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OPINION

The Target of Chemoprevention for Gastric Cancer

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ABSTRACT

Gastric Cancer (GC) is the fifth leading cancer in the world and the third leading cause of cancer-related death. The 5-year survival rate of advanced gastric cancer is less than 30%, it is very important to prevent gastric cancer. Current methods to prevent gastric cancer are eradication of H. pylori, early endoscopic diagnosis and early treatment. Chemoprevention of cancer is using of natural, synthetic, or biological substances to prevent, or reverse the development of cancer, thereby reducing the incidence and mortality of cancer. We will discuss the target of chemoprevention for gastric cancer based on the clue of regeneration of gastric mucosal epithelium from the perspectives of gastric stem cell proliferation and differentiation.

INTRODUCTION

Gastric Cancer (GC) is the fifth leading cancer in the world and the third leading cause of cancer-related death, responsible for almost 700,000 deaths in 2020 [1]. The incidence of GC varies widely across different geographic regions, with the highest incidence observed in East Asia, some Eastern Europe and South American countries, and the lowest in North America and Africa. Globally, over 70% of GC occurs in developing countries [2]. The incidence of gastric cancer showed a slow decline in North America and Western Europe, but it was still very high in Asia, Latin America and Eastern Europe [3]. The decline in North America and Western Europe has been mainly attributed to the decreased prevalence of *Helicobacter pylori* infection, but also to the progress in food storage and preservation, probably by allowing the reduction of salty and smoked food consumption [4,5]. The decline of gastric cancer concerns mainly distal GC, usually called "non-cardia" GC, while the incidence of proximal GC or "cardia cancer," has been steadily increasing [6].

Gastric cancer is believed to be a heterogeneous disease. Gastric cancer occurs in different location of stomach, and has different histological types and different epidemiology and physiopathology [7–9]. According to molecular classifications of GC, based on gene expression profile analysis, 4 types of gastric tumors can be distinguished: (1) positive for EBV, (2) MSI, (3) genomically stable, and (4) chromosomally unstable [10]. Each of these 4 types has a different molecular signature.

At present, the major measures of prevention for GC are eradication of *H. pylori*, early endoscopic diagnosis and early treatment. The National Cancer Institute (NCI) and several other institutions define chemoprevention as using of natural, synthetic, or biological substances to prevent, or reverse the development of cancer, thereby reducing the incidence and mortality of cancer. Current chemoprevention is based on the idea that cancer is a gene mutation disease [11], and pins hope on

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chemopreventive agents to inhibit tumor initiation and suppress the neoplastic transformation of initiated cells [12].

We will discuss the target of chemoprevention of gastric cancer from the perspectives of gastric stem cell proliferation and differentiation.

The regeneration of gastric mucosa epithelium

Gastric mucosa epithelium is in a dynamic regeneration process throughout life. Stem cells located in isthmus of gastric gland are responsible for gastric mucosal epithelial regeneration [13]. Gastric stem cells remain undifferentiated in a niche, and constantly self-renew and replicate [14,15]. Gastric stem cells can differentiate into various types of gastric epithelial cells and intestinal cells [16]. The proliferated gastric stem cells first differentiated into pre-parietal cells, pre-pit cells, pre-neck cells, and pre-enteroendocrine cells. Then the progenies mature gradually while they migrate along the axis of the gastric gland. The pre-parietal cells migrate up and down and become mature acid-secreting parietal cells gradually. The pre-pit cells migrate upward and become mature mucus-secreting pit cells. The pre-neck cells migrate downward and become mature mucus-secreting neck mucous cells and propepsin secreting chief cells. The pre-enteroendocrine cells migrate downward and become mature peptide-secreting enteroendocrine cells [17]. Mature cells age and die, the dead cells shed and be discharged from the gland. This process forms a dynamic cell flow in gastric gland.

Although gastric stem cells have the potential to differentiate into various gastric epithelial cells, they cannot spontaneously differentiate into mature cells. Gastric stem cells need a suitable cell differentiation microenvironment to differentiate and mature. Parietal cells play an important role in differentiation of gastric stem cell. Parietal cells are concentrated in the isthmus and scattered in other parts of the gastric gland. The synthesis of parietal cells is more active in the isthmus and neck regions. The mature parietal cells influence the differentiation process of gastric progenitor cells and regulate the migration and terminal differentiation of gastric pit cell and proenzyme cell lineages. In the absence of mature parietal cells, the number of pre-parietal cells, undifferentiated granulosa cells, precursors of gastric pit cells and proenzyme cells increased [18]. The parietal cells of the diphtheria toxin transgenic mice were damaged, and eventually gastric cancer almost inevitably developed, and the predominant cells of gastric cancer are the normally proliferating isthmus cells [18].

The risk factors of gastric cancer

Gastric mucosal injury and inflammation stimulate gastric stem cell proliferation and promote formation and progression of tumor [19].

High salt intake is associated with atrophic gastritis and intestinal metaplasia [20,21], and increases the risk of gastric cancer in patients with *H. pylori* infection [22]. Salt selectively destroys the parietal cells in the deep layer of gastric glands, and results in the immune response to H+/K+ -ATPase leading to the apoptosis of parietal cells near the surface of gastric glandular cavity [18].

H. pylori are considered to be important factor leading to the occurrence of gastric cancer [23], and eradication of *H. pylori* can reduce the risk of gastric cancer [24]. *H. pylori* do not directly lead to the occurrence of gastric cancer, *H. pylori* confined to gastric antrum mucosa lead to duodenal ulcer not gastric cancer [25]. *H. pylori* infection can induce plasma cells to produce antibodies to *H. pylori*, and the antibodies damage parietal cells through cross-reaction. Only when acid-secreting mucosa atrophy, *H. pylori* spread from gastric antrum to gastric body and whole stomach, and intestinal metaplasia, dysplasia and gastric cancer occur [26]. Once gastric acid-secreting mucosa atrophy, the carcinogenesis of gastric cancer is independent of *H. pylori* infection [27]. When atrophy of gastric acid-secreting mucosa reaches the "irreversible point", even elimination of *H. pylori* or mucosal resection, the occurrence of gastric cancer is inevitable [28,29]. The "irreversible point" may be the minimum of parietal cells. The gastrin stimulates parietal cells to secrete gastric acid and promotes gastric stem cells to proliferate. Gastrin usually increases in atrophic gastritis [30,31], and can enhance the carcinogenic effect of *H. pylori* [32].

High expression of IL-1β is closely associated with gastric cancer; Il-1β activates NF-κB to up-regulate the expression of iNOS and Bax genes that induces apoptosis of parietal cells [33]. Il-17a also induces apoptosis of parietal cells [34], high level of IL-17A is closely related to the severity of atrophic gastritis and gastric cancer both in human and mouse models [35-37]. Autoimmune gastritis produces antibodies to damage parietal cells, there is a higher risk of gastric cancer in autoimmune gastritis than in non-autoimmune gastritis [38].

Proton Pump Inhibitor (PPI) inhibits gastric acid secretion and promotes apoptosis of parietal cells through locking the covalent bond of H+/K+ -ATPase. Long-term use of PPI such as omeprazole increases the risk of gastric cancer [39].

There are many risk factors associated with gastric cancer; those factors can be divided into two categories. One is what stimulate gastric stem cell proliferation and promote the formation and progression of gastric tumor, such as gastric mucosal injury and inflammation. Another is what damage the parietal cells and increases the risk of gastric cancer. In contrast, metformin promotes the gastric stem cells to differentiate into mature parietal cells through the AMPK pathway, and prolongates the life span of mature parietal cells, the risk of gastric cancer in diabetes patients with long-term metformin treatment is lower [40]. In normal cell differentiation environment, the

factors that stimulate stem cell proliferation acted as tumor promoter can only lead to hyperplasia of tissue. Only when the differentiation environment destroyed, the factors that stimulate stem cell proliferation can promote the formation and progression of gastric tumor.

The origin and nature of gastric cancer

Gastric cancer is a malignant tumor occurred in gastric mucosa. Lauren divided gastric cancer into intestinal type gastric cancer with glandular structure and diffuse type gastric cancer without glandular structure [41], and believed that intestinal type gastric cancer originated from intestinal metaplasia, diffuse type gastric cancer originated from inherent gastric mucosa [42]. Correa believed that the intestinal type gastric cancer experienced the stages of atrophic gastritis, intestinal metaplasia, atypical hyperplasia and early cancer [42]. In fact, intestinal metaplasia is not prone to gastric cancer [43], and gastric cancer only occurs in acid-secreting mucosa atrophy [44]. The intestinal metaplasia also occurs in acid-secreting mucosa atrophy, but intestinal metaplasia is only a marker of gastric mucosa atrophies, not a precancerous lesion of gastric cancer [45,46], because gastric stem cells themselves can differentiate into intestinal cells [47].

The cells of gastric cancer are similar to their precursors in morphology and function [48]. Gastric cancer near the gastric pit is signed-ring carcinoma which cells are large and do not proliferate, and with abundant MUC5AC mucin of mature gastric mucous cells. Gastric cancer near the proliferation zone is a diffuse and poorly differentiated adenocarcinoma which cells are small and proliferate actively, and lack mucin [49,50]. Intestinal type gastric cancer has phenotypes of neck mucous cells and chief cells, and often contains MUC6 mucin of mature neck mucous cells [51]. Gastric neuroendocrine tumor usually presents glandular structures and its cells contain endocrine granules [52-54]. Gastric neuroendocrine carcinoma usually presents a diffuse growth pattern and its cells lack endocrine granules [55].

The gastric cancer only occurs in acid-secreting mucosa atrophy, and all the cells of gastric cancer are immature cells with morphology and function of their precursors. As acid-secreting mucosa atrophy, in the absence of mature parietal cells, the cell differentiation microenvironment alters. When the alteration of the cell differentiation microenvironment is not serious, gastric stem cells can differentiate into intestinal cells, and intestinal metaplasia occurs in gastric mucosa. The intestinal cells are terminally differentiated cells, so, intestinal metaplasia is not prone to gastric cancer. The intestinal metaplasia is not a precancerous lesion of gastric cancer. The intestinal metaplasia is just a mode of regeneration of gastric mucosa epithelium. When the cell differentiation microenvironment deteriorates, and the gastric stem cells could not differentiate into mature cells smoothly, accumulation of immature cells forms atypical hyperplasia and cancer.

With age, acid-secreting mucosa atrophies from gastric antrum up to gastric body along the lesser curvature of the stomach, and also atrophies from cardia to surrounding. Gastric antrum and cardia are two sites of high incidence of gastric cancer. With age, the site of distal gastric cancer gradually moves upward, and the incidence of gastric cardiac cancer increases. This article discusses cardiac carcinoma below the esophagogastric junction. Some cardia cancers in western countries include lower esophageal cancer which origins from Barrett's mucosa caused by reflux esophagitis. This part of cardiac cancer is beyond the scope of this article (Figure 1).

The gastric stem cells have the potential to differentiate into various gastric epithelial cells; the parietal cells provide a proper cell differential microenvironment for gastric stem cells. Factors that damage parietal cells acted as oncogenic agents disrupt cell differentiation microenvironment and increase the risk of gastric cancer. Factors that stimulate gastric stem cell proliferation acted as cancer promoter promote the formation and development of gastric tumors when cell differentiation microenvironment deteriorated.

The target of chemoprevention of gastric cancer

The goal of chemoprevention is to reduce the incidence and mortality of cancer by using natural synthetic or biological substances. Current chemoprevention is based on the idea that cancer is a gene mutation disease, and pins hope on inhibiting tumor initiation and suppressing neoplastic transformation of initiated cells. The decline in North America and Western Europe attributed to the decreased prevalence of *Helicobacter pylori* infection, but also to the progress in food storage and preservation, probably by allowing the reduction of salty and smoked food consumption [4,5]. In addition, the metformin accelerates gastric stem cells to differentiate into mature parietal cells and prolongs life span of the mature parietal cells; there is a lower risk of gastric cancer in patients receiving metformin [40]. These evidences support that the parietal cells provide a proper cell differential microenvironment for gastric stem cells, when acid-secreting mucosa atrophy, the cell differentiation microenvironment deteriorated, gastric stem cells could not differentiate into mature cells smoothly to lead to intestinal metaplasia, atypical hyperplasia and gastric cancer. So, the target of chemoprevention of gastric cancer should be protection for the parietal cells by using natural synthetic or biological substances.

CONCLUSION

Gastric cancers originate from regeneration of gastric mucosa epithelial. The gastric stem cells differentiate into various gastric epithelial cells in a proper cell differential microenvironment the parietal cells provided. Factors

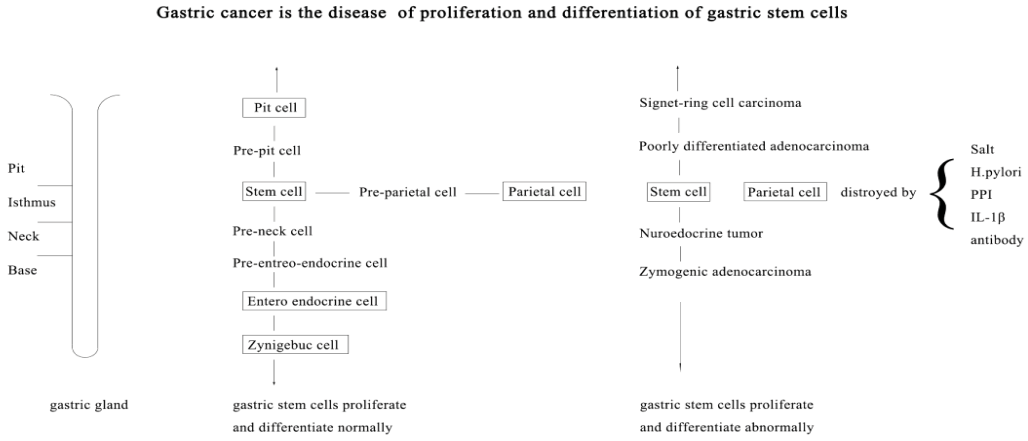

Figure 1 Gastric cancer is the disorder of proliferation and differentiation of gastric stem cells.

that damage parietal cells disrupt cell differentiation microenvironment and increase the risk of gastric cancer. Factors that stimulate gastric stem cell to proliferate promote the formation and development of gastric tumors when cell differentiation microenvironment deteriorated. To prevent gastric cancer, it is necessary to reduce gastric mucosal damage and protect the parietal cells. The target of chemoprevention of gastric cancer should be to protect for the parietal cells by natural, synthetic, biological substances.

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