Antimicrobial peptides as an alternative to antibiotics

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Introduction:

Antimicrobial resistance (AMR) is a new worldwide health issue that can make treating bacterial infections more difficult in certain situations. Since it is expected to kill roughly 10 million people year by 2050, the World Health Organization (WHO) named it one of the top ten global public health dangers confronting humanity (O'Neill, 2016). As a result, worldwide efforts have been made to slow the spread of AMR. As a result, in 2015, the Global Action Plan on Antimicrobial Resistance (GAP) was developed with the goal of putting national action plans into action to slow the spread of AMR. Furthermore, the WHO studies stress the significance of finding and creating new antibiotics and urge immediate action to prevent a crisis of antimicrobial resistance. Therefore, there is a need for novel drugs that are effective against pathogens, particularly those that cause nosocomial infections and have a propensity to develop multidrug resistance. Since antibiotic resistance is one of the biggest threats to world health, scientists are searching for novel strategies to combat it. A popular substitute for conventional antibiotics that has been extensively studied is antimicrobial peptides (AMPs).

The antimicrobial peptides (AMPs) are short, naturally occurring antimicrobial peptides (AMPs), also referred to as host defence peptides, are usually 12–50 amino acid residues long, have a net charge (from the abundance of Arg and Lys residues) and contain a significant percentage of hydrophobic residues (usually 50%), which enables them to fold into amphipathic conformations. They are present in a wide range of creatures, from microbes to humans, exhibit extraordinary structural and functional diversity and target a wide range of organisms (Bahar & Ren et al. 2013).

As secondary metabolites, these compounds are a component of innate immunity and are often ribosomally synthesized by epithelial cells in humans, but they can also be created by phagocytes, which are immune system cells. Tissues and mucous membranes contain these peptides; in fact, the latter are home to a wide variety of commensal or pathogenic microbes. Some of these peptides have a wide range of antimicrobial activity, meaning they can suppress or kill various microorganisms (MO), including viruses, protozoa, and Gram-positive or -negative bacteria and/or fungi. Over 3257 antimicrobial peptides have been described,

according to The Antimicrobial Peptide Database (Huan et al. 2020).

History: Lysozyme, which Alexander Fleming discovered in 1922, is believed to be the first example of a peptide having antibacterial activity. However, at the time of its discovery, the mechanism of action of lysozyme was not recognized as enzymatic destruction of the bacterial cell wall, placing it in a separate category than AMPs. Gramicidins are an antibacterial agent that Dubos identified from Bacillus thuringiensis soil in 1939. Several AMPs and antimicrobial proteins, including what are now known to be α-defensins from humans and rabbits, were described from leukocytes in the late 1970s and early 1980s. Over 5,000 AMPs have been identified and produced to date.

Characteristics of Antimicrobial Peptide:

The majority of AMPs share a number of characteristics, despite the fact that they are a diverse group of molecules with respect to sequence, structure, and origins.

1. Positive charge: This promotes its interaction with teichoic and lipoteichoic acids from the wall of Gram-positive bacteria or with the negatively charged lipopolysaccharide membrane of microorganisms.

2. Hydrophobic nature: The quantity of hydrophobic residues, such as tryptophan, valine, leucine, isoleucine, etc., in the peptide—50% for AMPs—is a crucial characteristic of all AMPs and is required for the insertion of the AMP into the cell/plasma membrane.

3 Amphipathicity: This describes how many hydrophilic and hydrophobic residues are present in the AMPs.

Mechanism of action: AMPs work by killing germs by membrane penetration, but they must interfere with crucial internal cellular functions that are necessary for macromolecular synthesis (such as RNA and DNA synthesis). Both receptor-mediated and non-receptor-mediated interactions are possible with membrane-targeting AMPs.

A. **Intracellular Mode of Action:** Aside from macromolecular synthesis, AMPs also impact a number of internal cellular functions, including the suppression of nucleic acid synthesis and metabolism, protein biosynthesis and metabolism, protein folding inhibitor, and cell wall production, all of which result in bacterial death.

B. **Direct killing through a membrane-permeabilizing mechanism:** When AMP reaches a specific concentration, its positively charged nature interacts with the negatively charged lipopolysaccharide membrane of bacteria, causing it to collect at the surface and self-assemble. At this point, the mechanism of AMPs is described by three models. Two major categories are used to classify the models:

a) **Transmembrane pore: which is further subdivided into t**he barrel-stave pore model and the toroidal pore model

b) **Non-pore models:** Carpet model

Barrel-stave pore: Lateral peptide-peptide

interactions akin to those of membrane protein ion channels result from the AMPs' initial attachment parallel to the cell membrane and eventual perpendicular insertion in the lipid bilayer. Since the hydrophilic residues produce the channel lumen and the hydrophobic portions interact with the membrane lipids, the peptide's amphipathic structure (α and/or β sheet) is necessary for this pore formation mechanism (Wimley, 2010).

Toroidal pore model: There are no particular peptide-peptide interactions in this scenario, even if the peptides are originally inserted in the lipid bilayer perpendicularly. Instead, the phospholipid head group and peptides create holes that cause a local curvature of the lipid bilayer (Figure 2B). The "toroidal pore" is the name given to this supramolecule. The bilayer's hydrophilic and hydrophobic configuration is upset (Kumar et al. 2018).

Carpet model: AMPs can also function in this scenario without creating particular membrane holes. A "carpet" is created when AMPs are adsorbed parallel to the lipid bilayer until they reach their maximum concentration and cover the entire membrane's surface. Although there is a large concentration of AMP molecules covering the outer membrane, there is no AMP binding in the inner layer. As a result, the membrane's integrity collapses and cytoplasmic contents, ions, and biomolecules leak out due to an imbalance in surface tension and charge across the membrane (Aisenbrey et al. 2019).

Advantages of Antimicrobial peptides:

- The most promising use of AMPs is as a therapeutic antibiotic alternative; they are more potent than traditional antibiotics due to their broad-spectrum antibacterial, antifungal, and antiviral properties.
- They can also be employed as anti-tumor medications.
- Rapidly kills the micro-organism and extremely low resistance levels.
- Capable of fast bactericidal activity at low concentrations
- Even effective against strains that exhibit resistance to traditional antibiotics; and even work in concert with common antibiotics to neutralize endotoxins.
- Compared to traditional antibiotics, these AMPs are harmless, have negligible to no cytotoxic effects, and are difficult to cause bacterial drug resistance (Rima et al. 2021).

Constraints:

- Stability under physiological settings (pH, serum, salt and particularly their vulnerability to protease degradation) (Svendsen et al. 2019).
- The cost of manufacture is high.
- Short half-lives, cytotoxicity and lack of specificity
- Reactions to allergies with repeated use.
- It is impossible to exclude out the development of bacterial resistance to AMPs, particularly if the microbe is frequently exposed to them (Nuding et al. 2013).
- **Conclusion:**

- There is a great need for a special class of antimicrobials due to the growing number of reports of multidrug resistance.
- Are less prone to resistance than conventional antibiotics.
- Constantly discovering natural AMPs from a variety of sources will increase the current AMP database.
- AMPs are potential agents with various structural and antimicrobial properties and represent one of the most promising future drug candidates for combating infections and drug resistance.

References

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