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REVIEW

Anticancer Effect of Lycopene in Gastric Carcinogenesis

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Gastric cancer ranks as the most common cancer and the second leading cause of cancer-related death in the world. Risk factors of gastric carcinogenesis include oxidative stress, DNA damage, *Helicobacter pylori* infection, bad eating habits, and smoking. Since oxidative stress is related to DNA damage, smoking, and *H. pylori* infection, scavenging of reactive oxygen species may be beneficial for prevention of gastric carcinogenesis. Lycopene, one of the naturally occurring carotenoids, has unique structural and chemical features that contributes to a potent antioxidant activity. It shows a potential anticancer activity and reduces gastric cancer incidence. This review will summarize anticancer effect and mechanism of lycopene on gastric carcinogenesis based on the recent experimental and clinical studies.
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Key Words: Anticancer effect, Lycopene, Gastric carcinogenesis

INTRODUCTION

Gastric cancer is one of the most common cancers in the world, following lung, breast and colorectal cancer.[1-3] Risk factors of gastric cancer include poor diet, smoking, family history, inflammation, and *Helicobacter pylori* infection.[4,5] Epidemiological studies have shown that diet including antioxidant nutrients plays an important role in prevention of cancer development.[6,7] Especially, consumption of lycopene reduced risk of several cancers.[8-10] However, compared to other cancers such as prostate cancer, anticancer effect of lycopene in gastric carcinogenesis has not been well studied. Lycopene is thought to be the active component in red fruits and vegetables such as tomatoes. In addition to its potential anticancer activity, lycopene supplementation decreased the occurrence of chronic diseases including type 2 diabetes, osteoporosis, and coronary heart disease.[11] Since lycopene has 11 conjugated double bonds, it functions as the most potent antioxidant among carotenoids.[12] Therefore, lycopene prevents the oxidative damage of DNA, lipids and proteins.[13] Other potential mechanisms of lycopene include cell cycle arrest, modulation of immune function, and induction of apoptotic cell death.[14] Lycopene also inhibited reactive oxygen species (ROS) production and decreased the phosphorylation of extracellular signal-regulated kinase (ERK), resulting in inhibition of cancer cell growth.[6,15-17] Here, we review the anticancer effect and mechanism of lycopene in gastric carcinogenesis based on the recent advances in experimental and epidemiologic studies.

ANTIOXIDANT ENZYME ACTIVITIES

Oxidative stress-mediated DNA damage and tissue injury are related to cancer development.[18,19] When the damaged cells divide, DNA duplication and cell metabolism become aberrant. Therefore, mutation is an important factor in carcinogenesis and oxidative damage could lead to carcinogenesis.[20,21] Several studies reported that antioxidants inhibit oxidative damage and decrease abnormal cell division.[22,23] Protective effect of antioxidants plays a critical role in prevention of cancer. Since gastrointestinal tract could easily be exposed to external and internal stimuli which produce ROS, the levels of antioxidants are especially important for preventing cellular damage. Antioxidants and

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antioxidant enzymes including glutathione (GSH), glutathione peroxidase (GPx), glutathione-S-transferase (GST) are involved in scavenging oxygen free radicals.[24] GSH protects essential cellular components from ROS-mediated damage and regulates cell proliferation. Lycopene, compared to other carotenoids and antioxidants such as α-tocopherol and β-carotene, is a powerful antioxidant with a singlet oxygen quenching activity.[25] Treatment of lycopene significantly reduced the extent of lipid peroxidation and enhanced the activities of GSH-dependent enzymes in gastric cancer rats.[26] Lycopene reduced oxidative injury by stimulating levels and activities of GSH, GST, GPx enzymes in gastric cancer animals.[27,28] These findings demonstrate that lycopene may have anticancer effect by increasing activities of antioxidant enzymes and reducing oxidative damage in gastric mucosa.

CELL PROLIFERATION AND APOPTOSIS

ERK signaling is involved in cell cycle checkpoints and mitosis. Therefore, ERK is considered as a major regulator of cell proliferation, apoptosis, and differentiation.[29,30] Lycopene increased G0-G1 phase and decreased S phase in human gastric cancer HGC-27 cells.[30] Lycopene inhibited phospholylation of ERK in gastric cancer cells as well as hepatocarcinoma cells.[30,31] Yang et al.[31] reported that enzymatic metabolite of lycopene, apo-8'-lycopena, suppressed protein expression of Rho small GTPases and inhibited focal adhesion kinase-mediated signaling pathway, such as ERK/p38 and phosphatidylinositol 3-kinase-Akt axis. These findings suggest that lycopene may contribute to anti-proliferative effects in gastric cancer cells by inhibiting activation of ERK and inducing cell cycle arrest.

Bcl-2 is considered as an important anti-apoptotic protein and regulates cell death.[32] Bcl-2 inhibits apoptosis by reducing caspase activation such as caspase 3 and 8.[33] Caspase 3, apoptosis-related cysteine peptidase, interacts with caspase 8. These proteins are involved in the programmed cell death induced by various stimuli.[34] Apoptosis regulator Bax protein, a member of Bcl-2 family proteins, promotes apoptosis. As a pro-apoptotic protein, Bax induces release of cytochrome C and other pro-apoptotic factors from the mitochondria, leading to activation of caspases.[35] Lycopene induced apoptosis in gastric cancer cells by decreasing Bcl-2 level and increasing the levels of Bax, caspase 3 and 8.[33,36]

A tumor suppressor gene p53 regulates the balance of cell proliferation and apoptosis. Several studies reported that p53 is overexpressed in gastric cancer.[37,38] In gastric mucosa of rats exposed to cigarette smoke, p53 is overexpressed.[39] Upon p53 is activated, p53 target gene such as p21, a cyclin-dependent kinase inhibitor, regulates cell cycle arrest in G1 and induces apoptosis.[40] Lycopene supplementation prevented changes in p53 expression in gastric mucosa of ferrets.[39] Therefore, lycopene may protect against the development of gastric cancer by inhibiting p53-dependent apoptosis and correcting the unbalance of apoptosis and cell proliferation.

HELICOBACTER PYLORI

Over half of the world's population is colonized with *H. pylori* which is a gram-negative bacterium.[41] *H. pylori* infection linked to chronic gastritis, gastric ulcers, and gastric cancer. One of the toxic factors in the pathogenesis of *H. pylori* infection is ROS. Nuclear factor-κB (NF-κB) is activated by ROS in the infected cells. NF-κB activation leads to induction of TNF-α and chemokines in *H. pylori*-infected gastric epithelial cells. *H. pylori*-induced TNF-α and interleukin-6 could alter gastric epithelial cell adhesion and result in migration of mutated epithelial cells.[42] TNF-α-inducing protein (Tipα) binds to nucleolin which is localized on the surface of gastric cancer cells.[43] Interaction between Tipα and nucleolin causes a cancer-oriented microenvironment that increases the risk of gastric cancer. *H. pylori* also induces activation of ERK,[44] which may be involved in hyper-proliferation of the infected cells.

H. pylori infection induced oxidative DNA damage.[45,46] Jang et al.[47] suggested that lycopene inhibited *H. pylori*-induced increases in ROS production and alterations in cell cycle distribution in gastric epithelial cells. In addition, *H. pylori* induced apoptosis with increased Bax and decreased Bcl-2 expression as well as cleavage of PARP-1.[47] PARP-1, as an enzyme of DNA damage recovery, has a role in repair of single-stranded DNA breaks. These findings suggest that lycopene may be beneficial for treatment of *H. pylori*-associated gastric disorders even though clinical trial of lycopene as an adjunctive therapy for *H. pylori* eradication had no effect.[48]

EPIDEMIOLOGIC STUDIES

As described above, in vitro and in vivo studies show anticancer effect of lycopene in gastric carcinogenesis. Many countries have implemented the clinical study of lycopene as the main component of tomato and tomato products An inverse association between tomato intake and gastric cancer incidence has been reported in some epidemiologic studies.

In China, meta-analysis study supports the negative relationship between tomato consumption and risk of gastric cancer.[49] The risk of gastric cancer was significantly reduced in people

consuming high lycopene compared to low intake group.[49] High serum levels of lycopene were significantly associated with reduced risk of developing gastric cancer.[50] In Finland cohort study, lycopene treatment did not affect the risk of gastric cardia cancer but decreased the risk of gastric noncardia cancer by <33%.[51] In a case-control study in Uruguay, tomato intake was strong inverse associations with stomach cancer development.[52] In Japan, plasma levels of lycopene were lower in *H. pylori*-positive controls.[53] *H. pylori* infection has been found to decrease the absorption of many nutrients. In the experiment by Ito et al.[54] serum levels of lycopene are associated with reduced risk of death from stomach cancer. They suggested that lycopene may be a promising biomarker to predict mortality from stomach cancer.

CONCLUSION

Lycopene from red fruits and vegetables has strong anticancer activity in gastric carcinogenesis. ROS have been implicated in the progression of several diseases including cancer. ROS cause severe cellular injury and promote tumor metastasis, angiogenesis, and invasion. As one of the most potent antioxidants, lycopene is effective in decreasing oxidative damage by activating antioxidant enzymes such as GSH, GPx and GST. Lycopene treatment inhibits cancer cell growth and induces apoptosis by suppressing ERK signaling pathway. Bcl-2 family and caspases are considered to be the most effective apoptotic regulators. Lycopene decreases Bcl-2 and increases Bax expression, which induce release of cytochrome C from mitochondria, leading to apoptosis. Lycopene treatment inhibits gastric cancer cell proliferation by increasing cell cycle arrest in G0-G1 phase. Moreover, lycopene prevents changes in p53 overexpression in gastric mucosa exposed to cigarette smoke. *H. pylori* infection is a high risk of gastric cancer. Lycopene inhibits *H. pylori*-induced increases in ROS levels and DNA damage in gastric epithelial cells. Korea is a high *H. pylori* prevalence and high gastric cancer incidence country. Since *H. pylori* infection rate in children is higher in Korea than other countries, consumption of red fruits and vegetables is recommended especially to the children to prevent *H. pylori*-associated gastric carcinogenesis.

Based on the studies, we propose a mechanism by which lycopene exerts protective effect against oxidative stress-mediated gastric carcinogenesis (Fig. 1). Smoking, inflammation, and *H. pylori* infection induce oxidative stress which leads to DNA damage, ERK activation and p53 overexpression, decreased activities of

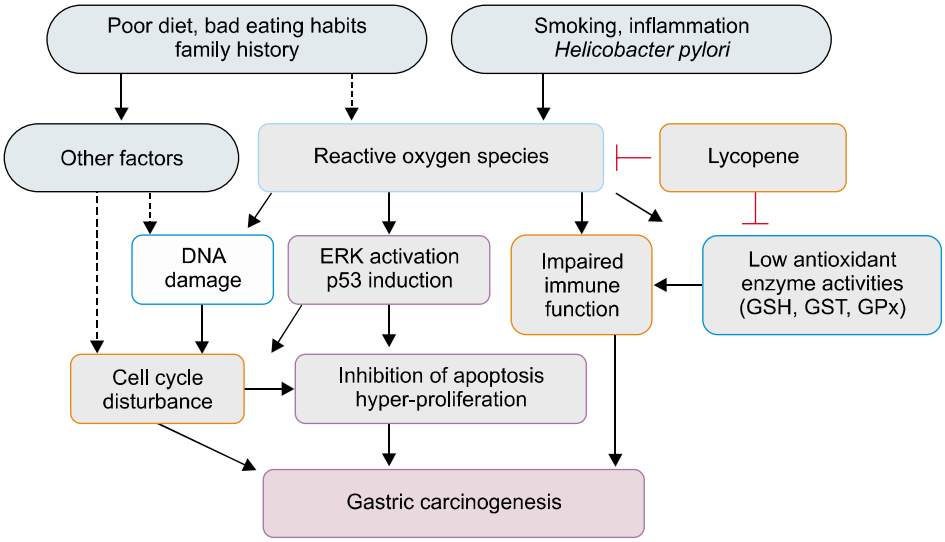

Figure 1. A schematic overview of the protective effect of lycopene against gastric carcinogenesis. Smoking, inflammation, and *Helicobacter pylori* infection induce oxidative stress which leads to DNA damage, ERK activation and p53 overexpression, decreased activities of antioxidant enzymes (GSH, GST, GPx) as well as impaired immune function. Low activities of antioxidant enzymes may decrease immune function of gastric mucosa. ERK activation and p53 overexpression induce cell cycle disturbances and inhibition of apoptosis as well as hyper-proliferation, resulting in gastric carcinogenesis. Poor diet, bad eating habits, and family history may be risk factors to induce DNA damage and cell cycle disturbances by affecting intrinsic factors or producing reactive oxygen species or oncogenic factors. Lycopene scavenges reactive oxygen species and stimulates activities of antioxidant enzymes, which protects gastric mucosa against oxidative stress-induced ERK activation, p53 induction, cell cycle disturbances, and impaired immune function. Therefore, lycopene may prevent oxidative stress-mediated gastric carcinogenesis. ERK, extracellular signal-regulated kinase; GSH, glutathione; GST, glutathione-S-transferase; GPx, glutathione peroxidase.

antioxidant enzymes (GSH, GST, GPx) as well as impaired immune function. Low activities of antioxidant enzymes may decrease immune function of gastric mucosa. ERK activation and p53 overexpression induce cell cycle disturbances and inhibition of apoptosis as well as hyper-proliferation, resulting in gastric carcinogenesis. Poor diet, bad eating habits, and family history may be risk factors to induce DNA damage and cell cycle disturbances by affecting intrinsic factors or producing ROS or oncogenic factors. Lycopene scavenges ROS and stimulates activities of antioxidant enzymes, which protects gastric mucosa against oxidative stress-induced ERK activation, p53 induction, cell cycle disturbances, and impaired immune function. Therefore, supplementation of lycopene or consumption of lycopene-containing fruits and vegetables may prevent oxidative stress-mediated gastric carcinogenesis.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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