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NF- κ B in Carcinoma Therapy and Prevention

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Abstract

Background—Nuclear factor- κ B (NF- κ B) includes a family of signal-activated transcription factors which normally regulate responses to injury and infection, but which are aberrantly activated in many carcinomas.

Objective—To review the activation and role of NF- κ B in pathogenesis and as a target for treatment and prevention in carcinoma.

Methods—Evidence from experimental, epidemiologic, pre-clinical studies and clinical trials cited in the literature are reviewed.

Results/conclusion—Cumulative evidence implicates NF- κ B in cell survival, inflammation, angiogenesis, spread and therapeutic resistance during tumor development, progression and metastasis of carcinomas. Non-specific natural and synthetic agents that inhibit NF- κ B have demonstrated activity and safety in prevention or therapy. NF- κ B activating kinases and the proteasome are under investigation for targeted prevention and therapy of carcinoma.

Keywords

aspirin; BMS-345541; bortezomib; carcinoma; CHS-828; dexamethasone; Inhibitor-kappaB; MLN-120B; NF-kappaB; NSAIDs; proteasome; sulindac

1. INTRODUCTION

Originally named for its ability to act as an enhancer element of the immunoglobulin kappa light chain gene in B-cells, NF- κ B's role has significantly expanded with demonstration of its contribution in other cells to development, injury, inflammation and the pathogenesis of malignancy. In cancer, NF- κ B activation has been linked to cell proliferation, survival, invasion, and angiogenesis, making it a potentially desirable target for therapy. Already, agents that inhibit NF- κ B have been shown to reduce tumor growth as well as induce apoptosis in malignant cells. Furthermore, NF- κ B has become a potential target for chemoprevention as there is increasing evidence of the critical role it plays in tumorigenesis. As our understanding of the molecules and mechanisms that regulate this pathway increases, so will our ability to selectively target and inhibit NF- κ B with existing and new agents. Recent development of specific small molecule inhibitors has yielded a plethora of agents for both preclinical and clinical studies. Additionally, greater understanding of the activity and uses of existing immunosuppressive and natural compounds that alter NF- κ B activity may lead to improved

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chemoprevention as well as adjuvant therapies to traditional cytotoxic agents and radiation regimens. Thus, interventions that target and attenuate NF- κ B activation may broaden our armamentarium in the fight against cancer for use as single agent or combination therapy.

2. NUCLEAR FACTOR- κ B (NF- κ B) COMPLEXES

2.1 NF- κ B family members

There are five members of the NF- κ B family, including NF- κ B1 (p105/p50), NF- κ B2 (p100/p52), REL A (p65), cREL, and RELB, which can associate with one another to form various heterodimeric and homodimeric combinations^{1, 2}. These proteins share a highly conserved REL homology domain that accounts for their ability to dimerize and bind specific DNA sequences in the promoters of many genes. This family of transcription factors is regulated through compartmentalization, with cytoplasmic sequestration in an inactive form maintained by C-terminal or distinct peptides (Inhibitor-kappaBs, I κ Bs), that contain ankyrin repeats which inhibit nuclear localization and DNA binding. Signal activation by phosphorylation and degradation of these I κ Bs enables nuclear translocation and promoter binding. Further post-translational modifications, including phosphorylation and acetylation of NF- κ B subunits, their co-factors and chromatin structure, can determine whether the complex serves to transactivate or repress gene function^{1, 2}.

2.2 Classical and alternative pathways

The signal activation of these NF- κ B and I κ B family members has been characterized into two main pathways; a classical or canonical pathway, and an alternative or non-canonical pathway^{1, 2}(Fig. 1). The classical pathway involves NF- κ B1 (p105) which is processed to p50 and bound to RELA (p65) and I κ B (inhibitor Kappa B) in the cytoplasm. I κ B α is phosphorylated at Serine 32 and 36 by the complex of IKKs (I κ B kinases) made up of IKK α , IKK β , and IKK γ . IKK α and IKK β are catalytic subunits that share a 52% overlap in their sequence, while IKK γ serves as a regulatory subunit, modulating the activity of the other IKK subunits. This phosphorylation step targets I κ B α for ubiquitination by an E3 ligase and degradation by the 26S proteasome, releasing the bound NF- κ B1 to be processed and to translocate to the nucleus^{1, 2}. Processing of the precursor of NF- κ B1 (p105) requires ubiquitin-dependent proteolysis of their C-terminus transcription modulating domain and ankyrin repeats to yield p50. A serine-threonine protein kinase, CK2, has also been shown to mark the I κ B α subunit for degradation by phosphorylation of its C-terminal end³. CK2 also contributes to the aberrant activation of IKK β and phosphorylation of I κ B α ⁴. The classical pathway is known to be stimulated by many proinflammatory cytokines including Tumor Necrosis Factor- α (TNF- α), Interleukin-1 (IL-1), bacterial LPS, and growth factors that act through Epidermal Growth Factor Receptor (EGFR), other growth factor receptors, and non-receptor tyrosine kinases^{1, 2, 5-7} (Bagain manuscript in preparation).

The alternative pathway, originally defined in cells of the hematopoietic lineage, is triggered by stimuli such as CD40L and lymphotoxin β receptor, which activate NF- κ B inducing kinase (NIK). NIK then induces IKK α /IKK α homodimers, which activates the processing of p100/RelB into NF- κ B2 p52/RelB heterodimers via the proteasome^{1, 2}. As in classical pathway signaling, the process appears to involve a ubiquitin-dependent process, however involvement of IKK β and IKK γ is not needed in the alternative pathway^{1, 2}.

The transactivating function of NF- κ B family members can be altered as a result of other post-translational modifications or interactions with various co-factors. RELA (p65) and other family members may be altered by phosphorylation at various sites on their domain. RELA has been shown to be phosphorylated at serine 536 by IKK β ⁸, at serine 529 by CK2⁹, and serine 276 by PKA¹⁰. Additionally, stress activated protein kinase (MSK1)¹¹ has been shown

to promote activation of RELA. Lastly a series of interactions with AKT, CBP/p300 and p14ARF/p53 may also differentially regulate NF- κ B activation or repression of downstream genes¹²⁻¹⁴.

3. NF- κ B AND CARCINOMA

3.1 NF- κ B, infection, inflammation, and carcinogens in the development of cancer

Experimental and epidemiologic evidence indicates that pathogen, carcinogen, and inflammation-induced activation of NF- κ B plays direct or indirect roles in cellular promotion, transformation and progression of both experimental and human cancers^{15, 16}. Evidence implicating pathogen-induced NF- κ B activation in the development of cancer originated with identification of the REV-T viral oncogene that causes avian reticuloendothelial lymphomatosis, v-Rel^{16, 17}, which shares a Rel transactivation domain with the mammalian homologues RELA (p65), cREL and RELB.

Figure 1 summarizes a number of alterations and signal pathways that have been implicated in activation of NF- κ B in human cancers (reviewed in ¹⁸). These include Epstein Barr virus gene *LMP-1*, and human T lymphocyte virus gene *Tax*, which encode proteins that activate NF- κ B and gene programs that contribute to the pathogenesis of lymphomas, nasopharyngeal carcinomas and adult T-cell leukemias, respectively. Human papilloma virus (HPV) genes *E6* and *E7* genes have also been implicated in NF- κ B activation, and are associated with premalignant and malignant lesions of the cervix, oropharynx and larynx, where HPV associated neoplasms are prevalent. In hepatocellular carcinoma, hepatitis B X protein and hepatitis C 5A and core proteins have been shown to activate NF- κ B. Gastric *H. pylori* and colonic bacteria in patients with ulcerative colitis have also been implicated in NF- κ B activation in epithelia and inflammatory leukocytes, and promotion of gastric and colon carcinomas.

Several known chemical and physical carcinogens implicated in the initiation and promotion of human cancer can also activate NF- κ B. Specifically, nicotine and carcinogens in tobacco and betel nut (areca), which are linked to the pathogenesis of both head and neck as well as lung malignancies, induce AKT and NF- κ B activation, promoting cell proliferation, survival and inflammation^{15, 16, 19}. Nicotine has been reported to directly activate these pathways via nicotinic receptors and AKT¹⁹. Chemotherapy and radiation-induced DNA damage has been reported to induce NF- κ B activation via a nuclear to cytoplasmic signaling mechanism involving sumoylation of the IKK complex²⁰. TNF, gamma radiation, and certain chemotherapeutic drugs, induce several NF- κ B target anti-apoptotic genes (TRAFs, IAPs and Bcl-2 and Bcl-X_L) that protect cells from therapeutic injury by these agents¹⁶.

3.2 Aberrant activation of NF- κ B in carcinoma

Aberrant activation of NF- κ B is prevalent in cell lines and tumor tissue specimens, and contributes to malignant progression and therapeutic resistance in most of the major forms of human cancer. As recently reviewed¹⁸, NF- κ B/RELBs are constitutively activated in human carcinomas of the breast, head and neck, esophagus, cervix, prostate, lung, colon and pancreas.

Aberrant activation of upstream tyrosine receptor and non-receptor kinases via IKKs or other kinases represents the most common etiology for NF- κ B activation in epithelial and lymphoid malignancies (Fig. 1)¹⁸. Autocrine or paracrine activation of NF- κ B resulting from overexpression of TGF- α , Epidermal Growth Factor (EGF), Her2/Neu, IL-1, Hepatocyte Growth Factor (HGF), and integrin family ligands and receptors, has been reported. EGFR and her2/neu signaling involving PI3K, IKK and CK2 has been demonstrated in breast cancer. IL-1/IL-1R, Transforming Growth Factor- α (TGF- α)/EGFR, PI3K, AKT, CK2 and IKK have been shown to mediate activation in head and neck squamous cell carcinomas. Activation via

CK2 and IKK is observed in colon carcinomas. PI3K/AKT and IKK are important in signal activation of NF- κ B and cell survival in many cancers. Constitutive activation of NF- κ B p52:p52 due to overexpression and association with the transactivating family member Bcl-3 has been detected in breast carcinomas (Fig. 1D).

Although established human carcinomas frequently demonstrate activation and a promotional role of NF- κ B, several experimental studies in murine models suggest that early in carcinogenesis, NF- κ B and IKKs may play an inhibitory rather than promotional role in carcinoma development. Inhibition of NF- κ B with activation of oncogenic ras in human keratinocytes was reported to promote development of malignant human epidermal lesions resembling squamous cell carcinoma in mice²¹. Targeted deficiency of IKK β in liver was reported to increase susceptibility of mice to diethylnitrosamine (DEN)-induced hepatocarcinogenesis²². Targeted deficiency of IKK γ /NEMO in liver parenchymal cells resulted in chronic liver disease resembling human nonalcoholic steatohepatitis and spontaneous hepatic carcinoma²³. However, others have reported that inhibition of NF- κ B inhibits murine and human squamous cell carcinoma tumorigenesis in mice¹⁸, or cholestatic hepatitis associated hepatocellular carcinomas in *MDR2* knockout mice²⁴. These differing results suggest the possibility that the cancer promoting role of NF- κ B in certain contexts may be tissue or carcinogenesis dependent, or may involve additional steps that are not well understood.

Among such steps, loss of the inhibitory effects of certain tumor suppressor genes may be important in function of NF- κ B as a prosurvival factor in carcinomas (Fig. 1). Evidence indicates that activation of functional ARF, ATR, and Chk2 normally mediates alternative phosphorylation of RELA, and p53 competes for CBP/p300, maintaining repression of NF- κ B prosurvival genes when the ARF-ATR-p53 pathway and proapoptotic target genes are activated¹⁴. Inactivation of this proapoptotic pathway by hypermethylation of p14ARF/p16INK4A or mutation or HPV inactivation of p53 are among the most common alterations in squamous cell carcinomas and other human cancers¹⁴. Loss of the inhibitory effects of TGF β signaling on NF- κ B and inflammatory gene expression represents another common event that is potentially important in development of squamous cell carcinomas²⁵. Loss of PTEN expression is associated with increased PI 3-kinase/AKT signal activation of NF- κ B and c-MYC in prostate carcinoma cells²⁶.

Direct mutation or altered expression of NF- κ B/I κ B molecules has only rarely been reported in human cancers, such as in Hodgkins lymphomas, where mutations of I κ B that favor activation have been identified^{27, 28}. Further, recent studies in human cancer indicate that the classical and alternate pathways may not be activated individually as identified in their tissues of origin in knockout mice (i.e. classical in epithelia and hematopoietic development, alternate pathway in lymphoid development)¹. In some circumstances, both pathways may be co-activated via the same mechanisms. Annunziata et al., demonstrated that various genetic or epigenetic alterations affecting NIK, TRAF3, CYLD, BIRC2/BIRC3, CD40, NFKB1, or NFKB2 are common and can promote activation of the classical and alternative pathways in human multiple myeloma (MM) tumors and cell lines²⁹. They provided evidence that NIK may activate not only the alternate pathway via IKK α , but also the classical pathway via a previously uncharacterized IKK β -dependent mechanism. As a result, many MM tumors were found to be sensitive to IKK β inhibitors. Additionally, Allen et al., recently demonstrated co-activation of classical and alternate pathway NF- κ B subunits in head and neck squamous cell carcinomas³⁰. They showed that proteasome inhibitor bortezomib more effectively inhibited nuclear localization of RELA and p50 than cREL or alternate pathway subunits NF- κ B2 or RELB in tumor specimens and lines from patients with HNSCC. In addition, IKK α has recently been implicated in promoting activation of the mTOR pathway³¹. Together, these results highlight the need to develop pharmacologic agents for IKK α and other targets in the alternate

pathway, in addition to IKK β and proteasome inhibitors, which have been the subject of greatest interest to date.

NF- κ B has been shown to regulate many of the genes differentially expressed and implicated in cell proliferation, survival, migration, and tumorigenesis and metastasis in cancer. NF- κ B related gene signatures have been identified and associated with malignant phenotype in squamous cell carcinomas³²⁻³⁷, Hodgkins and certain non-Hodgkins lymphomas^{38, 39}, and inflammatory breast cancer⁴⁰. Targets of NF- κ B important in cell proliferation and survival include prominent oncogenes such as cyclin D, Bcl-X_L, and Inhibitors of Apoptosis (IAPs)^{35-37, 41-43}. Expression of key angiogenesis factors and adhesion molecules such as GRO1, IL-8 and VEGF are directly or indirectly enhanced by NF- κ B activation^{5-7, 44}. Together, these genes contribute to the increase in proliferation, survival, inflammation and angiogenesis that leads to rapid tumorigenesis and metastasis.

4. MOLECULAR TARGETED THERAPY

As knowledge of the pathways and complexes involved in the activation of NF- κ B has grown, so has the list of possible targets for its inhibition. Several key targets exist including the IKK's, the 26S proteasome, CK2, and PPAR- γ . While all of these have been shown to play a role in NF- κ B activation, the contribution of each may vary from cancer to cancer and thus the efficacy of targeting them. These targets also vary in their specificity toward NF- κ B. Inhibition of the IKK's has been demonstrated to have a relatively specific inhibition of NF- κ B. In contrast, targets such as the proteasome, PI3K, PKA and CK2, while potentially efficacious for inhibiting NF- κ B, but also affect other pathways, making their therapeutic effects more complex to understand.

4.1 Proteasome Inhibition

For the canonical NF- κ B transcription factors (i.e., NF- κ B1/RELA) to be translocated from the cytoplasm to nucleus and bind DNA targets, I κ B must be ubiquitinated by the SCF- β -TrCP ubiquitin ligase complex and then degraded by the proteasome. The proteasome is a 26S multiprotein complex that consists of a 19S regulatory subunit and a 20S catalytic subunit that contains six unique ATP-dependent serine protease sites which hydrolyze proteins into small polypeptides, leading to their inactivation⁴⁵. Through its regulation of protein recycling, the proteasome is involved in many processes that are important in cancer such as cell-cycle progression, apoptosis and angiogenesis^{46,47}. Very specific and potent proteasome inhibitors have been engineered by coupling boronic acid to dipeptides⁴⁸. PS-341, or bortezomib, a dipeptide boronate, is the most well studied proteasome inhibitor that has currently entered clinical development³⁹. Bortezomib has been shown to inhibit proliferation as well as induce apoptosis in a variety of carcinomas, such as head and neck^{30, 46, 49}, prostate⁴⁷, pancreatic⁵⁰, gastric⁵¹, and ovarian⁵² carcinomas. The anti-tumor properties of bortezomib correlate in part with its ability to inhibit the degradation of the I κ B α ^{46, 53}. However, targeted NF- κ B inhibitors such as the IKK inhibitor PS-1145, do not entirely reproduce all of bortezomib's therapeutic activities, therefore implicating the significance of additional proteins which are also regulated by proteasome inhibitors⁵⁴. Global inhibition of protein degradation resulting in endoplasmic reticulum induced stress responses has recently been implicated in sensitivity and resistance to proteasome inhibition⁵⁰. New allosteric inhibitors of the proteasome are also in development which can preferentially inhibit the degradation of specific proteasome targets, such as I κ B α ⁵⁵. These results from preclinical studies as well as clinical trials demonstrate that proteasome inhibitors can potently inhibit proliferation and induce apoptosis in a variety of otherwise resistant cancer cells, and sensitize tumors to adjuvant chemotherapy and radiation therapy. However, the low response rates in monotherapy trials of proteasome inhibitors in patients with carcinomas have been disappointing, when compared to those in MM and other B cell malignancies¹⁸. Emerging evidence suggests that pre-existing

and/or induced activation of other prosurvival signal pathways and transcription factors in carcinomas contributes to resistance to proteasome inhibitors³⁰. In addition to the activation and relatively lesser effect of proteasome inhibition on the alternate pathway subunits, there is activation of other prosurvival pathways, including MAPK (ERK, JNK, p38) and STAT3, which are not inhibited by proteasome inhibitor therapy in tumors or cell lines from patients with head and neck squamous cell carcinoma^{30, 56}. Further studies reveal that proteasome inhibitors can induce JNK, ERK and AP-activation and in resistant human HNSCC and other malignancies⁵⁶. Proteasome inhibitors are also being studied in combination with other chemotherapy agents and radiation in which proteasome and NF- κ B inhibition enhances cytotoxicity^{18, 30, 57}.

4.2 IKK Inhibition

The IKK complex is a target shown to be a dedicated activator of NF- κ B activity^{1, 2}. Rational design and construction has yielded several potent and selective inhibitors. Most have a predominant effect on IKK β , but there are some that show activity against IKK α as well. CHS-828 is probably the most clinically advanced of the IKK β inhibitors. A phase I trial with single daily dose for 5 days every 28 days for refractory solid tumors showed dose limiting toxicities of nausea, vomiting, diarrhea, fatigue and urogenital tract mucositis⁵⁸. There were no observed tumor responses. A second trial CHS-828 was given 1 day every 3 weeks at increasing doses. At the 500mg dose, 2/3 of patients experienced a dose limiting toxic effect⁵⁹.

BMS-345541 targets the allosteric sites of IKK α and IKK β ⁶⁰. Yang has been able to show the of IKK inhibition as effective therapy in experimental melanoma models, achieving apoptosis through a mitochondrial mediated pathway⁶¹. In a subsequent study, via that knockdown of endogenous IKK β , Yang showed it significantly reduced the growth of the melanoma lesions and knockdown of either IKK α or IKK β prolongs the life span of immunocompetent mice⁶².

The inhibitor MLN120B showed activity against multiple myeloma cells in a SCID mouse model⁶³. It was able to cause 25% to 90% inhibition of cell growth in vitro and augment TNF induced toxicity. Additionally, MLN120B augmented growth inhibition initiated by doxorubicin and melphalan in multiple myeloma cell lines RPMI 8226 and INA6.

PS-1145, a beta-carboline, has shown activity in HeLa cells (cervical carcinoma) by reducing NF- κ B activity⁶⁴. In prostate cancer, PS-1145 has been able to reduce proliferation and invasiveness and attributable to NF- κ B activity reduction⁶⁵. Another study demonstrated that PS-1145 in combination with docetaxel resulted in cell death and lower IL-6 levels in prostate cancer.⁶⁶ However, PS-1145 and MLN 120B did not show significant anti-tumor activity in most cultured HNSCC lines (J Ricker, L Nottingham and C Van Waes, unpublished observations), and this was associated with incomplete NF- κ B inhibition, consistent with a role of non-canonical IKK α and NF- κ B activation observed in these cancers^{4, 30}.

BAY 11-7085, an irreversible inhibitor of I κ B α phosphorylation was shown to inhibit NF- κ B activation and have anti-tumor effects in vitro and in vivo against Caov-3 ovarian cancer models^{67, 68}. In combination with paclitaxel or cisplatin, Bay 11-7085 showed increased cell death, by reducing the normally induced NF- κ B activation. Additionally, further synergy against intra-abdominal dissemination and production of ascites in athymic nude mice inoculated intra-peritoneally with the ovarian cancer cell line, as the further evidence for the use of NF- κ B targeted inhibition in combination with cytotoxic agents.

Because IKK β plays an important role in macrophage IL-1 β response to pathogens, there remains concern that highly efficient or prolonged IKK β blockade could lead to unexpected complications. Also to date, no studies of specific IKK α inhibitor activity or toxicity in cancer

have been published. Considering that IKK α is part of the canonical IKK complex and implicated in several nuclear mechanisms that enhance expression of genes activated by the classical pathway, and is a key activator of the alternative pathway, its inhibition may also merit investigation as a modulator of NF- κ B targeted in cancer therapy.

4.3 CK2 Inhibition

CK2 (formerly casein kinase II) is a protein kinase with multiple substrates that include NF- κ B, WNT, PI3K and many other signal pathways⁶⁹. Initially, CK2 was shown to activate NF- κ B in the context of UV-radiation. We recently demonstrated it also plays a significant role in activation of IKK β and RELA in head and neck cancer cells⁴. CK2 and its targets regulate broad cellular processes, including maintenance of cell viability, protection of cells from apoptosis, and tumorigenesis, and elevated CK2 activity has been established in a number of cancers.

Most CK2 inhibitors, as derivatives of tetrabromobenzimidazole/triazole and indoloquinazolines have their selectivity by binding a small hydrophobic pocket adjacent to the ATP/GTP binding site. One study showed induction of cell death in anti-estrogen resistant human breast cancer cells by the protein kinase CK2 inhibitor DMAT⁷⁰. Specifically this study pointed to reduced amounts of BCL2 in estrogen independent breast cancer cells as a reason for CK2 susceptibility and not necessarily a reduction in NF- κ B. DMAT showed synergy in inhibiting tumorigenesis in vivo when combined with the tyrosine kinase inhibitor Imatinib while showing minimal kidney, liver and bone marrow toxicity⁷¹.

Apigenin is a natural plant flavone in parsley onions, oranges, tea and chamomile, making it a potential anti-oxidant and anti-inflammatory chemopreventative agent⁷². It exhibits CK2 inhibitory effects, stabilizing I κ B α and down regulating NF- κ B activity. It has been shown to have anti-CK2 activity in both prostate and breast cancer^{73, 74} and decreased the volume and weight of prostate tumor xenografts upon treatment⁷⁵.

A more novel approach to therapy using antisense oligonucleotides may yet provide another specific way of targeting this molecule. Ahmed and colleagues have shown therapeutic effects on prostate and head and neck cancer both in vivo and in vitro, with a relative increase in sensitivity of cancer cells compared to normal tissue^{76, 77}. Nanocapsule delivery mechanisms as vectors to promote tumor-specific uptake of the oligonucleotides may increase the selectivity and potency of antisense or siRNAs targeting CK2.

4.4 Selective estrogen receptor modulators (SERMS)

Selective estrogen receptor (ER) modulators, commonly referred to as SERMS, are a class of compounds that interact with subsets of estrogen receptors with discriminating tissue specificity. The relationship between estrogen receptor ligands and inflammation had long been known in clinical practice, in that excess estrogen, especially in pregnancy, was known to subdue symptoms of inflammatory diseases like Crohn's disease and ulcerative colitis. ER ligands have been developed which selectively inhibit NF- κ B and thereby inflammation without induction of the classic effects of estrogen⁷⁸. Estrogen has been hypothesized to promote breast cancer, and activated NF- κ B has been detected in a majority of breast cancers which lacked ER receptor expression. DNA bound NF- κ B was practically absent in ER positive specimens,⁷⁹ supporting the hypothesis of the negative effects of ER on NF- κ B activation. Tamoxifen, a SERM with wide clinical application, has been shown to inhibit TNF induced NF- κ B activation in human embryonic kidney cells and KBM-5 leukemic cell line, through inhibiting IKK activity and suppressing I κ B α degradation.⁸⁰

4.4 Peroxisome proliferator-activated receptor (PPAR)

Peroxisome proliferator-activated receptor (PPAR)- γ is a nuclear receptor and transcription factor of the steroid superfamily. It has recently been implicated as a regulator of cellular proliferation and inflammatory responses. The ligands of PPAR- γ include several prostanoids, such as 15-deoxy- $\Delta^{12,14}$ prostaglandin J₂ (15d-PGJ₂), polyunsaturated fatty acids, a variety of nonsteroidal anti-inflammatory drugs (NSAIDs), and a new class of oral antidiabetic agents, the thiazolidinediones (TZDs)^{81, 82}. Su et al demonstrated in colon carcinoma Caco-2 cells that 15d-PGJ₂ inhibits the nuclear translocation and subsequent DNA binding of NF- κ B via an I κ B- α -dependent pathway by inhibiting the immune response-induced degradation of I κ B- α .⁸³ PPAR- γ ligands can also inhibit tumor-associated angiogenesis by blocking the production of ELR+CXC chemokines, which is mediated through antagonizing NF- κ B activation.⁸⁴

5. ANTI-INFLAMMATORY AND IMMUNOMODULATING AGENTS

The connection between chronic inflammation and cancer has been at the center of many recent genetic and epidemiologic studies. Many NSAIDs have been studied for the anti-inflammatory role in chemoprevention, such as aspirin, sulindac, and more selective COX-2 inhibitors.⁸⁵ Additionally, other agents such as sulfasalazine and glucocorticoids have been shown to inhibit inflammation and NF- κ B activation.

5.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

While NSAIDs prevent the synthesis of prostaglandins by inhibiting cyclooxygenase (COX) activity, some of their anti-inflammatory and cancer-preventative effects may be independent of COX, through inhibition of NF- κ B activation. This inhibition can take place at multiple levels of the pathway, including IKK activity, proteasome-mediated degradation of I κ B, as well as the nuclear activity and DNA binding of the transcription factors. It has been demonstrated that high concentrations of aspirin and sodium salicylate can inhibit the LPS-induced NF- κ B-dependent transcription by preventing I κ B α degradation⁸⁶. This effect was later confirmed on TNF- α -induced activation of NF- κ B and attributed to the inhibition of both IKK α and IKK β kinase activity⁸⁷. IKK β inhibition is due to a competitive effect of aspirin and salicylates with ATP binding to IKK β , reducing the phosphorylation of I κ B and subsequent NF- κ B activation⁸⁶.

Anti-tumor and preventative effects of aspirin and other NSAIDs have been demonstrated in a number of studies. Aspirin inhibited the growth of colorectal carcinoma cell lines both *in vitro* and *in vivo*⁸⁸, and regular aspirin use has been shown to prevent colorectal adenomas, reducing the risk of colorectal carcinoma in clinical trials^{89, 89}. Variable inhibition of NF- κ B activity has been found with several other NSAIDs via inhibition of IKK activity. Independent of COX-inhibition, Sulindac inhibits growth of polyps and precancerous lesions in the colon, especially in association with familial adenomatous polyposis. Sulindac can prevent I κ B α degradation and subsequent NF- κ B nuclear translocation by inhibiting the catalytic activity of IKK β ⁸⁵. In NSCLC cells, sulindac enhanced TNF- α -mediated apoptosis by inhibiting NF- κ B activation⁹¹. Ibuprofen has been shown to inhibit the constitutive activation of IKK α and NF- κ B in androgen-independent prostate tumor cells⁹².

A novel mechanism for aspirin's inhibitory effects on NF- κ B-driven transcription has been recently suggested. In colon cancer cells, aspirin's long-term suppressive effects on NF- κ B were associated with the inhibition of I κ B α degradation to prevent relocalization of RELA into the nucleolus⁹³. By sequestering RELA away from target promoters, aspirin reduced the transcription of NF- κ B-dependent anti-apoptotic genes, promoting apoptosis⁹². Further, selective COX-2 inhibitor celecoxib suppressed NF- κ B activation, RELA phosphorylation,

and nuclear translocation in human non-small cell lung carcinoma by inhibiting IKK activity⁹⁴. The same study demonstrated that the COX-2 promoter, which is regulated by NF- κ B, was also inhibited by celecoxib. Thus, inhibiting NF- κ B has the additional anti-tumor effect of decreasing the expression of NF- κ B downstream target gene, *Cox-2*. Recently, Meloxicam, a preferential COX-2 inhibitor that has a higher degree of COX-1 inhibition than selective COX-2 inhibitors such as celecoxib, induced apoptosis in esophageal squamous cell carcinoma (SCC) in patients through inhibiting NF- κ B regulation of COX-2⁹⁵, which is similar to the mechanisms by which aspirin affected esophageal SCC TE-13 cells *in vitro*⁹⁶.

These results suggest that NSAIDs effects on NF- κ B activity may be both drug and cell type specific; that NSAIDs exhibit potential chemopreventative activity against various carcinomas such as lung cancer, colon cancer, prostate cancer, and esophageal cancer; and that such effects could be mediated at least partially by regulating NF- κ B activity^{96, 97}.

5.2 Sulfasalazine

Sulfasalazine, which has been routinely used for the treatment of rheumatoid arthritis and inflammatory bowel disease, is an anti-inflammatory derivative of 5-amino salicylic acid (5-ASA). Mechanistically, sulfasalazine has been shown to inhibit NF- κ B activation⁹⁸ via a direct inhibition of ATP binding to IKK α and β ⁹⁹. Further, while its metabolite 5-ASA lacks intrinsic IKK-inhibitor properties, it was shown to reduce p65 phosphorylation and NF- κ B-dependent transcription in Caco-2 cells, a colon adenocarcinoma cell line¹⁰⁰. Recently, in human renal cell carcinoma, sulfasalazine demonstrated inhibition of NF- κ B and blocked tumor cell growth by inducing cell apoptosis *in vitro*¹⁰¹. Clinical trials using sulfasalazine initiated to assess its anti-cancer potential for treatment in recurrent malignant gliomas have not demonstrated significant activity as a single agent.

5.3 Glucocorticoids

Glucocorticoids represent another class of agents with strongly established anti-inflammatory and anti-tumor activities, at least partially mediated through inhibition of NF- κ B¹⁰², such as inhibition of IKK activity, DNA binding, and transcription of the *I κ B α* gene¹⁰³. Glucocorticoids are commonly administered and have activity for the treatment of hematopoietic malignancies particularly dependent on NF- κ B activation, including certain leukemias, lymphomas and multiple myeloma. To date however, little evidence suggests similar efficacy of glucocorticoids in carcinoma therapy.

5.4 Immunosuppressive Agents

Like glucocorticoids, immunosuppressive agents have been studied less extensively in carcinomas than in lymphoid tumors. However, thalidomide and its analogues, classified as immunomodulatory drugs, have shown promising activity in hematological malignancies such as chronic lymphocytic leukemia and myelodysplastic syndromes as well as in some solid tumors such as prostate cancer, melanoma and progressive brain tumors¹⁰⁴. These agents have been shown to possess potent anti-NF- κ B properties. Thalidomide and its analogues have demonstrated perhaps the most promising results in multiple myeloma therapy¹⁰⁵.

Rapamycin and its derivative compounds, in complex with their cellular receptor FK506-binding protein (FKBP12), act on cell growth and proliferation mainly by inhibiting the mammalian target of rapamycin (mTOR)¹⁰⁶. However rapamycin might serve as a potent new agent to overcome drug resistance through its inhibition of NF- κ B. In melanoma cells, rapamycin inhibited IKK activity and decreased NF- κ B nuclear translocation induced by doxorubicin treatment.¹⁰⁷

6. NATURAL AGENTS AS INHIBITORS OF NF- κ B

Natural agents or their derivatives have been attractive sources of medicines for centuries. Most of them have been in use in crude formulations as folk medicines in diverse cultures all over the world. An added attraction of natural agents is that they are relatively inexpensive and culturally more accepted. There are a number of natural compounds which show inhibitory effects on NF- κ B that may warrant investigation of their potential for prevention of cancer or other diseases associated with inflammation.

Curcumin

Curcumin (diferuloylmethane) 1,7-bis-(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione, is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Turmeric is a member of the ginger family. Its rhizomes produce a brilliant yellow dye. The primary bioactive constituents in turmeric have been found to be the phenolic curcuminoids, the most important of which is curcumin (diferuloylmethane). The role of curcumin in inhibiting NF- κ B has been well studied in cancer cell lines, such as ovarian¹⁰⁸, breast¹⁰⁹, head and neck cancer¹¹⁰, lung¹¹¹, prostate¹¹² and others. Many head and neck squamous cell carcinomas constitutively express active NF- κ B, and treatment with curcumin inhibited NF- κ B as monitored by DNA binding, IKK activation, and p65 nuclear translocation, thus leading to suppression of expression of the NF- κ B regulated proteins Bcl-2, IL-6, cyclin D1, COX-2, MMP-9¹¹⁰. This was associated with inhibition of proliferation and induction of apoptosis in these cell lines^{110, 113}.

Resveratrol

Resveratrol, is a polyphenol (*trans*-3, 4', 5-trihydroxystilbene) abundant in red grapes, berries, and peanuts. As early as 1997, resveratrol was found to be a potent chemopreventive agent, blocking the initiation, promotion, and progression of tumors induced by the aryl hydrocarbon dimethylbenz(a)anthracene (DMBA).¹¹⁴ Since that time, resveratrol has been shown to inhibit the growth of a wide variety of tumor cells, including lymphoid and myeloid; cancers of breast, prostate, and thyroid; melanoma; head and neck squamous cell carcinomas; and ovarian and cervical carcinomas.

Resveratrol has been shown to mediate down-regulation of various proliferative and antiapoptotic gene products, including cyclin D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TRAF2 through suppression of constitutively active NF- κ B through inhibition of IKK and the phosphorylation of I κ B α and of p65 in human myeloma cell lines.¹¹⁵

Green tea and EGCG

Green tea is a common drink in many Eastern as well as Western countries, with remarkable anti-inflammatory and cancer chemopreventive effects found in many animal tumor studies, cell culture systems, and epidemiologic investigations.¹¹⁶ Epigallocatechin 3-gallate (EGCG), the major polyphenol present in green tea, has been shown to inhibit TNF- α induced degradation of I κ B and activation of NF- κ B in human epidermoid carcinoma (A431) cells and in normal human epidermal keratinocytes at high concentrations.¹¹⁷

Parthenolide

Parthenolide is a sesquiterpene lactone present in several medicinal plants that have been used in folk medicine for their anti-inflammatory and analgesic properties. *In vitro*, it inhibits NF- κ B by preventing the TNF- α -induced IKK β activation. Recently, parthenolide inhibited pancreatic cancer cell growth in BxPC-3, PANC-1, and MIA PaCa-pancreatic carcinoma cell lines¹¹⁸. Parthenolide treatment also increased the amount of the inhibitory protein, I κ B α , and

decreased NF- κ B DNA binding activity. The effect of this inhibition was found to be synergistic with sulindac, an NSAID.¹¹⁸

Kambekaurin—*Isodon japonicus* is a medicinal plant that has been used in folk medicine in China, Japan, and Korea as a remedy for gastrointestinal disorder, tumor, and inflammatory diseases. In an effort to identify the compound(s) that account for the anti-inflammatory property of *Isodon japonicus*, Hwang *et al* have reported several kaurane diterpenes from this plant with significant inhibitory effects on the NF- κ B activation, prominent among them being kambekaurin, in the treatment of cancer.¹¹⁹ Treatment of cells with kambekaurin prevented the tumor necrosis factor- α (TNF- α)-induced expression of antiapoptotic NF- κ B target genes encoding c-IAP1 (hiap-2) and c-IAP2 (hiap-1), members of the inhibitor of apoptosis family, and Bfl-1/A1, a prosurvival Bcl-2 homologue, and augmented the TNF- α -induced caspase 8 activity, thereby resulting in sensitizing MCF-7 cells to TNF- α -induced apoptosis.¹²⁰

Other Natural Inhibitors of NF- κ B

Silymarin and silibinin (a component of silymarin) form another class of compounds that can effectively target the NF- κ B pathway. Silibinin was shown to inhibit constitutive activation of NF- κ B in DU145 human prostate adenocarcinoma cells.¹²¹ It was also found to have chemopreventive effects on N-butyl-N-(4-hydroxybutyl) nitrosamine induced bladder cancers in mice.¹²²

CONCLUSIONS AND EXPERT OPINION

The alterations in multiple signal pathways shown to positively and negatively regulate NF- κ B activation are consistent with its frequent activation and important functional role in carcinoma. The redundancy in alterations that may lead to activation can also explain in part why drugs targeting receptors and kinases further upstream are effective primarily in cancers in which limited alterations and a dominant role of these signaling pathways are established. Agents with broad activities such as NSAIDs, corticosteroids and proteasome inhibitors have already demonstrated evidence of efficacy and safety in prevention or therapy of certain cancers, often before the role of NF- κ B among their mechanisms of action was identified. Similarly, many natural products initially identified as having beneficial dietary or anti-inflammatory medicinal effects have been shown to have inhibitory effects on activation of NF- κ B and NF- κ B associated inflammation, and are the subject of renewed interest, possibly as chemopreventative agents. The important role of CK2, IKKs, ubiquitinating enzymes and proteasome in integrating these signals and the final steps of activation have recently made these important molecules for study as potential targets for prevention and therapy.

Although there is now considerable evidence for the role of IKKs, NF- κ B and the proteasome in cancer, and beneficial therapeutic and preventative effects of inhibitors of these targets, their role in cellular homeostasis and immunity has been implicated in some of the toxicities and narrow therapeutic windows observed with these agents. Concerns about NF- κ B's and proteasome's broad expression and important functions as with DNA and hormone receptor targeted agents have not prevented careful development of some of the most important anti-cancer drugs, including corticosteroids, NSAIDs, proteasome inhibitors and SERMs, which have cytoplasmic or nuclear IKK or NF- κ B inhibitory effects. Libraries of siRNAs, natural, and synthetic products are currently being exploited for the discovery of key targets involved in NF- κ B activation in specific tissue and cancer subtypes, and to discover and identify drugs with different tissue selectivities and lower toxicity profiles for use in prevention or therapy. Combinations with existing cytotoxic drugs, radiation are also being explored to take advantage of sensitization that results from NF- κ B inhibition during DNA damage, in an effort to further enhance the efficacy of these agents. Increased appreciation and understanding of the activation

of several different prosurvival signal activated transcription factors in many carcinomas has resulted in improved understanding of the mechanism of drug resistance, and recognition of the need to investigate combinations of these targeted agents for preventive or therapeutic activity. Many natural products while active in GI tract or skin have been found to have poor systemic bioavailability. Efforts to utilize classical and newer engineering approaches in medicinal chemistry to modify these products holds promise for development of additional agents for systemic uses.

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Fig. 1. NF- κ B activation in pathogenesis of carcinoma. A. The classical pathway, involving p105 (NF- κ B1) and RelA activation. B. The alternative pathway stimulated through NIK and IKK α homodimers, involving NF- κ B2 and RelB. Abbreviations. NIK, NF- κ B inducing kinase; IL1R, interleukin 1 receptor; EGFR, epidermal growth factor receptor; TNFR, Tumor necrosis factor receptor; TRAF, TNF receptor-associated factor; TAK, transforming growth factor- β -activated kinase; FAK, focal adhesion kinase; CK2, casein kinase 2; PI3K, phosphatidylinositol 3-kinase; PDK, 3-phosphoinositide-dependent protein kinase; PKA, protein kinase A; MSK1, mitogen and stress activated protein kinase 1.

Fig. 2.

Targeting NF-κB in carcinoma. Red text highlights specific molecular targeted therapeutic agents. Pink text highlights anti-inflammatory agents that show inhibition of NF-κB. Orange text highlights natural compounds that exhibit anti-NF-κB properties. Abbreviations. NIK- NF-κB inducing kinase; IL1R, interleukin 1 receptor; EGFR, epidermal growth factor receptor; TNFR, Tumor necrosis factor receptor; TRAF, TNF receptor -associated factor; TAK transforming growth factor-β-activated kinase; FAK, focal adhesion kinase; CK2, casein kinase 2.