Free Radical Biology & Medicine 52 (2012) 2013–2037

Contents lists available at SciVerse ScienceDirect

Free Radical Biology & Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

Emerging avenues linking inflammation and cancer

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ARTICLE INFO

Article history:
Received 6 July 2011
Revised 14 February 2012
Accepted 16 February 2012
Available online 3 March 2012

Keywords:
Inflammation
Cytokines
DNA damage
Cancer
EMT
Epigenetics
miRNA
Free radicals

ABSTRACT

The role of inflammation in carcinogenesis has been extensively investigated and well documented. Many biochemical processes that are altered during chronic inflammation have been implicated in tumorigenesis. These include shifting cellular redox balance toward oxidative stress; induction of genomic instability; increased DNA damage; stimulation of cell proliferation, metastasis, and angiogenesis; deregulation of cellular epigenetic control of gene expression; and inappropriate epithelial-to-mesenchymal transition. A wide array of proinflammatory cytokines, prostaglandins, nitric oxide, and matricellular proteins are closely involved in premalignant and malignant conversion of cells in a background of chronic inflammation. Inappropriate transcription of genes encoding inflammatory mediators, survival factors, and angiogenic and metastatic proteins is the key molecular event in linking inflammation and cancer. Aberrant cell signaling pathways comprising various kinases and their downstream transcription factors have been identified as the major contributors in abnormal gene expression associated with inflammation-driven carcinogenesis. The posttranscriptional regulation of gene expression by microRNAs also provides the molecular basis for linking inflammation to cancer. This review highlights the multifaceted role of inflammation in carcinogenesis in the context of altered cellular redox signaling.

Contents

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doi:10.1016/j.freeradbiomed.2012.02.035

Inflammation and cancer—an overview

Inflammation, a host defense mechanism, is an immediate response of the body to tissue injury caused by microbial infection and other noxious stimuli. Acute inflammation is characterized by vasodilation, leakage of the vasculature, and infiltration of leukocytes into the site of infection to destroy invading pathogens and is followed by a rapid resolution phase and repair of the damaged tissue. Thus, acute inflammation plays a beneficial role against infection and injury. However, inadequate resolution of inflammation and uncontrolled inflammatory reactions can evoke a state of chronic inflammation, which is a common etiologic factor for various human ailments including cancer [1,2].

Since the 19th-century proposition of an inflammation–cancer connection [3], the persuasive role of inflammation in carcinogenesis has become more and more evident [4–6]. Numerous laboratory and population-based studies suggest that certain malignancies arise at tissues severely damaged by chronic inflammation. For example, cancers of stomach, liver, gallbladder, prostate, and pancreas are causally linked to gastric inflammation, chronic hepatitis, cholecystitis, inflammatory atrophy of the prostate, and chronic pancreatitis, respectively [5]. Colitis, a condition characterized by persistent colonic mucosal inflammation, often progresses to colorectal cancer [7]. In fact, inflammatory bowel disease increases the risk of colorectal cancer by 10-fold [8] and the management of colitis with anti-inflammatory therapy reduces this risk [9]. Although approximately 25% of all cancers have an etiologic background of chronic inflammation and/or infection [10], the overwhelming role of inflammation in changing genetic and epigenetic events associated with malignant conversion suggests that this figure would be greater than estimated.

Molecular details of the pathophysiologic role of chronic inflammation in the initiation, promotion, and progression stages of carcinogenesis are accumulating at a rapid pace. Mechanisms by which inflammation contributes to carcinogenesis include: (i) induction of chromosomal instability, (ii) alterations in epigenetic events and subsequent inappropriate gene expression, (iii) enhancement of cell proliferation, (iv) evasion from apoptosis, (v) stimulation of intratumoral neovascularization, (vi) invasion through tumor-associated basement membrane, and (vii) stirring up the metastatic movement [5,10–12]. Central to these altered biochemical processes is the elevated expression, overproduction, or abnormal activation of diverse mediators of inflammation. Such proinflammatory mediators include, but are not limited to, cytokines, chemokines, cyclooxygenase-2 (COX-2), prostaglandins (PGs), inducible nitric oxide synthase (iNOS), nitric oxide (NO), and advanced glycation end products.

During chronic inflammation, a wide array of intracellular signaling pathways, comprising cell surface receptors, cytoplasmic and nuclear kinases, adaptors and scaffold proteins, and transcription factors, are often deregulated, thereby leading to abnormal expression of proinflammatory genes involved in malignant transformation. In general, inflammation-driven activation of various protein kinases that include Janus-activated kinase (JAK), Akt, and mitogen-activated protein (MAP) kinases inappropriately transmits growth signals, allowing cells to acquire a malignant phenotype. Moreover, inflammation-induced aberrant activation of several transcription factors, such as signal transducer and activator of transcription (STAT), nuclear-factor-κB (NF-κB), activator protein-1 (AP-1), and hypoxia inducible factor-1α (HIF-1α), has been implicated in tumor growth, angiogenesis, and metastasis (Fig. 1). The roles of these transcription factors and upstream kinases in linking inflammation to cancer have been extensively reviewed [1,3,5].

Persistent local inflammation perturbs the homeostatic control of cell signaling pathways, which may predispose cells to premalignant and malignant conversion. Various types of inflammatory immune cells, host stromal cells, and cancerous cells within a tumor microenvironment also release a large excess of proinflammatory mediators, which accelerates tumor invasion and metastasis. The link between inflammation and cancer has two paradigms: one is inflammation-driven carcinogenesis (extrinsic mechanism) and the other involves accelerated cancer progression by tumor-derived inflammatory triggers (intrinsic mechanism) (Fig. 2).

Inflammation as a predisposing factor for carcinogenesis

The fact that chronic inflammation precedes tumorigenesis has been supported by a series of recent studies (Box 1). Inflammatory mediators such as NO and high-mobility-group box 1 proteins are produced in abundance in thyroiditis as well as in thyroid tumors, suggesting that inflammatory infiltrates may increase the risk of papillary thyroid cancer in patients with autoimmune lymphocytic thyroiditis [13]. RET/papillary thyroid carcinoma (PTC) 1 (RP3) is a fusion protein expressed not only in thyroid cancers but also in thyroid epithelial cells of patients with Hashimoto thyroiditis, an inflammatory condition that often progresses to thyroid cancer [14]. Exogenous overexpression of RP3 in primary normal thyrocytes induced the expression of genes encoding cytokines, chemokines, chemokine receptors, matrix-degrading enzymes, and adhesion molecules, all of which play crucial roles in setting a local inflammatory environment favorable for the development of papillary thyroid carcinoma [15]. Inhalation of asbestos fibers induces chronic inflammation that leads to the development of mesotheliomas. The levels of interleukin (IL)-6, IL-8, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) in peritoneal lavage fluid of severe combined immunodeficiency (SCID) mice were elevated at 7 days of intraperitoneal administration of malignant mesothelioma cells [16]. This led to the formation of free-floating tumor spheroids and subsequently adherent malignant mesothelioma [16].

Further evidence supporting the notion that inflammation precedes tumorigenesis has been provided in a murine model of prostatitis-associated prostate cancer [17]. According to this study, intraurethral inoculation of a uropathogenic *Escherichia coli* strain in mice induced a profound inflammatory response at 14 days postinoculation with a remarkable decrease in the level of NKX3.1, a homeodomain protein that functions as a prostate-specific transcription factor. A diminished expression of NKX3.1 in prostate cancer patients is conducive to prostate epithelial cell proliferation and advancing the Gleason grade, a system of grading the stages of prostate cancer. Thus, bacterial infection-induced prostate inflammation may stimulate the proliferation of prostate epithelial cells by decreasing the level of NKX3.1.

Role of reactive oxygen and nitrogen species in linking inflammation and cancer

A wide variety of inflammatory and immune cells (e.g., mast cells, neutrophils, leukocytes, macrophages, monocytes, eosinophils,