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Subject Review

Inflammation, a Key Event in Cancer Development

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Abstract

Several recent studies have identified nuclear factor-κB as a key modulator in driving inflammation to cancers. Besides this transcription factor, essential in regulating inflammation and cancer development, an inflammatory microenvironment inhabiting various inflammatory cells and a network of signaling molecules are also indispensable for the malignant progression of transformed cells, which is attributed to the mutagenic predisposition of persistent infection-fighting agents at sites of chronic inflammation. As a subverted host response to inflammation-induced tumors, the inflammatory cells and regulators may facilitate angiogenesis and promote the growth, invasion, and metastasis of tumor cells. Thus far, research regarding inflammation-associated cancer development has focused on cytokines and chemokines as well as their downstream targets in linking inflammation and cancer. Moreover, other proteins with extensive roles in inflammation and cancer, such as signal transducers and activators of transcription, Nrf2, and nuclear factor of activated T cells, are also proposed to be promising targets for future studies. The elucidation of their specific effects and interactions will accelerate the development of novel therapeutic interventions against cancer development triggered by inflammation.
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Introduction

The link between inflammation and cancers, rather than a recent concern, was noticed ~150 years ago. As early as 1863, Virchow indicated that cancers tended to occur at sites of chronic inflammation (1). Lately, it turned out that acute inflammation contributed to the regression of cancer (2). However, accumulated epidemiologic studies support that chronic inflammatory diseases are frequently associated with increased risk of cancers (1-3). The investigation aiming at the relationship between inflammation and cancers first led to the determination whether the reactive oxygen and nitrogen species generated by inflammatory cells, such as leukocytes recruited to the inflammatory foci to kill infectious agents, may cause mutagenic assaults and result in tumor initiation (4). Now, it has been realized that the development of cancers from inflammation might be a process driven by inflammatory cells as well as a variety of mediators, including cytokines, chemokines, and enzymes, which altogether establish an inflammatory microenvironment (3). Although this host response may suppress tumors, it may also facilitate cancer development via multiple signaling pathways (5). This review focuses on critical molecular players during the development from inflammation to carcinogenesis. We also discuss several potential targets, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and hypoxia-inducible factor-1α (HIF-1α), which have functions in both inflammatory responses and cancer development.

Inflammation: From Acute to Chronic

Inflammation is a physiologic process in response to tissue damage resulting from microbial pathogen infection, chemical irritation, and/or wounding (2). At the very early stage of inflammation, neutrophils are the first cells to migrate to the inflammatory sites under the regulation of molecules produced by rapidly responding macrophages and mast cells prestationed in tissues (3, 6). As the inflammation progresses, various types of leukocytes, lymphocytes, and other inflammatory cells are activated and attracted to the inflamed site by a signaling network involving a great number of growth factors, cytokines, and chemokines (3, 6). All cells recruited to the inflammatory site contribute to tissue breakdown and are beneficial by strengthening and maintaining the defense against infection (3).

There are also mechanisms to prevent inflammation response from lasting too long (7). A shift from antibacterial tissue damage to tissue repair occurs, involving both proinflammatory and anti-inflammatory molecules (7). Prostaglandin E_2 (8), transforming growth factor-β (9), and reactive oxygen and nitrogen intermediates (6) are among those molecules with a dual role in both promoting and suppressing inflammation. The resolution of inflammation also requires a rapid programmed clearance of inflammatory cells: neighboring macrophages, dendritic cells, and backup phagocytes do this job by inducing apoptosis and conducting phagocytosis (10-12). The phagocytosis of apoptotic cells also promotes an anti-inflammatory response, such as enhancing the production of anti-inflammatory mediator transforming growth factor-β (13-15). However, if inflammation resolution is dysregulated, cellular response changes to the pattern of chronic inflammation. In

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chronic inflammation, the inflammatory foci are dominated by lymphocytes, plasma cells, and macrophages with varying morphology (2). Macrophages and other inflammatory cells generate a great amount of growth factors, cytokines, and reactive oxygen and nitrogen species that may cause DNA damage (3). If the macrophages are activated persistently, they may lead to continuous tissue damage (16). A microenvironment constituted by all the above elements inhabits the sustained cell proliferation induced by continued tissue damage, thus predisposes chronic inflammation to neoplasia (1).

Cancer Development: An Overview

Cancer defines malignant neoplasms characterized by metastatic growth. It may occur in almost every organ and tissue relating to a variety of etiologic factors, such as genomic instability and environmental stress (2). A two-stage carcinogenesis model is first conceptualized in a mouse model of skin cancer (17). In this model, carcinogenesis is initiated by carcinogen-triggered irreversible genetic alteration and then promoted by dysregulated gene expression of initiated cells that resulted from epigenetic mechanisms and host-selective pressure (3). Once the proliferation advantage is obtained, cancer cells enter the progression stage in which their population expands rapidly (4). This model was subjected to criticism because it oversimplifies and failed to apply to all types of cancer (18). However, cancer development is still accepted as a multistep process, during which genetic alterations confer specific types of growth advantage; therefore, it drives the progressive transformation from normal cells to malignant cancer cells (19). Malignant growth is characterized by several key changes: self-sufficiency of growth signals, insensitivity to antigrowth signals, escaping from apoptosis, unregulated proliferation potential, enhanced angiogenesis, and metastasis (19). Each of these shifts is complicated and accomplished by combined efforts of various signaling processes. In later discussion, we will find out that inflammation may contribute to the formation of these cancer phenotypes.

Inflammation and Cancer: Evidence from Epidemiology and Clinical Studies

The association between inflammation and cancer was illustrated by epidemiologic and clinical studies (1, 3, 20). For instance, the risk of colorectal cancer was 10-fold greater if linked with inflammatory bowel disease, such as ulcerative colitis and Crohn's disease (21, 22). Moreover, the control of colitis by certain anti-inflammatory agent reduced colon cancer incidence (23, 24). In the context of the respiratory system, it was also suggested that cancer risk is positively associated with the severity and duration of inflammatory diseases (25, 26). For example, dysplastic progression in nasopharyngeal carcinoma was attributed to EBV (3, 16).

The cause of inflammation may be microbial infection or a noninfective physical and/or chemical irritant (2). In the gastrointestinal tract, gastric *Helicobacter pylori* infection is the leading cause of adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (3, 16). In the bile tract, cholangiocarcinoma was followed by chronic inflammatory infiltrate induced by *Clonorchis sinensis* infection (16). Within the hepatic system, chronic hepatitis caused by hepatitis B and C viruses predisposes into hepatocellular carcinoma, the third leading cause of cancer mortality globally (27). Moreover, human papillomavirus infection is the leading cause of penile and anogenital cancers. Schistosomiasis and human herpesvirus type 8 may increase the risk of bladder cancer and Kaposi's sarcoma, respectively (1, 28).

Chronic inflammation not caused by infection may also contribute to carcinogenesis. The risk of esophageal cancer, pancreatic cancer, and gallbladder cancer may be increased by inflammatory diseases, such as esophagitis, Barrett's metaplasia, and chronic pancreatitis (16, 29). Possible associations were also found in Marjolin's ulcer and skin carcinoma (16), asbestos and mesothelioma (16), silica, cigarette smoke, and bronchial cancer (16), chronic asthma and lung cancer (30-32), sarcoidosis and lung, skin, and liver cancer (33), ulcerative lichen planus and verrucous carcinoma (34, 35), foreskin inflammation/phimosis and penile cancer (36), and pelvic inflammatory disease or ovarian epithelial inflammation and ovarian cancer (16, 37). Chronic prostatitis, resulting from either persistent bacteria infection or noninfective stimuli, was associated with prostate cancer (38). Therefore, there is increasing evidence that supports the association between chronic inflammation and cancer development.

Mechanisms for the Association between Inflammation and Cancer

How does chronic inflammation develop to tumors? What are the important driving forces in this process? Studies from an animal model suggested a sequence of histopathologic events from chronic gastritis to gastric carcinogenesis (39). Chronic inflammation is characterized by sustained tissue damage, damage-induced cellular proliferation, and tissue repair (39). Cell proliferation in this context is usually correlated with "metaplasia," a reversible change in cell type (39). "Dysplasia," a disorder of cellular proliferation leading to atypical cells production, follows and is regarded as the previous event of carcinoma because it was usually found adjacent to the site of neoplasm (21). A recent study added further details into the above model and proposed a new paradigm that might be applied to all epithelial cancers (40). Within a mouse model of gastric cancer derived from *H. pylori* infection-induced chronic inflammation, bone marrow–derived cells were recruited to the site of chronic inflammation when the tissue-based stem cell compartment was exhausted by sustained chronic injury. These engrafted bone marrow–derived cells are more pliable and have a greater potential to develop into cancer through the putative "metaplasia, dysplasia, and cancer" process (40). However, a detailed mechanism applicable to all types of cancers is still unclear.

Mutagenic Potential of Inflammation

The chronic inflammation microenvironment is predominated by macrophages (3, 6). Those macrophages, together with other leukocytes, generate high levels of reactive oxygen and nitrogen species to fight infection (41). However, in a setting of continuous tissue damage and cellular proliferation, the

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persistence of these infection-fighting agents is deleterious (4). They may produce mutagenic agents, such as peroxynitrite, which react with DNA and cause mutations in proliferating epithelial and stroma cells (41, 42). Macrophages and T lymphocytes may release tumor necrosis factor-α (TNF-α) and macrophage migration inhibitory factor to exacerbate DNA damage (43). Migration inhibitory factor impairs p53-dependent protective responses, thus causing the accumulation of oncogenic mutations (44). Migration inhibitory factor also contributes to tumorigenesis by interfering Rb-E2F pathway (45). Within an ileocolitis-associated mouse cancer model, the high susceptibility to inflammation and cancer in hydroperoxide-reducing enzyme-deficient mice suggested that intracellular hydroperoxides might also contribute to tumor initiation (46).

Role of Inflammatory Cells in Tumor Development

Other than a single mutation, more genetic and epigenetic events are required to drive from initiated cells to malignant tumors (19). Some of these events are also found to be related to chronic inflammation. For instance, angiogenesis, a critical process in tumor progression (47), associates with chronic inflammation, such as psoriasis, rheumatoid arthritis, and fibrosis (19). In addition, the tumor inflammatory microenvironment can facilitate the breakage of the basement membrane, a process required for the invasion and migration of tumor cells (3). A wide population of leukocytes and other types of immune cells infiltrate to the developing tumor site and establish the tumor inflammatory microenvironment (5). Macrophages, neutrophils, eosinophils, dendritic cells, mast cells, and lymphocytes are also found to be key components in the epithelial-originated tumors (5, 16, 48).

The infiltration of immune cells to tumors may repress tumor growth (49-57). However, the increasing concern is that inflammatory cells act as tumor promoters in inflammation-associated cancers (3, 58, 59). Accumulated mutations in epithelial cells lead to dysregulation of their growth and migration. These dysregulated epithelial cells may also signal to recruit leukocytes (47). In addition, tumor cells may also produce cytokines and chemokines to attract immune cells to facilitate cancer development (3, 5, 47). In clinical studies, increased tumor-associated macrophages (TAM) density was found to associate with poor prognosis (60-65), whereas the role of other immune cells (e.g., dendritic cells, mast cells, and neutrophils) in tumor development is still under investigation because of inconsistent results (66-72).

TAMs contribute to tumor development through several mechanisms. TAMs release interleukin (IL)-10 and prostaglandin E_2, which suppress antitumor response (73). TAMs may also facilitate tumor growth by releasing angiogenic factors, such as vascular endothelial growth factor (VEGF), endothelin-2, and urokinase-type plasminogen activator (43, 74-80). A positive feedback loop may exist because both VEGF and endothelin-2 have chemotactic effects on TAMs (74, 81, 82). TAMs may produce IL-1, which up-regulates VEGF transcription (83). TAMs may also facilitate tumor cell invasion and metastasis by releasing matrix metalloproteinases (MMP-2 and MMP-9), which degrade the extracellular matrix and the basement membrane (43, 84). In addition, TAMs may induce TNF-α and iNOS, the role of which links inflammation to cancer and will be discussed later in detail. Moreover, TAMs release epidermal growth factor and other epidermal growth factor receptor family ligands to promote tumor cell proliferation and migration (61, 81, 85-87). A paracrine loop of epidermal growth factor might exist for macrophages to synergistically interact with tumors, enhancing metastasis (88). Several macrophage-associated inflammatory factors identified recently might contribute to the increase of tumor susceptibility (89). Activated mast cells generate angiogenic growth factors, such as VEGF/vascular permeability factor and basic fibroblast growth factor, specific angiogenic regulators histamine and heparin, MMP-9, and mast cell–specific proteases MCP-4 and MCP-6 (47, 69, 90-92). Therefore, activated mast cells are suggested to be involved in tumor angiogenesis, invasion, and metastasis. Inflammatory mast cells also enhance tumor progression by releasing cytokines and chemokines (47). Tumor-associated neutrophils enhance tumor angiogenesis, invasion, and metastasis in a similar manner to TAMs and mast cells (47, 93, 94). Neutrophils may also play a role in genetic instability of tumors (95).

T lymphocytes are recruited to tumors by a series of chemokines. At the premaligant lesion stage in a skin cancer model, the knockout of T cells resulted in the decreased leukocyte infiltration and reduced level of MMP-9 (96). Consistently, the increase of $CD4^+$ T cells was positively correlated with poor prognosis in both renal cell cancer and colorectal cancer (97, 98). Future studies should address the role of lymphocytes in cancer development. Recently, it was shown that transforming growth factor-β signaling in T lymphocytes suppressed colon tumor growth by inhibiting IL-6 (99).

Key Molecular Players in Linking Inflammation to Cancer

To address the details of transition from inflammation to cancers and the further development of inflammation-associated cancers, it is necessary to investigate specific roles of key regulatory molecules involved in this process (Table 1).

Cytokines. Cytokines, including IL, TNF-α, growth factors, and differentiation factors (colony-stimulating factors), are secreted or membrane-bound molecules that play a regulatory role in the growth, differentiation, and activation of immune cells (100). Cytokine signaling could contribute to the progression of tumors in two aspects: the stimulation of cell growth and differentiation and the inhibition of apoptosis of altered cells at the inflammatory site (43, 44).

The immune response to tumors is constituted by cytokines produced by tumor cells as well as host stromal cells. Tumor-derived cytokines, such as Fas ligand, VEGF, and transforming growth factor-β, may facilitate the suppression of immune response to tumors (58). Moreover, inflammatory cytokines have also been reported to facilitate the spectrum of tumor development (2, 58, 100). For example, there is accumulating evidence linking IL-6 to colon cancers (99, 101, 102). IL-6 was first found to play a regulatory role on the proliferation of intestinal epithelial cells (103). In colon cancer patients, IL-6

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Table 1. Key Molecular Players Linking Cancer to Inflammation

Potential linkers	Functions in linking inflammation to cancer	Refs.
Cytokines		
IL-6	Promote tumor growth	(99, 102)
TNF-α	Induce DNA damage and inhibit DNA repair	(108)
	Promote tumor growth	(2, 104, 109)
	Induce angiogenic factors	(110)
Chemokines	Promote tumor cell growth	(3)
	Facilitate invasion and metastasis by directing tumor cell migration and promoting basement membrane degradation	(19, 115-119)
NF-κB	Mediate inflammation progress, promoting chronic inflammation	(134, 135, 142)
	Promote the production of mutagenic reactive oxygen species	(128)
	Protect transformed cells from apoptosis	(157, 158)
	Promote tumor invasion and metastasis	(5, 160)
	Feedback loop between proinflammatory cytokines	(135, 136)
iNOS	Downstream of NF-κB and proinflammatory cytokines	(130, 163)
	Induce DNA damage and disrupt DNA damage response	(108, 166)
	Regulate angiogenesis and metastasis	(167)
COX-2	Produce inflammation mediator prostaglandins	(6, 171)
	Promote cell proliferation, antiapoptotic activity, angiogenesis, and metastasis	(175-181)
HIF-1α	Promote chronic inflammation	(194, 195)
	Induced by proinflammatory cytokines through NF-κB	(83, 196, 197)
	Enhance the glycolytic activity of cancer cells	(198)
	Contribute to angiogenesis, tumor invasion, and metastasis by transactivating VEGF	(198)
STAT3	Activated by proinflammatory cytokines	(199, 200)
	Promote proliferation, apoptosis resistance, and immune tolerance	(201, 202)
Nrf2	Anti-inflammatory activity	(204-206)
	Protect against DNA damage	(208, 210, 211)
NFAT	Regulate proinflammatory cytokine expression	(212-215)
	Required in cell transformation	Yan and Huang, unpublished data

serum levels were found to be strongly elevated and positively correlated to tumor load (101). An *in vitro* study also showed that IL-6 enhanced colony formation of human colon carcinoma cells in a dose-dependent manner, indicating its potential role in promoting cancer growth (102). The role of IL-6 in colon cancer progression has been confirmed *in vivo* by a recent study (99). Within this study, it was found that the IL-6 signaling was mediated by soluble IL-6 receptor derived by tumor cells rather than membrane-bound IL-6 receptor. The inhibition of IL-6 production and IL-6 signaling suppresses the growth of colon cancer (99).

A large number of studies suggest that TNF and chemokines are candidate linking molecules between inflammation and cancer (104-106). TNF, produced mainly by activated macrophages but also by tumor cells, binds to membrane-bound homotrimeric receptors TNFRI and TNFRII (107). In inflammation, TNF plays a critical role in both tissue destruction and damage recovery, maintaining the reversibility of microenvironments, stimulating cellular change, and tissue remodeling (104). TNF may initiate an inflammatory cascade consisting of other inflammatory cytokines, chemokines, growth factors, and endothelial adhesion factors, recruiting a variety of activated cells at the site of tissue damage (104). TNF has both anticancer and procancer actions (104). High-dose administration of TNF might destruct tumor vasculature and have necrotic effects in tumors (104). In contrast, TNF has been found to be required in chemical carcinogen-elicited skin carcinogenesis (105) and also is a major inducer for nuclear factor-κB (NF-κB) activation, which shows antiapoptotic activity (2). The contradictory roles of TNF in regulating cell death might be attributed to the diverse modifications of TNF receptor complexes triggering opposite pathways (106). In addition, TNF can induce DNA damage (108), inhibit DNA repair (108), and act as a growth factor for tumor cells (109). The ability of TNF to remodel tissues in inflammatory responses may also enable it to regulate the interactions of tumor cells with stroma as well as extracellular matrix. Furthermore, TNF-α may promote angiogenesis and tumor growth by inducing a range of angiogenic factors, thymidine phosphorylase, and MMPs (1, 104, 110, 111). Another role of TNF in linking inflammation to cancer might be its regulation of a network of chemokines (104).

Chemokines include the largest family of cytokines. They can be categorized into CC, CXC, XC, and CX_3C based on their relative positions of conserved cysteine residues. In the processes of inflammation, chemokines, usually induced by cytokines, are major soluble regulators that control the directional migration of leukocytes to the inflammatory site (96). It is well established that chemokines are involved in the promotion of cancer (96, 112, 113). Previous studies have shown that the expression of CXC receptor 2 might promote preneoplastic cell transformation under certain circumstances (114). It has also been reported that some specific chemokines can promote tumor cell growth (3). Moreover, chemokines also facilitate tumor invasion and metastasis in various cancer types (96, 112, 113) and the balance between chemokines with proangiogenic and angiostatic activities is critical in regulating angiogenesis (19). Mechanistically, chemokines may contribute to tumor invasion and metastasis by mediating the directional migration of tumor cells to specific distal organs via circulation in a similar manner to its control of leukocyte migration (19). They may also facilitate the metastasis of tumor cells by inducing the expression of MMPs and collagenases, which degrade the basement membrane (115-118). A recent study on CXCL-8 showed its role in the interaction between tumor cells and the host environment (119). Ras-transfected human cancer cells are able to produce CXCL-8, a chemokine encoded only in

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the human genome. After xenografted into nude mice, those cells secrete CXCL-8 in a paracrine manner, which can recruit host (mice)–produced inflammatory cells to initiate tumor inflammation and angiogenesis, thus facilitating cancer progression (119).

Nuclear Factor-κB. NF-κB is a collective term referring to dimeric transcription factors of the Rel family (120). In the cytoplasm, NF-κB exists in the form of an inactive NF-κB-IκB complex in which IκB inhibits NF-κB (121). In response to extracellular stimuli, such as cytokines, IκB is subjected to phosphorylation, ubiquitination, and proteolytic degradation via a canonical IκB kinase (IKK) complex-dependent pathway or a noncanonical NF-κB-inducing kinase pathway (120, 121). IκB degradation may be also through the phosphorylation by casein kinase 2 (122, 123). After IκB degradation, NF-κB is released and translocates to the nucleus (124), where it binds to the promoter regions of its target genes (125). The optimal NF-κB activation also involves the phosphorylation of NF-κB itself. For instance, recent studies showed that the phosphorylation of NF-κB/p65 on Ser^{536} is required for the polyubiquitination and degradation of IκBα, the predominant IκB protein (126). Suppression of this certain phosphorylation reduced the activation and nucleus translocation of NF-κB and functionally led to the resistance of JB6 cells to TNF-α-induced transformation (127).

Targets of transcription factor NF-κB include immune-mediating genes and inflammatory genes, antiapoptotic genes, cell proliferation regulation genes, and genes encoding negative regulators of NF-κB (128). Within the immune system, NF-κB is involved in the maturation of dendritic cells (129) and the development of lymphocytes (130-133). NF-κB acts as a critical mediator of inflammation progress, regulating the expression of a wide range of inflammatory molecules, such as cytokines and adhesion factors (134, 135). As an important regulator, NF-κB is subjected to tight control by several proteins, such as the zinc finger protein A20 (136). Aberrant and constitutive NF-κB activation plays a role in a variety of inflammatory diseases, including rheumatoid arthritis, atherosclerosis, asthma, inflammatory bowel disease, and *H. pylori*–associated gastritis (135, 136). The lack of IKKβ in keratinocytes enhances TNF-α-dependent inflammation (137). However, the inhibition of NF-κB in both enterocytes and a murine model of Crohn's disease results in a reduction of inflammatory response (138, 139). Recently, in a murine asthma model, the adenoviral delivery of a NF-κB inhibitory protein to lung epithelium results in the decrease of allergic airway inflammation (140). NF-κB is also required for neutrophil chemotaxis in intraepidermal inflammation (141). It has also been reported that NF-κB regulates inflammatory cell apoptosis and phagocytosis (7, 142). These results indicate that NF-κB may play a critical role in the establishment of chronic inflammation. In regard to carcinogenesis, NF-κB suppresses apoptosis by various mechanisms (128, 138, 143, 144). For instance, it has been shown that the proapoptotic activity of antineoplastic cyclopentenone prostaglandin involves NF-κB inhibition as well as the decrease of various NF-κB-dependent antiapoptotic proteins in malignant B cells (145). In mucosa-associated lymphoid tissue lymphoma, the inhibition of p53-mediated apoptosis was found through the activation of NF-κB pathway (146). In addition, NF-κB contributes to tumor development by stimulating cell proliferation, because it activates the expression of growth factor genes, proto-oncogene c-Myc, and cell cycle regulator cyclin D1 (128, 147, 148). NF-κB may also play an essential role in late-stage cancer development. It was found that NF-κB is required for the metastasis of injected cultured mammary epithelial cells transformed by Ras oncogene (149).

NF-κB is activated by inflammatory stimuli and its constitutive activation is found in cancer (128); as a result, it has long been suspected to be a critical promoter facilitating the development from inflammation into cancer (128). In squamous epithelium, bacterial lipopolysaccharide-induced human keratinocyte proliferation was found to be dependent on NF-κB activation and subsequent cyclin D1 up-regulation (150). NF-κB may also contribute to genomic instability in two aspects. It promotes the production of reactive oxygen species, which have a potential to cause mutations (128). On the other hand, the antiapoptotic activity of NF-κB prevents mutated precancerous cells from being eliminated (128). NF-κB might be involved in linking inflammation to cancer because of the association between NF-κB and the induction of proinflammatory cytokines, such as IL-6 and TNF-α, and chemokines, such as IL-8, adhesion molecules, MMPs, COX-2, and iNOS (130). Adhesion molecules, such as E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1, are responsible for the requirement of NF-κB in leukocyte adhesion and migration, which are important in both inflammation and the inflammatory microenvironment of cancer (151). The increase of adhesion molecules has also been found in certain types of cancer in clinical studies (152-155). This may be because those adhesion molecules are used by tumor cells to facilitate migration and positioning in the process of metastasis (3). Recently, it has been found that decoy receptor 3, a molecule associated with tumorigenesis as well as monocyte differentiation and function, up-regulates intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and IL-8, all of which promote monocyte adhesion (5). NF-κB activation is required for this up-regulation (5). MMPs, as mentioned before, facilitate tumor invasion by their proteolytic activity (128). Noticeably, it is suggested that certain feedback loops exist between proinflammatory cytokines (TNF-α, for instance) and NF-κB activation. In this putative feedback loop, NF-κB is activated by and induces the expression of proinflammatory cytokines (135, 136). This feedback loop may also be responsible for the constitutive activation and geographic spread of NF-κB from cell to cell found in inflammatory diseases and essential for the proposed role of NF-κB in linking inflammation with cancers. For instance, an autocrine system involving IL-1α has also been found to result in the constitutive expression of NF-κB within a metastatic human cancer model (156).

Recent studies using different animal models provided direct illustrations for the role of NF-κB at the tumor promotion stage in the development of cancers from chronic inflammation (157, 158). One study using two strains of genetically altered mice from a mouse model of colitis-associated cancer showed that the blockade of the IKKβ gene in the two different cells (myeloid lineage and epithelial cells) may both result in tumor

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regression but via different mechanisms (158). NF-κB activation is through IKK complex in inflammatory settings; therefore, NF-κB could not be activated after the knockout of IKKβ (159). NF-κB pathway inactivation, in the myeloid lineage that macrophages derive from, results in the reduction of both the tumor incidence and the sizes of occurred tumors, which is found to be due to the decrease of several proinflammatory factors facilitating tumor growth (158). The knockout of IKKβ in epithelial cells leads to the decrease of tumor incidence more often, but no effect on tumor sizes, which indicates that the lack of NF-κB pathway in epithelial cells increases epithelial apoptosis during very early tumor promotion (158). Consistently, NF-κB was also found to protect epithelial cells against inflammation-induced apoptosis in a cell-autonomous role (138). The similar conclusion was also derived from another inflammation-associated cancer model (157). In a Mdr2-knockout mouse strain that spontaneously develops hepatitis and hepatocellular carcinoma, NF-κB in hepatocytes is activated by the inflammatory process via the increase of TNF-α in endothelial and inflammatory cells within the microenvironment (157). After introducing a second knockout of NF-κB, it was found that the blockade of NF-κB does not affect the accumulation of premalignant hepatocytes but leads to the apoptosis of transformed hepatocytes, thus reducing the tumor formation to a great extent (157). Another recent study using a colon cancer cell line indicated a potential role of NF-κB in inflammation-induced metastasis (160). In a murine cancer metastasis model, the introduction of colon adenocarcinoma cell line caused lung metastases. The growth of such lung metastases was found to be stimulated by the injection of bacterial lipopolysaccharide. The knockout of NF-κB in the colon adenocarcinoma cells resulted in the regression of lipopolysaccharide-induced tumor metastases (160).

Inducible Nitric Oxide Synthase. iNOS, an enzyme-catalyzing NO production, was found to be overexpressed in chronic inflammatory diseases and various types of cancer (161). Recently, it was found in an animal model study that a selective NOS inhibitor prevents the progression of rat esophageal tumorigenesis, which is induced by the carcinogen *N*-nitrosomethylbenzylamine (162). NO is an important regulatory molecule in both inflammation response (163) and cancer development (164). Because iNOS is subjected to the induction by proinflammatory cytokines, such as TNF-α and IL-1β (163), and the transactivation by NF-κB (130), it may be a downstream effector of cytokines and NF-κB in linking inflammation to cancer. In an experimental model of colitis, TNF-α resulted in inflammation partially via the expression of iNOS triggered by TNF-α (165). Moreover, the blockade of lipopolysaccharide-induced NF-κB activation led to the inhibition of iNOS expression and NO generation and the inhibition of inflammation (161). Under the circumstances of chronic inflammation, the continuous generation of NO may lead to DNA damage, disruption of DNA repair, and cancer-prone post-translational modification (108, 166, 167). Increased NO production might result in p53 activation but also carcinogenic p53 mutations (163, 166, 168). Once the inflammation-associated tumors are formed, iNOS expression may be persistently stimulated by cytokines and NF-κB that are prevalent within the tumor inflammatory microenvironment (130). NO may also regulate angiogenesis, leukocyte adhesion and infiltration, and metastasis (167). A recent population-based study found that specific polymorphisms in the promoter region of iNOS gene led to higher promoter activities correlated with a higher incidence of gastric cancer in nonsmoking Japanese women (169). It was also suggested that, due to the higher promoter activities of iNOS, excess NO may be produced and cause chronic inflammation, which contributes to the *H. pylori*–induced gastric cancer (169). Noticeably, studies using a wide range of *in vitro* and *in vivo* models show that iNOS/NO signaling can also induce COX-2, which itself is a promising link between inflammation and cancer (167).

Cyclooxygenase-2. COX-2 expression may be induced by a wide range of stimuli, including lipopolysaccharide, proinflammatory cytokines, such as IL-1 and TNF, and growth factors, such as epidermal growth factor (128, 170). The products of COX-2 enzyme are prostaglandins, which are key mediators of inflammation (6, 171). Various nonsteroidal anti-inflammatory drugs affect COX-2 activity by covalent modification or competition for a substrate binding site, and the long-term use of nonsteroidal anti-inflammatory drugs was shown by population-based studies to reduce the risk of several cancers (170, 172-174). COX-2 is also overexpressed in various types of cancer and involved in cellular proliferation, antiapoptotic activity, angiogenesis, and an increase of metastasis (175-181). COX-2 pathway is induced by cigarette smoke in human lung fibroblasts, indicating a possible mechanism for the cigarette smoking–triggered cancer-prone inflammatory lung diseases (182). The functions of COX-2 in linking inflammation to cancer are now becoming the target of intense investigation. A recent study using an esophageal model of rats indirectly supports that the COX-2 induction might contribute to the progression of cancers from inflammation (183). In this study, COX-2 inhibitor celecoxib inhibits the COX-2 pathway and delays the developing progress from esophageal inflammation, metaplasia, to adenocarcinoma. However, inconsistency still exists in regard to the exact role of COX-2 in the development from inflammation to cancer. Another recent study in the context of Barrett's esophageal epithelium showed that COX-2 expression is independent of the degree of inflammation but related to the premalignant cells that already existed in the tissue (184). These results indicate that COX-2 expression may not be the driving force for the development from inflammation to cancer but rather play a role in enhancing cancer development in the scenario of chronic inflammation. This notion is supported by a recent immunohistochemical study of human prostate cancers in which the local chronic inflammation has been found to be able to up-regulate COX-2 expression in adjacent tumor cells and induced angiogenesis (185). However, inconsistent results were obtained in another recent study, which indicates that COX-2 may be sufficient to cause inflammation and the subsequent cancerous aberrations. Within this study, it was found that the forced expression of COX-2 transgene under the control of a keratin-5 promoter causes spontaneous inflammation-associated transitional cell

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hyperplasia and transitional cell carcinoma in urinary bladders of transgenic mice (186). Future research is needed to address the specific role of COX-2 in linking inflammation and cancer and to extend those findings to other types of inflammation-associated cancers. Arachidonic acids are the substrate for COX-2 to produce prostaglandins. Interestingly, arachidonic acids can be converted by another enzyme lipoxygenases to leukotrienes, which were suggested to be another missing link between inflammation and cancer (187).

Hypoxia-Inducible Factor-1α. HIF-1, widely accepted as a mediator of oxygen homeostasis, is a heterodimeric transcription factor (188). HIF-1α is oxygen sensitive at the protein level, whereas HIF-1β is constitutively expressed (189). In response to hypoxia, HIF-1 activates a wide range of hypoxia-responsive molecules, such as erythropoietin, iNOS, VEGF, glucose transporter-1, and other glycolytic enzymes (190). At sites of inflammatory lesions, hypoxia is a common feature resulting from metabolic shifts during inflammation (191). Therefore, HIF-1 may be implicated in inflammation. The role of HIF-1 in driving the progression of inflammation may be tissue specific. In a murine model of experimental colitis, HIF-1 in hypoxic epithelium attenuates clinical manifestations of inflammatory disease as an anti-inflammatory factor (192). However, HIF-1 plays an essential role in other models of inflammation, inducing leukocyte adhesion (193) and maintaining normal functions of myeloid cells recruited to sites of inflammation (194). HIF-1 also might promote chronic inflammation by preventing the hypoxic apoptosis of neutrophils and T lymphocytes (194, 195). The relationship between regulation of NF-κB and HIF-1 pathways is dependent on the status of cells (83, 194, 196, 197). The induction of NF-κB by hypoxia is dependent on the existence of HIF-1α (190), whereas in several normoxic cell lines, including cancer cells, HIF-1α is activated by proinflammatory cytokines, such as TNF-α and IL-1β, in a NF-κB-dependent manner (83, 196, 197). It is also found that COX-2 mediates IL-1β-induced HIF-1α by its product prostaglandin E_2 (83). HIF-1α plays an essential role in tumor development because it facilitates the phenotype of cancer cells with an enhanced glycolytic activity and increases the transcription of VEGF, a potent angiogenic factor that is important in tumor growth and metastasis (198). Although further studies are required to elucidate the interactions among proinflammatory cytokines, NF-κB, COX-2, and HIF-1, we hypothesize that HIF-1 is a candidate in linking inflammation and cancer. In the context of inflammation, HIF-1 induced by hypoxia may contribute to the establishment of cancer-prone chronic inflammation. Its persistent presence may result from NF-κB activation and/or COX-2-mediated induction by proinflammatory cytokines prevalent within the microenvironment. On the other hand, HIF-1 may also act as a promoter facilitating the development of inflammation-associated cancers.

Other Promising Links between Inflammation and Cancer. To add even more complexity to the whole picture of inflammation and cancer, there may be still some missing parts of the long-lasting puzzle. The transcription factor signal transducers and activators of transcription (STAT) might be one missing link. It is well known that cytokines can activate STAT family transcription factors by the signaling of Janus-activated kinases (199). The conformational change of cytokine receptor induced by the binding of their ligands causes the displacement of Janus-activated kinases, which subsequently phosphorylate and activate STAT transcription factors (200). The aforementioned IL-6, which was found to be involved in the progression of colon cancer, is a well-established inducer of STAT3. Because STAT3 has been found constitutively activated in various types of cancer (199), we speculate that the IL-6/Janus-activated kinase/STAT3 pathway might play a role in linking the inflammatory microenvironment and cancer development. Another member of the STAT family STAT5 is also activated by a wide range of cytokines, including IL-2, IL-3, IL-5, IL-7, IL-9, IL-15, and granulocyte-macrophage colony-stimulating factor, in a similar manner to that of STAT3. STAT5 is not associated with so many types of cancer as STAT3 is, and its activation seems to be specifically found in several types of leukemia (199). The function of STATs in cancer development is still under intense investigation, but it has been found that they can promote proliferation and apoptotic resistance in human myeloma cell lines (201) and contribute to the immune tolerance of tumor cells (202). Therefore, we suggest that STAT3 activation occurs after the occurrence of primary malignant cells and plays a role in promoting their development in an inflammatory microenvironment. Other than the STAT family transcription factors, there are still other possible linking molecules. The transcription factor Nrf2, which regulates a wide range of detoxifying and antioxidant genes, was identified as a critical system responding to cellular stresses (203). Interestingly, several *in vivo* studies showed that Nrf2 might play an anti-inflammatory role in inflammation (204-206). The regulatory role of Nrf2 in the resolution of inflammation was through the induction by a prostaglandin product of COX-2 (207). Nrf2 may also be induced by NO (208) and lead to the reduced susceptibility to apoptotic signals, such as TNF-α (209). As for carcinogenesis, Nrf2 was well established to protect against DNA damage and carcinogenesis (208, 210, 211). Moreover, nuclear factor of activated T cells (NFAT), which is expressed in both immune and nonimmune cells, plays an essential role in inflammatory responses by regulating the expression of a wide range of proinflammatory cytokines, such as IL-2, IL-3, IL-4, IL-5, IL-13, granulocyte-macrophage colony-stimulating factor, and TNF-α (212-215). The inhibition of NFAT in T cells resulted in a reduction of allergic pulmonary inflammation (216). In both T cells and colon carcinoma cells, NFAT was involved in the expression of COX-2, which has extensive functions in both inflammation and cancer development (217, 218). Recently, our group found that NFAT was required for TNF-α-induced COX-2 expression and cell transformation in mouse epidermal Cl 41 cells.[1] To date, the extensive roles of Nrf2 and NFAT suggest that they might be promising targets for addressing the puzzling link between inflammation and cancers.

[1] Yan and Huang, unpublished data.

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Concluding Remarks

Inflammation and cancer are both complicated pathologic processes under the control of many driving forces rather than a single one (3, 6, 19). In Fig. 1, we summarize the mechanisms underlying the involvement of inflammation in cancer development discussed in this review, although the mechanisms underlying their association still remain unraveled. The initial inflammation involves the recruitment of a wide range of immune cells to inflamed sites (16) as well as the release of various proinflammatory cytokines and other agents. These molecules function in a coordinative manner to commence an inflammatory cascade (3). The inflammation is precisely timed; however, the aberrations in the apoptosis and phagocytosis of *in situ* inflammatory cells may lead to an unresolved chronic inflammation (219, 220). In a setting of chronic inflammation, the persistent tissue damage and cell proliferation as well as the enrichment of reactive oxygen and nitrogen species contribute to a cancer-prone microenvironment (221). Cytokines, such as migration inhibitory factor, may also protect transformed cells from being arrested by tumor suppressor gene p53 (43, 44). The sinister role of inflammatory cells and molecules still persists after the tumors have been formed, when inflammatory cells are infiltrated into tumor sites. They are involved in the circumvention of tumor cells from host immune response or play an even more direct role to facilitate angiogenesis, tumor growth, invasion, and metastasis by themselves or by inducing other effector molecules, such as MMPs (3). Tumor cells may also release cytokines and chemokines to further enhance the tumor promotion of such a subverted host immune response (3, 5, 47).

Within such a generalized model, several transcription factors, enzymes, besides cytokines and chemokines, should be taken into extensive consideration for their critical regulatory functions during this complicated process. Recently, light has been shed on NF-κB. NF-κB mediates the development of cells participating in inflammatory responses (129, 130) and, more importantly, also drives the development of chronic inflammation by regulating apoptosis of inflammatory cells (7, 142). The proposed positive feedback loop that exist between NF-κB and cytokines, such as TNF-α, may imply the role of NF-κB as an essential regulator in the whole network (134, 135). In addition, this putative feedback loop may partially be the reason for the persistent and prevalent existence of all these signaling molecules in inflammatory tissues and results in the enhancement of their effects in cancer development. Recently, several studies have made a great progress in delineating the role of NF-κB in linking inflammation and cancer. These studies illustrated that NF-κB at the tumor promotion stage of inflammation-associated cancer is an antiapoptotic factor, which protects transformed cells against the elimination by several endogenous apoptotic factors (157, 158). The regulatory role of NF-κB in its downstream molecules, such as iNOS, COX-2, and HIF-1α, is also shown. These molecules themselves are pleiotropic in inflammation and cancers and thus are potential targets of the links between inflammation and cancers.

The whole story between inflammation and cancer is still far from being completely understood. For instance, the question regarding the intriguing feedback loop between cytokines and

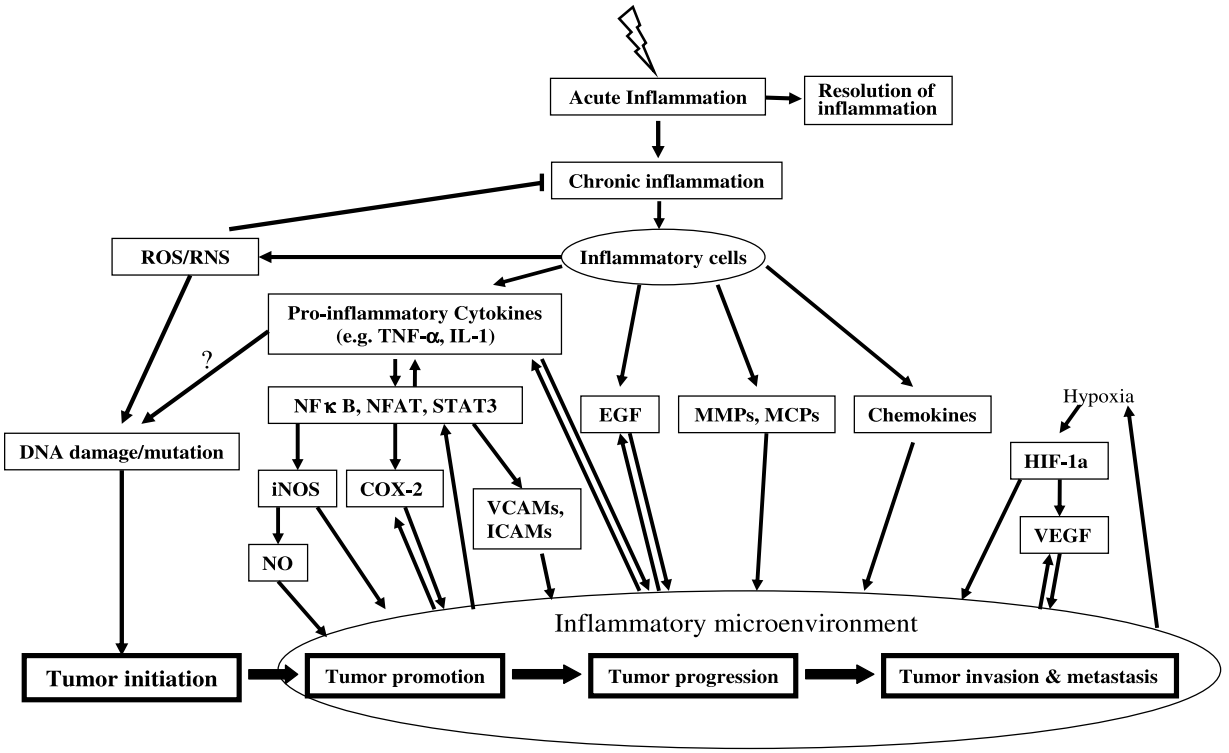

FIGURE 1. Microbial infection, chemical irritation, and tissue wounding. Summary of mechanisms for the involvement of inflammation in cancer development. Tumor promotion indicates the process during which initiated cells develop into benign lesions. Tumor progression defines the process during which benign tumors progress to malignant carcinomas.

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NF-κB is which activation is the initial event. In addition, animal models for inflammation-derived cancers and combination to molecular approaches, such as specific gene knockout mouse, will be helpful and necessary to address the questions in this field. Besides the delineation of an existing picture, another focus of our future study is to look for the missing links of this intriguing puzzle. We believe that the better clarification of mechanisms linking inflammation and cancers will be beneficial to the development of efficacious prevention and therapies of inflammation-associated cancers.

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