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Review

Host defense peptides and their antimicrobial-immunomodulatory duality

Lars Steinstraesser*, Ursula Kraneburg, Frank Jacobsen, Sammy Al-Benna

Laboratory for Molecular Oncology and Wound Healing, Department of Plastic Surgery, BG University Hospital Bergmannsheil, Ruhr-University Bochum, Buerkle-de-la Camp-Platz-1, 44789 Bochum, Germany

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ABSTRACT

Host defence peptides (HDPs) are short cationic molecules produced by the immune systems of most multicellular organisms and play a central role as effector molecules of innate immunity. Host defence peptides have a wide range of biological activities from direct killing of invading pathogens to modulation of immunity and other biological responses of the host. HDPs have important functions in multiple, clinically relevant disease processes and their imbalanced expression is associated with pathology in different organ systems and cell types. Furthermore, HDPs are now evaluated as model molecules for the development of novel natural antibiotics and immunoregulatory compounds. This review provides an overview of HDPs focused on their antimicrobial-immunomodulatory duality.

Contents

Introduction

Survival without the inherent shield of innate immunity seems to be virtually unattainable in a world filled with microorganisms. Surprisingly with a completely lack of acquired immune mechanisms plants, fungi, and invertebrates successfully survive protected by their innate defense mechanisms alone (Hancock and Scott 2000; Steinstraesser et al. 2009). Innate immunity as such constitutes an evolutionarily ancient mechanism founded on a relatively generic, but nevertheless quite effective defense strategy.

Beside the natural immediate anatomical barriers of the organism such as skin, this intrinsic resistance system relies primarily on pattern recognition receptors and associated signaling pathways, cytokines, the complement cascade, leukocytes, and importantly host defense peptides (HDPs) (Liu et al. 2009; Oppenheim et al. 2003).

The number of natural compounds with antimicrobial activities is extensive but largely includes three functional groups: (1) digestive enzymes destroying microbial structures (e.g., lysozyme), (2) peptides that are able to bind essential elements such as zinc or iron (e.g., calprotectin and lactoferrin, respectively), and (3) peptides that penetrate the microbial membrane (e.g., defensins and cathelicidins, as discussed below) (Yacoby and Benhar 2007; Deans et al. 2005; Ohlsen et al. 2008; Hancock 2001; Steinstraesser et al. 2004). Lysozyme as the first peptide with antimicrobial activity was identified by Alexander Fleming at the end of the 1920s. It is only in the past two decades, with the evolution in molecular biology techniques, that have allowed isolation and identification of individual peptides, and the establishment of their structural and functional features. To present, more than 1220 HDPs are known, including over 940 HDPs in eurkaryotic organisms, listed in three databases (Brahmachary et al. 2004; Fjell et al. 2007; Wang et al. 2009).

This aim of this review is to provide an overview of the current understanding of HDPs, with special emphasis on defensins and cathelicidins and their role in immunological defense in human.

* Corresponding author. Tel.: +49 234 302 3442; fax: +49 234 302 6379.
E-mail address: lars.steinstraesser@ruhr-uni-bochum.de (L. Steinstraesser).

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Defensins and cathelicidins are well studied and their potential both as natural antimicrobial compounds and as templates in development of novel synthetic antibiotics and immunoregulatory drugs is discussed.

The importance of an innate host defense

An immediate nonspecific defense system aimed at controlling potential infectious as well as noninfectious dangers effectively and efficiently is vital to ensure health. In the past immunologists believed that the immune system's main task was to discriminate between self and nonself. There is more to the immune system, as Matzinger describes in his "Danger-Model" concept, activation of an immune response is not only in response to microorganisms (nonself), but also as a reaction toward all other types of insults (or "danger signals"), including physical trauma, ionizing radiation, oxidative stress, ischemia, and extreme temperatures (Matzinger 1994). Innate immunity ensures an immediate mode of defense in virtually all living organisms. As an evolutionary co-development to prevent microbial colonization and tissue damage, the core of this innate immune response is comprised by multifunctional HDPs (Boman 2003; Kim et al. 2009).

A microbial pathogen has the potential to enter any part of a host organism. More often than not, the initial interaction takes place on the cutaneous surface or on the epithelial lining of the respiratory, gastrointestinal, reproductive, or urinary tracts (Hegedus et al. 2008; Tew et al. 2006; Chromek et al. 2006; Koczulla and Bals 2003; Tani et al. 2000; Thompson et al. 2006; Zhou et al. 2004a,b). Thus, epithelial cells of vertebrates produce HDPs as components of this first line of defense. Damaged skin can be the major portal of entry and allow multiplication and proliferation of pathogens; tetanus and burn wound infections are clear examples. As part of the inflammatory response, is an initial reaction by the innate immune cascade, which includes the production of HDPs by inflammatory cells such as neutrophils, and tissue phagocytes, including macrophages (Bhat and Milner 2007; Finlay and Hancock 2004; Jacobsen et al. 2005a,b; Sima et al. 2003).

HDPs tend to exhibit intrinsic specificity for microbial invaders and are relatively much less toxic for the metazoan host's cells. However, some are also active on eukaryotic cells. This specificity endows the animal with an "innate" immunity, in contrast to the better studied acquired immunity conferred by the clonal expansion of B- and T-cells. The importance of this system as a check on infection is evident when one considers that most bacteria have generation times of 20–30 min whereas the mounting of a specific immune response, dependent on the growth of mammalian cells, may take days or weeks.

The expression of many HDPs increases during infection and inflammation. For example, human β-defensin (hBD)-2 is upregulated in various cell types such as monocytes, epithelial cells and keratinocytes during bacterial infections and by stimulation from different bacterial components that activate the Toll-like receptor (TLR) to nuclear factor (NF)-kB pathway (Harder et al. 2004; Proud et al. 2004; Vora et al. 2004). In addition, decreased defensin levels in burn injury may facilitate infection and subsequent sepsis (Bhat and Milner 2007).

Furthermore, as a less important universal function of innate immune mechanisms HDPs are also expressed by less typical cell types such as endothelial cells and myocytes (Ganz 2005; Linde et al. 2007). It is perhaps better to consider the immune system, not only as an entity of "professional" immune cells surveying the body for potential intruders but as an integrated and inclusive entity of cells communicating and collaborating to ensure maintenance of homeostasis (Matzinger 2007).

HDPs have been isolated from a wide range of animal, plant, fungal and bacterial species (Hancock and Scott 2000). As they have successfully retained their antimicrobial activity for millions of years, certain HDPs act as natural antibiotics showing an exceptional broad-spectrum of activity, ranging from Gram-negative and Gram-positive bacteria to fungi and viruses (Hancock and Scott 2000; Hancock 2001; Steinstraesser et al. 2004; Zasloff 2002). There are distinctive different external and internal target mechanisms. One can distinguish between HDPs that permeabilize and/or disrupt the bacterial cell membrane and HDPs that translocate through the cell membrane and interact with a cytosolic target (Dorschner et al. 2006; Andres and Dimarcq 2007; Johansson et al. 1998; Oren et al. 1999). Broadly defined, HDPs have the capability of targeting any organism with a cholesterol-free, negatively charged membrane. Importantly, HDPs are able to kill transformed or cancerous cells, and this cytotoxicity tends to be neither species-specific nor selective (Oppenheim et al. 2003; Yang et al. 2002, 2004). For example, it has been shown that hCAP/LL-37 activates tumor cells resulting in increased cell growth both *in vitro* and *in vivo* (Coffelt et al. 2008; von Haussen et al. 2008). In contrast, Bose et al. demonstrated that hBD-1 induces rapid cytolysis of prostate cancer cells and that the PAX2 oncogene suppresses hBD-1 expression in prostate cancer (Bose et al. 2009).

HDPs characteristics, including angiogenesis, chemotactic functions, cytokine production, histamine release, lipopolysaccharide (LPS)-binding properties and other immunomodulatory activities can lead to antimicrobial activity and allow the appropriate activation of adaptive immune responses (Yang et al. 2002; Bals and Wilson 2003). For example, a linkage to initiation of an adaptive immune response has been observed for defensins, which act as direct chemoattractants for immature dendritic cells (Yang et al. 2002, 2004; Bowdish et al. 2005). Some defensins are opsonic and have the capability to modify hormonal reactions (Klotman and Chang 2006; Yang et al. 2007). Thus, HDPs are far more than "simple natural antibiotics," and appear to have central roles in a number of clinically relevant disease processes, including low grade inflammation, obesity, diabetes, and hyperlipidemia (Froy et al. 2007; Hollox 2008; Kougias et al. 2005; Nassar et al. 2007). A correlation between the severity of the disease and the level of HDP production has been demonstrated in several studies (Morrison et al. 2002; Niyonsaba et al. 2009). Morrison et al. could demonstrate increasing susceptibility to infections caused by *Staphylococcus aureus* in hBD-2 knockout mice and isolated Dermcidin (DCD) peptide DCD-1L, produced by eccrine sweat glands in the skin, has been shown to stimulate the production of cytokines/chemokines by human keratinocytes (Morrison et al. 2002; Niyonsaba et al. 2009). Reduced expression of DCD in sweat of patients with atopic dermatitis has been associated with high susceptibility of these patients to skin infections and altered skin colonization (Rieg et al. 2005). The physiological properties and regulation of HDPs may therefore be a key to explaining many complexities in medicine.

Structural characteristics of defensins and cathelicidins

By definition, HDPs include only gene-encoded, ribosomally synthesized polypeptide antimicrobial substances less than 100 amino acid residues in length (Ganz and Lehrer 1999). As the majority of fungal and bacterially derived peptide antibiotics are nonribosomally synthesized peptides incorporating atypical amino acids, the above definition distinguishes HDPs from this category (Ganz and Lehrer 1999). Natural antimicrobial substances are numerous and varying in size from relatively large protein complexes (e.g., the complement cascade) to small inorganic molecules (e.g., hydrogen peroxide) (Ganz 2005; Ganz and Lehrer 1999). According to their molecular composition, conformational structure, or predominant amino acid structure, HDPs can be divided into four main classes: linear α-helical structure without disul-

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fide bonds (for example, cathelicidins, magainins and cecropins), β-sheet structure stabilized by characteristic disulfide bridges (for example, α- and β-defensins), with predominance of one or more amino acids rich in arginine, glycine, histidine, praline, tryptophan, or particular combinations thereof (e.g., indolicidin), and loop-structured peptides with one disulfide bond (e.g., bactenecin) (Koczulla and Bals 2003; Hancock 1997; Andreu and Rivas 1998; van 't Hof et al. 2001; Hancock and Sahl 2006; Zhang and Falla 2009). The biological effect of HDPs is primarily dependent on their tertiary structure, and thus their structural characteristics are of direct interest (Sima et al. 2003).

Two major human classes of conventional HDPs are the defensins and cathelicidins. Classical defensin molecules encompass a family of small amphipathic variably arginine-rich cationic peptides, typically comprised of 29–45 amino acid residues. Defensins can be distinguished in α- and β-defensins; the disulfide connectivities in α-defensins are Cys1–Cys6, Cys2–Cys4 and Cys3–Cys5 (the number indicates the location of the Cys residue in the amino acid sequence from the N-terminus), while in β-defensin are Cys1–Cys5, Cys2–Cys4 and Cys3–Cys6 (Oppenheim et al. 2003; Ganz 2005; Matzinger 2007; Kesting et al. 2009). In human neutrophils, defensins comprise 30–50% of the granule proteins (Oppenheim et al. 2003; Matzinger 2007). Defensins have, however, also been identified in other cell types, including tissue macrophages, small intestinal epithelial cells, and cardiomyocytes (Linde et al. 2007; Scott et al. 2002; Steinstraesser et al. 2008; Wah et al. 2006). In human skin, defensins are produced mainly by keratinocytes, neutrophils, sudoriferous and sebaceous glands (Koczulla and Bals 2003) and are either expressed constitutively or after an inflammatory stimulus. The overall structure of the defensin peptides has been compared with a bent paperclip, intramolecular disulfide bridges between the NH_2-terminal and COOH-terminal regions of the peptide, creating a cyclic, triple-stranded, amphiphilic β-sheet structure, making up the characteristic "defensin-like" fold and spatially separated hydrophobic and hydrophilic regions. These three intramolecular disulfide bridges stabilize its β-sheet structures and increase resistance to proteolysis but also reduced in flexibility (Campopiano et al. 2004; Maemoto et al. 2004; Wu et al. 2003), although disulfide bridges are not necessarily essential for the antimicrobial activity of defensins (Wu et al. 2003).

To date, three different categories of vertebrate defensins have been described (in addition to the insect and plant defensins) based on size and structural differences in the cysteine linkage (secondary structure) (Boman 2003; Zasloff 2002). α-Defensins are the classical "neutrophil defensins," which were first described in the mid-1980s, whereas the slightly larger β-defensins were reported initially in the early 1990s (Ganz and Lehrer 1999). The Trieste Database contains 90 β-defensins and 55 α-defensins. More recently, γ-defensins have been described. α- and β-Defensins are widely distributed across species, but γ-defensins are only known to be expressed in granulocytes of the rhesus macaque and some other primates, including other Old World monkeys and orangutans (Crovella et al. 2005; Selsted and Ouellette 2005). Other great apes including humans and NewWorld monkeys do not express γ-defensins (Garcia et al. 2008; Nguyen et al. 2003; Selsted 2004; Tran et al. 2008). γ-Defensins are double-stranded small circular molecules, in contrast to α- and β-defensins, which are flat triple-stranded β sheets (Boman 2003). Alpha-defensins secreted by neutrophils can be detected in biological fluids (Panyutich et al. 1991, 1993, 1994). The concentration of α-defensins in human plasma under normal physiological conditions is about 40 ng/mL, as measured by ELISA (Panyutich et al. 1991). This concentration increases 2- to 4-fold in patients with an inflammatory syndrome and reaches micromolar concentrations in septic patients (Panyutich et al. 1993). In the plasma, α- and β-defensins bind unspecifically to high mass plasma proteins such as serum albumin, α2-macroglubulin and C1 complement, which decreases their anti-viral and anti-tumor activity (Panyutich and Ganz 1991). α- and β-Defensins have been found in human body fluids during inflammatory lung diseases, urinary tract infection and in tears after ocular surface surgery (Chromek et al. 2006; Thompson et al. 2006; Lemaitre et al. 1996).

The α-helical structured hCAP-18, also known as LL-37 is the only investigated antimicrobial peptide member of the cathelicidin family, which was first described 1995. Cathelicidins are found in varying numbers in numerous different species, including mammals (Scott and Hancock 2000; Zanetti 2004). A unifying feature of the cathelicidin peptides is a marked homology termed the catheline domain at the 50 regions, and a variable C-terminal antimicrobial domain, which is proteolytically released upon demand (Otte et al. 2009; Tomasinsig and Zanetti 2005). Cathelicidins typically are expressed by myeloid precursor cells, but expression also has been reported in mature circulating neutrophils and neonatal lymphoid tissue in some species (Zanetti 2004). They are stored as inactive propeptides and processed only upon stimulation, thus resulting in the release of active HDPs into the extracellular fluid (Scott et al. 2002; Zanetti 2004). It is mainly produced by leucocytes and epithelial and mucosal cells where it is stored in specific granules (Scott et al. 2002). Its cationic C-terminal 37 amino acid domain, LL-37 displays broad antimicrobial activity mediated through direct interaction with and disruption of the microbial cell membrane. The enzyme responsible for cleavage of the proprotein in neutrophils is serine proteinase 3. In skin, the serine proteases kallikrein 5 and 7 were recently reported to mediate alternative processing of hCAP18 generating several novel peptide fragments, suggesting that peptide profiles may differ between tissues and biological conditions. This opens up a potential new area of research since their functional profile may differ. In addition to being antimicrobial, LL-37 is implicated in diverse biological processes, such as angiogenesis, chemotaxis, cytokine production, histamine release and wound healings (Koczulla and Bals 2003; Jacobsen et al. 2005a,b; Scott et al. 2002; Shaykhiev et al. 2005; Steinstraesser et al. 2006). Moreover, the number of cathelicidin antimicrobial peptides varies among species, which most likely leaves different species with varying levels of resistance toward specific types of infections (Lee et al. 2005). It has been established that in humans, HDPs are required effector molecules in the TLR-induced antimicrobial response against intracellular mycobacteria in macrophages. Elucidation of these immune defense mechanisms utilized by human macrophages to combat pathogens provides possible targets for the development of new therapeutic strategies (Liu et al. 2009; Nizet et al. 2001). Interestingly, cathelicidins and defensins exhibit synergism, implying their combined role in the orchestration of the innate host defense, as further discussed below (Lee et al. 2005).

Host defense peptides—synthesis, expression, and mechanism of action

HDPs can be either constitutively expressed or induced in response to specific stressors such as infection and inflammation (Sima et al. 2003; Diamond et al. 2000; Hirsch et al. 2008, 2009). α-Defensins tend to be produced constitutively, whereas the majority of β-defensins are inducible (Hancock and Scott 2000; Scott and Hancock 2000). Moreover, α-defensins have evolved to operate mainly from within phagosomes, whereas β-defensins are produced primarily by epithelial cells (Boman 2003). Lipopolysaccharide (LPS) and the proinflammatory cytokines IL-1b and TNF-α promote HDP synthesis (Sima et al. 2003). Their production resembles that of peptide hormones, involving sizable precur-

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sor molecules and tissue-specific sequential proteolytic processing (Ganz 2005). After removal of the signal sequence, the proregion is disposed of, yielding the active HDP (Scott and Hancock 2000). Defensin molecules are produced as neutral preprodefensins, approximately 95 amino acids in size, which are not cytotoxic to the cell (Ganz 2005). The antimicrobial and cytotoxic functional properties of the mature defensins and other HDPs generally are thought to be associated with their pore-forming activities as multimers in biological membranes leading to self-promoted uptake (Ganz 2005; Scott and Hancock 2000), a mechanism that has been further described by the Shia–Matsuzaki–Huang model (Matsuzaki 1999; Shai 1999; Yang et al. 2000).

The antimicrobial activity of HDPs as membrane-agents, possessing a secondary α-helical peptide structure, depends on the presence of an ionic milieu that is comparable to the conditions found in mammalian body fluids (Dorschner et al. 2006; Johansson et al. 1998; Oren et al. 1999). The HDPs target the weakest spot of the microbial membrane for example the absence of cholesterol and negatively charged phospholipids on the outer leaflet of the cytoplasmic membrane) (Zasloff 2002). The positive net charge (+2 to +7 due to an excess of basic versus acidic amino acids) (Scott and Hancock 2000) facilitates binding of an increasing number of HDPs to the phospholipids on the bacterial surface until the bacterial membrane collapses completely (Boman 2003; Hale and Hancock 2007; Sallum and Chen 2008; Steiner et al. 1988). Cholesterol prevents membrane damage, and as this lipid is an essential part of eukaryotic membranes, it explains why normal concentrations of HDPs do not cause host-damage (Boman 2003). The membrane potential of eukaryotic cells (−15 mV) also is low compared with the bacterial transmembrane potential (−140 mV), which also minimizes interaction (Scott and Hancock 2000). Resistance to HDPs is rare, as it is particularly difficult for any microorganism to change its structural organization of surface phospholipids (Zasloff 2002). Some HDPs target intracellular sites in addition to the bacterial membrane (Jenssen et al. 2006; Xiong et al. 1999).

Although many HDPs for example defensins demonstrate direct antimicrobial activity against bacteria, fungi, eukaryotic parasites and/or viruses (Steinstraesser et al. 2005, 2008; Hirsch et al. 2008; Larrick et al. 1995), it has also been established that many also have a key modulatory role in the innate immune response and present an important link between the innate and adaptive immune responses (Zasloff 2002).

Various tissues and cell types in the body contain gene-encoded pattern recognition receptors (PRRs) and can mandate a number of different signaling pathways in response to stress, ultimately ensuring production of all necessary signaling and effector molecules required for an appropriate and immediate host defense. Host PRRs are generally surface proteins that immediately identify conserved molecular structures associated with microbial pathogens or other impending dangers. The repertoire of PRRs capable of regulating gene expression encompasses the TLRs and the virus-sensing RIG-I and Mda5 helicases (Onomoto et al. 2007; Yoneyama et al. 2005; Zou et al. 2009; Robinson et al. 2006). Other non-TLR recognition molecules, however, also have been described. The structures identified by a given PRR are classified either as pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Classical PAMPs include LPS and lipoteichoic acid (LTA) from Gram-negative and Gram-positive bacteria, respectively, viral double-stranded RNA (dsRNA), and fungal b-glucans (Robinson et al. 2006; Jo 2008). The term DAMPs is used here as a common name referring to PAMPs as well as endogenous alarm signals released by dying or injured cells (Matzinger 2007; Seong and Matzinger 2004). Matzinger's Danger Model defines "dangers" as anything (exogenous or endogenous) that has the potential to cause tissue stress or destruction (Matzinger 1994, 2007). Also in the category of innate sensors are the intracellular nod-like receptors (NLRs), which present a powerful combined defense at the plasma membrane (for example TLRs) as well as from within the cell (for example NLRs) (Benko et al. 2008; Fritz et al. 2006). Both TLRs and Nodg proteins can trigger the nuclear factor-kB (NF-κB) transcription factor, thus activating a highly stereotypical signaling pathway responsible for a range of different cellular responses including production of HDPs (Fritz et al. 2006). The NLRs have been linked to recognition of bacterial components as well as endogenous danger signals (Fritz et al. 2006). TLRs initially received considerable research interest, and consequently this group of PRRs is most well-described. Almost 20 different members have been reported in six major families, with each member recognizing different PAMPs. LPS is the classical ligand for TLR-4, whereas LTA and CpG oligodeoxynucleotides are recognized by TLR-2 and TLR-9, respectively (Dalpke et al. 2005). NF-κB signaling is one of the main down-stream pathways responsible for HDP production, although other signaling routes (including MAPKh and JAK/STATi signaling) have been implicated in their synthesis (Ji et al. 2009; Krisanaprakornkit et al. 2002). NF-κB is a transcription factor involved in the integration of numerous parallel signaling pathways and a variety of cellular responses central to an immediate and functional immune response, including the production of cytokines and cell adhesion molecules (Scott and Hancock 2000). Signalling through these pathways leads to transcriptional activation and subsequent production of HDPs. The TLRs and NLRs also result in activation of the inflammatory caspases, which comprise a field of research beyond the scope of this manuscript (Martinon and Tschopp 2007; Scott and Saleh 2007; Steinstrasser et al. 2007).

Biological activity of HDPs

HDPs are the first line of defense of inborn immunity in virtually all living species, and their high importance is evident by their abundance in circulating neutrophils (Scott and Hancock 2000). Substantial evidence accumulated in recent years indicates that mammalian defensins are multifunctional and, by interacting with host cell receptor(s), participate in both the innate and adaptive antimicrobial immunity of the host (Scott and Hancock 2000). HDPs participate in the inflammatory response by acting as chemoattractants for immune cells, including neutrophil recruitment by induction of IL-8 production and mobilization of immunocompetent T-cells as well as enhancers of cellular adhesion and the subsequent cellular transepithelial migration (Chertov et al. 1996; Hata and Gallo 2008; Van Wetering et al. 1997). Furthermore, studies suggest that defensins can enhance the cytotoxicity of NK-cells (Scott and Hancock 2000). The versatile nature of HDPs also includes roles in wound healing, possibly by induction of syndecank synthesis (Gallo et al. 1994), as well as modulation of the inflammatory response by inhibiting the activation of the classical complement pathway through C1q (Groeneveld et al. 2007; van den Berg et al. 1998). Given the ubiquitous production of HDPs in the organism, it is not surprising that many can be found in various types of body fluids and secretions (Sima et al. 2003). Plasma α-defensin concentrations of 40 ng/mL have been measured in normal human subjects, increasing in concentration to 41 mg/mL during infections (Zanetti 2004). Also, plasma concentrations of 170 mg/mL have been measured in sepsis, as have concentrations of 41,600 mg/mL in sputum from cystic fibrosis patients (Aarbiou et al. 2002; Soong et al. 1997). The antimicrobial activity of α-defensins *in vitro* generally relies on peptide concentrations from 10 to 100 mg/mL, although their contribution to tumor cell lysis occurs at higher concentrations (Zanetti 2004). HDPs are most likely secreted at higher concentrations in infected or otherwise diseased tissue, but their local concentrations have yet been inves-

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tigated (Zanetti 2004). Particular HDPs act as anti-inflammatory compounds in sepsis due to their LPS- and LTA-binding capacity (Scott and Hancock 2000), and, as well as neutralizing endotoxin, certain cathelicidins act directly to decrease the release of TNF-α (Bals et al. 1999; Braff et al. 2007). Some HDPs are inactivated by saline solutions, and others have decreased antimicrobial activity even at physiological fluid concentrations (Boman 2003; Yang et al. 2002). Extracellular release of certain defensins yields inactive HDPs, but parallel cathelicidin release ensures active functional synergism of HDPs (Chen et al. 2005). Such HDPs can also act in synergy with host molecules, such as proteins, lysozyme, and also conventional antibiotics, to kill microbes (Scott and Hancock 2000). Certain HDPs enhance wound healing through angiogenesis and epithelial growth, in addition to functioning as chemokines to attract both circulatory and migrating cells (Zasloff 2002; Chertov et al. 2000; De Smet and Contreras 2005; De et al. 2000; Lee et al. 2009). Defensins have chemotactic features toward monocytes, and function as "corticostatins" by reversibly interplaying with the adrenocorticotropic hormone receptor (Yang et al. 2007). Defensins can transfigure certain signalling pathways and cellular functions in the body by potent inhibition of protein kinase C (Charp et al. 1988). A role of β-defensins in sperm maturation also has been suggested (Zhou et al. 2004a,b).

Host defense peptides and human innate immune system modulation

At present, hCAP18/LL-37 is the only human cathelicidin described. As previously noted, the cathelicidin family has great variance but only the hCAP-18, with a cathelicidin gene on chromosome 3, can be produced as a pro-peptide. It is stored as a precursor in human neutrophil granules (Ganz 2004) and various cells and tissues such as B-cells, T-cells, lymphocytes, monocytes, natural killer cells and mast cells. The epithelia of the upper aerodigestive tract including the salivary glands, small intestine and certain parts of male (epididymis and testis) and female (vagina and cervix) reproductive tracts have been shown to express LL-37 (De et al. 2000; Agerberth et al. 2000). Furthermore, LL-37 is secreted in human wound, sweat, and airway surface fluids (Dorschner et al. 2001; Gallo et al. 2002; Ong et al. 2002; Sorensen et al. 1997) and is upregulated in response to cutaneous infection or injury (Dorschner et al. 2001; Turner et al. 1998).

As immune modulators, HNP-1, -2, and -3 upregulate tumor necrosis factor alpha (TNF-α) and IL-1 in human monocytes activated by bacteria (Braff et al. 2005a,b). Furthermore, HNP-1 and -2 have the ability to kill Gram-negative and Gram-positive bacteria directly (Lehrer et al. 1993), *Candida albicans* (Schroder and Harder 1999), as well as enveloped viruses such as members of the herpes family (Schroder and Harder 1999). HNP-5 has concentration-dependent microbicidal activity against *Escherichia coli*, *Listeria monocytogenes*, *Salmonella typhimurium*, and *C. albicans* (Porter et al. 1997).

hBD-1 was identified and purified from blood plasma of patients with renal disease in 1995 (Bensch et al. 1995). hBD-1 is constitutively expressed in different tissues with primary expression in the epithelial lining of the respiratory and urinary tracts (Valore et al. 1998; Zhao et al. 1996). Different studies have shown that hBD-1 expression can be up-regulated by lipopolysaccharides (LPS), heat-inactivated *Pseudomonas aeruginosa*, and interferon gamma (IFN-γ) (Valore et al. 1998; Duits et al. 2002). In contrast to many other antimicrobial peptides in cutaneous wounds, hBD-1 does not seem to be involved in a specific manner. However, it shows special activity against Gram-negative bacterial strains like *E. coli* and *P. aeruginosa* (Sorensen et al. 2005).

The initial isolation of hBD-2 occurred in 1997 from psoriatic skin lesions (Harder et al. 1997). The most prevalent expression of hBD-2 is observed in keratinocytes, the gastrointestinal tract, and respiratory tract (Bals et al. 1998; O'Neil et al. 1999). hBD-2 is stored in lamellar bodies of keratinocytes (Oren et al. 2003) and can be up-regulated directly by bacterial pathogens (Liu et al. 2002) or inflammatory cells like monocyte-, macrophage- (Fang et al. 2003; Tsutsumi-Ishii and Nagaoka 2003), and lymphocyte-derived cells (Selsted and Ouellette 2005). Several mechanisms and signalling pathways are involved in the expression of hBD-2. Detection of bacterial lipopolysaccharides (LPS) by CD14 and TLR-2 and subsequent activation of the NF-κB cascade induces hBD-2 (Birchler et al. 2001). Furthermore, human TLR-2 mediates induction of the antimicrobial peptide hBD-2 in response to bacterial lipoprotein (Birchler et al. 2001). HBD-2 signalling pathways involve NF-κB (Tsutsumi-Ishii and Nagaoka 2002) and mitogen-activated protein kinase (Krisanaprakornkit et al. 2002), including Src-dependent Raf-MEK1/2-ERK (93). The promoter of hBD-2 has binding sites for NF-κB and putative binding sequences for AP-1, NF-IL6, and STATs (Tsutsumi-Ishii and Nagaoka 2002; Wang et al. 2003). After upregulation, hBD-2 shows immune stimulating properties by chemoattracting immature dendritic cells and T cells to modify the adaptive immune reaction (Yang et al. 1999). As an inducible HDP, hBD-2 seems to be involved in wound repair by activating the intrinsic immunity after destruction of epidermal skin layers and inflammation (Schmid et al. 2001).

Mediators upregulating hBD-2 in epithelial tissue are proinflammatory cytokines like IL-1 (Liu et al. 2003), IL-22 (Wolk et al. 2006), bacterial lipopolysaccharide (LPS) (Kawai et al. 2002), and direct bacterial contact with epithelial cells (Harder et al. 2000). After activation, hBD-2 shows direct activity against *P. aeruginosa*, *E. coli*, and *C. albicans* (Singh et al. 1998). Furthermore, hBD-2 shows a synergistic effect with LL-37 in increased activity against *S. aureus* (Ong et al. 2002). In the setting of chronic skin disorders, Ong et al. showed a continuous upregulation of hBD-2 in psoriatic skin scale with a low susceptibility for skin infections (Ong et al. 2002). In burn wounds, decreased hBD-2 activity was shown, indicating that innate immune defects contribute to the risk of burn wound infection and sepsis (Milner and Ortega 1999).

hBD-3 was originally discovered from psoriatic skin lesions and isolated nearly simultaneously from two groups in 2001 (Garcia et al. 2001a,b; Harder et al. 2001). hBD-3 was further detected in many other tissues such as heart, liver, fetal thymus, and placenta cells (Garcia et al. 2001a,b; Dunsche et al. 2002). In skin, hBD-3 is stored like hBD-2 in lamellar bodies of keratinocytes (Sawamura et al. 2005). TNF-α, transforming growth factor alpha (TGF-β), insulin-like growth factor 1 (IGF-1), TLR-5, IL-1α, IFN-γ, TGF-β, and IGF-1 as well as various bacteria play an important role in activation of the synthesis of hBD-3 (Sawamura et al. 2005). After testing a large number of bacterial strains, the broad bactericidal activity of hBD-3 against Gram-positive and Gram-negative bacteria was reported, including multi-drug-resistant strains of *S. aureus* and *P. aeruginosa* (Maisetta et al. 2006).

hBD-4 is primarily expressed in testis and epididymis (Garcia et al. 2001a,b) and inducible in primary keratinocytes (Harder et al. 2004). These data are based on detection of mRNA and a partial characterization of this defensin relies on recombinant preparation by Garcia et al. (2001a,b). The activation of hBD-4 seems similar to hBD-2 and hBD-3 (Harder et al. 2004).

Human beta-defensins promote histamine release and prostaglandin-2 production in mast cells (Niyonsaba et al. 2002), connect the innate and adaptive immune system by chemoattraction of immature dendritic cells and T-cells (Yang et al. 1999), and increase the expression of TNF-α and IL-1 in human monocytes following activation by bacterial stimulus (Niyonsaba and Ogawa 2005).

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HDPs in human skin are primarily produced by keratinocytes, eccrin glands, and neutrophile granulocytes (Schroder and Harder 2006). Constitutively produced HDP of the human skin are dermicidin (Schittek et al. 2001), protease inhibitor antileucoprotease (Wiedow et al. 1998), RNAse 7 (Harder and Schroder 2002), psoriasin (Glaser et al. 2005), lysozyme (120), hBD-1 (69) and secretory phospholipase A2 (121). Inducible HDPs of the human skin are LL-37 (35) produced in keratinocytes, α-defensins (human neutrophil peptides 1 to 4) produced by neutrophils (Ganz 2003), and hBD-2 and -3 (Niyonsaba et al. 2005).

Host defense peptides in wounds

HDPs, synthesized in the skin at sites of potential microbial entry, provide a soluble barrier that acts as an impediment to infection (Braff et al. 2005a,b). If the skin is intact, bacterial growth will be controlled by bacteriostatic and bactericidal compounds such as psoriasin and RNase 7 (Schroder and Harder 2006). However, in injury and infection of the skin, expression of HDPs will be upregulated due to increased synthesis by keratinocytes and deposition from degranulation of recruited neutrophils.

In a wound, insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β) are stimulators for the human cathelicidin hCAP18/LL-37 to a comparable level as the proinflammatory cytokine interleukine-1 (IL-1) (Sorensen et al. 2003). Both play important roles in wound healing by activating epidermal cells and fibroblasts to form granulation tissue, mediate angiogenesis, and chemoattract macrophages and fibroblasts (Niyonsaba et al. 2006; Singer and Clark 1999). In a feedback mechanism, cathelicidin from activated leukocytes in pigs (PR-39) has shown a direct influence on dermal fibroblasts by increasing synthesis of the extracellular matrix proteoglycans, syndecan-1 and syndecan-4 (Chan and Gallo 1998), which are required for the activity of many growth factors (Proudfoot et al. 2001). In an animal model, syndecan production was delayed and ineffective wound repair (Gallo 2000) was reported. Heilborn et al. described a receptor K67-dependent, continuous increase of LL-37 produced by keratinocytes and granulocytes, with a peak maximum after 48 h and high expression in the wound fluid and wound tissue of healing skin. Expression decreased after wound closure, and a lack of LL-37 in chronic wounds was reported (Dorschner et al. 2001; Heilborn et al. 2003). Different authors have shown a protective function of LL-37 from invasive bacterial skin infections particularly against *P. aeruginosa*, *S. aureus*, and group A *Streptococcus* species (Dorschner et al. 2001; Ong et al. 2002). Comparing wild-type mice with Cnlp-deficient mice (targeted deletion of the cathelicidin gene), a prolonged period of wound healing and an increase in bacterial colonization for Cnlp-deficient mice was reported (Braff et al. 2005a,b). These findings were confirmed by Nizet and co-workers who reported a better outcome for wild-type mice versus Cnlp-deficient mice after challenge with necrotic skin infections of group A *Streptococcus* species (Nizet et al. 2001).

Ong et al. showed better immune response against *S. aureus* in patients with psoriasis caused by a higher LL-37 expression level, whereas patients suffering from topical dermatitis showed decreased expression (Ong et al. 2002; Leung et al. 2004). These findings may provide an explanation for the susceptibility of patients suffering from atopic dermatitis to skin infection compared with patients with psoriasis (Schroder and Harder 2006). We demonstrated a bactericidal effect of LL-37 in a rat animal model following transient adenoviral gene therapy to *P. aeruginosa*-infected burn wounds (Jacobsen et al. 2005a,b). LL-37 has a direct effect on wound healing by promoting neovascularization and angiogenesis. Koculla et al. showed the impact of LL-37 to angiogenesis in a chorionallantoic membrane assay and by a revascularization model in an animal after hind-limb ischemia. The authors found a direct effect of LL-37 by activating vessel growth in cultivated epithelial cells, and after injection of LL-37 in the ischemic limb of a rabbit, they noted increased blood supply. They found direct participation of the formyl peptide receptor like 1 (FPRL1) in activation of hCAP-18 and following neovascularization (Steinstraesser et al. 2006; Koczulla et al. 2003). We confirmed the angiogenetic effect of LL-37 in a skinfold chamber model in mice (Steinstraesser et al. 2006).

Another study analyzed visualization and localization of LL-37, HNPs, and hBD-1, -2, and -3, in normal and burned skin and determined the cell types in which these HDPs were localized using fluorescence microscopy. The authors showed that in normal skin, hBD-1 was localized to the perinuclear region of keratinocytes and hBD-2 was primarily localized to the stratum germinativum; human beta-defensin-3 was detected in the stratum spinosum, whereas HNP were randomly distributed in the papillary dermis. LL-37 was concentrated in the stratum corneum and along ducts.

In burned skin, hBD-1 was expressed in dermal glands, including hair shafts; hBD-2 and -3 were found in the remaining keratin layers and glands of the lower dermis; human neutrophil peptides were localized to hair shafts and in residual keratin layers. Interestingly, LL-37 was detected in very high concentrations in the epithelium of sweat ducts. The authors concluded that the cells in the lower dermal and subdermal regions of burned skin produce HDPs after burn injury to maintain a barrier against infection (Poindexter et al. 2006).

HNPs promote wound healing. Oono et al. showed that synthetic HNP-1 increases the expression of pro-collagen mRNA and protein in dermal fibroblast cultures. In contrast, the expression of matrixmetalloproteinase-1 was decreased. The authors suggest that HNP-1 may promote wound repair by enhancing extracellular matrix deposition (Oono et al. 2002). Another study showed mitogenic activity of HNPs in epithelial and fibroblast cell lines *in vitro* (Oono et al. 2002).

For β-defensins, Supp et al. showed expression of the hBD-1, -2, and -3 in keratinocyte cultures and split skin grafts from healthy and burned donors (Supp et al. 2004). Later studies reported that β-defensins stimulate migration and proliferation of epidermal keratinocytes and thus might promote cutaneous wound healing (Niyonsaba et al. 2006). In chronic and acute wounds, hBD-2 seems to be upregulated, whereas it is not detectable in healthy skin (Butmarc et al. 2004).

Expression of hBD-3 in keratinocytes is induced by skin infection with *S. aureus* via TLR-2 and EGFR (Sorensen et al. 2005; Menzies and Kenoyer 2006) and Kisich et al. demonstrated that the capacity of human keratinocytes to fight bacterial infections (*S. aureus*) depends on its hBD-3 expression (Kisich et al. 2007). We have demonstrated that gene transfer of hBD-3 to infected diabetic porcine wounds enhances wound closure by 25% (Hirsch et al. 2009).

HDP histone 1.2 is effective against *P. aeruginosa* wound infection in a rat burn model with a 3-fold reduction in bacterial burden infection (Jacobsen et al. 2005a,b). Concentrations of LL-37 and hBD-1, -2, and -3 change significantly in burn-traumatized skin. Whereas hBD-1 showed only a moderately lower expression in burn wounds compared with healthy tissue, hBD-2 expression changed drastically: burn wound tissue showed an upregulation of 380-fold compared with controls. Furthermore, hBD-3 showed a 10-fold increase in mRNA expression.

Tissue sections taken from the center of burn wounds showed no direct changes in LL-37 expression compared with comparable sections from unburned patients.

However, it became evident that in the edges of burn wounds a 10-fold reduction in LL-37 expression occurs. This might be due

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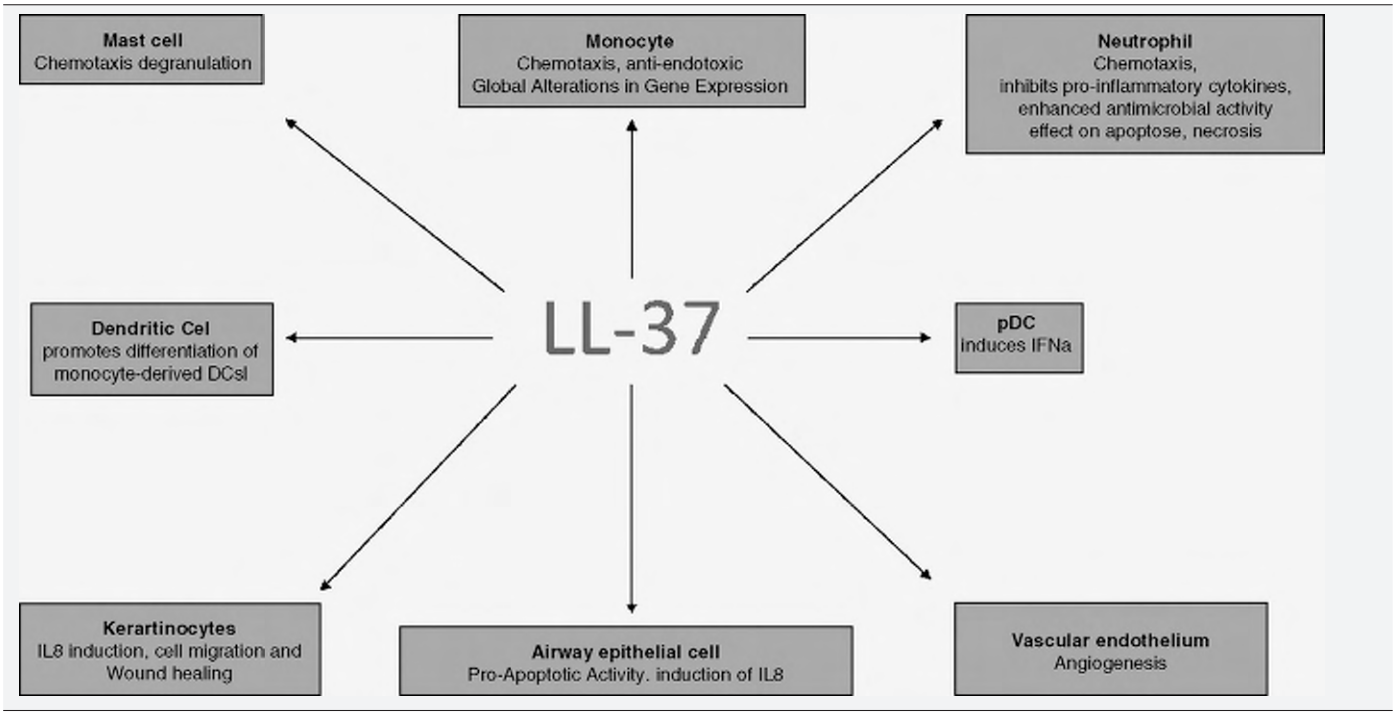
Table 1
Pluripotent activity of the human cathilicidin LL-37.



to the presence of more viable, thus traumatized cells, whereas in the center, cells are already dead (Kaus et al. 2008). These combined data show that HDPs play a major role in wound healing and wound infection. In contrast to clinically used antibiotics, HDPs have interesting features for topical application to treat wound infection and promote healing (Tables 1–3).

Finally, immunomodulatory peptides that act on the host rather than on the pathogen offer a unique opportunity to minimize the direct selective pressures for pathogen resistance. Recently, such an immunomodulatory peptide, an innate defence regulator IDR-1, was shown to protect mice against bacterial infections, including infections with multidrug-resistant pathogens, and this provides an

Table 2
Immunomodulatory properties of mammalian host defense peptides.

Cell or tissue type	Production and activity of host defense peptides
Hematopoietic cells	
Neutrophils (Nagaoka et al. 2008; Zheng et al. 2007)	The peptides LL-37 and defensins are produced by neutrophils and are later stored within neutrophil granules. LL-37 acts as a neutrophil chemoattractant, inhibits neutrophil apoptosis, promotes both chemokine induction and the antimicrobial functions of neutrophils, but limits pro-inflammatory cytokines
Mast cells (Bahri et al. 2010; Di Nardo et al. 2008; von Kockritz-Blickwede et al. 2008)	Mast cells produce LL-37 in the skin. LL-37 and β-defensins are mast cell chemoattractants and promote mast cell degranulation
Monocytes and macrophages (Elssner et al. 2004; Soehnlein et al. 2009; Yu et al. 2007)	In *vitro* and in *vivo* studies show LL-37 and β-defensins are monocyte chemoattractant. LL-37 is anti-endotoxic and promotes chemokine production and IL-1b secretion, but at the same time inhibits inflammatory responses to certain TLR ligands
Conventional dendritic cells (Bandholtz et al. 2006; Kandler et al. 2006; Morioka et al. 2008)	Defensins and cathelicidins are dendritic cell (DC) chemoattractants. LL-37 stimulates differentiation of monocyte-derived DCs, but inhibits DC maturation and activation by TLR-ligands β-Defensin 2 might promote DC activation as an endogenous TLR4 ligand. The adjuvant activities of defensins and cathelicidins in vivo might be mediated in part through their activity on DCs
Plasmacytoid dendritic cells (Ganguly et al. 2009; Lande et al. 2007)	LL-37 in complex with DNA oligonucleotides strongly induces IFNa production by plasmacytoid DCs. This might contribute to the pathology of psoriasis
Epithelial cells	
Keratinocytes (Coffelt et al. 2009; Tokumaru et al. 2005; Yahata et al. 2006; Yamasaki et al. 2007)	Due to LL-37 keratinocyte migration and production of IL-8 increase. Furthermore LL-37 inhibits keratinocyte apoptosis and modulates responses to TLR ligands. It might have wound healing activities in skin. Altered proteolytic processing of hCAP18 and LL-37 has been implicated in the pathology of rosacea
Bronchial epithelium (Barlow et al. 2010; Tjabringa et al. 2003)	On bronchial epithelial cells LL-37 stimulate cytokine and chemokine production and promote apoptosis
Intestinal epithelium (Otte et al. 2009; Wehkamp et al. 2007)	α-Defensins are produced by Paneth cells. LL-37 promotes mucin production and survival of intestinal epithelial cells. LL-37 plays an important role in the immune defenses of the gut. Reduced α-defensin production might contribute to Crohn's disease
Other cells	
Vascular endothelium (Steinstraesser et al. 2009; Shaykhiev et al. 2005)	LL-37 induces activation and proliferation of vascular endothelium and promotes angiogenesis
Mesenchymal stromal cells (Coffelt et al. 2009)	LL-37 acts as a chemokine for mesenchymal stromal cells and promotes the production of various cytokines, as well as VEGF and MMP2; this can contribute to angiogenesis and tumor progression
Cancer cells (von Haussen et al. 2008; Chuang et al. 2009)	LL-37 promotes migration and proliferation of lung, ovarian and breast cancer cells and LL-37 production by cancer cells in vivo promotes tumor growth. However, LL-37 also augments the anti-cancer therapeutic activity of CpG oligonucleotides

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Table 3
HDP in commercial development.

Drug	Description	Stage of development	Medical use
Immunomodulatory anti-infectives with antimicrobial actions			
hLF-1-11 (AM-Pharma)	Small peptide derived from human lactoferrin	Phase II	Allogeneic bone marrow stem cell transplantation-associated infections
Omiganan pentahydrocholoride/CP-226 (MX-226/CLS001; Migenix)	Synthetic HDP 12-mer analog of bactolysin, indolicidin derivative	Phase 3b	Prevention of catheter-related infections; dermatology-related infections
Ompebacan (Xoma)	21-Amino acid peptide derivativeof bactericidal/permeability-increasing protein	Phase I/II	Endotoxemia in haematopetic stem cell transpalnt recipients
Mersacidin	Bacteriocin	Preclinical	Gram-positive infections
BL2060	A synthetic compound comprising fatty acid and lysine copolymers	Lead optimization	Anti-infective
CSA-13	Cationic steroid (ceragenin) that mimics host-defense peptides	Preclinical	Anti-infective
Plectasin	Fungal defensin	Preclinical	Systemic anti-Gram positive, especially pneumococcal and streptococcal infections
PTX002 (33-mer peptide) PTX005 (12-mer peptide), PTX006 (N-acylated analog of PTX005) and PTX007 (a nonpeptidic structural analog of PTX005)		Discovery	Broad-spectrum antimicrobial antiendotoxin
Peptidomimetics	Derived from the arylamide, calixarene, hydrazide and salicylamide series	Discovery/ preclinical	Anti-infectives; antimicrobial polymers and coating materials
rBPI21		Phase IIIb	Anti-infective; allogeneic bone marrow stem cell transplantation-associated infections; prevention of burn infections
XOMA 629 (Xoma)	9-Amino acid peptide derivative of bactericidal/permeability-increasing protein	Phase IIa	Anti-infective, impetigo
Immunomodulatory anti-infectives peptides lacking antimicrobial action			
EA-230 (Exponential Biotherapies) Glutoxim/	Olgiopeptide fragment from Beta-hCG (4-mer, LQGV)	Phase II (Russia)	Sepsis
Glutoxim/NOV-002 (Pharma BAM/Noveios)	Hexapeptide with stabilized disulfide bond	Phase II (North America)	Tuberculosis, non-small cell lung cancer
IMX942 (Inimex)	5-Amino acid peptide, derivative of IDR-1 and indolcidin	Phase IA	Immunomodulation; treatment of fevers and neutropenia in chemotherapy patients
Immunomodulatory peptides			
DiaPep277 (DeveloGen)	HSP60 derivative of bactericidal/permeability-increasing protein	Phase IIA	Type 1 diabetes mellitus
RDP58 (Genzyme)	Semisynthetic D-amino acid decapeptide derived from HLA class I B2702	Post phase II	Inflammatory bowel disease
Anti-infecitve peptides with unknown immunomodulatory acitivity			
Pexiganan acetate (MSI-78)	Synthetic HDP 22-mer, magainin derivative	Phase IIII	Anti-infective; wound healing, topical antibiotic
PAC113 (Pacgen Biopharmaceuticals)	12-mer, based on the active segment of histatin 5 protein found in human saliva	Phase II	Oral candidiasis
CZEN-002	Synthetic 8-mer derived from -melanocyte-stimulating hormone	Phase IIb	Vulvovaginal candidiasis
HB-50	Synthetic natural peptide mimetic of cecropin	Preclinical	Anti-infective
MBI 594AN		Preclinical	Anti-infective
HB-107	19-Amino acid fragment of cecropin B	Preclinical	Wound healing
PMX-30063 (PolyMedix)	Defensin structural mimentic, non-peptide small molecule/copolymer	Phase IB	Antibitotic
HB-1345 (Helix BioMedix)	Lipohexapeptide	Pre-phase I	Acne
Iseganan (IB-367; Ardea Biosciences)	Synthetic protegrin-1 derivatetive, 17 amino acids	Phase III	Oral mucositis in radiation therapy patients

Modified from Steinstraesser et al. (2009).

important proof of principle for the immunomodulatory approach. The peptide was shown to act as a neutrophil chemoattractant and furthermore to induce chemokine production and promote cell recruitment *in vitro* and *in vivo*; these activities may account for some of its protective effects. Importantly IDR-1, as well as many natural HDPs, exerts anti-inflammatory and anti-endotoxic effects at the same time as antimicrobial functions.

Conclusion

Nature has created a significant depository of gene-encoded HDPs with enormous diversity in both structure and biological activity. These HDPs are rapidly emerging as attractive candidates for antimicrobial treatment and could provide us with potential templates for development of both antimicrobial and immunomodulatory therapies, often combining both activities in the same molecule. HDPs and their mimetics can be used synergistically with conventional antibiotics, and also to target resistant pathogens where conventional antibiotics fail. Importantly, immunomodulatory HDPs that target the host immune system rather than the pathogen also offer an excellent opportunity to minimize the risks of pathogen resistance to these compounds. Future basic and clinical research will tell if and when this new powerful "biological weapon" will become part of the health professionals' armentarium. Most important, future research must take advantage of and build on the diverse nature of HDPs and adhere to physiologically relevant conditions, ultimately validating, *in vivo*, their beneficial functions to treat pathogens.

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