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Review

Recent updates of marine antimicrobial peptides

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ABSTRACT

Antimicrobial peptides are group of proteins showing broad-spectrum antimicrobial activity that have been known to be powerful agents against a variety of pathogens. This class of compounds contributed to solving the microbial resistance dilemma that limited the use of many potent antimicrobial agents. The marine environment is known to be one of the richest sources for antimicrobial peptides, yet this environment is not fully explored. Hence, the scientific research attention should be directed toward the marine ecosystem as enormous amount of useful discoveries could be brought to the forefront. In the current article, the marine antimicrobial peptides reported from mid 2012 to 2017 have been reviewed.

Contents

1. Introduction

Antimicrobial peptides (AMPs) are molecules known to be essential components of the innate immune response that can also participate in certain organisms as immune modulators (Zanetti, 2004). The living organisms use the AMPs as an important vital tool for survival. They combat the invading pathogens to the host via a broad spectrum of antimicrobial activity that can vary according to the nature of the pathogens (Lehrer et al., 1983; Ganz et al., 1985; Zasloff, 1987). The wide spectrum is in part attributed to the diversity in the structures of AMPs that vary from alpha helix to beta strands (Hancock, 2001). AMPs play defensive role for the producing organisms. When it comes to their selective toxicity, the AMPs explore the differences in the lipid composition of the membrane between eukaryotic and prokaryotic organism that serves as their target of action sparing the host from harmful effects. Nevertheless, the selectivity of these molecules also rise from the effect of the uniform net charge and hydrophobicity which are characteristic trades for AMPs. The majority of these compounds have been described to be carrying a uniform positive

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charge ranging from +2 to +9, with only few reported to be anionic in nature (Zasloff, 2002).

The cationic nature accounts for the AMPs mechanism of action, as it enables their binding to the negatively charged lipopolysaccharides invading pathogen membrane via electrostatic attractive forces. During this interaction, the AMPs acquire an amphipathic confirmation that optimizes the binding to the pathogen's membrane. This kind of AMPs are classified to be membrane permeabilizing peptides due to their capability of forming pores in the membrane after their electrostatic interaction, thus resulting in expulsion of cellular content and subsequent cell death (Sengupta et al., 2008). In addition to the previously mentioned mechanism, AMPs can act by interfering with some vital cellular processes inhibiting them after their translocation across the cellular membrane. These peptides are classified as non membrane-permeabilizing peptides (Kondejewski et al., 1999; Brogden, 2005).

AMPs nowadays are an interesting field of research for potential drug candidates owing to their broad spectrum of activity and more importantly to the fact that AMPs may overcome the antimicrobial resistance. Since AMPs target the lipid components in the membrane of the invading pathogens, this interference with such a vital structure in microbes creates a barrier against resistance development. This fact has directed the effort of scientific research to exploit the vast world of AMPs where we can find more than 2000 AMPs reported in antimicrobial peptide databases [http://aps.unmc.edu/AP/main.php/].

Despite the promising activity of the AMPs, they suffer from the following drawbacks. (i) limited stability at certain pHs; (ii) disrupt the cellular membrane of eukaryotic organisms causing hemolytic side effects; (iii) elevated production cost and technical issues are limitations of their manufacturing (Mygind et al., 2005); (iv) lack of data on their toxicity, pharmacodynamics, and pharmacokinetics properties (Evans et al., 1999; Michalopoulos et al., 2005); (v) reduced activity in the presence of some cations such as calcium, iron and certain serum conditions (Smith et al., 1996; Thackray and Moir, 2003).

We have previously reviewed the chemical and biological properties of the marine AMPs reported from 2009 to June 2012 (El-Gamal et al., 2013). Herein, we reviewed the very recent research results in the field of marine AMPs, which were characterized and identified in the time period from July 2012 till 2017. We have classified marine AMPs according to their biological effects into antibacterial, antimycobacterial, antifungal, antiviral, and antiprotozoal.

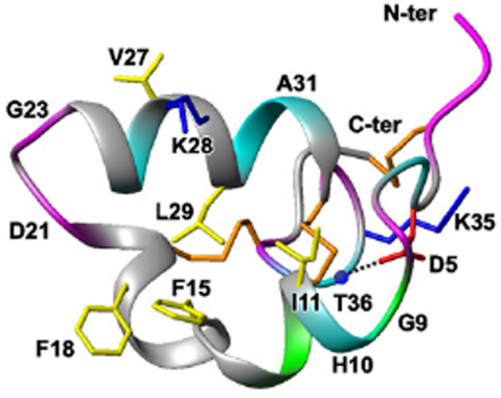

Fig. 1. Spatial structure and backbone dynamics of aurelin in aqueous solution (Shenkarev et al., 2012).

2. Antibacterial marine peptide

Almost there is no marine organism that does not produce natural antibacterial compounds as an essential line of defense to survive, hence marine antibacterial peptides is a rich class of antimicrobials with new discoveries.

Aurelin is an AMP derived from the mesoglea of a scyphoid jellyfish called *Aurelia aurita*. It is composed of 40 amino acid residues and described to be cationic in nature with a molecular weight of 4296.4 Da. It has demonstrated modest antibacterial activity against both Gram-positive and Gram-negative bacteria with MIC of 10 μM against the *Bacillus megaterium*, strain B-392, and 40 μM against *Micrococcus luteus*, strain Ac-2229 which were determined to be the most sensitive species to Aurelin. Fig. 1 shows that Aurlein is the first AMP to acquire Shk fold that enables Aurelin to have a diversity in its mechanism of action which can be attributed to two different mechanisms; (i) acting as a peptide toxin bocking K^+ channels, (ii) acting as a membrane active antimicrobial peptide (Shenkarev et al., 2012).

Mytimacin-AF is an AMP derived from marine mollusks, particularly from the mucus of *Achatina fulica* snail. It is characterized to be rich in cysteine as it is composed of 80 amino acid residues 10 of which are cysteines, and its molecular weight is 9711.41 Da. Mytimacin-AF showed activity against both Gram-positive and Gram-negative bacteria, however it was most potent against *Staphylococcus aureus* with minimum inhibitory concentration (MIC) value of 1.9 μg/ml. In addition, the most promising feature about mytimacin-AF is its activity against the human *Klebseilla pneumonia*, one of the most common hospital-acquired bacterial infections, what makes mytimacin-AF a very promising antibacterial agent (Zhong et al., 2013).

Myticusin-1 (TDHQMAQSACIGVSQDNAYASAIPRDCHGGKTCEGI CADATATMDRYSDTGGPLSIARCVNAFHFYKRRGEENVSYKPFVVSW KYGVAGCFYTHCGPNFCCCIS) is another cysteine-rich peptide derived from mussels. It was characterized and identified from the hemolymph of *Mytilus coruscus*. Its involvement in the host immune response has been proven, hence it plays a role in bacterial infection eradication. The cysteine amino acid comprises 10 out of 104 amino acid residues which makes myticusin −1 a long polypeptide chain with a molecular weight of 11,279.63 Da. This molecule has demonstrated greater potency against Gram-positive compared to Gram-negative bacteria, as it has recorded an MIC < 5 μM against a variety of tested Gram-positive strains including *S. aureus* compared to an MIC >10 μM against a variety of Gram-negative bacteria including *E. coli* (Liao et al., 2013).

EC-hepcidin3 (APAKCTPYCYPTHDGVFCGVRCDFQ), is a novel isoform that belongs to the hepcidin class of AMPs. This class is also known to be rich in cysteine, but this isoform is rather a four cysteinehepcidine unlike the typical eight cysteinehepcidin. It was cloned from the marine fish, the orange spotted grouper *Epinephelus coioides*. The purified Ec–hepcidin 3 has a theoretical molecular weight of 2798.2 Da. The kinetic studies proved that this molecule has a rapid and strong antibacterial activity against *Staphylococcus aureus* (MIC 1.5–3 μM, MBC 1.5–3 μM) and *Pseudomonas stutzeri* (MIC < 1.5 μM and minimum bactericidal concentration (MBC) < 1.5 μM) (Qu et al., 2013).

Marine's bacteria are also important source for AMP, Gageostatins A-C (Fig. 2). They are examples of three new non-ribosomal lipopeptide molecules that were derived from the broth of the bacterium *Bacillus subtilis*. These three molecules are consisting of heptapeptides and new fatty acid which is 3 beta hydroxy fatty acid and are anionic in nature with a uniform net charge of −3. Those molecules were tested as anticancer agents against a panel of six cancer cell lines; MDA-MB-231 breast cancer cell line, HCT-15 colon cancer cell line, PC-3 prostate cancer cell line,

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