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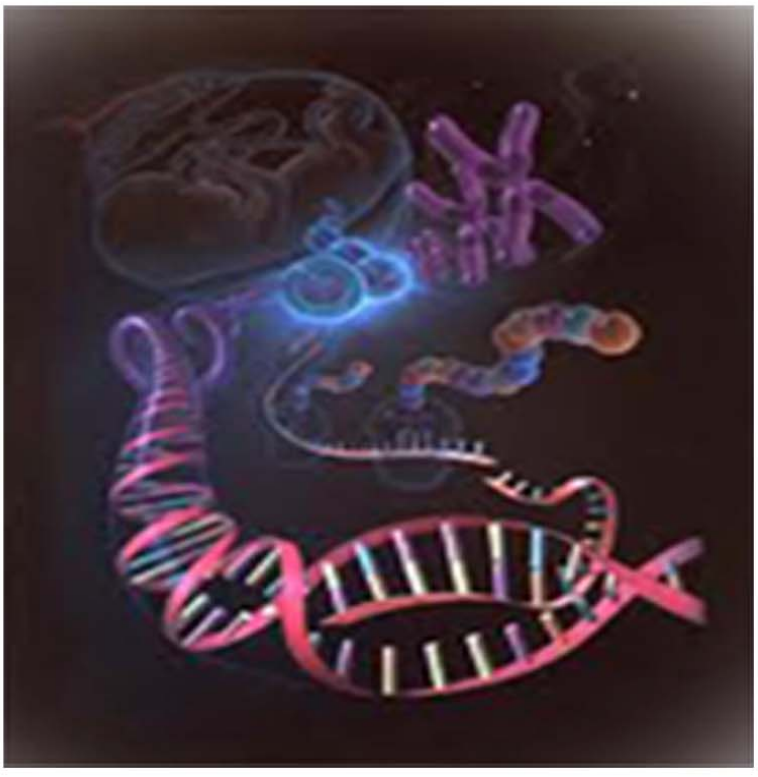

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Review Article

ANTIMICROBIAL PEPTIDES: A REVIEW

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Antimicrobial peptides (AMPs) are an important component of natural defenses of most of the living organisms against pathogenic organisms. During the past two decade several antimicrobial peptides have been isolated from wide variety of organisms both vertebrates and invertebrates, and plants as well as from bacteria and fungi. These peptides exhibit a broad range of activity against microorganisms including Gram-positive and Gram-negative bacteria, protozoa, yeast, fungi and viruses. Despite their broad divergences in sequences most of the antimicrobial peptides exhibit common mechanism of action, i.e., membrane permeabilization of the pathogens. Some of these peptides are under clinical trials for the treatment of diabetic foot ulcers and gastric helicobactor infections. This review will discuss the source, structure and mechanism of action with special reference to therapeutic applications of various antimicrobial peptides.

Keywords: Antimicrobial peptides, Structure, Mode of action

INTRODUCTION

Most of the living organisms are constantly exposed to potentially harmful pathogens in any climatic condition. The survival of these organisms depends on a network of host defense mechanisms involving various components (Bal, 2000). In addition to their normal immune responses, these organisms constitutively release a group of molecules termed as, Antimicrobial peptides (AMPs) or host defense peptides. These peptides constitute a primitive class of immune defense mechanism, and have remained conserved in wide range of eukaryotic organisms from human to insects in animals and plants. These peptides exhibit bactericidal, fungicidal, viricidal and tumouricidal properties and they have often been found to overcome bactericidal resistance making them promising agents for therapeutic drugs (Bal, 2000).

Antimicrobial peptides are generally between 12 and 50 (<100) amino acid residues-long with net positive charge ranging from +2 to +9. These are often characterized by multiple number of amino acids like proline, arginine, lysine, tryptophan and phenylalanine and a high proportion (>30%) of hydrophobic amino-acids. A common feature shared by these cationic AMPs is their ability to fold into amphipathic conformation upon interaction with membranes.

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SOURCES OF AMPS

More than 800 AMPs have been identified from various organisms and their sequences are deposited in the Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main.php). Besides animal and plants, bacteria itself produce AMPs and about 50 of them have been isolated from Gram-positive bacteria (Luders *et al*., 2003). They are called bacteriocins. These peptides exhibit activity against both Gram-positive and Gram-negative bacteria, in addition, they also show antibiotic activity against fungi (Mohammad *et al*., 1995) and protozoa (Aley *et al*., 1994). Their activities may be either narrow or broad spectrum, capable of targeting bacteria within the same species or from different genera.

The diversity of antimicrobial peptides discovered is so great that it is difficult to categorize them. However, it is common to classify antimicrobial peptides into four groups according to their secondary structure (Epand and Vogel, 1999, Van t Hoff *et al*., 2001).

1. α-helical: These are linear amphipathic peptides. The peptides are in disordered structure in aqueous solution but adopt an α-helical structure in hydrophobic solvents or on lipid surface, e.g., magainin, cecropinA, temporin. Magainin is most studied in this group. It is 23 amino acid long cationic peptide secreted on the skin of African clawed frog *Xenopus laevis* (Zasloff *et al*., 1987).

Some peptides of this group are hydrophobic α-helix with slight negative charge but these anionic peptides are less effective towards microbes compared to mammalian cells. One of the negatively charged and hydrophobic peptide is alamethicin (Duclohier and Wroblewski, 2001; Kikukawa and Araiso, 2002). This peptide surrounds ion transport channel after traversing through the lipid bilayer.

2. β-sheet: These peptides are cyclic with conserved motifs of six cysteine residues forming three disulfide bonds between C1-C4, C2-C5 and C3-C6. X-ray crystallography suggests that these peptides exist as dimers (Hill *et al*., 1991). The peptides of this group are human β-defensin-2 (Hancock, 2001), tachyplesins (Matsuzaki, 1999), protegrins (Harwig *et al*., 1995), and lactoferricin (Jones *et al*., 1994), gramicidin S (Prenner *et al*., 1999), polymyxin B (Zaltash *et al*., 2000), and tyrocidines (Bu *et al*., 2002). These peptides exist as β-sheet in solution and further stabilize on interaction with lipid surfaces. Defensin belongs to this group. X-ray crystallography (Hill *et al*., 1991) and NMR (Zhang *et al*., 1992) studies revealed that defensins either perturb the lipid bilayer or form channels in membrane. The aim of these studies was to understand the importance of disulfide linkage for the antimicrobial activity. Replacement of cysteine residues by certain other amino acids like Ala, Asp and Leu leads to inactivation of the peptide whereas analogs with aromatic residues Phe, Tyr and hydrophobic amino-acid like Leu, Met and Val retain broad spectrum antimicrobial activity (Tamamura *et al*., 1998).

3. AMPs rich in specific amino acids: The peptides belonging to this group are rich in certain specific amino acids. For example, histatin, a peptide found in saliva is rich in histidine residues (Brewer *et al*., 1998; Tsai and Bobek, 1998; Helmerhorst *et al*., 1999a). This peptide targets mitochondria of yeast cells, expressing its antifungal property

(Helmerhorst *et al*., 1999). The peptides produced by porcine neutrophils are rich in proline and arginine or proline and phenylalanine. Such peptides are PR-39 and prophenin which belong to cathelicidin family (Zhao *et al*., 1995; Linde *et al*., 2001). Tryptophan rich peptides include tritripticin (Lawyer *et al*., 1996) and indolicidin (Selsted *et al*., 1992). Indolicidin permeabilizes the outer membrane of *E. coli* (Falla *et al*., 1996; Subbalakshmi *et al*., 1998) to form channels.

4. Loop structures: Proline and arginine rich peptides can not form amphipathic structure, rather they form polyproline type II structures (Boman *et al.*, 1993; Cabiaux *et al*., 1994). Lantibiotics belong to this group. They have a ring structure with a thioether bond. Nisin is a lantibiotic used as antibacterial agent in food preservation due to its high activity against Gram-positive bacteria. This peptide has affinity for Lipid II which is a precursor in the bacterial cell wall synthesis. On binding to lipid membranes, the cyclic peptides can stack to form hollow β-sheet like tubular structures thereby increasing the membrane permeability. The peptides of this group are of great interest because of their short size, proteolytic stability, and ease of synthesis.

MECHANISM OF ACTION OF ANTIMICROBIAL PEPTIDES

Recently, it has been found that some intact proteins have no antimicrobial activity, but after proteolytic cleavage, the released segment exhibits antibacterial activity. For example, Lactoferrin, a milk protein, after digestion with pepsin releases a 25 residue-long peptide lactoferricin B which expresses a bacteriostatic potency unlike the intact protein.

The remarkable feature of AMPs is their cell specificity in that they kill microbes but are non-toxic to mammalian cells. This property of peptides is due to the difference in lipid composition between prokaryotic and eukaryotic cell membranes (Dathe and Wieprecht, 1999; Matsuzaki, 1999). The essential component of all biological membranes is phospholipid bilayers and it is only the phospholipids which display large diversity in membrane architecture (Kinnunen, 1991; De Kruiiff, 1997; Dowhan, 1997) and play important role during interaction with antimicrobial peptides (Lohner and Prenner, 1999; Lohner, 2001). Phosphatidylcholine (PC), phosphatidylethanolamine (PE) have no net charge while sphingomyelin (SM), a close analog of PC, containing a palmitoyl residue is also neutrally charged and commonly found in mammalian cytoplasmic membrane. Sterols like cholesterol and ergesterol found in eukaryotes, but rarely in prokaryotes, are also neutral. On the other hand, hydroxylated phospholipids such as, phosphatidylglycerol (PG), phosphatidylserine (PS) and cardiolipin (CL) have a net negative charge found in many pathogenic bacteria. The outer surface of Gram-negative bacteria contains lipopolysaccharides while Gram-positive bacteria contains acidic polysaccharides (teichoic acids) giving the surface of bacteria a negative charge. Thus, the net charge of a biomembrane is largely based on its phospholipid stoichiometry and architecture. Cationic antimicrobial peptides bind to membrane containing acidic phospholipids such as PG or PS due to strong electrostatic interaction (Matsuzaki *et al*., 1991, 1995 1998). The fluidity and curvature of lipid bilayer also

influence the lipid-peptide interaction. Fluid bilayers are more susceptible to the peptides. Cholesterol found in eukaryotic cell-membrane is responsible for fluidity and modulates the activity of the inserted peptides by hindrance (Matsuzaki *et al*., 1991). It has been suggested that the formation of hydrogen bonds between glutamates and cholesterol reduces the antibiotic activity.

The composition and architecture of prokaryotic and mammalian membrane is neither static nor symmetrical. Phospholipid is highly asymmetrically distributed in the cell membranes. Only 2% of total PE is oriented towards the outer membrane leaflet in the bovine erythrocyte. These differences in the asymmetric distribution, composition stoichiometry and saturation of phospholipid bilayer highly influence the membrane phase transition and fluidity. Lash *et al.* (1998) demonstrated that a polylysine peptide induces bacterial 1, 2-dimyristoyl-PE to separate from lippolysaccharide into a distinct domain. This means that interaction with peptides promotes abnormal asymmetry within or between phospholipid bilayer membranes.

Many antimicrobial peptides exist in unstructured conformation prior to interaction with the target cells, and after binding with pathogen membrane, peptides undergo conformational change to helical or other structures that effect antimicrobial activity. Tam *et al.* (2000) examined the influence of conformation on membranolytic selectivity of antimicrobial peptides. Unger *et al.* (2001) also provided additional insight into the structural basis for selective toxicity of AMPs. As compared to linear structure, the cyclized peptides are less efficient in initial binding to phospholipid membrane, and after binding to the lipid bilayer, these cyclized peptides convert to 75% of helical structure in comparison to their linear analogs. Oren *et al.* (1999) also shed light on the relationship between quaternary structure and selective toxicity among antimicrobial peptides. Human cathelecidin LL-37 is an antimicrobial peptide cytotoxic to both bacterial and mammalian cells. This peptide exists in equilibrium as monomer and oligomer in solution at low concentration but undergoes self association within zwitterionic and electronegative phospholipid membranes *in vitro*. The mechanism of action of LL-37 is detergent like, forming a structure membrane perturbation, this is referred as a carpet mechanism. Kol *et al.* (2001) demonstrated that the ability of peptides to induce phospholipid translocation is greater for peptides containing more lysine or histidine residues, compared to those containing tryptophan.

Antimicrobial peptide mediated cell killing may be rapid and in the case of some α-helical peptides, it is so quick that it is difficult to characterize the steps preceding cell death (Boman, 1995). Although, there is not any specific mechanism for antimicrobial activity some basic steps do occur. Among them, is the electrostatic bonding between the peptides and structures on the bacterial cell surface. Many peptides rapidly undergo highly structured amphipathic α-helical conformation upon interaction with the phospholipid bilayer. The frog skin peptide PGLa (the peptide which starts with glycine and ends with leucine amide) is in a disordered state but after being exposed to a membrane, it adopts a helical structure in the presence of PG and PE (Latal *et al*., 1997). Magainins only undergo a helical transition when interacting with anionic

membranes (Matsuzaki *et al*., 1991). In comparison, β-sheet antimicrobial peptides are in a much more ordered state in aqueous solution and membrane environments due to the constraint imposed by disulfide bonds. The secondary structure of tachyplesin, a b-sheet peptide, remains relatively stable on interaction with the target cell membrane. Antimicrobial peptides may self-associate following the initial interaction with the target membranes. These peptide-peptide interaction and peptide-lipid interaction within membranes create a complex structure, associated with specific antimicrobial mechanism of action. Peptides with well defined hydrophobic and hydrophilic domains efficiently orient themselves towards their respective membrane constituents or corresponding domains in adjacent peptides. This orientation facilitates the movement of amphipathic peptides deep into the hydrophobic membrane core.

Various models have been proposed as per the prevailing concepts of the mechanism of action of antimicrobial peptides.

The Barrel-Stave Mechanism

This mechanism describes the formation of transmembrane channels or pores by bundles of peptides. During binding, the hydrophobic residue/surface of α-helical or β-sheet peptides faces outward whereas the hydrophilic surface forms pore linings (Ehrenstein and Lecar, 1997; Breukink and Kruijiff, 1999). After binding, these peptides undergo conformational phase transition, forcing the polar phospholipid head groups to align, thus inducing membrane thinning. Subsequently, leakage of intracellular components causes cell death. This mechanism of action has been proposed for Alamethicin (Sansom, 1991, Beven *et al*., 1999, Yang *et al*., 2001).

The Carpet Mechanism

According to the carpet model, the peptides first bind onto the surface of the target microbial cell membrane covering it like a carpet. The initial interaction is due to electrostatic binding. In the second step, when this interaction reaches threshold concentration, the peptides cause membrane permeation leading to lysis of the microbial cell. The presence of negatively charged lipids is important for a peptide carpet to form as they help to reduce the repulsive electrostatic forces between positively charged peptides.

The Torroidal Pore Mechanism

Being one of the most well characterized peptide membrane interaction, it is also called the supra-molecular complex. It represents a membrane-spanning pore lined with polar peptide surfaces and phospholipid head groups. The α-helical peptides like magainins and PGLa are known to act by this mechanism. The hydrophobic residues of the bound peptides displace the polar head groups, creating a breach in the hydrophobic region of the membrane. This induces a positive curvature strain in the membrane (Hara *et al*., 2001). When the peptide reaches a threshold peptide to lipid ratio (estimated to be 1:30 for maganin), they orient themselves perpendicular to the membrane. At this point, helices begin to self associate so that their polar residues are away from the membrane hydrocarbon chains. This transient structure forms the dynamic peptide-lipid supra-molecular or torroidal pore complex.

Alternative Mechanism of Action: Intracellular Targets of Antimicrobial Peptides

In addition to their interactions act directly with lipid bilayers of the target membrane, antimicrobial

peptides might target intracellular molecules like DNA or enzymes. Bac5 and Bac7 inhibit protein and RNA synthesis of *E. coli* and *Klebsiella pneumonia*. Similarly, buforin II inhibits the cellular functions of *E. coli* by binding to DNA and RNA after penetrating the cell membrane (Park *et al*., 1998). Some antimicrobial peptides interfere with the metabolic processes of the microbes, e.g., a glycine rich peptide, attacin, blocks the transcription of the OMP gene in *E. coli* (Carlsson *et al*., 1991). It has also been presumed that many antimicrobial peptides may act synergistically with some host molecules for their active antimicrobial activity.

Therapeutic Property

The widespread increasing of observation of the bacterial resistance towards conventional antibiotics has led to an intensive search for more effective antimicrobial agents (Bonomo, 2000). AMPs are attractive alternative candidates for antibiotic treatment, because they offer several advantages over the currently used drugs. They combat pathogenic microbes by natural processes; target the fundamental structures such as bacterial membrane, and in most cases, target molecules within the cells. Due to this broad range of their targets the resistance towards these peptides would be difficult for the bacteria to develop.

Antimicrobial peptides are now being tested to gauge their response to local infections. Magainin pharmaceuticals, Inc (Plymouth Meeting, Pa) have taken the α-helical magainin variant MSI-78 into the phase-III clinical trial to test its efficacy against polymicrobic foot-ulcer infections in diabetics. It was reported that the trial demonstrated equivalency to the orally administered oflxacin with less side effect. Applied microbiology has initiated the trials to test the efficacy of the lantibiotic peptide nisin against the *Helicobactor pylori* in stomach cancer (http://www.businesswire.com/cnn/ambi.htm). Some peptides have been shown to be effective in systemic infections. α-helical-peptide (SMAP29) is effective against *Pseudomonas aeruginosa* in peritoneal infections, β-sheet-protegrin is effective against methicillin-resistant *Staphylococcus aureus* (MASA), vancomycin-resistant *Enterococcus faecalis* (VRE) and *P. aeruginosa* and indolicidin is effective against *Aspergillus* fungal infections (Ahmad *et al*., 1995). Human lactoferricin has also proved to be effective in systemic infections.

Current knowledge regarding the relationship between peptide structure, function and mechanism of action can be applied in semirational design of antimicrobial peptides with variance of microbicidal activity or altered target pathogen specificities.

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