

Short-term Intervention to Revert Premalignant Lesions as Strategy to Prevent Gastrointestinal Cancers

REVIEW

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“Prevention might be better than treatment in cancer treatment” is brief conclusion drawn from war on cancer through National Cancer Act of 1971 by U.S. President Richard Nixon. However, the clinical practice of chemoprevention is still in its infancy in spite of a wealth of data showing its effectiveness in experimental animals as well as in vitro mechanism research. Recent advances in either high throughput analysis including cancer genomes and tailored medicine or molecular targeted therapeutics, preventive strategies also should be changes as previous preventive strategies including phytochemicals, life-style modification, and some empirical agents. Furthermore, molecular targeted therapeutics achieved high goal of effectiveness under the concept of therapeutic or preventive “synthetic lethality”, of which extended application can be included within the scope of chemoprevention. Here, we will summarize several recent advances in chemopreventive strategy objected to justify optimism that chemoprevention will be an effective approach for the control of human cancer. *s*TRP (*short-term intervention to revert premalignancy*) strategy will be introduced for cancers in gastroenterology. (J Cancer Prev 2013;18:289-297)

Key Words: Chemoprevention, *s*TRP, Phytochemicals, Human cancer, Synthetic lethality

INTRODUCTION

Prof. Hong WK and Prof. Sporn MB, for the first time, defined chemoprevention as follows; chemoprevention is the use of pharmacologic or natural agents to inhibit the development of invasive cancer, for which either blocking the DNA damage that initiates carcinogenesis or arresting/reversing the progression of premalignant cells in 1997 (Fig. 1).¹ Since carcinogenesis is a process consisting of initiation, promotion and progression phases, this multi-stage sequence of carcinogenesis events has provided the opportunity for intervention to inhibit, revert or delay each process of carcinogenic stage before the development of invasive malignancy. Therefore, agents that can repress, detour, tackle, or revert this unpleasant journey to cancer

have great potential for chemoprevention. An ideal chemopreventive agent should have little or no toxicity, high efficacy in multiple sites, capability of oral consumption, known mechanisms of action, and low cost and feasibility of long-term administration, by which mostly natural products or phytochemicals had been identified. Until now, a variety of grains, cereals, nuts, soy products, olives, beverages such as chocolate, tea, and coffee, spices such as turmeric, garlic, ginger, black pepper, curcumin, and vegetables including cabbage, garlic, cauliflower, broccoli, tomatoes, and fruits such as, apples, grapes, and berries, and famous Korean red ginseng confer a protective effect against cancer, in which natural products contain a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids, gin-

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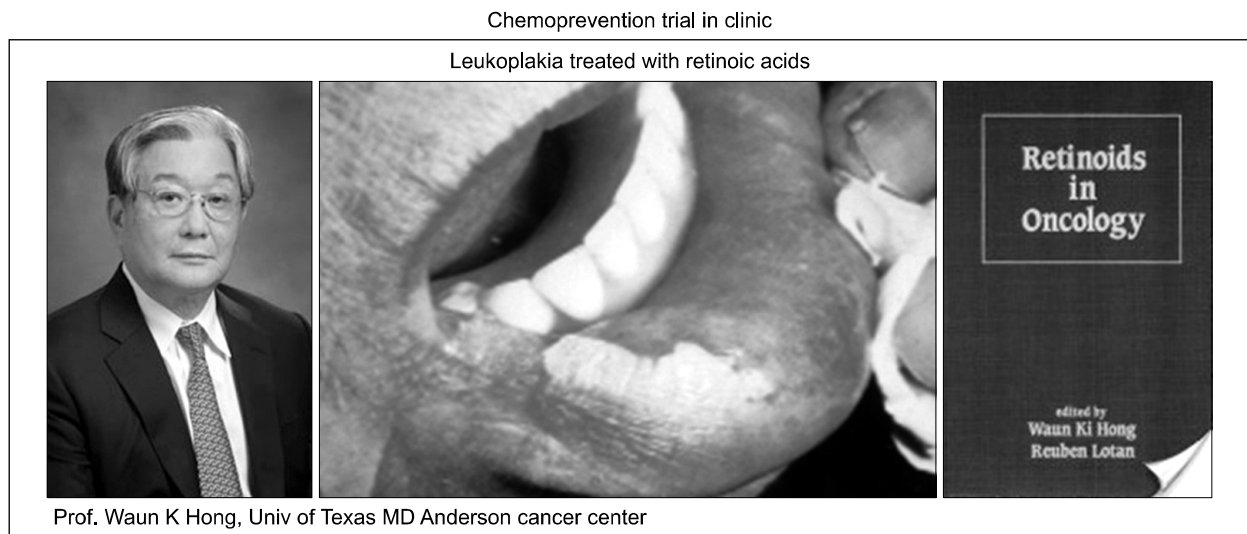


Fig. 1. Great achievement of chemoprevention by Prof. Hong WK (Univ of Texas MD Anderson Cancer Center). Prof. Hong WK (Univ of Texas MD Anderson Cancer Center) first tried the application of retinoic acid as differentiation therapy to revert leukoplakia, a precancerous lesion occurring at buccal area and achieve the disappearance of premalignant lesion.

senosides, and nitrogen containing as well as organosulfur compounds.² However, though very promising from publications, most are in the stage of preclinical or scientific interests, rather big gap in reality and evidence based medicine. To date, chemoprevention clinical trials with natural products conducted in cancer are very limited. Extensive clinical research is warranted to evaluate further safety and chemopreventive efficacy of natural products either alone or in combination with chemotherapeutic agents against cancer.³

The evidence that mutation in tumor suppressors such as BRCA1/2 makes cancer cells highly susceptible to inhibitors of a compensatory DNA repair pathway has broadened the range of possible therapeutic targets by extending it to gene products that are in a “synthetic lethality” relationship with oncogenes and tumor suppressors.⁴ Inhibition of such targets blocks specific buffer-mechanisms that are required for survival in the presence of defined oncogenic mutations, but not in their absence. This approach has led to identify compounds that are highly active in the presence of different types of mutated tumor suppressors and oncogenes. Further extended this concept “synthetic lethality”, Wu X and Lippman SM innovated new concept of “short-term intermittent therapy to eliminate premalignancy (SITEP) under the demise that intermittent dosing schedules might

reduce toxicity while retaining benefit escaping the limitation of synthetic lethality, which only targeted to enhance elimination of cancer cells.⁵ Therefore, a novel SITEP approach whereby short-term, intermittent therapy can eliminate premalignant cells via apoptosis induced by synthetic lethal interactions in higher efficacy, allowing personalized, selective elimination of premalignant clones without harming normal cells.⁵

Besides of cancers in other organ, cancers originating in gastroenterology including esophageal cancer, stomach cancer, colon cancer, and pancreatic cancer have premalignancy before developing invasive cancers, Barrett’s esophagus, chronic atrophic gastritis accompanied with intestinal metaplasia, dysplasia originating from chronic ulcerative colitis, and chronic fibrosing pancreatitis. If we can revert these premalignancies into non-tumorous conditions, that will be the best way of cancer prevention.

CHEMOPREVENTION; THE PAST AND THE PRESENT

Clifton Leaf present criticisms of past cancer research approaches in his article “Why we’re losing the war on cancer”⁶ and Lippman SM and Hawk ET in his article⁷ introduced the history of cancer prevention as exemplified; The multidisciplinary history of cancer prevention

recounted here begins with surgical and workplace recommendations of the 1700s and ends with 2009 results of the enormous Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer. The extraordinary panoply of clinical research includes numerous large and smaller chemoprevention studies of nutritional supplements, other dietary approaches, a *Bacillus Calmette-Guérin* trial in 1976, molecular-targeted agents, and agents to prevent infection-related cancers such as hepatitis B virus vaccine to prevent liver cancer in 1984. Also *Helicobacter pylori* (*H. pylori*) are defined as class I, definite, carcinogen for gastric cancer, but the question still remains whether its eradication can impart cancer prevention. Instead, clearing inflammatory activities surely warrant the prevention of infection-associated cancer, for instance, ulcerative colitis-associated colon cancer, Barrett's esophagus-associated esophageal cancer, and cholangitis-associated cholangiocellular carcinoma. This history of pioneering events may help in better understanding who we are and what we want to achieve as cancer prevention researchers and practitioners and the novel strategy will be introduced in later part of review article.

SYNTHETIC LETHALITY FOR THERAPEUTIC OR PREVENTIVE EFFICACY OF CANCER

Curing advanced cancer requires the simultaneous use of 2 or more drugs.⁸ Successful uses of combination chemotherapeutics and subsequent advances in cancer biology led to the recognition that frequent relapses after response to cancer therapy are because of multiple pathways that can enable resistant cancer cell populations to survive. With the increased understanding of the genetic origin of cancer and the recognition that the major phases of cancer development, a critical milestone for understanding carcinogenesis at a molecular level, the development of specific molecularly targeted therapies became possible. As representational example, the initial documented success with imatinib in targeting BCR-ABL for chronic myelogenous leukemia and in targeting *c-kit* for some gastrointestinal stromal tumors showed the potential of molecular-targeted, personalized therapy and continuous success in control of metastatic melanoma with a BRAF

inhibitor and against some cancers with an anaplastic lymphoma kinase (ALK) inhibitor have again heightened expectations for molecular targeting leading to no combination targeted therapy has yet emerged clinically from the targeted therapy development paradigm, which has important implications for the clinical implementation of "synthetic lethality". Synthetic lethality takes advantage of two out of following four potential field of influence including genetics, synergy, lineage, and host. In detail, cellular condition in which two or more non-allelic and non-essential mutations, which are not lethal on their own condition, but become deadly when present within the same cell. Therefore, the idea of therapeutic or preventive synthetic lethality rests on the premise that neoplastic cells develop mutations that normal cells do not and that inhibiting first one and then another critical pathway with a drug will be lethal to the cancer cells.⁹ Conclusively, the onset of synthetic lethality may provide a useful tool for amplifying the efficacy of drugs in anti-cancer regimens, for uncovering interdependence between genes and for identifying predictive factors that would be extremely useful to guide in the selection of more effective targeted drugs and drug combinations for each patient with advanced and intractable stage.¹⁰ In breast or ovary cancer, patients with mutated BRCA1 or 2, essential components of a repair pathway for repairing DNA double-strand breaks have become reliant on another DNA repair component, PARP1, for replication fork progression. In these patients, the exploitation of the addiction of cancer cells to a DNA repair pathway is based on synthetic lethality.¹¹ In patients with lung cancer, mutations and activation of KRAS occur frequently and are thought to be a primary driver of non-small cell lung cancers (NSCLC), chemotherapy is based on a synthetic lethal interaction among TNF-related apoptosis-inducing ligand (TRAIL), the second mitochondria-derived activator of caspase, Smac/DIABLO, and KRAS,⁹ leading to short-term, intermittent treatment with TRAIL and Smac-mimic induced apoptosis in tumor cells and reduced tumor burden in a murine model of KRAS-induced lung cancer. Synthetic lethality is exploited to overcome drug resistance to conventional chemotherapy in several types of solid tumors.

REVERTING PREMALIGNANCY ADOPTING SYNTHETIC LETHALITY AND *s*TRP

Since prevention by a single agent will be limited by both toxicity and potency, the concomitant use of multiple agents with different mechanisms of action is an exciting new field of investigation. The combination of a promoter of differentiation, an antiproliferative agent, and an inducer of apoptosis would be particularly appropriate for the treatment of advanced premalignant lesions in chemopreventive way.¹ As premalignancy and chemoprevention studies in head and neck cancer including oral cavity cancer, avoiding or cessation of alcohol and smoking, early detection of potentially malignant disorders or cancer, and early detection of recurrent and/or second primary tumor form the basis of prevention of oral cancer.¹² Similarly, the carcinogenesis process in head and neck cancer resulted from a dysregulation of cellular proliferation, differentiation, and cell death, chemoprevention efforts are all based on the correction of underlying molecular changes,¹³ requiring more details regarding re-regulation of growth and differentiation and possibly elimination of genetically and phenotypically aberrant clones to reverse carcinogenic process. Chemoprevention studies in upper aerodigestive tract cancers are based on these fundamental premises and the identification of molecular, genetic, biologic, and cellular changes.¹⁴ Since the use of poly-

phenols as a chemopreventive agent is a suitable tool for modulation of the oral carcinogenesis process, de Moura et al.¹⁵ conducted the use of polyphenols as a chemopreventive agent in oral carcinogenesis using *in vivo* and *in vitro* test systems and found that polyphenols are able to exert some chemopreventive action as a result of inducing cellular death, apoptosis, inhibition of tumor growth, and antioxidative properties, reaching to the conclusion that a new approach that would apply not only to polyphenols but also to other phytochemicals used as promising therapeutic agents against oral human diseases, especially cancer., prerequisite basis for *s*TRP strategy. Since chemoprevention, a novel approach for controlling cancer, involves the use of specific natural products or synthetic chemical agents to reverse, suppress or prevent premalignancy before the development of invasive cancer, several natural products, such as, grains, nuts, cereals, spices, fruits, vegetables, beverages, medicinal plants and herbs and their various phytochemical constituents including, phenolics, flavonoids, carotenoids, alkaloids, nitrogen containing as well as organosulfur compounds confer protective effects against wide range of cancers including colon cancer.¹⁶ However, identification of an agent with chemopreventive potential requires *in vitro* studies, efficacy and toxicity studies in animal models before embarking on human clinical trials (Fig. 2).

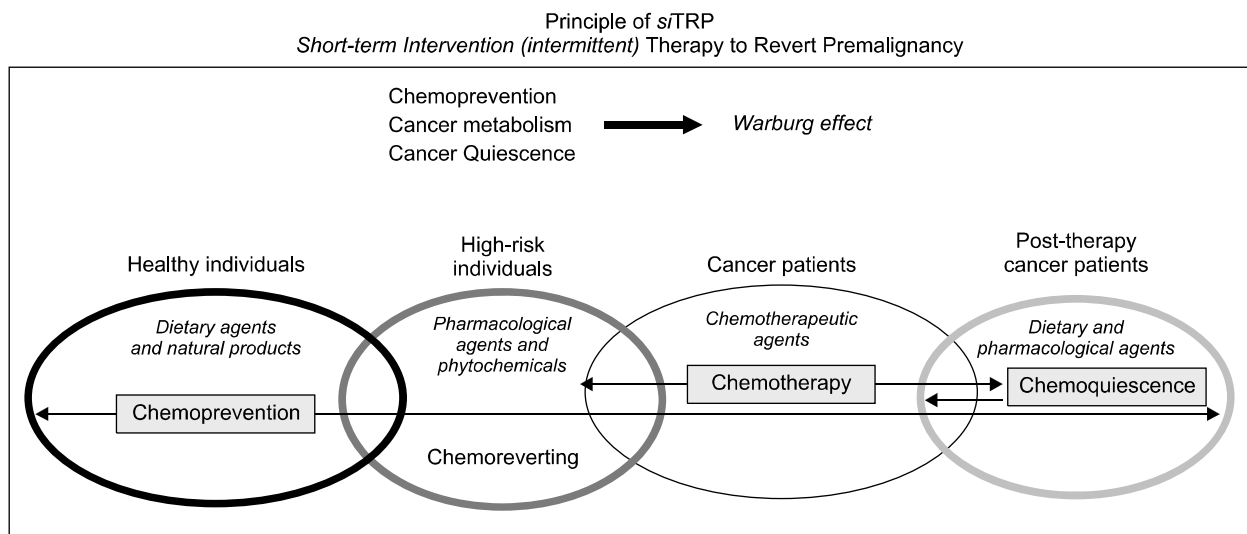


Fig. 2. *s*TRP (*short-term intervention To Revert Premalignancy*). *s*TRP aimed for chemoprevention via regulating Warburg effect as well as cancer quiescence.

APPLICATION OF *s*TRP IN GASTROENTEROLOGY

1. Barrett's esophagus

Barrett's esophagus is an acquired metaplastic changes in squamous epithelium lined esophagus featured with the normal stratified squamous epithelium lining of the esophagus is replaced by an intestinal-like columnar epithelium and its implication in a precursor lesion to esophageal adenocarcinoma threatened patients.¹⁷ Those with Barrett's have a 40 fold increased risk of esophageal adenocarcinoma.¹⁸ Although known to arise as a consequence of chronic gastroesophageal reflux, the cellular and molecular mechanisms underlying development Barrett's esophagus and its progression to cancer remain unclear.¹⁹ Though reflux disease is a key factor for development of Barrett's esophagus, other factors must underlie its development since it occurs in only a minority of reflux disease patients.²⁰ However, dominant pathogenic mechanism is that gastroduodenal content reflux from gastroesophageal reflux disease induces the inflammation-mediated progression from hyperplasia to metaplasia, and to adenocarcinoma,²¹ by which several pharmacological interventions are anticipated as cancer preventive way, including proton pump inhibitor (PPI including esomeprazole, rabeprazole, and pantoprazole), aspirin, NSAIDs, and some more anti-inflammatory agents. The effect of pharmacological and surgical intervention on the natural history of Barrett's is a subject of ongoing research, including the Barrett's Esophagus Surveillance Study and the aspirin and proton pump inhibitor (omeprazole) cancer chemoprevention trial with interesting results.²² The major questions surrounding Barrett's esophagus include validity of surveillance strategies, the optimal treatment and more importantly an agent that can prevent progression to cancer without unacceptable side effects. Though the main chemopreventive agents that show promise are aspirin and PPIs, other agents such as green tea, berries and antioxidants and diet also have been suggested.¹⁸ Improved characterization of the molecular mechanisms underlying Barrett esophagus is an incentive to undertake more basic science research in this field. Such research could also help with the development of chemoprevention

strategies for this precancerous condition.²³ Conclusively, hope and demand for continued improvement in the clinical trial infrastructure to facilitate testing of new pharmacological and endoscopic interventions for Barrett's esophagus is increasing as part of *s*TRP strategy.

2. *Helicobacter pylori*-associated chronic atrophic gastritis with intestinal metaplasia

Helicobacter pylori (*H. pylori*) are well recognised as a class I carcinogen because long-term colonization by this organism can provoke chronic inflammation and atrophy, which can further lead to malignant transformation. As animal model for *H. pylori*-associated gastric cancer, *H. pylori* infection enhances glandular stomach carcinogenesis in Mongolian gerbils (MGs) treated with N-methyl-N'-nitro-N-nitrosoguanidine and N-methyl-N-nitrosourea.²⁴⁻²⁶ A high-salt diet has been revealed to synergistically enhance development of stomach cancer with *H. pylori* infection; the latter exerts stronger promoting effects than the former. Heterotopic proliferative glands (HPG) frequently develop with *H. pylori* infection in the glandular stomach of infected gerbils, with a slightly dysplastic change of constituent cells. Eradication of *H. pylori* with antibiotics diminishes their enhancing effects. The earlier the eradication of *H. pylori* is undergone, the more effective is the prevention of gastric carcinogenesis in MGs. Cao et al.²⁷ investigated the effects of *H. pylori* eradication on cell turnover and changes of gastric tumors and concluded that eradication results in apoptosis and reduction of proliferation of HPGs in *H. pylori*-infected gerbils, these lesions thus being apparently reversible through regulation of cell kinetics. Lee et al.²⁸ evaluated the benefit of mass eradication of *H. pylori* infection in reducing premalignant gastric lesions for which mass eradication of *H. pylori* infection was started from 2004 for a Taiwanese population with prevalent *H. pylori* infection, who were >30 years of age. The main outcome measures were changes in the prevalence of *H. pylori* infection and premalignant gastric lesions, and changes in the incidence of premalignant gastric lesions and gastric cancer before (1995-2003) and after (2004-2008) chemoprevention. The present study demonstrated the application of mass eradication of *H. pylori* infection to a population in a small area with

highly endemic *H. pylori* infection and a high incidence of gastric cancer. Shortly after the implementation of treatment, significant reductions in *H. pylori* infection (79%) and gastric atrophy (77%) occurred. This remarkable effectiveness for atrophy (61%) persisted after adjustment for the effect of the declining incidence, possibly due to improvements in sanitation and hygiene. As results, the role of *H. pylori* eradication in reducing premalignant gastric lesions as well as invasive cancers has therefore gained attention. Stimulated with this result as well as other investigations, Japanese government decided to eradicate *H. pylori* in patients with chronic gastritis from this year and siTRP relevant to *H. pylori* infection will be reported around 5-10 years. However, real benefit of a microbial-based approach to cancer prevention in a population-wide, real-life setting thus remains unsubstantiated and non-microbial approach also should be considered because *H. pylori*-associated gastric inflammation still persists even after successful eradication and connection between inflammation and carcinogenesis should be modulated with additional intervention. Our group set

up new strategy of siTRP incorporating Korean red ginseng, probiotics, special extracts of licorice, and mesenchymal stem cells (MSCs, Fig. 3A) to rejuvenate atrophic gastritis into non atrophic change targeted to tackle the progression to *H. pylori* gastritis in high risk patients (Fig. 3B).

3. Colitis-associated cancer and colon adenoma

The risk of developing colorectal cancer is increased in patients with inflammatory bowel disease (IBD). Colitis-associated cancer represents a long-standing problem, with two new factors adding to its importance: the diffusion of inflammatory bowel disease in developing countries, and the increased availability of effective drugs that control ulcerative colitis delaying or abrogating the need for a curative colectomy.²⁹ Since persistent colon inflammation is the unique variable that factors in colitic cancer development, the search and release of anti-inflammatory/immune suppressive molecules to pursue the goal of cancer chemoprevention in on-going. Various chemopreventive agents have been clearly shown to

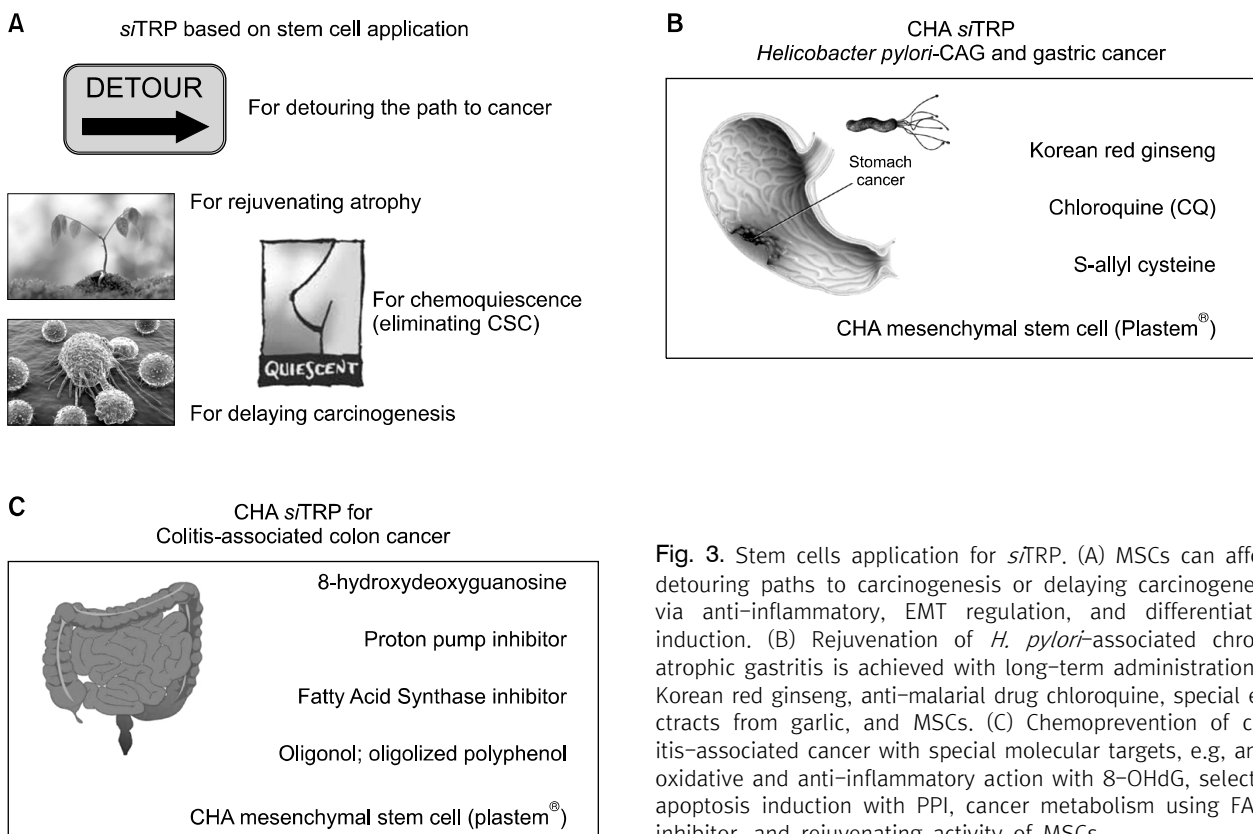


Fig. 3. Stem cells application for siTRP. (A) MSCs can afford detouring paths to carcinogenesis or delaying carcinogenesis via anti-inflammatory, EMT regulation, and differentiation induction. (B) Rejuvenation of *H. pylori*-associated chronic atrophic gastritis is achieved with long-term administration of Korean red ginseng, anti-malarial drug chloroquine, special extracts from garlic, and MSCs. (C) Chemoprevention of colitis-associated cancer with special molecular targets, e.g. anti-oxidative and anti-inflammatory action with 8-OHdG, selective apoptosis induction with PPI, cancer metabolism using FASN inhibitor, and rejuvenating activity of MSCs.

reduce the risk of colorectal adenoma and cancer in the general population and the problems associated with colonoscopic surveillance have led to increasing interest in utilising chemopreventive strategies to reduce the risk of colorectal cancer in patients with inflammatory bowel disease as well.³⁰ Because colitis-associated cancers arose in the setting of chronic inflammation, during which “inflammation-dysplasia-carcinoma sequence” prevails and anti-inflammatory agents can prevent carcinogenesis, we have published data regarding chemoprevention of colitic cancer using infliximab³¹ and 8-OHdG.³² Apart from colitic cancer, colorectal carcinogenesis is also based on a multi-step process characterized by molecular and cellular alterations that result in an identifiable precursor lesion, ie, the adenomatous polyp.³³ The transition from normal mucosa to adenoma and its subsequent progression to carcinoma are protracted events that offer opportunities for preventive interventions. In detail, regular and continued use of non-steroidal anti-inflammatory drugs (NSAIDs) and predominantly aspirin is associated with significant reductions in both colorectal adenoma and carcinoma incidence.³⁴ However, since long-term use of NSAIDs is associated with substantial GI toxicity and may cause an exacerbation in IBD patients, selective COX-2 inhibitors, with a better toxicity profile and no flare-up in IBD disease activity, are therefore attractive candidates for prevention.³⁵ Apart from aspirin and NSAIDs, calcium carbonate is the only other agent that has been shown to modestly reduce sporadic adenoma recurrence rates in a randomized trial. Folate and selenium are being actively studied based on provocative preclinical data.³⁶ Effective anti-inflammatory agents as well as biologics under colonoscopic surveillance can be included as *si*TRP strategy for colitic cancer and safe warrant novel NSAIDs as *s*/TRP strategy for colon adenoma (Fig. 3C).

4. Chronic fibrosing pancreatitis and pancreatic cancer

Chronic pancreatitis is characterized by progressive fibrosis, pain and loss of exocrine and endocrine functions and the long-standing chronic pancreatitis and its associated pancreatic fibrosis are the most common pathogenic events involved in human pancreatic carcinogenesis.³⁷ Since pancreatic cancer has an extremely poor prognosis

and the cellular mechanisms contributing to pancreatic cancer are relatively unknown, prevention of pancreatic cancer might be the better way to save patient life much more than the development of chemotherapeutics.³⁸ Pancreatic inflammation, mediated by cytokines, reactive oxygen species, and up-regulated pro-inflammatory pathways, may play a key role in the early development of pancreatic malignancy. Bai et al. investigated the effect of sulindac on inhibition of chronic pancreatitis in a cerulein induced chronic pancreatitis mouse model and found that sulindac was a promising reagent for the treatment of chronic pancreatitis via inhibition of inflammatory cell infiltration and stromal fibrosis³⁹ as well as additional finding that capsaicin also could be a promising agent for the chemoprevention of pancreatic carcinogenesis, possibly via inhibiting pancreatitis and mutant *Kras*-led ERK activation.⁴⁰ Similar to prevention of colon adenoma, the high level of COX-2 expression in pancreatic intraepithelial neoplasia lesions suggests that COX-2 could be a therapeutic target at a non-invasive stage of pancreatic carcinogenesis and NSAIDs as feasible chemopreventive agent in chronic pancreatitis.⁴¹ Redirection of interests toward pancreatic inflammation and mechanisms of pancreatic carcinogenesis may identify other novel anti-inflammatory agents or other ways to screen for or prevent pancreatic cancer.³⁸ Our group also added more evidence that antioxidant can tackle to way from chronic pancreatitis to pancreatic cancer.⁴² Potent antioxidant or anti-protease agents can be included as *s*/TRP agent for amelioration of chronic fibrosing pancreatitis.

PERSPECTIVE OF CANCER PREVENTION ADOPTING *si*TRP STRATEGY IN CLINIC

The continuing magnitude and burdening of the cancer problem make it imperative to develop an innovative preventive approach to this disease. As advances in the molecular and cellular biology of carcinogenesis continue, specific targets for preventive intervention are being profusely identified, and effective new chemopreventive agents are being synthesized and tested. As much as current molecular therapeutics and application of synthetic lethality, in the near future, molecular targeted

chemoprevention will shed the new hope for cancer conquest based on a mechanistic understanding of carcinogenesis and tailored chemoprevention. Especially further understanding of inflammatory mediators and stem cell biology, rejuvenation of chronic degenerative diseases as well as chemoprevention will be tried before irreversible change of carcinogenesis, so called, *s*TRP will be come true.⁴³ Results from our laboratory strongly suggested the high possibility of reverting into non-tumorous condition through short-term intervention. Among target for future chemoprevention, Kim et al.⁴⁴ provided an overview of the role of oxidative stress in inflammation-based GI tract diseases, including reflux esophagitis, *H. pylori*-associated gastritis, non-steroidal anti-inflammatory drug-induced enteritis, ulcerative colitis, and associated colorectal cancer. The challenging issue that ROS can contribute to diverse gastrointestinal dysfunction, or manifest dual roles in cancer promotion or cancer suppression will be the opportunity to enhance prevention of inflammation-based GI carcinogenesis.

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