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Self-renewal of the gastric epithelium from stem and progenitor cells

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1. ABSTRACT

The mammalian gastric mucosa and its glands are both of endodermal origin and together represent a tight barrier to the outside world. Here, two types of gastric units form homeostatic systems, i.e. fundic and antral units, showing continual bi-directional self-renewal via differentiation from stem and progenitor cells. This review describes recent developments concerning the different populations of gastric stem cells as well as the various gastric epithelial cell types and their self-renewal. Parietal cells, as the organizing centers of fundic units, are particularly important in regulating differentiation of the mucous neck-zymogenic cell lineage. Here, the morphogen Sonic hedgehog (SHH) plays a key role. Furthermore, dysregulated gastric self-renewal occurs in specific diseased states. For example, the TFF2/spasmolytic polypeptide expressing metaplasia (SPEM) is the result of a dysregulated trans-differentiation of the mucous neck-zymogenic cell lineage and SPEM can even evolve to intestinal metaplasia. Both metaplasic states represent premalignant conditions for the "intestinal" type of gastric cancer. Dysregulated differentiation also occurs in the course of chronic inflammation with SHH being a key target for inflammatory processes.

2. INTRODUCTION

The mammalian gastric epithelium is well known for its high cellular turnover rate, which is dependent on a series of differentiation processes (for reviews, see refs. 1, 2). Self-renewal (continuous regeneration) is an essential component of the multiple protection and defense mechanisms maintaining the surface integrity of the stomach. This sensitive organ represents a tight barrier to the outside world (i.e., the gastric juice and its contents including microbiota) and is permanently exposed to various endogenous and exogenous noxious agents.

As early as in 1953, progenitor cells were already suggested to reside within the isthmus of gastric glands (3). The gastric regeneration dynamics were first established in the mouse by Leblond and his co-workers in a series of elegant studies about 20 years ago (1, 4). However, the morphology and self-renewal of the human gastric epithelium differ in important details from the murine system (for review, see ref. 2). Today it is clear that the different secretory cells of the gastric mucosa all originate from multipotent somatic (adult) stem cells (SSCs) as well as from a pool of transit-amplifying cells. This homeostatic system is maintained by the bidirectional migration and differentiation of the various cell types followed by

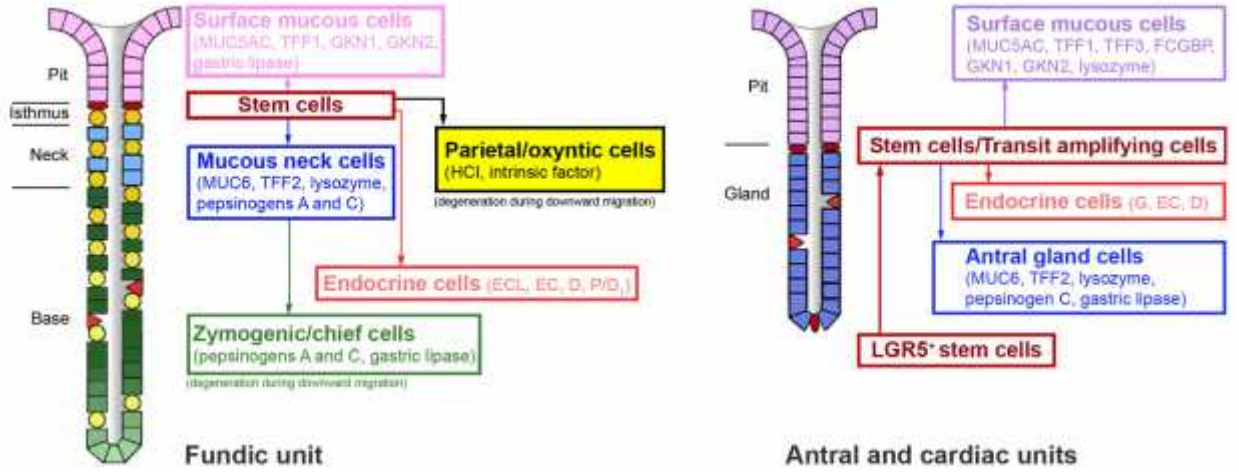

Figure 1. Schematic representation of the two gross types of human gastric units and their continual bidirectional self-renewal from stem and precursor cells. Shown are the major cell types and some of their characteristic secretory products such as mucins (MUC), TFF peptides, gastrokines (GKN), IgG Fc binding protein (FCGBP), lysozyme, gastric lipase, pepsinogens, intrinsic factor and hydrochloric acid (HCl) as observed in the fundic and antral units, respectively (modified and updated from ref. 2). Degeneration of parietal and zymogenic cells during downward migration in fundic units is indicated by decreasing coloring.

apoptosis of the mature cells at the pit or the bases of the glands, respectively.

Embryologically, the mammalian gastric epithelium is of endodermal origin and the specialized gastric epithelial cell types were first generated throughout endoderm organogenesis (5). Thus, it is not surprising that differentiation mechanism regulating this process and self-renewal in the mature stomach share common principles.

Currently, this knowledge becomes increasingly important for our understanding as dysregulated differentiation processes are the cause of gastric cancer (6). For example, dysregulated gastric self-renewal leads to metaplastic states, which are considered as premalignant conditions particularly for the "intestinal" type of gastric cancer (for reviews, see refs. 7, 8). Within the last few years, many important molecular details were described concerning gastric self-renewal, which justify an update of this medically relevant topic.

3. SELF-RENEWAL OF THE GASTRIC EPITHELIUM

Histologically, the human gastric mucosa and its glands are divided into three zones along the anterior-posterior (AP) axis: the cardiac zone, the fundus/corpus zone and the antral/pyloric zone. The gastric epithelium is covered by surface mucous cells (SMCs) which also line the ~3 million funnel-shaped gastric pits (also called foveolae). Gastric glands (divided into the isthmus, the neck and the base) open into the bottom of these pits (Figure 1). There are two gross types of gastric glands, i.e., a fundic type (in the fundus/corpus) and an antral type (in the cardia and antrum), which differ very much in their histology, renewal rates and bidirectional renewal profiles (Figure 1; for review, see ref. 2). The combination of a pit and a gland is called a gastric unit (9). The complex fundic units contain 5 principal mature epithelial cell types: the SMCs (also referred to as pit cells), the parietal cells (also called oxyntic cells), the mucous neck cells (MNCs), the zymogenic cells (also referred to as chief cells), and various endocrine cells (mainly enterochromaffin-like ECL, enterochromaffin EC, somatostatin-producing D, and ghrelin-producing P/D_1 cells). The antral units appear somewhat simpler and contain SMCs, antral gland cells (AGCs), and endocrine cells (mainly gastrin-producing G cells, but also D and EC cells). Each of the mature cell types is characterized by a highly specific expression profile. Established markers of these well differentiated cells are characteristic secretory proteins typical for their specialized biological functions (Figure 1).

3.1. Gastric stem and progenitor cells

The existence of multipotent gastric stem cells in the adult has been unambiguously demonstrated (9, 10). Surprisingly, the clonality of gastric units was shown to be different in the fundic and antral units of human (11).

The isthmus is clearly the region with the highest rate of proliferation. Here, undifferentiated cells lacking secretory granules ("granule-free cells") as expected for gastric SSCs were first identified in the mouse fundic and antral units (1). However, this cell type has no direct counterpart in the human gastric mucosa, where immature "mini-granule cells" were identified in fundic units that probably function as SSCs (12). Within this region, immature pre-SMCs, pre-MNCs, and pre-parietal cells were also characterized, which are typical progenitor cells. The differentiation programs of these lineages are blocked

by supraphysiological levels of activins, which belong to the transforming growth factor-ß (TGF-β) superfamily (13). Expression profiling of murine gastric progenitor cells in their niches at the isthmus revealed both common as well as distinctive features when compared with other stem cell populations (14, 15).

However, the situation in the fundic and antral units differs considerably. In the latter, additional cell populations with stem cell characteristics have been identified (for reviews, see refs. 16, 17). Besides stem cells at the isthmus also a second population of gastric stem cells has been characterized ($LGR5^+$) located at the base of antral (and probably also cardiac) units (18, 19). These $LGR5^+$ stem cells were also detected at the base of fundic units, but only in the neonatal stomach. Furthermore, a third population of cells with multilineage potential were identified mainly in antral glands at or below the isthmus (20). These cells are marked by the villin promoter and multiply after stimulation with interferon-γ, but do not contribute to renewal under normal conditions. They are thought to serve as a quiescent stem cell pool that is activated in response to inflammatory conditions.

The existence of multiple stem cell populations in the antral units might be connected with the fact that antral SMCs have a much higher turnover rate than fundic SMCs (21). Thus, it is not surprising that in human the number of proliferative cells is much higher in antral units when compared with fundic units (22). These proliferative cells are expected to serve mainly as transit-amplifying cells ultimately generating the mature cell types. The pool of fundic proliferative cells mainly consists of pre-SMCs, pre-MNCs, and MNCs (12); whereas the proliferative zone of antral units contains early SMCs and pre-AGCs (22).

3.2. Surface mucous cells

SMCs originate from progenitor cells at the isthmus from where they migrate to the luminal surface (1, 12). Typical components of the tight junction barrier are the claudins 3 and 5 (23). These cells are the major players during "restitution", i.e., the rapid repair of superficial lesions by cell migration (24), they typically respond to *Helicobacter pylori* infection (25), and they serve as the predominant hosts for the complex gastric bacterial microbiota (26). Only within the last years it has become clear that fundic and antral SMCs differ not only in their turnover rates (21), but also in their regeneration modes and expression profiles (22, 27, 28). For example, maturation of human antral SMCs occurs stepwise via a population of TFF3-positive cells close to the isthmus (27, 28). Furthermore, human fundic and antral SMCs differ in the expression of at least four secretory genes, i.e., gastric lipase, TFF3, FCGBP, and lysozyme (22).

Major drivers for the expansion of the SMC lineage are transforming growth factor α (TGF-α), which is a secretory product of SMCs, and gastrin (29-32). The trophic effect of gastrin is probably an indirect one and could occur, for example, via stimulation of heparin-binding EGF-like growth factor (HB-EGF) expression or REG1A expression (Figure 2). Furthermore, SMC differentiation is probably also controlled by TFF peptides. For example, Tff1-deficient mice show an expanded SMC population at the expense of parietal cells in the fundic units (33) and an amplification of SMCs and AGCs in the antral units (34). Proper differentiation of SMCs has been reported to depend also on the expression of the protease Furin (35), which is involved in proteolytic maturation of members of the TGF-ß family, such as bone morphogenetic protein-4 (BMP-4). Furthermore, formation of mucous granules in murine SMCs is dependent on functional synaptotagmin-like protein 2 (36) and Foxq1-dependent synthesis of the mucin MUC5AC (37) indicating that proper terminal differentiation of SMCs requires correct synthesis of the mucous secretory machinery.

SMCs also secrete the morphogen Indian hedgehog (IHH), which forms a steep gradient along the AP axis (increase from anterior to posterior, Figure 2) (32, 38, 39). Gastrin was proposed also as a regulator of IHH expression (32). IHH is expected to trigger proliferation of epithelial cells after crosstalk with mesenchymal cells via Wnt (32) and this might explain the higher turnover rates of antral SMCs when compared with fundic SMCs (21).

3.3. Parietal cells

Elegant studies using genetically manipulated mice revealed that the hydrochloric acid-producing parietal cells are the primary organizing centers of the fundic unit (for review, see ref. 40; for the expression profile of mouse parietal cells, see ref. 41). A loss of parietal cells leads to dysregulated renewal, i.e., a depletion of zymogenic cells and an increase in SMCs. Thus, parietal cells are expected to secrete regulatory factors controlling at least the differentiation of zymogenic cells (Figure 2). Of note, the parietal cell lineage is the only one that completes its terminal differentiation within the isthmus and parietal cells gradually degenerate during their downward migration (42-44). Here, the transcription factor GATA-4 has been shown to be critical, which is probably involved in the response to members of the TGF-ß superfamily (45). Another essential component for proper differentiation and survival of parietal cells is Huntingtin-interacting protein 1-related (Hip1r), which participates in vesicular trafficking, associated with acid secretion (46). Gastrin is a major stimulator of parietal cells. This occurs mainly indirectly via gastrin-triggered release of histamine from ECL cells (Figure 2) (29). However, parietal cells also contain the CCK_2 receptor and thus can in principle respond to gastrin directly.

One major regulatory factor secreted by parietal cells is SHH, a morphogen during embryonic development and a morphostat that plays a key role in the differentiation, proliferation, and maintenance of adult tissues (39, 47, 48). SHH expression is restricted to the fundic units where it forms a gradient with the highest expression in the parietal cells closest to the isthmus and gradually decreasing expression towards the base of the gland (Figure 2) (42, 44). In contrast, in the rat and mouse glandular SHH expression is not that restricted (39). Downregulation of SHH in antral units is probably regulated by the transcription factor GATA-4 (45). Gastrin stimulates SHH expression in parietal cells and its acid-depending

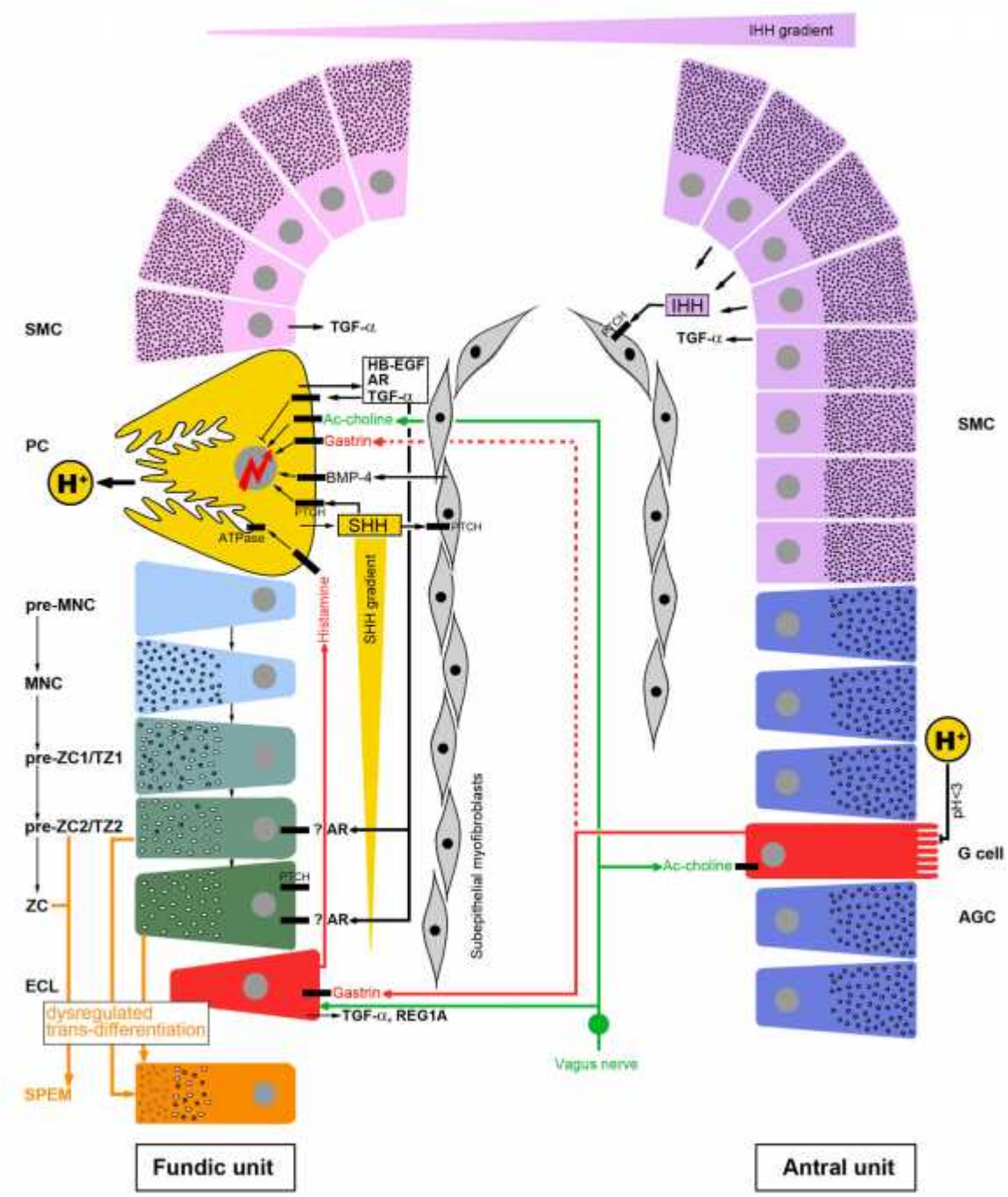

Figure 2. Pathways regulating the self-renewal of the two types of gastric units. Acid-secreting parietal cells (yellow) are the major organizing centres of fundic units and they are particularly essential for the maturation of the MNC-zymogenic cell lineage. The number and activity of parietal cells is pH-dependently regulated by gastrin, which is released into the blood stream (red line) from antral endocrine G cells (red). Gastrin is believed to act mainly indirectly by releasing histamine from fundic ECL cells (red), which in turn stimulates parietal cells, in a paracrine fashion (red line). In contrast, gastrin is considered as a relatively poor direct stimulant of acid secretion from parietal cells (dashed red line). Depicted is also the innervation of G cells, ECL cells, and parietal cells by the enteric nervous system (green lines). Typical secretory products of parietal cells are TGFα, AR, HB-EGF, and SHH. The morphogen SHH forms a gradient along the fundic gland axis and acts via its receptor PTCH typically located on mesenchymal cells, i.e., subepithelial myofibroblasts. A typical target of SHH signalling is BMP-4, which in turn signals back to epithelial cells. Zymogenic cells (green) arise from stepwise maturation and trans-differentiation of MNCs (blue). Dysregulated trans-differentiation results in SPEM formation (orange). The various cell types are explained on the left and right border, respectively. For abbreviations see list.

processing by pepsin A at the apical side (49). Of note, SHH expression is stimulated by the release of intracellular Ca^{2+} (50). However, SHH is finally released basolaterally (after a highly complex and unusual biosynthetic pathway; for review, see ref. 48) and SHH signaling via its receptor Patched (PTCH) is mainly paracrine from the epithelium to the mesenchyme (51). Here, subepithelial myofibroblasts respond to SHH and secrete BMP-4, which signals back to the epithelium, mainly to parietal cells (Figure 2) (52, 53). Of special note, PTCH has been reported to be localized also on parietal cells allowing autocrine stimulation (42) as well as on other epithelial cells (50). On parietal cells, one of the target genes is the H^+/K^+-ATPase (54). This explains why a loss of SHH expression in parietal cells induced hypochlorhydria, hypergastrinemia, and hyperproliferation of SMCs in mice (32). The latter effect is probably indirect due to the hypergastrinemia.

Furthermore, parietal cells secrete a number of EGF receptor ligands, including TGF-α, amphiregulin (AR), and heparin-binding EGF (HB-EGF). Interestingly, the individual ligands probably trigger different physiological responses (55). Of note, TGF-α inhibits hydrochloric acid secretion by parietal cells (56). Generally, both expansion of the SMC lineage (Dempsey *et al.* 1992/91) and proper maturation of the MNC-zymogenic cell lineage are affected by EGF receptor ligands, in particular by amphiregulin (55).

3.4. The mucous neck cell-zymogenic cell lineage

Murine as well as human MNCs, which originate from pre-MNCs, have been clearly shown to trans-differentiate during their downward migration to finally become zymogenic cells (Figure 1) (12, 57). MNC precursors can be recognized by their expression of mRNAs encoding MNC specific proteins, such as TFF2 (previously termed spasmolytic polypeptide), as shown in human (22), mouse (58), and rat (59). However, pre-MNCs do not express the corresponding TFF2 peptide, which only appear in mature MNCs.

Within the last years, remarkable progress has been made concerning the understanding of the stepwise maturation of zymogenic cells. Here, different precursors have been identified (transitional cells TZ1 and TZ2; see Figure 2) (60). Trans-differentiation from a mucous to a serous phenotype is accompanied by a drastic change of the secretory vesicles. Furthermore, there is an increasing gradient of moesin expression from MNCs to mature zymogenic cells on the apical membrane (61). The serous phenotype of mature zymogenic cells is probably characterized by the small GTPases Rab26 and Rab3D, which are expressed under the control of a cascade of transcription factors in the order Blimp1, Xbp1, and Mist1 (60, 62, 63). Another transcription factor important for differentiation of zymogenic cells is RUNX3, which also regulates claudin-1 expression (64, 65).

Proper maturation of the MNC-zymogenic lineage is strictly dependent on functional parietal cells, in particular on secretion of SHH (32) and BMP signaling (53). Amphiregulin is another secretory peptide of parietal cells, which is essential for the correct differentiation of zymogenic cells (55). Furthermore, histamine released from ECL cells has also been recognized to be essential for zymogenic cell differentiation (66). Lack of these ligands or inhibition of their signaling resulted in a disrupted differentiation (appearance of a mixed phenotype between MNCs and zymogenic cells) or premature differentiation of zymogenic cells. However, the precise mechanism how differentiation of the zymogenic lineage is controlled is not yet understood. The complex regulatory network of secretory ligands includes at least parietal cells (SHH, amphiregulin), mesenchymal cells (BMP-4), and ECL cells (histamine). Amphiregulin may act directly on the zymogenic lineage; whereas histamine, SHH, and BMP-4 may have only indirect roles. Thus, the schematic representation in Figure 2 lacks many important details, such as the roles of somatostatin, REG1A, and the crosstalk of the H_2, M_3, and CCK_2 receptors.

3.5. Antral gland cells

Based on their expression patterns, mucous AGCs resemble MNCs (Figure 1). For example, both secrete MUC6, TFF2, lysozyme, and pepsinogen C. However, human MNCs also secrete pepsinogen A, which is not expressed in AGCs (22). Of special note, in the mouse the dynamics of the self-renewal of AGCs is unique and does not follow a "pipeline pattern" as observed for the other gastric epithelial cells. Instead, AGCs differentiate gradually during their downward migration from the neck to the base; during this process many of these cells are lost, probably by extrusion into the lumen (67). Only a minority of cells reach maturity and thus this sequence was termed the "cascade pattern" of renewal (67).

In human, AGCs also differentiate gradually. First, in the proliferative region, lipase F, and pepsinogen C mRNAs are expressed; whereas MUC6 and TFF2 transcripts are detectable only after downward migration of these cells (22). Thus, AGCs mature from a serous phenotype to a mucous phenotype at the base of the glands. In the mouse, the transcription factor SPDEF has been shown to be required for terminal differentiation of AGCs (68).

3.6. Endocrine cells

It is now accepted that gastric endocrine cells are of endodermal origin, as all other gastric epithelial cells, and they originate from the same stem cells (69, 70). Despite expressing a common set of genes, neurons and enteroendocrine cells are clearly of divergent embryological origin (for review, see ref. 71). Interestingly, the regulation of endocrine cell differentiation varies significantly between the stomach and intestine (71, 72).

One of the master regulators of gastric endocrine differentiation is HES-1, which represses endocrine differentiation via the Notch pathway (73). Of note, in mice two gastric endocrine lineages exist, one depending on neurogenin3 (Ngn3); that includes gastrin- (G), somatostatin- (D), and glucagon- (A) producing cells. Whereas differentiation of serotonin- (EC), histamine- (ECL), and ghrelin-producing cells is Ngn3-independant

(72, 74). Furthermore, expression of the transcription factor NeuroD, a terminal endocrine differentiation marker, was shown to depend on Ngn3 (74). In the antrum, G and D cells differentiate via a common precursor (the G/D cell) and expression of the transcription factor ISL-1 is typical of differentiated D cells (75). In contrast, the transcription factor PDX-1 is essential for G cell maturation (76) with transcription factor Nkx6.1 being a downstream target of PDX-1. Further transcription factors involved in the maturation of antral EC, G and D cells are Nkx6.3, Pax4, and Pax6 (for review, see ref. 71).

3.7 Subepithelial mesenchymal cells

A sheet of subepithelial myofibroblasts (SMF), which are of mesodermal origin (77), surrounds the gastric epithelium. These cells are thought to be derived from bone marrow and/or locally activated fibroblasts in response to TGF-β (78). During embryonic, fetal, and adult life, the endoderm and mesoderm intensely communicate with each other in a bidirectional fashion. For example, elegant tissue recombination studies revealed that the mesoderm holds essential positional information for the correct differentiation of the epithelium (5, 79, 80). Here, secreted morphogens and the formation of gradients play a pivotal role (for review, see ref. 81). Typical morphogens in the stomach are members of the TGF-β superfamily (BMPs, activin) and the hedgehog family (SHH, IHH). For example, SHH is of endodermal origin (parietal cells) communicating with mesenchymal SMFs, which in turn release BMP-4 that signals back to the epithelial cells (Figure 2). Therefore, inhibition of BMP signaling causes parietal cell loss and dysregulated self-renewal of fundic units (53).

Generally, surrounding SMFs provide the microenvironment, topologically specifying epithelial cells, and thus are critical for gastric epithelial cell homeostasis. Of special note, SMFs generate also the specific microenvironment of SSCs called niches. These structures represent also a complex interface connecting the SSCs with the nervous and the blood system allowing a fine-tuned crosstalk between circadian rhythms, various environmental stimuli, and differentiation (82). The crosstalk between SSCs and SMFs is particularly well described for the intestine including Wnt, HH, Notch, PI3K, and BMP pathways (80, 83, 84). Furthermore, SMFs also regulate metastasis (84).

3.8. The anterior-posterior axis

The spatial organization of the gastric epithelium and its glands during embryonic development is rather complex, including at least the following four axes (85): (1) the AP axis from the cardia to the pylorus, (2) a lateral axis from the lesser to the greater curvature (left-right axis), (3) the dorsal-ventral axis, and (4) the individual gland axis from the pit to the base (radial axis). Initial patterning of the endoderm occurs mainly via the AP axis during development (5); whereas patterning along the radial axis is the last to occur during stomach development (86). Particularly these two patterning events continue throughout life and their precision is essential for correct self-renewal of adult fundic and antral units.

Major endodermal transcription factors along the AP axis defining gastric development are Sox2 and Pdx1; the latter being restricted to the antrum, duodenum, and pancreas (5, 87). Mesodermal transcription factors required for stomach development are, for example, Hoxa5, Barx1, Bapx1/Nkx3.2 and Nkx2.5; the latter crossing the pyloric sphincter (5, 85, 88). The mesodermal transcription factor Gata 3 plays a role in the formation of the epithelial stomach-intestine boundary (89). Furthermore, two secreted modulators of the TGF-β superfamily, i.e., mesodermal gremlin and endodermal nephrocan, are involved in pyloric border formation (89).

Fundic and antral units differ drastically (i.e., parietal cells mainly found in fundic units; different SMCs and different populations of endocrine cells present in fundic and antral units, respectively; fundic MNCs differ from AGCs). Thus far, the complex gene regulatory network along the AP axis responsible for the maintenance of a relatively sharp corpus-antrum-transitional zone in the adult is not understood in detail. Certainly a major regulator is PDX-1, which is expressed in G cells and AGCs and is essential for the maturation of G cells; also its expression is diametric to that of SHH (85). Furthermore, mesenchymal Hoxa5 also plays a role in regulating the regionalization of the stomach epithelium (88).

4. DYSREGULATED MUCOSAL SELF-RENEWAL

Dysregulated gastric self-renewal is typical of specific diseased states. For example, expansion of the SMC lineage (foveolar hyperplasia) has been observed in Menetrier's disease (56), in mice overexpressing TGF-α (56) and in mice with a loss of parietal cell function (40). Of note, foveolar hyperplasia in Menetrier's patients and in mice overexpressing TGF-α is accompanied by ectopic expression of the antral transcription factor PDX1 throughout the fundus (31).

Dysregulated gastric self-renewal has also been observed in Tff1-deficient mice which show an expanded SMC population at the expense of parietal cells in the fundic units (33) and amplification of SMCs and AGCs in the antral units (34). All Tff1-deficient mice spontaneously developed antropyloric adenoma and 30% of them showed carcinoma (90).

Furthermore, dysregulated gastric self-renewal can also lead to abnormal differentiation, where gastric epithelial cells are replaced by epithelial cells of other types (metaplasia). This is typically observed as a premalignant condition particularly in the "intestinal" type of gastric cancer, which is characterized by a hierarchy of well-defined lesions in the following order: chronic gastritis, gastric atrophy, metaplasia, and dysplasia (91). Nowadays, two metaplastic premalignant lineages are established, i.e., intestinal metaplasia (IM) and TFF2/spasmolytic polypeptide expressing metaplasia (SPEM; also known as pseudopyloric metaplasia or mucous metaplasia or antralization of the stomach) (for reviews, see refs. 7, 92). As a modification of the original model of intestinal type gastric cancer (91), both IM and SPEM are now considered

as commensals for the neoplastic process (93). Within the last years it has become clear that SPEM develops from both trans-differentiation of mature chief cells as well as on arrest of MNC trans-differentiation into chief cells (66, 94). This dysregulated trans-differentiation of the MNC-zymogenic cell lineage into SPEM was observed in various settings after parietal cell loss, in histamine-deficient mice, and in amphiregulin-deficient mice (55, 66, 93). Thus, a defective parietal cell function is expected to trigger the development of SPEM (see Figure 2). Furthermore, progression of SPEM to IM, e.g. in intestinal goblet cells, has been observed in amphiregulin-deficient mice (55) and this consecutive relationship is strengthened by gene expression profiling (95). By field cancerization, a single IM can then expand to form a dysplastic lesion (96). IM aberrantly expresses the intestine-specific transcription factor CDX2 that has been shown to repress SHH expression (97). Thus, SHH and CDX2 clearly have opposing roles, with SHH being essential for proper fundic unit differentiation and CDX2 being required for intestinal transformation. Taken together, SPEM is the result of a dysregulated self-renewal of zymogenic cells and this metaplastic state can even evolve to IM finally silencing the fundic differentiation program.

Dysregulated gastric self-renewal has also been observed in response to inflammatory conditions. For example, the proinflammatory cytokine interferon γ induced MNC hypertrophy and SPEM (98). Here, the dysregulated self-renewal probably occurs as a consequence of the disrupted organizer function of parietal cells, because inflammatory conditions have been shown to inhibit SHH expression and gastric acid secretion (44).

Homeostatic self-renewal of parietal cells is also disturbed by the proton pump inhibitor omeprazole (99). The reason for this might be that omeprazole also inhibits SHH expression, and this inhibition is even additive with that of IL-1β (44). Thus, there is a tight connection linking inflammation, acid suppression, and SPEM/self-renewal (100).

Only recently, SHH has been shown to act also as a macrophage chemoattractant during the immune response to *H. pylori* and mice with a parietal cell specific deletion of *Shh* did not develop gastritis (101). Thus, inflammation, immune response, acid secretion and self-renewal are intimately linked by SHH.

Chronic inflammatory responses play decisive roles at different stages of tumor development and for gastric cancer (7, 102). Here, dysregulated self-renewal in the course of chronic inflammation is the basis for the development of neoplasias (16, 103). Of special note, besides disrupting the organizer function of parietal cells, chronic inflammation (but not acute injury or acute inflammation) has also been reported to allow recruitment of bone marrow-derived cells to the gastric mucosa, which then progress to cancer (7, 104).

5. PERSPECTIVE

Understanding self-renewal of the gastric epithelium is a prerequisite for understanding gastric carcinogenesis (8). For example, stomach cancer was still the cause for 10% of total cancer-related deaths worldwide in 2008, with a clear preponderance in developing countries (105). Important future aims would be defining the bidirectional crosstalk between epithelial and mesenchymal cells in detail and how the different morphological axes are maintained in the adult stomach. Here, we still can learn a lot from embryology. This mesenchymal microenvironment also plays a key role for gastric stem cell homeostasis and the development of cancer stem cells (84). Furthermore, signals from the outside world, i.e., the complex gastric microbiota (at least 128 phylotypes) and the influence of diets represent important fields for future studies (26, 106, 107).

Applications in regenerative medicine will be a major challenge for translational studies. The directed differentiation of pluripotent stem cells (PSCs) into gastric antral units would be a first goal. For example, human PSCs have already been differentiated into liver hepatocytes, pancreatic endocrine cells, and intestinal tissue *in vitro* (108).

6. ACKNOWLEDGMENTS

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Abbreviations: AGC, antral gland cell; AP, anterior-posterior; AR, amphiregulin; BMP, bone morphogenetic protein; ECL, enterochromaffin-like cell; EGF, epidermal growth factor; HB-EGF, heparin-binding EGF-like growth factor; HH, Hedgehog; IHH, Indian hedgehog; IM, intestinal metaplasia; MNC, mucous neck cell; Ngn, neurogenin; PC, parietal cell; PSC, pluripotent stem cell; PTCH, Shh receptor Patched; SHH, Sonic hedgehog; SMC, surface mucous cell; SMF, subepithelial myofibroblast; SPEM, spasmolytic polypeptide expressing metaplasia; SSC, somatic stem cell; TFF, trefoil factor family; TGF, transforming growth factor

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