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Histogenesis of Small Intestine – A Review

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Abstract

In order to maintain nutrition and homeostasis and to support the developing organism's rapid growth, the small intestine mucosa must be able to control intestinal absorption as soon as possible after birth. This calls for the intestinal mucosa to be highly differentiated and capable of many of the physiological and biochemical processes that distinguish the small intestine mucosa of the adult by the time of birth. The histological changes taking place in the intestinal wall as it gets transformed from a primitive tube containing a stratified epithelium to a highly differentiated and organized structure during embryonic life are summarized in this review.

Keywords: Intestinal development, histological changes, intestinal epithelial cells, Brunner's glands, Peyer's patches, Enteric Nervous System, Intestinal lymphatic system.

Introduction

The oesophagus, stomach, small intestine, and large intestine are the four primary components of the gastrointestinal tract, which run from rostral to caudal. The primary segments are divided into secondary segments (from rostral to caudal): the proximal, middle, and distal parts of the oesophagus; the cardia, fundus, body, and antrum or pylorus of the stomach; the duodenum (with its first, second, third, and fourth parts), jejunum and ileum of the small intestine; and the cecum, appendix, ascending, transverse, descending, sigmoid, rectum, and anal canal segments of the large intestine. While the histologic transition between the primary segments may be abrupt, between the secondary zones they are actually zones of progressive change[1].

Small intestine is the principal organ for the absorption of nutrients from the consumed food. In addition to being an absorptive organ, the intestine also performs the action of a primary line of defense against the microorganisms that attempts to gain entry into the body through the gastrointestinal tract. The intestinal microstructure is designed by the nature in such a way that the intestine is capable enough to carry out its assigned functions. The

specializations of mucosal and submucosal layer serve to increase the surface area of absorption. These modifications include plica semilunaris, villi and microvilli on the enterocytes. Identical to the other regions of gastrointestinal tract, the intestinal wall is also comprised of four layers: namely mucosa, submucosa, muscularis externa and serosa. The mucosa is further subdivided into epithelium, lamina propria and muscularis mucosa[2].

The intestinal epithelium also differs from the rest of the gastrointestinal tract in the fact that it has various categories of cell types carrying out several functions namely: the enterocytes, the Paneth cells, the M cells, the goblet cells, the enteroendocrine cells, mucous cells and the stem cells[2]. In this review, the histogenesis of the small intestine while highlighting the microstructural adaptations of the intestine for carrying out its complex activity are summarized.

Review

The cranio-caudal and lateral folding of the embryo leads to the formation of an endodermal gut tube. This endodermal layer later forms the epithelial lining of the intestine. Concentric layers of mesenchyme surround the endodermal gut tube. These mesenchymal layers are derived from the splanchnic mesoderm which give rise to the rest of the layers of the intestinal wall[1]. The gastrointestinal tract of human beings undergoes lengthening, bending and looping to a great extent. This organ has a left – right asymmetrical pattern[3]. The development of the human intestine depends upon establishment of three axes: rostral-caudal, right-left and radial axes. The rostral-caudal axes are established by 7th week while the right to left axes is established only by 10th week. The radial gradient that is established from inside to outside is also established by 10th week[1]. The differentiation of the cells in the radial axes is brought about by the interaction with the underlying mesoderm[3]. It is convenient to divide the development of gastrointestinal tract into three arbitrary time period. The distinct definitive histology of each segment is created during the initial phase, which lasts up to the fourteenth postfertilization week. A few more histological structures develop between 14 and 30 weeks into the second phase. The third phase, which lasts for 30 to 40 weeks, is characterised by growth and continuous cell and structural maturation. In general, histogenesis progress from rostral to caudal[1].

Mucosa

The intestinal mucosa comprises of epithelium, laminar propria and muscularis mucosa. The timing of appearance of each of these layers has been described varyingly by different authors. The simple endodermal epithelium present in the bilaminar disc stage develops into a primitive stratified epithelium before 6 weeks of gestational age[1]. According to Mn S et al, in a fetus of gestational age 10 – 11 weeks, the mucosal lining is stratified. The transition of the stratified epithelium to simple columnar epithelium happens at around 13 weeks of gestational age of the fetus[4]. But Jerry and Colony Moxey has stated that the formation of secondary lumen takes place around 9 to 10 weeks of gestational age[5]. The convergent extension of the cells inside the pseudostratified epithelium similar to the process of gastrulation and neurulation may be responsible for the formation of secondary villi[3].

The villi are mucosal leaflike projections that extends from the mucosal surface into the lumen for a distance of about 0.5 – 1.5 mm. These villi are made up of a core that consists of an extension from lamina propria, a lacteal that is a central blind ending lymphatic capillary and an

extension of smooth muscle cells from the muscularis mucosa. This core is covered by simple columnar epithelium[6]. These villi start appearing as mesenchymal invaginations from the basal part of the epithelium. The time of appearance of villi is not uniform throughout the entire length of the small intestine. The appearance of villi progress from proximal to distal[4]. Trier JS et al has stated that the villi appear in the proximal intestine about 1 week prior to its appearance in the distal part of the intestine. Complete appearance of villi in the entirety of small intestine happens around 14 weeks of gestation. While the villi attain a considerable size in the proximal duodenum, the villi start appearing in the ileum[5].

The intestinal glands or the crypts of Leiberkuhn are tubular structures that extends from the muscularis mucosa, traverse through the entire length of the lamina propria and eventually open at the base of villi. These glands are lined by simple columnar epithelium which is in line with the epithelium of villi. The primordial crypts make their appearance around 11 to 12 weeks of gestational age while they become the mature crypts with the presence of a central lumen around the end of 12 weeks[5].The intestinal epithelium consists of various category of cells, each with a peculiar function and a time of appearance.

Enterocytes

The enterocytes or the absorptive cells are tall columnar cells that have a basal nucleus. The supranuclear golgi cisternae, ribosomes and the rough endoplasmic reticulum aid in the secretory function of the cell. These cells also carry modifications that aid in the absorptive function of the cell. They have apical microvilli and lateral plicae. The mitochondria are elongated. The smooth endoplasmic reticulum lines the apical portion of the cytoplasm to help in the absorption of fatty acids and glycerol[6]. These cells start to line the surface of intestinal villi around 10 to 20 weeks of gestational age. The cytoplasm of these absorptive cells contain collections of glycogen and lysosome like meconium corpuscles. These corpuscles are found in abundance and in larger dimension in the distal than the proximal part of the small intestine. The enterocytes are also characterized with invaginations of the apical plasma membrane along with associated tubules and vesicles[5].

Paneth cells

The Paneth cells are located in the base of the intestinal glands. These cells consist of a basophilic basal cytoplasm, supranuclear golgi apparatus and acidophilic refractory secretory vesicles in the apex[6]. The Paneth cells were first noted to be differentiating from the base of the crypts in 11 to 12 week of gestational age. These Paneth cells were identified by the presence of abundant granular endoplasmic reticulum (supranuclear eosinophilic granules[1]). At the time of differentiation, the Paneth cells are found to have secretory granules that are smaller in size. There is an increase in the number of the granular endoplasmic reticulum and increase in the size of secretory granules from 12 weeks of gestation upto 22 weeks of gestation.

Goblet cells

Goblet cells are unicellular glands that has an increasing quantity from duodenum to ileum. Under transmission electron microscopy, these cells have an intense eosinophilic base due to the heterochromatic nuclei, mitochondria, rough endoplasmic reticulum and a mucinogen granule in the apex[6].The goblet cells are present even when the intestinal epithelium is stratified in nature[5]. In a study conducted by Pfoze and Rajshree in an attempt to find the time of appearance of goblet cells, the goblet cells started to appear around 9 weeks of gestation

in some specimens. Around 12 weeks of gestation, the goblet cells have made its appearance in almost all the studied specimens. The goblet cells are characterized by the distended theca containing mucin granules located below the apical membrane. The presence of goblet cells among the epithelial cells increases distally from the duodenum. The proportion of goblet cells increase as the intestine becomes exposed to the microorganisms[7].

Enteroendocrine cells

The enteroendocrine cells also have an early appearance even before the formation of villi or crypts. By 12 weeks of gestational age many subtypes of enteroendocrine cells were clearly distinguishable in the intestinal epithelium. A primitive enteroendocrine cell is characterized by presence of small heterogeneous granules (200 – 300 nm) with central cores of fluctuating electron density and frequently surrounded by an electron-lucent halo. These primitive cells are often found in the early ages of gestation and are most numerous in the stratified epithelium. The enteroendocrine cells with larger granules measuring upto 1μm are classified as precursor cell. These precursor cells were also found in early gestational stage around 9 to 10 weeks of gestation and in the stratified epithelium. These precursor cells are also present when the epithelium becomes columnar both in the proximal and the distal part of the intestine. Some cells share characteristics of the precursor cells and the mature enteroendocrine cell and are termed as transitional cells. These cells may represent the developmental stage of the adult enteroendocrine cell[5].

Lamina propria

Lamina propria is composed of loose connective tissue with nerves, blood vessels and lymphatics embedded in them[1]. The lymphatic tissue is often present as aggregates. These aggregates are more in ileum and in the anti-mesenteric border. They are given the name as Peyer's patches or aggregated nodules[6]. The presence of eosinophils and mast cells were noted in the lamina propria from 16-20 weeks[1].

Peyer's patches

At the same time, Salva et al described that the lymphoid tissues start appearing around the second trimester and is found in higher quantity by the time of third trimester. At around 14-16 weeks of gestational age, Baginskys et al found some discrete populations of T and B cells. According to them, the maturation of these groups into Peyer's patches happen around 19 weeks of gestational age. According to Grand RJ, the Brunner's glands and Peyer's patches start developing around 14 weeks and 20 weeks respectively[4]. J S Cornes conducted a study with the specimens of small intestine obtained from fetus of varying gestational age and studied the developmental pattern of the Peyer's patches. They described that the Peyer's patches are generally oval or rectangular in outline and are initially found in the jejunum upto the ileocecal junction. The patch with largest surface area was present in the ileocecal junction while the longest patch was seen in the proximal ileum. The longest patch measured about 9.9 cm. With increase in size of the patches, there appeared to be an increase in the follicular content of the Peyer's patches. Cornes found the longest patch to be having around 980 follicles and the smallest patch to be containing 10 to 20 follicles. Around 24 weeks of gestation, the author found about 45 Peyer's patches but the lymphopoiesis was said to start in the fetal small intestine around 15 weeks of gestation. The authors opinion is that the Peyer's patches continue to grow upto 10 years of life of an individual[9]. In a study conducted by Jo spencer et al, there were no aggregates of lymphoid tissue present in the 11-12 weeks of gestational age.

Infrequent observation of lymphoid aggregates was noted around 14 weeks of gestational age. But the discrimination between the B cell and the T cell population was possible from 19 weeks of gestational age[10].

Muscularis mucosa

Separating the mucosa from the submucosa is a thin, double layer of smooth muscle called the muscularis mucosae. It comprises an inner circular and outer longitudinal layer of smooth muscles. In routine hematoxylin & eosin, the layer that is mostly visible is the inner circular layer. The outer longitudinal layer is prominently visible in cases of intestinal obstruction. The smooth muscle cells from the muscularis mucosa extend into the lamina propria and attach themselves to the basement membrane[1].

Submucosa

The submucosa is made up of loose connective tissue that contains nerves, ganglia, blood vessels, dispersed smooth muscle fibres and lymphatics. These structures are best developed where the primary segments meet, such as the junctions of the duodenum, terminal ileum, appendix, and anorectal region. The nerve plexus in the submucosa are divided into two: Plexus of Meissner and Plexus of Henle. The Meissner's plexus is superficial and present just beneath the muscularis mucosa while the Henle's plexus is deep and located along the inner surface of the inner circular layer of muscularis propria[1].

Brunner's glands

Brunner's glands are branched tubular glands that have both zymogen and mucin secreting characteristics[6]. Reports from the experiments of Schumacher et al said that the Brunner's glands start to develop around 3 – 5 months of gestational age. On the other hand, Salva et al concluded the time of appearance to be around the third trimester[4]. Botros et al investigated the development of Brunner's glands in fetus of gestational age ranging from 10 weeks to full term. They reported the first evidence of appearance of Brunner's glands as few cords of epithelial cells from the mucosa of the duodenum. These cords of epithelial cells develop into simple tubular down growths at around 16 weeks of gestation. The tubular down growths start maturing into Brunner's glands from 20 weeks of gestation starting from the proximal part of the duodenum near the pyloroduodenal junction. At birth, the Brunner's glands of the new-born resemble the Brunner's glands of adults in both structure and histochemical properties[8].

Muscularis externa

The muscularis externa or the muscularis propria is composed of inner circular and outer longitudinal layer separated by a thin intermuscular septum containing a nerve plexus called the Auerbach's plexus. Recent research has shown that both layers of the muscularis propria express smoothelin strongly and diffusely, in contrast to the muscularis mucosae, which often exhibit poor to absent immunohistochemistry staining[1].

Xuelai Liu et al studied the development of muscle layers in the human foetuses ranging from gestational age of 6 to 12 weeks. Their findings suggested that the inner circular smooth muscle layer starts to develop around 8 to 9 weeks of gestation followed by the outer longitudinal muscle layer which starts to appear around 10 weeks of gestation. The muscular layer present in the mucosa is seen only after 11 to 12 weeks of gestation. They also noted a difference in the morphology between the muscular layers in the muscularis externa and muscularis mucosa. The muscularis mucosa was seen branching into the glands of lamina propria and was also found to have increased thickness[11].

Myenteric plexus

The plexus of nerves in the muscular layer appears earlier than the smooth muscle cells. The Auerbach's plexus develops around 9 weeks while the smooth muscles start appearing around 12 weeks of gestational age[4]. The electron microscopy of the ganglia of the myenteric plexus reveals it to be a very compact structure that is surrounded by a basal lamina isolating it from the adjacent connective tissue and the blood vessels. This arrangement is found to be more similar to the central nervous system than the autonomic ganglia. With a few chromatin condensations adhered to the nuclear envelope, the nucleoplasm is finely granular. Throughout the entire length of the small intestine the nerve bundles are surrounded by the Schwann cells. The enteric glial cells are structurally similar to the central astrocytes. The ratio between the nucleii of glial cells and neurons in the myenteric ganglia is 2:1. The interstitial cells located outside the ganglia are flattened with long laminar processes. Baumgarten et al. described three profiles of neurons present in the myenteric plexus. These are characterized on the basis of the vesicles present in the nerve endings. First type has numerous agranular vesicles, second type has vesicles that are intensely osmiophilic with a diameter of 50 to 90 nm and the last type has vesicles of size 85 to 160 nm with a large granule of medium electron density. The enteric nervous system develops from the neural crest cells migrating from the vagal and the sacral region of the neural tube. Since the intestinal peristalsis is observed in the fetal small intestine around 12 weeks of gestation, implying that the transit of the neural crest cells takes place around this time[12].

Interstitial cells of Cajal

The interstitial space between the nerve endings and the smooth muscle cells is occupied by the interstitial cells of Cajal (ICC). These interstitial cells are said to maintain specialized relations with the surrounding structure forming an anatomical unit called as NE-ICC-SMC units[13]. S E Lee et al investigated the distribution and appearance of ICC in the stomach and duodenum of rats. They described the existence of two types of ICC. One in the Auerbach's plexus (ICC-AP) and one in the deep muscular plexus (1CC-DMP). The authors describe ICC-AP as irregular oval shaped cells containing electron dense nucleus with a less dense cytoplasm when compared to the ICC-AP of the stomach. But the ICC-AP of the duodenum has numerous mitochondria and slender processes. The cytoplasm of the ICC-DMP are spindle shaped with its orientation along the smooth muscle cells. The cytoplasmic organelles such as the golgi apparatus, rough endoplasmic reticulum and the mitochondria appear to be well developed in the cytoplasm of the perinuclear region. The ICCs had multi directional processes that established connections with the nerve endings and also had extensions among the smooth muscle cells[14].

Intestinal lymphatic system

The intestinal lymphatics along with the regulation of tissue fluids also have importance in the transport of luminal substances like dietary fat absorbed from the consumed food. The intestinal lymphatic system consists of two separate, non-communicating lymphatic networks: one that contains the lacteals that drain the villi and the submucosal lymphatic network that connects them, and the other that does the same for the lymphatics that drain the intestine muscular layer. The common collecting lymphatics of these two systems are located close to the mesenteric border of the intestine. Studies employing scanning electron microscopy on rat small intestine lymphatic corrosion casts showed the existence of

longitudinally oriented muscle cells linked to the lacteals[15].

Morphometry

Bagyanski et al conducted a morphometric analysis of the developing concentric structure of the human fetal intestinal tube. After week 12, the epithelial thickness remained nearly constant over the whole length of the intestine due to the stabilisation of the rate of epithelial cell proliferation. Week 18 of the gestational age shows a significant transformation of the short, sparse, and irregularly orientated microvillar surface into a well organised brush border complex. The growth of the villi and crypts, which occurs when the epithelial cells move in distinct cohorts, may be related to the bilayered appearance of the intervillar epithelium at week 12 and the shifting desmosome pattern between weeks 12 and 18 of gestational age. Between weeks 12 and 18 of gestational age, there was a large region-specific thickening of the submucosal layer, which was accompanied by intense vascularization, pointing to an increased oxidative metabolism during this fetal stage[16].

Conclusion

The small intestine of the developing fetus undergoes a complex development to perform the function of absorption of nutrients while keeping the primary line of defence intact. The small intestine also undergoes functional maturation after birth as it is exposed to the microorganisms and starts its function in the absorption of nutrients. This review summarises the histological characteristics of each layer of the intestinal tube according to their time of development. The understanding of the developmental aspects of intestine in greater detail helps understand the pathogenesis of disease involving the intestine.

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