Review

Role of Antimicrobial Peptides in Inflammatory Bowel Disease

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Abstract: Inflammatory bowel diseases (IBD) are characterized by a chronic relapsing inflammation of the gastrointestinal mucosa. The etiology and pathogenesis of these disorders such as Crohn's disease and ulcerative colitis are incompletely understood. Recently, antimicrobial peptides, which are expressed by leukocytes and epithelia, have been implicated in the pathogenesis of IBD. Antimicrobial peptides are pivotal for intestinal defense, shaping the composition of the luminal flora and contributing thereby to the maintenance of intestinal homeostasis. Apart from their antimicrobial activity affecting commensal bacteria, immunomodulatory properties of antimicrobial peptides have been identified, which link innate and adaptive immune response. There is increasing evidence that alterations in mucosal levels of these peptides contribute to IBD pathogenensis.

Keywords: inflammatory bowel disease; defensin; cathelicidin

1. Introduction

The etiology of inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), has not been understood in detail. These diseases are characterized by chronic relapsing inflammation of the gastrointestinal mucosa. The etiology is multifactorial with immune,

genetic and environmental factors contributing to the onset and perpetuation of IBD [1,2]. Recent characterization of IBD susceptibility genes has demonstrated the importance of epithelial barrier function including adaptive and, most importantly, innate immune responses. Further substantial advances in the understanding of the molecular pathogenesis of IBD have come from the identification of environmental factors. Numerous studies have identified commensal bacteria and their products, rather than pathogenic organisms, as drivers of dysregulated immune responses in IBD. In this regard, adherent bacteria have been detected in the mucosa of CD patients, and antibiotics as well as probiotics have been proven to ameliorate the symptoms and clinical course in IBD [3]. Accumulating evidence indicates a microbial contribution to IBD and supports a key role of the antimicrobial mucosal barrier in the pathogenesis of IBD.

Antimicrobial peptides (AMP) have been identified as essential peptides in the maintenance of intestinal barrier function and immune homeostasis. Human peptides detectable in the gastrointestinal tract are divided into α- and β-defensins (HD and HBD, respectively) and the cathelicidin LL-37 based on their amino-acid sequences. Of at least six human α-defensins that are expressed within the gut mucosa, HD1-4, also referred to as Human Neutrophil Peptide 1 to 4, are predominantly secreted from azurophilic granules of polymorphonuclear leukocytes. Accordingly, the presence of these peptides in the gastrointestinal mucosa is dependent on the recruitment of neutrophils into the mucosa. HD5 and HD6 are contained in apically-oriented secretory granules of Paneth cells, which reside at the base of the crypts of Lieberkühn in the small intestine. In addition to α-defensins, only four of the human β-defensins (hBD1 to 4) have been found in epithelia of diverse gastrointestinal tissues, including those of the stomach, small intestine and colon [4]. Biologically-active defensins are released upon proteolytic processing of their proforms by certain enzymes, including trypsin for HD5 and HD6 in humans [5]. In addition to defensins, mucosal gastrointestinal cell lineages also express LL-37/h-CAP18, the only cathelicidin detected in humans. LL-37 is constitutively expressed in various immune cells, whereas its expression in intestinal epithelia is inducible.

Apart from these major groups, antimicrobial properties have been attributed to a multitude of other small molecules. These include elafin and the secretory leukocyte protease inhibitor (SLPI), which exert broad spectrum bactericidal activity against Gram-negative and Gram-positive bacteria with additional activity against selected viruses and fungi being noted [6]. Moreover, at least 17 members of the chemokine family have been shown to exert direct antibacterial activity. Epithelial-derived chemokines with constitutive expression include CLL14, CCL15 and CCL20/macrophage-inflammatory protein-3α [7]. Finally, bactericidal/permeability-increasing protein (BPI) is another anti-infective molecule present in the intestinal mucosa. BPI is diffusely expressed along the crypt-villous axis and epithelial BPI levels decrease along the length of the intestine. Although epithelial cells express markedly less BPI protein than neutrophils, this peptide contributes significantly to bacterial killing and attenuates bacterial-elicited proinflammatory signals [8].

2. Immunoregulatory and Non-Antimicrobial Functions of Antimicrobial Peptides

There is accumulating evidence that antimicrobial peptides and particularly defensins influence the gut immune system through multiple mechanisms, *i.e.*, it has been shown that HD1 attracts monocytes, T cells and immature dendritic cells to inflammatory sites [9,10]. Therefore, these peptides are

no longer regarded as "mere" natural antibiotics. Notably, this phenomenon is not restricted to α-defensins. Recently, chemoattractive properties have been described for β-defensins and the cathelicidin LL-37 [11-13]. In this aspect, recruitment of immune cells is not only mediated directly by chemoattractive properties of the antimicrobial peptides, but also by eliciting the expression and release of co-stimulatory molecules, cytokines and chemokines through receptor-dependent mechanisms on variable cell types [13,14]. Moreover, HBD-2 and HBD-3 have been characterized as signaling ligands *per se* for some membrane-bound pathogen-recognition receptors, including the toll-like receptors 4 and 2, respectively. Furthermore the expression of the co-stimulatory molecules CD80, CD86 and CD40 is significantly and consistently increased in a MyD88-dependent manner following exposure of monocytes and dendritic cells to recombinant HBD-3 [15]. Finally, neutrophil-derived defensins, HBD-2 and LL-37 have been involved as positive regulators of cell survival, neovasculogenesis and wound healing [13,16,17].

3. Expression of Antimicrobial Peptides in Inflammatory Bowel Disease

Changes in the bacterial flora and its adherence to intestinal lineages, as well as the long standing observation that antibiotics cause clinical improvement, have led to the hypothesis that a primary defect in antibacterial mechanisms is pivotal for the development of chronic intestinal inflammation. Numerous clinical studies have linked chronic intestinal inflammation to an altered expression and secretion of AMPs. Currently, there are several limitations to our understanding of the regulatory mechanisms maintaining appropriate expression of AMPs in intestinal disease. However, a defective bacterial clearance due to impaired defensin and IgA production has been identified in IBD and particularly in CD. These alterations contribute to epithelial cell damage and increased epithelial permeability and broaden the spectrum of pathogenetic relevant mechanisms, which hitherto included a decreased expression of certain tight junction proteins such as claudins or junction adhesion molecule-A (JAM-A) and a concomitant up-regulation of other pore-forming proteins (*i.e.*, claudin-2) [18,19].

3.1. Crohn's Disease

3.1.1. Ileal Crohn's Disease

In the small intestine, phasic propulsive motility, a hostile environment rich in pancreatic and bile secretion and effectors of the innate and adaptive immune system keep the bacterial load low in healthy individuals. Among the antibacterial peptides detected, Paneth cell derived α-defensins HD5 and HD6 constitute the most abundant released granule components. A hundredfold excess in HD5 expression levels has been found in comparison to other AMPs released such as secretory phospholipase 2 (SPLA2), lysozyme, trypsin or antitrypsin [20]. Studies in transgenic animals have not only proven the antibacterial capacities of HD5 and but have furthermore revealed, that HD5 shapes the composition of microbial species present in the small intestine [21].

Interestingly, in a clinical study by Wehkamp and collaborators, decreased expression of both HD5 and 6 was clearly linked to the development of CD-associated lesions in the small intestine [20]. An antibacterial deficiency specifically in Paneth cell α-defensins is detectable in the majority of mucosal

extracts from patients with ileal CD. A major breakthrough was the discovery of a link between frameshift mutations of the NOD2/caspase15 recruitment domain and a marked deficiency of HD5 and HD6 in patients with ileal but not colonic CD or ulcerative colitis [20,22]. However, the NOD2 mutation is present in only one-third of patients with ileal CD in Western countries and is rarely detectable in Japanese cohorts. In search for alternative mechanisms, recent studies have revealed a deficiency of Wnt/Tcf-4 in ileal CD [23]. Tcf-4 mRNA expression levels were significantly decreased in the muocsa of ileal CD patients and this decrease strongly correlated with diminished HD5 expression [23]. Wnt signaling is crucial for Paneth cell maturation and differentiation and regulates specifically the expression of MMP7 and Paneth cell α-defensins [24]. Notably, there was no association being detected between Tcf-4 expression and the inflammatory score, IL8 levels or NOD2 mutations. However, Tcf-4 deficiency was specific for ileal but not colonic CD. More recently, a polymorphism in the Tcf-4 promoter region has been linked to ileal CD—independent of the NOD2 status in the subjects studied. Hence, alterations in Tcf-4 expression seem to represent another genetic basis for Paneth cell defensin deficiency in ileal CD [25].

3.1.2. Colonic Crohn's Disease

Accumulating evidence points to a major role of β-defensins in inflammatory processes of the colon. However, recent data from a mouse model indicate, that Paneth cell cryptidins synthezised in the ileum retain their structure and functionality in the colonic lumen [26]. Furthermore, Paneth cell metaplasia has been noted in inflamed areas of the colon [27] suggesting additional antibacterial protection in these areas.

Regarding β-defensins, a decreased HBD1 expression has recently been associated with colonic involvement of CD [28]. Furthermore, it has been shown that dysregulated peroxisome proliferator-activated receptor (PPAR)-γ production results in reduced antimicrobial activity of the mucosa against major components of the microbiota in mice, whereas the PPAR-γ agonist rosiglitazone triggered epithelial HBD1 expression *in vitro* and *in vivo* [28]. A pathogenetic relevance of HBD1 expression in colonic CD is furthermore supported by the recent detection of the single nucleotide polymorphism (SNP) rs1800972 in the promoter region of the human DEFB1 gene with positive regulation of HBD1 expression. In support, individuals bearing this SNP seem to be protected towards the development of colonic CD [28,29].

Crohn's colitis has also been associated with a deficient expression of HBD2 and HDB3, which represent the predominantly induced antimicrobial peptides in the colon. Genes for both peptides are located on chromosome 8p23.1 with a highly-polymorphic DNA number detected in the healthy population. Nevertheless, a shift towards lower DNA copy numbers (3 in UC *vs.* 4 in healthy individuals) of this gene cluster has been identified in colonic CD by genome wide copy number profiling [30]. Three or less gene copy numbers were paralleled with diminished mucosal HBD2 mRNA expression and furthermore associated with a significantly higher risk for the development of colonic CD [30]. In addition, a reduced expression of elafin has been observed in CD, which also points to a protease-antiprotease imbalance explaining at least in part the penetrating, transmural phenotype in CD [31].

Taken together, these findings challenge the perspective that diminished defensin expression is merely the result of epithelial cells loss in inflammatory conditions as discussed below [32].

3.2. Ulcerative Colitis

Data on a mechanistic role of AMPs in UC are far less conclusive. Of the peptides studied so far, expression of the inducible beta-defensins HBD2 and HBD3 was increased up to 1,000-fold or 300-fold, respectively in active UC [12,31]. Accordingly, mucosal extracts of patients with active UC displayed a significantly increased antimicrobial activity towards various organisms of the intestinal flora. Cathelicidin LL-37 also showed induction in inflamed tissues of UC [33]. In summary, and in contrary to the observations made in CD, these data suggest an intact bacterial shield in UC patients [22].

Finally it should be noted, that decreased mucosal AMP expression is proposed to be a consequence of epithelial and enterochromaffine cell damage and loss rather than a primary effect [32]. Arijs and co-workers correlated the epithelial cell mass and the number of Paneth cells with the expression levels of HBD1, HD5 and 6, respectively. Results from their study suggest that mucosal cell loss is responsible for the decreased alpha-defensin or beta-defensins expression in ileal and colonic CD respectively, which is in accordance with a previously published report [34]. The authors concluded that decreased expression of antimicrobial peptides in CD is not a primary defect causing the disease, but rather a consequence of epithelial cell loss in the ileum and colon as well as a loss of Paneth cells in the ileum in an active phase of the disease. In established IBD, decreased secretion of AMPs as a consequence of epithelial cell damage and loss may then contribute to the perpetuation of inflammation. As a consequence, the ongoing bacterial invasion of the mucosa cannot be controlled although Paneth cell metaplasia might result in an increased production of some of the AMPs in the colon.

4. Conclusions

Current understanding of IBD etiology is that abnormalities in mucosal innate immune response cause a loss of tolerance to commensal microbiota and alterations in the composition of the gut microbiota. The host immune system is subsequently overwhelmed by bacterial antigens which lead to chronic immune-mediated intestinal injury. Supported by numerous clinical studies, a dysregulated expression and processing of AMPs seems to be the key mechanism. Whether the abnormalities in defensin expression in the mucosa in IBD are primary defects or the consequence of inflammatory cell damage is still debated. In addition, the role of further AMPs in the pathogenesis of chronic inflammation needs to be clarified.

However, given the essential role of defensins in maintaining intestinal homeostasis, correcting defensin deficiency might represent a new and alternative therapeutic avenue. Furthermore, drugs and diets which modulate or reconstitute the expression of defensins may protect against the onset of colitis or the development of colitis-associated cancer by maintaining sufficient levels of these multifactorial antimicrobial peptides. Strategies discussed so far and potential molecules include PPAR-γ agonists as well as activators of nuclear receptors such as vitamin D and PPAR-β. Reconstitution of immunological capacities might open new therapeutic avenues eagerly awaited by patients and physicians alike.

Acknowledgements

References

1. Podolsky, D.K. Inflammatory bowel disease. *N. Engl. J. Med.* **2002**, *347*, 417-429.
2. Xavier, R.J.; Podolsky, D.K. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* **2007**, *448*, 427-434.
3. Sartor, R.B. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: Antibiotics, probiotics, and prebiotics. *Gastroenterology* **2004**, *126*, 1620-1633.
4. Cunliffe, R.N.; Mahida, Y.R. Expression and regulation of antimicrobial peptides in the gastrointestinal tract. *J. Leukocte Biol.* **2004**, *75*, 49-58.
5. Gosh, D.; Porter, E.; Shen, B.; Lee, S.K.; Wilk, D.; Drazba, J.; Yaday, S.P.; Crabb, J.W.; Ganz, T.; Bevins, C.L. Paneth cell trypsin is the processing enzyme for human defensin-5. *Nat. Immunol.* **2002**, *3*, 583-590.
6. Sallenave, J.M. Secretory leukocyte protease inhibitor and elafin/trappin-2: Versatile mucosal antimicrobials and regulators of immunity. *Am. J. Respir. Cell. Mol. Biol.* **2010**, *42*, 635-643.
7. Kotarsky, K.; Sitnik, K.M.; Stenstad, H.; Kotarsky, H.; Schmidtchen, A.; Koslowski, M.; Wehkamp, J.; Agace, W.W. A novel role for constitutively expressed epithelial-derived chemokines as antibacterial peptides in the intestinal mucosa. *Mucosal. Immunol.* **2010**, *3*, 40-48.
8. Canny, G.; Cario, E.; Lennartsson, A.; Gullberg, U.; Brennan, C.; Levy, O.; Colgan, S.P. Functional and biochemical characterization of epithelial bactericidal/permeability-increasing protein. *Am. J. Physiol. Gastrointest. Liver. Physiol.* **2006**, *290*, G557-G567.
9. Territo, M.C.; Ganz, T.; Selsted, M.E.; Lehrer, R. Monocyte-chemotactic activity of defensins from human neutrohils. *J. Clin. Invest.* **1989**, *84*, 2017-2020.
10. Yang, D.; Chen, Q.; Chertov, O.; Oppenheim, J.J. Human neutrophil defensins selectively chemoattract naive T and immature dendritic cells. *J. Leukocyte Biol.* **2000**, *68*, 9-14.
11. Garcia, J.R.; Jaumann, F.; Schulz, S.; Krause, A.; Rodriguez-Jiminez, J.; Forssmann, U.; Adermann, K.; Klüver, E.; Vogelmeier, C.; Becker, D.; Hedrich, R.; Forssmann, W.G.; Bals, R. Identification of a novel, multifunctional beta-defensin (human beta-defensin 3) with specific antimicrobial activity. Its interaction with plasma membranes of Xenopus oocytes and the induction of macrophage chemoattraction. *Cell Tissue Res.* **2001**, *306*, 257-264.
12. Garcia, J.R.; Krause, A.; Schulz, S.; Rodriguez-Jiminez, J.; Klüver, E.; Adermann, K.; Forssmann, U.; Frimpong-Boateng, A.; Bals, R.; Forssmann, W.G. Human beta-defensin 4: A novel inducible peptide with a specific salt-sensitive spectrum of antimicrobial activity. *FASEB J.* **2001**, *15*, 1819-1821.
13. Otte, J.-M.; Zdebik, A.E.; Brand, S.; Chromik, A.M.; Strauss, S.; Schmitz, F.; Steinstraesser, L.; Schmidt, W.E. Effects of the cathelicidin LL-37 on intestinal epithelial barrier integrity. *Regul. Pept.* **2009**, *156*, 104-117.

14. Diamond, G.; Beckloff, N.; Weinberg, A.; Kisich, K.O. The role of antimicrobial peptides in innate host defense. *Curr. Pharm. Des.* **2009**, *15*, 2377-2392.

15. Funderburg, N.; Lederman, M.M.; Feng, Z.; Drage, M.G.; Jadlowsky, J.; Harding, C.V.; Weinberg, A.; Sieg, S.F. Human β-defensin-3 activates professional antigen-presenting cells via Toll-like receptors 1 and 2. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 18631-18635.

16. Baroni, A.; Donnarumma, G.; Paoletti, I.; Longanesi-Cattani, I.; Bifulco, K.; Tufano, M.A.; Carriero, M.V. Antimicrobial human beta-defensin-2 stimulates migration, proliferation and tube formation of human umbilical vein endothelial cells. *Peptides* **2009**, *30*, 267-272.

17. Chavakis, T.; Cines, D.B.; Rhee, J.S.; Liang, O.D.; Schubert, U.; Hammes, H.P.; Higazi, A.A.; Nawroth, P.P.; Preissner, K.T.; Bdeir, K. Regulation of neovascularization by human neutrophil peptides (alpha-defensins): A link between inflammation and angiogenesis. *FASEB J.* **2004**, *18*, 1306-1308.

18. Vetrano, S.; Rescigno, M.; Cera, M.R.; Correale, C.; Rumino, C.; Doni, A.; Fantini, M.; Sturm, A.; Borroni, E.; Repici, A.; Locati, M.; Malesci, A.; Dejana, E.; Danese, S. Unique role of junctional adhesion molecule-a in maintaining mucosal homeostasis in inflammatory bowel disease. *Gastroenterology* **2008**, *135*, 173-184.

19. Zeissig, S.; Bürgel, N.; Günzel, D.; Richter, J.; Mankertz, J.; Wahnschaffe, U.; Kroesen, A.J.; Zeitz, M.; Fromm, M.; Schultze, J.D. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* **2007**, *56*, 61-72.

20. Wehkamp, J.; Salzman, A.; Porter, E.; Nuding, S.; Weichenthal, M.; Petras, R.E.; Shen, B.; Schaeffeler, E.; Schwab, M.; Linzmeier, R.; Feathers, R.W.; Chu, H.; Lima, H.J.; Fellermann, K.; Ganz, T.; Stange, E.F.; Bevins, C.L. Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 18129-18134.

21. Salzman, N.H.; Hung, K.; Haribhai, D.; Chu, H.; Karlsson-Sjöberg, J.; Amir, E.; Teggatz, P.; Barman, M.; Hayward, M.; Eastwood, D.; Stoel, M.; Zhou, Y.; Sodergren, E.; Weinstock, G.M.; Bevins, C.L.; Williams, C.B.; Bos, N.A. Enteric defensins are essential regulators of intestinal microbial ecology. *Nat. Immunol.* **2010**, *11*, 76-83.

22. Nuding, S.; Fellermann, K.; Wehkamp, J.; Stange, E.F. Reduced mucosal antimicrobial activity in Crohn's disease of the colon. *Gut* **2007**, *56*, 1240-1247.

23. Wehkamp, J.; Wang, G.; Kübler, I.; Nuding, S.; Gregorieff, A.; Schnabel, A.; Kays, R.J.; Fellermann, K.; Burk, O.; Schwab, M.; Clevers, H.; Bevins, C.L.; Stange, D.E. The Paneth cell alpha-defensin deficiency of ileal Crohn's disease is linked to Wnt/Tcf-4. *J. Immunol.* **2007**, *179*, 3109-3118.

24. van Es, J.H.; Jay, P.; Gregorieff, A.; van Gijn, M.E.; Jonkheer, S.; Hatzis, P.; Thiele, A.; van den Born, M.; Begthel, H.; Brabletz, T.; Taketo, M.M.; Clevers, H. Wnt signalling induces maturation of Paneth cells in intestinal crypts. *Nat. Cell Biol.* **2005**, *7*, 381-386.

25. Koslowski, M.J.; Kübler, I.; Chamaillard, M.; Schaeffeler, E.; Reinisch, W.; Wang, G.; Beisner, J.; Teml, A.; Peyrin-Biroulet, L.; Winter, S.; Herrlinger, K.R.; Rutgeerts, P.; Vermeire, S.; Cooney, R.; Fellermann, K.; Jewell, D.; Bevins, C.L.; Schwab, M.; Stange, E.F.; Wehkamp, J. Genetic variants of Wnt transcription factor TCF-4 (TCF7L2) putatice promotor region are associated with small intestinal Crohn's disease. *PLoS One* **2009**, *4*, e4496.

26. Mastroianni, J.R.; Ouellette, A.J. Alpha-defensins in enteric innate immunity: Functional Paneth cell alpha-defensins in mouse colonic lumen. *J. Biol. Chem.* **2009**, *284*, 27848-27856.

27. Cunliffe, R.N.; Rose, F.R.; Keyte, J.; Abberley, L.; Chan, W.C.; Mahida, Y.R. Human defensin 5 is stored in precursor form in normal Paneth cells and is expressed by some villous epithelial cells and by metaplastic Paneth cells in the colon in inflammatory bowel disease. *Gut* **2001**, *48*, 176-185.

28. Peyrin-Biroulet, L.; Beisner, J.; Wang, G.; Nuding, S.; Oommen, S.T.; Kelly, D.; Parmentier-Decrucq, R.; Dessein, R.; Merour, E.; Chavatte, P.; Grandjean, T.; Bressenot, A.; Desreumaux, P.; Colombel, J.F.; Desvergne, B.; Stange, E.F.; Wehkamp, J.; Chamaillard, M. Peroxisome proliferator-activated receptor gamma activation is required for maintainance of innate antimicrobial immunity in the colon. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 8772-8777.

29. Kocsis, A.K.; Lakatos, P.L.; Somogyvári, F.; Fuszek, P.; Papp, J.; Fischer, S.; Szamosi, T.; Lakatos, L.; Kovacs, A.; Hofner, P.; Mándi, Y. Association of beta-defensin 1 single nucleotide polymorphisms with Crohn's disease. *Scand. J. Gastroenterol.* **2008**, *43*, 299-307.

30. Fellermann, K.; Stange, D.E.; Schaeffeler, E.; Schmalzl, H.; Wehkamp, J.; Bevins, C.L.; Reinisch, W.; Teml, A.; Schwab, M.; Lichter, P.; Radlwimmer, B.; Stange, E.F. A chromosome 8 gene cluster polymorphism with low human beta-defensin 2 gene copy number predisposes to Crohn's disease of the colon. *Am. J. Hum. Genet.* **2006**, *79*, 439-448.

31. Schmid, M.; Fellermann, K.; Fritz, P.; Wiedow, O.; Stange, E.F.; Wehkamp, J. Attenuated induction of epithelial and leukocyte serine antiproteases elafin and secretory leukocyte protease inhibitor in Crohn's disease. *J. Leukocte Biol.* **2007**; *81*, 907-915.

32. Arijs, I.; De Hertogh, G.; Lemaire, K.; Quintens, R.; van Lommel, L.; van Steen, K.; Leemans, P.; Cleynen, I.; van Assche, G.; Vermeire, S.; Geboes, K.; Schuit, F.; Rutgeerts, P. Mucosal gene expression of antimicrobial peptides in inflammatory bowel disease before and after first infliximab treatment. *PLoS One* **2009**, *4*, e7984.

33. Schauber, J.; Rieger, D.; Weiler, F.; Wehkamp, J.; Eck, M.; Fellermann, K.; Scheppach, W.; Gallo, R.L.; Stange, E.F. Heterogeneous expression of human cathelicidin hCAP18/LL-37 in inflammatory bowel diseases. *Eur. J. Gastroenterol. Hepatol.* **2006**, *18*, 615-621.

34. Simms, L.A.; Doecke, J.D.; Walsh, M.D.; Huang, N.; Fowler, E.V.; Radforf-Smith, G.L. Reduced alpha-defensin expression is associated with inflammation and not NOD2 mutation status in ileal Crohn's disease. *Gut* **2008**, *57*, 903-910.