THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
Popular Article
June, 2023; 3(06), 1104-1107

Antimicrobial Peptides: from host defence to therapeutics

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https://doi.org/10.5281/zenodo.8078858

Abstract

Our over-reliance on antibiotics, their overuse and inappropriate prescription has created a serious antimicrobial resistance (AMR) crisis such that the world is on the verge of entering the 'post antibiotics era'. According to CDC, AMR is an urgent global threat affecting health care, veterinary, aquaculture, fisheries, and agriculture industries. The discovery of antimicrobial peptides (AMPs) and the magic bullet 'antibiotics' were contemporary but the former didn't gain attention for therapeutic exploitation. The renewed interest in antimicrobial peptides is a consequence of increasing cases of AMR.This article outlines the diversity, physicochemical properties, mechanism of action, and therapeutic potential of AMPs.

Keywords: Antibiotics, Antimicrobial Peptides, Interaction, Potential

Overview

Antimicrobial peptides (AMPs) are naturally occurring host defense peptides produced by every domain of life ranging from prokaryotes to multicellular organisms including humans and plants as part of their innate defense mechanism. These evolutionarily conserved effector molecules are found abundantly in organs exposed to the external environment or at the passage of pathogen entry. These biological molecules are either expressed constitutively or upregulated during infections. They show broad-spectrum antibiotic activity, targeting bacteria, fungi, viruses, parasites, and even cancerous cells. In most organisms, AMPs are multifunctional molecules that not only provide resistance against pathogen attack but are also involved in other biological functions like immune modulation, wound healing, inhibiting cancer cell growth, and/or functioning as signaling molecules such as hepcidins that are also involved in iron regulations **(**Shi and Camus, 2006; Raju ***et***

al., 2020**).** These characteristic features make them an attractive candidate for application in medicine, like dermatology, ophthalmology, and cancer therapy.

About 90 years have passed since the discovery of 1st naturally occurring AMP viz., Lysozyme, in the human body by Alexander Fleming (Fleming, 1922). Characterization of the first AMP in prokaryotes dates back to 1939 when René Dubos isolated 'gramicidin', from a soil bacterium, *Bacillus brevis*,and found that it protects mice from *Pneumococci* infection (Dubos, 1939), and today gramicidins have become one of the most commercialized AMP (Cheng *et al.,* 2014). Hirsch reported the first animal-originated AMP 'defensin' in 1956, isolated from the leukocytes of rabbits (Hirsch, 1956). AMPs have also been isolated from plants, for example, purothionin obtained from *Triticumaestivum* and was found to be effective against fungi and some phytopathogenic bacteria (Balls *et al.,* 1942; De Caleya*et al.,* 1972). There are a number of databases documenting AMPs classification, prediction, design, and structure, one such database is the antimicrobial peptide database (APD). APD is continuously being updated and currently is in the APD3 version with a total of 3217 AMP entries.

Structure and Diversity

AMPs are predominantly chains of α-amino acids (2-100 mer) joined by a peptide bond. This diverse group of oligopeptides displays some standard characteristic features such as amphipathicity, net positive charge (+1 to +5), hydrophobicity (30-70%), and low molecular weight (<13kDa) **(**Chaturvedi*et al.,* 2020; Ganet *al.,* 2021**)**. Its primary structure is simple however, on the basis of secondary structure, AMPs are classified into four structural groups: α-helix, β-sheet, linearly extended, and loop. They are synthesized biologically, synthetically, or by a combination of both.

Mechanism of Action

Unlike antibiotics, AMPs attacks multiple target sites on the pathogen. They either work by disrupting the membrane or through immunomodulation. Membrane-disrupting AMPs such as buforin II are selectively cytotoxic to pathogens due to the fundamental difference in cell membrane composition of bacteria and host. In contrast to the host, the bacterial surface is negatively charged and so is the cancer cell (Mahlappu*et al.,* 2016; Gong *et al.,* 2020; Gan *et al.,* 2021). Initially, the cationic AMPs strongly interacts with the negatively charged surface of microbes through electrostatic interaction, followed by amphiphilic and hydrophobic interactions. Once the AMPs adheres to the surface it follows one or a combination of 3 membrane disrupting models, viz., (i) Barrel stave model, (ii) toroidal pore model, (iii) carpet model, ultimately disrupting the membrane integrity, while some may also interfere with the crucial intracellular processes (Kumar *et al.,* 2018). Some AMPs like defensin, cathelicidin, lactoferrin, and anti-LPS factor, exhibit additional

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Published **25.06.2023**

immunomodulatory properties, indirectly killing the pathogen by modulating the host's immune system. They are involved in recruiting APC to the site of infection, inducing the expression of anti-inflammatory cytokines while suppressing the expression of pro-inflammatory cytokines, binds to lipopolysaccharide, influence differentiation of T-cells and beyond (Gan *et al.*, 2021).

Therapeutic Potential

AMPs are emerging as a potential new class of antibiotics to combat AMR as they display multi-modal, rapid killing mechanisms thus reducing the probability of developing AMP resistance. Some AMPs also display synergistic effects by facilitating the activity of other antimicrobial compounds. Furthermore, AMPs like β-defensin, histatins and LL-37, have also shown efficacy against multi-drug resistant and biofilm-forming microorganisms (Hancock and Diamond, 2000; Le et al., 2022).

Nisin, gramicidin, polymyxins, daptomycin, and melittin are some of the commercialized AMPs. Nisin (From *Lactococcuslactislactis)*,is usedas a food preservative or as a treatment for stomach ulcers and colon infections(Gharsallaoui et al., 2016; Dijksteel*et al.,* 2021). Polyoxin (from *Streptomyces cacaoi*) is used as a fungicide (El-Naggar, 2021). Lactoferricin B (isolated mainly from bovine milk) is used as a controlling agent of mastitis (Weigel and Shook, 2018) whileGramicidin is a constituent of ophthalmic solutions.

Conclusion

Antimicrobial peptides are broad spectrum antimicrobial compounds with strong immunomodulatory and anti-cancer properties. They have become an ideal candidate for next generation anti-infective mainly due to its amenability to bioengineering. The field of AMP needs to be further explored and developed with the advancement of science to design AMP-based therapeutic approach in treating bacterial infections and in cancer therapies.

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