

HOST DEFENSE PEPTIDES IN BRIEF

Suzana Popovic

University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Microbiology and Immunology

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Corresponding author:

Suzana Popovic

Faculty of Medical Sciences, University of Kragujevac,
Department of Microbiology and Immunology,
Svetozara Markovica 69, 34000 Kragujevac, Serbia

E-mail: popovic007@yahoo.com

ABSTRACT

Host defense peptides (HDPs) are an indispensable part of innate immunity. These multifunctional peptides, immanent in all living organisms, have diverse roles in host defense due to their antimicrobial and immunomodulatory properties. HDPs show activity against a broad spectrum of Gram⁺ and Gram⁻ bacteria, fungi, mycobacteria, and some enveloped viruses. Their numerous roles as effector molecules of innate immune response and a link between innate and adaptive immunity, contribute to their antimicrobial properties. Furthermore, HDPs conduce to the resolution of inflammation and participate in wound healing. The increasing incidence of antimicrobial drug resistance and the need for agents that can modulate immune response have put these peptides into the spotlight of researchers' interest as potential therapeutics. In this review, we will present principal informations about the properties and the functions of host defense peptides, as well as their prospective applications.

Keywords: Host defense peptides; antimicrobial; antitumor; immunomodulatory.



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INTRODUCTION

Host defense peptides (HDPs), found in almost all species, from bacteria to humans, represent a heterogeneous group of peptides with a multiplicity of properties. Although they vary in amino acid sequences and structure, some features are in common for all members of this family. They are composed of 12 to 50 amino acids with a positive net charge (+2 to +9) due to lysine or arginine residues, and about 50% hydrophobic residues. HDPs have diverse biological and functional properties, still, the most common characteristic is their antimicrobial effect. Cationic and amphiphilic features enable strong interaction with membranes, especially with negatively charged membranes of microorganisms. Host defense peptides with antimicrobial properties are also referred to as antimicrobial peptides (AMPs). HDPs are most often bifunctional. In addition to their broad-spectrum antimicrobial action, HDPs exert diverse immunomodulatory activities, both pro-inflammatory and anti-inflammatory. As such, HDPs are the first-line defense against pathogens and an indispensable part of innate immunity.

Physiologically active cationic peptides were first described in 1956 by Skarnes and Hirsch as peptides with antimicrobial activity (1, 2). Ten years later Zeya and Spitznagel introduced term defensins for several basic proteins found in polymorphonuclear leukocyte lysosomes, due to their participation in host defense (3, 4). At the beginning of the 1980's, in studies of the African frog *Xenopus laevis* oocyte system, it was observed that despite the nonsterile surgical procedures, cut margins of the wound didn't develop an infection, and normal healing of lesions occurred. Later on, Zasloff extracted two components with antibacterial activity from the skin of *Xenopus laevis* and called them "magainins" (5). Since then, a large number of natural peptides displaying a diversity of functions related to host defense have been isolated from cells and tissues of virtually all living organisms. They were found to be present in bacteria, fungi, and in all multicellular organisms as an inherent part of non-specific immunity. In bacteria, these molecules, called bacteriocins, provide survival in nutrient-poor environments by inhibiting adjacent microorganisms (6). Herbal peptides with the activities toward phytopathogens have been found in all plant organs. In mammals peptides participating in host defense reside in granulocytes, skin, and mucous membranes of the gastrointestinal, urogenital and respiratory tract. The antimicrobial peptide database (APD, <http://aps.unmc.edu/AP/main.php>) so far contains 337 bacteriocins, 18 fungi, 346 plant, and 2264 animal host defense peptides with antimicrobial and immunomodulatory activities.

CLASSIFICATION

HDPs are classified based on their primary and secondary structure. In mammals, three major families have been described: defensins, cathelicidins, and histatins (7). Defensins are further divided into three groups: α -defensins, β -defensins, and θ -defensins. They are widely expressed on the skin

and mucous membranes, in Paneth's cells of the small intestine and stored in granules of neutrophils. The cathelicidins, found only in mammals, are immanent mostly in lymphoid tissue, but are also found in epithelial and brain tissue. The only cathelicidin found in humans is LL-37 (8). This multifunctional peptide is present predominantly in leukocytes, but also in different cells of various tissues and body fluids. Histatins are histidine-rich peptides present in saliva and, due to their bactericidal and fungicidal activity, participate in maintaining of oral health.

ANTIMICROBIAL ACTIVITY

The first contact between the peptide and bacteria is electrostatic. Peptidoglycan and cell wall-associated proteins, as well as cytoplasmic membrane surface, bear negative net charges. Electrostatic attraction between the negatively charged bacterial envelope and cationic peptides leads to peptide accumulation in the cell wall and interaction with the membrane surface. After binding to the membrane some peptides disrupt its structure and thus increase membrane permeability, or form pores, which leads to cell lysis. Others traverse the membrane, enter the cell and bind to vital molecules, inhibit the activity of enzymes participating in the synthesis of the cell wall, DNA, RNA, and proteins (9-11), or activate microbial autolytic systems (12). Since the surface of bacteria is more negatively charged than the eukaryotic cell membrane, peptides show a selective affinity for bacteria. Cholesterol present in the membrane of eukaryotic cells contributes to HDPs selectivity as well, by preventing peptide binding.

There are several mechanisms of HDPs antiviral action. They can act directly on the viral envelope (13) or interfere with viral adsorption and/or entry into the cell (14). Some HDPs that have the ability to translocate through the cytoplasmic membrane of eukaryotic cells, or others, that are produced and stored in cellular organelles, can activate host antiviral mechanisms inside an infected cell, or block expression of viral genes (15, 16). α -defensin HNP-1 inhibits replication of HIV-1 and influenza virus and inactivates vesicular stomatitis virus, adenovirus, HSV, CMV, and papillomavirus (17-19). Some other HDPs, such as cathelicidin LL-37 and neutrophil peptide Alpha-defensin-1, block HIV-1 infection either through down-regulation of HIV-1 coreceptor CXCR4(20) or by inhibition of virus replication in infected cells (21). θ -defensin Retrocyclin 2 inhibits avian influenza H5N1 virus through interference with viral mRNA transcription (22).

A number of HDPs have shown strong fungicidal properties(23). Most HDPs, that affects a broad spectrum of microorganisms, including fungi, bacteria, and viruses, act nonspecifically and exert their activity by inducing membrane lysis (24-27). HDPs that have primarily or exclusively antifungal properties are less immanent. These peptides have diverse specific targets. Members of the echinocandin family are inhibitors of β -glucan synthase, the enzyme involved in the generation of the cell wall in *Candida*, *Aspergillus*, *Cryptococcus*, and *Pneumocystis* species. Preclinical and clinical



studies have shown these peptides and their analogs as promising agents for the treatment of invasive and systemic *Candida* and *Aspergillus* infections(28, 29). Synthase inhibitors, such as Nikkomycins, interrupt the synthesis of chitin, a cell wall component essential for the structural integrity of the fungus. These HDPs have shown significant activity against *Candida albicans*, *Candida immitis*, and *Blastomyces dermatitidis*(30, 31). Aureobasidins alter the assembly of actin and chitin and interrupt the synthesis of sphingolipids in *Candida* spp. and *Cryptococcus neoformans* (32, 33). Some members of the defensin family with marked antifungal effects target the fungus-specific membrane glucosylceramide and induce the generation of toxic reactive oxygen species (34, 35). Histatins exert strong candidacidal activity (36-38) and significant activity against *Cryptococcus neoformans* and *Aspergillus fumigates* (39, 40). Histatin 5 is highly selective for fungi, acting on specific intracellular targets (41).

Only a minority of HDPs have been tested against parasites known to cause infections in humans. Since the cell membrane of protozoan parasites has a higher proportion of anionic phospholipids than mammalian cells, it seems that the antiprotozoan action of HDPs is also based on electrostatic binding and disruption of the plasma membrane. NK-lysin, a peptide found in cytoplasmic granules of porcine cytotoxic T cells and natural killer cells (the human analog is termed granulysin), interacts with the membrane of erythrocytes infected with *Plasmodium falciparum*, permeabilizes it, and kills intracellular parasites (42). NK-lysin also potentially inactivates *Trypanosoma cruzi* by permeabilization of the parasite plasma membrane (43). Magainins and cecropins tested against a variety of *Plasmodium* species (44) have the potential to inhibit the normal development of oocysts and disrupt the sporogonic development of *Plasmodium*. Bovine lactoferrin peptides exhibited potent *in vitro* anti-giardial activity (45).

The mechanisms of HDPs antimicrobial activity are shown in Table 1.

Table 1. Mechanisms of HDPs antimicrobial activity

Antibacterial			
Mechanism of action	HDPs	Target organism	Reference
Permeabilization of the outer and the inner membrane	HNP4	<i>E. coli</i> , <i>E. aerogenes</i> , <i>En. faecalis</i> , <i>S. aureus</i> , <i>B. cereus</i>	(46)
Membrane dysfunction	Lactoferrin	<i>V. cholerae</i> , <i>S. typhimurium</i> , <i>E. coli</i> .	(47)
Inhibition of cell wall synthesis	BMAP-28	<i>A. baumannii</i>	(48)
	Polymixin E	<i>E. coli</i> , <i>P. aeruginosa</i>	(49)
	RTD-1	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	(50)
	Mersacidin	<i>B. cereus</i> <i>M. luteus</i> <i>S. simulans</i>	(51) (52)
	Seminalplasmin	<i>E. coli</i>	(53)
	HNP-1	<i>C. difficile</i>	(54)
	hBD3	<i>S.aureus</i> , <i>E. faecium</i>	(55) (10)
Inhibition of DNA, RNA and protein synthesis	tPMP-1 and tPMP-2	<i>S.aureus</i>	(11)
	Pleurocidin	<i>E. coli</i>	(56)
	Apidaecins, oncocins	<i>E. coli</i>	
Activation of the microbial autolytic systems	RTD-1 and RTD-2	<i>S. aureus</i> , <i>S. simulans</i> , <i>S. carnosus</i>	
Antiviral			
Viral envelopes lysis	LL-37	<i>Vaccinia virus</i>	(13)
Interference with viral adsorption and/or entry into the cell	Dermaseptins	HSV1	(14)
	HNPs-1 - 3, HD-5	HPV	(17)
	HNP-1	HSV1	(18)
	NP-1	HSV2	(19)
	HD5	HIV1	(57)
	β -defensin-2 and HBD-3	HIV1	(58)
Inhibition of replication	Melittin, Cecropin	HIV1	(15)
	Alpha-defensin-1	HIV1	(20)
	β -defensin-2, HBD-3	HIV1	(58) (21)
	LL-37	HIV1	(59)
Blocking expression of viral genes	HNP-1 and HBD-2	HIV1	(16)
	LL-37, mCRAMP	<i>Influenza A virus</i>	(22)
	Retrocyclin 2	H5N1	(60)
	HNP2, HDP	HSV2	



Antifungal			
Membrane lysis	Cecropin B, Dermaseptin	<i>A. flavus</i> , <i>A. fumigates</i> , <i>A. niger</i> , <i>F. moniliforme</i> , <i>F. oxysporum</i>	(24)
Inhibition of fungal chitin synthase	Ranalexin, Magainin II	<i>Candida spp</i> , <i>Cryptococcus</i>	(27)
Inhibition of sphingolipid synthesis	Nikkomycins X and Z	<i>C. immitis</i> , <i>B. dermatitidis</i>	(30, 31)
Disruption of actin assembly and chitin delocalization	Aureobasidin A	<i>S. cerevisiae</i>	(32)
Induction of reactive oxygen species	Aureobasidin A	<i>S. cerevisiae</i>	(61)
	RsAFP2	<i>C. albicans</i>	(62) (63)
	HsAFP1	<i>S. cerevisiae</i>	(64)
Induction of ion fluxes	DmAMP1		(65)
Cell cycle progression impairment	RsAFP2	<i>N. crassa</i>	(66)
	Psd1	<i>N. crassa</i>	
Antiparasitic			
Membrane permeabilisation	NK-lysin	<i>P. falciparum</i>	(42)
		<i>T. cruzi</i>	(43)
Oocyst development and sporozoite production	Magainin 2, Cecropin B	<i>Plasmodium spp.</i>	(44)
Membrane disruption, morphological changes, apoptosis induction	bLF	<i>G. intestinalis</i>	(45)

ROLE IN IMMUNITY

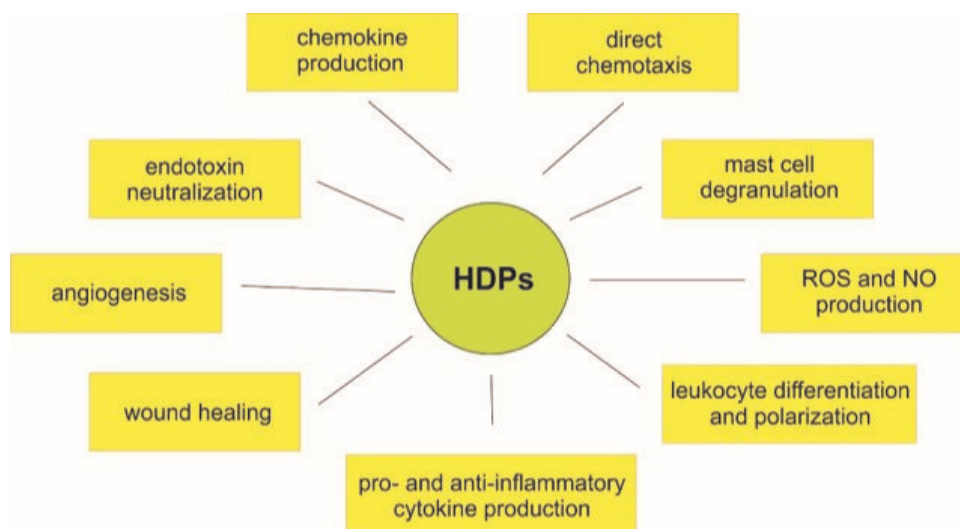
In addition to antimicrobial potency, HDPs have a variety of functions related to host defense (Figure 1.). They act as signaling molecules that coordinate innate and adaptive immune response and promote subsequent healing of injured tissue and neovascularization of the wound (67-71). Their numerous immunomodulatory functions include the ability to act as chemokines and/or to induce the production of chemokines that attract neutrophils, monocytes, T cells, and mast cells to the infection site (72). HDPs stimulate mast cell degranulation which results in increased permeability of blood vessels and enables the recruitment of leukocytes to the site of inflammation (73, 74). In an inflammatory environment, they increase the production of ROS and amplify the respiratory burst in macrophages (75) and neutrophils (76). HDPs can modulate host gene expression (77) thus influencing the production of pro- and anti-inflammatory cytokines. Also, they may facilitate maturation and function of dendritic cells and enhance adaptive immune response (78). Importantly, these peptides can bind LPS and neutralize them, or block the binding of LPS to macrophage receptors (79, 80), thus preventing an excessive proinflammatory response that can result in tissue damage (81).

The immunomodulatory activity of HDPs is not unidirectional. Depending on stimuli, HDPs can exert a dual impact on the immune response. Popovic et al. have shown that

brevinin-2-related peptide-ERa (B2RPERa), isolated from *Hylarana erythraea*, induces proliferation of resting peripheral blood mononuclear cells, but limits proliferative response to concanavalin A (82). The dual effect of LL-37 is well documented. *In vitro* experiments showed that this cathelicidin, expressed in human myeloid and epithelial cells, completely inhibited the expression of proinflammatory genes, but did not affect the expression of chemotactic mediators in LPS-activated macrophages (83). Furthermore, this peptide influenced the differentiation of dendritic cells: LL-37 increased their endocytic capacity, modified expression and function of receptors involved in phagocytosis, increased expression of costimulatory molecules and production of Th1 cytokines, promoting Th1 cell response (84). In contrast, simultaneous treatment of immature dendritic cells with LL-37 and TLR-ligands inhibited their maturation (85). As studies have shown that the expression of this peptide is increased during infection or inflammation, it seems that LL-37, and possibly some other HDPs, acts as a negative feedback signal that promotes local immune response to infection, and prevents systemic hyperproliferative response. The crucial role of HDPs in both prevention and resolution of infection has also been shown in animal models (81, 86, 87).



Figure 1. Immunomodulatory properties



ANTITUMOR ACTIVITY

In recent years it became evident that HDPs exhibit promising antitumor activity and may have therapeutic value. A variety of peptides tested *in vitro* for their ability to kill cancer cells showed an outstanding direct cytotoxic effect on leukemia, lymphoma, bladder, ovarian, cervical, breast, lung, and oral squamous carcinoma cells (88-96). The advantage of HDPs over conventional chemotherapeutics is their selectivity for cancer cells. That discrimination is based on the difference in expression of cell surface molecules such as phosphatidylserine, heparan sulfate, or sialic acid (97, 98), variance in membrane fluidity, and the presence of a high number of microvilli that increase the surface of the cancer cell. Interaction between HDPs and cancer cells is electrostatic. Owing to their cationic amphipathic structure, HDPs interact with negatively charged molecules that are more abundantly expressed on cancer cells. Damaging of the cell membrane can be apparent within minutes. Certain HDPs do not disturb cell membrane integrity, but translocate through the membrane of the cancer cell to the cytosol and interact with cellular components, preferentially with mitochondria whose membrane contains more phosphatidylserine compared to a normal cell, and trigger apoptosis (99). Conducively, cancer cells change the microenvironment lowering pH, and that can be of benefit for optimal activity of HDPs. Since HDPs kill cancer cells rapidly in non-receptor mediated mode, targeting molecules that have important roles in the progression of cancer, the emergence of resistance is less possible. In addition to the direct cytotoxic effect, HDPs participate in the immune response to cancer as a part of innate immunity and the connection between innate and adaptive immune response (100).

Based on *in vitro* experiments, a variety of HDPs has been tested *in vivo* in animal models. A rising number of *in vivo* studies on mice showed that certain HDPs administered intratumorally (101, 102), peritumorally (103), subcutaneously (104), or applied in the form of sprays or ointment in case of melanoma (105) had direct antitumor activity, inhibited

tumor growth and increased the survival time of experimental animals. Intratumoral injections of NRC-03 and NRC-07, a pleurocidin family HDPs, to breast cancer-bearing immunodeficient NOD SCID mice resulted in significant inhibition of tumor growth. Furthermore, histologic analysis of peptide-treated tumors revealed larger necrotic zones than that of control animals. Importantly, intratumoral delivery of peptides had no deleterious side-effects (106). Shan et al. have shown that five days of administration of magainin II-bombesin conjugate directly in the tumor of mice bearing MCF-7 tumor grafts resulted in reduced tumor masses alongside extensive necrotic areas (107).

Since therapeutic use of HDPs requires maintaining of *in situ* concentrations sufficient to kill cancer cells, new approaches to overcome this problem involve vector-mediated delivery of genes encoding HDPs into cancer cells (108), or targeting cancer cells with immunoconjugates containing HDPs (109). Importantly, the membranolytic activity of HDPs and the resulting increase in permeability of cancer cell membrane can be used to enhance the cytotoxic activity of conventional chemotherapeutics (110, 111).

TROUBLESHOOTING

The role of HDPs in host defense is complex and their multiple functions can be utilized for designing future therapeutic agents. However, there are several crucial limitations to their therapeutic use. One of the problems is the insufficient specificity of certain HDPs. While some HDPs selectively kill microorganisms and cancer cells, others are more or less cytotoxic for healthy eucaryotic cells and may have severe hemolytic activity. Consequently, administration of HDPs may result in systemic toxicity.

One of the prerequisites for the therapeutic use of HDPs is sufficient stability that will allow peptides to complete



their action. Fast inactivation by gastrointestinal enzymes rule out oral administration. In the blood, HDPs are bind and inactivated by serum albumins and low-density proteins, or degraded by serum enzymes. The strategy for overcoming this problem is employment of different delivery systems like liposomes, nanoparticles, nanotubes, etc (112).

In addition, although HDPs exert their antimicrobial action in non-receptor mediated mode (113), several mechanisms leading to diminution of susceptibility to HDPs have been described in some fungi (114) and bacteria (115). Those mechanisms include reduction of negative net charge of outer envelopes, up-regulation of proteolytic enzymes that degrade or modify HDPs, or engagement of efflux pumps. The same strategies are found to be exploited by cancer cells as well.

One more obstacle that has to be overcome is the high cost of peptide production. Additionally, chemical synthesis has to provide high yield and high purity of correctly folded peptides. Nowadays recombinant technology, using bacteria, yeast, plant, and mammalian cells as host cells, is employed in most for cost-effective production of large-scale peptides.

Currently, a number of investigations are directed toward designing peptide analogs with advanced performances. As the features and the functions of HDPs are determined by amino acid composition, modifications of peptide structure have been utilized to enhance desired functions and to modulate other properties, such as selectivity and stability (116-120). Excision, insertion, or substitution of amino acid residues in native peptides can effectively improve electrostatic attraction and consequently selectivity for microorganisms or cancer cells, along with stability and resistance to proteases. Another possibility that is intensively investigated is the creation of truncated analogs attained by the excision of biologically active regions of natural HDPs. In recent years combinatorial libraries are employed for computer-aided modeling and designing small peptides with better performances relative to naturally occurring HDPs (121, 122). A number of new HDP analogs with enhanced properties have been generated and tested in ongoing laboratory studies (123-125) and clinical trials. Omiganan, an indolicidin analog with antimicrobial and anti-inflammatory activities, is in phase III clinical trials for the prevention of catheter infections (126) and phase II trials for the treatment of papillomavirus-induced genital lesions (127). Pexiganan (a synthetic variant of magainin) is currently tested in phase III clinical studies for the treatment of infections of diabetic foot ulcers (128). PAC-113, derived from histatin found in human saliva, is investigated for the treatment of oral candidiasis in immunocompromised patients (129). hLF1-11, derived from human lactoferrin, along with antimicrobial activity, has demonstrated immunomodulatory properties (130), and currently, its efficacy in the protection and prevention of infection during allogeneic stem cell transplantation is assessing in clinical trials. Oncolytic peptide LTX-315, derived from the segment of bovine lactoferricin that has been identified as important for its anticancer properties, in phase I/II studies showed strong and selective anticancer activity (131, 132).

CONCLUSION

The emergence of antimicrobial drug resistance, lack of adequate treatment for some infectious diseases, insufficient efficiency of anticancer drugs, the increasing emergence of the diseases that originate from disturbed immunity, are unsolved problems of modern medicine. The abundance of HDPs in living organisms and the multiplicity of their functions in host defense offer the paramount possibilities. Despite the aforementioned problems, these peptides can be used at least as the models for designing improved, more efficient molecules, with necessary therapeutic properties.

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CONFLICT OF INTEREST

The author have no conflicts of interest to declare.

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