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Molecular mechanisms underlying chronic inflammation-associated cancers

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Abstract

Although it is now accepted that chronic inflammation plays an essential role in tumorigenesis, the underlying molecular mechanisms linking inflammation and cancer remain to be fully explored. Inflammatory mediators present in the tumor microenvironment, including cytokines and growth factors, as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS), have been implicated in the etiology of inflammation-associated cancers. Epithelial NADPH oxidase (Nox) family proteins, which generate ROS regulated by cytokines, are upregulated during chronic inflammation and cancer. ROS serve as effector molecules participating in host defense or as chemo-attractants recruiting leukocytes to wounds, thereby influencing the inflammatory reaction in damaged tissues. ROS can alter chromosomal DNA, leading to genomic instability, and may serve as signaling molecules that affect tumor cell proliferation, survival, metabolism, angiogenesis, and metastasis. Targeting Noxs and their downstream signaling components may be a promising approach to pre-empting inflammation-related malignancies.

Keywords

NADPH oxidase; Inflammation; Reactive oxygen; Cancer

1. Introduction

As early as 1863, Rudolf Virchow noted leukocyte infiltrates in tumor tissue, suggesting that cancer may arise from chronic inflammation [1]. Epidemiological data indicate that over 25% of all cancers are related to chronic infection and other types of unresolved inflammation [2,3]. Mounting evidence supports the hypothesis that chronic inflammation is an important risk factor for the development of cancer. Table 1 illustrates some examples of infection- and inflammation-associated cancers.

Inflammation is a normal host response to tissue damage inflicted by infections or other stimuli. Whereas most pathogens provoke an acute inflammatory response that results in complete clearance of the irritants in a suitable host, inadequate resolution of inflammation and an unchecked inflammatory reaction can evoke chronic inflammation, predisposing the host to various diseases, including cancer. Inflammation contributes to tumor initiation by

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7. Conflict of Interest

None.

inducing DNA damage and chromosomal instability. It promotes tumor development by enhancing tumor cell proliferation and resistance to apoptosis. Inflammation also stimulates angiogenesis and tissue remodeling, both of which contribute to tumor cell invasion and metastasis [4–6]. All of these altered biochemical processes are effected by chemical mediators of inflammation present in the tumor microenvironment. Tumors are heterogeneous, complex structural entities in which cancer cells are embedded in an extracellular matrix and vascular network, surrounded by a wide variety of innate and adaptive immune cells, and stromal cells [4,5]. This diverse cell network communicates by means of direct contact or cytokine and chemokine production, and acts in both autocrine and paracrine fashions to govern tumor growth and progression [3,4].

During chronic inflammation, a wide array of intracellular signaling pathways, comprising cell surface receptors, kinases, and transcription factors, are often dysregulated, leading to abnormal expression of pro-inflammatory genes involved in malignant transformation. Inflammation activates a variety of protein kinases, including members of the Janus-activated kinase (JAK), phosphatidylinositol-3-kinase (PI3K/AKT), and mitogen-activated protein kinase (MAPK) families to alter cellular proliferation. Inflammation-induced aberrant activation of certain transcription factors, such as signal transducer and activator of transcription (STAT) family members, nuclear factor kappa B (NF- κ B), activation protein-1 (AP-1), and hypoxia inducible factor-1 α (HIF-1 α), has also been implicated in tumor growth, angiogenesis, and metastasis [3–5]. This manuscript discusses the link between inflammation and carcinogenesis focusing on mediators involved in oxidative stress.

2. Role of redox-regulated transcription factors in inflammation-associated carcinogenesis

The expression of pro-inflammatory mediators is transcriptionally regulated by a variety of redox-sensitive transcription factors (TFs), including NF- κ B, AP-1, STAT1/STAT3, HIFs, and Nrf2. The following section briefly reviews the involvement of these TFs in linking inflammation with cancer.

2.1. NF- κ B

NF- κ B is a heterodimeric protein mainly composed of p65 and p50 subunits. It is a ubiquitous redox-regulated TF that is retained in the cytoplasm by forming an inactive complex with its cytosolic repressor I κ B [7,8]. Oxidative and pro-inflammatory stimuli activate NF- κ B through phosphorylation-dependent proteasomal degradation of I κ B α , thereby facilitating nuclear accumulation of NF- κ B. Upon nuclear localization, NF- κ B binds to the κ B elements located in the proximal promoter region of genes encoding pro-inflammatory mediators, such as cytokines [9], INOS [10], and COX-2 [11], that are involved in inflammation-associated carcinogenesis. The NF- κ B signaling pathway can be activated by pro-inflammatory stimuli (IL-1, TNF- α), viruses, genotoxic stress, the toll-like receptor (TLR)-MyD88 complex, oncogenes in tumor cells, growth factors, and hypoxia and acidic conditions in solid tumors [3,12,13]. NF- κ B is constitutively active in most tumors and in chronic inflammatory conditions such as inflammatory bowel disease (IBD) and gastritis [14,15]. NF- κ B-targeted gene products include: anti-apoptotic proteins (BCL-2, BCL-X_L), inflammatory mediators (TNF- α , IL-6, IL-8, COX-2), effectors of invasion and metastasis (adhesion molecules, matrix metalloproteinases [MMPs]), promoters of DNA damage (reactive oxygen species [ROS], reactive nitrogen species [RNS]), inducers of cell proliferation (c-MYC, cyclin D1), and angiogenic factors (VEGF, angiopoietin) [3,4]. In a colitis-associated cancer model and *Mdr2*-knockout mice, NF- κ B has been shown to play a pivotal role linking inflammation to cancer as well as to cholestatic hepatitis and

hepatocellular carcinoma [16,17]. The activation of NF- κ B has also been shown to be a critical event in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma that is associated with chronic inflammation by *Helicobacter pylori* [18]. NF- κ B-regulated genes play a major role in modulating the level of intracellular ROS; in monocyte and microglial cells NF- κ B mediates LPS/IFN- α -induced NADPH oxidase 2 (Nox2) expression [19]. LPS also induces Nox1 expression in mouse macrophages and guinea pig gastric mucosal cells in an NF- κ B-dependent manner [20]. Our laboratory found that NF- κ B is involved in LPS/IFN- α -induced Dual oxidase (Duox)/DuoxA2 expression in human pancreatic cancer cells [21]. NF- κ B also regulates many detoxifying enzymes, such as MnSOD [22], catalase [23], and thioredoxin-1 and thioredoxin-2 [24]. Conversely, ROS can affect the activity of NF- κ B in many ways. For example, ROS have been shown to activate NF- κ B through alternative I κ B α phosphorylation or by direct oxidation of NF- κ B, inhibiting DNA binding [23].

2.2. Stat3

STAT3 is a redox-sensitive TF that serves as a molecular switch between inflammation and cancer [25,26]. STAT3 can be activated by phosphorylation of Tyr705 in response to various stimuli, followed by the formation of a STAT3 dimer that translocates to the nucleus and binds to the promoter regions of genes encoding inflammatory and cell cycle regulatory proteins [27,28]. STAT3 supports oncogenesis through mechanisms ranging from activation of genes crucial for proliferation and survival to enhancement of angiogenesis and metastasis [29]. Many cytokines and growth factors activate STAT3, including the IL-6 family, EGF family members, VEGF, IL-23, IL-21, PDGF as well as oncogenic proteins, such as Src and Ras. Activated nuclear STAT3 has been detected in many forms of malignancy, including breast, colon, gastric, lung, head and neck, skin, and prostate cancer [26,29]. Myeloid cell-derived IL-6 can enhance the proliferation of tumor-initiating cells and can protect normal and premalignant intestinal epithelial cells from apoptosis in STAT3-dependent manner, promoting colitis-associated cancer progression [30]. Obesity can increase IL-6 and TNF- α production, which causes hepatic inflammation and activates STAT3 to promote hepatocellular carcinoma [31]. STAT3 is redox-sensitive, and ROS scavengers and inhibitors of Nox generally inhibit STAT3 activity. Oxidation of a conserved cysteine in the DNA-binding domain as well as C-terminal transactivation domains of STAT3 by H₂O₂ blocks binding to consensus serum-inducible elements [32,33].

2.3. HIFs

Hypoxia inducible factors are members of the bHLH-PAS family of proteins that bind to canonical DNA sequences (hypoxia responsive elements, or HREs) in the promoter or enhancer of target genes [34]. They consist of an O₂-labile α subunit and a constitutively-expressed β subunit. Hydroxylation of two conserved proline residues within the O₂-dependent degradation domain of the α subunit catalyzed by proline hydroxylases (PHDs) under normal conditions mediates HIF-1 α degradation via the 26S proteasome [35]. When stabilized under hypoxia, HIF-1 α translocates to the nucleus, dimerizes with HIF-1 β , recruits co-activators CBP/p300, and binds to the HREs, driving gene transcription involved in adaptation to hypoxic stress [36]. At least 150 genes encoding proteins that regulate metabolism, survival, motility, angiogenesis, hematopoiesis, and other functions have been identified as being HIF-regulated [37,38]. Elevated expression of HIF-1 α was detected in the colonic epithelium of patients with IBD as well as colorectal tumors [39]. Overexpression of HIF-1 α (59.2%) is frequently detected in human pancreatic carcinoma, whereas it is almost absent in normal pancreatic tissue. Moreover, HIF-1 α expression is significantly associated with tumor size and microvessel density [40]. HIF-1 α is regulated by various inflammatory mediators (TNF- α , IL-1 α , TGF- α) and growth factors (EGF) in addition to oxygen [41–44]. Nox-derived ROS have been shown to regulate HIF-1 α stability

through inhibition of PHD activity by oxidation of Fe^{2+} to Fe^{3+} , decreasing the availability of Fe^{2+} , the cofactor for PHDs [45]. ROS can also activate ERK, p38, and PI3K/AKT pathways increasing HIF-1 α synthesis under both normoxic or hypoxic conditions [46]. HIF-1 α also modulates macrophage inflammatory responses by regulating important inflammatory cytokines, including CXCR4, VEGF, and IL-8 [37].

3. Role of ROS and NADPH oxidases in inflammation, tumor initiation, promotion, and progression

ROS, including superoxide ($\text{O}_2^{\bullet-}$), H_2O_2 , and the hydroxyl radical, are produced by the partial reduction of oxygen. Under physiological conditions, formation of ROS is counterbalanced by endogenous antioxidant defense systems including superoxide dismutase, glutathione peroxidase, catalase, peroxiredoxins, and thioredoxin. When ROS production exceeds cellular antioxidant capacity, oxidative stress can damage DNA, proteins, and lipids [47–49]. The phagocyte NADPH oxidase, Nox2, was the first identified enzyme that generates ROS as its primary function [50]. NADPH oxidase (Nox)/dual oxidase (Duox) membrane proteins catalyze the purposeful generation of ROS in non-phagocytic cells, including vascular endothelium and tumor cells [51]. The Nox family, comprised of seven enzymatic isoforms, produces ROS by the NADPH-dependent, one-electron reduction of oxygen to superoxide. Isoform-specific conversion of superoxide to hydrogen peroxide is unique to Nox4 and the Duoxs. Structurally, each Nox/Duox protein associates with the plasma membrane through 6 transmembrane (TM) helices and allows for NADPH oxidation through a C-terminal FAD/NADPH oxidase domain (Fig. 1). The Nox5 isoform varies from its Nox counterparts by an amino-terminal EF-calcium binding region. A Duox-specific extracellular peroxidase-like domain and two cytosolic calcium binding sites define the structural characteristics unique to the two Duox family members [52–55].

3.1. Noxs and inflammation

Oxidative stress plays a critical role in modulating the immune response to inflammatory stimuli. Recent evidence suggests that the source of at least some of the ROS that accompany acute and chronic inflammation in many organs is one or more members of the Nox family [56,57]. Nox2 has been identified as a primary component of the microbicidal oxidase system of phagocytes; its deficiency is associated with chronic granulomatous disease [50]. Nox1 is expressed in both normal and malignant colonic tissue [58]. Nox1-induced $\text{O}_2^{\bullet-}$ at the luminal surface of the colon has been suggested to enhance host defense [59]. Duox2 is found in bronchial epithelium and throughout the gastrointestinal tract [60,61]. In airway mucosal cells, Duox2 plays an important role in the generation of H_2O_2 for host defense against a variety of pathogens [62,63]. Duox2-induced ROS are indispensable for gut antimicrobial activities in *Drosophila* [64]. An epithelial cell Duox2-derived H_2O_2 gradient at the site of wounds mediates leukocyte recruitment [65]. Duox2 expression is significantly increased in patients with IBD compared to healthy control subjects [66]. Many pro-inflammatory mediators, such as cytokines and growth factors, can induce the expression or regulate the activity of Nox isoforms [67–70], as outlined in Table 2. Inflammatory response-related TFs, such as STAT1, IRF1, GATA-1 (for Nox2) [71,72], GATA-6 (for Nox1) [73,74], NF- κ B (for Nox1, Nox2, and Duox2) [21,67,75], are involved in regulating Nox family member expression. Hypoxia, common both in inflammation and solid tumors, can also induce Nox expression. The human Nox4 and Nox2 promoters have putative HREs to which HIFs bind under hypoxic conditions. Both Nox4 and Nox2 mRNAs are enhanced *in vitro* and *in vivo* in response to HIF stabilization [76–78]. We also found that Nox1 expression across a panel of 60 human tumor cell lines correlates significantly with certain inflammatory and immune response pathways, suggesting that Nox1-mediated ROS production is involved in inflammation [79]. Hepatitis C virus induces Nox1 and Nox4

expression in hepatocytes *in vitro* and in the human liver. These Nox proteins have been implicated as persistent, endogenous ROS generators that might contribute to hepatitis C virus-related pathologies [80].

3.2. Nox-mediated oxidative DNA damage in inflammation and tumorigenesis

Recent studies implicate Nox-mediated ROS as a modulator of the inflammatory response and DNA damage in the context of tumorigenesis. A direct link between enhanced ROS production by Nox homologues leading to oxidative DNA damage and genetic instability was demonstrated when overexpression of the human Nox1 complex increased steady-state levels of DNA 8-oxo-7,8-dihydroguanine and caused a threefold increase in the HPRT mutation rate in HeLa cells [81]. Nox-mediated tumorigenesis was observed when rats administered testosterone and 17 β -estradiol developed dysplasia and stromal inflammation of the lateral lobe of the prostate [82]. The inflammatory stroma showed an increased expression of Nox1, 2, and 4, and an accumulation of 8-hydroxy-2'-deoxyguanosine, and 4-hydroxy-2-nonenal (HNE)-modified protein adducts [82]. These oxidative by-products are indicative of hormone-induced, oxidative stress-related inflammation and DNA damage potentially underlying the dysplastic transformation of prostate epithelial cells. Our laboratory found that both IFN- γ and LPS can synergistically induce Duox2/DuoxA2 expression in human pancreatic cancer cell lines, which leads to increased ROS production, and DNA damage [21]. In patients with chronic pancreatitis and pancreatic cancer, Duox2 expression is significantly increased, suggesting that Duox2-mediated ROS may play an important role both for host defense and in the development of cancer [83]. Nox1- and Nox4-mediated, ROS-induced genomic instability has been reported for Ras oncogene-related DNA damage and senescence [84–86]. Up-regulation of Nox expression at sites of inflammation and DNA damage and recent reports of DNA damage activating the Nox1-Rac1 pathway [87], strongly suggest that Nox-mediated oxidative stress may be involved in nuclear signaling, DNA damage, and subsequently, the fate of the cell [88]. The detection of a functional and nuclear-localized splice variant of Nox4 (Nox4D) whose overexpression induced DNA damage further supports this concept. By modulating genomic integrity, Nox-dependent ROS formation increases the likelihood of developing tumor-initiating cells with the potential to give rise to pre-neoplastic lesions, and eventually to neoplasia.

3.3. Nox-derived ROS in tumor promotion

Tumor cells produce significant amounts of ROS [51], derived in part from Nox isoforms. Although high concentrations of ROS are toxic, optimal ROS levels promote cell proliferation [89,90]. Nox-derived ROS increase growth factor-mediated tyrosine autophosphorylation by inactivating protein tyrosine phosphatases (PTPs), leading to hyperphosphorylation and activation of receptor tyrosine kinases (RTKs) and other downstream kinases. The cysteine residues within the catalytic domain of PTPs are highly susceptible to H₂O₂-induced oxidation and inactivation [91–93]. In HepG2 and A431 human cancer cells, high levels of intrinsic ROS can inactivate PTP1B and regulate cell proliferation, contributing to the transformed phenotype [94]. Nox1 is highly expressed in colon cancer; stable knockdown of Nox1 expression in HT-29 human colon cancer cells results in decreased ROS levels, and a corresponding increase in phosphatase activity, which in turn inhibits MAPK signaling. Decreased MAPK activity is associated with significant inhibition of cyclin D1 and a G1/S block in the cell cycle. Decreased Nox1 expression also contributes to a significantly diminished growth rate and blood vessel density in HT-29 xenografts [152]. We found that diphenylene iodonium (DPI) also decreases ROS production and inhibits the growth of Caco2 and HT-29 cells at concentrations of 10–250 nM. The decreased tumor cell proliferation was caused by a profound block in cell cycle progression at the G1/S interface, accompanying p27 up-regulation and decreases in cyclin D1, A, and E expression. DPI also significantly decreased the growth of both HT-29 and LS-174T human

tumor xenografts [95]. Nox1 has additionally been reported to mediate cell survival through NAD-dependent histone deacetylase sirtuin 1 activation, which inactivates p53, ultimately impairing p53-mediated transcriptional induction of pro-apoptotic proteins, such as Bax [96,97]. Further, activation of the Wnt- β -catenin signaling pathway by Nox1-derived ROS promotes cell proliferation by oxidizing and inactivating nucleoredoxin (NRX), a redox-sensitive, regulatory protein modulating Wnt- β -catenin signaling [98].

3.4. Role of Nox-derived ROS in angiogenesis

Angiogenesis is necessary for solid tumor growth past a diameter of ~1–2 mm. Compartmentalized, Nox-derived ROS appear to coordinate the angiogenic switch by increasing VEGF production by tumor cells. These processes are initiated when a tumor experiences hypoxia [48]. However, under normoxic conditions, both Nox4 and mitochondrial-derived ROS are involved in enhancing HIF-1 α and VEGF expression in ovarian cancer cells [99]. In Ras-transformed colon cancer cells, Nox1-derived ROS increase ERK-dependent phosphorylation of the transcription factor SP1, which is responsible for the up-regulation of VEGF mRNA and neo-vascularization in nude mice [100]. Our laboratory has found that Nox1-derived ROS are essential for angiogenesis *in vivo*; stable knockdown of Nox1 expression in HT-29 colon cancer cells significantly decreases VEGF expression and blood vessel density in HT-29 xenografts [152].

3.5. A role for Noxs in tumor cell invasion and metastasis

Metastasis is a crucial aspect of tumorigenesis; 90% of cancer mortality is caused by metastasis [4]. It is a multistep process that requires intracellular changes such as epithelial to mesenchymal transition (EMT), extracellular matrix degradation, reduced cell adhesion, and increased migration [48]. Noxs can influence tumor cell migration and invasion in response to stimulation by soluble mediators present in the tumor microenvironment. TGF- β induces Nox4 expression and ROS generation in human breast epithelial cells; Nox4 derived ROS may be critical for the progression of the EMT in the breast epithelium [101]. Protein localization studies showed that Nox1 and Nox4 often co-localize with Src and the Src family of kinases in invasive microdomains, such as invadopodia and focal adhesions, where they form an active redox signaling platform to coordinate cell adhesion, migration, and invasion [102–106]. LPS induces ROS production in colon cancer cells via NF- κ B dependent up-regulation of Nox1 and Nox2 protein expression. The LPS-Nox1 redox signaling axis also plays a crucial role in facilitation of colon cancer cell adhesion and metastasis [107].

4. Involvement of epithelial and stromal cells in oxidative stress-driven tumor progression

Many solid tumors exist in an oxidative milieu, resulting from an increased basal metabolic activity of the tumor cells, mitochondrial dysfunction due to a hypoxic tumor microenvironment, uncontrolled oncogene-dependent growth factor and/or cytokine signaling, as well as enhanced ROS generation as a consequence of upregulated expression of Noxs, COXs, and lipoxygenases (LOXs) [108]. Decreased expression of certain antioxidant enzymes (catalase, glutathione peroxidase, and/or superoxide dismutase) in cancer cells also may contribute to oxidative stress [109]. Oxidative stress can influence both cancer and stromal cells. For tumor cells, ROS can: (1) result in DNA damage and genomic instability that promotes tumor initiation and progression, (2) modulate intracellular signaling pathways controlling cell proliferation and survival, (3) influence cell motility, invasiveness, angiogenesis, and metastasis, and (4) mediate tumor cell resistance to many anticancer drugs [4,108].

Besides acting directly on tumor cells, ROS have also been shown to have profound effects on stromal cells in the tumor microenvironment, particularly on cancer-associated fibroblasts (CAFs). CAFs originate either from resident tissue fibroblasts which infiltrate growing tumors, or from bone marrow mesenchymal stem cells. These fibroblasts need to be activated through a process called mesenchymal–mesenchymal transition (MMT), converting them into myofibroblasts or CAFs, contractile cells able to affect tumor progression through the secretion of cytokines and the deposition of extracellular matrix [108].

Pro-inflammatory cells of the tumor microenvironment play important roles in the development of several different tumor histologies. Sustained activation of pancreatic stellate cells (PaSCs) is responsible for the fibrotic process associated with both chronic pancreatitis and pancreatic cancer [110]. Both exogenous ROS released by damaged pancreatic acinar cells or leukocytes recruited in response to pancreatic injury, and endogenous ROS derived from PaSCs and Nox activity in pancreatic duct cells have been implicated in the regulation of PaSC proliferation, chemokine production, and expression of α -smooth muscle actin (α -SMA) and collagen [110,111]. In a tumor-stroma model of skin carcinogenesis, TGF- α 1 initiates ROS-dependent, myofibroblast transdifferentiation. ROS modulate protein kinase C activity and the secretion of HGF, IL-6, and VEGF, ultimately enhancing the invasive capacity of the skin tumor [112].

Mutations in the *BRCA1* (breast cancer type 1 susceptibility) gene strongly predispose toward the development of breast and ovarian cancers. Inactivation of *BRCA1* induces high levels of oxidative stress. *BRCA1*-deficient epithelial cancer cells produce large amounts of H_2O_2 , which induces oxidative stress and glycolysis in CAFs. These CAFs then provide lactate to epithelial cancer cells for oxidative mitochondrial metabolism. Importantly, this metabolic symbiosis phenotype is reversed by genetic replacement of the wild type *BRCA1* gene in epithelial cancer cells, or by the administration of the antioxidant n-acetyl cysteine (NAC) [113]. In another oxidative stress-based model of tumor-stromal co-evolution, breast cancer cells induce a loss of caveolin-1 in adjacent fibroblasts, which triggers nitric oxide production, mitochondrial dysfunction, and oxidative stress in fibroblasts. Oxidative stress in fibroblasts then promotes further DNA damage and genetic instability in cancer cells, by way of a bystander effect. Thus, oxidative interactions between breast cancer cells and fibroblasts lead to a more aggressive phenotype (mutagenic evolution) [114].

5. Strategies to overcome chronic inflammation-associated cancer

The prevalence of cancer related to chronic infection has been estimated to be 1.9 million cases per year, or 17.8% of the global cancer burden [115]. Hence, development of effective therapies to prevent the adverse effects of cancer-causing pathogens, such as the successful vaccines against hepatitis B virus (HBV) and human papilloma virus (HPV), will contribute significantly to decreasing morbidity from hepatocellular and cervical carcinoma, respectively [116]. In like manner, eradication of chronic *H. pylori* infection with antimicrobials is likely to reduce the incidence of gastric cancer [18,116]. For each of these infectious diseases, chronic inflammation plays a role in the pathological basis for tumor development; accordingly, smoldering inflammation has been proposed as the 7th hallmark of cancer.

Recent preclinical studies have suggested that early detection and timely treatment of inflammatory stress might be a useful strategy to interdict the carcinogenic process in patients suffering from chronic inflammation of the prostate or pancreas that is not clearly related to an infectious pathogen [117]. Well known anti-inflammatory drugs, such as aspirin, non-steroidal anti-inflammatory agents (NSAIDs), cyclo-oxygenase-2 (COX-2)

inhibitors (e. g. celecoxib), and glucocorticoids (e.g. dexamethasone) have all been demonstrated to reduce tumor incidence or progression and reduce mortality when employed in a variety of preclinical model systems, as well as in man [4,6,116].

5.1. Tumor-promoting inflammation: therapeutic targets

Chemical mediators of inflammation, including a wide variety of cytokines, are present in the tumor microenvironment. Chemokines, growth factors, COX-2, and prostaglandins are the critical mediators of chronic inflammation-associated cancer. Strategies to specifically inhibit the production and/or function of inflammatory mediators are actively being investigated for their therapeutic activity. For example, lenalidomide, a structural analogue of thalidomide, which suppresses the production of several inflammatory cytokines without exhibiting marked cytotoxic activity against tumor cells *in vitro*, has substantial therapeutic efficacy in patients with advanced multiple myeloma when combined with dexamethasone [118]. Phase I/II trials of antagonists of IL-6, IL-6 receptor, CCL2, CCR4, and CXCR4 for several epithelial and hematopoietic malignancies are ongoing [6]. Clinical trials of TNF- α antagonists in patients with advanced cancer have also demonstrated therapeutic benefit [119,120], as have agents blocking IL1 α and its receptor [121].

Constitutively-activated transcription factors, such as NF- κ B, STAT3, HIF-1 α , and AP-1, induce the expression of genes that stimulate tumor cell proliferation and survival. Among these, STAT3 has emerged as a critical regulator of tumor-associated inflammation, and it is a promising target for inflammation-associated cancer therapy. In addition to the well-known promotion of tumor cell proliferation and survival, angiogenesis, and invasion by STAT3, activated STAT3 can negatively regulate Th1-type immune responses and promote expansion of myeloid-derived suppressor cells (MDSCs) and regulatory T-cell functions in the tumor micro-environment, restraining anti-tumor immune responses. Thus, targeting STAT3 has the potential to not only inhibit tumor growth directly, but also to alter the immunological environment so as to favor control of tumor proliferation. Approaches currently under study to inhibit STAT3 activation include targeted delivery of STAT3 siRNAs into immune cells, the systemic delivery of STAT3 antisense molecules targeting tumor cells, as well as the development of small molecule inhibitors directed against both upstream and downstream mediators of the STAT3 pathway [29,122].

Oxidative stress plays an important role in both chronic inflammation and carcinogenesis. Considerable effort has been directed toward the development of therapeutics for reactive oxygen species (ROS)-related diseases [123]; these efforts have focused on suppressing ROS generation using small molecule antioxidants, as well enzyme mimetics of the antioxidant proteins superoxide dismutase and catalase [124]. The ROS scavenger NAC has been shown to slow tumor progression in a p53-dependent mouse lymphomagenesis model by reducing ROS-mediated genomic instability [125]. HIF-1 α -dependent antitumor effects of NAC and vitamin C in a Myc-dependent mouse tumor model have also been reported [126]. The Nox inhibitors diphenylene iodonium and 2-di-thienyl iodonium have been shown to decrease the growth of both HT-29 and LS-174T human colon cancer xenografts *in vivo* [95]. The Nox4 inhibitor fulvene-5 potently inhibits Nox4 and blocks the growth of endothelial tumors in mice [127]. Thus, there is considerable preclinical evidence that modulation of oxidant stress levels in tumor cells can alter their proliferative potential; verification of these approaches in human malignancies awaits future clinical investigation.

6. Summary

Chronic inflammation creates a microenvironment in which cancer cells, various immune cells, and stromal cells coexist. These diverse cellular species communicate by secreting inflammatory mediators such as cytokines and growth factors. As illustrated in Fig. 2,

cytokines or growth factors can exert their effect on premalignant cells directly, by engaging their cognate receptors, thereby activating downstream kinases and TFs to regulate an array of genes involved in cell proliferation, survival, metabolism, angiogenesis, and metastasis. All of these events lead to enhanced tumor growth. Cytokines and growth factors can also upregulate the expression and enhance the activity of Nox family members in epithelial cells, increasing ROS production in the tumor microenvironment, which damages genomic DNA and may produce mutational hits that can initiate tumor formation in a chronic inflammatory background. ROS additionally can propagate cytokine and growth factor signals via oxidation of redox-sensitive cysteine residues located in the catalytic domains of PTPs, or by directly targeting cysteine residues in transcription factors. Considering the essential role of cytokines, growth factors, and ROS generating Nox enzymes in tumor initiation, promotion, and progression, targeting each of these components may provide a novel strategy to fight both chronic inflammation and cancer.

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Abbreviations

ROS	reactive oxygen species
Nox	NADPH oxidase
Duox	dual oxidase
RNS	reactive nitrogen species
MMP	matrix metalloproteinase
VEGF	vascular endothelial growth factor
COX-2	Cyclooxygenase 2
IBD	inflammatory bowel disease
SOCS1	suppressor of cytokine signaling-1
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
STAT1	signal transducers and activators of transcription
HIF1	hypoxia-inducible factors
Nrf2	nuclear factor erythroid-2 related factor
INOS	Inducible Nitric Oxide Synthase
LPS	lipopolysaccharide
PHD	proline hydroxylase
PTP	protein tyrosine phosphatase
RTK	receptor tyrosine kinase
DPI	diphenylene iodonium
DTI	di-2-thienyliodonium chloride
EMT	epithelial to mesenchymal transition
PMA	phorbol 12-myristate 13-acetate

ILs	interleukins
EGF	epidermal growth factor
PDGF	platelet-derived growth factor
IGF-1	insulin-like growth factor 1
TGF-β	transforming growth factor beta

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Fig. 1. Schematic view of the conserved structural features of the NADPH oxidase proteins. Each isoform contains 6 putative TM domains (white cylindrical loops), with C-terminal FAD (green) and NADPH binding domains (red). The NADPH binding domain structural models were created by the SWISS-MODEL program server with hNOX2 (PDB: 3A1F) as the template, visualized by Pymol software. (A) NOX1-4 are depicted with loop regions labeled based on established designations: extracellular loops A, C, E and intracellular loops B and D. (B) The NOX5 isoform shares the same structural motif as NOX1-4, with a novel N-terminal calcium binding region, composed of 4 EF-hand calcium binding sites (orange squares). (C) DUOX1-2 are unique to the NADPH oxidase family, as both isoforms contain an extracellular N-terminal peroxidase homology domain (orange) and two cytosolic calcium binding sites.

Fig. 2. Role of cytokines, growth factors, and Noxs in tumor initiation, promotion, and progression. Schematic representation showing cytokines and growth factors are secreted by inflammatory cells and stromal cells in the tumor microenvironment during chronic inflammation; they engage their cognate receptors to activate downstream kinases and transcription factors such as NF- κ B, STAT, and HIFs. These TFs can up-regulate the expression, and enhance the activity of Noxs. They can also regulate target genes involved in cell cycle control, apoptosis, metabolism, angiogenesis, and metastasis. On the other hand, Nox-derived ROS can oxidize redox-sensitive cysteine residues in the catalytic domain of PTPs and inactivate their ability to limit the propagation of cytokine-derived signals. ROS can also directly oxidize the cysteine residues in some TFs and regulate their

transcriptional activity. [PTP, protein tyrosine phosphatase; ROS, reactive oxygen species; HIFs, hypoxia-inducible factors; Noxs, NADPH oxidases].

Table 1

Cancers associated with infection and inflammation.

Infection/inflammation	Cancer	Reference
Helicobacter pylori	Gastric cancer	[128]
Inflammatory bowel disease	Colorectal cancer	[129]
Hepatitis B/C virus	Hepatocellular carcinoma	[130]
Prostatitis	Prostate cancer	[131]
Pancreatitis	Pancreatic cancer	[132]
Human papillomavirus	Cervical cancer	[133]
Chronic obstructive pulmonary disease	Lung cancer	[134]
Schistosoma haematobium	Bladder cancer	[116]

Table 2

Cytokines and growth factors involved in Nox expression and regulation of activity.

Nox	Cytokines	Growth factors	References
Nox1	IL-13, TGF- β , IFN- γ , TNF- α	EGF, PDGF, phorbol myristate acetate (PMA)	[135–139]
Nox2	IL-1 β , IFN- γ , TGF- β , TGF- α	EGF, PDGF, PMA	[111,135,140,141]
Nox3			
Nox4	TGF- β , TNF- α , IL-13	EGF, IGF-1, PDGF, PMA	[101,135,136,142,143]
Nox5		PMA	[144]
Duox1	IL-4, IL-13	PMA	[145–148]
Duox2	IL-1 α , IL-4, IL-13, IFN- γ	PMA	[21,149–151]