



Molecules in focus

Human β -defensin 1: A restless warrior against allergies, infections and cancer

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ABSTRACT

Human β -defensin 1 (hBD-1) is probably the most important antimicrobial peptide in epithelial tissues. Its alleles and/or altered gene expression have been associated with at least 20 human diseases. hBD-1 is a tumor suppressor and *DEFB1* is the only innate immunity gene that shows long-term balanced selection and heterozygote advantage. It is unique in its constitutive expression, but is still capable of upregulation upon inflammatory or microbial stimuli. The present minireview focuses on hBD-1 properties, biological function, its proposed pathogenic mechanisms and the potential uses of elicitors, inhibitors or the peptide itself in the treatment of hBD-1-related human diseases including allergies, infections and cancer.

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1. Introduction

Antimicrobial peptides are an innate immunity component including cathelicidin LL-37, dermcidin, psoriasin and defensins among others. In humans, there are two families of defensins, α and β . The name “defensin” is derived from the Latin *defendo*, meaning “to repel”, in reference to their properties against pathogenic microorganisms. Human β -defensin-1, was identified in 1995, through purification of hemodialysate fluid from renal disease patients. Research has primarily focused on hBD-1 antimicrobial properties (Pazgier et al., 2006) although other functions have been reported (Table 1).

The present minireview focuses on hBD-1 properties, biological function, its proposed pathogenic mechanisms and the potential uses of *DEFB1* elicitors, inhibitors or the peptide itself in the treatment of *DEFB1*-related human diseases including allergies, infections and cancer.

2. Structure

The *DEFB1* gene (GeneID: 1672; www.ncbi.nlm.nih.gov/gene) spans 7448 bp, at locus 8p23.2–p23.1. *DEFB1* is the most telomeric β -defensin (for those on chromosome 8), and is located amid a cluster of α -defensins. The structures of most human β -defensin genes show a common organization with two exons and one large intron. The unique feature of *DEFB1* is that the pro-peptide segment is in exon 1 and not in exon 2 as in all other β -defensins (Pazgier et al., 2006) (Fig. 1). *DEFB1* is generally considered as a unique copy gene, although some individuals exhibit duplicons (Cagliani et al., 2008). The 10 most relevant *DEFB1* Single Nucleotide Polymorphisms (SNPs) in human diseases known to date are shown in Fig. 1. The 214 annotated polymorphisms (dbSNP build 130) in *DEFB1* can be referred to www.genome.ucsc.org.

The hBD-1 peptide structure has an α/β stabilized scaffold with three disulfide bridges (Fig. 2), two β -sheets and an α -helix at the N-terminus (Pazgier et al., 2006, 2007). Based on hBD-1 pro-peptide nomenclature (Fig. 2C), the residues N36, V38, R61, K63, K65, K68 define most of the in vitro anti-*Escherichia coli* activity; while interaction of the D33, N36, S40, K54, Q56 and K65 residues with CCR6 is relevant for chemotactic properties (Pazgier et al., 2007). N36 and K65 residues are relevant in both chemotactic and antimicrobial properties. As expected, these functions are distributed according to the surface of the hBD-1 tertiary structure rather than N- or C-terminus polarization probably because hBD-1 is not a linear peptide. Cysteines are probably relevant for chemotactic proper-

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Table 1

Known hBD-1 functions. hBD-1 is involved in cell development, antimicrobial, allergic and tumor suppressor pathways, among others. Inferred results are indicated with a question mark.

Function	Acts upon	Mode of action/repercussion	Reference
Antimicrobial	Retrovirus (HIV)	Induces CCL5 (RANTES) release in PBMC, inhibits infectivity by 50% Indirectly by hBD-3 induction (CXCR4 antagonist)	Sun et al. (2005) Kalus et al. (2009)
	Adenovirus (Av1CF2)	Inhibits replication?	Ding et al. (2009)
	Fungi?	Membrane lysis?	Prado-Montes de Oca et al. (2009)
	Gram-positive bacteria	Membrane lysis	Pazgier et al. (2006)
	Gram-negative bacteria	Membrane lysis	Pazgier et al. (2006)
	<i>Mycobacterium tuberculosis</i>	Membrane lysis	Fattorini et al. (2004)
	<i>Mycobacterium leprae</i> ?	Membrane lysis? NF- κ B mediated upregulation?	Prado-Montes de Oca et al. (2009)
Tumor suppressor	Cancer cells	Induction of caspase-mediated apoptosis	Bullard et al. (2008) and Sun et al. (2006)
Immunomodulator	Dendritic cells	Chemoattraction and maturation by CCR6, activation by TLRs? Maturation through receptor-mediated internalization? Enhancing antigen presentation binding to microbial debris?	Prado-Montes de Oca et al. (2007) and Presicce et al. (2009) Yang et al. (2007) Yang et al. (2007)
	T cells	Chemoattraction by CCR6	Yang et al. (2007)
	B cells, eosinophils	Elevate IgE levels and blood eosinophils count?	Prado-Montes de Oca et al. (2007)
Glucose metabolism	All hBD-1-expressing cells?	Constitutive hBD-1 expression?	Barnea et al. (2008)
Cellular differentiation	Keratinocytes	Involved as transcription factor? Protection against apoptosis in epithelia reorganization?	Bick et al. (2007) Sayama et al. (2005)

ties (hBD-1 is a competitive ligand for CCR6) (Yang et al., 2007), but not for antimicrobial properties, as is the case for hBD-3. As a quaternary structure, hBD-1 is capable of in vitro dimerization by weak intermolecular salt bridges but any in vivo function it might have is yet unknown (Pazgier et al., 2006).

3. Expression, activation and turnover

hBD-1 is considered the most important antimicrobial peptide in epithelial defense against infection (Zhu et al., 2003), is the only β -defensin gene with constitutive expression in skin keratinocytes, urinary and respiratory tract epithelial cells, in addition, and is capable of upregulation through microbial or inflammatory stimuli (Yang et al., 2007). The highest hBD-1 concentrations have been found in the kidney and female repro-

ductive tract, especially in pregnant women. Other expression sites include epithelial cells of the testis, gingival tissue, small intestine, cornea, mammary gland, and astrocytes among others (Pazgier et al., 2006) (a more complete information of *DEFB1*-expressing cells is available at <http://www.ebi.ac.uk/microarray-as/atlas> and <http://www.ncbi.nlm.nih.gov/GEO>).

Upregulation of *DEFB1* influences hBD-3 expression when the –44G allele (rs1800972 or 668) is present. A possible repercussion of this SNP is that the –44C allele alters hBD-1 mRNA secondary structure (Kalus et al., 2009) as well as a nuclear factor kappa B1 (NF- κ B1 or p50/p105) binding site (Prado-Montes de Oca et al., 2009). The –44G allele may be important in constitutive expression and relevant in IFN- γ -dependent induction (Kalus et al., 2009) (Fig. 1). This might explain the rare heterozygote advantage in the regulatory region of this gene (Cagliani et al., 2008). The *DEFB1*

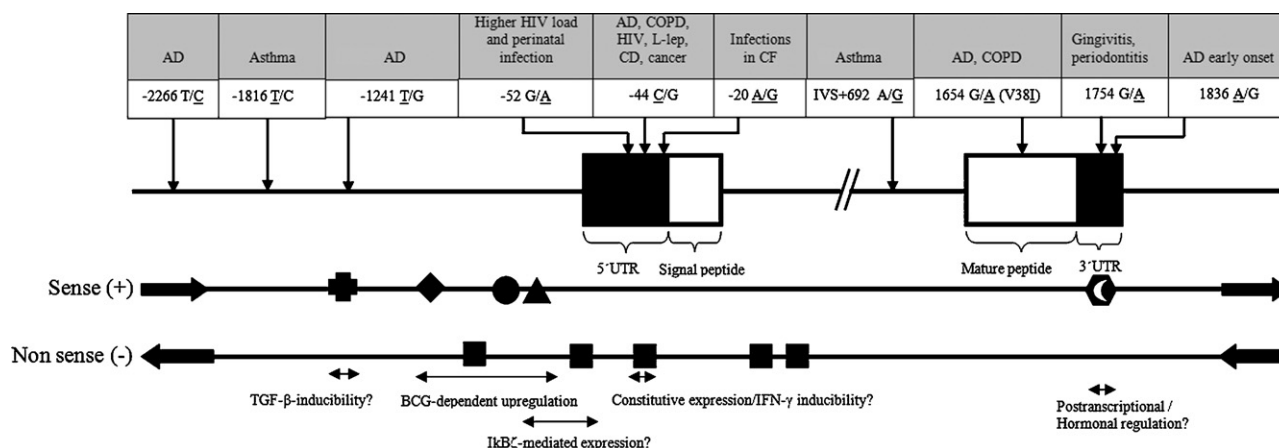


Fig. 1. *DEFB1* gene schematic representation with their putative regulatory sequences. First row shows exons (rectangles), including 5'UTR and 3'UTR (black rectangles) and flanking sequences. Biomedical-relevant SNPs and disease-associated alleles/genotypes (underlined) are in boxes. The second and third rows show putative response elements to transcription factors in the sense and non-sense DNA strands: NF- κ B1 (p50/p105, square); activator protein-1 (AP-1, circle); CCAAT enhancer binding protein beta (CEBP- β , triangle), α -globin transcription factor CP2 (TFCP2, rhombus), Sma- and mad-related protein (SMAD, cross), miRNA binding site (moon); Estrogen Receptor 1 (ESR1, hexagon). Data are adapted from GeneRIF (www.ncbi.nlm.nih.gov), Defensins Knowledgebase (<http://defensins.bii.a-star.edu.sg/>), Prado-Montes de Oca et al. (2009); Sherman and Froy (2008); Zhu et al. (2003); and for (ESR1), Prado-Montes de Oca E., unpublished results. AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; L-lep, lepromatous leprosy; CD, Crohn's disease.

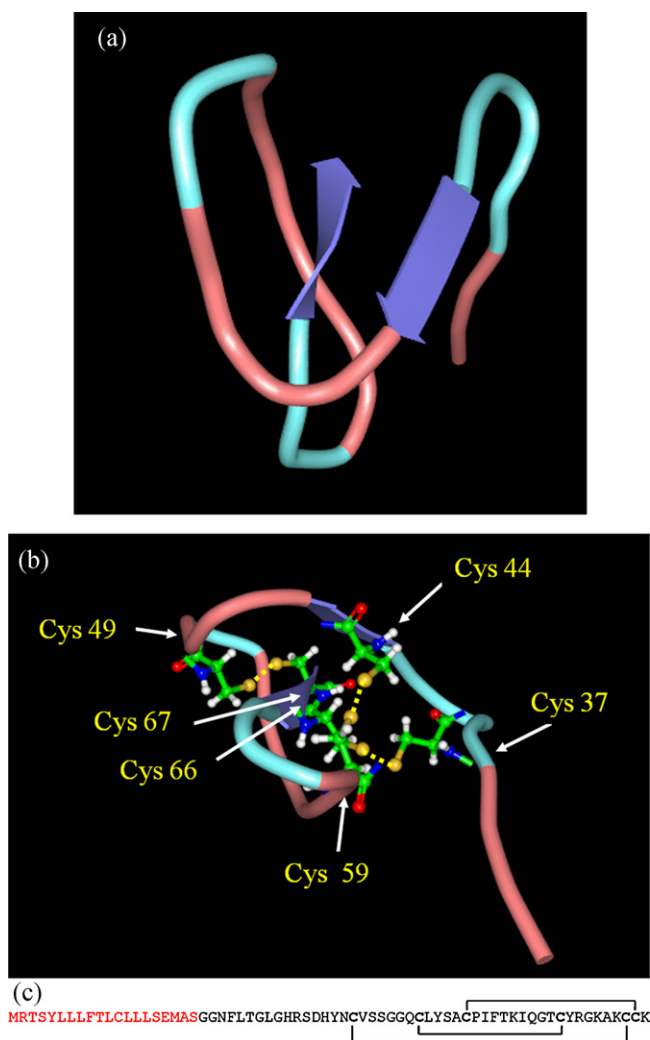


Fig. 2. Human β -defensin 1 structural model and peptide sequence. (A) Structure of mature form of human β -defensin 1 peptide (PDB ID: 1IJVA, www.pdb.org). (B) Rotated image to show disulfide bridge connections; for clarity only cysteine residues are shown in a ball and stick model. Three disulfide bridges at the cysteines 1–5, 2–4 and 3–6 (a β -defensins hallmark pattern) at residues 22–51, 29–44, 34–52 of the pro-peptide, superimposed on the secondary structure backbone. Secondary structures: α -helix (pink); β -sheets (purple); loops (cyan). Atoms: carbon (green); hydrogen (white); oxygen (red); nitrogen (blue); and sulfur (yellow). (C) hBD-1 pro-peptide sequence. Signal peptide sequence (red) and mature peptide (black) showing disulfide bridge connectivity (brackets) between cysteines (bold). (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

proximal promoter contains CCAAT/enhancer binding protein- β (C/EBP β) (Zhu et al., 2003) adjacent to a NF- κ B binding site (Prado-Montes de Oca et al., 2009), a relevant feature for I κ B zeta(I κ B ζ)-induction (Fig. 2) (Matsuo et al., 2007) (Fig. 1).

Stromal cell-derived factor 2-like protein 1 (SDF2L1) is an endoplasmic reticulum protein probably involved in hBD-1 processing and/or sorting, after which it is probably transferred to chaperones or protein disulfide isomerases for correct folding (Tongaonkar and Selsted, 2009) and processed to maturity by signal peptidase (Beckloff and Diamond, 2008) which cleaves 20 residues at N-terminus (Fig. 2C). When hBD-1 enters the nucleus, it most probably follows a passive entry route through the nuclear pore complex (NPC) or by coupling with karyopherin- α and - β which interact with the NPC because even hBD-1 dimers (Pazgier et al., 2006) are below the NPC 20 kDa cutoff. The biological meaning of nuclear import is unknown, but hBD-1 may act as a transcription factor (Bick et al., 2007) (Table 1).

Beta-defensins are primarily produced by various epithelia and secreted by the producing cells in mature forms. Amino-terminal processed hBD-1 fragments ranging from 38 to 47 residues have been identified in void urine and bound to carrier macromolecules in blood plasma, all with different microbicidal potencies. It is still unknown if these variants are produced in all hBD-1-expressing tissues, or which enzyme produces these amino-processed forms (Pazgier et al., 2006), because hBD-1 is cleaved in a very similar manner when exposed to chymotrypsin (Zucht et al., 1998) or Matrix Metalloproteinase 7 (MMP-7 or matrylsin) (Wilson et al., 2009). MMP-7 cleaves six amino acids from the amino terminal of the 47-residue hBD-1 precursor form, but not of the 39-residue hBD-1 or mature peptide, probably because they are protected by their native three-dimensional folding (Wilson et al., 2009).

4. Biological function

4.1. Antimicrobial function

As occurs with other defensins, hBD-1 is thought to control microbial flora on epithelial surfaces (Zhu et al., 2003). The *defb1* knockout mouse model exhibits significantly higher counts of *Staphylococcus* sp. in the bladder than in wild-type counterparts and less efficient lung clearance, especially at higher *Haemophilus influenzae* doses (Pazgier et al., 2006). The hBD-1 has a wide, direct and indirect, antimicrobial spectrum (Table 1) while hBD-1-chemoattracted iDCs can also phagocytize and kill pathogens and enhance antigen presentation (Yang et al., 2007).

Even though hBD-1 is considered the least active of the β -defensin family against HIV, *DEFB1* reduces in vitro HIV infectivity up to ~50% (Sun et al., 2005) and acts indirectly through hBD-3 upregulation which is a HIV-1 coreceptor CXCR4 antagonist (Kalus et al., 2009). Furthermore, hBD-1 is the only β -defensin which induces release of CC motif chemokine ligand 5 (CCL5 or RANTES) in peripheral blood mononuclear cells (PBMC) (Sun et al., 2005). The CCL5 is a ligand of the CC motif chemokine receptor 5 (CCR5) and a promising target for AIDS therapy. This property of hBD-1 suggests that it may have a potentially more important role than other defensins in limiting HIV (Kalus et al., 2009; Sun et al., 2005).

hBD-1 may also play a fundamental role in human biology by protecting breast-fed infants from infectious diseases such as diarrhea, and protecting mothers from lactational mastitis (Cagliani et al., 2008). Overall, hBD-1 may provide constitutive protection against potential pathogenic organisms on all internal and exposed mucosal epithelia. A number of reports suggest that insufficient hBD-1 expression by the -44C allele in the presence of pathogens leads to poor innate immunity response against infectious microorganisms (Prado-Montes de Oca et al., 2009). For relevant *DEFB1* SNPs in diseases susceptibilities see Fig. 1.

4.2. Immunoregulatory function

Both hBD-1 and hBD-2 selectively chemoattract human immature dendritic cells (iDCs) and memory T cells in vitro. Their chemotactic activities involve the chemokine receptor CCR6 which mediates innate signaling from innate through adaptive immunity (Yang et al., 2007). Chemoattraction of DCs facilitates antigen uptake, processing and presentation, leading to the induction of antigen-specific immune responses. DCs are known to be important cells in immune response type (autoimmune, allergic, etc.) and initiation. In addition to its chemoattraction properties, hBD-1 may also be involved in DC maturation and/or activation via CCR6 and Pattern Recognition Receptors such as Toll-like receptors (TLRs), probably having a major effect on the skin inflammation and/or skin responsiveness in any allergic reaction (Prado-Montes de Oca

et al., 2007; Yang et al., 2007). Furthermore, HNP-1 and hBD-1 promote the activation and maturation of the monocyte-derived DCs, and up-regulate the CD91 scavenger receptor expression on the DCs surface, probably amplifying their own effects via an autocrine loop (Presicce et al., 2009). *DEFB1* SNPs have been associated with several inflammatory and allergic diseases (Table 1 and Fig. 1).

4.3. Tumor suppressor function

DEFB1 has been proposed as a tumor suppressor because it promotes cancer cells apoptosis and is absent in most tumor samples (Bullard et al., 2008; Sun et al., 2006). In addition, when present, hBD-1 accumulates in the nucleus and is associated with malignancy and lower expression, probably via promoter autoregulation (Pantelis et al., 2009; Wenghoefer et al., 2008). Binding of the *PAX2* oncogene homeodomain to the *DEFB1* promoter suppresses hBD-1 expression (Bose et al., 2009). Some cancer samples have been associated with SNP C at –44 site and correlate with lower *DEFB1* expression patterns (Table 1 and Fig. 1).

4.4. Glucose metabolism

DEFB1 expression correlates with insulin and glucose levels, suggesting a relevant role in the presence of low intracellular glucose or hypoinsulinemia. Constitutive hBD-1 expression may be glucose dependent in otherwise healthy individuals (Barnea et al., 2008) (Table 1).

4.5. Cellular differentiation

When hBD-1 enters the nucleus, it probably acts as a relevant transcription factor when corneum stratum is in the differentiation process, thus protecting keratinocytes from apoptosis during epithelial reorganization (Bick et al., 2007; Sayama et al., 2005).

5. Potential therapeutic approaches and industrial applications

5.1. Recombinant hBD-1

Even when *DEFB1*-recombinant *E. coli* and *Saccharomyces cerevisiae* are available (Cipakova and Hostinova, 2005), it remains expensive to produce and purify antimicrobial peptides for therapeutic applications. Nevertheless, many antimicrobial peptides are currently in clinical trials as immune regulators (Easton et al., 2009).

5.2. *DEFB1* elicitors

Physical, chemical and biological elicitors are an alternative to direct administration of antimicrobial peptides because they produce overexpression of these host defense peptides, boosting internal armament against pathogens. Even when *DEFB1* expression is mainly constitutive, its currently identified elicitors to date include amino acids such as L-isoleucine and its analogs, and albumin (Prado-Montes de Oca, 2009) among others (Prado-Montes de Oca E, in preparation).

DEFB1 elicitors have potential applications in treatment of diseases probably caused or aggravated by defensin deficiency, such as Crohn's disease, lepromatous leprosy, and cancer. They may even have application in HIV/AIDS prophylaxis since an hBD-1 elicitor could help to protect mucosae from infection by diminishing HIV binding and internalization (Sun et al., 2005) (Table 1).

5.3. *DEFB1* inhibitors

Research on molecules which block hBD-1 will help to identify hBD-1 signaling events and expression regulation. One promising approach is the use of substances that mimic hBD-1 inhibitory molecules (Prado-Montes de Oca, 2009), or application of miRNAs strategies (Castanotto and Rossi, 2009) in treatment of diseases caused by or associated with *DEFB1* upregulation such as acne, psoriasis, chronic periodontitis, scleroderma and chronic sialadenitis (Gene RIF at www.ncbi.nlm.nih.gov; and Defensins Knowledgebase at <http://www.defensins.bii.a-star.edu.sg/>).

6. Concluding remarks

Its wide antimicrobial spectrum and tumor suppressor properties indicate hBD-1 to be an elemental molecule in host defense and cell cycle regulation. Future research challenges include demonstrating if *DEFB1* elicitors, inhibitors or hBD-1 itself alleviate disease symptoms and can therefore be used as alternative therapies in treating different human diseases. What is clear is that research into the functions of human β -defensin 1 is still incipient, and that future discoveries hold great promise.

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Space limitations required the reference list be kept to a representative sample, however, interested readers can easily find the primary reports in the quoted reviews. This work was supported by the Fondos Sectoriales de Ciencia Básica SEP-CONACYT (CB-2008-01-105813). The author receives a research stimulus from the Sistema Nacional de Investigadores (SNI 41290, CONACYT, Mexico) and received a training fellowship from the Wellcome Trust (UK) in 2009. Thanks to Dr. AE Islas Rodríguez (Universidad de Guadalajara) and Dr. LD Possani (IBT, UNAM) for their motivation and support in their labs. Thanks also to Dr. L Figueroa (CIBO-IMSS, Guadalajara, Mexico) for the review of an earlier version of this manuscript and for constant support.

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