Regulation of Gastrointestinal Mucosal Growth

Second Edition

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Regulation of Gastrointestinal Mucosal Growth

Second Edition

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COLLOQUIUM SERIES ON INTEGRATED SYSTEMS PHYSIOLOGY: FROM MOLECULE TO FUNCTION TO DISEASE #69

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ABSTRACT

The mammalian gastrointestinal mucosa is a rapidly self-renewing tissue in the body, and its homeostasis is preserved through the strict regulation of epithelial cell proliferation, growth arrest, and apoptosis. The control of the growth of gastrointestinal mucosa is unique and, compared with most other tissue in the body, complex. Mucosal growth is regulated by the same hormones that alter metabolism in other tissues, but the gastrointestinal mucosa also responds to host events triggered by the ingestion and presence of food within the digestive tract. These gut hormones and peptides regulate the growth of the exocrine pancreas, gallbladder epithelium, and the mucosa of the oxyntic gland region of the stomach and the small and large intestines. Luminal factors, including nutrients or other dietary factors, secretions, and microbes that occur within the lumen and distribute over a proximal-to-distal gradient, are also crucial for maintenance of normal gut mucosal regeneration and could explain the villous-height-crypt-depth gradient and variety of adaptation, since these factors are diluted, absorbed, and destroyed as they pass down the digestive tract. Recently, intestinal stem cells, cellular polyamines, and noncoding RNAs are shown to play an important role in the regulation of gastrointestinal mucosal growth under physiological and various pathological conditions. In this book, we highlight key issues and factors that control gastrointestinal mucosal growth and homeostasis, with special emphasis on the mechanisms through which epithelial renewal and apoptosis are regulated at the cellular and molecular levels.

KEY WORDS

gastrointestinal mucosa; gut mucosal growth; epithelial renewal; proliferation; growth arrest; apoptosis; mucosal atrophy; polyamines; intestinal stem cells; luminal factors

Preface to the Second Edition

As with any new edition of a book, we hope that the second edition is better than the previous one. We feel strongly that this second edition is such an improvement, because there has been significant progress in the field since the first edition published in 2010. Although the way of presentation and philosophy remain the same as in the first edition, the basic outline of materials now includes a new chapter on posttranscriptional regulation of gut epithelial integrity by non-coding RNAs. Since non-coding RNAs, including microRNAs (miRNAs) and long ncRNA (lncRNAs), are a novel class of regulators that modulate gut epithelial homeostasis, this addition is a significant improvement. Moreover, we also highlight the new advances in the control of gut mucosal regeneration and protection by intestinal epithelial-specific stem cells, luminal microbiota, and cellular polyamines under physiological and various pathological conditions. We further analyze the mechanisms by which these factors modulate gut epithelial cell division, migration, differentiation, apoptosis, and cell-to-cell interaction.

In addition to these new findings included in the present edition of the book, a number of corrections which previously escaped the author's attention have been made right; about 95 new references have been added, and two new figures and one table illustrating the new text have been added. It is hoped that readers will find the new material to be useful and provocative for their work and understanding of this key research area.

We greatly appreciate our own students, residents, and research fellows who point out errors and areas of ambiguity. Several colleagues from our institution and other universities have added their suggestions and criticisms during the revision as well. We are thankful for their interest and help. Finally, we wish to thank Mr. Joe Cho and Mr. Jovan Carreon, Morgan & Claypool Life Sciences, for their help and communication, and Drs. D. Neil Granger and Joey Granger for organizing this book series on *Integrated Systems Physiology*.

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CHAPTER 1

Introduction

The epithelium of mammalian gastrointestinal (GI) mucosa is a rapidly self-renewing tissue in the body, and its integrity depends on a complex interplay between processes involved in cell proliferation, differentiation, migration, and apoptosis. Under physiological conditions, undifferentiated epithelial cells continuously replicate in the proliferating zone within the crypts and differentiate as they migrate up the luminal surface of the colon and the villous tips in the small intestine. To maintain stable numbers of enterocytes, cell division must be dynamically counterbalanced by apoptosis, a fundamental biological process involving selective cell deletion to regulate tissue homeostasis. Apoptosis occurs in the crypt area, where it maintains the critical balance in cell number between newly divided and surviving cells, and at the luminal surface of the colon and villous tips in the small intestine, where differentiated cells are lost. This rapid dynamic turnover rate of the intestinal epithelium is tightly controlled at different levels by numerous intracellular and extracellular factors.

Consistent with most other tissues in the body, the regulation of the growth of GI mucosa is unique and affected by the same hormones such as insulin, growth hormone, thyroxine, and cortisol that alter metabolism in other tissues. However, the GI mucosa also responds to a host of events triggered by the ingestion and presence of food within the digestive tract. Food directly interacts with the GI mucosa and results in the release of several gut hormones that specifically regulate only tissues of the GI tract and alter the rate of mucosal growth. Compared with gut hormones, various factors theorized to affect the mucosa within the lumen are less well defined. These factors include secretions (especially those of the pancreas and liver), luminal nutrition, and additional dietary constituents that stimulate growth independent of their nutritive value. Although physiological significance of these factors remains to be fully investigated, the common property of these stimulants, which accounts for their scientific interest, is that they occur within the lumen, distributed over a proximal-to-distal gradient. These luminal factors are diluted, absorbed, and destroyed as they pass down the GI tract, therefore, their effects on the mucosa also decrease distally. For many years, this mechanism has been proposed to explain the villous-height-crypt-depth gradient and a variety of adaptations that occurs after exposure of portions of the gut to luminal contents, such as GI bypass surgery.

2 REGULATION OF GASTROINTESTINAL MUCOSAL GROWTH

In this section, we overview the new advance in the regulation of GI mucosal growth, particularly the involvement of intestinal stem cells (ISC) in epithelial renewal and cellular signals that are activated during adaptation and control epithelial cell division and apoptosis. We examine the trophic properties of a variety of gut peptides and luminal factors and some of the hypotheses invoked to explain the gradient-oriented nature of mucosal growth. We also review the roles of cellular polyamines in GI mucosal growth and analyze in some detail the mechanisms by which polyamines regulate expression of various growth-related genes at both transcription and posttranscription levels. Finally, we highlight the importance of novel class of regulators, non-coding RNAs (ncRNAs) including microRNAs (miRNAs) and long ncRNA (lncRNAs), in the regulation of gut epithelial cell proliferation, apoptosis, migration, and cell-to-cell interactions and further analyze the mechanisms through which ncRNAs modulate the stability and translation of target mRNAs.

CHAPTER 2

Intestinal Architecture and Development

The architecture of GI tract and its developmental features of different segments have been well defined. Several excellent review articles in this area are readily available [1–5]. Here, we only provide a brief overview on GI architecture and its developmental aspects that are relevant to our understanding of GI mucosal growth and regulation.

2.1 MUCOSAL WALL ARCHITECTURE

The primary functions of GI tract include digestion and absorption of nutrients, secretions, and immunoresponse. The unique architecture of the GI tract facilitates these functions including multiple levels of infolding that result in an immense surface area thus allowing maximal nutrient absorption. The wall of the intestine is conventionally described in terms of its component layers and these layers are not separated entirely one another, but are joined together by connective tissue and by the neural and vascular elements. All segments of the GI tract are divided into four layers: the mucosa (epithelium, lamina propria and muscular mucosae), the submucosa, the muscularis propria (inner circular muscle layer, intermuscular space, and outer longitudinal muscle layer), and the serosa (Figure 1). Mucosa is the innermost layer, which is structurally and functionally the most complex and important area. The mucosal surfaces of the body are the areas where important absorptive function occurs. The mucosa consists of three layers. The first layer facing the intestinal lumen is made up of epithelial cells, which is a single layer in the GI tract and is attached to a basement membrane overlying the second layer, the lamina propria which consists of subepithelial connective tissue and lymph nodes, underneath which is the third and deepest layer called muscularis mucosae. This is a continuous sheet of smooth muscle cells that lies at the base of the lamina propria. The entire mucosa rests on the submucosa, beneath which is the muscularis propria. The outermost layer is named as the serosa or, it lacks an outer layer of mesothelial cells, the adventitia. The submucosa consists of a variety of inflammatory cells, lymphatics, autonomic nerve fibers and ganglion cells. This area is also a branching and distribution zone for arteries and small venous channels.

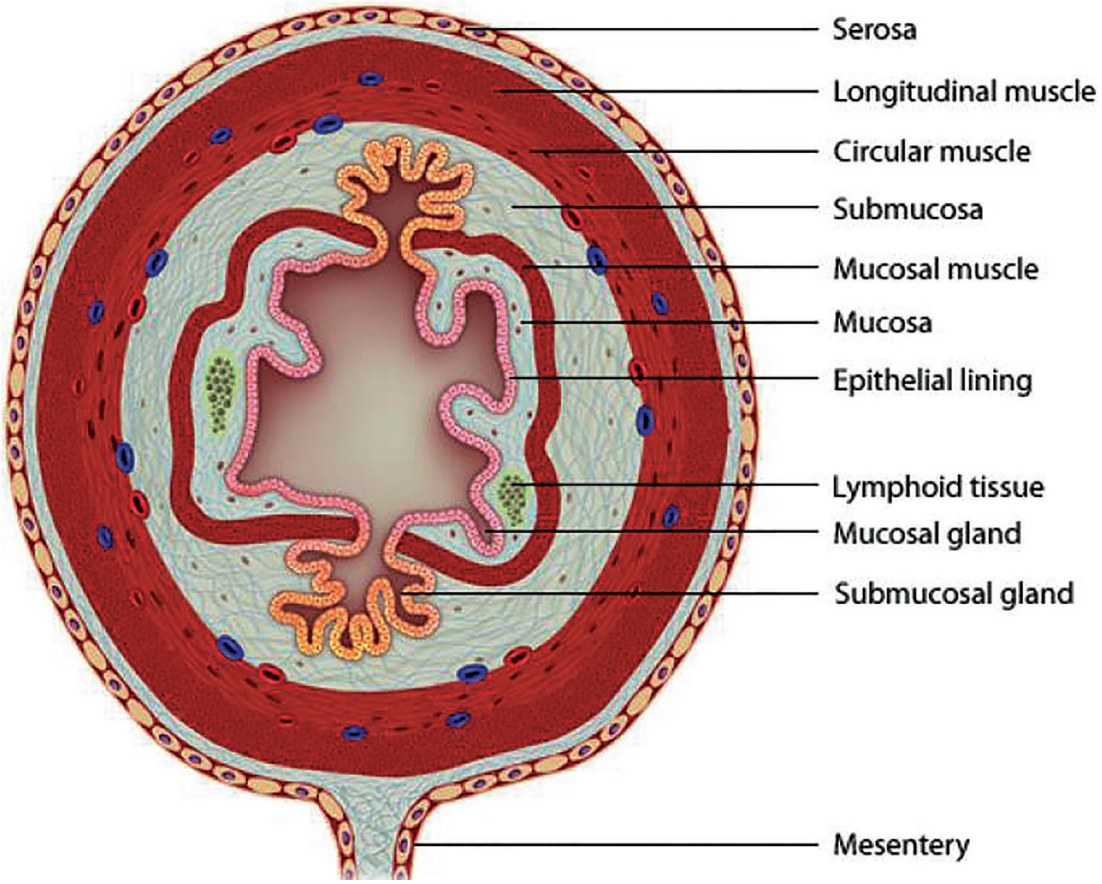

FIGURE 1: Architecture of the gut mucosal wall. Four-layered (mucosa, submucosa, muscularis mucosa and serosa) organization of the digestive tract. Used with permission from www.myVMC.com.

In GI tract, the muscularis propria contains smooth muscle cells organized into a tightly coiled, inner circular layer and outer longitudinal layer as shown in Figure 1. The smooth muscle cells are arranged in parallel arrays. Between the outer and inner layers of the muscularis propria are prominent autonomic neural fibers and ganglionic clusters that forms a myenteric plexus. The major functions of the muscularis propria are to propel food through the gut by contractile peristaltic waves initiated and regulated by various neural and hormonal events [2, 6]. Flow is regulated by peristalsis mechanisms and by sphincters located in the upper esophagus, in the distal portions of the esophagus, stomach, and ileum and in the anus. Most part of the intestine is lined on its outer surface by a sheath of protective layer, the serosa which consists of a continuous sheet of squamous

epithelial cells, the mesothelium separate from the underlying longitudinal muscle layer by a thin layer of loose connective tissue (Figure 1). The serosal layer forms a natural barrier to the spread of inflammatory and malignant processes [7, 8].

2.2 DEVELOPMENT AND FUNCTIONS

The development of the mammalian GI system is preprogrammed, but this can be altered during the intrauterine and early postnatal life [6, 9, 10]. There are two major steps involved in the development of the GI tract: formation of the gut tube and formation of the individual organs with their specialized cell types. Genes regulating both phases are being identified and well characterized in published comprehensive reviews [6, 11, 12].

Esophagus: The esophagus is the foremost part of the GI tract that can be identified as a distinct structure early in human embryogenesis. This organ elongates during subsequent development relatively more rapidly than the fetus as a whole [2, 6, 13]. The major events during the formation of esophagus are at 10 weeks, ciliated columnar epithelium appears followed by the replacement of stratified squamous epithelium around 20–25 weeks, a process that begins in the midesophagus and proceeds further [14]. Studies by Hitchcock et al. [9] show the development of esophageal musculature and innervation in fetuses of 8–20 weeks gestation and in infants 22–161 weeks of age. The esophagus is well supplied with lymphatics that form a richly anastomosing network in the lamina propria and submucosa. Although the esophagus is described as a tube, it is oval and has a flat axis anterior to posterior with a wider transverse axis. The primary functions of the normal esophagus are the propulsion of food from the mouth to the stomach and the prevention of significant reflux of gastric contents into the esophagus. The propulsive function is affected by involuntary peristalsis in the muscularis propria that unlike the remainder of the GI tract is formed of two types of muscle fibers such as striated and smooth muscles [2, 15]. When it is on the resting state, the esophagus is a collapsed tube, and the elastic tissue in its walls accounts for its distensability. During swallowing, the lumen dilates and the folds flatten so that the esophagus can normally accommodate the passage of even large amounts of food bolus.

Stomach: The stomach receives food from esophagus and is a J-shaped reservoir of the digestive tract, in which ingested food is soaked in gastric juice that contains digestive enzymes and acids [2, 12]. The prenatal ultrasound examinations have revealed that the stomach grows in a linear fashion from 13 to 39 weeks and that the characteristic anatomic features such as greater curvature, fundus, body and pylorus are identified as early as 14 weeks [6]. Stomach located in the left upper

quadrant of the abdomen, its upper portion lies beneath the dome of the left hemi-diaphragm. Stomach is divided into four zones, each of which has a specific microscopic mucosal structure. The "cardia" is the narrow portion of the stomach immediately distal to the gastroesophageal junction. The remainder of the stomach is divided into proximal and distal parts. The proximal portion is the body or corpus and the distal part is named as pyloric antrum which is demarcated from the duodenum by the pyloric sphincter. Pyloric sphincter is closed in the resting state to prevent the reflux of intestinal contents into the stomach (Figure 2). The arterial blood supply to the stomach involves many different branches among which, splenic artery, common hepatic and left gastric arteries are important. Venous drainage from the stomach is through the portal system to the liver. Deeper in the epithelial wall is a rich lymphatic network that drains to regional perigastric lymph nodes and to nodes in the omentum, around the head of the pancreas and in the spleen [16]. In the stomach, solid food is fragmented and mixed by peristalsis. A semi-liquid material (chime) is formed and released in small, regulated bursts into the duodenum by rhythmic openings of the pyloric sphincter. Cells in the corpus and fundus of the stomach also produce hydrochloric acid and intrinsic factors necessary for the absorption. Although it occurs predominantly in the small intestine, some digestion does occur in the stomach. Certain gastric mucosal cells produce pepsinogens, the proteolytic enzymes that are secreted in an inactive form but they are then activated by the acid environment of the gastric lumen during food intake. In addition, production of the hormone gastrin is also another major gastric function. The development of gastric glands (fundic-type or oxyntic) occurs very early during human fetal life (10–12 weeks of gestation) [6, 17, 18]. The advance and detailed description of development, gastric endocrine cells, and functions of the stomach are described in the recent review articles [6, 13, 19].

Small Intestine: The intestinal tract followed by the stomach consists of the small intestine including duodenum, jejunum, and ileum, and the large intestine or colon (Figure 2). The development of small intestine consists of three successive phases: morphogenesis and cell proliferation, cell differentiation, and cellular and functional maturation [6, 20]. Organogenesis of the intestine is completed by 13 weeks of gestational period [21]. Duodenum is the first portion of the small intestine and extends approximately 25 to 30 cm from the pyloric sphincter to a fibrous and muscular band, the ligament of Treitz. From the distal part of the stomach, duodenum enters the retroperitoneum, curves, and then enters into peritoneal cavity. Jejunum and ileum are located between the Trietz and the ileocecal sphincter. First one third of this segment of the small intestine is referred as the jejunum, whereas the remainder is named as the ileum. Structure and function of jejunum and ileum are different and occur gradually during the development. The blood supply for the three segments of small intestine derives from the celiac, superior, and inferior mesenteric arteries, respectively.

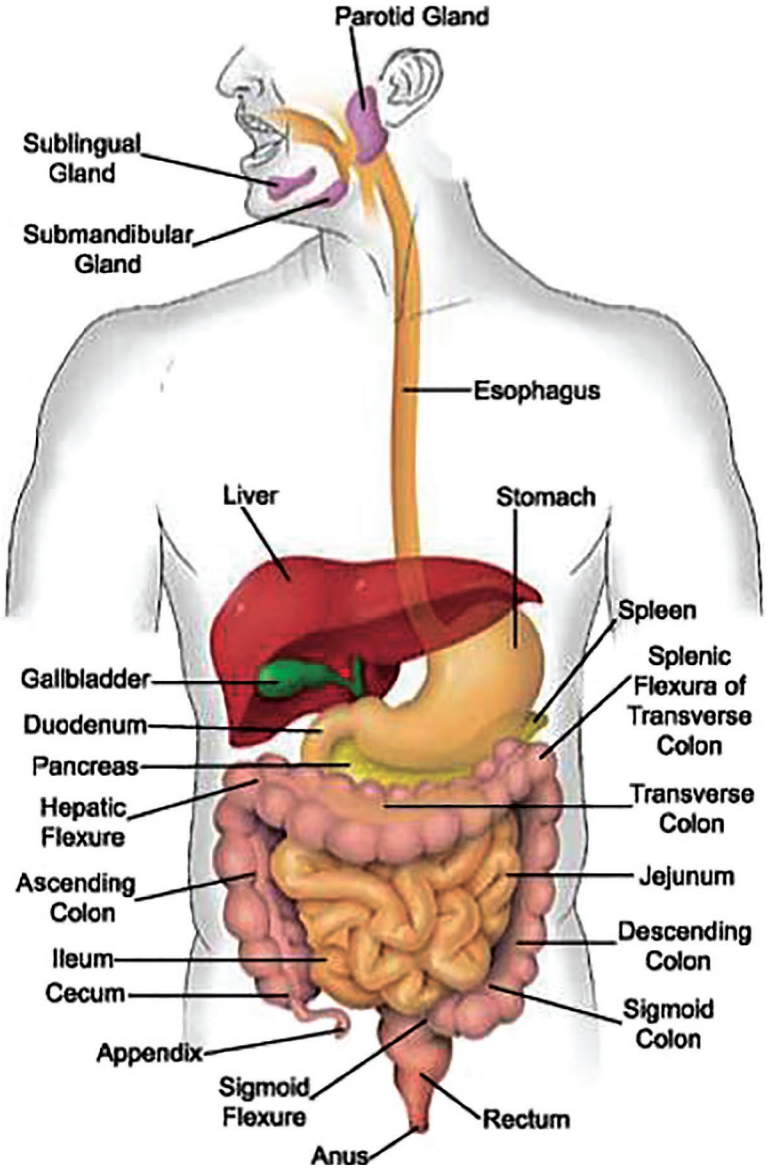

FIGURE 2: Architecture of human digestive system. Adapted from http://www.vitallywell.net/digestive-enzymes.html.

The cecal and appendiceal diverticulum appear during 6 week of gestation, marking the margin between the small and large intestine. The inner surface of the small intestine is covered with a simple columnar epithelium exhibiting invaginations, known as the crypts of Liberkuhn, which are comprised predominantly of proliferating cells, and finger like projections called villi that contain the majority of differentiated absorptive cells [2, 6, 19]. The epithelial lining initiates and modulates the basic activities attributed to the small intestine like terminal digestion of nutrients and transport of nutrients, water, and ions. The epithelial surface is expanded by villous thickness and crypts present between villi. The adult small intestinal epithelium is composed of four different cell lineages. Differentiated cells such as enterocytes, enteroendocrine and goblet cells occupy the villi, while another type of differentiated cells, the Paneth cells, reside at the bottom of the crypts and secrete antimicrobial agents. The remaining part of the crypts constitutes the stem cells and proliferating progenitor compartment [20, 21].

Large Intestine: The large intestine or colon arches around the small intestine, commencing in the right ileac region. In adult humans, the colon is approximately 1.5 m in length. The parts of the large intestinal anatomic divisions from proximal to distal end include the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectum, and anus. The structure of the colon in many respects overlaps that of the small intestine as described previously [2, 6, 22]. Development of the colon is marked by three important cyto-differentiative stages which include the appearance of primitive stratified epithelium to a villous architecture with developing crypts at about 12–14 weeks of gestation and followed by the remodeling of the epithelium at around 30 weeks when villi disappear and the adult-type crypt epithelium is established [6]. Concurrent with the presence of villous morphology the colonic epithelial cells express differentiation markers similar to those in small intestinal enterocytes [22]. As seen in the small intestine, lymphoid nodules that distort the normal mucosal architecture are present in the colon, and the colonic epithelium also rapidly renews by itself. Undifferentiated crypt cells appear to be the progenitor for all cell types in colon. In contrast to the small intestine, the mucosa of the large intestine is not covered with villous projections but it contains deep tubular pits that increase in depth toward the rectum and extends as far as the muscularis mucosa. Colonic mucosal epithelial cells include absorptive cells, goblet mucus cells, undifferentiated columnar crypt cells, caveolated cells, Paneth cells, and M-cells present in the colonic mucosa and are almost identical to those cells present in the small intestine. The major functions of the colon are to reclaim luminal water and electrolytes.

CHAPTER 3

Characteristics of Gut Mucosal Growth

The GI epithelium is a complex system that consists of multiple cell types undergoing continual renewal while maintaining precise interrelationships [23–28]. Under biological conditions, a huge number of cells are exfoliated regularly throughout the lumen of the GI tract, and these sloughed cells are almost immediately replaced by new cells from the stem cell compartment. These stem cells or proliferative progenitors in the crypts generate epithelial cells that differentiate during their migration toward the villous region. A wide variety of dietary, growth factors, hormonal and transcriptional factors are involved in the regulation of GI mucosal growth and development [24, 25, 28]. A well-controlled cascade of signals maintains mucosal growth by the shedding of senescent and apoptotic cells at the surface of the GI epithelium [26, 28, 29]. The overall mucosal integrity depends on dynamic balance between cell production and cell loss. A defect in cell production leads to the development of mucosal atrophy and results in a decrease in absorption, whereas mucosal hyperplasia results from excess production of newborn cells. Hyperplasia can cause hypersecretion and increase the risk to cancers [10, 27, 29].

The mucous neck cells are located throughout the stomach, predominantly in the upper portion (neck or isthmus) of each gland, immediately below the glandular junction [2, 27] and are considered as gastric epithelial progenitor cells. In each gland, mucous neck cells form the zone of epithelial cell renewal, giving rise to new surface faveolar mucous cells as well as the other cell types within the glands. It has been thought by many investigators for years that parietal (oxyntic) cells are unable to divide [30] and are replaced by newly formed cells migrating slowly down the gland and differentiating into acid producing cells [31]. Based on results obtained from cultured human gastric corpuses from 12–17 weeks of gestation, the proliferative compartment of the mucosa from which the differentiated cells arise is the neck portion at the base of the glandular compartments [2, 6]. Most parietal cells occupy the mid portion of the gastric glands and are important in the processes of differentiation and development of the stomach. In the mouse, parietal cells survive for ~90 days, which is the time period for migration to the bottom of the gland [27, 32]. Another type cells located in the gastric glands are zymogen (chief) cells that are concentrated at the base of the gastric glands. After injury, zymogen cells are derived from stem cells, but they are replaced by