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Inflammation and cancer: How hot is the link?

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Abbreviations:
ALL, acute lymphocytic anemia
AML, acute myelogenous leukemia
B-CLL, B-cell chronic lymphocytic leukemia
CLL, chronic lymphocytic leukemia
COX, cyclooxygenase
EBV-LMP1, Epstein-Barr virus-latent membrane protein
EGFR, epidermal growth factor receptor
HBV, hepatitis B virus
HCL, hairy cell leukemia
HCV, hepatitis C virus
HPV, human papilloma virus
IκB, inhibitory subunit of NF-κB
IL, interleukin
iNOS, inducible nitric oxide synthase
LOX, lipoxygenase

ABSTRACT

Although inflammation has long been known as a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes loss of function, there has been a new realization about its role in a wide variety of diseases, including cancer. While acute inflammation is a part of the defense response, chronic inflammation can lead to cancer, diabetes, cardiovascular, pulmonary, and neurological diseases. Several pro-inflammatory gene products have been identified that mediate a critical role in suppression of apoptosis, proliferation, angiogenesis, invasion, and metastasis. Among these gene products are TNF and members of its superfamily, IL-1α, IL-1β, IL-6, IL-8, IL-18, chemokines, MMP-9, VEGF, COX-2, and 5-LOX. The expression of all these genes are mainly regulated by the transcription factor NF-κB, which is constitutively active in most tumors and is induced by carcinogens (such as cigarette smoke), tumor promoters, carcinogenic viral proteins (HIV-tat, HIV-nef, HIV-vpr, KHSV, EBV-LMP1, HTLV1-tax, HPV, HCV, and HBV), chemotherapeutic agents, and γ-irradiation. These observations imply that anti-inflammatory agents that suppress NF-κB or NF-κB-regulated products should have a potential in both the prevention and treatment of cancer. The current review describes in detail the critical link between inflammation and cancer.

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MAPK, mitogen-activated protein kinase
MMP, matrix metalloproteinase
NF-κB, nuclear factor-κB
PPAR-γ, peroxisome proliferator activated receptors
RCC, renal cell carcinoma
TGFα, transforming growth factor
TNF-α, tumor necrosis factor
VCAM-1, vascular cell adhesion molecule 1
VEGF, vascular endothelial growth factor

1. Introduction

Common wisdom says ''most things in life are a double-edged sword''. While they are in our favor at one dose or under one condition; they may be disfavor at another dose or under another condition. This is analogous to what Alexander Fleming (discoverer of penicillin) once said: if the soil causes the disease; the cure to the disease also lies in it. For instance, while TNF mediates rheumatoid arthritis, the soluble form of its receptor (enbrel) is used for its treatment. Similarly, while T helper (Th)-1 secreted cytokines mediate inflammation, Th-2 produced cytokines suppress it. Also it is noted that while pro-oxidants produced in the body mediate inflammation, antioxidants (such as glutathione) suppress this response. Inflammation is a part of the host response to either internal or external environmental stimuli. This response serves to counteract the insult incurred by these stimuli to the host. This response can be pyrogenic, as indicated by fever. When acute inflammation or fever is manifested for a short period of time, it has a therapeutic consequence. However, when inflammation becomes chronic or lasts too long, it can prove harmful and may lead to disease. How is inflammation diagnosed and its biomarkers is not fully understood, however, the role of pro-inflammatory cytokines, chemokines, adhesion molecules and inflammatory enzymes have been linked with chronic inflammation (Fig. 1). Chronic inflammation has been found to mediate a wide variety of diseases, including cardiovascular diseases, cancer, diabetes, arthritis, Alzheimer's disease, pulmonary diseases, and autoimmune diseases [1]. The current review, however, will be restricted to the role of chronic inflammation in cancer. Chronic inflammation has been linked to various steps involved in tumorigenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis [2,3]. That inflammation is a risk factor for most type of cancers is now well recognized (Table 1; [4–16]). The present review will discuss the various inflamma-

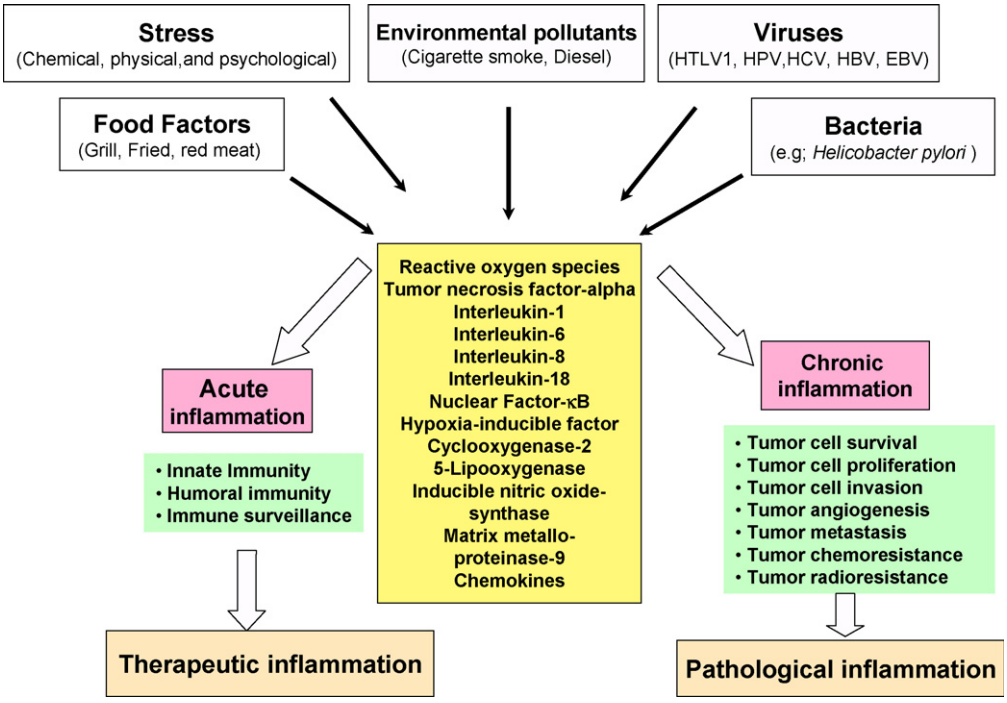

Fig. 1 – Different faces of inflammation and its role in tumorigenesis.

Table 1 – Inflammation as a risk factor for most cancers

Inducer	Inflammation	Cancers	% Predisposed that progress to cancer	References
Tobacco smoke	Bronchitis	Lung cancer	11–24	[4]
Helicobacter pylori	Gastritis	Gastric cancer	1–3	[5]
Human papillomavirus	Cervicitis	Cervical cancer	<1	[6]
Hepatitis B & C virus	Hepatitis	HCC	10	[7]
Bacteria, GBS	Cholecystitis	Gall bladder cancer	1–2%	[8]
Gram-uropathogens	Cystitis	Bladder cancer	<1	[9]
Tobacco, genetics	Pancreatitis	Pancreatic cancer	≤10%	[10]
GA, alcohol, tobacco	Esophagitis	Esophageal cancer	15	[11]
Asbestos fibers	Asbestosis	Mesothelioma	10–15	[12]
Epstein-Barr virus	Mononucleosis Hodgkin's disease	Burkitt's lymphoma	<1	[13]
Gut pathogens	IBD	Colorectal cancer	1	[14]
Ultraviolet light	Sunburn	Melanoma	≤9%	[15]
Infections, STD	PIA	Prostate cancer	?	[16]

GA, gastric acid; GBS, gall bladder stones; HCC, hepatocellular carcinoma; STD, sexually transmitted diseases; PIA, prostate inflammatory atrophy.

tory intermediates responsible for the steps leading to formation of tumors, their growth and metastasis.

2. Role of tumor necrosis factor in tumorigenesis

Tumor necrosis factor (TNF-α) was first isolated as an anticancer cytokine by our group more than two decades ago [17]. Experience since then has indicated that when expressed locally by the cells of the immune system, TNF-α has a therapeutic role. However, when dysregulated and secreted in the circulation, TNF-α can mediate a wide variety of diseases, including cancer [17]. TNF-α has itself been shown to be one of the major mediators of inflammation [18]. Induced by a wide range of pathogenic stimuli, TNF-α induces other inflammatory mediators and proteases that orchestrate inflammatory responses. TNF-α is also produced by tumors and can act as an endogenous tumor promoter [18]. The role of TNF-α has been linked to all steps involved in tumorigenesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis, as outlined below (Fig. 2).

2.1. *TNF-α can induce cellular transformation*

A number of reports indicate that TNF-α induces cellular transformation, proliferation, and tumor promotion [2,18–20]. Komori's group reported that human TNF-α is 1000 times more effective than the chemical tumor promoters okadaic acid and 12-*O*-tetradecanoylphorbol-13-acetate in inducing cancer [21]. They further found that TNF-α substantially enhanced cellular transformation initiated with 3-methylcholanthrene in fibroblasts. Moreover, TNF-α induced growth of v-Ha-ras transfected but not of non-transfected cells. Okadaic acid itself induced the secretion of TNF-α from fibroblasts cells, thus suggesting that the chemical tumor promoters could also induce the secretion of TNF-α, which in turn can act as an endogenous tumor promoter in vivo [21].

2.2. *Tumor cells produce TNF-α and mediate proliferation*

Although initially thought to be a product only of macrophages, TNF-α has now been shown to be produced by a wide variety of tumor cells, including those of B cell lymphoma [22,23], cutaneous T cell lymphoma [24], megakaryoblastic leukemia [25], adult T cell leukemia [26], AML [27], CLL [28], ALL [29], breast carcinoma [30], colon carcinoma, lung carcinoma, squamous cell carcinoma, pancreatic cancer [31,32], ovarian carcinoma

Table 2 – TNF as an autocrine and paracrine growth factor

Autocrine growth factor	
Chronic B cell malignancies	[175–178]
Chronic myeloid leukemia (CML)	[28]
B cells-chronic lymphocytic leukemia (CLL)	[22,39]
Hairy cell leukemia	[178]
Juvenile chronic myelogenous leukemia	[179]
B cells from ALL, MDS, AML patients	[27]
Macrophage differentiation	[180]
B-lymphoblastoid cells	[181]
Acute myelogenous leukemia (AML)	[29]
Neuroblastoma (SKNF-1 & SKNBE)	[38]
Ovarian tumor cells	[33]
Mantle cell lymphoma	[182]
Cutaneous T cell lymphoma	[24]
Glioblastoma	[183]
Skin fibroma	[184]
Paracrine growth factor	
Fibroblasts	[185]
Astrocytes	[186]
Thymocytes	[187]
Hairy cell leukemia (HCL)	[188,189]
B-cell chronic lymphocytic leukemia (B-CLL)	[190]
Normal B cells	[191]
Megakaryblastic leukemia (CMK)	[192]
Clonogenic cells (AML)	[193]
Promyelomonocytic leukemia (HL-60)	[194]
Acute myeloblastic leukemia	[195,196]
Astrocytoma (U-373)	[197]

[33–35], the cervical epithelial ovarian cancer [36], glioblastoma [37], and neuroblastoma [38]. In most of these cells, TNF-α acts as an autocrine growth factor however; in some cell types TNF-α induces the expression of other growth factors, which mediate proliferation of tumors (Table 2). For instance, in cervical cells TNF-α induces amphiregulin, which induces the proliferation of cells [36], whereas in pancreatic cells TNF-α induces the expression of epidermal growth factor receptor (EGFR) and transforming growth factor (TGF-α), which mediates proliferation [32]. TNF-mediated down-regulation of ERBB2 in pancreatic tumor cells is accompanied by an increase in growth inhibition at low doses of TNF. This decrease of ERBB2 is a singular example of a modulation of this growth factor receptor by TNF-α and represents a striking model of cytokine receptor transregulation in the growth control of malignant pancreatic epithelial cells [31]. Schmiegel and coworkers reported that TNF-α induced the expression of TGF-α and EGFR in human pancreatic cancer cells. The simultaneous induction of a ligand/receptor system by TNF-α suggests that this cytokine modulates autocrine growth-regulatory pathways in pancreatic cancer cells [32]. Both IL-1α and TNF-α stimulate proliferation of immortal and malignant cervical epithelial cells by an EGF receptor-dependent pathway requiring autocrine stimulation by amphiregulin [36].

TNF-α is frequently detected in human tumors and associated with a poor prognosis, loss of hormone responsiveness, and cachexia/asthenia. An interesting link between TNF-α and malignancy has been identified in human ovarian carcinoma. The gene for TNF-α was found to be expressed in 45 of 63 biopsies of human epithelial ovarian cancer [35]. TNF-α mRNA was found in epithelial tumor cells and infiltrating macrophages, whereas TNF-α protein localized primarily to a subpopulation of macrophages within and in close proximity to tumor areas. The coexpression of TNF-α and its receptor in ovarian cancer biopsies suggests the capacity for autocrine/paracrine action. TNF-α is also constitutively produced by B-cell chronic lymphocytic leukemia (B-CLL) and hairy cell leukemia (HCL) cells and may play a regulatory role in the progression of the neoplastic clone in B-cell chronic lymphoproliferative disorders [39]. Tsukasaki's group found that TNF-α polymorphism is associated with increased susceptibility to development of ATL/lymphoma in human T-lymphotropic virus type 1 (HTLV-1) carriers [26]. Genetic polymorphism leading to increased TNF-α production may enhance susceptibility to ATL among HTLV-1 carriers.

2.3. *TNF-α can induce invasion and angiogenesis of tumor cells*

Although loss of cell–cell adhesion and gain of invasive properties play a crucial role in malignant progression of epithelial tumors, the molecular signals that trigger these processes have not been fully elucidated. TNF-α has been shown to confer an invasive, transformed phenotype on mammary epithelial cells [30]. TNFα has been reported to induce angiogenic factor upregulation in malignant glioma cells [40]. This upregulation in turn promotes angiogenesis and tumor progression. There is a marked upregulation (RNA and protein) of TNF-α, IL-8, and, to a lesser extent, vascular endothelial growth factor (VEGF) in U251 glioma cells after stimulation with TNF-α. TNF-α stimulates epithelial tumor cell motility, which is a critical function in embryonic development, tissue repair, and tumor invasion [41]. TNF-α could enhance invasiveness of some carcinomas or stimulate epithelial wound healing in vivo [42]. TNF-α has been even reported to mediate macrophage-induced angiogenesis [43]. The angiogenic activity produced by activated murine peritoneal macrophages is completely neutralized by a polyclonal antibody to TNF-α, suggesting that immunological features are common to TNF-α and the protein responsible for macrophage-derived angiogenic activity.

2.4. *Role of TNF-α and its receptor in cancer development*

The role of both TNF-α and its receptors has been examined in cancer development. Various approaches, including genetic deletion, transgenic models, and the use of antibodies and

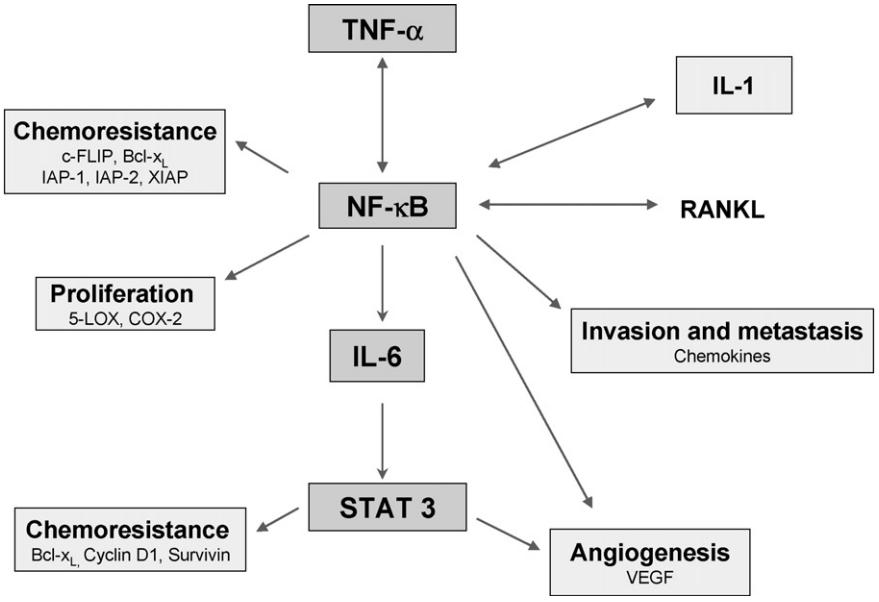

Fig. 2 – Inflammatory networking in cancer.

soluble receptors as decoys, have been used to gain insight into the role of TNF in tumor development. TNF receptor (TNFR-1)-mediated signaling is required for skin cancer development induced by NF-κB inhibition [44]. This suggests a critical role of local TNFR1-mediated signaling and associated inflammatory response cooperating with repressed keratinocyte NF-κB signaling in driving skin cancer development. An essential role of TNFR p55 has been found in the liver metastasis of intrasplenic administration of colon 26 cells [45]. TNFR p55-mediated signals can upregulate both VCAM-1 expression in the liver and subsequent liver metastasis after intrasplenic tumor injection. Moreover, TNF-$\alpha^{-/-}$ and TNFR1$^{-/-}$ mice are resistant to chemically induced carcinogenesis of the skin [46], and development of liver metastasis in experimental colon cancer [47]. TNF-α drives a lymphoproliferative disorder in FasL$^{-/-}$ mice [48], and inhibition of stromal cell TNF-α decreases the incidence of inflammation-induced liver tumors [49]. Interestingly, endogenous and exogenous TNF-α administration showed enhancement of metastasis in an experimental fibrosarcoma metastasis model [50]. Mice injected with fibrosarcoma cells showed enhanced metastasis to the lungs in the presence of exogenous TNF. Neutralization of endogenous tumor-induced TNF led to a significant decrease of the number of pulmonary metastases.

3. Role of interleukins in tumorigenesis

Several inflammatory interleukins have been linked with tumorigenesis, which suggests that inflammation is associated with cancer development (Table 3). These interleukins include IL-1, IL-6, IL-8, and IL-18. Interleukins mediate different steps in the pathway leading to tumorigenesis. Secretion of IL-1α promotes growth of cervical carcinoma [36] and can also induce anchorage independence in embryo fibroblasts and tumor cell revertants [51]. Autocrine production of interleukin IL-1β promotes growth and confers chemoresistance in pancreatic carcinoma cell lines [52]. High levels of IL-1β have been identified as a key mediator of this activation in two of the chemoresistant pancreatic cell lines. IL-1β secretion into the tumor milieu also induces several angiogenic factors from tumor and stromal cells that promotes tumor growth through hyperneovascularization in lung carcinoma growth in vivo [53]. IL-6 acts as a paracrine growth factor for multiple myeloma, non-Hodgkin's lymphoma, bladder cancer, colorectal cancer, and renal cell carcinoma (RCC) [54–58]. Autocrine IL-6 production in RCC has been linked with the involvement of p53. RCC cell lines containing mutant p53 produced higher levels of IL-6 than those containing wild-type p53 [58].

Another important pro-inflammatory cytokine IL-8 has been reported to promote growth and metastasis of wide variety of tumors. Expression of IL-8 by human melanoma cells and human ovarian cancer cells correlates with their metastatic potential [59–61]. IL-8 has been detected in astrocytomas, anaplastic astrocytomas, glioblastomas, and central nervous system cervical carcinoma metastasis. Thus, IL-8 secretion could be a key factor involved in the determination of the lymphoid infiltrates observed in brain tumors and

Table 3 – Role of inflammatory interleukins and chemokines in tumorigenesis

Cancer	Interleukines and chemokines	Mechanism(s)	References
Cervical carcinoma	IL-1α and TNF	Growth	[36]
Fibroblasts	IL-1α and TNF	Anchorage independence	[51]
Pancreatic carcinoma	IL-1α	Metastasis	[198]
Lung carcinoma	IL-1α	Angiogenesis	[199]
Pancreatic carcinoma	IL-1β	Chemoresistance	[52]
Lung carcinoma	IL-1β	Growth	[53]
NHL	IL-2, IL-6, TNF	Autocrine growth	[55]
Bladder cancer	IL-6	Transformation	[56]
Multiple myeloma	IL-6	Proliferation	[54]
RCC	IL-6	Autocrine growth	[58]
Colorectal cancer	IL-6 polymorphism	Increased risk	[57]
Melanoma	IL-8	Tumor growth	[59,60]
Prostate cancer	IL-8 polymorphism	Angiogenesis	[200]
Gastric cardia carcinoma	IL-8 polymorphism	Higher risk	[63]
Glioblastoma	IL-8	Lymphoid infiltration	[62]
Ovarian tumors	IL-8	Disease progression	[201]
Tumor	IL-8	Growth, angiogenesis	[64]
Melanoma	IL-18	Metastasis	[202]
LGL leukemia	RANTES, MIP-1β & IL-18	Risk	[65]
Breast cancer	CXCR4, CCR7	Metastasis	[68]
Melanoma	CXCR4, CCR7, CCR10	Metastasis	[68]
Ovarian carcinoma	CXCR4/CXCL12	Invasion and growth	[61]
RCC	CCR3	Higher risk	[73]
Pancreatic carcinoma	MIP-3α, CCR6	Cell invasion	[74]
Ovarian carcinoma	CXCR4, SDF1	Proliferation	[72]
Prostate carcinoma	CXCL14	Inhibits tumor growth	[75]

NHL, non-Hodgkin's lymphoma; RCC, renal cell carcinoma; LGL, large granular lymphocytes.

the development of cerebrospinal fluid pleocytosis in persons with meningoencephalitides [62]. Polymorphisms in the IL-8 gene contributes to a high risk of gastric cardia adenocarcinoma (GCC) and esophageal squamous cell carcinoma (ESCC) among the population of Linxian in north-central China [63]. IL-8 has been found to be transcriptional target of Ras signaling. Ras-dependent IL-8 secretion was required for the initiation of tumor-associated inflammation and neovascularization [64]. Constitutive production of IL-18, RANTES, and MIP-1β, has been linked to disease progression in large granular lymphocyte (LGL) leukemia [65].

4. Role of chemokines in tumorigenesis

Chemokines are a family of proteins that have pleiotropic biological effects. Chemokines can play several roles in cancer progression, including angiogenesis, inflammation, cell recruitment, and migration, and have a well-known role in regulating the recruitment and trafficking of leukocytes to sites of inflammation. Chemokines are grouped into four classes based on the positions of key cysteine residues: C, CC, CXC, and CX3C. The stimulation of angiogenesis and tumor growth – directly or indirectly through the recruitment of tumor-associated macrophages – are typical situations in which chemokines promote tumor development. On the other hand, chemokines could be used to the benefit of cancer patients, as they act in the recruitment of dendritic cells (DC) or/and effector cells or for their angiostatic properties. However, chemokine-mediated recruitment of immature DC within tumors, due to factors produced by the tumor milieu, could lead to the induction of immune tolerance, and therefore novel strategies to eradicate tumors based on chemokines should attempt to avoid this risk [66].

Evidence from murine models and human tumours suggests that CC chemokines are major determinants of macrophage and lymphocyte infiltration in melanoma, carcinoma of the ovary, breast, and cervix, and in sarcomas and gliomas [67]. Chemokine receptors CXCR4 and CCR7 are highly expressed in human breast cancer cells, malignant breast tumors, and metastasis [68]. Their respective ligands CXCL12/SDF-1α and CCL21/6Ckine exhibit peak levels of expression in organs representing the first destinations of breast cancer metastasis. In breast cancer cells, signaling through CXCR4 or CCR7 mediates actin polymerization and pseudopodia formation and subsequently induces chemotactic and invasive responses. In vivo, neutralizing the interactions of CXCL12/CXCR4 significantly impairs metastasis of breast cancer cells to regional lymph nodes and lung. Malignant melanoma, which has a metastatic pattern similar to that of breast cancer but also a high incidence of skin metastases, shows high expression levels of CCR10 in addition to CXCR4 and CCR7. Thus chemokines and their receptors have a critical role in determining the metastatic destination of tumor cells.

Melanoma growth stimulatory activity/growth-regulated protein (MGSA/GRO), a CXC chemokine, plays an important role in inflammation, wound healing, growth regulation, angiogenesis, and tumorigenesis. Constitutive expression of MGSA/GROα in melanoma tumors is associated with constitutive NF-κB activity. Exogenous addition or continuous expression of MGSA/GROα in immortalized melanocytes enhances NF-κB activation [69]. Ovarian cancers express CXCR4 chemokine receptors [70]. CXCR4 ligand, CXCL12 (stromal cell-derived factor 1), was expressed in ovarian cancer cell line IGROV [71]. The chemokine CXCL12 may have multiple biological effects in ovarian cancer, stimulating cell migration and invasion through extracellular matrix, as well as DNA synthesis and establishment of a cytokine network in situations that are suboptimal for tumor cell growth. CXCR4 activation also induced EGFR transactivation in an ovarian cancer cell line [72]. It has been demonstrated that CXCR4 and SDF-1 induces proliferation in ovarian cancer cells, and this correlated with epidermal growth factor (EGF) receptor transactivation.

The functional chemokine receptor CCR3 has been shown to be upregulated in human RCC [73]. Mip-3α and its receptor, CCR6, promote pancreatic cancer cell invasion [74]. Co-localization of Mip-3α and its CCR6 receptor promotes pancreatic cancer cell invasion of type IV collagen. Recent studies suggest that inflammatory processes may be involved in the development or progression of prostate cancer. CXCL14 (BRAK) RNA expression has been observed in normal and tumor prostate epithelium and focally in stromal cells adjacent to cancer [75].

5. Overexpression of cyclooxygenases can mediate tumorigenesis

Cyclooxygenase (COX)-2, an inducible enzyme with expression regulated by NF-κB, mediates tumorigenesis. COX-2, the inducible isoform of prostaglandin H synthase, has been implicated in the growth and progression of a variety of human cancers. Recent epidemiologic studies have shown a 40–50% reduction in mortality from colorectal cancer in individuals who take nonsteroidal anti-inflammatory drugs on a regular basis compared with those not taking these agents. One property shared by all of these drugs is their ability to inhibit COX, a key enzyme in the conversion of arachidonic acid to prostaglandins. Enhanced COX-2 expression has been found in colon cancer tissues from subjects with clinically diagnosed colorectal cancer [76–78]. Cyclooxygenase regulates colon carcinoma-induced angiogenesis by two mechanisms: COX-2 can modulate production of angiogenic factors by colon cancer cells, while COX-1 regulates angiogenesis in endothelial cells. It has been also reported that COX-2 and mPGES were induced in the COX-1-expressing fibroblasts in human familial adenomatous polyposis polyps [79,80].

COX-2 expression in human tumors can be induced by various growth factors, cytokines, oncogenes, and other factors. IL-1β has been reported to upregulate COX-2 expression in human colorectal cancer cells via multiple signaling pathways [81]. Treatment of HT-29 cells with IL-1β induced expression of COX-2 mRNA and protein, and inhibitors of the ERK 1/2, JNK, P38 MAPK, and NF-κB signaling pathways, blocked the ability of IL-1β to induce COX-2 mRNA. COX-2 overexpression reduces apoptotic susceptibility by inhibiting the cytochrome c-dependent apoptotic pathway in human colon cancer cells [82]. Paradoxically, COX-2 overexpression can also inhibit death receptor 5 expression and confers

resistance to TRAIL-induced apoptosis in human colon cancer cells [83].

COX-2 is expressed at an intermediate or high level in epithelial cells of invasive breast cancers [84]. Expression of COX-2 in breast cancer correlates with poor prognosis, and COX-2 enzyme inhibitors reduce breast cancer incidence in humans. COX-2 overexpression has been also found in the mammary gland of transgenic mice induced mammary cancer [85]. COX-2 also plays an important role in the progression of human lung adenocarcinoma [86]. COX-2 overexpression also leads to enhanced in vitro expression of both CXC ligand CXCL 8 and CXCL5 NSCLC angiogenic peptides, in the NSCLC cell lines [87]. COX-2 mRNA has been found to be nearly 150-fold greater in patients with HNSCC compared with normal oral mucosa from healthy volunteers [88]. COX-1 expression in all carcinoma tissues was associated with enhanced expression of COX-2 RNA and protein [89].

COX-2 and iNOS expression has been observed in human ovarian tumors and in tumor-associated macrophages [90]. COX-2 expression levels in tumor specimens from patients with low- and high-grade astrocytomas indicated a correlation between the percentage of COX-2 expression and patient survival [91]. These findings indicate that high COX-2 expression in tumor cells is associated with clinically more aggressive gliomas and is a strong predictor of poor survival. Subbarayan et al. compared and contrasted the expression levels and subcellular distribution patterns of COX-1 and COX-2 in normal prostate (prostate epithelial cell (PrEC), prostate smooth muscle (PrSM), and prostate stromal (PrSt)) primary cell cultures and prostatic carcinoma cell lines (PC-3, LNCaP, and DU145). The basal COX-2 mRNA and protein levels were high in normal PrEC and low in tumor cells, unlike many other normal cells and tumor cells. They concluded that COX-2 expression may be important to PrEC cell function. Although it is low in stromal and tumor cells, COX-2 expression is induced by TNF-in these cells, and this responsiveness may play an important role in prostate cancer progression [92].

COX-2 is also expressed in 93% of melanomas, with a moderate to strong expression in 68% [93]. Increased expression of COX-2 plays a functional role in the development and progression of malignant epithelial cancers. [94]. COX-2 appears to play an important role in gastrointestinal as well as pancreatic carcinogenesis, and COX-2 overexpression has been demonstrated both in esophageal adenocarcinomas and in the metaplastic epithelium of Barrett's esophagus. It has been reported that inhibition of COX-2 suppresses growth and induces apoptosis in human esophageal adenocarcinoma cells [95]. COX-2 expression has been reported in 91% of the squamous cell carcinomas (SCCs) and in 78% of the esophageal adenocarcinomas (ADCs) [96]. It has also been found that both COX isoforms may be involved in the pathogenesis of esophageal adenocarcinoma, as they are linked to the expression of important modulators of angiogenesis (VEGF-A) and lymphangiogenesis (VEGF-C) [97]. COX-2 mRNA and protein expression has been found in 9 of 10 cases of adenocarcinoma of the pancreas but not in nontumorous pancreatic tissue [98]. Human gastric adenocarcinoma tissues also contain significantly higher levels of COX-2 mRNA as compared with paired gastric mucosal specimens devoid of cancer cells [99]. COX-inhibiting drugs have antitumor activity in canine and rodent models of urinary bladder cancer. COX-2 expression was not found in normal urinary bladder samples but was detected in (86%) of invasive transitional cell carcinomas of the urinary bladder and in 75% of cases of carcinoma in situ [100]. These results indicate that COX-2 may play a role in bladder cancer in humans.

6. Overexpression of lipoxygenase mediates tumorigenesis

5-Lipoxygenase (5-LOX) is a key enzyme in the metabolism of arachidonic acid to leukotrienes. Several studies suggest that there is a link between 5-LOX and carcinogenesis in humans and animals. In addition to the important role of leukotrienes as mediators in allergy and inflammation, these compounds are also linked to pathophysiological events in the brain, including cerebral ischemia, brain edema, and increased permeability of the blood-brain barrier in brain tumors. Abundance of the mRNA for arachidonate 5-LOX, which is the rate-limiting enzyme in leukotriene synthesis, has been investigated in a series of human brain tumors. 5-LOX transcript is expressed in human brain tumors and 5-LOX gene product may play a role in human tumor-induced brain edemas [101].

The arachidonic acid-metabolizing enzymes COX-2 and 5-LOX are also overexpressed during the process of colonic adenoma formation promoted by cigarette smoke. Ye et al. investigated whether there exists a relationship between COX-2 and 5-LOX and whether dual inhibition of COX-2 and 5-LOX has an anticarcinogenic effect in the colonic tumorigenesis promoted by cigarette smoke. It has been found that pretreatment of colon cancer cells with cigarette smoke extract promoted colon cancer growth in the nude mouse xenograft model and inhibition of COX-2 or 5-LOX reduced the tumor size [102]. They further found that exposure to the mainstream smoke of unfiltered cigarettes enhanced the 5-LOX protein expression in the inflammation-associated colonic adenomas [103]. Such expression was accompanied by an upregulation of MMP-2 and VEGF, the key angiogenic factors for tumorigenesis. 5-LOX inhibitors decreased the incidence of colonic adenoma formation and reduced angiogenesis, MMP-2 activity, and VEGF protein expression in the colons of these animals. Overexpression of 15-lipoxygenase-1 (15-LOX-1) in human prostate cancer cells has been reported to increase tumorigenesis [104].

Moreover, inhibitors of 5-LOX (MK-886) have been reported to prevent NNK-induced formation of tumors [105]. Possible mechanisms of action of these inhibitors include inhibition of tumor growth and lipoxygenase-mediated activation of NNK. 1-([5-(3-methoxy-4-ethoxy carbonyloxyphenyl)-2,4-pentadienoyl]aminoethyl)-4-diphenylmethoxypiperidine (TMK688) is a potent and orally active 5-lipoxygenase inhibitor having anti-histamine activity in its moiety. TMK688 inhibits epidermal cyclooxygenase activity with potency similar to its inhibiting 5-lipoxygenase. Oral administration of TMK688 inhibited two-stage skin carcinogenesis as well as complete skin carcinogenesis [106]. Thus anti-tumor promoting action of TMK688 may most probably be related to its anti-lipoxygenase activity.

Table 4 – Role of inflammatory enzymes, COX2, LOX and MMPs in tumorigenesis

Tumor	Enzyme	References
Breast cancer	COX-2	[84,85,203]
Cervical carcinoma	COX-1	[89]
Ovarian tumors	COX-2, iNOS	[90,204]
Glioma	COX-2	[91]
Prostate cancer	COX-2	[92]
Melanoma	COX-2	[93,94]
Esophageal adenocarcinoma	COX-2	[95]
Esophageal SCC and AC	COX-2	[96]
Urinary bladder	COX-1, COX-2	[100]
Pancreatic carcinoma	COX-2	[98]
Head and neck SCC	COX-2	[88,205]
Lung carcinoma	COX-2	[86,87]
Gastric carcinoma	COX-2	[99]
Colorectal cancer	COX-2	[76,77,80,82,83]
Brain tumors	5-LOX	[101]
Colon cancer	COX-2, 5-LOX	[103]
Prostate cancer	15-LOX1	[104]
Skin cancer	5-LOX	[106]
Skin cancer	MMP-9	[108]
Breast cancer	MMP-1, MMP-9	[109,110]
Colon cancer	MMP-7	[111]

7. Role of matrix metalloproteinases (MMPs) in tumorigenesis

Matrix metalloproteinases (MMPs) are key modulators of many biological processes during pathophysiological events, such as skeletal formation, angiogenesis, cellular migration, inflammation, wound healing, and cancer [107]. MMP-9/gelatinase B is upregulated in angiogenic dysplasias and invasive cancers of the epidermis in a mouse model of multi-stage tumorigenesis elicited by HPV16 oncogenes. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis [108]. In tumors, MMP-9 expression has been attributed to infiltrating inflammatory cells. Transgenic mice lacking MMP-9 show reduced keratinocyte hyperproliferation at all neoplastic stages and a decreased incidence of invasive tumors. Carcinomas that arise in the absence of MMP-9 exhibit a greater loss of keratinocyte differentiation, indicative of a more aggressive and higher-grade tumor. In gene expression profiles associated with poor outcome of patients with breast tumors, 2 of the 70 genes identified were found to be MMP-1 and MMP-9 [109]. In a recent study, patient survival, gene overexpression and RNAi validation data showed that MMP-1 is the second most important gene in a 95-gene expression profile in determining the metastatic potential of breast cancer to produce lung metastases [110]. MMP-7 also promotes cancer invasion by proteolytic cleavage of the extracellular matrix substrates and activates other MMPs, such as proMMP-2 and proMMP-9, to facilitate tumor invasion [111]. A role of COX-2, 5-LOX, and MMPs in tumorigenesis is summarized in (Table 4).

8. Role of hypoxia-inducible factor-1 in inflammation

Hypoxia-inducible factor-1 (HIF-1) is a heterodimeric transcriptional complex composed of an alpha subunit and a beta subunit. The HIF-1α subunit is generally unstable and undergoes proteasomal degradation in normoxia, whereas the β subunit is permanently present in nuclei irrespective of the state of oxygenation [112]. Recent studies have shown that a number of peptidic and nonpeptidic mediators of inflammation can activate HIF-1 even under normoxic conditions [113]. These include cytokines, hormones such as insulin or IGF-1 and IGF-2, and vasoactive peptides, such as angiotensin II [114]. Among cytokines IL-1β and TNF-α were first shown to increase HIF-1α activity in the human hepatoma cell line HepG2 [115]. HIF-1α stimulates the expression of several genes encoding proteins that promote inflammatory reactions. These include erythropoietin, vascular endothelial growth factor (VEGF) and VEGF-receptor, iNOS, COX-2, glucose transporters, and a number of glycolytic enzymes [112]. The accumulation of HIF-1α in the absence of apparent hypoxic stimulation has been demonstrated in a number of different cancers, in contrast to benign tumors and normal tissue [6]. Thus, HIF-1α is important for conferring a growth and survival advantage to tumor cells, particularly under conditions of metabolic stress.

9. Inducible nitric oxide (NO) synthase (iNOS) and inflammation

iNOS is one of three key enzymes generating nitric oxide (NO) from the amino acid L-arginine [116]. iNOS gene expression and subsequent mRNA translation is controlled by various agonists, especially pro-inflammatory mediators. The most prominent cytokines involved in iNOS stimulation are TNF-α, IL-1β, and IFN-γ [117]. The expression of iNOS is regulated by transcription factors including NF-κB, activator protein 1, signal transducer and activator of transcription, 1α interferon-regulatory protein 1, nuclear factor interleukin-6, and high-motility group I (Y) protein [118]. iNOS has been implicated in different stages of cellular changes that lead to malignancy: transformation of normal cells; growth of transformed cells; angiogenesis triggered by angiogenic factors released from tumor cells or from the surrounding tissue; and metastasis of malignant cells [119]. In a variety of human malignant tumors, e.g. breast, lung, prostate, bladder, colorectal cancer, and malignant melanoma, expression of iNOS can be observed [120]. Further studies are required to determine the role of the NO/iNOS pathway in tumorigenesis and to establish the utility of iNOS inhibitors as chemoprevention agents.

10. Role of oxidative stress in tumorigenesis

Reactive oxygen intermediates, also generically referred to as oxidants, are derivatives of molecular oxygen such as superoxide, hydrogen peroxide, hypochlorous acid, singlet oxygen, and the hydroxyl radical. Under normal circumstances, phagocyte-derived oxidants serve a protective function by killing invading bacteria and parasites. However, they can also have detrimental effects, causing tissue damage and contributing to the development or progression of numerous diseases including cancer [121]. Chronic inflammation is accompanied by increased production of tissue reactive

oxygen and nitrogen intermediates. ROS can alter signal transduction cascades as well as induce changes in transcription factors such as NF-κB and AP-1 that mediate immediate cellular stress responses [122]. The proneoplastic activity of reactive oxygen species is mainly due to their ability to cause DNA damage [123]. Proteins and lipids are also significant targets for oxidative attack, and modification of these molecules can increase the risk of mutagenesis [124]. Agents that either scavenge reactive oxygen intermediates or prevent their formation inhibit induction of DNA damage, mutagenesis, and transformation by inflammatory phagocytes. This forms the basis for the theory that dietary antioxidants can inhibit the development or progression of cancer [125].

11. Dual role of peroxisome proliferator-activated receptor gamma (PPARγ) in inflammation and cancer

The orphan nuclear receptor, PPARγ, is one of three of a family of receptors (PPARα, β and γ) [126]. It is expressed in numerous cell types including adipocytes, epithelial cells of the breast, colon, and lung, and macrophages among others [127]. A growing body of evidence suggests that activated PPARγ might also possess anti-inflammatory and immunomodulatory capacities [128]. Several anti-inflammatory mechanisms have been suggested, including inhibition of NF-κB, AP1, and STAT transcription factors by PPARγ [129]. However, Chawla et al. reported that PPARγ is not essential to elicit the anti-inflammatory effects that result from treatment with the known PPAR agonists 15dPGJ 2or rosiglitazone [130]. PPARγ has also been implicated both as a tumor suppressor and tumor promoter. It is expressed in many cancers, including lung, breast, and prostate, and PPARγ ligands are generally antiproliferative in these settings [131]. However, Sarraf et al. reported that PPARγ contributes to suppression of colon cancer [132]. The combination of receptor overexpression in tumors and known physiological effects of its ligands on cancer cells makes PPARγ a viable target of future chemotherapeutic agents.

12. NF-κB activation mediates tumorigenesis

TNF, interleukins, chemokines, COX-2, 5-LOX, and MMP-9 are all regulated by the transcription factor NF-κB. Although this factor is expressed in an inactive state in most cells, cancer cells express an activated form of NF-κB. This activation is induced by a wide variety of inflammatory stimuli and carcinogens, and the gene products regulated by it mediate tumorigenesis as indicated above [1,133]. Only few of the recent evidences linking NF-κB and cancer will be reviewed here.

12.1. *Genetic evidence about the role of NF-κB in tumorigenesis*

NF-κB activity is triggered in response to infectious agents and pro-inflammatory cytokines via the IκB kinase (IKK) complex. Using a colitis-associated cancer model, it has been shown that although deletion of IKKβ in intestinal epithelial cells does not decrease inflammation, it leads to a dramatic decrease in tumor incidence without affecting tumor size [134]. Pikarsky et al. reported that NF-κB constitutes an important missing link between cancer and inflammation. The Mdr2-knockout mouse strain, which spontaneously develops cholestatic hepatitis followed by hepatocellular carcinoma, serves as a prototype of inflammation-associated cancer. It has been shown that the inflammatory process triggers hepatocyte NF-κB through upregulation of TNFα in adjacent endothelial and inflammatory cells. Suppressing NF-κB inhibition through anti-TNFα treatment or induction of IκB-super-repressor in later stages of tumor development resulted in apoptosis of transformed hepatocytes and failure to progress to hepatocellular carcinoma [49].

Mice lacking IKKβ only in hepatocytes has been found to exhibit a marked increase in hepatocarcinogenesis caused by diethylnitrosamine (DEN) [135]. Decreased hepatocarcinogenesis was also found in mice lacking IKKβ in both hepatocytes and hematopoietic-derived Kuffer cells. These mice exhibited reduced hepatocyte regeneration and diminished induction of hepatomitogens, which were unaltered in mice lacking IKKβ, suggesting that IKKβ provides an inflammatory crosstalk between hepatocytes and hematopoietic-derived cells that promote chemical hepatocarcinogenesis. Co-culture of macrophages with ovarian or breast cancer cell lines led to TNFα-dependent activation of JNK and NF-κB pathways in tumor cells but not in benign immortalized epithelial cells [136]. Tumor cells with increased JNK and NF-κB activity exhibited enhanced invasiveness. Inhibition of the NF-κB pathway by TNFα-neutralizing antibodies, an NF-κB inhibitor, RNAi to RelA, or overexpression of IκB inhibited tumor cell invasiveness. This suggests that TNF-α, via NF-κB and JNK, induces macrophage migratory inhibitory factor (MIF) and extracellular matrix metalloproteinase inducer CD147 (EMMPRIN) in macrophage to tumor cell co-cultures and leads to increased invasive capacity of the tumor cells [120].

12.2. *Activation of NF-κB by carcinogens*

Cigarette smoke (CS) contains several carcinogens known to initiate and promote tumorigenesis and metastasis [137]. Treatment of human histiocytic lymphoma cells with CS activated NF-κB in a dose- and time-dependent manner. Thus CS can activate NF-κB in a wide variety of cells, and this may play a role in cigarette smoke-induced carcinogenesis. The role of EBV latent infection in development of lymphoid and epithelial malignancies such as nasopharyngeal carcinoma (NPC) is mediated via NF-κB activation pathway. The EBV latent membrane protein 1 (LMP1) acts as a constitutively active tumor necrosis factor receptor and activates cellular signaling pathways such as c-Jun-NH(2)-terminal kinase, cdc42, Akt, and NF-κB. Activation of NF-κB p50 homodimer/Bcl-3 complexes has been found in nasopharyngeal carcinoma [138]. Constitutive activation of NF-κB in human melanoma cells has been linked to activation of Akt kinase suggesting that activation of Akt may be an early marker for tumor progression in melanoma. The chemokines CXC ligand 1 (CXCL1) and CXCL8, but not CXCL5, are highly expressed in most melanoma cell lines, suggesting that the constitutive

production of chemokines is highly correlated to endogenous NF-κB activity [139]. Dhawan's group reported that constitutive activation of Akt in melanoma leads to upregulation of NF-κB and tumor progression [140].

Numerous studies have indicated that tumor cells exhibit an elevation in constitutive production of the pro-inflammatory cytokines TNF-α, IL-1α, IL-6, GM-CSF, and KC (the murine homologue of chemokine Groα). The basis for constitutive expression of these cytokines after tumor progression in vivo is unknown. Regulation of the expression of these pro-inflammatory cytokines involves transcription factor NF-κB, which can be activated by cytokines such as TNF-α. The host environment promotes the constitutive activation of NF-κB and pro-inflammatory cytokine expression during metastatic tumor progression of murine squamous cell carcinoma [141]. The gastric pathogen *Helicobacter pylori* is associated with progression to gastric cancer. *H. pylori* induces plasminogen activator inhibitor 2 in gastric epithelial cells via activation of NF-κB and RhoA, which in turn mediates invasion and apoptosis [142]. Suganuma et al. found that *H. pylori* membrane protein 1 (HP-MP1) induces release of inflammatory cytokines and TNFα, which acts as both initiator and tumor promoter, and produced tumors in nude mice [143]. Helicobacter infection has been shown to induce inflammation and colon cancer in SMAD3-deficient mice [144]. Brandt and coworkers showed that the *H. pylori* immunodominant protein, CagA which causes gastritis and carcinoma induces IL-8 in a dose and time dependent manner and this induction occurs via a Ras → Raf → Mek → Erk → NF-κB signaling pathway in a Shp-2- and c-Met-independent manner [145].

12.3. *NF-κB as a growth factor for tumor cells*

The role of NF-κB as a growth factor for tumor cells is well documented. Ludwig's group investigated the role of specific point mutations of the ret proto-oncogene in multiple endocrine neoplasia (MEN) types 2A and 2B, for familial medullary thyroid carcinoma (MTC) syndromes, and for sporadic MTC. They found that NF-κB is constitutively active in C-cell carcinoma and is required for ret-induced transformation [146]. RET-induced NF-κB and IKKβ activity requires Ras function but involves neither the classical MAPK/ERK pathway nor the PI-3K/Akt pathway. In contrast, RET-induced NF-κB activity is dependent on Raf and MEKK1. Inhibition of constitutive NF-κB activity results in cell death of TT cells and blocks focus formation induced by oncogenic forms of RET in NIH 3T3 cells. These results suggest that RET-mediated carcinogenesis critically depends on IKK activity and subsequent NF-κB activation. Constitutive activation of NF-κB in human cutaneous T cell lymphoma cells was mediated through the autocrine production of TNF [24]. Constitutive activation of NF-κB in human cutaneous T cell lymphoma cell has been reported to mediate the proliferation of these cells [147].

Breast cancer metastasis suppressor 1 (BRMS1) functions as a metastasis-suppressor gene in breast cancer and melanoma cell lines. BRMS1 inhibits gene expression by targeting NF-κB [148]. Suppression of both constitutive and TNF-induced NF-κB activation by BRMS1 may be due to inhibition of IκBα phosphorylation and degradation. These results suggest that at least one of the underlying mechanisms of BRMS1-dependent suppression of tumor metastasis includes inhibition of NF-κB activity and subsequent suppression of uPA expression in breast cancer and melanoma cells. The anti-apoptotic response and enhanced cellular proliferation observed in neoplastic cells on overexpression of metallothionein (MT) is also mediated via NF-κB signaling pathway. MT caused transactivation of NF-κB through a specific interaction with the p50 subunit of NF-κB, thus mediating the antiapoptotic effects of MT [149]. Lack of molecular targets in estrogen receptor-negative (ER-negative) breast cancer is a major therapeutic hurdle. Biswas et al. studied NF-κB activation in human breast cancer specimens and its role in cell proliferation and apoptosis [150]. These findings substantiate the hypothesis that certain breast cancer cells rely on NF-κB for aberrant cell proliferation and simultaneously avoid apoptosis, thus implicating activated NF-κB as a therapeutic target for distinctive subclasses of ER-negative breast cancers.

12.4. *NF-κB suppression mediates chemosensitivity*

Extensive research in the last few years suggests that NF-κB activation mediates resistance to cytokines, chemotherapeutic agents, and γ-irradiation, whereas suppression of NF-κB can sensitize tumor cells to these agents. For instance, it has been found that inhibition of NF-κB activation confers sensitivity to TNF-α by impairment of cell cycle progression in six human malignant glioma cell lines [151]. p65 DN protein was used to inhibit NF-κB activation. Similarly, expression of a dominant-negative mutant IκBα in human head and neck squamous cell carcinoma inhibits survival, pro-inflammatory cytokine expression, and tumor growth in vivo [152]. Inhibitors of NF-κB activation can block the neoplastic transformation response. Both TNF and PMA activated NF-κB and induced cell transformation, whereas NF-κB blockers suppressed the transformation. These results suggest that NF-κB activation may be required for transformation whether induced by TPA or by TNF. Inhibition of NF-κB through adenoviral delivery of a modified form of IκBα, a specific inhibitor of NF-κB, has been reported to sensitize chemoresistant tumors to the apoptotic potential of TNF-α and to the chemotherapeutic compound CPT-11, resulting in tumor regression [153].

A central mediator of a wide host of target genes regulated by the NF-κB has emerged as a molecular target in cancer-associated bone destruction. Gordon and coworkers investigated NF-κB-dependent mechanisms in breast cancer cells that regulate tumor burden and osteolysis in bone [154]. They stably transfected cells of the bone-seeking MDA-MB-231 breast cancer cell line with a DN-IκBα to block NF-κB. Blockade of NF-κB signaling in MDA-MB-231 cells decreased in vitro cell proliferation, expression of the pro-inflammatory, bone-resorbing cytokine interleukin-6, and in vitro bone resorption by tumor/osteoclast co-cultures while reciprocally upregulating production of the proapoptotic enzyme caspase-3. Dong et al. used molecular profiling of transformed and metastatic murine squamous carcinoma cells by differential display and cDNA microarray, which found altered expression of multiple genes related to growth, apoptosis, angiogenesis, and the NF-κB signaling pathway [155]. Loercher's group examined the role of NF-κB in the cumulative changes in gene expression

with transformation and progression of the murine SCC and after switching off NF-κB by a DN-IκBα(M) by profiling with cDNA microarray. They found that NF-κB directly or indirectly modulated expression of programs of genes functionally linked to proliferation, apoptosis, adhesion, and angiogenesis. These results also provide evidence that NF-κB is an important modulator of gene expression programs that contribute to the malignant phenotype of SCC [156].

12.5. *Role of NF-κB in tumor metastasis*

Metastasis of cancer cells is a complex process involving multiple steps, including invasion, angiogenesis, trafficking of cancer cells through blood vessels, extravasations, organ-specific homing, and growth. While MMP, UPA, and cytokines play a major role in invasion and angiogenesis, chemokines such as SDF-1α and their receptors such as CXCR4 are thought to play a critical role in motility, homing, and proliferation of cancer cells at specific metastatic sites. NF-κB signal blockade resulted in the downregulation of prometastatic MMP-9, a UPA, and heparanase and reciprocal upregulation of anti-metastatic TIMP-1 and -2 and PAI 2 [157]. NF-κB promotes breast cancer cell migration and metastasis by inducing the expression of the chemokine receptor CXCR4 [158]. NF-κB regulates the motility of breast cancer cells by directly upregulating the expression of CXCR4. The cell surface expression of CXCR4 and the SDF-1α-mediated migration are enhanced in breast cancer cells isolated from mammary fat pad xenografts compared with parental cells grown in culture. A further increase in CXCR4 cell surface expression and SDF-1α-mediated migration was observed with cancer cells that metastasized to the lungs. Taken together, these results implicate NF-κB in the migration and the organ-specific homing of metastatic breast cancer cells. Huang et al. reported that blockade of NF-κB signaling also inhibits angiogenesis and tumorigenicity of human ovarian cancer cells by suppressing expression of VEGF and IL-8 [159].

The transcription factors p53 and NF-κB have been implicated in apoptosis induced by DNA-damaging agents, but the relationship between these two factors at the molecular level is largely unknown. Downregulation of NF-κB is required for p53-dependent apoptosis in X-ray-irradiated mouse lymphoma cells and thymocytes. Apoptosis-resistant mutant sublines from a radiosensitive mouse lymphoma 3SB cell line that undergoes p53-dependent apoptosis after X-ray irradiation were isolated and analyzed for NF-κB activity. A similar downregulation of NF-κB activity by X-rays was observed in thymocytes derived from p53 wild-type and heterozygous mice but not in thymocytes from p53 homozygous knock-out mice. These results suggest that NF-κB inactivation is p53 dependent and is required for X-ray-induced apoptosis in thymic lymphoma cells and normal thymocytes [160].

The molecular mechanisms responsible for the progression of malignant transformation in Barrett's esophagus are still poorly understood; however, the activation of NF-κB represents the central event in the neoplastic progression associated with Barrett's esophagus The increased NF-κB activity has been linked to increased IL-8 and COX-2 expression [161].

13. Inflammation is a double-edged sword

While most evidence presented above suggest that pro-inflammatory cytokines and enzymes play a major role in mediating tumorigenesis, there is evidence to suggest that blockade of inflammatory pathways could prove to be harmful. First, administration of TNF blockers to patients with rheumatoid arthritis increases the risk for developing lymphomas [162]. Second suppression or deletion of NF-κB has been shown to promote carcinogenesis [163–167]. Third, NF-κB activity is modulated by tumor suppressors such as p53 and ARF [168,169]. Fourth, NF-κB destabilizes tumor suppressor p53 [170]. Fifth, NF-κB subunits could induce the expression of tumor suppressor genes such as p53 [171]. Lastly, NF-κB has been shown to regulate the expression of Fas, Fas ligand, and TRAIL [17,172,173], all of which play an important role in innate immunity. These evidences suggest that while under some conditions, inflammatory mediator promote tumorigenesis; their total suppression could have negative effects.

14. Conclusions

Overall this review provides evidence for a strong link between chronic inflammation and cancer. Thus inflammatory biomarkers as described here can be used to monitor the progression of the disease. These biomarkers can also be exploited to develop new anti-inflammatory drugs to prevent and treat cancer. These drugs can also be used as adjuvant to the currently available chemotherapy and radiotherapy, which by themselves activate NF-κB and mediate resistance. Numerous anti-inflammatory agents including those identified from natural sources have been shown to exhibit chemopreventive activities [125,174], and thus can be used not only for prevention but also for therapy of cancer. The lack of toxicity associated with the natural agents combined with their cost provides additional advantages.

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