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REVIEW

Translating Developmental Principles to Generate Human Gastric Organoids

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SUMMARY

This review discusses the basics of stomach morphology, function, and development, and explains the technical process of generating human gastric organoids. Important gaps in understanding why epithelial-mesenchymal interactions are essential for the development and overall function of the human stomach are highlighted.

Gastric diseases, including peptic ulcer disease and gastric cancer, are highly prevalent in human beings. Despite this, the cellular biology of the stomach remains poorly understood relative to other gastrointestinal organs such as the liver, intestine, and colon. In particular, little is known about the molecular basis of stomach development and the differentiation of gastric lineages. Although animal models are useful for studying gastric development, function, and disease, there are major structural and physiological differences in human stomachs that render these models insufficient. To look at gastric development, function, and disease in a human context, a model system of the human stomach is imperative. This review details how this was achieved through the directed differentiation of human pluripotent stem cells in a 3-dimensional environment into human gastric organoids (HGOs). Similar to previous work that has generated human intestine, colon, and lung tissue in vitro, HGOs were generated in vitro through a step-wise differentiation designed to mimic the temporal-spatial signaling dynamics that control stomach development in vivo. HGOs can be used for a variety of purposes, including genetic modeling, drug screening, and potentially even in future patient transplantation. Moreover, HGOs are well suited to study the development and interactions of nonepithelial cell types, such as endothelial, neuronal, and mesenchymal, which remain almost completely unstudied. This review discusses the basics of stomach morphology, function, and developmental pathways involved in generating HGOs. We also highlight important gaps in our understanding of how epithelial and mesenchymal interactions are essential for the development and overall function of the human stomach. *(Cell Mol Gastroenterol Hepatol 2018;5:353–363; https://doi.org/10.1016/j.jcmgh.2017.12.014)*

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The stomach's main role is to digest macronutrients. Chemical and mechanical digestion breaks down and prepares macronutrients for proper absorption once they are emptied into the intestine. The stomach also plays a part in regulating satiety.[1] A diverse set of endocrine cells secrete a variety of hormones and neuropeptides, including gastrin, ghrelin, and somatostatin, to regulate appetite and gastric acid secretion.

The 2 main regions of the human stomach are the proximal corpus/fundus and the distal antrum[1–3] (Figure 1). In the corpus, the epithelium is organized into fundic glands that contain mucus-producing cells along the surface and within the gland, acid-secreting parietal cells, pepsinogen-secreting chief cells, stem cells, endocrine cells, and rare tuft cells.[2] The antrum gland unit also contains mucus cells along the surface and within the gland, endocrine cells, including gastrin-producing cells that are unique to the antrum, and rare tuft cells, but has far fewer parietal and chief cells.[4] It does, however, contain LGR5+ stem cells that give rise to all other cell types within the antrum.[2] Both gland units are organized into 3 basic sections: a deep base, medial isthmus, and surface pit. Although undifferentiated stem cells make up the isthmus of both fundic and antral glands, the isthmus is nearer to the surface in fundic glands and nearer to the base in antral glands. Parietal, chief, and endocrine cells reside in the base of fundic glands, whereas endocrine and LGR5+ stem cells, along with rare parietal and chief cells, reside in the base of antral glands. Rare tuft cells can be found on the surface of both types of glands.[1,2]

Stomach Morphology Across Species

Historically, functional studies of gastric development, lineage commitment, and disease have predominantly

Abbreviations used in this paper: BMP, bone morphogenetic protein; e, embryonic day; ECL, enterochromaffin-like; ENS, enteric nervous system; ENCC, enteric neural crest cell; GI, gastrointestinal; HDGC, hereditary diffuse gastric cancer; HGO, human gastric organoid; hPSC, human pluripotent stem cell; PSC, pluripotent stem cell; Shh, Sonic hedgehog; 3-D, 3-dimensional.

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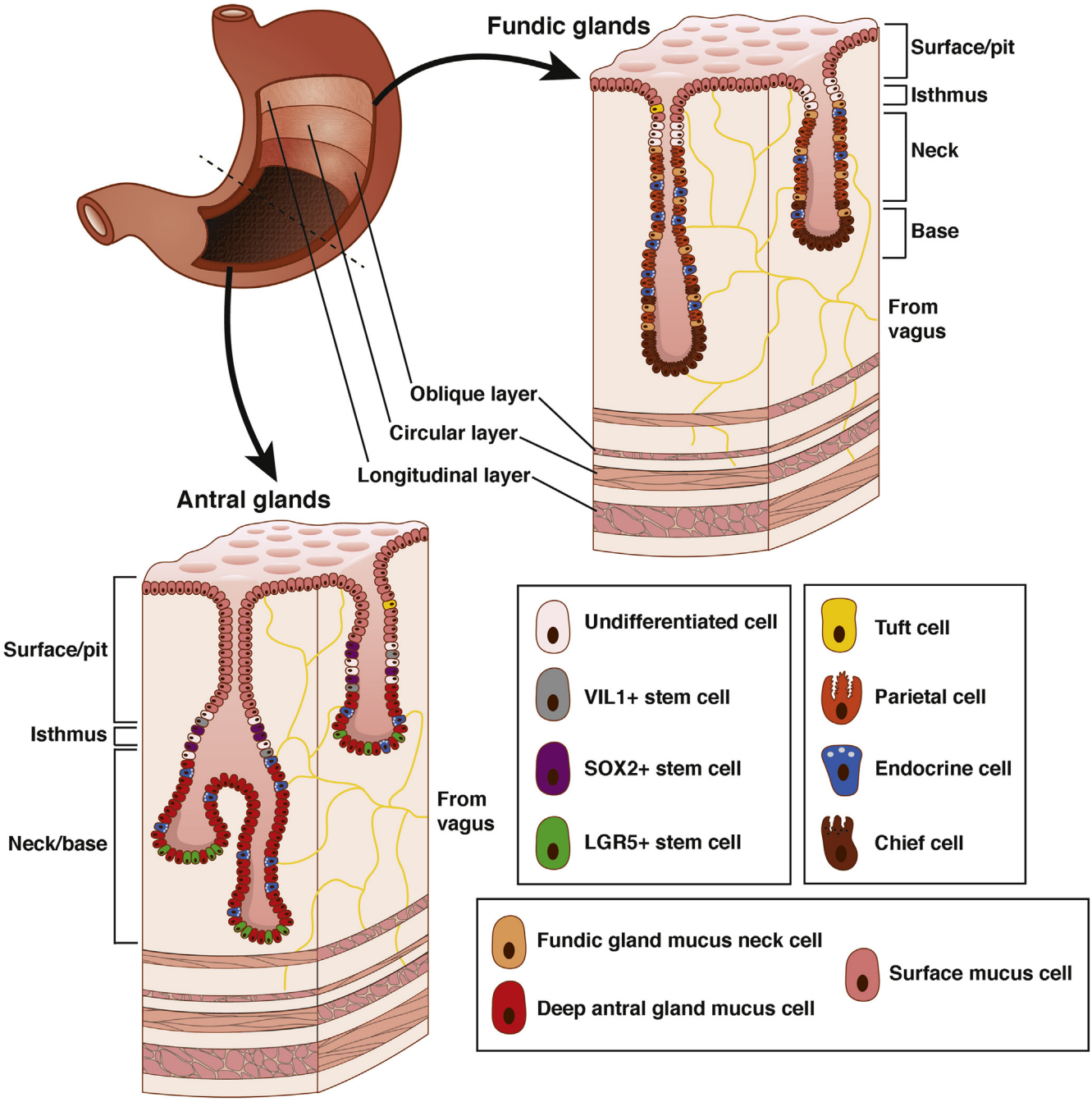

Figure 1. Morphology and germ layer contributions of the adult stomach with specific cell types of the antral and fundic glands. The adult stomach comprises an endoderm-derived epithelial lining surrounded by mesoderm-derived smooth muscle and ectoderm-derived nerves and glia. Fundic glands are comprised of chief cells (brown) in the base, parietal (orange), endocrine (blue), and mucus (tan) cells throughout the neck, stem cells (white) in the isthmus, and mucus (pink) and tuft (yellow) cells on the surface. Antral glands comprise endocrine (blue), mucus (red), and LGR5+ (green) stem cells within the base, VIL1+ (grey), SOX2+ (purple), and other (white) stem cells in the isthmus, and mucus (pink) and tuft (yellow) cells along the surface. Myenteric neurons innervating the submucosa and muscle layers of the stomach not only stimulate hormonal secretion, including gastrin, somatostatin, and histamine, to aid in chemical digestion, but also play a role in regulating muscular contraction to aid in mechanical digestion.

used murine models. However, stomach morphology and regionalization differ greatly across species.[1,2] Unlike the human stomach, the murine stomach contains an additional region, the forestomach, that is anterior to the corpus/fundus and contains a stratified squamous, rather than glandular, epithelium.[2] In addition, parietal cells are absent from murine antral gland units.[1] It is likely that the embryonic development of the stomach similarly differs