Review Article

Antimicrobial Peptides (AMPs)

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Abstract

Antimicrobial peptides (AMPs) are extensive group of molecules that produced by variety tissues of invertebrate, plants, and animal species which play an important role in their immunity response. AMPs have different classifications such as; biosynthetic machines, biological sources, biological functions, molecular properties, covalent bonding patterns, three dimensional structures, and molecular targets.

These molecules have multidimensional properties including antimicrobial activity, antiviral activity, antifungal activity, anti-parasite activity, biofilm control, antitumor activity, mitogens activity and linking innate to adaptive immunity that making them promising agents for therapeutic drugs. In spite of this advantage of AMPs, their clinical developments have some limitation for commercial development. But some of AMPs are under clinical trials for the therapeutic purpose such as diabetic foot ulcers, different bacterial infections and tissue damage. In this review, we emphasized on the source, structure, multidimensional properties, limitation and therapeutic applications of various antimicrobial peptides.

Keywords: Antimicrobial peptides, Antibiotics, Infections

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Introduction

Natural antibiotics that produce by a variety of tissues and cell types organisms against pathogenic microorganisms are considered as antimicrobial peptides[1,2]. Nowadays antibiotic resistance has become a major public health problem around the world and so other antimicrobial agents against organisms should be used[3]. Antimicrobial peptides (AMPs) play an important role in innate immune responses against infections in different organisms[4]. The role of antimicrobial peptides in innate immunity was demonstrated by Metchnikoff[5]. For example some AMPs that produced by insects can protect them from variety of pathogens such as bacteria, viruses or fungi. α-defensins that isolated from mammalian leukocytes showed that this line of defense is not exclusively be found in the organisms that lack an acquired immune system[6,7]. Because of their potentially usefulness in clinical applications, many researches are undergoing for development of peptide antibiotics as a new class of anti-infective drugs[8].

AMPs have general structural features that are shared by a majority of AMPs such as length, net charge and hydrophobicity. They are commonly composed of less than 100 amino acid residues (generally between 12 to

50 amino acids) and show different net charges from 0 to +7 and hydrophobic percentages between 31–70%[7,9]. Antimicrobial peptides can be produced by a variety of sources including insects, amphibians, echinoderms, crustaceans, plants, mammals, bacteria, fungi, and fishes. More than 2453 AMPs from various organisms have been identified in the antimicrobial peptide database including 244 AMPs from bacteria (i.e., bacteriocins), 2 from archaea, 7 from protists, 13 from fungi, 311 from plants, and 1835 from animals (http://aps.unmc.edu/AP/main.php).

Discovery of AMPs

The discovery of AMPs dates back to 1922, when Alexander Fleming discovered human lysozyme in saliva. In 1939, another AMP, gramicidin, was discovered by Hotchkiss and Dubos[7,10]. The discovery of antimicrobial peptides in later years has continued until today. For example some of important AMPs which have been discovered until now include Plant Kalata B1 in 1973, cecropins that produced by insects in 1980, magainin from frog in 1987, defensins that produced by human cells and mammalian cells in 1985[7].

Classification of AMPs

There are various classifications of antimicrobial peptides based on: The biosynthetic machines, biological sources, biological functions, molecular properties, covalent bonding patterns, 3 dimensional structures, molecular targets.

According to the biosynthetic machines natural peptides can be classified as gene coded and non-gene coded. Based on biological sources AMPs can classified as bacterial AMPs (bacteriocins), plant AMPs, and animal AMPs that animal AMPs are further classified into insect AMPs, amphibian AMPs, fish AMPs, reptile AMPs, and mammal AMPs. According to the biological functions AMPs can act as antibacterial, antifungal, antiviral, antiparasite, anticancer, anti- protest, insecticidal, spermicidal, chemotactic, antioxidant and protease inhibitors.

In the absence of three-dimensional (3D) structural information, AMPs can be classified based on peptide properties such as charge (cationic, neutral, and anionic peptides), hydrophobicity (hydrophobic, amphipathic, and hydrophilic peptides), and length (ultra-small (2-10 aa), small (10-24 aa), medium (25-50 aa), and large (50-100 aa).

One of the universal classification systems (UC) according to the covalent bonding patterns leads to four classes of antimicrobial peptides, UCLL: linear one-chain peptides (e.g. LL-37 and magainins) or two linear peptides not connected via a covalent bond, UCSS: sidechain-linked peptides (e.g. disulfide-containing defensins or ether bond-containing lantibiotics). A sidechain-sidechain connection can occur within a single peptide chain or between two different peptide chains, UCSB: polypeptide chains with a sidechain to backbone connection, UCBB: circular polypeptides with a peptide bond between the N- and C-termini that found in bacteria (like AS-48), plants (cyclotides), and animals (theta-defensins). According to the 3dimentional structures the types of secondary structures are used for the classification of AMPs into four families: α- helix, β- sheet, extended and loop.

AMPs can be broadly classified into two families based on the molecular targets: cell surface targeting peptides (e.g. nisins and temporins) that including both membrane-targeting and non-membrane targeting peptides which can be further classified based on specific targets such as cell wall/carbohydrates, lipids/membranes, and proteins/receptors. Second family includes intracellular targeting peptides that can be further classified based on the specific target molecules (e.g. proteins (Pro-rich peptides), DNA, and RNA)[11,12].

Multidimensional properties of AMPs

Beside antimicrobial activity, AMPs show other properties like biofilm control, antitumor property, mitogens activity and linking the innate immunity to the adaptive immunity.

Antimicrobial activity

AMPs have antimicrobial activity against bacteria, viruses, fungi and parasites with different mechanisms.

AMPs with antibacterial activity

AMPs show selective toxicity against bacteria comparing to eukaryotes. There are more negatively charged phospholipids in the membrane of bacteria compared to eukaryotic cells which composed of lipids without any net charges. These differences can lead to electrostatic interactions between cationic antimicrobial peptide and cytoplasmic membrane of bacteria. Some anionic peptides form a salt bridge through reaction of metal ions with negatively charged components of microbial membranes[13,14]. Unlike conventional antibiotics, peptide antibiotics target microbial cellular membranes which are different in various species of microorganisms from plants and animals. These important characteristics of peptide antibiotics effectively reduce the possibility of development of resistance against them[8].

Mechanisms of antibacterial activity

AMPs perform antibacterial activity with the following method.

Membrane disruption

AMPs can form pore in the bacterial membrane with three mechanisms:

Barrel-stave model: monomer peptides get aggregated on the surface and inserted into the cell membrane and form pore. This mechanism is well explained by analyzing a lantibiotic peptide nisin.

Toroidal-pore model: peptide molecules are inserted into the membrane and inducing the lipid monolayers to continuously bend through the pore. For example melittin, LL-37 and MSI-78 can form pore with this mechanism.

Carpet model: AMPs covering cell membranes of bacteria like a carpet, in threshold concentration reduce electrostatic force that causes membrane permeation and lysis of the microbial cell. For example magainins act by this mechanism[4,15].

Some AMPs influx into cell and inhibit cell wall, DNA, RNA, and protein synthesis[16].

Inhibition of cell wall synthesis

Cell wall is a unique structure in bacterial cells that provides structural integrity. Because of the absence of cell wall structure in eukaryotic cells, prevention of cell wall synthesis is an attractive target for antibacterial peptides. In particular, lipid II which is an important precursor of peptidoglycan synthesis was shown to be an attractive target for antibacterial compounds. Several AMPs like Class I bacteriocins, nisin, Pep5, Mersacidin, Lcn972 and defensins can be target cell wall[17].

Inhibition of protein, RNA and DNA synthesis

Some AMPs can penetrate into the cell without disrupting cell membrane and target intracellular components such as protein and acid nucleic synthesis. Some AMPs like buforin II binds to DNA and RNA which have been studied in *Escherichiacoli*o rPR-39 which can block DNA and protein synthesis and have multidimensional properties like wound repair, chemo attraction, angiogenesis, and inflammation[17].

AMPs with antiviral activity

They can act in different ways including: blocking of viral receptors, inhibition of adsorption by binding of antimicrobial peptides to the viral proteins, interaction with co-receptors like CXCR4, inhibition of cell fusion by interfering of ATPase activity of protein, inhibition of gene expression, inhibition of peptide elongation and activation of an immune modulatory pathway[2].

AMPs with antifungal activity

AMPs can target fungal cell membrane or their intracellular components like cell wall, DNA, RNA and proteins[3].

AMPs with anti-parasite activity

Mechanism of antimicrobial peptides action is similar to others and they can disrupt cell membrane or target intracellular components like protein, RNA or DNA synthesis[3].

Biofilm control

Microorganisms can attach to the artificial implants surfaces and become resistant to environmental condition[18]. Antimicrobial peptides can be used as a therapeutic agent for biofilm control. Electrostatic interaction between antimicrobial peptides and cell surfaces could prevent biofilm formation. They can be effective in different ways for example preventing biofilm formation dose dependently like LL-37 orcoating on implants surfaces to stop biofilm formation like Tet-20, histatin 5 and lactoferrin.

In addition they can be used against drug resistant bacteria like nisin A and lacticin Q which can be effective against biofilm formation of a MRSA *(Methicillin Resistant Staphylococcus aureus*) strain. Some antimicrobial peptides can increase the sensitivity of ,l m. biofilm cells to other antibiotics like lactoferrin in which in combination with vancomycin can be used for the removing of *S. epidermidis* biofilms on contact lenses[3].

Antitumor activity

Cancer is one of the most important reasons of morbidity and mortality throughout the world. In recent decades other therapies, such as chemotherapy, radiation, surgery, or hormone ablation are more used for cancer therapy but they are not successful in more than 50% of patients. Therefore there is an urgent need for new therapeutic agents. Several antimicrobial peptides have been studied as potential candidates for anticancer drugs. These molecules interact with different bilayers depending on the physical properties of membranes consisting of different lipid molecules. Their mechanism of action usually implicates the disruption of cancer cell membranes. These membranes are similar to membranes of bacterial cell with respect to their anionic characteristics. The cancer cell membrane has a negatively charged lipid phosphatidyl serine (PS) on their outer leaflet which differentiates them from normal cells that have a neutral charge due to the zwitterionic phosphatidyl choline and sphingomyelin. For example, LAH4 is an antimicrobial peptide that is shown to have both antibiotic and DNA delivery capabilities and it is a membrane-active peptide. The experimental studies indicate the greater tendency of LAH4 to interact with anionic membrane that can be useful data in order to confirm on its anticancer properties. Because of their different mechanism, resistance and cytotoxicity are less likely to arise for these peptides. Therefore AMPs are also expected to cause fewer side-effects than chemotherapeutic agents. As a result, AMPs are good candidates for development of new anticancer drugs and completing the usual anticancer therapy[19].

Also it is shown that anticancer peptides (ACPs) can kill cancer cells with other mechanism. Another mechanism of killing of cancer cells is the induction of mitochondrial pathway of apoptosis by either the cytochrome C release into the cytoplasm or the activation of the caspase cascade. Furthermore fluidity of cancer cells is greater than normal cells, which enhance the lytic activity of ACPs by enhancing the membrane destabilization. In addition because of the higher number of microvilli in the surface area of the tumorous cells membrane comparing non-tumorous cells, an increased number of peptides can bind to the surface area of the tumorous cells membrane[2,20].

Mitogens activity

Mitogens properties of antimicrobial peptides was first introduced by Murphy *et al.* Defensins have several properties, one of these properties is ability to stimulated growth of fibroblasts and epithelial cells *in vitro* in concentration range required for antimicrobial activity. In other words, defensins can also induce a wound healing process besides preventing microbial infection[21]. A similar result was obtained by Aarbiou et al., for lung epithelial cells. In this study defensins enhanced proliferation of A549 lunge epithelial cells at 4–10 μg/ml by the MAP kinase path way and independent of the EGF-receptor[22]. Moreover another study suggested that human α-defensins have an effective role in the proliferation of both the normal and tumor cells in kidney. According to this study human α-defensins present in normal kidney and biopsies of renal carcinoma tissue. This study also showed that defensins were present at a concentration not exceeding 25g/ml stimulated DNA syntheses[23].

Link innate to adaptive immunity

Not only antimicrobial peptides have direct effect on bacterial membranes, but also are able to modulate other components of innate immunity. Gene expression of antimicrobial peptides has been controlled by immunity related transcription factors and by innate immunity cells including neutrophils, mast cells and eosinophils. So, they initiate signaling cascade of NAPDH oxidase-dependent mechanism that leads to the disintegration of the nuclear and cellular membrane[24]. For example, defensin also known as the regulator of innate immunity and secreted by a variety cells such as phagocytic cells and lymphocytes[26]. In the other hand, they can be effective as chemo attractants for monocytes and neutrophils. Moreover, defensins can produce several cytokines such as TNF and IL-1 in monocytes and induct IL-8 in lung epithelial cells[24]. As pretreatment of the cells with pertussis toxin, phospholipase C, phosphoinositide-3-kinase and Rho kinase inhibitors suppresses cell migration it is presumed that antimicrobial peptide-induced chemotaxis is mediated through G-protein-coupled receptors[25]. First study in 1996 by demonstrated that defenisns had chemotaxic activity in both nonspecific phagocytes and cells that involved in acquired immune response[24].

Antimicrobial peptides limitations

Despite of many advantage of AMPs which include broad-spectrum activity, rapid onset of activity, and relatively low possibility of resistance emergence, they still have some limitations for pharmaceutical development including; potential toxicity, conditions (susceptibility to proteases and extreme pH), lack of selectivity against specific strains, high produce cost and bacterial resistance[27]. Besides since AMPs have many similar features with eukaryotic nuclear localization signal peptides and because of their ability to translocate into cells, they can cause toxicities, including apoptosis, mast-cell degranulation or extracellular DNA transfer[28].

However it could be said that the main reason for unwilling of pharmaceutical industry in promoting the clinical use of these peptides as a class of antibacterial therapeutics is their high production cost. The synthesis of AMPs costs five to twenty times as high as that of conventional antibiotics[28]. The production of recombinant proteins in bacteria is by far the simplest and most inexpensive means to produce large amounts of peptide of interest[8]. On the other hand, after production of these peptides another problem for their pharmaceutical development is their stability.

Protein and peptide stability is the result of a balance between the intramolecular interactions of protein functional groups and their interactions with the solvent environment. Addition of co-solvents into the protein solution can modify this balance[29]. The addition of co-solvents to solutions of peptides and proteins can result in a variety of effects such as denaturation, increased or decreased solubility, and secondary structure formation[30]. Protein transition from unfolded states to its native state is one of the most important biophysical processes. It is also of interest because of the important role it plays in the mechanisms and control of a lot of cellular processes. These include regulation of complex events during the cell cycle and translocation of proteins across biomembranes to their appropriate organelles[31].

Application of antimicrobial peptides

Despite of restrictions mentioned about the use of antimicrobial peptides for therapeutic purposes, some of them are used as therapeutic agents[32]. For example they can be effective in combination with conventional antibiotics. Because of their synergic activity in association with other antibiotics, they have desirable effect in reducing the minimal inhibitory concentration (MIC) and minimal bactericidal concentrations (MBC) of those antibiotics. Several applications have been demonstrated for therapeutic application including: as single anti-infective agents, in combination with conventional antibiotics or antivirals to promote any additive or synergistic effects, as immune stimulatory agents that enhance natural innate immunity and as endotoxin neutralizing agents to prevent the potentially fatal complications associated with

bacterial virulence factors that cause septic shock[33].

In general, most of the researches about antimicrobial peptide devoted to tropical therapy due to the uncertainty about their long-term safety when administered systemically. On the other hand, in systematic studies it is shown that in spite of their activity *in vitro*, they can be effective in infection of animal models only at very high doses[28].

Below are some of AMPs that are used in drug development:

1. Magainin is a 22-amino-acid linear antimicrobial peptide, isolated from the skin of the African clawed frog (*Xenopuslaevis*) which is in the phase 3 of clinical trial by companies Dipexium Pharma (White Plains, New York)/MacroChem/Genaera for Diabetic foot ulcers[34].
2. Omiganan a synthetic cationic peptide derived from indolicidin which is in the phase 2 of clinical trial by company BioWest Therapeutics/Maruho (Vancouver) for Rosacea[34].
3. NVB302 a Class B lantibiotic which is in the phase 1 of clinical trial by company Novacta (Welwyn Garden City, UK) for C. difficile infection[34].
4. Avidocin and purocin a modified R-type bacteriocins from Pseudomonas aeruginosa which is in the preclinical by company Avid Biotics (S. San Francisco, California) and are narrow spectrum antibiotics for human health and food safety[34].

IMX924 a synthetic 5-amino-acid peptide innate defense regulator which is in the preclinical by company Iminex (Coquitlam, British Columbia, Canada) and is effective in Gram-negative and Gram-positive bacterial infections and improves survival and reduces tissue damage[34].

Conclusion

AMPs are one of the important components of innate defense in a wide variety of organisms, from bacteria to humans. AMPs include a broad range of peptides with different chemical structures and conformations which all have certain properties in common. Their modes of action are very different and they demonstrate a great ability to exert a diverse range of antimicrobial effects. During recent years it has become evident that increasing bacterial drug resistance has created an urgent need for new classes of antibiotics. AMPs seem to represent promising properties for overcome this threat. On the other hand, AMPs have shown other potential and desirable therapeutic properties like antiviral, anticancer and contraceptive activities. Thus, understanding the diverse biological properties of AMPs can be very importance for clinical development of AMPs-based therapeutics.

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