Nuclear factor-κB: The enemy within

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Numerous lines of investigation suggest that nuclear factor NF-κB, a proinflammatory transcription factor, could promote tumorigenesis. Various inflammatory agents, carcinogens, tumor promoters, and the tumor microenvironment activate NF-κB. NF-κB proteins themselves and proteins regulated by it have been linked to cellular transformation, proliferation, apoptosis suppression, invasion, angiogenesis, and metastasis. Constitutively activated NF-κB is common in wide variety of tumors. Furthermore, there exists genetic evidence that NF-κB mediates tumorigenesis. Thus, suppression of NF-κB activation should be effective in the prevention and treatment of cancer.

Background

The history of gram-negative bacteria, lipopolysaccharides (LPS, also called endotoxins), tumor necrosis factor (TNF), and NF-κB is very closely intertwined and is linked to inflammation. Fever, an inflammatory response, whether induced by viral infection, bacterial infection, or another environmental stimulus, invariably leads to loss of appetite and temporary infertility. More than a century ago, the German physician Brunes showed that gram-negative bacterial infection can produce tumor regression. Bacterial extracts have been used until recently, under the name "Coley's toxins," for cancer treatment (Aggarwal, 2003). The antitumor principle in Coley's toxins was identified as LPS, a constituent of the bacterial cell wall that interacts with the cellular receptor TLR4, leading to TNF production from host macrophages (Aggarwal, 2003). TNF turned out to be the most potent activator of NF-κB.

NF-κB was discovered by Baltimore and coworkers in 1986 as a *f*actor in the *n*ucleus of *B* cells that binds to the enhancer of the *k*appa light chain of immunoglobulin (Sen and Baltimore, 1986). It has since been shown to be expressed ubiquitously in the cytoplasm of all cell types, from *Drosophila* to man. It translocates to the nucleus only when activated, where it regulates the expression of over 200 immune, growth, and inflammation genes.

The activation of NF-κB is a double-edged sword. While needed for proper immune system function, inappropriate NF-κB activation can mediate inflammation and tumorigenesis. That duality is especially striking in relation to cancer, a proinflammatory disease (Balkwill and Mantovani, 2001). Most inflammatory agents mediate their effects through the activation of NF-κB (see Figure 1A), and the latter is suppressed by anti-inflammatory agents. Similarly, most carcinogens and tumor promoters activate NF-κB, whereas chemopreventive agents suppress it, suggesting a strong linkage with cancer (for references, see Bharti and Aggarwal, 2002). Paradoxically most agents, including cytokines, chemotherapeutic agents, and radiation, that induce apoptosis also activate NF-κB (Beg and Baltimore, 1996), indicating that NF-κB is a part of the cells' autodefense mechanism and thus may mediate desensitization, chemoresistance, and radioresistance (Wang et al., 1999a). How NF-κB activation mediates tumorigenesis will be addressed in this minireview.

Inactive NF-κB is present in the cytoplasm of all cells; only when it is activated and translocated to the nucleus is the usual sequence of events generated. Currently, NF-κB is known to consist of a family of Rel-domain-containing proteins; e.g., Rel A (also called p65), Rel B, c-Rel, p50 (also called NF-κB1), and p52 (also called NF-κB2). Phosphorylation-dependent cleavage of p100 produces p52, whereas p105 is cleaved to form p50. Similarly, a family of anchorin-domain containing proteins—IκBα, IκBβ, IκBγ, IκBαε, bcl-3, p105, and p100—keep NF-κB in its inactive state within the cytoplasm. In the cytoplasm, NF-κB consists of a heterotrimer of p50, p65, and IκBα. The phosphorylation, ubiquitination, and degradation of IκBα releases the p50-p65 heterodimer, which then translocates to the nucleus and binds its specific 10 base pair consensus site GGGPuNNPyPyCC. IκBα is phosphorylated at serine residues 32 and 34 by IκBα kinase (IKK), which consists of IKKα, IKKβ, and IKKγ (also called NEMO). Gene deletion studies have indicated that IKKβ is needed for NF-κB activation by TNF and most other agents.

NF-κB is constitutively active in most tumor cell lines, whether derived from hematopoietic tumors or solid tumors. It is rarely found to be constitutively active in normal cells except for proliferating T cells, B cells, thymocytes, monocytes, and astrocytes. Constitutively active NF-κB has been identified not only in human cell lines but also in tumor tissues derived from patients with multiple myeloma (Feinman et al., 1999), acute myelogenous leukemia (Griffin, 2001), acute lymphocyte leukemia (Kordes et al., 2000), chronic myelogenous leukemia (Baron et al., 2002), and prostate (Palayoor et al., 1999) and breast cancers (Nakshatri et al., 1997). Suppression of NF-κB in these tumor samples inhibits proliferation, causes cell cycle arrest, and leads to apoptosis (for references, see Bharti and Aggarwal, 2002), indicating the crucial role of NF-κB in cell proliferation and survival. What causes the constitutive activation of NF-κB in tumor cells is incompletely understood. Mutation of IκBα (Wood et al., 1998), enhanced proteosomal activity (Miyamoto et al., 1994), or enhanced inflammatory cytokine expression (O'Connell et al., 1995) have all been cited.

Several carcinogens, such as 7,12 dimethyl-benz(a)anthracene (DMBA) and cigarette smoke, and tumor promoters, such as phorbol ester, can induce NF-κB activation (Banerjee et al., 2002; Anto et al., 2002). TNF, which can mediate carcinogene-

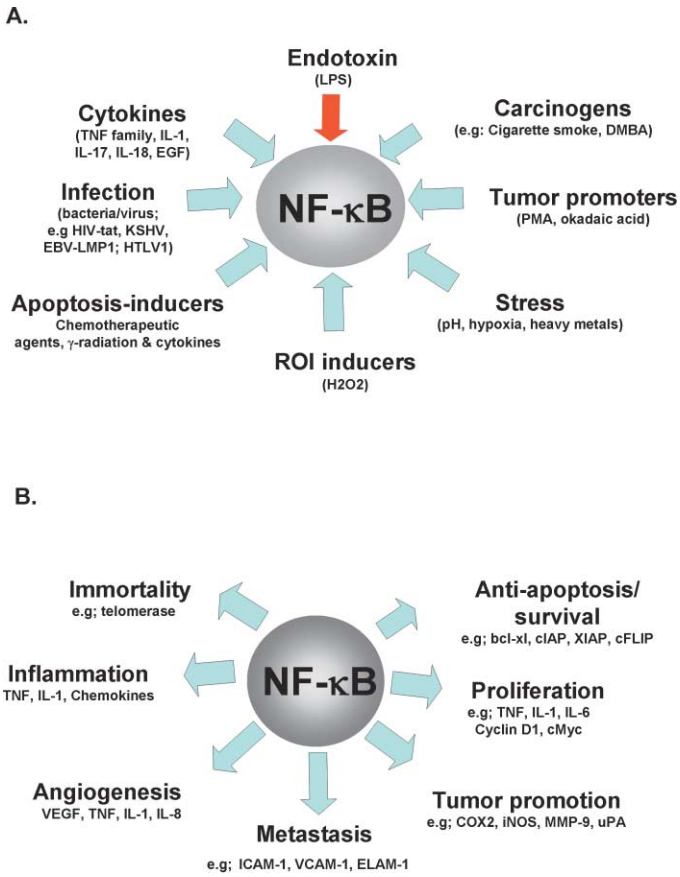

Figure 1. Inducers of NF-κB activation and tumorigenic genes regulated by NF-κB

A: Activation of NF-κB by inflammatory agents, carcinogens, tumor promoters, viral proteins, stress, chemotherapeutic agents, and γ radiation.
B: Expression of numerous genes involved in cell survival, proliferation, angiogenesis, inflammation, invasion, and metastasis is regulated by activation of NF-κB.

sis through induction of proliferation, invasion, and metastasis of tumor cells (Shishodia et al., 2003; Chen et al., 2002), is perhaps the most potent activator of NF-κB. The constitutive activation of NF-κB in tumor cells has numerous consequences, as described below.

NF-κB proteins are oncogenes

Certain members of the NF-κB family are oncogenic. Among the Rel/NF-κB family members, c-Rel consistently transforms cells in culture, is itself activated by a retroviral promoter insertion in an avian B cell lymphoma, and is frequently amplified in Hodgkin's lymphomas, diffuse large B cell lymphomas, and some follicular and mediastinal B cell lymphomas (Gilmore et al., 2004). The avian Rev-T retrovirus encodes the v-Rel oncoprotein. v-Rel induces rapidly fatal lymphoma/leukemia in young birds, and v-Rel can transform and immortalize a variety of avian cell types in vitro. v-Rel is frankly oncogenic in animal model systems. The potent oncogenicity of v-Rel is the consequence of a number of mutations that have altered its activity and regulation (Gilmore, 1999).

NF-κB activation can induce cellular transformation

Several oncogenes mediate their effects by activating NF-κB. Among them is oncogenic Ras, which is constitutively active in several tumor types (Mayo et al., 2001; Balmain and Pragnell, 1983), including prostate (Kim et al., 2002) and colon cancer. Similarly, c-*myc*, which can mediate tumorigenesis (Kim et al., 2000), is regulated by NF-κB. Pim-2, which is a transcriptionally regulated oncogenic kinase, promotes cell survival through activation of NF-κB (Fox et al., 2003). Various viral proteins that mediate tumorigenesis also signal through NF-κB activation. These include Kaposi's sarcoma-associated herpes virus (KSHV), EBV latent membrane protein (LMP)-1, and human T lymphocytic leukemia virus (HTLV)-1.

NF-κB activation mediates cellular proliferation

Numerous NF-κB-regulated cytokines are growth factors for tumor cells. IL-1β is a growth factor for AML, TNF is a growth factor for Hodgkin's lymphoma, cutaneous T cell lymphoma, and gliomas (Pahl, 1999); and IL-6 is a growth factor for multiple myeloma (Kawano et al., 1988), among others. Both IL-1 and TNF mediate their proliferative effects through activation of NF-κB (Osborn et al., 1989). EGF, a growth factor for many different solid tumors, activates NF-κB (Biswas et al., 2000). HER2, a growth factor receptor, is overexpressed in breast, prostate, and other cancers; it too mediates its effects in part through NF-κB activation (Bhat-Nakshatri et al., 2002; Myers et al., 1996). Thus, both cytokines and cytokine receptors either are regulated by NF-κB or mediate proliferation through activation of NF-κB. Certain cell cycle proteins, such as cyclin D1, needed for entry of cells from G1 to S phase, are also regulated by NF-κB.

NF-κB activation can mediate cellular invasion and angiogenesis

Tumor invasion is regulated by numerous NF-κB-regulated gene products, including matrix metalloproteinases (MMP), urokinase type of plasminogen activator (uPA), interleukin-8 (IL-8), and other chemokines (see Figure 1B) (Farina et al., 1999; Bond et al., 1998; Novak et al., 1991). It has been reported that MMP-9 expression is regulated transcriptionally through NF-κB elements within the *MMP-9* gene (Farina et al., 1999). Bond et al., using an adenovirus that overexpresses the inhibitory subunit IκBα, found that NF-κB activation was an absolute requirement in upregulation of MMP-9. uPA, another critical protease involved in tumor invasion and metastasis, is transcriptionally activated by PMA, IL-1, and TNFα. Activation requires the induction of NF-κB activity and the decay of IκBα (Novak et al., 1991). Wang et al. reported that uPA was overexpressed in pancreatic tumor cells through constitutive RelA activity (Wang et al., 1999b). The uPA promoter contains an NF-κB binding site that directly mediates the induction of uPA expression by RelA.

Among the growth factors that regulate angiogenesis are the chemokines (e.g., MCP-1, IL-8), and growth factors (e.g., TNF, VEGF) produced by macrophages, neutrophils, and other inflammatory cells (Loch et al., 2001). The production of these angiogenic factors is regulated by NF-κB activation (Chilov et al., 1997). NF-κB mediates the upregulation of IL-8 and VEGF expression in bombesin-stimulated PC-3 cells (Levine et al., 2003). NF-κB expression has been implicated in

VEGF expression and the regulation of microvessel density in human colorectal cancer (Yu et al., 2003). These studies further underscore the role of NF-κB activation in mediating angiogenesis.

NF-κB activation can mediate metastasis

Metastasis requires the migration of cancerous cells into and out of the vessel walls that transport them to other parts of the body. The ability to penetrate vessel walls is mediated by specific molecules expressed on the endothelial cells of the blood vessels in response to a number of signals from inflammatory cells, tumor cells, etc. Metastasis itself is mediated through the expression of various adhesion molecules, including ICAM-1, VCAM-1, and ELAM-1 (van de Stolpe et al., 1994), which are in turn regulated by NF-κB (Figure 1B). The inducible nitric oxide synthase (iNOS) has also been closely linked with metastatic ability of the tumor (Thomsen and Miles, 1998), and it too is regulated by NF-κB.

Helbig et al. have demonstrated that NF-κB regulates the motility of breast cancer cells by directly upregulating the expression of the chemokine receptor CXCR4 (Helbig et al., 2003). Fujioka et al. showed that inhibiting constitutive NF-κB activity by expressing mutant IκBα (IκBαM) suppressed liver metastasis (Fujioka et al., 2003). These results all implicate NF-κB in the migration and organ-specific homing of metastatic breast cancer cells.

NF-κB links inflammation and cancer

Numerous lines of evidence exist to suggest that inflammation mediates tumorigenesis (Vakkila and Lotze, 2004; Taketomi et al., 1997). Clinically, Taketomi et al. demonstrated that an activated inflammation in a nontumorous portion of the liver was a significant risk factor for recurrence in patients with small hepatocellular carcinoma (Taketomi et al., 1997). The inflammation is mediated through adhesion molecules, such as ICAM-1. In animal studies, Pidgeon et al. noted that surgical removal of a primary tumor is often followed by rapid growth of previously dormant metastases (Pidgeon et al., 1999). They hypothesized that LPS was responsible for this effect. As proof, BALB/c mice that received a tail vein injection of 4T1 mouse mammary carcinoma cells were subjected to surgical trauma or an LPS injection (intraperitoneal). These animals showed an increase in lung metastasis five days later compared to anesthetized controls. Tumor cell proliferation increased and apoptosis decreased within lung metastases. Circulating levels of the angiogenic cytokine VEGF were also elevated in these groups and correlated with increased plasma levels of LPS. Endotoxin treatment directly upregulated VEGF production in vitro. These data indicated that endotoxin introduced during surgery enhanced the growth of metastases.

Harmey and colleagues also showed that LPS increased the growth of experimental metastases in a murine tumor model (Harmey et al., 2002). BALB/c mice bearing 4T1 lung metastases given an i.p. injection of LPS had increased lung weight and a higher incidence of pleural lesions. LPS injection increased angiogenesis both in vivo and in vitro, and vascular permeability in lung tissue was increased after LPS injection. LPS increased inducible iNOS and MMP-2 expression in lung tumor nodules. 4T1 cells transfected with green fluorescent protein (4T1-GFP) injected via the lateral tail vein appeared in lung tissue on treatment with LPS, but not if the competitive NOS inhibitor N(G) methyl-L-arginine was also given. They concluded that LPS-induced growth and metastasis of 4T1 experimental lung metastases are associated with increased angiogenesis, vascular permeability, and tumor cell invasion/migration with iNOS expression.

Genetic evidence that inflammation can mediate tumorigenesis was reported recently by Michael Karin's group (Greten et al., 2004; Luo et al., 2004), in which they manipulated the levels of NF-κB in the tumors and its microenvironment. The first report by Greten et al. examined IKKβ- mediated inflammation and tumorigenesis in a mouse model of colitis-associated cancer (CAC). Tissue-specific deletion of IKKβ in enterocytes and myeloid cells reduced the incidence and development of CAC, but by different mechanisms. Deletion of IKKβ in enterocytes greatly decreased colitis-associated tumor incidence without affecting tumor size. Enterocyte-specific deletion of IKKβ did not prevent dextran sulfate sodium salt (DSS, an inflammatory agent)-induced inflammation, but enhanced p53-independent apoptosis during early tumor promotion. Exposure to azoxymethane (AOM, a procarcinogen) and DSS led to IKK activation in control epithelial cells but not in IKK knockout cells. p53, Mdm2, p21, and JNK were unaltered; expression of bcl-2 family members accounted for the difference in apoptosis. This suggested that the expression of IKKβ in enterocytes is important during early stages of tumor initiation and/or promotion.

Karin's group found that deletion of IKKβ in myeloid cells decreased tumor growth without affecting apoptosis (Greten et al., 2004). It also reduced the expression of IL-1α, IL-1β, IL-6, KC, MIP2, TNF, COX2, and ICAM-1 in macrophages. Tumor incidence was reduced by half. Although tumor morphology was similar, the percentage of smaller tumors was higher. Apoptotic and proliferation indices did not change. While enterocyte-specific deletion of IKK increased COX2 and MMP-9, myeloid-specific deletion of IKKβ decreased their expression. Thus, IKKβ promoted tumor growth in myeloid cells through production of tumor-promoting paracrine factors, rather than inhibition of tumor cell apoptosis. Thus, in myeloid cells, IKKβ is involved in production of inflammatory mediators that promote tumor growth. Which growth factors were involved was not reported. Thus, IKKβ in enterocytes contributed to tumor initiation and promotion by expressing antiapoptotic protein (such as bcl-2), whereas IKKβ in myeloid cells contributed through expression of tumor growth factors.

In the second report, featured in this issue of *Cancer Cell*, Karin and coworkers showed that activation of NF-κB by endotoxin in cancer cells produces inflammation-induced tumor growth through expression of TNF, whereas inhibition of NF-κB mediates tumor regression through TRAIL (Luo et al., 2004). To demonstrate this, they used an experimental murine cancer metastasis model in which an adenocarcinoma cell line generates lung metastasis. Its growth is stimulated by injection of LPS. They found that LPS induced metastatic growth in this model through TNF production by host hematopoietic cells and NF-κB activation in tumor cells. Suppression of NF-κB in both colon and mammary carcinoma cells converted the LPS-induced growth response to LPS-induced tumor regression.

The tumor regression response was TNF-independent but TRAIL-dependent. LPS induced TRAIL receptor in NF-κB deficient cells.

Luo et al. transfected a CT26 colon cancer cell line, which metastasizes to lung, with an IκBα "super-repressor." LPS increased the weight of the lungs and number of tumor nodules in BALB/c mice injected with CT26, but the IκBα super-repressor significantly decreased lung weight and number of nodules. They concluded that NF-κB activation is required for LPS-induced tumor growth. LPS enhanced the proliferation of the tumor, and NF-κB suppression led to apoptosis. LPS also shortened the life span of the animals injected with control cells line, but not of those injected with the super-repressor transfected line. LPS induced Bcl-x_L, cIAP-1, cIAP2, MMP-9, and PCNA in tumors derived from animals injected with control cell line, but not in tumors from IκBα super-repressor cells.

Further investigation revealed that TNF mediates LPS-induced tumor growth and NF-κB activation. LPS activated NF-κB in the host cell (most likely macrophages) and induced circulating TNF within 2 hr. No LPS-induced NF-κB activation was noted in *Tlr4*$^{lps\text{-}d}$ mutant mice (LPS receptor). To examine the role of TNF production/TNF signaling in tumor growth, bone marrow from WT, type 1 TNF receptor-deficient (*Tnfr1*$^{-/-}$) or TNF-deficient (*Tnf*$^{-/-}$) mice was transplanted into lethally irradiated BALB/c mice to generate chimeric mice, which were then inoculated with CT26 tumor cells. The lung tumor burden in chimeric mice reconstituted with either WT or *Tnfr1*$^{-/-}$ bone marrow was significantly higher after LPS challenge. However, LPS did not increase tumor burden in lungs from mice reconstituted with *Tnfα*$^{-/-}$ bone marrow. This correlated with NF-κB activation. These results suggest that TNF production by host hematopoietic cells is required for activation of NF-κB in cancer cells and stimulation of tumor growth.

How does suppression of NF-κB mediate tumor regression? The authors found that LPS-induced regression of NF-κB-deficient tumors is mediated through production of TRAIL. A role for TNF in LPS-induced tumor regression was ruled out, as no difference in tumor burden was noted when CT/IκBα (AA)-cells were inoculated in WT or *Tnf*$^{-/-}$ mice. Because tumor-bearing lungs, not the tumors, from mice inoculated with either CT or CT/IκBα (AA)-cells had elevated expression of Fas and TRAIL after LPS administration, the authors proposed that TRAIL mediates LPS-induced regression. Because Fas is not expressed by CT26 cells, a role for FasL was ruled out. It is intriguing to note that LPS did not induce TRAIL in the tumor, but did induce in tumor-bearing lungs, suggesting that the source of TRAIL was the lungs of the mice. Also, the LPS-induced expression of TRAIL was, if anything, slightly higher in mice bearing CT/vector than those with CT/IκBα (AA) tumors. The lack of difference in LPS-induced TRAIL expression between CT/vector and CT/IκBα (AA) suggests that NF-κB does not have a role in TRAIL expression. Anti-TRAIL antibodies reversed the LPS-induced tumor regression in mice bearing CT/IκBα (AA) tumors. What effect anti-TRAIL antibody has on LPS-induced tumor growth in mice bearing CT 26 tumor was not examined. The question is important, because while TRAIL inhibits the growth of some cell types, it promotes proliferation of other cell types (Secchiero et al., 2003).

Luo et al. further showed that LPS induced DR5 expression (TRAIL receptor II) in tumors from mice bearing CT/IκBα (AA) but not CT/vector, suggesting NF-κB does not have a role in DR5 expression either (Luo et al., 2004). This contradicts published reports that NF-κB activation is needed for DR5 expression (Ravi et al., 2001). Luo's group concluded that JNK-mediated p53 phosphorylation was responsible for DR5 expression. Overall, these results provide evidence, at the genetic level, that inflammatory response generated through the activation of NF-κB plays a critical role in tumorigenesis.

NF-κB activation prevents tumorigenesis

It is possible that NF-κB has different roles in different cell types. Seitz et al. found that in normal epidermis, NF-κB proteins existed in the cytoplasm of basal cells and then localized to the nuclei of suprabasal cells, suggesting that NF-κB mediates the switch from proliferation to growth arrest and differentiation (Seitz et al., 1998). Functional blockade of NF-κB created by expressing dominant-negative NF-κB inhibitory proteins in transgenic murine and human epidermis produced hyperplastic epithelium in vivo. Consistent with this, application of a pharmacologic inhibitor of NF-κB to intact skin induced epidermal hyperplasia. In contrast, overexpression of active p50 and p65 NF-κB subunits in transgenic epithelium produced hypoplasia and growth inhibition. These data suggest that spatially restricted NF-κB activation occurs in stratified epithelium and indicate that NF-κB activation in this tissue, in contrast to its role in other settings, is important for cellular growth inhibition.

van Hogerlinden et al. showed that selective inhibition of NF-κB signaling in murine skin, by targeted overexpression of a super-repressor form of IκBα, results in an increased basal frequency of apoptotic cells and the spontaneous development of squamous cell carcinomas (van Hogerlinden et al., 1999). The presence of hyperplasia and hair follicle degeneration demonstrated an important role for Rel/NF-κB signaling in normal epidermal development and homeostasis. Transgenic skin, in addition, showed an enhanced sensitivity to UV-induced apoptosis. These data suggest an involvement of the Rel/NF-κB signaling pathway in apoptosis and cancer development of the skin.

Dajee et al. showed that NF-κB blockade triggered invasive human epidermal neoplasia (Dajee et al., 2003). The inhibition of NF-κB enhanced apoptosis in certain tumors, and blockade of NF-κB predisposed murine skin to squamous cell carcinoma. They showed that in normal human epidermal cells, NF-κB triggered cell-cycle arrest. Thus, these reports suggest that suppression of NF-κB could be tumorigenic under some conditions.

Conclusion

That inflammation plays a major role in tumorigenesis is becoming evident. Most, if not all, of the inflammatory effects are mediated through NF-κB activation. Its activation controls the expression of genes that mediate transformation, proliferation, invasion, angiogenesis, and metastasis on the negative side of the ledger, and apoptosis, immunity, and hematopoiesis on the positive side. While numerous pharmaceutical companies are developing inhibitors of NF-κB for the treatment of cancer, these inhibitors should be tested with

caution in view of the dual nature of NF-κB, in which either its activation or inactivation may lead to tumorigenesis, depending upon circumstances. Cancer is a proinflammatory disease, as indicated by the fact that aspirin, an established NF-κB blocker and an anti-inflammatory agent, has now shown promise in the treatment of certain cancers. Blockers of NF-κB that are nontoxic, such as plant polyphenols, should be beneficial not only in prevention but also in the treatment of cancer.

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