Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.57.008939

Paneth Cells: Development, Morphology, Function and Clinical Importance

Mukaddes Esrefoglu*

Department of Histology and Embryology, Faculty of Medicine, Bezmialem Vakıf University, Turkey

***Corresponding author:** Mukaddes Eşrefoğlu, Department of Histology and Embryology, Faculty of Medicine, Bezmialem Vakıf University, Fatih Istanbul, Turkey

ARTICLE INFO

Received: May 06, 2024

Published: June 13, 2024

Citation: Mukaddes Esrefoglu. Paneth Cells: Development, Morphology, Function and Clinical Importance. Biomed J Sci & Tech Res 57(1)-2024. BJSTR. MS.ID.008939.

ABSTRACT

Paneth cells (PCs) first described in the late 19th century are columnar epithelial cells of the intestinal glands. PCs are easy to recognize based on their locations and the presence of numerous apical granules. PCs are crucial in the defense against pathogens thus maintaining intestinal flora and in the protection of nearby stem cells thus maintaining epithelium. Besides they can eliminate certain bacteria and trophozoites by their phagocytic ability and engulf the neighboring apoptotic intestinal epithelial cells. The altered integrity increases the risk of developing inflammatory bowel diseases. PCs capture the attention of scientists, especially in terms of the role of their antimicrobials in arbitrating host-microbe interactions and the mechanism by which PCs mediate in the crypt stem cell niche. This review will provide a brief glimpse into the history, development, morphology, function, and clinical importance of PCs.

Keywords: Paneth Cell; History; Development; Morphology; Function

Abbreviations: PCs: Paneth Cells; TCF: T Cell Factor; TLR: Toll-Like Receptor; SLPI: Secretory Leukocyte Inhibitor; EGF: Epidermal Growth Factor; TGF: Transforming Growth Factor; PRRs: Pattern Recognition Receptors; NOD: Nucleotide-Binding Oligomerization Domain; IBD: Inflammatory Bowel Diseases; UC: Ulcerative Colitis; CD: Crohn's Disease; GBA: Gut-Brain Axis; LRRK2: Leucine-Rich Repeat Kinase 2; XBP1: Xbox- Binding Protein-1; IL: Interleukin

Introduction

The intestinal glands occupying nearly the whole lamina propria are tubular glands extending from the lamina muscularis mucosa to the base of the intervillous space. The glandular epithelium comprises various cell types including enterocytes, goblet cells, enteroendocrine cells, Paneth cells (PCs), intermediate cells, and stem cells. Stem cells and PCs are located at the base of the intestinal glands. PCs are easily recognized due to their zymogen granule content that is strongly acidophilic in staining characteristics (Figure 1A) (Esrefoglu [1]). In the small intestines of mice, rats, and humans, the distribution of PCs is heterogeneous, with fewer numbers in the duodenum and higher numbers towards the ileum (Darmoul, et al. [2,3]). PCs are located all along the entire length of the small intestine in healthy individuals, but they can also be detected throughout the colon and esophagus in diseased individuals (Cheng, et al. [4-6]). PCs are unique cells because they not only exhibit protein-synthesizing properties but also unexpectedly phagocytose certain harmful bacteria and protozoa. Even though they are epithelial cells with an endodermal origin, they are surprisingly capable of phagocytosis, which helps to maintain hemostasis in the intestinal milieu by controlling the intestinal flora. More than a century ago, Gustav Schwalbe (1844-1916) who was a well-known German anatomist, histologist, and anthropologist first described glandular cells with acidophilic granules (Schwalbe, et al. [7,8]).

Schwalbe was the first to describe PCs in the Archiv für mikroskopische Anatomie in 1872. In addition to anthropological research, he made scientific studies on the nervous system, lymphatic system, and eye. Descriptions such as 'Schwalbe's spaces', 'Schwalbe's nucleus', 'Schwalbe's ring', and 'Schwalbe's line' refer to his name. In 1888, Joseph Paneth (1857-1890), an Austrian histologist and physiologist, reported the results of his detailed morphological analysis of PCs (Paneth, 1988) (Bykov [8]). By microscopic examination of the crypts of Lieberkuhn in the small intestine, he identified the cells known eponimically as Paneth's cells. He made this discovery two years be-

fore his death at age 33 because of tuberculosis. Between 1960 and 1970 research on these cells was accelerated because of the recognition of the antimicrobial nature of their apical granules (Bykov, et al. [8-10]). The results of electron microscopic observation focused on secretory granules, lysosomes, and endoplasmic reticulum first appeared in 1964 (Behnke, et al. [11]). Through secretory products and their capacity for phagocytosis, PCs manage the intestinal microbiota, maintaining commensal microbes and eliminating noncommensal ones. Dysbiosis, characterized by an increase in non-widely distributed bacteria, can be the result of a reduction of PC secretion (Zhang, et al. [12]). PCs still capture the attention of scientists, especially in terms of the role of their antimicrobials in arbitrating host-microbe interactions and the mechanism by which PCs mediate in the crypt stem cell niche.

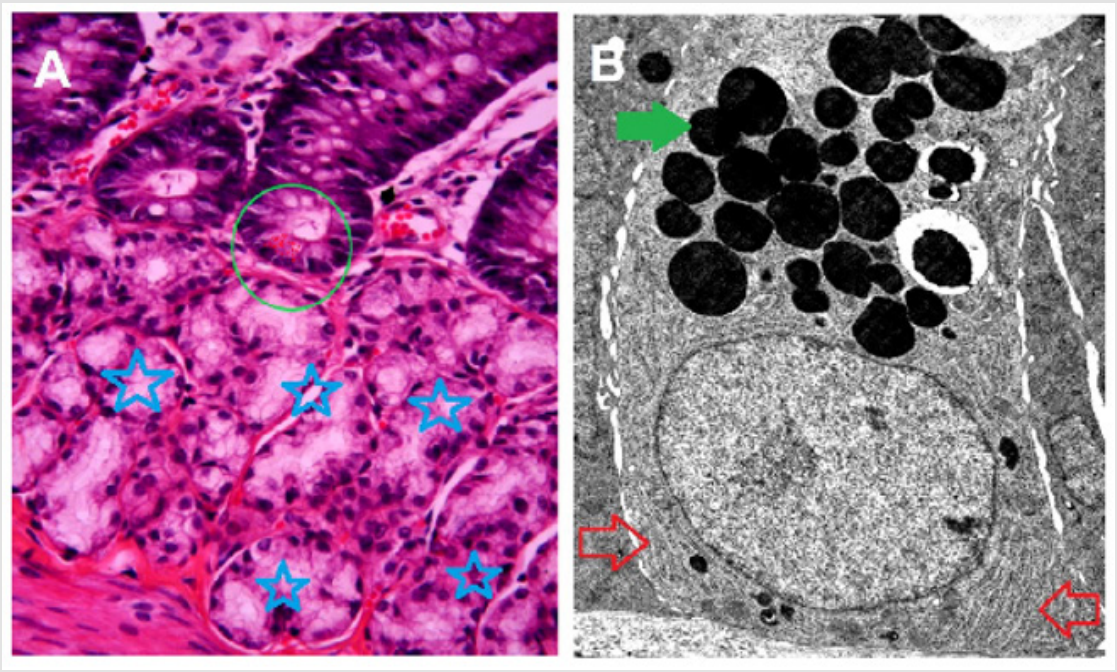

Figure 1: Light (A) and electron microscopic (B) features of PCs.

A. At the base of the intestinal glands of the duodenum PCs with acidophilic granules are obvious. In the submucosa Brunner's glands are marked (asterisks).

B. In the human intestinal gland, a PC containing perinuclear rough endoplasmic reticulum (clear arrows) and apical zymogen granules (arrow) is observed. Hematoxylin & eosin; X 40, Uranyl acetate & lead citrate; X 6.300; respectively.

Microscopic Features of Paneth cells

PCs are pyramidally shaped epithelial cells with a broader base and narrower apical pole. The nucleus is generally oval-shaped, sometimes irregular in outline, and the nucleolus is a dense sponge-like structure (Eltahawy, et al. [13]). They possess an extensive rough endoplasmic reticulum, supra-nuclear Golgi apparatus, many mitochondria, and apical-orientated cytoplasmic granules (Porter, et al. [1,14,15]). PCs are distinguishable from the other cells of the epithelium because of their unique location and eosinophilic apical granules. At the electron microscopic level electron-dense apical granules and extensive network of endoplasmic reticulum are conspicuous (Esrefoglu, et al. [1,15,16]) (Figure 1B). Various histochemical staining techniques, including eosin, periodic acid Schiff's stain, phloxine-tartrazine (Lendrum [17]), fluorescent staining (Fano, et al. [18]), and pokeweed lectin binding (Evans, et al. [19]) intensely stain the PC granules. PC-specific components, primarily lysozyme (Erlandsen, et al. [20,21]), and more recently defensins (Porter, et al. [22]) or type-2 secretory phospholipase A2 (Nevalainen, et al. [23]), have allowed for more accurate labeling for PCs. The granules include more than 50 substances, including trypsinogen, IgA, TNF-alpha, alpha 1-antitrypsin, human alpha defensin 5 and 6, lysozyme, secretory phospholipase A2, osteopontin, and catecholamines. The main ingredient of the granules is human alpha defensin 5, which accounts for roughly 90% of the mixture (Porter, et al. [14]).

Comparative ultrastructural analysis of Satoh et al. (Satoh, et al. [24]) revealed that granule morphology varies among the species. It was discovered that PCs from hares, guinea pigs, humans, monkeys, and bats have secretory granules with homogenous electron-dense components. In humans, (Figure 1B), monkeys, and bats, immature granules near the Golgi apparatus sometimes show bipartite substructure.

Development of Paneth cells

The origin of the epithelial derivatives of the intestines is the endodermal germ layer. The proximal part of the duodenum is derived from the foregut whereas the distal part of the duodenum, jejunum, and ileum are derived from the midgut (Esrefoglu [25]). PC differentiation is the result of intricate interactions between several factors. The Wnt pathway and the expression of SRY-Box transcription factor 9 (Sox9), one of its targets, are the main factors influencing differentiation (Bastide, et al. [26,27]). A favorable environment is created for the progenitor cells to differentiate into PCs by the high concentration of Wnt and the limited supply of Notch (Farin, et al. [28-30]). A distinct differentiation profile is induced by Wnt activation, which stabilizes and translocates β-catenin to the nucleus where it interacts with several T cell factor (TCF) molecules. TCF4 is a PC maturation regulator that induces a PC gene program in the developing gut of the mice (van Es, et al. [31]). Sox9 and SAM-pointed domain-containing ETS transcription factors are involved in both PC and goblet cell differentiation (Bastide, et al. [26,32]). Since most research on stem cell niche and PC differentiation has been performed in rodents, some different factors can be effective in humans. Hence, in human and mouse organoids important differences in niche factors have been detected (Sato, et al. [33]). In humans, the intestinal glands appear around the 10th gestational week, soon PCs appear between the 11 to 13.5th weeks in the small intestines and also in the colon (Moxey, et al. [34-37]).

Except for pathological situations, they are restricted to the small intestine until after 17 weeks of gestation (Mallow, et al. [37]). The development of PCs can be observed by examining their cytoplasmic granules, which enlarge and become heterogeneous after 20 gestational weeks (Moxey, et al. [34]). Until a sufficient number of matured and functional PCs is reached at term, the number of PCs progressively increases with a considerably more rapid expansion after the 29th week (Umar [38]). The expression of human alpha-defensin 5 (HD5) which is a marker of the immune competence of PCs increases after the 29th week of gestation (Heida, et al. [39]). Between weeks 29 and 37, the number of PCs and the level of HD5 rapidly increases (McElroy, et al. [40]). Since epithelial maturation of the intestines is not completed at birth, growth factors and cytokines derived from breast milk, interstitial fluid, and systemic circulation help to complete maturation during postnatal life (Montgomery, et al. [41]). PC expression is low in the human, mice, and rat newborns, PC numbers and secretory products significantly increase during the postnatal period (Bry, et al. [37,42,43]), independently of exposure to microorganisms (Bry, et al. [42]). A steady count of PCs per crypt is established in early adulthood. Several factors have been suggested to impact the total number of PCs including gestational age at birth, the manner of delivery, nursing (Porter, et al. [14]), the weaning diet and duration, dietary preference, and medical problems (Umar, et al. [4,38]).

In a healthy person, the number of PCs remains relatively constant for up to 20 years (Stappenbeck, et al. [44]) which is five to fifteen PCs per crypt. PCs are especially prevalent in the terminal ileum which has the highest load of microorganisms (Luvhengo, et al. [45]). PCs undergo apoptotic cell death at the end of their lifespan which is longer than that of the enterocytes (Günther, et al. [46]). Apoptosis is characterized by abundant expression of pro-apoptotic protein ARTS (apoptosis-related protein in the TGF-β signaling pathway) in PCs (Koren, et al. [47]).

Secretory Activity of Paneth cells

As mentioned above, PCs with extensive rough endoplasmic reticulum, prominent Golgi apparatus, many mitochondria, and numerous granules are typically protein-secreting cells. More than 50 ingredients are present in the granules, including trypsin, trypsinogen, IgA, TNF-alpha, alpha 1-antitrypsin, human alpha-defensin 5 and 6 (HAD5 and HAD6), lysozyme, heavy metal ions such as zinc, copper and selenium, etc. (Porter, et al. [14]). PCs release their granules into the crypt lumen via exocytosis in a manner of merocrine secretion in response to a range of stimuli, such as bacterial cell surface molecules (Ayabe, et al. [48]), acetyl cholinergic agonists (Satoh, 1998), and other Toll-like receptor agonists (Rumio, et al. [49]). The release of granules by PCs in response to heat-killed or live bacteria (Satoh Y, et al. [50-52]) or microbial products such as lipopolysaccharide and lipoteichoic acid (Ayabe, et al. [48]) increases the concentration of luminal antimicrobials. Following degranulation of PCs, granules are replenished immediately, usually within 24 hours (Zhang, et al. [12]). The results of the study by Vaishnava et al. [53] indicate that PCs use cell-autonomous MyD88-dependent toll-like receptor (TLR) activation to identify enteric bacteria. This activation causes the development of a comprehensive antimicrobial program that includes RegIIIγ, RegIIIβ, CRP-ductin, and RELMβ. According to their findings, the translocation and spread of bacteria across the mucosal barrier are inhibited by PC-intrinsic MyD88 activation. To protect the host against infections by *Listeria monocytogenes*, *S. aureus*, and *Toxoplasma gondii*, MyD88-dependent pathways are critical (Scanga, et al. [54,55]).

In humans, two classes of antimicrobial peptides which are cathelicidins and defensins have been identified. In the neonatal period, cathelicidins possessing antibacterial, antiviral, and antifungal activities are exclusive (Lueschow, et al. [56]). Defensins are classified as alpha-defensins which are also known as cryptidins in mice and beta-defensins. Alpha-defensin is produced by PCs and neutrophils, and beta-defensins are produced by epithelial cells (Gassler, et al. [57,58]). The alpha-defensins are produced as pre-pro-peptides. Pro-defensins undergo proteolytic cleavage to become active alpha-defensins after losing their signal peptide during the transition from the ER into the secretory vesicles. In human PCs, trypsin which is stored as trypsinogen and activated after or during secretion is responsible for the proteolytic maturation (Ghosh, et al. [59]). Only two enteric alpha-defensins which are HD5 and HD6, are produced by the human body despite the genome encoding ten alpha-defensins (Patil, et al. [60]). Humans express neutrophilic alpha-defensins, which are not expressed in mice (Shanahan, et al. [61]). HD5 possesses lec-

tin-like characteristics and acts as a harpoon by rupturing bacterial membranes. Human HD6 is different from the other alpha-defensins in terms of its binding properties. Rather than being bactericidal or bacteriostatic, HD6 works by first attaching itself to the proteins on the surface of the bacteria. This initial binding leads to a gradual binding to the anchoring ligand, which in turn creates self-assembling peptide nanofibrils and nano nets that encircle the targeted bacteria.

The captured bacteria cannot invade the mucosa (Bevins, et al. [62-64]). Since HD5 and HD6 can influence DNA and RNA replication and resemble viral coats, they possess indirect antiviral effects (Bevins, et al. [65,66]). Some of the other less well-defined antimicrobial proteins produced by PCs are the weakly antimicrobial secretory leukocyte inhibitor (SLPI), immunoglobulin A (IgA), and M (IgM) (Bergenfeldt, et al. [67-69]). Secretory IgA, released from the PC cytoplasm inhibits the adhesion and adsorption of viruses and bacteria in the intestinal mucosa (Wang, et al. [70]). Moreover, PCs are a significant source of cathepsin G, which destroys pathogens, regulates the immune response, and sterilizes the intestinal epithelium (Zamolodchikova, et al. [71]). Interestingly, microorganisms stimulate PCs to release a large amount of lysozyme and cathepsin G, which in turn kill harmful pathogens and mediate homeostasis of the intestinal flora (Burclaff, et al. [72]). PCs release chemicals such as lysozyme, secretory phospholipase A2, and c-type lectins in addition to antimicrobial peptides. An enzyme called lysozyme is specifically responsible for hydrolyzing peptidoglycan found in bacterial cell walls. The lysozyme C gene, which is expressed in PCs, is the only lysozyme that humans encode (Bevins, et al. [14,58,62]). PCs have a constitutive expression of bactericidal secretory phospholipase A2, which is particularly effective against Gram-positive bacteria (Bevins, et al. [62,73]).

C-type lectins bind glycan chains of peptidoglycans on the walls of Gram-positive bacteria (Holly, et al. [58, 74]). As a member of the C-type lectins family, pancreatitis-associated protein binds sugar moieties on microbial surfaces resulting in enhanced binding to phagocytes (Lasserre, et al. [52,75]). Unlike defensins, c-type lectins are expressed after the induction of Toll-like receptor pathways (Bevins, et al. [62]). Antimicrobial peptides produced from PCs help to keep the gut microbiota in a healthy state and guard against bacterial infections. (Clevers, et al. [76]). Antimicrobial peptides either cause pathogens' cell membranes to become micellized or inflict damage to the membrane's surface, opening up sizable holes that pierce deeper into the hydrophobic cell membrane (Porter, et al. [14,77]). For a variety of enzymatic activities in PCs, heavy metal ions may be necessary. Moreover, they may enhance the antimicrobial activity of PCs by acting as direct harmful compounds at high concentrations or by working in concert with other antimicrobial components of PCs (Wilson, et al. [78,79]). Zinc is not only directly antibacterial but also contributes to PC antimicrobial activities (Wallaes, et al. [80]).

Paneth Cells and Stem Cell Niche

PCs respond to autocrine, paracrine, or endocrine signals in addition to performing autocrine, paracrine, and endocrine tasks. Close relationships and direct communication take place between PCs and the first tier of intestinal stem cells, also known as Lgr5+ cells or crypt-base columnar cells (Sato, et al. [33]). The Lgr5+ intestinal stem cells have the least capacity to repair any damage to their DNA (Luvhengo, et al. [45]). The secretory products of PCs tightly regulate the proliferation and differentiation of the Lgr5+ intestinal stem cells in the niche area. To maintain the regular replacement of short-lived exfoliating surface epithelial cells, PCs protect and control the activity of Lgr5+ intestinal stem cells and their derivatives (Sato, et al. [33]). Secretions from PCs in the proximal parts of the small intestine influence the growth and function of distally situated stem cells and their derivatives (Salzman [81]). By delivering growth-promoting molecules including Wnt3a, Dll4, epidermal growth factor (EGF), and transforming growth factor-α (TGF-α) as well as metabolites like lactate and cyclic ADP ribose, PCs support the stem cell niche (Sato, et al. [33,82]). PCs can facilitate communication between specific bacterial communities and stem cells. The stem cells produce lactic acid which binds to the lactate G-protein-coupled receptor on PCs.

The binding increases Wnt3a expression in PCs, which in turn enhances Wnt signaling in stem cell niches (Lee, et al. [83]). The other role of the PCs is to nourish the intestinal stem cells (Booth, et al. [84.85]). PCs use the glycolytic pathways to obtain energy, while intestinal stem cells use the mitochondria's aerobic metabolism to produce ATP. The lactic acid produced by a PC is transferred into adjacent intestinal stem cells for utilization in metabolism. PCs can detect the body's fed state and then modify intestinal stem cell activity under that sensation (Luvhengo, et al. [45]). Under the influence of peristalsis, PCs secrete their main products together with water and chloride ions to bathe the crypt environment in a manner that is favorable to the functioning of intestinal stem cell tiers (Porter, et al. [14,33,84]). By producing antimicrobial peptides, PCs also aid in sterilizing the stem cell zone, safeguarding intestinal stem cells. (Bevins [86]).

Unexpected Phagocytotic Activity of Paneth Cells

Professional phagocytes like neutrophils and macrophages use phagocytosis as their primary method of eliminating microorganisms. On the other hand, phagocytotic activity is an unexpected engagement for the epithelial cells. Epithelial cells, however, also demonstrate potent phagocytic ability—a process referred to as "internalization"—when combating a range of bacterial infections (Plotkowski, et al. [87,88]). Spiral-formed bacteria and trophozoites of the *flagellate Hexamita muris* were identified in the digestive vacuoles of PCs from rats (Erlandsen, et al. [89]). *S. Typhimurium* was also demonstrated in the PCs of infected mice (Bel, et al. [90]). Thus, epithelial cells can be considered as facultative or non-professional phagocytes. Phagocytosis capacities and methods of the epithelial cells are quite different from those of the professional phagocytes. Professional phagocytes recognize the pathogen-related molecules using pattern recognition receptors (PRRs) and actively phagocytose them. A significant part of the process is antibody-mediated opsonization (Mosser, et al. [91]). Nonprofessional phagocytes do not express opsonic phagocy-

tosis-related receptors. Instead, the host cells actively participate in the internalization process by allowing the pathogen to enter them. The pathogens use two distinct mechanisms which are the "zipper" and "trigger" mechanisms to enter the epithelial cells (Günther, et al. [92]). In the zipper mechanism, cell adhesion to the host membrane is facilitated by host surface proteins such as cadherins and integrins (Veiga, et al. [93]).

The attachment of pathogens causes the reorganization of the actin cytoskeleton, which leads to internalization. The zipper mechanism is used for internalization by a wide range of bacteria, including *Listeria monocytogenes*, *Staphylococcus aureus*, *Helicobacter pylori*, and *Yersinia enterocolitica* (Günther, et al. [92,93]). In the trigger mechanism, soluble chemicals secreted by the pathogens cause the reorganization of the actin cytoskeleton resulting in the formation of a phagocytic cup and ultimately internalization. Actin fiber organization results in the formation of membrane ruffles which enfold the pathogen, fuse, and eventually form a pathogen-containing vesicle. Examples of bacteria using this trigger mechanism are *Salmonella sp.* and *Shigella sp.* colonizing intestinal epithelial cells (Günther, et al. [92,93]). The epithelium expresses various PRRs that actively recognize the invading microorganism, so the epithelium releases cytokines and chemokines in response to the invasion (Günther, et al. [92]). To prevent dysbiosis and/or harmful microbial invasion, PCs include PRRs, which comprise nucleotide-binding oligomerization domain-like (NOD) and TLR receptors. These receptors are used by PCs to continuously sample the composition of the microbiome in the intestinal lumen. (Lievin-Le Moal, et al. [77]). The main principles of phagosome maturation in professional and non-professional phagocytes are relatively similar. In both cell types, after the engulfment of the pathogen, phagosome fuses with lysosome, and phagolysosome formation occurs (Blanchette, et al. [94]).

However, in non-professional phagocytes, phagolysosome formation is slower than in professional phagocytes. Furthermore, lysosome numbers in non-professional phagocytes are much lower than those in professional phagocytes (Saftig [95]). Non-professional phagocytes do not prioritize phagocytosis as much as professional phagocytes do, besides these cells cannot eradicate microorganisms with the same level of effectiveness. Efferocytosis which removes apoptotic cells by phagocytes was recently identified as a new function of PCs. Shankman et al. (Shankman, et al. [96]) illustrated that PCs can effectively engulf the neighboring apoptotic intestinal epithelial cells, hence reducing local inflammation and contributing to gut homeostasis. CD95 receptors expressed on the basolateral surface of intestinal epithelial cells can trigger apoptosis in the intestine (Strater, et al. [97]). PCs secrete CD95 ligands to drive apoptosis of epithelial cells suggesting the potential role of PCs in regulating epithelial integrity (Moller, et al. [98]). The apoptotic epithelial cells at the villus tip are shed into the lumen (Blander, etb al. [99]), and other apoptotic epithelial cells are engulfed by professional and non-professional phagocytes (Arandjelovic, et al. [100,101]). PC deletion leads to apoptotic cell increase and efferocytosis disappearance in crypts under homeostasis and irradiation conditions (Shankman [96]).

Relationship Between Paneth Cells and Diseases

Anatomical, functional, and pathological alterations in PCs are anticipated as the cause or consequence of digestive disorders, given the important role that PCs play in maintaining the stem cell niche and the microbial ecology. Before, during, or following the onset of the disease, the number, position, distribution, and microscopic features including organelle and granule morphology and quantity may change resulting in PC dysfunction. Alteration in the composition of the gut microbiota is called 'dysbiosis' which is characterized by an increased number of pathobionts, but fewer symbionts and is closely related to the altered integrity of PCs. Oxidative stress, bacteriophage induction, and the secretion of bacterial toxins can trigger rapid shifts among intestinal microbial groups thereby yielding dysbiosis (Weiss, et al. [102]). Dysbiosis increases the risk of developing inflammatory bowel diseases (IBD) such as ulcerative colitis (UC), Crohn's disease (CD), necrotizing enterocolitis (NEC), and indeterminate colitis (Tomasello, et al. [103-106]). Besides, metabolic disorders such as obesity and diabetes type II are associated with intestinal dysbiosis (Weiss, et al. [102]). Moreover, microbial intestinal dysbiosis has been suggested to play a prominent role in the pathogenesis of central nervous system-related disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis. The interrelation between dysbiosis and the increased prevalence of neurodegenerative diseases is attributed to the disrupted integrity of the intestinal barrier leading to the transition of pathogens and toxic metabolites into the circulation causing the dysregulation of the Gut-Brain Axis (GBA) (Chidambaram, et al. [107]).

Inflammatory bowel diseases including UC and CD are both related to dysbiosis. In UC, the pathogens recognized as foreign by the PCs lead to an inflammatory response in the bowel wall (Salzman [81]). CD is an IBD that affects mainly the ileum and colon. The etiology of CD comes from genetic and environmental factors, and it affects mostly the immune response and intestinal barrier (Torres, et al. [108]). CD is associated with abnormal bacterial adherence to the intestinal mucosal surface and abnormal composition of colonizing microbiota in the intestine, two phenomena that implicate abnormal PCs (Sartor, et al. [109,110]). Recent studies have shown that abnormal PC morphology and/or decreases in a-defensins are present in 50% of pediatric CD patients (Perminow, et al. [111,112]). Thus, in CD, the ability of PCs to secrete sufficient antimicrobial peptides to prevent dysbiosis is diminished (Simms, et al. [113]). Wehkamp and colleagues (Wehkamp, et al. [114]) reported that α-defensin expression in PCs is reduced in ileal CD compared with expression in either healthy controls or individuals with other categories of inflammatory bowel disease. The gene that is mostly associated with CD is NOD2 (Wang, et al. [69]). As mentioned above, NOD and TLR receptors, the PRRs, are crucial for PCs to prevent dysbiosis and/or harmful microbial invasion (Lievin-Le Moal, et al. [77]). NOD2 is associated with autophagy, response

against bacteria, regulation of alpha-defensin expression, and AMP sorting in PCs (Yang, et al. [115]). In PCs, NOD2 can upregulate the expression of HD5 and HD6 through the nuclear factor-κB pathway and can downregulate the expression of HD5 and HD6 through the mitogen-activated protein kinase pathway.

CD is associated with mutations in NOD2 resulting in an insufficient response against bacteria, decreased secretion of AMPs, or the targeting of these peptides to lysosomes (Ogura, et al. [115,116]). Increased risk of developing CD is associated with the abnormalities of other autophagy-related genes including autophagy-related 16-like 1 (ATG16L1), leucine-rich repeat kinase 2 (LRRK2), immunity-related GTPase family member M (IRGM1) (Wang, et al. [69]) and Xbox-binding protein-1 (XBP1) (Yang, et al. [115]). Thachil and colleagues (Thachil, et al. [117]) reported that autophagy is specifically activated in PCs from CD patients, independently of mucosal inflammation or disease-associated variants of Atg16L1 or IRGM. In these cells, activation of autophagy in PCs was associated with a significant decrease in the number of secretory granules. NOD2 is associated with the recruitment of ATG16L1 which is expressed by PCs as well as antigen-presenting cells and T lymphocytes (Cadwell, et al. [104]). ATG16L1 is a gene involved in the formation of autophagosomes (Yang, et al. [115]). ATG16L1 deficiency is related to abnormal exocytosis (Cadwell, et al. [104]). LRRK2 gene important to maintain the normal inflammatory response in the intestines (Wallings, et al. [118]) is also related to an increased risk of developing CD (Wallings, et al. [115,118]). IRGM, a protein related to inflammation and autophagy, inhibits NLRP3 inflammasome, reducing the transcription of proinflammatory cytokines, such as interleukin (IL)-1β, IL-18, and TNF-α. Several large-scale genome-wide association studies genetically linked IRGM to CD and other inflammatory disorders in which the IRGM appears to have a protective function (Mehto et al. et al. [119]).

IRGM gene variations are associated with increased susceptibility to CD (Parkes, et al. [120]). Finally, transcription factor XBP1 abnormalities are also associated with the risk of developing CD (Yang, et al. [115]). In PCs, the deletion of XBP1 results in endoplasmic reticulum stress, autophagy, and spontaneous ileitis (Adolph, et al. [105]). KCNN4, another gene that encodes for the Ca2+-activated potassium channel KCa3.1 is associated with CD susceptibility (Simms, et al. [121]). Abnormalities in the KCa3.1 channel may disrupt PC granule secretion and may result in a deficiency of PC AMPs in small intestinal crypts. These results support the idea that PC functional problems are the initiators of ileal CD in patients. For preterm infants, one of the leading causes of morbidity and mortality, and the most devastating intestinal complication, is the development of NEC (Patel, et al. [122]). Theories have been suggested to explain this delay including feeding practices, the development of microbial dysbiosis, the accumulation of mesenteric hypoxic events (Hackam, et al. [123]), and disruption in the function or quantity of PCs (McElroy, et al. [41]). Premature infants do not possess a full complement of the functional PC population. As PCs are essential to regulate the intestinal bacterial flora, disruption of normal PC function, especially in the immature intestine could very well be involved in developing the NEC (Lueshcow, et al. [56]). Decreased numbers of lysozyme-positive PCs were documented in infants with surgical NEC compared to similar-aged surgical controls (Coutinho, et al. [124,125]).

As the premature infant is exposed to foreign antigens, there is an increase in the production of inflammatory cytokines (Lueshcow, et al. [56]) creating a more aerobic state leading to a competitive advantage for Proteobacteria. As the microbiome becomes more dysbiotic, it suppresses anti-inflammatory mechanisms but increases intestinal inflammation (Elgin, et al. [126]). Increasing inflammation can then lead to a loss in PCs (Brown, et al. [127]). This limited number of PCs has limited capacity for protection via AMPs (Satoh, et al. [50]). As AMP reduction reaches a critical threshold, bacterial invasion of the epithelial tissue begins to occur (Sherman, et al. [128]). Salzman et al. found that in NEC patients, PC numbers were increased and expression of defensin HD5 mRNA was not paralleled by a similar increase in HD5 peptide (Salzman, et al. [129]). They suggested that the lower peptide levels in PC could reflect a defect in protein synthesis or an increase in secretion. UC is a chronic immune-mediated inflammatory disorder of the colon that is hypothesized to be related to exposure to environmental risk factors leading to inappropriate immune responses to enteric commensal microbes in genetically susceptible individuals (Du, et al. [130]). Patients with UC have disturbances in the composition of their gut microbiota, coined "microbial dysbiosis," with a reduction in bacterial diversity (Nagalingam, et al. [131,132]). In UC, the colonic antimicrobial barrier, formed by a mucus layer retaining the AMPs, is impaired despite the upregulated epithelial peptide production (Ostaff et al. et al. [133,134]).

Nevertheless, the pathogenesis of UC is complex, and the interaction between the host and intestinal microbiota may be a key factor. Under normal circumstances, the host's innate and adaptive immunity prevents the invasion of harmful bacteria while tolerating the normal microbiota. However, if the microbiota is imbalanced, immunity is compromised. The intestinal mucosal immune response is overstimulated, which can lead to disease (Shen, et al. [135]). The shifts in the balance of the mucosal microbiota in UC towards increased proportions of pro-inflammatory bacteria, especially Enterobacteriaceae, and decreased proportions of anti-inflammatory bacteria, such as *Bacteroides spp.,* may initiate and exacerbate inflammation (Jalanka, et al. [136]). Decreased expression of antimicrobial defensin β 1 (DEFB1), a key effector of the innate immune system (Planell, et al. [137]) linked to an increased Enterobacteriaceae abundance may cause activation of the mucosal immune system and activity of the inflammatory disease (Jalanka et al. [136,138,139]).

Conclusion

PCs are crucial in the defense against pathogens thus maintaining intestinal flora and in the protection of nearby stem cells thus maintaining the epithelium. Although phagocytotic activity is an unex-

pected engagement for the epithelial cells, PCs can eliminate certain bacteria and trophozoites by their phagocytic ability. Besides, these cells can effectively engulf the neighboring apoptotic intestinal epithelial cells, hence reducing local inflammation and contributing to gut homeostasis. The altered integrity of PCs results in dysbiosis characterized by an increased number of pathobionts versus symbionts. Dysbiosis, in turn, increases the risk of developing inflammatory bowel diseases such as ulcerative colitis, Crohn's disease, and necrotizing enterocolitis. PC morphology and function are the major research focus in areas including inflammatory bowel diseases, infection diseases, and regenerative medicine.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.57.008939

Mukaddes Eşrefoğlu. Biomed J Sci & Tech Res

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