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Review

The multifaceted Paneth cell

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Abstract. Paneth cells (PCs) were described over a century ago as granulated cells located at the base of small intestinal crypts, the 'crypts of Lieberkühn.' Various histochemical staining procedures were developed that identified PCs based on their distinctive granule-staining pattern. Early on, PCs were proposed to perform a specialized function other than absorption of digested nutrients, the predominant task of the small intestinal epithelium. Since then, many constituents of the PC granules have been biochemically characterized. The presence of various granule-associated antimicrobial substances and their release upon microbial challenge suggest that PCs function as specialized defense cells in the small intestine. Altered resistance to microbial infection in animal models with disrupted or augmented PC function provides further support for the host defense role of PCs. Other PC components suggest that PCs may also participate in the regulation of lumenal ionic composition, crypt development, digestion, and intestinal inflammation.

Key words. Innate immunity; pancreas; inflammatory bowel disease; antimicrobial peptide; cytokine; matrilysin; trypsin.

Introduction

This review summarizes reports on the biology and function of Paneth cells (PCs) gained from a variety of research perspectives, and proposes a model for PCs as multifunctional cells. Whereas the antimicrobial properties of PCs are now well established, the suggested additional roles are more speculative.

PCs are granulated cells in small intestinal crypts

PCs are found at the bottom of the small intestinal crypts [1, 2], also called crypts of Lieberkühn (fig. 1). On average, there are 5–15 PCs in each crypt [3, authors' observations]. Various histochemical stains (fig. 2), including periodic acid Schiff's stain, eosin, phloxine-tartrazine [4, 5], Blancofor BA or fluorescent staining [6], and pokeweed lectin binding [7], intensely stain the basic PC granules, when properly fixed [8], and have been used to identify PCs in vertebrates [6, 9–11]. By such histochemical criteria, the small intestines of humans, primates, rodents, horses, and pigs are abundantly populated with PCs (table 1). Comparative ultrastructural analysis revealed that granule morphology varies among the species [12]. More precise staining for PCs was achieved with immunohistochemistry employing antibodies against PC-specific components, mostly lysozyme [8, 14] and, more recently, defensins [15] or type-2 secretory phospholipase A2 (sPLA2) [16]. We noted that in some circumstances such as ulcerative colitis in humans, the typical histochemical staining of granules is absent while staining of granule-as-

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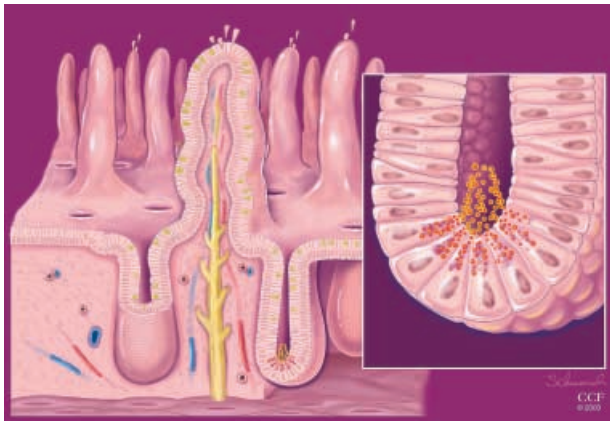

Figure 1. Schematic diagram of the small intestinal villus-crypt architecture. Intestinal stem cells reside at the neck of the crypt. Immature epithelial cells derived from the stem cells migrate either toward the villi tips or toward the crypt base. Cells migrating toward the villus differentiate into either absorptive enterocytes, goblet cells, or enteroendocrine cells. At the villus tips, cells ultimately die by apoptosis and are sloughed. Cells that migrate toward the crypt base differentiate into Paneth cells. *Inset* Paneth cells release their secretory vesicles into the narrow crypt lumen. See text for details. (Illustration by D. Schumick, Department of Medical Illustration, Cleveland Clinic Foundation, 2000.)

sociated proteins is still detectable by immunohistochemistry [B. Shen and C. L. Bevins unpublished data]. A similar discrepancy was found previously comparing lysozyme immunostain with histochemical staining in celiac disease [17]. Hence, the reported absence of PCs in an animal species or disease setting must be interpreted with caution since it may mean only the absence of histochemically stainable granules in PCs. In mice, rats, and humans, the expression of PCs is inhomogeneous in the small intestine, with lower numbers in the duodenum and higher number towards the ileum [C. L. Bevins unpublished data; 18, 19]. Sometimes, cells with some morphologic features of PCs are observed in the villi and are named intermediate cells [20, 21]. The ontogeny and function of these cells is still not clarified. Outside mammals, cells similar to PCs have been found in frog intestine [22].

PCs are long-lived cells that undergo postnatal proliferation and maturation

PCs are pyramidally shaped columnar epithelial cells that originate from the multipotent intestinal stem cells [23,

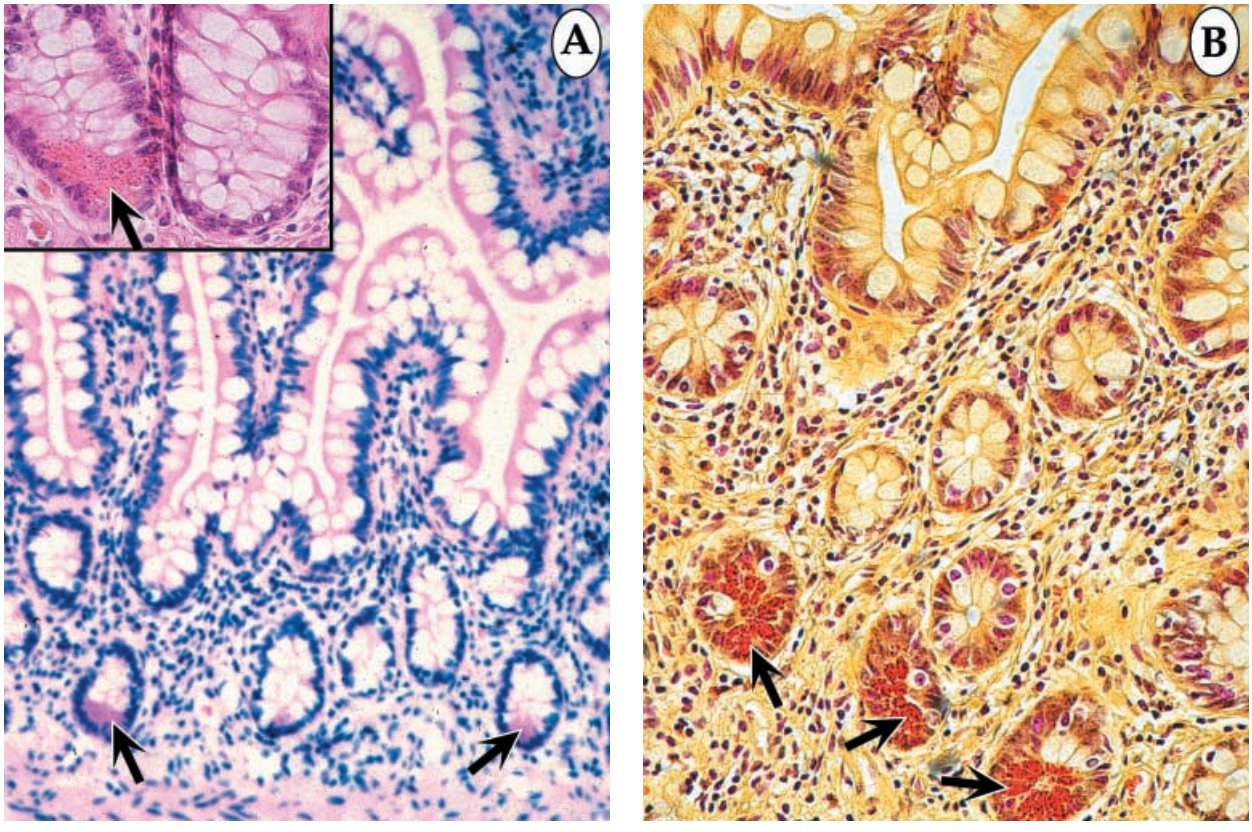

Figure 2. Histology of the human small intestinal crypts. (*A*) Low-power view of paraffin-embedded section of normal adult ileum stained with hematoxylin and eosin [reproduced with permission from *J. Biol. Chem.* (1992) **267:** 23216–23225]. Arrows denote Paneth cells at the base of the crypts. *Inset* Higher-power view of Paneth cells. Arrow denotes Paneth cell secretory granules. (*B*) Paraffin-embedded section of adult ileum stained with phloxine-tartrazine [B. Shen, unpublished data]. Arrows denote Paneth cells.

Table 1. Distribution of Paneth cells in vertebrates. In most cases, PCs were identified by the presence of granules after histochemical staining. However, since in some cases, PC-specific products are detected only by immunohistochemistry, the reported lack of PCs needs to be interpreted with caution.

Abundant	Rare reports	Reported as absent
Human [1], monkey [12, 160, 173], mouse [174–176], rat [177, 178], rabbit [12], guinea pig [12, 117], hamster [12, 129, 179], horse [53, 186], bat [12], opossum [38, 181, 182], squirrel [183-185], pig [13, 187, 188], frog (PC homologue) [22]	Cat* [11, 189], dog* [63, 189], mole [185], anteater [190], echidna [191]	Cow [185], sheep [8, 185], ostrich [192], sloth [193], seal [194], crocodile [195], colubrid snake [196]

* Controversial.

24] located at the interface of the villus and the crypt. The stem cells also give rise to three other lineages – enterocytes, goblet and enteroendocrine cells – that migrate upward and populate the villi. During maturation and differentiation, PCs migrate downward to the bottom of the crypt and fill with numerous prominent apical cytoplasmic granules [3, 25], which can be released into the crypt lumen [26, 27]. Epithelial cell migration may be influenced by human intestinal trefoil factor that has been localized in PCs [28]. PC differentiation is accompanied by cytokeratin 21 expression in rat [29] and may be signaled through Rac1 [30]. In contrast to absorptive villous enterocytes that turn over rapidly (2–3 days), PCs have a longer turnover period of about 18–23 days [31–33]. In humans, PCs first appear at 13.5 weeks of gestation in the colon and small intestine, and after 17 weeks of gestation they are confined to the small intestine only [34]. In mice, PCs appear after birth when the intestinal crypts are formed. In humans, mice, and rats, PC expression is low in the newborn but PC numbers and products increase substantially postnatally [3, 34–36], independently of exposure to microorganisms [3] and possibly promoted by epidermal growth factor [37]. As shown in rats and opossum, PC development may also be stimulated in newborns by corticosteroids [36, 38]. The presence of a prolactin receptor in PCs [39] suggests that PC development and maturation in the postnatal period could be influenced by prolactin (and other hormones) in breast milk [40, 41].

Systems to study the cell biology of PCs

Studies of the cell biology of PCs have been limited by the need to work with primary tissue because PC-derived cell lines are not yet available. Interestingly, true PC neoplasia is rarely found in clinical medicine, possibly related to the expression of the tumor suppressor gene adenomatous polyposis coli (APC) [42]. However, neoplastic PCs with incomplete differentiation may be underreported, since they may lack the characteristic granules used for histochemical identification. Techniques to characterize granule content, surface-bound, and cytoplasmic components include immunohistochemistry, in situ hybridization, tissue extraction, and intestinal washes with subsequent RNA or protein analysis (table 2). To explore the biology of PCs in primary organ cultures, multiple experimental systems have been developed including tissue-engineered neointestine [43], isolated ileal loops and tissue cultures of hyperplastic PCs derived from these [44–46], xenografts of fetal gut [47, 48], autograft neomucosa in ectopic sites [49], and isolated crypts [50]. Recently, PC-enriched fractions have been prepared from single-cell suspensions of isolated crypts by flow cytometry. Although biological properties of these cells are not yet characterized, this method may provide opportunities for direct studies on single PCs [T. Ayabe and A. J. Ouellette, unpublished data]. Transgenic mice with altered PCs [51, 52] and oral infection models in various animals have been used to study PC function in the living animal [53–57]. In humans, ileal pouches constructed (as a pseudocolonic reservoir) following total proctocolectomy and ileal neobladders (as a urinary bladder replacement) following cystectomy have provided opportunities to study PC secretion in vivo [58–61; C. L. Bevins and D. Ghosh, unpublished data]. In summary, most of our knowledge about the composition and function of PCs has been gained indirectly from studies of complex tissues, and more studies on isolated PCs would be invaluable.

PCs are filled with antimicrobials

Immunohistochemistry by light and electron microscopy localized to PC granules several substances with well-documented antimicrobial activity. For example, defensins [15, 27, 62], lysozyme [63–65], and sPLA2 [16, 66] are antimicrobial (poly)peptides directed against cell walls of target microbes (fig. 3). Other granule proteins with possible but less well defined antimicrobial roles include the weakly antimicrobial secretory leukocyte inhibitor (SLPI) [67] and immunoglobulin IgA [68] that

Table 2. Paneth cell components.

Subcellular location	molecule	comments	species	references
Granule-associated	lysozyme, phospholipase A2, SLPI	~ 14.5 kD; antimicrobial	H, M	16, 65–67, 205
	defensins	~ 3.5 kDa; antimicrobial; induction of epithelial chloride secretion	H, M, R	15, 27, 76, 77
	IgA	~ 160 kDa as monomer; antimicrobial	H, R	68
	heavy metal ions (cadmium, copper, selenium, zinc)	regulation of metalloenzyme activities, antimicrobial?	H, M, R	151–153, 155, 158, 159
	zinc-binding protein	~ 90 kDa	H, R	156
	TNF-α	proinflammatory	H, M	92–95
	AE2 anion exchanger	~ 140 kDa integral membrane protein; three isoforms; Cl^-/HCO_3^- exchanger	M	118
	prostaglandin E2	proinflammatory; secretagogue	R	96
	trypsin and trypsinogen	~ 24 and ~ 26 kDa; Arg- and Lys-specific protease; 3 isoforms; human defensin processing? digestive function?	H	106, unpublished data
	laminin receptor	~ 67 kDa; possible receptor for encephalitis viruses and prion proteins; belongs to family of ribosomal proteins	H	197
	Rab3D	Ras-like monomeric GTP-binding protein; regulated exocytosis?	R	198
	phospholipase B/lipase	Ca^{2+}-independent phospholipase; catalytic domain of an ~ 150 kDa membrane enzyme	R	132
	carboxylic ester hydrolase	~ 100 kDa; glycoprotein; pancreatic carboxylesterase; digestive function?	H	125
	DNAse I	~ 30 kDa; removal of extracellular DNA; possibly involved in apoptosis	H	133
Cytoplasmic	zinc	see above; DNA transcription and RNA translation	H, R	151, 199
	EGF	growth factor for epidermal and epithelial cells	H, R	109
	CRHSP28	~ 28-kDa-calcium-regulated heat-stable protein; role in Ca^{2+}-mediated exocrine secretion	R	122
	cytokeratin 21	~ 49-kDa type I cytokeratin; in differentiated intestinal epithelia; homologue to human keratin 20	R	29
	prolactin receptor	~ 67 kDa; member of the cytokine receptor superfamily; signal transduction; produced by PCs?	H	39
	glutathione-S-Transferase	~ 25 kDa; GST theta1; conjugation of reduced glutathione to a wide range of exogenous and endogenous hydrophobic electrophiles	H	165
Basolateral membrane	MRP	~ 190-kDa multidrug-resistance associated protein; export of glutathione-conjugated substrates	M	163
Lysosome	osteopontin	~ 40-kDa protein; same as urinary stone protein; cell-matrix interaction	H	97
	enzymes	unspecific acid phophatase (~ 45 kDa); E600 resistant esterase (~ 43 kDa, hydrolysis of cholesteryl esters and triglycerides), β-glucuronidase (~ 72 kDa, dermatan and keratan sulfate degradation, glycosylhydrolase); β-glucosaminidase (~ 61 kDa, degradation of terminal N-acetyl-glucosamine, glycosyl hydrolase)	R	177
Endoplasmic reticulum	protein disulfide isomerase	~ 55-kDa protein; also named cellular thyroid-binding protein, p55; rearrangement of disulfide bonds	H, R	200, 201
Golgi	NADPase activity	distinct ultrastructural location of a ubiquitous enzyme	R	202
unspecified	HIP/PAP	~ 16-kDa stress protein; same as pancreatitis-associated protein; C-type lectin	H, M,	69, 70, 203
	trypsin-inhibitors	α1-antitrypsin ~ 43 kDa; Mpgc60 (postnatally upregulated) ~ 7 kDa; pancreatic secretory trypsin inhibitor (PSTI) ~ 6 kDa	H, M	105, 107, 108, 204
	matrilysin	~ 27-kDa protein; also known as MMP7; zinc metalloprotease; mouse defensin processing?	M	206
	CD15	carbohydrate antigen (3-fucosyl-N-acetyllactosamine); also named Lewis X, lex, SSEA-1, X-hapten, 3-FAL; expressed in phagocytes, various epithelial cells, some activated lymphocytes, and some tumor cells; cell adhesion molecule; involved in phagocytosis?	H	207

Table 2. (continued)

Subcellular location	molecule	comments	species	references
	pancreatic lipase related-protein 2	~ 50-kDa protein; lipase with digestive function; role in cytotoxic T-lymphocyte function? in contrast to strong in situ hybridization, immunohistochemistry is weak	M	121
	CRS	cryptdin -related sequences; gene product unknown; antimicrobial?	M	208
	REG protein	~ 19-kDa glycoprotein (P19); similarities to C-lectin family; precursor of the ~ 14-kDa unglycosylated polypeptide (P14, also named pancreatic stone protein or pancreatic thread protein); role in cell matrix association; downregulation upon differentiation; communication with immune cells	H	209
	FAS ligand (CD95 L)	~ 30-kDa membrane protein; apoptosis inducing in FAS+ cells	H	103, 104
	TGF-β1	~ 42 kDa; controls cell growth; anti-inflammatory	R	91
	APC	~ 300 kDa; adenomatous polyposis coli protein; tumor suppressor; cell-contact and cytoskeleton-associated protein with signaling functions	M	42
	CD1	family of ~ 50-kDa membrane glycoproteins (CD1a–e); associates with beta-2-microglobulin; lipid and glycolipid antigen presentation to T cells; involved in intracellular infection, possibly in autoimmune disease	M	100
	CD44 variant 6	~ 80-kDa glycoprotein; involved in matrix adhesion, lymphocyte activation, and lymph node homing	H	112
	metallothionein	~ 6-kDa; heavy metal binding through the numerous cysteine residues	R	155, 210
	α1 E voltage-gated Ca^{2+} channels	Ca^{2+} channel	H	126
	VIP receptor; cAMP-activated Cl^- conductance	activation of Cl^- currents after stimulation	GP	117
	guanylin	~ 2-kDa; endogenous activator of intestinal guanylate cyclase; validity has been questioned in recent reviews	H	211–214

H: human, M: mouse, R: rat, GP: guinea pig. In addition to original literature, ExPasy Swiss Protein and TrEMBL Databases were used for molecule description.

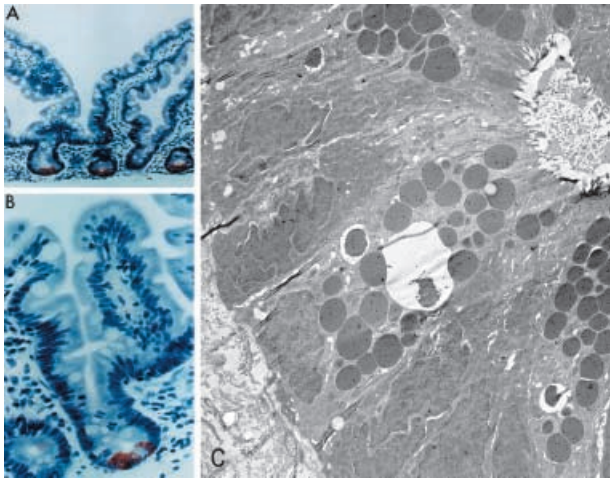

Figure 3. Immunohistochemistry demonstrating human defensin HD5 in Paneth cell granules. (*A*) Immunoperoxidase staining of formalin-fixed normal human small intestine biopsy with rabbit polyclonal antibodies against HD5 and Harris hematoxylin counterstain, low power. There is specific staining (brown color product) of Paneth cells in the crypt base. (*B*) Same under higher magnification. (*C*) Transmission electron micrograph of normal human ileum crypt after immunogold labeling of HD5 shown to be concentrated in the granules of PCs [reproduced with permission from *Infection and Immunity* (1997) **65:** fig. 2 p. 2392 and fig. 3 p. 2393].

may bind to and block microbial pathogenic factors such as pili or toxins. PCs also contain pancreatitis-associated protein, PAP (also known as hepatocarcinoma-intestine-pancreas protein, HIP) [69, 70], belonging to a family of C-type lectins that bind sugar moieties on microbial surfaces with consequent aggregation or enhanced binding to phagocytes. Upon exposure to viable or heat-killed bacteria [53, 68] or to microbial products such as lipopolysaccharide and lipoteichoic acid [50, 71], PCs release their granules, resulting in increased concentrations of antimicrobials in the intestinal lumen. Hence, PCs may be important in controlling microbial density in the small intestine where microbial nutrients in the form of digestate are plentiful. Supporting this notion, much lower densities of microbial colonization have been observed in small than in large intestine that lacks PCs. Phagocytic activity of PCs was proposed in early reports, based on ultrastructural analysis of PCs [72, 73] and expression of the granulocytic surface antigen CD15 [74]. However, microbes could rarely be detected in PCs. The role of PCs in intestinal immunity was questioned when two lines of transgenic mice with ablated PC developed normally and had no increase in intestinal colonization when maintained in a barrier facility [51]. Interestingly, in one lin-

eage, the lack of recognizable Paneth cells was accompanied by an increased number of intermediate cells in the crypts, which had upregulated defensin-containing granule production. It will be of great interest to test the response of these transgenic mice to microbial pathogens.

More recently, other transgenic approaches have supported a role for PCs in host defense. In transgenic mice lacking matrilysin [52], the enzyme that activates mouse PC defensins, orally administered bacteria survived in greater numbers and were more virulent. Conversely, transgenic mice with additional human defensin expression in their PCs demonstrated dramatically increased survival after challenge with *Salmonella typhimurium* [N. Salzman, D. Ghosh and C. L. Bevins, unpublished data]. These bacteria naturally cause a systemic typhoid fever-like disease in mice, but in humans cause only localized gastroenteritis. In vitro, human PC defensin HD5 is active against *S. typhimurium* [75] but cryptdins, the mouse PC defensins, are much less active against this pathogen [76, 77]. Thus, current evidence supports an important role for PCs in defense against pathogens ingested through food and water-borne routes, in the protection of nearby stem cells, and as regulators of microbial density in the small intestine.

PCs release their numerous granules upon microbial, hormonal, cholinergic, and cytokine stimulation

The degranulation of PCs in response to heat-killed or viable bacteria was noted more than 15 years ago [53, 68]. Recently, quantification of cryptdin secretion in isolated crypts showed that mouse PCs degranulated in response to a variety of microbial substances, including lipopolysaccharide, lipoteichoic acid, and mycobacterial antigens [50].

In addition, PC degranulation seems to be integrated with oral ingestion and regulated by gastrointestinal hormones. PCs secrete upon stimulation with cholecystokinin-pancreozymin [78] and long-term exposure to cholecystokinin and gastrin induced PC hypertrophy and increased lysozyme levels in the intestine [79]. In mice, insulin and glucagon have been shown to inhibit PC secretion and increase their granule content [80]. In mice, PCs accumulate their granules during fasting [81]. However, PCs conceivably also respond to the presence of macromolecules per se, possibly through an osmoreceptor. A third type of PC secretion, possibly linked to parasympathetic autonomic nervous system activity, follows G protein-mediated cholinergic stimulation [82]. PCs secrete in response to cholinergic agonists, including bethanechol [71, 82], pilocarpine [83, 84], and carbamylcholine [85, 88]. Accordingly, cholinergic inhibition by atropine blocked PC secretion (and molecule uptake) in mice and rats [83, 86], and vagotomy in rats caused profound ultrastructural rearrangement in PC organization and an increase in secretory granules and relative number of their immature forms [87].

As isolated PCs have not yet been analyzed and no PC cell line is available, it is not clear whether PCs respond to all these stimuli directly or react to secondary signals produced by the other epithelial cells lining the intestinal tract. Exocytosis upon systemic administration of tumor necrosis factor (TNF)-α [89] or interferon (IFN)-α [90] in mice or rats supports the idea that PCs also respond to indirect signals of infection. We venture to speculate that PC secretion is tightly linked to increased numbers of bacteria in the small intestine and PC secretion may be already stimulated upon oral ingestion. The latter response we envisage as an anticipatory defense mechanism that may help combat potential pathogenic bacteria likely to accompany food and water.

PCs may communicate inflammation to other host defense cells

PCs are reported to produce various cytokines and mediators of inflammation. By in situ hybridization, mRNAs have been detected for transforming growth factor (TGF)-β in normal rats [91] and for TNF-α in humans and mice [92–95]. By immunohistochemistry, prostaglandin E2, a pleiotropic mediator of inflammation, was found in PCs [96], as was osteopontin [97], a glycosylated phosphoprotein with recently proposed functions in cell-mediated immunity [98, 99]. PCs may also play a role in antigen presentation, as they express CD1 [100]. However, single reports based on in situ hybridization must be viewed with caution, as PCs have been found to nonspecifically bind nucleic acid probes [101].

Removal of diseased cells and downregulation of immune responses through apoptosis is another arm of host defense [102]. PCs express FAS ligand (or CD95) at their basolateral membrane [103, 104] and could induce apoptosis in FAS+ immune cells of the surrounding tissue. In conclusion, PCs not only play a role in innate host defense as effector cells producing antimicrobial factors and releasing them into the intestinal lumen but may also communicate and coordinate host defense signals with other cell types.

Secretion-associated posttranslational processing by PCs

Mature PCs not only contain preformed substances that are released on demand, but also molecules that mediate or are subject to posttranslational processing. Human defensin HD5 is stored in PCs as a precursor molecule [21, 61], together with trypsinogen (C. L. Bevins and D. Ghosh, un-

published data). Upon degranulation, trypsinogen is cleaved to trypsin and proHD5 is N-terminally cleaved by trypsin. Of note, the various N-terminally truncated forms of HD5 vary in their antimicrobial activity (E. Martin Porter and D. Ghosh, unpublished data). Once released, trypsin may also activate and/or degrade other compounds. The activity of PC trypsin may be tightly regulated as suggested by the observation that PCs also contain inhibitors of trypsin and other serine proteases: pancreatic secretory trypsin inhibitor [105, 106], α_1-antitrypsin [107], and Mpgc60 [108]. Regulated posttranslational processing at the time of degranulation may allow additional modulation of granule-associated bioactivity.

The role of PCs in crypt development and homeostasis

Crypt formation in small intestine requires stem cell proliferation, cell differentiation, migration, and polarization. PCs may support these processes since they produce human intestinal trefoil factor [28] that promotes cell migration, epidermal growth factor (EGF) [109] that stimulates the growth of epithelial cells, and osteopontin [97], a regulator of cell matrix interaction, cell polarization, and cell migration [110]. Osteopontin has also been involved in cell migration as an integral component of CD44-ERM [111] and CD44 variant 6 that has also been demonstrated in PCs [112]. In addition, PCs store zinc that has been implicated in coordinate regulation of mitosis and apoptosis [113, 114]. However, PCs do not seem indispensable for crypt formation, since in mice with ablated PCs small intestinal crypts appear morphologically normal [51].

Several PC-associated substances may regulate ionic currents in epithelial cells. Certain murine PC defensins act as anion channels [115, 116]. In guinea pig PCs, VIP receptor and cAMP-dependent chloride current were detected with whole cell patch clamp analysis [117]. Anion exchanger AE2 has been detected on the membrane of secretory granules in mouse PCs [118] and prostaglandin E2 that has been demonstrated in rat PCs [96] can act as a secretagogue in addition to its proinflammatory activity [119, 120]. Hence, PCs may influence the ion composition of the intestinal crypt and lumen.

Relationship of PCs to pancreatic cells

Many PC constituents were earlier described in pancreatic cells. Characteristic exocrine pancreatic cell products including pancreatic lipase-related protein [121], CRHSP28 (a cytoplasmic protein involved in calcium-dependent secretion) [122], pancreatitis-associated protein (PAP, same as human C-lectin hepatocarcinoma-intestine-pancreas protein, HIP) [69, 70], pancreatic stone protein (same as pancreatic thread protein, also a member of the C-type lectin family) [123], pancreatic glycoprotein p19 (precursor of pancreatic stone protein) [124], carboxylic ester hydrolase [123, 125], and trypsin are also found in PCs [106, 124]. In addition, both the islet cells of Langerhans and PCs express the α1E long isoform of a voltage-gated Ca^{2+} channel [126]. Similar unusual filamentous inclusions have been reported in cancerous pancreatic cells and neoplastic PCs [127]. During chronic pancreatitis, after pancreatic duct ligation in hamsters and in diabetic mice, PCs become hyperplastic [128–131]. Considering that pancreatic lipase-related protein 2 [121], pancreatic carboxylesterase [125], phospholipase B/lipase [132], and DNAse I [133] have been localized in PCs, PC secretions may have digestive functions in small intestinal regions distant from the pancreas, where digestive enzymes originating from the pancreas may have undergone autodegradation and degradation through microbial products. However, several other digestive enzymes including chymotrypsin, amylase, and lipase are reportedly not expressed in the small intestine [134]. Thus, the lipolytic and proteolytic PC enzymes together with the deoxyribonuclease activity may be primarily targeted to microbe degradation, possibly enhancing the activity of PC-derived antimicrobials. Alternatively, lytic enzymes may participate in the activation or inactivation of signaling molecules in the intestine. Finally, the relatedness between PCs and pancreas raises the question whether the pancreas is more important in host defense than previously appreciated.

Intestinal metaplasia and inflammatory bowel disease involve PCs

Although in the normal digestive tract, PCs are confined to the small intestine, in various disease states, they frequently appear aberrantly throughout the alimentary tract. Expression of small intestinal epithelium in aberrant sites is referred to as intestinal metaplasia (table 3), and termed complete if PCs are present. Intestinal metaplasia with PC expression can also occur within adenomas (benign or malignant). Less frequently, intestinal metaplasia has been reported in the cervix [135] and occasionally in the respiratory tract [136]. Formation of intestinal metaplasia is often preceded by chronic inflammation, e. g. in the stomach following a chronic infection with *Helicobacter pylori* [137–139]. Hence, intestinal metaplasia could reflect a specific form of host defense response.

Inflammatory bowel disease (IBD) is sometimes characterized by PC hyperplasia [140–142]. PCs may respond to the potent inflammatory stimuli characteristic of this disease. In rats, IFN-α [90], and in mice, systemic administration of TNF-α caused secretion of PC granules

Table 3. Diseases with PC alterations.

Disease	PC Involvement	References
Intestinal metaplasia	occurrence of PCs outside the small intestine; most often in stomach or esophagus	135, 136, 140, 215, 216
Inflammatory bowel disease	PC metaplasia, hyperproliferation	141, 142, 217, 218
Necrotizing enterocolitis (NEC)	PC cell increase and mRNA increase for HD5 and TNF; low lysozyme levels	94, 145, 146
Celiac disease	varying reports: reduced numbers of PCs; normal PC numbers with reduced lysozyme content; reduced PC numbers and reduced lysozyme tissue content; lack of α_1-antitrypsin; PC hyperplasia	17, 219–222
Familial adenomatosis polyposis (FAP)	over 90% of adenomas contain PCs; increased numbers of PCs also in flat mucosa in FAP patients; possible involvement of PC-derived epidermal growth factor in duodenal adenomas	223–226
Acrodermatitis enteropathica, zinc deficiency	ultrastructural changes that are reversible with zinc supplementation; similar filamentous inclusions also found in neoplastic PCs	127, 147–150
Autism in children associated with gastrointestinal symptoms	increased PC numbers in duodenal crypts	227

[89]. Considering that many PC antimicrobials, including sPLA2 and defensins, are cytotoxic at high concentrations [143, 144], their secretion could contribute to tissue damage. Furthermore, PCs contain TNF-α and could contribute to the high proinflammatory cytokine concentrations seen in IBD. In addition, PCs express at their basolateral membrane FAS-ligand that is involved in apoptosis of immune cells in IBD [103].

Another disease in which PCs are implicated is necrotizing enterocolitis (NEC). Newborns express lower numbers of PCs a condition further aggravated in premature infants. Based on the concurrent increased risk for NEC in premature infants, an association of PC immaturity with NEC was proposed. In support of this concept, a decreased lysozyme content was found by immunostain in NEC patients [145]. We found that in NEC patients, increased PC numbers and expression of defensin HD5 mRNA were not paralleled by a similar increase in HD5 peptide [146]. As lysozyme or defensin levels were not measured in the lumen, the lower peptide levels in PC could reflect a defect in protein synthesis or increase in secretion. In another study, high amounts of TNF-α transcripts were observed in PCs indicating that PCs could be major contributors to tissue inflammation [94].

In acrodermatitis enteropathica and other forms of zinc deficiency, PCs show typical ultrastructural alterations that disappear after zinc replacement [127, 147–150]. This supports the notion that PC homeostasis depends on zinc but the specific mechanism is uncertain.

A possible role of PCs in heavy metal metabolism, delivery, and detoxification

Several heavy metals, including zinc and selenium, have been demonstrated in PCs [151–153]. They also express various heavy metal ion-binding proteins including metallothionein [154, 155] or zinc-binding proteins such as the cysteine-rich intestinal protein (CRIP) [156]. Heavy metal ions may be required in PCs for various enzymatic processes. For example, matrilysin in mouse PCs is a zinc-dependent metalloprotease that has been postulated to be instrumental in defensin processing in mice [52]. Alternatively, the accumulation of heavy metals in PCs could also support their antimicrobial function, either as direct toxic substance at high concentrations or in synergism with other antimicrobial components of PCs [157]. On the other hand, PCs could also be a selective site for heavy metal ion uptake, transport, and export as reflected in the accumulation of cadmium, copper, or mercury in PCs after alimentary overload [155, 158–160] or after intraperitoneal injection [161]. Heavy metals can be excreted through multidrug resistance proteins [162]. In murine intestine, a multidrug resistance-associated protein (MRP) is found predominantly in the basolateral membrane of PCs [163] raising the possibility that PCs may use this molecule to transport heavy metals into the body. The same molecule may also be involved in export of other toxic compounds [164]. Glutathione S-transferase, an important drug-detoxifying enzyme also found in PCs may function to self-protect and possibly contribute to detoxification [165].

PC changes after irradiation and chemotherapy

Irradiation or chemotherapy can severely damage the intestinal epithelium and after such treatment, patients often suffer from severe acute gastrointestinal disease. The rapidly dividing stem cells and villous enterocytes are most affected [166]. However, PCs can be damaged as well and alterations range from inclusion structures to dose- and time-dependent complete loss of PCs [167–169]. Sublethal exposure to radiation or methotrexate was reported to induce a reversible increase in PC numbers [170], increased lysozyme content [166, 171], and PC metaplasia

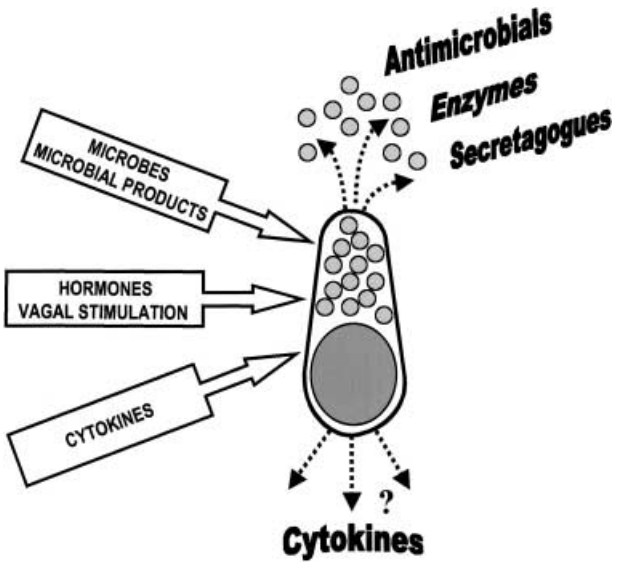

Figure 4. Stimuli and responses in Paneth cells. PCs respond to a variety of stimuli by releasing their numerous granules into the intestinal lumen. They may also secrete cytokines to the surrounding tissue.

[172] pointing to a potentially important function of PCs in the regeneration of intestinal mucosa.

Summary and outlook

PCs seem to respond to a broad range of stimuli with a rather uniform response, degranulation into the intestinal lumen (fig. 4). The diversity of stimuli and the complexity of PC granule composition suggest that PCs may have multiple functions. Many studies have supported the concept that PCs function in intestinal host defense through their production and release of antimicrobial factors. Other functions of PCs, less well supported by experimental data and more speculative may include regulation of inflammation, participation in stem cell protection and crypt formation, and possibly in digestion and detoxification. Future studies should be directed at more specific documentation of each of the multiple proposed roles of PCs, and how these functions are fulfilled in animals that lack PCs naturally or through genetic manipulation.

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