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REVIEW

Stem cells in gastric cancer

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Abstract

Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide. Cancer stem cells (CSCs), which were first identified in acute myeloid leukemia and subsequently in a large array of solid tumors, play important roles in cancer initiation, dissemination and recurrence. CSCs are often transformed tissue-specific stem cells or de-differentiated transit amplifying progenitor cells. Several populations of multipotent gastric stem cells (GSCs) that reside in the stomach have been determined to regulate physiological tissue renewal and injury repair. These populations include the Villin+ and Lgr5+ GSCs in the antrum, the Troy+ chief cells in the corpus, and the Sox2+ GSCs that are found in both the antrum and the corpus. The disruption of tumor suppressors in Villin+ or Lgr5+ GSCs leads to GC in mouse models. In addition to residing GSCs, bone marrow-derived cells can initiate GC in a mouse model of chronic *Helicobacter* infection. Furthermore, expression of the cell surface markers CD133 or CD44 defines gastric CSCs in mouse models and in human primary GC tissues and cell lines. Targeted elimination of CSCs effectively reduces tumor size and grade in mouse models. In summary, the recent identification of normal GSCs and gastric CSCs has greatly improved our understanding of the molecular and cellular etiology of GC and will aid in the development of effective therapies to treat patients.

Key words: Cancer stem cells; Gastric cancer; Lgr5; Villin; Troy; Sox2; CD133; CD44; E-cadherin

Core tip: Cancer stem cells (CSCs) play important roles in cancer initiation, dissemination and recurrence. The recent identification of normal gastric stem cells and gastric CSCs has greatly improved our understanding of the molecular and cellular etiology of gastric cancer and will help with the design of effective treatments. In this article, we review the literature on the recent progress in the identification and characterization of normal gastric stem cells and gastric CSCs and discuss the implications for the treatment of gastric cancer.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer and the second most deadly cancer worldwide, with one million newly diagnosed patients and 600000 deaths each year[1-3]. Approximately 70% of all GC cases occur in East Asia, Central and Eastern Europe, South Africa, and Central and South America[3,4]. GCs are grouped into two major histological types: the well-differentiated intestinal-type (IGC) and the undifferentiated diffuse-type (DGC)[5]. The IGC type occurs more frequently (60%-80%) in the distal part of the stomach (antrum) and in aged patients, while the DGC type is more common in younger patients[6]. The mechanism that underlies GC initiation and progression is not well understood, but both genetic and environmental factors contribute to GC development. Epidemiologic studies have demonstrated that an excessive intake of salt, a low intake of vegetables and fruits, and smoking are risk factors for GC. Notably, infection with the gram-negative bacterium *Helicobacter pylori* (*H. pylori*), a type I carcinogen according to the WHO classification, is strongly associated with both GC subtypes[7,8]. The detailed molecular mechanisms on how *H. pylori* infection leads to GC are under intense investigation and have been reviewed elsewhere[2,9]. In this article, we focus on recent progress in the identification of normal and cancer stem cells (CSCs) in the stomach and discuss the implications for the treatment of GC.

CANCER STEM CELL HYPOTHESIS

Human primary tumors often contain phenotypically heterogeneous cells. Two hypotheses, the clonal evolution hypothesis and the CSC hypothesis, have been proposed to explain the observed cellular heterogeneity, initiation, progression and metastasis of tumors[10,11] (Figure 1). In the clonal evolution hypothesis, cellular heterogeneity is generated by genetic instability, such as changes in chromosomal number or mutations in the tumor cell genome. Cells with genetic compositions that confer growth advantages are selected and clonally expanded[10] (Figure 1A). In contrast, the CSC hypothesis proposes that only a small fraction of cancer cells, namely CSCs, resides at the top of the cellular hierarchy and govern tumor heterogeneity; these cells divide to generate identical CSCs (self-renewal) and differentiate into phenotypically heterogeneous, but typically less proliferative, tumor cells (Figure 1B). The presence of CSCs was first demonstrated in human acute myeloid leukemia as a CD34+CD38- population. Interestingly, normal hematopoietic stem cells also express identical cell surface markers, which led to the hypothesis that CSCs are transformed tissue-specific stem cells or de-differentiated transit amplifying progenitor cells[11,12]. The existence of CSCs was soon demonstrated in solid tumors from several organs, including brain, breast, colon, prostate, liver, pancreatic, skin, and in areas of the head and neck[13-23].

Experimentally, CSCs are characterized by their capacity for tumor propagation, which is the generation of tumors that are full phenocopies of the primary tumors after they are serially transplanted into immunocompromised recipient mice. The tumor-propagating capacity can also be evaluated by *in vitro* clonogenic assays, such as the spheroid colony-forming or co-culture assays. These surrogate assays allow for the measurement of self-renewal and differentiation of cells of interest at the single-cell level and therefore serve as good complementary strategies to the mouse xenograft approach[24].

CSCs are responsible for cancer metastasis because of their tumor-propagating capacity. In human pancreatic cancer, only the CXCR4-expressing fraction of CD133+ CSCs is able to metastasize. The depletion of these cells from the CSC pool abrogates the metastatic phenotype, but does not affect tumorigenic potential[22]. In colorectal cancer, metastatic capacity is restricted to the CD26+ subpopulation of CSCs, and the presence of this subpopulation predicts subsequent liver metastasis in patients with primary colon cancer[25].

CSCs are more resistant to chemo- and radiotherapies, and therefore likely contribute to cancer recurrence. It is believed that, similar to normal tissue-specific stem cells, a quiescent subpopulation of CSCs exists[26,27]. These CSCs are more resistant to chemo- and radiotherapies because of their quiescent nature. In addition, CSCs express high levels of cellular efflux pumps and anti-apoptotic proteins, low levels of reactive oxygen species, and are more efficient in the repair of DNA damage[28-31]. Consequently, CSCs are often enriched after chemotherapy or radiotherapy[22,25,29,32,33] and cause cancer recurrence[26].

MULTIPOTENT STEM CELLS IN THE STOMACH

The stomach can be divided into three distinct anatomic regions: the cardiac region; the corpus; and the pyloric antrum. The basic structural elements of the gastric epithelium are gastric units, each of which is composed of a planar surface epithelium, tubular invaginations of the surface epithelium called pits, and tubular extensions of the pits called glands. The glands can be further divided into the isthmus, neck and base[34] (Figure 2A). The pits occupy the apical portion of the invaginations and contain mucus-producing pit cells. The isthmus connects the pit and the associated gland and contains cells that are morphologically undifferentiated, secretory, granule-free and highly proliferative. The neck is below the isthmus and contains mucus-producing neck cells. The base region is located at the very bottom of the gland and contains slowly dividing, digestive enzyme-producing chief cells[35-39] (Figure 2A). Gastric units of the corpus and antrum are similarly organized, except that the units of the corpus consist of more acid-producing parietal cells and gastric hormone-producing enteroendocrine cells.

In a series of classical electron microscopic auto-radiographic experiments, Karam and Leblond suggested that the morphologically immature, granule-free isthmus cells are actively dividing multipotent gastric stem cells

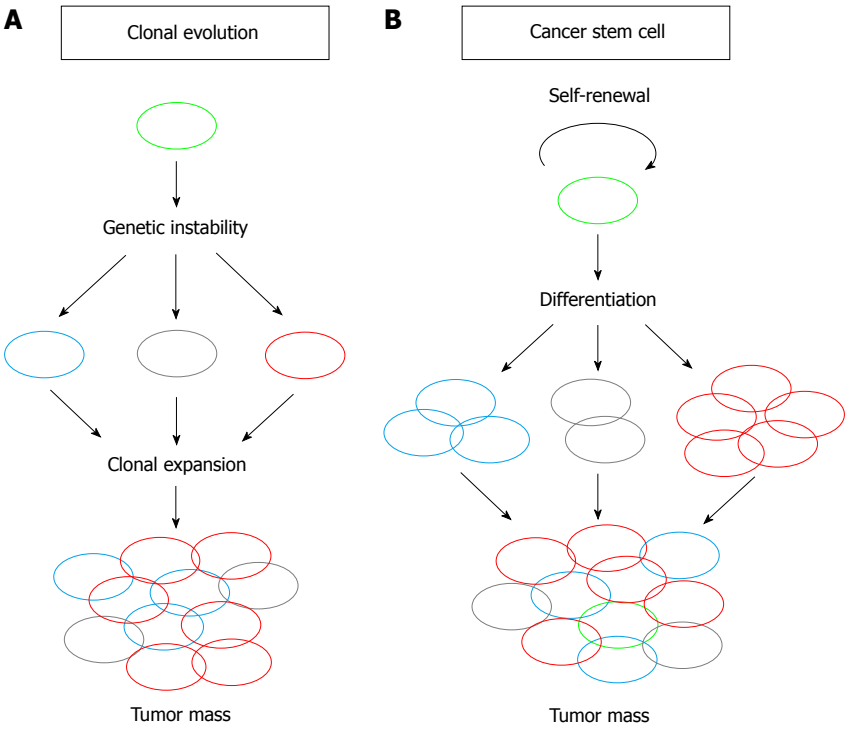

Figure 1 Hypotheses that explain the cellular heterogeneity, initiation and progression of cancer. A: In the clonal evolution hypothesis, cellular heterogeneity is generated by genetic instability, such as changes in chromosomal number or mutations in the genome of the tumor cells. Those cells with genetic compositions that confer growth advantages will be selected and preferentially expanded; B: In the cancer stem cell (CSC) hypothesis, CSCs reside at the top of the cellular hierarchy and govern tumor heterogeneity. CSCs divide to generate identical CSCs (self-renewal) and differentiate into phenotypically heterogeneous, but usually less proliferative, tumor cells. It is believed that CSCs are often transformed tissue-specific stem cells or de-differentiated transit amplifying progenitor cells.

(GSCs) in the mouse and human stomach[35-40]. However, the potential of these putative stem cells to differentiate into fully committed pit, neck and zymogenic cells was not rigorously demonstrated. The existence of GSCs that replenish all of the populations of the gastric units was not convincingly demonstrated until lineage-tracing experiments were performed. These experiments used either X-chromosome inactivation as a clonality marker or transgenic mice that carry a β-galactosidase (lacZ) reporter[41-43].

The molecular markers that define multipotent GSCs were only discovered very recently. The first biomarker that labels GSCs is Villin, an epithelial cell-specific, calcium-regulated actin-binding protein that modulates the reorganization of microvillar actin filaments[44]. Qiao *et al*[45] discovered that transgenic mice that express a *Villin* promoter-driven LacZ or GFP reporter labeled a rare population of cells in the antrum that are long-lived and capable of multi-lineage replenishment (Figure 2A). Compared with the highly proliferative, putative GSCs in the isthmus[35], the *Villin* promoter-marked gastric stem cells (V-GSCs) likely represent a different cell population because they are quiescent and located in the lower third of the antral glands[45]. Recently, Clevers and colleagues identified another population of GSCs that expresses the G protein-coupled receptor Lgr5 (also known as Gpr49)[46]. The Lgr5+ GSCs (L-GSCs) are found at the base of the corpus and antral glands in the neonatal stomach, but become restricted to the antral glands in adults (Figure 2A). Similar to the V-GSCs, L-GSCs also give rise to all cells that comprise the gastric units, but are highly proliferative. Intriguingly, purified L-GSCs can form long-lived gastric organoids that highly resemble gastric units in cell culture, which demonstrate a remarkable proliferative and differentiation potential[46]. The co-existence of active and quiescent stem cells has been demonstrated in several tissue types[27]. It has been hypothesized that the active stem cells are responsible for physiological tissue renewal, while the quiescent stem cells serve as a reserve population primarily for injury repair[27]. Whether the V-GSCs and L-GSCs exhibit distinct capacities with respect to tissue renewal and injury repair of the antral epithelium has not been investigated.

Because both V-GSCs and L-GSCs are primarily found in the antrum, but not in the corpus, the main body of the stomach[45,46], it is intriguing as to the identity of the corpus stem cells. Recently, Clevers and colleagues demonstrated that a subpopulation of fully committed zymogenic chief cells, which reside at the base of the gastric glands of the corpus, are multipotent and can generate all cell lineages of the stomach epithelium[47] (Figure 2A). This population of chief cells expresses Troy, a member of the tumor necrosis factor receptor superfamily[48]. Troy+ cells divide slowly and become more active after cytotoxic drug-induced tissue injury[47].

In addition to the Troy+ cells, Sox2+ cells also represent GSCs in the corpus as well as the antrum. During embryonic development, Sox2 is highly expressed in the foregut region and plays essential roles in the

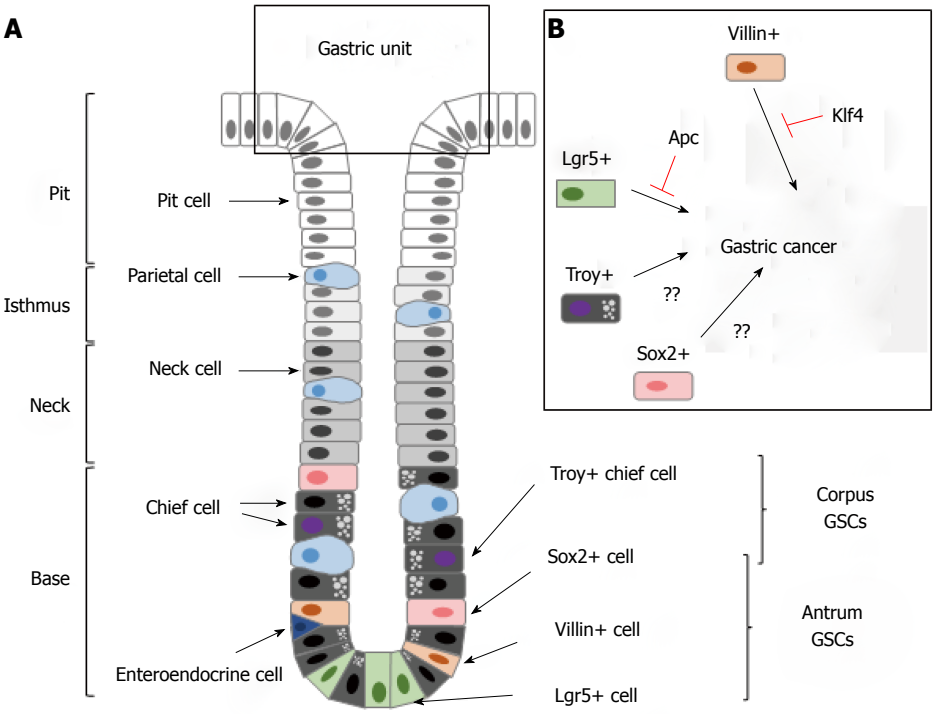

Figure 2 Stem cells that reside in gastric units. A: An illustration of a gastric unit and the presence of several populations of gastric stem cells (GSCs), all of which can replenish the entire cellular population of the gastric units. In the antrum, Villin+ and Lgr5+ GSCs represent the quiescent and actively dividing stem cells, respectively. Villin+ GSCs are located in the lower third, while Lgr5+ GSCs are often found at the base of the gastric unit. In the corpus, populations of Troy+ chief cells that reside in the base are multipotent GSCs. Sox2+ GSCs are present in both the antrum and the corpus; B: The transformation of GSCs that reside in the stomach can lead to gastric cancer. The inactivation of Klf4 in Villin+ GSCs or of Apc in Lgr5+ GSCs can lead to gastric cancer in the antrum in mouse models. It is remains unclear whether the transformation of Troy+ or Sox2+ GSCs can cause gastric cancer in the corpus. GSCs: Gastric stem pcells.

patterning of the stomach[49]. Genetic tracing experiments have demonstrated that these Sox2+ cells are capable of generating all cell types that comprise the gastric units. Selective ablation of Sox2+ cells leads to the disruption of the physiological renewal of the gastric epithelium[50].

CANCER STEM CELLS IN GASTRIC CANCER

Evidence that supports the existence of CSCs in GC has emerged in recent years. Because CSCs are often transformed from tissue-specific stem cells[51-53], whether GC originates from cancerous GSCs is an intriguing question (Figure 2B). Two general approaches were used to identify the putative gastric CSCs. One approach involved genetic manipulation and tracing of specific cell populations in mouse models of GC. Another approach involved the identification of cells with tumor-propagating capacities within human primary gastric tumors or tumor-derived cell lines using mouse xenograft models.

Villin promoter-marked cancer stem cells and the Klf4 tumor suppressor

Because V-GSCs are enriched within the lesser curvature of the antrum[45], the frequent anatomical site of human GC[54], it has been hypothesized that the transformation of V-GSCs could lead to GC. Klf4 is a Kruppel-like, zinc finger transcription factor that is highly expressed in the gut and plays critical roles in the reprogramming of terminally differentiated somatic cells into induced pluripotent stem cells[55]. Klf4 down-regulation is associated with human GC initiation and progression, which alludes to its role as a tumor suppressor[56]. The deletion of Klf4 in mouse stomach using a *Foxa3-Cre* transgene, which expresses Cre recombinase in all cells of the glandular stomach, leads to widespread hypertrophy and premalignant metaplasia in the antrum and corpus within 6 mo[57]. Interestingly, Klf4 deletion specifically in the V-GSCs with a *Villin-Cre* transgene leads to pronounced hypertrophy between 35 to 50 wk and spontaneous gastric adenomas by 80 wk[58]. Furthermore, these lesions were only observed in the antrum of the stomach where most V-GSCs reside. In this model, tumor initiation is greatly accelerated by the administration of the chemical mutagen N-nitroso-N-methylurea (NMU). It is noteworthy that in this mouse model, the gastric adenomas do not progress into adenocarcinomas even in the presence of NMU, which suggests that additional genetic mutations are required for cancer progression. Nonetheless, these data demonstrated that the transformation of the V-GSCs can initiate GC and that Klf4 plays a critical role in the suppression of tumorous growth of normal GSCs[58] (Figure 2B).

The mechanism by which Klf4 suppresses the conversion of normal stem cells to CSCs could provide important insight into the molecular etiology of GC.

Klf4 can suppress cell proliferation by activating the expression of cyclin-dependent kinase-inhibitors such as p21 and p27[57,59,60]. Klf4 can suppress the expression of Klf5, a pro-proliferation transcription factor from the Kruppel-like family in esophageal tissues[61]. Klf4 deletion also leads to increased expression of the pro-proliferative factor FoxM1 in gastric tissue[58]. Together, these mechanisms can contribute to the transformation of V-GSCs upon Klf4 deletion.

Lgr5+ cancer stem cells and Wnt-driven transformation

Similarly, whether the rapidly dividing L-GSCs can transform into CSCs was examined. Inactivating mutations in *Apc* are frequently found in human colorectal cancer and IGC[62-64]. Mice with germline *Apc* mutations develop multiple adenomas in the small intestine[65]. *Apc* deletion in Lgr5+ crypt stem cells using an *Lgr5* promoter-driven CreER recombinase leads to rapid stem cell transformation and the appearance of macroscopic adenomas in the intestine within 3 to 5 wk[52]. In the same mouse model, Barker *et al*[46] specifically disrupted *Apc* in L-GSCs. Upon the administration of tamoxifen, L-GSCs were rapidly transformed, and microscopic adenomas were detected in the antrum within 2-3 wk. However, it is unclear whether these adenomas would eventually progress into adenocarcinomas as it was necessary to sacrifice the animals used in the study due to the tumor load in the intestine[46]. These studies demonstrated that the Lgr5+ stem cells in the stomach and intestine could be tumor-initiating cells (Figure 2B).

Bone marrow-derived gastric stem cells

Because inflammatory signals, which are often caused by infection with the bacterium *H. pylori* and may predispose individuals to GC, can recruit bone marrow-derived cells (BMDCs), Wang and colleagues hypothesized that GC originates from BMDCs[66]. Using a mouse model, these authors demonstrated that chronic infection with *H. felis* resulted in intense bone marrow-derived inflammation and repopulation of the stomach with BMDCs, which subsequently progressed through metaplasia and dysplasia to intra-epithelial cancer. In contrast, BMDCs are not recruited to the stomach under circumstances of acute injury or acute inflammation. Thus, this study demonstrated that gastric CSCs can also have a bone-marrow origin[66].

Other gastric cancer stem cell markers

CD133: CD133 (also known as prominin-1) belongs to the prominin family of pentaspan membrane proteins and resides within plasma membrane protrusions, such as epithelial microvilli[67]. A glycosylated form of CD133, the AC133 antigen, was first identified as a marker that is strictly expressed by CD34+ hematopoietic stem cells[68,69] and later by normal and cancer stem cells of several solid organs[14,15,17,18,70-72]. In the mouse intestine, CD133+ cells located at the base of the crypts co-express Lgr5 and are capable of generating all cells of the intestinal epithelium; therefore, they represent the multipotent stem cell population[51]. The activation of canonical Wnt signaling in CD133+ cells in the crypt by the forced expression of a stable form of β-catenin led to intestinal cancer[51]. Recently, CD133+ cells were identified in the stem cell zone of normal human gastric glands[73]. However, it is still unclear whether these gastric CD133+ cells perform stem cell functions[73]. CD133+ cells can be found in over half of human gastric tumors and in both diffuse and intestinal subtypes; additionally, CD133 expression is associated with a poor prognosis[74-76].

CD44: CD44 was first described as a lymphocyte homing receptor and is expressed in many cell types[77]. It is the major cell surface receptor for hyaluronate[78], the most abundant component of the extracellular matrix[79]. CD44 is encoded by a single gene with 20 exons and can generate a variety of structurally distinct molecules because of alternative splicing of the primary transcripts, *N*- and *O*-linked glycosylation, and glycosaminoglycan modification[80-82]. The most commonly expressed isoform, CD44s, has seven extracellular domains, one transmembrane domain and one cytoplasmic domain[83]. Alternatively spliced exons can be incorporated into the extracellular domains to generate variant isoforms[82]. CD44 became a valid cancer marker when one variant isoform, CD44v, which is only expressed by a fraction of embryonic epithelial cells[84], was found to be associated with the metastatic potential of tumor cells[85]. CD44 was subsequently demonstrated to be specifically expressed by tumor-propagating cells that were isolated from human cancer cell lines and solid tumors[13,21,86]. It has been suggested that CD44 has key functions in CSCs, including the following: the mediation of adhesion and homing to the stem cell niche; the indirect enhancement of the expression of anti-apoptotic proteins and surface efflux pumps; the regulation of the cellular redox status; and the response to the activation of the canonical Wnt pathway[87-89].

CD44+ cells were found in 65 out of 100 human primary gastric adenocarcinomas, but were absent in normal human gastric tissues[90]. In addition, CD44+ tumors are more common in the intestinal subtype and are associated with a worse outcome[90]. Consistently, a CD44+ subpopulation was identified in multiple established human GC cell lines. Compared with CD44- cells, purified CD44+ cells are superior in the generation of spheroid colonies in culture, are more resistant to radiation and DNA damage-inducing drugs, and are more tumorigenic when they are injected into the stomachs of immunocompromised mice; they can also give rise to CD44- cells, and therefore represent putative gastric CSCs[91]. In cases of sporadic and hereditary DGC, a CD44v6 variant was expressed at levels that inversely correlated with the expression of E-cadherin[92]. Another variant isoform, CD44v8-10, has been demonstrated to be a CSC marker in primary GC tumors. Purified CD44v8-10+ cells possess a tumor-propagating capacity when they are serially transplanted

into immunocompromised mice. Importantly, the knock-down of total CD44 by shRNA dramatically reduced the tumor-propagating capacity of these cells, and only the re-introduction of the CD44v8-10 variant, but not the CD44s isoform, rescued the tumor-propagating capacity[93]. Recently, the CD44 variant v9 was reported to be a predictive marker for cancer recurrence in patients with GC who received curative endoscopic submucosal dissection[94]. In a mouse model of gastric neoplasia, where the canonical Wnt and prostaglandin E_2 pathways were co-activated in the gastric epithelium, disruption of the CD44 gene significantly reduced tumor size and grade. This result suggests that CD44 is not simply a marker of gastric CSCs, but it is also actively involved in tumor growth and progression[89].

H. PYLORI AND GASTRIC STEM CELLS

H. pylori is classified by WHO as a type I carcinogen, and its infection is strongly associated with the incidence of both IGC and DGC[7,8]. Whether gastric CSCs are the primary targets of *H. pylori* infection has been investigated. In addition to the recruitment of BMDCs to the stomach to initiate GC[66], infection with *H. pylori* also transforms GSCs. *H. pylori* infection of gastric epithelial cells disrupts the epithelial apical junctional complex and induces the transition to a mesenchymal phenotype[95], which is often associated with tumor invasion, metastasis and drug resistance[96]. Bessède *et al*[97] demonstrated that only the CD44+ cells of cultured human gastric epithelial cells can be induced to assume a mesenchymal phenotype by *H. pylori* infection. Compared with CD44- and uninfected CD44+ cells, the infected CD44+ cells are able to form spheroid colonies more readily in culture and are more tumorigenic in a mouse xenograft model, which suggests that *H. pylori* preferentially transforms GSCs. There is also evidence to suggest that *H. pylori* bacteria can evolve to establish symbiosis with gastric stem or progenitor cells. Giannakis *et al*[98] isolated *H. pylori* strains before and after a single human host progressed from chronic atrophic gastritis (ChAG) to gastric adenocarcinoma over a 4-year interval. The cancer-associated strain was less fit in a mouse model of human ChAG, but readily established itself within a mouse gastric epithelial progenitor-derived cell line (mGEP). Transcriptional profiling that compared control and infected mGEP cells revealed that infection of the cancer-associated *H. pylori* strain regulates cell signaling, metabolism and tumor suppressor genes in a very different way from the ChAG-associated strain. This observation suggests that adaptation of *H. pylori* to GSCs is critical for the progression of ChAG to GC.

CDH1, EPITHELIAL-MESENCHYMAL TRANSITION AND STEM CELL-LIKE FEATURES

The identification of genetic mutations in patients with GC has greatly advanced our understanding of the disease etiology. Several studies have generated a comprehensive list of mutations in IGC and DGC through cancer genome/exome sequencing[63,99,100]. Here, we only focus on *CDH1* mutations, which are strongly associated with DGC and likely contribute to the acquisition of stem cell-like features through the mediation of epithelial-mesenchymal transition (EMT).

CDH1 encodes the epithelial cell-expressed, calcium-dependent, cell adhesion membrane protein E-cadherin. E-cadherin regulates the architecture of the epithelium *via* the mediation of cell-cell adhesion and the regulation of biological processes, such as signal transduction and cytoskeletal remodeling. E-cadherin consists of five extracellular cadherin repeats, a single transmembrane domain and a well-conserved cytoplasmic domain. The extracellular domain is responsible for the adhesive recognition and interaction with extracellular domains from adjacent cells; the cytoplasmic domain contains the docking site for β-catenin and a variety of other effectors, such as tyrosine kinase receptors, phosphatases and cytoskeleton regulators[101,102].

Loss-of-function mutations of *CDH1* have been frequently found in sporadic DGC but not in IGC[103,104]. Immunohistochemistry for E-cadherin in DGC samples further confirmed that E-cadherin levels are usually low or undetectable, which suggests that the loss of E-cadherin leads to DGC. Germline mutations in *CDH1* were found in three Maori kindred with hereditary diffuse gastric cancer (HDGC), which provides genetic evidence that a deficiency in *CDH1* increases the susceptibility to DGC[105]. Germline inactivating mutations in *CDH1* were subsequently verified in patients with HDGC from other ethnic groups and were determined to account for 30% of all HDGC cases[106-108]. The penetrance of *CDH1* germline mutations is 67%-83%[109]. In patients with HDGC, the germline mutation only affects one *CDH1* allele. The second *CDH1* allele is inactivated by mechanisms that include methylation-mediated transcriptional silencing, somatic mutations or loss of heterozygosity[109-114]. The extracellular fragment of E-cadherin, which results from the cleavage of the functional membrane-bound form, is soluble and serves as an important prognostic marker for GC[115].

How E-cadherin deficiency causes DGC is not fully understood. Based on the known properties of E-cadherin, several mutually non-exclusive mechanisms have been proposed. One mechanism is that the loss of E-cadherin enhances canonical Wnt signaling. Because a fraction of β-catenin is normally anchored to the membrane *via* the cytoplasmic tail of E-cadherin, the down-regulation of E-cadherin may release this fraction into the cytoplasm, which likely enhances the nuclear transcriptional activity of β-catenin/TCF. This model is supported by the observation that the levels of E-cadherin inversely correlate with the transcriptional activity of β-catenin during mouse embryonic development[116]. However, the model is challenged by the observations that the loss of E-cadherin is insufficient to modulate

Wnt signaling in cultured cell lines[117], and tumors are initiated in a β-catenin-independent manner in a mouse pancreatic cancer model[118]. Most importantly, *APC* mutations, which lead to enhanced Wnt signaling, are associated with IGC and colorectal cancer, but are rarely found in DGC[63]. This fact suggests that a deficiency in E-cadherin initiates DGC in a manner independent of the canonical Wnt pathway. Another proposed mechanism is that a deficiency of E-cadherin leads to the loss of contact inhibition and unchecked proliferation of epithelial cells. This hypothesis is supported by the findings that E-cadherin inhibits EGF signaling by direct binding to the kinase receptor EGFR[119-122], which lies upstream of the proliferation-promoting Ras-Erk pathway. Consistent with this idea, mouse xenografts derived from poorly differentiated human GC samples were often amplified at the EGFR locus and were responsive to the EGFR monoclonal antibody Cetuximab[123]. Another potential mechanism is that the loss of E-cadherin induces the acquisition of mesenchymal features by epithelial cells, which are more stem cell-like[124,125], more invasive and resistant to genotoxic insult[96]. The functional loss of E-cadherin is a hallmark of EMT. It has been demonstrated that pre-cancerous mammary epithelial cells acquire stem cell-like features after they transition into mesenchymal cells, at which time they express stem cell markers and are capable of forming spheroid colonies in culture[124]. However, it is currently unclear whether the EMT that results from a *CDH1* deficiency contributes to DGC initiation and progression.

IMPLICATIONS FOR THE TREATMENT OF GASTRIC CANCER

Because CSCs can propagate tumors that are a phenocopy of the primary lesion, the residual CSCs that survive standard chemotherapy and surgery are sufficient for cancer recurrence. This situation is exacerbated by the increased resistance of CSCs to cytotoxic drugs and irradiation. Due to their tumor-propagating capacity, CSCs are also considered the source of metastasis. Therefore, the development of strategies that specifically eliminate CSCs could be more effective, but less toxic than standard therapeutic strategies. For example, CSCs may be induced to differentiate by reagents such as retinoic acid (RA) and its derivatives. RA can induce the differentiation of the CD133+ CSCs isolated from human glioblastoma cell lines and reduce their *in vitro* spheroid colony-forming capacity and tumorigenicity in a mouse xenograft model[126-128]. It has also been reported that RA induced the differentiation of CD44+ breast CSCs and reduced their *in vitro* sphere-forming capacity[129]. Because CD133 and CD44 are expressed by CSCs of many cancers, strategies for the elimination of CD133+ and/or CD44+ cells have been tested in cell culture and animal models. The knock-down of CD133 in human melanoma cells led to a decreased *in vitro* spheroid colony-forming capacity and metastatic potential[130]. The elimination of CD44+ cells in cultured GC cells and in transgenic mice reduced tumor-propagating capacity, tumor size and tumor grade[89,93]. Furthermore, cytotoxic antibodies against CD133 effectively inhibited the proliferation of cultured hepatocellular carcinoma cells and GC cells. Intriguingly, these antibodies significantly reduced the tumor mass of hepatocellular carcinoma in a mouse xenograft model[131]. Paclitaxel-loaded nanoparticles conjugated to CD133 antibodies effectively eliminated liver CSCs in cultured liver cancer cells and induced tumor regression in mouse xenografts[132]. Although the efficacy of these approaches requires further validation, a combinatorial approach of specific elimination of CSCs together with standard chemotherapy and surgical methods to remove the tumor mass will likely have a profound impact on the future treatment of patients with GC.

CONCLUSION

In summary, several populations of GSCs have been identified that regulate physiological tissue renewal and injury repair of the gastric epithelium. In the antrum, both the quiescent *Villin*-expressing GSCs and the actively proliferating Lgr5+ GSCs can differentiate into all types of fully committed gastric somatic cells[45,46] (Figure 2A). The transformation of either stem cell population leads to GC in mouse models[46,58] (Figure 2B). In the corpus, Troy+ chief cells and Sox2+ cells can replenish the entire cellular population of the gastric units (Figure 2A). However, whether GC originates from these cells remains unclear[47,50] (Figure 2B). Bone marrow-derived cells (BMDCs) can also cause GC in a mouse model of chronic *Helicobacter* infection[66]. In addition, cells that express CD133 or CD44, markers that define CSCs of solid tumors in many tissues, are frequently identified in human GC[74-76,89,90]. The targeted elimination of the CD133+ or CD44+ cells in mouse models of GC or in human GC-derived cell lines often reduces tumor formation[89,93].

The recent progress in the identification of normal and CSCs in the stomach has provided critical insights into the molecular and cellular etiology of GC. However, many unanswered questions remain. First, all of the GSC populations (Villin+, Lgr5+ Troy+ and Sox2+ cells) have been identified in mouse models. Whether similar GSCs are present in the human stomach and whether the transformation of these cells leads to GC need to be experimentally verified. Second, it remains unclear whether Troy+ cells, Sox2+ cells or a yet unidentified cell population comprise the CSCs in the corpus. The current data have only demonstrated that V-GSCs and L-GSCs in the antrum can convert to CSCs in mouse models. Third, it remains unclear whether tumors that originate from distinct GSC populations are identical. Does the transformation of a certain population of GSCs preferentially give rise to IGC or DGC? Do different tumor suppressors, such as Klf4 in V-GSCs and *Apc* in L-GSCs, prevent GC *via* the suppression of common

or distinct molecular pathways? In addition, whether *H. pylori* infection plays a role in the transformation of human GSCs remains to be determined. If so, what is the molecular pathway that is affected by *H. pylori*? Answers to these questions will greatly improve our understanding of the molecular and cellular etiology of GC and will help with the development of more effective therapeutic strategies.

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