International Journal of Science, Environment and Technology, Vol. 7, No 5, 2018, 1666 – 1670

ISSN 2278-3687 (O)
2277-663X (P)

Review Article

ANTI-MICROBIAL PEPTIDES: A BRIEF REVIEW

Prasanta Kumar Koustasa Mishra[1*], Anupama Jena[2] and Indhu MS[1]

[1]Ph.D. Scholar, Division of Biochemistry, [2]Ph.D. Scholar, Division of Extension Education, Indian Veterinary Research Institute, Izatnagar, Bareilly-243122

E-mail: prasantmodel@gmail.com (**Corresponding author*)

Abstract: Alternatives targeting pathogenic microbes is the need of the hour for antibiotics resistance strains. Anti-microbial peptides (AMPs) can be a suitable tool to address the menace of genetically upgraded pathogenic microbes. The peptides are smaller stretches of amino acids which target different types of pathogens as per their compositions. While insertion into membrane is the prime mechanism but these peptides can nullify the pathogenicity of microbes by many different ways. Such peptides are abundantly distributed across the nature and artificially synthesized peptides do further increase the repository volume. In this review, the AMPs are discussed very briefly based on their types and mechanism of actions.

Keywords: AMPs, antibiotic resistance, pathogenicity, mechanism of action.

Introduction

AMPs are small protein (peptides) that can kill or inhibit the growth of various microbes. The peptide can be of varied length starting from 6 to 50 amino acids (Zasloff, 2002) or maximum up to 100 residues (Xiao *et al*., 2015). The first anti- microbial peptide (AMP) was reported in 1980 from African clawed frog *Xenopislaevis* as in the form of maginin. It is an important component of innate immune system. Unavailability of adaptive immunity in plants and in lower forms of life necessarily requires such defense strategies. In mammals, the AMPs are distributed throughout their body in different cell types and tissues such as neutrophils, epithelial cells, mesenchymal tissues, articular cartilage and mucosal epithelial cells (Zasloff*.,* 2002). In case of mammals, the AMPs can be categorized under three main classes as (i) defensin (ii) cathelicidines and (iii) histatin (Smet and Contreras, 2005).

Classification of AMPs

AMPs can be classified into various types or sub-types based on their structure, function and mode of action.

1. Structural classification:

This is based on the secondary conformations these molecules adopt and include α-helix forming, β-sheet forming, loop former and extended conformations. Protegrin, maginin,

*Received Sep 9, 2018 * Published Oct 2, 2018 * www.ijset.net*

cyclic and coiled indolicidin do belong to α-helix forming group. whereas defensins are grouped under β-sheet forming proteins.

2. Functional classification:

Based on the target organisms

2.1. Anti-viral:

They do act by integrating into viral envelope or into the host cell membrane. AMP can act upon, both DNA and RNA viruses (Robinsons *et al*., 1998). Defensin like molecule can bind to glycoprotein of herpes simplex virus making it incapable of binding to the host cells. Some AMP do also target host protein synthesis machinery in order to modify it in such a way that the proteome of the host cell will mostly be diverted towards elimination of viruses e. g. NP-1.

2.2. Anti-bacterial

Positively charged peptides can easily target the bacterial surface (Shai, 2002). They do also possess amphipathic residues which help in getting inserted into the membrane. Reports regarding non-membrane targeting AMPs have emerged like Buforin-II, which binds to the intracellular components compromising bacterial survival machinery (Park *et al*., 1998). Certain AMPs are effective against antibiotic resistance bacteria like MRSA (Methicillin resistance *Staph. aureus*). Nisin is an example which acts by inhibiting cell wall synthesis.

2.3. Anti-fungal:

In contrast to bacterial cell membrane, positively charged chitin is a component of fungal cell wall. Interestingly, AMPs active against fungi contain neutral and polar amino acids instead of charged residues present in anti-bacterial AMPs (Jenssen*et al*., 2006). Indolicin is an example of anti-fungal peptide.

2.4. Anti-parasitic:

Maginin has anti-parasitic effect against *Paramecium caudatum* (Chen and Harrison, 2013). Cathelicidin was effective against free living *Caernohabditis elegans,* by forming a pore on it.

3. Based on mechanism of action:

According to mechanism of action, they are grouped under two categories: (i) membrane acting and (ii) non-membrane acting.

3.1. Membrane acting:

The cationic part helps them to interact with target membrane whereas the amphipathic region helps in insertion of molecules into the membrane (Madani*et al.,* 2011). Various

hypothesis and models have been postulated which may individually or in combination may justify the mechanism of action of surface acting AMPs. The carpet like action was described, where initial spreading on membrane followed by pore formation was observed. The thinning effect of membrane was further explored where the insertion of AMP into the membrane decreases the density of phospholipids present in that region. They can also form aggregate by changing their orientation over the membrane which facilitates entry into the membrane. Apart from these, there are reports suggesting barrel stave and toroidal pore shaped conformation formed by AMPs to gain access into target cells.

3.2. Non-membrane acting:

AMPs may act inside the cell rather than acting on surface (Otvos Jr, 2005). Amps like PR-39 can inhibit DNA and protein synthesis by acting as a proteolytic agent. Indolicin targets DNA synthesis and kills bacteria. A protease from *Bacteriocidesgingivalis* was inhibited by Histatin-5 thus retarding its infection. Another AMP, eNAP-2 had anti-serine protease activity. But the intracellular action of AMP too raises questions regarding its internalization process. It was suggested that AMP can be internalized by direct penetration or by endocytosis. The later can be further classified as macro-pinocytosis or as receptor mediated endocytosis.

Limitations of AMPs:

Like every other biological molecule, AMPs are also prone to degradation. Safe administration into host is a big challenge in that case. Again, being a foreign peptide, it may elicit some level of immune responses in the host. Till date, these peptides are only tested for their anti-microbial effect but they may bring certain changes in the host which may be useful or harmful. Surprisingly, reports are emerging showing resistance of microbes towards these peptides which may further put a big question on the reliability of these molecules as a therapeutic agent.

Present status and future scopes of AMPs

They are mostly preferred for their fast response to microbial challenge. But the practical application in current therapeutics for management of bacterial infection is very limited. Polymyxin was proven to be a successful translation from AMP to a real world therapeutic agent. This antibiotic compound is derived from *Bacillus polymyxa* is important in treating drugs resistance infections caused by gram -ve bacteria. Also, the topical use of the antibacterial has been reported. Apart from these, various other AMPs are under clinical trial (Mostly phase –II/ III) like pexiganan, which was used in the treatment of diabetes

induced foot ulcer (Lipsky *et al*., 2008). Indolicidin derivative omiganan was found to be useful for catheter infections and rosacea. Synthetic AMPs were also tried and were effective against gram -ve skin infections and impetigo. Systemic administration of hLF-11 (N-terminal 1-11 cationic fragment of human lactoferrin) was shown to be effective against bacterial and fungal infection in immune-compromised stem cell recipients. Anti-fungal AMPs like Novexatin and ZEN-002 were curative against toenailsand vaginal candidiasis infection respectively. In a recent study, LL-37 was administered as a local treatment of venary leg ulcers. In addition, it also acts as chemo-attractant and helps in secretion of pro inflammatory cytokines. Increase in immune response was targeted by supplementing Vitamin D3, which had stimulating effect on endogenous AMP production (Mohamed *et al*., 2016).

Though most of the AMPs are under preclinical or clinical trial but they do have a promising role as next generation therapeutics.

References:

[1] Zasloff, M. 2002. Antimicrobial peptides of multicellular organisms. Nature. ***415***: 389-395.

[2] Xiao, H., Shao, F., Wu, M., Ren, W., Xiong, X., Tan, B. and Yin, Y. 2015. The application ofantimicrobial peptides as growth and health promoters for swine. J. Ani Sci. Biotech. **6**: 19-26.

[3] Smet, K. and Contreras, R. 2005. Human antimicrobial peptides: defensins, cathelicidins and histatins.Biotechnol. Lett. **27**: 1337-1347.

[4] Robinson, W.E., McDougall, B., Tran, D. and Selsted, M.E. 1998. Anti-HIV-1 activity of indolicidin, an antimicrobial peptide from neutrophils. J. Leukocyte Biol.**63**: 94-100.

[5] Shai, Y. 2002. Mode of action of membrane active antimicrobial peptides. Peptide Sci. **66**: 236-248.

[6] Park, C.B., Kim, H.S. and Kim, S.C. 1998. Mechanism of action of the antimicrobial peptide buforin II: buforin II kills microorganisms by penetrating the cell membrane and inhibiting cellular functions. Biochem. Biophys. Res. Comm. **244***:* 253-257.

[7] Jenssen, H., Hamill, P. and Hancock, R. E. 2006. Peptide antimicrobial agents. Clin. Microbial. Rev. **19**: 491-511.

[8] Chen, L. and Harrison, S.D. 2007. Cell-penetrating peptides in drug development: enabling intracellular targets. Biochem. Soci. Transact. **35**: 821-825.

[9] Madani, F., Lindberg, S., Langel, Ü., Futaki, S. and Gräslund, A. 2011. Mechanisms of cellular uptake of cell-penetrating peptides. j. Biophys. **12:** 127-132

[10] Otvos Jr, L. 2000. Antibacterial peptides isolated from insects. J. Pept. Sci, **6**: 497-511.

[11] Mohamed, M.F., Abdelkhalek, A. and Seleem, M.N. 2016. Evaluation of short synthetic antimicrobial peptides for treatment of drug-resistant and intracellular *Staphylococcus aureus*. Sci. Rep. **6**: DOI: 10.1038/srep29707

[12] Lipsky, B.A., Holroyd, K.J. and Zasloff, M. 2008. Topical versus systemic antimicrobial therapy for treating mildly infected diabetic foot ulcers: a randomized, controlled, double-blinded, multicenter trial of pexiganan cream. Clin. Infect. Dis. **47**: 1537-1545.