Chronic Inflammation and Cancer

ABSTRACT: A substantial body of evidence supports the conclusion that chronic inflammation can predispose an individual to cancer, as demonstrated by the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma. Chronic inflammation is caused by a variety of factors, including bacterial, viral, and parasitic infections, chemical irritants, and nondigestible particles. The longer the inflammation persists, the higher the risk of associated carcinogenesis. This review describes some of the underlying causes of the association between chronic inflammation and cancer. Inflammatory mediators contribute to neoplasia by inducing proneoplastic mutations, adaptive responses, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis. All these changes confer a survival advantage to a susceptible cell. In this article, we discuss the contribution of reactive oxygen and nitrogen intermediates, prostaglandins, and inflammatory cytokines to carcinogenesis. A thorough understanding of the molecular basis of inflammation-associated neoplasia and progression can lead to novel approaches to the prevention and treatment of cancer.

Chronic inflammation may be a causative factor in a variety of cancers. In general, the longer the inflammation persists, the higher the risk of cancer. Hence, acute inflammation, such as occurs in response to a transient infection, is not regarded as a risk factor for the development of neoplasia, although many of the same molecular mediators are generated in both acute and chronic inflammation. In general, inflammatory leukocytes such as neutrophils, monocytes, macrophages, and eosinophils provide the soluble factors that are thought to mediate the development of inflammation-associated cancer, although other cells, including the cancer cells themselves, also participate.

Inflammatory mediators include metabolites of arachidonic acid, cytokines, chemokines, and free radicals. Chronic exposure to these mediators leads to increased cell proliferation, mutagenesis, oncogene activation, and angiogenesis. The ultimate result is the proliferation of cells that have lost normal growth control. Animal models provide experimental evidence that chronic inflammation can promote cancer and further insights into possible mechanisms.

This review will summarize the clinical association between chronic inflammation and cancer and will describe the inflammatory factors and pathways that are thought to be proneoplastic. Emphasis will be placed on examining the role of the reactive oxygen and nitrogen intermediates, cytokines, and prostaglandins.
Inflammatory Conditions That Predispose to Cancer

TABLE 1

A wide array of chronic inflammatory conditions predispose susceptible cells to neoplastic transformation (Table 1).[1-17] Most of the resulting tumors are of epithelial cell origin (carcinomas). The most widely studied and best established of these links are colon carcinoma associated with inflammatory bowel disease (chronic ulcerative colitis and Crohn's disease), esophageal adenocarcinoma associated with reflux esophagitis (Barrett's esophagus), hepatitis predisposing to liver cancer, schistosomiasis causing an increased risk of bladder and colon carcinomas, and chronic Helicobacter infection leading to cancer of the stomach. Some increase in the incidence of lymphoma is also seen, particularly mucosa-associated lymphoid tissue (MALT) lymphoma.

Inflammatory Bowel Disease and Colon Carcinogenesis

Much of our understanding of the association between chronic inflammation and cancer is illustrated through inflammatory bowel disease and colon carcinogenesis. Patients with either chronic ulcerative colitis or Crohn's disease have a five- to sevenfold increased risk of developing colorectal carcinoma.[18] It is generally thought that the colitis must persist for at least 8 years to significantly increase the risk of cancer.[2] Neoplasia generally appears after a median duration of approximately 15 years. Increased cancer incidence is associated with increased duration of the inflammation. Like other forms of cancer, colon carcinogenesis is a multistage process. It begins with focal proliferation of dysplastic cells, the formation of benign adenomatous polyps, and potential progression to malignant adenocarcinomas.[19] Mutations in oncogenes and tumor-suppressor genes (p53, APC, and Ki-ras) are found in a high percentage of colon cancers.[20] The molecular nature of the mutations differs in colon cancers associated with chronic colitis compared to sporadic and familial colon carcinoma, suggesting different mechanisms of mutagenesis. The cancers that develop are found predominantly at the sites of the inflammation and not at distant sites.[2] Chronic intake of anti-inflammatory drugs decreases the incidence of colon carcinogenesis associated with inflammatory bowel diseases (see below).

Chronic Inflammation

Animal models demonstrate experimentally that chronic inflammation predisposes to the development of various forms of cancer. For example, marmosets have a high incidence of spontaneous colitis and a high incidence of colon cancer as well. Skin cancer is induced by administration of carcinogens such as dimethylbenzanthracine (DMBA) followed by repeated administration of tumor promoters such as phorbol myristate acetate (PMA) or benzoyl peroxide, which induce inflammation and the production of various inflammatory mediators.[21] Intraperitoneal introduction of mineral oils (eg, pristane) or plastic discs into BALB/c mice promotes the formation of chronic granulomatous tissue and the development of plasmacytomas.[22] In these animal models, the tumors generally arise in the inflammatory tissue, indicating that local inflammatory mediators are responsible for their development. In some cases, there is strong evidence suggesting a genetic basis for the susceptibility to tumor development. For example, in the mouse plasmacytoma model, BALB/c mice are uniquely susceptible to developing plasma cell tumors.
in response to pristane, whereas most other strains are not. Similarly, SENCAR mice are uniquely susceptible to developing skin tumors in response to DMBA and PMA. These findings provide a basis for identifying critical genes and factors that contribute to tumor development and may explain why, for example, some individuals with chronic inflammatory conditions and carcinogen exposure (eg, smokers) develop cancer while others do not.

As shown in Table 1, the types of chronic inflammation that lead to cancer are varied. In some cases, the progenitors of the inflammation are known. These include chronic bacterial and parasitic infections, chemical irritants, and nondigestible particles. In other cases, the underlying cause of the chronic inflammation is unknown. This is true for inflammatory bowel disease, sialadenitis, and lichen sclerosis. Some of the known chronic inflammatory agents will be described below. Of these, parasitic infections are perhaps the best described. It seems that any parasitic infection that persists or recurs over many years can predispose to cancer. Thus, bacterial, viral, and parasitic infections can all lead to cancer if left unchecked.

**Bacterial Infections**
The strongest association between chronic bacterial infection and the development of cancer involves the organism *Helicobacter pylori*, which is associated with at least a twofold increased risk of adenocarcinoma of the stomach.[23,24] In addition, *H pylori* infection is thought to increase the incidence of MALT lymphoma.[25] Strong experimental evidence that *Helicobacter* infection is carcinogenic comes from studies showing that gerbils infected with *H pylori* develop active chronic gastritis followed by a high incidence of gastric adenocarcinoma. *Helicobacter* infection in humans is always accompanied by mucosal inflammation (gastritis) with an influx of lymphocytes, plasma cells, and neutrophils. The robust immune response to *H pylori* generally fails to clear the infection, thus resulting in a chronic inflammatory response thought to be a key element of the carcinogenic activity of the bacterium. Unless treated, *H pylori* infection and the associated gastritis persist for decades. Eradication of *H pylori* infection with antibiotics may also eliminate the excess risk for cancer, but this has not yet been established.

**Parasitic Infections**
Several parasitic infections are known to increase the risk of cancer. Schistosomiasis is prevalent primarily in Third World countries and is difficult to treat because contaminated water supplies lead to reinfection.[10] Chronic schistosomiasis induces cystitis and fibrosis and increases the incidence of carcinoma of the bladder, liver, and rectum, and follicular lymphoma of the spleen, with different strains of the parasites infecting specific organs and leading to the various cancers.[10] Liver flukes (*Opisthorchis* and *Clonorchis*), introduced by eating raw fish, infect the bile duct and lead to chronic cholangitis associated with an increased incidence of cholangiocarcinoma.[11] Chronic infection and inflammatory diseases may also contribute to the development of Hodgkin’s disease and non-Hodgkin’s lymphoma.[26]
Viral Infections
Many different viruses cause an increased incidence of cancer. Those most commonly associated with chronic inflammation are the hepatitis B and C viruses, which lead to chronic active hepatitis and hepatocellular carcinoma.[13] Epstein-Barr virus (EBV) is associated with B-cell non-Hodgkin’s lymphoma, and may contain a chronic inflammatory component.[27] Other viral infections can also increase the incidence of cancer, but the role of inflammatory mediators is less clear. For example, the human papillomavirus, herpes simplex virus 2, and cytomegalovirus have been implicated in cervical and other carcinomas.[28] Among RNA retroviruses, the human immunodeficiency virus (HIV) predisposes to the development of non-Hodgkin’s lymphoma, squamous cell carcinomas, and Kaposi’s sarcoma,[29] while the human T-cell lymphoma virus causes adult T-cell leukemia. Unlike the other parasitic infections described here, viruses implicated in inducing neoplasia directly infect the cells that ultimately undergo neoplastic transformation. Hence, it is difficult to determine whether these agents act by causing a chronic inflammatory condition, by directly transforming the cells that they infect, or both. Most of these viruses induce chronic increased proliferation of the infected cells, thus predisposing to neoplastic transformation (see below). For example, EBV causes sustained proliferation of peripheral B lymphocytes, but when coupled with a secondary mutation can result in malignant transformation, such as occurs with the chromosomal translocations that activate the c-myc oncogene in Burkitt’s lymphoma. The hepatitis viruses are thought to give rise to hepatocellular carcinoma by causing liver damage and regeneration together with the generation of secondary inflammatory mediators.[13]

Noninfectious Causes of Chronic Inflammation
Various noninfectious agents also cause chronic inflammation associated with an increased risk of cancer. For example, esophageal reflux causes chronic exposure of the esophageal epidermis to irritation by gastric acids. This leads to reflux esophagitis, or Barrett’s esophagus, and subsequent development of esophageal carcinoma.[12] Excess fecal bile acids in patients with primary sclerosing cholangitis and ulcerative colitis are
associated with an increased risk of colorectal carcinoma. A recent publication demonstrated that ursodiol (Actigall), a drug that reduces the colonic levels of deoxycholate and other bile acids (used to treat cholangitis), significantly reduces the incidence of neoplasia.[30] Chronic irritation of the liver by alcohol causes cirrhosis and hepatocellular carcinoma.[31] Nondigestible agents such as asbestos, coal, and silica dust lead to chronic inflammation in the lung because of the inability of the immune system to remove the substances. Such sterile inflammations increase the incidence of epithelial cancers including mesothelioma and lung carcinoma.[32] Experimental evidence that chronic sterile inflammation can cause cancer comes from studies in BALB/c mice that received intraperitoneal administration of nondigestible, nongenotoxic mineral oils or plastic disks. The mice developed a high incidence of B lymphocytic (plasma cell) tumors but no epithelial cancers.[22]

Cigarette smoke is a complex proneoplastic agent that may act, in part, by inducing a chronic inflammatory condition. Smoking not only causes chronic bronchitis, but also delivers an array of genotoxic carcinogens (eg, nitrosamines, peroxides) into the lungs. Hence, at present, it is unclear to what degree chronic bronchitis, mutagens in the smoke, and other factors contribute to the high incidence of lung carcinoma among smokers.

There are limitations, however, to using epidemiology to understand the causes of cancer. Definitive evidence that chronic inflammation predisposes to cancer requires identification of the causative inflammatory mediators as well as the agents that prevent neoplastic transformation through inhibition of the inflammatory process. The remainder of this review will focus on the mechanisms whereby inflammatory mediators promote neoplastic transformation.

**General Mechanisms of Proneoplastic Activity**

Tumorigenesis is generally a protracted and complex process involving different developmental stages often referred to as initiation, promotion, and progression.[33] Much of our understanding of these steps derives from studies of epidermoid carcinogenesis such as skin and colon cancer. Initiation is thought to involve a primary mutation in the DNA leading to a cell with increased potential for growth but still dependent on additional genotypic and phenotypic changes to achieve complete transformation. Frequently, initiation is induced by genotoxic carcinogens that directly damage the DNA, while promotion involves clonal expansion of initiated cells. In early skin carcinogenesis studies, promotion was thought to be caused primarily by epigenetic mechanisms that stimulated expansion of a preneoplastic population of mutated cells.[34] However, it is now apparent that promotion involves genetic as well as epigenetic changes.[33] Progression is the advancement of an early neoplastic clone of cells into a fully malignant phenotype via both genetic and epigenetic mechanisms. Malignant cells have minimal requirements for normal growth factors and are relatively unresponsive to normal growth regulation, resulting in the uncontrolled growth that is the hallmark of cancer.

Because tumor cells contain more than one mutation, it may be difficult to know which should be classified as causing initiation, promotion, or progression, although this distinction may not be relevant. In this review, we will use the terms tumor promoter/promotion in a generic sense; ie, as any proneoplastic activity. Several general mechanisms of proneoplastic activity are recognized and are summarized as follows.

**Mutagenesis**

The establishment of a mutation is a sine qua non of cancer: All cancer cells contain permanent changes to the DNA such that the transformed phenotype is inherited following multiple cell divisions. Under normal conditions, mutation of a critical gene results in a loss of cellular homeostasis and the ultimate death of the cell. Proneoplastic mutations, on the other hand, confer a selective growth or survival advantage to the cell. As a result, a cell that "should" die manages to survive sufficiently to undergo secondary changes, permitting growth under conditions in which a normal cell would either die or be static. Most notable among proneoplastic mutations are those that result in increased expression of oncogenes (eg, myc, ras, abl, bcl-2) or decreased activity of tumor-suppressor genes (eg, p53, Rb).[33]

Neoplastic alterations of these genes derive from point mutations, deletions, and chromosomal translocations. Almost all tumor cells have an affected identifiable oncogene or suppressor gene. Their gene products have diverse mechanisms of action involving different metabolic pathways in the cell. However, they all commonly confer a selective growth or survival advantage to the cell. Phenotypic changes representative of proneoplastic mutations include a decreased need for metabolites and growth factors, abnormal signal transduction, inappropriate expression of receptors for available growth factors (epidermal growth factor receptor, HER2/neu), dysregulation of cell-cycle checkpoints, and resistance to apoptosis.[33]
Cell Proliferation
It is widely thought that any agent that causes increased cell proliferation increases the risk of neoplastic transformation. The rationale for this concept is that DNA synthesis associated with cell division is necessary to convert a potentially transient change in the DNA into a permanent one. That is, for a mutation to occur, the damage to the DNA must survive the many DNA repair processes and must be readable by DNA polymerase, which creates and locks in the mutation. DNA damage that blocks DNA synthesis results in cell death, thus eliminating the possibility of a mutation in that cell. In addition, although replicative DNA synthesis is a precise process, errors do occur, and these can lead to the incorporation of a mutation. If, by chance, this mutation results in a selective growth or survival advantage to the cell, it may become a precancerous lesion.

Adaptation
Cells have the ability to turn on and off the genes that help them survive toxic signals (e.g., induction of P450 enzymes for metabolism of toxic chemicals and drugs). This adaptation to an adverse growth environment is usually transient and allows normal cells to survive until the potentially toxic condition is alleviated. However, under circumstances of prolonged stress, such as during chronic inflammation, a mutation may lock in the growth-advantaged phenotype. Hence, prolonged exposure to stress can result in selection of preneoplastic cells. Some examples of adaptive changes in a cell are increased expression of antioxidant enzymes, matrix metalloproteinases, and growth factor receptors; increased anaerobic respiration; and de novo synthesis of angiogenic factors.

Angiogenesis
One exciting new concept in cancer treatment comes from the understanding that tumorigenesis requires new blood vessel formation (angiogenesis, neovascularization) in solid tissues. Normal tissues have a fixed blood supply and do not incur angiogenesis unless undergoing developmental changes (e.g., embryogenesis, menstrual cycle) or recovering from a wound. Tumors, on the other hand, must develop a new blood supply in order to survive. Studies in experimental tumor models suggest that the inhibition of angiogenesis can impede tumor growth and metastasis and can cause preformed tumors to necrose and regress. Chronic inflammation is closely associated with angiogenesis, as granulation tissue requires an extended vascular supply. [35] Macrophages, platelets, fibroblasts, and tumor cells themselves are a major source of angiogenic factors such as basic fibroblast growth factor, vascular endothelial growth factor, inflammatory cytokines (e.g., tumor necrosis factor [TNF]-alpha, interleukin [IL]-1-beta, IL-6, chemokines (e.g., IL-8, GRO-alpha), prostaglandins-1 and -2, and nitric oxide. [35]

Inhibition of Apoptosis
Except during development and tissue regeneration, normal tissues exhibit a precise balance between the rate of cell division and cell death. Disruption of this balance in favor of excess growth signals possible oncogenesis. Because dead or dying cells are rarely detected in normal tissue, it is thought that normal (programmed) cell death occurs through a controlled process called apoptosis. Apoptotic cells have unique morphologic and biochemical characteristics that distinguish them from necrotic cells. [36] The main physiologic difference between apoptosis and necrosis is in how the cells affect the surrounding tissues: Cells dying by apoptosis are recognized and taken up by phagocytic cells before they have an opportunity to lyse and release their content into the tissue. [37] The phagocytes degrade the cells with minimal environmental disturbance and no induction of inflammation. In contrast, cells dying by necrosis lyse before being taken up by phagocytes, [38] thereby causing an inflammatory response that can cause incidental damage to the surrounding tissue.

Treatment with chemotherapeutic drugs or depletion of growth factors usually kills tumor cells by inducing apoptosis, [39] whereas high levels of oxidants, chemicals, or severe hypoxia usually induce necrotic death. Cells that have become resistant to apoptosis have a greatly increased risk of being or becoming neoplastic. An appreciation for the strong association between reduced apoptosis and tumorigenesis was advanced by the discovery that the oncogene bcl-2, which mediates B-cell tumorigenesis, acts by inhibiting normal B-cell apoptosis.

We now know that many different oncogenes act by inhibiting apoptosis, thereby conferring a survival advantage to preneoplastic and malignant cells. By the same token, normal tumor-suppressor genes such as p53 and Rb promote apoptosis in response to toxic stimuli, inducing appropriate death in a damaged cell. [40] Any agent that prevents cells from dying in response to toxic stimuli can have the effect of promoting tumorigenesis by allowing proliferation of an abnormal cell.

Proneoplastic Inflammatory Mediators
Inflammatory cells secrete soluble factors that can contribute to the promotion of tumorigenesis.
through all of the above mechanisms. This provides a strong basis for understanding how chronic inflammation can predispose to the development of cancer. The remainder of this review will focus on the role of three different types of inflammatory mediators that have documented ability to serve as tumor promoters: (1) reactive oxygen and nitrogen molecules, (2) cytokines, and (3) prostaglandins. Although these mediators are often studied and discussed in isolation, there is significant interaction and synergy among them—for example, prostaglandins induce expression of certain inflammatory cytokines, which can, in turn, induce production of reactive oxygen and nitrogen species.

Reactive Oxygen and Nitrogen Intermediates

When phagocytes (neutrophils, eosinophils, monocytes, macrophages) are exposed to an inflammatory stimulus (eg, bacteria), they become activated and begin to generate large quantities of reactive oxygen and nitrogen intermediates.[41] Reactive oxygen intermediates, also generically referred to as oxidants, are derivatives of molecular oxygen such as superoxide, hydrogen peroxide, hypochlorous acid, singlet oxygen, and the hydroxyl radical. Under normal circumstances, phagocyte-derived oxidants serve a protective function by killing invading bacteria and parasites. However, they can also have detrimental effects, causing tissue damage and contributing to the development or progression of numerous diseases including cancer.[41] The same is true for reactive nitrogen intermediates, which are generated by inflammatory phagocytes through the enzymatic synthesis of nitric oxide by an inducible nitric oxide synthase and the subsequent interaction with molecular oxygen or reactive oxygen intermediates.[42]

Proneoplastic Mechanisms—Our best understanding of the proneoplastic activity of reactive oxygen and nitrogen intermediates comes from their ability to induce damage to DNA.[43,44] Exposure of cells to activated phagocytes leads to oxidative and nitrosative modification of bases, and single-strand breaks.[45-47] Despite the presence of a wide array of mechanisms to repair oxidatively damaged DNA, the repair process is slow and not always complete.[48] Further processing of damaged DNA leads to proneoplastic mutations, including point mutations, deletions, sister chromatid exchanges, and chromosomal translocations.[49] Proteins[50] and lipids[51] are also significant targets for oxidative attack, and modification of these molecules can increase the risk of mutagenesis. For example, oxidative modification of lipids can cause mutagenesis through the formation of genotoxic lipid peroxidation by-products that react with the DNA.[44,52] Protein oxidation may indirectly promote mutagenesis through oxidative modification of DNA polymerase or inhibition of DNA repair enzymes. Agents that either scavenge reactive oxygen and nitrogen intermediates or prevent their formation inhibit induction of DNA damage, mutagenesis, and transformation by inflammatory phagocytes. This forms the basis for the theory that dietary antioxidants can inhibit the development or progression of cancer.

This review focuses on the DNA-damaging effects of reactive oxygen and nitrogen intermediates, but other proneoplastic mechanisms may also be important. For example, chronic exposure to low levels of reactive oxygen intermediates stimulates signal transduction and cell proliferation. In addition, subtoxic levels of reactive oxygen intermediates induce activation of genes that support escape from normal growth controls, including induction of genes that code for antioxidant enzymes such as catalase and superoxide dismutase. Overexpression of these proteins can result in adaptation and survival in the face of high levels of oxidants that should be cytotoxic.[53] These mechanisms may play an important role in oxidant-mediated tumorigenesis and have been reviewed elsewhere.[52]

Superoxide, Hydrogen Peroxide, and the Hydroxyl Radical—Reactive oxygen and nitrogen intermediates have varying degrees of reactivity and diffusability that influence their mutagenic potential.[43] Superoxide is the primary product of the phagocytic oxidative burst and is generated by a membrane-associated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[41] Superoxide is not particularly reactive with biomolecules and cannot diffuse across cell membranes. It rapidly dismutates—either spontaneously or catalytically through the action of superoxide dismutase—to hydrogen peroxide, which also is not particularly reactive on its own. However, hydrogen peroxide can diffuse significant distances and cross cell membranes like water. The biological danger from superoxide and hydrogen peroxide comes when there is a redox-active transition metal present, such as iron (Fe) or copper (Cu). Interaction of Fe^{2+} or Cu^{1+} with hydrogen peroxide generates highly reactive radicals such as the hydroxyl or ferryl radicals. Superoxide serves as a source of hydrogen peroxide and acts also to maintain the transition metals in the reduced state, thus supporting radical formation. The hydroxyl radical is too reactive to diffuse any significant distance and will react with the first molecule with which it comes in contact. Hence, the site where the hydroxyl radical is formed is also the site of its damage.

DNA contains a significant amount of bound iron and copper. When phagocyte-derived hydrogen
peroxide diffuses into the nucleus of the target cell, it interacts with the transition metal on the DNA, forming a radical and giving rise to strand breaks and base modifications.

**Peroxy nitrite**—In addition to its pivotal role in supporting the formation of the hydroxyl radical, superoxide has the additional effect of reacting with nitric oxide to generate peroxynitrite.[42] Unlike nitric oxide and superoxide, which have limited reactivity with biomolecules, peroxynitrite and its hydrogenated counterpart peroxynitrous acid react with most biomolecules yet have a significant diffusion distance as well—a potent combination. Peroxynitrite generated outside of the cell can cause damage to the DNA inside the nucleus. In this regard, the formation of peroxynitrite may be one of the most dangerous products of activated phagocytes. Note that in order for peroxynitrite to be formed, both NADPH oxidase and nitric oxide synthase must simultaneously be active in the cell. Reactive nitrogen intermediates can induce DNA damage and mutations via several different mechanisms.[42] Like the hydroxyl radical, peroxynitrite has the ability to bring about DNA base modifications, strand breaks, and mutations through oxidative mechanisms. In addition, the products of nitric oxide synthesis have a second important pathway for inducing mutations that comes from the formation of nitrosamines through N-nitrosation of secondary amines. N-nitrosamines are highly mutagenic and carcinogenic and, hence, may be particularly important mediators of carcinogenesis induced during chronic inflammation.[47]

**Hypochlorous Acid**—In addition to synthesizing superoxide and nitric oxide, activated neutrophils, monocytes, and eosinophils generate large quantities of hypochlorous acid, the active ingredient in household bleach. The formation of hypochlorous acid from hydrogen peroxide and chloride is catalyzed by myeloperoxidase, which comprises approximately 5% of the total protein of neutrophils, or by the homologous eosinophil peroxidase. Hypochlorous acid is a strong oxidant that also has the ability to diffuse across cell membranes, and although it is not thought to cause DNA strand breaks, it can cause DNA base modifications leading to mutations.

**Lines of Evidence**—Support for the theory that phagocyte-derived oxidants contribute to mutagenesis and carcinogenesis comes from several lines of evidence.

1. **Inflammatory phagocytes have the capacity to induce oxidative and nitrosative DNA damage and mutagenesis in neighboring cells.** Thus, co-incubation of cells with activated neutrophils or macrophages fosters the induction of strand breaks and oxidative base damage. The most common mutations induced by reactive oxygen and nitrogen intermediates are base modifications leading to point mutations. Prominent among these is 8-oxo-2-deoxyguanosine (8-oxodG), which is misread by DNA polymerase to generate GC-to-TA transversions.[43] In addition, oxidants cause the formation of gross chromosomal abnormalities such as sister chromatid exchanges, deletions, and inversions.[54]

2. **Incubation with activated neutrophils or macrophages results in neoplastic transformation of fibroblasts and epithelial cells.[55,56]** The induction of chromosomal damage and neoplastic transformation by activated phagocytes can be inhibited with antioxidant compounds, indicating that oxidants are mediators of phagocyte-mediated cell transformation.[54,55]

3. **The types of mutations found in some tumor cells are reflective of oxidative damage.** For example, the GC-to-TA transversions that are induced by reactive oxygen and nitrogen intermediates are commonly found in Ras codons 12, 13, and 61, leading to activation of the oncogene, and in "hot spots" in the tumor-suppressor genes p53 and Rb.[47] This represents a possible common mechanism of tumor promotion by these agents. Compounds that inhibit tumor promotion in the mouse skin cancer model also inhibit the respiratory burst of phagocytes.

4. **Tumor promoters such as PMA and benzoyl peroxide are known for their ability to activate the oxidative burst of neutrophils and macrophages, and PMA causes oxidative base damage in the skin.[57]** This represents a possible common mechanism of tumor promotion by these agents. Compounds that inhibit tumor promotion in the mouse skin cancer model also inhibit the respiratory burst of phagocytes.

5. **Chronic inflammation is accompanied by increased production of tissue reactive oxygen and nitrogen intermediates.** Evidence of this process is documented in studies of the markers of oxidative activity in vivo. Thus, oxidatively and nitrosatively modified DNA and proteins are present in chronically inflamed tissue or the body fluids of patients with chronic inflammatory conditions. The likely source of the oxidative activity is the polymorphonuclear neutrophils and macrophages recruited as part of the inflammatory response. Markers of oxidative damage are also elevated in tumor tissues,[58] but it is unclear whether these are caused by oxidants generated by inflammation-associated leukocytes or whether the damaging oxidants come from the tumor cells themselves.[59]

In addition, the inducible form of nitric oxide synthase, thought to be responsible for the generation of nitric oxide in inflamed tissues, is up-regulated in chronically inflamed tissues, including gastric tissue associated with *H pylori* infection.[47] While increased expression of inducible nitric oxide
synthase is seen in inflammatory bowel disease, it is unclear whether it actually promotes or attenuates the inflammatory condition, because knockout mice display an increased susceptibility for colitis.[60]

Overall, although there is some disagreement as to whether phagocyte-derived oxidants contribute to tumorigenesis,[61] there is a significant body of experimental data supporting the conclusion that they do.

**Prostaglandins**
Evidence from human and animal studies suggests that prostaglandins contribute to the development of cancer.[62,63] Prostaglandins such as prostaglandin E (PGE) are lipid mediators of the inflammatory immune response and are derived from oxidative metabolism of arachidonic acid. These lipids are synthesized in large quantities by inflammatory cells in response to both acute and chronic inflammatory stimuli.

Two different cyclooxygenase (COX) enzymes catalyze the rate-limiting first step in prostaglandin synthesis.[64] COX-2 is expressed during inflammation. Its primary site of synthesis is inflammatory monocytes and macrophages, but it is also expressed in noninflammatory cells such as fibroblasts, epithelial cells, and endothelial cells. In vitro expression of COX-2 is induced by bacterial cell products and inflammatory cytokines. Notably, prostaglandin synthesis can also be stimulated by peroxynitrite,[65] thereby providing for synergy between these two procarcinogenic inflammatory mediators. Experimental induction of COX-2 in animal models is accomplished with agents that induce chronic inflammation such as administration of azoxymethane to rats. COX-1 is a constitutive enzyme expressed in most cell types and is associated with regulation of housekeeping functions such as gastric acid secretion.

**Lines of Evidence**—Two significant findings represent strong evidence that prostaglandins mediate human inflammation-associated carcinogenesis. First, the incidence and progression of colon cancer is diminished by long-term intake of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or sulindac.[62,66,67] These drugs share the ability to inhibit cyclooxygenase activity and prostaglandin synthesis. Although this may not be their only mechanism for inhibiting tumor development,[62] it is a likely mechanism because other activities of NSAIDs, such as inhibition of angiogenesis,[68] require high drug concentrations that are unlikely to be achieved at therapeutic doses in humans.

Second, COX-2 is elevated in inflammatory bowel diseases and is associated with an increased risk of colon carcinogenesis. The endogenous agents responsible for inducing COX-2 expression in the inflamed colonic mucosa are unknown as yet. COX-2 is also overexpressed in 85% of adenocarcinomas, suggesting that there is a link between COX-2 activity and tumor growth. The likely cellular sources of prostaglandins in tumor tissue are the inflammatory monocyctic cells that infiltrate the colonic mucosa. PGE is also elevated in the tumor tissue and blood of patients with colon cancer. If these prostaglandins promote tumor growth, then NSAIDs may not only prevent colon carcinogenesis but may also provide a means of limiting tumor progression.[63]

**Animal Models**—Important evidence that prostaglandins promote carcinogenesis also comes from animal models showing that experimentally induced tumor formation or progression can be inhibited by NSAIDs. In a murine model of colon carcinogenesis associated with familial adenomatous polyposis, it was demonstrated that knockout of the COX-2 gene or administration of a selective COX-2 inhibitor reduced the incidence of colon carcinogenesis.[69] Similarly, inhibition of chemically induced colon carcinogenesis by COX-2 inhibitors has been demonstrated in a rat model.

Animal models suggest that other inflammation-associated cancers may also be promoted by prostaglandins. For example, pristane-induced plasma cell tumorigenesis in BALB/c mice is inhibited by the administration of indomethacin in the drinking water.[22] Injection of pristane into the peritoneal cavities of BALB/c mice induces a chronic inflammatory condition associated with a massive influx of neutrophils and macrophages.

COX-2 expression is elevated in macrophages, and this is associated with elevated peritoneal PGE levels.[70] Treatment of mice with indomethacin significantly inhibits tumor development and, as expected, completely inhibits PGE production by the inflammatory macrophages.[71] The levels of indomethacin achieved in the peritoneal cavity are low (µm range) and are unlikely to inhibit enzymes other than the cyclooxygenases (E. Shacter, J. Wax, and M. Potter, unpublished results, 1992).

Skin carcinogenesis in experimental mouse models also involves PGE, and here, too, NSAIDs are preventive. Similarly, progression of mouse mammary tumorigenesis is inhibited by administration of NSAIDs.[72] Mammary tumors are often infiltrated with inflammatory macrophages, which, together with the tumor cells themselves, are potent sources of endogenous PGE.
Mechanisms of Tumorigenesis—Many different mechanisms have been proposed to explain how prostaglandins promote tumorigenesis.[63] These mechanisms are briefly described below.

1. Prostaglandins can stimulate cell proliferation.
2. PGE induces synthesis of cytokines such as IL-6 that serve as tumor growth factors.
3. Synthesis of prostaglandins is coupled with formation of DNA-reactive by-products with mutagenic potential; eg, formation of malondialdehyde from prostaglandin G.
4. COX enzymes can catalyze the oxidative metabolism of xenobiotics, leading to the formation of genotoxic mutagens.
5. Prostaglandins can induce angiogenesis, which is required for growth and metastasis of tumors.
   Some evidence of this comes from the demonstration that NSAIDs inhibit angiogenesis in vitro. It has been suggested that these drugs may not be acting entirely through the inhibition of PGE synthesis because the addition of exogenous PGE fails to overcome the inhibitory effect of the NSAIDs.[68]
   However, the concentrations of NSAIDs required to inhibit prostaglandin-independent angiogenesis in vitro are quite high (eg, 250 to 500 µM of indomethacin) and are unlikely to be achieved in vivo. In contrast, inhibition of prostaglandin synthesis by NSAIDs occurs at concentrations that are achieved in vivo (eg, 1 µM or less for indomethacin).[73]
6. In addition to serving as proinflammatory mediators, prostaglandins are also immunosuppressive. By inhibiting the functions of T cells and macrophages, they may decrease immune surveillance and thereby allow nascent tumor cells to escape detection by the immune system.
7. Prostaglandins may inhibit apoptosis of tumor cells by increasing expression of the antiapoptotic oncogene bcl-2 or by removing arachidonic acid, which is thought to be proapoptotic.
8. Prostaglandins can stimulate cell signaling through peroxisome-proliferator-activated receptor delta, a transcription factor that regulates proliferation-associated genes.

Cytokines

Inflammatory cells secrete a large number of cytokines and chemokines that can promote the outgrowth of neoplastic cells. These factors are produced in response to proinflammatory stimuli such as bacterial lipopolysaccharide. Neoplastic cells have a reduced need for normal metabolic factors, but they often require the presence of specific cytokines in order to proliferate, at least in the early stages of tumor development. Many tumor cells developing in chronically inflamed tissue cultivate a growth advantage by acquiring the ability to proliferate in response to cytokines. They may express growth factor receptors abnormally or alter their response to the factors by undergoing cell division instead of differentiation.

Examples of tumor cell cytokine dependence in human disease are the growth dependence of AIDS- and EBV-associated B-cell lymphomas, B-cell leukemias, and multiple myeloma on the inflammatory cytokines IL-6[74] and IL-15,[75] and the dependence of malignant mesothelioma on platelet-derived growth factor. Monocytes, macrophages, and T cells are major sources of cytokines that promote outgrowth of preneoplastic and malignant cells, in addition to autocrine growth factor production by the tumor cells themselves.

Tumor-Progression Mechanisms—Cytokines can contribute to tumor progression by mechanisms other than direct stimulation of cell growth. One such mechanism involves inducing the production of reactive oxygen and nitrogen intermediates. For example, TNF-alpha is known to enhance the formation of reactive oxygen intermediates by neutrophils and other cells. IL-1-beta, TNF-alpha, and interferon (IFN)-gamma stimulate expression of inducible nitric oxide synthase and the formation of nitric oxide in cholangiocarcinoma. This process has been shown to cause DNA damage and inhibit DNA repair in tumor cells.

IL-8 can promote tumorigenesis through two different mechanisms. One involves induction of angiogenesis, possibly through the synthesis of matrix metalloproteinases. In addition, IL-8 recruits inflammatory neutrophils to the site of inflammation and may thereby increase formation of reactive oxygen and nitrogen intermediates. Some cytokines may also promote tumorigenesis by inducing immunosuppression, as is suggested for transforming growth factor-beta.

Animal Models—Several animal models have demonstrated the role of inflammatory cytokines in tumorigenesis associated with chronic inflammation. Pristane-induced plasma cell tumors in mice require IL-6 for their growth; macrophages in the chronically inflamed tissue provide the IL-6.

Production of IL-6 in this system is stimulated by PGE2 and inhibited by the administration of indomethacin.[70,71] As noted above, the PGE2 is probably derived from COX-2, which is elevated in inflammatory macrophages from pristane-treated mice. Knockout of the IL-6 gene inhibits experimental plasmacytomagenesis.[76]

A second experimental system for elucidating the role of inflammatory cytokines in tumorigenesis is seen with TNF-alpha, which is induced by tumor promoters in experimental skin carcinogenesis.
models. Knockout of the TNF-alpha gene in mice significantly inhibits the development of skin tumors in response to DMBA and phorbol esters.[77] IL-8, an inflammatory CXC chemokine derived from monocytes, macrophages, and endothelial cells, is implicated in the progression and metastasis of tumors in the colon, bladder, lung, and stomach.

**Treatment and Prevention**

Many of the inflammatory mediators described in this review promote both the initiation and progression of cancer. As such, it should be possible to devise strategies to slow or prevent tumorigenesis and tumor progression.

**NSAIDs and Novel Agents**

Chronic intake of NSAIDs may reduce carcinogenesis by inhibiting production of prostaglandins, cytokines, and angiogenic factors. Note that NSAIDs do not eliminate inflammation but rather act by reducing the production of selected inflammatory factors. Hence, unlike steroids, they do not suppress elements of the immune response that are necessary for tumor depletion such as T cells, NK cells, and macrophages. COX-2 selective inhibitors may provide a safer method for chemoprevention than older NSAIDs such as aspirin and indomethacin, which also inhibit COX-1 activity and cause gastric lesions.

Potential therapies for tumors that depend on inflammatory cytokines for growth or metastasis may derive from modalities that either remove the cytokines (eg, monoclonal antibodies or soluble receptors), block cytokine receptors, or target toxins to tumor cells bearing high levels of growth factor receptors. All these approaches are currently being explored in clinical trials.

**Dietary Antioxidants**

Eating a diet rich in fruits and vegetables is thought to be the best and safest means of preventing cancer. Epidemiologic studies suggest that diets high in fruits and vegetables are strongly associated with a lower incidence of different forms of cancer. This approach to cancer prevention has been reviewed elsewhere.[78]

Because fruits and vegetables contain high levels of antioxidant compounds (eg, carotenoids, polyphenols, vitamin C), and because oxidants have a known capacity to promote neoplastic transformation, it has been postulated that consumption of antioxidant supplements may prevent some forms of cancer. More definitive evidence that reactive oxygen and nitrogen intermediates derived from inflammatory phagocytes can lead to tumorigenesis will depend on the completion of an intervention trial demonstrating that interference with radical formation or activity reduces tumor development or progression.

The Food and Nutrition Board of the Institute of Medicine recently examined the role of oxidants in disease in order to determine whether dietary antioxidants inhibit the development of chronic diseases such as atherosclerosis and cancer (see [http://books.nap.edu/books/0309061873/html/index.html](http://books.nap.edu/books/0309061873/html/index.html)). The panel of experts concluded that, at present, there are insufficient human data to conclude that dietary antioxidants, such as vitamins C and E, carotenoids, and selenium, can prevent cancer. The lack of supportive evidence is due, in part, to the complexities of designing and conducting a suitable intervention trial and to the long-term nature of tumor development. Trials that are of short duration or that are conducted in older individuals may only be looking at tumor progression and not initiation events.

If oxidants are involved primarily in initiation through the induction of DNA damage, and this occurs years (or decades) before tumor outgrowth begins, then administration of antioxidants over a narrow window of time later in life would likely be ineffective. Studies of NSAID inhibition of colon cancer indicate that the drugs must be taken for many years in order to lower tumor incidence. The same may hold true for antioxidant supplements.

**Antioxidants Plus Chemotherapy**

In addition to inhibiting de novo carcinogenesis, antioxidants may improve cancer treatment by enhancing antineoplastic therapy. Solid tumors are often infiltrated with inflammatory phagocytes, and tumor tissues can contain higher than normal levels of reactive oxygen intermediates.[58,79] It has recently been discovered that oxidants can interfere with the induction of apoptosis by chemotherapeutic agents (eg, etoposide, doxorubicin, fluorouracil) and that these effects can be overcome with antioxidant compounds.[38,80] Hence, the oxidative stress associated with inflammation in tumor tissue may interfere with cancer treatment.

The experimental findings are relevant in light of the fact that oncologists generally advise their patients not to take antioxidant supplements while receiving chemotherapy. The basis for this recommendation comes from the theory that most chemotherapeutic drugs act by generating intracellular oxidants to kill the target tumor cells, mostly by inducing apoptosis. Thus, any agent that interferes with the pro-oxidant activity of the drugs might interfere with efficacy.
In reality, while some of the ancillary damage caused by chemotherapeutic agents is thought to occur through an oxidative mechanism (eg, cardiac and kidney damage induced by doxorubicin and cisplatin, respectively), it is unclear whether this is true for tumor killing. In fact, most antineoplastic drugs kill tumor cells by interfering with DNA metabolism through nonoxidative mechanisms. Consistent with this view, several reports in the literature suggest that antioxidants can prevent unwanted tissue damage without interfering with efficacy.[81] Moreover, the possibility that oxidants derived from chronic inflammation within a preexisting tumor might interfere with cancer treatment merits further investigation.

References:


78. Blumberg JB: Considerations of the scientific substantiation for antioxidant vitamins and


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