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Patterning the gastrointestinal epithelium to confer regional-specific functions

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ABSTRACT

The gastrointestinal (GI) tract, in simplest terms, can be described as an epithelial-lined muscular tube extending along the cephalocaudal axis from the oral cavity to the anus. Although the general architecture of the GI tract organs is conserved from end to end, the presence of different epithelial tissue structures and unique epithelial cell types within each organ enables each to perform the distinct digestive functions required for efficient nutrient assimilation. Spatiotemporal regulation of signaling pathways and downstream transcription factors controls GI epithelial morphogenesis during development to confer essential regional-specific epithelial structures and functions. Here, we discuss the fundamental functions of each GI tract organ and summarize the diversity of epithelial structures present along the cephalocaudal axis of the GI tract. Next, we discuss findings, primarily from genetic mouse models, that have defined the roles of key transcription factors during epithelial morphogenesis, including p63, SOX2, SOX15, GATA4, GATA6, HNF4A, and HNF4G. Additionally, we examine how the Hedgehog, WNT, and BMP signaling pathways contribute to defining unique epithelial features along the cephalocaudal axis of the GI tract. Lastly, we examine the molecular mechanisms controlling regionalized cytodifferentiation of organ-specific epithelial cell types within the GI tract, concentrating on the stomach and small intestine. The delineation of GI epithelial patterning mechanisms in mice has provided fundamental knowledge to guide the development and refinement of three-dimensional GI organotypic culture models such as those derived from directed differentiation of human pluripotent stem cells and those derived directly from human tissue samples. Continued examination of these pathways will undoubtedly provide vital insights into the mechanisms of GI development and disease and may afford new avenues for innovative tissue engineering and personalized medicine approaches to treating GI diseases.

1. Introduction

The gastrointestinal (GI) tract is an epithelial-lined muscular tube extending from the oral cavity to the anus. Organs of the Gl tract including the esophagus, stomach, small intestine, and colon function in coordination with the pancreas, liver, and gall bladder to perform the life-sustaining tasks of digestion and absorption. The GI tract also contains the body's largest reservoir of lymphoid tissue and an enteric nervous system with more neurons than the spinal cord. The general architecture of GI tract organs is conserved with all embryonic germ layers contributing to tissues of each organ (Fig. 1). The innermost mucosal layer consists of an endoderm-derived epithelium. The epithelium is supported by lamina propria, a connective tissue layer, and muscularis mucosae, a thin, smooth muscle layer, both derived from mesoderm. Underlying the mucosa is the submucosa, which contains mesoderm-derived loose collagenous tissue, adipose tissue, and large blood and lymphatic vessels. Ectoderm-derived enteric ganglia also reside within the submucosa. The muscularis externa, a thick layer of mesoderm-derived muscle containing additional enteric ganglia, wraps around the mucosal and submucosal layers and generates the peristaltic forces that move contents through the gut. Generally, the muscularis externa consists of smooth muscle; however, the esophagus and anal sphincter contain skeletal muscle. Finally, the GI tract is covered by a mesoderm-derived adventitia or serosa.

Although the general three-dimensional structure of GI organs is conserved, each organ, and even specific regions within an organ, perform specialized functions that together culminate in efficient nutrient assimilation. In particular, unique features of each organ's epithelium provide the foundation for the regional-specific organ functions essential for digestion and absorption. The structure of the epithelium and the presence of organ-specific epithelial cell types drive regional-specific functions along the GI tract. The goal of this review is to explain how key transcription factors and signaling pathways contribute to regionalization of the GI epithelium. Investigations using

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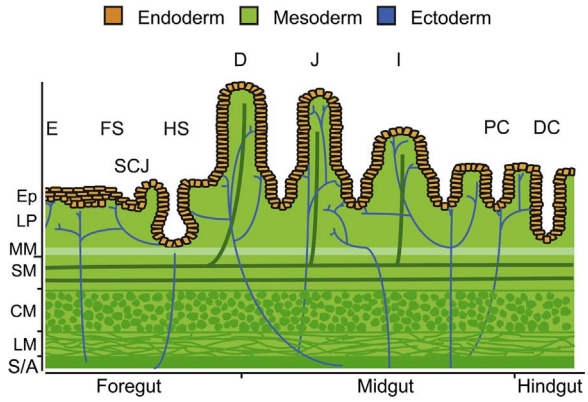

Fig. 1. All embryonic germ layers contribute to the tissue layers of GI organs. Divided into three regions, the endoderm (orange) gives rise to the innermost epithelial layer of all GI organs. The stratified squamous epithelium of the esophagus (E) and forestomach (FS) as well as the simple columnar epithelium of the hindstomach (HS) and proximal duodenum (D) of the small intestine originate from foregut endoderm. The junction between the stratified squamous epithelium and simple columnar epithelium is referred to as the squamocolumnar junction (SCJ). Midgut endoderm gives rise to the simple columnar epithelium of the distal duodenum, jejunum (J), and ileum (I) of the small intestine as well as to the simple columnar epithelium of the proximal colon (PC). The simple columnar epithelium of the distal colon (DC) arises from hindgut endoderm. Beneath the epithelium (Ep), the lamina propria (LP), muscularis mucosae (MM), submucosa (SM), vasculature, lymphatics, and muscularis externa (CM, circular muscle; LM, longitudinal muscle) layers develop from mesoderm (green). The enteric nervous system is derived from ectoderm and ganglia reside within the submucosa and the muscularis externa (blue). The gut tube is covered by a mesoderm derived adventitia (A) or serosa (S). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

genetically modified mouse models have been the primary source of information regarding the mechanisms through which specific transcription factors and signaling pathways orchestrate regionalization of the GI epithelium during development. More recently, studies using in vitro three-dimensional organoid cultures have also shed light on regionalizing mechanisms. The first half of this review will discuss how transcription factors and upstream signaling pathways shape the various three-dimensional structures of each GI organ's epithelium. The second half will discuss how transcription factors and upstream signaling pathways control specific cytodifferentiation programs in the GI tract, with particular attention given to the gastric epithelium and the intestinal epithelium.

2. Generating uniquely structured epithelia along the cephalocaudal axis of the GI tract

2.1. The diversity of epithelial structures within the GI tract

Before discussing the molecular mechanisms underlying architectural patterning of the GI epithelium, we must first appreciate the structural differences that exist among epithelia of the GI tract and how each GI organ's epithelial structure directly supports its unique digestive and absorptive functions. The esophagus is essentially a muscular tube that transports ingested materials from the oral cavity to the stomach. Its epithelium is stratified, with multiple cell layers providing the protection needed in the face of the frictional forces generated by the passage of undigested and partially digested materials. In rodents, the esophageal epithelium is keratinized, and it extends into the proximal stomach forming a gastric region known as the forestomach. Absent in human stomach, the rodent forestomach serves as a holding zone for food and is responsible for some degree of mechanical digestion (San Roman and Shivdasani, 2011). The simple columnar nascent epithelium of the esophagus/forestomach undergoes morphogenesis during development to give rise to a mature multilayered epithelium that consists of a basal layer of proliferating cells and suprabasal layers of differentiated cells (Fig. 1) (Zhang et al., 2016).

There is a distinct change in the epithelial architecture of the GI tract at the transition from the esophagus/forestomach to the glandular hindstomach (Fig. 1). As the site of chemical and mechanical digestion, the simple columnar glandular epithelium of the stomach is ideally suited for highly efficient secretion of acid and production of digestive enzymes. The boundary between the stratified squamous epithelium of the esophagus/forestomach and the simple columnar epithelium of the glandular stomach is referred to as the squamocolumnar junction (SCJ) (Fig. 1). Understanding how these different epithelial structures are generated and maintained at the SCJ is essential because metaplasia occurs in these tissues in GI diseases including Barrett's esophagus, esophageal adenocarcinoma, and gastric adenocarcinoma.

The small intestine is the site of nutrient absorption and is also a fundamental component of the innate immune system. Essential for the function of the small intestine is the large surface area of its simple columnar epithelium, which has many folds with deep grooves, called crypts, and finger-like projections, called villi (Fig. 1) (Chin et al., 2017; Noah et al., 2011; Thompson and Battle, 2014; Walton et al., 2016a). The small intestine can be divided into three functional regions: duodenum, jejunum, and ileum. The epithelial cells of the duodenum synthesize digestive enzymes, which are secreted or localized to the brush border membrane. These enzymes, together with bile produced by the liver and pancreatic digestive enzymes, complete the digestion of proteins, fats, and carbohydrates (Binder and Reuben, 2005; Jeejeebhoy, 2002). The jejunal epithelium accomplishes the bulk of nutrient absorption (Binder and Reuben, 2005; Davis and Attie, 2008; Jeejeebhoy, 2002). The ileal epithelium is responsible for absorption of vitamin B12 in addition to bile salts, which are recycled to the liver (Binder and Reuben, 2005; Davis and Attie, 2008; Jeejeebhoy, 2002). Understanding how the small intestinal epithelium is appropriately regionalized should provide fundamental insights into short bowel syndrome (SBS) and may lead to new SBS treatment options.

Similar to the small intestine, the function of the epithelium of the large intestine is absorption. Lined by a simple columnar epithelium arranged as crypts but lacking villi, these epithelial cells primarily absorb water and electrolytes (Fig. 1) (Jeejeebhoy, 2002). Like the small intestine, the large intestine can also be divided into three regions: cecum, colon, and rectum. Although the epithelia of the small and large intestines share many features, the presence of villi and Paneth cells in the small intestine is one distinguishing feature. Understanding how the epithelium of these organs is specialized and regionalized is important considering that this process can be disrupted in disease. For example, Paneth cell metaplasia, or the abnormal presence of Paneth cells in the large intestine, sometimes occurs in inflammatory bowel disease and colorectal cancer (Tanaka et al., 2001; Wada et al., 2005).

2.2. Key transcription factors and signaling molecules that control structural patterning of GI tract epithelia

2.2.1. p63, master regulator of stratified squamous epithelial morphogenesis

The transcription factor p63 is considered to be a master regulator of stratified squamous epithelium development (Fig. 2) (Daniely et al., 2004; Koster et al., 2004; Mills et al., 1999; Romano et al., 2012; Senoo et al., 2007; Wang et al., 2011; Yang et al., 1999; Yu et al., 2005). p63 is required to establish stratified epithelia and, therefore, is typically absent from columnar epithelia. Studies of p63 knockout mouse embryos reveal that proper epithelial morphogenesis in the esophagus and forestomach requires p63, with its absence posteriorizing this domain (Wang et al., 2011). Specifically, esophageal or forestomach epithelium lacking p63 fails to stratify and instead remains columnar. Columnar-cell type cytokeratins persist in p63-/- esophagus and forestomach in place of stratified-cell type cytokeratins. Alterations in