

IN THE SPOTLIGHT

NF- κ B in Cancer: A Matter of Life and Death

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Summary: Activation of NF- κ B has been linked to various cellular processes in cancer, including inflammation, transformation, proliferation, angiogenesis, invasion, metastasis, chemoresistance, and radioresistance. Although acute inflammation mediates innate and humoral immunity, chronic inflammation has been linked to tumorigenesis. Thus, inhibition of NF- κ B has therapeutic potential in sensitization of tumors to chemotherapeutic agents; however, generalized suppression of NF- κ B can result in serious host toxicity with minimum effect on the tumor. *Cancer Discovery*; 1(6); 469-71. ©2011 AACR.

Commentary on Enzler et al., p. 496 (5).

INTRODUCTION

Among all the transcription factors, no transcription factor has been examined more extensively than NF- κ B. NF- κ B controls the expression of more than 500 different gene products that have been closely linked to inflammation, cellular transformation, tumor cell survival, proliferation, invasion, angiogenesis, and metastasis (1). In addition, this transcription factor is activated in response to a wide variety of stimuli that are shown to be lifestyle risk factors, such as stress (physical, psychological, mechanical, or chemical), tobacco, radiation, asbestos, dietary agents, environmental pollutants, obesity, and various infectious agents closely linked to cancer.

Multiple growth factors linked to proliferation of tumors also activate NF- κ B. Among all growth factors, TNF- α is one of the most potent activators of NF- κ B. In addition, epidermal growth factor receptor, which is linked to the growth of almost one third of all cancers, also acts in part through NF- κ B activation (Fig. 1). The NF- κ B activation pathway typically involves activation of NF- κ B inhibitor α (I κ B α) kinase kinase (known as IKKK), leading to activation of I κ B α kinase, phosphorylation, ubiquitination, and degradation of I κ B α , nuclear translocation of the p50 and p65 subunits of NF- κ B, and consensus DNA binding culminating in NF- κ B target gene transcription. Although canonical NF- κ B activation is mediated through the activation of I κ B α kinase β , noncanonical activation involves I κ B α kinase α .

Although NF- κ B is a major mediator of both innate and humoral immunity, its activation in organs other than the immune system can cause havoc. In most normal cells, NF- κ B exists in its inactive form, but constitutive activation of NF- κ B has been noted in almost all cancers. Why NF- κ B is constitutively active in most tumor cells is not fully

understood. Mechanisms that lead to constitutive activation of NF- κ B differ from those of inducible NF- κ B activation and may vary from one tumor type to another. Some of the potential mechanisms of constitutive NF- κ B activation in different tumor cells have been reviewed recently (2). Crosstalk between NF- κ B and various other transcription factors has also been well documented. Most tumor cells are highly “addicted” to the activated form of NF- κ B because its inactivation usually leads to the inhibition of tumor cell growth, mostly through the suppression of antiapoptotic and proliferative gene products.

Different types of cancer exploit inflammatory components to improve their lifespan in organs. An array of growth factors and cytokines (e.g., interleukin-1 [IL-1], TNF- α , IL-6, VEGF) supports malignant cell progression and contributes to suppress the body’s immune defense. Strategies to modulate the host microenvironment offer new approaches for anticancer therapies. In light of the crucial link between inflammation and cancer, molecules with antitumor and anti-inflammatory features are being looked at with fresh eyes.

The activation of NF- κ B in various immune cells, including T cells, B cells, macrophages, dendritic cells, and neutrophils, leads to expression of proinflammatory cytokines required for proliferation. However, NF- κ B-mediated activation in the immune system has the potential to suppress tumor growth, in part through the production of growth inhibitory cytokines. An acute proinflammatory microenvironment, as defined by the arrival of neutrophils, blood monocytes, and dendritic cells, plays a critical role in tumor regression. It is chronic inflammation, however, that is known to mediate tumorigenesis. Although M1-type macrophages, activated by IFN- γ , promote the adaptive immune response through the secretion of proinflammatory cytokines, M2-type macrophages activated by IL-4 and IL-13 have been linked to anti-inflammatory signaling and wound healing. NF- κ B thus plays an important role in the immune response regardless of the specific macrophage type. Care must therefore be taken with NF- κ B inhibition because tumor-associated macrophages are a major component of inflammatory infiltrates in intratumoral or peritumoral tissue of most solid tumors. Yet, although acute activation of NF- κ B has therapeutic potential, chronic activation can lead to tumorigenesis (3). How to selectively block NF- κ B activation in the tumor remains unclear.

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doi:10.1158/2159-8290.CD-11-0260

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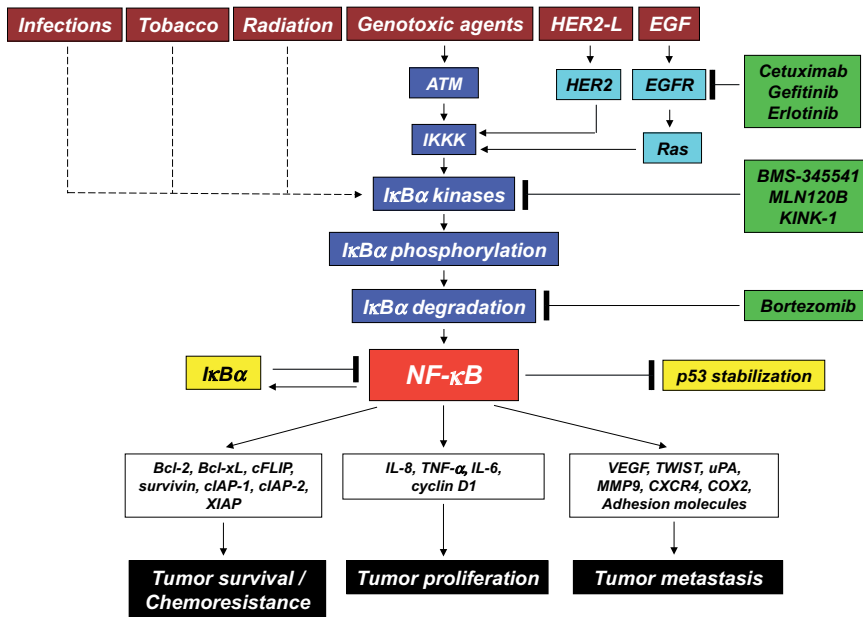


Figure 1. Pathways leading to NF-κB activation in tumor cells and consequent roles of NF-κB activation in tumorigenesis. ATM, ataxia-telangiectasia mutated; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HER2-L, HER2 ligand.

Paradoxically, in addition to lifestyle factors, NF-κB is also activated by most chemotherapeutic agents and radiation used for the treatment of cancer, which then leads to chemoresistance and radioresistance and possibly progression and metastasis of the tumor. Thus, agents that can down-regulate NF-κB are expected to sensitize the tumors to chemotherapy and radiation and prevent metastasis (4). Patients with constitutively active NF-κB normally respond poorly to treatment; therefore, NF-κB status is thus a predictor of overall survival.

In their article in this issue of *Cancer Discovery*, Enzler et al. (5) demonstrate that the NF-κB signaling pathway is linked to both induction of chemoresistance and host toxicity mediated through two distinct cell type-specific mechanisms. These studies were performed in a melanoma chemotherapy model chosen because the role of NF-κB in the growth and chemoresistance of melanoma is well established (6). The authors performed three distinct sets of experiments. First, they showed in a human melanoma xenograft model that doxorubicin cannot inhibit the growth of the tumor. Furthermore, they found that an IκBα kinase inhibitor (BMS-345541) sensitized the tumor to the chemotherapeutic agent but was highly toxic to the host, in part because of generalized suppression of NF-κB. Second, they showed that after tumor-specific suppression of NF-κB with a repressor of IκBα kinase, doxorubicin induced tumor regression with little damage to the host. Third, when NF-κB was specifically down-regulated in host myeloid cells, doxorubicin caused necrotic tumor lesions through the recruitment of IL-1β-producing neutrophils into the tumor, resulting in increased host mortality with minimum tumor regression. They found that polymorphonuclear leukocytes from these animals produced IL-1β, which caused necrotic lesions in the tumor. The inhibition of NF-κB in the melanoma cells was responsible for the antitumor effects, whereas myeloid-specific inhibition of NF-κB was responsible for the toxicity.

Thus, the authors concluded that although tumor-specific suppression of NF-κB is beneficial, generalized suppression of NF-κB is harmful.

These studies are very well done and once again demonstrate the importance of NF-κB in tumor suppression. The studies clearly indicate that NF-κB activation is a “double-edged sword.” Although this transcription factor has therapeutic effects when inhibited in a tumor-specific manner, it could have devastating effects if it is inhibited nonspecifically in the host. As is the case for most cancers, constitutive NF-κB plays a critical role in melanoma [e.g., Schon et al. (7)]. Similar to studies by Enzler et al. (5), Schon et al. (7) also reported that an IκBα kinase β inhibitor (KINK-1) could potentiate the effect of doxorubicin against human melanoma in a xenograft model. When they used camptothecin instead of doxorubicin, sensitization of the tumor was similar. Pulmonary metastasis was also suppressed by down-regulation of NF-κB. The authors noted minimum host toxicity, perhaps because they used a very low dose (3 mg/kg) of the IκBα kinase inhibitor. Although they used different IκBα kinase inhibitors, Enzler et al. (5) showed that an IκBα kinase inhibitor alone (125 mg/kg) was highly effective in suppressing tumor growth, whereas Amschler et al. (8) showed that IκBα kinase inhibitor alone (3 mg/kg) had no effect on tumor growth, thus suggesting a dose-dependent effect. It is thus possible that the host toxicity observed by Enzler et al. (5) was in part attributable to the high dose used. Amschler et al. (8) reported chemosensitization of melanoma (B16F10) to camptothecin in mice (C57BL/6) when they administered a proteasome inhibitor (bortezomib) that also inhibits NF-κB activation and has been approved by the Food and Drug Administration for use in patients with multiple myeloma. These studies demonstrate that inhibition of NF-κB in the melanoma cells can sensitize the tumors to chemotherapeutic agents. Inhibition of NF-κB in the immune system such as macrophages, however, may exhibit toxicity to the host.

These studies have enormous clinical implications because the NF- κ B activation pathway is correlated with response to doxorubicin in patients with breast cancer (9). Similarly, NF- κ B activation has also been associated with resistance to chemoradiation and poor outcome in patients with esophageal carcinoma (10). Furthermore, NF- κ B activation has also been shown to predict the response and survival of patients with irinotecan-refractory metastatic colorectal cancer treated with cetuximab (an antibody against epidermal growth factor receptor) and irinotecan (11). Collectively, these studies suggest the critical role that NF- κ B plays in patients treated with various chemotherapeutic agents, emphasizing again that selective inhibition of NF- κ B is critical.

Although suppression of NF- κ B in the host system may exhibit harmful effects, suppression of NF- κ B in the tumor is beneficial. It is possible that the answer lies in dialing down versus completely suppressing NF- κ B. Like most other molecular targets, it is the dysregulation of NF- κ B that mediates tumorigenesis and chemoresistance. Thus, low doses of chemical inhibitors may be sufficient for sensitization of tumors to chemotherapeutic agents, as shown by Schon et al. (7). Furthermore, other agents, for example, natural products such as curcumin (the yellow pigment in turmeric) that are known to suppress NF- κ B activation both *in vitro* and *in vivo*, are pharmacologically safe, highly affordable, and can chemosensitize a variety of tumors (12–14); these alternatives to the dilemma should be considered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Walter Pagel for carefully editing the manuscript and providing valuable comments. B.B. Aggarwal is the Ransom Horne, Jr., Professor of Cancer Research.

Grant Support

This work was supported by a core grant from the NIH (CA-16-672) and a program project grant from the NIH (CA-124787-01A2).

Received October 6, 2011; accepted October 6, 2011; published online November 17, 2011.

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