

Cationic Host Defence Peptides: Multifaceted Role in Immune Modulation and Inflammation

Ka-Yee Choi Leola N.Y. Chow Neeloffer Mookherjee

Manitoba Centre for Proteomics and Systems Biology, Departments of Internal Medicine and Immunology, University of Manitoba, Winnipeg, Man., Canada

Key Words

Inflammation • Host defence peptides • Antimicrobial peptides • Host defence • Immunomodulation

Abstract

Host defence peptides (HDPs) are innate immune effector molecules found in diverse species. HDPs exhibit a wide range of functions ranging from direct antimicrobial properties to immunomodulatory effects. Research in the last decade has demonstrated that HDPs are critical effectors of both innate and adaptive immunity. Various studies have hypothesized that the antimicrobial property of certain HDPs may be largely due to their immunomodulatory functions. Mechanistic studies revealed that the role of HDPs in immunity is very complex and involves various receptors, signalling pathways and transcription factors. This review will focus on the multiple functions of HDPs in immunity and inflammation, with special reference to cathelicidins, e.g. LL-37, certain defensins and novel synthetic innate defence regulator peptides. We also discuss emerging concepts of specific HDPs in immune-mediated inflammatory diseases, including the potential use of cationic peptides as therapeutics for immune-mediated inflammatory disorders.

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Introduction

Antimicrobial peptides were described more than 25 years ago. The peptides cecropins were isolated from the pupae of the moth *Hyalophora cecropia* in 1980, followed by the discovery of magainins from the skin of the African clawed frog (*Xenopus laevis*) and defensins from mammalian neutrophils [1]. Cationic antimicrobial peptides have been described in a wide variety of species including plants, insects, amphibians and mammals [2]. Research has predominantly been focused on the structures, functions and potential uses of these peptides as 'alternate' antibiotic-like therapeutics against infections. Various models are proposed for the microbicidal activities of antimicrobial cationic peptides, which include interaction with the negatively charged membrane components of microbes resulting in pore formation, induction of non-specific membrane permeabilization, binding to intracellular targets and disruption of bacterial biofilms [3, 4]. Natural cationic antimicrobial peptides can indeed protect against a wide range of infections, including bacterial, viral and parasitic [5–8]. However, it is now appre-

K.-Y.C. and L.N.Y.C. contributed equally to this paper.

Table 1. Examples of immunomodulatory functions of HDPs and IDR peptides

Biological function	Peptide	Ref. No.
Direct chemotaxis of cell types such as neutrophils, monocytes, DCs, T cells and eosinophils	LL-37, PR-39, HNP-1, HNP-2, hBD-1 and hBD-2	52 53 54 55 56
Induction of chemokine expression, e.g. MIP-1 β /CCL4, IL-8/CXCL8, MCP-1/CCL2 and MIP-3 α /CCL20	LL-37, hBD-2, hBD-3, IDR-1 and IDR-1002	57 58 11 40 10 59 15 22
Regulation of chemokine receptor expression, e.g. IL-8RB and CXCR4	LL-37	22
Suppression of neutrophil apoptosis	LL-37 and hBD-3	60 24
Induction of anti-inflammatory cytokines, e.g. IL-10 and IL-1RA	LL-37, IDR-1 and IDR-1002	20 35 10 22
Suppression of pro-inflammatory mediators, e.g. TNF- α , IL-1 β , IL-6, MIP-1 α and nitric oxide	LL-37, IDR-1 and IDR-1002	20 10 15 22
Activation of ERK1/2 and p38 MAPK signalling pathways	LL-37 and hBD-2	61 40 62 63
Modification of DC differentiation, endocytic capacity, phagocytic receptor expression and cytokine secretion	LL-37 and HNP-1–3	28 27 25 26
Enhancement of phagocytosis	HNP-1–3	64
Induction of autophagy	LL-37	18
Promotion of wound/vascular healing	LL-37, HNP-1, hBD-2 and hBD-3	65 66
Regulation of angiogenesis and arteriogenesis	LL-37 and PR-39	67 68
Activation and degranulation of mast cells	LL-37 and hBD-2–4	61 69
Regulation of T and B lymphocyte response	CRAMP	29
Adjuvant-like functions	BMAP-28, indolicidin, bactenecin 2A and IDR HH2	70 71 72
Protection against immune-mediated inflammation in synovial fibroblasts	IDR-1002	20
Protection against inflammatory shock or sepsis in vivo	LL-37	73 22

ciated that the direct microbicidal activity of certain cationic antimicrobial peptides, e.g. human LL-37 and human β -defensin (hBD)-2, is antagonized in the presence of physiological salt concentrations and in the presence of anionic polysaccharides [6, 9]. Moreover, two recent studies have conclusively shown that synthetic cationic peptides (based conceptually on natural antimicrobial cationic peptides) with no direct microbicidal properties can protect against various infections in vivo [10, 11]. Consistent with this, various studies, primarily in the last decade, have demonstrated that several cationic antimicrobial peptides have multifunctional roles as immune effector molecules, provide a link between innate and adaptive immunity, contribute to resolution of inflammation, maintain homeostasis and aid in wound healing [reviewed in 1, 12–14] (table 1). Thus, it is likely that the antimicrobial functions of cationic peptides are largely due to their role in host immunity [5, 6, 15]. Therefore, the term host defence peptide (HDP) is currently used for natural cationic peptides, which takes into account their overall biological functions both as antimicrobial and immunomodulatory compounds.

HDPs are gene encoded and vary in size, sequence and structure. They are typically 12–50 amino acids in length with a net positive charge of +2 to +9 and amphipathic with 40–50% hydrophobic residues [1]. HDPs are expressed both in circulating leukocytes and structural cells such as epithelial cells [16]. The structures of HDPs can be broadly classified as (1) amphipathic α -helix (e.g. cathelicidin LL-37), (2) β -sheet structures with disulphide bonds (e.g. protegrin), (3) extended structures (indolicidin) and (4) loop structures with one disulphide bond (e.g. bactenecin). To date, more than 1,200 HDPs have been described (<http://aps.unmc.edu/AP/main.php>). Defensins and cathelicidins are the two best characterized groups of HDPs in mammals. These peptides are expressed as larger precursor pre-pro-proteins, the structures of which allow for transcriptional and post-transcriptional regulation for tightly controlled expression [16]. The pre-pro-proteins are proteolytically processed by endogenous proteases to generate biologically active mature HDPs. For example, the sole human cathelicidin is expressed as an 18-kDa pre-pro-protein, hCAP18, which is cleaved by a serine protease to form the biologically active 37-amino acid, α -helical, amphipathic peptide LL-37. Depending on the specific HDP and the cell type, the expression of these peptides can be constitutive or inducible, and their expression is typically induced by pathogens or other inflammatory effectors such as cytokines [16, 17]. Examples of physiological concentrations

and sources of certain HDPs are shown in table 2. Recent studies have also demonstrated that metabolites, such as the active metabolite of vitamin D3, can induce the expression of human cathelicidin LL-37 and hBD-4, which in turn contributes to protection against the intracellular pathogen mycobacteria, possibly by aiding in the process of autophagy [18]. Early research with cationic HDPs was focused on their 'direct' antimicrobial activity. Interest in this area was propelled by the potential of developing novel antibiotic-like therapeutics, especially for antibiotic-resistant pathogens. However, research in the last decade has solidified the critical role of HDPs as immune effector molecules for both innate and adaptive immune responses.

In recent years, small synthetic cationic peptides have been designed based on the widely diverse sequences of HDPs used as templates [19]. These novel synthetic cationic peptides are known as innate defence regulator (IDR) peptides and typically exhibit enhanced immunomodulatory activities. IDR peptides described in recent studies (table 3) are essentially linear derivatives of cathelicidins, were selected based on their ability to stimulate chemokine production in human peripheral blood-derived mononuclear cells, were shown to protect against endotoxin and infectious challenge and, in contrast to the natural cathelicidins, exhibit limited cytotoxicities [10, 11, 20, 21]. In this review, we will focus on the immunomodulatory and anti-inflammatory role of HDPs defined so far, with emphasis on cathelicidins and novel synthetic IDR peptides, and further discuss the therapeutic potential of these peptides in immune-mediated inflammatory diseases.

Diverse Immunity-Related Biological Effects

Various studies have demonstrated that HDPs and their synthetic derivatives, IDR peptides, have multifaceted roles in immunity (summarized in table 1). A primary function associated with certain HDPs is in the facilitation of chemotaxis of immune cells. HDPs, e.g. human cathelicidin LL-37 and defensins human neutrophil peptide (HNP)-1, HNP-2, hBD-1 and hBD-2, can either directly or indirectly promote recruitment of different immune cells such as neutrophils, monocytes, immature dendritic cells (iDCs), T lymphocytes, eosinophils and neutrophils to the site of infection. Human cathelicidin LL-37, human α -defensins HNP-1 and HNP-2, murine β -defensins and porcine cathelicidin PR-39 are direct chemoattractants for cell types such as iDCs, neutrophils

Table 2. Examples of normal physiological concentrations of human HDPs

HDP	Source	Physiological concentration	Ref. No.
LL-37	plasma (circulating levels in healthy controls)	27.2 \pm 4.9 ng/ml	74
LL-37	maternal plasma	1.74 ng/ml	75
LL-37	cord blood (from normal delivery)	1.11 ng/ml	75
LL-37	neonatal tracheal aspirate	1–4 ng/ml	76
hBD-2	neonatal tracheal aspirate	250–750 pg/ml	76
HNP-1–3	saliva	1.3 \pm 0.22 μ g/ml	77
HNP-1–3	bronchoalveolar fluid	12.9 \pm 15 ng/ml	78
HNP-1–3	plasma	323 \pm 173 ng/ml	78

Table 3. Sequences of immunomodulatory IDR peptides

IDR peptide	Sequence	Ref. No.
IDR-1	KSRIVPAIPVSSL-NH ₂	10
IDR-1002	VQRWLIVWRIRK-NH ₂	11
IDR-1018	VRLIVAVRIWRR-NH ₂	21
IDR HH-2	VQLRIRVAVIRA-NH ₂	79

and T lymphocytes (table 1). Moreover, at low to modest physiological concentrations, HDPs such as LL-37, hBD-2 and hBD-3 can promote chemotaxis of immune cells indirectly by inducing the production of chemokines such as MCP-1/CCL2, MIP-1 β /CCL4, RANTES/CCL5, MIP-3 α /CCL20, Gro- α /CXCL1 and IL-8/CXCL8 from both immune cells and structural cells such as epithelial cells and gingival fibroblasts (table 1). Similarly, synthetic derivatives, i.e. IDR-1 and IDR-1002, can also induce chemokine production [10, 11]. Induction of chemokines by IDR peptides appears to be cell type dependent; for example, IDR-1002 can induce the production of chemokines from immune cells such as macrophages but not from stromal synovial fibroblasts [11, 20]. In addition, HDPs such as LL-37 can up-regulate the expression of chemokine receptors such as IL-8RB, CXCR4 and CCR2 in macrophages [22]. Human defensins hBD-1 and hBD-2 chemoattract dendritic cells (DCs) and T lymphocytes via the chemokine receptor CCR6, which is preferentially expressed on iDCs and memory T cells [23]. Thus, it can be summarized that a critical innate immune function of certain HDPs and IDR peptides is the promotion of immune cell recruitment to the site of infection, which

directly contributes to the clearance of infections. Another innate immune mechanism by which HDPs can protect against bacterial invasion is by prolonging the life span of neutrophils. It has been demonstrated that cathelicidin LL-37 and human defensin hBD-3 suppress neutrophil apoptosis (table 1). LL-37 induces the expression of the anti-apoptotic protein Bcl-XL and inhibits caspase-3 activity to suppress neutrophil apoptosis [24]. As neutrophils phagocytose and destroy infectious agents, suppressing apoptosis of neutrophils would aid in host defence mechanisms for resolution of bacterial infections.

Apart from innate immune effector functions, HDPs serve as an important link between the innate and adaptive immune systems. Human HDP LL-37 is a potent modifier of DC differentiation from circulating hematopoietic precursor cells and pre-DCs (monocytes and plasmacytoid cells) and can influence adaptive immunity by interaction with iDCs [25, 26]. LL-37 up-regulates the endocytic capacity of iDCs, modifies the expression of phagocytic receptors and enhances the secretion of Th1-inducing cytokines in mature DCs [26]. Similarly, defensins, e.g. human hBD-3 and HNP-1 to -3, can initiate the maturation of DCs, up-regulate the expression of co-stimulatory molecules and activate professional antigen-presenting cells [27, 28]. Interestingly, it has been demonstrated that effects on DCs mediated by the defensins HNP-1 to -3 are typically observed with low concentrations of defensins that do not have direct antimicrobial activity [28]. This observation also aligns with the recent paradigm that the anti-infective mechanism mediated by some HDPs is largely due to the modulation of host immunity. As iDCs can be activated by innate immune mediators and function as antigen-presenting cells to subsequently activate subsets of T and B lymphocytes for the development of the adaptive immune response, it may be proposed that one of the anti-infective mechanisms of HDPs is to influence the differentiation and subsequent change in DC phenotype to promote a robust adaptive immune response. Apart from influencing antigen-presenting cells for the initiation and polarization of adaptive immunity, certain HDPs were shown to have direct effects on lymphocytes. A recent study has demonstrated that the murine cathelicidin CRAMP can directly alter T and B cell responses and plays a role in regulating adaptive immune responses [29]. Similarly, human defensins HNP-1 to -3 can enhance the proliferation and cytokine responses of CD4⁺ T lymphocytes from murine spleen and Peyer's patches [30]. The ability of HDPs to influence adaptive immunity is further supported by studies that

show that the HDPs BMAP-28 and indolicidin and IDR peptides such as HH-2 have the potential to enhance production of antigen-specific serum antibodies, thus demonstrating adjuvant-like properties (table 1). HDPs are known to promote several other immune-related functions, which include promotion of wound healing, angiogenesis (capillary growth) and arteriogenesis (growth of pre-existing vessels), induction of mast cell degranulation and release of histamine and prostaglandin D₂ (see table 1 for specific examples). Unfortunately, the relationship between the structures of the various HDPs and how this relates to the diverse immunity-related functions mediated by these endogenous peptides is not yet resolved.

Research in the last decade has demonstrated direct effects of cationic peptides on immune cells such as macrophages, DCs and T cells, as well as on structural cells, e.g. epithelial cells. These peptides influence both innate and adaptive immune functions. The paradox associated with HDP-mediated immune functions is that even though these peptides promote innate immune effector mechanisms which include certain 'classical' inflammatory responses required for resolution of infections, they also contribute to the resolution of inflammation, thus protecting against the detrimental effect of excessive inflammation (discussed below). Overall, direct effects of HDPs on immune functions contribute to a wide range of biological effects from infection control to wound healing and maintaining homeostasis.

Modulation of Inflammation

Several *in vivo* models of infections and sepsis have shown that HDPs such as cathelicidins LL-37 and BMAP-28 and defensin hBD-2, as well as the synthetic IDR peptides IDR-1 and IDR-1002, can modulate host immune responses for the resolution of pathogen-induced inflammation [10, 11, 31–33]. In a recent study, we also demonstrated that IDR-1002 can suppress immune-mediated inflammation under conditions that contribute to tissue destruction in inflammatory arthritis [20]. The anti-inflammatory activity of these cationic peptides appears to be targeted and selective. HDPs such as LL-37 and hBD-3 have been demonstrated to target inflammatory pathways such as Toll-like receptor to NF- κ B in the presence of exogenous inflammatory stimuli, resulting in selective suppression of pro-inflammatory responses, while maintaining or enhancing critical immune responses such as cell recruitment and movement and crucial anti-inflam-

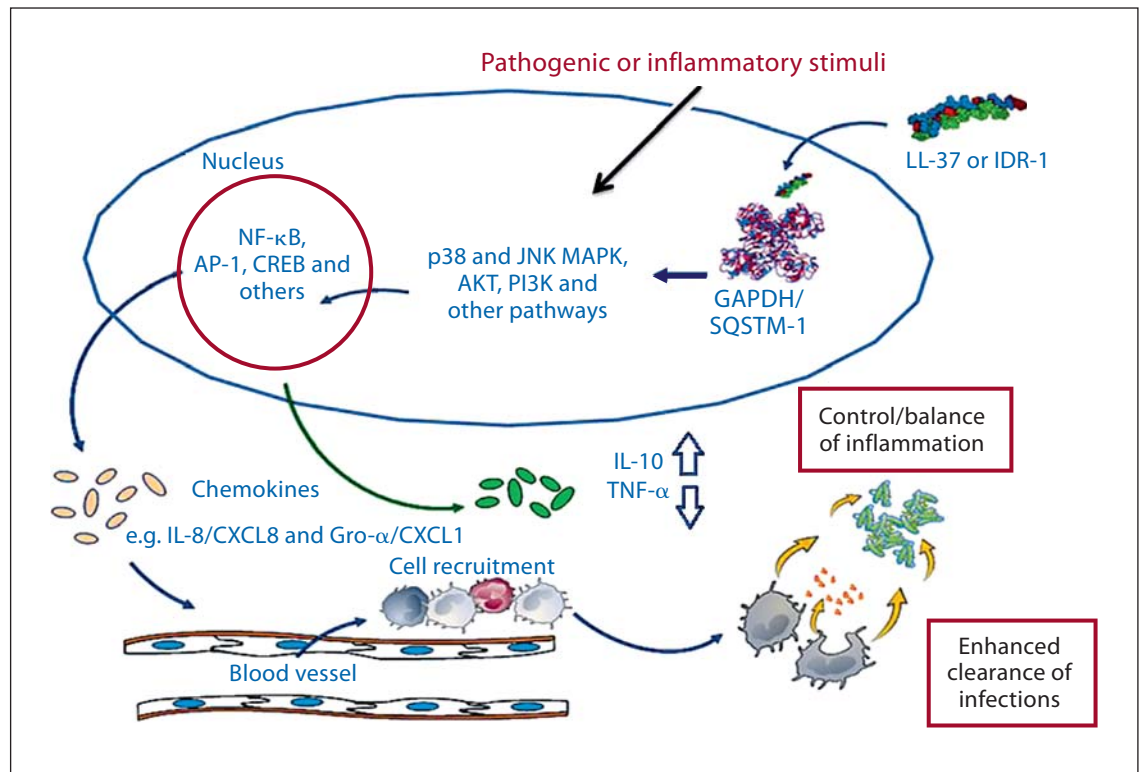


Fig. 1. Mechanism of immunomodulatory activity of LL-37 and IDR-1. Intracellular uptake of LL-37 and IDR-1 is hypothesized to be mediated by an atypical endocytic process. Interaction of these peptides with intracellular receptors such as GAPDH and sequestosome (SQSTM)-1 facilitates alteration of pathogen- or inflammatory mediator-induced signalling pathways, leading to alteration of transcription factor activity with different kinetics. The overall downstream effect is selective control of inflammatory responses and enhanced pathogen clearance. Modified from Mookherjee et al. [35, 40] and Yu et al. [41].

matory mechanisms [15, 34]. Similar selective anti-inflammatory activity has also been described for the IDR peptides IDR-1 and IDR-1002 [10, 11, 20]. Cathelicidin peptides such as LL-37, BMAP-28 and mimetics IDR-1 and IDR-1002 have been shown to suppress specific pro-inflammatory responses such as induction of tumour necrosis factor (TNF)- α , IL-1 β , NF- κ B1 (p105/p50), TNF- α -induced protein-2, MMP-3 and nitric oxide in the presence of either pathogenic or immune-mediated inflammatory stimuli, without suppressing production of certain chemokines that are required for cell recruitment and movement. In contrast, these peptides enhance or maintain crucial anti-inflammatory responses such as TNF- α -induced protein-3 (also known as A20), the NF- κ B inhibitor NF κ BIA, expression of IL-10 and the IL-1 antagonist IL-1RA [10, 11, 15, 20, 35–37]. Mechanistic studies to date have demonstrated that the anti-inflammatory or immunomodulatory activity of these peptides

is very complex and involves intracellular uptake, endocytic mobilization and interaction with several receptors, resulting in altered signalling pathways (such as NF- κ B, p38 and JNK MAPK, and PI3K) and transcription factor activities with different kinetics. Intracellular uptake has been shown to be important for the immunomodulatory activity of LL-37 [38], and intracellular uptake was also observed for IDR-1002 [20]. Even though putative cell surface receptors, including Gi-coupled protein receptors, have been described for both LL-37 and IDR-1002 [11, 38, 39], it is not yet determined whether the intracellular uptake of these peptides is receptor mediated. In addition, intracellular proteins, e.g. GAPDH and sequestosome-1, were demonstrated to be direct interacting protein partners or receptors for the HDP LL-37 and IDR peptide IDR-1, respectively, thus contributing to peptide-mediated immune responses [40, 41]. Taken together, it may be speculated that these peptides interact with mul-

Table 4. Altered expression of HDPs in immune-mediated inflammatory diseases

Inflammatory disease	Induction	Suppression	Ref. No.
Crohn's disease	–	hBD-2, hBD-3 and LL-37	80
RA and osteoarthritis	LL-37 and hBD-3	–	81
Systemic lupus erythematosus	LL-37	–	82
Asthma	–	hBD-2	83
Chronic obstructive pulmonary disease	hBD-1	–	84
Bronchiolitis obliterans syndrome	hBD-2, HNP-1–3 and LL-37	–	85 86
Atopic dermatitis	–	dermcidin and LL-37	87 88
Psoriasis	hBD-2 and LL-37	–	43
Rosacea	LL-37	–	89

multiple receptors, with the interactions mediating different events dependent on cell type and perhaps the exogenous stimuli. Peptides such as LL-37 and IDR-1 may be taken up by an atypical endocytic pathway, possibly similar to that described for other cationic cell-penetrating peptides [25, 38], followed by interaction with intracellular partners such as GAPDH and sequestosome-1, leading to the alteration of immune signalling mechanisms and resulting in the modulation of inflammatory responses in the presence of exogenous inflammatory stimuli (fig. 1). Specific receptor interaction of HDPs and IDR peptides and how this mediates different immune functions is not yet completely resolved. The targeted and selective anti-inflammatory activity described for specific HDPs (e.g. LL-37 and BMAP-28) and IDR peptides (IDR-1 and IDR-1002) overall results in a net balancing of inflammation and maintains the protective anti-infective responses without excessive harmful inflammation. Therefore, these peptides may prove to be valuable therapeutic agents for controlling the destructive effects of inflammatory diseases without abrogating host defence mechanisms.

Distribution and Potential Application of HDPs in Immune-Mediated Inflammatory Diseases

Inflammation is an essential element of innate immunity, a breakdown in the regulation of which contributes to progressive tissue and organ damage associated with the pathology of a wide range of chronic inflammatory diseases such as rheumatoid arthritis (RA), asthma, chronic obstructive pulmonary disease, inflammatory bowel disease and atherosclerosis. The etiology and molecular mechanisms of these diverse chronic inflammatory diseases are poorly understood. Altered expression of various HDPs has been reported in immune-mediated chronic inflammatory diseases (summarized in table 4). Human hBD-2 is suppressed in Crohn's disease and allergic airway inflammation but found to be elevated in psoriasis (table 4). Likewise, cathelicidin LL-37 is suppressed in Crohn's and atopic dermatitis but elevated in systemic lupus erythematosus (SLE) and RA (table 4). A recent study has also demonstrated that patients with SLE develop autoantibodies to LL-37 and proposed that LL-37-self DNA complex is crucial in the chronic activation of plasmacytoid dendritic cells central to the pathogenesis of SLE [42]. Aggregates of LL-37 and extracellular self-DNA fragments have been shown to be taken up by plasmacytoid dendritic cells, triggering a robust interferon response [43]. These studies indicate that dysregulation of certain HDPs may be linked to the pathology of chronic inflammatory diseases.

A common element associated with chronic inflammatory diseases is the dysregulation of the cytokine and chemokine balance. Several critical pro-inflammatory cytokines are elevated in chronic inflammatory diseases such as TNF- α , IL-1 β , IL-15 and IL-23. Therefore, current therapeutic strategies for these diseases include targeting inflammatory cytokines such as TNF- α [44]. However, these current therapies often result in an increased risk of infections, including reactivation of tuberculosis, and the potential for development of cancers due to comprehensive immune suppression [45]. Therefore, there is a need to explore alternate therapeutic strategies, ideally a therapy that can suppress the elevated inflammatory responses without neutralizing immune mediators required for the resolution of infections and neoplasms. As discussed above, certain HDPs and IDR peptides can selectively regulate the inflammatory process while maintaining responses required for the resolution of infections. The ability of these peptides to result in a net balancing of inflammation, without compromising host immunity required for resolution of infections, makes them attractive

candidates as potential therapeutics for controlling the destructive effects of the inflammatory processes in immune-mediated chronic inflammatory diseases.

Recent studies have demonstrated that some HDPs and IDR peptides can alter immune-mediated cellular responses. For example, human cathelicidin LL-37 differentially alters cytokine-induced responses in blood-derived mononuclear cells, synergistically enhances certain responses induced by IL-1 β and GM-CSF [46] and, in contrast, suppresses the interferon- γ -induced cellular response which is critical in Th1-polarized immune responses [47]. The duality of the pro- and anti-inflammatory properties of LL-37 was also demonstrated in psoriasis, which is a Th1-mediated inflammatory autoimmune disease, and it was hypothesized that LL-37-related peptides can act both as regulators and effectors in psoriasis [48]. In addition, a recent study has shown that LL-37 can interfere in the activation of AIM2 inflammasome, IL-1 β production and autoimmune inflammation in psoriasis [49]. Based on these studies, it can thus be speculated that these HDPs or their synthetic IDR derivatives may be beneficial for the development of therapeutics for chronic inflammatory diseases, perhaps with a bias toward Th1-polarized chronic inflammatory diseases, which could also be peptide dependent. Consistent with this, the cathelicidin HDP rCRAMP was shown to heal gastric ulcers in an animal model of colitis [50]. Similarly, we have recently demonstrated that a 12-amino-acid cationic IDR peptide, IDR-1002, designed from a bovine cathelicidin, can indeed selectively limit immune-mediated pro-inflammatory responses, under conditions such as those that contribute to tissue destruction in RA [20], which is also largely a Th1-polarized autoimmune inflammatory disease. The IDR-1002 peptide exhibits a targeted and distinct immunomodulatory activity on both immune cells, e.g. macrophages and neutrophils (demonstrated both *in vitro* and *in vivo* studies) [11], and stromal cells, e.g. human fibroblast-like synoviocytes [20]. In addition to the early proof-of-concept studies discussed above, a cationic peptide therapeutic, Omiganan (Migenix Pharmaceuticals), has been demonstrated to be effective against rosacea in phase II clinical trials. Even though investigating the use of HDPs and their synthetic IDR derivatives for controlling the destructive effects of sustained inflammation in chronic inflammatory diseases is in its infancy, these early studies have shown promise and therefore warrant further exploration. However, there are multiple challenges associated with the development of cationic peptide therapeutics. The first involves bioavailability. Cationic peptides are

potentially vulnerable to proteases, for example trypsin-like enzymes that have a propensity for basic residues, which is a characteristic feature of cationic HDPs. Several studies have provided solutions to circumvent this problem, such as the use of D-amino acids, chemical modifications of the cationic peptides to make them protease resistant, use of a non-peptide backbone and formulations using liposomes to mask the peptides [51]. Secondly, there is the issue of potential toxicity; however, it appears that small IDR peptides designed from natural HDPs have significantly lower toxicity [10]. There is a lack of pharmacokinetic or toxicology data for cationic peptides, and this is essential for further development of these peptides as therapeutics. The third challenge is the cost of goods, as the cost of manufacturing synthetic peptides is significantly high. Exploring new methods for producing recombinant cationic peptides and designing smaller bioactive IDR peptides may be effective in lowering the cost for cationic peptide therapeutics. Overall, the development of cationic peptide therapeutics is focused on designing small IDR peptides, based conceptually on HDPs, with optimized bioactivity and lower cytotoxicity.

Summary

HDPs are widely distributed natural molecules that play a critical role in anti-infective immunity. Research in the last decade has demonstrated that the biological roles of natural HDPs are very diverse and influence multiple aspects of immunity. It is now well appreciated that the mechanism of the multifaceted role of HDPs in immunity is complex, involving various signalling pathways, and is often determined by physiological conditions, the cellular environment and the extracellular milieu. Specific interacting cellular partners or receptors for various HDPs or IDR peptides, the process of endocytic uptake of the peptides and how this mediates diverse immune functions need to be completely resolved. Moreover, there is limited understanding of the structure and immunomodulatory activity relationship for these peptides. Nevertheless, the paradoxical effect of certain HDPs in enhancing innate immune responses to control infections and at the same time their ability to control inflammation makes these peptides attractive candidates for both anti-infective and anti-inflammatory therapeutics. The multifaceted roles of HDPs and their synthetic mimics, i.e. IDR peptides, have resulted in research into their use as antimicrobials, anti-inflammatory agents and adjuvants and in wound healing. However, there are

some challenges in the development of cationic peptide therapeutics, including limited bioavailability, associated toxicity and high manufacturing costs. Overall, cationic HDPs and IDR peptides represent an exciting avenue in immunomodulatory therapeutics, which, although still in its infancy, warrants further exploration.

Disclosure Statement

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