

Targeting Inflammatory Pathways by Dietary Agents For Prevention and Therapy of Cancer

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ABSTRACT

Chronic infections, obesity, alcohol, tobacco, radiation, environmental pollutants, and high-calorie diet have been recognized as major risk factors for the most common types of cancers. All these risk factors are linked to cancer through inflammation. While acute inflammation that persists for short-term mediates host defense against infections, chronic inflammation that lasts for long-term can predispose the host to various chronic illnesses, including cancer. Linkage between cancer and inflammation is indicated by numerous lines of evidence; first, transcription factors NF- κ B and STAT3, two major pathways for inflammation, are activated by most cancer risk factors; second, an inflammatory condition precedes most cancers; third, NF- κ B and STAT3 are constitutively active in most cancers; fourth, hypoxia and acidic conditions found in solid tumors activate NF- κ B; fifth, chemotherapeutic agents and gamma irradiation activate NF- κ B and lead to chemo-resistance and radio-resistance; sixth, most gene products linked to inflammation, survival, proliferation, invasion, angiogenesis, and metastasis are regulated by NF- κ B and STAT3; seventh, suppression of NF- κ B and STAT3 inhibits the proliferation and invasion of tumors; and eighth, most chemo-preventive agents mediate their effects through inhibition of NF- κ B and STAT3 activation pathways. Thus suppression of these pro-inflammatory pathways may provide opportunities for both prevention and treatment of cancer. The potential of dietary agents in regulation of these inflammatory cell signaling pathways and their role in prevention and therapy of cancer, is discussed.

Key words: inflammation, NF- κ B, STAT3, Cancer

INTRODUCTION

Common wisdom says “most things in life are a double-edged sword”. While they are in our favor at one dose or under one condition; they may be disfavor at another dose or under another condition. This is analogous to what Alexander Fleming (discoverer of penicillin) once said: if the soil causes the disease; the cure to the disease also lies in it. For instance, while TNF mediates rheumatoid arthritis, the soluble form of its receptor (enbrel) is used for its treatment. Similarly, while T helper (Th)-1 secreted cytokines mediate inflammation, Th-2 produced cytokines suppress it. Also it is noted that while pro-oxidants produced in the body mediate inflammation, antioxidants (such as glutathione) suppress this response. Inflammation is a part of the host response to either internal or external environmental stimuli. This response serves to counteract the insult incurred by these stimuli to the host. This response can be pyrogenic, as indicated by fever. When acute inflammation or fever is manifested for a short period of time, it has a therapeutic consequence. However, when inflammation becomes chronic or lasts too long, it can prove harmful and may lead to disease. How is inflammation diagnosed and its

biomarkers is not fully understood, however, the role of pro-inflammatory cytokines, chemokines, adhesion molecules and inflammatory enzymes have been linked with chronic inflammation. Chronic inflammation has been found to mediate a wide variety of diseases, including cardiovascular diseases, cancer, diabetes, arthritis, Alzheimer’s disease, pulmonary diseases, and autoimmune diseases. The current review, however, will be restricted to the role of chronic inflammation in cancer. Chronic inflammation has been linked to various steps involved in tumorigenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis. That inflammation is a risk factor for most type of cancers is now well recognized. The present review will discuss the various inflammatory intermediates responsible for the steps leading to formation of tumors, their growth and metastasis.

I. NF- κ B Activation Mediates Tumorigenesis

TNF, interleukins, chemokines, COX-2, 5-LOX, and MMP-9 are all regulated by the transcription factor NF- κ B. Although this factor is expressed in an inactive state in most cells, cancer cells express an activated form of

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NF- κ B. This activation is induced by a wide variety of inflammatory stimuli and carcinogens, and the gene products regulated by it mediate tumorigenesis as indicated above. Only few of the recent evidences linking NF- κ B and cancer will be reviewed here.

II. Genetic Evidence About the Role of NF- κ B in Tumorigenesis

NF- κ B activity is triggered in response to infectious agents and pro-inflammatory cytokines via the I κ B kinase (IKK) complex. Using a colitis-associated cancer model, it has been shown that although deletion of IKK β in intestinal epithelial cells does not decrease inflammation, it leads to a dramatic decrease in tumor incidence without affecting tumor size. Pikarsky et al. reported that NF- κ B constitutes an important missing link between cancer and inflammation. The Mdr2-knockout mouse strain, which spontaneously develops cholestatic hepatitis followed by hepatocellular carcinoma, serves as a prototype of inflammation-associated cancer. It has been shown that the inflammatory process triggers hepatocyte NF- κ B through upregulation of TNF α in adjacent endothelial and inflammatory cells. Suppressing NF- κ B inhibition through anti-TNF α treatment or induction of I κ B-super-repressor in later stages of tumor development resulted in apoptosis of transformed hepatocytes and failure to progress to hepatocellular carcinoma.

Mice lacking IKK β only in hepatocytes has been found to exhibit a marked increase in hepatocarcinogenesis caused by diethylnitrosamine (DEN). Decreased hepatocarcinogenesis was also found in mice lacking IKK β in both hepatocytes and hematopoietic-derived Kuffer cells. These mice exhibited reduced hepatocyte regeneration and diminished induction of hepatomitogens, which were unaltered in mice lacking IKK β , suggesting that IKK β provides an inflammatory crosstalk between hepatocytes and hematopoietic-derived cells that promote chemical hepatocarcinogenesis. Co-culture of macrophages with ovarian or breast cancer cell lines led to TNF α -dependent activation of JNK and NF- κ B pathways in tumor cells but not in benign immortalized epithelial cells. Tumor cells with increased JNK and NF- κ B activity exhibited enhanced invasiveness. Inhibition of the NF- κ B pathway by TNF α -neutralizing antibodies, an NF- κ B inhibitor, RNAi to RelA, or overexpression of I κ B inhibited tumor cell invasiveness. This suggests that TNF α , via NF- κ B and JNK, induces macrophage migratory inhibitory factor (MIF) and extracellular matrix metalloproteinase inducer CD147 (EMMPRIN) in macrophage to tumor cell co-cultures and leads to increased invasive capacity of the tumor cells.

III. Activation of NF- κ B by carcinogens

Cigarette smoke (CS) contains several carcinogens known to initiate and promote tumorigenesis and metastasis. Treatment of human histiocytic lymphoma cells with CS activated NF- κ B in a dose- and

time-dependent manner. Thus CS can activate NF- κ B in a wide variety of cells, and this may play a role in cigarette smoke-induced carcinogenesis. The role of EBV latent infection in development of lymphoid and epithelial malignancies such as nasopharyngeal carcinoma (NPC) is mediated via NF- κ B activation pathway. The EBV latent membrane protein 1 (LMP1) acts as a constitutively active tumor necrosis factor receptor and activates cellular signaling pathways such as c-Jun-NH(2)-terminal kinase, cdc42, Akt, and NF- κ B. Activation of NF- κ B p50 homodimer/Bcl-3 complexes has been found in nasopharyngeal carcinoma. Constitutive activation of NF- κ B in human melanoma cells has been linked to activation of Akt kinase suggesting that activation of Akt may be an early marker for tumor progression in melanoma. The chemokines CXC ligand 1 (CXCL1) and CXCL8, but not CXCL5, are highly expressed in most melanoma cell lines, suggesting that the constitutive production of chemokines is highly correlated to endogenous NF- κ B activity. Dhawan's group reported that constitutive activation of Akt in melanoma leads to upregulation of NF- κ B and tumor progression.

Numerous studies have indicated that tumor cells exhibit an elevation in constitutive production of the pro-inflammatory cytokines TNF- α , IL-1 α , IL-6, GM-CSF, and KC (the murine homologue of chemokine Gro α). The basis for constitutive expression of these cytokines after tumor progression in vivo is unknown. Regulation of the expression of these pro-inflammatory cytokines involves transcription factor NF- κ B, which can be activated by cytokines such as TNF- α . The host environment promotes the constitutive activation of NF- κ B and pro-inflammatory cytokine expression during metastatic tumor progression of murine squamous cell carcinoma. The gastric pathogen *Helicobacter pylori* is associated with progression to gastric cancer. *H. pylori* induces plasminogen activator inhibitor 2 in gastric epithelial cells via activation of NF- κ B and RhoA, which in turn mediates invasion and apoptosis. Suganuma et al. found that *H. pylori* membrane protein 1 (HP-MP1) induces release of inflammatory cytokines and TNF α , which acts as both initiator and tumor promoter, and produced tumors in nude mice. *Helicobacter* infection has been shown to induce inflammation and colon cancer in SMAD3-deficient mice. Brandt and coworkers showed that the *H. pylori* immunodominant protein, CagA which causes gastritis and carcinoma induces IL-8 in a dose and time dependent manner and this induction occurs via a Ras-->Raf-->Mek-->Erk-->NF- κ B signaling pathway in a Shp-2- and c-Met-independent manner.

IV. NF- κ B as a Growth Factor for Tumor Cells

The role of NF- κ B as a growth factor for tumor cells is well documented. Ludwig's group investigated the role of specific point mutations of the ret proto-oncogene in multiple endocrine neoplasia (MEN) types 2A and 2B, for familial medullary thyroid carcinoma (MTC) syndromes, and for sporadic MTC. They found that NF- κ B is

constitutively active in C-cell carcinoma and is required for ret-induced transformation. RET-induced NF- κ B and IKK β activity requires Ras function but involves neither the classical MAPK/ERK pathway nor the PI-3K/Akt pathway. In contrast, RET-induced NF- κ B activity is dependent on Raf and MEKK1. Inhibition of constitutive NF- κ B activity results in cell death of TT cells and blocks focus formation induced by oncogenic forms of RET in NIH 3T3 cells. These results suggest that RET-mediated carcinogenesis critically depends on IKK activity and subsequent NF- κ B activation. Constitutive activation of NF- κ B in human cutaneous T cell lymphoma cells was mediated through the autocrine production of TNF. Constitutive activation of NF- κ B in human cutaneous T cell lymphoma cell has been reported to mediate the proliferation of these cells.

Breast cancer metastasis suppressor 1 (BRMS1) functions as a metastasis-suppressor gene in breast cancer and melanoma cell lines. BRMS1 inhibits gene expression by targeting NF- κ B. Suppression of both constitutive and TNF-induced NF- κ B activation by BRMS1 may be due to inhibition of I κ B α phosphorylation and degradation. These results suggest that at least one of the underlying mechanisms of BRMS1-dependent suppression of tumor metastasis includes inhibition of NF- κ B activity and subsequent suppression of uPA expression in breast cancer and melanoma cells. The antiapoptotic response and enhanced cellular proliferation observed in neoplastic cells on overexpression of metallothionein (MT) is also mediated via NF- κ B signaling pathway. MT caused transactivation of NF- κ B through a specific interaction with the p50 subunit of NF- κ B, thus mediating the antiapoptotic effects of MT. Lack of molecular targets in estrogen receptor-negative (ER-negative) breast cancer is a major therapeutic hurdle. Biswas et al. studied NF- κ B activation in human breast cancer specimens and its role in cell proliferation and apoptosis. These findings substantiate the hypothesis that certain breast cancer cells rely on NF- κ B for aberrant cell proliferation and simultaneously avoid apoptosis, thus implicating activated NF- κ B as a therapeutic target for distinctive subclasses of ER-negative breast cancers.

V. NF- κ B Suppression Mediates Chemosensitivity

Extensive research in the last few years suggests that NF- κ B activation mediates resistance to cytokines, chemotherapeutic agents, and γ -irradiation, whereas suppression of NF- κ B can sensitize tumor cells to these agents. For instance, it has been found that inhibition of NF- κ B activation confers sensitivity to TNF- α by impairment of cell cycle progression in 6 human malignant glioma cell lines. p65 DN protein was used to inhibit NF- κ B activation. Similarly, expression of a dominant-negative mutant I κ B α in human head and neck squamous cell carcinoma inhibits survival, pro-inflammatory cytokine expression, and tumor growth in vivo. Inhibitors of NF- κ B activation can block the neoplastic transformation response. Both TNF and PMA

activated NF- κ B and induced cell transformation, whereas NF- κ B blockers suppressed the transformation. These results suggest that NF- κ B activation may be required for transformation whether induced by TPA or by TNF. Inhibition of NF- κ B through adenoviral delivery of a modified form of I κ B α , a specific inhibitor of NF- κ B, has been reported to sensitize chemoresistant tumors to the apoptotic potential of TNF- α and to the chemotherapeutic compound CPT-11, resulting in tumor regression.

A central mediator of a wide host of target genes regulated by the NF- κ B has emerged as a molecular target in cancer-associated bone destruction. Gordon and coworkers investigated NF- κ B-dependent mechanisms in breast cancer cells that regulate tumor burden and osteolysis in bone. They stably transfected cells of the bone-seeking MDA-MB-231 breast cancer cell line with a DN-I κ B α to block NF- κ B. Blockade of NF- κ B signaling in MDA-MB-231 cells decreased in vitro cell proliferation, expression of the pro-inflammatory, bone-resorbing cytokine interleukin-6, and in vitro bone resorption by tumor/osteoclast co-cultures while reciprocally upregulating production of the proapoptotic enzyme caspase-3. Dong et al. used molecular profiling of transformed and metastatic murine squamous carcinoma cells by differential display and cDNA microarray, which found altered expression of multiple genes related to growth, apoptosis, angiogenesis, and the NF- κ B signaling pathway. Loercher's group examined the role of NF- κ B in the cumulative changes in gene expression with transformation and progression of the murine SCC and after switching off NF- κ B by a DN-I κ B α (M) by profiling with cDNA microarray. They found that NF- κ B directly or indirectly modulated expression of programs of genes functionally linked to proliferation, apoptosis, adhesion, and angiogenesis. These results also provide evidence that NF- κ B is an important modulator of gene expression programs that contribute to the malignant phenotype of SCC.

VI. Role of NF- κ B in Tumor Metastasis

Metastasis of cancer cells is a complex process involving multiple steps, including invasion, angiogenesis, trafficking of cancer cells through blood vessels, extravasations, organ-specific homing, and growth. While MMP, UPA, and cytokines play a major role in invasion and angiogenesis, chemokines such as SDF-1 α and their receptors such as CXCR4 are thought to play a critical role in motility, homing, and proliferation of cancer cells at specific metastatic sites. NF- κ B signal blockade resulted in the downregulation of prometastatic MMP-9, a UPA, and heparanase and reciprocal upregulation of antimetastatic TIMP-1 and -2 and PAI 2. NF- κ B promotes breast cancer cell migration and metastasis by inducing the expression of the chemokine receptor CXCR4.

NF- κ B regulates the motility of breast cancer cells by directly upregulating the expression of CXCR4. The cell surface expression of CXCR4 and the SDF-1 α -mediated migration are enhanced in breast cancer cells isolated from

mammary fat pad xenografts compared with parental cells grown in culture. A further increase in CXCR4 cell surface expression and SDF-1 α -mediated migration was observed with cancer cells that metastasized to the lungs. Taken together, these results implicate NF- κ B in the migration and the organ-specific homing of metastatic breast cancer cells. Huang et al. reported that blockade of NF- κ B signaling also inhibits angiogenesis and tumorigenicity of human ovarian cancer cells by suppressing expression of VEGF and IL-8.

The transcription factors p53 and NF- κ B have been implicated in apoptosis induced by DNA-damaging agents, but the relationship between these two factors at the molecular level is largely unknown. Downregulation of NF- κ B is required for p53-dependent apoptosis in X-ray-irradiated mouse lymphoma cells and thymocytes. Apoptosis-resistant mutant sublines from a radiosensitive mouse lymphoma 3SB cell line that undergoes p53-dependent apoptosis after X-ray irradiation were isolated and analyzed for NF- κ B activity. A similar downregulation of NF- κ B activity by X-rays was observed in thymocytes derived from p53 wild-type and heterozygous mice but not in thymocytes from p53 homozygous knock-out mice. These results suggest that NF- κ B inactivation is p53 dependent and is required for X-ray-induced apoptosis in thymic lymphoma cells and normal thymocytes.

The molecular mechanisms responsible for the progression of malignant transformation in Barrett's esophagus are still poorly understood; however, the activation of NF- κ B represents the central event in the neoplastic progression associated with Barrett's esophagus. The increased NF- κ B activity has been linked to increased IL-8 and COX-2 expression.

VII. Regulation of NF- κ B by Dietary Agent

These observation provides evidence for a strong link between chronic inflammation and cancer. Thus inflammatory biomarkers as described here can be used to monitor the progression of the disease. These biomarkers can also be exploited to develop new anti-inflammatory drugs to prevent and treat cancer. These drugs can also be used as adjuvant to the currently available chemotherapy and radiotherapy, which by themselves activate NF- κ B and mediate resistance. Numerous anti-inflammatory agents including those identified from dietary sources have been shown to exhibit chemopreventive activities and thus can be used not only for prevention but also for therapy of cancer. The lack of toxicity associated with the natural agents combined with their cost provides additional advantages

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