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Mini-review

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.

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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 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), phosphati-

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 erthroid-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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dylinosito-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-κB), activation protein-1(AP-1), and hypoxia inducible factor-1α (HIF-1α), 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-κB, 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-κB

NF-κB 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 IkB [7,8]. Oxidative and pro-inflammatory stimuli activate NF-κB through phosphorylation-dependent proteasomal degradation of IkBα, thereby facilitating nuclear accumulation of NF-κB. Upon nuclear localization, NF-κB binds to the kB 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-κB 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-κB is constitutively active in most tumors and in chronic inflammatory conditions such as inflammatory bowel disease (IBD) and gastritis [14,15]. NF-κB-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-κB 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-κB 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-κB-regulated genes play a major role in modulating the level of intracellular ROS; in monocyte and microglial cells NF-κB 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-κB-dependent manner [20]. Our laboratory found that NF-κB is involved in LPS/IFN-α-induced Dual oxidase (Duox)/DuoxA2 expression in human pancreatic cancer cells [21]. NF-κB 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-κB in many ways. For example, ROS have been shown to activate NF-κB through alternative IkBα phosphorylation or by direct oxidation of NF-κB, inhibiting DNA binding [23].

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]

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 H_2O_2 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 O_2-labile α subunit and a constitutively-expressed α subunit. Hydroxylation of two conserved proline residues within the O_2-dependent degradation domain of the α subunit catalyzed by proline hydroxylases (PHDs) under normal conditions mediates HIF-1a degradation via the 26S proteasome [35]. When stabilized under hypoxia, HIF-1α translocates to the nucleus, dimerizes with HIF-1α, 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-1α was detected in the colonic epithelium of patients with IBD as well as colorectal tumors [39]. Overexpression of HIF-1α (59.2%) is frequently detected in human pancreatic carcinoma, whereas it is almost absent in normal pancreatic tissue. Moreover, HIF-1α expression is significantly associated with tumor size and microvessel density [40]. HIF-1α is regulated by various inflammatory mediators (TNF-α, IL-1α, TGF-α) and growth factors (EGF) in addition to oxygen [41–44].