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Strategies employed in the design and optimization of synthetic antimicrobial peptide amphiphiles with enhanced therapeutic potentials ☆

Zhan Yuin Ong, Nikken Wiradharma [1], Yi Yan Yang *

Institute of Bioengineering and Nanotechnology, 31 Biopolis Way, The Nanos, Singapore 138669, Singapore

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ABSTRACT

Antimicrobial peptides (AMPs) which predominantly act via membrane active mechanisms have emerged as an exciting class of antimicrobial agents with tremendous potential to overcome the global epidemic of antibiotics-resistant infections. The first generation of AMPs derived from natural sources as diverse as plants, insects and humans has provided a wealth of compositional and structural information to design novel synthetic AMPs with enhanced antimicrobial potencies and selectivities, reduced cost of production due to shorter sequences and improved stabilities under physiological conditions. In this review, we will first discuss the common strategies employed in the design and optimization of synthetic AMPs, followed by highlighting the various approaches utilized to enhance the therapeutic potentials of designed AMPs under physiological conditions. Lastly, future perspectives on the development of improved AMPs for therapeutic applications will be presented.

Contents

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* Corresponding author.
E-mail address: yyyang@ibn.a-star.edu.sg (Y.Y. Yang).
[1] Currently at Brigham and Women's Hospital, 65 Landsdowne St, Cambridge MA 02139, USA.

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1. Introduction

The global epidemic of antibiotics resistanct infections coupled with a decline in the number of new antibiotics entering the clinical development pipeline has greatly necessitated the exploration for alternative classes of antimicrobial agents [1]. In the last two decades, antimicrobial peptides (AMPs), with their potent and broad spectrum antimicrobial activities which also extend to various antibiotics-resistant microbes such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), multi-drug-resistant *Pseudomonas aeruginosa* and multi-drug-resistant *Mycobacterium tuberculosis* have emerged as a promising class of antimicrobial agents that could potentially revolutionize infectious disease treatments. Since the initial discovery of AMP mixtures, named gramicidins from soil *Bacillus brevis* in 1939, a myriad of AMPs has been identified and isolated from various natural sources including plants, invertebrates, amphibians and mammals [2,3]. To date, more than 2300 naturally occurring AMP sequences have been catalogued in various AMP databases [4–6]. Although vast sequence and structural diversities exist, AMPs share several common features including cationicity, amphipathicity and the acquisition of secondary α-helical, β-sheet, looped, extended and mixed structures in membranous environments (Fig. 1) [3,7], which taken together are believed to be central to the antimicrobial mechanisms of AMPs .

In general, positively charged AMPs accumulate at membrane surfaces via electrostatic interactions with the anionic phosphate head groups of membrane lipids to achieve a critical concentration beyond which insertion of the hydrophobic moieties of interfacially active AMPs into lipid bilayers occurs to mediate direct membrane disruptions via the barrel-stave pore, toroidal pore, disordered toroidal pore and/or carpet mechanisms, leading to cytoplasmic leakage, membrane depolarization, membrane lysis and cell death (Fig. 2) [8–10]. In the barrel-stave model, AMPs insert perpendicularly into the membrane bilayer to form pores, lining the pore lumen via parallel hydrophobic–hydrophilic associations with the phospholipid chains. The toroidal pore model, on the other hand, similarly proceeds via perpendicular membrane entry of the AMPs, but involves the inward folding of the membrane lipids such that continuous channels between the inner and outer leaflets are attained. The disordered toroidal pore model deviates from the standard toroidal pore mechanism in that less regular pore structures are formed and the peptides are mainly oriented parallel to the plane of the membrane. In the carpet mechanism, the AMPs bind parallel to the membrane surface and act to permeate and disperse the membrane in a detergent-like manner without pore formation once above a threshold concentration. Besides direct membrane-lytic antimicrobial activities, recent compelling evidence has also established that AMPs exhibit indirect antimicrobial mechanisms via translocation to internal cellular targets where they mediate metabolic inhibition through alteration of cytoplasmic membrane septum formation and the inhibition of cell wall, nucleic acid or protein synthesis or enzymatic activities after transmembrane pore formation in the microorganisms [8] as well as by mediating immunomodulatory effects in the host [11].

Despite the early promise of AMPs such as melittin, magainin and cathelicidins isolated from natural sources as alternatives to antibiotics, many of them are not optimal for therapeutic applications due to their long sequences translating into high production costs, limited supply, low potency, susceptibility to in vivo enzymatic degradation and salt inactivation as well as high hemolytic activities and cytotoxicities. The wealth of sequence and structural information provided by the naturally occurring AMPs, however, has provided significant leads for the creation of a new generation of more potent and less toxic synthetic AMP congeners in therapeutic applications [12,13]. In this review, we will provide an overview to the general approaches adopted in the design of fully synthetic AMPs and discuss the strategies to improve the therapeutic applications of AMPs under physiological conditions.

2. Design approaches towards synthetic AMPs development

General approaches adopted in the design and structural–activity relationship (SAR) studies of synthetic AMPs include sequence modifications from naturally occurring template peptides, de novo minimalist design of amphipathic peptides as well as the use of bioinformatics and combinatorial libraries to aid in the identification of new lead sequences [14,15].

2.1. Template modification

The reservoir of potent and broad spectrum AMPs available from species as diverse as plants, insects, amphibians and mammals present in nature provides an excellent and convenient resource for the design

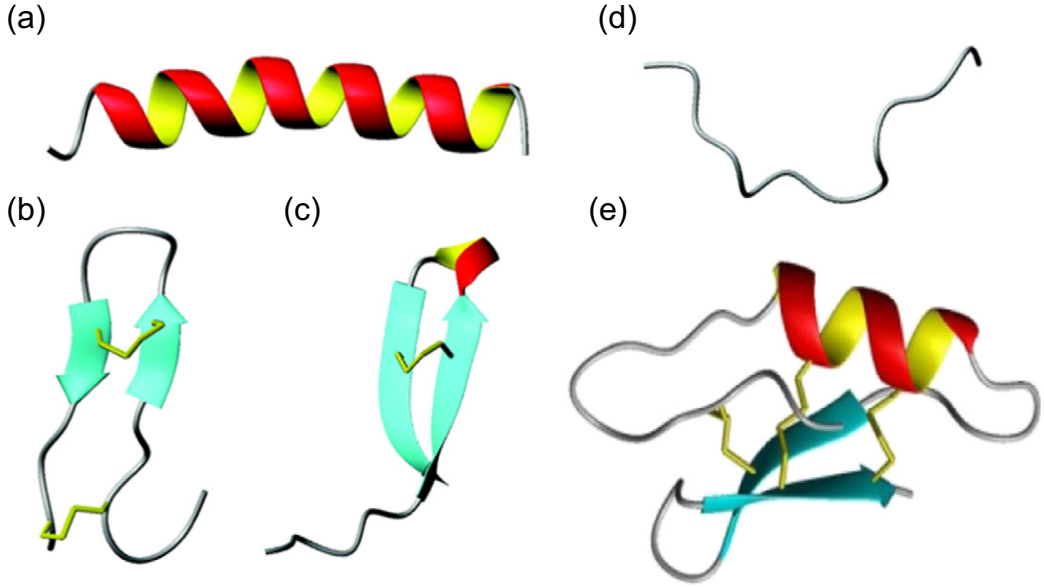

Fig. 1. Common structural classes of antimicrobial peptides: (a) α-helix, (b) β-sheet, (c) looped, (d) extended and (e) mixed secondary structures. Disulfide linkages are indicated by yellow bonds. Adapted with permission from Ref. [7], Copyright (2006) the American Society for Microbiology and Ref. [165], Copyright (2009) MDPI AG (Basel, Switzerland).