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Review

Antimicrobial Peptides and Their Therapeutic Aspect

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Abstract

Antimicrobial peptides which are already known for several decades and are an important element of the natural immunity obtained from practically all living organisms ranging from bacteria, insects, and plants to vertebrates, are supposed to be promising candidates for the various treatments. These agents came into focus as new treatment strategies for bacterial infections. The existing scenario of antimicrobial resistance shows concern about a post-antibiotic era with no antimicrobial treatment options. Antimicrobial peptides are short and generally positively charged peptides found in a large diversity of living forms. These are multifunctional effectors of the natural immune system of mucosal surfaces and present antimicrobial activity against a range of pathogenic viruses, microorganisms, and fungi with great possibility of novel antibiotics. Therapeutic applications are hindered by their low stability, toxicity, and high manufacturing cost. An approach to studying the pharmacokinetics of antimicrobial peptides in animals has been developed. Most antimicrobial peptides can destroy infectious organisms directly, whereas others act by altering the host defense mechanisms. Several antimicrobial peptides are at present being evaluated in experimental trials as new anti-infectives, but also as new pharmacological agents to amend the immune response, help wound healing, and check post-surgical grip. There are still plenty of ways and constraints to develop these peptides for experimental applications, and the original formulation and strategies for the application in various aspects of treatment.

Keywords: Antimicrobial Peptides, Homology Modeling, Omiganan, Pexiganan, Resistance

Introduction

Antimicrobial peptides (antimicrobial peptides) commonly known as endogenous polypeptides came into existence quite early but got recognition in 1980. Over 2700 of these innate immune molecules have been discovered in all life forms, ranging from bacteria to humans are found worldwide and guard hosts against infective and pathogenic microbes. These host defense peptides hold an essential role in maintaining immunity. In the mid-1990s, Brogden *et al*. identified the first anionic antimicrobial peptides in X. Laevis and characterized several other such peptides in ruminants, including sheep and cattle. In the early 1990s, facts stated that lysozyme is capable of showing antimicrobial activity linking non-enzymatic mechanisms, similar to antimicrobial peptides, thought to be among the first of the peptides to be discovered. Keeping this in view investigators considered the possibility that antimicrobial peptides may play a role in the defense systems of organisms deficient in an adaptive immune system.

Antibiotics are one of the intriguing discoveries of the twentieth century. Beginning with the first antibiotic penicillin, a diverse range of antibiotics is used against several life-threatening infections. With due course of time increase in resistance toward usual antibiotics in the "post-antibiotic era," became immaterial. As there is a limited number of available antibiotics, with each having almost similar spectrum and mechanism of action, exhaustive nonclinical and experimental research is now invested into the finding of new and non-conventional anti-infective therapies, with adjunctive or preventive approaches including antibodies targeting a virulence factor, probiotics, and vaccines (Czaplewski *et al.,* 2016).

In due course of time, antimicrobial peptides have quickly captured interest as novel drug candidates along with immuno-modulatory properties (Fjell *et al.,* 2012), which make them unique compounds for the progress of novel therapeutics. These peptides have already been introduced into the market, and many are at present being tested in clinical trials which provides a reason for hopefulness for the preface of novel antimicrobial peptide-based drugs in several indication areas. Antimicrobial peptides hold promise as potential pharmacological agents being broad-spectrum alternatives to conventional antibiotics, the focus of their applied therapeutic aspects being evaluated (Gee *et al.,* 2013; Ravi *et al.,* 2011).

In the antimicrobial peptide database, about 2300 antimicrobial peptides have been reported, and around 500-600 candidates are in preclinical processes however, none has received FDA approval for therapeutic use, except a few approved only for topical use.(Imran and Amjad, 2017) Although there is no drug currently in the market based on antimicrobial peptides, however, their selectivity, natural antimicrobial properties, and low propensity to develop antimicrobial resistance make them a striking and promising candidate for clinical development as new antibiotics. Different strategies including chemical, computational, and bioinformatics tools used to improve their antibiotic drug development process.

Structure of Antimicrobial Peptides

Antimicrobial peptides are short peptides with 8 to 50 amino acids, low molecular weight, most of which are cationic, with net positive charge mainly due to an excess of positively charged amino acids arginine, lysine, and histidine, contain 50 % hydrophobic amino acids and constitute an antimicrobial peptideshipathic structure, having multiple hydrophobic residues with broad-spectrum antimicrobial activity. Being cationic in nature, they interact only with the negatively charged membrane of microorganisms, distressing the membrane structure. After binding to the membrane, they undergo a conformational change, which allows the peptide to translocate into the interior of the bacterial cell. (Imran and Amjad, 2017). Holding a critical role in host protection these peptides are considered to be one of the crucial factors in the development of complex organisms from primitive cellular living forms. In invertebrates, these antimicrobial peptides play major defense molecules of innate immunity whereas in vertebrates it serves both as modulators of the adaptive immune system and effectors in innate immunity (Brogden, 2005)

Classification

On the basis of chemical structures and sequence diversity they are classified as follows:

1. Alpha helical structure
2. Beta strand/sheet peptides
3. Mixed helical sheets
4. Extended non-linear sheets

Mechanism of Action

There are many proposed mechanisms of action for antimicrobial peptides, but the exact mechanism is still unclear. Electrostatic forces between the cationic antimicrobial peptides and the negatively charged bacterial surface are critical determinants The hydrophobicity, cationic charge, amino acid sequence, and size, manipulate their contact with negatively charged bacterial membranes. (Yeung *et al.,* 2011)

a) Interaction with Bacterial Membrane

The cytoplasmic membranes of both Gram-positive and Gram-negative bacteria are rich in the phospholipids phosphatidylglycerol, cardiolipin, and phosphatidylserine, which have negatively charged head groups, highly attractive for positively charged antimicrobial peptides (Yeaman and Yount, 2003; Ebenhan *et al.*, 2014). After interacting with the bacterial membrane, interactions between antimicrobial peptides and the mammalian cell membrane are mainly hydrophobic interactions, which are relatively weak compared to the electrostatic interactions taking place between antimicrobial peptides and bacterial membranes. Interference with the physical integrity of the microbial membrane and translocated across the membrane into the cytoplasm of bacteria act on intracellular targets (Hancock and Sahl, 2006). This process of membrane interaction plays a major role in the direct antimicrobial activity of antimicrobial peptides both in the case of membrane target or intracellular target (Jenssen *et al.,* 2006; Nguyen *et al.,* 2011; Giuliani *et al.,* 2007)

b) Membrane Disruption and Intracellular Targets in Bacterial Cells

Antimicrobial peptides translocate through the outer membrane which forms a permeability barrier for many macromolecules, partly due to the divalent cations Ca^{2+} and Mg^{2+} that bind to the phosphate groups of the inner core of lipopolysaccharides and thereby provide stabilization of the outer leaflet (Clifton *et al.,* 2015).In contact with the cytoplasmic membrane, these peptides form a peptides hipathic secondary structure, which ultimately leads to membrane permeabilization. According to the "**barrel-stave model,"** the peptides insert upright into the bilayer later result in the formation of a peptide-lined trans-membrane pore. In this pore, the peptides are associated with the hydrophobic side facing the lipid core of the membrane and the hydrophilic regions facing the interior region of the pore. According to the "toroidal-pore model," the inclusion of peptides forces the phospholipid to bend constantly from one leaflet to the other, resulting in a pore lined by both peptides and the head groups of the phospholipids. As per the "carpet model," accumulation of peptides on the membrane surface causes tension in the bilayer that ultimately leads to disruption of the membrane and formation of micelles. (Tokumaru *et al.,* 2005)

Therapeutic Aspect

Due to the complex and multi-target mechanism of action, antimicrobial peptides are distinguishable from conventional antibiotics and making them an ideal candidate to generate new antimicrobials. A number of factors such as their synergistic effects with conventional antibiotics, relatively small size, neutralizing endotoxin ability, and minimum inhibitory concentration [MIC], manifest that they are highly prone to kill bacterial cells.

The rapid bactericidal activity of antimicrobial peptides makes them promising candidates for therapeutic anti-infective. Furthermore, several antimicrobial peptides have a broad range of action, which is an advantage in certain therapeutic areas, such as complicated skin and soft tissue infections, as these areas are prone to multiple microbial infections reported in recent times (Dryden, 2010).

Only a few antimicrobial peptides are approved for clinical use, Polymyxins are last-resort drugs for intravenous treatment of drug-resistant infections caused by Gram-negative pathogens, but they are also applied on skin tissue formulations for avoidance and cure of restricted area infections (Zavascki *et al.,* 2007). There are numerous antimicrobial peptides currently under clinical development for the treatment of various bacterial pathogens Pexiganan, a 22-amino-acid membrane disruptor analog of the Xenopus peptide magainin has been evaluated as a topical cream for treating bacterial infections associated with diabetic foot ulcers in two-phase III clinical trials (Lipsky *et al.,* 2008), and additional clinical trials are currently ongoing. Omiganan is a derivative of indolicidin, which was isolated from bovine neutrophils, and has been assessed as a topical gel in clinical trials for catheter infections. LTX-109 is a synthetic antimicrobial peptide mimetic, which has been to date evaluated for local application in uncomplicated Gram-positive skin infections (Nilsson *et al.,* 2015). Several antimicrobial peptides

are currently under clinical development for therapeutic indications other than antimicrobials or antifungal agents. One of the most well-known of these peptides is LL-37, which has recently been evaluated in phase I/II clinical trials as a local treatment to enhance the curing of venous leg ulcers (Grönberg *et al.,* 2014) The mechanisms by which LL-37 promotes wound healing are still not clear, but are likely to entail several wound repairs mechanism such as re-epithelialization, increased blood circulation, and inflammation. Re-epithelialization is likely moved by means of the antimicrobial attractant effects of LL-37 (Shaykhiev *et al.,* 2005; Tokumaru *et al.,* 2005). There are several attempts ongoing to use agents to increase the endogenous production of antimicrobial peptides by the body to boost the innate immune responses and thereby combat infections.

Commonly, topical therapy is preferred over drug administration in skin diseases to stay away from systemic unfavorable effects. However, the topical application requires sufficient tissue penetration (Stein and Wells, 2010). In a recent study, a synthetic cationic peptide was found to kill more than 99% of E. coli in planktonic culture. Besides, this synthetic peptide reduced the number of persister cells in mature biofilms by up to 98% at 40 µM. The combination of this peptide with ofloxacin (5 µg/mL) resulted in the complete eradication of viable cells in E. coli biofilms including persister cells. Thus, the combination of conventional antibiotics with antimicrobial peptides may offer a synergy to control drug-tolerant infections antimicrobial peptides have also been tested against the biofilms of drug-resistant bacteria. In a study nisin A and lacticin Q were tested against mature biofilms of an MRSA strain, S. aureus MR23. Nisin A at 40 µM was found to kill more than 95% of biofilm cells while lacticin Q at 80 µM killed around 90% of the biofilm cells. (Okuda *et al*., 2013)

The therapeutic use of antimicrobial peptides concluded that most of the claimed antimicrobial peptides were characterized not only as potent antibiotics but also as effective modulators of inflammation or neutralizers of pathogenic toxins (Kosikowska and Lesner, 2016). The broad range of immune-modulatory activities exerted by antimicrobial peptides includes stimulation of chemotaxis, modulation of immune cell differentiation, and initiation of adaptive immunity, together contributing to the bacterial clearance of the host. The immunomodulatory activities further include suppression of toll-like receptors (TLR)- and/or cytokine-mediated production of pro-inflammatory cytokines and anti-endotoxin activity, together preventing excessive and harmful pro-inflammatory responses including sepsis. (Lai and Gallo, 2009; Van der Does *et al.,* 2010). Omiganan is a derivative of indolicidin, which was isolated from bovine neutrophils, and this antimicrobial peptide has been assessed as a topical gel in clinical trials for catheter infections.

Resistance to Antimicrobial Peptides

They have a low susceptibility to develop resistance still due to cell surface modifications with reduced anionic charge, which inhibits peptide to aggregate on the membrane, degradation by proteolytic enzymes, variation in cell wall hydrophobicity, membrane fluidity, and membrane-bound efflux pump also cause expulsion of the peptides showing reduced effect and development of resistance against microbes. Bacterial resistance against antimicrobial peptides has already been reported holding the risk that bacteria that evolve resistance against externally applied antimicrobial peptides might develop cross-resistance to host antimicrobial peptides or antibiotic therapy (Dobson *et al.,* 2014; Kubicek-Sutherland *et al.,* 2017), such as *S. aureus* which was not responsive after treatment with pexiganan (Conlon, 2015). Resistance of bacteria to antimicrobial peptides might develop due to the modification of lipo-polysaccharides in Gram-negative and lipoteichoic acid in Gram-positive bacteria (Joo *et al.,* 2016). The release of proteases resulting in proteolytic degradation of the peptides is the most possible way of developing of a resistance mechanism. The inactivation of antimicrobial peptides by bacterial proteases strongly depends on the peptide structure, given a higher susceptibility to degradation of linear peptides compared to cyclic peptides containing disulfide bonds. Resistance mechanisms that contribute to virulence *in vivo* are modification of cell surface structures and efflux transporters whereas only a few studies demonstrated a contribution of proteases to *in vivo* antimicrobial peptides resistance.

Challenges to Develop Antimicrobial peptides for Clinical Applications

These antimicrobial peptides despite showing various advantages over conventional antibiotics in being broad spectrum activity with sensitivity against drug-resistant strains, mode of action without involving specific binding sites. Particularly skin and soft tissue infections are an attractive target for the application of antimicrobial peptides since topical treatment circumvents potential systemic adverse effects and can achieve high drug concentrations. Furthermore, only their direct antimicrobial effect is affected by bacterial resistance to the target site, whereas their

immuno-modulatory properties stay unaffected (Stein and Wells, 2010). There are several challenges in the usage of these peptides such as high production costs, potential toxicity, susceptibility to proteases (also in the wound fluid), and unknown pharmacokinetics (Dutta and Das, 2015). The major question for the clinical use of antimicrobial peptides is their low stability in tissues E.g., toward bacterial proteases, to endogenous proteases such as trypsin-like proteases that are abundant in the body (e.g., in wound exudate). The majority of naturally occurring antimicrobial peptides have unfavorable pharmacokinetic properties such as a very short half-life of only 1–2 h, mainly due to degradation by proteases. Therefore, before any clinical use, peptides should be properly seen for optimum skin penetration and the effects of enzymes on the skin on peptide action. A molecular weight lower than 500 Da and moderate lipophilicity and aqueous solubility are ideal characteristics for successful transdermal delivery. Antimicrobial peptides used for topical application should not be absorbed systemically into the circulation and provoke any allergic reactions. In chronic wounds the excessive release of pro-inflammatory cytokines delays wound healing, retaining the process in the inflammatory phase. So far very few antimicrobial peptides have been thoroughly characterized and accepted in clinical trials, and from those even fewer have been approved by the US Food and Drug Administration (FDA). (Malanovic and Lohner. 2016).

The low metabolic stability of antimicrobial peptides, which is an inherent risk of therapeutic peptides in general, is considered another key factor limiting their clinical application. antimicrobial peptides that neutralize bacterial pathogenicity factors or control and balance the host immune response rather than acting directly on bacteria, might be favorable to improve the outcome of infections on the one side by enhancing levels of immune cells and chemokines that are clearing infections and on the other side by decreasing pathogenicity factor-induced secretion of pro-inflammatory cytokines (Mansour *et al.*, 2015; Brandenburg *et al.*, 2016). With a large number of antimicrobial peptides going through clinical development, there is still a considerable discrepancy between the list of antimicrobial peptides claimed as potent drug candidates and the actual result of the clinical trials (Kosikowska and Lesner, 2016).

Strategies to Overcome the Challenges

Several strategies exist to improve the bioavailability of antimicrobial peptides for topical application. The antimicrobial peptide action becomes most important, since their activity to neutralize bacteria is not direct but rather through the inhibition of pathogenicity factors or by controlling the host immune response. To improve the efficacy of the antimicrobial peptide, different strategies have been proposed including the chemical modification of antimicrobial peptides by including non-natural or D -amino acids in their structure, shortening the peptides lengths, or inducing amidation at the N-terminus to avoid peptide degradation like liposome encapsulation or the function at the surface of wound dressings for topical delivery. Several antimicrobial peptides have been synthesized and produced with promising topical effects, both *in vitro* and *in vivo*, on infected wounds.

New antimicrobial peptides Design by Homology Modelling

Designing synthetic antimicrobial peptides by homology modeling within the same class might also provide a better understanding of the activity-structure relationship. It is possible to broaden the target spectrum of antimicrobial peptides by homology modeling. A conserved sequence, which corresponds to an α-helical region, among these antimicrobial peptides was found, by aligning multiple sequences. This regular region was altered by inserting the GKLI sequence into its main sequence, and the novel synthetic peptide obtained showed actions against *E. coli* O157 with a more stable structure compared to other lactoferrin antimicrobial peptidesins.

Conclusion

Overall, antimicrobial peptides present hopeful alternatives to standard therapies as anti-infective and immune-modulatory agents with mechanisms of action that are less prone to resistance induction compared to common antibiotics. The discovery and commercial development of next-generation therapeutic peptides and peptide mimetics is predicted to be accelerated by the most recent advances in the overall understanding of their mechanism of action, resistance patterns, and useful formulation strategies. *In vivo* studies could be performed to increase the activity of antimicrobial peptides to treat infections caused by multidrug-resistant Gram-positive and Gram-negative bacteria. Despite the great efforts that were made by several researchers to design new peptides with enhanced properties, only a few antimicrobial peptides have been introduced to the market or are in clinical trials. Most of the studies conducted concentrate on topical therapy for indications such as chronic wounds revealing the promising

therapeutic applicability of antimicrobial peptides for these medical indications. Several antimicrobial peptides currently undergoing the last stage of clinical development in different therapeutic areas, confirm the therapeutic benefit of these novel candidates. In coming years we could hope for market authorization of several new antimicrobial peptides-based drugs.

Contribution by Authors

RP: The attainment of data and decisively revising the manuscript; AS: Significant contribution to the conception and design, the acquisition of data and critically revising the manuscript; NS: Critically revising the manuscript; NK: Substantial contribution to the conception and design; SKS: Critically revising the manuscript; RR: Critically revising the manuscript.

Conflict of Interests

There is no conflict of interest.

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