REVIEW ARTICLE

Mechanisms for nicotine in the development and progression of gastrointestinal cancers

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ABSTRACT Long-term smoking is major risk factor for a variety of cancers, including those of the gastrointestinal (GI) tract. Historically, nicotine and its derivatives are well known for their role in addiction, and have more recently been documented for their carcinogenic role in a number of human cancers. The cellular and molecular pathways activated by nicotine mimic physiological and environmental carcinogenesis in cancers throughout the GI tract potentiating cancer growth and/or inducing the formation of cancer on their own. Thus, it is important to unlock the carcinogenic mechanisms induced by nicotine in these systems, and underscore nicotine's potential as an environmental hazard. This review outlines the specific pathways demonstrated to mediate nicotine's carcinogenic mechanism in the GI tract. The abundance of cell and animal evidence calls for increased epidemiologic and case-control evaluation of nicotine's role in cancer.

KEY WORDS Nicotine; nitrosamines; gastrointestinal neoplasms; smoking; catecholamines; nicotinic acetylcholine receptors; carcinogen; autocrine signaling; angiogenesis; proliferation; migration

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Introduction

The World Health Organization (WHO) reports that in the 20th century, tobacco abuse resulted in the deaths of one hundred million people, and the deaths of one billion this next century if abuse is left unabated (1). Currently, there are more tobacco-related deaths than for AIDS, tuberculosis and malaria combined. In the United States, over 400,000 cancer-deaths are caused each year by cigarette smoke (2). It is well-known that cigarette smoke increases the risk of chronic obstructive pulmonary disease, heart disease, and lung and esophageal cancers (3-6). Cigarette smoke is also known for increasing the risk of cancers throughout the gastrointestinal (GI) tract. It is the strongest risk factor for gastric cancers in Taiwan and increases tumorigenesis in the intestinal tract, liver, and colon (4,7-9). In the pancreas, there is strong evidence from epidemiological and case control studies showing that cigarette smoke is a major, if not the most important risk factor for pancreatic cancer (10-23).

Cigarette smoke contains multiple compounds that exert effects on the GI tract. Of these compounds, nicotine has been extensively studied for its biological effects on mood, appetite, and task performance; and owing to its interaction with nicotinic receptors in the brain, is highly addictive (24-26). Nicotine is rapidly absorbed through the skin, alveoli, and the GI tract and distributed rapidly throughout the body. The nicotine metabolites 4-methylnitrosamino-1-3-pyridyl-1-butanone (NNK), and N'nitrosonornicotine (NNN), are particularly known for their carcinogenic properties (27-29). In rats, NNN has been identified as a causative agent of esophageal cancer (30). In adenocarcinoma cells of the colon, NNK promotes the upregulation of nuclear factor-kappa B(NF-κB) binding and an increase in the cancer-promoting homomeric nicotinic acetylcholine receptor (nAChR), α_7-nAChR (31).

nAChRs are ligand-gated transmembrane ion channel

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receptors that bind and respond to nicotine (32). Twelve genes encode the nAChRs, which are discretely expressed throughout various functional areas of the CNS (27,33,34). Upon nicotine binding, the conformation of the nAChR subunits changes to open a central pore and allow the flow of ions such as calcium (Ca^{2+}). Ca^{2+} entry reduces the negative charge across the plasma membrane (depolarization) resulting in activation of the voltage-gated Ca^{2+} channels and further Ca^{2+} influx. This process results in activation of downstream pathways and neurotransmitter release. Until recently, it was thought that nAChRs exist only in the nervous system. However, increasing evidence suggests that nAChRs are expressed in virtually all mammalian cells and are evolutionarily conserved (35). Outside of the nervous system, nAChRs regulate a complex network of stimulatory and inhibitory signals that regulate a number of processes such as growth, angiogenesis, neurogenic release of factors, and modulation of the microenvironment (36). While different members of the nAChR family may trigger converging signaling pathways, they often have diverse and even opposing actions. The two most important and evolutionarily-conserved of these are the α_7-homomeric nicotinic receptor (α_7-nAChR), and the α_4/β_2-heteromeric nicotinic receptor ($\alpha_4\beta_2$-nAChR), which cooperatively promote breast and prostate cancer by increasing dopamine synthesis (36). On the other hand, in most cancers, these receptors have opposing actions. In the lung, α_7-nAChR promotes cancer by increasing catecholamine synthesis, and $\alpha_4\beta_2$-nAChR suppresses catecholamine-induced cancer progression by GABA release (36).

There is increasing evidence that nicotine and its derivatives activate and promote key processes in the carcinogenesis of GI cancers (9). Over the past two decades, experimental models using animals, cell cultures, and clinical data have identified nicotine as a carcinogen for virtually all GI organs (9). Although other chemicals found in cigarette smoke contribute to the development of cancer, we focus on nicotine in this review.

Role of nicotine in esophageal and oral cancer

In vitro experiments on squamous epithelium give insight into the carcinogenic pathways nicotine induces to promote esophageal and oral cancers. Esophageal and oral cancer is commonly promoted by an epithelial-mesenchymal transition (EMT) of the keratinocyte lining (squamous epithelium) of the esophagus. In esophageal keratinocyte culture, nicotine has been shown to cause structural alterations in nAChRs by displacing the local neurotransmitter Ach (37). In this study, nicotine caused a downstream change in the transcriptional/translational control of cell cycle and differentiation genes including Ki-67, PCNA, p21, cyclin D1, and p53 (37). A change in the expression of nAChR subunits α_3, α_5, α_7, and β_2, and β_4 was also induced by nicotine as demonstrated by RT-PCR and immunoblotting (37). Multiple studies have demonstrated the oncogenic roles of the α_7-nAChRs in keratinocyte cultures (38-42). Chernyavsky *et al.* studied the carcinogenic mechanisms of nAChR-receptor activation and demonstrated increased NF-κB and SLURP1 activity and eferession, and changes in keratinocyte morphology, following α_7-nAChR stimulation (40). Nicotine displays oncogenic activity by triggering increased production and release of growth factors. Zong *et al.* demonstrated that nicotine increases COX-2 and MMP2 activity, and enhances cell migration and invasion (42). Additionally, nicotine alters fragile histidine triad gene (FHIT) gene expression through methylation. In cellular models of squamous cell carcinoma (SCC), promoter methylation of tumor suppressor p16 and FHIT induces the development of squamous cell carcinoma of the esophagus (43-45). Methylation of the FHIT promoter in nicotine-treated cells conferred a growth and proliferative advantage through altered expression of genes such as anti-apoptotic genes p53 and p16 (43-45). Furthermore, re-expression of FHIT protein was seen in esophageal squamous epithelial cells following smoking cessation of nicotine exposure (43-45).

Role of nicotine in gastric cancer

Nicotine is a major risk factor for gastric cancer (46). In the recent years, *in vitro* investigation into inflammatory messengers and growth signals has provided mechanistic information about nicotine's carcinogenic properties in the stomach. The pioneering studies performed by Dr. Cho's laboratory have provided data on the signaling pathways of nicotine uses to promote gastric cancer growth. Shin and Cho demonstrated that nicotine increases the proliferation and migration of gastric cancer cells by inducing COX-2, prostaglandin E2, VEGF release, and activates ERK, and stimulates cancer cell angiogenesis through a COX-2-dependent increase in VEGF and VEGF receptor (2,47-50). These studies are intriguing since the same signaling pathways mediate the formation of gastric cancer by the bacterium *Helicobacter pylori* (33,34). The ERK-mediated 5-Lipoxygenase (5-LOX) pathway was also investigated for its role in the pathogenesis of gastric cancer cells (49). Here, nicotine induced 5-LOX expression to promote cell growth and invasion (49). Inhibiting 5-LOX using the protein inhibitor MK886 caused a decrease in invasion and triggered cell cycle arrest by decreasing the relative transcription of cyclin D1, Cyclin E, p-RB, DP-1, and E2F (49). Additionally, 5-LOX blockade resulted in the inactivation of E-cadherin and activation of transcriptional repressor Snail,

indicating an epithelial-mesenchymal transition (EMT) (49). In support of this, a recent study demonstrated an increased number of migratory cells during nicotine stimulation in a transwell migration assay (51). Nicotine was shown to induce a marked downregulation of E cadherin and upregulation of ZEB-1 and Snail (51). Nicotine has also been shown to decrease the expression of anti-proliferative genes through induction of a microRNA (miRNA) pathway. One group determined that nicotine regulates the expression of microRNAs (miRNA) 16 and 21 in gastric cancer cells, through activation of NF-κB by prostaglandin E receptors (EP2 and EP4) (52). Knockdown of NF-κB markedly reduced cell proliferation, and miRNA-16/21 expression; and knockdown of EP2 and EP4 impaired the NF-κB/miRNA pathway (52).

Early *in vivo* work showed that long-term administration of nicotine to rats increased gastric cancer incidence and caused the initiation of gastric tumors at an early stage (53). A more recent follow-up study by Shin *et al*. performed using human gastric xenografts on rats, showed increased expression of ERK, COX-2, and VEGF following nicotine administration (54). Reducing the expression of COX-2 attenuated tumor growth and neovascularization (54).

Clinical evidence for human markers of gastric cancer has been presented in association studies on gastric cancer patients. A study investigating the association between different TNF genetic variants and cancer induced by smoking, found a significant association between TNF-alpha-857 genetic variant and gastric cancer which was propounded by smoking (55). Another study found a correlation between clinical evidence of tumor severity (e.g., invasion of tumor, metastasis, and clinical stage) and uPAR expression in gastric cancer patients (56). Since nicotine increases the expression of uPA/uPAR, it is likely that uPAR could be another clinical key carcinogenic player induced by nicotine (49).

Role of nicotine in colon cancer

Key processes for the progression of colon cancer including proliferation, migration, angiogenesis, and escape from apoptosis have been demonstrated by *in vitro* treatment of nicotine. Nicotine has been shown to increase proliferation by changing the expression of receptors and their phosphorylation patterns in several different mitogenic pathways. One study showed enhanced phosphorylation of epidermal growth factor receptor (EGFR) and increased expression of 5-LOX in colon cancer cells following nicotine exposure (31). By blocking these receptors (EGFR and/or 5-LOX), the proliferation induced by nicotine stimulation was inhibited. Similarly, the upregulation of acetylcholine and noradrenaline receptors was induced by nicotine and enhanced the proliferation of colorectal carcinoma cells (57,58). Nicotine was shown to increase the expression of β_1- and β_2-adrenoceptors causing increased expression/production of VEGF, COX-2, PGE2 and micro vessel densities. Inhibition of β-adrenergic receptors by atenolol abrogated these effects (57,58). Additional studies have demonstrated that nicotine/smoking stimulates angiogenesis and neovascularization in colon cancer through increases in VEGF, 5-LOX, COX-2, and MMP2/9 (57-60). A nicotine/α_7-nAChR pathway has been shown to play an important role in colon cancer cell migration by induction of fibronectin (61). In this report, nicotine and COX-2 were necessary for induction of fibronectin as demonstrated by siRNA knockdown and chemical inhibition of COX-2 and α_7- nAChR (61). Since nicotine increases growth factor synthesis and receptor expression, autocrine signaling may likely be another important oncogenic mechanism for the development and progression of colon cancer. Although this likely occurs through some of the pathways previously discussed, an autocrine pathway for nicotine carcinogenesis has been proposed in human colon cancer cells for SLURP-1 (62). This short study reported that nicotine induces a decrease in the release of an antiproliferative autocrine peptide SLURP-1, an endogenous α_7-nAChR ligand.

Role of nicotine in pancreatic cancer

Studies have demonstrated that nicotine works through various mechanisms to activate key mitogenic MAPK cascades in the development of pancreatic cancer (63). The activation of receptors and/or cellular targets for nicotine results in downstream phosphorylation of MAPKs including p42, JNK, and ERK 1/2 resulting in the induction of mitogenic transcription factors such as ELK 1 (63-65). One working model depicting the development of pancreatic adenocarcinoma by chronic nicotine exposure elegantly diagramed an important pathway leading to angiogenesis, proliferation and migration, and apoptosis (66). In this model, nicotine causes a change in the expression of nicotinic receptors, increasing α_7-nAChR and decreasing $\alpha_4\beta_2$-nAChr; leading to increased noradrenaline, and decreased GABA, respectively (66). This contributes to cellular changes by increasing β-adrenergic activation of CREB, ERK 1/2, and AKT, and decreasing GABA an inhibitor of adenylyl cyclase activity a key regulator of MAPK activity (66). From a signaling perspective, this pathway is analogous to the addiction pathway induced by nicotine in the brain and in a number of cancers including small-cell lung cancer SCLC and pulmonary neural endocrine cells (36). A pathway diverging from the α_7

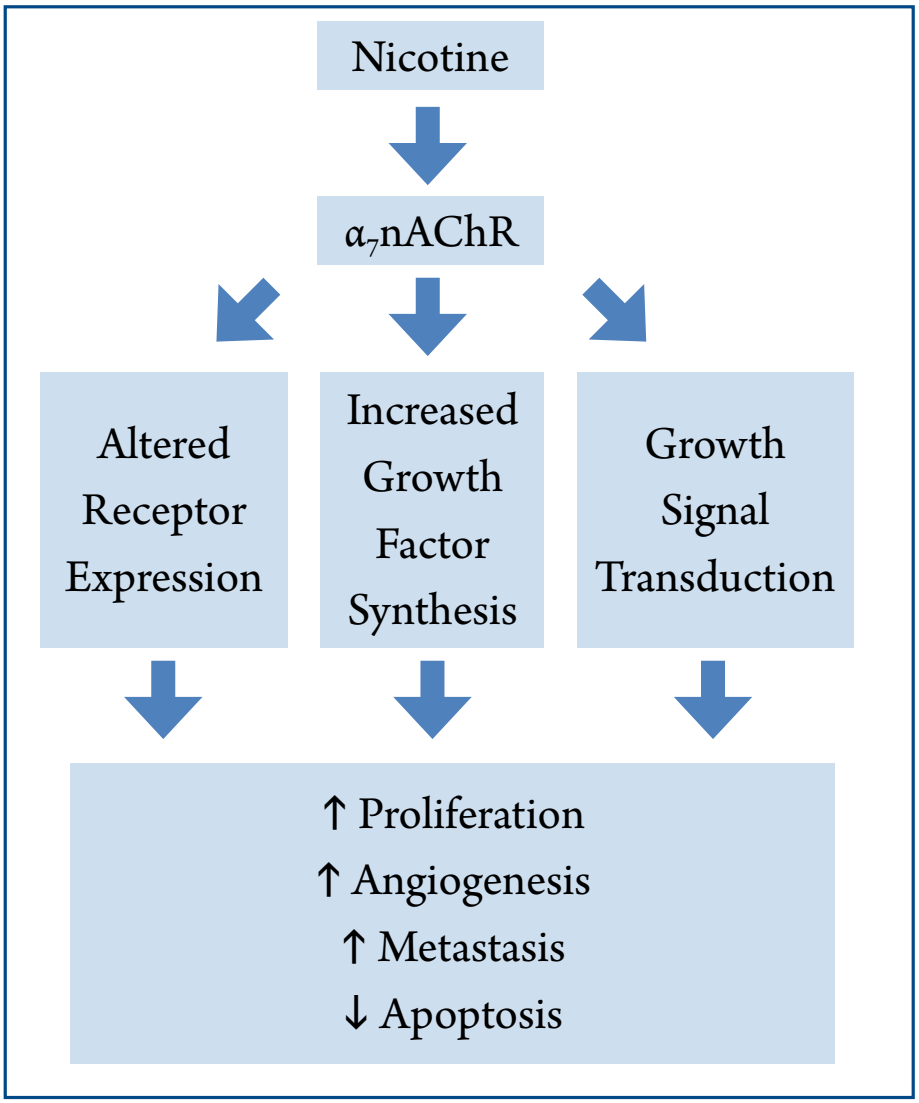

Figure 1. Overview of the major mechanisms nicotine enhances cancer in the GI tract. Nicotine stimulation through the α7-nAChR induces a change in the expression of surface receptors, release of growth factors, and directly invokes transduction of growth pathways. This leads to an increase in mediators of cell proliferation, angiogenesis, and metastasis, and a decrease in apoptosis.

nAChR has also been described (67). This study demonstrated that NNK stimulation of α_7-nAChR transactivated the EGFR receptor, increasing cAMP and ERK 1/2 in immortalized pancreatic duct cells (67).

In addition to changing the expression levels of surface receptors and intracellular signal peptides, nicotine induces the progression of pancreatic cancer by stimulating increases in autocrine/paracrine secretion. One group investigating the effect of nicotine on pancreatic adenocarcinoma cell migration and angiogenesis, demonstrated that nicotine induced osteopontin (OPN) mRNA expression mRNA (68). Follow-up work by the same group showed nicotine increased MMP-9 and VEGF mRNA expression, which was dependent on osteopontin (69). In a similar fashion, the pro-inflammatory cytokine, monocyte chemoattractant protein (MCP-1), was induced and secreted upon nicotine exposure, as shown by RT-PCR, and ELISA, and appeared to colocalize with OPN in confocal images (70). Furthermore, IHC staining in human pancreatic tissue showed colocalization of MCP-1 and OPN in malignant ducts compared to normal pancreatic ducts (70).

Role of nicotine in liver carcinogenesis

In comparison to other cancers of the GI tract, there is limited information about nicotine's effects on liver carcinogenesis. While smoking is not listed as a major risk factor for hepatocellular carcinoma (HCC), it is to a lesser degree associated with HCC by itself, and profoundly associated with HCC in certain liver conditions and/or diseases (71,72). For example, studies on patients with primary sclerosing cholangitis (PSC), have reported a significant association between HCC and smoking/nicotine abuse (73,74). *In vivo* models have demonstrated that nicotine derivatives act as liver carcinogens. One study evaluating the carcinogenicity of nitrosamine derivatives found that subcutaneous injection of NNK induced lung and liver tumors in rats (75).

Summary

A number of factors controlled by cholinergic and adrenergic signaling plays critical roles in determining the pathophysiology of the GI tract. While it is important to remember that many endogenous and environmental signals trigger carcinogenic mechanisms in the GI, we emphasized the mechanisms (Figure 1) nicotine and its derivatives trigger in experimental models of cancer. First, nicotine-signaling potently modulates the cell's receptor profile at the plasma membrane. Chronic nicotine exposure causes an increase in α_7-nAChR and a decrease in $\alpha_4\beta_2$-nAChR expression. While the α_7-nAChR promotes cancer through increased catecholamine production, the $\alpha_4\beta_2$-nAChR suppresses the development of cancer via GABA inhibition of β-adrenergic signaling (36). A similar increase in expression of β-adrenergic receptors and the non-neuronal receptors including uPAR, VEGFR, Prostaglandin receptors and EGFR is triggered by nicotine exposure. Second, nicotine induces synthesis of hormones and cytokines important for the growth, metastasis, and invasion of cancer. This is exemplified by VEGF, which mediates the growth of cancer arising in nearly all GI organs; and the pro-inflammatory cytokine COX-2, most known for its role in the development of gastric cancer. Finally, nicotine and its derivatives may themselves activate mitogenic pathways such as the MAPKs, either directly, or through signal-transduction by cholinergic signaling.

Perspective and future directions

While nicotine supports the growth of GI cancers in cells and animal models, there is insufficient epidemiological evidence that nicotine by itself causes cancer in humans. One study reported five-year surveillance data of 3,320 Canadian patients taking nicotine-replacement therapy (NRT) and found that usage of the drug could not predict the occurrence of cancer in this population (76). Thus, there is a need for further studies with greater than five years follow-up. Since GI disturbances are the most common adverse effect in NRT trials, it will be interesting to learn whether long-term NRT is associated with increased GI cancer risk (77). Moreover, since nicotine acts through some of the same processes, which promote other types of cancer, it is likely nicotine will accelerate the growth of cancer in co-morbid conditions of the GI tract.

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