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**Review**

# Mammalian cells of the small intestine : a review

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**ABSTRACT:**

The digestive tract is an essential organ in living organisms, and assumes a fundamental role in food processing and absorption. The small intestinal mucosa is characterized by continuous villi and crypts that, in the adult, are lined by mature epithelial cells that form the functional epithelial compartment of differentiated cells. The epithelial lining of the small intestine consists of different types of cells, absorptive enterocytes, goblet cells, Paneth cells and enteroendocrine cells. The goblet cells are unicellular exocrine mucous glands, dispersed among the columnar cells of the epithelium of the villi and crypts of Lieberkühn. The enterocytes were principal type of epithelium cells; most of these cells were dark, tall and cylindrical cells, while a few cells were pale in the epithelium of the entire length of the villi and crypts of Lieberkühn. Paneth cells are highly adapted small-intestinal epithelial cells, where many physiological roles are organized. These cells are located at the base of the crypts of Lieberkühn and the enteroendocrine cells are unicellular endocrine glands, lie in the villi and crypts of the small intestinal mucosa.

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## INTRODUCTION

The epithelial membrane lining the small intestine of mammals is both the path for absorption of nutrients and an effective barrier between both the surrounding factors and circulation. Growth of the surface region for nutrient absorption often raises the possibility of possible pathogens colonizing the mucosa. Lieberkühn crypts (intestinal crypts), which are delusional intestinal mucosal invaginations, are optimal microniches for microbial growth. Nonetheless, the small intestine bacterial density is relatively lower than that of the intestinal tract (Ouellette, 2005; Ergun *et al*., 2003).

The small intestine epithelium consists of enterocytes, enteroendocrine cells, goblet cells and Paneth cells. Paneth cells, sited in crypts of Lieberkühn, originate from a certain crypt stem cells that produce all lineages of intestinal epithelium (Garabedian *et al*., 1997; Ouellette, 2005). A notable organ is the gastrointestinal tract. Not only does it digest most of our food into smaller units but it is also littered with kilograms of microorganisms that live with us and our immune response in dynamic state. A digestive tract can be traced to early metazoa and Cambrian evolution long even before emergence of an adaptive immune system (Erwin and Valentine, 2013).

Goblet cells inhabit all through the Gastro Intestinal (GI) tract and are capable of producing and preserving a preventive mucus mattress like layer through the synthesis and secretion of high molecular weight glycoproteins known as mucins. Secretion-producing goblet cells (mucocytes), containing mucopolysaccharides, play a significant defensive role against chemical burns and microorganisms (barrier function), and also transporting substances between the gastrointestinal tract and the mucosal microvilli (Sgambati *et al*., 1996). The allocation of these cells has been intensively researched in mammals, primarily mammalion; even so, the goblet cell functional studies are still contentious, particularly in young animals of various species.

Paneth cells with round or oval nuclei were defined as pyramidal cells. They have been seen alongside less different infed cell types in the lower third of the intestinal crypts. Paneth cells contain various secretory granules that can be soiled with acid dye molecules at the cell apex (Cormack, 1987). In the small intestine, Paneth cells express granules into the epithelium of the Lieberkuhn crypts in which their component proteins take part in mucosal immunity (Ouellette, 2005). The granules hold a combination of associated proteins with innate immunity roles which include lysozymes, secretory phospholipase A2, and so called cryptdin alpha-defensins.

Entero Endocrine Cells (EECs) are hormone-secreting cells that are sparsely distributed in the digestive tract wall and constitute approximately one percent of the intestinal epithelial cells. The intestinal enteroendocrine system can be regarded as a colon in three broad regions in the gastric, proximal intestinal and distal intestinal. Thus, every part has a particular pattern of distribution of the EEC forms. Much of these cells exhibit neurocrine contact processes with neighboring cells (Sgambati *et al*., 1996).

### Digestive tract of mammals

The digestive tracts of various mammalian species are adjusted to the most effective use of the food they eat (Stufflebeam, 1983). The intestinal system is vital in living organisms and plays a key role in the handling and uptake of food (Parish, 2011; Hill *et al*., 2008). It was reported that the microscopic section of small intestine contains numerous goblet cells. The intestine plays an important role in the metabolism and absorption of ingested food and the eradication of undigested food and microbes. The responsive consistency of the intestinal mucosal epithelial cells varies depending on coordinated mucus layer oversight, intercellular tight junction, epithelial cells, and adaptive and innate immune response from the organism (Lievin-Le and Servin, 2006; Dharmani *et al*., 2009).

The gastric mucosa epithelium is made up of four major cell types - absorptive enterocytes, goblet cells, Paneth cells, and enteroendocrine cells - which undergo continuous regeneration cycles. The small intestinal epithelium is composed of two different compartments. The lower crypt composed of multipotent stem cells currently lying at the lower part of the crypt, frequently detected by the stem cell marker Lgr5, and rapidly spreading transit magnifying cells differentiating into mature cell lines (absorptive, goblet, and enteroendocrine cells) during migration towards the villus capsule. Paneth cells reside at crypt bottoms and differentiates (Van and Clevers, 2009).

Small intestinal mucosa is known for its villi and crypts that, in adults, are filled by mature epithelial cells forming the functional epithelial region of specialized cells which are no longer capable of differentiating and can be classified according to their function: a) enterocytes, the predominant lineage (90 per cent of total cells), with the sharp luminal brush border that absorbs nutrients b) 8 % to 10% goblet cells that naturally produce a defensive mucus shield, (c) enteroendocrine cells that make up around 1% of the epithelium and contain gastrointestinal chemicals, and (d) Paneth cells that naturally produce antibacterial compounds (Rossano *et al*., 2016).

The small intestine of ox and sheep, lie in the right half of the abdominal cavity with a few coils caudal and ventral to the rumen, while in horse they are chiefly in the dorsal part of the left half of abdominal cavity (Dyce *et al.*, 2010). The structure of the mammalian small intestine consists of four layers or tunicae: the mucosa, submucosa, myometrium and serosa (Ponder *et al*., 1985). This organ is distributed across the diverse monolayer epithelium, which consists of many distinct cell types. They are four primary cells in the intestinal epithelium *viz*: absorptive enterocytes, goblet cells, Paneth cells and enteroendocrine cells (Roth *et al*., 1990; Formeister, 2009). The mucosa had finger like projections (villi) which are heavy, crowded and lined by simple columnar epithelium and goblet cells. The mucosa had finger-like extensions (villi) that were thick, crowded and filled with clear columnar epithelium and goblet cells. Each villus' lamina propria was composed of a thin layer of cells with loose connective tissue, whereas the lower villi layer comprised of Lieberkühn's crypts forming the Paneth cells, such cells were filled with acidophilic cytoplasmic granules (Luay and Najlaa, 2017). Generally in small intestine of all animals they are small cells, with ovoid nucleus lying in the basal half of the intestinal villi and crypts of Lieberkuhn and considered as stem cells for columnar absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells (Gartner and Hiatt, 2000; Eroschenko, 2008).

All mammals' duodenum gets three various bodily secretions, *viz:* liver bile, pancreatic juice from the pancreas, and intestinal juice from the intestinal wall glands (Seeley *et al.*, 2006; Frandson *et al.,* 2009). In ruminants, these secretions elevate the pH of the ingesta from 2.5 to 7 or 8 (Umphrey and Staples, 2003). The enzymes found in the brush-border layer of one humped camel's small intestinal epithelial cells are the intestinal disaccharides (maltase, glucoamylase, sucrase, α-amylase, lactase and cellobiase) (Mohamed *et al*., 2007). El-Sayed (2006) and Hassan and Moussa (2015) reported that extensive mucous membranes were found in the duodenum and multiple goblet cells owing to the unavailability of Brunner's glands in duodenum submucosa. The mucosa had very tall simple mucosal folds which were lined with simple columnar epithelium that invaded with goblet cells and the lamina propria displaying groups of sub mucosa tubuloalveolar seromucous glands. The glands of duodenal were lined by a simple columnar epithelium that was similar to that lined in the duodenal lumen, containing stem cells, absorptive columnar cells, goblet cells and Paneth cells, except that the Paneth cells was not observed in the epithelium of duodenal lumen, the granular contents of

Paneth cells showed in the lumen of the crypts of Lieberkuhn (Abdel-Magied and Taha, 1994). There were numerous, tall columnar cells, with oval nuclei, lie in the epithelium of the villi and crypts of Lieberkuhn of the different parts of the one humped camel small intestine (Abdel-Magied and Taha, 1994). Microvilli, are cytoplasm extensions that cover the apices of the intestinal absorptive cells as brush border, in human small intestine they appear as rod shaped structures separated from each other by spaces (Marsh and Swift, 1969), and the enteric microvilli of the human beings are coated with a conspicuous layer composed of fine filaments radiating from the outer dense leaflet of the mucous membrane (Bacha and Bacha, 2000).

The villous epithelium in the one humped camel small intestine is a high simple columnar type, with deep furrows in the apical surface containing stem cells (regenerative cells), absorptive cells (enterocytes), goblet cells and enteroendocrine cells and average thickness of it is 30 - 40 µm (Abdel-Magied *et al*., 1994), in all mammals (Bacha and Bacha, 2000; Young *et al*., 2006). Those cells that had been spattered by Grimelius technique for argyrophilia and Singh argentaffin reaction 10 could be noted all throughout entire rat small intestine. Cells were dispersed as single elements across a large prevalent group of non-endocrine epithelial cells inside the columnar epithelium of the gut Grimelius positive cells which were most commonly observed in the first part of the duodenum and slowly decreased towards the jejunum, but eventually they were marginally increased in the last part of the ileum. In contrast, the middle section of the jejunum displayed a small rise in those cells (Masoud *et al*., 2014). The epithelium covering the free surface of the mucous membrane consists of simple columnar cells. Three types of cells were distinguished: columnar absorptive cells, goblet cells and enteroendocrine cells (Bacha and Bacha, 2000)

**The goblet cells**

The goblet cells are unicellular exocrine mucous glands, dispersed among the columnar cells of the epithelium of the villi and crypts of Lieberkuhn; the apical portion of it becomes distended due to mucigen droplets that accumulate as large globules, and the nucleus is irregularly oval or triangular in the basal part of the cell of small intestine of one humped camel (Abdel-Magied *et al*., 1994). The number of goblet cells decreases at the tip of the villi, and are less abundant in the duodenum, while increase in the ileum of most mammals (Junqueira and Carneiro, 2005; Seeley *et al*., 2006; Samuelson, 2007). The density of goblet cells in the caudal part is two to three times greater than that in the cranial part of the small intestine of ruminants and horse (Dellmann and Eurell, 1998). Their number in the duodenum of Tibetan goat is higher than that of Tibetan sheep (Ergun *et al*., 2010).

Goblet cells, were seen as unicellular mucous, globular shaped glands dispersed among the columnar cells in the villi and crypts of Lieberkuhn epithelium. Their nucleus were close to the base, the cells appeared white vacuolated when viewed with hematoxylin and eosin stains (Garabedian *et al*., 1997). Goblet cells were observed in the initial periods of development (at 9–10 weeks of pregnancy in the human fetal small digestive tract) and moderately undifferentiated oligomucous and mature goblet cells are noticeable in both columnar epithelium viz: stratified and simple; in any case, when the villi have grown, most goblet cells are vague from those noticed in the intestine of the adults.

The morphology of the goblet cell is formed by the distended theca which contains the mucin granules found under the apical membrane. In mice deficient in the major goblet cell mucin (Velcich *et al.,* 2002), the percentage of goblet cells among epithelial cell types rises medially from duodenum (4 percent) to distal colon (16 percent), comparable to the growing number of microbial species present in the proximal intestine to colon (Karam, 1999). The microbe-free mice's intestine has fewer and smaller goblet cells especially in

comparison to those of conventionally raised mice, implying the goblet cell microbial amplitude (Deplancke and Gaskins, 2001). Goblet cells synthesize and secrete bioactive molecules such as secretory and membrane-bound mucins, trefoil peptides, resistin -like molecule β (RELMβ), and Fc-γ Binding Protein (FcγBP), which are the components of mucus (Dharmani *et al*., 2009). Such molecules are naturally produced by two pathways, constitutive or basal secretion, or stimulated or controlled secretion, which is a low-level persistent secretion depending on the cytoskeletal motion of secretory granules, which involves exocytosis of granules in response to external stimuli (Davis *et al*., 2008). In Buffalo calves, the goblet cells were reasonable in number from the cranial to the terminal portion of the ileum. The nuclei in the form of oval or round had 1-2 nucleoli situated at the bottom of the cells and the cytoplasm is mildly eosinophilic and granular. Lieberkühn's crypts consist of undifferentiated columnar cells, and the number of goblet cells were less or nil (Barnwal and Yadava, 1975).

The mucosa of the camel small intestine was lined by simple columnar epithelium consisting of surface absorptive cells and goblet cells. A fewer number of goblet cells were observed at the tip of the villi. Goblet cells inhibit all through the intestine and were important for the production and maintaining the preventive mucous layer by producing and discharging high molecular weight glycoproteins called mucins (Deplancke and Gaskins, 2001; Kim and Khan, 2013). The mucus layer above the epithelium naturally produced by the goblet cells facilitates the degradation of gut contents and offers the first line of protection against physical and chemical damage caused by ingested food, microbes and microbial items. The key component of the mucus is the naturally produced mucins, large glycoproteins with a strongly polymeric backbone protein complexes, connected to multiple hygroscopic and hydrophilic side chains of oligosaccharides that contribute to the formation of gel-like strucure (Hollingsworth and Swanson 2004, Andrianifahanana *et al*., 2006).

**The absorptive cells**

The absorptive cells in pig were present in variable sizes depending on the position they occupy. Thus, in the Lieberkuhn glands epithelium, they are small, cuboidal in shape, with an average height of 25 µm at villi basis, while reaching 35 µm on the villi apex. Absorptive cells or the enterocytes were principal cells of epithelium; most of these cells were dark and tall, cylindrical cells, while a few cells were pale in the epithelium of the entire length of the villi and crypts of Lieberkuhn. The number of pale cells increased towards the epithelium of the villi apex, the nucleus of enterocytes was pale ovoid situated near the cell base (Garabedian *et al*., 1997). The absorbent cells are columnar or prismatic, with a centrally located, vertically elongated nucleus of 20 to 26 µm in height. The luminal surface is customized in forming a microvilli, with a striated boundary. The cell foundations rest on a thin but prominent basal layer, tightly connected to the lamina propria's connective tissues/fibres. The goblet cells are unicellular glands that are dispersed abnormally among the cylindrical absorptive cells that secrete the mucus. (Abdel-Magied *et al*., 1994).

**The Paneth cells**

The Paneth cells are pyramidal-shaped cells, in ruminants, horses and humans small intestine (Eurell, 2004). They are large columnar cells with basically positioned oval nuclei and small cytoplasmic granules apically positioned in the duodenum of the one humped camel (Abdel-Magied and Taha, 1994) and in the human small intestine, they are wedge shaped (Subbuswamy, 1973). In most mammals, the secretory epithelial cells (Paneth cells) are situated in the base of crypts of Lieberkühn (Porter *et al*., 2002). Although Garabedian *et al*. (1997) showed that the Paneth cells of the mice originated from intestinal stem cells and differ-

entiate during a downward migration to reach their definite location at the bottom of Lieberkühn crypts.

Substances such as α-defensins, lysozyme and phospholipase A2 (sPLA2) which possess antimicrobial activity were synthesized by the Paneth cells (Porter *et al*., 2002). Moreover, the Paneth cells regulate the count of endogenous flora, be a part of crypt formation and development and helps in phagocytosis, digestion and detoxification and also protects the proliferative compartment (Porter *et al*., 2202; Bevins, 2004; Ouellette, 2005).

The distribution of Paneth cells shows considerable variation among mammals. The small intestinal epithelium of the ruminants, man and monkeys contains abundant numbers of these cells in the crypts of Lieberkuhn, while they are devoid in the dog and pig (Dellmann and Eurell, 1998). In the small intestine of sheep, they are located in the crypts of Lieberkuhn and more numerous in the base than that in the higher parts of the crypts of Lieberkuhn and is characterized by acidophilic granules (Ergun *et al.*, 2003). The Paneth cells are seen to uniformly line at the base of the equine intestinal glands (Takehana *et al.*, 1998) and in human as granulated cells located at the base of small intestinal crypts (about 5-15 Paneth cells in each crypt), and these cells increases from the beginning of the duodenum towards the jejunum, but in the ileum it is less dense than that in the duodenum (Porter *et al*., 2002). Paneth cells are profoundly developed small intestinal epithelial cells, which perform a number of physiological roles. First depicted over a century ago by standard histology based on their secretory granules which are instantly perceptible, these cells are found at the base of Lieberkühn's crypts as small invaginations covering the mucosal surface along the entire small intestine. Work in the course of recent decades has showed that such cells combine and produce huge amounts of antimicrobial peptides and proteins.

Paneth cells can legitimately encounter enteric microorganisms by actuating a cell-autonomous MyD88 dependent Toll Like Receptor (TLR), which triggers articulation of different antimicrobial elements (Bevins and Salzman, 2011). Paneth cells are long-lived cells; they migrate downwards to the base of crypts after differentiating from stem cells. On the other hand, Ouellette *et al*. (2000), Cunliffe and Mahida (2004), Coutinho *et al*. (1998), Hecht (1999), Hornef *et al*. (2004) and Harwig *et al*. (1995) described the shape of Paneth cells as pyramidal with apical granules. It is rich in essential molecules which are associated with the innate immunity, such as α-defensins, lysozyme, Phospholipase A2 and other compounds implicated in the control of the structure, cell proliferation, digestive and detoxification phases of the intestinal endogenous flora (Bevins, 2004; Ouellette, 2005; Porter *et al*., 2002). In sheep, Ergun *et al*. (2010) reported that the Paneth cells were characterized by acidophilic granules which as seen in the crypts of Lieberkuhn.

In a previous study in the sheep by Ergun *et al.* (2003), Paneth cells can be recognized as acidophilic granules that were found in the crypts of Lieberkühn. These cells were present at the base and neck regions of the crypts, but none was found in the villi. The round or oval shaped nuclei were present at the base of the cells with the granules in the apical cytoplasm. On the other hand, Ahmed *et al.* (2009) revealed that the epithelium of *Varanus niloticus* covering the villi was simple columnar with goblet cells and no Paneth cells were seen in it. The lamina propria is rich in lymphocyte and eosinophils. In sheep, Ergun *et al.* (2003) revealed that no Paneth cells are encountered in the villi of the small intestines. On other aspect, Deschner (1997) revealed that the human Paneth cells are not limited to the bases of the crypts but also to the entire length of the crypts and even in the villi.

**The enteroendocrine cells**

The enteroendocrine cells are unicellular endocrine organs, that lie in the villi and crypts of the duo-

denal mucosa. In one humped camel, the EEC's *viz*: 5-hydroxytryptamine, cholecystokinin and somatostatin immunoreactive cells were flask-shaped with apices pointing towards the lumen and the peptide tyrosine - tyrosine and substance P were other immunoreactive cells which were mainly rounded or basket-shaped (Al-Haj *et al*., 2007). In Bactrian camel (Eerdunchaolu, *et al.*, 2001), in sheep (Oomori *et al*., 1980; Calingasan *et al*., 1984), in Philippine carabao, *Bubalus bubalis* (Maala *et al.,* 1989; Baltazar *et al*., 1998), in Indian buffaloes (Mishra and Das, 2000) and in horses (Kitamura *et al*., 1984), they are numerous in the epithelial surface, intestinal glands and lamina propria of the duodenal wall.

Heidenhain (1870) had first ascertained enteroendocrine cells in the stomach of rabbits and dogs in18$^{th}$ century. Soon afterwards these cells were documented in different animal species throughout the gastrointestinal tract. Their basal area were in the epithelium and the existence of concentrated granulosa cells at the base of the cell recommended that they were endocrine cells releasing bodily fluids into the propria of the epidermis and not into lumen. In 1905, Schmidt recognized these cells in the duodenum and named them as chromaffin cells because of their ability to bind to potassium dichromate. (Sadeghi *et al*., 2014).

The enteroendocrine cells were viewed as yellowish orange cells located at the bottom of Lieberkühn's intestinal glands or crypts by solvents containing potassium dichromate. Those changes are identical to adrenal medulla reactions. In the utter lack of a reduction agent, some of these cells precipitate silver salts, and were called argentaffin cells. They exist as very common individual cells and tend to be a small aspect of the epithelium, but were estimated to be numerous in the human intestine. (Al-Haj *et al*., 2007).

Enterocytes are primary intestinal epithelial cells and basic columnar epithelial cells which assume key jobs in the assimilation of nutrients (for example ions, water, sugar, peptides, and lipids) and in immunoglobulin bodily liquids. Goblet cells make up around 10 per cent of all EECs. Goblet cells secrete mucus, which greases the passage of food into the intestines and protects the wall against digestive enzymes (Kim and Ho, 2010). Neuroendocrine cells, upon stimuli, can discharge intestinal hormones or proteins into the bloodstream to activate nervous reactions (Noah *et al*., 2011). It is also known that neuroendocrine cells act as chemoreceptors, initiate digestive process, detect toxic chemicals and and initiating protective responses (Cox, 2016).

**Other cells**

Other revealed cell types involve exocrine cells, and endocrine cells. Exocrine cells were situated in the small intestinal mucosa, secreting bodily fluid, peptidase, sucrase, maltase, lactase, lipase, and enteropeptidase (Noah *et al*., 2011). Cholecystokinin and secretin are discharged by endocrine cells. Their discharges are mostly controlled by chyme: the more noteworthy the amount of chyme present, the higher the secretions in the intestine (Rindi *et al*., 2004).

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