Chronic Inflammation and Cancer: The Role of the Mitochondria

We review the evidence implicating a strong association between chronic inflammation and cancer, with an emphasis on colorectal and lung cancer.

Introduction

Virchow is credited with suggesting the causal link between inflammation and cancer in the 19th century.[1] He based his conclusion on the astute observation that tumors often developed in the setting of chronic inflammation and that inflammatory cells were present in tumor biopsy specimens. Accumulating evidence that has emerged in the last decade or so has shed light on the underlying mechanisms accounting for the strong association between chronic inflammation and each step of tumorigenesis.[reviewed in 2-8] Notably, nearly 90% of all cancers are due to environmental factors and somatic mutations, whereas causal germ-line mutations are infrequent.[6] Nearly 20% of cancer deaths worldwide are attributed to chronic infection and/or inflammation, with gastrointestinal and lung cancers accounting for a substantial portion of the total burden.[1,9] An estimated 30% of cancers may be linked to exposure to tobacco and/or other airborne pollutants, and 20% can be attributed to chronic infections.[9] In general, a normal adaptive immune response is anti-tumorigenic; however, dysregulated innate and/or adaptive immune responses can be pro-tumorigenic. Human neutrophils can induce malignant transformation, which suggests that phagocytic cells are carcinogenic.[10] Mantovani et al[3,4] proposed that genetic instability resulting from cancer-related inflammation represents the seventh hallmark of tumorigenesis, in addition to the six proposed by Hanahan and Weinberg[11] (limitless replication, sustained angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, and tissue invasion/metastasis).

In this review, we summarize the current knowledge supporting the association between chronic inflammation and cancer, highlighting the information that has been published since our 2002 ONCOLOGY review.[2] We then review the emerging evidence regarding important molecular and cellular pathways that link chronic inflammation to cancer. Emphasis will be placed on the pivotal role of the mitochondria in coordinating life- and death-signaling pathways important in inflammation-associated cancer. Collectively, the studies we review are revealing the crucial mechanisms that underlie inflammation-associated cancer and that may prove useful for developing novel cancer preventative and therapeutic strategies.

TABLE 1

Cancers Associated With Chronic Inflammation
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Epidemiological evidence firmly supports a link between chronic inflammation and cancer that occurs in various organs (Table 1). The inflammatory conditions implicated are quite diverse; they include a wide array of chronic infections, exposure to noxious agents that trigger inflammation (eg, gastric acid reflux, tobacco, asbestos), and auto-immune conditions. Inflammation-associated cancer consists of white blood cells, notably tumor-associated macrophages (TAM) and T lymphocytes; increased generation of reactive oxygen species (ROS)/reactive nitrogen species (RNS); altered cytokine/chemokine expression; and augmented molecular signaling via nuclear factor kappa B (NFkB), signal transducer and activator of transcription proteins (STATs), cyclooxygenase-2 (COX-2), and others.[reviewed in 2-8] In this section we focus on two widely studied cancers linked to chronic inflammation: colorectal cancer and lung cancer.

The best-established link between chronic inflammation and cancer is seen in colorectal cancer that develops in patients with inflammatory bowel disease (IBD; eg, ulcerative colitis and Crohn disease). These patients have a five- to seven-fold increased risk of developing colorectal cancer.[12-15] Nearly 43% of patients with ulcerative colitis develop colorectal cancer after 25 to 35 years.[15] Therapeutic strategies for the treatment or prevention of IBD aim to reduce the endogenous levels of tumor necrosis factor (TNF)-α, which is a key pathophysiologic element of the disease.[16] NFkB regulates multiple pathways involved in inflammation-associated cancer (eg, cytokine expression, angiogenesis, apoptosis, and COX-2 expression). TNF-α regulates NFkB, in part by receptor-mediated activation of inhibitory κB kinases (IKK) that stimulate degradation of proteins responsible for retaining the transcription factor in the cytosol, thereby enabling the translocation of NFkB to the nucleus. In a murine model of IBD, the development of colitis-associated colorectal cancer can be inhibited either by blocking TNF-α expression or by generating mice with colon epithelial cells that are deficient in IKK-β.[16,17] These findings in mice concur with the clinical observation that inhibition of the NFkB-regulated protein COX-2 by nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk for colorectal cancer in humans with IBD by nearly 80%.[18,19] The synthesis of prostaglandin E2 (PGE2) by COX-2 induces the production of inflammatory cytokines such as interleukin (IL)-6.[20] Exposure to inflammatory cytokines (eg, IL-6, IL-10) causes the activation of the signal-transducing STAT proteins that work in conjunction with NFkB to regulate many genes involved in tumorigenesis.[reviewed in 4,21-23] The importance of STAT3 in colorectal cancer is evident in the finding that the development of tumors in a murine model of IBD is reduced in STAT3-deficient mice and through pharmacologic inhibition of IL-6.[22] The STAT pathway also regulates erythropoiesis and angiogenesis, both of which augment the availability of oxygenated blood to otherwise hypoxic tumors.[4,21-23] This pathway would provide an indirect mechanism for STAT-mediated tumor promotion. Collectively, these investigations provide the molecular basis for future studies on the role of inflammatory signaling through TNF-α, NFkB, STAT3, IL-6, and other signaling proteins in the etiology of inflammation-associated cancer. Hopefully, the information gained will prove useful in the management of colorectal cancer as well as IBD.

Lung cancer causes nearly 1 million deaths worldwide every year and is the leading cause of cancer deaths.[24] Although tobacco exposure is evident in nearly 90% of all patients with lung cancer, other chronic airway inflammatory conditions (eg, asbestosis, silicosis, exposure to airborne particulate matter (PM), idiopathic pulmonary fibrosis, tuberculosis, etc) are all independent risk factors for lung cancer and may account for a proportion of the non-smoking related cases.[25] Tobacco smoke contains nearly 5000 reactive chemicals, including over 1015 free radicals in the gas phase and 1018 free radicals per gram in the tar phase.[25] These include H2O2, •OH, and organic radicals.[25] As reviewed in detail elsewhere,[26-28] chronic inflammation has a pivotal role in the pathogenesis of chronic obstructive pulmonary disease (COPD). Smokers with COPD have a 1.3- to 6-fold increased risk of lung cancer compared with smokers without COPD, and this is likely due to persistent lung inflammation.[2,27,29] A meta-analysis demonstrated a strong indirect relationship between forced expiratory volume in 1 second (FEV1) and lung cancer risk.[30] Low-grade emphysema, without airway obstruction, is an independent risk factor for the development of lung cancer.[31] Although beyond the scope of this review, some of the potentially important molecular mechanisms underlying cancer associated with tobacco-induced inflammation include the production of ROS, inflammatory signaling (eg, via TNF-α, NFkB, IL-6, and others), single nucleotide polymorphisms in inflammatory cytokines (IL-1α and IL-1β), and increased ceramide and epithelial growth factor receptor (EGFR) signaling.[26-28] Interestingly, COPD-like inflammation induced by nontypeable Haemophilus influenza, which is the most common bacteria colonizing the airways of patients with COPD, promotes K-Ras-induced lung cancer in mice.[32] Notably, a recent study
showed that mitochondrial metabolism is crucial for allowing mitochondrial ROS production at the Qo site of complex III, and that mitochondrial metabolism and ROS production were both required for mediating K-Ras-induced lung cancer in mice.[33] Macrophage migration inhibitory factor, an inflammatory cytokine, is produced at sites of bleomycin-induced lung injury in mice and functions to prevent apoptosis and promote tumor growth.[34] These innovative studies reveal insights into the pathogenesis of lung cancer occurring in the setting of emphysema-associated inflammation and should provide a rationale for future novel treatment strategies. Additional studies are necessary to understand why inflammation persists after smoking cessation as well as how inflammation in patients with COPD modulates disease expression.[29,35]

Lung cancer can also result from chronic pulmonary inflammation and fibrosis following exposure to other environmental toxins (eg, asbestos, silica, PM, beryllium). Further, a large cohort analysis of data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed that pulmonary scarring was associated with an elevated lung cancer risk (hazard ratio 1.5; 95% confidence interval 1.2-1.8).[36] In this section we highlight the role of asbestos. Asbestos is a term for a group of naturally occurring hydrated silicate fibers whose resilient strength and chemical properties make them ideal for a variety of building and insulation purposes. Asbestos causes an estimated 100,000 to 140,000 lung cancer deaths per year worldwide and contributes to nearly 5% to 7% of all lung cancers.[37,38] There are two classes of asbestos fibers: (1) serpentine fibers—curly-stranded structures, among which chrysotile is the principal commercial variety, and (2) amphibole fibers—straight, rod-like fibers (eg, crocidolite, amosite, tremolite, and others). Compared to chrysotile, amphibole fibers are more fibrogenic and carcinogenic, in part because their biopersistence in the lung results in chronic inflammation. Asbestos is an established carcinogenic agent that can induce chronic inflammation of the lung and pleura, ROS production, DNA damage, and cell death in all the major lung target cells (eg, bronchial and alveolar epithelial cells [AEC], mesothelial cells).[see for review: 39,40] Substantial investigations have shown that the extent of AEC injury and lack of sufficient AEC repair are important determinants of pulmonary inflammation and fibrosis following exposure to a wide variety of noxious agents, including asbestos.[40] There is a direct correlation between the levels of asbestosis seen in asbestos workers and the risk of developing lung cancer.[41] Asbestos-induced ROS cause DNA damage, such as single- or double-strand breaks, intra- and inter-strand cross-linking, and base damage.[see 42,43 for reviews] Repair of these lesions in most instances will restore the physiologic DNA structure, but abnormal DNA repair may result in gene mutations, chromosomal aberrations, and ultimately cell transformation. Early studies in our group showed that the repair of complex, inflammation-associated DNA damage, such as that caused by the exposure of cells to activated neutrophils, is slow compared to the repair of single-strand breaks, suggesting that residual DNA damage may lead to mutations or other cellular abnormalities that can promote tumorigenesis.[44] ROS-induced DNA damage is implicated in mediating the synergistic effect between asbestos and cigarette smoke for lung cancer risk.[see for review: 45,46] Convincing evidence, reviewed elsewhere,[40] has established that asbestos induces AEC apoptosis via the mitochondria-regulated (intrinsic) death pathway and involves mitochondrial ROS production. Interestingly, studies in transgenic mice suggest that Rac1-mediated mitochondrial H2O2 production from asbestos-exposed alveolar macrophages is necessary for the induction of pulmonary fibrosis.[47] However, further studies are required to better understand the molecular mechanisms underlying the link between asbestos-induced inflammation/pulmonary fibrosis and lung cancer.

One possibility is that diverse environmental stimuli, including asbestos and other lung carcinogens (eg, silica), but not inert particulates, cause pulmonary inflammation and fibrosis via activation of Nalp3 inflammasomes, which can stimulate caspase-1.[48,49] Nalp3 is a member of the NLR family of over 20 proteins. These proteins contain multiple functional domains, including an N-terminal protein-protein interaction domain that is necessary for caspase activation, a caspase recruitment domain (CARD), a central nucleotide-binding domain, and a C-terminal leucine-rich repeat domain.[50] Nalp3 inflammasome formation occurs when activated Nalp3 recruits caspase-1 and ASC, an adaptor molecule, via CARD-CARD interactions. Asbestos- and silica-induced lung inflammatory cell recruitment, cytokine production (eg, of IL-1β and others), and silicosis are all reduced in mice deficient in Nalp3, ASC, or caspase-1.[48,49] Moreover, by using specific pharmacologic inhibitors and targeted murine knockouts, it was found that the factors that appear essential for Nalp3 inflammasome activation include fiber uptake into phagocytic cells, an intact actin cytoskeleton, and ROS generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase during phagocytosis. Thus, asbestos- and silica-induced Nalp3 inflammasome activation may be a novel therapeutic target for treatment/prevention of the underlying causes of
Mechanisms Underlying Inflammation-Associated Cancer

Inflammation-Associated Cancer: Facts & Questions

The last decade has witnessed much insight into inflammation-associated cancer; however, major gaps in our understanding remain. Table 2 highlights some of what we know regarding inflammation-associated cancer, as well as some of the critical questions that require further investigation to definitively prove a causal role for inflammation-associated cancer in tumorigenesis. In this section, we summarize the emerging evidence highlighted in Table 2. We focus on recent studies indicating an important role for the mitochondria, especially mitochondrial ROS production, as an upstream regulator of cancer-related signaling pathways that promote inflammation and tumorigenesis.[reviewed in 51,52]

Inflammatory Cells in Tumorigenesis

Although a wide variety of cancers are associated with chronic inflammation and/or infection (see Table 1), it is unclear whether chronic inflammation is sufficient to induce cancer in the absence of a carcinogen. Further, acute inflammation is not associated with cancer, and not all chronic inflammatory conditions augment cancer risks (eg, psoriasis, rheumatoid arthritis, asthma), for reasons that are uncertain.[6] A causal role for inflammation in cancer is suggested by the finding that IL-10 deficiency promotes somatic mutations in a murine IBD model in the absence of exogenous carcinogens.[53] There are some data suggesting that ROS derived from either inflammatory/immune cells[54,55] or the mitochondria of epithelial cells[33] act as the central endogenous carcinogens that drive cancer-promoting signaling pathways important in inflammation-associated cancer, as depicted in the Figure. It is unclear whether ROS/RNS produced by neutrophils and macrophages are sufficient to induce the kinds of epithelial cell DNA damage that result in tumorigenesis. Inflammatory cells also release cytokines, such as TNF-α, that can promote chronic oxidative stress in affected tissue. Further investigations are required to formally verify a causal relationship between chronic inflammation/infection and cancer, as well as to determine whether ROS are the only endogenous carcinogens.

As reviewed in detail elsewhere[7,14,56], one of the most compelling arguments linking inflammation-associated cancer to tumorigenesis is the observation that drugs that inhibit the production of prostaglandins during inflammation reduce the risk of various cancers, such as colorectal, esophageal, gastric, lung, breast, and ovarian cancer. These drugs include nonspecific NSAIDs, such as aspirin, and selective COX-2 inhibitors. COX-2 is an inducible form of cyclo-oxygenase that is activated in chronic inflammation. It is highly expressed in nearly all tumors.[7] COX-2 expression is necessary and sufficient to induce tumorigenesis in multiple in vitro...
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and animal models.[reviewed in 2,7] It mediates the production of certain inflammatory cytokines that can act as tumor promoters, such as IL-6.[57] Randomized clinical trials show that NSAIDs decrease colon adenoma formation, an important precursor of colorectal cancer.[7,56] In breast cancer cells, COX-2 overexpression induces oxidative stress as well as chromosomal abnormalities (eg, fusions, breaks, and tetraploidy) that contribute to tumorigenesis.[58] Despite these remarkable advances in our understanding, no anti-inflammatory strategy is currently approved to prevent or treat cancer, although several are under development (eg, anti-IL-6 therapy for multiple myeloma).

As reviewed in detail elsewhere[3,59], additional studies are required to determine which patient populations are appropriate for cancer preventative agents that target COX-2 or other relevant signaling pathways.

The tumor microenvironment contains a wide variety of inflammatory and immune cells, cytokines, and chemokines that have pro- and anti-tumorigenic activity, the balance of which likely dictates clinical outcome.[2-8] Experimental in vivo evidence unequivocally establishing the role of particular immune/inflammatory cells and cytokines/chemokines in tumorigenesis is lacking.[6] The most common immune cells in tumors are tumor-associated macrophages (TAMs) and T cells. TAMs, which are the major source of cytokine production in the tumor microenvironment, promote tumorigenesis in several ways. They produce protein factors that stimulate tumor cell growth, directly and indirectly (eg, by stimulating angiogenesis), and they stimulate metastasis by producing matrix-degrading enzymes.[5,6] TAMs are classified either as M1 or M2 macrophages, depending on their response to various stimuli. M1 TAMs respond to interferon (IFN)-γ or microbial exposure by expressing high levels of cytokines involved in anti-tumor and anti-microbial activity (eg, TNF-α, IL-1, IL-6, IL-12, IL-23), while M2 TAMs are proangiogenic/tissue-remodeling macrophages that display reduced expression of IL-12 and increased expression of the anti-inflammatory cytokine IL-10 following exposure to IL-4, IL-10, or IL-13.[3,6] The M1 and M2 TAM phenotypes are plastic, based on their gene expression profiles.[6] The protumorigenic effects of TAMs are suggested by the finding that TNF-α-deficient mice are protected against drug-induced skin cancer.[60,61] Also, TAMs augment Wnt signaling via a TNF-α-dependent pathway in gastric cancer; this pathway is necessary for growth and for epithelial-mesenchymal cell transition that is important in metastasis.[62] Phase 1 and II clinical trials are underway examining the role of TNF-α antagonists in patients with renal cancer[63] as well as advanced cancers.[64] As reviewed in detail elsewhere,[5] studies in transgenic mice have established a protumorigenic role for IL-1. The finding of increased skin and colitis-related cancers occurring in mice deficient in the atypical chemokine receptor D6 establishes a prominent role for CC chemokines in tumorigenesis.[65] In this context, it is not surprising that a high tumor TAM content generally foreshadows a poor prognosis.[66]

T cells can also impact cancer outcomes. Increased levels of CD8+ cytotoxic T lymphocytes and CD4+ helper 1 (Th1) cells portend a better prognosis in certain tumors (eg, colon, melanoma, pancreatic, multiple myeloma, lung) and comprise a therapeutic approach to the treatment of these cancers.[6] In contrast, a T-cell deficiency can augment tumor formation.[6] Additional investigation is necessary to determine why certain T-cell subsets are pro-tumorigenic in one cancer but anti-tumorigenic in another. Also, it is unknown whether there is a common upstream inflammatory signal (eg, mitochondrial ROS production) that is activated in all malignancies, and if so, whether this regulates the balance between TAM and T-cell pro- and/or anti-tumorigenic activities.

Inflammation and Oncogenes/Tumor Suppressor Genes

Similar to Ras, the Myc oncoproteins are mutated in many human cancers and alter mitochondrial function (eg, increased electron transport, oxygen uptake, and ROS production) in a way that induces the rapid cell growth that is a crucial element of tumorigenesis.[51] Growth factors and chemokines produced in the setting of inflammation-associated cancer augment Myc overexpression in cancer cells, thereby driving Ras activation and abnormal DNA synthesis.[4] In a murine Myc model of pancreatic cancer, the initial wave of angiogenesis is mediated by the inflammatory cytokine IL-1β.[69] Interestingly, a recent gene expression profile study showed that the Myc network of transcription programs accounts for most of the similarity between embryonic stem cells and cancer cells.[70] Myc activation can trigger mitochondria-regulated apoptosis, whereas Myc-induced DNA damage and cellular transformation are prevented by mitochondria-targeted antioxidants.[71,72] Thus, the emerging evidence suggests that the mitochondria are important downstream effector organelles in both Myc- and Ras-induced oncogenic transformation (see Figure).

The tumor suppressor protein p53 is an important transcriptional factor for multiple proteins involved in the cellular DNA damage response, and it is likely important in inflammation-associated cancer.[see for review 73] Following DNA damage caused by oxidative stress (eg, that resulting from...
exposure to tobacco, asbestos, etc), an intact p53 response prevents mutations from accumulating by increasing the expression of genes that inhibit cell growth, thereby increasing the time available for DNA repair. However, if DNA damage is extensive, p53 activation can augment apoptosis by inducing pro-apoptotic genes while inhibiting expression of anti-apoptotic genes, ultimately causing mitochondrial dysfunction and intrinsic apoptosis. Because of its central role in directing cellular life and death outcomes, it is not surprising that mutations in p53 gene family members are common in human tumors.[73] Mitochondrial ROS block wild-type p53 function and promote the formation of p53 mutations.[reviewed in 4,51] Mutations in p53, some from inflammation-associated oxidative stress, are evident in the epithelium of cancer cells and in inflamed, but non-dysplastic epithelial cells.[74] This suggests that genomic changes can result from chronic inflammation. Altered p53 expression has also been implicated in the pathophysiology of pulmonary fibrosis, including that due to asbestos, as well as in pulmonary fibrosis-associated bronchogenic lung cancer.[75-80] For example, increased p53 protein expression is detected in the bronchial and alveolar epithelium of humans with idiopathic pulmonary fibrosis and in rodents exposed to asbestos.[75-80] Furthermore, increased p53 levels are detected in lung cancers of patients with asbestosis.[81] and p53 point mutations are widely evident in the respiratory epithelium of smokers and asbestos-exposed individuals.[82] p53 mediates asbestos-induced, mitochondria-regulated apoptosis in lung epithelial cells, and this is blocked in cells incapable of producing mitochondrial ROS.[80] Notably, loss of p53 results in mtDNA depletion, altered mitochondrial function, and increased H2O2 production.[83] Considerable evidence, reviewed in detail elsewhere,[51] has established that p53 is a crucial regulator of mitochondrial function, including ROS generation and mtDNA repair following oxidative damage, as well as mitochondrial biogenesis and mtDNA replication. Although formal evidence is lacking, it is likely that loss of wild-type p53 function augments the deleterious effects induced by Ras and Myc on mitochondrial function described above.[51] Thus, p53 has a key role in regulating the response to cellular DNA damage caused by exposure to oxidative stress, and likely plays a role in the pathogenesis of inflammation-associated cancer. Future investigations are required to better understand how the Ras, Myc, and p53 pathways are interconnected.

As reviewed in detail elsewhere,[4,8] chronic inflammation can effect each of the six hallmarks of tumorigenesis identified by Hanahan and Weinberg,[11] including limitless replicative potential, sustained angiogenesis, evasion of apoptosis, self-sufficiency in growth signaling, insensitivity to anti-growth signals, and tissue invasion/metastasis. The evasion of immune surveillance mechanisms and genetic instability due to inflammation-associated cancer have each been proposed as the seventh hallmark of cancer—again emphasizing the role of inflammation in cancer.[4,84] Inflammation-associated cancer induces oxidative stress that can lead to DNA damage and cellular stress, which in turn cause abnormalities in mitosis (eg, through chromosomal abnormalities) and metabolism (eg, through the Warburg effect, or increased glucose uptake for glycolysis).[8] Although beyond the scope of this review, nearly 30 different cancer therapies targeting these assorted mechanistic hallmarks of inflammation-associated cancer are in various stages of development.[reviewed in 8] A crucial unresolved issue is whether inflammatory signaling in susceptible tissues (eg, the lungs of smokers) can be altered so as to favor adaptive immunity (anti-tumorigenic activity) rather than pro-tumorigenic activity.

**Inflammation, ROS, and the Mitochondria**

α, IL-1β, NFκB, STAT3, and COX-2) decreases the incidence and spread of certain tumors (eg, colorectal cancer). In general, inflammatory immune components necessary at one stage of tumorigenesis may be completely dispensable during another stage.[3,6] Also, adaptive transfer of inflammatory cells or overexpression of certain cytokines promotes tumor formation.[3]

The major sources of ROS in the setting of inflammation-associated cancer include (1) NADPH oxidase present in phagocytes and other cells and (2) mitochondria. In non-phagocytic cells, over 95% of ROS formed during normal metabolism originate from the electron transport chain (ETC) in the inner mitochondrial membrane in close proximity to mtDNA.[51] ROS-induced mtDNA damage is implicated in a wide range of pathologic processes, including carcinogenesis, aging, and degenerative diseases.[85,86] Emerging studies suggest that mitochondrial ROS form crucial intermediates between environmental and host stimuli that result in inflammation-associated cancer (see **Figure**). Mitochondrial metabolism via the pentose phosphate shunt and mitochondrial ROS production from the Qo site of complex III in the ETC are necessary for K-Ras–induced tumorigenesis.[33] Hypoxia, as occurs in solid tumors, stimulates the expression of HIFs, which are important transcription factors involved in coordinating the cellular response to hypoxia. They regulate mitochondrial metabolism and ROS production, yet at the same time, mitochondrial ROS
regulate HIF expression. [reviewed in 51,87] Accumulating evidence establishes that asbestos fibers induce lung epithelial cell apoptosis via the mitochondria-regulated death pathway and that mitochondrial ROS have a causal role. [40] A recent study showed that a Helicobacter pylori toxin, vacuolating cytotoxin A, induces mitochondria-regulated apoptosis by juxtaposing the mitochondria with endosomes. [88] This finding implicating the mitochondria provides a potential mechanistic link between chronic Helicobacter infections and gastric cancer. Thus, the available information supports the hypothesis that the levels of mitochondrial ROS are important in regulating the balance between normal physiologic signaling (low mitochondrial ROS levels) compared with the signaling in inflammation-associated cancer that promotes tumorigenesis (high mitochondrial ROS levels). In this regard, mitochondria-targeted antioxidants present attractive agents for cancer prevention or treatment. [51] However, the mechanisms of action of these antioxidants may not be as expected. For example, in recent studies, we found that mitoquinone inhibits tumor cell growth, but that, instead of acting as an antioxidant, it appears to act by inducing ROS formation in cancer cells, causing the induction primarily of autophagy instead of apoptosis. [89] Further studies are required to deepen our understanding of the potential therapeutic benefits of mitochondria-targeted redox agents for inflammation-associated cancer.

Given the close proximity of mtDNA to the mitochondrial ETC and the lack of protective histones, mtDNA resulting from oxidative stress may be important in the pathogenesis of inflammation-associated cancer. For example, with asbestos, lung mesothelial cell mtDNA damage is evident following exposure to a four-fold lower concentration of crocidolite asbestos than the crocidolite doses required to cause nuclear DNA damage. [90] Also, several lines of evidence implicate mtDNA oxidative injury as a key trigger of apoptosis that may be important in inflammation-associated cancer, including: (1) that cell death is more closely associated with mtDNA oxidative lesions than with nuclear DNA lesions, (2) that mtDNA damage precedes ATP depletion and mitochondrial dysfunction, (3) that enhancing mtDNA repair blocks cell death, and (4) that deficiency of mtDNA repair enhances cell death. [reviewed in 51,86] Base excision repair (BER) is the principal pathway for repairing oxidative mtDNA damage. [83] Epidemiological data suggest that the levels of 8OHdG, the most common DNA base change arising from oxidative stress, is linked with various cancers and neurodegenerative diseases. [85,86,91-94] 8OHdG induces mutations in replicating cells by preferentially mispairing with adenine during DNA synthesis, thereby increasing the incidence of G:C to T:A transversions. DNA glycosylases have a key role in BER pathways: they recognize the oxidized DNA adduct and excise the damaged base. 8-oxo-guanine DNA glycosylase (Ogg1), which is responsible for repairing 8OHdG, has a dual function: it preferentially recognizes 8OHdG opposite cytosine and then excises it via its apurinic/apyrimidic lyase activity. All mtDNA BER repair proteins, including Ogg1, are nuclear-encoded and imported into mitochondria. [83] Overexpression of mitochondria-targeted Ogg1 blocks intrinsic apoptosis in ROS-exposed vascular endothelial and asbestos-exposed HeLa cells. [90,95,96] We recently extended these findings to AEC exposed to oxidative stress (asbestos or H2O2). [97] Further, using Ogg1 mutants incapable of 8OHdG DNA repair, we showed that Ogg1 functions in a role independent of DNA repair by preserving mitochondrial aconitase levels. Mitochondrial aconitase has a dual role: (1) it serves as an iron-sulfur– containing tricarboxylic acid cycle enzyme that is a mitochondrial redox-sensor susceptible to oxidative degradation and (2) it maintains mtDNA by mechanisms that are independent of its catalytic activity. [98-100] Mitochondrial aconitase co-precipitates with frataxin, an iron chaperone protein that is as good as Ogg1 at preventing aconitase oxidative inactivation. [97,101] Given the importance of p53 in inflammation-associated cancer, it is of interest that Ogg1 is under transcriptional regulation by p53. [102,103] Collectively, these findings suggest critical crosstalk between the mitochondria (ROS, aconitase, Ogg1, etc) and p53 that is likely important in inflammation-associated cancer.

Activation of oncogenic transcription factors can be triggered through pattern recognition receptors, by exposure to components of bacteria, viruses, and interestingly, mtDNA. [104,105] Chronic inflammation /infection can lead to extensive cellular damage in target organs (e.g., necrotic epithelial cells and macrophages in tumors), and this results in the release of damage-associated molecular pattern (DAMP) or pathogen-associated molecular pattern (PAMP) molecules. [reviewed in 6,56] DAMPs include IL-1α, high mobility group B1 molecule (HMGB1), and other molecules that work in concert to facilitate inflammation. [59] The underlying mechanisms are the subject of ongoing studies. Circulating mtDNA and mitochondrial DAMPs can be detected in patients with trauma, a finding that may account for the increased risk of multi-organ dysfunction in these patients. [105] These investigations illustrate the diverse mechanisms by which alterations in the mitochondria can impact inflammation-associated cancer. It is unclear whether epithelial cells or
immune/inflammatory cells are the primary source of DAMPs in tumors. It will be of interest to determine whether chronic inflammation/tissue injury results in the release of mtDNA, and if so, whether this is crucial for driving inflammation-associated cancer. Further studies are necessary to better understand the precise molecular details by which mitochondrial respiration, mitochondrial ROS production, and mtDNA damage affect specific components of inflammation-associated cancer.

**Inflammation and Tumor-Promoting Signaling Pathways**

Tumor cells, carcinogen-exposed epithelial cells, and inflammatory cells utilize NFkB, a tightly regulated transcription factor, to activate a number of genes coding for proteins involved in inflammation-associated cancer, including cytokines, growth factors, adhesion molecules, angiogenic factors, proto-oncogenes (eg, Myc), COX-2, and nitric oxide synthase.[reviewed in: 3,6,7,106] NFkB, a dimer of two Rel-family proteins (p50 and p65), is activated in the cytoplasm by diverse cellular conditions including excess ROS, hypoxia, and HIF-1α. It is also regulated autonomously by genetic alterations that lead to phosphorylation of its inhibitor protein (IkBα). The phosphorylation of IkBα results in the proteolytic degradation and subsequent translocation of IkB to the nucleus, where it binds to and regulates the DNA.[106] NFkB is also activated downstream of signaling by inflammatory cytokines (eg, TNF-α, IL-1β) as well as by the toll-like receptor–MyD88 pathway that is stimulated by microbes and tissue damage.[4] NFkB can have divergent effects in various models of carcinogenesis that likely relate to the balance between activating downstream pro- and anti-tumorigenic effects.[106-109] Murine transgenic studies have established a key role for NFkB signaling pathways in colitis-associated cancer, liver cancer, and breast cancer metastasis.[reviewed in 4,7,14] NFkB activation by TNF-α augments nuclear entry of Wnt/β-catenin in inflammation-associated gastric cancer,[110] as well as in colonic crypt cells[111]—a finding that is likely crucial for promoting tissue invasion/metastasis. Asbestos causes prolonged, dose-dependent transcriptional activation of NFkB-dependent genes in vitro and in vivo by a ROS-dependent mechanism.[reviewed in 112] In murine models that inhibit IKKβ-dependent NFkB activation, acute inflammation is exacerbated while chronic intestinal inflammation is attenuated.[113] These findings underscore how critical the context of inflammation (eg, acute vs chronic) is in regulating the pro-inflammatory and anti-apoptotic effects of NFkB. The collective evidence suggests that NFkB has primarily pro-tumorigenic effects but that an anti-inflammatory role can occur. Further studies are necessary to determine the precise role of pharmacologic and genetic targeting of the NFkB-dependent pathways in various cancer preventative and treatment strategies.

STAT3, like NFkB, is a transcription factor that is often constitutively activated in tumors and immune cells. It mediates a number of crucial tumorigenic signaling pathways (eg, cell proliferation, apoptosis, Myc expression, evasion of immune surveillance).[reviewed in 4] The STAT family contains seven members, but STAT3 has been most closely implicated in inflammation-associated cancer.[reviewed in 21] STAT3 signaling is essential for stem-cell renewal as well as for persistent NFkB activation in tumor cells.[114,115] Further, mitochondrial STAT3 is essential for Ras-dependent oncogenic transformation.[116] The molecular mechanism(s) that account for the presence of STAT3 in the mitochondria are unclear, but apparently do not depend on increased STAT3 transcriptional activity, nor on changes in mtDNA-encoded proteins. Rather, the presence of mitochondrial STAT3 appears to be mediated by greater mitochondrial ETC activity. A firm role for STAT3 in colitis-associated cancer is suggested by the finding of a reduced incidence of colon cancers in STAT3-deficient mice.[reviewed in 14] Also, a colitis-inducing strain of *Bacteroides fragilis* that is implicated in colorectal cancer is a potent activator of STAT3 in humans and mice.[117] Mutations in EGFR result in downstream IL-6 production and STAT3 phosphorylation in lung adenocarcinomas.[118,119] Although the precise molecular details await further study, the available experimental evidence supports an important role for the interconnected signaling cascade of NFkB–IL-6–STAT3 in the development of inflammation-associated cancer.

**Conclusions**

Cancer-related inflammation remains a significant challenge to healthcare providers, as well as to investigators studying the basic mechanisms underlying tumorigenesis. Largely because the pathogenesis of inflammation-associated cancer is incompletely understood, there are currently limited therapeutic techniques for modifying cancers that occur in the setting of chronic inflammation. The accumulating evidence links a wide variety of chronic inflammatory conditions to diverse groups of cancers (see Table 1), providing firm support for the role of inflammation-associated cancer as an important event in the pathogenesis of cancer. It may even be
the seventh hallmark of cancer, as suggested by Mantovani et al.[4] In this review, we summarized the evidence implicating a growing number of key molecular and cellular pathways mediating cancers that occur in the setting of chronic inflammation (see Figure). In particular, we reviewed current knowledge implicating the mitochondria, especially mitochondrial ROS, as a central regulator in inflammation-associated cancer. As summarized in Table 2, there is much that we know about what promotes inflammation-associated cancer, but there remain a number of crucial missing pieces of experimental evidence that will be necessary to definitively prove a causal relationship between inflammation and cancer. In this regard, future in vivo studies utilizing novel targeted murine transgenic approaches, such as those described herein, will be necessary to advance our understanding of the field. Strategies aimed at enhancing mitochondrial DNA integrity and/or increasing mitochondrial antioxidant defenses may prove beneficial in reducing malignant transformation after exposure to noxious agents (eg, tobacco, PM) and host mutations that result in inflammation-associated cancer. Importantly, the significance of these investigations is that they provide the molecular rationale for developing urgently needed and novel strategies for cancer prevention and treatment.

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