



## A human mode of intestinal type gastric carcinoma

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### ABSTRACT

Gastric cancer is a malignant tumor originating from the gastric mucosa epithelium. Intestinal type gastric cancer is frequently taken on elderly men, and there are many high incidence areas around the world. Intestinal type gastric cancer often is accompanied by gastric mucosal atrophy, intestinal metaplasia. The clinical manifestation involves hypergastrinemia, low stomach acid, PG I/II progressive decreasing, anemia, and protein energy malnutrition.

The neck cells of gastric glands act as tissue stem cells to regenerate the gastric glands. In addition to secreting gastric acid and intrinsic factor, the parietal cells also have the function of inducing differentiation of themselves and gastric epithelial cells. When the function of parietal cells is normal, the neck cells differentiate into mature cells, and the glands regenerate intact. When the function of parietal cells is defective, the neck cells maybe differentiate into mature intestinal cells, and the gastric glands will regenerate in form of the intestinal metaplasia. When the function of parietal cells is lost, the neck cells can not differentiate into mature cells successfully, and the accumulation of immature cells in gastric mucosal tissue forms atypical hyperplasia of different degrees and cancers of various differentiation grades.

Any factors that can reduce the function of parietal cell could result in intestinal type gastric carcinogenesis. Adrenal cortical hypofunction can make the parietal cell hypofunction, hypohematopoiesis, protein synthesis rates reducing and protein degradation rates increasing. The patients develop gastric cancer, and come with lack of gastric acid and intrinsic factor, anemia, protein energy malnutrition.

Autoimmune gastritis can produce parietal cell antibodies to damage parietal cells. Patients with autoimmune gastritis gastric exhibit hypergastrinemia, lack of gastric acid and internal factor, higher incidence of gastric cancer.

*H. pylori* can damage gastric parietal cells directly and indirectly. When declining in quantity of parietal cells, the patients exhibit hypergastrinemia, low gastric acid, mucosa atrophy, intestinal metaplasia and gastric cancer.

Medicine that inhibits the function of parietal cells also could increase the risk of gastric cancer development.

The distribution of mucosa atrophy, intestinal metaplasia and intestinal type gastric cancer is opposite with the distribution of parietal cells in stomach. With age the quantity of parietal cells decreases, the atrophy area of gastric mucosa extends upward from antrum to body and downward from cardia to body along lesser curvature, and the location of distal gastric cancer moves upward and the gastric cardiac cancer increase.

### Introduction

Gastric cancer is a malignant tumor originating from gastric mucosa epithelium. Lauren divided gastric cancer into diffuse type gastric cancer and intestinal type gastric cancer. The diffuse type gastric cancer exhibits diffuse growth pattern, and the differentiation of cancer cell is usually poor. The morbidity of diffuse type gastric cancer is stable. The diffuse type gastric cancer exhibits family aggregation and heritability, and is more frequently taken on young female. The intestinal type gastric cancer exhibits sporadic and environment-related pattern, and is more frequently taken on elderly men. The intestinal type gastric cancer

is always accompanied by atrophic gastritis, intestinal metaplasia, and has many high incidence area around the world [1,2].

The morbidity and mortality of gastric cancer are in the second place in malignant neoplasm in China. The incidence of gastric cardiac cancer is high in northwest China, and the incidence of gastric antrum cancer is high in east coastal area of China. The incidence of atrophic gastritis, intestinal metaplasia is high in the high risk area of gastric cancer, and the location of atrophic gastritis, intestinal metaplasia and gastric cancerous lesions is mainly in lesser curvature of stomach.

The gastric cancer is related to diet, depression and *Helicobacter pylori* infection, and the patients have anemia, asitia, fatigue,

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emaciation, protein energy malnutrition, hypergastrinemia and low gastric acid.

Correa believed that gastric carcinogenesis is a gradual transition from the mature to the embryonal phenotype because of genetic mutation. The gastric carcinogenesis is from atrophic gastritis to metaplasia to dysplasia to carcinoma [3]. But it is difficult to explain all the manifestations by gene mutation. Shaoqing Lai believed carcinogenesis is consequence of failure of tissue development [4].

This study shows that all the manifestations of gastric cancer are closely related to parietal cell damage.

**Theory: A human mode of intestinal type gastric carcinoma**

The neck cells of gastric glands act as tissue stem cells to regenerate gastric glands. The neck cells proliferate and differentiate to maintain the structure stability of the gastric glands.

The gastric parietal cells secrete gastric acid and intrinsic factor, and they also have the function of inducing differentiation of themselves and gastric epithelial cells.

When the function of parietal cells is normal, the neck cells differentiate into mature cells smoothly, and the glands regenerate intact. When the function of parietal cells is defective, the neck cells maybe differentiate into mature intestinal cells, and the gastric glands will regenerate in form of the intestinal metaplasia. When the function of parietal cells is lost, the neck cells can not differentiate into mature cells successfully, and the accumulation of immature cells in gastric mucosal tissue forms atypical hyperplasia of different degrees and cancers of various differentiation grades.

The regulation of parietal cell function is a negative feedback mechanism. Any factors that reduce the function of parietal cell may be the causes of intestinal type gastric carcinogenesis.

For example, adrenal cortical hypofunction may be the causes of intestinal type gastric cancer. Because adrenal cortical hypofunction can make the parietal cell hypofunction, as well as hypoematopoiesis, protein synthesis rates reducing, protein degradation rates increasing. And those would make patients lack of gastric acid and intrinsic factor, gastric carcinogenesis, anemia and protein energy malnutrition.

Autoimmune gastritis can produce parietal cell antibodies damaging parietal cells. Autoimmune gastritis gastric would make Patients hypergastrinemia, lack of gastric acid and internal factor, higher incidence of gastric cancer.

*H. pylori* infection can stimulate plasma cells to produce antibodies which can damage parietal cells through cross-reaction. The inflammatory mediators also can induce parietal cells apoptosis. When *H. pylori* colonize at gastric antrum, the parietal cells have not been damaged. There are hypergastrinemia, high gastric acid and duodenal ulcer, without mucosa atrophy, intestinal metaplasia and gastric cancer. When *H. pylori* spread to body or whole stomach, the parietal cells have been damaged. There are hypergastrinemia, low gastric acid, mucosa atrophy, intestinal metaplasia and gastric cancer.

Medicine that inhibits the function of parietal cells also could increase the risk of gastric cancer development.

The distribution of mucosa atrophy, intestinal metaplasia and intestinal type gastric cancer is opposite with the distribution of parietal cells in stomach. The composition of gastric glands and quantity of parietal cell are different in different part of stomach. The composition of gastric glands and quantity of parietal cell in different part of stomach see Fig. 1. The quantity of parietal cells decreases with age. And the atrophy area of gastric mucosa extends upward from antrum to body and downward from cardia to body along lesser curvature, also extends downward from lesser curvature to great curvature. The extension direction of atrophy of gastric mucosa see Fig. 2. With age the location of distal gastric cancer moves upward and the gastric cardiac cancer increase.

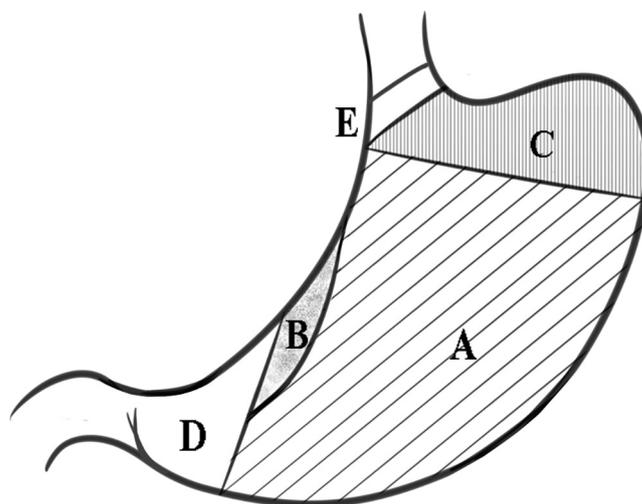


Fig. 1. The quantity of gastric parietal cells in different parts of stomach. (A) Gastric body gland. Parietal cells account for 100%. (B) A narrow area of lesser curvature, parietal cells account for 75%. (C) Gastric fundus gland, parietal cells account for 50%. (D) Gastric pyloric gland, parietal cells account for 0–1%. (E) Gastric cardiac gland, parietal cells account for 25%.

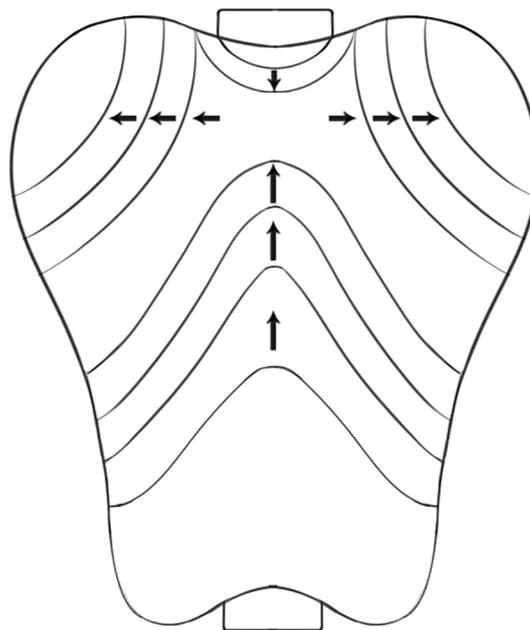


Fig. 2. The extension direction of atrophy of gastric mucosa with age.

**Data: Supporting evidences**

1. The evolution from chronic atrophic gastritis to intestinal metaplasia to atypical hyperplasia is related to the changes in the number of chief cell, parietal cell, G cell and D cells of the gastric gland [5].
2. The decline in quantity of parietal cell affects the division and migration of chief cell and mucous cell, and is accompanied with gastric gland disappearing and stem cell increasing [6]. Parietal cells have the function of inducing themselves and gastric epithelial cells differentiation [7].
3. Autoimmune gastritis can produce parietal cell antibodies to damage parietal cells. The patients with autoimmune gastritis gastric exhibit hypergastrinemia, the lack of gastric acid and internal factor, higher incidence of gastric cancer [8,9]. Type B gastritis do not produce parietal cell antibody, and there is no gastric mucosal atrophy, intestinal metaplasia, and gastric cancer.

4. When *H. pylori* colonize at gastric antrum, the patients exhibit hypergastrinemia, high gastric acid and duodenal ulcer, without mucosa atrophy, intestinal metaplasia and gastric cancer. When *H. pylori* spread to gastric body or whole stomach, the patients exhibit hypergastrinemia, low gastric acid, and are more prone to mucosa atrophy, intestinal metaplasia and gastric cancer [10–12]. *H. pylori* infection can stimulate plasma cells to produce antibodies which can damage parietal cells through cross-reaction. Interleukin-1 (beta IL-1 $\beta$ ) and TNF $\alpha$ , activate NF- $\kappa$ B to up-regulate iNOS and Bax gene expression to induce apoptosis of parietal cells [13–15].
5. Long-term use of PPI such as omeprazole inhibiting gastric acid secretion increases the risk of gastric cancer development [16].
6. The minor curvature of gastric cardia is relatively fixed, on which most early gastric cardiac cancer occurs [17]. The carcinogenesis of gastric cardiac cancer is the same as that of distal gastric cancer [18]. Precancerous lesions and early cardiac cancer can reverse in vivo [19].

## Discussion

If the function of gastric parietal cells is studied deeply to make clear how the parietal cell to induce of gastric epithelial cells differentiation, there will be more evidences to verify this hypothesis.

Most of manifestations of gastric cancer are all in a day's work. But scientists are accustomed to focus on gene mutation to find the cause of gastric cancer. The manifestations become mystery to perplex oncologists.

*H. pylori* infection can reduce acid reflux, but *H. pylori* are not probiotics. *H. pylori* damage the parietal cells directly and indirectly and increase risk of gastric cancer. Evidences show to eradicate *H. pylori* before an irreversible point, the atrophy of gastric mucosa and intestinal metaplasia can reverse in vivo; and to eradicate *H. pylori* after the point, the process of gastric carcinogenesis cannot stop even eradicate the cancerous lesions [20,21]. The irreversible point should be minimum quantity of parietal cells. This suggests it is important to eradicate *H. pylori* timely. Long-term use of PPI such as omeprazole inhibiting gastric acid secretion increases the risk of gastric cancer development. We should reevaluate the effectiveness and potential risk of triple therapy and quadruple therapy including PPI.

It is believed that the carcinogenesis of gastric cardiac cancer is different from that of distal gastric cancer. By our studies, the carcinogenesis of gastric cardiac cancer and distal gastric cancer is the same. There is no parietal cell at gastric antrum, so gastric cancer easily occurs in gastric antrum. As the gastric mucosa atrophying upward and downward along the small curvature of the stomach with age, the location of distal gastric cancer will move upward and the incidence of gastric cardiac cancer increase. Gastric antrum is the emptying part of the stomach, and gastric cardia is stomach entrance. The mucosa on those areas is easily damaged by coarse food. The damage can act as tumor promoter to promote tumor growth. The people in northwest China are accustomed to eat baked pasta; the people in east China are accustomed to eat cooked corn. Maybe the dietary habit is one of causes why the location of gastric cancer is different in different area people.

## Declaration of interests

The author Shaoqing Lai has no conflict of interests.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2018.12.009>.

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