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Exploring the microscopic terrain of the small intestinal epithelium: a comprehensive overview of general architecture and the present understanding of intestinal stem cells

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Abstract

This paper provides a comprehensive overview of the microscopic landscape of the small intestinal epithelium, focusing on its general structure and the current state of knowledge regarding intestinal stem cells. The small intestine's epithelial layer is intricately organized, comprising various cell types with specialized functions, including goblet cells, enterocytes, enteroendocrine cells, Paneth cells, microfold cells (M cells), and tuft cells. These cells collectively contribute to essential physiological processes such as digestion, absorption, and immune response regulation. The review delves into the role of intestinal stem cells, residing in the crypts, and their significance in maintaining tissue homeostasis and regeneration. Understanding the microscopic intricacies of the small intestinal epithelium is crucial for unraveling its physiological functions and exploring potential therapeutic avenues.

Running title: Small Intestinal Epithelium and Stem Cell Insights

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Gross anatomy structure of human intestine

The human intestine is a vital organ in the digestive system that is responsible for absorbing nutrients from ingested food. Consisting of the small and large intestines, this coiled tube plays a crucial role in breaking down and processing nutrients for absorption into the bloodstream [1-3].

The small intestine, composed of the duodenum, jejunum, and ileum, serves as the primary site for nutrient absorption. Within its structure, specialized formations such as villi and microvilli increase the surface area to facilitate efficient absorption. The large intestine, which includes the cecum, colon, and rectum, primarily functions to absorb water and facilitate the formation of feces [4,5].

The intricate anatomical structure of the human intestine is fortified by an extensive network of blood vessels, lymphatic vessels, and a diverse array of cells, including intestinal stem cells that are critical for regeneration and maintenance. Understanding this complex structure is essential for comprehending the complexities of the digestive process and addressing diverse gastrointestinal conditions. The initial structure of the gut tube undergoes differentiation into three distinct segments known as the foregut, midgut, and hindgut. The foregut is responsible for the development of the upper gastrointestinal tract, comprising the upper alimentary canal that eventually matures into the esophagus, stomach, and initial portion of the duodenum. The midgut is responsible for the development of the majority of the small intestine, including additional segments of the duodenum, jejunum, and ileum. The hindgut plays a role in the development of the lower digestive tract, including the large intestine[6,7].

The development of the gut tube is closely regulated by genes and growth factors that control the differentiation of cells and the formation of anatomical structures. This complex transformation of the gut tube is necessary for the proper functioning of the digestive system, allowing for the later processes of digestion and absorption of nutrients in the developing organism [8].

A thorough comprehension of the structure and anatomy of the intestine is of great clinical importance. This has been confirmed by numerous anatomical studies conducted on human cadavers, fetuses, and in vivo during therapeutic procedures performed on living individuals [3]. The purpose of this work is to familiarize the reader with the intricate microanatomical structure of the small intestine epithelium and to outline the main areas of research. In this article, we conducted a literature review specifically on intestinal stem cells (ISC).

General significance (physiology) of the small intestine epithelium

It is widely recognized that this tissue plays a crucial role in the functioning of the digestive system [9].

The primary functions of the small intestine epithelium are digestion and absorption of nutrients. Nutrient absorption requires a large surface area which is achieved by the creation of three morphological phenomena. The first involves the formation of folds by the mucosal and submucosal layers, most prominently observed in the proximal segment of the small intestine and diminishing in the middle part. The second phenomenon is the creation of intestinal crypts and glands. Lastly, microvilli, which are submicroscopic finger-like projections on the apical surfaces of epithelial cells, greatly contribute to the increase in surface area of the epithelium [9].

Another important function of the small intestine epithelium is its barrier function. The epithelium separates the internal environment of an organism from the intestine lumen, preventing harmful substances like toxins, pathogens, and antigens from entering the bloodstream[10].

This is accomplished through several mechanisms. Tight connections between epithelial cells create a physical barrier, preventing substances from leaking between cells. In addition, epithelial cells release mucus that forms a protective layer, preventing pathogens from adhering to the surface of the epithelium. The epithelium also contains immune cells known as intraepithelial lymphocytes, which help with immunological surveillance and defending against pathogens [11].

The intestinal epithelium plays a significant role in producing hormones that regulate digestion and nutrient absorption. It produces cholecystokinin (CCK), which stimulates the release of digestive enzymes from the pancreas and bile from the gallbladder. It also produces secretin, which controls the secretion of bicarbonate from the pancreas to neutralize stomach acid [12].

It is worth noting that the epithelium of the small intestine also interacts with the gut microbiota, a diverse community of microorganisms inhabiting the intestines. Epithelial cells possess specialized receptors that can identify and react to certain molecules produced by the gut microbiota. This mutual interaction assists in maintaining a harmonious community of microorganisms in the intestines and plays a role in promoting gut health and immune function. Maintaining intestinal homeostasis depends on the complex interactions between the microbiota, intestinal epithelium, and the host immune system [13]. The epithelium also plays a role in secreting compounds that can impact microbial colonization and stimulate or modulate immune responses [13].

Clinical significance of the intestinal epithelium in infectious diseases

The intestinal epithelium plays a critical role in infectious diseases by acting as the first line of defense against attacking pathogens and participating in various immune responses. As a physical barrier,

it separates the intestinal lumen from the underlying tissues, effectively preventing harmful microorganisms, toxins, and antigens from entering the bloodstream. When this barrier is compromised, pathogens can breach it, leading to the development and spread of infections [14].

The intestinal epithelium is equipped with pattern recognition receptors (PRRs) that are able to identify certain molecular patterns found in pathogens, such as components of bacterial cell walls or viral nucleic acids [15]. These receptors activate signaling pathways that initiate immune responses to control and eliminate invading pathogens [16].

The intestinal epithelium secretes a protective mucus layer that covers its surface. This layer contains antimicrobial substances and serves as a physical barrier, aiding in capturing and expelling pathogens. It also includes antibodies called secretory IgA, which can neutralize pathogens and prevent their adherence to epithelial cells [17]. The intestinal epithelium contains various immune cells, including specialized cells known as intraepithelial lymphocytes (IEL) and antigen-presenting cells (APCs), such as dendritic cells. These immune cells help to detect and eliminate pathogens directly within the epithelial layer. Additionally, they initiate immune responses by presenting antigens from pathogens to other immune cells in the underlying tissues, resulting in the activation of systemic immune responses. The majority of the intestinal immune system is located in the subepithelial compartment. Dendritic cells (DCs) present collected antigens to T cells to initiate action or induce tolerance. Meanwhile, macrophages regulate the intercellular space and also induce phagocytosis [17]. The intestinal epithelium interacts with the microbiome. The microbiota helps to maintain the integrity of the epithelial barrier, competes with pathogens for nutrients and colonization sites, and stimulates the development and functioning of the immune system. Disturbances in the composition of the gut microbiota can impact the function of the epithelial barrier and increase susceptibility to infections [16].

In summary, the intestinal epithelium plays an integral role in infectious diseases as it is the largest and one of the most crucial components of the human immune system [18]. It functions as a physical barrier, identifies pathogens, stimulates immune responses, engages with the gut microbiota, and regulates immune homeostasis. A comprehensive understanding of the intricate interactions involving the intestinal epithelium can offer valuable insights into the development of effective strategies for preventing and treating infectious diseases.

Clinical significance of the small intestine epithelium in autoimmune diseases

The epithelium of the small intestine holds clinical significance in autoimmune diseases, especially those affecting the gastrointestinal tract. It acts as a physical barrier and is involved in immune regulation and tolerance. The epithelium plays a crucial role in maintaining immune regulation and barrier function, and its dysfunction can contribute to the development of autoimmune diseases. Understanding these mechanisms helps in the development of targeted therapies for autoimmune conditions.

For example, in celiac disease, there is atrophy, or shrinking, of intestinal villi due to an autoimmune process directed against the epithelial structures of the intestine. Disrupted nutrient absorption in individuals with celiac disease can lead to various clinical symptoms and deficiencies [19].

Clinical significance of the small intestine epithelium in absorption disorders

Improper absorption may result from congenital defects in the transport system of the small intestine epithelium, acquired defects, or surgical procedures [20]. Digestive and absorption disorders are closely linked and collectively referred to as malabsorption syndrome. These disorders are classified into congenital, genetically predisposed, and acquired forms. Morphological abnormalities may vary depending on the underlying disorder, including a normal mucosal lining with an increased number of intraepithelial lymphocytes (viral enteritis, food allergies), shortened villi with crypt hyperplasia (celiac disease (CD)), and a completely flat mucosal lining (autoimmune enteropathy) [20,21]

The intestine and aging

The brain-gut axis may play a role in maintaining the structure of intestinal villi and facilitating nutrient absorption. Previous studies have suggested that age-related phenotypes, such as brain dysfunction, can affect the development of intestinal senescence [22]. Cellular senescence is a stress-induced process in which cells stop dividing but continue to function. Senescent cells remain metabolically active and have the ability to secrete various molecules [23].

Detailed structure of the small intestinal epithelium

The epithelium of the small intestine is composed of various cell types, differentiated from epithelial stem cells residing at the base of the intestinal crypts [24]. Within the epithelium of the small intestine, distinct cell types perform specialized functions. Goblet cells produce mucin glycoproteins, which contribute to the formation of mucus. Enterocytes, the main and abundant type of epithelial cells, play a significant role in the functions of the intestine. Enteroendocrine cells are involved in hormonal signaling, and Paneth cells, located at the base of the crypts, secrete antimicrobial peptides (AMPs). M cells, or microfold cells, play a role in capturing and presenting antigens to immune cells.

Additionally, tuft cells, also known as brush cells, are thought to contribute to promoting type 2 immunity against intestinal parasites. The variety of cells in the small intestine is crucial for its complex functions and defense mechanisms [25].Prior research has indicated a continuous evolutionary process of the intestinal epithelium driven by proliferation, cellular differentiation, and apoptosis. These dynamic regulatory mechanisms play a important role in preserving homeostasis and maintaining the functions of the small intestine [26]. Within the intestinal lumen, there are actively renewing stem cells at a weekly frequency. These stem cells play a pivotal role in regenerating the intestinal epithelium [27]. The assessment of the dynamics of small intestinal epithelial cell renewal varies among some researchers. Some authors argue that these cells undergo regeneration at a much more rapid pace, occurring approximately every 2 to 5 days [28].

It can be observed that the epithelium is a highly dynamic regenerative tissue within the human body. Consequently, despite the constancy of the cells that make up the intestine, there is a continual fluctuation in the types of individual cells present within its structure [29]. In their detailed presentation of the small intestinal epithelium, Takahashi and Shiraishi highlight the layered arrangement of various cell types along the villi and crypts. The structure of the small intestinal epithelium comprises crypts, enteroendocrine cells, goblet cells, and enterocytes. The researchers meticulously distinguished the structural components within the crypts, including Paneth cells, Lgr5+ cells, undifferentiated cells, and transit-amplifying cells. It is important to note that these cells migrate during their lifespan, moving either towards the base of the crypt or the lumen of the small intestine [29]. Columnar cells were first described by Chong and Leblond (1974) [30] at the base of the intestinal crypts.

These cells interact with Paneth cells, which have multiple functions such as producing bactericidal substances responsible for controlling intestinal stem cells [29]. In a study that used single-cell RNA sequencing (scRNAseq) of the small intestine and its regions (duodenum, jejunum, and ileum), Burclaff et al. were able to identify marker expressed by intestinal stem cells, including LGR5, SCL12A2, ASCL2, and RGMB [27]. In addition, the study focused on structural components related to vesicles, including M cells, which are microfolded cells that transport antigens to immune cells. When describing structures in the intestinal epithelium, it is important to mention specialized receptors that can serve as targets for various therapeutic substances[27]. According to Tian et al. [28], small intestinal epithelial stem cells can be divided into two groups: columnar cells expressing Lgr5 located primarily at the base of the intestinal crypts, and cells located above them (above the base of the crypts) expressing Bmi1.

Small intestine stem cells

The epithelium of the small intestine, known to be one of the most rapidly regenerating tissues along with blood and skin undergoes cellular regeneration within a few days. This remarkable regenerative property is attributed to the presence of multipotent intestinal stem cells (ISCs). Through the use of genetic mapping strategies, researchers have categorized two distinct groups of epithelial stem/progenitor cells within the small intestine [31].

These stem cells have been characterized based on their location and cyclic dynamics. Cells expressing markers such as Lgr5 (leucine-rich repeat-containing G protein-coupled receptor 5), CD133, and Sox9 are known as crypt base columnar cells (CBCs). These rapidly changing cells, also referred to as columnar cells, exhibit a slender morphology and are situated at the base of the intestinal crypts. Topographically, CBCs intertwine among Paneth cells, with the latter acting as a supportive niche for the former.

These stem cells have been defined based on their location and cycling patterns. Cells expressing markers such as Lgr5, CD133, and Sox9 are known as crypt base columnar cells (CBCs). These rapidly changing cells, also known as columnar cells, have a thin appearance and are found at the base of the intestinal crypts. Topographically, CBCs are intertwined with Paneth cells, which serve as a supportive niche for them [28]. Studies have shown that from this population of stem cells, terminally differentiated tissues of the intestinal epithelium (IEC) emerge. These differentiated tissues include absorptive enterocytes, goblet cells, Paneth cells, enteroendocrine cells, as well as immune and neuronal cells [32]. Unfortunately, the Lgr5-expressing cell population is highly sensitive to the effects of intestinal damage [31].

The capacity for rapid cell division in progenitor cells presents a significant challenge in preserving the intestinal milieu throughout an organism's life. The increased vulnerability of rapidly multiplying Lgr5+ cells to genomic insults leads to the accrual of harmful mutations, greatly decreasing their chances of long-term viability. This highlights the delicate balance needed to sustain the regenerative abilities of the intestinal lining and emphasizes the need for protective mechanisms to ensure the continued functional integrity of these crucial cellular components [33]. Tian et al. identified a secondary pool of progenitor cells in the small intestine, characterized by Bm1 or MTERT expressions. These cells have a slower metabolic turnover and are essential for maintaining the proper functioning and stability of the crypt environment. This revelation enhances our understanding of the intricate dynamics within the intestinal epithelium, emphasizing the indispensable role played by these cells in preserving the equilibrium and vigor of the crypt microenvironment [28]. Located at a position +4 from the crypt

base, they exhibit resilience to acute and genotoxic stress. Most importantly, they possess the capacity to replace damaged CBC cells, which are susceptible to injuries in the small intestine [32]. Available scientific data suggests that following an injury, the initially activated cells express the Bmi1 gene; the next step involves the regeneration of cells expressing Lgr5 [34]. We observe a balance between the rapid, active cycle of Lgr5 cells and the quiescent cycle of +4 ISC, crucial during injuries, allowing for continuous self-renewal and regeneration in response to damage [34].

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Additionally, when Lgr5+ CBC cells are absent, Bmi1-expressing cells have the ability to transform into all types of intestinal cells without transitioning through intermediate stages typical of Lgr5+ CBC cells. This provides potential for the regeneration of intestinal segments lacking populations of Lgr5-expressing cells. It is important to note that in present research, there is a concerning dependency indicating that +4 cells are only present in the proximal segments of the small intestine, particularly in the duodenum. Tian et al. suggest that this may be due to a lack of increased labeled sites with Bmi1-expressing cells in more distal crypts, leading to suspicion that there may be yet undiscovered progenitor cells in the distal small intestine and colon [28]. The functionalities of stem cells may be influenced by various factors, including the enteric nervous system (ENS) and the immune system [32].

Recent studies have demonstrated the impact of acetylcholine (Ach) on reducing the proliferative activity of Lgr5-positive cells[29,32].

Acetylcholine (Ach) is recognized as a major neurotransmitter in the enteric nervous system (ENS). Its effect on Lgr5-positive cells involves reducing cyclin D1 transcript levels and decreasing the expression of the M3 receptor gene, thereby inhibiting the differentiation of these cells [36]. The importance of acetylcholine in maintaining intestinal homeostasis highlights its regulatory role in balancing and stabilizing the intestinal environment. By regulating the transcription of cyclin D1 and suppressing the expression of the M3 receptor gene in Lgr5-positive cells, acetylcholine restrains their proliferative activity and differentiation. This mechanism contributes to the overall equilibrium within the intestine, emphasizing the interplay between neural signaling, cellular processes, and the maintenance of intestinal function [37]. Recent research has uncovered the impact of innate lymphoid cells (ILC) through the secretion of interleukin 22 (IL-22). This interleukin has been found to have a positive effect on the proliferation and expansion of intestinal stem cells (ISC)[38]. Cells of the immune system play a complex role in influencing the behavior of intestinal stem cells (ISC). Notably, helper T cells (Th) play a role in remodeling the intestinal epithelium. A study conducted by Hou et al. revealed that the presence of Th2 cells and their associated cytokines IL-14 and IL-13 have inhibitory effects on the proliferation of ISC. On the other hand, regulatory T cells and their associated cytokines contribute to the expansion of ISC. These interactions demonstrate the complex interplay between immune cells and ISC, which regulates the dynamics of intestinal tissue [34].

Not only do ISC receive signals from their own organism, but they can also be influenced by substances produced by bacteria or fungi. These cells have a high expression of innate immune receptors, such as protein 2 receptor (NOD2) and toll-like receptor 4 (TLR4) [39].

The niche in which ISC are located is key for their survival. The tissue is made up of a mesenchymal component, which includes fibroblast cells, myofibroblasts, and smooth muscle cells, as well as an epithelial component that includes Paneth cells. The mesenchymal component secretes vital signals to preserve the function of ISCs, while the epithelial component is responsible for supplying necessary signals to maintain ISC balance in the small intestine. Research has shown that the epithelial component, especially Paneth cells, release signaling molecules that are essential for maintaining the ISC niche [34].

Conclusions

Intestinal stem cells play a fundamental role in the maintenance and regeneration of the small intestine and are integral to the overall health and function of this vital organ. Positioned within the crypts of Lieberkühn, these cells possess a remarkable capacity for self-renewal, continuously dividing to generate progenitor cells that differentiate into various cell types essential for intestinal function. As the foundational elements of the epithelial lining, these stem cells make vital contributions to the ongoing regeneration of intestinal cells and the mucosal layer, which is crucial for the absorption of nutrients. Additionally, intestinal stem cells play a pivotal role in responding to injury and damage, facilitating the repair and regeneration of compromised tissue. The study of these cells can thus offer valuable insights into the effective management of conditions affecting the small intestine, such as inflammatory bowel diseases, and other disorders that compromise tissue integrity. In doing so, it not only deepens our understanding of important biological processes but also reveals potential interventions for the improvement of intestinal health.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare no conflict of interest.

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