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Defensins in Ulcerative Colitis

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1. Introduction

Defensins and cathelicidins are the two major endogenous antimicrobial peptide families in mammals, which are abundant components of phagocytic leukocytes and are released by epithelial cells at mucosal surfaces. Defensins are antimicrobial peptides produced at a variety of epithelial surfaces. In the small intestine Paneth cells secrete α -defensins and additional antimicrobial peptides at high levels in response to cholinergic stimulation and when exposed to bacterial antigens. In the intestinal tract α - and β -defensins contribute to host immunity and assist in maintaining the balance between protection from pathogens and tolerance to normal flora. However, attenuated expression of these defensins compromises host immunity and hence may alter the balance toward inflammation. Altered defensins production is suggested to be an integral element in the pathogenesis of ulcerative colitis (UC). Recent years, the defensins have attracted great attention because of their roles in the organism defense system. This review highlights the current knowledge of defensins, distribution, structures, the diverse functions in the immune response and the changes of defensins expression in UC and the potential role in the pathogenesis of UC.

2. Structures of defensins

Antimicrobial peptides are gene-encoded natural antibiotics produced by virtually every life form studied (Boman, 1995; Zasloff, 2002). In mammals, defensins are a major (if not predominant) group of antimicrobial peptides. In the 1980s, Lehrer et al. first found a series of small molecules cationic peptides with similar structures to rabbit and human neutrophil cytoplasmic granules, which were first named "defensins" (Lehrer et al., 1980). A fundamental characteristic of defensins peptides is the presence of three intramolecular disulfide bonds (Ganz, 2003). The defensins are thus subdivided into three subgroups (designated α -, β -, and θ -defensins). The subgroups are based largely on the connectivity of three cystine linkages (Table 1), but structural features of the gene and precursor are also further distinguishing characteristics.

The three-dimensional structures of several α - and β -defensins have been determined by both nuclear magnetic resonance (NMR) and X-ray crystallography techniques (Hill et al., 1991; Zhang et al., 1992; Pardi et al., 1992; Skalicky et al., 1994; Zimmermann et al., 1995;

Sawai et al., 2001). Although crystal structures of some defensins are made up of dimers or multimers, it has not been yet clear whether these multimers are the biologically relevant to different forms of defensins.

Defensins	Peptide size	Cysteine Linkages	Size	Expression Sites	Expression Patterns	Species Distribution
α -defensins	30~34 aa	1-6, 2-4, 3-5	90-105 aa	Neutrophils, Macrophage, Paneth cells, Reproductive epithelia	Mostly constitutive	Primates Rodents Rabbits
β -defensins	36~44 aa	1-5, 2-4, 3-6	60-70 aa	Mucosal epithelia and Skin, Ruminant, Heterophils, Epididymis	Mostly inducible	Primates Rodents Ruminants Birds Crustaceans
θ -defensins	18 aa (two connected hemi-peptides of 9 aa each)	1-1', 2-3, 2'-3'	90 aa	Neutrophils	Constitutive	Non-human primates

Table 1. Comparison of α -defensins, β -defensins and θ -defensins

The 3D structures of α - and β -defensins contain a canonical triple-stranded antiparallel β -sheet motif. Solution and crystallographic analyses of β -defensins have revealed that the α - and β -defensins folds are similar as the amphipathicity is produced by the distribution of polar and hydrophobic side chains on the peptide surfaces. However, both β -defensins possess short α -helical segments that α -defensins lack. There is no evident relationship between β -sheet content and antimicrobial activity, and knowledge of the general structural factors that modulate the antimicrobial spectrum and activity of defensins is for the most part lacking.

The solution structures of closed circular rhesus θ -defensin-1 (RTD-1) and its open chain analog (oRTD-1) have been determined by two-dimensional NMR. RTD-1 and oRTD-1 adopt very similar structures in water, containing an extended β -hairpin, structure with turns at one end in oRTD-1 or in both ends in circular RTD-1. The double stranded β -sheet region of the two molecules is flexible, and, because the structures and flexibilities of RTD-1 and oRTD-1 are similar, the reduced antimicrobial activity of oRTD-1 relative to circular RTD-1 is attributable to the charged N- and C-termini of the oRTD-1 molecule (Trabi et al., 2001; Ouellette, 2006). In contrast to many antimicrobial peptides, RTD-1 has no amphiphilic character, even though surface models of RTD-1 exhibit a certain clustering of positive charges.

3. Characteristics of defensins distribution

Defensins are abundant in cells and tissues that are involved in host defense against microbial infections. Notably, the specific tissue distribution of defensins diverged rapidly during vertebrate evolution (Table 2). To date, 12 different human α -defensins and 48

human β -defensins, 22 mouse α -defensins and 26 mouse β -defensins have been identified and isolated (<http://defensins.bii.a-star.edu.sg>). In the alimentary tract of mammals, α -defensins are highly expressed and largely confined to the small intestine, whereas β -defensins are found to be inducible expression at sites of infection or inflammation.

Species	Neutrophil defensins	Paneth cell defensins	Epithelial cell defensins
Human	α	α	α and β
Rhesus monkey	α and θ	Not determined	β
Mouse	none	α	α and β
Rat	α	α	β
Pig	Not detected in granule extracts	Not determined	β
Cow	β	none	β
Chicken	β	Not determined	β

Table 2. Diverse patterns of defensins expression in vertebrates

In human, α -defensins are expressed primarily in neutrophils, NK cells, certain T cell subsets, and in Paneth cells of the small intestine, where they may regulate and maintain microbial balance in the intestinal lumen. Moreover, low levels of α -defensins expression have been observed in epithelial cells of digestive tract, urogenital tract of mammalian and the kidney of rabbit. Human α -defensin-1, -2, -3, and -4, also known as neutrophil polypeptide (HNP), are located primarily in neutrophils, while human α -defensin-5 and -6 (HD-5, HD-6) are secreted by the small intestinal Paneth cells. Mature α -defensins consist of 29-36 amino acids including six conserved cysteine residues.

β -defensins are the most widely distributed, being secreted by leukocytes and epithelial cells of many kinds. For example, they can be found on the tongue, skin, cornea, salivary glands, kidneys, esophagus, and respiratory tract. It has been suggested that some of the pathology of cystic fibrosis arises from the inhibition of β -defensins activity on the epithelial surfaces of the lungs and trachea due to higher salt content. β -defensins were first found from tracheal epithelium cells of cattle and in granulocytes of cattle (Diamond et al., 1991). The first human β -defensin (HBD-1) was discovered in 1995, which is mainly expressed in kidney, urogenital tract and other epithelial cells (Bensch et al., 1995). In 1997 Harder et al. first isolated and purified HBD-2 from the skin of psoriasis patients (Harder et al., 1997), and it is mainly expressed in damaged skin, oral mucosa and epithelium of infected lungs. HBD-3 is observed to be mainly expressed in human keratinocytes and airway epithelial cells. HBD-4 is mainly expressed in testis, uterus, neutrophils, thyroid, lung and kidney. In addition, HBD-5 and HBD-6 are only present in testicular cells (Harder et al., 2001; Garcia et al., 2001). β -defensins are composed of 36-42 amino acid residues, containing 6 conserved cysteine residues.

θ -defensins are rare and thus far have been found only in the leukocytes of the rhesus macaque (Tran et al., 2008), and the olive baboon, *Papio anubis*, being vestigial in humans and other primates (Angie & Michael 2008; Garcia et al., 2008). Interestingly, θ -defensins are negative in humans and New World monkeys (Garcia et al., 2008; Nguyen et al., 2003). θ -defensins are macrocyclic octadecapeptides expressed only in old world monkeys and orangutans, and produced by the pair-wise, head-to-tail splicing of nonapeptides derived from their respective precursors. Rhesus θ -defensin-1 (RTD-1) is a unique cyclic antimicrobial peptide first identified in rhesus macaque leukocytes (Tang et al., 1999), and

produced by a novel post-translational processing pathway involving the excision of two 9-amino-acid oligopeptides from a pair of propeptides that is further stabilized by three disulfide bonds. θ -defensins possess broad antimicrobial properties *in vitro* against bacteria, fungi, and viruses (Owen et al., 2004; Tran et al., 2008; Wang et al., 2004). Nevertheless, they exhibit very low levels of toxicity *in vitro* (Tran et al., 2008) and *in vivo*, indicating that they may have utilities as therapeutic agents.

4. Biosynthesis of defensins

4.1 Regulation of α -defensins biosynthesis

α -defensins genes map to 8p21–8pter through 8p23 in human and are syntenic in mice (Ouellette, 2006; Ouellette et al., 1989b; Patil et al., 2004; Sparkes et al., 1989), which are expressed predominantly in myeloid cells or in Paneth cells (Selsted & Ouellette, 1995).

4.1.1 Transcriptional regulation

Myeloid α -defensins mRNA are expressed almost exclusively in the bone marrow, where they are found at the highest levels in promyelocytes and at lower levels in myeloblasts and myelocytes (Yount et al., 1995). Enteric α -defensins occur exclusively in Paneth cells in normal small bowel (Cunliffe et al., 2001; Ouellette et al., 1999; Ouellette et al., 2000; Porter et al., 1997b; Selsted et al., 1992). Myeloid and Paneth cell α -defensins genes differ in that genes expressed in cells of myeloid origin consist of three exons, whereas those expressed in Paneth cells have only two exons (Bevins et al., 1996; Huttner et al., 1994; Jones & Bevins, 1992; Jones & Bevins, 1993; Lala et al., 2003). In Paneth cell α -defensins genes, the 5'-untranslated region and the preprosegment are coded by exon 1, but an additional intron interrupts the 5'-untranslated region of myeloid α -defensins gene transcripts (Ouellette & Selsted, 1996).

The differentiation of Paneth cells is determined by continuous Wnt signaling via the frizzled-5 receptor, and transcription of α -defensins genes in Paneth cell is mediated by β -catenin/TCF-4 recognition sites in the 5'-upstream regions of the gene transcription start sites as well as upstream of the gene coding for matrix metalloproteinase-7 (MMP-7), the mouse α -defensins convertase (Andreu et al., 2005; He et al., 2004; Pinto & Clevers, 2005; Van et al., 2005). Monocytes and NK cells also contain α -defensins mRNAs and peptides, but regulatory elements equivalent to β -catenin/TCF-4 sites in Paneth cell α -defensins genes remain to be found in myeloid α -defensins gene promoters.

4.1.2 Posttranslational activation of α -defensins

Both α - and β -defensins are initially synthesized as preprodefensins, consisting of a characteristic amino terminal signal sequence, a propiece, and the mature peptide at the carboxy terminal end of the prepropeptide. The processing and release of α -defensins seem to be peptide- and host species-specific. α -defensins have been isolated from primate leukocytes and neutrophils of several rodents including rats, rabbits, guinea pigs, and hamsters. Myeloid α -defensins RNAs are expressed almost exclusively in the bone marrow, where they occur at the highest levels in promyelocytes and at lower levels in myeloblasts and myelocytes. Although neutrophils contain high levels of α -defensins peptides, defensins mRNAs are degraded during neutrophil differentiation. In contrast, circulating monocytes contain both α -defensins mRNAs and peptides. The proteolytic pathway required to produce mature HNPs from their proforms is active only in myeloid cells (Valore & Ganz,

1992). Newly synthesized proHNPs are processed to mature defensins and then the mature peptides are stored in cytoplasmic granules. The propeptide of proHNPs is important for the normal cellular trafficking during defensins biosynthesis and functions as an intramolecular inhibitor of defensins cytotoxicity (Liu & Ganz, et al., 1995; Valore et al., 1996).

Unlike human neutrophil defensins, Paneth cell defensins HD-5 and HD-6 are stored as precursor in the secretory granules of Paneth cells (Ghosh et al., 2002). The biosynthesis of Paneth cell pro- α -defensins involves post-translational proteolytic activation. Although the enzymes that mediate pro- α -defensins processing in myeloid and epithelial cells are likely to differ, the overall processing schemes are similar in that all are processed from precursor by specific proteolytic cleavage steps.

Evidences have been shown that α -defensins are present in murine Paneth cells under germ-free conditions (Salzman et al., 2007; Ouellette & Lualdi, 1990; Putsep et al., 2000), and in human Paneth cells prenatally (Mallow et al., 1996). These findings indicate that α -defensins expression is independent on bacterial stimulation. In contrast, expression of Reg3 γ and angiogenin in Paneth cells is closely associated with the presence of microbes in the intestinal lumen.

Transcription levels of α -defensins in Paneth cells are directed, in part, through factors intimately linked to cellular differentiation (Batlle et al., 2002). Clevers and colleagues have shown that Tcf7-L2 (also known as Tcf-4) is a key transcription factor for α -defensins expression in Paneth cells. Activity of this transcription factor is linked to Wnt/ β -Catenin signaling gradients in the crypt and appears to represent a master regulator for Paneth cell differentiation (Van et al., 2005). Defensins expression is found to be low in human neonates (Mallow et al., 1996), unweaned mice (Ouellette & Cordell, 1988; Ouellette et al., 1989a) and rats, but increases dramatically with maturation. Aside from this developmental pattern, α -defensin expression is relatively constitutive under most conditions. However, levels vary significantly in association with some disease states (Kelly et al., 2004; Wehkamp et al., 2004, 2005).

Additional regulatory mechanisms of α -defensins activity are granule secretion and proteolytic processing of precursor peptides (Bevins, 2004). Paneth cells secrete their dense secretory granules into the crypt lumen in response to bacterial products (including muramyl dipeptide, a component of bacterial peptidoglycan), but not to fungal or protozoal stimuli (Qu et al., 1996; Ayabe et al., 2000). These findings suggest that *in vivo* control of α -defensins secretion in Paneth cells may be linked to microbial sensors. Interestingly, recent studies have identified that Paneth cells could express nucleotide oligomerization domain (NOD)2 (a critical intracellular pattern recognition receptor for muramyl dipeptide), whose precise functions in Paneth cells are yet to be clearly determined (Lala et al., 2003; Rumio et al., 2004; Kobayashi et al., 2005). Cholinergic agonists can also stimulate α -defensins secretion by a mechanism that appears to involve both increased cytosolic Ca²⁺ and mIKCa1 potassium channels (Satoh et al., 1995; Ayabe et al., 2002).

Proteolytic processing is an important step in regulating expression of active Paneth cell-derived defensins. Paneth cell-derived α -defensins, like myeloid-derived α -defensins, are initially expressed as amino acid prepropeptides. After removal of the N-terminal signal sequence, the Paneth cell-derived α -defensins propeptides require processing by an endopeptidase to produce a mature active peptide. However, there are differences in this general theme when comparing with rodents and primates. MMP-7 (also known as matrilysin), an endoprotease expressed in mouse Paneth cells, is essential for processing of the α -defensins propeptide to active mature peptides in mice (Wilson et al., 1999; Ouellette,

2005; Selsted & Ouellette, 2005). MMP-7 processes the α -defensins propeptides to their active mature peptide counterparts at precisely the same cleavage site *in vitro* as identified *in vivo* (Selsted et al., 1992; Shirafuji et al., 2003). Polymorphic isoforms of α -defensins containing mutations at MMP-7 cleavage site exist in some mouse strains, which influence post-translational processing and yield differences in mature peptides. Characterization of Paneth cell-derived α -defensins suggests that MMP-7 is also the endoprotease responsible for processing in rats (Qu et al., 1996). In rhesus macaques, characterization of Paneth cell-derived α -defensins indicates that trypsin is likely the endoprotease responsible for processing in these primates as well (Tanabe et al., 2004a, 2004b). In contrast, MMP-7 is not detected in human Paneth cells, and trypsin is the endoprotease expressed in Paneth cells, which is responsible for processing of α -defensins propeptides (Ghosh et al., 2002).

In humans Paneth cell-derived α -defensins are stored in secretory granules as propeptides (Ghosh et al., 2002; Cunliffe, et al., 2001). The propeptide trypsinogen is also stored in these same Paneth cell granules. Current hypotheses point that trypsinogen is activated to trypsin after secretion, which then converts proHD5 into mature HD5 in either the crypt or intestinal lumen. In contrast, some of the α -defensins pool in mouse Paneth cells is processed intracellularly and stored as mature MMP-7-cleaved peptides (Ouellette, 2005; Selsted & Ouellette, 2005). Since proteolytic processing is central to the biology of Paneth cell α -defensins, it will be interesting to determine how and why rodents and primates diverged in their mechanisms for achieving this important post-translational modification.

Evidence for the key role of Paneth cell α -defensins in host defense against orally ingested pathogens comes from murine models. Targeted disruption of the MMP-7 gene, which encodes the processing endoprotease of murine Paneth cell α -defensins precursors, has shown to impair the ability of mice to produce active cryptdin. Compared to their wild-type littermates, the MMP-7 null mice cannot effectively clear orally administered noninvasive *Escherichia coli*, and they succumb more rapidly to lower doses of virulent *Salmonella enterica* serovar Typhimurium. However, MMP-7 may have other biological functions that could have altered the susceptibility to these bacterial challenges. Therefore, Salzman et al. utilized a complementary approach to analyze Paneth cell α -defensins function (Salzman et al., 2003). Mice were genetically engineered to express the human Paneth cell α -defensins HD5. Under transcriptional control of HD5's own endogenous promoter, these transgenic mice expressed HD5 in Paneth cells. Expression levels of the transgene were similar to those of the endogenous α -defensins (cryptdins), pointing that this murine model can assess the biological effects of physiologically relevant levels of HD5. The transgenic mice were more resistant to orally administered *Salmonella*. Thus, these two models point to a central role for Paneth cell α -defensins in innate immunity of the small intestine against orally ingested pathogens.

4.2 Regulation of β -defensins biosynthesis

It is likely that β -defensins gene products are produced and stored as mature peptides because pro- β -defensins have not been recovered from natural producing cells and insect cells, in which transfected with β -defensins cDNA always release bioactive mature β -defensins (Aono et al., 2006; Shi, 2007). HBD-1 is constitutively expressed in the epithelial cells in the small intestine and colon and its expression is not influenced by inflammation or bacterial infection. Despite normally absent, HBD-2 and HBD-3 can be induced in normal colon epithelial cells (O'Neil et al., 1999; Fahlgren et al., 2004). Induction of HBD-2 is an NF-

κ B-dependent process in the intestinal epithelium because blocking NF- κ B activation could inhibit the upregulation of HBD-2 in response to IL-1 stimulation or bacterial infection (O'Neil et al., 1999; Voss et al., 2006). Unlike professional phagocytes and Paneth cells, epithelial cells expressing β -defensins do not have visible granules. How β -defensins are stored and released from intestinal epithelial cells remains obscure.

4.3 Regulation of θ -defensins biosynthesis

Rhesus θ -defensins peptides assemble from two distinct precursor molecules with each hemi-precursor contributing a nine-amino acid moiety to the final RTD-1 peptide, although the molecular mechanisms that catalyze or facilitate θ -defensins assembly in primates are not understood (Tang et al., 1999). Rhesus pro-RTDs are products of different genes that resemble the three-exon myeloid α -defensins genes, except that they are truncated by stop codons in exon 3. In addition to heterodimeric RTD-1, homodimeric θ -defensins RTD-2 and -3 have also been isolated from monkey neutrophils (Tran et al., 2002; Leonova et al., 2001). α -defensins gene mutations that give rise to the θ -defensins genes (DEFT) apparently arise in Old World monkeys, because rhesus DEFT homologs have not been found in prosimians or in New World monkeys (Lehrer, 2004). Humans, chimpanzees, and gorillas lack θ -defensins, because the DEFT genes of those species harbor mutations that create premature stop codons in the prepro regions of the precursors. However, at least one mutant human DEFT gene still is actively transcribed, and its nonfunctional mRNA accumulates to high abundance at several sites of expression (Cole et al., 2002).

5. Role of defensins in immune response

In the gastrointestinal tract, these peptides have bactericidal activity by forming micropores in the phospholipid bilayer of bacterial membranes, causing loss of structural integrity and collapse of the bacterial cells. This antimicrobial quality allows defensins to protect the host epithelium and stem cells from virulent pathogens and also help to regulate the number and composition of commensal microbiota (Ramasundara et al., 2009).

5.1 Defensins in innate immunity

The innate immunity is the most primitive defense system against pathogens, which has not only the generalized mechanical barriers and antibacterial action, but also includes functional defense barrier built by phagocytosis and inflammatory response.

5.1.1 Antibacterial activity

Defensins have a broad antibacterial spectrum, which can effectively kill Gram-negative and -positive bacteria, fungi, spirochetes, and some parasites. Importantly, α -defensins have stronger activity against Gram-positive bacteria, while the β -defensins have stronger activity against Gram-negative and -positive bacteria. HBD-3 has stronger bactericidal activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Actinomyces in vitro* (Maisetta et al., 2005).

The α - and β -defensins expressed in the alimentary tract of human and mice have activity profiles and expression patterns that overlap with other mammalian peptides (Table 3). Intestinal α -defensins have microbicidal activities against many Gram-positive (*L. monocytogenes*, *S. aureus*) and Gram-negative bacteria (*E. coli*, *S. typhimurium*). Similarly, HD5

is active against many bacterial species and the fungus *C. albicans* (Porter et al., 1997a; Ghosh et al., 2002; Ericksen et al., 2005). Surprisingly, initial reports indicate that HD6 has very poor antibacterial activity *in vitro*, despite similar ionic charge properties as HD5 (Ericksen et al., 2005). The most abundant β -defensins, expressed chiefly in the stomach and colon, also have bactericidal activity *in vitro*. HBD-2 is microbicidal against *P. aeruginosa*, *E. coli* and *C. albicans*, but less activity against Gram-positive *S. aureus* (Harder et al., 1997). In contrast, the more cationic HBD-3 has activity against *S. aureus* (Harder et al., 2001) and is less sensitive to the ionic composition of the assay medium. HBD-1 has antibacterial activity (Valore et al., 1998), but it is not potent *in vitro* like HD6.

Defensins	Mr (kDa)	Tissue distribution	Stimuli
HNP 1-4	3.5-4.5	Sparse lamina propria neutrophils in active inflammation seen in scattered intestinal epithelial cells	Increased in active inflammation but possibly a result of increased neutrophilic influx
HD-5, HD-6	3.5-4.5	Paneth cells and some villous epithelial cells in normal duodenum, jejunum and ileum Paneth cell metaplasia	Constitutively expressed, however processing is required for biological activity
HBD-1	3.5-4.5	Colonic epithelia (and some other mucosal epithelia)	Constitutively expressed
HBD-2, -3, -4	3.5-4.5	Colonic epithelia (and some other mucosal epithelia) Colonic plasma cells	IL-1 α and entero-invasive bacteria
Cryp-4	5.1	Paneth cells	Uncertain

Table 3. Defensins in the gut of human and mouse

5.1.2 Chemotactic activity

Various defensins have been reported to have chemotactic activity for monocytes, T cells and dendritic cells. In the case of HBD-1 and HBD-2, which attract memory T cells and immature dendritic cells, the chemoattractant activity might be due to defensins binding to the chemokine receptor CCR6. Although the physiological importance of this interaction has not yet been shown, the high concentrations of HBD-2 in inflamed skin make it probable that this defensins could compete effectively with the natural CCL20, despite the higher affinity of the latter for the CCR6. Recent structural analysis of CCL20 has indicated marked similarities to HBD-2 in the putative receptor binding region of CCL20. The role of this region in the chemotactic activity of HBD-2 needs to be confirmed by mutating the amino-acid residues that are suspected to be involved in its interaction with CCR6. Human neutrophil defensins HNP1-3 have been reported to be chemotactic for monocytes, naive T cells and immature dendritic cells (Territo et al., 1989; Chertov et al., 1996; Yang et al., 1999; 2000), but a specific receptor has not yet been identified. Mouse β -defensin-2 acted as a peptide adjuvant when it was linked to a non-immunogenic tumour antigen (Biragyn et al., 2002). This immunostimulatory activity was shown to depend on TLR-4 and its ability to induce dendritic-cell maturation. It is not yet certain how this receptor can bind with mouse β -defensin-2 as well as the many other ligands attributed to it, or whether some of

these molecules function as efficient carriers for lipopolysaccharide, the main ligand of TLR-4.

5.1.3 Paneth cell defensins regulate innate immune responses by NOD2 or TLRs

TLRs which are the major pattern recognition receptors of innate immunity, by recognizing pathogen associated molecular patterns, activating the innate immune system to produce proinflammatory cytokines and defensins resist damage caused by pathogens (Elphick & Mahida, 2005). NOD2 is a new pattern recognition molecule, participating in the anti-bacterial and anti-invasion effect of host cell by the identification of intracellular bacterial components. The absence of NOD2 leads to the disorder of NF- κ B, resulting in imbalance of cytokine production and defensins secretion disorders. Kobayashi et al. found that the levels of two cryptdins expression were significantly reduced when NOD2 gene mutated in mice (Kobayashi et al., 2005). NOD2 mutations have impact on Paneth cell α -defensins expression, whereas α -defensins are the main effector molecule which Paneth cells play a major role in innate immunity. Therefore, intestinal epithelium could regulate the expression of defensins secretion to activate and regulate innate immune responses by NOD or TLRs through pattern recognition receptors.

5.1.4 Blocking ACTH activity

Evidences have demonstrated that some defensins have a role in inhibiting the effects of adrenocorticotrophic hormone (ACTH) by binding to ACTH receptor (Zhu et al., 1987, 1989; Solomon et al., 1991; Tominaga et al., 1990). Although such activity could inhibit the production of the immunosuppressive hormone cortisol, and could therefore be useful in responding to infections, the physiological role of this *in vitro* interaction has not yet been shown.

5.1.5 Other activities of defensins

It has been reported that defensins have the ability to activate nifedipine-sensitive calcium channels in mammalian cells (MacLeod et al., 1991; Bateman et al., 1996). The structural basis of this effect is not understood. Certain mouse Paneth cell defensins could promote chloride secretion, probably by forming channels in the apical membrane of epithelial cells (Lencer, et al., 1997; Merlin et al., 2001). This activity is limited to a subset of mouse Paneth cell defensins, and its structural basis is not yet known.

5.2 Defensins in acquired Immunity

Evidences have demonstrated that α - and β -defensins have chemotactic activities, indicating that defensins are involved in attracting T cells recycling and promoting immature dendritic cells and monocytes homing to the site of infection. HNP-1 and HNP-2 could enhance severe immune deficiency (SCID) mice T cell recycling (Lillard et al., 1999). Intraperitoneal administration of human neutrophil peptide (HNP) significantly increased the production of keyhole limpet hemocyanin (KLH)-specific IgG1, IgG2a and IgG2b antibodies 14 days after immunization. These results indicate that defensins function as potent immune adjuvants by inducing the production of lymphokines, which promote T cell-dependent cellular immunity and antigen-specific Ig production, and that defensins appear to act as neutrophil-derived signals that promote adaptive immune responses (Tani et al., 2000).

Increasing data have shown that β -defensins participate in acquired immunization mainly by chemotactic induction or direct activation of antigen presenting cells, such as dendritic cells, to activate the T cells, resulting in enhanced specific immune response (O'Neil et al., 1999). Previous study has confirmed that defensins contribute to host defense by disrupting the cytoplasmic membrane of microorganisms (Yang et al., 1999, 2000). Human α -defensins are also chemotactic for immature dendritic cells and memory T cells. Human α -defensins was selectively chemotactic for cells stably transfected to express human CCR6, a chemokine receptor preferentially expressed by immature dendritic cells and memory T cells. The α -defensin-induced chemotaxis is sensitive to pertussis toxin and inhibited by antibodies to CCR6. The binding of iodinated LARC, the chemokine ligand for CCR6, to CCR6-transfected cells was competitively displaced by α -defensins. Thus, α -defensins may promote adaptive immune responses by recruiting dendritic and T cells to the site of microbial invasion through interaction with CCR6. In addition, defensins are also able to activate macrophages via TLR signaling and trigger acquired immune system. Evidence has shown that in cooperation with the IL-1 related protein kinase (IRAK), β -defensin-2 as TLR-4 endogenous ligand could combine with TLR4, leading to NK- κ B activation and migration to the nucleus to activate cytokine gene transcription, upregulation of costimulatory molecules expression and dendritic cells maturation, thereby activate T cells, trigger a strong specific immune response (Biragyn et al., 2002; Means et al., 2000).

6. Role of defenins in the pathogenesis of UC

Inflammatory bowel disease (IBD) is chronic, relapsing and debilitating conditions that have significant impact on quality of life. IBD includes two main conditions, UC and Crohn's disease (CD), which are defined based on characteristic endoscopic and histological findings. UC is characterised by superficial inflammation limited to the mucosa of the colon. In contrast, CD is characterised by discontinuous skip lesions that can occur anywhere in the gastro-intestinal tract with transmural inflammation and non-caseating granulomas.

The pathogenesis of IBD is not clearly understood, and its presentation regarding disease localization, progression and response to therapies is unpredictable. In the intestinal tract, defensins contribute to host immunity and assist in maintaining the balance between protection from pathogens and tolerance to normal flora. However, attenuated expression of defensins compromises host immunity and hence may alter the balance toward inflammation. Altered defensins production is suggested to be an integral element in the pathogenesis of IBD (Table 4).

Defensins	Ulcerative colitis	Ileal Crohn's disease	Colonic Crohn's disease
HNP 1-4	upregulate (infection)	Unknown	Unknown
HD-5, HD-6	Upregulate, Paneth cell metaplasia	Downregulate, especially NOD2 mutation patient	Upregulate, Paneth cell metaplasia
HBD-1	Downregulate	Downregulate	Downregulate
HBD-2, -3	Upregulate (infection)	No obvious change	No obvious change
HBD-4	Upregulate	No obvious change	No obvious change
Cryp-2	Upregulate	Unknown	Unknown
Cryp-4	Unknown	Unknown	Downregulate

Table 4. Defensins expression in ulcerative colitis, and colonic and ileal Crohn's disease

6.1 α -defensins in UC

6.1.1 Paneth cell-derived α -defensins in UC

α -defensins are highly expressed by Paneth cells (Fig. 1). These cells are located at the base of the crypts of Lieberkühn and are distributed from the duodenum to the ileum. Their location in the crypts suggests an essential role of protecting the epithelial stem cells, located in close proximity. Paneth cells are filled with large apically located granules (Fig. 1A) and have ultrastructural hallmarks (an extensive endoplasmic reticulum and well-developed Golgi) of prototypical secretory cells. The development of small intestine gland is imperfect in newborn BALB/c mice, and no Paneth cells were seen 4 days before. However, Paneth cells could be detected in small intestine gland 6 days after birth (Fig. 1C). In addition to α -defensins, human Paneth cells also secrete lysozyme, Reg 3 γ , and phospholipase A2 (Ouellette & Bevins, 2001). Of these antimicrobials, the α -defensins are the most abundant. In addition, mouse Paneth cells also express numerous cryptdin-related peptides (Fig. 1B) and angiogenin (Ouellette & Bevins, 2001; Hornef et al., 2004).

Numerous data have proven that intestinal luminal microbes play an important role in the pathogenesis of IBD (Janowitz et al., 1998; Sartor, 2001; Marteau et al., 2004; Strober et al., 2007). NOD2, the aforementioned intracellular peptidoglycan receptor for muramyl dipeptide is the first susceptibility gene identified for IBD (Hugot et al., 2001; Ogura et al., 2001). Mutations in NOD2 are likely responsible for the genetic predisposition to disease in approximate one third of patients with CD, especially for ileal disease (Bonen & Cho, 2003; Hugot 2004). NOD2 is expressed in macrophages and Paneth cells. Since Paneth cell antimicrobials may affect the microbial composition of the small intestine, deleterious changes in the bacterial microbiota that result from altered Paneth cell function might contribute to the pathogenesis of IBD (Ouellette & Bevins, 2001; Fellermann et al., 2003).

Wehkamp et al. have reported that low levels of Paneth cell α -defensins mRNA and protein are present in inflamed ileum of CD patients as compared to non-IBD controls (Wehkamp et al., 2004, 2005). Interestingly, the specific decrease in α -defensins is more pronounced in CD patients with NOD2 gene mutation. Consistent with this, Kobayashi et al. reported a decrease expression of Paneth cell α -defensins (cryptdin) and cryptdin related sequences in NOD2-knockout mice (Kobayashi et al., 2005). As compared to wild-type controls, the NOD2-knockout mice are more susceptible to gastric, but not systemic, challenges with the Gram-positive bacterium *Listeria monocytogenes*. The decreased expression of Paneth cell antimicrobials in the NOD2-knockout mice is proposed to underlie the increased susceptibility.

6.1.2 α -defensins by colonic Paneth cells

Evidences have shown that HD-5 and HD-6 are not present in normal colonic mucosa. However, Cunliffe et al. detected HD5 in the colonic crypt region of IBD samples (Cunliffe et al., 2001). The appearance of these defensins is due to the phenomenon of Paneth cell metaplasia during colonic inflammation. HD-5 mRNA expression is enhanced in both idiopathic and nonidiopathic inflammatory states of the large bowel, whereas HD-6 is specifically related to CD and UC. Immunohistochemical staining has confirmed that the presence of HD-5 in colonic epithelium may be of importance in maintaining the mucosal barrier and controlling microbial invasion in IBD (Yamaguchi et al., 2009).

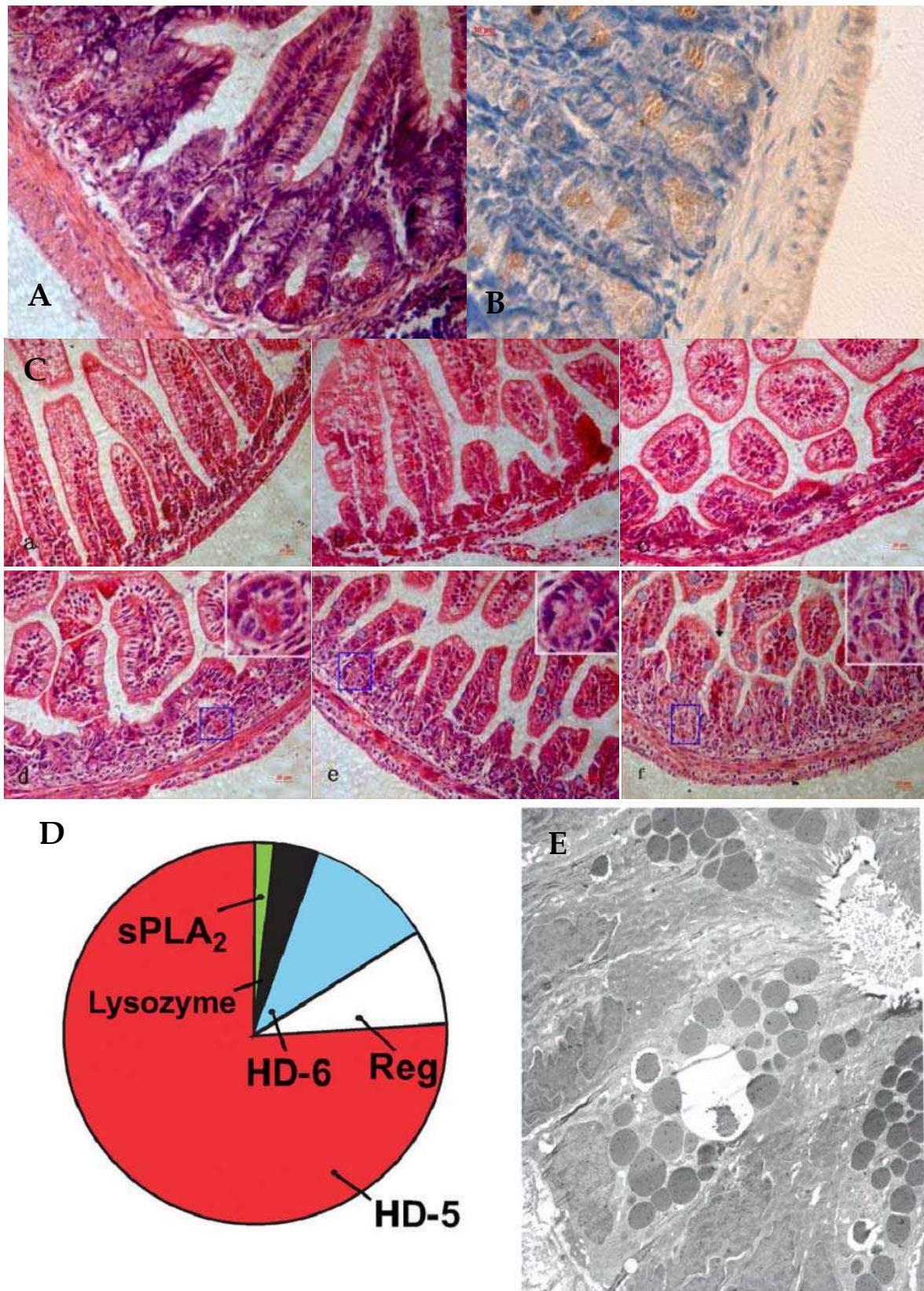


Fig. 1. Paneth cell granules contain α -defensins

A: Hematoxylin-eosin stain of small intestinal crypt shows Paneth cell granules (Bright Red) containing α -defensins in ileum of BALB/c mice. Abundant large secretory vesicles of

Paneth cells are adjacent to the crypt lumen. Scale bar = 20 μm .

B: Immunohistochemical staining demonstrates Cryptidins-4 in the granules of Paneth cell in the ileum crypts of BALB/c mice. Scale bar = 10 μm .

C: The Paneth cells in intestine of newborn BALB/c mice. The development of small intestine gland is imperfect in newborn BALB/c mice, and no Paneth cells were seen 4 days before. However, Paneth cells could be detected in small intestine gland 6 days after birth.

a: duodenum, 4 days; b: jejunum, 4 days; c: ileum, 4 days; d: duodenum, 10 days; e: jejunum, 10 days; f: ileum, 10 days. Scale bar = 20 μm

D: Real-time PCR analysis of mRNA encoding Paneth cell α -defensins (HD-5 and HD-6) antimicrobial peptides in human ileum.

E: Immunogold electron microscopy localizes HD5 to Paneth cell secretory granules.

Transmission electron micrograph of human ileum crypt with immunogold staining for HD5. Defensin-rich granules were found exclusively in Paneth cells

6.1.3 Other α -defensins in the gut

Human HNP-1, -2, -3, and -4 have been found to be present in the granules of polymorphonuclear cells and intestinal epithelial cells, where they participate in systemic innate immunity (Cunliffe, 2003). Cunliffe and colleagues have observed that the mRNA levels of HNP-1, -2, and -3 are significantly increased in inflamed mucosa of IBD patients compared with controls (Cunliffe, 2003), indicating that α -defensins are also involved in the pathogenesis of IBD.

Evidences have shown that expression of HNP-1, -2 and -3 mRNA is highly increased in inflamed colon of UC patients than in healthy controls. Further research also proved that the expression levels of HNP1-3 mRNA, NO and MDA is significantly higher in colonic mucosa of UC patients than in that of normal controls. The expression of HNP-1, -2, and -3 mRNA is correlated with the levels of NO and MDA in the inflamed mucosa in UC patients, the induction of HNP-1, -2, and -3 is involved in the process of inflammation and damage of UC. HNP-1, -2, and -3, NO and MDA might have synergistic effects on colonic inflammation (Cunliffe et al., 2002, 2003). These HNPs are also significantly increased in sera of IBD patients compared with controls, and being significantly correlated with CD activity index, peripheral white blood cell counts, serum CRP values and TNF- α levels (Yamaguchi et al., 2009).

6.2 β -defensins in UC

6.2.1 Inducible β -defensins in UC

Evidences have shown that expression of the inducible β -defensins is significantly increased in inflamed mucosal of UC patients compared with controls. Moreover, HBD-2 expression has also been found to be significantly increased in inflamed colon of UC patients compared with that in controls and CD patients (Wehkamp et al., 2002). In mucosal biopsies, HBD-1 expression is marginally decreased in both CD and UC patients, while HBD-2 is increased exclusively in UC but not in CD. Interestingly, expression of HBD-3 is found to be strongly correlated with HBD-2 in UC (Wehkamp et al., 2003).

6.2.2 Colonic β -defensins

It has been reported that epithelial cells and plasma cells in the lamina propria of colon express HBD. Importantly, expression of HBD-1 is constitutively, while expression of HBD-

2, -3, and -4 is induced by various inflammatory and bacterial stimuli. The pathway responsible for induction of HBD is not completely understood, however it has been presumed that NOD2 signaling is involving in triggering transcription expression of HBD genes (Voss et al., 2006). Colonic plasma cells also express HBD-2, -3 and -4, but it is unclear whether this expression is constitutive or inducible (Rahman et al., 2007).

Previous studies have found that colonic mucosa HBD-1 expression is decreased in UC, and this reduction may result in the decrease of antibacterial activity of mucosal immune system, leading to bacterial invasion secondary inflammatory response. Further studies suggest that defensins deficiency is due to mucosal surface destruction as a result of inflammatory changes, indicating that reduced defensins expression is a symptom of the disease and not the cause (Ramasundara et al., 2009).

Relative low level of HBD-2 expression is found in epithelial cells of normal colon, but significantly increased in inflamed colon (O'Neil et al., 1999). In feces from healthy control individuals, low levels of HBD-2 were detectable, which are also markedly increased under inflammatory conditions (Kapel et al., 2009). In a study by Wehkamp and associates, HBD-2 mRNA was detectable in only 18% of control biopsies compared to 34% in CD and 53% in UC (Wehkamp et al., 2002). In addition, there was increased HBD-2 expression in inflamed compared to non-inflamed areas of CD patients and similarly in UC (Wehkamp et al., 2003). O'Neil and colleagues also demonstrated that HBD-2 mRNA was expressed by colonic epithelial cells in response to stimulation by proinflammatory mediators IL-1 α and enteroinvasive bacteria (O'Neil et al, 1999; Fahlgren et al, 2003). In addition, HBD-3 and HBD-4 are expressed minimally in normal intestinal epithelium, and that there was no difference in expression for patients with colonic CD. In contrast, there was a significant increase of HBD-3 and HBD-4 in UC (Fellermann et al., 2006; 2007).

Overall, HBD-1 is constitutively expressed in normal intestinal epithelial cells and play foundational defense roles in the mucosal immune, while HBD-2, -3 and -4 could be induced to express in inflamed mucosa of UC patients and play a defense role in inflammation response.

7. Defensins therapy in UC

Imbalance of intestinal mucosal immunity is an important condition for the pathogenesis of UC, and the defensins is an important factor to maintain the immune response in intestinal mucosa. Defensins play an important role in the prevention and treatment of mucosal inflammation. Consistent with this, evidences have proven that defensins could inhibit the development of neonatal colitis in mice caused by *Escherichia coli* (Sherman et al., 2005). Moreover, defensins also have certain effects on the inhibition of bacterial translocation and control of intestinal infection, which may substitute for antibiotics in the prevention of bacterial infection and some inflammatory diseases. Therefore, monitoring of defensins will help us to evaluate the severity of inflammation (Hiratsuka et al., 1998). A new approach using defensins therapy may shed some light on management of infectious and inflammatory conditions such as UC. HBD-1-expressing *Escherichia coli* clone has been generated, and defensins protein with biological activity is purified (Cipakova et al., 2004, 2005). HBD-2 gene was also cloned from the lesions of human condyloma acuminatum, and an expression vector was constructed and transformed into *Escherichia coli* (Fang et al., 2002). These approaches may allow us to have a clinical trial in the treatment of UC in the future.

8. Outlook

Since innate immune responses in the gut are directed against luminal bacteria, a defect in the expression and/or function of defensins could give rise to an increase in frequency and severity of intestinal infections. Such a deficiency could lead to gradual bacterial invasion, inflammation and a loss of tolerance to gut bacteria. Although this presumes that a defensins deficiency is a primary event in the pathogenesis of IBD, it is also possible that the deficiency is a secondary event, occurring as a consequence of the disease. The pathogenesis of UC is not clear, but increasing data have suggested that the abnormalities of the intestinal mucosal immune system play a decisive role in the occurrence and development, while the intestinal defenses play an important role in maintaining the balance of mucosal immunity. Defensins function as the effective and regulatory molecules of the immune system in the gut. Further study on the relationship between defenses and UC will be conducive to understanding the pathogenesis of UC, but also provide new approaches for the treatment.

9. References

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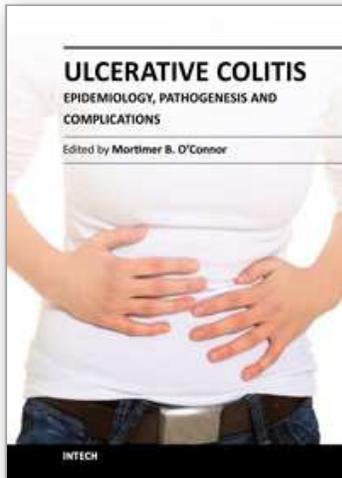
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This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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