



Eating Right to Block Left Premalignant Lesion of GI Cancers

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Short Communication

Cancer prevention, chemoprevention, cancer delay, and chemoquiescence

Prof. WK Hong and prof. MB Sporn in their publication at "Science" journal [1] defined chemoprevention as cancer prevention using pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage or by reversing the progression of premalignant cells. Their efforts to achieve "chemoprevention" were highlighted more because that though "war on cancer" was declared by President Richard Nixon in 1971, cancer statistics from the American Cancer Society and other sources suggested the failure of this war, leaving strong message that a "prevention strategy" might be much better than drastic war on cancer [2]. Recently, increasing emergence of Cancer Stem Cell (CSC) researches led to the feasibility of removing Tumor Initiating Cells (TICs), metastasis initiating cells, and underlying CSCs, after which the concept "chemo quiescence" is also stressed in oncology as ultimate purpose of cancer cure. With the advancement of molecular targeted therapeutics or non-invasive removal of cancer such as endoscopic treatment [3], the studies regarding molecular targeted prevention of cancer is increasingly achieved and with scientific achievements telling that chronic inflammation is one of core hallmarks in carcinogenesis, several strategies had been applied and studied that anti-inflammatory intervention can be faithful strategy to prevent cancer [4]. Especially in Gastrointestinal (GI) tract, the prevention of Barrett' esophagus, *Helicobacter pylori* (*H. pylori*)-associated Chronic Atrophic Gastritis (CAG) with intestinal metaplasia, and long-term inflammatory bowel diseases can be possible with the introduction of either synthetic or natural agents [5]. In detail, the major barrier to more successful cancer immunotherapy is the Tumor Microenvironment (TME), where chronic inflammation played a predominant role in carcinogenesis, cancer cell proliferation, angiogenesis, and immunosuppression. Increasing understanding of cancer-related inflammation has significantly advanced to inhibition of inflammatory mediators or their signaling molecules, blocking of myeloid cells recruitment, and modulation of immunosuppressive functions, and re-education of TME [6]. In this short communication, we have introduced, among novel approaches for GI cancers with proton pump inhibitor, smad7 anti-sense oligonucleotide, non-steroidal anti-inflammatory drug, autophagy regulator, natural or dietary agents in correcting TME under the theme that eating right can be right way for cancer prevention.

siTRP (short-term intervention to revert premalignant lesions) strategy as part of chemoprevention

The continuing magnitude and burdening of the cancer problem make it imperative to develop an innovative preventive approach to this disease. In detail, as advances in the molecular and cellular biology of carcinogenesis continue, specific targets for preventive intervention are being profusely identified, and higher effective chemo preventive agents are being synthesized and tested [7]. As much as the developments of molecular targeted therapeutics and creation of synthetic lethality concept, in the near future, molecular targeted cancer prevention will be come true for cancer conquest. Especially, further understanding of inflammatory mediators and cancer stem cell biology, rejuvenation of chronic degenerative diseases as well as chemo quiescence will be tried before irreversible change of carcinogenesis. Our group nominated these strategies as siTRP. Results from our laboratory strongly suggested the high possibility of reverting premalignant lesions into non-tumorous condition through short-term effective intervention. Inflammation-based GI tract

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diseases, including reflux esophagitis, *H. pylori*-associated gastritis, non-steroidal anti-inflammatory drug-induced enteritis, ulcerative colitis, and associated colorectal cancer, are ultimate target [8].

Eating right to prevent cancer through reverting premalignant lesions

Though recent advances in cancer immunotherapy, for example, immune checkpoint blockade therapy, have dramatically changed the therapeutic strategy against advanced malignancies, the unmet medical need in cancer immunotherapy is that only a subset of patients shows a good response [9]. Therefore, the efforts to correct TME are still prerequisite and nutrients or natural products can contribute greatly to this concern correcting TME. In order to achieve this, eating right seems to be answer and the strategy to leave premalignant lesions as it seems to be potential way. Some examples will be introduced in this communication.

Artemisia and green tea extracts: Since the discovery of *H. pylori* infection as the major cause of gastro duodenal disorders including acute and chronic gastritis, gastro duodenal ulcer, CAG, and gastric cancer almost three decades ago, the possibility of preventing these clinical diseases through eradicating *H. pylori* has been the focus of active research. Our group set strong hypothesis that non-microbial, dietary approach might be the alternate, for which several interventions of nutritional components can aim rejuvenation of CAG [10]. The experience and outcome regarding nutritional application to rejuvenate gastric atrophy was reported with the following natural agents including *Artemisia* and green tea extract, Korean red ginseng, garlic extracts, cancer preventive kimchi, n-3 Polyunsaturated Fatty Acids (PUFA), special form of licorice, and probiotics. Among these, we evaluated the efficacy of long-term dietary administration of *Artemisia* and green tea extracts on *H. pylori*-initiated, high-salt-promoted chronic atrophic gastritis and gastric tumorigenesis mouse model [11]. As reported, the erythematous and nodular changes and mucosal ulcerative and erosive lesions were noted in the control group at 24 weeks, while *Artemisia* and green tea extracts showed significantly ameliorated pathologic lesion compared to the control group. After the 36 weeks, scattered nodular masses with some central ulcers and thin gastric surface were noted in the control stomach, whereas no tumorous lesion and milder atrophic changes were observed in *Artemisia* and green tea extracts groups. On molecular analysis, increased expressions of COX-2, TNF- α , IL-6, lipid peroxide, and activated STAT3 relevant to *H. pylori* infection were significantly decreased with *Artemisia* and green tea extracts administration ($p < 0.01$), whereas HSP70 was significantly increased. 15-PGDH expressions, core tumor suppressor involved in carcinogenesis, were significantly decreased with *H. pylori* infection ($p < 0.05$), but significantly increased in *Artemisia* and green tea extract group ($p < 0.05$). Conclusively, long-term dietary intake of *Artemisia* and green tea extracts can be an effective strategy either to rejuvenate *H. pylori* atrophic gastritis or to suppress tumorigenesis.

Cancer preventive kimchi (cpkimchi) for GI cancer: Our group developed cpkimchi and administered to chronic *H. pylori*-initiated, high salt diet-promoted, gastric tumorigenesis mice model. As results, the erythematous and nodular changes, mucosal ulcerative and erosive lesions noted in the stomach of 24 weeks wild type mice were significantly ameliorated with cpkimchi administration. After 36 weeks, scattered nodular masses, some ulcers, and thin nodular gastric mucosa were noted in *H. pylori*-infected wild type mice, but

these gross lesions were significantly attenuated in cpkimchi group. On molecular analysis, significant expressions of COX-2 and IL-6, activated NF- κ B and STAT3, increased apoptosis, and marked oxidative stresses were noted in *H. pylori*-infected WT group, but these were all significantly attenuated in cpkimchi group. With interest, cpkimchi extracts afforded significant selective induction of apoptosis only in cancer cells, led to inhibition of *H. pylori*-induced proliferation, while no cytotoxicity through significant HO-1 induction in non-transformed gastric cells. Conclusively, daily dietary intake of cpkimchi can be an effective way either to rejuvenate *H. pylori*-atrophic gastritis or to prevent tumorigenesis supported with the concerted actions of anti-oxidative, anti-inflammatory, and anti-mutagenic mechanisms [12].

ω -3 PUFAs: Using *Fat-1* transgenic mice, which can synthesize ω -3 PUFAs due to presence of 6-desaturase, we compared the serial gastric pathologies after *H. pylori* infection. As results, *Fat-1* TG mice showed significantly attenuated gastritis as well as gastric tumorigenesis compared to wild type littermates, signifying that long-term intake of ω -3 PUFAs can provide protection from *H. pylori*-associated CAG and gastric cancer [13]. Though general eradication in patients with chronic gastritis was intervened in Japan as drastic effort to decrease *H. pylori*-associated gastric cancer, non-microbial and nutritional intervention can be an alternate to these cost-expensive and skewed strategies can be preferred [10]. Conclusively, we recommend that eating right to prevent left premalignant lesions.

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