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Review Article

NF-κB and cancer: a paradigm of Yin-Yang

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Abstract: Recent studies have clearly linked nuclear factor-kappaB (NF-κB), a transcription factor that plays a central role in regulating immune and inflammatory responses, to tumor development, progression, and metastasis as well as tumor therapy resistance. However, it still remains largely unknown on how the tightly regulated NF-κB becomes constitutively activated in tumorigenesis and how the original cancer immunosurveillance function of NF-κB is transformed to be tumorigenic. To address these important issues for cancer prevention and treatment, we discuss current understanding of the molecular mechanisms and molecules involved in the oncogenic activation of NF-κB. We also discuss current understanding of how NF-κB coordinates the inflammatory and malignant cells in tumorigenesis.

Keywords: A20, cancer, cancer immunology, cancer immunosurveillance, CYLD, deubiquitination, IκB, IKK, microRNA, NF-κB, oncogene, oncogenesis, PDLIM2, tumor, tumorigenesis, tumor suppressor, ubiquitination, WWOX,

Introduction

The NF-κB family

Nuclear factor-κB (NF-κB) plays a central role in the regulation of diverse biological processes, including immune responses, development, cell proliferation and survival. Deregulated NF-κB has been linked to a variety of human diseases, particularly cancers [1-3]. The NF-κB family consists of five closely related DNA binding proteins: RelA (p65), RelB, c-Rel, NF-κB1/p50 and NF-κB2/p52, which function as various homodimers and heterodimers. All five NF-κB members share a highly conserved 300-amino-acid-long N-terminal Rel homology domain (RHD), which is responsible for their dimerization, nuclear translocation, DNA binding and also interaction with the inhibitors of NF-κB (IκBs) (**Figure 1**). But they show huge difference in their C-terminal sequences and also synthesis modes. While RelA, RelB and c-Rel have transactivating domain (TAD) at their C-termini and are synthesized directly as mature forms, p50 and p52 lack a TAD and are generated from large precursor proteins, p105 and p100, respectively. Interestingly, p105 and p100 contain a C-terminal ankyrin repeat domain (ARD), the characteristic domain of IκB. Indeed, both p105 and p100 function as IκB-like inhibitors of NF-κB [4, 5].

The IκB family

The IκB family comprises eight members and shares one common structural feature: presence of an ARD, which can bind to the RHD of NF-κB (**Figure 1**). While IκBα and IκBε function as potent NF-κB inhibitors by sequestering NF-κB dimers in the cytoplasm, other IκB proteins including IκBβ are not simple inhibitors of NF-κB but rather cofactors displaying both positive and negative effects on NF-κB-mediated gene transcription [6, 7]. For example, Bcl-3, which was originally identified as an oncogene from B-cell chronic lymphocytic leukemias (B-CLLs), has a typical TAD in its C-terminal. Bcl-3 is constitutively translocated into the nucleus where it interacts with p50 or p52 homodimers, which lack TAD, to facilitate transcription of NF-κB target genes. The nuclear translocation of Bcl-3 requires its K63-linked polyubiquitination (via the lysine 63 of ubiquitin) [8]. Bcl-3 may also repress transcription of NF-κB target genes. In this case, Bcl-3 promotes p50 homodimer occupancy of the κB site-containing promoters by

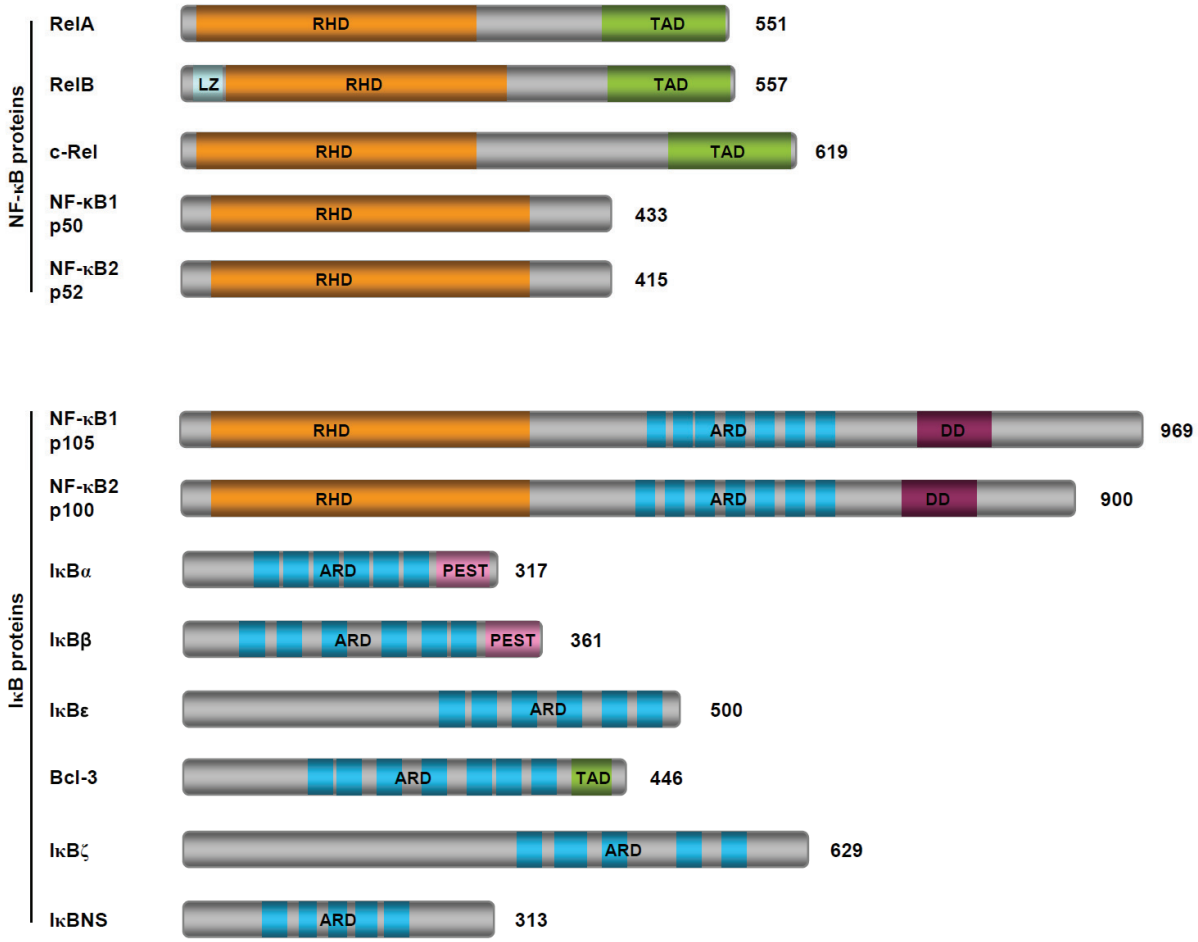

Figure 1. Schematic representation of members of NF-κB and IκB families. The NF-κB family can be divided into two subfamilies. One subfamily consists of three members: RelA, RelB and c-Rel, which contain TADs at their C-termini and are synthesized directly as mature forms; the other one consists of two members: NF-κB1/p50 and NF-κB2/p52, which lack a TAD and are generated from large precursor proteins p105 and p100, respectively. Typical NF-κB dimers are usually composed of one member from each subfamily, such as RelA/p50 and RelB/p52, although all NF-κB members may form various homo- or hetero-dimers. Of note, the p50 or p52 homodimers repress NF-κB target gene expression due to lack of a TAD. The IκB family can be classified into three subfamilies: the typical IκB proteins (IκBα and IκBε), the precursor proteins (p100 and p105) and the atypical IκB proteins (BCL-3, IκBβ, IκBε and IκBNS). The typical subfamily just simply functions as NF-κB inhibitors. The precursor subfamily is also required for generation of the NF-κB members p50 and p52, besides being NF-κB inhibitors. While the processing of p105 to p50 is a constitutive event, the processing of p100 to p52 is tightly controlled. The atypical subfamily may function as co-activator or co-repressor of NF-κB depending on different situations [6, 7]. RHD: Rel homology domain; TAD: transactivating domain; ARD: ankyrin repeat domain; DD: death domain; LZ: leucine zipper; PEST: PEST containing sequence.

inhibiting ubiquitination and degradation of p50, therefore preventing replacement by active NF-κB dimers [9].

NF-κB signaling pathways

In unstimulated cells, NF-κB dimers usually exist as latent complexes with the IκB proteins in the cytoplasm. There are two major mechanisms leading to NF-κB activation: the canonical and non-canonical NF-κB pathways, which are based on the inducible degradation of IκBα and processing of p100 to generate p52 (selective degradation of the C-terminal IκB-like sequence of

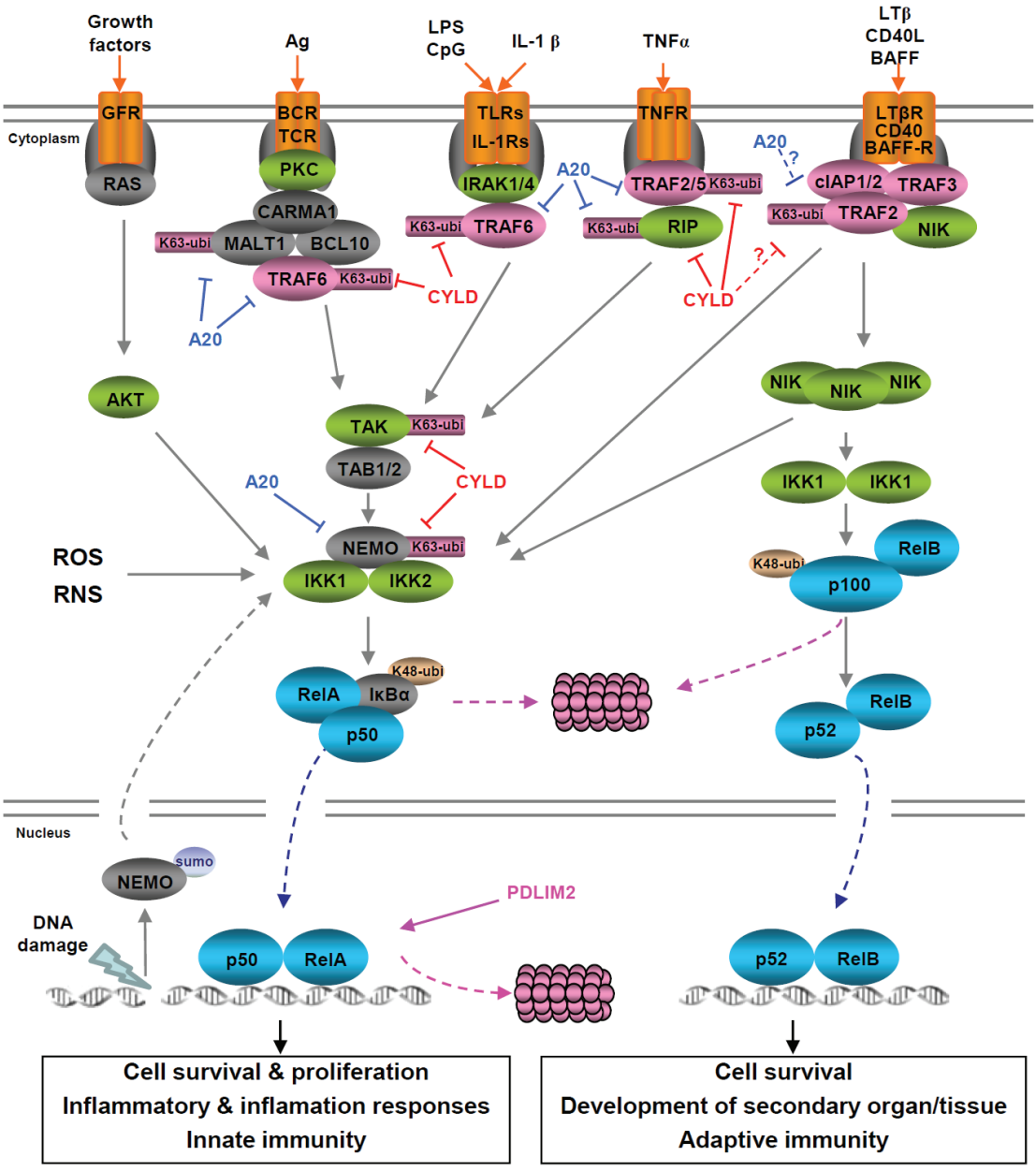

Figure 2. NF-κB signaling pathways. Although the canonical and non-canonical signaling pathways primarily activate the RelA/p50 and RelB/p52 dimers, respectively, all NF-κB members can be activated by either pathway or both. In fact, the RelA/p50 dimers may be sequestered in the cytoplasm by p100 and can be activated through p100 processing. On the other hand, NF-κB dimers containing p52 may be sequestered in the cytoplasm by IκBα and can be activated through IκBα degradation. Furthermore, activation of the canonical NF-κB signaling pathway can be induced through inducible degradation of IκBβ, IκBε and p105, a process similar to the inducible IκBα degradation, although their degradation dynamics can be different.

p100), respectively (**Figure 2**).

Pathways leading to NF-κB activation

Canonical NF-κB pathway: The canonical pathway can be rapidly activated by a plethora of stimuli, such as inflammation cytokines and antigens. These NF-κB inducers induce assembly of a multimolecular complex that includes the RING-finger E3 ubiquitin ligase tumor necro-

sis factor receptor associated factor 6 (TRAF6), leading to TRAF6 auto-polyubiquitination [10, 11]. The K63 ubiquitinated TRAF6 then recruits and catalyses K63-linked ubiquitination of the transforming growth factor-β-activated kinase 1 (TAK1) and the IκB kinase (IKK) complex [which consists of two catalytic subunits, IKK1 (IKKα) and IKK2 (IKKβ), and a regulatory subunit, NEMO (NF-κB essential modulator, IKKγ)], so that TAK1 can phosphorylate and activate IKK. Once activated, IKK phosphorylates specific serines (S32 and S36) within IκBα, triggering its K48-linked ubiquitination by the E3 ubiquitin ligase β-transducin repeat-containing protein (β-TrCP) and degradation by the 26S proteasome. The released NF-κB translocates into the nucleus to regulate expression of a wide range of genes, particularly those involved in cell proliferation, survival, adhesion and migration. In addition to IκB degradation, many other regulatory mechanisms are also important for canonical NF-κB activation, such as phosphorylation, acetylation, prolyl isomerization and/or methylation of the prototypical NF-κB member RelA. These post-translational modifications prevent RelA from binding to IκBα, facilitate its DNA binding and transcriptional coactivator recruitment, and/or increase its stability [6].

Non-canonical NF-κB pathway: In contrast to the canonical pathway, the noncanonical NF-κB pathway is induced only by a handful of stimuli including B-cell activating factor (BAFF), lymphotoxin β (LTβ), CD40 ligand, TNF-like weak inducer of apoptosis (TWEAK) and receptor activator of NF-κB ligand (RANKL) [6]. In addition, activation of the noncanonical NF-κB pathway is slow and depends on protein synthesis of NF-κB -inducing kinase (NIK) [12]. Although its mRNA expression is relatively abundant, the protein level of NIK is normally very low because of its constitutive degradation via a TRAF3-dependent mechanism [12, 13]. TRAF3 functions as a scaffold between NIK and TRAF2, which in turn recruits cellular inhibitors of apoptosis 1 and 2 (c-IAP1/2) into the NIK complex. Within the complex, c-IAP1 or c-IAP2 acts as the E3 ubiquitin ligase to mediate NIK polyubiquitination and proteolysis, thereby keeping its abundance below the threshold required for its function. In response to noncanonical NF-κB stimuli, either TRAF2 and TRAF3 or c-IAP1 and c-IAP2 are degraded by the proteasome, resulting in stabilization and accumulation of the newly synthesized NIK, thereby allowing NIK proteins to form oligomers and cross-phosphorylate each other for their activation [12-19]. Self-activated NIK in turn activates the IKK complex and specifically recruits IKK1 into the p100 complex to phosphorylate p100, leading to p100 ubiquitination by the β-TrCP E3 ubiquitin ligase and processing by the proteasome to generate p52 [20-23]. The processed product p52 together with its NF-κB binding partner translocates into the nucleus to induce or repress gene expression. Moreover, NIK-activated IKK may also induce IκBα degradation to activate the canonical NF-κB pathway [24].

Termination of NF-κB activation

Activation of the NF-κB pathways is tightly regulated and rapidly curtailed following the initial activating stimulus. Transient activation of NF-κB is physiologically important because persistent activation can result in deleterious or even fatal conditions, such as acute inflammation, septic shock or at a cellular level, inappropriate cell growth and survival leading to cancer. It is therefore not surprising that feedback inhibition mechanisms to terminate NF-κB activation occur at almost all the levels or regulations that led to the initial activation.

Consistent with the central role of IKK in the activation of both canonical and non-canonical NF-κB pathways, several mechanisms are employed to inactivate IKK. Once activated, IKK also phosphorylates themselves and upstream activators, such as RIP in the canonical NF-κB pathway and NIK in the non-canonical NF-κB pathway, in addition to the IκB proteins. The autophosphorylation of the IKK catalytic subunits at multiple C-terminal serines is supposed to cause IKK conformational alteration and phosphatase recruitment, resulting in dephosphorylation of the IKK activation loops and IKK inactivation [25]. Phosphorylation of RIP and NIK, similar to IκB phosphorylation, leads to K48-linked ubiquitination and degradation of these IKK activators [26, 27]. The ubiquitination of RIP is mediated by A20 (TNFAIP3, TNFα-induced protein 3), a known target of NF-κB activation [28], providing a distinct feedback inhibition mechanism. In addition to as an E3 ubiquitin ligase for RIP K48-linked ubiquitination and degradation, A20 exerts at least two additional functions in the termination of NF-κB activation: on one hand functions as a deubiquitinase (DUB) to remove K63-linked ubiquitin

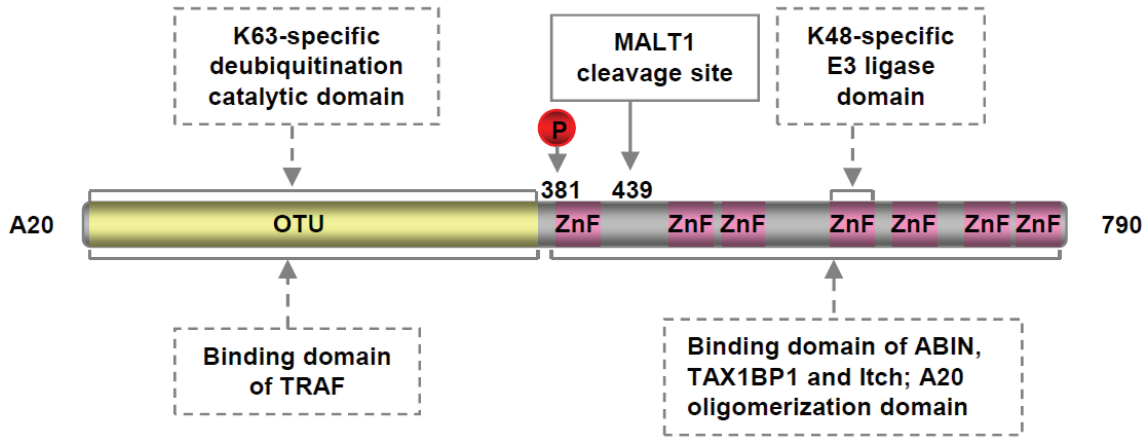

Figure 3. Domain structure of A20. OUT: ovarian tumour domain; ZnF: zinc finger.

chains from multiple NF-κB signaling molecules such as TRAF2/6, RIP, MALT1 and NEMO, and on the other hand blocks continuous K63-linked ubiquitination of these key NF-κB regulators by disrupting the interaction between the K63 ubiquitin ligases TRAF2/6 and their E2 ubiquitin conjugating enzymes Ubc13 and UbcH5c [26, 29-32]. As stated above and shown in **Figure 2**, K63-linked ubiquitination of NF-κB signaling molecules is critical for the assembly of signaling complex and subsequent activation of IKK/NF-κB. The K48-ubiquitin ligase and the K63-ubiquitin deubiquitinase activities of A20 are mediated by its C-terminal zinc finger containing domain and N-terminal ovarian tumor (OTU) domain, respectively [26, 33, 34]. Interestingly, A20 is also a target of IKK activation for phoshorylation. In this case, IKK-mediated phosphorylation increases the K63-specific DUB activity of A20, suggesting another level of feedback inhibition mechanism of IKK/NF-κB activation [35] (**Figure 3**). Besides A20, another deubiquitinase termed cylindromatosis (CYLD) also plays an important role in the termination of IKK/NF-κB activation. Like A20, CYLD is a target gene of NF-κB activation and can remove K63-linked ubiquitin chains from multiple activated IKK/NF-κB signaling molecules, including TRAF2/6, RIP, TAK, NEMO and Bcl-3 [36-38].

However, the best known and most critical feedback inhibition mechanism is to replenish the pool of IκB proteins via NF-κB activation itself. Same to many NF-κB repressors such as A20 and CYLD, all the IκB family members except IκBβ are direct targets of NF-κB. Newly synthesized IκB, particularly IκBα, enters the nucleus to bind to and transport NF-κB dimers back to the cytoplasm to reconstitute the status quo ante [39].

Recent studies, however, indicate that this feedback inhibition mechanism is neither sufficient nor necessary for the turnoff of NF-κB activation, at least in certain situations [40]. Instead, ubiquitination-mediated proteasomal degradation of activated NF-κB members directly in the nucleus provides a more rapid but also essential mechanism for NF-κB termination. Two different E3 ubiquitin ligases have been reported to be involved in the nuclear degradation of RelA: suppressor of cytokine signaling 1 (SOCS1) and PDZ-LIM domain-containing protein 2 (PDLIM2). The SOCS1 ligase complex, which consists of Elongins B and C, Cul2 and SOCS1, requires COMMD1 (MURR1) for its function in RelA ubiquitination and degradation [41-44]. COMMD1 binds to both SOCS1 and RelA and therefore enhances the interaction between SOCS1 and RelA. Accordingly, knockdown of COMMD1 stabilizes nuclear RelA and enhances NF-κB activity in response to TNF stimulation or certain stress stimuli [44, 45]. PDLIM2, a ubiquitously expressed nuclear protein with a strong shuttling activity between the nucleus and the cytoplasm, terminates NF-κB activation using two distinct but related mechanisms: it not only functions as an E3 ubiquitin ligase to promote nuclear RelA ubiquitination but also shuttles RelA to the nuclear matrix for the proteasome-mediated degradation [46, 47]. Importantly, PDLIM2 knockout mice are more sensi-

tive to septic shock due to enhanced p65 activation and subsequently augmented production of inflammatory cytokines [46].

Crosstalk between NF-κB pathways

Although the canonical and non-canonical NF-κB signaling pathways are fundamentally different, they do interact with each other at multiple levels. As described above, all known non-canonical NF-κB stimuli are also able to activate the canonical pathway, although most of canonical NF-κB stimuli are unable to activate the non-canonical pathway. However, activation of the canonical NF-κB pathway does facilitate activation of the non-canonical NF-κB pathway, e.g. transcriptional upregulation of p100 and non-canonical NF-κB stimuli such as CD40L and TWEAK. Interestingly, recent studies indicate that activation of the non-canonical NF-κB pathway may facilitate or repress activation of the canonical pathway depending on cell-context. For example, non-canonical NF-κB activation by the viral oncoprotein Tax leads to transcriptional repression of the tumor suppressor WWOX, which selectively inhibits Tax activation of the canonical NF-κB by blocking IKK1-mediated RelA phosphorylation [48]. On the other hand, NIK-dependent induction of CYLD by RANKL has been reported to be critical in repressing osteoclastogenesis through downregulation of the TRAF6 signaling pathways including the canonical NF-κB activation [49]. Furthermore, both signaling pathways activate some common NF-κB members and regulate some common target genes. In addition to the signaling interactions, the two pathways also cooperate functionally. Whereas one of the main functions of canonical NF-κB activation is to regulate innate immunity, the major function of non-canonical NF-κB activation is to control adaptive immunity. Another common property of the two NF-κB pathways is that they both have been linked to various human pathogenesis, particularly cancer, although it still remains largely unknown whether and how the two signaling pathways cooperate during tumorigenesis.

Yin-Yang imbalance of NF-κB activation in cancer

The involvement of NF-κB in oncogenesis has been long suggested since the discovery of c-Rel and its viral derivative v-Rel [50, 51]. The v-Rel oncoprotein induces acute lymphoid malignancies in young chickens as well as T-cell lymphomas in transgenic mice [52]. Subsequent work has indicated that persistent activation of NF-κB is associated with various human cancers. More recent studies involving genetically modified mice have clearly demonstrated the significance of the IKK/NF-κB signaling in tumorigenesis. For example, conditional deletion of IKK2 or RelA in intestinal or lung epithelial cells results in significant, although not complete, inhibition of tumor genesis and progression in mouse models of colitis-associated cancer and lung carcinomas, respectively [53, 54]. On the other hand, transgenic mice conditionally expressing c-Rel in mammary gland or a constitutive processing form of p100 in lymphocytes develop mammary tumors and lymphomas, respectively [55, 56]. However, the molecular mechanisms by which the NF-κB signaling pathways become constitutively activated during cancer pathogenesis still remain obscure. Both NF-κB pathways are tightly regulated by both negative (yin) and positive (yang) regulators. Logically, disruption of the delicate balance between those yin-yang factors due to excess of yang and/or shortage of yin should result in persistent activation of NF-κB. In some cancers, the constitutive activity of NF-κB is clearly caused by genetic alterations in genes encoding NF-κB members and their inhibitors IκBs. In most cases, however, the deregulated NF-κB activity is attributed to overactivation of the positive regulators and/or inactivation of the negative regulators of the IKK/NF-κB signaling.

NF-κB versus IκB

Activating mutations of NF-κB members and their co-factors: As mentioned above, the link between NF-κB and cancer was initially suggested by the acute oncogenicity of the v-Rel oncoprotein, a close kinship to c-Rel. Soon thereafter, all five NF-κB members have been found to be overactivated in human cancers (**Table 1**). One mechanism leading to aberrant activation of NF-κB involves the genetic alterations of the *nf-κb* genes themselves, which include gene amplifications, mutations, deletions and chromosomal translocations, a major cause of oncogene activation.

Consistent with their global functions, genetic alterations of either the *rela* gene or the *nf-κb1* gene are only infrequently found in human tumors, although overexpression and overactiva-

Table 1. Alteration of NF-κB and IκB in cancer

Genes	Locus	Alteration	Tumor type	References
rela	11q13	amplification	various types of lymphomas, including diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma and follicular large cell lymphoma; solid tumors such as squamous head and neck, breast and stomach adenocarcinoma	[51,190-192]
		rearrangement	B-cell non-Hodgkin's lymphoma and multiple myeloma	
		splicing variant	non-small cell lung carcinoma	
		amino acid substitution	multiple myeloma	
		overactivation	various types of cancers	
relb	19q13.32	rearrangement	adult T-cell leukemia cell lines	[193]
c-rel	2p13-p12	amplification	diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and follicular large cell lymphoma	[51,190,194,195]
		rearrangement	follicular lymphoma and diffuse large B-cell lymphoma	
		overexpression	follicular lymphoma, diffuse large cell lymphoma and non-small cell lung carcinoma	
nf-kb1	4q24	rearrangement	acute lymphoblastic leukemia	[51,196]
		overexpression	various cancers including non-small cell lung carcinoma, colon, prostate, breast and brain cancer	
nf-kb2	10q24	rearrangement	cutaneous T-cell lymphoma, B-cell non-Hodgkin's lymphoma, B-cell chronic lymphocytic leukemia and multiple myeloma	[51,196-199]
		overexpression	cutaneous T-cell lymphoma, breast and colon carcinoma	
bcl3	19q13.1-q13.2	rearrangement	B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma	[51,200,201]
		overexpression	B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma	
ikbα	14q13	mutation	Hodgkin's disease	[51,85]
ikbε	6p11	mutation	Hodgkin's disease	[88]

tion of both RelA and p50 (due to activation of the NF-κB signaling, see discussion below) are common not only in tumors but also in other human diseases. Currently, a definitive correlation between the genetically altered *rela* and *nf-κb1* genes and human tumorigenesis remains to be established.

A much clearer link between *nf-κb* genetic alterations and tumorigenesis has been observed in the studies of *c-rel* and *nf-κb2*. Amplification of the *c-rel* gene has been often detected in various non-Hodgkin's B-cell lymphomas such as diffuse lymphomas with a large cell component (DLLC), follicular large cell lymphomas and mediastinal thymic B-cell lymphomas (**Table 1**). The *c-rel* gene also undergoes rearrangement in some DLLCs and in a few follicular lymphomas [51]. Interestingly, the resulting C-terminal deletion of c-Rel because of the gene rearrangement is reminiscent of that of the *v-rel* oncogene. Although the involved mechanism remains to be investigated, overexpression of c-Rel has often been reported in solid tumors as

well, such as breast and lung cancers [57, 58]. Given the tumorigenesis in c-Rel transgenic mice and the oncogenic potentials of *v-rel*, there is no doubt that amplification and rearrangement of the *c-rel* gene contribute to, if not cause, the lymphomagenesis.

Unlike its closest relative *nf-κb1*, the human *nf-κb2* gene is frequently involved in chromosomal translocations or small deletions associated with development of various lymphomas and leukemias, such as cutaneous T-cell lymphoma (CTL), B-cell non-Hodgkin lymphoma (B-NHL), B-cell chronic lymphocytic leukemia (B-CLL), multiple myeloma (MM) and adult T-cell leukemia/lymphoma (ATL) [51, 59]. In fact, the *nf-κb2* gene is the first NF-κB member that was found to undergo genetic alterations in human tumors. In all cases studied, such gene rearrangements always lead to deletions of the C-terminal processing-regulatory sequences together with part of ankyrin repeats [6]. Since these C-terminal sequences are essential for repressing p100 nuclear translocation and constitutive processing, these truncated p100 mutants undergo constitutive processing in association with the κb site-containing promoters in the nucleus [20, 60, 61]. The genetic mutation of the *nf-κb2* gene results in the loss of IκB-like function of p100 in two ways: genetic deletion and biochemical degradation (protein processing) of C-terminal ankyrin repeats. The genetic mutation also results in the gain of transcriptional function in two related mechanisms, because these p100 truncation proteins and their processed products p52 regulate transcription of common and distinct target genes [60]. Although these constitutive processing forms of p100 show strong oncogenicity both in vitro and in vivo [56, 60, 62], the involved mechanisms remains unclear. Homozygous knockout of the *nf-κb2* gene leading to deficiency of both p100 and p52 proteins in mice is not tumorigenic [63, 64], suggesting that the simple loss of the IκB-like function is not sufficient to account for the oncogenicity of the truncated p100 proteins. Interestingly, overexpression of p52 in the absence of p100 in p100 knockin mice causes marked gastric and lymphocyte hyperplasia and early postnatal death [65]. On the other hand, p52 transgenic mice expressing wild type p100 only leads to development of thymoma at extremely low rate, although over 50% mice develop inflammatory autoimmune disease by 8-month age [66]. Furthermore, mice selectively expressing the human *nf-κb2* gene in mammary epithelial cells by the β-lactoglobulin milk protein promoter exhibit ductal thickening and hyperplasia only when the transgene expression and p100 processing to p52 are repeatedly induced through multiple pregnancies [67]. Thus, it seems plausible that both loss of IκB-like function of p100 and gain of transcriptional function of p52 contribute to the oncogenicity of C-terminally truncated p100 proteins. This idea is also consistent with the fact that aberrant processing to p52 of p100 has been found in many types of tumors [6]. The transcriptional function of truncated p100 proteins themselves also plays a role in the oncogenesis, given the strong transforming abilities of the mutants.

Another piece of evidence linking activating mutations of the *nf-κb* genes to tumorigenesis comes from chromosomal translocations of the Bcl-3 oncoprotein, a coactivator of p50 and p52 (**Figure 1**). Bcl-3 was originally identified through cloning of the t(14;19) breakpoint junction, which occurs in a subset of B-cell chronic lymphocytic leukemias (B-CLLs) [68]. Of note, the rearranged *bcl-3* gene remains intact but is transcriptionally activated, resulting in overproduction of the Bcl-3 protein and presumably elevated transactivation activity of the p50 or p52 complexes. Overproduction of Bcl-3 independent of its gene translocation has also been observed in various tumors including breast cancer, colorectal cancer, hepatocellular carcinoma, melanoma, nasopharyngeal carcinoma, and different lymphomas [69-74]. In fact, overexpression of Bcl-3 is often associated with tumor progression and poor prognosis. The contribution of Bcl-3 overexpression to tumorigenesis is further suggested by the findings that expression of exogenous Bcl-3 leads to cell transformation in vitro and transgenic mice overexpressing Bcl-3 in B cells develop lymphadenopathy and splenomegaly with excess number of B cells [75, 76].

Inactivating mutations of IκB proteins: The first hint to a tumor suppressive function of the prototypical NF-κB inhibitor IκBα came from the finding that inactivation of IκBα by *iκbα* antisense transcript is sufficient to transform mouse fibroblasts [77]. Although later studies showed that *iκbα* knockout fibroblasts are not transformed [78, 79], the tumor suppressive role of IκBα cannot be overlooked, as defective activity of IκBα is often associated with persis-

tent NF-κB activation in many human tumors. Importantly, overexpression of a super-repressor form of IκBα induces tumor cell apoptosis and inhibits tumorigenesis in numerous animal models [48, 80-82]. In most cases, the I κBα deficiency in tumors is because of the enhanced protein degradation mediated by constitutively activated IKK. However, a subset of Hodgkin's lymphomas (HLs) are associated with genetic mutations or deletions of the *iκbα* gene, which lead to generation of nonfunctional or unstable IκBα mutants [93-87]. Similar to *iκbα*, the *iκbε* gene also undergoes somatic mutations in some Hodgkin's lymphomas, generating nonfunctional IκBε mutants [88]. Interestingly, simultaneous inactivations of both the *iκbα* gene and the *iκbε* gene are also detected in certain Hodgkin/Reed–Sternberg (HRS) cells. Given the non-redundant functions of IκBα and IκBε in the control of a subset of NF-κB target genes [78, 89], these findings suggest the importance of coordination among NF-κB members and also their target genes in tumorigenesis.

NF-κB activators versus NF-κB terminators

Overactivation of NF-κB activators: Although activating mutations of the NF-κB proteins and inactivating mutations of the IκB proteins have been defined in human tumors, they are mainly limited to lymphoid malignanices and only account for a small number of leukemias and lymphomas. On the other hand, constitutive degradation of IκBs due to the elevated activation of IKK, the primary NF-κB-activating kinase, has been found not only in lymphoid malignancies but also in most solid tumors, suggesting one common mechanism for the NF-κB oncogenic activation. As yet, however, no oncogenic mutations of IKK have been detected. Instead, persistent existence of NF-κB stimuli, particularly proinflammatory cytokines and growth factors in the tumor microenvironment, has been suggested to be involved in the oncogenic activation of IKK/NF-κB (**Table 2**). Interestingly, many of these NF-κB inducers are also target genes of NF-κB activation, thereby providing an autocrine or paracrine mechanism for persistent NF-κB activation.

Another important mechanism contributing to oncogenic NF-κB activation involves overexpression and activating mutations of IKK/NF-κB upstream activators. One example is the genetic mutations of the CARMA1/MALT1/Bcl10 complex, which is essential for antigen-induced IKK/NF-κB activation. Chromosome translation of the *bcl10* gene [t(1:14)(p22:q32)] and the *malt1* gene [t(11:18)(q21:q21)] are frequently found in B-cell lymphomas of mucosa-associated lymphoid tissue (MALT), while missense mutations of the *carma1* gene are detected in about 10% activated B cell-like (ABC) diffuse large B cell lymphomas (ABC-DLBCLs) and in about 4% germinal center B cell-like (GCB)-DLBCLs [90-98]. Interestingly, the genetic mutations of these signaling proteins always result in their overexpression and/or enhanced abilities in IKK/NF-κB activation, which is required for the survival of tumor cells [95-99].

As stated above, stabilization and accumulation of the NIK kinase will lead to activation of both canonical and non-canonical NF-κB pathways. It is thus not surprising that overexpression of the NIK protein has been linked to various tumors such as multiple myeloma, adult T-cell leukemia, melanoma, pancreatic carcinoma, breast cancer and lung cancer. Several mechanisms may contribute to the oncogenic expression of NIK: inactivating mutations of NIK negative regulators TRAF2/3 and c-IAP1/2, activating mutations of NIK and its positive activators CD40 and LtβR, as well as epigenetic activations of NIK mRNA transcription [100-102]. In support of the role of NIK overexpression in tumorigenesis, a recent study show that expression of exogenous NIK is sufficient to transform rat fibroblasts and knockdown of NIK reverses the tumor phenotype of those malignant cells with high expression of NIK [103, 104]. It is important to reiterate that the oncogenic action of NIK depends on NF-κB activation. Interestingly, NIK can also be stabilized and activated through K63-linked ubiquitination, which is mediated by an atypical E3 ubiquitin ligase termed zinc finger protein 91(ZFP91) [105]. Giving the findings that ZFP91 is overexpressed in 93% acute myelogenous leukemia (AML) and required for cancer survival [105, 106], ZFP91-mediated stabilization may stand for another mechanism of NIK oncogenic activation.

In addition to deregulation of those central NF-κB signaling molecules, activation of many well-known oncoproteins also persistently activates IKK/NF-κB (**Table 2**). For instance, oncogenic mutations of the *ras* gene, which occur in over 30% of human tumors, induce IKK/NF-κB indi-

Table 2. NF-κB activating and adaptor molecules in cancer

	NF-κB pathway	Cancer linkage	References
Growth Factors			
EGF	canonical	stimulates tumor cells proliferation; modulates tumor-associated angiogenesis and bone metastasis; regulates resistance to chemotherapy	[202-204]
NGF	canonical	promotes survival and proliferation of breast cancer cells	[205]
TGFβ	canonical	causes adenoma and adenocarcinoma; induces epithelial to mesenchymal transition in cancer	[206-209]
Kinases			
IRAK	canonical	its polymorphism correlates with prostate cancer risk; its expression correlates with lung cancer development	[210-212]
RIP	canonical	mediates proliferation of human head and neck squamous cell carcinoma	[213]
MEKKs	canonical	essential for cancer cell survival	[214, 215]
Tpl2	canonical	promotes cell migration and transformation	[216-218]
TBK1	canonical	highly expressed in cancer; essential for KRAS-dependent cancer cells survival	[219, 220]
MLK3	canonical	critical for cancer cell migration and invasion; highly expressed in breast cancer cells	[221, 222]
Raf	canonical	oncoprotein involved in various cancers; essential for the progression of metastatic melanoma and breast epithelial cancer	[223, 224]
TAK1	canonical	required for progression and metastasis of breast cancer cells; required for R-RAS mediated transformation of mammary epithelial cells; suppresses procarcinogenic pathway in liver cancer	[225-227]
PKCs	canonical	promotes tumor progression and invasion	[228-230]
AKT	canonical	activated in multiple types of cancer; promotes cancer progression	[231, 232]
PKR	canonical	promotes cancer progression and metastasis	[233, 234]
PAK1	canonical	overexpression and/or hyperactivation in cancer; promotes tumor progression and invasion	[235, 236]
CK2	canonical	promotes tumorigenesis	[237]
NIK	both canonical and noncanonical	shows oncogenicity in vitro; elevated expression in various types of cancer	[103, 104, 238, 239]
Adaptors			
Ras	canonical	promotes cancer proliferation, metastasis and invasion; commonly mutated in various cancers	[240, 241]
FADD	canonical	elevated in and associated with aggressive lung cancer	[242]
MyD88	canonical	crucial for tumour promotion in models of spontaneous and carcinogen-induced intestinal tumorigenesis; required for RAS-mediated carcinogenesis	[243, 244]
Bcl10	canonical	aberrant expression found in primary cutaneous marginal zone B-cell lymphoma	[245]
MALT1	canonical	contributes to tumorigenesis in diffuse large B-cell lymphoma of the activated B-cell subtype	[246]
CARMA1	canonical	oncogenic mutation of CARMA1 is found in diffuse large B cell lymphoma; overexpressed in primary gastric B-cell lymphoma	[247, 248]
Viral oncoproteins			
HTLV-1 Tax	both canonical and noncanonical	promotes cell transformation and tumor progress	[249]
EBV LMP-1	both canonical and noncanonical	promotes cell transformation, tumor progress and migration in EBV-associated cancer	[250, 251]
Herpesvirus Tio	both canonical and noncanonical	essential for transformation of primary human T cells	[252-254]
KSHV K13	both canonical and noncanonical	promotes cell transformation and tumor progress	[118, 255]

EGF: epidermal growth factor; NGF: nerve growth factor; TGFβ: transforming growth factor beta; ROS: reactive oxygen species; HTLV-1: human T-cell lymphotropic virus type 1; EBV: Epstein-Bar virus; LMP-1: latent membrane protein 1; Tio: two in one; KSHV: Kaposi's sarcoma-associated herpesvirus; K13: FADD-like interleukin-1 beta-converting enzyme (FLICE) inhibitory protein (vFLIP)

rectly through the AKT and Raf kinases, another two famous oncogenes that can induce tumors when expressed in transgenic mice [107, 108]. It seems that activation of NF-κB is one crucial mechanism of Ras-mediated tumorigenesis, because inhibition of NF-κB activation by transgenically expressing the super-repressor form of IκBα or genetically silencing RelA significantly blocks Ras-mediated tumorigenesis and tumor progression [54, 80].

Similar to cellular oncogenes, many viral oncoproteins also target NF-κB for their oncogenicities [6, 59]. The first and best example is the Tax oncoprotein encoded by the human T-cell leukemia virus type I (HTLV-I), an etiological agent of an acute T-cell malignancy termed adult T-cell leukemia/lymphoma (ATL) [109]. By directly interacting with NEMO, Tax activates IKK to phosphorylate IκBα, resulting in IκBα degradation and canonical NF-κB activation [110-114]. In parallel, Tax specifically recruits IKK1 into the p100 complex to activate the non-canonical NF-κB pathway independent of NIK [115, 116]. The significance of NF-κB activation in Tax-mediated tumorigenesis has been well defined. Whereas HTLV-I or Tax mutants selectively defective in NF-κB activation lose the transforming ability, blockage of Tax activation by overexpression of p100 or the super-repressor form of IκBα prevents HTLV-I/Tax-mediated transformation [109]. However, the most impressive in vivo data supporting a role of NF-κB in Tax-mediated pathogenesis is from studies on Tax transgenic mice in the presence or absence of endogenous p100/p52 [48]. In this model, genetic knockout of the *nf-κb2* gene, leading to no expression of both p100 and p52 proteins, significantly delays Tax-mediated tumorigenesis in mice. Later on, NF-κB has been found to be targeted for human tumorigenesis by many tumor viruses including Kaposi sarcoma-associated herpesvirus (KSHV), and Epstein-Barr virus (EBV) [6, 59]. KSHV can induce several different clinical variants of Kaposi's sarcoma, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) through expression of a viral version of the cFLIP protein named vFLIP, which resembles Tax in the NF-κB activation [117, 118]. On the other hand, EBV encodes a potent oncoprotein named latent membrane protein 1 (LMP1), which acts like a constitutively activated member of the TNFR/CD40 superfamily for the activation of both canonical and non-canonical NF-κB pathways [119].

Inactivation of NF-κB terminators: NF-κB is controlled by a delicate counterbalance between its activators and terminators, guaranteeing an inducible but transient activation of NF-κB. Thus, disruption of this fine balance by inactivation of NF-κB terminators represents another important mechanism of oncogenic activation of NF-κB. In fact, rapidly increasing evidence indicates that many NF-κB terminators actually function as tumor suppressors (**Table 3**).

Consistent with its role in NF-κB termination, genetic knockout of the deubiquitinase A20 leads to severe spontaneous multiorgan inflammation and cachexia in mice and importantly inactivating mutations of A20 have been detected in several human autoimmune disorders including Crohn's disease, Coeliac disease, psoriasis, rheumatoid arthritis, systemic lupus erythematosus and diabetes [120, 121]. Although the premature death of A20 knockout mice prevented the detection of a potential tumorigenic effect, the tumor suppressor role of A20 has been well suggested recently. The first clue came from the identification of the *a20* gene as a target gene of 6q23.3-q24.1 deletion in ocular adnexal marginal zone B cell lymphoma (MZBCL) [122]. Soon thereafter, A20 was found to be frequently inactivated by deletion, promoter methylation or somatic mutations in a variety of lymphomas, including Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma (FL), Burkitt's lymphoma, natural killer cell lymphoma and adult T cell leukaemia/lymphoma (ATL) [34, 123-126]. Interestingly, the inactivating mutations often involve both alleles of the gene, suggesting that a complete inactivation of A20 favors cell survival and tumorigenesis. Except the genetic and epigenetic inactivations, A20 is also negatively regulated at the protein level by the paracaspase MALT1, which cleaves and inactivates A20 to enhance NF-κB activation [127]. As we already discussed, MALT1 is a proto-oncoprotein that is constitutively activated in certain lymphomas. Notably, the oncogenicity of MALT1 is through targeting NF-κB. In direct support of the tumor suppressor role of A20, reconstitution of A20 decreases NF-κB activation and induces growth arrest and apoptosis of A20-deficient lymphoma cell lines [124, 128, 129].

Table 3. NF-κB signaling repressors in cancer

Gene Name	Effects on NF-κB Module	Cancer linkage	References
CYLD	targets multiple NF-κB signaling molecules	tumor suppressor; mutated, deleted or down-regulated in various cancers	[100, 130, 131, 134, 136-138]
A20	targets multiple NF-κB signaling molecules	tumor suppressor; mutated, deleted or down-regulated in various lymphomas	[124-128, 256]
PDLIM2	promotes nuclear RelA degradation	potential tumor suppressor; epigenetically downregulated in various types of cancer	[144-147]
WWOX	inhibits HTLV-1 Tax induced RelA phosphorylation and NF-κB activation	inhibits tumor growth; deleted or downregulated in various types of cancer	[257-263]
CHFR	negatively regulates RelA transcriptional activity	potential tumor suppressor; silenced in various cancer	[264]
LZAP	impairs RelA phosphorylation and transcription activity	inhibits cellular proliferation and clonogenic growth; downregulated in human head and neck squamous cell carcinomas	[265]
NLBP	inhibits RelA transcription activity	inhibits cell invasion; downregulated in invasive cancer cells	[266]
PIAS1	blocks the DNA binding activity of RelA	tumor suppression function; downregulated in multiple myeloma and colon cancer	[267-269]
LDOC1	inhibits TNF-α and PMA induced NF-κB activation	sensitizes pancreatic cancer cells to apoptosis; downregulated in pancreatic cancer	[270]
OPTN	inhibits NF-κB activation; competes with NEMO for ubiquitinated RIP binding	its mutation is linked with some forms of glaucoma	[271, 272]
MENIN	interacts with RelA, p50 and p52; represses RelA transcriptional activity	tumor suppressor; is mutated or deleted in parathyroid tumors	[273]
ARF	represses RelA transcriptional activity by ATR- and Chk1-dependent phosphorylation	central component of the cellular defense against oncogene activation	[274]
RKIP	interacts with NIK, TAK1 and IKKs; inhibits TNF-α induced IKK activation	inhibits prostate cancer metastasis	[275-277]
KEAP1	induces IKK2 degradation and inhibits IKK2 phosphorylation	functions as tumor suppressor, and mutated in multiple types of cancer	[278-280]
PP2A	dephosphorylates MEKK3; inhibits LPS induced IKK2 and NF-κB activation	involved in growth suppression, enhances apoptosis, restores differentiation, impairs clonogenic potential	[281, 282]

Abbreviation: CHFR: checkpoint with forkhead and ring finger domains; LZAP: LXXLL/leucine zipper-containing alternative reading frame (ARF)-binding protein; NLBP: novel LZAP-binding protein; PIAS1: protein inhibitor of activated STAT, 1; LDOC1: leucine zipper, down-regulated in cancer 1; OPTN: optineurin; MENIN: multiple endocrine neoplasia I; ARF: cyclin-dependent kinase inhibitor 2A (p16); ATR: ataxia telangiectasia mutated (ATM) and Rad3-related checkpoint kinases; Chk1: checkpoint kinase 1; RKIP: Raf-kinase inhibitor protein; KEAP1: kelch-like ECH-associated protein 1; PP2A: serine/threonine protein phosphotase 2A.

CYLD, another deubiquitinase (DUB) that plays a key role in NF-κB termination, was originally identified as a tumor suppressor that is mutated in familial cylindromatosis, an autosomal-dominant predisposition to multiple tumors of skin appendages including multiple familial trichoepithelioma and Brooke-Spiegler syndromes [130]. The genetic mutations of the *cyld* gene involve loss of heterozygosity (LOH) and mutations (**Figure 4**). Interestingly, in all cases the allele lost is the wild-type allele inherited from the parent not carrying mutations and all

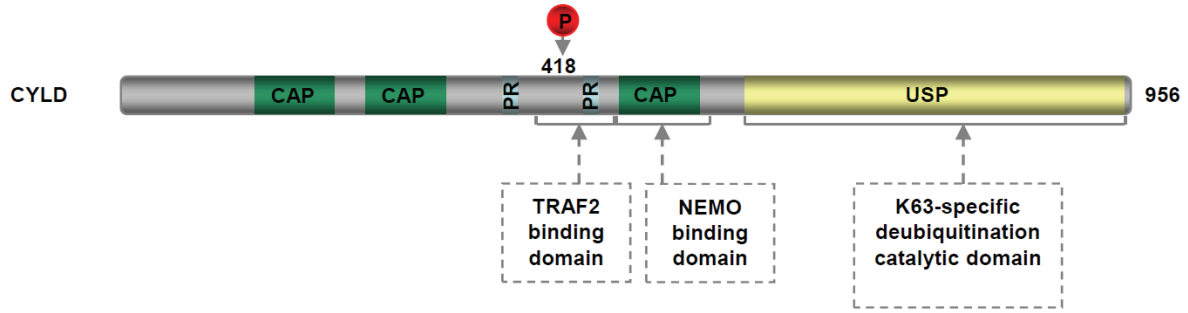

Figure 4. Domain structure of CYLD. CAP: cytoskeletal-associated protein-glycine-conserved repeats; PR: proline-rich region; USP: ubiquitin carboxy-terminal hydrolases domain.

mutations predict absence, truncation or mutation of the encoded protein, leading to loss of the DUB activity of CYLD [131-134]. These findings suggest the importance of the DUB activity in the tumor suppressor function of CYLD. However, the direct evidence came from a more recent study showing a strong tumorigenicity of a CYLD point mutant defective in the deubiquitinating function that mimics the identified mutations of *cyld* in human tumors [135]. In addition to skin cancers, inactivating mutation or downregulation of CYLD has been detected in several human cancers including colon cancer, hepatocellular carcinoma (HCC), T-cell acute lymphoblastic leukemia (T-ALL), multiple myeloma (MM) and melanoma, and is inversely correlated with NF-κB activation, tumor progression and patient's survival [100, 136-138]. Thus, inactivation of CYLD DUB catalytic activity by any mechanism contributes to tumorigenesis by promoting unchecked NF-κB activity and enhanced cell survival. Consistent with the tumor suppressor role of CYLD, *cyld*-deficient mice exhibit increased susceptibility to cilitis-associated tumorigenesis and chemically induced skin tumors [8, 139]. Mechanistic studies further indicate that CYLD deficiency leads to sustained NF-κB activity by increasing K63-linked ubiquitination and/or nuclear translocation of NF-κB activators/co-activator such as TRAF2, NEMO and Bcl-3. Interestingly, recent studies show that CYLD is negatively regulated by miR-181b, a microRNA (miRNA) that is upregulated during cellular transformation and in acute lymphocytic leukemia (ALL) [140, 141]. More importantly, expression of miR-181b inhibits CYLD, leading to increased NF-κB activity required to maintain cell transformation. These studies provide a different mechanism for the oncogenic deregulation of CYLD and NF-κB.

Like A20 and CYLD, PDLIM2 is also required for the termination of NF-κB, although the involved mechanisms are totally different [46] (**Figure 5**). Thus, it should be no surprise if PDLIM2 is linked to tumor suppression. Indeed, recent studies indicate that expression of PDLIM2 is significantly downregulated in several NF-κB-associated tumors, including adult T-cell leukemia/lymphoma (ATL), breast cancer and colorectal cancer [142-147]. More importantly, expression of exogenous PDLIM2 or reinduction of endogenous PDLIM2 inhibits constitutive NF-κB activation and suppresses the in vitro anchorage-independent growth and in vivo tumor formation of these malignant cells [144, 146, 147]. In contrast, PDLIM2 mutants defective in NF-κB repression lose the tumor suppressive function. It is noteworthy that in the case of ATL,

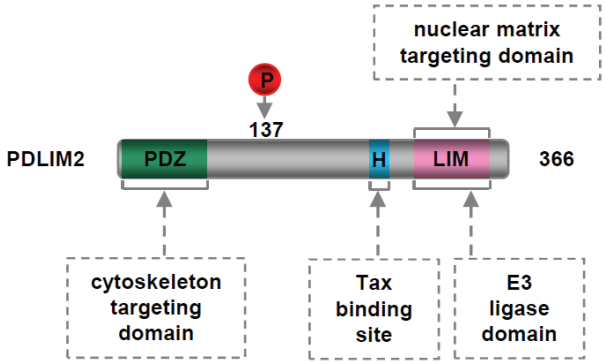

Figure 5. Domain structure of PDLIM2. PDZ: postsynaptic density 65-discs large-zonula occludens 1; H: putative α-helix motif; LIM: abnormal cell lineage 11-islet 1-mechanosensory abnormal 3.

Table 4. NF-κB regulating microRNAs in cancer

miRNA	Targets in NF-κB Signaling	Alteration in Cancer	Cancer linkage	Other Targets Linked to Cancer	References
	NF-κB members				
miR-9	NF-κB1	epigenetically down-regulated	gastric cancer and clear cell renal cell carcinoma	E-cadherin	[283-286]
miR-125b	Bcl-3	downregulated	human liver cancer, melanoma, glioma, ovarian cancer, bladder cancer and breast cancer	LIN28B2; MUC1; E2F3; Endothelin-1; BAK1; BMF; CYP24; p53	[165, 166, 170, 287-292]
	NF-κB activators				
miR-15a, miR-16	IKK1	downregulated; deleted	chronic lymphocytic leukemia, multiple myeloma, lung squamous cell carcinoma and ovarian cancer	BMI-1	[293-297]
miR-223	IKK1	downregulated	chronic lymphocytic leukemia and acute myeloid leukemia	E2F1	[296, 298, 299]
miR-218	IKK2	downregulated	glioma, gastric cancer and lung squamous cell carcinoma	ROBO1; LASP1	[300-304]
miR-199a	IKK2	downregulated	breast cancer, melanoma and bladder cancer	MET; KRT7	[163, 305-307]
miR-146a	IRAK1 TRAF6	downregulated	breast cancer and pancreatic cancer	-	[308-310]
	NF-κB inhibitors				
miR-181b-1	CYLD	upregulated	acute lymphocytic leukemia	-	[140, 141]
miR-301a	NRF	upregulated	pancreatic tumor	-	[311]

which is mediated by the HTLV-I retrovirus, the tumor suppression role of PDLIM2 is much more complicated, since PDLIM2 also promotes ubiquitination and degradation of the viral oncoprotein Tax, a potent NF-κB activator that is largely responsible for HTLV-I-mediated pathogenesis [144]. In fact, Tax inhibition plays a predominant role in PDLIM2-mediated ATL suppression [47, 109]. One mechanism contributing to the oncogenic PDLIM2 downregulation involves the methylation of the *pdlim2* promoter [145-147]. Although not reported yet, the genetic alterations of the *pdlim2* gene could also be involved in the PDLIM2 downregulation in tumors, as the *pdlim2* gene is located at chromosome 8p21.1, a region that frequently undergoes allelic loss in a number of tumor types including breast, colon, live, lung, *stomach*, prostate and ovarian cancer [143, 148-157]. Furthermore, the activity of PDLIM2 is regulated by protein phosphorylation [158, 159], suggesting another potential mechanism for PDLIM2 inactivation in tumor.

In addition to those 'traditional' repressors, NF-κB is negatively regulated by many miRNAs, which induce mRNA degradation or inhibit mRNA translation of NF-κB or its key signaling components (**Table 4**). Downregulation or deletion of these miRNAs has been detected in a broad range of human tumors including leukemias, lymphomas and solid tumors. For instance, miR-125b, which targets the *bcl-3* oncogene, is downregulated in multiple types of tumor, including hepatocellular carcinoma (HCC), breast cancer, oral cancer, bladder cancer, anaplastic thyroid carcinomas, metastatic cutaneous malignant melanoma, head and neck squamous cell carcinomas (HNSCC) and ovarian cancer [160-166]. In fact, the downregulation of miR-125b is often associated with tumor progression and patient's survival. In support of the tumor suppressor role of miR-125b, expression of exogenous miR-125b blocks the tumorigenicity of these malignant cells. Interestingly, the tumor suppression effect, at least the anti-growth activity of miR-125b can be antagonized by expression of Bcl-3 [166]. It should be pointed out that some NF-κB repressor miRNAs including miR-125b are already known target genes of NF-κB [167-171], further supporting the idea that disruption of feedback inhibition of NF-κB is a common and important mechanism of NF-κB pathogenic activation and human tu-

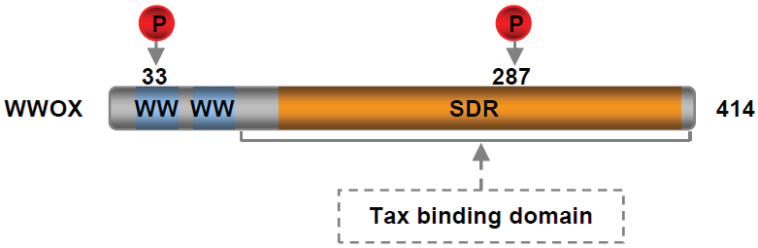

Figure 6. Domain structure of WWOX. WW: WW domain; SDR: short-chain dehydrogenase/reductase domain.

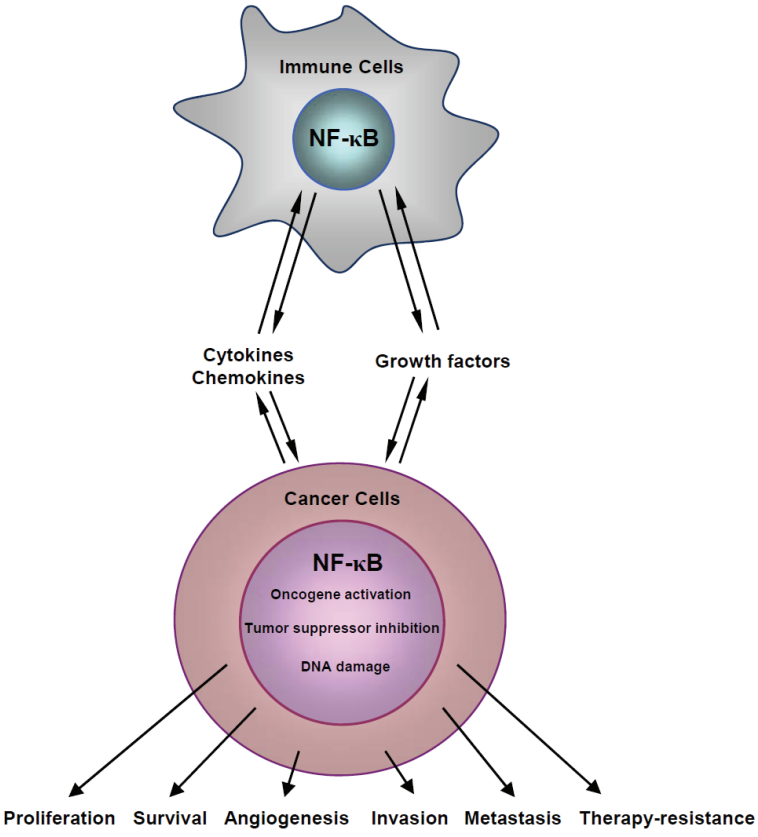

Figure 7. Current model depicting the NF-κB-dependent interaction between inflammatory cells and malignant cells in tumorigenesis.

been little progress on whether and how the two signaling pathways cooperate during tumorigenesis. Using the Tax viral oncoprotein as a model, a recent study provides the first example of how the deregulated canonical and non-canonical NF-κB pathways collaborate in tumorigenesis [48]. While Tax activation of the canonical NF-κB pathway induces p100 expression, Tax-induced p100 processing to generate p52 (activation of the non-canonical NF-κB pathway) leads to transcriptional downregulation of the WW domain-containing oxidoreductase (*wwox*), a tumor suppressor gene that has been linked to various tumors including breast cancer, ovarian tumor, lung cancer, gastric carcinoma, pancreatic adenocarcinoma, hematopoietic neoplasia and squamous cell carcinoma [172] (**Figure 6**). Notably, WWOX specifically inhibits Tax-induced activation of the canonical, but not the non-canonical NF-κB pathway. Mechanistic studies indicate that WWOX blocks Tax-induced IKK1 recruitment to RelA and subsequent RelA phosphorylation at serine 536, which is required for RelA transcriptional activity. In contrast, WWOX Y33R, a mutant unable to block the IKK1 recruitment and RelA phosphorylation, loses the ability to inhibit Tax-mediated tumorigenesis. It can be speculated that many targets genes other than *nf-κb2* and *wwox* may also contribute to the oncogenic coordination between the two pathways. Since both NF-κB activation and WWOX inactivation are associated with many different cancers in addition to Tax-associated tumorigenesis, it is of interest to investigate whether and how they cross-talk in general tumorigenesis.

morigenesis.

Oncogenic interplay between NF-κB pathways

Both the canonical and non-canonical NF-κB pathways have been linked to tumorigenesis and in many cancers they are simultaneously deregulated. However, until recently there has

Role of NF-κB in tumorigenesis

As a transcription factor, NF-κB is involved in all stages of tumorigenesis from initiation all the

way to metastasis by regulation of expression of various tumor-related genes (**Figure 7**). Like tumor itself, however, the role of NF-κB in tumorigenesis is complex and dynamic. During tumor initiation, NF-κB within pre-malignant cells and possibly also their neighbors is activated to induce expression of chemokines and cytokines, leading to the recruitment and activation of immune cells, particularly myeloid cells. Activated immune cells in turn produce a large amount of pro-inflammatory cytokines/chemokines and growth factors, such as IL-1, IL-6, TNF, and EGF, which is also through NF-κB activation within the cells [1]. These secreted cytokines, growth factors and other bioactive molecules act on both malignant and inflammatory cells in an autocrine and/or paracrine manner, generating a complex inflammatory and protumorigenic microenvironment. The NF-κB-mediated inflammation contributes to DNA damage and induction of oncogenic mutations (activating mutations of oncogenes and/or inactivating mutations of tumor suppressor genes) in pre-malignant cells through both NF-κB dependent [induction of the 'mutagenic' enzyme activation-induced cytidine deaminase (AID) and suppression of DNA damage gatekeepers such as p53] and independent [production of reactive oxygen and nitrogen species (ROS and RNS)] mechanisms [173-176], facilitating tumor initiation and progression. Furthermore, NF-κB, which is activated by NF-κB-induced cytokines and growth factors as well as inflammation-induced ROS/RNS and DNA damage, regulate the transcription of genes involved in cell survival, proliferation, angiogenesis, invasion and metastasis, promoting tumor growth and progression. Thus, NF-κB participates in tumorigenesis in both extrinsic (inflammatory cells) and intrinsic (tumor cells) ways.

Conclusions and perspectives

There is no doubt that NF-κB plays a critical role in tumorigenesis. However, many key issues have not been addressed yet. First, the significance of the NF-κB members themselves in tumorigenesis has been rarely studied. Most evidences linking NF-κB to tumorigenesis are from studies on the knockout of NF-κB regulators. As we already know, almost all known NF-κB regulators, such as IKK, A20, CYLD, and PDLIM2, also regulate signaling pathways other than NF-κB, and many of them have already been linked to tumorigenesis [34, 177-180]. Thus, the functions of these regulators in tumorigenesis may not be attributed to NF-κB. Second, the mechanisms by which NF-κB interacts with other signaling pathways in tumorigenesis remain largely unknown. In fact, how the two NF-κB pathways cooperate in tumorigenesis still remains unclear. In this regard, overexpression of the super-repressor forms of IκBα or knockout of *rela* or *nf-κb2* or even IKK components fails to completely block, although significantly reduces, tumor genesis and progression in different tumor models. On the other hand, NF-κB is known to crosstalk with many other tumor-related signaling pathways such as autophagy, STAT3 and p53 [1, 2, 177, 181-184]. Third, most studies are focused on the net effect of NF-κB activation on tumor tumorigenesis. As an old Chinese saying goes, everything has both yin and yang aspects, and so does NF-κB. Although NF-κB activation contributes to tumorigenesis in general, it may also play a negative role in certain stages of tumorigenesis and even exert a net negative effect on tumorigenesis in certain situations. One mechanism of NF-κB-mediated tumor suppression involves its original function in immunity and immunosurveillance. Currently, it is still unknown how the anti-tumor activity is suppressed and transformed to be protumorigenic. Paradoxically, the survival function of NF-κB may also contribute to tumor suppression by preventing tissue damage and oxidant accumulation as well as the activation of other signaling pathways such as c-Jun N-terminal kinase (JNK). Indeed, a tumor suppressive function of NF-κB has been suggested in several skin and liver cancer models [185-189]. Furthermore, very few of downstream targets of NF-κB that play a critical role in tumorigenesis have been clearly and comprehensively identified. Future genetic studies, particularly those involved in the inducible and conditional transgenic mice, and computational modeling analysis will help understand the complex and dynamic role of NF-κB in tumorigenesis and help design personalized treatments for cancer patients.

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