivo models (Richardson et al. 2003). Accumulating evidence(s) indicate that most chemotherapeutic agents and radiation therapy induce the activation of NF-κB and its mediator genes in different type of cancers, which leads to the chemo- or radioresistance observed in tumors (Li and Sethi 2010). The idea of using bortezomib to inhibit NF-κB activation, in combination with either chemotherapy or radiotherapy, has been tested in variety of cancers. It has been demonstrated that bortezomib could block the chemotherapy- or radiation-induced NF-κB activation, which led to dramatic augmentation of chemo- or radiosensitivity in colorectal cancer cells and a human colon cancer xenograft model (Cusack et al. 2001; Russo et al. 2001).

In the clinical setting, the addition of bortezomib to doxorubicin-based chemotherapy resulted in a significantly higher response and improved the survival of patients with DLBCL (Dunleavy et al. 2009). These effects were associated with the inhibition of NF-κB activation and consequent suppression of NF-κB-regulated genes. Proteasomal ubiquitination regulates the degradation of multiple important proteins involved in cancers including p53, JUN, and β-Catenin (Hershko and Ciechanover 1998), and it is reasonable to believe that the inhibition of NF-κB is not the only mechanism behind the anti-tumor effects of proteasome inhibitors. In fact, it has been reported that bortezomib mediates anti-myeloma activity by inducing p53 phosphorylation and expression, and activating the JNK and caspase-8-dependent apoptotic pathway (Hideshima et al.

2003; Mitsiades et al. 2002a). Besides the synthetic peptide aldehydes, to which bortezomib belongs, the natural compound lactacystin was previously identified as having the ability to irreversibly block the activity of the proteasome via a covalent modification (Voorhees and Orlowski 2006). Indeed, the lactacystin derivative PS-519 (MLN519) is in clinical development for its anti-inflammatory properties; however, other proteasome inhibitors have only been studied in preclinical settings (Adams 2004).

Natural products

Compounds derived from natural products, which have diverse molecular mechanisms of action, have also exhibited inhibitory effects on NF-κB signaling (Aggarwal and Shishodia 2006; Nakanishi and Toi 2005; Surh 2003). A flavonoid-based compound, flavopiridol, blocks the translocation of p65 into the nucleus through inhibition of IKK (Takada and Aggarwal 2004), whereas another extensively investigated phytochemical, curcumin, suppresses NF-κB activation by inhibiting the NIK/IKK signaling complex (Glaser et al. 1973; Plummer et al. 1999). In addition, some studies suggested that curcumin downregulates NF-κB activation by inhibiting Notch-1 signaling (Wang et al. 2006) or disrupting the function of the ubiquitin proteasome system (Dikshit et al. 2006). Similarly, the green tea polyphenol epigallocatechin-3-gallate (EGCG) causes the blockade of the catalytic activities of the proteasome complex, resulting in intracellular accumulation of IκBα (Aktas et al. 2004; Nam et al. 2001). Some natural compounds such as andrographolide (from plant *Andrographis paniculata*) and sesquiterpene lactone helenalin (from plant *Arnica montana and Arnica chamissonis foliosa*) can directly interact or modify the p50 or p65 subunit of the NF-κB complex, respectively, and thus prevent the binding of NF-κB to DNA (Lyss et al. 1998; Xia et al. 2004). Resveratrol (from various natural sources such as grapes, berries, *or Polygonum Capsidatum*) acts as a potent pharmacological agonist of the NAD-dependent deacetylase SIRT1, which in turn inhibits NF-κB transcription by directly deacetylating the RelA/p65 protein (Yeung et al. 2004). Many of these compounds demonstrated promising anticancer properties in preclinical studies, and a few of which have been evaluated in clinical studies. There are several ongoing phase II and phase III clinical trials utilizing curcumin for chemoprevention or as a cancer therapy (Jurenka 2009), and preliminary results from a phase II trial reported beneficial effects of curcumin in patients with advanced pancreatic cancer (Dhillon et al. 2008). It should be noted that some of the therapeutic effects of natural agents may be mediated through pathways other than NF-κB, due to their pleiotropic nature of interfering with numerous molecular targets (Basseres and Baldwin 2006).

Concluding remarks

Several agents such as thalidomide and arsenic trioxide, which are able to inhibit NF-κB function, are currently in clinical use for cancer treatment; however, their NF-κB inhibitory effects have only been indentified after their approval for clinical use. The most well-known case of exploring chemotherapeutics with the intention, at least in part, to target NF-κB is the development of the proteasome inhibitor bortezomib. Since it gained FDA approval in 2003, bortezomib has been used clinically for relapsed multiple myeloma and later for mantle cell lymphoma. In fact, the available NF-κB inhibitors usually present only limited therapeutic efficacy when used as a single agent therapy. There are multiple preclinical studies and clinical trials that successfully demonstrated that NF-κB inhibitors markedly potentiate the effects of chemotherapeutic drugs or radiation, highlighting the promising potential of NF-κB inhibitors as adjuvant therapy. It is very important to take note that prolonged NF-κB inhibition might bring undesirable side effects that comprise the activation or efficacy of the immune system of the patients. Thus, NF-κB inhibition should be transient and reversible to avoid long-term immunosuppression, which makes it more practical to use NF-κB inhibitors in cancer therapy, rather than chemoprevention. In addition, NF-κB inhibitors should be tested and used with caution because NF-κB may promote tumorigenesis under certain circumstances (Perkins 2004; Shishodia and Aggarwal 2004). More detailed understanding of NF-κB signaling and its different roles in diverse tumor types needs to be further addressed in future studies in order to provide new insights into the rational drug design for specific NF-κB inhibition.

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Conflict of interest None.

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