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Review

Inflammation: Gearing the journey to cancer

Joydeb Kumar Kundu [a,1], Young-Joon Surh [a,b,*]

[a] National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Seoul 151 742, South Korea
[b] Cancer Research Institute, Seoul National University, Seoul 110-799, South Korea

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ABSTRACT

Chronic inflammation plays a multifaceted role in carcinogenesis. Mounting evidence from preclinical and clinical studies suggests that persistent inflammation functions as a driving force in the journey to cancer. The possible mechanisms by which inflammation can contribute to carcinogenesis include induction of genomic instability, alterations in epigenetic events and subsequent inappropriate gene expression, enhanced proliferation of initiated cells, resistance to apoptosis, aggressive tumor neovascularization, invasion through tumor-associated basement membrane and metastasis, etc. Inflammation-induced reactive oxygen and nitrogen species cause damage to important cellular components (e.g., DNA, proteins and lipids), which can directly or indirectly contribute to malignant cell transformation. Overexpression, elevated secretion, or abnormal activation of proinflammatory mediators, such as cytokines, chemokines, cyclooxygenase-2, prostaglandins, inducible nitric oxide synthase, and nitric oxide, and a distinct network of intracellular signaling molecules including upstream kinases and transcription factors facilitate tumor promotion and progression. While inflammation promotes development of cancer, components of the tumor microenvironment, such as tumor cells, stromal cells in surrounding tissue and infiltrated inflammatory/immune cells generate an intratumoral inflammatory state by aberrant expression or activation of some proinflammatory molecules. Many of proinflammatory mediators, especially cytokines, chemokines and prostaglandins, turn on the angiogenic switches mainly controlled by vascular endothelial growth factor, thereby inducing inflammatory angiogenesis and tumor cell-stroma communication. This will end up with tumor angiogenesis, metastasis and invasion. Moreover, cellular microRNAs are emerging as a potential link between inflammation and cancer. The present article highlights the role of various proinflammatory mediators in carcinogenesis and their promise as potential targets for chemoprevention of inflammation-associated carcinogenesis.

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* Corresponding author at: National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Seoul 151 742, South Korea. Tel.: +82 2 880 7845; fax: +82 2 874 9775.
E-mail address: surh@plaza.snu.ac.kr (Y.-J. Surh).
[1] On leave from Faculty of Pharmacy, University of Dhaka, Dhaka 1000, Bangladesh.

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1. Role of chronic inflammation in cancer

1.1. Chronic inflammation as a predisposing factor for malignant transformation of cells

Chronic inflammation represents a major pathologic basis for the majority of human malignancies. The role of inflammation in carcinogenesis has first been proposed by Rudolf Virchow in 1863, when he noticed the presence of leukocytes in neoplastic tissues [1]. Since the Virchow's early observation that linked inflammation and cancer, accumulating data have supported that tumors can originate at the sites of infection or chronic inflammation [2]. Approximately, 25% of all cancers are somehow associated with chronic infection and inflammation [3]. Although inflammation acts as an adaptive host defense against infection or injury and is primarily a self-limiting process, inadequate resolution of inflammatory responses often leads to various chronic ailments including cancer [4,5].

Multiple lines of evidence from laboratory and population-based studies suggest that organ-specific carcinogenesis is partly associated with a persistent local inflammatory state [6–9]. For instance, the development of carcinomas of stomach, liver, gallbladder, prostate and pancreas has been attributed to *Helicobacter pylori*-induced gastric inflammation, chronic hepatitis, cholecystitis, inflammatory atrophy of the prostate and chronic pancreatitis, respectively [5,10,11]. Patients suffering from inflammatory bowel disorders, such as ulcerative colitis and Crohn's disease, have an increased risk of developing colorectal cancer [6,12,13], while the management of colitis with anti-inflammatory drugs reduces this risk [14]. Table 1 lists some examples of chronic inflammatory conditions that are considered to ultimately turn into cancers.

1.2. Inflammation-associated carcinogenesis: roles of reactive oxygen and nitrogen species

Sustained cellular injuries can cause inflammation, which may lead to carcinogenesis. Various inflammatory and innate immune cells (e.g., mast cells, neutrophils, leukocytes, macrophages, monocytes, eosinophils, dendritic cells, phagocytes, and natural killer cells) are often recruited at the site of infection or inflammation. In response to proinflammatory stimuli, activated inflammatory/immune cells generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can function as chemical effectors in inflammation-driven carcinogenesis. Thus, one of the plausible mechanisms by which chronic inflammation can initiate tumorigenesis is the generation of ROS and/or RNS in the inflamed tissue and subsequent DNA damage leading to activation of oncogenes and/or inactivation of tumor suppressor genes. Chronic exposure to ultraviolet (UV) B radiation is known to precipitate inflammatory tissue damage and skin cancer [15]. Mutational changes in *ras* and *p53* have been observed in many

Table 1
Chronic inflammation/infection as the cause of various cancers

Infection/Inflammatory conditions/stimuli	Characteristic neoplasia	References
Chronic pancreatitis	Pancreatic carcinoma	[268]
E. coli infection of prostate	Atypical hyperplasia and dysplasia of prostate	[269]
Chronic prostatitis	Prostate cancer	[270]
Inflammation of lung (caused by infection, particulate inhalation, diesel exhaust, smoking, etc.), lung fibrosis	Lung cancer	[271–274]
Kaposi's sarcoma herpes virus (KSHV)/Human herpes virus-8 (HHV8)	Kaposi's sarcoma	[275]
Endometriosis	Endometrial adenocarcinoma	[276]
Pelvic inflammatory disease	Ovarian cancer	[277]
Barrett's esophagitis	Esophageal cancer	[72]
Inflammatory bowel disease	Colorectal cancer	[6,12,13]
Chronic gastritis (usually with *H. pylori* infection)	Gastric cancer	[278]
Infection with Hepatitis virus B and C, hepatic fibrosis	Hepatocellular carcinoma	[10,202]
Telangiectatic features with inflammatory syndrome	Telangiectatic adenoma and hepatic malignancy	[279]
Thyroidtis	Papillary thyroid carcinoma	[280]
Asbestos	Malignant mesothelioma	[281]
Hemophagocytic lymphohistiocytosis (Epstein-Barr virus infection)	T cell lymphoma	[282]
Schistosomiasis	Bladder cancer	[283]
Primary sclerosing cholangitis	Cholangiocarcinoma	[284]
Chronic cholecystitis	Gall bladder carcinoma	[5]

types of human cancer [16,17]. The activation of *ras* oncogene and loss-of-function of *p53* tumor suppressor gene have been implicated in UVB-induced mouse skin carcinogenesis [18]. ROS-induced DNA damages including DNA strand breaks, DNA base modifications, and DNA cross-links result in the replication errors and the genomic instability and hence contribute to tumor initiation [19,20]. Nitric oxide (NO), another reactive species, plays a role in inflammation-associated carcinogenesis by direct modification of DNA and inactivation of DNA repair enzymes [21]. 8-Oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), a major biochemical hallmark of oxidative and mutagenic DNA damage [22], has been found to be produced in association with *H. pylori*-induced gastric [23] and tumor necrosis factor-α (TNF-α)-induced pulmonary carcinogenesis [24]. Peroxynitrite, a product formed by a reaction between NO radical and superoxide anion, causes DNA damage by forming 8-nitroguanine (8-NG) [25,26], which is another potential biomarker of inflammation-associated cancers [27]. Thus, oxidative and nitrosative DNA damage products, such as 8-oxo-dG and 8-NG, have been implicated in the initiation of inflammation-driven carcinogenesis [28]. ROS and RNS can induce lipid peroxidation to generate other reactive species, such as manoldialdehyde and 4-hydroxynonenal (4-HNE), which are capable of forming DNA-adducts [29]. 4-HNE forms an adduct preferentially at the codon 249 of the *p53* gene [30].

Elevated intracellular ROS (e.g., superoxide anion, H_2O_2, and hydroxyl radical) and RNS (e.g., peroxynitrite, NO, and *S*-nitrosothiols) also cause alterations in cellular protein functions, such as perturbation of DNA-protein cross-links and post-translational modification of proteins involved in maintaining cellular homeostasis. For example, NO has been shown to hyperphosphorylate and inactivate retinoblastoma protein resulting in increased proliferation of human colon cancer cells [31]. Moreover, in a mouse model of colitis, the hyperphosphorylation of Rb has been blunted in colons of inducible nitric oxide synthase (iNOS)-null mice as compared to the wild-type littermates, suggesting that NO is involved in Rb hyperphosphorylation [31]. In colon tissues from patients with ulcerative colitis, a positive correlation between the expression of iNOS and the phosphorylation of p53 at serine 15 residue, as well as the activation of p53 transcriptional activity has been noted [32]. Nitrosative stress also plays a critical role in inflammation-associated carcinogenesis by activating activator protein-1 (AP-1), a representative redox-sensitive transcription factor [33], which is involved in cell transformation and proliferation [34,35]. Paradoxically, ROS and RNS can cause apoptotic or necrotic cell death [36,37].

1.3. Role of inflammation in cancer epigenetics

Apart from direct mutational changes in the genomic DNA, epigenetic alterations that can influence gene expression via other mechanisms, such as DNA methylation and histone modifications, also contribute to inflammation-associated carcinogenesis [3,38,39].

1.3.1. Inflammation, DNA methylation and cancer

DNA methylation, the covalent addition of a methyl group to the 5-position of cytosine base in the DNA, represents a critical epigenetic control of gene expression. The perturbation of methylation patterns as either aberrant loss of cytosine methylation in transforming genes or inappropriate gain of cytosine methylation in tumor suppressor genes has been involved in various human malignancies [39,40]. The most predominant aberrant DNA methylation is hypermethylation that typically occurs at the CpG islands located in the promoter regions of tumor suppressor genes [38,39]. Promoter hypermethylation of tumor suppressor genes, such as *p16, von-Hippel Lindau* (*VHL*), *adenomatous polyposis coli* (*APC*), *breast cancer susceptibility gene* (*BRCA1*), *retinoblastoma* (*Rb*), *E-cadherin* (*CDH1*), *p73, p53*, and *p57*, results in transcriptional silencing [38,41,42]. By analyzing the methylation status of 11 candidate cancer-related genes in cutaneous squamous cell carcinomas, Murao et al. have demonstrated that the promoter hypermethylation of *CDH1*, *p16*, *Rb1* and *p14* results in the loss of respective protein production [41]. Therefore, the epigenetic silencing of tumor suppressor genes by promoter CpG island hypermethylation perturbs cell cycle control, apoptosis, DNA repair and cell adhesion, and is recognized as an important mechanism in the tumorigenesis [39]. However, global hypomethylation of certain genes, e.g., insulin-like growth factor-2 (IGF-2), can also result in genomic instability, accelerating malignant transformation [3,43].

Several studies have demonstrated the role of infection/chronic inflammation in altered DNA methylation patterns [39,40,44–49]. The CpG hypermethylation of E-cadherin gene in intestinal metaplasia in patients infected with *H. pylori* suggests DNA hypermethylation as an early event in developing gastric cancer [44]. Moreover, *H. pylori* infection has been shown to cause DNA hypermethylation of another tumor suppressor *p16*, suggesting the involvement of epigenetic alterations in inflammation-associated cancers [47]. Gene silencing via promoter hypermethylation in tumor suppressor genes *p16*, *RUNX-3*, *MLH1* and *HPP1* has been observed in ulcerative colitis and Barretts esophagus, which are closely associated with gastric carcinogenesis [46,48]. In areas of tissue inflammation, activated neutrophils and eosinophils release HOCl and HOBr, which react with DNA to produce 5-chlorocytosine and 5-bromocytosine, respectively [40]. Neither methyl-binding proteins nor DNA methyltransferase-1 (DNMT-1) can distinguish between these inflammation-damaged 5-halocytosines and 5-methylcytosine. Thus, the formation and persistence of 5-halocytosine residues in the DNA of cells at the site of inflammation may lead to inappropriate *de novo* DNA methylation and represents another important link between inflammation and cancer development [40]. The role of DNA hypermethylation in inflammation-associated tumorigenesis has been addressed in a recent study by Hodge et al. [45]. According to this study, treatment of human multiple myeloma KAS 6/1 cells with a proinflammatory cytokine interleukin (IL)-6 resulted in increased expression of DNMT-1 and hypermethylation of the *p53* promoter. Demethylation of the hypermethylated *p53* promoter by use of the DNMT inhibitor zebularine restored the normal *p53* function [45]. In contrast, a decrease in the CpG island methylation of epidermal growth factor receptor (EGFR) gene in IL-6-transfected malignant cholangiocytes led to increased EGFR mRNA and protein expression, thereby promoting growth of cholangiocarcinoma cells [49]. Furthermore, the epigenetic silencing of suppressor of cytokine signaling (SOCS) conferred resistance to apoptosis in cholangiocarcinoma cells via sustained inflammatory signaling mediated by IL-6/signal transducer and activators of transcription (STAT-3) and subsequent expression of myeloid cell lymphoma-1 (Mcl-1) [50].

1.3.2. Inflammation, histone modification and cancer

One of the well-established epigenetic mechanisms of gene expression control involves chromatin remodeling via histone modification. Histone deacetylase (HDAC) and histone acetyl transferases (HATs), two opposing classes of enzymes, are responsible for transcriptional regulation of a variety of cancer-related genes [51,52]. The acetylation of lysine residues on the N-terminus of histones by HATs activates gene transcription, while removal of an acetyl group from lysine residues in histone tails by HDACs results in transcriptional repression of genes [53,54]. Thus, HDACs and HATs generally act as transcriptional co-repressors and

co-activators, respectively [53,54]. Besides being subjected to deacetylation or acetylation, histones are post-transcriptionally modified by other mechanisms. These include methylation, phosphorylation, sumoylation, etc., which can also alter gene expression [53,54]. Inappropriate activation/inactivation of HDACs and HATs has been implicated in chronic inflammatory responses as well as in carcinogenesis [51,52]. Exposure of human bronchial epithelial cells (BEAS-2B) to the diesel exhaust particulate matter induced the transcriptional activation of a representative proinflammatory gene *cyclooxygenase-2* (*COX-2*) by promoting acetylation of histone-4 via degradation of HDAC-1 [55]. Moreover, pharmacological inhibition of HDACs with trichostatin-A enhanced bacterial lipopolysachaaride (LPS)-induced transcriptional activation of *COX-2* in bone marrow-derived macrophages [56]. Overexpression of HDAC-1 or HDAC-8 abrogated LPS-induced *COX-2* mRNA expression [56,57]. Likewise, the activation of NF-κB and expression and release of IL-8 and IL-6 in human alveolar epithelial (A549) cells by H_2O_2 were associated with increased acetylation of histone 4 and decreased expression and activity of HDAC-2 [58]. Transcriptional activation of NF-κB and IL-8 induced by proinflammatory stimuli, such as LPS and TNF-α, was dependent on p38 mitogen-activated protein (MAP) kinase- and inhibitory kappa B kinase (IKK)-α-mediated phosphorylation of histone-3 [59,60]. Therefore, the inflammation-induced alterations in histones and the resultant upregulation of COX-2 and NF-κB suggest that inflammation may disrupt the cellular epigenetic machinery, thereby contributing indirectly to genetic instability of cancer cells.

2. Major mediators linking inflammation and cancer

Chronic inflammation is implicated in all stages of carcinogenesis, i.e., initiation, promotion and progression. In a persistently inflamed tissue, excessive generation of ROS can cause genomic instability which leads to initiation of cancer [3,61]. A single initiated cell undergoes proliferation to produce a clone of mutated cells which form premalignant mass, the event generally termed tumor promotion. Some of the preneoplastic cells encounter additional mutations and become malignant. This process is referred to as tumor progression. Proliferating tumor cells, their surrounding host stromal cells and tumor-infiltrating inflammatory/immune cells create a tumor microenvironment that reflects a persistent inflammatory state [1,62]. Within the tumor microenvironment, various proinflammatory mediators participate in a complex inflammatory signaling that facilitates extravasation of tumor cells through the stroma, thereby fostering tumor progression [1,62] (Fig. 1). Inflammation acts as a key regulator of tumor promotion and progression by several mechanisms including acceleration of cell cycle progression and cell proliferation, evasion from apoptotic cell death, and stimulation of tumor neovascularization [63,64]. Among the major molecular players involved in the inflammation-to-cancer axis, the notable members are cytokines, chemokines, COX-2, prostaglandins, prostanoid receptors (EP 1–4), iNOS, NO, and NF-κB. Table 2 represents the mechanisms by which the key inflammatory mediators contribute to carcinogenesis.

2.1. Cytokines

Cytokines including ILs, TNF-α, growth factors and differentiation factors are secreted or membrane bound small protein molecules that regulate diverse physiological processes, such as growth, development, differentiation, wound healing and immune response [61,65]. Cytokine signaling is initiated upon binding of specific cytokines to cell-specific cognate receptors followed by activation of intracellular kinases, such as Janus-activated kinase (JAK), phosphatidylionositol-3-kinase (PI3/K)/Akt, IKK, and MAP kinases, with subsequent activation of transcription factors, predominantly STAT, NF-κB, and AP-1 [66,67]. The pleiotropic nature of cytokine functions is evident from cross-regulation of one cytokine by other cytokines, differential response of the same cytokine depending on the cell type, and synergistic or antagonistic effects elicited by combined cytokine stimulation of cells [68]. Despite a complex nature of their function, cytokines can broadly be classified as inflammatory

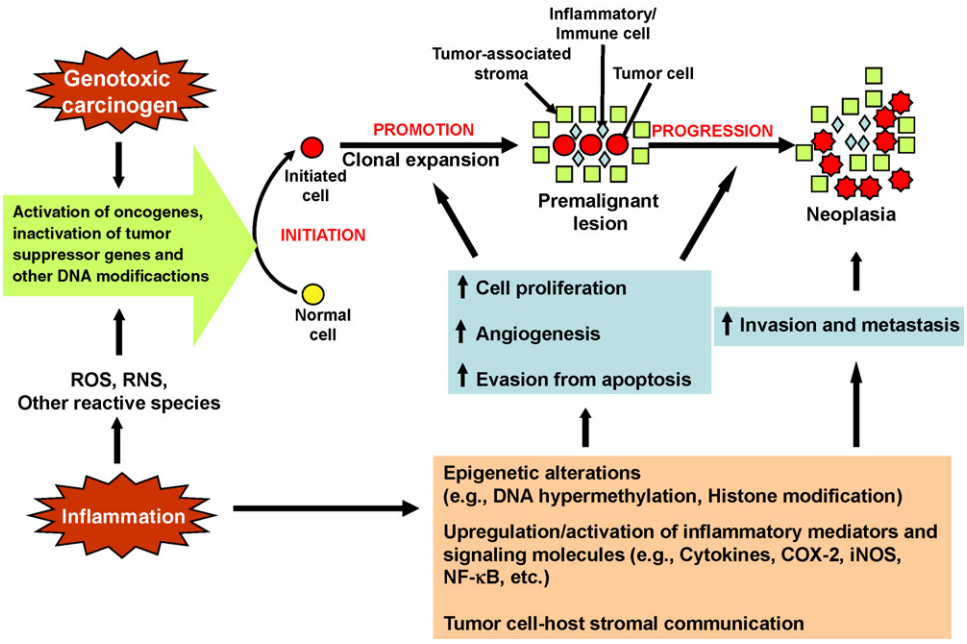

Fig. 1. A journey to cancer: inflammation as the driving force. Inflammation is implicated in multi-stage carcinogenesis. ROS/RNS or other reactive species derived from inflammatory stress can attack DNA and cause mutations in oncogenes/tumor suppressor genes or other genetic alterations. This will lead to initiation of carcinogenesis. Inflammation also contributes to promotion and progression stages by stimulating the proliferation of initiated or premalignant cells, enhancing angiogenesis and metastasis, rendering precancerous or neoplastic cells resistant to apoptosis, etc., through epigenetic mechanisms.

Table 2
Key mediators linking inflammation and cancer

Signaling molecules	Role in inflammation-associated cancer
Proinflammatory cytokines	Overexpressed in inflamed, hyperplastic, metaplastic tissues and adenocarcinomas Induce DNA damage Stimulate inflammatory angiogenesis through production/expression of proangiogenic molecules, such as VEGF, VEGFR, IL-8, NO, ICAM-1 and VCAM-1 Activate proinflammatory signaling mediated via JAK-STAT and NF-κB and help to maintain inflammatory tumor microenvironment Stimulate cell proliferation and inhibit apoptosis
Chemokines	Attract inflammatory and immune cells to the tumor microenvironment Promote tumor cell migration and facilitate invasion and metastasis Enhance extravasation of tumor cells through stromal tissue Stimulate inflammatory angiogenesis by upregulating proangiogenic factors, such as VEGF and MMP
COX-2	Catalyzes biosynthesis of lipid mediators of inflammation Helps to maintain a persistent inflammatory state in the premalignant and malignant lesion Overexpressed in various inflammation-associated cancers Promotes cell proliferation and block apoptosis Accelerates angiogenic process by triggering PGE_2 signaling and expression of VEGF and stabilization of HIF-1α
PGE_2	Promotes tumorigenesis in experimental animals Excessively produced as a consequence of COX-2 induction in inflamed, hyperplastic, and dysplastic tissues, and carcinomas Augments cell proliferation, suppresses apoptosis Induces proangiogenic factors and promotes inflammatory angiogenesis Activates proinflammatory signaling pathway with in the tumor microenvironment
iNOS	Is elevated in precancerous and cancerous lesions Induces nitrosative or oxidative DNA damage Produces proinflammatory mediators, e.g., NO, by catalyzing arginine metabolism Acts as a downstream effector of NF-κB and inflammatory cytokine-mediated signaling
NO	Promotes tumor growth by stimulating cell proliferation Causes *S*-nitrosylation of important proteins involved in inflammation and cancer Causes DNA damage by nitration of nucleotide bases
NF-κB	Increases expression/production of proinflammatory mediators and amplifies the inflammatory signal transduction Augments the expression of antiapoptotic proteins and helps transformed cells to escape apoptosis Promotes invasion and metastasis

(e.g., IL-1, IL-6, IL-17) and anti-inflammatory (e.g., IL-10) ones. Some cytokines have been reported to play a role in inflammation-associated carcinogenesis [69–72]. For example, mice genetically modified to disrupt SOCS3 exhibit enhanced colonic crypt formation, crypt proliferation, and the increased number and the size of colon tumors after challenge with dextran sulfate sodium (DSS) or azoxymethane (AOM) plus DSS [71]. While persistent local inflammation leads to cell transformation, a tumor cell further augments inflammatory responses in its vicinity by secreting cytokines and chemokines, thereby creating a positive loop between inflammation and cancer. Both cytokines and chemokines facilitate the communication between tumor cells and tumor-associated host stromal tissue, thereby accelerating tumor progression [62,73,74].

2.1.1. TNF-α

As a representative inflammatory cytokine with pleiotropic functions, TNF-α plays a dual role in carcinogenesis. While a high concentration of TNF-α is destructive to tumor vasculature and causes necrosis, it may stimulate the growth of fibroblasts and certain tumor cells. For example, TNF-α acts as a growth stimulator for epidermal growth factor (EGF)- or serum-depleted cervical cancer cells, but it inhibits proliferation of normal cervical keratinocytes [75]. The expression of TNF-α has been detected in various human cancers including those of breast, prostate, colorectum, bladder, lymphoma and leukemia [1,76,77]. Several preclinical studies have suggested TNF-α as an endogenous tumor promoter. For example, mice lacking TNF-α [78] or TNF-α receptor [79] are resistant to skin carcinogenesis. In addition, pharmacologic inhibition of TNF-α production by pentoxifyline inhibited chemically induced papilloma formation in mouse skin [80]. In comparison to normal tissues, a significant increase in the levels of TNF-α was observed in gastric lesion [81] and inflamed colonic mucosa [70] specimens obtained from patients with *H. pylori* infection and inflammatory bowel disease, respectively. Moreover, the expression of TNF-α was increased in Barrett's metaplasia, a precancerous lesion that progresses to adenocarcinoma [72].

2.1.2. IL-6

IL-6 is another major proinflammatory cytokine that participates in inflammation-associated carcinogenesis [82]. IL-6 modulates the expression of genes involved in cell cycle progression and inhibition of apoptosis, primarily via the JAK-STAT signaling pathway [69]. An elevated level of IL-6 has been implicated in the pathogenesis of various cancers [83–85]. Conversely, mice lacking IL-6 are less susceptible to development of plasmacytoma, which is a malignant disorder of plasma cells [86]. Jeng et al. [87] demonstrated that betel quid, a potential oral carcinogen, induced oral mucosal inflammation and elevated the expression of IL-6, TNF-α and PGE_2 in gingivial keratinocytes. In craniopharyngiomas, a local inflammatory state between tumor cells and parenchyma exists due to enhanced infiltration of leukocytes and tumor cell-derived cytokines, especially IL-6, at the adjacent tissue [88]. Moreover, analysis of biopsy specimens from inflammation-associated gastric cancers has revealed that the levels of IL-1β and IL-6 are highly elevated in tumors as compared to adjacent normal mucosa [84]. The serum levels of IL-6 have been found to be significantly increased and positively correlated to tumor burden in colon cancer patients [89]. Likewise, IL-6 stimulated the anchorage-independent growth of human colon carcinoma cells, suggesting its potential role in tumorigenesis [85]. It has been reported that the inhibition of IL-6 production and IL-6-trans-signaling mediated via soluble IL-6 receptor accounts for transforming growth factor-β suppression of colon cancer

progression [90]. In addition, *ras*-induced secretion of IL-6 has been shown to be required for the growth of *ras*-transformed human kidney cells implanted *in vivo* [91]. Moreover, in IL-$6^{-/-}$ mice, there was a delayed onset and a reduced multiplicity of skin papillomas compared to those in IL-$6^{+/+}$ mice, when treated with 7,12-benz[*a*]anthracene (DMBA) plus 12-*O*-tetradecanoylphorbol-13-acetate (TPA) [91]. Since mouse skin tumors formed by topical application of DMBA followed by TPA have *ras* mutation [92], the above findings suggest that IL-6 is essential for *ras*-driven tumorigenesis. The development of colitis-associated colon cancer was suppressed by genetic ablation of IKKβ in myeloid cells, which was associated with the reduced expression of IL-6 mRNA [93]. IL-6 contributes to the growth of cholangiocarcinomas by decreasing promoter methylation of EGFR and upregulating growth promoting genes [49]. Moreover, incubation of cholangiocarcinoma cells with anti-IL-6 neutralizing serum reduced the phosphorylation of Akt and diminished the expression of antiapoptotic protein Mcl-1, suggesting that IL-6 regulates Akt-mediated survival signals [94].

2.1.3. Other proinflammatory cytokines

Other proinflammatory cytokines including IL-1 and IL-17 may also play roles in inflammation-associated carcinogenesis [69,95]. The IL-1 family consists of proinflammatory and immunoregulatory cytokines, such as IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1Ra) [95]. IL-1 ligands interact with transmembrane receptors, such as IL-1RI and IL-1RII [96,97]. IL-1α, expressed in both normal tissue and several tumor cells, is a regulatory cytokine that can induce the activation of transcription factors, including NF-κB and AP-1, and promotes the expression of genes involved in cell survival, proliferation, and angiogenesis [98,99]. The elevated production of IL-1α by epithelial cells derived from human benign prostate hyperplasia has been implicated in increased proliferation of these cells [100]. A low concentration of IL-1β has been shown to induce local inflammatory responses followed by activation of protective immune response, while a high concentration of IL-1β leads to inflammation-associated tissue damage and tumor invasiveness [101]. Treatment of human colon cancer (HCA-7) cells with IL-1β induced cell proliferation via activation of ERK and upregulation of COX-2, which was blocked by a vitamin D analogue Ro26-2198 [102]. Exogenously administered prostaglandin E_2 (PGE_2) augmented the transcriptional activity of the IL-1α promoter and significantly stabilized IL-1α mRNA in colon cancer cells [103]. Knockdown of the IL-1α by small-interfering RNA resulted in a reduction of VEGF secretion in colon cancer cells and an inhibition of tube formation by human umbilical vein endothelial cells (HUVEC) [103]. A significant correlation between VEGF production and secretion of IL-1 and IL-6 in human pituitary tumor cells suggests the role of these cytokines in the growth of pituitary adenomas [104].

Another cytokine IL-7 has been reported to act as a growth factor in cutaneous T cell lymphoma [105]. This particular proinflammatory cytokine produced by 'Th17' subtype of T cells has recently been recognized as a key player in inflammation and cancer [69]. The role of IL-17 in inflammation-associated cancer relies largely on its proangiogenic property. For example, IL-17-overexpressing human cervical cancer [106], fibrosarcoma [107] and human non-small cell lung cancer [108] showed higher oncogenic growth *in vivo*.

2.2. Chemokines

Chemokines are soluble chemotactic cytokines, which are classified as four major groups, i.e., CXC, CC, XC and CX_3C primarily based on the positions of conserved cysteine residues [1,61,109]. In chronic inflammation, chemokines are usually produced by proinflammatory cytokines. The central role of chemokines is to recruit leukocytes at the site of inflammation [61]. Most tumor cells can produce CXC and CC chemokines, which again differ in selectivity for particular leukocytes. While lymphocytes represent a common target of both CXC and CC, neutrophils are targeted only by CXC chemokines. CC chemokines can also act on other leukocyte subtypes, such as monocytes and eosinophils as well as dendritic cells and natural killer cells [1]. Like cytokines, chemokines also act by interacting with specific receptors expressed by both infiltrated leukocytes and tumor cells in an autocrine or a paracrine fashion [1,61].

Several studies have reported the involvement of chemokines and chemokine receptors in cell proliferation, migration, invasion and metastasis of different types of tumors [110–113]. Overexpression of CXCL-1/GROα, CXCL-2/GROβ or CXCL-3/GROγ promotes soft agar colony formation and transformation of melanocytes in culture as well as tumorigenicity of transplanted melanoma cells in nude mice [112]. Treatment of cultured melanoma cells with anti-IL-8Rβ antibody inhibited the cell growth [114]. Chemokine regulation of tumor angiogenesis results from a balance between proangiogenic and angiostatic activities [61,115]. Besides their role in chemoattraction of leukocytes, chemokines direct the migration of tumor cells to the distal organs via circulation [110]. The metastatic potential of chemokines is attributed to their ability to induce the expression of matrix metalloproteinases (MMPs), which facilitate tumor invasion [61,113]. A stromal cell derived factor (SDF-1)/CXCL-12 promoted the migration of colon adenocarcinoma (CT26) cells in culture and the growth of implanted CT26 cells in BALB/c mice *in vivo* through angiogenesis-dependent induction of tumor cell proliferation and inhibition of apoptotic cell death [111]. Moreover, silencing of endogenous CXCR4 gene expression by CXCR4-shRNA resulted in the inhibition of the proliferation, adhesion, chemotaxis and invasion of mucoepidermoid carcinoma cells [116].

2.3. COX-2 and prostaglandins

COX-2, an inducible form of cyclooxygenase, serves as an interface between inflammation and cancer [117,118]. In response to various external stimuli, such as proinflammatory cytokines, bacterial LPS, UV, ROS and phorbol ester, COX-2 is transiently elevated in certain tissues [118]. Abnormally elevated COX-2 causes promotion of cellular proliferation, suppression of apoptosis, enhancement of angiogenesis and invasiveness, etc., which account for its oncogenic function [64] (Fig. 2).

2.3.1. COX-2

Aberrant induction of COX-2 has been implicated in the pathogenesis of various types of malignancies [119–121]. Mice genetically engineered to overexpress *COX-2* in mammary glands, skin or stomach were found to be prone to develop malignancies of these organs [122–124], while *COX-2* knockout mice are less susceptible to intestinal tumorigenesis [125], skin papillomagenesis [126] and mammary carcinogenesis [127]. Either administration of the COX-2-selective inhibitor rofecoxib or the functional inactivation of the *COX-2* in adenomatous polyposis coli $(APC)^{\Delta 716}$ knockout mice, a murine model of human adenomatous polyposis, reduced both the number and the size of intestinal polyps [125,128], lending support to an association between abnormal upregulation of COX-2 and tumorigenesis. In a chronic UV-induced skin carcinogenesis model, the lack of one allele of *COX-2* resulted in a 50–65% reduction in the tumor multiplicity and a marked decrease in the tumor size in SKH-1 hairless mice, while transgenic mice that overexpress *COX-2* under the control of a keratin 14 promoter developed 70% more tumors than wild-type mice [129]. Furthermore, forced expression of *COX-2* under the control of

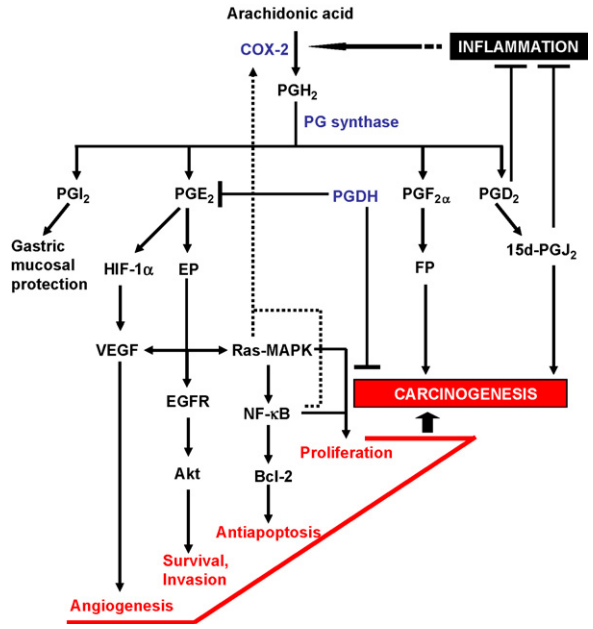

Fig. 2. Role of COX-2 and PGs in inflammation-induced carcinogenesis. Inflammatory signaling triggers induction of COX-2 expression and subsequently production of an array of prostaglandins. While some prostaglandins, especially PGE_2, are implicated in carcinogenesis, others (e.g., PGI_2) have cytoprotective effects. Still another group of prostaglandins, including PGD_2 and 15d-PGJ_2, have dual effects on carcinogenesis. PGDH by inactivating PGE_2 can protect against carcinogenesis and is recognized as a tumor suppressor. EP and FP denote PGE_2 and $PGF_{2\alpha}$ receptors, respectively.

keratin-5 promoter showed spontaneous inflammation-associated transitional cell hyperplasia and carcinomas of the bladder in mice [130]. Pharmacological inhibition of COX-2 by celecoxib retarded the progression of esophageal inflammation to metaplasia and adenocarcinoma in rats [131]. However, Abdalla et al. [132] have demonstrated that COX-2 expression is independent of the degree of inflammation in Barrett's esophageal epithelium, but it enhances the development and progression of cancer in a state of chronic inflammation. The involvement of COX-2 in the early stage of esophageal squamous cell carcinogenesis is evident from the observation that COX-2 expression is elevated during dysplasia, carcinoma *in situ* and invasive squamous cell carcinomas [133]. Suppression of COX-2 expression and activity in esophageal squamous carcinoma cells by either pharmacologic intervention or RNA interference resulted in decreased production of PGE_2 and reduced tumorigenesis in nude mice [133].

Overexpression of COX-2 in human basal cell carcinoma cells (BCC) by stable transfection upregulated the expression of antiapoptotic Mcl-1 and Bcl-2 proteins, and increased levels of angiogenic factors including VEGF-A and basic fibroblast growth factor (bFGF), thereby increasing resistance to apoptosis and promoting angiogenesis [134]. This study also revealed that inoculation of COX-2 overexpressing BCC cells into severe combined immunodeficient (SCID) mice led to an increased tumor volume in comparison to those inoculated with control cells harbouring the blank vector [134]. Pharmacological inhibition of COX-2 induced apoptosis in hepatocellular carcinoma cells via activation of death receptor-mediated signaling, downregulation of antiapoptotic protein Mcl-1, localization of proapototic protein Bax to mitochondria, release of cytochrome *c* and subsequent casapse activation [135]. In another study, the development of Barrett's adenocarcinoma was positively correlated with increased expression of COX-2 and antiapoptotic protein Bcl-2 [136]. In contrast, elevated expression and nuclear accumulation of COX-2 were associated with p53-dependent apoptosis of human breast cancer MCF-7 and MDA-MB-231 cells treated with a chemopreventive agent resveratrol [137]. Similarly, the induction of apoptosis in H-*ras*-transformed human mammary epithelial (MCF-10A) cells by ET-18-OCH_3, an alkylphospholipid type antitumor agent, was causally linked to upregulation of COX-2 and subsequent production of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) and transcriptional activation of peroxisome-proliferator activated receptor-gamma (PPAR-γ) [138]. However, stable transfection of *COX-2* in normal MCF-10A cells increased proliferation and resistance to apoptosis, decreased differentiation and enhanced cell transformation characterized by epithelial to parenchymal transition [139]. Therefore, the role of COX-2 in apoptosis is influenced by the nature of stimuli and/or the cell type.

2.3.2. PGE_2 and prostanoid (EP 1–4) receptors

COX-2 promotes the breakdown of arachidonic acid to produce a series of prostaglandins, which are key mediators of inflammatory responses [64]. Some proinflammatory prostaglandins, such as PGE_2, $PGF_{2\alpha}$, and 15d-PGJ_2, have been reported to play roles in carcinogenesis [140–142]. Several studies have demonstrated that PGE_2 is capable of promoting mouse skin and colon carcinogenesis [140,141]. Topical application of 15d-PGJ_2 potentiated papillomagenesis in a two-stage mouse skin carcinogenesis model [143]. Elevated levels of PGE_2 have been observed in various types of human cancers [142,144,145]. PGE_2 promotes cell proliferation and tumor-associated neovascularization, and inhibits cell death, thereby favoring tumor growth [146]. Intraperitoneal administration of PGE_2 enhanced AOM-induced formation of colon tumors, especially adenocarcinomas, in F344 rats [147], preferentially by increasing cell proliferation and suppressing apoptosis. Treatment of APC^{min} mice with PGE_2 caused a dramatic increase in the size and the number of intestinal adenomas [148]. Moreover, administration of PGE_2 blocked non-steroidal anti-inflammatory drug-induced adenoma regression in APC^{min} mice [149]. In addition, the functional inactivation or loss of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme that degrades PGE_2, was correlated with increased tumorigenesis in several organs including colon, lung and bladder [150–153].

The role of PGE_2 in tumorigenesis has also been corroborated by several other studies conducted with mice lacking EP 1–4 receptors. In fact, PGE_2 functions by interacting with its cognate EP receptors. Homozygous deletion of EP1 and EP4 receptors, but not EP3 receptor, resulted in a partial decrease in AOM-induced aberrant crypt foci formation in mice [154,155]. Similarly, homozygous deletion of EP2 receptor reduced the size and the number of intestinal polyps formed in $APC^{\Delta 716}$ mice [156]. Pharmacological blockade of EP1 and EP4 receptors by specific antagonists diminished carcinogen-induced aberrant crypt foci formation in wild-type mice and intestinal polyp formation in APC^{min} mice [154,155]. In another study, the abrogation of EP4 receptor function by a specific inhibitor L-161982 resulted in decreased proliferation of human colon cancer HCA-7 cells which was associated with suppression of PGE_2-induced activation of extracellular signal regulated protein kinase (ERK) and cyclic AMP response element-binding protein (CREB) [157]. Moreover, exposure of various cancer cells to exogenous PGE_2 enhanced cellular proliferation [158–160]. In addition to PGE_2, an increased autocrine signaling mediated via PGF-2α and PGF-2α receptor (FP) in colorectal adenocarcinoma resulted in enhanced cell motility and invasiveness [161].

2.4. iNOS and NO

Another important inflammatory mediator linking chronic inflammation and cancer is NO, which is produced endogenously

during arginine metabolism by different isoforms of NOS [162]. During inflammation, induced expression of iNOS in macrophages and epithelial cells leads to production of NO. The expression of iNOS and the level of NO have been shown to be elevated in various precancerous lesions and carcinomas [163,164]. Our previous study demonstrated that topical application of phorbol ester induced iNOS expression and subsequent NO production, which in turn induced COX-2 expression via NF-κB activation in mouse skin [165]. Pretreatment of mouse skin with aminoguanidine, an inhibitor of iNOS, suppressed chemically induced mouse skin papilloma formation, suggesting that iNOS and NO play a role in tumorigenesis [165]. In cytokine-stimulated macrophages, iNOS enhanced the activity of COX-2 via *S*-nitrosylation [166]. In response to inflammatory cytokines (e.g., TNF-α and IL-1β) or other inflammatory stimuli (e.g., phorbol ester, UVB, LPS and DSS), iNOS is transactivated by some transcription factors including NF-κB [64,167]. The overexpression of iNOS has been detected in Barrett's mucosa, a premalignant condition arising from chronic reflux esophagitis and colorectal adenomas or carcinomas [168]. Analysis of clinically isolated prostate cancers has shown that strong iNOS expression is positively correlated with rapid cancer cell proliferation, dedifferentiation and progression to advance-stage cancer [169]. With the biopsy specimens from patients with stomach carcinoma and *H. pylori*-induced gastritis, Reider et al. have demonstrated that elevated expression and activity of iNOS are associated with the development of intestinal metaplasia [170]. The overexpression of iNOS in colon tissues from patients with ulcerative colitis suggests that iNOS may contribute to the pathogenesis of colitis-related neoplasia [164,171]. Colonic adenocarcinomas from mice receiving a single intraperitoneal dose of AOM or 1,2-dimethylhydrazine followed by 2% DSS in drinking water for two weeks exhibited elevated expression of iNOS and nitrotyrosine, which were suppressed by administration of either a COX-2 inhibitor or ligands of PPARα or PPARγ [172,173]. Similarly, overexpression of iNOS was associated with enhanced DSS-induced colon carcinogenesis in APC^{min+} mice as compared to $APC^{+/+}$ mice [174]. Treatment with ONO-1714, a specific iNOS inhibitor, attenuated DSS-induced colonic adenocarcinomas in APC^{min+} mice [175].

Although, genetic ablation of iNOS decreased mouse lung tumorigenesis by 80%, a distinctive role of iNOS in inflammation-associated lung carcinogenesis was not evident as the rate of macrophage infiltration in butylated-hydroxy toluene-induced chronic lung inflammation remained unaffected even in the absence of iNOS [176]. Furthermore, Zhang et al. [177] demonstrated that the induction of iNOS might confer protection against colitis-induced adenocarcinomas as evidenced by significantly augmented dysplasia, the increased number of mucosal polyps and submucosal invasion in $IL\text{-}10^{-/-}/iNOS^{-/-}$ double knockout mice compared to those observed in $IL\text{-}10^{-/-}$ animals. Moreover, the development of lymphomas in $p53^{-/-}NOS2^{-/-}$ or $p53^{-/-}NOS2^{+/-}$ mice were faster than that in $p53^{-/-}NOS2^{+/+}$ mice, and the formation of sarcomas and lymphomas were faster in $p53^{+/-}NOS2^{-/-}$ or $p53^{+/-}NOS2^{+/-}$ mice compared with that in $p53^{+/-}NOS2^{+/+}$ mice [178]. According to this study, $p53^{-/-}NOS2^{+/+}$ mice showed a higher apoptotic index and a decreased proliferation index as compared to *p53* and *iNOS* double knockout mice. Based on these findings, Hussain et al. suggested that NO radical could suppress tumorigenesis [178]. Seril et al. [179] examined the role of iNOS in a DSS-induced and iron-enhanced ulcerative colitis in $iNOS^{-/-}$ mice. There was no significant difference in the incidence and the multiplicity of well-differentiated adenocarcinomas in $iNOS^{-/-}$ and $iNOS^{+/+}$ mice. Moreover, the levels of nitrotyrosine in inflammatory and epithelial cells of the colon in both treatment groups were identical. However, an increase in endothelial NOS (eNOS) in lamina propria macrophages and blood vessels suggests that in the absence of iNOS, other factors, such as eNOS may play a role in nitrosative stress and ulcerative colitis-related neoplasia [179].

Thus, NO derived from a distinct NOS exerts differential effects on carcinogenesis depending on the available concentration, the interaction with other free radicals, metal ions and proteins, and the type of a target cell [180]. NO can exert both apoptotic and anti-apoptotic effects [181–183]. Treatment with a NO donor *S*-nitroso-*N*-acetylpenicillamine (SNAP) inhibited proliferation of HUVEC and human coronary artery endothelial cells [182], but SNAP stimulated proliferation of mouse clonal osteogenic (MC3T3-E1) cells [183]. The complex mechanisms underlying NO-induced apoptosis depends on a variety of factors, including the concentration of NO, redox status and the type of a target cell [180].

NO and its derivative peroxynitrite play roles in inflammation-associated carcinogenesis [3,184] by inducing damage to DNA, post-translational modification of key oncoproteins, suppression of DNA repair enzymes, promotion of cell proliferation, inhibition of apoptosis, enhancement of tumor microcirculation, angiogenesis and metastasis, and suppression of host antitumor defense [164,178,184–187]. The role of NO and peroxynitrite in causing DNA damage and initiation of tumorigenesis was described in the previous section 1.2. NO can also prevent apoptosis by targeting caspases [188]. Torok et al. [189] have reported that NO inhibits etoposide-induced apoptosis of human cholangiocarcinoma cells via *S*-nitrosylation of caspase 9. Using a mouse model of colitis, Ying et al. demonstrated that NO-mediated hyperphosphorylation and inactivation of Rb led to increased cell proliferation [31].

The inhibition of DNA repair enzymes, such as human thymine-DNA glycosylase [190] and 8-oxoguanine DNA glycosylase [191], by NO allows cells with mutated or damaged genes to escape apoptosis. This may favor the clonal expansion of critically damaged cells and tumorigenesis [192,193]. One of the key players in the NO-driven tumor promotion is the tumor suppressor and DNA damage sensor *p53*. While NO induces accumulation and post-translational modification (phosphorylation and acetylation) of p53 and subsequent growth arrest in cancer cells expressing wild-type p53, it promotes clonal expansion of cells harboring mutant p53 (213). NO contributes to tumor growth via transactivation of hypoxia-inducible factor-1α (HIF-1α) [194], which is stabilized by *S*-nitrosylation [195] and induction of VEGF [196]. The trans-repression of iNOS expression and NO production in mice with wild-type p53 [197] and increased expression of iNOS in p53 knockout mice [198] suggest that the loss of wild-type p53 by oxidative or nitrosarive stress during chronic inflammation may hamper p53-mediated negative regulation of iNOS, thus augmenting NO production and subsequent stimulation of NO-dependent angiogenic process.

2.5. NF-κB

A wide array of DNA-binding proteins are aberrantly activated in response to inflammatory stimuli, which can cause inappropriate induction of various proinflammatory genes in tumor cells, tumor-associated stromal cells and in surrounding host tissues. Different transcription factors are abnormally turned on or switched off in various human malignancies. Among these, NF-κB has been most extensively investigated because of its ubiquitous presence and multiple functions. For example, improper activation of NF-κB contributes to tumorigenesis either by transactivating several target genes that have inflammatory (e.g., *COX-2*, *iNOS*, and *TNF-α*), anti-apoptotic (e.g., *cIAP1*, *cIAP2*, *XIAP*, *Bcl-2*, *Bcl-3* and *Bcl-X_L*), cell cycle regulatory (e.g., *cyclin D1*) and proangiogenic (e.g., *VEGF* and angiopoetin) functions or by

down-regulating apoptosis-inducing genes (e.g., *p53*, *Bax*, and *Bad*) [35,199,200].

Recently, NF-κB has been identified as a potential molecular bridge between inflammation and cancer [201]. The induction of proinflammatory cytokines (e.g., IL-6 and TNF-α), chemokines (e.g., IL-8), COX-2, iNOS, MMP and several adhesion molecules are mediated via transcriptional activation of NF-κB. The NF-κB-dependent activation of cell adhesion molecules, such as vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM), which have been found to increase in various cancers, are involved in leukocyte adhesion and migration within the inflammatory tumor microenvironment. While the cytokine expression is regulated primarily by NF-κB, the tumor cell-derived cytokines further stimulate NF-κB-mediated transcription of proinflammatory genes in tumor cells, tumor-associated stromal cells and host tissues, thereby creating a sustained chronic inflammatory state within the tumor microenvironment [61]. The role of NF-κB in chronic inflammation-driven tumor promotion has been shown in different experimental models. In a mouse model of colitis-associated colorectal cancer, inactivation of NF-κB via genetic ablation of one of its key upstream regulators IKKβ resulted in the reduced tumor incidence and the size of tumors due to the ultimate lack of proinflammatory mediators [93]. *In vivo* studies using rodent models of inflammatory liver disease and cell-targeted perturbation of NF-κB activity revealed the role of NF-κB in driving 'inflammation-fibrosis-cancer' axis in the course of developing hepatocellular carcinoma [202]. Knockout of IKKβ in liver and hematopoietic cells substantially reduced diethylnitrosamine-induced elevation of TNF-α and IL-6, and suppressed tumorigenesis in mice [203]. Inactivation of NF-κB in multi-drug resistance-2 (mdr2)-null mice by overexpressing a super-repressor of IκBα enhanced apoptosis of transformed hepatocytes, and attenuated tumorigenesis [201]. In addition, LPS-induced colon adenocarcinoma progression was regressed after deletion of NF-κB [204]. Saccani et al. [205] demonstrated that overexpression of p50-NF-κB inhibitory homodimer blocked M1-type antitumor response by tumor-associated macrophages (TAM), which exist predominantly as M2 phenotype in established tumors and acts as a critical player in the protumoral function of inflammation. While TAM isolated from murine fibrosarcoma and human ovarian carcinoma lacked M1 type responsiveness due to massive nuclear localization of p50-NF-κB, TAM isolated from $p50^{-/-}$ mice exhibited normal production of M1 cytokines responsible for reduced growth of implanted tumors [205].

3. Inflammatory angiogenesis in cancer

The role of inflammation in angiogenesis has been evolutionarily recognized in physiological processes, such as development of uterine and intestinal vasculature [206]. Angiogenesis is also essential for the growth and survival of solid tumors, and their progression to invasive phenotypes. The concept of angiogenesis as a mechanism of growth and survival of tumor cells was first introduced by Folkman et al., who proposed that tumor cells could sense their distance from the normal vasculature and release angiogenic signals [207]. Since then, enormous efforts have been made to understand the molecular mechanisms underlying tumor angiogenesis. It is now recognized that a tumor is not merely a mass of transformed cells, but are a complex entity composed of transformed cells, normal parenchymal and epithelial cells, extracellular matrix, stromal fibroblasts, immune cells (e.g., lymphocytes, macrophages, dendritic cells, mast cells, neutrophils) and vascular cells (e.g., pericytes, endothelial cells and smooth muscle cells), which create a tumor microenvironment [62,208]. While inflammation can promote development of cancer, components of the tumor microenvironment may produce an intratumoral inflammatory state. In the early stage of tumorigenesis, tumor cells disrupt the homeostasis in the surrounding normal tissue by diverse mechanisms including direct cell–cell contact, communication between cell and extracellular matrix and secretion of various factors, which accelerate the inflammation within the premalignant tissues. Tumor cells often secrete cytokines that cause infiltration of certain inflammatory cells in the tumor microenvironment. Various proinflammatory mediators (e.g., cytokines, chemokines, growth factors, prostaglandins, etc.) released by these inflammatory cells function in an autocrine or a paracrine manner to further trigger inflammatory signaling, tumor cell to host stroma communication, and chemoattraction of more inflammatory immune cells in the microenvironment. Many of these proinflammatory mediators promote angiogenesis, thereby accelerating tumor growth. Tumor-associated macrophages, mast cells and neutrophils play an important role in tumor angiogenesis by secreting VEGF, IL-8, TNFα, MMPs and other factors that increase vascular permeability [209–211]. Thus, chronic inflammation-driven tumor angiogenesis and a sustained 'inflammation-cancer-inflammation' loop proves Dvorak's early proposition that tumors are wounds that never heal [212]. The role of various proinflammatory mediators in tumor angiogenesis will be discussed further.

3.1. Role of cytokines in inflammation and tumor angiogenesis

Cytokines, such as TNF-α and IL-1, are the polypeptide messengers of inflammation that drives tumor angiogenesis [74]. While cytokines produced by cancer cells provide optimal conditions for cell growth within the tumor microenvironment, cytokines secreted by stromal cells may influence the behavior of malignant cells [213,214]. TNF-α and IL-1, present in host stromal cells surrounding breast, prostate, bladder and colorectal cancer, stimulate tumor growth [213,215]. Factors that mediate a proangiogenic effect of TNF-α include VEGF, VEGFR, bFGF, IL-8, platelet activating factor, P-selectin, NO and intracellular adhesion molecules [216–219]. Co-culture of IL-1β-expressing Lewis lung carcinoma cells with macrophages synergistically augmented neovascularization and the migration of HUVEC with marked increases in the production of VEGF-A, IL-8, monocyte chemoattractant protein-1, and MMP-9 via activation of NF-κB and AP-1 signaling pathways, suggesting that macrophages recruited into tumors could interact with cancer cells and play a critical role in promoting angiogenesis [220]. Incubation with IL-20, a proangiogenic cytokine, significantly induced the migration of HUVEC, vascular tube formation on Matrigel and tumor angiogenesis *in vivo* [221]. IL-20 induced expression of other angiogenic factors, such as bFGF, VEGF, MMP-2, MMP-9, and IL-8 and enhanced the phosphorylation of ERK1/2, p38, and JNK [221]. Hagemann et al. [222] have demonstrated that macrophage migration inhibitory factor (MIF), a key regulator of immune and inflammatory responses, plays a critical role in inflammation-associated cancer. Stable knockdown of MIF in the murine ovarian cancer (ID8) cells decreased the expression of IL-6, VEGF and keratinocyte chemoattractant, and reduced the infiltration of macrophages and endothelial cells in tumor ascites [222]. Mice injected intraperitoneally with MIF-RNAi-expressing ID8 cells showed reduced ascites burden and prolonged survival compared to those injected with ID8 mock control cells [222].

3.2. Chemokines in inflammatory angiogenesis

Chemokines are key components which regulate leukocyte recruitment and function in the tumor microenvironment

[223,224]. Chemokines, such as CXCL2, stimulate prostate cancer growth through the regulation of macrophage infiltration and enhanced angiogenesis within the tumor [225]. The CXCR4/CXCL12 signaling results in PI3K/Akt-mediated expression of VEGF, a key molecule responsible for angiogenesis and tumor progression [223]. CXCL12, secreted by stromal cells, promotes angiogenesis by recruiting endothelial cell precursors to the growing tumor via the activation of MMP-9 [226]. Another chemokine IL-8 (also known as CXCL-8) acts as a mediator of tumor angiogenesis. The increased proliferation of endothelial cells stimulated with conditioned media obtained from Bcl-xl-overexpressing human glioblastoma and melanoma cells is diminished in the presence of IL-8 neutralizing antibody [227]. In addition, treatment with IL-8 neutralizing antibody reduced *in vivo* vessel formation in mice inoculated with matrigel containing these cells or conditioned culture media, supporting the role of IL-8 in tumor angiogenesis [227].

3.3. Role of COX-2 and prostaglandins in tumor angiogenesis

Besides cytokines and chemokines, COX-2 and some of its products also participate in inflammatory angiogenesis via mechanisms involving increased expression of VEGF, promotion of vascular sprouting, migration and tube formation, induction of MMPs, and activation of EGFR-mediated angiogenesis [228,229]. A significant positive correlation between elevated COX-2 and VEGF expression, and resultant increase in tumor vascularization and microvessel density were observed in tumors from patients with head and neck cancer [230]. Moreover, incubation of human epidermoid carcinoma (A-431) and squamous cell carcinoma (SCC-9) cells with LPS resulted in increased *COX-2* mRNA expression and PGE_2 production as well as increased *VEGF* mRNA and protein expression, which was abolished by co-incubation of cells with COX-2 inhibitors [230]. Subsequent studies also demonstrated VEGF as a key mediator in the COX-2 angiogenic pathway [231–234]. HIF-1α is considered to function as a molecular link between COX-2 and VEGF in the course of angiogenesis [233,235]. Increased VEGF expression in COX-2-overexpressing gastric cancer (AGS) cells was reduced after transfection with antisense HIF-1α, while expression of HIF-1α and VEGF was increased in wild-type AGS cells incubated with exogenous PGE_2, suggesting that the COX-2/PGE_2/HIF-1α/VEGF pathway contributes to tumor angiogenesis associated with gastric cancer [235]. Alternatively, PGE_2 was shown to upregulate VEGF expression in gastric cancer (MKN28) cells via activation of the EGFR-MAP kinase signaling pathway [236]. Moreover, a reduced growth of implanted tumor in $EP3^{-/-}$ mice [237], suppression of PGE_2-induced VEGF expression in AGS cells by the EP receptor antagonist SC19220 [235], and impaired vascular branch formation and motility of endiothelial cells derived from $EP2^{-/-}$ mice [238] suggest the potential role of the COX-2/PGE_2/EP/VEGF axis in tumor angiogenesis.

4. OncomiR: linking inflammation and cancer?

4.1. Role of miRNA in cancer

In the field of epigenetics, microRNAs (miRNAs or miR) have emerged as a novel class of gene expression regulators. The miRNAs constitute a large family of non-coding-, small size- (19–22 oligonucleotides), and gene-silencing RNAs, which negatively regulate gene expression via translational repression and/or mRNA degradation. miRNAs are transcribed by RNA polymerase II forming a long primary transcript (pri-miRNA), which is processed into a short hairpin structure (pre-miRNA) by nuclear RNase enzymes and exported to cytoplasm by exportin 5 [239–241]. Once in the cytoplasm, the primary miRNA (pre-miRNA) undergoes further processing by Dicer to produce mature miRNA and subsequently is incorporated into the RNA-induced silencing complex (RISC) [242]. The mature miRNAs specifically bind to 3′-untranslated region (UTR) of target mRNAs leading to either mRNA degradation or inhibition of translation [243]. A growing body of evidence suggests that miRNA can play a significant role in the process of tumorigenesis [240,244]. Several miRNAs have already been demonstrated to behave as oncogenes or tumor suppressor genes in many types of cancer [245], and are referred to as 'oncomiRs' [246,247]. Dysregulated miRNA levels have been shown to be associated with several types of malignancies including those of colon, breast, lung and leukocyte-derived tumors, such as pediatric Burkitt's lymphoma and chronic lymphocytic leukemia (CLL) [248]. The microarray analysis of different miRNAs has revealed that a high hsa-mir-155 and low expression of hsa-let-7a-2 miRNA are correlated with poor survival of lung adenocarcinomas, suggesting that the expression profiles of these miRNAs are diagnostic and prognostic markers of lung cancer [249]. The 3′-UTR of *ras* oncogene contains complementary sites for let-7 miRNA, which negatively regulates *ras*. The expression of let-7 miRNA is lower in lung tumors than that in the normal lung tissue, while Ras is overexpressed in lung tumors, suggesting a tumor suppressor function of let-7 miRNA [250]. Other miRNAs, such as miR-15 and miR-16, induce apoptosis in CLL cells by targeting antiapoptotic protein Bcl-2 [251]. Lehmann et al. [252] have demonstrated that aberrant hypermethylation-dependent inactivation of miR-9-1 gene is an early event in the development of human breast cancer.

4.2. miRNA as a novel link between inflammation and cancer

The relationship between inflammation and miRNA in connection to tumorigenesis has just been started to be explored. Treatment of human monocytes with inflammatory cytokines resulted in the upregulation of miR-146 in an NF-κB-dependent manner and the induced miR-146 inhibited expression of TNF-receptor-associated factor 6 and IL-1 receptor-associated kinase 1, which are downstream molecules in the proinflammatory cytokine signaling pathway [253]. The induction of let-7a miRNA in human malignant cholangiocytes stably transfected with IL-6 contributes to the constitutive phosphorylation of STAT-3, another key molecule that links inflammation and cancer [254]. Alternatively, IL-6 enhances the growth of human cholangiocarcinoma cells by downregulating miR-370 [254]. Therefore, uncovering the role of miRs in linking inflammation and cancer appears to have promise for future research.

5. Components of inflammatory signaling cascades as targets for chemoprevention

Chemoprevention is a practical approach of preventing cancer by using relatively non-toxic chemical entities to halt, reverse or delay the carcinogenic process [119]. One of the promising strategies for chemoprevention is to alleviate inflammatory responses, which is implicated in all stages of tumorigenesis [255]. Numerous synthetic and natural compounds with anti-inflammatory properties have been identified as attractive chemopreventive arsenal [119,255]. At the molecular level, the chemopreventive activities of anti-inflammatory substances are often attributed to their ability to target the components of proinflammatory signaling pathways, especially those mediated by a panel of upstream kinases and transcription factors [256].

In a case–control study, comprising 188 patients with ulcerative colitis-associated cancer and matched controls, post-inflammatory

pseudopolyps were recognized as a predictive factor for cancer, and intervention with anti-inflammatory medication reduced the risk of colorectal cancer [257]. According to a randomized, placebo-controlled, double-blind study, patients receiving a selective COX-2 inhibitor celecoxib showed significantly reduced occurrence of colorectal adenomas within 3 years of surgical removal of colorectal adenomatous polyps [258]. Selective inhibitors of COX-2 and iNOS have been shown to exert chemopreventive effects in various experimental tumor models [165,172,175,259,260]. Etodolac, a COX-2 inhibitor, markedly reduced the occurrence of colitis-associated neoplasia in p53-deficient mice treated with DSS [261]. In a DSS-induced chronic colitis model, mice receiving nimesulide for 120 days following DSS treatment showed significantly reduced levels of dysplasia and colon cancer [259]. Dietary administration of nimesulide also suppressed AOM-initiated and DSS-promoted colonic epithelial malignancy and attenuated the expression of COX-2, iNOS and nitrotyrosine in female ICR mice [172]. Another COX-2 inhibitor celecoxib diminished cutaneuos inflammation and tumor formation in mouse skin irradiated with UVB [120] and esophageal inflammation-metaplasia-adenocarcinoma sequences in rats [131]. The latter study demonstrated that celecoxib abrogated COX-2 expression and PGE_2 production in the stroma of inflamed esophageal epithelia [131]. Topical application of celecoxib lowered the incidence and the multiplicity of DMBA-initiated and TPA-promoted skin papillomas and diminished TPA-induced COX-2 protein and mRNA expression in mouse skin by blocking p38 MAP kinase-mediated activation of AP-1 [262]. In addition, celecoxib inhibited TNF-α-induced activation of JNK, p38 MAP kinase and ERK as well as COX-2 promoter activity [263]. The inhibition of COX-2 by celecoxib caused the lowering of bFGF-2-induced rat corneal neovascularization and suppression of the growth of colon cancer (HT-29 and HCT116 cells) xenograft in immunocompromised mice [264]. Moreover, inhibition of elevated COX-2 by celecoxib resulted in the loss of intratumoral PGE_2 levels and inhibition of the growth of human head and neck xenograft tumors [265]. The suppression of chemically induced papillomagenesis by aminoguanidine in female ICR mouse skin [165] and the reduction in AOM-induced aberrant crypt foci formation by SC-51 or aminoguanidine in F344 rats [260] suggested that selective inhibition of iNOS might confer prevention against experimental carcinogenesis.

Numerous anti-inflammatory phytochemicals have also been shown to interfere with different stages of inflammatory signaling cascades, thereby preventing experimentally induced tumorigenesis. Examples of the extensively investigated chemopreventive anti-inflammatory phytochemicals are epigallocatechin gallate (EGCG) from green tea, resveratrol from grapes and red wine, organosulfur compounds from garlic, curcumin from turmeric, gingerol from ginger, capsaicin from hot chili pepper, sulforaphane from broccoli, etc. [119,256]. Studies conducted with cultured cells and animal models have demonstrated that anti-inflammatory phytochemicals exert chemopreventive effects by targeting the components of inflammatory signaling pathways [256]. For instance, the antitumor promoting effects of EGCG have been attributed to its inhibitory effect on the expression of COX-2 and iNOS, production of PGE_2, NO, IL-8, and TNF-α, activation of MAP kinases and the transactivation of transcription factors including NF-κB and AP-1 in cells or tissues exposed to diverse proinflammatory stimuli [256]. The chemopreventive effect of curcumin is largely attributable to its suppressive effects on cellular signaling mediated via NF-κB and AP-1, and the upstream kinases, and subsequent downregulation of aforementioned proinflammatory mediators [256]. In a mouse model of colitis-associated cancer, curcumin diminished AOM-initiated and DSS-promoted colon carcinogens and abrogated DSS-induced COX-2 expression and NF-κB activation [266]. Likewise, the suppression of COX-2 and iNOS expression via modulation of MAP kinase, IKKs, NF-κB and AP-1 by resveratrol accounts, in part, for the molecular basis of its anti-inflammatory and anti-tumor promoting activities [256]. Martin et al. [267] have reported that resveratrol significantly ameliorated trintirobenzene sulfonic acid-induced chronic experimental colitis in rats by suppressing the aberrant expression of COX-2, activation of NF-κB, and overproduction of PGE_2 and TNF-α [267]. There is now growing interest in developing effective chemopreventive regimens by single or combined use of some of well-defined edible anti-inflammatory phytochemicals.

6. Conclusion

Despite enormous effort to conquer cancesur over the last few decades, the outcome of conventional strategies, such as chemotherapy and radiotherapy, to combat cancer appears unsatisfactory as the incidence and the mortality of cancer, in general, are not decreasing worldwide. The concept of chemoprevention, therefore, appears to be a realistic and fundamental approach to fight cancer. Illuminating an inflammation-cancer link corroborates that chemoprevention can be achieved, partly, by targeting the aberrant inflammatory process. Numerous anti-inflammatory agents of natural and synthetic origin have been shown to inhibit inflammation-associated carcinogenesis. In an attempt to dissect the molecular basis of inflammation-driven carcinogenesis, several key mediators of inflammatory signaling have been identified, and substantial progress has been made in clarifying the role of molecular switches to link chronic inflammation and cancer. Some important molecular players in a complex network of inflammatory or anti-inflammatory signaling include transcription factors, such as NF-κB, AP-1, HIF-1α, STAT3, and nuclear factor erythorid-2-related factor-2 (Nrf-2), and their upstream regulators. Moreover, cellular miRNA has also emerged as another potential link between inflammation and cancer. However, rigorous studies are still necessary to characterize the pleiotroic behavior of host immune cells, resolve various complications and elucidate missing links between inflammation and cancer. Nonetheless, based on the current knowledge of our understanding the tumor cells-host stroma communication, persistent inflammatory states of the tumor microenvironment and the role of inflammatory signaling molecules in the whole process of oncogenesis flares the hope of achieving chemoprevention or chemotherapy by targeting the components of specific inflammatory signaling.

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