

Endogenous Inhibitors of Nuclear Factor- κ B, An Opportunity for Cancer Control

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Abstract

Excessive and prolonged activation of nuclear factor- κ B (NF- κ B) has been linked to numerous human diseases, especially cancer, because of the elevated expression of genes encoding antiapoptotic proteins, cytokines, chemokines, cell adhesion molecules, and so on. Eukaryotic cells have developed multiple mechanisms to keep this ubiquitous transcription factor in check. In addition to the inhibitor of κ B family proteins, a number of endogenous molecules that negatively regulate the activation or activity of NF- κ B have been identified. These molecules include A20, CYLD, cyPG15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂, Foxj1, Twist proteins, and β -arrestins. The extended list of these endogenous inhibitors of NF- κ B may provide new opportunities for the development of novel strategies for the intervention of malignant transformation. The question to be asked is how NF- κ B is sustained activated in a number of cancers in which so many antagonists are surrounded.

Introduction

Carcinogenesis is a malfunction of the cells in the human body. It is caused by one or more intracellular biochemical changes, most frequently in combination with external factors (1). Originally it was thought that cancer is the result of genetic disorders ranging from point mutations to insertions and deletions of chromosomal DNA. The completion of Human Genome Project and the potential for gene-based therapies have raised expectations that in the future gene-targeted cancer therapy will lead to efficient and specific treatments. However, a number of nongenetic factors, such as the regulation of gene expression, post-transcriptional modification, and the kinase-based signal transduction, cannot be ignored (2). In this regard, the delineation of nuclear factor- κ B (NF- κ B) signaling and function has made a profound impact on our understanding of carcinogenesis (3). This knowledge should make it possible to target NF- κ B as a unique strategy for carcinogenic control.

The transcription factor NF- κ B has been the focus of investigation by a number of biologists for nearly 2 decades after its discovery by Drs. Sen and Baltimore (4). During the past decade, tremendous progress has been made in our understanding of how this transcription factor is activated. Two major pathways account for the activation of NF- κ B (5). In response to inflammatory stimuli, the canonical pathway is initiated by the activation of IKK β subunit of the IKK complex that phosphorylates inhibitor of κ B α (I κ B α) and targets it for ubiquitin-dependent proteasomal degradation. The alternative pathway is triggered mainly by B cell-activating factor (BAFF) or lymphotoxin that selectively activates NF- κ B-inducing kinase (NIK) and the IKK α subunit of IKK complex, resulting in the phosphorylation-dependent proteolytic removal of the I κ B-like COOH-terminus of NF- κ B2 (p100). Both pathways are affected by a number of other signaling pathways that cross-talk with NF- κ B, either positively or negatively.

Multiple kinases, adapter proteins, and modifying molecules, mainly ubiquitin and small ubiquitin-like modifier (SUMO), play a critical role in these two pathways. In the nuclei, the activated NF- κ B undergoes several different modifications, including phosphorylation, acetylation, and even SUMOylation, on its subunits. The transcriptional activity of NF- κ B for a given gene is further affected by the location, number, and fidelity of canonical NF- κ B binding sites (κ B elements), the neighboring enhancer or repressor elements, the availability of cofactors, the accessibility of κ B element because of the modification of histone proteins in the nearby chromatin structure, and the redox status of local microenvironment.

Evidence indicating the contribution of NF- κ B to cancer has been firmly established by the observation of persistent NF- κ B activation in many types of malignancies (3, 6). The antiapoptotic activity of NF- κ B appears to be the most important mechanism mediating the carcinogenic effect of NF- κ B. Thus, there are excellent reasons to believe that curbing NF- κ B would be an effective weapon in the arsenal against cancer. More than 100 compounds have been shown to be potent inhibitors of activation or activity of NF- κ B. The typical compounds include proteasome inhibitors, antioxidants, nonsteroidal anti-inflammatory drugs, and reagents suppressing immune system. However, the poor specificity of these compounds makes clinical application difficult. In addition to the I κ B family proteins, the identification of several endogenous NF- κ B inhibitors has raised hope for a relatively specific inhibition of NF- κ B signaling. These endogenous inhibitors of NF- κ B fall into two groups. The first group acts on the activation signaling pathways by interfering with the activation of IKK kinase or the ubiquitination of I κ B proteins. The second group mainly affects the transcriptional activity of nuclear-translocated NF- κ B by competing with cofactors or directly preventing the tethering of histone acetyltransferases (HATs) by NF- κ B subunit RelA/p65. In this brief review, I will discuss several molecules that recently have been shown to down-regulate the activation or activity of NF- κ B.

cyPG15-Deoxy- $\Delta^{12,14}$ -prostaglandin J₂

Cyclopentenone prostaglandins are metabolic products of arachidonic acid. cyPG15-Deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂) is formed by dehydration and isomerization of the cyclooxygenase metabolite prostaglandin D₂. As a natural ligand and agonist of the peroxisome proliferator-activated receptor γ (PPAR γ), the anti-inflammatory activity of 15d-PGJ₂ was originally attributed to the activation of PPAR γ that antagonizes the transcriptional activity of NF- κ B (7, 8). Further studies suggest that 15d-PGJ₂ inhibits I κ B α phosphorylation and degradation through inhibition of the kinase activity of IKK β (9, 10). In HeLa cells, which do not express PPAR γ , 15d-PGJ₂ inhibited tumor necrosis factor α (TNF- α)-induced IKK activity in a dose-dependent manner (11). A characteristic structure of 15d-PGJ₂ and its metabolites is the cyclopentenone ring containing an electrophilic reactive α , β unsaturated carbonyl group. This structure is not required for the interaction with PPAR γ but appears to be able to form Michael adducts with cellular nucleophiles, such as cysteine 179 of IKK β within the activation loop (11). The cyclopentenone ring

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structure of 15d-PGJ₂ also is accountable for the covalent modification of the cysteine residues in p50 and p65 subunits, which impairs the DNA binding activity of NF- κ B (9).

CYLD

CYLD is a tumor suppressor gene found in cylindromatosis, a disease associated with numerous benign skin adnexal tumors that occur in hair follicles and cells of the sweat and scent glands (12). Genetic analysis revealed mutations in CYLD in the germline of cylindromatosis families and sporadic cylindromatosis cases. The CYLD gene product is a protein with 956 amino acids harboring three glycine-rich regions found in some cytoskeleton-associated proteins and two COOH-terminal motifs that share similarity with the cysteine and histidine boxes found in ubiquitin COOH-terminal hydrolases. The mutation of *CYLD* gene creates premature stop codons or frameshift alterations, leading to proteins truncated in the COOH terminus and missing the ubiquitin-specific protease domain. In the upstream of NF- κ B activation cascade, TRAF2 and NEMO/IKK γ , a component of the IKK kinase complex, are conjugated with polyubiquitin chains by Ubc13/Uev1(Mms2) ubiquitin-conjugating enzyme complex that catalyzes the formation of a lysine 63 (K63)-linked polyubiquitin chain (13, 14). The majority of ubiquitination in which the proteins are ubiquitinated with K48 polyubiquitin chains targets proteins for proteasomal degradation (e.g., I κ B α , p53, and Cdc25C; ref. 15). However, this is not the case of TRAF2 and NEMO, which are ubiquitinated by polyubiquitin chains assembled through K63. The K63 ubiquitination of TRAF2, NEMO, and possibly TRAF6 triggers assembly and activation of IKK complex. Recent studies suggest that CYLD is capable of deubiquitinating K63 polyubiquitin chain on TRAF2 and NEMO by direct interaction with these two proteins, leading to the disassembly of IKK complex and the inhibition of NF- κ B activation (16–18). Loss of the deubiquitinating activity of the mutated CYLD correlates with a sustained activation of NF- κ B, which is accountable for the predisposition of cylindromatosis.

A20

A20 is a zinc finger protein originally identified as an NF- κ B-regulated adapter protein associated with TNF- α receptor complex. The inhibitory activity of A20 on NF- κ B activation first was observed in the breast carcinoma cell line MCF7S1 treated with TNF- α or interleukin 1 (IL-1; ref. 19). It is intriguing to note that A20 enhances the recruitment of IKK complex to the TNF- α receptor but decreases the activity of IKK (20). The ability of A20 to block NF- κ B activation was mapped to its COOH-terminal zinc finger domains, which interact with IKK (20), whereas the TRAF binding domain is located in the NH₂ terminus (21). A recent study by Wertz *et al.* (22) suggested a dual function for A20 in the regulation of protein ubiquitination involved in NF- κ B signaling. A20 participates in deubiquitination through a deubiquitinating enzyme domain found in the NH₂-terminal half of the protein. This domain is able to remove K63-linked ubiquitin chains from receptor interacting protein (RIP), an important component of TNF receptor complex. In contrast, the fourth zinc finger at the COOH terminus serves as an ubiquitin ligase by conjugating RIP with K48-linked ubiquitin chains for proteasomal degradation. A detailed biochemical study indicated that the removal of K63-linked ubiquitin chains on RIP by NH₂-terminal deubiquitinating enzyme domain of A20 is a prerequisite for the A20 COOH-terminal zinc finger 4-mediated RIP degradation through K48-linked ubiquitin chains. The K63-ubiquitinated RIP may stabilize association of proximal signaling components with IKK complex. Therefore, the removal of K63 ubiquitin chains from RIP by A20 and the degradation of RIP caused by the addition of K48-linked ubiquitin chains will terminate

NF- κ B signaling. However, A20 appears to be unable to deubiquitinate K63-linked ubiquitin chains on TRAF2 or NEMO (23).

SUMO

SUMO is the best-characterized member of a growing family of ubiquitin-related proteins, and it shares 18% sequence identity with ubiquitin (24). Conjugation of protein with SUMO, SUMOylation, has profound impact on protein transportation, location, and stability. A number of cellular processes, including mitosis, DNA repair, and gene transcription, require protein SUMOylation. Vertebrate species are known to express four members of SUMO: SUMO1, SUMO2, SUMO3, and SUMO4 (25). It has been shown that >50 proteins are conjugated by SUMO, among which the SUMOylation of RanGAP1, I κ B α , p53, PCNA, c-Jun, PML, and histone deacetylases are extensively studied. A common feature of the proteins modified by SUMO is the Ψ KXE motif, in which Ψ is a large hydrophobic residue, K is lysine, X is any residue, and E is glutamic acid. This motif possibly serves as a binding site of Ubc9, a SUMO-conjugating enzyme (E2). The first evidence indicating negative regulation of SUMO on NF- κ B signaling was provided by Desterro *et al.* (26), who showed that I κ B α was modified by SUMO1 on K21, a site which can be conjugated with a K48-linked ubiquitin chain by β TrCP-SCF ubiquitin ligase. Thus, modification of I κ B α by SUMO protects I κ B α from ubiquitin-mediated degradation and consequently prevents the activation of NF- κ B, especially under hypoxic conditions (27). This conclusion is further supported by a recent identification of a functional variant of SUMO4 (28). In this variant, a conserved methionine (Met55) was substituted by valine residue (M55V) as a result of a single nucleotide polymorphism-associated type I diabetes (28). Substitution of Met55 with Val substantially decreased the inhibitory effect of SUMO4 on NF- κ B activation, presumably because of its poor ability of conjugation with I κ B α . NEMO, a component of IKK kinase complex, also can be modified by SUMO in the nucleus under genotoxic stress conditions (29). However, the SUMOylation of NEMO does not inhibit but rather activates NF- κ B by providing nuclear export signals for NEMO, which assembles IKK complex in cytoplasm.

β -Arrestins

The arrestin family consists of four members: β -arrestin1, β -arrestin2, α -arrestin, and s-arrestin (30). β -Arrestin1 and β -arrestin2 are ubiquitously expressed in virtually all of the cell types, whereas α -arrestin and s-arrestin are found exclusively in the visual system. All of the arrestins interact with seven-membrane-spanning receptors after their phosphorylation by G protein-coupled receptor (GPCR) kinases. Under physiologic conditions, the main function of β -arrestins (β -arrestin1 and β -arrestin2) is to desensitize the second-messenger signaling mediated by β 2-adrenergic receptor, a subtype of GPCR. The overall structure of the β -arrestin1 and β -arrestin2 is similar, with an arrestin domain at the NH₂ terminus, followed by a COOH-terminal arrestin domain and a potential nuclear export signal domain, which is responsible for the cytosolic localization. The sequence identity is as high as 77% and 78% in the NH₂- and COOH-terminal arrestin domains, respectively. Gene knockout studies suggest that deletion of β -arrestin1 and β -arrestin2 produces remarkably similar effects, suggesting redundant functions in the regulation of cellular functions. In addition to the regulation of GPCR signals, increasing evidence suggests that β -arrestins also serve as modulators for a number of intracellular signaling pathways, including p53, mitogen-activated protein kinase, transforming growth factor β , insulin-like growth factor I, phosphatidylinositol 3'-kinase-Akt, and Wnt5a (30).

Working with different types of cell lines, Gao *et al.* (31) and

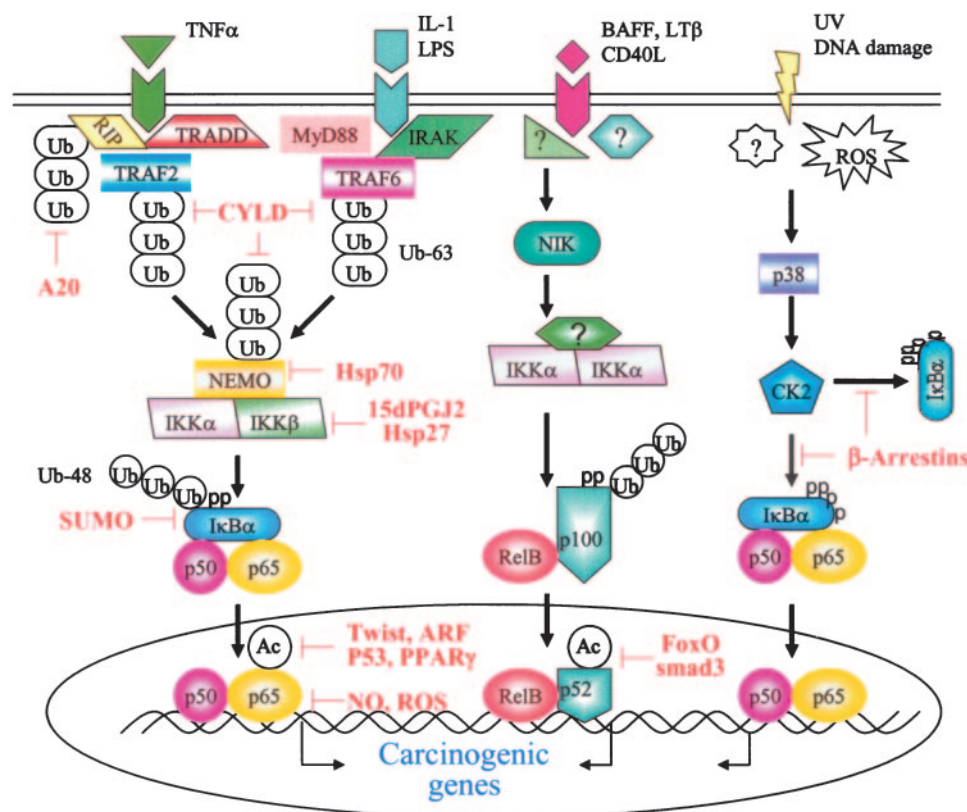


Fig. 1. Inhibition of NF- κ B activation or activity by endogenous inhibitors. Black arrows denote the signaling pathways for NF- κ B activation. Red lines indicate the inhibition of signaling points by endogenous NF- κ B antagonists (red). Ub-63 and Ub-48 indicate the polyubiquitin chains assembled through lysine 63 and lysine 48, respectively. NO, nitric oxide; ROS, reactive oxygen species; p, phosphorylation; Ac, acetylation. (Adapted in part from Ben-Neriah and Schmitz [47].)

Witherow *et al.* (32) discovered that either β -arrestin1 or β -arrestin2 can ablate signal-induced activation of NF- κ B transcription factor. A direct interaction of β -arrestins with I κ B α protein was observed in the yeast two-hybrid and immunoprecipitation assays. Furthermore, β -arrestins are able to interact with IKK α , IKK β , or NIK in an over-expression system (32). These observations suggest possible effect of β -arrestins on either I κ B α phosphorylation or degradation. Because β -arrestins inhibit NF- κ B activation in response to broad extracellular stimuli, including TNF- α , carbachol, and pervanadate, it is likely that β -arrestins affect general NF- κ B activation signaling, such as I κ B α degradation. A series of deletion mutant experiments indicated that I κ B α stabilization is determined by the NH₂-terminal 1 to 60 amino acid of β -arrestin2 that interacts with the COOH-terminal PEST domain of I κ B α protein (31). The IKK kinase and casein kinase 2 can phosphorylate the PEST domain of I κ B α protein under conditions of oxidative stress or DNA damage (33). The phosphorylation of PEST domain of I κ B α mainly regulates the basal or inducible turnover of free I κ B α protein in a proteasome-independent manner. Thus, the binding of β -arrestins with the COOH terminus of I κ B α will make the PEST domain inaccessible for either IKK or casein kinase 2, leading to the stabilization of I κ B α protein, especially the unassociated cytosolic I κ B α protein.

Nuclear Antagonists

It has been known for a decade that liberation of NF- κ B from its inhibitors in cytosol and translocation of NF- κ B to nucleus alone are not sufficient to induce NF- κ B-dependent transcription. The NF- κ B complex must undergo further modifications, most importantly, the phosphorylation and acetylation of NF- κ B subunits, for its maximal activity. Both p50 and RelA/p65 are phosphorylated in response to extracellular signals (34, 35), which enhance the binding of HATs or displace transcriptionally repressive histone deacetylase complexes (HDACs) to either RelA/p65 or p50. The majority of nuclear antag-

onists of NF- κ B, such as p53 (36), ARF (37), Twists (38, 39), N-CoR (40), and PPARs (41), can either compete with NF- κ B for HATs or recruit HDACs to NF- κ B to negatively regulate the acetylation of p50 or RelA/p65, leading to the decrease of DNA binding activity and transcription activity of NF- κ B. The forkhead box-containing proteins (Fox), Foxj1 and FoxO3a, recently have been shown as nuclear antagonists of NF- κ B (42, 43). Foxj1 and FoxO3 are able to up-regulate the expression of I κ B β or I κ B ϵ that can bind to and ferry the NF- κ B complex from nucleus to cytosol. An alternative mechanism of Foxj1 and FoxO3 on NF- κ B is possibly through Smad3, a nuclear protein belonging to transforming growth factor β signaling pathway (44). Smad3 not only can interact with NF- κ B subunit (45) but also can recruit HDAC1 to repress the acetylation and function of NF- κ B (44, 46).

Summary

In addition to the endogenous NF- κ B inhibitors described above, a number of other factors have been reported as negative regulators of NF- κ B. These factors include heat shock protein 70, heat shock protein 27, nitric oxide, PTEN, SOCS1, IL-4, IL-10, IL-11, IL-13, and PISA3. The discoveries of more endogenous NF- κ B inhibitors will unequivocally provide more opportunities for the effective control of NF- κ B activation or activity in the process of carcinogenesis. The question that follows is, how does NF- κ B dodge these surrounding endogenous inhibitors in the malignantly transformed cells? It is unlikely that all of these endogenous inhibitors are simultaneously disabled to render a cell to undergo transformation. It is more likely that these endogenous inhibitors are effective in the control of NF- κ B activation or activity only in the early stage of cancer cells, during which the number of mutations is limited. As the cancer progresses, these endogenous inhibitors may be less able to control NF- κ B activation or activity because of the accumulation of multiple carcinogenic signals.

It is undisputable that NF- κ B is important for tumor development. However, it also should be noted that some data suggested tumor suppressive activity of NF- κ B (6), depending on the involvement of signaling pathways for activation, composition of NF- κ B subunits, availability of other tumor suppressors, and cell types. The benefit of endogenous *versus* exogenous inhibitors of NF- κ B is that these inhibitors may be capable of distinguishing different NF- κ B signaling pathways, NF- κ B dimers, or NF- κ B cofactors (Fig. 1). This is especially critical if NF- κ B inhibition is to evolve as an important factor in cancer therapies. Obviously we need to ablate the tumor-promoting activity rather than the tumor-suppressive activity of NF- κ B.

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