What stem cells have to do with stomach cancer

The surface of the stomach is lined by a delicate single-layered sheet of epithelial cells (termed the gastric mucosa and its glands), which represents a tight barrier to the outside world (i.e., the gastric juice and its contents including a variety of microorganisms, such as *Helicobacter pylori*) and is also essential for the digestion of food. The stomach consists of two major parts (Fig. 1), a proximal fundus/corpus region with fundic glands producing the gastric acid, and the distal antrum with antral glands releasing the peptide hormone gastrin. During evolution, a series of protection and repair mechanisms have been developed because the gastric mucosa is permanently exposed to different noxious agents. These mechanisms include the formation of a complex mucous gel containing mucins, secretion of antimicrobial peptides, acute inflammatory processes, rapid repair by cell migration (restitution) within minutes to hours, and continual self-renewal of the various cell types by differentiation from progenitor cells and adult (somatic) stem cells (Fig. 1). The latter process takes days to months depending on the cell type.

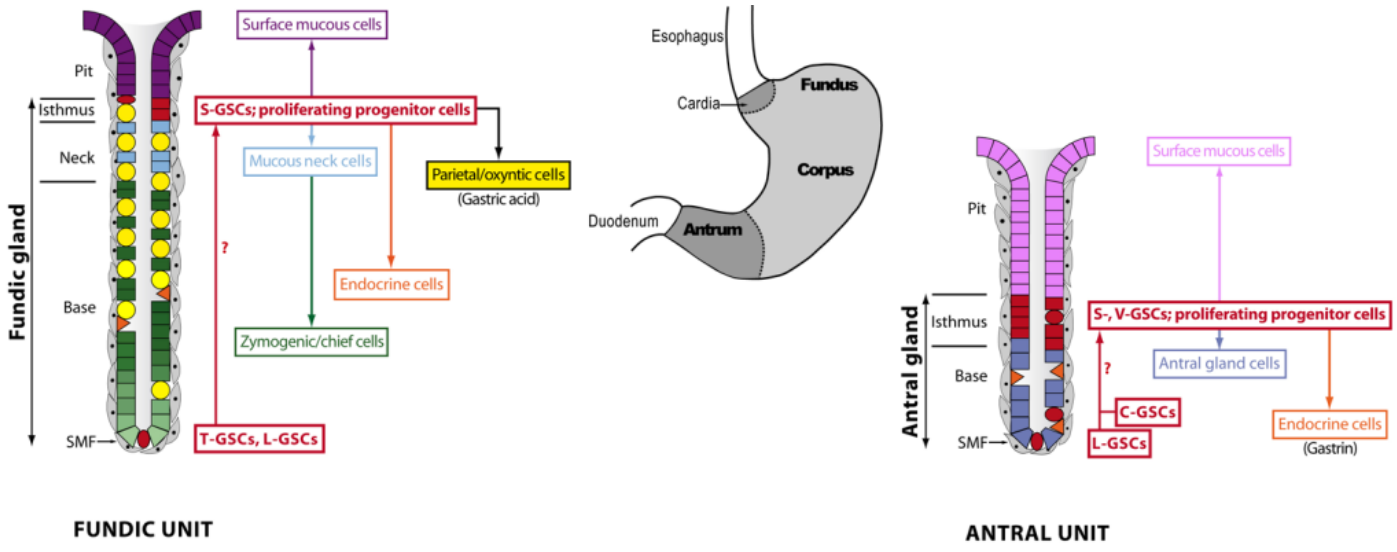

Fig. 1. Schematic representation of the two gross types of human gastric units and their continual, bidirectional self-renewal from various gastric stem cell (GSC) populations. Shown are the major epithelial cell types in the fundic and antral units, respectively. The mature epithelial cell types originate by differentiation from the proliferative region in the isthmus and migrate bidirectionally towards the pit and gland base, respectively. The various GSC populations are marked in red: C, CCK2 receptor+; L, Lgr5+; S, Sox2+; T, Troy+, V, villin+. Also displayed are the subepithelial myofibroblasts (SMF; modified from Hoffmann W. 2015).

Only within the last few years it has become clear that gastric glands contain an unexpected variety of stem cell populations, which are even different in fundic and antral glands (Fig. 1). Of note, the

isthmus is no longer thought to serve as the exclusive stem cell reservoir. Thus far, the relation and the hierarchy, respectively, between the different gastric stem cell (GSC) populations in a single gastric unit have not been established.

Some 90% of primary tumors in adult humans arise from epithelia mainly on the base of chronic inflammation because of their high regenerative capacity and the existence of adult stem cells. Gastric cancer is still a leading cause of cancer-related mortality worldwide (10% of total cancer deaths in 2008) in spite of declining incidence. Gastric cancers are essentially adenocarcinomas (90%) and 50% of these epithelial tumors are classified histologically as the "intestinal" type. Gastric cancer is promoted by environmental factors such as smoked meat, chilli peppers, alcohol, and smoking. However, the most striking risk factor is infection with *H. pylori* causing chronic inflammation (gastritis). For the intestinal type of adenocarcinomas, a well-defined sequence of events (the "Correa cascade") has been known for a long time, starting from chronic gastritis and proceeding to gastric atrophy (loss of parietal and zymogenic cells), intestinal metaplasia (aberrant occurrence of intestinal cells in the stomach), and dysplasia. Within the last years it turned out that also a second type of metaplasia (the "spasmolytic polypeptide-expressing metaplasia"/SPEM) is involved in gastric carcinogenesis.
Tumors consist of a heterogeneous, hierarchical population of cancer cells. Importantly, only cancer stem cells (CSCs) can initiate tumor formation. Thus, CSC-targeted therapies might be promising future strategies to cure gastric cancer. Currently, there are three origins of gastric CSCs discussed, i.e., (i) dedifferentiation of metaplasias, (ii) transformation of normal adult GSCs, and (iii), to a lesser extent, engraftment of bone marrow-derived mesenchymal stem cells under the conditions of chronic inflammation. Thus, gastric cancer is now regarded as a disease resulting from the dysregulated differentiation of certain stem and progenitor cells mainly due to a chronic inflammatory environment. Understanding the self-renewal of the gastric mucosa is an important contribution in understanding gastric carcinogenesis and in developing new gastric cancer therapies.

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