Chemoprevention of Gastrointestinal Cancer: The Reality and the Dream

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Despite substantial progress in screening, early diagnosis, and the development of noninvasive technology, gastrointestinal (GI) cancer remains a major cause of cancer-associated mortality. Chemoprevention is thought to be a realistic approach for reducing the global burden of GI cancer, and efforts have been made to search for chemopreventive agents that suppress acid reflux, GI inflammation and the eradication of *Helicobacter pylori*. Thus, proton pump inhibitors, statins, monoclonal antibodies targeting tumor necrosis factor-alpha, and nonsteroidal anti-inflammatory agents have been investigated for their potential to prevent GI cancer. Besides the development of these synthetic agents, a wide variety of the natural products present in a plant-based diet, which are commonly called phytoceuticals, have also sparked hope for the chemoprevention of GI cancer. To perform successful searches of chemopreventive agents for GI cancer, it is of the utmost importance to understand the factors contributing to GI carcinogenesis. Emerging evidence has highlighted the role of chronic inflammation in inducing genomic instability and telomere shortening and affecting polyamine metabolism and DNA repair, which may help in the search for new chemopreventive agents for GI cancer. **(Gut Liver 2013;7:137-149)**

Key Words: Chemoprevention; Gastrointestinal neoplasms; Phytoceuticals; Molecular target

INTRODUCTION

1. The general principle for chemoprevention of gastrointestinal (GI) cancers

1) General concept of chemoprevention

Since the incidence of new cancer cases as well as the rate of cancer mortality are increasing worldwide,[1] the prevention of cancer is ranked as a prime importance to reduce the global burden of cancer. The perception of preventing cancer was first outset by Wattenberg[2] in 1960s, after which a wide array of population-based as well as preclinical studies has been conducted to evaluate the cancer prevention potential of diverse classes of natural as well as synthetic compounds. In 1976, Sporn[3] first coined the term "chemoprevention" that refers to the use of nontoxic chemical substances of either natural or synthetic origin to delay, retard or reverse the process of carcinogenesis. Over the last few decades, numerous preclinical and clinical studies demonstrated the success of the chemoprevention strategy in curbing the cancer incidence and mortality. Chemoprevention is the strategy to intervene multistage carcinogenesis process, which comprises of apparently three distinct phases: initiation, promotion, and progression. Tumor initiation is a rapid and irreversible process that involves damage of cellular DNA by various known and unknown carcinogens. Many carcinogens, either endogenous or exogenous, are inactive per se and are activated through biotransformation inside the body. Biotransformation is a process of eliminating relatively non-polar carcinogenic substances by converting them into water soluble entities, hence called detoxification. Extensive metabolic activation of carcinogens and compromised detoxification leads to the accumulation of highly reactive carcinogens, which cause covalent modification of genomic DNA, thereby activating various oncogenes and inactivating tumor suppressor genes, which leads to the initiation of cell transformation. Therefore, chemopreventive agents that can either inhibit carcinogen activation or promote detoxification are generally termed as anti-initiating agents or blocking agents. Tumor promotion, a reversible process, is the clonal expansion of initiated or transformed cells to grow as a population of preneoplastic cells forming the benign tumor. Abnormal biochemical reactions encompassing inappropriate amplification and/or inactivation of cell signal-

ing pathways underlie tumor promotion stage that often spans over 10 years. Thus, the normalization of aberrant cell signaling pathways by chemopreventive agents can reverse or halt the journey of premalignant cells to become malignant. Tumor progression involves malignant conversion of preneoplastic cells with characteristic features of increased angiogenesis, invasion and metastasis.[4,5] In summary, cancer can be prevented by intervening any of these three stages of carcinogenesis and chemopreventive agents that can interfere with tumor promotion or progression are known as suppressing agents. The aforementioned stage-specific prevention of cancer is a simplistic view of chemoprevention strategy. Conclusively, accumulating evidence of the success of chemopreventive agents in reducing the risk of various cancers suggests that chemoprevention is the first line of defense against carcinogenesis.[6]

2) The basis for chemoprevention of GI cancers

GI cancers include cancers of the esophagus, stomach, intestine, colon, rectum, pancreas, and liver. Among these, the esophageal squamous cell carcinoma accounts for approximately one-sixth of all cancer-related mortality worldwide.[7] Esophageal adenocarcinoma (EAC) has received considerable attention because of the dramatically increased incidence in the past 2 decades and the poor prognoses with a 5-year survival rate of 10% to 20%.[8,9] In spite of relative decline in the incidence and mortality, gastric cancer is still the fourth most common cancer worldwide and ranks the third most common cause of cancer-related deaths.[10] Likewise, hepatocellular carcinoma (HCC) remains as the fifth common cancers and a major cause of cancer-related deaths.[11] Pancreatic cancer, the most lethal form of GI cancer, is the fourth leading cause of cancer mortality with an overall median 5-year survival rate of only 5%.[12] Colorectal cancers are also increasing worldwide with an estimate of 1,200,000 new cases in the year 2011 and half of them are going to die from the disease.[13,14] Based on the looming scenario of cancer mortality, chemoprevention appears to be the forefront in fighting against GI cancers. Majority of the GI cancers have etiologic link with dietary and life style factors, of which point is critical basis for prevention. For instance, the association between gastric cancer and high salt diet intake or *Helicobacter pylori* infection, the positive corelation between HCC and aflatoxin-B1 contaminated food consumption or chronic hepatitis virus infection or excessive alcohol consumption, and the causal relationship between colon cancer and the intake of burnt meat are notable examples. Thus, GI cancers can be prevented by changing dietary habit and life style. Whereas the maintenance of proper hygiene, abstinence from alcohol and smoking, increasing physical activity and avoidance of high salt and brunt food intake are commonly advocated, the pharmacological intervention for chemoprevention of GI cancers have been sought for over last several decades. Since oxidative stress and chronic inflammation, in general, play a key role in car-

cinogenesis, antioxidants, and anti-inflammatory agents have been shown to prevent various GI cancers. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been extensively investigated for the chemoprevention of colorectal cancers.[15,16]

MOLECULAR BASIS IMPLICATED IN THE PREVENTION OF GI CANCERS

1. Inflammation and oxidative stress

Despite having unique etiology, all forms of GI cancers share the common mechanisms of oxidative stress-induced damage of genomic DNA, modification of cellular proteins and lipids, altered cell signaling and persistent local tissue inflammation. Whereas oxidative stress incites local tissue inflammation, persistent inflammation leads to the generation of reactive oxygen species (ROS). Excessive ROS as well as reactive nitrogen species (RNS) perturbs cellular homeostasis by inducing genetic and epigenetic changes and amplifying and/or inactivating cell signaling network, thereby inducing premalignant transformation of cells. ROS and RNS generate other reactive species, such as malondialdehyde and 4-hydroxynonenal (4-HNE), which can cause DNA damage by forming DNA adducts,[17] thereby initiating the tumor formation. For example, 4-HNE forms $1,N^6$-ethenodeoxyadenosine (εdA) and $3,N^4$-ethenodeoxycytidine (εdC) DNA adducts in inflamed human pancreas and colon, respectively.[18] DNA damage caused by oxidative stress is a major contributor to colorectal cancer development in ulcerative colitis patients.[19] Peroxynitrite, a powerful oxidant, causes DNA damage through the formation of 8-nitroguanine (8-NG).[20,21] In addition, elevated expression of nitrative and oxidative DNA lesion products, 8-NG and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), and iNOS was detected in inflammation sites of HCC, gastric cancer and cholangiocarcinomas.[22] The incidence of EAC in patients with Barrett's esophagus with dysplasia is increased by 30- to 125-fold.[23] Likewise, inflammatory bowel diseases (IBD) (ulcerative colitis and Crohn's disease) are associated with about 10-fold increase in the risk of colorectal cancer[24] and the use of anti-inflammatory therapy reduces this risk.[15] The fact that inflammation precedes tumor development has recently been reported in a mouse model of pancreatic cancer.[25] According to this study, authors developed a method to tag pancreatic cancer cells in order to track the movement of these cells. It was found that tagged pancreatic cells acquired mesenchymal phenotype and appeared in circulation much before the development of pancreatic tumor, and these cells were seeded into liver. This phenomenon was aggravated in the presence of pancreatitis and was most abundant at the inflammatory foci.[25] Mouse pancreatic ductal adenocarcinomas arising from pancreatic acinar cells, which are resistant to transformation by oncogene activation or tumor suppressor gene inactivation, have been reported to form pancreatic intraepithelial neoplasia when exposed to limited bouts of nonacute pancreatitis and harbor K-ras oncogene.[26]

2. Genomic instability

Inflammation in the GI epithelial cells induces genomic instability as a mechanism of turning into tumor development. Barrett's esophagus and EACs showed 64% and 43% changes in chromosome 11 and 12, respectively. Nondysplastic multilayered epithelium and Barrett's esophagus retaining normal levels p53 and adenomatous polyposis coli showed aneusomy of these chromosomes, suggesting that inflammation caused genomic instability prior to the inactivation of tumor suppressor genes.[27] The loss of heterozygosity at chromosome three and microsatellite instability at chromosome 12 were observed in 50% and 62%, respectively, in chronically inflamed, nondysplastic epithelium of ulcerative colitis patients, corroborating the fact that inflammation induces microsatellite instability as an initial event for dysplasia and consequent development of colonic adenocarcinoma.[28] Likewise, chronic pancreatitis was found to exhibit increased incidence of microsatellite instability[29] and chromosomal instability.[30] In the early stage of hepatocarcinogenesis, infection with hepatitis C leads to hepatic inflammation that is characterized by aneuploidy in hepatocyte DNA.[31]

3. Telomere shortening

Several studies have reported that certain forms of GI cancers are associated with telomere shortening. For instance, the relative telomeric repeat content was substantially reduced in inflamed liver tissues as well as in HCC.[32] The risk of gastric cancer was increased by 2-fold in *H. pylori*-infected patients, who had shortened telomere.[33] Likewise, telomere shortening was noted in colon biopsies from ulcerative colitis patients with low grade dysplasia.[34]

4. Impaired DNA repair system

Mice deficient in alkyladenine DNA glycosylase (AAG), a base excision repair enzyme, exhibited more intense gastric lesions as upon infection with *H. pylori*.[35] The AAG-mediated DNA repair protected mice against dextran sodium sulphate-induced colon carcinogenesis.[35] In a murine colitis model, homozygous deletion of mismatch repair gene *MSH2* caused 60% incidence of high-grade dysplasia or adenocarcinoma as compared to 29% of the animals harboring wild type *MSH2*. Moreover, tumors in $MSH2^{-/-}$ mice exhibited high index of microsatellite instability than that in wild type mice, suggesting that deficient mismatch repair plays a key role in inflammation-associated colon carcinogenesis.[36] A similar phenomenon was observed in mice deficient of another mismatch repair gene *hMlh1*. The incidence of colon tumors in male and female *Mlh1*-null mice challenged with DSS was 63% and 44%, respectively. However, *Mlh1* heterozygous and wild type mice were free from tumors. Thus, a strong association exists between *Mlh1* deficiency and colon carcinogenesis.[37] Edwards *et al.*[38] reported that colon tumors in mice lacking the heterotrimeric G protein alpha subunit Giα2

showed increased microsatellite instability arising from epigenetic silencing of *Mlh1*. Homozygous deletion of 8-oxoguanine glycosylase (Ogg1), a base excision repair enzyme, increased the susceptibility to DSS-induced colitis and the formation of colorectal adenocarcinomas as compared to *Ogg1* wild type animals.[39] The Ogg1 activity was inhibited by NO in human cholangiocarcinoma cells.[40] In contrast to the protective role of DNA repair enzymes in GI carcinogenesis, Hofseth *et al.*[41] demonstrated that AAG and *apurinic/apyrimidinic* endonuclease (APE1) are elevated in colonic epithelium of ulcerative colitis patients as compared to normal epithelium. The elevated levels of AAG and APE1 were associated with increased microsatellite instability in inflamed colon tissue. One possible mechanism may be the role of APE1 in enhancing inflammatory signaling by functioning as a redox chaperone to cause thiol reduction of proinflammatory transcription factors nuclear factor-kappaB and AP-1, thereby increasing DNA binding of these transcription factors.[42]

5. Polyamine metabolism

The imbalance in cellular polyamine pool is also associated with GI carcinogenesis. Significant reduction in colonic adenomas in patients receiving a combination of diferuloylmethane, polyamine biosynthesis inhibitor, and sulindac suggest that increased polyamine synthesis contributes to colon carcinogenesis.[43] Gobert *et al.*[44] reported that *H. pylori* infection, the major cause of gastric cancer, induces the expression and activity of enzymes utilized for polyamine biosynthesis. Moreover, increased cellular polyamine pool has been noted in tumor cells.[45] In contrast, spermine has been reported to inhibit lipopolysaccharide-induced expression of iNOS, formation of nitrotyrosine, and the release of inflammatory mediators in mice.[46] Moreover, increased catabolic depletion of polyamine pool led to acute pancreatitis,[47] which was prevented by treatment with a polyamine analogue.[48] Whereas the induction of polyamine catabolic enzymes, such as spermidine/spermine-N^1-acetyltransferase, N^1-acetylpolyamine oxidase, and spermine oxidase may prevent carcinogenesis by depleting cellular polyamine pool, H_2O_2 generated as a by-product of polyamine catabolism may cause DNA damage leading to cell transformation.[49,50] Thus, more rigorous investigation is warranted to delineate the role of polyamine metabolism in GI carcinogenesis.

6. Activation-induced cytidine deaminase (AID)

Recently the role of AID, an enzyme that naturally functions as a DNA and RNA sequence editor, in GI carcinogenesis has been reported. The expression of AID is elevated in chronic inflammatory conditions, such as ulcerative colitis[51] and *H. pylori*-induced gastritis.[52] It has been reported that increased levels of AID causes mutation of many tumor-related genes[53] in hepatocytes of hepatitis C virus infected patients[54] and in gastric epithelial cells in patients with *H. pylori* infection.[52] The expres-

sion of AID is increased in response to several cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-4, and IL-13 in colonic epithelial cells.[51] Shimizu et al.[55] and Marusawa et al.[56] strongly concluded that AID might play an integral role in inflammation-associated GI carcinogenesis and is therefore a potential target molecule for the prevention and treatment of cancers since the activity of AID as a genome mutator provides a new avenue for studies aimed at understanding mutagenesis mechanisms during carcinogenesis.

REALITY OF CANCER PREVENTION ACCORDING TO AGENTS

1. Prevention of GI cancers with proton pump inhibitors (PPIs) beyond acid suppression

Another class of agents studied for the chemoprevention of GI cancers is PPI, which act beyond authentic acid suppression. Epidemiological studies suggest that PPIs can reduce the risk of neoplastic progression in patients with Barrett's esophagus.[57,58] Miyashita et al.[59] reported that subcutaneous administration of rabeprazole protected against the development esophageal cancers in a rat surgical reflux model. Contrary to these observations, a case control study from the UK demonstrated an increased risk of EACs in patients receiving PPI therapy for GI reflux disease symptoms or Barrett's esophagus.[60] Although the controversy hailed over the tumorigenic potential of PPIs, Obszynska et al.[61] have conducted a large clinical trial and reported that long term use of PPIs has no clinical evidence of extending esophagus length and is clinically safe. The major concern with PPIs is the hypergastrinemia that might play role in inducing colorectal tumorigenesis after the use of PPIs. However, our recent study demonstrated that intraperitoneal administration of omeprazole reduced the incidence and the multiplicity of colitis-associated colon tumors in C57BL/6 mice.[62] Our study revealed that omeprazole can block the trophic effect of gastrin on colonic epithelial cells.[63] Moreover, the ability of PPIs in inducing apoptosis in gastric cancer cells[64] or the enhanced eradication of H. pylori with a combination of lansoprazole, amoxicillin, and rebamipide[65] suggest the potential of PPIs in the chemoprevention of GI cancers.

2. Prevention of GI cancers with NSAIDs

A notable example is the emergence of aspirin or NSAIDs in the prevention and therapy of colorectal cancer.[66] According to a recent randomized placebo-controlled chemoprevention trial, regular administration of aspirin reduced the polyp formation and disease progression in young patients with high risk of familial adenomatous polyposis (FAP).[67] Regular intake of a low dose aspirin has also been shown to reduce the risk of sporadic colorectal cancers in patients with IBDs.[68] A randomized controlled trial comprising 17,285 participants reported that daily aspirin can prevent distant metastasis of certain cancers.[69] In a prospective human study, Vaughan et al.[70] demonstrated that NSAIDs can reduce the risk of neoplastic progression in Barrett's esophagus, a metaplastic disease that serves as the precursor for EACs. The clinic- or hospital-based studies demonstrated that aspirin, but not nonaspirin NSAIDs, reduced the risk of developing pancreatic cancer.[71-73] The history of developing aspirin or NSAIDs is rather long (Fig. 1A), starting from drastic trepanation to the discovery of the efficacy of willow tree bark on the relief of pain as well as inflammation by Hipocrates. These experiences were completed by Dr. John Vane, who got Nobel Prize through the identification of prostaglandin and cyclooxygenase (COX) as core mechanisms of aspirin and NSAIDs. These great achievements were proven to be chemopreventive way of NSAIDs in diverse GI cancers including colon cancer and gastric cancer (Fig. 1B). Diverse mechanisms of NSAIDs on GI cancer prevention had been identified (Fig. 1C), including COX dependent mechanisms and COX-independent mechanisms (Fig. 1).

3. Prevention of GI cancers with natural products

Although several monoclonal antibodies targeting specific gene products have been developed as chemotherapeutic agents, only few studies have demonstrated their chemoprevention potential. We have recently reported that infliximab, a monoclonal antibody against TNF-α, can prevent the development of colitis-associated colorectal cancers in rodents.[63] Besides these synthetic products, a large body of evidence suggests that regular consumption of fruits and vegetables can prevent different forms of GI cancers (Table 1).[74-132] Because it is estimated that two thirds to three quarters of gastric cancer worldwide are associated with H. pylori infection,[133] it seems that the eradication of H. pylori and the control of gastric inflammation induced by the pathogen are essential in the prevention of gastric cancer. Previous our studies have shown that Korea red ginseng could rescue H. pylori-induced cytotoxicity,[76] suppress H. pylori-induced 5-lipoxygenase pathway,[77] and attenuate gastric inflammation through augmented eradication rates of H. pylori in the clinical study.[78] These results suggest that Korean red ginseng administration after the eradication of H. pylori would be helpful to prevent H. pylori-associated inflammation and carcinogenesis. Moreover, Korean red ginseng powder also has shown to the inhibitory effects on aberrant crypt foci formation and the preneoplastic lesions in the rat colon treated with azoxymethane.[79] In addition to Korean red ginseng, a wide variety of antioxidant and anti-inflammatory substances present in our regular plant-based diet are effective in preventing GI cancers. Examples include, but not limited to, epigallocatechin gallate (EGCG) from green tea,[134,135] anthocyanins from raspberry,[136] curcumin from turmeric,[137,138] resveratrol from grapes,[44,80-83] etc. Tea and tea constituents, especially EGCG from green tea has well known to the cancer preventive activities in various models for GI carcinogenesis.[134,135] Chemopreventive activities of EGCG were associated with the inhibition of tumorigenic

A

The history: NSAID as anti-inflammatory agents

Trepanation

Before hippocrates

Willow tree — Bark extracts — Salicin

Salicylic acid — Aspirin

First prepared by Gilm in 1859, introduced by Dreser into medicine in 1899.

Fellix Hoffman, PhD (1900 early)

NSAID & *coxibs* (mid 1990)

CELEBREX 100mg

John Vane, PhD (Nobel prize at 1982)

B

NSAIDs administration for chemoprevention

Hepatitis vaccination/ NSAIDs

Cholangiocarcinoma in the intra- and extrahepatic biliary tracts:
• Liver fluke (O*pisthorchis viverrini*) infection
• Hepatolithiasis
• Choledochal cyst

PPI/NSAIDs

Oesophageal adenocarcinoma:
• Barrett's oesophagus mainly induced by GERD

Gallbladder carcinoma:
• Cholelithiasis
• Cholecystitis possibly associated with *Helicobacter* species (*H. bilis, H. pullorum*) infection

Gastric adenocarcinoma:
• Chronic gastritis caused by *Helicobacter pylori* infection

Antiparasites/ NSAIDs

H. pylori eradication/ NSAIDs

Familial adenomatous polyposis

Obstructive colon cancer

C

Modes of chemopreventive action of aspirin and NSAIDs in GI cancer

COX dependent mechanisms
- Inhibition of COX-2 gene expression via interaction with transcription factors; NF-κB, STAT3
- Inhibition of the Wnt/β-catenin pathway by 'replacement' of defective APC function; inhibition of PPAR-δ
- Inhibition of COX-2-dependent PGE_2 formation
- Antagonism of PGE_2-mediated immunosuppression via EP2/EP4PGE receptors
- Inhibition of COX-2/peroxidase-mediated activation of (co)carcinogens
- Generation of 'aspirin-triggered lipoxins (ATL)'
- Inhibition of generation of further lipid mediators; sphingosine-1-phosphate
- Inhibition of COX-1-dependent prostaglandin formation

COX independent mechanisms
- Modulation of oncogen-induced expression of transcription factors; VEGF, others
- Interaction with DNA mismatch-repair genes
- Restauration of apoptosis by 'sensitizing' tumour cells to apoptotic stimuli; TRAIL
- Induction of proapoptotic NSAID activated gene-1; NAG-1
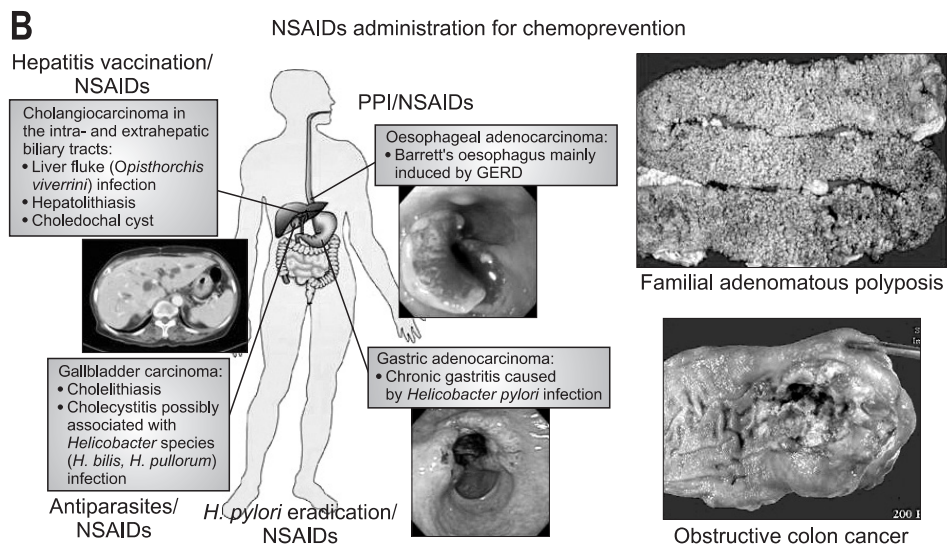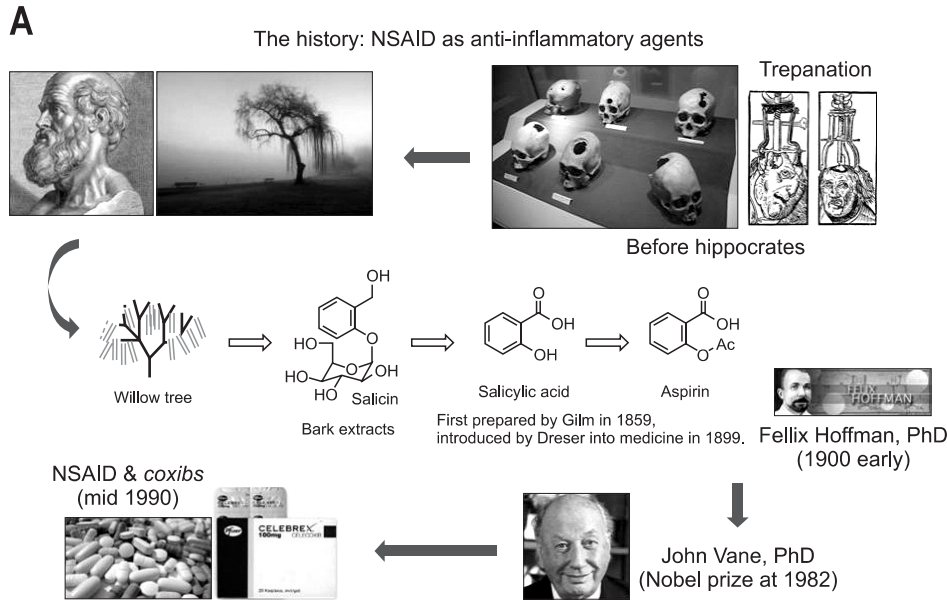- Energy depletion by uncoupling of oxidative phosphorylation

Fig. 1. Chemopreventive actions of nonsteroidal anti-inflammatory drugs (NSAIDs). (A) The history of the development of NSAIDs as chemopreventive agents has shown that they can inhibit tumor development in some cancers, although various side effects, such as gastrointestinal (GI) bleeding and renal disorders, have been shown to occur. Selective cyclooxygenase (COX)-2 inhibitors (coxibs) were originally developed as anti-inflammatory drugs to avoid the side effects of NSAIDs. (B, C) Similar to NSAIDs, the coxibs also proved to have an inhibitory effect on tumorigenesis in many experimental studies using cell lines and animal models. Because a randomized study for polyp chemoprevention with celecoxib in familial adenomatous polyposis (FAP) patients demonstrated a significant reduction in the number of colorectal polyps, the clinical use of celecoxib was approved for FAP patients. (C) The role of COX-2 in carcinogenesis of the GI tract and the chemopreventative mechanisms of NSAIDs, including coxibs, are shown.
PPI, proton pump inhibitor; NF-κB, nuclear factor kappa B; STAT3, signal transducer and activator of transcription-3; APC, adenomatous polyposis coli; PGE, prostaglandin E2; EP, prostaglandin E receptor; VEGF, vascular endothelial growth factor.
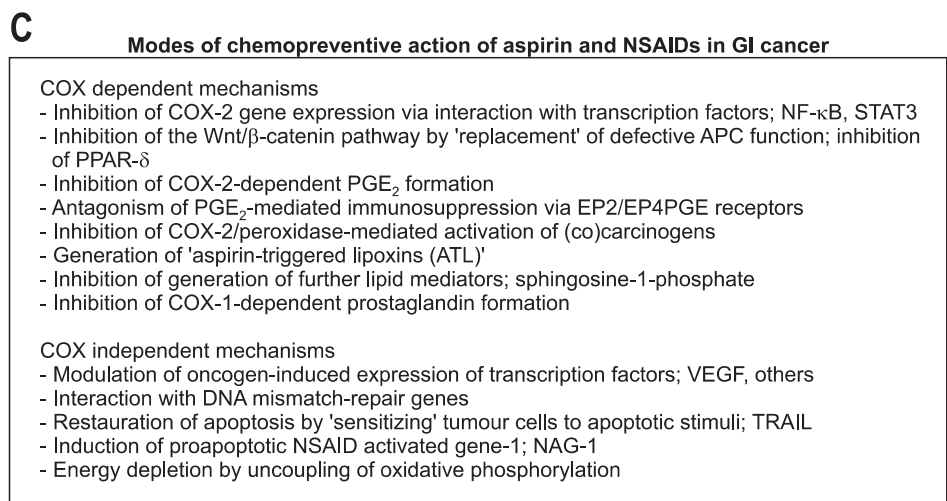
Table 1. Promising Phytoceuticals for Gastrointestinal Cancer Types

Phytoceuticals	Targets and cancer types
Korean red ginseng	Helicobacter pylori eradication[74] Gastric cancer[75,78] Colon cancer[79]
Green tea and EGCG	Esophageal cancer[91-93] Gastric cancer[94-98] Colon cancer[84,85,99-104]
Resveratrol	Esophageal tumorigenesis[81] Gastric cancer[80,105-108] Pancreatic cancer[83] Colon cancer[82,89,90,109-114]
Curcumin	Esophageal cancer[115,116] Gastric cancer[117-121] Colon cancer[86-88,99,122-128]
Diallyl trisulfide	Gastric cancer[129,130] Colon cancer[131,132]

EGCG, epigallocatechin gallate.

signaling including β-catenin, c-Myc, pAkt, cyclin D1, etc.[84,85] However, a few studies which covered different areas in Japan did not observe a relationship between green tea consumption and stomach cancer.[139,140] Several clinical trials with curcumin have been reported in GI cancers,[141,142] among which curcumin could decrease lymphocytic glutathione-S-transferase[86] and prostaglandin E2 production[87] in patiens with colorectal cancer and reduce polyp number and size in patients with FAP.[88] Resveratrol has potent anti-inflammatory and anticarcinogenic effect through mainly scavenge of free radicals, by which its unique aromatic structure.[143] Several studies demonstrates that resveratrol suppresses proliferation of colon cancer cells[82,89] and gastric cancer cells.[80] Liang et al.[90] suggested the cell cycle arrest at G2/M phase through inhibition of Cdk7 kinase activity as a mechanism of apoptosis in cancer cells treated with resveratrol.

4. Prevention of GI cancers with other promising agents

Focus has also been given to statins for the chemoprevention of GI carcinogenesis. A population-based case control study
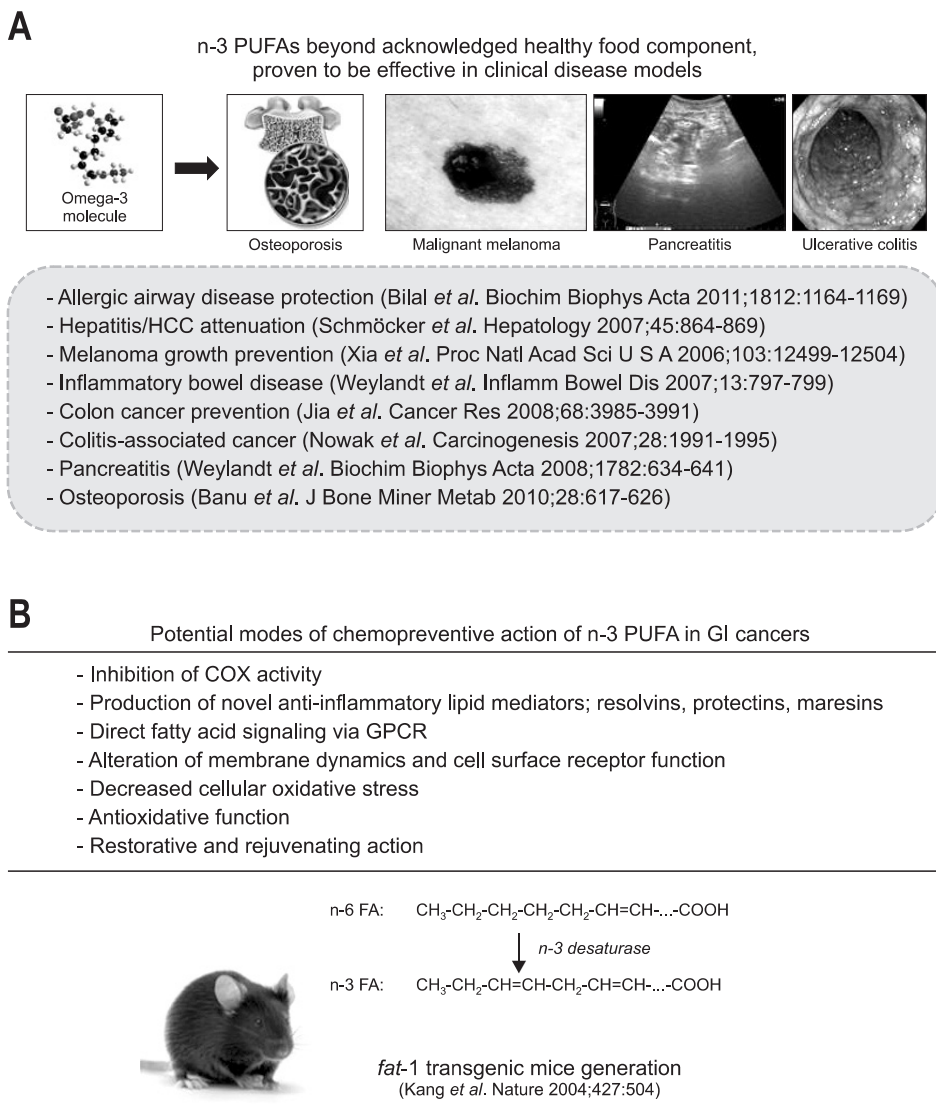
A

n-3 PUFAs beyond acknowledged healthy food component, proven to be effective in clinical disease models

- Allergic airway disease protection (Bilal et al. Biochim Biophys Acta 2011;1812:1164-1169)
- Hepatitis/HCC attenuation (Schmöcker et al. Hepatology 2007;45:864-869)
- Melanoma growth prevention (Xia et al. Proc Natl Acad Sci U S A 2006;103:12499-12504)
- Inflammatory bowel disease (Weylandt et al. Inflamm Bowel Dis 2007;13:797-799)
- Colon cancer prevention (Jia et al. Cancer Res 2008;68:3985-3991)
- Colitis-associated cancer (Nowak et al. Carcinogenesis 2007;28:1991-1995)
- Pancreatitis (Weylandt et al. Biochim Biophys Acta 2008;1782:634-641)
- Osteoporosis (Banu et al. J Bone Miner Metab 2010;28:617-626)

B

Potential modes of chemopreventive action of n-3 PUFA in GI cancers

- Inhibition of COX activity
- Production of novel anti-inflammatory lipid mediators; resolvins, protectins, maresins
- Direct fatty acid signaling via GPCR
- Alteration of membrane dynamics and cell surface receptor function
- Decreased cellular oxidative stress
- Antioxidative function
- Restorative and rejuvenating action

n-6 FA: $CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH=CH\text{-}...\text{-}COOH$

n-3 desaturase

n-3 FA: $CH_3\text{-}CH_2\text{-}CH=CH\text{-}CH_2\text{-}CH=CH\text{-}...\text{-}COOH$

fat-1 transgenic mice generation
(Kang et al. Nature 2004;427:504)

Fig. 2. Chemopreventative actions of n-3 polyunsaturated fatty acids (PUFAs). (A) Diverse clinical effects of n-3 PUFA beyond the prevention of atherosclerosis or the use of healthy food supplements have been demonstrated. (B) Antitumoric actions of n-PUFAs. Thus far, the following effects of n-3 PUFA have been documented: inhibition of cyclooxygenase (COX) activity; production of novel anti-inflammatory lipid mediators, such as resolvins, protectins, maresins, etc.; direct fatty acid signaling via G protein-coupled receptors (GPCR); alterations of membrane dynamics and cell surface receptor functions; decreased cellular oxidative stress; anti-oxidative function; and restorative and rejuvenating actions. (C) Future prospects for the use of n-3 PUFAs in the prevention of various gastrointestinal (GI) diseases, such as gastric ulcers, ulcerative colitis, gastric cancer and colon cancer. Additional detailed clinical trials should be performed to rank n-3 PUFAs as potent chemopreventive agents.

C

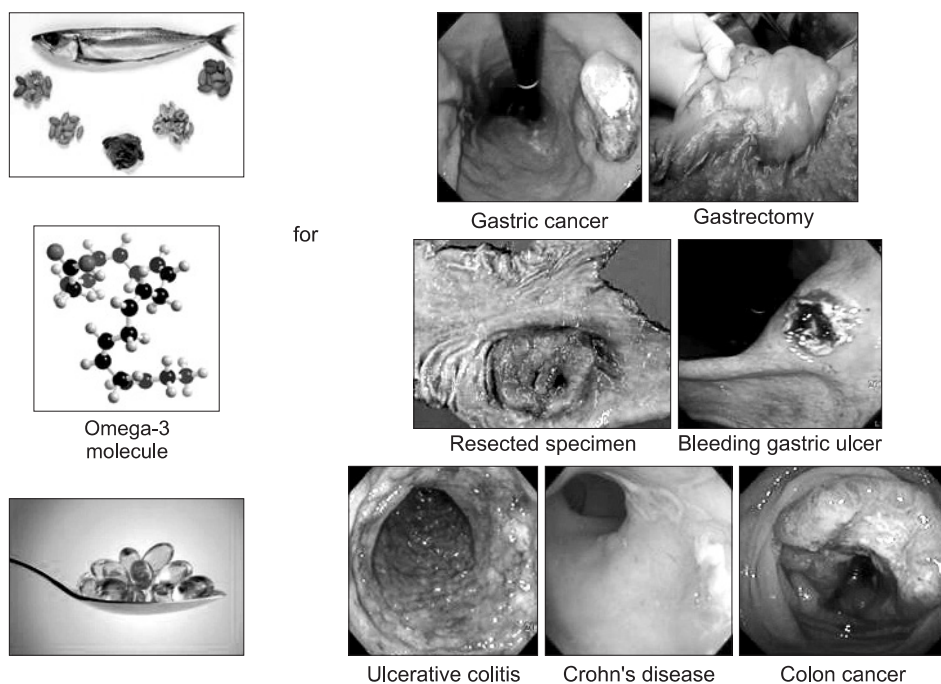Application of n-3 PUFA for chemopreventive action of GI cancers

for

Omega-3
molecule

Gastric cancer

Gastrectomy

Resected specimen

Bleeding gastric ulcer

Ulcerative colitis

Crohn's disease

Colon cancer

Fig. 2. Continued.

suggests the ability of statins in reducing the risk of gastric cancer.[144] In contrast, lovastatin did not show any beneficial effects in patients with advanced gastric cancer.[145] Moreover, administration of pravastatin failed to inhibit *H. pylori*-induced gastric cancer in rodents.[146] Likewise, statins were found to have no protective effects against colorectal cancers.[147] However, simvastatin was found to inhibit the proliferation and growth of HCC cells *in vitro*.[148,149] Additional studies are warranted to establish the potential of statins in the chemoprevention of GI cancer. In addition, prebiotics, selectively fermented food ingredients that induce specific changes in the composition or activity in the GI microbiota, has been acknowledged as beneficial to the host well being and health, showed a protective effect and may be the useful for colon cancer prevention and treatment.[150] Similarly, probiotics can carry broad spectrum of GI cancer prevention, particularly *H. pylori*-associated gastric cancer and IBD-associated colon cancer.[151] Recently we have published cancer preventive effect of exogenous 8-hydroxydeoxyguanosine against colitis-associated cancer, where we have shown that strong anti-inflammatory and antioxidative agents administered at early phase of inflammation-associated carcinogenesis could suppressed inflammation-based mutagenic actions strongly, supporting the thesis that top-down strategy might be better in a wide spectrum of cancer prevention rather than bottom-up strategy.[152] As seen in Fig. 2, accumulating evidences are available showing that n-polyunsaturated fatty acids (n-PUFAs) were very essential in either ameliorating carcinogenesis-associated inflammation or spurting rejuvenation to revert precancerous lesion.[153-155] In order to clearly document the cancer preventive efficacy of n-3 PUFA, Kang *et al*.[156] generated *fat-1* transgenic

mice, which was made through over-expressing n-3 desaturase (Fig. 2B), and proved the chemopreventive actions of n-PUFA in diverse clinical diseases from inflammation based GI diseases to diverse GI cancers (Fig. 2A). Several mechanisms by which n-3 PUFA can exert the chemopreventive effects have recently been identified; inhibition of COX activity,[154] production of novel anti-inflammatory lipid mediators; resolvins, protectins, maresins, etc,[157] direct fatty acid signaling via G protein-coupled receptors,[158] alteration of membrane dynamics and cell surface receptor function,[159] decreased cellular oxidative stress,[160] antioxidative function,[161] and restorative and rejuvenating action (Fig. 2B).[162] Currently our group is continuing to prove the efficacy of n-3 PUFA to halt the progression of precancerous to cancer lesions in gastroenterology (Fig. 2C).

CONCLUSIONS

In spite of advancement and development in screening and early diagnosis as well as minimally invasive treatment technology, GI cancers still remain a leading cause of death worldwide, a challenge for the clinicians to search more effective preventive strategies. The increasing burden of cancer treatment as evidenced with the failure of cancer act to conquest has led to a significant paradigm shift in more intense efforts from treatment to prevention. As potential candidates postulated as having a chemopreventive effect on GI cancers, aspirin, and NSAID had been most widely studied and has gained universal acknowledgement. However, complications such as peptic ulceration, upper GI bleeding, and perforation as well as increased cardiovascular threatening posed serious threats to the routine

administration of NSAIDs for the purpose of cancer prevention, still awaiting serious improvement in formulation for chronic use. Finally though a balance between the risks and benefits must be struck accompanied with extensive clinical trials to weight advantage, the safety, cost effectiveness and optimal dose will be solved in a near future. Another hope comes from cancer metabolism, for instance, Warburg effect can shed promising chance for cancer prevention. As shown in the main text, we have high levels of evidence that PPI as well as acid pump antagonist might be evolved to cover the villainous characteristics of cancer cells into a virtuous feature of noncancer cells. Finally, natural products or phytoceuticals cover the long journey to the prevention of cancers through chronic safe administration.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

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