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Antimicrobial Peptides: Classification, action and therapeutic potential.

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Abstract

Microbial resistance to conventional antibiotics is one of the most outstanding medical and scientific challenges. Antimicrobial resistance is an alarming threat to public health at the global level. This is due to acquired resistance to antimicrobial agents by microorganisms associated directly to the indiscriminate use of antibiotics. To combat the ill effects of antibiotic resistance several substances known as antimicrobial peptides have been used. Antimicrobial peptides (AMPs) are an essential part of innate immunity that evolved in most living organisms over 2.6 billion years to combat microbial challenge. The naturally occurring peptides are seen as a promising alternative to regular antibiotics, because they are still effective defence mechanism against bacteria despite exposure throughout the centuries. These AMPs use different mechanisms to kill the microbial pathogens. Different classes of the AMPs have been discovered that have proved to be of immense advantage in combating different pathogens. This review shall give a brief discussion regarding the classification, mode of action and therapeutic potential of AMPs.

Keywords:- Antimicrobial Peptides, resistance, therapeutic.

I. Introduction

These days, most bacterial infections are easily treated with antibiotics, however increasing bacterial resistance against these medicines is starting to complicate treatment. Microbial resistance to conventional antibiotics is one of the most outstanding medical and scientific challenges of our times. Antimicrobial resistance is an alarming threat to public health at the global level. Current estimates of the associated burden vary greatly depending on the

method of data collation and analysis [De Kraker 2016], but a recent report commissioned by the United Kingdom government estimated that, by 2050, 10 million people will die every year due to antimicrobial resistance unless appropriate counter measures are taken [O' Neill].

The increase in infections associated with microorganisms resistant to conventional antibiotics is a major concern for the clinical treatment of diseases and future public health problem. This is due to acquired resistance to antimicrobial agents by microorganisms associated directly to the indiscriminate use of antibiotics. Therefore, several studies have been conducted to discover substances that present effective antimicrobial activity. Thus, natural compounds represent a promising alternative for this purpose, in evidence, are the secondary antimicrobial peptides (AMP). Antimicrobial peptides and proteins (AMPs) are a group of diverse class of naturally occurring molecules that are produced by all multicellular organisms as a first line of defense. AMPs in nature are produced either by ribosomal translation of mRNA or by nonribosomal peptide synthesis (Hancock and Chapple, 1999). While nonribosomally synthesized peptides are mainly produced by bacteria, the ribosomally synthesized AMPs are genetically encoded and produced by all species of life, bacteria included (Hancock and Chapple, 1999). These proteins can have broad activity to directly kill bacteria, yeasts, fungi, viruses and even cancer cells. The antimicrobial peptides (AMP) are components of the innate immune system of various multicellular organisms that were maintained during the course of evolution [Xu et al., 2015]. AMP are a group of molecules that enhance immune responses from the first line protection and modulate inflammatory responses induced by pathogens [Kim et al., 2013].

II. Classification

Based on primary and secondary structural differences, antimicrobial potentials and effects on host cells, AMPs can be divided into different families. In mammals, three families have been described: defensins, cathelicidins and histatins. In addition to these three main families of AMPs other AMPs have also been discovered such as hepcidin, RNase 7 etc.

Defensins

Defensins are widely expressed, show bactericidal, antifungal and antiviral activity and are enriched mainly in cells and tissues involved in host defense [Dale 2002; Alexander et al., 1999]. Mammalian defensins are cationic, relatively arginine-rich nonglycosylated peptides with a molecular mass of 3.5–4.5 kDa and contain six cysteine residues that form three characteristic intramolecular disulfide bridges [Lehrer et al., 1991].The defensins are secreted

into the biological fluids, urine, bronchial fluids, nasal secretions, saliva and gingival crevicular fluid. The human defensin (HD) family can be further divided into two subfamilies, including α-defensin and β-defensin subfamilies.

In the α-defensin subfamily, four of the six α-defensins that includes human neutrophil peptide -1, -2, -3, and -4, are synthesized and stored in neutrophil granules while the other two α-defensins, HD-5 and -6, are synthesized and stored in the granules of paneth cells, specialized epithelial cells located at the crypts of Lieberkuhn of the small intestine.[Jung et al., 2011]. In the β-defensin subfamily, four human β-defensins (hBD), hBD-1, -2, -3, and -4, are principally expressed in epithelial cells that cover some tissues and organs, predominantly skin and the mucosal surfaces of gastrointestinal, respiratory, and urogenital tracts.[Marshall 2000].

Cathelicidins

Cathelicidins are defined by a highly conserved N-terminal cathelin pro-domain and a structurally variable antimicrobial domain at the C-terminus. Peptide antibiotics that belong to the cathelicidin family contains a highly conserved signal sequence and pro-region ('cathelin' = cathepsin L inhibitor) but show substantial heterogeneity in the C-terminal domain encoding the mature peptide, which can range in size from 12 to 80 or more amino acid residues [Zanetti et al., 1995]. The first cathelicidin AMP was sequestered from bovine neutrophils. The only cathelicidin in humans, LL-37, an α-helical peptide is derived from proteolytic processing of a predecessor peptide human cationic antimicrobial protein-18, and comprehends two leucines at its N-terminus.

Histatins

The third main family of AMPs in mammals is the histatins that includes various small, cationic, histidine-rich peptides. These are secreted by the parotid and sub-mandibular salivary glands in man and some higher primates and are present in saliva at concentrations in the range 50±425 ·M (Helmerhorst et al 1997).The primary structures of the major family members (histatins 1 and 3) has been determined and revealed lengths of 38 and 32 amino acid residues. Smaller members of the histatin family, including histatin 5 (24 residues), originate from histatin 1 and 3 by post-translational processing.

III Mechanism of Action

The fundamental differences between microbial and mammalian membranes is to protect mammalian cells against AMPs and enable selective action of these peptides (Yeaman and Yount, 2003). Many AMPs display a direct and rapid antimicrobial activity by causing disruption of the physical integrity of the microbial membrane and/or by translocating

across the membrane into the cytoplasm of bacteria to act on intracellular targets [Hancock and Sahl, 2006]. The microbial membrane is the target of these peptides and there are numerous models to explain their mechanism of action ranging from pore formation to general membrane disruption. The interaction between the AMP and the target membrane is critical to the specificity and activity of these peptides. Antimicrobial peptides act on the microbes by different modes. The different modes of action include [Park et al., 2011]:

i) Lipopolysacchride neutralization or disaggregation.

ii) Induction of membrane permeability.

iii) Inhibition of cytoplasmic proteins related to cell division or survival.

iv) Inhibition of macromolecular synthesis through interaction with nucleic acids.

v) Anti- biofilms Activity of antimicrobial peptides against biofilm of multi-drug resistant bacteria.

IV . Therapeutic Applications

Many AMPs have potent activity against bacteria, including those that are resistant to conventional antibiotics. Their activity is often relatively-specifically directed against certain genera or groups of bacteria, which could limit damaging effects on a patient's commensal flora. The rapid bactericidal activity of AMPs makes them promising candidates for therapeutic anti-infectives. There are numerous AMPs currently under clinical development for the treatment against various bacterial pathogens. Antimicrobial peptides (AMP) have attracted interest as potential targeting vectors for the development of PET tracers designed for the detection of infection. Due to their role in the body as a natural microbicide, these antimicrobial peptides are selectively cytotoxic to bacteria, whilst showing minimal cytotoxicity towards cells of the host organism[Thomas et al., 2014]. AMPs are primarily chemotactic for immune and non-immune cells. Defensins including α-defensins (e.g., HNP1-3) and β-defensins (human β-defensin 3 and 4; HBD3 and 4) recruit phagocytes, neutrophils granulocytes and monocytes to the site of inflammation [Lai and Gallo 2009]. Many other AMPs have been found to play an effective role in many diseases by activating different immune responses. Many defensins attract inflammatory cells such as neutrophils, B-cells, and macrophages, and activate these and other cell types, including epithelial cells. They liberate inflammatory mediators such as IL-8, interferon-g, IL-6, IL-10, and LTB4. Also defensins might also exhibit anti-inflammatory activities by induction of the secretion of IL-10 or SLPI or by facilitating the binding of microorganisms to epithelia with subsequent clearance of the microorganisms by a bactericidal activity of the cell[Van wetering et al., 2000; Lillard et al.,

1999]. Antimicrobial Peptides might not only act as antibiotics but also as modulators of immune system.

V. Conclusion

Antibiotic resistance has proved to be a global burden. Emergence of antibiotic resistant strains of different pathogens has lead to discovery of antimicrobial peptides.From the last few decades antimicrobial peptides have emerged as major effector substances of the innate immune system involving a number of activities , that not only includes endogenous antibiotics but also mediators of inflammation. Much work needs to be done in the area of interaction of AMPs with the host cells so as to unveil different defense mechanisms provided by AMPs.

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