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Review Article

Antimicrobial peptides as potential anti-biofilm agents against multidrug-resistant bacteria

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Abstract Bacterial resistance to commonly used drugs has become a global health problem, causing increased infection cases and mortality rate. One of the main virulence determinants in many bacterial infections is biofilm formation, which significantly increases bacterial resistance to antibiotics and innate host defence. In the search to address the chronic infections caused by biofilms, antimicrobial peptides (AMP) have been considered as potential alternative agents to conventional antibiotics. Although AMPs are commonly considered as the primitive mechanism of immunity and has been extensively studied in insects and non-vertebrate organisms, there is now increasing evidence that AMPs also play a crucial role in human immunity. AMPs have exhibited broad-spectrum activity against many strains of Gram-positive and Gram-negative bacteria, including drug-resistant strains, and fungi. In addition, AMPs also showed synergy with classical antibiotics, neutralize toxins and are active in animal models. In this review, the important mechanisms of action and potential of AMPs in the eradication of biofilm formation in multidrug-resistant pathogen, with the goal of designing novel antimicrobial therapeutics, are discussed.

Introduction

Chronic wound infections as a result of pressure sores, venous legs ulcers and diabetic foot ulcers are typically caused by multiple genera of bacteria, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are strong biofilm formers.[1] The presence of biofilm has now been identified as the cause of poor healing of these

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wounds. While physical debridement can assist the healing of these wounds, biofilm-focused therapeutic approaches can promote more rapid healing in a large percent of patients.[2] Thus, a biofilm-centric approach to reduce the ability of these pathogens to form biofilms is urgently needed to enable more effective subsequent healing by the body or treatment with antibiotics. In the search for an effective agent that can treat chronic infections, antimicrobial peptides (AMPs) have been shown to demonstrate antimicrobial, anti-attachment and anti-biofilm properties.

AMPs are essential components of innate immunity in humans and other higher organisms, contributing to the first line of defense against infections.[3] Despite co-evolution with bacteria, AMPs have retained their advantage and bacteria have yet to develop wide-spread resistance. As such, there is growing interest in the therapeutic application of these molecules. Their amino-acid sequences, net-positive charge, amphipathicity, and very small size allow AMPs to bind to and disrupt membranes of microbes. Other researches have shown that AMPs can also inhibit cell wall, nucleic acid, and protein biosynthesis.[4]

Classification of AMP

AMPs are generally made up of 10—50 amino-acid residues and are divided based on the composition of their amino-acid, size and conformational structures. Due to the increasing number of AMPs, there are 13 databases of AMPs to date, which manage information and conduct peptide analysis (Fig. 1).[5]

Structurally, AMPs can be classified in four major classes: β-sheet, α-helical, loop and extended peptides,[6] with the first two classes being the most common in nature. Among the best studied AMPs are magainins, magainin 2 and PGLa, which are α-helical peptides that were originally isolated from the skin of the African frog *Xenopus laevis*.[7] In humans, the two most well characterized families of host defence peptides are cathelicidins and defensins. Cathelicidins are AMPs bearing an amino-terminal cathepsin L inhibitor domain (cathelin), and produced by leukocytes,[8] while defensins are a highly complex group of open-ended cysteine-rich peptides widely distributed in nature and found both in vertebrates and invertebrates. On the basis of their size and pattern of disulfide bonding, mammalian defensins are classified into α-, β- and θ-defensins.[9]

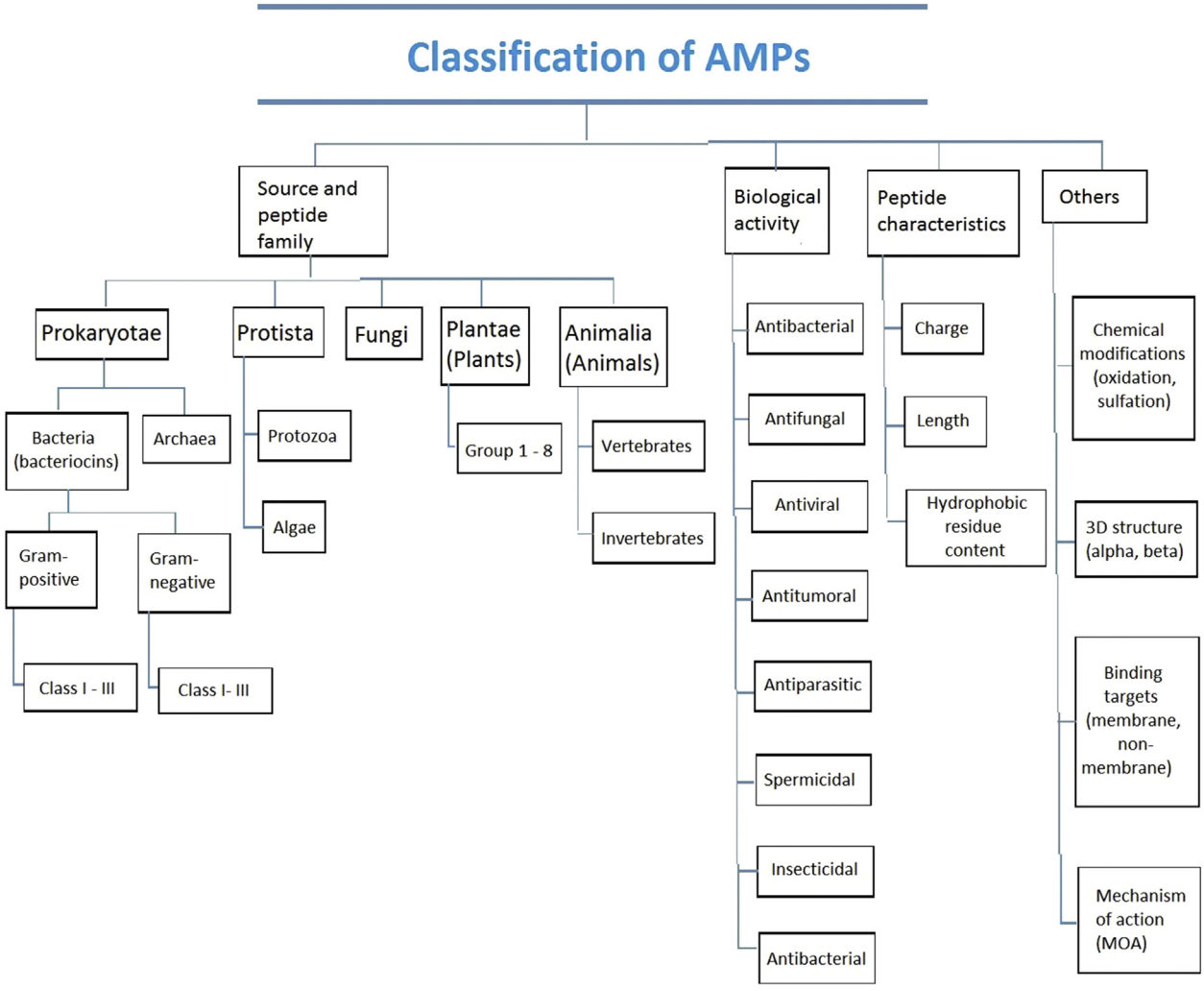

Figure 1. Classification of AMPs based on various referring factors.