Targeting Inflammatory Pathways for Prevention and Therapy of Cancer: Short-Term Friend, Long-Term Foe

Bharat B. Aggarwal, R.V. Vijayalekshmi, and Bokyung Sung

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 cancer. All these risk factors are linked to cancer through inflammation. Although 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 nuclear factor-κB (NF-κB) and signal transducers and activators of transcription 3 (STAT3), two major pathways for inflammation, are activated by most cancer risk factors; second, an inflammatory condition precedes most cancers; third, NF-κB and STAT3 are constitutively active in most cancers; fourth, hypoxia and acidic conditions found in solid tumors activate NF-κB; fifth, chemotherapeutic agents and γ-irradiation activate NF-κB and lead to chemoresistance and radioresistance; sixth, most gene products linked to inflammation, survival, proliferation, invasion, angiogenesis, and metastasis are regulated by NF-κB and STAT3; seventh, suppression of NF-κB and STAT3 inhibits the proliferation and invasion of tumors; and eighth, most chemopreventive agents mediate their effects through inhibition of NF-κB and STAT3 activation pathways. Thus, suppression of these proinflammatory pathways may provide opportunities for both prevention and treatment of cancer.

Cancer is now generally believed to be a preventable disease. Only 5% to 10% of all cancers are caused by inheritance of mutated genes and somatic mutations, whereas the remaining 90% to 95% has been linked to lifestyle factors and environment (1). Almost 30% of all cancers have been attributed to tobacco smoke, 1 35% to diet (2), 14% to 20% to obesity (3), 18% to infections (4), and 7% to radiation and environmental pollutants (5). The underlying mechanisms by which these risk factors induce cancer are becoming increasingly evident. One process that seems to be common to all these risk factors is inflammation.

The great German pathologist Rudolph Virchow (1821-1902) once remarked: “that chronic irritation which is manifested by a chronic inflammation is a key promoter of cancer.” Inflammation (derived from Latin word “inflammatio,” to set on fire), a complex biological response to harmful stimuli, was characterized by the first century Roman physician Cornelius Celsus as that which consists of heat (calor), redness (rubor), pain (dolor), and swelling (tumor). There are two stages of inflammation, acute and chronic. Acute inflammation is an initial stage of inflammation (innate immunity) mediated through activation of the immune system; it helps the body ward off infections, it lasts for short period and generally is regarded as therapeutic inflammation. If the inflammation persists for a long period of time, however, the second stage of inflammation, i.e., chronic inflammation sets in (6). Although this chronic inflammation has been now linked with most chronic illnesses, including cancer, cardiovascular diseases, diabetes, obesity, pulmonary diseases, and neurologic diseases (7), the current review focuses on the role of inflammatory pathways in tumorigenesis. Nuclear factor-κB (NF-κB) and signal transducers and activators of transcription 3 (STAT3) are two most important transcription factors in inflammatory pathways that play major roles in tumorigenesis and thus can be considered targets for prevention and therapy of cancer (6, 8).

NF-κB was discovered in 1986 as a nuclear factor that binds to the enhancer region of the κB chain of immunoglobulin in B cells. It has been shown since, however, to be a ubiquitous transcription factor present in all cell types. In its resting state, this factor resides in the cytoplasm as a heterotrimer consisting of p50, p65, and IκBα (Fig. 1). On activation, the IκBα protein, an inhibitor of NF-κB, undergoes phosphorylation, ubiquitination, and degradation. p50 and p65 are then released to be
translocated to the nucleus, bind specific DNA sequences present in the promoters of various genes, and initiate transcription. The kinase that causes the phosphorylation of IκBα is called IκBα kinase or IKK. Whereas IKKβ mediates the classic/canonical NF-κB activation pathway, IKKα mediates the noncanonical pathway. What causes the activation of IKK is not well-understood. More than a dozen different kinases have been described that can activate IKK including AKT, mitogen-activated protein/extracellular signal-regulated kinase kinase 1 (MEKK1), MEKK3, transforming growth factor–activating kinase 1, NF-κB–activating kinase, NF-κB-inducing kinase, protein kinase C, and the double-stranded RNA-dependent protein kinase PKR. Various gene products that have been shown to mediate inflammation, cell survival,
cell proliferation, invasion, angiogenesis, and metastasis are regulated by NF-κB. Similarly, most agents that promote inflammation and proliferation activate NF-κB. These include endotoxin, carcinogens (such as cigarette smoke), radiation, chemotherapeutic agents, hyperglycemia, tumor promoters, inflammatory cytokines [e.g., tumor necrosis factor (TNF) and interleukin (IL)-1] and growth factors [e.g., epidermal growth factor (EGF); ref. 9].

STAT3 is another transcription factor that is normally present in the cytoplasm of most cells. In response to certain inflammatory stimuli (e.g., IL-6) and growth factors (e.g., EGF), STAT3 undergoes sequential tyrosine phosphorylation, homodimerization, nuclear translocation, DNA binding, and gene transcription. Several protein kinases that cause specific phosphorylation of STAT3 have been identified, including Janus-activated kinase 1, 2, and 3. Similarly, protein phosphatases that cause the dephosphorylation of STAT3 also have been identified. Gene products linked with survival (e.g., Bcl-xL), proliferation (e.g., cyclin D1), and angiogenesis (e.g., vascular endothelial growth factor) are regulated by STAT3 activation (8).

Clinical-Translational Advances

Most carcinogens activate NF-κB and STAT3 pathways. Most carcinogens, including cigarette smoke (10), polycyclic hydrocarbons (11), asbestos (12), alcohol (13), sun light (14), and UV light (15), have been shown to activate the proinflammatory NF-κB pathway. Almost all infectious agents linked with cancer activate NF-κB. For instance, human papillomavirus (16), HIV (17), human herpes virus (18), EBV (19), hepatitis B virus (20), hepatitis C virus (21), and Helicobacter pylori (22) have been shown to activate NF-κB. The roles of human papillomavirus in cervical cancer, human herpes virus in lymphoma, hepatitis B virus and hepatitis C virus in hepatocellular carcinoma, Helicobacter pylori in gastric cancer and HIV, and EBV in leukemia, are well-documented. Hyperglycemia associated with diabetes and obesity, a risk factor for various cancers, has been shown to mediate NF-κB activation (23). Moreover, most growth factors (such as EGF) and growth factor receptors such as EGF receptor and HER2 have been shown to mediate NF-κB activation (24, 25). TNF, the proinflammatory cytokine that has been linked with survival, proliferation, invasion, and metastasis of tumors, is one of the most prominent activators of NF-κB (26).

How all these diverse agents activate NF-κB is not fully understood (Fig. 1). That cigarette smoke and EGF activate NF-κB through a mechanism different from that of TNF has been shown in our laboratory (27, 28). Whereas TNF-induced NF-κB activation was found to be IKK dependent, for example, EGF activated NF-κB through an IKK-independent mechanism (28). Similarly, the mechanism of NF-κB activation by UV, the major risk factor for melanoma, has been shown to be different from that of TNF (29). Most solid tumors exhibit hypoxic and acidic conditions in their core; both of these conditions can lead to NF-κB activation (30). Proinflammatory cytokine IL-6, whose expression is regulated by NF-κB, is a potent activator of the STAT3 pathway (31). STAT3 is also activated by EGF and other growth factors linked to tumorigenesis (32). Although NF-κB and STAT3 activation by most agents is transitory, however, long-term exposure is likely to make it irreversible. These lines of evidence strongly support the hypothesis that carcinogen-induced NF-κB activation could lead to tumorigenesis.

Inflammation precedes most cancers. The suffix “itis” is used typically to denote inflammation. Bronchitis, colitis, celiacitis, gastritis, and hepatitis, for example, reflect inflammation of the bronchus, colon, cervix, stomach, and liver, respectively. It seems that most cancers, especially solid tumors, are preceded by inflammation of a given organ. For instance, people who smoke cigarettes develop bronchitis, and 15% to 20% of these people develop lung cancer (33). Similarly, people who have colitis are at high risk of developing colon cancer (34). Infection with Helicobacter pylori can induce gastritis, which in its chronic form can lead to gastric cancer (35).

Proinflammatory stimuli such as TNF, IL-1, IL-6, cyclooxygenase-2, and 5-lipoxygenase, all regulated by the NF-κB pathway, have been shown to be expressed in bronchitis, colitis, celiacitis, gastritis, or hepatitis. Overexpression of cyclooxygenase-2, for example, has been shown in colitis, bronchitis, and gastritis (36). We have recently shown that TNF is overexpressed in head and neck squamous cell carcinoma and mediates tumor cell proliferation (37). Similarly, TNF expression and its proliferative role have been shown in mantle cell lymphoma (38), acute myeloid leukemia (39), cutaneous T-cell lymphoma (40), and glioblastoma (41). IL-6, whose expression is regulated by NF-κB, has been shown to induce proliferation of multiple myeloma cells through activation of the STAT3 pathway (42).

Inflammatory cells that express activated NF-κB and secrete inflammatory cytokines have been shown to contribute to tumor initiation and progression (43). For instance, inhibition of TNF production by nonparenchymal cells (Kupffer and endothelial cells) prevented NF-κB activation in hepatocytes and in early tumors; and reduced tumor multiplicity (44). Greten et al. (45) reported that deleting IKKβ in myeloid cells caused suppression of NF-κB activation, diminished expression of inflammatory cytokines, and thus leading to a significant decrease in tumor size.

NF-κB and STAT3 are constitutively activated in most tumor cells. In a majority of tumor cell lines, both solid and hematologic tumors, NF-κB has been shown to be constitutively active (46). What causes the constitutive activation of NF-κB in these tumor cells is not fully understood. Many different mechanisms have been described, including overexpression of growth factor receptors, mutation of IκBα such that it cannot bind to NF-κB, constitutive activation of ras protein, high proteolytic activity directed to IκBα, and autocrine secretion of inflammatory cytokines. In most of these tumor cells, constitutive activation of NF-κB is responsible for proliferation, because inhibition of NF-κB leads to abrogation of proliferation (47). Constitutive activation also has been linked to chemoresistance and radioresistance (48). Constitutive activation of STAT3 has been reported in various tumor cell lines (8) and is known to mediate proliferation of these cells.

Constitutive activation of NF-κB and STAT3 is encountered in samples from cancer patients (8, 48). We found that constitutive activation of NF-κB and STAT3 in CD134+ cells from patients with multiple myeloma (49). Similarly, we showed constitutive activation of NF-κB in samples from patients with lung cancer (50) and pancreatic cancer (51).

Organ-specific conditional knock-in and knockout of the inflammatory intermediates promote cancer. Using mice bearing
mutations in the genes coding for the IKKβ and IKKα catalytic subunits, Karin and his colleagues (52–54) examined the role of the NF-κB pathway in tumorigenesis. They found that mice lacking IKKβ only in hepatocytes or hematopoietic-derived Kupffer cells showed a marked increase in hepatocarcinogenesis induced by diethylnitrosamine (53). Interestingly, although tumorigenic function of IKKβ was found to be mediated via NF-κB, the metastatic function of IKKα was found to be independent of NF-κB (54). Moreover, they showed that processes that occur within inflammatory cells are essential for cancer development and progression (53).

To determine the role of NF-κB in inflammation-induced tumor growth, Luo et al. (52) used an experimental murine cancer metastasis model in which a colon adenocarcinoma cell line metastasizes to the lungs when stimulated by lipopolysaccharide. They found that endotoxin-induced metastatic growth response depends on TNF-α production by host hematopoietic cells, leading to NF-κB activation in tumor cells. Inhibition of NF-κB in colon led to tumor regression. The latter depends on TRAIL receptor induction in NF-κB-deficient cancer cells. These findings support the role of inflammatory pathways in tumor development.

Most genes linked with tumorigenesis are regulated by NF-κB and STAT3. NF-κB plays a pivotal role, not only in immune response and inflammatory reaction but also in regulating expression of genes involved in characteristic processes leading to tumorigenesis, such as cell survival, proliferation, invasion, angiogenesis, and metastasis (9).

Numerous genes have been described that are regulated by NF-κB and mediate survival of tumor cells. These include cFLIP, (55) Bcl-XL (56), Bcl-2 (57), XIAP (58), c-IAP1 (59), c-IAP-2 (59), and survivin (60), all of which negatively regulate apoptosis. Some of the genes that are regulated by NF-κB and are linked with proliferation of tumors include cyclin D1 (61), c-myc (62), and cyclooxygenase-2 (63). Other genes such as matrix metalloproteinase-9 (64), vascular endothelial growth factor (65), CXCR4 (66), and TWIST (67), which have been closely associated with invasion, angiogenesis, and metastasis, also are regulated by NF-κB. STAT3 is known to regulate the expression of Bcl-XL (68), Mcl-1 (69), survivin (70), cyclin D1 (71), vascular endothelial growth factor (72), and TWIST (73). Most proinflammatory genes that have been linked with carcinogenesis also are regulated by NF-κB and STAT3, including TNF (74), RANKL (75), IL-1 (76), IL-6 (77), IL-8 (78, 79), and cell surface adhesion molecules such as intercellular adhesion molecule-1, ELAM-1, and VCAM-1 (80). Thus genes regulated by NF-κB and STAT3 are clearly implicated in tumorigenesis.

Most chemotherapeutic agents and γ-radiation activate NF-κB and mediate chemoresistance and radioresistance. Several chemotherapeutic agents have been shown to activate NF-κB, including paclitaxel, vinblastine, vincristine, doxorubicin, daunomycin, 5-fluorouracil, cisplatin, and tamoxifen in human lung cancer, cervical cancer, and in T cells (81–83). Ionizing radiation also has been shown to activate this transcription factor in various tumor cells including human myeloid leukemia cells (84). The mechanism by which chemotherapeutic agents activate NF-κB, however, differs from that of γ-radiation. Activation of NF-κB by ionizing radiation induced tyrosine phosphorylation of IkBα, whereas that by chemotherapeutic agents involves serine phosphorylation (85). Activation of NF-κB by these agents has been linked in turn with chemoresistance and radioresistance (48). Thus suppression of the NF-κB pathway provides a unique window of opportunity to overcome chemoresistance and radioresistance. Activation of the NF-κB pathway by these agents is selective; none of them activate the STAT3 pathway.

Inhibitors of proinflammatory pathways have therapeutic potential. Because the NF-κB and STAT3 pathways play a critical role in tumorigenesis and in induction of resistance of tumor cells to currently available therapy, inhibitors of these pathways have enormous potential. Several inhibitors of NF-κB and STAT3 have been reported (8, 48). Some of these inhibitors are “proof of principle” type, others are rationally designed, and still others have been identified from natural products known to have antiinflammatory activities. For instance, a peptide derived from the phosphorylation domain of p65 can block NF-κB activation and enhance the effect of chemotherapeutic agents (86). Similarly, proteasome inhibitors that were rationally designed as a NF-κB inhibitor, when combined with chemotherapy, can potentiate its effects in multiple myeloma (87, 88). For instance, Velcade, a proteasome inhibitor, has been shown to suppress the NF-κB activation of multiple myeloma cells in culture (89). However, there is no data to indicate that Velcade could inhibit NF-κB activation in the patients. Similarly, thalidomide has been shown to suppress NF-κB activation in cell culture and inhibit cell growth (90). Such data in the patients treated with thalidomide analogues, is lacking.

Numerous agents identified from natural sources can block the NF-κB pathway, including curcumin, resveratrol, ursoic acid, capsaicin, silymarin, guggulsterone, and plumbagin (91–97). Several of these agents also suppress the STAT3 pathway (98–103), suggesting that they exhibit multiple targets. In addition to agents from natural products, synthetic and semisynthetic agents also inhibit the NF-κB or STAT3 pathway. For example, the semisynthetic compound flavopiridol has been reported its activity on NF-κB and STAT3 suppression. Pharmacologically, these agents have been shown to be quite safe, and thus, they can be used not for just prevention but also therapy. In human clinical trials, curcumin has been shown to actually down-regulate both the NF-κB and STAT3 pathways (104). To our knowledge, curcumin is the only agent among all those tested in patients that has been shown to down-regulate both the NF-κB and STAT3 pathways (49, 51, 104). By this property, therefore, curcumin has been shown to have potential in the treatment of human pancreatic cancer (51), familial adenomatous polyposis (105), inflammatory bowel disease (Crohn’s disease; ref. 106), irradiable bowel disease (107), and other proinflammatory diseases (108) in clinical trials. Further clinical trials are needed to fully realize the potential of the inflammatory pathways described here in the treatment of human cancers.

Conclusion

Whether the objective is prevention or therapy of cancer, the targets are the same. The evidence described here clearly shows that inflammatory pathways are critical targets in both prevention and therapy of cancer. Therefore, identification of agents/drugs that can suppress these pathways has enormous potential. Most drugs fail because they are monотargeted, toxic, ineffective, and unaffordable by many. Because of cross-talk
between the pathways, cancers are caused by dysregulation of multiple pathways. Thus, agents that can suppress NF-κB, STAT3, and other pathways (e.g., PI3K/AKT, HIF-1) are likely to be more effective drugs. Because of their safety and ability to affect multiple targets, natural products are likely to have a special place in the preventive and therapeutic armamentarium for cancer. Although there are plenty of preclinical data to support such claims, only clinical studies can fully validate them.

Disclosures of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Molecular Pathways


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