Cigarette smoking and gastrointestinal diseases: The causal relationship and underlying molecular mechanisms (Review)

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Abstract. Cigarette smoking is an important risk factor for gastrointestinal (GI) disorders, including peptic ulcers, inflammatory bowel diseases, such as Crohn's disease and cancer. In this review, the relationship between smoking and GI disorders and the underlying mechanisms are discussed. It has been demonstrated that cigarette smoking is positively associated with the pathogenesis of peptic ulcers and the delay of ulcer healing. Mechanistic studies have shown that cigarette smoke and its active ingredients can cause mucosal cell death, inhibit cell renewal, decrease blood flow in the GI mucosa and interfere with the mucosal immune system. Cigarette smoking is also an independent risk factor for various types of cancer of the GI tract. In this review, we also summarize the mechanisms through which cigarette smoking induces tumorigenesis and promotes the development of cancer in various sections of the GI tract. These mechanisms include the activation of nicotinic acetylcholine receptors, the formation of DNA adducts, the stimulation of tumor angiogenesis and the modulation of immune responses in the GI mucosa. A full understanding of these pathogenic mechanisms may help us to develop more effective therapies for GI disorders in the future.

Contents

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1. Introduction

Cigarette smoking is the most preventable risk factor for human health. According to a WHO report, 1.3 billion individuals are active smokers worldwide and smoking kills six million individuals each year; eventually, half of these smokers die due to smoking-related diseases (1). To this end, cigarette smoking is known to be associated with cardiovascular diseases (2), cancers (3,4), lung diseases (5), chronic renal disorders (6) and other diseases remained to be defined. It has been regarded as a main killer and induces serious problems in humans with major concerns in public health.

Over 5,000 ingredients are found in cigarette smoke (7,8). Among these, at least 150 compounds found in cigarette smoke are known to induce free radicals and possess toxic and carcinogenic activities. Based on their structures, these toxic and carcinogenic ingredients are divided into several chemical classes. These include alkaloids, phenolic compounds, volatile aldehydes, polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TNSAs), as well as heavy metals (8). These chemical induce high levels of oxidative stress in smokers (7), and trigger and augment lipid peroxidation, which causes low-density lipoprotein (LDL) oxidation and atherosclerosis (9). These active ingredients also cause a high incidence of lung cancer accounting for approximately 90% of small cell lung cancer (SCLC) cases and 70% of non-small cell lung cancer (NSCLC) cases worldwide (10).

A number of studies have provided evidence that cigarette smoking is a major cause of gastrointestinal (GI) disorders, which include chronic inflammation, such as peptic ulcers and inflammatory bowel disease (IBD), and cancers of the GI tract (1,3-8). In this review, we mainly discuss the relationship between smoking and GI disorders, and the underlying mechanisms through which cigarette smoke and its active ingredients affect the pathogenic processes of some of these diseases of the GI tract.

2. Cigarette smoking increases the risk of ulcers and inflammatory diseases of the GI tract

Cigarette smoking increases the risk of peptic ulcer disease. Peptic ulcers are histologically identified as necrosis of the mucosa, which produces lesions. This disease is mainly caused

by *Helicobacter pylori* (*H. pylori*) infection, as well as the excessive use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen (11). Cigarette smoking is also considered to be one of the major contributors to ulcer diseases. A large US population-based study (1997-2003) revealed that the prevalence of ulcer disease in current and former smokers (11.43 and 11.52%) is almost doubled that of never smokers (6.00%) (12). It is also clear that the risk of peptic ulcers is associated with the quantity of tobacco use (13).

According to clinical observations, cigarette smokers are more likely to develop ulcers which are more difficult to heal (14). The risk of peptic ulcers also increases in smokers who have a large daily intake of tobacco compared with never smokers (15). However, cigarette smoking is not an independent ulcerogenic. It adversely affects the gastroduodenal mucosal protective mechanisms and increases the risk of *H. pylori* infection (14). Cigarette smoking allows the reflux of harmful duodenal contents back into the stomach. Furthermore, smokers appear to be at higher risk of becoming infected with *H. pylori*. This increased risk may be due to the adverse effects of smoking on the reduction of antioxidants or the defensive immune system locally present in the gastroduodenal mucosa. All these actions can interfere with the natural defensive mechanisms against *H. pylori* infection in the stomach and duodenum.

Effects of smoking on IBD. IBD is known as chronic inflammation of the GI tract, particularly the colon and small intestine. IBD includes Crohn's disease and ulcerative colitis (16). Cigarette smoking exerts a dichotomous effect in the progression of IBD. Smokers seem to be more likely to develop Crohn's disease, with a higher recurrence after surgery and poor response to medications (17,18). However, people who smoke have a lower risk of developing ulcerative colitis (19). Cigarette smoking is known as an independent risk factor for Crohn's disease. As early as 1984, a case-control study involving 82 patients with Crohn's disease and matched controls was conducted in the UK to determine the relationship between Crohn's disease and cigarette smoking (20). Patients with this disease were more likely to have a smoking habit. The relative risk for smokers to develop Crohn's disease was significantly higher than in non-smokers (20). In a separate study involving 2,795 patients with Crohn's disease, patients were classified into non-smokers, light smokers (1-10 cigarettes/day) and heavy smokers (>10 cigarettes/day). Researchers found that the percentage of years with active Crohn's disease for non-smokers, light smokers and heavy smokers were 37, 46 and 48%, respectively. Besides, the number of years of immumosuppressant mediation was higher in the heavy smokers than the light smokers and non-smokers (36 vs. 34 vs. 32%, respectively) (21). These results suggest that smoking may worsen the severity of the disease and prolong the disease course and drug treatment with immunosuppressants.

Conversely, smoking has been demonstrated to reduce the risk of ulcerative colitis. Mounting evidence has indicated that patients with ulcerative colitis tend to be non-smokers (22). In a population-based incident cohort study, smoking was more common in male patients (P=0.002), and positively correlated with an increased risk of Crohn's disease [odds ratio, 1.96; 95% confidence interval (CI), 1.63-2.37; P<0.001]. By contrast, current smoking was protective against ulcerative colitis (odds ratio, 0.33; 95% CI, 0.27-0.41). In addition, in ulcerative colitis, cigarette smoking was associated with less extensive disease (P=0.01) and a decreased need for colectomy (P=0.06) (23). The underlying mechanisms of action of smoking and its bidirectional effects on the progression of Crohn's disease and ulcerative colitis have not yet been fully elucidated and further studies are required using human and animal models.

Possible mechanisms of action of smoking in inflammatory diseases of the GI tract. As discussed, cigarette smoking is a major risk factor for the development of inflammation-related diseases, such as ulcers and Crohn's disease. In Fig. 1, the mechanisms of action of smoking in these disorders include the alteration of mucosal cell proliferation, change of blood flow in the inflammatory sites, the increase of viral or bacterial infections and the dysfunction of the immune system in the GI mucosa.

Smoking induces cell death in the mucosa. The mucosa is the inner layer of the GI tract, which surrounds the lumen. The innermost layer is known as the epithelium, which forms a continuous layer of protection against noxious agents from the lumen. The induction of cell apoptosis is an adverse effect of cigarette smoking, which results in tissue injury and dysfunction in the GI tract. A number of studies have shown that cigarette smoke can induce cell apoptosis in the esophagus and gastric mucosa (24), as well as in the inner layers of the small intestine and colon (25). Exposure to cigarette smoke induces a time- and concentration-dependent increase in apoptosis in the gastric mucosa (26). Pre-treatment with allopurinol (a xanthine oxidase inhibitor) or dimethyl sulfoxide (DMSO) (a hydroxyl free radical scavenger) can block the apoptotic activity induced by smoking, and does not affect the p53 level of the mucosa (26), suggesting that the apoptosis induced by cigarette smoking is mediated through reactive oxygen species (ROS) and occurs independently of the p53 pathway. Chronic exposure to cigarette smoke can also induce apoptosis in the follicle-associated epithelium, possibly through the CCL20-CCR6 cascade (25). Benzo(e)pyrene, a toxic compound found in cigarette smoke, also causes cell death in human retinal pigment epithelial cells (ARPE-19), and induces apoptosis through the involvement of multiple caspase pathways (27).

Smoking inhibits epithelial cell renewal in the GI tract. Epithelial cell renewal in the GI tract is an effective progress for protecting the surface epithelial cells from various aggressive factors coming from the lumen. The effects of cigarette smoking on cell renewal in the GI tract have been reviewed by a number of studies showing that cigarette smoke and its active ingredients not only inhibit mucosal cell proliferation, but also induce cell apoptosis during ulcer healing (8,24). Cell renewal is a protective process for the GI tract, the dysfunction of which plays a vital role in ulceration and ulcer healing (28). We have previously reviewed that cigarette smoke and its active ingredients can suppress mucosal cell proliferation and induce apoptosis during ulceration and the healing processes (8,24).

Epidermal growth factor (EGF). In our previous studies we demonstrated that cigarette smoke or its extracts significantly inhibit mucosal cell proliferation in human and animal mucosal cells, associated with the reduction of EGF and poly-

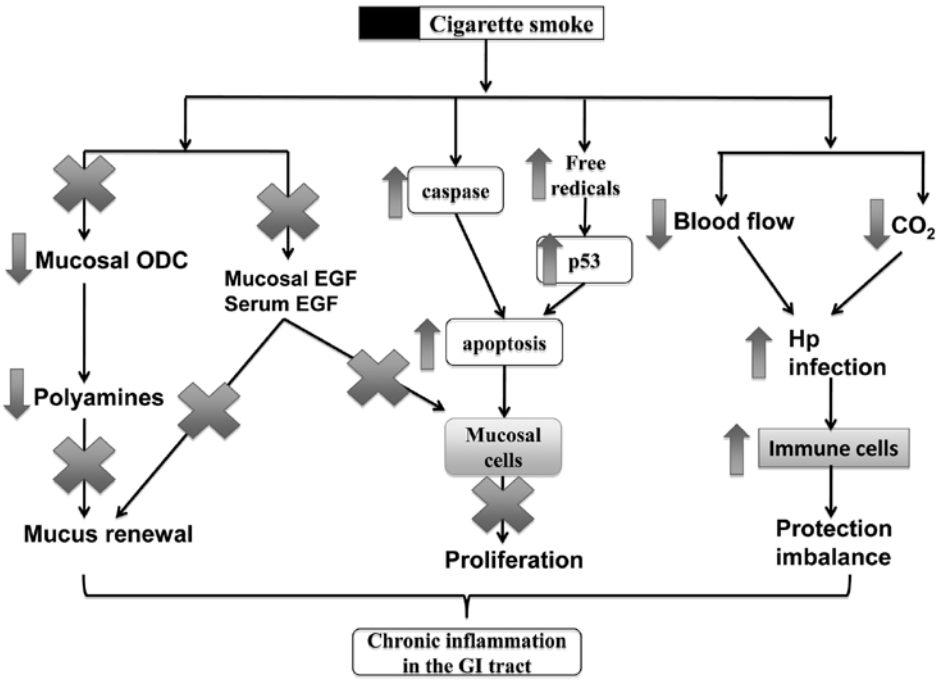

Figure 1. Possible mechanisms of action of cigarette smoke in inducing chronic inflammation in the GI tract. GI, gastrointestinal; ODC, ornithine decarboxylase; EGF, epidermal growth factor; Hp, *Helicobacter pylori*.

amine release (29,30). EGF plays an important role in mucosal cell proliferation and modulates mucosal integrity. During ulceration, the synthesis of EGF, as well as its expression are markedly upregulated in epithelial cells adjacent to the ulcer crater (31). Data from our previous study also demonstrated that cigarette smoke significantly inhibited EGF synthesis and its mRNA expression in salivary glands and gastric mucosa in rats with acetic acid ulcers (29). In addition, gastric ulcer healing was also delayed along with a reduced mucosal cell proliferation, suggesting that the delay of ulcer healing induced by cigarette smoke is possibly caused by the reduction of EGF release at the ulcer site.

Polyamines. Polyamines are found to be associated with mucosal cell proliferation during the ulcer healing process (32,33). Polyamines are involved in EGF-mediated cell proliferation and acid secretion in the stomach (34). Ornithine decarboxylase (ODC) is the primary enzyme for the biosynthesis of polyamines, including putrescine, spermine and spermidine. To further elucidate the association between smoking and peptic ulcer disease, in previous studies, we also examined ODC activity, which is crucial for promoting mucosal growth and has gastroprotective effects during gastric ulcer healing. Following the intragastric administration with cigarette smoke extracts once daily for three days, ulcer sizes were markedly enlarged and the myeloperoxidase activity was also increased. Cigarette smoke also significantly inhibited cell migration and cell proliferation with a reduction in ODC activity in an *in vitro* wound model. Moreover, the inhibitory effect on cell proliferation and ODC activity induced by cigarette smoke may be reversed by exogenous spermidine, indicating that the delayed wound healing in the stomach induced by cigarette smoke was at least in part due to a reduction in polyamine synthesis (30,32).

Smoking interferes with GI mucosal protective mechanisms

Stomach acid secretion. Under normal conditions, large amounts of hydrochloric acid exist in the stomach, which help to break down food into smaller particles for further digestion in the digestive tract. Gastric acid is neutralized in the duodenum by sodium bicarbonate produced by the pancreas. The increased secretion of stomach acid and/or a reduction in sodium bicarbonate production in the pancreas can interfere with the protective mechanisms of the gastric mucosa and the inner layer of the duodenum, where ulcers are normally formed. Ample evidence suggests that smoking can increase the production of gastric acid, accompanied by a reduction in bicarbonate production. The role of cigarette smoke and its active compounds, such as nicotine on acid production and sodium bicarbonate production has been reviewed (35). Researchers have found that the intravenous injection of nicotine hydrogen tartrate (0.012-0.020 mg/kg body weight) increases the concentration of hydrogen and chloride ions in the gastric juice (36). In an early study, Ligny *et al* (37) demonstrated that the magnitude of acid secretion was associated with the number of cigarettes smoked. They also found that tobacco smoking over a long period of time stimulated vagus nerves and induced functional parietal cells to increase pentagastrin-induced acid output in smokers.

Biliary reflux. Bile is a digestive fluid produced by the liver, and normally flows into the duodenum, where it digests fats and removes toxins. Bile salts also function as detergents and damage the mucosal barrier. The pylorus is a one-way valve between the stomach and the duodenum that prevents bile and other contents of the small intestine going back into the stomach (38). In a clinical study, it was demonstrated that cigarette smoking induces pyloric incompetence and increases the duodenogastric reflux (39), which may be due to the reduction

in basal pyloric pressure induced by smoking (40), leading to mucosal injury in the stomach.

Pancreatic bicarbonate secretion. Pancreatic bicarbonate plays an important role in neutralizing extra acid coming from the stomach. The increased secretion of gastric acid, as well as a reduction in sodium bicarbonate production would interfere with the protective mechanisms in the stomach and the duodenum, possibly leading to the development of ulcers in these organs. Several clinical studies have shown that the secretion of bicarbonate is diminished after cigarette smoking (41,42). Furthermore, the degree of inhibition on basal pancreatic secretion has been shwon to have a good correlation with the blood nicotine concentrations in humans (43).

Smoking increases susceptibility to H. pylori infection. *H. pylori* is known as one of the most common infectious bacteria found in humans (44). Growing evidence points to a potential association between *H. pylori* infection and GI disorders, including gastroduodenal ulcers and cancer (45). Although some researchers have found that cigarette smoking is negatively associated with *H. pylori* infection, particularly in younger subjects (46), other epidemiological and experimental studies have indicated that smoking is also a risk factor for *H. pylori* infection at least under certain clinical conditions (47,48).

Free radicals. Free radicals have been related to a wide spectrum of GI disorders, including ulcers, IBDs and GI cancers. Oxygen-derived free radicals play an important role in the pathogenesis of peptic ulcers and IBD induced by smoking, alcohol, as well as NSAIDs (49-51). Cigarette smoke contains large amounts of free radicals (52). The quinone/hydroquinone complex, for example, is an active redox system which is capable of decreasing molecular oxygen to produce superoxide, eventually transforming to hydrogen peroxide and hydroxyl radicals (52). The blood concentrations of free radicals in smokers are higher than those of non-smokers, indicating that smoking-induced free radicals promote gastric mucosal injury (53).

Smoking regulates immune cells in the GI tract. The GI tract is also protected by the local mucosal immune system operating in the GI mucosa against various internal and external pathogens (8). Chronic exposure to cigarette smoke and its active ingredients has also been demonstrated to lead to alterations in the immune system (54). Macrophages, neutrophils, lymphocytes and dendritic cells may be involved in the pathogenesis of inflammatory disorders in the GI tract. A research group found that chronic smoke exposure was positively associated with immune cell accumulation in Peyer's patches. The total number of dendritic cells, $CD4^+$ T cells (including regulatory T cells) and $CD8^+$ T cells was significantly increased following exposure to cigarette smoke for 24 weeks (25). Furthermore, the expression of chemokines, including CCL9 and CCL20 was also upregulated, which may play an important role in the pathogenesis of Crohn's disease. Smoke exposure also increases xanthine oxidase activity and histamine release in the gastric mucosa. This may further lead to neutrophil aggregation and vascular damage, thus promoting gastric ulcers in rats (55).

3. Smoking increases the risk of cancer of the GI tract

As stated in the previous section, tobacco smoking induces various chronic inflammatory diseases of the GI tract, including ulcers. It is clearly understood that chronic inflammation can cause tumor initiation through the induction of genomic instability, leading to mutagenesis (56). In addition, cigarette smoke contains a broad spectrum of toxic and carcinogenic components, such as aromatic amines, phenolic compounds, alkaloids, PAHs, TNSAs, as well as heavy metals (7,8). Among these, aromatic amines are thought to be the inducers of bladder cancer, and TNSAs are thought to contribute to lung cancer in smokers (57). Nicotine, taken as an example, is known as the most active ingredient in cigarette smoke, which is as high as 0.3-5% of the dry weight in tobacco leaves (58). It has been found that nicotine plays an important role in gastroduodenal ulceration (35) and Crohn's disease. Furthermore, it also promotes cancer development in the esophagus (59), stomach (4), colon (60) and liver (61).

Epidemiological studies

Cigarette smoking causes esophageal cancer. Cigarette smoking is one of the risk factors for esophageal cancer (62-65). Recently, a cohort study with a 20-year follow-up period conducted by Japanese researchers found that individuals who began smoking at a younger age and consumed larger amounts of alcohol more had a higher risk of developing esophageal cancer compared with the normal population. The esophageal cancer mortality risk was as high as 9.33 (95% CI, 2.55-34.2) for smokers who began smoking between the ages of 10 and 19 years and consuming three units of alcohol per day (64).

Cigarette smoking and cancer of the oral cavity. Supporting data have demonstrated that cigarette smoking is a major risk factor for cancer of the oral cavity (66-68). A recent study demonstrated that the odds ratios for current smokers and former smokers were 11.8 (95% CI, 8.6-16.3) and 2.2 (95% CI, 1.6-3.1), respectively when compared to non-smokers. The risk of developing cancer of the oral cavity increased with the quantity and duration of cigarette smoking (66). In addition, the risk of developing cancer of the oral cavity in former smokers decreased with time. The buccal mucosa and the floor of the mouth were the most sensitive sites with lesions induced by smoking (67).

Cigarette smoking and gastric cancer. The relationship between the occurrence of stomach cancer and cigarette smoking has been studied since the 1950s. Cigarette smoking has been considered as one of the key risk factors for gastric cancer, which increases the incidence of the disease by approximately 1.5- to 2.5-fold among current smokers (69). Nicotine, the active compound in cigarette smoke, has been demonstrated to be capable of promoting gastric tumor growth and neovascularization (3). In a 20-year follow-up study involving 18,244 middle-aged and older men conducted in Shanghai, China, researchers found that the risk of gastric cancer was statistically significantly higher in ever smokers [hazard ratio (HR), 1.59; 95% CI, 1.27-1.99] than in non-smokers (70). Furthermore, among the non-drinkers, the ever smokers experienced an 80% higher risk of gastric cancer (HR, 1.81; 95% CI, 1.36-2.41). All these observations indicate that cigarette smoking may exert independent effects on the development of gastric cancer.

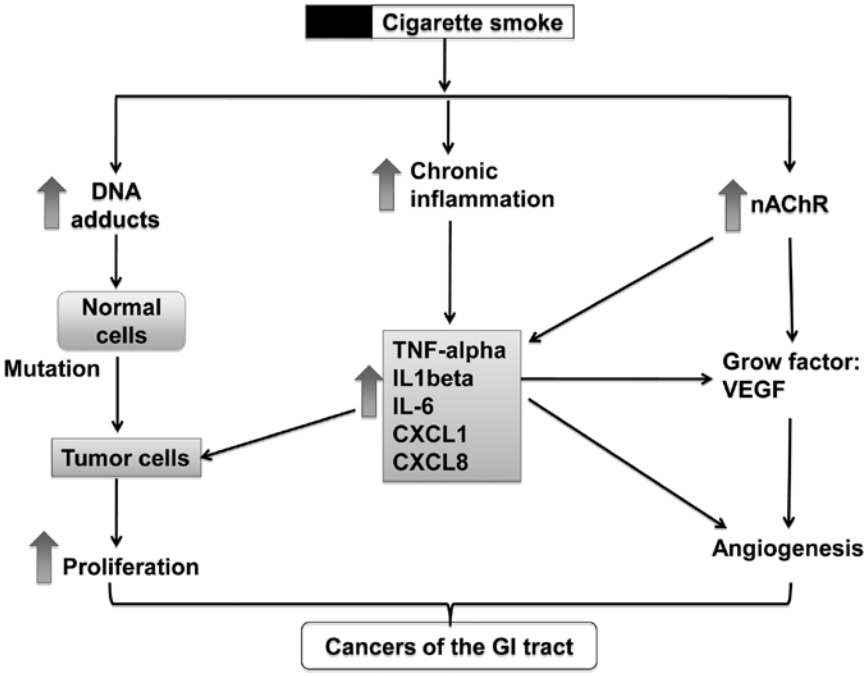

Figure 2. Proposed mechanisms of action of cigarette smoke in tumorigenesis in the GI tract. GI, gastrointestinal; TNF, tumor necrosis factor; IL, interleukin; nAChR, nicotinic acetylcholine receptors; VEGF, vascular endothelial growth factor.

Cigarette smoking causes pancreatic cancer. Tobacco consumption is considered an established risk factor for pancreatic cancer (71,72). In a 10-year cohort study, researchers found that cigarette smoking was related to an increased risk of the disease [relative risk (RR), 1.7; 95% CI, 1.6-1.9] and mortality (RR, 1.6; 95% CI, 1.4-1.7) in patients with pancreatic cancer (72).

Cigarette smoking causes colorectal cancer. Phipps *et al* (74) carried out a study in 1,968 patients with stage III colon cancer in order to examine the relationship between smoking and cancer outcome. They found that smoking history was significantly associated with a shorter disease-free survival (DFS), and time to recurrence (73) in patients with colon cancer (74). Compared with never-smokers, ever smokers experienced a significantly shorter DFS with a three-year DFS proportion of 70 vs. 74% (HR, 1.21; 95% CI, 1.02-1.42). Compared with never-smokers, participants who were former or current smokers were older and were more likely to be male, and to have colon tumors that were dMMR and/or BRAF mutated (74).

Possible effects of smoking on tumorigenesis in the GI tract. Cigarette smoke contains a broad spectrum of toxic and carcinogenic components, such as aromatic amines, phenolic compounds, alkaloids, PAHs, TNSAs, as well as heavy metals (7,8). These toxic and carcinogenic ingredients induce tumorigenesis in the GI tract through several possible mechanisms, including the activation of nicotinic acetylcholine receptors (nAChRs), the formation of DNA adducts, stimulation of tumor angiogenesis, the involvement of immune response and others (Fig. 2). Normally, these mechanisms co-exist and have synergistic effects on the promotion of tumorigenesis. For example, nicotine can activate the nAChRs on cancer cells and induce the release of growth factors, such as vascular endothelial growth factor (VEGF) and IL-1β into the tumor microenvironment, which can increase tumor angiogenesis and therefore promote tumor growth.

nAChRs. nAChRs are a family of ligand gate ion channels that function as the key regulators of nicotinic and cholinergic signaling in cells (75). nAChRs are known to participate in cellular adhesion and migration through the interactions with rapsyn and herparan sulphate proteoglycan (76,77). Increasing evidence suggests that nicotine and its derivatives, such as N-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonee can directly activate nAChRs to promote cell growth and angiogenesis and inhibit the drug-induced apoptosis of cancer cells (75).

A recent study demonstrated that nicotine activates Yes-associated protein 1 (YAP1) through nAChR-mediated signaling in esophageal squamous cell cancer (ESCC) (76). Zhao *et al* (76) reported that nicotine administration increased cell proliferation and migration, and promoted resistance to apoptosis in ESCC. In addition, nicotine administration was also found to induce the nuclear translocation and activation of YAP1 in ESCC. Nicotine signaling can also inhibit the interaction of YAP1 with p63 that contributes to the inhibitory effects of nicotine on cell apoptosis. The association between cigarette smoking and YAP1 activation was also observed in clinical esophageal cancer samples (76). These results suggest that nicotine may be the active compound in cigarette smoke responsible for carcinogenesis in the esophagus.

In our previous studies, we found that nicotine in cigarette smoke may be the most active ingredient responsible for the tumorigenesis of colon cancer cells (78,79). Nicotine was demonstrated to stimulate the proliferation of human colon adenocarcinoma HT-29 cells through the activation of α7-nAChR followed by the catecholamine-synthesis pathway and adrenaline release and finally, β-adrenergic activation (78).

Furthermore, in an animal study, nicotine was shown to promote tumor growth, mainly by activating the β-adrenoceptors and the subsequent expression of cyclooxygenase-2, prostaglandin E2, and VEGF in tumor tissues (79). These results demonstrate for the first time the contributory role of α7-bAChR and β-adrenoceptors in the tumorigenesis of colon cancer with significant involvement of some stress hormones.

Formation of DNA adducts. Many toxic compounds in cigarette smoke can interact with DNA to form DNA adducts, which are believed to be another important mechanism for carcinogenesis induced by cigarette smoke (80). Among various ingredients in cigarette smoke, TNSAs are known as the responsible compounds for the formation of DNA adducts (81). In an early clinical study, Dyke *et al* (81) found that in males only, DNA adducts in gastric tumor tissues from smokers were significantly higher than in those from non-smokers. Nitrosamines and other nitroso compounds in cigarette smoke are capable of covalently interacting with DNA, which alters the normal biological function of DNA and eventually induces carcinogenesis in the GI tract and in urinary bladder (81,82). To date, the formation of DNA adducts has been found in cancer tissues from the oral cavity (83), esophagus (84), stomach (81), pancreas (85) and colon (86).

The tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) has been demonstrated to be one of contributors for smoke-induced pancreatic cancers. It is clear that NNK can react with DNA to form DNA methyl and pyridyloxobutyl adducts (87). These DNA adducts can induce an activating point mutation of the Ki-ras gene in codon 12, which is common in human pancreatic adenocarcinomas (88,89). Askari *et al* (89) further demonstrated that NNK induced the transactivation of the EGF receptor, increased the accumulation of intracellular cyclic AMP, and activated the phosphorylation of mitogen-activated protein kinase (MAPK) and ERK1/2. These results indicate that the NNK-mediated β-adrenergic cAMP-dependent signaling pathway may contribute to the development of pancreatic carcinogenesis in smokers.

Chronic inflammation. The relationship between cancer and inflammation was perceived as early as the 19th century. It is clear that chronic inflammation predisposes to cancer at the proximity of the site of inflammation (90). Chronic inflammation in the GI tract can be caused by *H. pylori* infection, autoimmune diseases, such as IBD and inflammatory conditions, such as peptic ulcers. Various types of immune cells are involved in the formation of the tumor inflammatory microenvironment, such as macrophages, neutrophils, mast cells and lymphocytes. During the inflammatory process, various inflammatory components acting as messengers of inflammation are released by the immune cells and tumor cells in the microenvironment of the neoplastic tissues. These include cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1 and IL-6, and chemokines, such as CXCL8. Cigarette smoking is a risk factor for the development of chronic inflammation in the GI tract as reviewed in the previous section, which also promotes inflammation-associated adenoma/adenocarcinoma formation (91).

Cytokines: *a) TNF-α*. TNF-α, as a pro-inflammatory cytokines, can not only induce hemorrhagic necrosis of tumors, but also has protumoral functions. It has been found that a high dose of TNF can destroy the tumor vasculature and cut-off the supplement of O_2 and nutrition for tumor growth to exert necrotic effects in tumors (92). However, TNF-α can also induce DNA damage (93), suppress DNA repair (93) and promote the growth of tumor cells (94). Increasing evidence also suggests that TNF-α enhances tumor growth and invasion, angiogenesis, leukocyte recruitment and facilitates epithelial to mesenchymal transition (90). The bidirectional role of TNF-α in tumor progression and cell death is due to the fact that TNF can bind to different membrane-bound homotrimeric receptors, TNFRI and TNFRII, to trigger opposite pathways (95). As regards tumor promotion, TNF-α can inhibit the expression of glycogen synthase kinase-3β, and consequently activate the Wnt/β-catenin signaling pathway to induce tumor development (96). Furthermore, TNF family members can also suppress the immune response in the tumor environment, which may be due to the inhibition of the major histocompatibility complex class II in tumor-associated macrophages through the decoy receptor-3 (97).

b) IL-6. IL-6 plays an important role in tumor development, such as colorectal cancer, in the GI tract (98). Clinical data have shown that IL-6 serum levels from patients with colorectal cancers are significantly increased and positively correlate with tumor load, including tumor size and liver metastases (98). It was demonstrated that two major signaling pathways, the signal transducers and activators of transcription 1 and 3 (STAT1/3) and the Src-homology tyrosine phosphatase 2 (SHP2)-Ras-ERK, are involved in the IL-6-mediated proliferation of intestinal epithelial cells (99). In addition, IL-6 can also promote tumor growth by increasing the colony formation of human colon carcinoma cells (100). These biological actions of IL-6 in colorectal cancer progression were further elucidated by mediating through the soluble IL-6 receptors derived from tumor cells rather than from the membrane-bound receptors (101).

c) IL-1β. IL-1β has been found to be capable of promoting tumor cells to metastasize, by activating the cancer-related inflammation cascade (102,103). In models of 3-methylcholanthrene-induced carcinogenesis, it was IL-1β, rather than IL-1α in the tumor microenvironment that was capable of determining the invasive potential of malignant cells, including increased tumor adhesion and invasion, angiogenesis and immune suppression (104). Microenvironmental IL-1β is a required factor for tumor invasiveness and angiogenesis, which may contribute to the production of TNF-α and vascular endothelial cell growth factor by IL-1β (105). Recently, Carmi *et al* (106) found that myeloid cells released IL-1β and induced endothelial cells to produce proangiogenic factors, such as VEGF, and subsequently provided the inflammatory microenvironment for tumor progression and angiogenesis. Furthermore, they also observed that IL-1β inhibition significantly reduced tumor growth by suppressing inflammation and inducing the maturation of immature myeloid cells into M1 macrophages (106).

Chemokines. Chemokines in the tumor microenvironment are another important factors for modifying tumor growth, and promoting angiogenesis (107) and tumor metastatic spread (108). CXCL1 (growth-regulated oncogene α) for example, produced by human colorectal cancer cells is capable of inducing microvascular endothelial cell migration and tube formation *in vitro*. PGE2-induced CXCL1 in the tumor microenvironment has also been found to increase microvessel density and stimulate

LS-174T cell proliferation in an *in vivo* model (109). Together with CXCL-1, the angiogenic chemokine CXCL8 (IL-8) was also significantly unregulated in tumor tissues from patients with colorectal cancer (110). CXCL8 signals are mainly activated through the interaction with CXCR1 and CXCR2 present in cancer cells and other cells. To date, CXCR1 and CXCR2 receptors are widely expressed in cancer cells, tumor-associated macrophages, neutrophils and endothelial cells (111). Therefore, the increased CXCL8 levels caused by cigarette smoking could nurture the tumor microenvironment to promote cancer growth (112). Studies have shown that CXCL8 induces cell proliferation by the activation of classical MAPK and downstream phosphorylation of ERK1/2 in neutrophils and cancer cells (113,114). CXCL8 also regulates angiogenesis by the induction of matrix metalloproteinase 9 (MMP-9) through the activation of VEGFR-2 in endothelial cells, and subsequently promotes cancer growth and metastasis (115).

4. Conclusions

Mounting evidence demonstrates that cigarette smoking can induce pathogenic and carcinogenic processes in the GI tract. These may lead to severe chronic inflammation and subsequently, the development of cancer at the inflammation sites. Clinical and experimental data have also shown that cigarette smoking is a main risk factor for the induction of inflammatory diseases, such as ulcers and Crohn's disease. Cigarette smoke and its active compounds impair the fundamental structure of the GI tract through the induction of cellular apoptosis and the inhibition of mucosal cell renewal. Cigarette smoke also interferes with the protective mechanisms of the GI tract by decreasing the blood flow in the mucosa and modulating the mucosal immune system. Furthermore, cigarette smoke also inhibits the synthesis and release of EGF and polyamines and thereby, mucus secretion, which plays an important role in protecting mucosal integrity. Chronic inflammation induced by cigarette smoke exposure releases various inflammatory components, including the cytokines, TNF-α, IL-1 and IL-6, and the chemokines, CXCL1 and CXCL8. These inflammatory components are capable of promoting tumor growth, tumor adhesion and invasion. Moreover, these mediators also induce angiogenesis and immune suppression in the tumor microenvironment. Along with the induction of chronic inflammation, cigarette smoke and its active ingredients can directly activate nAChRs, and form DNA adducts to initiate tumorigenesis in the GI tract. In conclusion, cigarette smoke is a detrimental factor affecting the pathogenesis and tumorigenesis of certain disorders in the GI tract. Detailed mechanistic studies may aid in the development of more effective therapies for various disorders of the GI tract.

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