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Gastric Epithelial Stem Cells

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Abstract

Advances in our understanding of stem cells in the gastrointestinal tract include the identification of molecular markers of stem and early progenitor cells in the small intestine. Although gastric epithelial stem cells have been localized, little is known about their molecular biology. Recent reports describe the use of inducible Cre recombinase activity to indelibly label candidate stem cells and their progeny in the distal stomach, (ie, the antrum and pylorus). No such lineage labeling of epithelial stem cells has been reported in the gastric body (corpus). Among stem cells in the alimentary canal, those of the adult corpus are unique in that they lie close to the lumen and increase proliferation following loss of a single mature progeny lineage, the acid-secreting parietal cell. They are also unique in that they neither depend on Wnt signaling nor express the surface marker Lgr5. Because pathogenesis of gastric adenocarcinoma has been associated with abnormal patterns of gastric differentiation and with chronic tissue injury, there has been much research on the response of stomach epithelial stem cells to inflammation. Chronic inflammation, as induced by infection with *Helicobacter pylori*, affects differentiation and promotes metaplasias. Several studies have identified cellular and molecular mechanisms in spasmolytic polypeptide–expressing (pseudopyloric) metaplasia. Researchers have also begun to identify signaling pathways and events that take place during embryonic development that eventually establish the adult stem cells to maintain the specific features and functions of the stomach mucosa. We review the cytologic, molecular, functional, and developmental properties of gastric epithelial stem cells.

Keywords

Stomach Stem Cells; Epithelial Self-Renewal; Tissue Metaplasia

The self-renewing epithelium of the stomach body contains 4 types of terminally differentiated cells that are replaced at different rates: oxyntic (parietal) cells, zymogenic (chief) cells, surface mucous foveolar (pit) cells, and hormone-secreting enteroendocrine cells. Mucous neck cells can function in a secretory capacity and as an intermediate progenitor for chief cells (Figures 1–3).[1–10] The gastric antrum has few parietal or chief cells but has a separate population of alkaline, mucus-producing cells near the base of gland

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units that, in terms of molecular marker expression, resemble corpus mucous neck cells (Figure 1).[11,12] A transitional zone separates the stereotypic corpus and antral/pyloric epithelia and has features of each.[13] There is consensus that all gastric mucosal cells originate from stem cells,[2,14] although stem cell properties differ in the corpus and antrum. Gastric epithelial stem cells share many properties with intestinal epithelial stem cells, which have been studied more extensively, but it is also becoming clear that they differ in fundamental respects.

Stem cells in adult tissues can regenerate all the resident cell types within a lineage, and stem cell research is often motivated by the desire to harness their potential for regeneration of lost or damaged tissue. In developed countries, there is little need for therapeutic replacement of stomach mucosa, but aberrant differentiation of the gastric epithelium occurs during tumorigenesis. Thus, understanding normal and abnormal gastric epithelial stem cell biology may help reveal the origins of gastric cancer, the second leading cause of cancer death worldwide.[15] We review how stem cells might contribute to metaplasia, and eventually cancer, following inflammation or injury.

Tissue-based adult stem cells can be defined by 3 properties we describe as location, allocation, and relocation (Figure 4); in other words, characterizing their anatomic and molecular niches (location within the tissue), identifying molecular markers (allocation from other cells), and establishing assays for their regenerative properties (experimental relocation to a new niche to show the capacity to regenerate all lineages of that tissue).[16] We know most about the location of stomach epithelial stem cells but less about their molecular properties or ways to measure their regenerative potential.

Stem Cell Properties

Location

In the late 1940s, Leblond et al identified the location of ^{32}P-labeled nucleotides that were incorporated into nuclei of live cells.[17] In the stomach, radiolabeled cells appeared just below the pits or foveolae, the microscopic openings of gastric gland units into the stomach lumen. The investigators concluded that this region of anatomic narrowing, the isthmus, was the site of cellular renewal in undamaged tissue (Figures 1 and 2). The isthmus is found toward the upper third of the typical glandular unit in the gastric corpus and in the lower third of typical units in the antrum. These studies indicated that one or a few cells in the isthmus constantly regenerate cells that migrate bidirectionally, up to the mucosal surface and down to the gland base, as they differentiate into mature cells of the gastric unit (Figure 3). However, because earlier studies had focused on regeneration after tissue injury, researchers did not investigate the continuous renewal of healthy mucosa until years later.[18]

In 1966, Richard Corpron analyzed his own findings with those from the few available ultrastructural studies of the rat gastric corpus and concluded that “nondifferentiated cells” in the isthmus were the source of all other mucosal cells.[19] These cells had a high nucleus-to-cytoplasm ratio, open chromatin, lack of granules, underdeveloped rough endoplasmic reticulum, many free ribosomes, and few mitochondria (Figure 2). Although Corpron did not use the term “stem cell,” he did localize and identify cells with undifferentiated morphology as the probable origin of all other epithelial cells. Leblond et al continued in this area of research, using light and electron microscopy to identify different cell types and patterns of differentiation and migration in gastric antral units of mice.[12,20] They proposed that undifferentiated, “granule-free” cells in the isthmus represented gastric stem cells and, based on their abundance, that each unit contained, on average, a single stem cell. Karam and Leblond and others used morphologic and labeled nucleotide incorporation assays in tissues from mouse[6–9] and rat[21] gastric bodies to study the bidirectional migration and

differentiation from morphologically undifferentiated cells in the isthmus. Karam et al subsequently used morphologic and ultrastructural analyses to delineate those patterns in the human gastric body.[22] Again, cells with stem-like activity were found in the isthmus and appeared immature, with high nucleus/cytoplasm ratios, open chromatin, small and scant organelles, and many ribosomes. Unlike their granule-free counterparts in rodents, the most undifferentiated cells in humans had mini-granules, without distinct morphologic features to allow assignment to any mature lineage.

We know little about the gastric epithelial stem cell niche. Myofibroblasts in the scant mesenchyme between gland units are proposed to regulate stem cell activity,[23] but this has not been tested. Endothelial cells or pericytes within the capillary network might also interact with the stem cell compartment because the extensive capillary network throughout the normal corpus is reduced as stem cells expand during metaplasia.[4] In the isthmus, undifferentiated cells and precursors, especially of the mucous neck lineage, usually appear close or immediately adjacent to mature parietal cells[5,24] (Figure 2). The significance of this proximity is unclear, but parietal cells might influence stem cell proliferation, at least following certain types of injury.

Allocation

Surface markers of hematopoietic stem and progenitor cells allow their isolation by flow cytometry, setting a standard for stem cells in other tissues. Molecular markers of gastric epithelial stem cells have not been sufficiently characterized for isolation from or identification within their niche. In early studies,[25,26] Gordon et al used microarrays to detect increased expression of factors in the insulin-like growth factor signaling pathways and RNA-binding proteins in stomachs of mice with increased stem/progenitor cell proliferation relative to normal controls.[5] Subsequently, microdissected isthmus regions from parietal cell–deficient mice (which have increased progenitor/stem cell proliferation) showed increased transcript levels of the doublecortin-like serine-threonine kinase (*Dcamkl1*) gene, a proposed marker of intestinal stem cells.[27] *Dcamkl1* is expressed in cells scattered throughout the isthmus of normal corpus units and in a larger population following parietal cell ablation. Although these cells lack molecular markers of advanced differentiation, they have dendritic processes, tufted microvilli (in the small intestine), and a relatively low nucleus/cytoplasm ratio, which are features distinct from normal isthmal progenitors.

The state-of-the-art way to identify stem cell activity in an adult tissue without purifying stem cells in vitro and subsequently testing their regenerative capacity is by lineage labeling (lineage tracing). Candidate stem cells are marked genetically by indelibly inducing expression of a reporter gene using genetic recombination of genomic sequence that otherwise would prevent expression (eg, inducing lacZ in the ROSA26 locus). After recombination, any cells derived from the labeled cell can be traced by their shared expression of the reporter.[28] If recombination occurs in a stem cell with constant turnover and traceable migration of cell lineages, such as the gastric epithelium, all the cells in a unit will eventually reveal their origin from a stem cell expressing the reporter gene. Provided the initial recombination event occurs only in a certain cell and not in any of its progeny, this approach indicates stem cell activity in that cell. Lineage labeling studies should thus help determine whether DCAMKL1 or other putative markers specifically mark a gastric stem cell population.[29]

Using such lineage labeling, Qiao et al found rare cells that expressed a transgene regulated by an intestine-specific promoter (villin, not usually expressed at detectable levels in stomach) at varying positions between the isthmus and base of some antral units. Following crosses to the R26 reporter line, the investigators showed that stimulation with interferon

gamma caused these cells to regenerate all the cells within a given antral unit,[30] indicating stem cell activity. Because few gland units carry these cells and they seem to replicate only after cytokine stimulation, villin is not likely to be a marker of most antral stem cells. However, those cells that expressed Cre under control of the villin promoter in this study might represent a rare stem-like population that regulates the gastric epithelium in response to specific signals such as injury or inflammation.

More recently, Barker et al used lineage labeling to show that cells that express the intestinal stem cell marker LGR5 and are located at the base, rather than the isthmus, of glands can give rise to all antral unit cells.[31] As with $Lgr5^+$ intestinal stem cells, which replicate rapidly, $Lgr5^+$ cells at the base of antral glands incorporate labeled nucleotides and express markers of cell proliferation. It is often assumed that stem cells in all tissues resemble hematopoietic stem cells, which are believed to divide infrequently.[32] Although some researchers consider replicative quiescence to be a cardinal property of stem cells, stem cells in a rapidly renewing tissue might indeed divide rapidly, as $Lgr5^+$ cells do. Mouse $Lgr5^+$ cells have more differentiated morphology than granule-free isthmus cells, with more abundant basal endoplasmic reticulum and apical microvilli. Compared with the cells marked by expression of the villin-regulated trans-gene, they show stem cell properties more frequently but also lack the morphology or long-term nucleotide retention associated with native isthmal stem cells. As the antral epithelium expands in part by branching or fission from the base of gland units,[11,14,33] basal $Lgr5^+$ cells might contribute to formation of new units by gland fission from the base; studies are needed to determine if this is the case.

Although Lgr5-expressing cells are also detected in the neonatal mouse corpus, they disappear soon after birth and become confined to the antral-pyloric mucosa.[31] It is important to identify the cells that replenish the corpus stomach epithelium.

Wang et al recently described a mouse line that expresses tamoxifen-inducible Cre recombinase under control of the *Tff2* promoter. Crosses with the R26 reporter strain revealed that parietal and zymogenic, but not surface or foveolar, cells arose from cells that express the transgene,[34] indicating that a population of corpus progenitor cells can give rise to parietal and zymogenic lineages. Transgene expression was confined to these progenitors, which are located in the isthmus, and normal mucous neck cells expressed trefoil factor 2 (TFF2) protein but not the transgene.

Relocation

Stem cells from the bone marrow or mammary gland regenerate tissues on transplantation in animal models.[35,36] These types of experiments are not easy to perform with gastric epithelial stem cells because of the lack of markers and because it is difficult to create animal models where gastric or intestinal mucosa is denuded to host exogenous cells as a test of their regenerative capacity. Ex vivo assays have therefore been developed. $Lgr5^+$ cells isolated from the antrum of adult mice generate long-lived colonies that resemble gastric units in morphology and carry all resident epithelial lineages.[31] The best evidence for stem cell activity within these colonies comes from the isolation of single cells from primary outgrowths that generate secondary and tertiary colonies, indicating self-renewal. This finding presents opportunities to optimize culture conditions and characterize the minimal requirements for ex vivo growth and differentiation. Markers of each gastric lineage make it possible to assess the full differentiation potential of individual progenitors; additional markers might be identified to isolate and characterize corpus and antrum subpopulations with stem or progenitor properties. It is, however, possible that the greater cellular diversity and 3-dimensional complexity of corpus glands, compared with their antral counterparts,[24] will limit their potential to be replicated in tissue culture.

Proliferation (Label Retention)

Because gastric stem cells might proliferate infrequently, investigators have investigated whether labeled nucleotides, incorporated during S phase, remain concentrated in the nuclei of stem cells for long periods. Although label retention has received much attention in characterizing intestinal stem cells in the +4 position,[37,38] there is little evidence for long-term, label-retaining cells in the stomach. Labeled nucleotide analogues incorporated in the stomach epithelium usually mark cells near the isthmus in the short-term, followed by bidirectional migration into neighboring nuclei; only differentiated cells are labeled next, and the marker eventually disappears,[20,39] indicating that gastric stem cells might proliferate rapidly. Because the isthmus in antral gland units lies close to the base, bidirectional migration is harder to monitor. Basal $Lgr5^+$ cells seem to divide frequently and repopulate gland units in undamaged mucosa.[31] After tissue injury, additional cells might be recruited that have progenitor or stem cell functions. For example, cytokines can induce quiescent cells that express the Cre transgene under control of the *villin* promoter to enter the cell cycle.[30] Without stimulation, however, these cells do not differentiate in normal mice.

Unitary Origin and Clonality of Gastric Units

The concept that all mature gastrointestinal epithelial cell lineages arise from a common stem cell, once known as the Unitarian Theory,[40] has been validated in the stomach.[2] However, it is not known if an individual gastric unit is replenished from a single monoclonal stem cell. Evidence supporting the Unitarian Theory came from Thompson et al, who found that all lineages within a gland shared the same XX or XY genotype in XX-XY chimeric mice. Those studies indicated that gastric enteroendocrine cells also derive from the same stem cell and not from a lineage that originated in the embryonic neural crest.[2] Nomura et al followed expression of an X-linked *LacZ* transgene that female mice inactivate randomly during development; cells are blue or white, depending on X chromosome inactivation in stem cells and their progeny.[33] In adult mice, most units were totally blue or white, indicating monoclonality. However, because some units could derive from 2 (or more) stem cells of the same genotype, the investigators estimated that at least 3 of 4 mouse gastric glandular units are monoclonal. Because X-chromosome inactivation occurs in early embryos, Bjerknes and Cheng investigated whether cell lineage generating activity in the adult stomach might result from progenitors that remained after development. They used chemical mutagenesis experiments in adult mice to determine whether single adult stem cells yielded entire units that included the same mutation or if units arose from 2 or more stem cells, based on their mixture of mutant and wild-type cells.[14] Although they found evidence that most glands arose from a single stem cell, even 48 weeks after mutagen exposure, some units carried mutant cells of only a single lineage, indicating that new cells had arisen continually along only that lineage. In light of known cell renewal rates, those cells could not have been derived from a multipotential stem cell. Hence, some units might maintain long-lived progenitors that are committed to replenishing cells of only a single lineage. Nomura et al[33] did not report mixed glands with a single labeled lineage, perhaps because long-lived progenitors arise only in adults, long after X chromosome inactivation.

Human gastric gland units are architecturally more complex than units of mice, with multiple glands feeding like tributaries into a single pit. McDonald et al followed spontaneous mutations in a mitochondrial gene, *Cytochrome c oxidase*, to examine their propagation and stem cell and progenitor cell dynamics in human gastric units.[41] Although the mutation was occasionally confined to a single cell type, adult gastric glands were found to derive from multipotential and clonal stem cells, at least in basal states. Local injury and cytokine stimulation might, of course, alter stem cell dynamics, affecting differentiation potential and clonality of stem and progenitor cells until homeostasis is restored.

Unique Aspects of the Gastric Stem Cell

Studies of other tissues that have continuously self-renewing cells, such as the skin, blood, intestine, and mammary gland, have led to better characterization of stem cells than in the stomach. In particular, identification of LGR5 and BMI-1 as markers of intestinal cells with stem cell–like properties,[38,42] and Musashi and Prominin1/CD133 as markers of a broader crypt population,[43,44] helped advance characterization of intestinal stem cells that respond to Wnt and Notch signals.[45] Candidate molecular markers of small intestine stem cells label crypt cells either deep in the base, interspersed among Paneth cells, or just above the Paneth cell zone in the canonical +4 tier.[45] In each case, labeled crypt cells also had the least differentiated morphology and were among the first to incorporate labeled nucleotides, providing a satisfying agreement between morphologic and molecular features. In the antral stomach, by contrast, LGR5, which marks cells with apparent stem function, does not coincide with the anticipated location, morphology, or nucleotide uptake, whereas the few cells marked by the villin transgene do have some of the predicted properties. These distinctions may force reconsideration of core assumptions in the field.

The gastric corpus epithelium differs from the rest of the digestive tract in important ways. The stem cell niche is nearer the lumen than in the base of the glands (Figure 1); hence, it is likely to be more exposed to surface irritants and requires bidirectional migration of its daughter cells. Cell lineages in the stomach epithelium vary greatly in life span: from 3 to 5 days for mouse surface-associated mucous cells to several months for zymogenic cells, whereas the life span of mature intestinal cells ranges from 3 to 5 days for enterocytes to about 2 weeks for Paneth cells.[20] The marked variation in gastric corpus epithelial turnover rates exerts asymmetry in the demand for various stem cell progeny; stem cells must generate many more precursors of pit cells than of chief cells in each differentiation cycle. It is not clear how stem cells allocate progeny toward individual lineages or respond to differential demands for daughter cells in any tissue. Stem cell activities, or at least proliferative activities, in the gastric corpus mucosa are sensitive to loss of mature progeny; parietal cell injury causes pseudo-pyloric (spasmolytic polypeptide–expressing) metaplasia, an altered differentiation pattern wherein proliferative activity shifts deeper into the gland base (see the following text).

Although intestinal progenitors depend on Wnt stimulation and stop dividing immediately on withdrawal of Wnt signals,[46] the steady-state gastric corpus does not depend on this signaling pathway. There have been few reports indicating that Wnt signaling occurs in most of the adult stomach and, unlike intestinal cancers, which have dysregulated Wnt signaling, gastric cancers rarely carry mutations in Wnt pathway genes or show signs of constitutive Wnt activation.[47] In light of the fundamental similarities between stomach and intestinal epithelial organization and turnover, and the origin of each in a common primordium, it is surprising that each has distinct means of homeostatic regulation. Studies of antral stem cells indicate that the gastric antrum/pylorus might be a hybrid of corpus and intestine.[48] These cells express the Wnt-dependent intestinal stem cell marker LGR5.[26] Moreover, Apc^{Min} and Apc^{1322T} mice, which develop intestinal polyps as a result of inactivation of the Wnt-regulatory gene *Apc*, develop a few adenomas in the gastric antrum but not in the corpus.[49,50] Furthermore, loss of Apc in $Lgr5^{+}$ cells rapidly results in formation of antral but not corpus adenomas.[31] These observations indicate that the antrum has Wnt-responsive stem cells that are distinct from those that mediate corpus mucosal self-renewal. Furthermore, antral stem cells rarely generate parietal or chief cells. On the other hand, the basal mucous neck cells they do generate resemble the duodenal Brunner's gland cell in morphology and mucus production. Intestinal epithelial progenitors seem also to depend on Notch signaling, responding to chemical or genetic inhibition of the Notch pathway with

profound cell cycle arrest and goblet call metaplasia[51,52]; a parallel dependence among gastric progenitors has not been investigated.

Response of Gastric Epithelial Progenitor Cells to Injury

Categories of Injury

For the purpose of this review, we consider gastric mucosal injury in 2 broad categories: focal (repairable damage that does not change the cellular differentiation pattern) and diffuse (chronic damage that alters cell differentiation). Toxin ingestion, bile reflux, and certain infectious agents usually induce the first type of injury, resulting in focal erosions or full-thickness ulcerations that are rapidly repaired by increased proliferation in neighboring units and migration of surface cells; these eventually reestablish normal differentiation in damaged units.[53] It is unclear, though, how new stem cells emerge after extensive injury. The second pattern of injury results in abnormal differentiation (metaplasia) in humans, most commonly from chronic infection with *Helicobacter pylori* or from parietal cell destruction in autoimmune gastritis.[54–57] In mice and other animals, metaplasia can be induced by *Helicobacter* species or by direct destruction of parietal cells.[24,26,58–61] Metaplasias are associated with cancer and seem to reflect a permanent alteration in the behavior of stem and progenitor cells.

Intestinal Metaplasia

The gastric mucosa can adopt various aberrant differentiation patterns, resulting, in rare instances, in cells with pancreatic acinar or ciliated bronchial features; however, the most well-characterized pattern of metaplasia involves conversion of gastric into intestinal-type epithelium. This change is easily detected by analysis of specimens by histopathology, based on the markedly different cellular organization and histochemical staining patterns of gastric and intestinal epithelia. Patterns of intestinal metaplasia can vary from instances where the gastric mucosa mimics the morphology of small or large bowel epithelium perfectly to varying degrees of intestinal differentiation of indeterminate type. The extent of metaplasia can vary from partial intestinalization, in which patches of cells express intestinal markers but contain normal gastric epithelium,[55] to diffuse, in which large portions of the stomach resemble the intestine. Gastric units can also be partially intestinal, with whole or parts of gland branches affected, with sharp interfaces between cells with gastric and intestinal morphologies.[41,55] Most animal models for experimental or spontaneous metaplasia have limited tissue conversion, with only focal changes in mucin content or gene expression; they do not undergo the dramatic changes in differentiation patterns observed by histologic analysis of human intestinal metaplasia lesions. Although intestinal metaplasia causes changes in stem and progenitor cells, it is not clear whether native gastric stem cells are the initial source of the changes and metaplasia results from their reprogramming into an intestinal type or if differentiated gastric cells first acquire intestinal properties and then stem cell properties. The stomach epithelium of mice converts readily into the intestinal type on transgenic expression of CDX2, a transcription factor that regulates intestinal development and differentiation.[62,63] This observation indicates that intestinalization of gastric stem cells might be the initiating event in intestinal metaplasia. Additional animal models are needed to improve research into the molecular and cellular pathogenesis of intestinal metaplasia.

The most common gastric adenocarcinomas have intestinal features; just as Barrett's metaplasia is characterized by intestinalization of the esophagus or gastric cardia,[64] intestinal metaplasia has been proposed as an intermediate step in the development of gastric cancer.[57,65] However, this interpretation may be facile, because different types of intestinal

metaplasia have different degrees of association with malignancy, and early-stage gastric cancers can arise in nonintestinalized epithelium.[66–68]

Spasomolytic Polypeptide (TFF2)-Expressing Metaplasia

Pathologists observed more than a century ago that certain types of gastric corpus injury alter the balance between enzyme- and mucus-secreting cells.[69,70] Pseudopyloric metaplasia, so named because increases in mucus and loss of mature parietal and chief cells make the corpus resemble the pylorus or antrum, is associated with increased cell proliferation (Figure 5). Understanding of the condition advanced when Goldenring et al observed that human metaplastic stomach expressed high levels of spasmolytic polypeptide (TFF2) at the base of corpus gastric units, although TFF2 is normally expressed at lower levels in mucous neck cells in upper and mid portions of the units (Figure 5).[54,55,71] Animal models have been developed with this pattern of pseudopyloric features (or spasmolytic polypeptide–expressing metaplasia [SPEM]) in Mongolian gerbils and mice; in all cases, including humans, parietal cells are lost, zymogenic cells are lost or dedifferentiate, and TFF2 expression extends from the isthmus to the gland base.[24,55,60,72,73]

Some studies suggest that gastric tumorigenesis might have a stronger correlation with SPEM than with intestinal metaplasia,[54,74] although these metaplasias often occur together.[55,75] Also, SPEM is by definition a corpus lesion, whereas cancer is believed to arise more commonly in the antrum or in the transitional area between antrum and corpus. However, because SPEM resembles the antrum histologically, cancers arising in corpus tissue that converted to SPEM might appear to pathologists to arise in the antrum; this would result in overestimation of the prevalence of antral tumors.

Parietal cell loss in humans correlates with SPEM.[74] Virtually any intervention that disrupts parietal cells in animals—parietal cell–specific expression of a toxic transgene,[26,59] knockout of genes required for development or activity,[61] or injection of agents that are toxic to parietal cells[73]—leads to SPEM. Parietal cell loss rapidly expands the proliferative compartment in the isthmus, including cells that are morphologically indistinguishable from normal granule-free presumptive stem cells (Figures 2 and 5).[25,26] It is unclear if this change in stem cell behavior is associated with permanent or transient changes in gene expression. In addition, chief cells lose expression of at least one marker of maturity (the transcription factor MIST1, also known as BHLA15), reenter the cell cycle, re-express progenitor neck cell markers like TFF2, and begin to react with the lectin GSII.[24,60] Expression of secretory chief cell markers (eg, pepsinogen C) is maintained in these TFF2-expressing metaplastic cells (Figure 5). A recent study of hundreds of specimens indicated that the same chief cell changes in expression of MIST1 and other genes occur in human tissues.[55,75] It is unclear what proportion of the SPEM cells arise de novo, from altered stem cells, or from transdifferentiation of chief or even mucous neck cells (Figure 5). A recent study used genetic lineage tracing in tamoxifen-inducible, *Mist1-Cre* knock-in mice to show that mature, *Mist1*-expressing chief cells can give rise to metaplastic cells in SPEM.[76]

Although little is known about molecular mechanisms that control the fate of stem cells during SPEM, as mentioned previously, expansion of presumptive isthmal stem cells in SPEM was exploited to identify genes expressed by gastric stem and progenitor cells.[5] Loss of the epidermal growth factor family member Amphiregulin leads to SPEM,[77] and chief cells that differentiate in the absence of the transcription factor XBP1 or parietal cell–secreted Sonic Hedgehog have significantly increased numbers of basal cells that have a SPEM pattern of coexpression of mucous neck cell markers (such as TFF2) and chief cell markers. Sonic Hedgehog might normally signal chief cells to increase expression of XBP1, whose transcriptional targets inhibit SPEM.[78,79] XBP1 induces MIST1 expression,[79] and

MIST1 is lost in SPEM.[24,55] Studies in experimental models of SPEM will increase our understanding of its mechanism and mediators.

The Relation of Gastric Metaplasias to *Helicobacter* infection

Human gastric cancer is commonly associated with *H pylori* infection and intestinal metaplasia, and there has been much interest in identifying the mechanisms of their relationships. However, the role of gastric epithelial stem cells is uncertain.[80] As for all epithelial tumors, it is unclear whether gastric adenocarcinoma develops through alterations in the native stem cell population or of less primitive cells in the transit-amplifying or mature cell compartments (eg, via progression from metaplasia; Figure 5). Distinguishing between these possibilities will help elucidate the role of stem cells in tumorigenesis and improve our ability to isolate and monitor these cells. Mice have different immune responses to *Helicobacter* infection from humans and rarely develop metastatic gastric tumors but continue to be used as models of gastric cancer because they can be genetically manipulated and infected with various *Helicobacter* species, and cell lineages can be traced from stem cell populations when stem cell–specific markers are available. *H pylori* infection initially and briefly increases apoptosis of surface and proliferative cells and then expands the proliferative cell zone to deeper in the gland, presumably as a compensatory response (similar to the pattern in chemically induced SPEM; Figure 5); mucosal atrophy and SPEM ensue in the next 12 to 18 months.[58] *Helicobacter felis* infection, of C57/B6 mice in particular, leads more consistently to high-grade dysplasia and the development of large antral tumors months later.[58] The parietal cell loss that is characteristic of SPEM precedes development of invasive cancer in mouse models and most humans, but it is not clear if tumors eventually arise from the resulting metaplastic stem and chief cells or if the pattern of metaplasia and achlorhydria associated with parietal cell loss merely increases the propensity of other cells to form tumors.[80]

Other Injury-Induced Changes in Progenitor Activity

Other progenitor cells have activity during chronic stomach injury that leads to metaplasia. In myeloablated C57BL/6 mice infected with *H felis*, bone marrow–derived cells contributed significantly to the resulting metaplastic epithelium.[81] After these mice received transplants of bone marrow from ROSA26R (expressing LacZ as a reporter) or from *β-actin-EGFP* (expressing green fluorescent protein) mice, LacZ+ or green fluorescent protein–positive bone marrow–derived cells were detected in the gastric mucosa. However, more recent experiments suggest that those mesenchymal stem cells may not originate from the blood but from keratin-19–expressing mesenchymal cells.[82] During chronic inflammation, failure of gastric stem cells might lead to recruitment and engraftment of mesenchymal cells, whether from bone marrow–derived populations or already resident in the stomach epithelial stem cell niche; these cells might contribute to metaplasia, dysplasia, and cancer. The study did not exclude the possibility of fusion between mucosal and bone marrow cells, a common source of the erroneous concept that stem cells in other tissues have a circulating source; although bone marrow–derived cells in the stomach mucosa were diploid, fused cells shed excess chromosomes.[83] Importantly, even if cells that appear in response to gastric injury are fusions of mucosal and blood-derived cells, the observations indicate an unusual amalgamation of cell lineages that may ultimately affect stem cell properties.

Altered Gastric Epithelial Differentiation in Other Conditions

Certain uncommon chronic disorders also alter gastric epithelial differentiation in ways that alter stem cells. Ménétrier's disease, which involves chronic over-stimulation by epidermal growth factor ligands, leads to expansion of foveolar pit cells.[84] The Zollinger–Ellison syndrome of gastrin hypersecretion leads to excess proliferation of parietal and/or zymogenic precursors. Although these disorders can be modeled in mice, it is not clear if

selected cell types are affected or if changes in stem cells promote their differentiation along a specific lineage.

Developmental Origins of the Gastric Stem Cell Compartment

It is important to learn how prospective stem cells are distinguished from their neighbors during development, come to occupy a unique niche, and establish the property of self-renewal. Not much is known about this process in any tissue type; in the small intestine of fetal mice, cell proliferation is initially disseminated throughout nascent villi but becomes confined to the intervillus space over the span of 1 to 2 days in midgestation.[85] These intervillus cells subsequently invade the underlying mesenchyme to form crypts during the first 2 to 3 weeks of life in mice and in the third trimester of pregnancy in humans. Although we can visualize this transition, we have limited insight into its molecular and physiologic basis and even less understanding of development of the gastric stem cell niche. Early stomach endoderm retains a certain plasticity; if juxtaposed experimentally with intestinal mesenchyme, it can develop into a villiform intestine.[86] This developmental potential becomes restricted in midgestation, when the homeodomain transcription factor BARX1, whose expression in the digestive tract is restricted to the stomach mesenchyme, promotes stomach-specific differentiation of the overlying endoderm.[87,88] This specification somehow determines the properties of future stem cells, creating an environment that promotes stomach-specific differentiation. Generation of gastric identity in the fetus requires inhibition of canonical Wnt signaling in the nascent epithelium (Figure 6). Stomach expression of *Barx1* is restricted to embryos; the mesenchyme in neonatal and adult stomachs lacks Barx1 but still supports and regulates the overlying gastric epithelium in perpetuity. In adult transgenic mice, expression of the intestinal homeodomain protein CDX2 converts the stomach epithelium into the intestinal type, defined by the presence of intestine-specific goblet cells.[62,63] Mechanisms that repress transcriptional regulation by CDX2 must therefore be important in maintaining gastric epithelial and, by extension, gastric stem cell identity.

In the intestinal epithelium, stem or progenitor cell activity represents a balance between Wnt and Notch signaling, which promote cell replication, and bone morphogenetic protein BMP4 signaling, which reduces proliferation and promotes cell differentiation.[45] The corresponding regulators of the adult gastric stem cell are not known. However, disruption of BMP2, BMP4, and BMP7 signaling, through deletion of their receptor BMPR1A, leads to hyperplastic polyp formation in the antrum, but not the corpus,[89,90] indicating again the parallel between regulation of stem cell activity in the antrum and intestine.

Maturation of the stem cell compartment continues after birth. Nomura et al studied mosaic $LacZ^+$ gastric glands[33]; although monoclonal gland units were observed in adult mice, most units in stomachs of fetal and newborn mice contained mixed populations of blue and white cells. These observations reflect a gradual and seemingly stochastic process of gland evolution toward monoclonality, which is sometimes called purification and is similar to the clonal restriction of intestinal crypts.[91] One mechanism for progression toward monoclonality might be that, as gastric units propagate by branching or fission, those with 2 competing stem cells are more likely to branch, with one progenitor forming the new unit and the other supplying the original unit. Surprisingly, experimental and mathematical modeling studies have indicated that intestinal crypt stem cells divide symmetrically and stochastically, not with the asymmetry observed in stem cell divisions in some other tissues.[92,93] Similarly, symmetric divisions among gastric stem cells probably account for the emergence of monoclonality within individual gastric glands; the pace is likely to be slower than in the intestine because stomach stem cells self-renew more slowly.

Future Directions

Each gastric unit in the stomach is served by a tiny population of monoclonal stem cells that enable lifelong epithelial self-renewal. Despite their fundamental similarities with intestinal stem cells, which are increasingly well characterized, gastric stem cells are poorly understood, although they are likely to be involved in the pathogenesis of gastric cancer, which is a global health problem. In the oxyntic mucosa of the gastric corpus, they probably lie in the isthmus and cycle slowly, generating progeny that migrate bidirectionally, differentiate into mature resident lineages, and have variable life spans. A lack of molecular markers presents the most significant barrier to research on corpus stem cells. Identification of markers of stem cells in normal and diseased states, and reliable methods for ex vivo culture and expansion of gastric corpus stem cells, are priorities for this field of research. In the simpler mucosa of the gastric antrum, stem cells lie closer to the gland base, produce fewer types of progeny, and seem to have hybrid characteristics between corpus and intestinal stem cells. At least one subset, if not the whole population, of antral stem cells bears the surface marker LGR5 and replicates briskly, perhaps daily, in adult mice, where it can contribute to all mature epithelial lineages over long periods. The recent expansion and differentiation of these cells in culture should lead to experiments to define their growth requirements and signaling pathways and determinants of whether these cells undergo continued replication or lineage commitment. Because stem cells throughout the stomach respond continually to external cues and local tissue injury, they must occupy a sophisticated niche that conveys homeostatic signals as well as information about infection and inflammation. Some combination of intrinsic and niche-derived cues likely converts gastric cells with proliferative potential into cells with aberrant, metaplastic differentiation patterns that lead to dysplasia and carcinoma. Although our knowledge about stem cell niches is limited, few areas in basic gastroenterology research present greater interest or challenges. It is important to develop methods to isolate and culture stem cells that express well-validated molecular markers. Such progress will advance understanding of stem cell properties and the responses to infection and tissue damage that induce metaplasia and cancer in the gastric epithelium.

Abbreviations used in this paper

SPEM	spasmolytic polypeptide–expressing metaplasia
TFF2	trefoil factor 2

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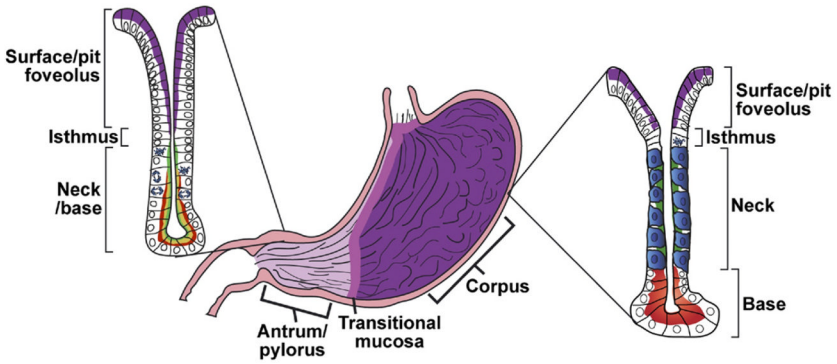

Figure 1.

Typical anatomy and histology of a mammalian stomach. There are a number of variations in mammalian gastric anatomy. For example, mice have a forestomach with keratinized squamous epithelium, whereas humans have a pronounced cardiac region with simpler mucous glands that mark the transition region between the esophagus and corpus. However, the most prominent regions in most mammals are a proximal corpus, encompassing most of the stomach volume, and a distal antrum or pylorus. The corpus epithelium is organized into repeating gastric units that are invaginations from the surface and contain multiple cell lineages in 4 distinct zones. In the diagram, acid-secreting parietal cells are *blue*, digestive enzyme secreting zymogenic (chief) cells are *red*, mucous neck cells are *green*, and the mucus-secreting pit cells nearest the surface are *purple*. In the antrum, the gastric units are simpler, with few parietal or zymogenic cells. Antral units contain 2 distinct types of mucous cells: those lining the surface (*purple*) are similar to the surface cells of the corpus, and those nearer to the base have properties intermediate between zymogenic cells and mucous neck cells of the corpus (*red-yellow*). The interfaces between esophagus and corpus and between corpus and antrum are not abrupt but marked by transitional mucosae. Endocrine cells (not depicted) are also present throughout the corpus and antrum epithelium.

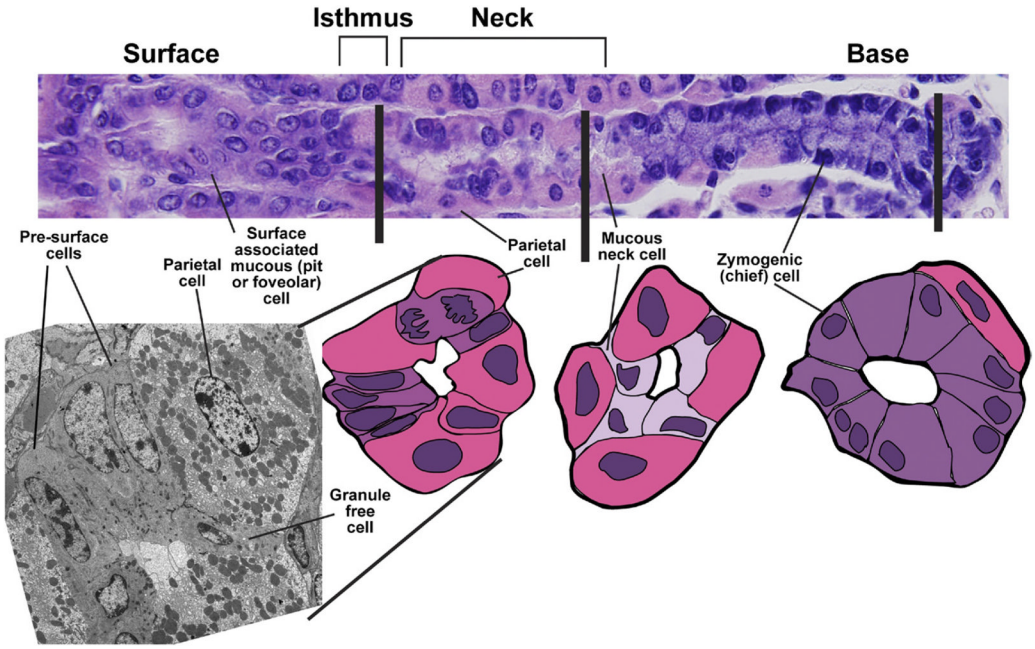

Figure 2.

Microanatomy of a corpus gastric unit. (*Top*) A typical mouse gastric unit, stained by H&E, with the gastric lumen to the left and musculature to the right. Below that are transverse sections through the isthmus (note the dividing cell), neck, and base. Cartoons traced from actual H&E tissue sections are shown. Note the close apposition of progenitor cells in the isthmus and mucous neck cells in the neck with mature parietal cells. (*Left*) A transverse transmission electron micrograph of a section through the isthmus. A granule-free (presumptive gastric epithelial stem) cell is notable for its high nuclear-cytoplasmic ratio and absence of distinguishing granules. Presurface cells, the precursors to surface mucous (pit or foveolar) cells, are distinguished by early granules that are characteristic of this lineage. Again, mature parietal cells are prominent in the isthmus.

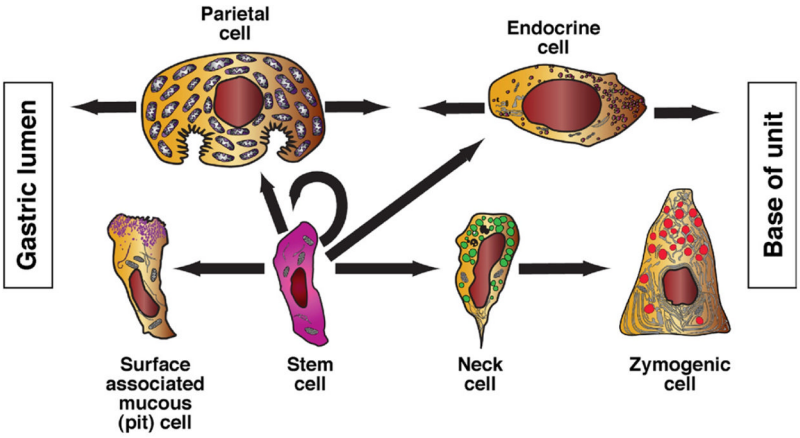

Figure 3.
Origins of principal corpus epithelial lineages. The self-renewing stem cell gives rise to each of the principal epithelial lineages of the corpus. There is ultrastructural evidence for the transient intermediates for each lineage (eg, presurface cells depicted in Figure 2); however, available evidence indicates greater complexity in the zymogenic lineage, which arises from a long-lived (≥1 week in mice) intermediate, the mucous neck cell, with its own distinct ultrastructure and probable function.

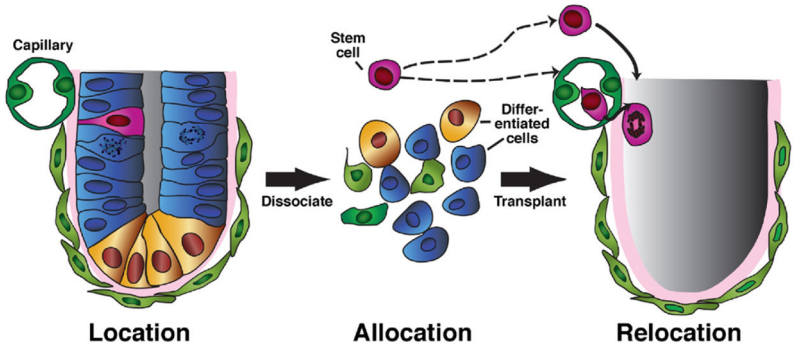

Figure 4.

Approaches to investigate stem cell biology. A stem cell (*pink*) can be characterized by understanding its niche (location), meaning the cells that surround it and affect its activity. Stem cells can also be characterized by identification of molecular markers, which allow their distinction and isolation (allocation) from differentiated cells. Finally, stem cells can be assayed for functional activity based on their ability to regenerate all the normal lineages of a specific tissue (relocation). Ideally, relocation experiments are performed in vivo (eg, serial transfer of hematopoietic stem cells to irradiated recipients). However, tissue culture approaches have also been useful for isolating and demonstrating the properties of stem cells. In several tissues, including the gastric antrum, single cells have been shown to function as stem cells. However, isolation procedures in all tissues only enrich the fraction of single cells that have stem cell capacity; pure populations of single cells, each with complete stem cell activity, have not yet been isolated.

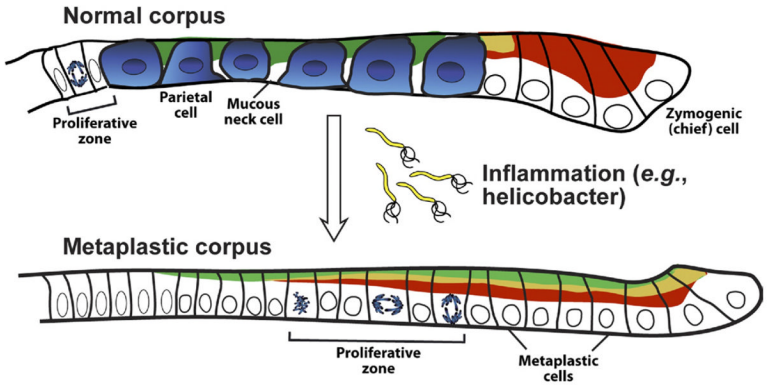

Figure 5.

Cellular mechanisms of SPEM. Chronic inflammation of the corpus in mammals leads to characteristic changes in differentiation in the gastric unit. Parietal cells are lost (atrophy), and the zymogenic chief cell lineage is reprogrammed so that genes that are normally expressed only in mucous neck cells, such as spasmolytic polypeptide/TFF2 (shown in *green*), are expressed at high levels in cells at the base. The zymogenic cell–specific transcription factor MIST1 (not depicted) is lost, but other zymogenic cell markers (such as pepsinogen C; *red*) are coexpressed with neck cell markers. Proliferation is increased and occurs more basally in the unit. The pattern of basal proliferation and coexpression of neck and zymogenic cell genes is similar to the histologic pattern in the normal antrum and pylorus, which is why it is called pseudopyloric metaplasia. The most common metaplasia-inducing inflammation is caused by *H pylori* infection, although autoimmune gastritis (in which autoantibodies target parietal cells) can cause the same metaplasia pattern.

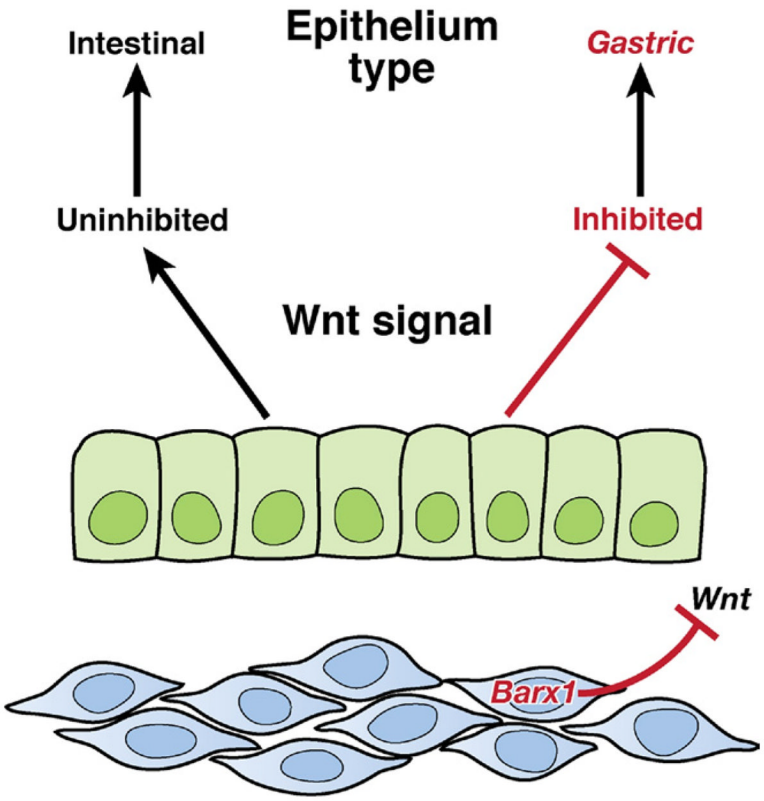

Figure 6.

Molecular basis of stomach epithelial specification in embryos. Expression of the homeodomain transcription factor Barx1 is restricted to the developing mesenchyme, which underlies the nascent gastric epithelium. Barx1 regulates transcription of many factors, including the secreted inhibitors of Wnt signaling that repress the canonical Wnt pathway in the overlying endoderm. This repression promotes stomach epithelial differentiation at the expense of intestinal differentiation, which would occur in the absence of Barx1-induced Wnt blockade.