Chronic inflammation and gastrointestinal cancer

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ABSTRACT

Chronic inflammation has been identified as an important risk factor in the development of the gastrointestinal (GI) tract cancers, and the underlying molecular mechanisms have been studied extensively. Chronic inflammation is able to trigger cellular events to promote malignant transformation of normal epithelial cells in the GI tract to cancer. Host inflammation responses in carcinogenesis are through multiple mechanisms such as reactive oxygen and nitration species from mononuclear phagocytes and leukocytes, immune response and pro-inflammatory cytokines. Nuclear factor-κB (NF-κB) has been considered as the central mediator of the immune response. Activation of NF-κB by phosphorylation leads to translocation of NF-κB protein to the nucleus, and in turn regulates the transcription of several pro-inflammatory cytokines and chemokines. Furthermore, chronic inflammation creates an environment for genomic and epigenetic changes. In this review, we summarize the important molecular mechanisms that link chronic inflammation and GI tract cancer, including esophageal, gastric and colonic cancers, focusing on infective and noninfective agents such as gastroesophageal reflux disease, Helicobacter pylori gastritis and inflammatory bowel disease.

Key words: Cancer, gastrointestinal tract, immune response, inflammation

Introduction

It is now widely accepted that inadequately resolved chronic inflammation could increase cancer risk. The etiology of inflammation varies and could result from infection with viruses, bacteria or parasites. Alternatively, it may be noninfective but caused by a physical or chemical irritant. For example, hepatitis B and C viruses account for more than 80% of hepatocellular carcinoma cases in the world, while human papillomavirus infection is the leading cause of anogenital cancer, and Helicobacter pylori has been considered as the major cause of gastric adenocarcinoma and is known to significantly increase the risk of gastric mucosa-associated lymphoid tissue lymphoma. Moreover, there are numerous examples of noninfective agents being associated with inflammation and development of cancers. Several pathological conditions in the gastrointestinal (GI) tract such as gastroesophageal reflux disease (GERD), inflammatory bowel diseases (IBDs), chronic pancreatitis, and cholangitis-related cholangiocarcinoma illustrate this link.[1] As a barrier to the environment and as the main organ system for digestion and absorption of food, the GI tract is exposed to many substances and stimulants.

Some of these, such as alcohol and acid, can cause GI cancers by linking to chronic inflammation [Table 1].[2,3] Thus, in this review, we discussed emerging concepts and provided specific examples for the role of chronic inflammation in the development of GI cancers, including esophageal, gastric and colonic cancers, since they have been investigated most thoroughly.

Role of Chronic Inflammation in Cancer Development

Immune response and cytokines in cancers

Chronic inflammation is characterized by the infiltration of mononuclear cells, such as macrophages, lymphocytes and plasma cells in damaged tissue, together with tissue destruction and attempts to repair. In this inflammatory state, local activation of the immune system occurs. Natural killer cells, monocytes, macrophages, dendritic cells, mast cells and granulocytes usually elicit the first immune response and initiate inflammation. Of the many cell types active during chronic inflammatory response,

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How to cite this article: Ida S, Watanabe M, Baba H. Chronic inflammation and gastrointestinal cancer. J Cancer Metastasis Treat 2015;1:138-43.

Received: 27-07-2015; Accepted: 11-08-2015.
Macrophages are one of the key players. Recent studies showed that tumor-associated macrophages (TAMs) were dispersed throughout tumor lesions and contributed to tumor growth, invasion and metastasis by producing various mediators. In general, TAMs are found within and surrounding most tumor cells and can, when activated, release numerous factors to influence the behavior of tumor cells and the local tissue microenvironment. Interferon (IFN)-γ induces “classical” activation of macrophages, while anti-inflammatory mediators such as interleukin (IL)-10, IL-4 and IL-13 provoke “alternative” activation of macrophages, which are referred as M1 and M2 macrophages respectively.

M2 macrophages are oriented toward promoting tumor progression, tissue repair and angiogenesis as well as suppressing adaptive immunity in tumors, whereas M1 macrophages, as classically or alternatively activated macrophages, are activated by lipopolysaccharides and IFN-γ, and can secrete high levels of IL-12 and low levels of IL-10.

**Reactive oxygen species, nitric oxide and cyclooxygenase-2**

Chronic inflammation creates a microenvironment locally to induce genomic instability in cells. At the site of chronic inflammation, cells are exposed to oxygen and nitrogen radicals from mononuclear phagocytes and leukocytes. These radicals can cause DNA damage. For example, nitric oxide and its products may exert oncogenic effects via several mechanisms, including inhibition of DNA mismatch repair, protein damage, induction of hypermethylation, inhibition of apoptosis, mutation of DNA and disruption of cellular repair functions such as those involving the p53 pathway. Release of reactive oxygen and nitrogen species is enhanced by pro-inflammatory cytokines such as tumor necrosis factor (TNF), IL-1β and IFN-γ.

Another inducible enzyme with carcinogenic properties that is active in inflamed and malignant tissues is cyclooxygenase-2 (COX-2). Strong epidemiological evidence implicates that COX-2 plays a role in the pathogenesis of a number of epithelial malignancies, including esophageal, gastric and colorectal cancers (CRCs). 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.

**Nuclear factor-κB**

Inflammatory responses contribute to carcinogenesis through multiple mechanisms. As mentioned above, reactive oxygen species, COX-2 and some cytokines interact with each other in a complex manner during development and progression of an inflammatory environment. One such mediator is the transcription factor nuclear factor-κB (NF-κB), which is a key mediator of inflammation and involved in the regulation of apoptotic and oncogenic gene expression and activation. NF-κB has often been described as the central mediator of the immune response and as being critically involved in cancer-associated inflammation and the tissue repair response. Aberrant activation of NF-κB protein was associated with inflammation and cancer in mouse models and in human GI cancers. Activation of NF-κB plays an important role in integrating multiple stress stimuli and regulating immune responses. Bile acids, particularly deoxycholic acid, have been shown to activate the NF-κB pathway. NF-κB activation through phosphorylation leads to translocation into the nucleus, and in turn regulates the transcription of several pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8, and chemokines such as CXCL-1 and CXCL-2.

Thus, chronic inflammation could lead to carcinogenesis by sustaining pro-inflammatory oncogenic signaling, angiogenesis and immune suppression.

**Esophageal Cancer**

There are two major histological subtypes of esophageal cancer, that is, esophageal squamous cell carcinoma
(ESCC) and esophageal adenocarcinoma (EAC). Tobacco smoking and alcohol consumption are the two major risk factors in ESCC, with a risk of heavy smokers drinkers for 50 times greater in the induction of ESCC. Tobacco smoking and alcohol consumption have been associated with the field of cancerization in the upper aerodigestive tract. For example, Oka et al. demonstrated that tobacco smoking was likely to induce global DNA hypomethylation and site-specific CpG island promoter hypermethylation in the normal-appearing esophageal mucosa. Both these mutations are representative of DNA methylation alterations occurring in cancer cells. In addition, we also previously reported that global DNA hypomethylation in normal esophageal mucosa was observed in ESCC patients who habitually smoked, suggesting epigenetic field defect after exposure to risk factors. Recently, deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2), which causes the so-called alcohol flushing response, has been revealed to increase the risk of alcohol-related ESCC. In East Asian populations, there is a variant of ALDH2 in which the glutamate at position 487 is replaced with lysine, resulting in an inactive protein. Consumption of hot beverages is also suspected to cause chronic inflammation in esophageal squamous cell mucosa. In addition, the influence of human papillomavirus in increasing ESCC risk is still under debate.

Gastroesophageal reflux disease (GERD), cigarette smoking and obesity are all risk factors in EAC. EAC develops through chronic exposure to gastroesophageal reflux, Barrett’s esophagus, dysplasia and adenocarcinoma as a sequence. Increased exposure of the esophagus epithelium to refluxed gastric and bile acid, particularly deoxycholic acid, has a critical role in promoting the development of Barrett’s esophagus and EAC. NF-κB is a key regulator of the inflammatory process that has been shown to be activated in EAC. Several studies report that NF-κB was activated by bile acid components and subsequently involved in the development of metaplasia of Barrett’s esophagus and cancer.

**Gastric Cancer**

Gastric adenocarcinoma is the second leading cause of cancer-related death in the world. H. pylori causes chronic gastritis, and the relationship between H. pylori-induced chronic inflammation and cancer is one of the best-elucidated factors. Indeed, H. pylori induces active chronic gastric inflammation, which progresses to gastric adenocarcinoma, resulting in approximately 660,000 worldwide new cases of gastric cancer per year. However, only a few percentage of infected persons do develop neoplasia.

Several recent studies described that cytotoxin associated gene A (Caga)-positive H. pylori strains were identified to be particularly carcinogenic. Compared to CagA-negative strains, H. pylori strains that harbor the CagA pathogenicity islands (PAI) are associated with a significantly increased risk of distal gastric cancer. After attached to gastric epithelial cells, H. pylori CagA-positive strains eject the CagA protein directly into the gastric epithelial cells. After translocation, CagA undergoes tyrosine phosphorylation by Src and Abl kinases and the tyrosine phosphorylated-CagA binds to the Src homology 2 (SHP-2) domain, leading to morphologic alterations such as cell scattering and elongation. Furthermore, CagA-activated SHP-2 deregulates the MAP kinase signaling cascade. The CagA protein of certain H. pylori strains can stimulate expression of IL-8 by activating NF-κB, thereby contributing to neutrophil infiltration in the gastric mucosa. In addition, chronic inflammation caused by H. pylori infection contributes to neoplastic transformation by establishing a positive feedback loop via the signal transducer and activator of transcription (STAT) 3-dependent COX-2 induction, which in turn influences STAT3 regulation via IL-6.

Another mechanism of H. pylori-induced gastric carcinogenesis is genomic alteration and gene mutation. For example, prevalence of the TP53 mutation in gastric cancer is, on average, approximately 40%. Previous studies have shown that various genetic alterations occur in the gastric mucosa during chronic gastritis, suggesting an importance of the accumulated genomic mutations induced by H. pylori infection in the development of gastric cancer. Activation-induced cytidine deaminase (AID), a member of the cytidine deaminase family that functions to edit genomic DNA, is an enzyme essential for somatic hypermutation and class-switch recombination in immunoglobulin genes. However, inappropriate AID expression acts as a genomic mutagen to contribute to tumorigenesis. Infection with CagA PAI-positive H. pylori ectopically induced high expression of AID via NF-κB activation in human gastric epithelial cells, leading to multiple mutations in the host genome, such as those found in TP53. The accumulation of nucleotide alterations will lead to the development of gastric cancer.

Recently, exciting data showed an association of H. pylori infection with cancer stem cell population. The leucine-rich repeat-containing G-protein coupled receptor (Lgr5) is known as the stem cell marker of GI cancers, including gastric cancer. Lgr5-positive epithelial cells have higher levels of oxidative DNA damage than in Lgr5-negative cells from patients with H. pylori-positive gastric cancer, indicating that H. pylori specifically targets Lgr5-positive epithelial cells.

Other inflammatory risk factors that either act independently of H. pylori infection or further enhance its effects have been also identified. For example, chronic gastritis caused by bile reflux can cause intestinal metaplasia as a neoplastic precursor lesion in gastric cancer. Moreover, T-cell-mediated autoimmune
gastritis fosters the development of intestinal type gastric cancer.\textsuperscript{[53,54]} Thus, these risk factors lead to a state of chronic inflammation and then development of gastric cancer.

**Colorectal Cancer**

CRC is one of the leading causes of cancer-related deaths in the world. CRC is one of the most serious complications of IBD, including ulcerative colitis and Crohn’s disease. The relative risk of CRC in patients with colitis is two to eight times higher than the general population.\textsuperscript{[55]} Although it is clear that chronic inflammation is a CRC risk factor, pathogenesis of colitis-associated cancer (CAC) is still uncertain.

CAC develops in chronically inflamed mucosa and is believed to develop in a colitis-dysplasia-carcinoma sequence. The chronic inflammation in IBD often results in increased re-epithelialization of cells and cell turnover in the colonic mucosa and thus, leads to increased risk of errors in DNA repair and cell cycle regulation. Oxidative stress and impaired DNA mismatch repair are combined with proliferation, invasion and angiogenesis, thereby promoting cell growth signaling. In contrast with sporadic CRC, \textit{p53} mutations occur in the early stages and APC mutations occur in the late stages of the genesis of CAC.\textsuperscript{[56,57]}

Moreover, obesity-related inflammation has been considered to be a plausible link between obesity and cancer.\textsuperscript{[58]} In general, survival of cancer cells is critically dependent on their interaction with neighboring non-malignant cells.\textsuperscript{[59]} The contribution of the tumor stroma to cancer cell survival has been widely studied. The adipocytes surrounding tumor lesions are one of the major components of the tumor stroma. Furthermore, adipose tissue can secrete signaling molecules such as adipocyte-derived cytokines (termed adipokines), pro-inflammatory cytokines, proangiogenic factors and extracellular matrix constituents.\textsuperscript{[60]} From a clinical viewpoint, obese individuals are at an increased risk of developing colon cancer, in addition to the fact that increased adiposity is associated with morbidity and mortality.\textsuperscript{[58,61]} In IBD, many inflammatory cytokines are involved in carcinogenesis, as evidenced by the elevated circulating levels of IL-6 and TNF. TNF is highly elevated in the colon of C57/BL6 mice fed with a high fat diet.\textsuperscript{[62]} Moreover, treatment with TNF-neutralizing monoclonal antibodies decreased growth of colon cancer xenografts and tumor incidence in azoxymethane (carcinogen)-treated leptin-deficient mice.\textsuperscript{[63]} These studies demonstrated that local inflammation mediated by TNF had a key role in tumor initiation in obese rodents.

Most recently, the gut microbiota has been also implicated in the initiation and promotion of CAC.\textsuperscript{[54,64]} It is thought that microbe-driven intestinal inflammation as an etiological factor contributes to CAC development; however, better understanding of the underlying molecular mechanism needs further investigation.

**Conclusion**

In this review, we have discussed the links between chronic inflammation and cancer development, with special reference to GI cancers. Future studies will determine the role for this novel anti-inflammation treatment modality in the prevention of GI cancers.

**Financial support and sponsorship**

This work was supported by Scientific Research (C) (KAKENHI) (15K10080) from the Japanese Society for the Promotion of Science.

**Conflicts of interest**

There are no conflicts of interest.

**References**


49. Kinoshita K, Nonaka T. The dark side of activation-induced...


