Acta Scientific Veterinary Sciences (ISSN: 2582-3183)

Volume 3 Issue 8 August 2021

Short Communication

Antimicrobial Peptides as Potential Alternative to Antibiotics

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Received: June 01, 2021

Published: July 14, 2021

Introduction

Antibiotic resistance is one of the most serious challenges to global health, so researchers are looking for new ways to fight it. Antimicrobial peptides (AMPs) are one among the widely researched alternatives to standard antibiotics [3]. Antimicrobial peptides (AMPs), also known as host defense peptides, are short, naturally occurring, typically 12-50 amino acid residues long, possess a net charge (due to an abundance of Arg and Lys residues) and have a considerable proportion of hydrophobic residues (usually 50%) which allows them to fold into amphipathic conformations. They're found in a vast variety of life forms (microorganisms to humans), display remarkable structural and functional diversity and have broad spectrum of targeted organisms [1].

History

In 1922, Alexander Fleming discovered lysozyme, which is thought to be the first instance of a peptide with antimicrobial activity. However, lysozyme's mechanism of action was not understood to be enzymatic degradation of the bacterial cell wall at the time of its discovery, putting it in a different group than AMPs. Dubos isolated an antimicrobial agent from a soil *Bacillus thuringiensis* in 1939 and named gramicidins [4]. In the late 1970s and 1980s several AMPs and antimicrobial proteins were reported from leukocytes, including what are now known to be α -defensins from rabbits and humans. Till date more than 5,000 AMPs have been discovered and synthesized [6].

Biosynthesis and release

AMPs are synthesized as an inactive pre-proproteins precursor, which allow for transcriptional and posttranscriptional regulation of the mature biologically active peptides. The precursor proteins are proteolytically cleaved by specific proteases such as serine proteinase-3 to generate the biologically active mature form of the peptide.

Structure and classification of AMPs

Majority of ADPs have been classified into three major structural groups defined as (a) α-helical (e.g., magainin), (b) β-stranded (e.g., α- and β-defensins), (c) extended (e.g., indolicin) (Figure 1) [7].

Figure 1: Structural diversity of antimicrobial peptides.

Common properties of antimicrobial peptides

Although AMPs are a diversified group of molecules in terms of sequence, structure and sources, there are various features that are common to most AMPs.

Positive charge

This favors its interaction with the lipopolysaccharide membrane (negatively charged) of microorganism, or with teichoic and lipoteichoic acids from the wall of Gram positive bacteria [10].

Hydrophobic nature

It is very important feature for all AMPs and is the number of hydrophobic residues like tryptophan, valine, leucine, isoleucine, etc. within the peptide (50% for AMPs) and is needed for the insertion of the AMP within the cell/ plasma membrane [2].

Amphipathicity

It refers to the abundance of hydrophobic and hydrophilic residues within the AMPs.

Mechanism of action of AMPs

AMP kills microorganisms through membrane permeation method, although they have to affect important internal cellular processes required from macromolecular synthesis (i.e. RNA, DNA synthesis). The membrane targeting AMPs can have both receptor mediated as well as non-receptor mediated interactions [7].

Intracellular mode of action

AMPs also affect several internal cellular processes from macromolecular synthesis such as inhibition of nucleic acid synthesis and metabolism; protein biosynthesis and metabolism; protein folding inhibitor; cell wall biosynthesis thus killing the bacteria**.**

Direct killing by membrane permeabilizing mechanism of action

AMP being positively charged interacts with negatively charged lipopolysaccharide membrane of bacteria and accumulates at the surface and get self-assembled on the bacterial membrane after reaching a certain concentration. At this stage three models are used to describe the mechanism of AMPs. The models are classified under two broad categories:

- **Transmembrane pore:** This can be further subdivided into the:
- The barrel-stave pore model and
- The Toroidal pore model.
- **Non-pore models:** Carpet model.

Figure 2: Various models have been used to describe the action of AMPs.

The barrel-stave pore

The AMPs are initially attaches parallel to the cell membrane but eventually insert perpendicularly in the lipid bilayer leading to lateral peptide-peptide interactions similar to that of membrane protein ion channels (Figure 2A). Amphipathic structure of the peptide (α and/or β sheet) is required in this pore formation mechanism as the hydrophobic regions interact with the membrane lipids and hydrophilic residues form the lumen of the channels [9].

The toroidal pore model

In this model, the peptides are insert perpendicularly initially in the lipid bilayer but there is no specific peptide-peptide interactions. Rather the peptides induce a local curvature of the lipid bilayer with the pores which is formed by peptides and by the phospholipid head group (Figure 2B). This supramolecule is known as the "toroidal pore". There is disruption of the hydrophilic and hydrophobic arrangement of bilayer [7].

The carpet model

In this model, AMPs can also act without forming specific membrane pores. AMPs are adsorbed parallel to the lipid bilayer until they reach maximum concentration covering whole surface of the membrane, thus forming a "carpet" (Figure 2C). While the outer membrane is covered with high concentration of AMP molecules,

the inner layer is free of AMP binding. This results in imbalance of surface tension and charge over the membrane leading to collapse of membrane integrity and leakage of the cytoplasmic contents, ions and biomolecules [8].

Advantages of antimicrobial peptides

- The most appealing application of AMPs is their use as therapeutic substitute of antibiotics.
- They are more effective over the conventional antibiotics as they have broad-spectrum antibacterial, antifungal and antivirus activities.
- Can be used as anti-tumour drugs.
- Rapid onset of killing and have very low levels of resistance.
- Potent with fast bactericidal activity at low bactericidal concentration, even effective on strains which show resistance towards conventional antibiotics and even have synergistic effects with typical antibiotics to neutralize endotoxin.
- These AMPs are safe with very less to no cytotoxic effects and are hard to induce bacterial drug resistance compared to the conventional antibiotics [5].

Limitations

- Physical stability at physiological conditions (proteases, serum, salt, pH etc).
- High production cost.
- Allergic reactions after repeated application.
- Natural resistance.

Conclusion

- With increasing reports of multidrug-resistant, a unique category of antimicrobials is in extreme demand.
- AMPs are potential agents with various structural and antimicrobial properties and represent one among the foremost promising future drug candidate for combating infections and drug resistance.
- Are less susceptible to resistance as compared to standard antibiotics.
- The continuous discovery of natural AMPs from numerous sources will further expand the current AMP database.

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