**VIEWPOINT**

**Paneth's disease**

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**Abstract**

In about 70% of patients Crohn's disease (CD) affects the small intestine. This disease location is stable over time and associated with a genetic background different from isolated colonic disease. A characteristic feature of small intestinal host defense is the presence of Paneth cells at the bottom of the crypts of Lieberkühn. These cells produce different broad spectrum antimicrobial peptides (AMPs) most abundantly the α-defensins HD-5 and -6 (DEFA5 und DEFA6). In small intestinal Crohn's disease both these Paneth cell products are specifically reduced. As a functional consequence, ileal extracts from Crohn's disease patients are compromised in clearing bacteria and enteroadherent *E. coli* colonize the mucosa. Mechanisms for defective antimicrobial Paneth cell function are complex and include an association with a NOD2 loss of function mutation, a disturbance of the Wnt pathway transcription factor TCF7L2 (also known as TCF4), the autophagy factor ATG16L1, the endosomal stress protein XBP1, the toll-like receptor TLR9, the calcium mediated potassium channel KCNN4 as well as mutations or inactivation of HD5. Thus we conclude that small intestinal Crohn's disease is most likely a complex disease of the Paneth cell: Paneth's disease.

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**1. Introduction**

The etiology of Crohn's disease and ulcerative colitis is still enigmatic. Crohn's disease is linked to the "pathogen poor" living conditions in the Western world. There is convincing evidence that the development of Crohn's disease is associated with good hygiene standards. These patients also are characterized by the frequent use of antibiotics during childhood even before they developed the disease. In developing countries, infectious intestinal diseases are common, and yet idiopathic inflammatory bowel diseases, especially Crohn's disease, practically do not exist. Interestingly, the first occurrence of Crohn's disease often starts after a bacterial infection. These observations suggest a weakened defense against these microbes. It is general consensus that in both forms of IBD, intestinal microbiota trigger the disease in genetically susceptible individuals. The classical interpretation of this bacteria-triggered chronic inflammatory disease is a loss of mucosal tolerance towards the bacteria responsible for the inflammatory process. In contrast, we hypothesized, that the host with inflammatory bowel disease may be more likely to contract...
an intestinal infection because of a defective innate immune defense which weakens the mucosal barrier against the entry of microbes.\textsuperscript{3,4} Along these lines, IBD was generally found to be associated with mucosal adherent bacteria.\textsuperscript{5–7} A mere dysregulation of inflammatory cells in the mucosa would not explain this phenomenon. Moreover, it is now generally accepted that the commensal flora plays a central role in triggering and perpetuating the disease process (Figs. 1 and 2).

In this article we discuss the concept that small intestinal Crohn’s disease is a disease entity linked etiologically to a specialized protective cell, the Paneth cell residing in this bowel segment. The concept is compatible with the clinical observation that disease location is the only clinical parameter which is stable over time.\textsuperscript{8} Small intestinal disease appears to be genetically different from the form with isolated colonic involvement und the multiple hits affecting the Paneth cell in Crohn’s disease suggest its central role in the disease process.

2. Innate immunity and the barrier of the small intestine

The intestinal tract is the largest surface in humans. It is constantly colonized by a remarkable community of commensals and is occasionally challenged by pathogenic microbes. Yet intestinal infections or translocation of bacterial agents is the exception rather than the rule and mostly limited to highly pathogenic bacteria or predisposing disease states. The nutrient rich small intestinal luminal content at body temperature provides especially ideal growing conditions for microbes. Still, their numbers remain at a surprisingly low level directly at the mucosa. To maintain these almost germfree conditions, mucosal integrity and proper function is a vital question. Therefore epithelial cells not only serve as a physical barrier but are responsible for powerful chemical and biological immune interfaces.

The effective action of the barrier system depends on different arms of the epithelial innate immunity and provides an immediate and continuous response to microbes.\textsuperscript{9} On intestinal surfaces this includes the expression of a variety of microbial “pattern recognition receptors” (PRR) (such as “Toll like receptors” (TLR’s) and “Nucleotide-binding oligomerization domain containing molecules” (NOD’s)), different defense coordinating signaling molecules. The secreted mucins interacting with different epithelial bactericidal effectors such as defensins and cathelicidins have an important role in the first line of intestinal defense.\textsuperscript{10} Different constitutive and inducible antimicrobial peptides (AMPs) generate a competent weapon arsenal towards any kind of microbial threat.\textsuperscript{3} AMPs show activity against bacteria, enveloped viruses, protozoa and fungi and thereby help to limit invasion and adherence of both pathogens and commensal bacteria. Common AMP characteristics are biochemical properties like a low molecular mass around 3–4 kD, a positive charge and disulfide bonds.\textsuperscript{11} Their mechanisms of action are not yet completely understood but depend on the cationic charge which mediates integration into and disruption of negatively charged microbial membranes.\textsuperscript{12}

3. A special role for Paneth cells and their defensins

The original description of granular cells at the bottom of small intestinal crypts was published by Gustav Albert Schwalbe, in the Archiv für mikroskopische Anatomie in 1872 while he was “Privatdocent” at the University of Freiburg. The cells were named after Joseph Paneth from Vienna, the author of the second paper on these cells appearing 16 years later in the same journal. Paneth acknowledged Schwalbe and actually used one of his drawings in his article. More than 130 years later it has become clear that Paneth cells originate directly from the crypt stem cells which are close neighbours near the crypt base. The decisive factors directing the fate of stem cells and the production as well as differentiation of Paneth cells reside in the Wnt
proliferation of progenitor cells into secretory Paneth cells at the bottom of the crypts. Wnt (wingless type) signaling derived from a small number of asymmetrically dividing stem cells at the base of the crypts. Wnt (wingless type) signaling derived from intestinal subepithelial myofibroblasts (ISMF) also promotes proliferation of progenitor cells into secretory Paneth cells residing at the base of the crypts, in direct neighborhood of epithelial stem cells. Modified from Gregorieff et al.\textsuperscript{14}

Paneth cells escape from the mesenchyme to cell surface receptors the target cells release intracellular \(\beta\)-catenin which interacts with TCF4 (T-cell factor 4). The resulting complex binds to DNA and regulates transcription of diverse genes. Probably the most important targets are the antibacterial defensin genes.\textsuperscript{13,14} Currently the most convincing role of the Paneth cell is the production of a stream of antibacterial secretions keeping the small intestinal crypt lumen sterile, thus protecting the vital neighboring stem cells.

The most abundant, constitutively expressed defensins in the small intestine are the \(\alpha\)-defensins human defensin (HD) -5 and -6 (DEFA5 und DEFA6) found in Paneth cells (PCs).\textsuperscript{15} Besides HD-5 and -6, PCs also store several other innate antibiotic peptides (e.g. lysozyme, regenerating islet-derived 3 gamma (RegIII\(\gamma\)) and phospholipase A2 group IIA (sPLA\(_2\)), also known as PLA\(_2\)G2A) in cytoplasmatic granules.\textsuperscript{16,17} In quantitative terms the two \(\alpha\)-defensins are by far the most prevalent antimicrobial PC products and expression levels of HD5 exceed those of lysozyme and sPLA\(_2\) by a factor of up to 100\textsuperscript{18} whereas the ratio of HD-5 to HD-6 is about 3:1.\textsuperscript{17} Investigations on human \(\alpha\)-defensin antibacterial activity revealed an effective killing capacity of HD-5 against \textit{S. aureus} as well as gram negative bacteria whereas HD-6 exhibited little antibacterial potential \textit{in vitro}.\textsuperscript{19} Both also seem to have antiviral activity but studies are still emerging.\textsuperscript{20}

The release of PC antimicrobial peptides into the intestinal lumen follows stimulation of PRRs with "pathogen-associated molecular patterns" (PAMPs) or "microbe-associated molecular patterns" (MAMPs). These are bacterial products including lipopolysaccharide (LPS) (which activates TLR4) and muramyl dipeptide (MDP) (which is recognized by NOD2).\textsuperscript{21} In addition, the release of PC defensins appears to be mediated by bacterial cell wall glycolipids independent of TLR4.\textsuperscript{22} TLR9, another important Paneth cell PRR, recognizes unmethylated cytidine–phosphate–guanosine (CpG). It has been shown that oral administration of oligonucleotides containing a CpG sequence lead to extensive PC degranulation and protect mice against subsequent treatment with \textit{S. typhimurium}.\textsuperscript{23} The functional importance of PC \(\alpha\)-defensins, called cryptdins in mice, is also illustrated by other models. Mice lacking their cryptdin-processing enzyme are incompetent in producing mature versions of the AMPs and as a consequence are highly susceptible to orally administered bacterial pathogens.\textsuperscript{24} On the other hand, human HD5 transgenic mice are protected against \textit{S. typhimurium} infection substantiating a potent \textit{in vivo} activity of this specific human peptide.\textsuperscript{25} A more recent study using mice expressing "myeloid differentiation primary response gene" (MyD88) specifically in PCs provided additional evidence for their essential role in sensing and controlling commensal and pathogenic bacteria. PC-intrinsic MyD88, an important cytoplasmatic TLR signaling compound triggered a complex antimicrobial program which sufficiently limited bacterial penetration into the mucosa.\textsuperscript{26} Moreover newly published data might have major importance in understanding PC-defensin function along the intestinal tract since it was demonstrated that cryptdins resist propeptolysis \textit{in vivo} preserving activity even in the distal colonic lumen.\textsuperscript{27}

4. Paneth cell differentiation: Location and organization in the intestinal crypt

The human intestinal epithelial lining undergoes cell renewal at an extraordinary rate, outrunning all other tissues of the organism.\textsuperscript{14,28} All its cell types descend from multipotent stem cells located at the base of the crypts, right above and/ or between the Paneth cells. The intestinal adult stem cells self-renew and give rise to daughter cells that form an adjacent zone of rapidly cycling progenitors. These increase their pool by undergoing 4–6 rounds of divisions before differentiating into multiple lineages creating up to 300 cells/crypt/day.\textsuperscript{29,30} The crypt necks and the villus regions consist of post-mitotic cells and make up the biggest area of the intestinal epithelium. Besides absorptive cells, there are three classes of secretory cells: goblet cells, which secrete mainly mucus, enteroendocrine cells, with various subtypes secreting different hormones and as mentioned, specifically in the small intestine: Paneth cells.\textsuperscript{31} PCs escape the general upwards flow of differentiating cells and migrate downwards or stay at the crypt base where they reside for 3–6 weeks.\textsuperscript{30}

The maintenance of the proliferating region is subject to the activity of Wnt signalling. All intestinal proliferation and differentiation events underlie a complicated system of sending and receiving various signals, the most important being integrated in the Wnt pathway.\textsuperscript{32} There is not only a
pool of differently operating Wnt molecules, but also various receptors, as well as intracellular compounds and signalling cascades. One of these, the β-catenin depending cascade (called “canonical Wnt pathway”), depends on activation of Fzrizzled as well as “low density lipoprotein receptor-related protein” (LRP) 5 or 6 receptors by Wnt ligands and subsequent accumulation of cytoplasmatic β-catenin. Cytoplasmatic β-catenin is stabilized by different events mediated by Frizzled and LRP5/6 activation. As a result accumulated β-catenin enters the nucleus where it activates the transcription of target genes. This last steps is dependent on a cooperation with transcription factors of the “lymphoid enhancer-binding factor” (Lef)/“transcription factor (T-cell specific, HMG-box)” (TCF) family.

The group of Hans Clevers clearly demonstrated a critical dependence of the Paneth cell gene program on transcription factor 7-like 2 (TCF7L2, also known as TCF4), a canonical Wnt pathway component of particular importance in the embryonic mouse intestine. A conditional Fzrizzled-5 deletion in adult mice lead to conspicuous mispositioning of PCs and abrogated expression of Wnt/TCF4 target genes, including cryptdins. Those findings are corroborated by studies linking conditional APC loss in mice to enhanced intestinal progenitor commitment towards the Paneth cell lineage. A rather new study using hypomorphic β-catenin mice completes the picture by illustrating a high PC sensitivity to changes in canonical Wnt dosage. It could be demonstrated that a mild reduction in β-catenin mRNA levels severely disrupted Paneth cell development but effects on general intestinal cell proliferation were limited.

5. NOD2 and small intestinal disease

A key finding which changed the field was the discovery of the first important susceptibility gene in Crohn’s disease. About a third of patients with Crohn’s disease have a mutation in the NOD2 gene, which encodes an intracellular bacterial pattern-recognition receptor (for a review see 35). Further clinical analyses have revealed that this mutation is associated with the clinical phenotype of ileal Crohn’s disease, whereas it is not associated with the colonic type of Crohn’s disease (for a review see 36). The discovery of this loss of function mutation in the NOD2 gene represents a major advance. Initially, fitting well with the former common understanding of the disease, the pathophysiology of NOD2 in Crohn’s disease was proposed to link to immunological dysregulation in monocytes. Alternatively, it was hypothesized that intestinal epithelial cells (Voss et al., 2006) and especially Paneth cells, which have also been demonstrated to extensively express NOD2 (Lala et al., 2003; Ogura et al., 2003), might be compromised in their antibacterial response. Along these lines, it has been shown that intestinal epithelial cells transfected with mutated NOD2, are not able to respond appropriately to an in vitro challenge with Salmonella and the mechanism has been detailed consequently. As emphasized above, mutations in the NOD2 gene, especially SNP13, was not associated with overall Crohn’s disease but with ileal localization of disease. This finding was the first genetic evidence for the clinical phenotype of this location suggesting that different genetic mechanisms cause inflammation at different sites. As compared to monocytes, which are widely distributed, Paneth cells and their main effector molecules (defensins HD5 and HD6) are normally restricted to the small intestine. Since NOD2 is predominantly expressed in the small intestinal Paneth cell, we hypothesized that the phenotype of ileal affection in Crohn’s disease is linked to Paneth cell antimicrobial host defense. Thus, our work was based on the idea, that different disease locations (e.g. ileal versus colonic) are due to location specific defects in host innate immunity. As stated above, these barrier defects would allow the mucosal entry of commensal and or pathogenic bacteria and then trigger a secondary inflammatory response.

6. The Paneth cell and Crohn’s disease

The evidence for a link between the Paneth cell and ileal Crohn’s disease is manifold and comprises genetics, microbiology, as well as functional aspects. The initial hint to the Paneth cell was the observation that NOD2, the first gene clearly associated with (ileal) Crohn’s disease was heavily expressed in Paneth cells. We then reported that ileal but not isolated colonic Crohn’s disease is associated with a diminished synthesis of Paneth cell defensins. This was then extended and confirmed by showing the same deficiency in American patients where the functional relevance of this defect in terms of diminished bacterial killing was also demonstrated. Expression of a total of eight other Paneth cell products remained unchanged or increased when compared with controls. Functionally, the deficit in PC α-defensins affects antibacterial host defence capacity, as mucosal extracts of ileal Crohn’s disease patients exhibit weekend killing activity against different bacteria. Using a transgenic HD-5 mouse model it could also be shown, that changes in defensin expression had an impact on luminal microbiota. Those results on the in vivo mode of HD-5 operation suggested a role in fine-tuning the intestinal flora composition and preventing bacterial invasion. The defect was found in patients with an ileal phenotype both in the presence and in the absence of current inflammation. Similarly, a recent study we performed in a Norwegian pediatric population revealed low ileal HD-5 as well as TCF4 which was independent of interleukin-8 expression, i.e. inflammation. In Australia the low Paneth cell defensin production was confirmed but suggested to be secondary to inflammation. We next prospectively tested if the grade of inflammation indeed changed Paneth cell defensin expression within ileal Crohn’s disease and did not observe an inflammation related decrease (Fig. 3). In the meantime, several additional genetic associations have been found which clearly advance this cell to the centre stage in Crohn’s disease. Among other arguments, these genetic associations argue strongly in favour of a primary role of low Paneth cell defensins in ileal disease.

6.1. NOD2: loss of function and low Paneth cell defensin production

Although Paneth cell defensins were diminished in most of our ileal Crohn’s disease patients, the subgroup with a loss of function mutation (SNP 13) were characterised by a
particularly low expression level. This was apparent in two independent investigations in both German and American patients. In another study in the United Kingdom the levels of HD-5 in the effluent of ileostomy patients with Crohn’s disease was also lowest in the cohort with a NOD2 mutation. The role of NOD2 as an intracellular receptor for bacterial muramylpeptide in regulating Paneth cell defensin formation was confirmed in NOD2-knockout mice and also in patients following small intestinal transplantation.

6.2. Wnt pathway TCF4: defective Paneth cell differentiation in Crohn’s disease

The hypothesis that the Wnt pathway could be involved in Crohn’s disease was based on its role in Paneth cell differentiation and defensin formation, as mentioned above. As NOD2 provides a mechanism for decreased levels of defensins in some patients, we hypothesized that a disturbed epithelial differentiation in Paneth cells via Wnt signalling could explain the decrease in NOD2 wildtype patients. We could show that this is indeed the case and patients with ileal Crohn’s disease are characterized by low Wnt Tcf-4. Like HD-5,
TCF4 expression was low irrespective of current inflammation. In accordance with this association in patients, heterozygotic Tcf-4 knockout mice also had lower Paneth cell cryptidins and revealed a disturbed antimicrobial killing in the small intestine. To test if this link was also determined by genetics, we sequenced the Tcf7L2 gene and found an association which we then prospectively tested in different European IBD cohorts. Importantly, this association in the promoter region was linked to ileal but not colonic Crohn's disease or ulcerative colitis. The odds ratio was highest in the group with stenosing ileitis. These findings characterize another underlying mechanisms in the aetiology of ileal Crohn's disease and demonstrate the primary nature of Paneth cell defects in patients (Fig. 4).

6.3. ATG16L1: altered Paneth cell granule exocytosis

A mutation in this gene was also found to be associated with Crohn's disease, especially with an ileal phenotype. The link was confirmed in many studies and was the first to point to a role of autophagy. Autophagy is principally a degradation mechanism of cellular structures but also appears to be involved in the breakdown of phagocytosed or invasive bacteria. Quite surprisingly in knockout mice with Paneth cells defective in ATG16L1 the granule exocytosis pathway was abnormal. Notably, patients with Crohn's disease homozygous for the mutation the Paneth cell granules displayed alterations similar to the knockout mice. Although other mechanisms may also be relevant, this finding best explains the association of the risk alleles with ileal disease.

6.4. XBP1: expressed in Paneth cells during endosomal stress

XBP1 is a key transcription factor for the endosomal stress response which may be activated during inflammation. Deletion of this factor in mice results in spontaneous enteritis and increased susceptibility to induced colitis secondary to Paneth cell dysfunction, as well as an overreaction to bacterial products. An association of genetic XBP1 variants was identified in patients with Crohn's disease, but also in those with ulcerative colitis.

6.5. TLR9: Paneth cell receptor interacting with NOD2

TLR9 is a receptor for CpG-DNA which is prominently expressed by the Paneth cell. In cells homozygous for NOD2 mutations the response to this ligand is drastically diminished suggesting an interaction between both receptors. Although the initial suggestion of an independent link between a TLR9 mutation and Crohn's disease was not confirmed in a second study, there was significant epistasis between these mutations: the frequency of the -1237C mutation was significantly higher in patients with at least one NOD2 mutation and further increased in those homozygous for NOD2 mutations. The functional relevance for host-bacterial interaction in Crohn's mucosa is still unclear, however.

6.6. KCNN4: Calcium mediated potassium channel and possibly secretion of Paneth cell antimicrobials

Very recently, work by Simms et al. showed an association of the potassium intermediate/small conductance calcium-activated channel KCNN4 located in the IBD linkage region on chromosome 19q13 with ileal Crohn's disease in Australian and New Zealand individuals. Interestingly, the KCNN4 encoded KCa3.1 protein has an important role in T lymphocyte Ca(2+) signaling as well as Paneth cell secretion and shows significantly reduced mRNA levels in NOD2 mutated patients. These data from Australia could be another mechanism for a defect in Paneth cell antimicrobial host defense and a possible therapeutic target.

Figure 4  Different known associations and mechanisms for defects in Paneth cell function in small intestinal Crohn's disease. The original photography is from Joseph Paneth in 1888, Archiv für mikroskopische Anatomie.
6.7. Paneth cell defensin mutation and inactivation in Crohn’s disease

Apparently, although this has not been studied systematically, mutations in HD-5 are rare. Nevertheless, in a small study such a mutation has been found, not surprisingly, in a patient with Crohn’s disease. Interestingly, the replacement of arginine at position 13 to histidine, as observed in this patient, reduced bacterial killing and thus was functionally relevant. 66

Other reports have suggested that the disulfide bridges in HD-5 which normally protect the peptide against proteolytic degradation are defective in the peptide isolated from the ileum of Crohn’s disease patients. This might lead to rapid degradation and inactivation, since trypsin is normally secreted by Paneth cells to activate the propeptide. Finally, it has been reported that the luminal processing of HD-5 is impaired in Crohn’s disease where it may persist in a complex with chymotrypsin and trypsin (Elphick et al., 2008).

7. Consequences for clinical treatment

For acute flares of Crohn’s disease the conventional approach is the use of steroids. A newer second line alternative are so called biologics, such as antibodies against TNF-α. To maintain remission, different immunosuppressant agents are established. The two main drugs are azathioprine as well as methotrexate which – if tolerated – help to prevent some flares in a proportion of patients. 67 Unfortunately, however, the current anti-inflammatory therapy remains far from satisfactory for both patients and physicians, mostly because of substantial side effects and uncontrolled relapses.

The new insights in the etiologial role of innate immune effector molecules like defensins and other antimicrobial peptides could have a substantial influence on future therapeutic strategies. As demonstrated recently, current standard treatments do not seem to have substantial effects on the expression of the main antimicrobial defensins. 53 For the treatment of IBD, future strategies should aim to strengthen protective innate immunity, especially in case of disease remission. Although different studies have shown that antibiotics may be effective in certain situations, their role in treatment is currently limited 68: antibiotic therapy is currently used mostly in treating fistula as well as maintenance therapy after surgery. Their modest effectiveness is probably due to the fact that the luminal bacterial flora is only modified but not eliminated from the mucosa. Also, the reported efficacy of Trichuris suis therapy in Crohn’s disease provokes the testable question of whether the stimulation of Paneth cell defensins or other antimicrobials by parasitic worms might be an explanation for their therapeutic effect. Probiotic bacteria like E. coli Nissle 1917, other therapeutic probiotic E. coli (Symbioflor) as well as Lactobacilli have been shown to strongly induce antimicrobial peptides. 69–71 In case of E. coli Nissle (Mutaflor), the oldest known (in use since World War I, 1917) and probably the best studied probiotic strain, this induction is mediated by a specific flagellin. 72 Its efficacy in maintaining remission in ulcerative colitis has been shown to be as effective as standard treatment with mesalazine in a placebo controlled, double-blind study. 73,74 Even though E coli Nissle is clearly effective in ulcerative colitis, probiotic treatment in Crohn’s disease seems to be less useful. A possible but speculative explanation could be a general defect in the upregulation of defensins and other protective host molecules. Probiotic bacteria are the first therapeutic agents for IBD that have been shown to induce the production of antimicrobial peptides and this might be an important mechanism to prevent bacterial invasion into the mucosa. It is likely, however, that other therapeutic agents like worm eggs, specific bacterial, food or artificial components could have similar effects. We believe that future, innovative drugs should aim to bolster protective innate immunity especially in the disease free remission phase to maintain remission.

8. Conclusion

It is apparent from this brief discussion that there is good evidence for an important role of ileal defensins in Crohn’s disease involving this localization. The mechanisms leading to a function defect are extremely complex, imply both genetic and structural mechanisms and are likely to be additive in some cases. The multiple genetic links suggest a primary role of defensin deficiency allowing bacterial invasion and render it highly unlikely that the defence is defective only secondary to inflammation. Rather, the presence of various bacterial strains found at and in ileal Crohn’s mucosa including adherent E. coli or M. paratuberculosis is likely a direct consequence of the defective chemical antibacterial barrier. Recently it has been found that ileal derived Paneth cell HD-5 is still intact and bactericidal in the colon lumen of the mouse. If true in man, this would explain the involvement of the proximal colon in many of the patients with ileal disease through alterations of the luminal flora in case of deficient HD-5. In conclusion, if any particular cell type is pathogenetically linked to ileal and possibly ileocolonic Crohn’s disease, the Paneth cell is a perfect candidate.

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Paneth’s disease


