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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Stomach Organ and Cell Lineage Differentiation: From Embryogenesis to Adult Homeostasis

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SUMMARY

This review details the current understanding of gastric specification during development and adult homeostasis.

Gastric diseases cause considerable worldwide burden. However, the stomach is still poorly understood in terms of the molecular–cellular processes that govern its development and homeostasis. In particular, the complex relationship between the differentiated cell types located within the stomach and the stem and progenitor cells that give rise to them is significantly understudied relative to other organs. In this review, we highlight the current state of the literature relating to specification of gastric cell lineages from embryogenesis to adulthood. Special emphasis is placed on substantial gaps in knowledge about stomach specification that we think should be tackled to advance the field. For example, it has long been assumed that adult gastric units have a granule-free stem cell that gives rise to all differentiated lineages. Here, we point out that there are also other models that fit all extant data, such as long-lived, lineage-committed progenitors that might serve as a source of new cells during homeostasis. ***(Cell Mol Gastroenterol Hepatol 2016;2:546–559; http://dx.doi.org/10.1016/j.jcmgh.2016.05.006)***

Keywords: Granule-Free; Lineage Tracing; Metaplasia.

The adult stomach produces acid and enzymes that aid in food digestion and kill microbes, and it regulates delivery of food to the small intestine. The stomach also works remotely via its endocrine cells, which send distal signals to help coordinate hunger/satiety and Ca^{++} homeostasis.[1] The stomach comprises tissues originating from all 3 embryonic germ layers including the ectodermally derived enteric nerves, mesodermally derived smooth muscle and mesenchymal cells, and the endodermally derived epithelium lining the lumen of the stomach. In this review, we largely focus on the processes governing epithelial development and homeostasis. The glandular epithelium in most mammals is arranged into 2 principal compartments: corpus and antrum (Figure 1). Both compartments are composed of a single layer of epithelial cells arranged into invaginated units. The principal cellular constituents of corpus units include the surface mucous (pit/foveolar) cells, acid-secreting parietal cells, mucous neck cells, digestive-enzyme secreting (zymogenic) chief cells, endocrine cells, and isthmal cells with undifferentiated features that likely serve as multipotent stem cells. The antral units can contain some chief and parietal cells depending on the species, but primarily are composed of pit/foveolar cells on the surface and deep glandular cells that express markers of both mucous neck cells and chief cells (Figure 1). Scattered throughout the corpus and antrum are the rarer endocrine cells, each type named for the predominant hormone they secrete (eg, gastrin-secreting G cells of the antrum).

Understanding cellular development in the normal stomach should help us better understand the origins of gastric cancer, one of the most common causes of cancer death worldwide.[2] Most gastric cancer is initiated in the setting of chronic infection with the bacterium *Helicobacter pylori*, which is estimated to infect more than half the world's population.[3] In addition to increasing the risk for gastric cancer, it is also the cause of most ulcers of the stomach and duodenum. Those patients at risk for gastric cancer show a response to infection with *H pylori* characterized by an overall loss of specific differentiated cell lineages, a condition known pathologically as *chronic atrophic gastritis*. Molecular and cellular mechanistic studies have shown that chronic atrophic gastritis is not characterized simply by a chronic inflammatory infiltrate (gastritis) and the loss of acid-secreting parietal cells (oxyntic atrophy), but also by changes in differentiation of the chief cells (metaplasia).[4–6] A thorough understanding of the processes that control the specification of cells within the gastric epithelium during development and adult homeostasis could be crucial to deciphering the disease etiology, particularly the metaplastic changes that arise after *H pylori* infection. However, currently in the stomach, in both the adult and embryonic state, there is a rudimentary understanding of the cell lineage relationships. Furthermore, there is also a marked lack of lineage-specific markers and genetic tools for studying development and differentiation. In this review,

Abbreviations used in this paper: **BMP, bone morphogenetic protein; ECL, enterochromaffin-like; FGF, fibroblast growth factor; RA, retinoic acid; Shh, sonic hedgehog.**

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2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2016.05.006

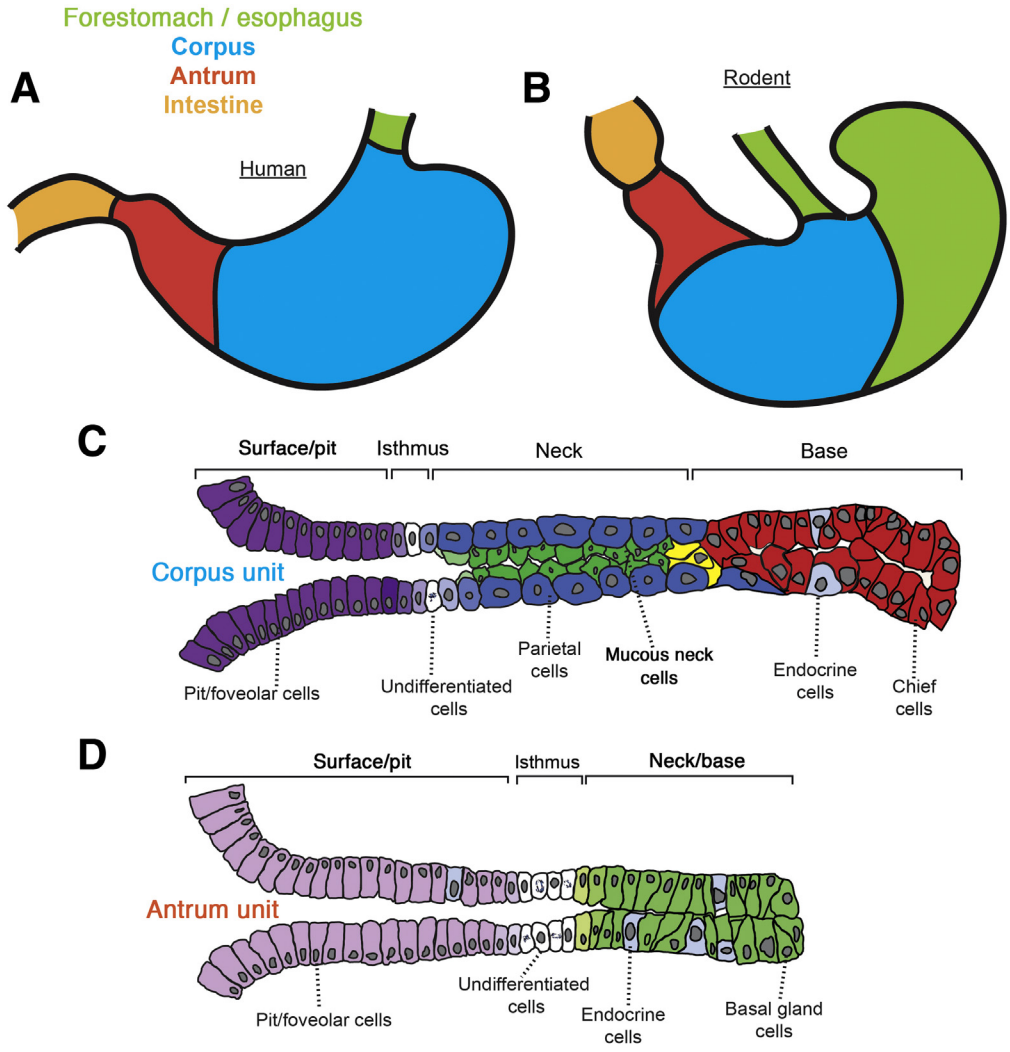

Figure 1. Architecture of the adult stomach and the organization of corpus and antral units. (*A*) The adult human stomach is composed entirely of glandular epithelium (*blue, red*), whereas (*B*) the adult rodent stomach contains a squamous-epithelium–lined forestomach (*green*), in addition to a glandular stomach. (*C*) Adult corpus units contain pit/foveolar cells (*purple*), isthmal stem cells (*white*), parietal cells (*blue*), mucous neck cells (*green*), endocrine cells (*light blue*), and chief cells (*red*). Cells transitioning from neck to chief cells are indicated in *yellow*. (*D*) Antral units primarily contain pit/fovelar cells (*light purple*), proliferative isthmal stem cells (*white*), basal gland cells (*light green*) similar to mucous neck cells with a hint of chief cell differentiation, and endocrine cells (*grey*). Note that up to half of human antral gastric units also contain parietal cells (not shown).

we highlight the relatively limited information we have about stomach specification, starting with the embryo and continuing through adulthood.

One caveat is that most of the work on mammalian gastric development has been in rodents. Much work also has been performed in nonmammalian model organisms such as in chicks. The degree to which human gastric development follows the same rules as rodents—let alone nonmammalian vertebrates—is not known in most cases. Because of our relatively close ancestry, it is likely that most developmental patterns will be similar between human beings and these model organisms. However, there are some known differences. For example, the human stomach is lined entirely by glandular units while the rodent stomach contains an additional anatomic compartment known as the forestomach, which is not glandular at all, but rather is lined with squamous epithelium (Figure 1). In the human stomach, up to half of antral units harbor parietal cells, whereas they are absent from antral units in the rodent.[7] In addition, chief cells in the rodent express gastric intrinsic factor, whereas intrinsic factor is expressed by parietal cells in human beings.[8]

Early Specification

Gastric specification in the mouse begins during gastrulation with derivation of the endodermal germ layer that eventually will seed the epithelial lining of the digestive, respiratory, and urogenital systems. The endoderm germ layer is formed by the ingression of epiblast cells through the primitive streak. As the cells exit the primitive streak, they arrange into a single-layered epithelial sheet on the outside of the embryo (embryonic day [E]6–E7.5). This sheet forms pockets at the anterior (future foregut) and posterior (future hindgut) end of the embryo and progressively zippers into a complete gut tube. Zippering of the gut tube, mesodermal growth, and embryonic turning transform the endodermal sheet on the outside of the embryo into an internal tube consisting of 3 major regions: foregut, midgut, and hindgut (E7.5–E9).[9] Regional and subsequent organ identity is assembled within the naive, as yet unspecified, gut tube through the integration of signaling inputs from mesodermal tissues located apposed to the endoderm and the endodermal progenitors themselves.[10] One recognizable