Chapter 1

Immunomodulatory Cationic Peptide Therapeutics: A New Paradigm in Infection and Immunity

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Natural cationic host defence (antimicrobial) peptides are widely distributed gene encoded molecules with diverse structures. There are more than 1200 natural Host Defence Peptides (HDPs) described to date. Due to the multifunctional roles defined for such peptides there is a keen interest in the potential therapeutic applications of HDPs and their synthetic mimics, Antimicrobial peptides and Innate Defence Regulator (IDR) peptides. These peptides constitute two broad classes of potential therapeutics; (i) with direct antimicrobial and/or anti-biofilm activity, and (ii) with immune-modulating and/or anti-inflammatory activity. Exploiting the immunomodulatory functions of these peptides represents a new therapeutic approach for resolution of infections and inflammatory disorders.

Introduction

More than two decades ago cationic peptides, discovered in the skin of frogs, lymph of insects and in human neutrophils, were demonstrated to be actively antimicrobial compounds (*1*). Even though cationic host defence (antimicrobial) peptides were initially defined as natural microbicidal agents, it is now increasingly appreciated that collectively these peptides are multifunctional immune effector

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and regulatory molecules that protect against infections, maintain homeostasis, support healing while suppressing potentially harmful inflammation, and provide a functional link between innate and adaptive immunity (*2*). Therefore here we use the collective term Host Defence Peptides (HDPs), which accurately encompasses their diverse biological functionality while the more common term Antimicrobial peptides (AMPs) is used only to describe direct antibiotic activity.

HDPs are gene encoded ribosomally synthesized molecules, typically 12-50 amino acids in length with a net positive charge ranging from +2 to +7 with ≥ 30 % hydrophobic residues (*3*). Based on their conformational structures in membrane-like environments, these peptides can be broadly divided into four categories; amphipathic α-helix (e.g. cathelicidin CRAMP), β-sheets stabilized by disulphide bridges (e.g. protegrin), peptides with extended structures (e.g. indolicidin), and peptides with loop structures (e.g. bactenecin) (*4*) (Fig. 1). HDPs are widely distributed in Nature, being found in plants, insects and mammals. Well characterized families of HDPs in vertebrates are the cathelicidins and defensins defined by their conserved prepro sequences and semi-conserved disulphide arrays respectively. HDPs are expressed in cell types such as phagocytic leukocytes, epithelial cells and keratinocytes, and in a most tissues and body fluids (*5–8*). There are more than 1200 natural HDPs described to date, with >900 defined from eukaryotes (http://aps.unmc.edu/AP/main.php). The vast repertoire of natural HDPs thus provides an extensive template for the design of short synthetic derivatives. These synthetic derivatives can be designed to maintain or enhance biological activity with limited associated host cytotoxicity and are known as Antimicrobial (AMPs) or Innate Defence Regulator (IDR) peptide (*9–11*). Traditional development approaches have concentrated on developing directly antibiotic, topically-applied AMPs. However there is an increasing appreciation that the IDR peptides show much more promise for systemic usage. As these peptides protect against a wide range of infections, and confer anti-infective immunity by modulating innate and adaptive immune responses, there is a growing interest in the therapeutic development.

AMPs are well described elsewhere (*1–4*, *12*). Basically there have been a broad range of clinical trials on these molecules that effectively mimic two well established bacterial-derived cationic peptide drugs polymyxin B and gramicidin S. However although one, Omiganan, showed statistically significant activity in Phase III clinical trials as a topical agent to prevent catheter colonization and tunnel infections, none have as yet been awarded new drug approval. Newer methods of peptides screening and production are leading to broad spectrum antimicrobial peptides with excellent *in vitro* activity that are short and/or protease resistant (*1*). The basis for protection may be more complex than previously thought since Omiganan has also demonstrated significant efficacy in Phase II trials against Rosacea, an inflammatory non-infectious skin condition. This appears to indicate that even AMPs have the potential to work as immune modulators. Other avenues for exploitation of the action of cationic peptides on bacteria include the ability of some peptides to reduce biofilm formation at sub-MIC concentrations (*13*) and their ability to retain antimicrobial activity even when covalently bound to surfaces (*14*).

There are at least three avenues where the potential of immunomodulatory HDPs can be exploited for therapeutic development. It has been demonstrated that HDPs and IDR peptides with no direct microbicidal activity can protect against a wide variety of infections, through selective modulation of the innate immune response (*9*, *15*, *16*). This provides a distinct advantage in developing these molecules as therapeutics to treat infections that can circumvent problems of antimicrobial resistance. Non-microbicidal cationic peptides that protect against infections through their immunomodulatory properties do not exert selective pressure to develop resistance as they are directed at the host rather than the pathogen and work by selectively enhancing host immune mechanisms. It is extremely likely that such a treatment would be developed to treat infections as an *adjunctive* therapy in combination with conventional antibiotics (*16–18*). Secondly, the ability of HDPs and IDR peptides to suppress certain pro-inflammatory pathways and up-regulate anti-inflammatory mechanisms while maintaining efficient innate immune responses (*9*, *16*, *19*), makes them useful as potential anti-inflammatories for acute and chronic inflammatory disorders, and to suppress pathogen-induced inflammation. These could serve as therapeutics agents that might limit the escalation of inflammation without compromising host immunity. Third, HDPs and IDR peptides, through their action on innate immunity, have been demonstrated to modulate the adaptive immune response (*20–22*) and thus can be developed as potential adjuvants for vaccines (*11*, *23*, *24*). Table I summarizes some of the cationic peptide-based therapeutics in clinical development. In this chapter we discuss design strategies for IDR peptides, and summarize the progress and challenges associated with the development of HDPs and IDR peptides as anti-infective and immunomodulatory therapeutics and adjuvants.

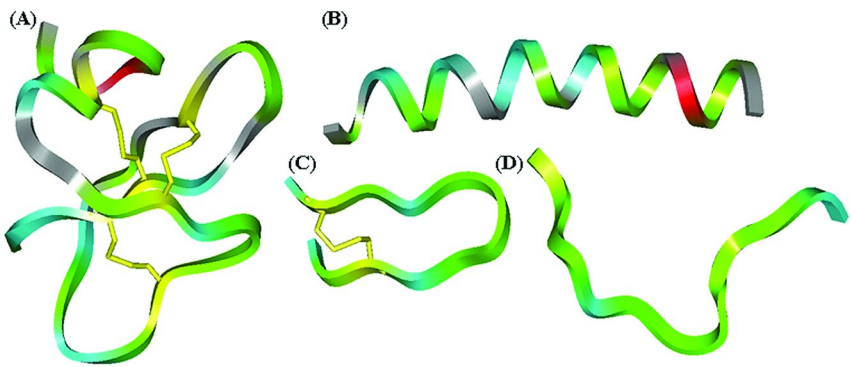

Figure 1. ***Structures of cationic peptides.*** *Cationic peptides can be broadly divided into four categories;* ***(A)*** *peptides with loop structures,* ***(B)*** *amphipathic α-helix,* ***(C)*** *β-sheets stabilized by disulphide bridges and* ***(D)*** *peptides with extended structures.*

Table I. Host defence peptide-based therapeutics in clinical development (*84*)

Peptide-Based Drug	***Company***	***Trial Phase***	***Proposed Clinical Use***
Omiganan (MX-226 / MBI-226)	Migenix	III & II	Treatment of catheter infections, topical antiseptic, and anti-inflammatory for acne and rosacea.
Pexiganan acetate (MSI-78)	MacroChem	III	As topical antibiotic.
Iseganan (IB-367)	Ardea Biosciences	III	Treatment of oral mucositis in radiation therapy patients.
Delmitide (RDP58)	Genzyme	Post II	Treatment of inflammatory bowel disease.
hLF1-11	AM Pharma	I / II	Treatment of fungal infections and bacteremia in immunocompromised patients e.g. patients undergoing hematopoetic stem cell transplants.
Opebacan	Xoma	I / II	For endotoxemia in recipients of hematopoetic stem cell transplants.
PAC-113	Pacgen Biopharmaceuticals	II	Treatment of fungal infections.
AP-214	Action Pharma A/S	II	Treatment of sepsis and use in post-surgical organ failure.
CD-NP	Nile Therapeutics	II	For use in organ failure.
Ghrelin	Miyazaki University, Japan Papworth Hospital, UK.	II	Treatment of airway inflammation, chronic respiratory infections and in cystic fibrosis.
OP-145	OctoPlus N.V.	II	Treatment of chronic bacterial otitis media.
Xoma-629	Xoma	IIa	Impetigo.
CZEN-002	Zengen	IIb	Treatment of vulvovaginal candidiasis.
Hexapeptide-7	Helix BioMedix	I	For wound healing and skin regeneration.
Vasoactive intestinal peptide (VIP)	State University of New York	I	Treatment of respiratory tract infections and of sepsis.

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Table I. (Continued). Host defence peptide-based therapeutics in clinical development (*84*)

Peptide-Based Drug	*Company*	*Trial Phase*	*Proposed Clinical Use*
IMX942	Inimex	Ia	Treatment of nosocomial infections and in febrile neutropenia.
PMX-30063	PolyMedix	Ib	As an antibiotic.

Synthetic Variants: Antimicrobial and Innate Defence Regulator (IDR) Peptides

Traditional approaches to peptide design have involved systematic variations in the structure of a base molecule, usually to optimize a limited range of parameters such as cationic charge, hydrophobicity, and hydrophobic moment. When performed in conjunction with structural modelling or structure determination of the base molecule, such design methods can yield useful increases in activity (*1*). Although this approach was used for almost all clinically developed peptides to date, there are some limitations for this approach including (i) each amino acid change in a small peptide yields a change in secondary structure making it nearly impossible to accurately relate activity to structure, this is especially concerning since the same pair of adjacent amino acids will have very different atomic properties when sited within different secondary structures (e.g. α-helices, β-sheets or turns, polyproline helices and random structures, all of which have been found in natural HDPs) (*25*), (ii) the starting structure effectively guides the final output, and to some extent limits the value of this approach, as it limits molecular diversity, (iii) such optimizations are usually limited to tens of peptides whereas up to 10,000 compounds are required to enable development of successful drugs, and (iv) there are many more structural parameters that are influential than the three properties discussed above (*26*). A game changer was the development of technologies for much higher throughput, cost effective production of small peptides using robotic synthesis on peptide arrays (so called SPOT synthesis) (*27*). This enables broad screening and the rapid development of optimized peptides when used in combination with newer approaches involving chemi-informatics. In these procedures, the structural properties of peptides (determined by a series of conventional and inductive "descriptors" that are calculated from the primary sequence and are sensitive to structure) were related, using machine learning approaches, to measured activities, and used to quite accurately predict the activity of a 100,000 virtual peptides. Application of these procedures led to the identification of 9 amino acid peptides with broad spectrum activity against many pathogens, superior activity against highly resistant Superbugs than conventional agents, and an ability to protect against systemic infections (*26*).

Similar procedures have not been pursued with IDR peptides and traditional and random design approaches predominate. In this case, we have found that chemokine induction by monocytes is a reasonable surrogate for anti-infective immunomodulatory activity (*28*), whilst suppression of LPS-induced TNF-α production works to screen for anti-inflammatory properties (*19*).

Cationic Peptides as Broad Spectrum Antimicrobials

Many HDPs including cathelicidins, defensins and hepcidin, have been demonstrated to protect against bacterial, viral and parasitic infections (*15*, *29–34*). Several studies provide evidence to correlate the expression of HDPs with susceptibility or resistance to bacterial infections (*35–37*). Although these studies are often interpreted as being due to direct antimicrobial activity, the data often does not discriminate between this and stimulation of protective innate immunity. Lack or low expression of certain HDPs in humans results in increased susceptibility to infections. For example, patients with morbus Kostmann have deficiencies in cathelicidin-LL37 and α-defensins HNP1-3 and suffer from frequent periodontal infections (*36*). Similarly, patients with specific granule deficiency display an almost complete deficiency of defensins, and suffer from frequent severe bacterial infections (*38*). In contrast, in animal studies, mice expressing human LL-37 or human defensin 5 (HD-5) show increased resistance to bacterial challenge (*37*, *39*). Similarly, the lantibiotic duramycin has been demonstrated to be effective as a potential treatment in cystic fibrosis (*40*). It has also been suggested that vitamin D-mediated induction of human HDP LL-37 contributes to innate immune responses to infections and wounds, in that the CAMP gene which encodes for human cathelicidin LL-37 was shown to be a direct target of vitamin D / vitamin D receptor complex and increased susceptibility to infections associated with vitamin D deficiency may thus be due to the lack of appropriate HDP expression (*41–43*). Taken together it is apparent that the absence of one or more HDPs leads to increased susceptibility to infections, while induction or exogenous introduction of HDP protects against infections.

In general, when HDPs are present at very high concentrations, such as in the granules of phagocytes, in intestinal crypts or adjacent to degranulating phagocytes, they might have direct antimicrobial properties (*15*, *16*, *21*); however most HDPs are strongly antagonized by physiological divalent cation concentrations (2 mM Mg^{2+}, Ca^{2+}) and anionic polysaccharides like heparin (*15*). Mechanistically, polycationic AMPs work against Gram negative bacteria by binding to the polyanionic lipopolysaccharide (LPS) on the surface bilayer of the bacterial outer membrane, followed by translocation by the self promoted uptake mechanism (*44–47*). Then they bind to the outer monolayer of the cytoplasmic membrane and at appropriate concentrations trigger localized perturbations of the membrane, as described in a variety of different models (*47*). The actual lethal event differs between peptides and target organisms and seems to involve considerable complexity, involving often several of the following: disruption of membrane integrity, collapse of membrane potential and loss of intracellular

pH homeostasis, interference with membrane associated biosynthetic enzymes involved in e.g. cell wall biosynthesis and cell division, and/or translocation into the cell and inhibition of cytoplasmic functions including macromolecular synthesis and the function of specific enzymes (*47*, *48*). These events all likely involve relatively low affinity interactions with targets that complement the cationic amphipathic HDPs in being anionic or hydrophobic, explaining the ionic inhibition of HDP activity. Therefore, it has been proposed that for those HDPs that are strongly antagonized by physiological salt concentrations or are present in relatively low levels, their anti-infective protective functions might be largely due to the modulation of immune responses in the host (*15*, *17*, *19*, *29*, *49*), since immunomodulatory functions occur readily at physiological salt concentrations (such as those found in tissue culture medium and *in vivo*). It has also been demonstrated that a synthetic IDR-1 derivative of bovine bactenecin, without any direct antimicrobial activity, confers protection in several animal models of bacterial infection (*9*). Similarly in a mouse model of *Pseudomonas aeruginosa* infection, a truncated version of human cathelicidin peptide LL-37 was able to decrease the level of bacterium-induced injury (*50*). Other immunomodulatory IDR peptides, in particular IDR-1002, have been demonstrated to be protective against a range of infections in animal models (*10*). Consistent with this, a wide range of immunomodulatory functions have been demonstrated to be mediated by natural HDPs and IDR peptides both *in vitro* and in animal models, including direct and indirect recruitment of critical immune cells, modulation of cytokine and chemokine production, anti-endotoxin and anti-inflammatory activities, barrier repair and wound healing, and modulation of dendritic cell differentiation and T-cell polarization (*9*, *10*, *12*, *19*, *22*, *51–53*). Mechanistic studies have demonstrated that such interactions are complex with a number of receptors, intracellular uptake, and several pathways and transcription factors controlling the expression of hundreds of genes.

The immunomodulatory functions of HDPs contributing to anti-infective immunity cannot be considered in isolation as HDPs have been shown to work in synergy with other immune effector molecules. For example, HDP such as human LL-37 can function synergistically with cytokines including the granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-1β (*54*, *55*). The presence of GM-CSF increases the magnitude of LL-37-induced phosphorylation of extracellular signal-regulated kinase1/2 (ERK1/2) and p38 MAPK in peripheral blood-derived monocytes and thus may reduce the threshold concentration of LL-37 required to activate these pathways (*15*, *54*). MAPK ERK1/2 and p38 are involved in various immune responses including initiation of innate immunity and activation of adaptive immunity (*56*). Therefore, it is likely that during an infection, HDPs can act synergistically with specific cytokines to amplify immunomodulatory effects required for the overall resolution of infections.

Cationic Peptides as Selective Immunomodulatory Agents

The biological roles of HDPs include a wide range of immunomodulatory functions (*12*, *51*). It is thus not surprising that dysregulation or altered HDP expression has been linked to various immune-mediated chronic inflammatory diseases. For example decreased expression of human β-defensins is associated with the pathogenesis of inflammatory bowel disease, Crohn's in children and psoriatic plaques (*57–59*). Similarly, reduced expression of cathelicidin LL-37 and dermcidin are linked to increased risk of atopic dermatitis (*60*, *61*). In contrast, over expression of LL-37 is linked to psoriasis (*62*), and increased accumulation of defensins is seen in the synovial fluid of patients with rheumatoid arthritis (*63*). Simiarly several studies using transgenic mouse models and bioengineered tissues have demonstrated that cationic peptides not only can protect against various infections but also contribute significantly to resolution of inflammation (reviewed in Dybvig et al, 2011 (*64*)). Consistent with this several studies have shown that HDP and IDR peptides can 'selectively' regulate inflammatory processes, enhancing certain pro-inflammatory pathways such as chemokine expression, immune cell recruitment, cellular differentiation and other responses required for the resolution of infections, while suppressing pro-inflammatory cytokine production in response to bacterial TLR agonists and up-regulating anti-inflammatory mechanisms (*9*, *10*, *16*, *19*, *23*, *49*, *53*, *65–67*) (Fig. 2).

Previous studies have demonstrated surface binding, cellular uptake and endocytic mobilization of HDP in monocytic cells and epithelial cells, and has suggested that cellular uptake is essential for the immunomodulatory activities such as chemokine induction (*68*, *69*). Both intracellular interacting protein partners, like SQSTM-1 and GAPDH, and cell surface receptors, including various Gi-coupled receptors, have also been described for HDP such as cathelicidin LL-37 and IDR peptides (*10*, *68*, *70*, *71*). However, the mechanisms of receptor interaction for HDP and IDR peptides are yet to be completely resolved. It is possible that there are a variety of moderate affinity receptors rather than a single high affinity receptor. After binding to the membrane or surface receptors, an atypical endocytic uptake pathway appears to facilitate the internalization of HDP and IDR peptides, in a manner analogous to the structurally related cell penetrating peptides (*69*, *72*, *73*), followed by interaction with the intracellular receptors (*68*, *70*). These interactions appear to facilitate modulation of immune signalling pathways, both in the absence and presence of a subset of endogenous immune effectors or exogenous bacterial TLR agonists, resulting in the 'selective' modulation of inflammatory responses.

Endotoxin-induced specific inflammatory responses such as TNF-α, IL-1β and IL-6 production, NF-κB1 (p105/p50) and TNF-α-induced protein-2 (TNFAIP2) expression, and the activation of NF-κB/Rel family of transcription factors, which plays a critical role in the inflammatory process are significantly suppressed by HDPs and IDR peptides (*9*, *19*, *66*). HDPs can also influence key signalling pathways such as MAPK ERK1/2, PI3 kinase, and AP-1 etc (*66*). In contrast, HDP were shown to maintain or enhance cellular responses that antagonize inflammation such as the expression of TNF-α-induced protein-3 (TNFAIP3/A20) and anti-inflammatory mediators such as IL-10, and the

NF-κB inhibitor NFκBIA (*9*, *10*, *19*, *66*). HDP can induce the production of chemokines, for example MCP-1, IL-8 and several others, and up-regulate the surface expression of chemokine receptors such as for example IL-8RB and CXCR-4, in various cell types suggesting that these peptides promote immune cells recruitment (*52*). Indeed, HDP can either directly or indirectly promote recruitment of a variety of immune cells including neutrophils, monocytes, immature dendritic cells, mast cells, T-cells, eosinophils and neutrophils (*16*, *21*, *23*, *71*). In addition, HDPs can directly influence cellular differentiation and modification. For example, human cathelicidin LL-37 was shown to up-regulate the endocytic capacity of premature dendritic cells and modify the expression of phagocytic receptors and enhance the secretion of Th-1 inducing cytokines in mature dendritic cells (*22*). It has also been suggested that HDPs, in particular cathelicidin peptides, can influence brain immunity by stimulating glial cell activation, cytokine production and aid brain cell protection by inducing neurotrophic factors (*74*). Other immunomodulatory roles associated with HDPs include mast cell stimulation (*75*), promotion of angiogenesis (*76*) and wound healing (*77*).

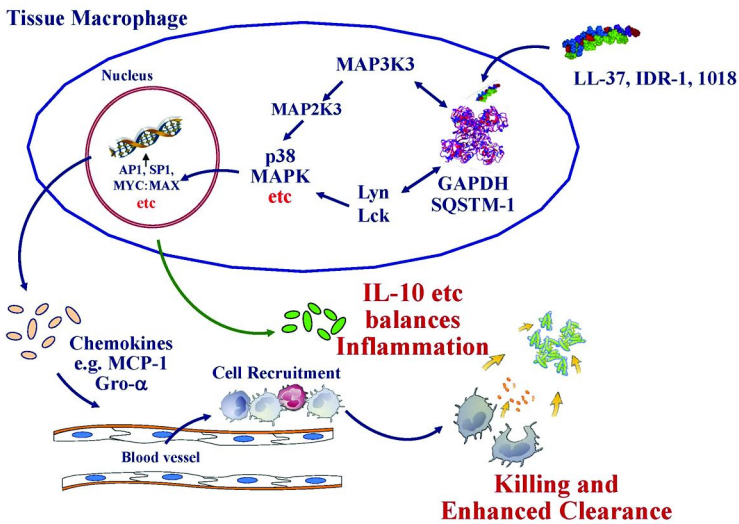

Figure 2. ***Mechanism of action of immunomodulatory HDPs and IDR-peptides.*** *Internalization of HDPs and IDR peptides is facilitated by an atypical endocytic uptake, followed by interaction with the intracellular receptors. These interactions appear to facilitate modulation of various immune signalling pathways, mediates various immunomodulatory responses and overall results in the 'selective' modulation of inflammatory responses. Modified from J. Immunol. 183, 2688-2696 (2009), Mol. Biosystems 5, 483-496 (2009) and J. Biol. Chem. 284, 36007-36011 (2009).*

Overall, the diverse and paradoxical immunomodulatory functions exhibited by HDP can lead to rebalanced / controlled inflammation with a net anti-infective response in the host. This suggests that HDPs and IDR peptides might also be promising therapeutic agents to treat immune-mediated inflammatory disorders. An important consideration regarding current therapeutics used for chronic inflammatory diseases is the increased associated risk of infections and neoplasms due to compromised immune functioning (*78*, *79*). The targeted anti-inflammatory function of HDPs and IDR peptides makes them attractive candidates as potential therapeutics for chronic inflammatory disorders. A distinct advantage of developing these peptides as anti-inflammatory agents is their potential to selectively suppress escalation of inflammation without hampering innate immune responses required for resolution of infections.

Cationic Peptides as Vaccine Adjuvants

The ability of HDPs to modulate aspects of the innate immune system has made them potential candidates as vaccine adjuvants, since it is well known that innate immunity instructs adaptive immunity. Thus the appropriate stimulation of innate immunity promotes a transition to enhanced and appropriately polarized antibody or cellular immune responses to foreign antigens. The HDP activities mentioned above involving the regulation of cytokine responses, enhancing and modulating DC and lymphocyte recruitment and maturation, as well as T_H cell polarization, all play a major role in the development of an effective adaptive immune response. Animal studies have shown that the use of human neutrophil defensins and LL-37 as adjuvants led to significant enhancement of adaptive, antigen-specific, immunity (*80*, *81*). Recent studies have investigated the effects on adaptive responses by IDR peptides used in combination with CpG ODNs. Indolicidin, a bovine HDP, and its analogs when co-formulated with CpG ODN and polyphosphazene, significantly enhanced antigen-specific humoral responses and promoted cell-mediated immunity in cattle, compared to CpG ODN with emulsigen®, an adjuvant that is often used in veterinary vaccines (*82*). In this instance it was suggested that the polyphosphazene created a depot, peptides enhanced immune cell recruitment, and CpG led to activation of those immune cells. Similarly, IDR-HH2 peptide in complex with CpG ODN, within a pertussis toxoid vaccine formulation, synergistically induced the production of chemokines and significantly enhanced the production of protective toxoid-specific antibodies in mice (*83*). This formulation demonstrated responses indicative of a balanced T_H1/T_H2 response. Intriguingly, potent immune responses were observed even after a single application of adjuvanted pertussis toxoid and animals became protected against pertussis infections with this formulated vaccine. These studies demonstrate the strong potential for using HDPs and IDR peptides as vaccine adjuvants to promote an effective, long-lasting and balanced protective response.

Emerging Technologies Facilitating the Development of Cationic Peptide Therapeutics

AMPs have already navigated their way through clinical trials and although they have shown efficacy in Phase III trials, none has to date obtained new drug approval. IDR peptides are also in clinical trials Phase I/II (*84*). Some challenges in the development of AMP and IDR peptide therapeutics are bioavailability, potential toxicity, usage systemically, and manufacturing costs. These areas that need to be addressed for the development of cationic peptides as viable therapeutics. Some HDPs may be liable to proteases (*12*), for example chymotrypsin-like enzymes can attack proteins at basic residues that are a hallmark feature of HDPs (*12*). IDR peptides appear to be effective even in the face of this concern. Several solutions to resolve this issue has been proposed. For example, the use of unusual or D-(rather than natural L-) amino acids, the development of cyclic peptides with strained peptide bonds, or chemical modification of peptides to create protease resistant molecules can be employed (*1*, *12*, *85*, *86*). Alternatively, improved formulations such as in liposomes to mask the peptide and the use of non-peptidic backbones to create protease-resistant mimetics could also help to resolve sensitivity to proteases (*12*, *85*, *86*). These approaches could also assist in making peptides work systemically. Also, it has been documented that high concentrations of certain HDPs are cytotoxic to a variety of eukaryotic cell types (*21*). For example, HNP-1 induces progressive lung dysfunction in a dose dependent manner in mice (*87*). Nevertheless it seems possible to make peptides with low toxicity in animal models, although there is a lack of published toxicology data in animals. Finally, The high cost of manufacturing HDPs is a significant challenge, as the laboratory and commercial scale costs of even modest sized peptides can range from $100 to $600 per gram which is an average daily dose for most systemic applications (*12*, *88*). Nevertheless even these issues are likely to be overcome as the development of effective small peptides of 9-12 amino acids (*9*, *10*, *26*), reductions in commercial scale costs, and new recombinant methods (*89*), all have the potential for substantially lowering costs. Thus the focus in the development of HDPs for clinical applications is on small peptides, performing extensive structure activity relationship studies to assist in limiting potential toxicity, and lowering the cost of drug production.

Summary/Conclusion

HDPs and synthetic derivative AMPs and IDR peptides are rapidly emerging as potential novel therapeutics that can directly kill pathogens and/or modify immune responses to control infections and inflammation. Apart from their anti-infective properties, a wide range of immunomodulatory functions have been defined for HDPs and IDR peptides that result in a net suppression of potentially harmful pro-inflammatory responses along with enhancement of effective immunity enabling resolution of infections. The multiple molecular modes of action associated with these peptides make these attractive candidates as potential therapeutics for at least four clinical avenues; as direct antimicrobials and anti-biofilm agents, as anti-inflammatories, in wound healing and as adjuvants.

The distinct advantages of developing these cationic peptides as therapeutics are two fold; (i) their ability to circumvent or avoid problems of microbial resistance, and (ii) their frequent ability to control inflammation without compromising the host's anti-infective immunity. However, there are some challenges in the process of developing peptide therapeutics, essentially limited bioavailability, unknown toxicities and high cost of production. Future directions in the development of cationic peptide therapeutics would perhaps focus on short IDR peptide derivatives of HDPs, with optimization of desired biological activities and limited cytotoxicity, while exploring the best mode of delivery to make the peptides bioavailable. Overall cationic AMPs and IDR peptides represent an exciting new approach as immunomodulatory therapeutics.

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