Inflammation and Cancer

II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy

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Inflammation and Cancer. II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. Am J Physiol Gastrointest Liver Physiol 286: G515–G520, 2004; 10.1152/ajpgi.00475.2003.—It is well established that cancer arises in chronically inflamed tissue, and this is particularly notable in the gastrointestinal tract. Classic examples include Helicobacter pylori-associated gastric cancer, hepatocellular carcinoma, and inflammatory bowel disease-associated colorectal cancer. There is growing evidence to suggest that this association is not coincidental but may indeed be causal. In this review, we discuss the role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy and outline some of the possible mechanisms involved.

chronic inflammation; carcinogenesis; reactive oxygen species; cyclooxygenase-2; cytokines; cytokine polymorphisms

THE LINK BETWEEN INFLAMMATION and cancer was first suggested by Rudolph Virchow in 1863, when he demonstrated leukocytes in neoplastic tissue. Virchow’s original hypothesis has been revisited by many research groups, and there are now ample data to corroborate inflammation-mediated oncogenesis (6). The epidemiological data available are very impressive and show a clear association between chronic inflammatory conditions and subsequent malignant transformation in the inflamed tissue (Table 1).

The gastrointestinal system is the site of a significant proportion of these tumors. Starting in the pharynx and moving distally, cancers arise in chronically inflamed gastrointestinal tissues and organs. The etiology of the inflammation varies and can be infective, such as a virus, bacteria, or parasite, or it may be a noninfective irritant, either physical or chemical. For example, Epstein-Barr virus is the etiological agent responsible for the progression of early dysplastic change into severe dysplasia in nasopharyngeal carcinoma. Hepatitis B (HBV) and C (HCV) viruses account for >80% of cases of hepatocellular carcinoma worldwide, and human papilloma virus (HPV) infection is the leading cause of anogenital cancer. The gram-negative bacterium Helicobacter pylori has been identified as the major etiological factor in gastric adenocarcinoma, and it is also known to significantly increase the risk of gastric mucosa-associated lymphoid tissue (MALT) lymphoma. Parasites such as Clonorchis sinensis cause a chronic inflammatory infiltrate of the biliary tract and are linked to subsequent cholangiocarcinoma.

There are numerous examples of noninfective irritants being associated with the development of malignant disease. Within the gastrointestinal tract, chronic esophagitis including Barrett’s metaplasia, chronic pancreatitis, and chronic cholecystitis are all inflammatory conditions that increase the risk of cancer. Thus it is apparent that chronic inflammation is a common underlying theme in the development of many gastrointestinal malignancies. But what are the mechanisms through which these inflammatory stimuli may act to induce cancer? To examine this, we must first give a brief outline of chronic inflammation.

CHRONIC INFLAMMATION

Chronic inflammation may progress from acute inflammation if the injurious agent persists, but more often than not, the response is chronic from the outset. In contrast to the largely vascular changes of acute inflammation, chronic inflammation is characterized by infiltration of damaged tissue by mononuclear cells such as macrophages, lymphocytes, and plasma cells, together with tissue destruction and attempts at repair.

The macrophage is the key player of the chronic inflammatory response. This is due to the great number of bioactive products it releases (Table 2). These mediators form part of the body’s powerful defense against invasion and injury. The downside, however, is that persistent or pathological macrophage activation can result in continued tissue damage. This underlies a variety of disease processes from rheumatoid arthritis to atherosclerosis.

THE INFLAMMATORY INFILTRATE OF TUMORS

In tumors, many of the cell types active in chronic inflammation can be found in the surrounding stroma and also within the neoplasm itself. In 1891, mast cells were reported as histological findings at the tumor periphery, and today, there is no doubt that many neoplasms, particularly those that are epithelial in origin, have a significant inflammatory cell component. This includes a diverse leukocyte infiltrate of macrophages, neutrophils, eosinophils, and mast cells often in association with lymphocytes (5). Tumor-associated macrophages are dispersed throughout many tumors, whereas the distribution of dendritic cells may vary according to their level of maturity. For example, in breast cancer, mature dendritic cells were found to be confined to the peritumoral area, whereas immature dendritic cells were interspersed in the tumor mass. Dendritic cells originate from monocytes in the presence of...
A cardinal feature of inflamed tissues, including those of the gastrointestinal tract, is the generation of nitric oxide (NO) through inducible nitric oxide synthase (iNOS). NO reacts with superoxide to form peroxynitrite (ONOO−) and nitrosating species such as NO− (nitrates), NO2− (nitrites), and N2O3. NO and its products may exert oncogenic effects via several mechanisms including direct DNA and protein damage, inhibition of apoptosis, mutation of DNA, and cellular repair functions such as p53 and also via promotion of angiogenesis (17).

Another inducible enzyme with carcinogenic properties that is active within inflamed and malignant tissues is cyclooxygenase-2 (COX-2). Several mechanisms of COX-2-mediated intestinal carcinogenesis have been elucidated. These include inhibition of apoptosis, modulation of cellular adhesion and motility, promotion of angiogenesis, and immunosuppression (21, 29). There is also strong epidemiological evidence implicating COX-2 in the pathogenesis of a number of epithelial malignancies including gastric and colorectal cancer. Inhibitors of the enzyme are associated with a reduction of up to 50% in the morbidity and mortality of colorectal cancer (21). Among the most potent inducers of COX-2 are the key proinflammatory cytokines IL-1α, IL-1β, and TNF-α.

### IMMUNE RESPONSE AND CYTOKINES IN GASTROINTESTINAL MALIGNANCY

Immune response undoubtedly has a significant impact on the potential for malignancy, and this is highlighted by the findings that severe combined immunodeficiency and T cell-deficient mice infected with Helicobacter do not develop the same degree of tissue injury despite high levels of gastric bacterial colonization (10, 24). The importance of CD4 lymphocytes, in particular, is also demonstrated by experiments that show that B cell-deficient Helicobacter-infected mice are not protected from severe atrophy and metaplasia (24). In colorectal adenomas and carcinomas, there is a predominance of CD4- and CD3-positive cells (16). Thus CD4 T lymphocytes and their cytokine products are extremely important in the malignant transformation of chronically inflamed tissue.

Focusing on individual cytokines has generated further evidence to support the role of inflammation in gastrointestinal carcinogenesis. For example, IFN-γ knockout mice are protected from gastric atrophy, whereas IL-10-deficient mice develop severe atrophic gastritis and a chronic enterocolitis (18, 26). Interestingly, many of the IL-10-deficient mice with chronic enterocolitis go on to develop colorectal cancer similar to human inflammatory bowel disease-associated neoplasia.

IL-1, similar to many other proinflammatory cytokines, is capable of inducing COX-2 and iNOS expression. In the gallbladder, IL-1α and TNF-α were found to directly affect

<table>
<thead>
<tr>
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<tbody>
<tr>
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</tr>
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<td>Asbestos and mesothelioma, Silica, cigarette smoke and bronchial cancer, Chronic asthma and bronchial cancer</td>
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**Table 1. Chronic inflammatory conditions and associated cancers according to system**

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**Table 2. Products released by macrophages (4)**

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Neutral proteases</th>
</tr>
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<tbody>
<tr>
<td>Elastase</td>
<td>Collagenase</td>
</tr>
<tr>
<td>Plasminogen activator</td>
<td>Acid hydrolases</td>
</tr>
<tr>
<td>Phosphatases</td>
<td>Lipases</td>
</tr>
<tr>
<td>Plasma proteins</td>
<td>Complement components (e.g., C1 to C5, properdin)</td>
</tr>
<tr>
<td>Coagulation factors (e.g., factors V, VIII, tissue factor)</td>
<td>Reactive metabolites of oxygen</td>
</tr>
<tr>
<td>Eicosanoids</td>
<td>Lipid mediators, cytokines, chemokines (IL-1, TNF, IL-8)</td>
</tr>
<tr>
<td>Growth factors (PDGF, EGF, FGF, TGF-β)</td>
<td>Nitric oxide</td>
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**G516 INFLAMMATION AND GI MALIGNANCY**

**WHY ARE INFLAMMATORY CELLS SO CLOSELY ASSOCIATED WITH TUMORS?**

It is known that neoplastic cells are capable of attracting several different cell types into the tumor microenvironment through secretion of extracellular proteases, proangiogenic factors, and cytokines. IL-10 is secreted by tumor cells as well as macrophages, and among other effects, it inhibits cytotoxic T cells and thus aids in suppressing the immune response against the tumor (6). Chemokines, which comprise the largest family of cytokines, are characterized by their ability to induce migration and activation of leukocytes to specific sites. This includes tumor stroma and the CC chemokine, macrophage chemotactic protein (MCP)-1, which has been shown to be a major determinant of monocyte/macrophage infiltration in tumors. Tumor epithelial areas have also been found to express MCP-1, whereas additional chemokines such as MIP-1β and regulated on activation normal T-expressed and presumably secreted may be detected in the stroma and regulate the infiltration of other inflammatory cells including T cells. Furthermore, chemokines may stimulate cells to release proteolytic enzymes, aiding the digestion of extracellular matrix and providing a path for further inflammatory cell migration, tumor growth, and metastasis. It is important to appreciate, however, that in many preneoplastic conditions such as those outlined in Table 1, an inflammatory cell infiltrate is already well established and driving protumor effects.

**REACTIVE OXYGEN SPECIES, NITRIC OXIDE, AND CYCLOOXYGENASE-2**

A cardinal feature of inflamed tissues, including those of the gastrointestinal tract, is the generation of nitric oxide (NO) through inducible nitric oxide synthase (iNOS). NO reacts with superoxide to form peroxynitrite (ONOO−) and nitrosating species such as NO− (nitrates), NO2− (nitrites), and N2O3. NO and its products may exert oncogenic effects via several mechanisms including direct DNA and protein damage, inhibition of apoptosis, mutation of DNA, and cellular repair functions such as p53 and also via promotion of angiogenesis (17).
epithelial cell absorptive function, similar to the proinflammatory agents LPS and PGE2 (23). The same study went on to suggest that this diminished absorptive capacity may predispose to gallstone formation on a background of inflammation. Thus chronic inflammation, mediated by cytokines such as IL-1 and TNF-α, may not just be a consequence of gallstones but a precursor.

The molecular mechanisms involved in the pathogenesis of hepatitis C virus (HCV)-associated hepatocellular carcinoma also depend on cytokines. HCV core protein interacts with STAT3, the signal transducer and activator of transcription 3 protein, which mediates cytokine signaling and the local cytokine profile (3). NF-κB, another transcription factor that is known to activate inflammatory pathways and proinflammatory cytokines, is also stimulated in HCV infection. Both these factors have additional tumor-promoting potential in that STAT-3 has growth-stimulatory effects and NF-κB can inhibit apoptosis.

NF-κB

Reactive oxygen species (ROS), COX-2, and cytokines interact in a complex manner in the development and progression of an inflammatory environment. They share several intracellular pathways and mediators through which their physiological and pathological effects are exerted. One such mediator is NF-κB, a ubiquitous transcription factor involved in the regulation of various inflammatory, apoptotic, and oncogenic genes. It has often been described as a central mediator of the immune response, particularly because a large variety of bacteria and viruses can lead to its activation. The activation of NF-κB leads to the expression of inflammatory cytokines, chemokines, immune receptors, and cell surface adhesion molecules.

Further evidence supporting inflammation’s role in the initiation and promotion of gastrointestinal malignancy comes from the fact that constitutive expression of NF-κB has been identified in a number of gastrointestinal (GI) malignancies including hepatocellular carcinoma and colorectal cancer.

CYTOKINE POLYMORPHISMS AND GASTROINTESTINAL MALIGNANCY

Genetic polymorphisms have emerged in recent years as important determinants of disease susceptibility and severity. This is particularly true for cytokine gene polymorphisms and gastrointestinal malignancy. Perhaps the most compelling evidence for the role of inflammation in GI malignancy comes from studies showing that proinflammatory cytokine gene polymorphisms increase the risk of cancer and its precursors. An excellent example of this is the role of these polymorphisms in the pathogenesis of H. pylori-induced gastric cancer. H. pylori causes its damage by initiating chronic inflammation in the gastric mucosa. This inflammation is mediated by an array of pro- and anti-inflammatory cytokines. Genetic polymorphisms directly influence interindividual variation in the magnitude of cytokine response, and this clearly contributes to an individual’s ultimate clinical outcome. In the case of H. pylori infection, we speculated that the most relevant candidate genes would be ones whose products were involved in handling the H. pylori attack (innate and adaptive immune responses) and ones that mediated the resulting inflammation. Because such a list of candidate genes would be prohibitively extensive, we further narrowed the search by selecting genes that were most relevant to gastric physiology and, in particular, gastric acid secretion. H. pylori-induced gastritis is associated with three phenotypes that correlate closely with clinical outcome. The first is an antrum-predominant/corpus-sparing pattern associated with high acid secretion and increased risk of duodenal ulcer disease. Second is mild mixed antrum/corpus gastritis with no major effect on acid secretion and, generally, no serious clinical outcome. The last is a corpus-predominant or severe pangastritis pattern that is associated with gastric atrophy, hypochlorhydria, and an increased risk of gastric cancer. Inhibition of gastric acid pharmacologically can lead to a shift from an antrum-predominant pattern to a corpus-predominant one with onset of gastric atrophy. Thus it was clear that an endogenous agent that was upregulated in the presence of H. pylori, has a profound proinflammatory effect, and was also an acid inhibitor would be the most relevant host genetic factor to be studied. IL-1β fitted this profile perfectly, for not only is it one of the earliest and most important proinflammatory cytokines in the context of H. pylori infection, it is also the most powerful acid inhibitor known (11). We have shown that proinflammatory IL-1 gene cluster polymorphisms (IL-1B encoding IL-1B and IL-1RN encoding its naturally occurring receptor antagonist) increase the risk of gastric cancer and its precursors in the presence of H. pylori (12). Individuals with the IL-1B-31°C or -511*T and IL-1RN*2/*2 genotypes are at increased risk of developing hypochlorhydria and gastric atrophy in response to H. pylori infection. This risk is extended to gastric cancer itself with a two- to threefold increased risk of malignancy compared with subjects who have the less proinflammatory genotypes (12, 13). The association of IL-1 gene cluster polymorphisms and gastric cancer has been confirmed in other reports (14).

In addition to IL-1 gene cluster polymorphisms, proinflammatory genotypes of TNF-α and IL-10 have also been identified as risk factors for gastric cancer, and, as is the case with IL-1 gene cluster polymorphisms, this is restricted to noncardia adenocarcinomas (13). We have shown that having an increasing number of proinflammatory genotypes (IL-1B-511*T, IL-1RN*2/*2, TNF-α-308*A, and IL-10 ATA/ATA) progressively increases the risk of gastric cancer. Indeed, by the time three to four of these polymorphisms are present, the risk of gastric cancer is increased 27-fold (13). The fact that H. pylori is a prerequisite for the association of these polymorphisms with malignancy demonstrates that in this situation, inflammation is indeed driving carcinogenesis. It is likely that other proinflammatory cytokine gene polymorphisms will be relevant to gastric cancer initiation and progression. This exciting field has expanded greatly over the past few years, and the search is now fully on for the full complement of risk genotypes that dictate an individual’s likelihood of developing cancer. This approach has now been adopted for many other cancers as described below.

In Japanese patients with chronic HCV infection, the IL-1B-511 T/T genotype has been associated with an increased risk of progression to hepatocellular carcinoma (27). Because the T/T proinflammatory genotype is related to greater IL-1B production, it is feasible that risk of malignant transformation is higher. IL-1B leads to the production of PGE2 and hepatocyte growth factor and has angiogenic influence via inducible NO
and COX-2 expression. Furthermore, the degree of HCV-induced liver inflammation and fibrosis has been correlated with hepatic expression of Th1 cytokines.

At present, there is relatively little information on the relationship between other gastrointestinal malignancies and cytokine polymorphisms. Some studies have addressed the influence of polymorphisms on cancer outcome. Barber et al. (1) found that possession of a genotype resulting in increased IL-1β production was associated with shortened survival in pancreatic cancer. Park et al. (22) investigated TNF-A and -B polymorphisms in 136 colorectal cancer patients and 325 healthy controls in an Asian population. Their results indicated that TNF-B*1/TNF-B*1 genotypes showed an increased risk for colorectal cancer. De Jong and colleagues (9) recently performed pooled analyses on 30 polymorphisms in 20 low-penetrance genes and identified an additional three studies investigating TNF-A polymorphisms and colorectal cancer. Associations were detected for the a2, a5, and a13 TNF-α alleles and colorectal cancer.

MECHANISMS OF INFLAMMATION-ASSOCIATED TUMOR DEVELOPMENT IN THE GI TRACT

The mechanisms employed by ROS, COX-2, and cytokines to promote neoplasia are well described in the literature and, due to space limitations, will only be discussed briefly here. These mechanisms include direct DNA damage, inhibition of apoptosis, subversion of immunity, and stimulation of angiogenesis. In addition, chronic inflammation in the GI tract is also known to affect proliferation, adhesion, and cellular transformation (Table 3).

Deregulation of cellular proliferation is one of the hallmarks of cancer cells and is the outcome of interaction between a variety of endogenous and exogenous factors that are active during the inflammatory process. These include luminal contents, bacteria, inflammatory cytokines, and mediators such as the matrix metalloproteinases. Direct mechanical irritation can also lead to epithelial proliferation, and when this is combined with the effects of an additional inflammatory stimulus, such as a bacterium for example, the resulting hyperproliferation can push the tissue further along the pathway toward cancer. H. pylori infection, although initially enhancing apoptosis, ultimately leads to a compensatory proliferation (30). Pathways through which H. pylori may influence apoptosis include those involving COX-2 and peroxisome proliferator-activated receptor-γ (15). Proinflammatory cytokines, particularly TNF-α, are also able to modulate apoptosis through altering the levels of the pro- and antiapoptotic proteins Bcl-2 and Bax.

As well as affecting proliferation and apoptosis, the same mediators impact on cellular adhesion and angiogenesis. Cancer cells responding to proinflammatory cytokines released from macrophages may exploit the same mechanism used by leukocytes to migrate through the vasculature. Upregulation of cell adhesion molecule expression is seen on exposure of colon cancer cells to LPS, and COX-2 has also been shown to promote cell adhesion (26, 28).

Macrophages are important sources of VEGF, and studies have shown that this can be augmented in tumors by the humoral antitumor immune response (2). Thus a Th2 environment promotes angiogenesis, and conversely, CMI/Th1 immune responses tend to be inhibitory. Although infection and inflammation initially generate Th1 cytokines, a cycle involving COX-2-mediated upregulation of Th2 cytokines and subsequent chronic downregulation of the Th1/Th2 cytokine balance in favor of angiogenesis, and COX-2 itself has proangiogenic activity. Hypoxia is a potent inducer of VEGF, and this is mediated by the transcription factor hypoxia-inducible factor-1α (HIF-1α). The VEGF gene contains a number of HIF-1α-binding sites in its regulatory region, and HIF-1α is able to activate the VEGF promoter. Liu and colleagues (19) demonstrated that PGF2α production via COX-2-catalyzed pathways plays a critical role in HIF-1α regulation by hypoxia. They showed that tumors treated with a COX-2 inhibitor were smaller, with increased apoptosis, decreased microvessel density, and decreased tumor VEGF levels. ROS, NO, certain cytokines, and growth factors are also regulators of HIF-1α expression, and this may explain their proangiogenic activity. The significance of HIF-1α in inflammation has been highlighted by Cramer et al. (7), who revealed that it controls the redness and swelling of injured tissues and the ability of leukocytes to enter inflamed areas. In the low oxygen concentration of injured, inflamed, or neoplastic tissue, HIF-1α is required to generate ATP in leukocytes and thus enable them to function. It also increases the production of NO, which acts back to further increase HIF-1α activity. Thus acting through HIF-1α in a hypoxic environment, various inflammatory mediators including growth factors, NO, cytokines, chemokines, COX-2, and its products may “switch” on angiogenesis. They may do this via the generation of VEGF, either directly or indirectly, and may also aid the process by activating other factors such as proteases, which degrade the extracellular matrix. Therefore, it is not difficult to see that in chronic GI inflammation, the development of hypoxic areas may increase the generation of proangiogenic stimuli that tip the balance in favor of angiogenesis and further drive tissues toward carcinogenesis.

Finally, in addition to impacting on cellular proliferation, apoptosis, adhesion, and angiogenesis, the stimuli and mediators of chronic inflammation can cause cellular transformation. A number of viruses such as HBV, Epstein-Barr, and HPV are known to directly bind to certain genes and affect protein activity, including transcriptional factors and oncogenes. Animal models have also demonstrated that bacteria can lead to ultrastructural changes within the colonic epithelia and subsequent hyperplasia (20). This may precede the development of colonic adenomas.

Table 3. Mechanisms of inflammation-associated tumor development in the gastrointestinal tract

| Stimulation of cellular proliferation—increases probability of mutations, (e.g., in cellular proto-oncogenes, DNA, and cellular repair mechanisms) |
| Inhibition of apoptosis |
| Cellular adhesion |
| Stimulation of angiogenesis |
| Cellular transformation |
In Fig. 2, we have attempted to provide an overview of how chronic inflammation in the GI tract may ultimately lead to malignancy. This takes into account the various cellular processes and pathways through which inflammation and its by-products are thought to exert their effects.

In summary, in this review, we have discussed the links between chronic inflammation and carcinogenesis of the GI tract. There is ample epidemiological evidence to support this link, but increasingly, the basic molecular pathways of this association are being uncovered. Inflammatory cells produce a number of inflammatory mediators including proinflammatory cytokines, chemokines, growth factors, and NO, many of which share transcriptional factors such as HIF-1 and NF-kB. These may act independently or in combination, leading to the activation of COX-2. At the center are 5 cellular mechanisms that could form a pathway to malignant transformation, either independently or more likely in concert. COX-2 is known to impact on each of them and is placed in an inner layer because of the growing evidence supporting its central role in gastrointestinal carcinogenesis. However, the relationships among NO, cytokines, and activation of COX-2 and their impact on cellular mechanisms are not purely linear. As described in the review, all of these factors are capable of exerting effects independent of COX-2, and thus this layer may not always be a necessary component in revealing the final core of pathways to cancer.
wide range of mediators including proinflammatory cytokines, chemokines, ROS, growth factors, and eicosanoids. COX-2 may be a linchpin in orchestrating many of the mutagenic effects of these products, and this is supported by studies showing the chemopreventative benefits of COX inhibitors. Cytokine gene polymorphisms undoubtedly contribute to individual risks of malignancy, but their importance lies in their contribution to the understanding of inflammation-mediated carcinogenesis. The fact that chronic inflammation impacts crucial cellular processes such as proliferation, adhesion, apoptosis, angiogenesis, and transformation highlights its pivotal role in the pathogenesis of GI malignancy.

REFERENCES