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Review Article

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Multifaceted link between cancer and inflammation

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Synopsis

Increasing evidence from epidemiological, preclinical and clinical studies suggests that dysregulated inflammatory response plays a pivotal role in a multitude of chronic ailments including cancer. The molecular mechanism(s) by which chronic inflammation drives cancer initiation and promotion include increased production of pro-inflammatory mediators, such as cytokines, chemokines, reactive oxygen intermediates, increased expression of oncogenes, COX-2 (cyclo-oxygenase-2), 5-LOX (5-lipoxygenase) and MMPs (matrix metalloproteinases), and pro-inflammatory transcription factors such as NF-κB (nuclear factor κB), STAT3 (signal transducer and activator of transcription 3), AP-1 (activator protein 1) and HIF-1α (hypoxia-inducible factor 1α) that mediate tumour cell proliferation, transformation, metastasis, survival, invasion, angiogenesis, chemoresistance and radioresistance. These inflammation-associated molecules are activated by a number of environmental and lifestyle-related factors including infectious agents, tobacco, stress, diet, obesity and alcohol, which together are thought to drive as much as 90% of all cancers. The present review will focus primarily on the role of various inflammatory intermediates responsible for tumour initiation and progression, and discuss in detail the critical link between inflammation and cancer.

Key words: activator protein 1 (AP-1), hypoxia-inducible factor 1α (HIF-1α), matrix metalloproteinase (MMP), nuclear factor κB (NF-κB), oncogene, signal transducer and activator of transcription 3 (STAT3)

INTRODUCTION

Inflammation is a complex process that involves widespread changes in cellular and molecular components of physiology. Although controlled inflammation is a necessary process required for an array of processes including tissue repair, wound healing and for defence against invading foreign pathogens, chronic, uncontrolled inflammation is harmful and has now been linked to a number of human ailments [1,2]. The critical role of chronic inflammation in cancer was first proposed by Rudolf Virchow in 1863, when he observed the presence of leucocytes in neoplastic tissues [3,4]. Virchow postulated that an inflammatory milieu promotes a cellular environment that drives the initiation and development of carcinogenesis [1,5]. Within the tumour microenvironment, a network of various pro-inflammatory mediators participate in a complex signalling process that facilitates extravasations of tumour cells through the stroma, thereby promoting tumour progression [6,7]. While acute inflammation is primarily a self-limiting process and has potential therapeutic consequences, prolonged chronic inflammation is mostly detrimental [2,8]. Chronic inflammation is now dubbed by the popular press as a 'secret killer' and has been widely associated with diseases such as atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's disease and various cancers [1,3,4].

It is a well-accepted paradigm now that environment- and lifestyle-related factors play a critical role in development of 90% of all cancers [4,9]. For example, almost 30% of all cancers have been attributed to tobacco smoke, 35% to diet,

Abbreviations used: AP-1, activator protein 1; CCR7, CC chemokine receptor 7; COX-2, cyclo-oxygenase-2; CXCL14, CXC chemokine ligand 14; CXCR, CXC chemokine receptor; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, EGF receptor; HIF-1α, hypoxia-inducible factor 1α; HPV, human papillomavirus; JAK, Janus kinase; IGF-1, insulin-like growth factor; IκB, inhibitory κB; IKK, IκB kinase; IL, interleukin; 5-LOX, 5-lipoxygenase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor κB; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; ROS, reactive oxygen species; SCC, squamous cell carcinoma; STAT3, signal transducer and activator of transcription 3; TAM, tumour-associated macrophage; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

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14–20% to obesity, 18% to infections and 7% to radiation and environmental pollutants [10]. The molecular mechanism(s) by which these risk factors induce cancer are becoming increasingly evident and one major process that seems to be common between all these risk factors is inflammation. Chronic inflammation acts as a key regulator of tumour promotion and progression by several mechanisms including accelerated cell proliferation, evasion from apoptosis, enhanced angiogenesis and metastasis [11]. The mechanism(s) for cancer development in the presence of chronic inflammation involves the continuous presence of cytokines, chemokines, ROS (reactive oxygen species), oncogenes, COX-2 (cyclo-oxygenase-2), 5-LOX (5-lipoxygenase), MMPs (matrix metalloproteinases) and activation of important transcription factors such as NF-κB (nuclear factor κB) and STAT3 (signal transducer and activator of transcription 3), AP-1 (activator protein 1) and HIF-1α (hypoxia-inducible factor 1α) [8,12]. In the present review, we will focus on the role of various pro-inflammatory mediators in cancer and provide novel insights into the intricate link between chronic inflammation and cancer.

ROLE OF TNF (TUMOUR NECROSIS FACTOR) IN INFLAMMATION-DRIVEN CANCERS

TNFα was first isolated as an anticancer cytokine more than two decades ago, but when its antitumour activity was tested on cancer patients, a paradoxical tumour-promoting role of TNFα became apparent [13–15]. At present, the pro-inflammatory role of TNFα has been linked to all steps involved in tumorigenesis, including cellular transformation, survival, proliferation, invasion, angiogenesis and metastasis [15,16].

TNFα has been reported to be produced by a wide variety of tumour cells, including those of B-cell lymphoma [17], megakaryoblastic leukaemia [18], adult T-cell leukaemia [19], breast carcinoma [20], colorectal cancer, lung cancer, SCC (squamous cell carcinoma), pancreatic cancer [21,22], ovarian carcinoma [23], the cervical epithelial cancer [24], glioblastoma [25] and neuroblastoma [26]. The pro-inflammatory potential of TNFα has also been analysed in various animal models of cancer. In a genetic model of liver cancer, TNFα produced by myeloid cells promoted inflammation-associated tumours [27] and also in a chemical-induced model of colorectal cancer, TNFα produced by macrophages has been implicated in inflammation and subsequent tumour development [15]. Endogenous and exogenous TNFα showed an enhancement of metastasis in an experimental fibrosarcoma metastasis model [28]. Elevated levels of TNFα have also been detected in various cancer patients. For example, the TNFα gene was found to be expressed in 45 of 63 biopsies of human epithelial ovarian cancer [23]. Moreover, it has been found that, in CLL (chronic lymphocytic leukaemia) patients, TNFα level was significantly higher as compared with the healthy control population and it also acted as a predictor of patient survival [29]. Thus, novel strategies that neutralize systemic TNFα may be useful in cancer treatment and prevention.

ROLE OF IL (INTERLEUKIN) IN INFLAMMATION AND CANCER

Several ILs have been linked with inflammation and subsequent cancer development. These ILs include IL-1, IL-6, IL-8 and IL-17. IL-1α, which is expressed in both normal tissue and several tumour cells, is a regulatory cytokine that can induce the activation of transcription factors, including NF-κB and AP-1, and promote the expression of various genes involved in cell survival, proliferation and angiogenesis [30]. Also, direct evidence for the role of IL-1β in human cancer has been found in multiple myeloma. IL-1β when released by myeloma cells can induce the production of IL-6 by bone marrow stromal cells and function as an autocrine growth factor for myeloma cells [31]. IL-1β also up-regulates HIF-1α protein through a classical inflammatory signalling pathway involving NF-κB and COX-2, culminating in up-regulation of VEGF (vascular endothelial growth factor), a potent angiogenic factor required for tumour growth and metastasis [32]. In another study, surgical removal of the ovarian tumour and resolution of ascites in patient was found to be directly associated with decrease in serum levels of IL-1β [33].

IL-6 is another major pro-inflammatory cytokine that has been implicated in inflammation-associated carcinogenesis [34,35]. IL-6 modulates the expression of genes involved in proliferation, survival and angiogenesis via the JAK (Janus kinase)–STAT signalling pathway [36]. RCC (renal cell carcinoma) cell lines containing mutant p53 have been found to produce higher levels of IL-6 than those containing wild-type p53 [37]. Moreover, the analysis of biopsy specimens from inflammation-associated gastric cancers has revealed that the levels of IL-1β and IL-6 are highly elevated in tumours as compared with adjacent normal mucosa [38]. An overproduction of IL-6, indicated by increased plasma CRP (C-reactive protein) levels, has also been found in 37% of multiple myeloma patients at diagnosis and is associated with disease aggressiveness, myeloma-cell proliferation and poor prognosis [39]. Increased serum levels of IL-6 have been observed to be positively correlated with tumour burden in colorectal cancer patients with high significance [40]. In another study, inflammatory markers were measured at baseline in 52 patients with stage IV colorectal cancer, and significantly elevated levels of IL-6 and gp130 were observed in these patients and inflammatory markers paralleled clinical outcome [41].

Constitutive expression of IL-8 mRNA and secreted IL-8 protein has been observed in various tumour cell lines and animal models, thus suggesting that IL-8 secretion could be a key factor involved in proliferation, angiogenesis and metastasis of cancer cells [42]. It has been reported that acidic pH can induce elevation in IL-8 expression in human ovarian cancer cells and transcription factors; AP-1 and NF-κB were found to be responsible for this

process [43]. Huang et al. [44] have further found that the neutralizing antibodies to IL-8 can inhibit angiogenesis, tumour growth and metastasis of human melanoma, suggesting the potential utility of anti-IL-8 as a modality to treat melanoma and other solid tumours either alone or in combination with conventional chemotherapy or other antitumour agents. In another report, tumour-derived IL-8 has been shown to induce the differentiation and activation of osteoclasts, underpinning the characteristic osteolytic metastasis of breast cancer cells that have disseminated to the bone [45]. Furthermore, Maxwell et al. [46] determined whether hypoxia can increase IL-8 and IL-8 receptor expression in prostate cancer cells and whether this contributes to a survival advantage in hypoxic cells. Indeed, they found that IL-8, CXCR1 (CXC chemokine receptor 1) and CXCR2 mRNA expression in prostate cancer PC3 cells was up-regulated in response to hypoxia in a time-dependent manner. They also found that the inhibition of IL-8 signalling potentiated etoposide-induced cell death in hypoxic PC3 cells [46]. These results indicate that IL-8 signalling confers a survival advantage to hypoxic prostate cancer cells, and therefore strategies to inhibit IL-8 signalling may sensitize hypoxic tumour cells to conventional treatments. IL-17, another important cytokine, has also been found to act as a growth factor in cutaneous T-cell lymphoma and a key regulator of angiogenesis [47]. IL-17-overexpressing human cervical cancer [48], fibrosarcoma [49] and human NSCLC (non-small cell lung cancer) preferentially exhibit higher oncogenic growth *in vivo* [50].

ROLE OF CHEMOKINES IN INFLAMMATION AND CANCER

Chemokines are soluble chemotactic cytokines that are grouped into four classes based on the positions of key cysteine residues: C, CC, CXC and CX3C [8,51,52]. Several studies have reported the involvement of chemokines and chemokine receptors in cell proliferation, migration, and invasion and metastasis of different types of tumours [53–55].

The chemokine receptors CXCR4 and CCR7 (CC chemokine receptor 7) are highly expressed in human breast cancer cells, malignant breast tumours and metastasis [56]. In breast cancer cells, signalling through CXCR4 or CCR7 mediates actin polymerization and pseudopodia formation and subsequently induces chemotactic and invasive responses [56]. It has been reported that CXCR4 and SDF-1 (stromal-cell-derived factor 1) induces proliferation in ovarian cancer cells, and this correlated with EGFR [EGF (epidermal growth factor) receptor] transactivation. The functional chemokine receptor CCR3 has been shown to be up-regulated in human RCC [57]. CXCL14 (CXC chemokine ligand 14) [BRAK (breast and kidney chemokine)] RNA expression has been observed in normal and tumour prostate epithelium and focally in stromal cells adjacent to cancer [58]. *In vivo*, neutralizing the interactions of CXCL12/CXCR4 significantly impairs metastasis of breast cancer cells to regional lymph nodes and lung [59]. Thus chemokines and their receptors have a critical role in determining the metastatic destination of tumour cells. A list of various ILs and chemokines associated with cancer initiation and promotion is briefly summarized in Table 1.

ROLE OF ONCOGENES IN INFLAMMATION-DRIVEN CANCER

Oncogenes are altered versions of normal cellular genes, the so-called proto-oncogenes, involved in the regulation of cell growth [60,61]. Recently, it has become increasingly evident that pleiotropic effects of oncogenes also include the induction of a pro-tumour microenvironment, through the persistent promotion of an inflammatory milieu [61–63]. For example, Liu et al. [64] have shown that HRAS- and KRAS-G12V induce the expression of various cytokines, including IL-1α, IL-1β, IL-6, CXCL8 and IL-11 in human ovarian cells [64]. Moreover, transcription factor NF-κB is activated in Ras-transformed ovarian epithelial cells and this activation is responsible for the increased expression of CXCL8 [65]. Furthermore, Ancrile et al. [66] have demonstrated that IL-6 acts downstream of Ras in a paracrine fashion to promote angiogenesis. Recent reports indicate that Myc oncogene can also orchestrate a complex inflammatory program [67]. Myc activation in β-cells rapidly induces the expression and release of the pro-inflammatory cytokine IL-1β that, in turn, mediates the release of VEGF-A from mast cells and onset of tumour angiogenesis [68]. Mast cell activation is required not only for angiogenesis during outgrowth of Myc-dependent islet tumours but also for tumour maintenance and the inhibitors of mast cell function trigger hypoxia and cell death of tumour and endothelial cells [69]. Moreover, four mutually exclusive genetic lesions have been identified in papillary thyroid carcinoma, covering approx. 80 % of the cases: rearrangements of *Ret* or *Trk* genes and activating mutation of *Ras* or *Braf* genes [70]. Thus, several oncogene-driven inflammatory pathways are activated in various human cancers and are likely to play a key role in various stages of carcinogenesis.

ROLE OF OXIDATIVE STRESS IN CHRONIC INFLAMMATION AND CANCER

Reactive oxygen intermediates, also generically referred to as oxidants, are derivatives of molecular oxygen such as superoxide, H_2O_2, hypochlorous acid, singlet oxygen and the hydroxyl radical [71–73]. Chronic inflammation is often accompanied by increased production of tissue reactive oxygen intermediates [74]. ROS can alter signal transduction cascades as well as induce changes in transcription factors such as NF-κB, NF-E2/rf2 or Nrf2 (nuclear factor erythroid 2/related factor 2) and AP-1 that mediate immediate cellular stress responses [75,76]. The

Table 1 Role of ILs and chemokines in cancer
MIP-3α, macrophage inflammatory protein-3α.

Cancer type	Inflammatory mediator	Mechanism(s)	Reference
Bladder cancer	IL-6	Transformation	[193]
Multiple myeloma	IL-6 poly	Proliferation	[194]
Colorectal cancer	IL-6	Increased risk	[195]
Melanoma	IL-18	Metastasis	[196]
Pancreatic carcinoma	IL-1α	Metastasis	[197]
Prostate cancer	IL-8 poly	Angiogenesis	[198]
Lung carcinoma	IL-1α	Angiogenesis	[32]
Melanoma	IL-8	Tumour growth	[199]
Glioblastoma	IL-8	Angiogenesis	[200]
RCC	IL-6	Autocrine growth	[37]
Pancreatic carcinoma	IL-1β	Chemoresistance	[201]
Ovarian tumours	IL-8	Disease progression	[202]
Tumour	IL-8	Growth, angiogenesis	[203]
Lung carcinoma	IL-1β	Growth	[204]
Breast cancer	CXCR4 and CCR7	Metastasis	[56]
Melanoma	CXCR4 and CCR7,	Metastasis	[56]
Ovarian carcinoma	CXCR4/CXCL12	Invasion and growth	[43]
RCC	CCR3	Higher risk	[57]
Pancreatic carcinoma	MIP-3α and CCR6	Cell invasion	[205]
Ovarian carcinoma	CXCR4 and SDF1	Proliferation	[206]
Prostate carcinoma	CXCL14	Inhibits tumour growth	[58]

pro-neoplastic activity of ROS is mainly due to their ability to cause DNA damage [77]. Oxidative damage to DNA has also been linked to aflatoxin B-induced p53 and Ras gene mutations in hepatocarcinogenesis [78] and in UV-induced mouse and human skin cancers [79]. Agents that either scavenge reactive oxygen intermediates or prevent their formation inhibit the 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 [80–82].

OVEREXPRESSION OF COX CAN MEDIATE INFLAMMATION-ASSOCIATED CANCERS

COX-2, an inducible enzyme regulated by NF-κB, is known to mediate tumorigenesis [11,83]. COX-2, the inducible isoform of prostaglandin H synthase, has been implicated in the growth and progression of a variety of human cancers. COX-2 has been shown to regulate colorectal cancer-induced angiogenesis by two mechanisms: COX-2 can modulate the production of angiogenic factors by colon cancer cells, while COX-1 regulates angiogenesis in endothelial cells. It has been found that COX-2 and mPGES (membrane-associated prostaglandin E synthase) were induced in the COX-1-expressing fibroblasts in human familial adenomatous polyposis polyps [84]. Administration of the COX-2-selective inhibitor rofecoxib or the functional inactivation of the COX-2 in adenomatous polyposis coli knockout mice, a murine model of human adenomatous polyposis, reduced the number and the size of intestinal polyps [85,86], thereby indicating the correlation between the abnormal up-regulation of COX-2 and tumorigenesis.

COX-2 expression in human tumours can be induced by growth factors, cytokines, oncogenes and other factors. For example, IL-1β has been reported to up-regulate COX-2 in human colorectal cancer cells via multiple signalling pathways [87]. COX-2 has also been implicated in the progression of human lung adenocarcinoma. Steady-state levels of COX-2 mRNA were high in well-differentiated adenocarcinoma samples but low in poorly differentiated adenocarcinoma, SCC and small cell lung cancer. COX-2 overexpression enhanced the *in vitro* expression of both CXC ligand CXCL8 and CXCL5, NSCLC angiogenic peptides in the NSCLC cell lines [88]. COX-2 expression was observed to be strong in the SCCs and weak in oesophageal ADCs (adenocarcinomas) [89]. COX-2 expression levels in tumour specimens from patients with low- and high-grade astrocytomas indicated a correlation between the percentage of COX-2 expression and patient survival [90]. Overexpression of COX-2 is also associated with a poor prognosis in patients with SCC of the uterine cervix treated with radiation and concurrent chemotherapy [91]. Levels of COX-2 expression were also found to be a significant prognostic factor for patients with multiple myeloma [92]. Overall survival of those patients

with negative or weak-to-moderate COX-2 expression was significantly better than that of patients with strong COX-2 immunoreactivity. These findings indicate that high COX-2 expression in tumour cells is associated with clinically more aggressive tumours and is a strong predictor of poor survival.

OVEREXPRESSION OF 5-LOX LINKS INFLAMMATION AND CANCER

5-LOX is a key enzyme in the metabolism of arachidonic acid to leukotrienes [93]. Several studies suggest that there is a link between 5-LOX and carcinogenesis in humans and animals [93–95]. 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 tumours [96]. The 5-LOX transcript is expressed in human brain tumours and the 5-LOX gene product may play a role in human tumour-induced brain oedema [96].

Studies also indicate that the exposure to the mainstream smoke of unfiltered cigarettes enhanced the 5-LOX protein expression in the inflammation-associated colonic adenomas [97]. Such expression was accompanied by an up-regulation of MMP-2 and VEGF, the key angiogenic factors for tumorigenesis and 5-LOX inhibitors were found to decrease the incidence of colonic adenoma formation and reduced angiogenesis, MMP-2 activity and VEGF protein expression [97]. In addition, the increased expression of 5-LOX has been linked with the progression and development of cancer of the pancreas [98], breast [99] and kidney [100].

ROLE OF MMP IN INFLAMMATION AND CANCER

MMPs are a multigene family of zinc-dependent endopeptidases that share a similar structure and which collectively have the capacity to degrade ECM (extracellular matrix) [101]. MMPs are now also implicated in the EMT (epithelial to mesenchymal transition), a hallmark of cancer progression to metastasis [102]. It has been observed that MMP-9 is a potent regulator of the angiogenic switch in a pancreatic tumour model [103]. MMP-9 is up-regulated in angiogenic dysplasias and invasive cancers of the epidermis in a mouse model of multi-stage tumorigenesis elicited by HPV16 (human papillomavirus 16) oncogenes [104]. In gene expression profiles associated with poor outcome of patients with breast tumours, two of the 70 genes identified were found to be MMP-1 and MMP-9 [105]. In another study, patient survival, gene overexpression and RNAi (RNA interference) 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 [106]. Expression of MMP-9 has also been correlated with prognosis, aggressiveness and survival in cancer of the lung [107], stomach [108] and oesophagus [109], RCC and in NHL (non-Hodgkin's lymphoma) [110]. A role of COX-2, 5-LOX, and MMPs in cancer is briefly summarized in Table 2.

Table 2 Role of inflammatory enzymes (COX2, 5-LOX and MMP-9) in cancer
AC, adenocarcinoma.

Tumour	Enzyme	References
Breast cancer	COX-2	[207,208]
Glioma	COX-2	[90]
Prostate cancer	COX-2	[209]
Melanoma	COX-2	[210,211]
Oesophageal adenocarcinoma	COX-2	[212]
Oesophageal SCC and AC	COX-2	[89]
Urinary bladder	COX-2	[213]
Pancreatic cancer	COX-2	[214]
Head and neck SCC	COX-2	[215]
Lung carcinoma	COX-2	[216,217]
Gastric carcinoma	COX-2	[218]
Colorectal cancer	COX-2	[84,219]
Brain tumours	5-LOX	[96,220]
Colorectal cancer	COX-2 and 5-LOX	[221]
Pancreatic cancer	MMP-9	[103]
Skin cancer	MMP-9	[104]

ROLE OF TRANSCRIPTION FACTOR NF-κB IN CHRONIC INFLAMMATION AND CANCER

The transcription factor NF-κB, first discovered by David Baltimore in 1986, is present in the nucleus and binds the promoter of immunoglobulin κ chain in B-cells. In mammalian cells, the NF-κB family of transcription factors is composed of homodimers and heterodimers derived from five distinct subunits, RelA (p65), c-Rel, RelB, p50 (NF-κB1) and p52 (NF-κB2). All family members share a highly conserved RHD (Rel homology domain; ~300 amino acids) responsible for DNA binding, dimerization domain and interaction with IκBs (inhibitory κBs), the intracellular inhibitor of NF-κB [111–113]. In unstimulated cells, the majority of NF-κB complexes are predominantly cytoplasmic and in an inactive form due to their binding to the IκB family of proteins that prevent DNA binding and as a consequence prevent nuclear accumulation [114]. Generally, the inactive NF-κB/IκBα complex is activated by phosphorylation on two conserved serine residues within the N-terminal domain of the IκB proteins. Phosphorylation of these conserved serine residues in response to stimulation leads to the immediate polyubiquitination of IκB proteins by the SCF-β-TrCP (transducin repeat-containing protein-β-transducin repeat-containing protein) complex. This modification subsequently targets IκB proteins for rapid degradation by the 26S proteasome [115]. Activation of

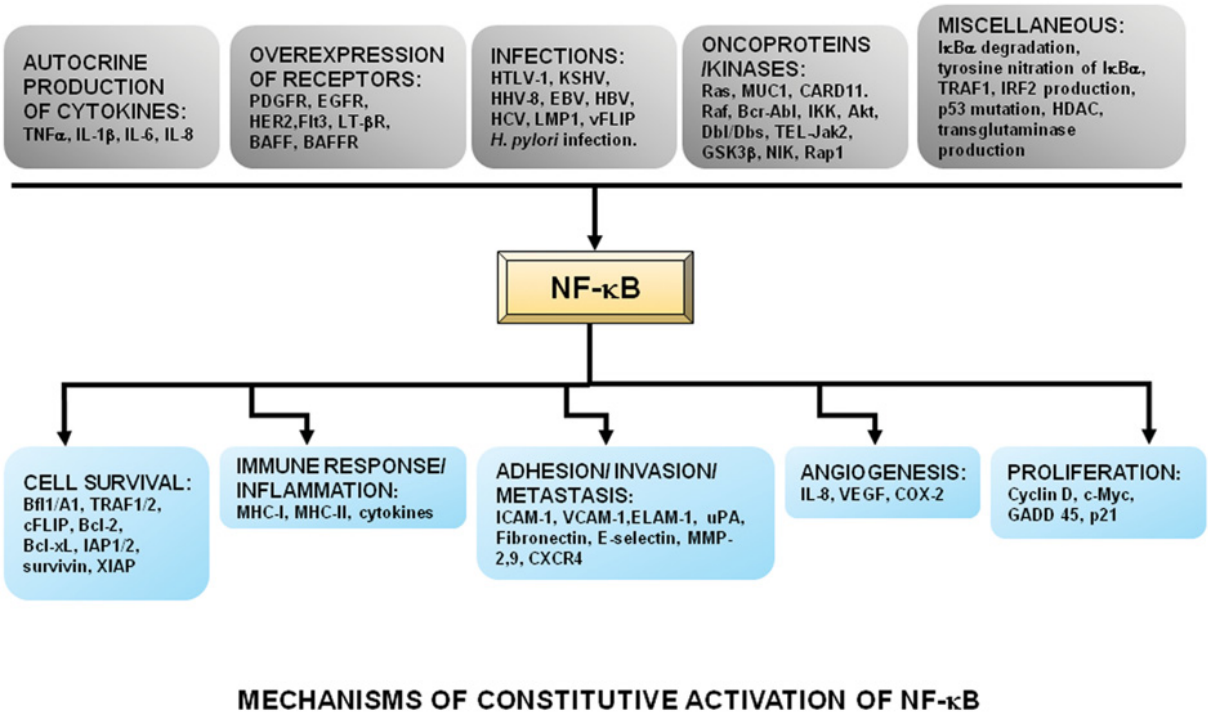

Figure 1 **Mechanisms of constitutive activation of NF-κB**

Abbreviations: BAFF, B-cell activating factor belonging to the TNF family; BAFFR, B-cell activating factor belonging to the TNF family receptor; CARD11, caspase recruitment domain family 11; Dbl/Dbs, transforming protein isolated from diffuse B-cell lymphoma; EBV, Epstein Bar virus; ELAM-1, endothelial cell leucocyte adhesion molecule 1; Flt3, fms-related tyrosine kinase 3; GADD, growth arrest and DNA-damage inducible; GSK3β, glycogen synthase kinase 3β; HBV, hepatitis B virus; HCV, hepatitis C virus; HDAC, histone deacetylase; HER2, erythroblastic leukaemia viral oncogene; HHV-8, human herpes virus 8; HTLV-1, human T-cell leukaemia virus type 1; ICAM-1, intracellular adhesion molecule 1; IRF2, interferon regulatory factor 2; KSHV, Kaposi's sarcoma-associated herpes virus; LMP1, latent membrane protein 1; LT-βR, lymphotoxin β receptor; MUC1, mucin 1; PDGFR, platelet-derived growth factor receptor; TEL-Jak2, telomere maintenance-Janus kinase 2; TRAF, TNF-receptor-associated factor; uPA, urokinase plasminogen activator; VCAM-1, vascular cell adhesion molecule 1; vFLIP, viral FADD-like interleukin-1β-converting enzyme (FLICE)/caspase-8-inhibitory protein; XIAP, X-linked inhibitor of apoptosis.

the NF-κB signalling cascade is a consequence of degradation of IκB proteins, allowing nuclear accumulation of NF-κB, due to DNA binding [116–119]. NF-κB is activated by many divergent stimuli, including pro-inflammatory cytokines (e.g. TNFα, IL-1), T- and B-cell mitogens, bacteria, LPS (lipopolysaccharide), viruses, viral proteins, double-stranded RNA and physical and chemical stresses. Activated NF-κB binds to specific DNA sequences in target genes, designated as κB elements, and regulates transcription of over 400 genes involved in inflammation, immunoregulation, tumour cell proliferation, invasion, metastasis, angiogenesis, chemoresistance and radioresistance [120–124].

Numerous studies have indicated that tumour cells exhibit constitutive production of the pro-inflammatory cytokines TNFα, IL-1α, IL-6, GM-CSF (granulocyte/macrophage colony-stimulating factor) and KC (keratinocyte chemoattractant) [2,125]. Production of tumour-promoting cytokines by immune/inflammatory cells that activate NF-κB, along with other transcription factors such as AP-1 and STAT3 in premalignant cells to induce genes that stimulate cell proliferation and survival, is a major tumour-promoting mechanism [2,125]. For instance, inhibition of TNFα production by non-parenchymal cells (Kupffer and endothelial cells) prevented NF-κB activation in hepatocytes and in early tumours and reduced tumour multiplicity [27]. Greten et al. [126] reported that deleting IKKβ (IκB kinase β) in myeloid cells caused suppression of NF-κB, activation and diminished expression of inflammatory cytokines, thus leading to a significant decrease in tumour size. The host environment promotes the constitutive activation of NF-κB and pro-inflammatory cytokine expression during metastatic tumour progression of various cancers [113,127,128].

What causes the constitutive activation of NF-κB in various tumour cells is not fully understood. Many different mechanism(s) have been described, including overexpression of growth factor receptors, mutation of IκBα such that it cannot bind to NF-κB, constitutive activation of Ras protein, high proteolytic activity directed to IκBα, and autocrine secretion of inflammatory cytokines (Figure 1). It has also been shown that IκB proteins do not bind and export NF-κB that is phosphorylated at p65. Indeed phosphatases of p65 such as WIP1 (wild-type p53-induced phosphatase) have recently been identified with removed phosphates

from p65 and make NF-κB more submissive to IκB-mediated nuclear export [129]. Constitutive activation of NF-κB also has been linked to chemoresistance and radioresistance in various tumour cell lines and in animal models [113,124]. It is also well known that it blocks the function of p53 tumour suppressor by causing its degradation [130–132]. Activation of IKKs in response to inflammatory stimuli has also been shown to deregulate cell cycle [133]. Thus the activation of NF-κB represents the central event in linking the process of chronic inflammation to different aspects of tumorigenesis. Indeed agents that simultaneously target the p53 and NF-κB pathway should be developed further in the treatment of cancers [134–136].

An association between the development of cancer and inflammation is further strengthened by studies of the role of NF-κB in tumour-infiltrating leucocytes [137]. For example, myeloid-lineage-specific inactivation of the gene encoding IKKβ was found to inhibit cancer-related inflammation in the intestine, as well as colitis-associated cancer, providing evidence that inflammatory cells are involved in carcinogenesis [126]. Defective NF-κB has also been reported in T-lymphocytes of patients with RCC [138]. In established advanced tumours, which typically have an inflammatory milieu [139], TAMs (tumour-associated macrophages) have delayed and defective NF-κB activation [140]. Inhibition of NF-κB activation in TAMs has also been reported to correlate with impaired expression of NF-κB-dependent inflammatory functions [141] and to exhibit the alternatively activated, 'M2', phenotype [137]. Evidence suggests that homodimers of the p50 subunit of NF-κB (a negative regulator of the NF-κB pathway) are responsible for this slow activation of NF-κB in TAMs and for the pro-tumour phenotype of these cells [142]. Thus, NF-κB seems to function as a 'rheostat' whose function can be tuned to different levels, predisposing individuals towards developing cancer, and enables TAMs to maintain the inflammatory milieu [137]. Although several experimental and clinical results clearly indicate inflammation having a pro-tumour consequence, some reports also demonstrate the inverse. For example, a marked chronic inflammatory response is not associated with an increased risk of developing melanoma [143]. Also, in certain tumours, the presence of inflammatory cells is associated with better prognosis [144]. These observations appear to reveal that inflammatory cells can destroy tumour cells, in addition to normal tissue cells. Taken together, evidence indicates that NF-κB is an important determinant of the balance between the pro-tumour and anti-tumour properties of macrophages [142,145] and thus NF-κB could be targeted to 're-educate' tumour-promoting macrophages towards an anti-tumour role [145].

ROLE OF STAT3 IN INFLAMMATION AND CANCER

STAT3 was originally identified as a DNA-binding protein that responds to stimulation by EGF and IL-6 and has an important role in their signalling [146,147]. On activation, STAT3 undergoes phosphorylation-induced homodimerization, leading to nuclear translocation, DNA binding and subsequent gene transcription [148]. The phosphorylation is mediated through the activation of non-receptor protein tyrosine kinases called JAKs. JAK1, JAK2, JAK3 and TYK2 have been implicated in the activation of STAT3 [147,149]. Constitutive activation of STAT3 has been observed in many kinds of solid tumours and haematological malignancies [4,150] and this persistently active STAT3 is thought to contribute to oncogenesis by modulating the expression of a variety of genes involved in cell proliferation, invasion, metastasis and angiogenesis [151,152].

Chronic inflammatory conditions that drive carcinogenesis can also be attributed to genetic alterations that directly affect the STAT3 pathway [149]. The importance of constitutively active mutations in GP130, which encodes a subunit of the IL-6 receptor, has been demonstrated in human inflammatory HCC (haemofiltrate CC chemokine) [153]. A critical role for STAT3 in inflammation-induced adenocarcinomas was also demonstrated using a transgenic mouse model with a constitutively active GP130 in epithelial cells [154]. Studies in mice with GP130 mutations demonstrated that an increase in GP130 and STAT3 signalling led to inflammation-associated gastric tumorigenesis [155]. Several infectious agents also exert their tumorigenic effects through STAT3 activation and depend on STAT3 for their oncogenic potential [149]. For instance, infection with *Helicobacter pylori*, which is associated with gastric cancer, activates STAT3 through its cytotoxin-associated gene A in host cells [156]. In addition, a critical role of STAT3 activation in mediating UV-light-induced skin cancer in a transgenic mouse model and cigarette-smoke-associated cancer development has also been demonstrated [157,158].

STAT3 can also act in close liaison with NF-κB to mediate various steps involved in initiation, promotion and development of cancer [159]. Moreover, NF-κB and STAT3 control both distinct and overlapping groups of genes involved during tumorigenesis [149]. Global profiling of STAT3-dependent genes in mouse lung cells revealed a large number of genes whose expression is controlled by STAT3, among which a number of typical NF-κB target genes are also present [160]. Furthermore, in a recent study, it was demonstrated that obesity-promoted hepatocellular carcinoma development was dependent on enhanced production of the tumour-promoting cytokines IL-6 and TNFα, which cause hepatic inflammation and activation of the STAT3 [161]. Thus STAT3 activation pathway also is an important contributor to inflammation-induced cancers, making it an attractive target for treating and/or preventing inflammation.

ROLE OF AP-1 IN INFLAMMATION AND CANCER

The transcription factor AP-1 produced by 18 different dimeric combinations of proteins from the Jun (c-Jun, JunB and JunD) and Fos (c-Fos, FosB, Fra-1 and Fra-2) families, plays a critical role

in variety of cellular processes, including inflammation, proliferation, differentiation and apoptosis [162–164]. When activated, AP-1 recognizes and binds to the TRE (TPA response element) or cAMP response element within the promoter region of target genes [165]. Activation usually occurs both transcriptionally and post-translationally in response to a broad range of external stimuli, including growth factors, pro-inflammatory cytokines, chemokines, ECM and is mediated predominantly through the MAPK (mitogen-activated protein kinase) [ERK (extracellular-signal-regulated kinase), JNK (c-Jun N-terminal kinase) and p38 MAPK] cascade [166,167]. In addition to being activated by oncogenic signal transduction cascades, AP-1 is itself strongly oncogenic [168]. Endogenous c-*fos* and c-*jun* are also oncogenes as indicated by their potential to morphologically transform murine fibroblasts, causing density- and anchorage-independent growth in these cells [169,170]. Moreover, inhibition of Fos and Jun expression in murine fibroblasts and erythroleukaemia cells has indicated that AP-1 is required for cell proliferation and cell-cycle progression [164].

AP-1 is also overexpressed in a large number of tumours and transformed cell lines and targeted inhibition of its activity in these model systems suggest a pivotal role for AP-1 in oncogenic transformation and progression [163,164]. Dominant-negative constructs of c-*fos* and c-*jun* can reverse the transformed phenotype induced by activated Ras and also inhibit the invasiveness and tumorigenesis of keratinocytes [171]. Several AP-1 target genes are also implicated in the invasive phenotype, including the MMPs MMP-1, MMP-3 and MMP-9 [172], the ECM-associated protein osteonectin/SPARC (secreted protein acidic and rich in cysteine) [173], the PKC (protein kinase C) substrate SSeCKS (Src-suppressed C-kinase substrate) [174] and the angiogenic factor, autotaxin [175]. Interestingly, suppression of c-*jun* activity by using a dominant-negative c-*jun* in basal keratinocytes or conditional inactivation of c-*jun* in the liver resulted in the inhibition of the development of chemically induced papillomas and liver tumours respectively [176,177]. Moreover, using mice overexpressing c-*fos*, Wang et al. [178] showed an intimate relationship between c-*fos* expression levels and chondrogenic tumour development. Furthermore, AP-1 has also been found to interact with pro-inflammatory transcription factor NF-κB, and the dominant-negative Jun has been reported to inhibit both AP-1 and NF-κB activity in HPV-immortalized human keratinocytes [179]. Thus AP-1 acts as a master regulator of gene expression in response to oncogenic signal transduction cascades in a wide variety of tumour cell and animal models and can be considered as an important target for novel anti-cancer therapies.

ROLE OF HIF-1α IN INFLAMMATION AND CANCER

HIF-1 is a heterodimeric transcriptional complex composed of an α-subunit and a β-subunit [180,181]. 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 [182]. Recent studies have shown that a number of peptidic and non-peptidic mediators of inflammation can activate HIF-1α even under normoxic conditions [183]. These include cytokines, hormones such as insulin or IGF-1 (insulin-like growth factor 1) and IGF-2, and vasoactive peptides, such as angiotensin II [183]. Among various cytokines, TNFα and IL-1β were first shown to increase HIF-1α activity in the human hepatoma cell line HepG2 [184]. HIF-1α stimulates the expression of several genes encoding the proteins that promote inflammatory reactions. These include erythropoietin, VEGF and VEGF receptor, iNOS (inducible nitric oxide synthase), COX-2, glucose transporters and a number of glycolytic enzymes [185,186]. Moreover, the accumulation of HIF-1α in the absence of apparent hypoxic stimulation has been demonstrated in a number of different cancers, in contrast with benign tumours and normal tissues. For example, immunohistochemical analyses of tissue sections have shown HIF-1α to be highly expressed in many tumour types including pancreatic, head and neck, breast, renal, ovarian, bladder, brain, colorectal and prostate [185]. HIF-1α overexpression has also been found to correlate with increased angiogenesis and metastasis and thus can be used as a marker to predict outcome in patients with metastatic cancers [181]. Thus, targeting the HIF-1α pathway provides an attractive strategy to treat various hypoxic and metastatic tumours.

CONCLUSION AND PERSPECTIVES

There is growing evidence, as described above, which is highly suggestive that chronic inflammation is a critical mediator of various aspects of development of cancer. It is becoming imminently clear that chronic inflammation contributes to carcinogenesis at all three stages: initiation, proliferation and progression. Some of the agents that have the potential to suppress these pro-inflammatory mediators and are being tested include TNFα blockers (such as thalidomide, enbrel, humira and remicade), IL-1 blockers (canakinumab and anakinra), NF-κB inhibitors (such as curcumin, resveratrol and roscovitine) and COX-2 inhibitors (such as celecoxib). However, while most evidence discussed above indicates that pro-inflammatory cytokines, enzymes, oncogenes and transcription factors play a pivotal role in mediating tumorigenesis, the existing literature also suggests that inhibition of pro-inflammatory pathways is not always beneficial. For example, in a skin cancer mouse model, the pro-inflammatory transcription factor NF-κB has been reported to inhibit tumour formation [187]. Furthermore, in Mdr2-knockout mice, bile duct tumours are rarely found, despite extensive inflammation, NF-κB activation and abundant proliferation of bile ducts in portal spaces [27]. Another recent report indicates that inhibition of NF-κB activation can accelerate hepatocellular carcinoma development and enhance proliferation of tumour-initiating cells [188]. And finally, administration of TNFα blockers to patients

with rheumatoid arthritis have been found to increase the risk for developing lymphomas [189], thereby suggesting that inhibition of pro-inflammatory pathways can act as a double-edge sword.

Therefore novel strategies such as identification of specific adaptors of IKK complex like ELKS [190] and Rap1 [191] will allow development of better inhibitors of IKK and hence NF-κB which are less likely to have adverse side effects. Moreover, genetic studies in patients with hyper-IgE syndrome identified dominant-negative STAT3 gene mutations as the probable cause of the disease in few patients [192]. Thus a detailed elucidation of the underlying mechanism(s) will help us to better understand the interaction between tumour cells and their inflammatory microenvironment, and consequently how to interfere and block such pro-tumour biomarkers with minimum toxic effects. Targeted therapies that can interfere with the recruitment of bone-marrow-derived cells or specifically directed at specific components of the tumour microenvironment can also be utilized in the future as treatment regimens for inflammation-driven cancers.

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