


The transcription factor NF- κ B: control of oncogenesis and cancer therapy resistance

Marty W. Mayo, Albert S. Baldwin *

Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA

Received 30 November 1999; accepted 5 January 2000

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Abstract

Discovered in 1986 as a DNA binding activity that recognized the immunoglobulin light chain intronic enhancer, NF- κ B has been studied intensively for its role in controlling expression of genes involved in immune and inflammatory function [1,2]. However, more recently, NF- κ B has been implicated in controlling cell growth and oncogenesis. The link between NF- κ B and cancer stems, in part, from the fact that this transcription factor is capable of inducing gene products that control proliferative responses and that suppress apoptotic cascades, such as those induced by tumor necrosis factor (TNF), expression of oncoproteins, and genotoxic stress. This latter observation is likely to be important in developing new approaches aimed at improving the efficacy of cancer chemotherapy. © 2000 Elsevier Science B.V. All rights reserved.

1. Activation and regulation of NF- κ B

NF- κ B factors are dimers of Rel family of proteins. There are presently five members of the NF- κ B family: p50/p105 (NF- κ B1), p52/p100 (NF- κ B2), c-Rel, RelB, and p65 (RelA). These proteins are characterized by their Rel homology domains which control DNA binding, dimerization and interactions with inhibitory proteins known as I κ B (reviewed in [1,2]). Several I κ B genes (I κ B α , I κ B β , I κ B ϵ) have been identified and their gene products have been shown to function to retain NF- κ B proteins in the cytoplasm [1,2]. The I κ B proteins physically interact with NF- κ B to block the nuclear localization sequences of NF- κ B, thus regulating both transient and persistent nuclear levels of NF- κ B. Another member of the I κ B family, Bcl-3, interacts with p50 and p52

subunits of NF- κ B, but rather than functioning to inhibit NF- κ B transcriptional activity, Bcl-3 functions to stimulate transcription and to promote nuclear localization [1,2]. In most cell types, NF- κ B complexes are largely cytoplasmic and transcriptionally inactive until a cell receives the appropriate stimuli. In response to pro-inflammatory cytokines, such as TNF and interleukin-1 (IL-1), or bacterial lipopolysaccharide (LPS) the I κ B proteins become phosphorylated on two serine residues located within the N-terminal region [1,2]. Phosphorylation occurs on Ser-32 and Ser-36 of I κ B α and on Ser-19 and Ser-23 of I κ B β . Phosphorylation of the I κ B proteins results in rapid ubiquitination and subsequent proteolysis by the 26S proteasome. Proteasome-dependent degradation of the I κ B proteins results in the liberation of NF- κ B allowing this transcription factor to accumulate in the nucleus where it activates the expression of specific gene targets [1,2].

Recently, a large molecular weight complex responsible for phosphorylating I κ B α and I κ B β was

* Corresponding author. Fax: +1-919-966-0444;
E-mail: jhall@med.unc.edu

purified and genes encoding several of the protein subunits were identified (reviewed in [3–5]). The first two subunits to be identified were called I κ B kinase (IKK) α and β . These two proteins contain a Ser/Thr kinase domain in the N-terminal portion of the protein, a leucine zipper, which is responsible for heterodimer formation, and a helix-loop-helix domain in the carboxy-terminal region. Although these proteins can form stable homodimers *in vitro*, it is believed that the majority of the kinase activity is associated with the formation of IKK α /IKK β heterodimers. In addition to IKK α and IKK β , another protein subunit has also been associated with the IKK complex called IKK γ or NEMO (NF- κ B essential modulator). IKK γ is present in the IKK complex and is essential for IKK α /IKK β kinase activity perhaps by acting as a structural complex that links the IKK complex to upstream signaling pathways (reviewed in [4,5]).

In addition to I κ B-dependent regulation, NF- κ B transcriptional activity is also positively modulated through signaling events that result in direct phosphorylation of NF- κ B subunits. For example, it has been shown [6] that phosphorylation on Ser-276 by the catalytic subunit of protein kinase A (PKA_c) can contribute to the intrinsic transcriptional capacity of the p65 subunit of NF- κ B. Interestingly, PKA_c was found associated with NF- κ B and I κ B in the cytoplasm and was able to phosphorylate p65 only after I κ B degradation [6]. The phosphorylation of p65 on Ser-276 increases intrinsic transcriptional activity by facilitating interaction with the transcriptional co-activators, CBP (cAMP-responsive element binding protein (CREB)-binding protein) and the closely related factor p300 [6]. Our laboratory has also demonstrated that TNF can stimulate signaling cascades that lead to the phosphorylation of the p65 in the C-terminal transactivation domain 1 (TAD1) on Ser-529 [7]. Similar to phosphorylation on Ser-276, TNF-induced phosphorylation of p65 at Ser-529 does not affect nuclear translocation signals or modulate DNA-binding activity but instead increases the transcriptional potential of p65. Interestingly, a site-directed mutant of p65 (Ser-276 to Ala) is still phosphorylated at Ser-529 in response to TNF treatment [7], suggesting that multiple physiological stimuli modulate p65 through distinct phosphorylation sites to control transcriptional activity. Since the C-terminus of p65 has been shown to interact with basal

transcriptional apparatus proteins like TBP, TFIIB, and TAF105 as well as coactivators, including CBP and p300 [1,2,6], it remains to be elucidated whether the phosphorylation status of the TAD1 domain is involved with regulating interactions with these regulatory proteins. Therefore, as with several transcription factors, NF- κ B is under dual control through mechanisms which govern the regulation of nuclear levels and others which modulate intrinsic transcriptional capacity.

2. NF- κ B is activated during oncogenic transformation and tumorigenesis

Accumulating evidence indicates that NF- κ B plays an important role in the development of cancer and metastasis. Retroviruses that encode v-Rel, a viral homolog of c-Rel, are highly oncogenic and cause aggressive tumors in chickens (reviewed in [8,9]). Interestingly, genes that encode c-Rel, NF- κ B2 (p100/p52), p65/RelA and Bcl-3 proteins are all located within regions of the genome that are involved in rearrangements or amplifications. The gene for c-Rel has been found amplified in some cancer cell lines and rearranged in others [8,9]. The *Bcl-3* gene was originally identified as a [t(14,19)(q32;q13.1)]chromosomal translocation in a subset of B-cell chronic lymphocytic leukemias [10] and is overexpressed in certain B-cell neoplasms [11]. The t(10,14) chromosomal translocation breakpoint associated with NF- κ B2 originally found in a case of B-cell non-Hodgkin's lymphoma [12] is found in number of lymphoid neoplasms, particularly cutaneous lymphomas [13]. Moreover, expression of lymphoma-associated, but not normal p52, induced tumorigenic potential in 3T3 cells in a SCID mouse experiment [14]. In another experiment, it was shown that mice with a homozygous deletion of the C-terminal ankyrin repeats of the p100 precursor exhibited increased lymphocyte proliferation and gastric hyperplasia [15]. Mutations in the I κ B α gene have been detected in Hodgkin's lymphoma [16] and are suggested to contribute to constitutively active NF- κ B in Hodgkin's cells. This observation suggests a tumor suppressor for this inhibitory protein as well as an involvement of NF- κ B in this disease (also see below).

NF- κ B is also directly linked to cellular transformation independent of chromosomal translocation events. For example, it has been shown that NF- κ B is activated by a number of viral transforming proteins and, in some cases, is required for virus-induced transformation. Thus, the Tax protein from the human T-cell leukemia virus-I (HTLV-I) transcriptionally activates NF- κ B. It appears that Tax activates NF- κ B through direct interactions with the IKK complex [17–21]. Activation of NF- κ B was shown to be required for transformation of rat fibroblasts by the HTLV-I Tax protein [22]. In addition, other viral transforming proteins, such as the Epstein–Barr virus (EBV) encoded proteins, EBV protein nuclear antigen 2 (EBNA2) and the latent membrane protein (LMP), the Simian virus-40 (SV-40) encoded large-T, and adenovirus encoded E1A, all stimulate NF- κ B transcriptional activity [23]. Consistent with NF- κ B being involved in transformation and tumorigenesis, many human derived solid tumor cell lines display increased nuclear levels and/or increased NF- κ B-dependent reporter activity in comparison to non-transformed control cell lines [24–27].

More recent evidence confirms the involvement of NF- κ B in oncogenesis. First, it was shown that inhibition of NF- κ B by expression of a modified form of I κ B α (super-repressor I κ B α) blocked focus formation induced by oncogenic H-Ras in NIH3T3 cells [28]. Second, it was shown that the oncogenic fusion protein BCR-ABL activated NF- κ B and that tumorigenesis driven by BCR-ABL could be blocked by expression of the super-repressor I κ B α [29]. Additionally, NF- κ B was shown to be activated in Hodgkin's lymphoma and inhibition of NF- κ B blocked growth of these cells [26]. As mentioned earlier, there are numerous reports of NF- κ B being activated in a variety of tumor cell lines grown in vitro (see [24–27]). For example, the classic form of NF- κ B (p50-p65) has been shown to be activated (i.e. nuclear) in breast cancer cell lines and in some breast tumors [25]. We agree with the observations that NF- κ B appears to be dysregulated in breast cancer, but in contrast to these studies, we find that human breast tumors display an accumulation of nuclear p52 and Bcl-3 rather than p65 [30]. More evidence for the involvement of NF- κ B in cellular transformation comes from Nancy Colburn and colleagues who find that AP-1 and NF- κ B cooperate to promote

proliferation and transformation [31,32]. Recently it has been shown that inhibition of NF- κ B in head and neck squamous cell carcinoma inhibits cell survival and tumor growth [27].

3. How do oncogene products activate NF- κ B?

The ability of oncogenic Ras and Raf to activate NF- κ B has been intensively studied by our group and others. Compared to parental control cells, NF- κ B nuclear levels were not increased in Ras- or Raf-transformed cells even though an NF- κ B-dependent reporter exhibited a strong increase in activity in the transformed cells [28,33]. This enigma was explained by showing that Raf- and Ras-transformed cells display elevated NF- κ B transcriptional activity through the ability of these oncoproteins to target the transactivation domain of the p65 subunit of NF- κ B [28,33]. Surprisingly, it was shown that dominant negative forms of Raf did not strongly inhibit the ability of Ras to activate NF- κ B-dependent transcription [33]. Thus, it was concluded that the major pathway through which oncogenic Ras activated NF- κ B did not go through Raf. Several mechanisms have been found to potentially explain this result. First, inhibitors of the stress-activated kinase, p38 [33,34], and of the kinase, Akt (L. Madrid, A.B. and M.M., submitted), block the ability of Ras and/or Raf to activate NF- κ B. Akt is downstream of PI3K and is associated with promotion of cell survival (reviewed in [35]). In each of these cases, the activation of NF- κ B-dependent expression is associated with the stimulation of p65 transcriptional activity. Second, the ability of Raf to activate NF- κ B appears to involve the secretion of an autocrine factor which stimulates NF- κ B transcriptional activity [33,34]. Additionally, it has been found that induction of oncogenic Ras can stimulate a transient accumulation of NF- κ B via the induction of IKK activity (L. Madrid, A.B. and M.M., submitted). The ability of oncogenic Ras to activate IKK may be dependent on Akt, since other groups have recently indicated that Akt can function to activate NF- κ B in an IKK-dependent manner [36–38]. However, Akt activity, alone, is insufficient to induce NF- κ B nuclear translocation (L. Madrid, A.B. and M.M., submitted). Additionally, we have found that the ability

of Akt to stimulate p65 transcriptional activity (not involving induced nuclear translocation) is at least partially dependent on IKK function (L. Madrid, A.B. and M.M., submitted). Current work in the laboratory is directed towards understanding the signaling pathways utilized by Ras to potentially stimulate phosphorylation of the p65 C-terminal transactivation domain.

In addition to Ras and Raf, other oncogene products are known to activate NF- κ B. For example and as described above, HTLV-I Tax activates NF- κ B at least partly through binding to IKK and stimulating nuclear translocation of NF- κ B [17–21]. Her2/Neu is known to activate an NF- κ B-dependent reporter [39], but it was not shown whether this was through nuclear accumulation of NF- κ B or through stimulation of transactivation function. The BCR-ABL oncoprotein involved in chronic myelogenous leukemia is known to activate NF- κ B through a relatively weak stimulation of nuclear translocation and through the targeting of the transcriptional activation domain [29].

4. What is the role of NF- κ B in oncogenesis?

Relevant to issues involving oncogenesis and resistance to chemotherapy, it has been shown that NF- κ B activation can suppress cell death pathways [40]. Thus, consistent with the role of NF- κ B as an anti-apoptotic factor, NF- κ B activation is required to protect cells from the apoptotic cascade induced by TNF and other stimuli [41–45]. NF- κ B has been shown to activate TRAF1 and 2 and c-IAP1 and 2 to block caspase-8 activation [46]. Other anti-apoptotic genes have been shown to be activated by NF- κ B and include the Bcl-2 homolog A1/Bfl-1, IEX-1, and XIAP [47–51]. Of significant interest are the observations that NF- κ B can antagonize p53 function, possibly through the cross-competition for transcriptional co-activators [52].

Based on the observations which demonstrate that cells upregulate NF- κ B in response to TNF in order to overcome apoptosis, we speculated that one mechanism whereby NF- κ B functions to promote oncogenesis was to suppress a transformation-associated apoptosis. Thus, we tested whether NF- κ B was required to suppress the apoptotic potential associated

with oncogenic H-Ras expression. Inhibition of NF- κ B, via the expression of the super-repressor I κ B α , led to the induction of apoptosis when an oncogenic allele of H-Ras (RasV12) was expressed [53]. Other evidence has been presented that inhibition of NF- κ B in transformed cells can induce apoptosis (see [25,54]). In addition to being required to suppress transformation-induced apoptosis, we and others have recently shown that NF- κ B can promote cell growth through the transcriptional upregulation of the cyclin D1 gene [55,56]. Since NF- κ B has potent effects on cell survival and growth, NF- κ B most likely will also be found to control other aspects of cell cycle progression. Relative to other aspects of oncogenic control, NF- κ B is known to regulate expression of cell adhesion molecules [1,2] and cell surface proteases (such as MMP-9, [57]). Therefore, it is speculated, but not proven, that NF- κ B can control metastasis. This idea is supported by the fact that Cdc42 and Rac induce integrin-mediated invasiveness through PI3K [58], and we and others have shown that Rac and PI3K are involved in NF- κ B activation (see above). Recently, it was shown that animals null for TNF are inhibited in their ability to undergo skin carcinogenesis [59]. Since NF- κ B positively upregulates TNF gene expression and since TNF activates NF- κ B [1,2], these results [59] may correlate with a role for NF- κ B in skin carcinogenesis (see below, however). Consistent with this, it has been suggested that the upregulation of NF- κ B in squamous cell carcinoma of the head and neck promotes proinflammatory cytokine production and possibly metastasis [27,60].

Gene regulation by NF- κ B is presumed to control its major oncogenic functions. As described above, NF- κ B activates an anti-apoptotic response that suppresses the ability of oncogenic Ras to induce apoptosis. Additionally, it has been shown that the activation of NF- κ B by growth factors suppresses the apoptotic response induced by c-myc expression during growth factor deprivation [38]. It is presently unclear which of the anti-apoptotic genes that are regulated by NF- κ B may perform this function. However, it should be noted that most tumors exhibit a general resistance to cell death pathways and the upregulation of anti-apoptotic genes is most likely relevant to the development of oncogenesis. For example, members of the IAP family of anti-apoptotic

proteins are upregulated in a variety of cancers [61], and it is known that NF- κ B regulates expression of some of the IAP genes (see above). Additionally, as stated above, NF- κ B promotes cell-cycle progression via the upregulation of cyclin D1.

What other NF- κ B-regulated genes may contribute to oncogenesis? It has been reported that NF- κ B regulates the gene encoding tenascin-C, an extracellular matrix protein involved in cell attachment and cell growth [62]. NF- κ B is known to regulate ICAM-1 [1,2], a cell adhesion molecule found upregulated in several cancers. For example, ICAM-1 is upregulated in approximately 70% of primary melanoma lesions and in about 90% of metastatic lesions [63]. ICAM-1 expression was associated with a reduction in disease-free intervals and in patient survival [63]. Cox-2, a protein involved in inflammation, is found upregulated in more aggressive forms of colorectal cancer [64], is known to be transcriptionally activated by NF- κ B [1,2] and is known to promote angiogenesis [65]. The upregulation of iNOS and the enhanced production of nitric oxide has also been proposed to enhance tumor progression and angiogenesis [66,67]. NF- κ B has also been shown (reviewed in [1]) to induce expression of the c-myc and c-myb proto-oncogenes and of gro α (melanoma stimulatory factor). Hypoxia is present in regions of malignant tumors and is thought to influence tumor progression through angiogenic processes [68] and hypoxia/reperfusion is known to induce NF- κ B activation (see [1]). Thus, the activation of NF- κ B may contribute to a pro-malignant phenotype by upregulating gene products that control cell adhesion and angiogenesis in addition to those promoting cell proliferation and survival.

5. NF- κ B is a target of chemopreventive compounds

Evidence that NF- κ B is involved in many inflammatory diseases (see [1,2] and in oncogenesis has led a number of investigators to determine if NF- κ B is a specific target of pharmaceutical and dietary compounds known to prevent disease. Thus, it has been shown that NF- κ B is inhibited by aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) treatments [69–71], which are known to block the initiation and/or progression of certain cancers, par-

ticularly colorectal cancer (reviewed in [71]). Interestingly, aspirin and sulindac both inhibit the activation of the I κ B kinase complex (see [70,71]). Several dietary chemopreventive compounds, including flavonoids, curcumin, and resveratrol, are known to block NF- κ B activation ([72,73] and M. Holmes-McNary and A.B., submitted). These studies make it likely, therefore, that NF- κ B is a functionally relevant target of chemopreventive drugs and dietary compounds which prevent cancer.

6. Roles for NF- κ B as a tumor suppressor and in pro-apoptotic signaling

Although there is clear data that NF- κ B is involved in many aspects of oncogenesis, in part, by the ability of this transcription factor to block apoptosis, there is evidence in the literature that indicates that NF- κ B may prevent oncogenesis and promote apoptosis. Recently it was shown that inhibition of NF- κ B in the skin via expression of the super-repressor form of I κ B α led to squamous cell carcinomas and increased apoptosis [74]. Since NF- κ B along with IKK α has been proposed to be involved in controlling differentiation of skin [4,75], the loss of NF- κ B may promote oncogenesis in this particular setting. Again, it is likely that the subunit composition of NF- κ B is important in determining relevant aspects of cellular growth control. Potentially relevant to this point and, as described above, the activation of NF- κ B that occurs in breast cancer is not the p50-p65 heterodimer but rather complexes that contain p50, p52 and Bcl-3 [30]. Thus, different NF- κ B complexes may control growth and differentiation in different cell types or in response to different stimuli.

Consistent with idea that NF- κ B activation can promote pro-apoptotic effects, the gene encoding Fas ligand (FasL) has been shown to be transcriptionally regulated by both AP1 and NF- κ B in response to chemotherapeutic agents and to T-cell activation signals [76,77]. In these studies, T-cells can be induced to undergo apoptosis in response to etoposide or T-cell activation signals through the NF- κ B-dependent upregulation of FasL. Thus, the inhibition of NF- κ B provided cell protection from genotoxic-induced or T-cell activation-induced Fas-directed death signalling [76,77]. Consistent with the

dysregulated NF- κ B transcriptional activity in human cancers, some transformed cells derived from solid tumors display constitutive FasL expression [78]. Interestingly, these cells are resistant to Fas-induced apoptosis, because they either downregulate Fas expression or they have intracellular mechanisms to suppress Fas-induced apoptosis [78]. In fact, it has been shown that oncogenic Ras downregulates Fas gene expression [79]. Thus, overexpression of FasL has been proposed to be a potential mechanism by which solid tumors avoid the cellular immune system by inducing Fas-mediated apoptosis in tumor infiltrating T-cells. It is intriguing to speculate that the activation of NF- κ B in tumor cells could lead to upregulation of FasL expression as well as the associated resistance to apoptosis.

7. A role for NF- κ B in chemoresistance

The realization that NF- κ B can inhibit apoptosis led us to examine whether NF- κ B plays a role in blocking the efficacy of cancer chemotherapies and radiation. Since NF- κ B is activated in a number of cancers, it may be that it provides a level of chemoresistance prior to cancer therapy. Additionally, we showed [41] that HT1080 fibrosarcoma cells exposed to ionizing radiation and to the chemotherapy daunorubicin exhibited enhanced activation of NF- κ B. Inhibition of NF- κ B leads to dramatically enhanced apoptosis in response to ionizing radiation or daunorubicin treatment as compared to the control cells. HT1080 fibrosarcoma tumors grown in nude mice were induced to undergo apoptosis when infected with an adenovirus expressing a modified form of I κ B α along with systemic delivery of chemotherapy CPT-11 [80]. Other tumors (for example, those derived from the colorectal tumor cell line, LOVO) showed basically identical responses to the combined treatment. In fact, LOVO tumors could be eliminated with CPT-11 systemic treatment and with adenoviral delivery of I κ B α either every 5 or 10 days (J. Cusack, R. Liu and A.B., submitted). In contrast to our studies, Bours and colleagues showed that stable expression of the super-repressor form of I κ B α did not yield enhanced cytotoxicity in response to chemotherapy, despite the ability of genotoxic agents to activate NF- κ B [81]. We have analyzed two of the

cell lines used in these in vitro studies, and have found that transient inhibition of NF- κ B via the adenoviral delivery of I κ B α strongly enhanced the apoptotic response to CPT-11 ([82] and J. Cusack, R. Liu and A.B., submitted). Thus, we propose that the stable inhibition of NF- κ B via the expression of I κ B α may select for variant cell types that have upregulated an NF- κ B-independent anti-apoptotic pathways. This concept is supported by the fact that numerous cancer cells die upon infection with the super-repressor form of I κ B α (M.M., unpublished and see [54]). Thus, the only consistent way to block NF- κ B in these types of experiments is through transient inhibition of NF- κ B, which is the way that it must be accomplished in future developments of cancer therapy. Present studies are focused on the treatment of a variety of cancers with systemic (small molecule) inhibitors of NF- κ B in combination with chemotherapy.

8. Summary

The activation of NF- κ B by virtually every known oncogene product is consistent with a role for this transcription factor in oncogenesis. Direct evidence, using both in vitro and in vivo models, indicates that NF- κ B is required for oncogenesis probably at multiple levels. Our evidence is that NF- κ B plays an important role in the early events of oncogenesis, probably functioning primarily in protecting against transformation-associated apoptosis. In most late stage tumor cells, NF- κ B is clearly not the only survival factor, because its inhibition does not induce apoptosis in many of these tumor cells. This observation suggests that other secondary events have occurred to upregulate NF- κ B-independent cell survival pathways. Additionally, NF- κ B contributes to cell progression through the upregulation of cyclin D1 with the corresponding hyperphosphorylation event on the tumor suppressor protein, Rb. NF- κ B activation also potentiates proliferation by blocking differentiation in certain settings, and this phenomenon may also promote oncogenesis. NF- κ B is known to regulate certain genes associated with metastasis, such as MMP9, tissue plasminogen activator, and ICAM-1. Thus, a more relevant role for NF- κ B in later stage oncogenesis may be to promote metastasis

and angiogenesis. Although many tumor cells display elevated nuclear NF- κ B, the transcriptional potential of NF- κ B appears to be further upregulated in response to certain types of chemotherapy. Inhibition of NF- κ B in parallel with chemotherapy treatment strongly enhances the apoptotic potential of the chemotherapy. This observation indicates that NF- κ B plays an important role in inducible chemoresistance and establishes NF- κ B inhibition as an important new adjuvant approach in chemotherapy.

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