Anti-microbial Peptides: New Weapon against Bacteria

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Abstract

Antimicrobial peptides (AMPs), also known as host defense peptides, are short and generally positively charged peptides found in a wide variety of life forms from microorganisms to humans. Most AMPs have the ability to kill microbial pathogens directly, whereas others act indirectly by modulating the host defense systems. Against a background of rapidly increasing resistance development to conventional antibiotics all over the world, efforts to bring AMPs into clinical use are accelerating.

Keywords

Anti-microbial Peptides, Host defense systems, Pathogens

Introduction

20th Century was marked by the undeniable success in the field of treatment and prophylaxis of infectious diseases. However with advancements in treatment protocols and drugs being used, the bacteria are also evolving. The spread of drug-resistance is of major concern and poses a serious threat to the existing medical doctrine founded on the effective use of antibiotics. In 2015, the Global Action Plan on anti-microbial resistance was endorsed at the 68th World Health Assembly which emphasizes more on development of new compounds and methods effective against multi-drug resistant microbes.

Anti-microbial peptides

They are evolutionary conservative tools of the innate immunity providing immediate response to a large set of various pathogen. They were firstly discovered by Dubos in 1939 from soil bacillus. Hotchkins and Dubos fractioned and identified it as Gramicidine. AMPs are oligopeptides are generally cationic and amphipathic molecules with varying number of amino acids with a broad spectrum of target range.
So far more than 800 AMPs have been discovered.

**Structure**

**α-Helical symmetry**

Contains 12-40 amino acid residues and helix stabilizing residues such as alanine, leucine and lysine but never cysteine.

**β-sheet symmetry**

Typically contains 2-10 cysteine residues that from intrachain disulphide bonds which allows then adopt the **β-sheet** conformation.

**Loop structures**

Proline and arginine rich peptides. They cannot form amphipathic structure. Rather they form polyproline type II structure. The peptides of their group are of great interest due to their short sizes, proteolytic stability and ease of synthesis.

**Other structures**

Rich in certain specific amino acids. For example- Histatine- peptide rich in histidine residues.

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**Some anti-microbial peptides and their sources**

| Class          | Representatives                  | Host                     |
|----------------|----------------------------------|--------------------------|
| **α-helical**  | LL-37                            | Mammal: human            |
|                | Cecropins                        | Insect: moth             |
|                | Melittin                         | Insect: honey bee        |
|                | Magainins                        | Amphibian: frog          |
|                | Fowllicidins                     | Ave: chicken             |
| **β-sheet**    | Thanatin                         | Insect: soldier bug      |
|                | Tachylesins                      | Arthropod: horseshoe crab|
|                | Protegrins                       | Mammal: pig              |
|                | Plant defensin VrD2              | Plant: mung bean         |
|                | Plectasin                        | Fungus: ebony cup        |
|                | Insect defensin A                | Insect: northern blow fly|
|                | α-defensin                       | Mammal: human            |
|                | β-defensin                       | Mammal: human            |
|                | θ-defensin                       | Mammal: rhesus monkey    |
| Flexible       | Indolidicidin                    | Mammal: cow              |
|                | Trirpticin                       | Mammal: pig              |
|                | Histatins                        | Mammal: human            |
|                | PR-39                            | Mammal: pig              |
Classification of AMPs based on the ionic structure

### Classification of AMPs

| CLASS                        | EXAMPLE  | STRUCTURE | ORIGIN     |
|------------------------------|----------|-----------|------------|
| Anionic peptides             | Dermicidin | Asp & Glu | Human      |
| Cationic peptides            | Cecropin | Helical   | insects    |
|                              | LL37     | Helical   | Human      |
| Cationic peptides with specific amino acids | PR 39 | Pro & arg rich | Pig |
|                              | Prophenin | Pro & Phe | Pig        |
|                              | Indolicidin | Trp rich  | cattle     |

### Cont....

| Peptides that forms disulphide bridges | Brevinins | 1-disulphide bridge | Amphibians |
|----------------------------------------|-----------|---------------------|------------|
| Tachyplesin                            | 2-disulphide bridges | Horse shoe crab    |
| Defensins                              | 3-disulfide bridges | Human              |
| NK-lysin                               | 3-disulfide bridges | Pig                 |
| Drosomycin                             | More than 3-disulfide bridges | Fruitfly |
| Fragmented peptides                    | Lactoferricin | 14-42 a.acids | Human     |
Mechanism of action

The basic mechanism of action of anti-microbial peptides is the alteration of cell membrane permeability which leads to the loss of cellular components resulting into cell death.

Variation models have been proposed to the prevailing concepts of mechanism of action on anti-microbial peptides.

The following mechanism of action is being followed –

**Barrel-Stave model**

Formation of transmembrane channels or pores by bundles of peptides.

During binding, hydrophobic residue/surface of alpha-helical and beta-sheet peptides face outwards whereas the hydrophilic surface for the pore-lining. After binding these peptides undergo conformational changes, facing the polar phospholipids head group to align, thus inducing membrane thinning eventually leading to leakage and cell death.

**Carpet model**

Due to electrostatic binding, the peptides cover the membrane like a carpet and when the electrostatic interaction reaches a threshold concentration, peptides cause membrane permeation leading to lysis of microbial cell.

**Torroidal pore**

Represents a membrane spanning pore lined with polar peptide surface and phospholipids head group. The alpha-helicals like magainins and PGA act by this mechanism. The hydrophobic residues bond peptides displace polar head groups thus creating a breach in hydrophobic region of membranes.

**Anti-microbial peptides and their uses**

**Plays a major role in maintenance of innate immunity**

![Graph showing Spectrum of biological activity of AMPs](image)

**Therapeutic potential**

Magainin pharmaceutical Inc. have taken the α-helical magainin variant MSI-78 into Phase-III clinical trials to test it’s efficacy against polymicrobial foot ulcer infection in diabetes.

Trials initiated to test Lantibiotic Nisin against *Helicobacter pylori* in stomach cancer.

α-helical peptide SMAP29 is effective against *P.aeruginosa* in peritoneal infections.

Beta sheet protegrins is effective against MRSA, VRE and *P.aeruginosa*.

**Food preservation and as a feed additive**

Peptides such as PR-39 have been shown to inhibit the growth of *S. typhimurium* by interfering with it’s DNA synthesis.
Similarly another peptide named Sphenicin has action against many gram positive and negative bacteria and thus helps in decreasing microbial spoilage of food.

Similarly there are peptides such as protamine and magainins which have almost identical mechanism of action and reduce food spoilage.

**Feed additive**

In a recent study on piglets, it was concluded that antimicrobial peptides can also be used as a feed additive.

Piglets were fed a diet rich in antimicrobial peptides such as AMP-P5, Cercopins, Colicin, Lactoferrin.

All of them showed a positive effect on immune status of the animals, and apparent digestibility and also reduced the quantity of coliforms from the digestive tract which might cause a disease condition.

**AMP as a drug fighting against bacteria**

IN 2016 Lam *et al*., described SNAPPS

**SNAPPS** stands for-
- Structurally Nanoengineered Antimicrobial Peptide PolymerS

SNAPPS are a unique class of star shaped AMPs with activity against broad range of Gram negative bacteria.

SNAPPS are built from short chains of lysine and valine,

These peptide arms are conjugated at one end to a core of poly (amidoamine) and each core may be linked to 16-32 arms resulting into a positively charged protein star about 20nm across.

The goal of this project was to replace chemically synthesised SNAPPS with fully synthetic biological fusion proteins.

**Criteria for selecting core proteins**

The monomer must be expressible in *E.coli*.

The monomer must self-assemble into a homomultimeric complex.

The complex must have size between 4-25 nm.

The complex must have known structure deposited in PDB.

The N- and or C-termini of the monomers should be free.

The set of complexes should be of diverse shapes.

**Different antimicrobial peptides and their sources**

| PEPTIDE       | ORIGIN                              | ACTION                        |
|---------------|-------------------------------------|-------------------------------|
| DEFENSIN      | *Crassostrea gigas* (oyster)        | Anti-bacterial, anti fungal   |
| ALYTESERIN    | *Allytes obstetricus* (Toad)        | Anti-bacterial, cytotoxic     |
| ARENSIN       | *Pardachirus pavoninus* (fish)      | Cytotoxic                      |
| PalG1         | Cow rumen                          | Anti-bacterial                 |
| PONERICINS    | *Pachycondyla goeldii*              |                               |
| CECROPINS     | *Hyalophora cecropia* (cecropia moth)| Anti-bacterial                |
| SQUALAMINE    | Deep water sharks                   |                               |
| NISIN-34aa    | *Lactococcus bacteria*              | Anti-bacterial                 |
| PUROTHIONINE  | *Triticum aestivum* plant           | Anti-bacterial, cytotoxic      |
| TYROCIDINE    |                                    | Anti-bacterial, cytotoxic      |
Resistance to AMPs

1. Substitution modification
2. Acylation of membrane proteins
3. Activation of some proteolytic enzymes and proteins
4. Efflux pump and modification of targets

**Fig. 1** Substitution modification

![Substitution modification](image1)

**Fig. 2** Acylation of membrane proteins

![Acylation of membrane proteins](image2)
Conclusion of the study is as follows:

AMPs are multi-purpose and multi-functional peptides with very wide-spectrum use and biological activity.

Based on their natural AMPs, their synthetic analogs can be developed.

They can be used as prebiotic and antibiotics or feed additives to improve the microflora.

Can be developed into synthetic analogs to be used as a mode of treatment against cases of infection with Drug Resistant bacteria as the causative pathogen and can revolutionise treatment protocols all around the world.

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