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Review Article

Types of Antimicrobial Peptides

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Abstract

Natural antimicrobial peptides (AMPs) have high therapeutic potential and have bactericidal, anti-inflammatory and anticancer action, with high selectivity for bacterial cells compared to mammalian cells. The use of AMPs is at an early stage, with most of the work being in vitro and with very few animal studies. AMPs probably interact with the cell membrane of target bacteria, resulting in disruption or interference of microbial biosynthetic pathways. These AMPs can also boost cellular and humoral immune responses and have been shown to be chemotaxic for monocytes, T lymphocytes, and dendritic cells. Their nature makes them susceptible to degradation by proteolytic enzymes; however, their chemical modification or encapsulation could protect the peptides (PPs) from enzymatic degradation.

Keywords: antimicrobial activity, bacteria, antibiotic resistance; viral infections, defense peptides

Background

Since their discovery, antibiotics have been used in animal production both to promote growth and to prevent and treat contagious diseases.

However, due to potential associated problems, such as antibiotic resistance and the threat of antibiotic residues in animal products that adversely affect human health, the continued use of antibiotics in feed has become one of the most important problems in animal production. The use of antibiotics as feed additives has already been banned by the European Union. Numerous scientific papers have been published on alternatives to antibiotics in feed, with the use of plants, enzymes, probiotics, oligosaccharides, etc. Recently, AMPs have been shown to be an interesting alternative to antibiotics [1].

AMPs (also known as host defense PPs) are 1 to 5 kDa PPs encoded by small genes that have a broad spectrum of activity against gram-positive and gram-negative bacteria, fungi, and mycobacteria [2].

These are natural proteins produced by all organisms that can be classified according to the composition and structure of amino acids (AAs) into 5 classes: anionic PPs, linear cationic PPs α-helix, cationic PPs enriched with specific AAs, anionic PPs and cysteine-containing cysteine and form disulfite bonds and anionic and cationic PPs as large protein fragments.

AMPs, also called host defense PPs (HDPSs), are part of the innate immune response found in all classes of life. These PPs are powerful broad-spectrum antibiotics that have the potential as new therapeutic agents. AMPs have been shown to kill bacteria in Gram-negative and Gram-positive viruses, sheaths, fungi, and even transformed or cancerous cells. Unlike most conventional antibiotics, it seems that AMPs frequently destabilize biological membranes, can form transmembrane channels, and can also enhance immunity as immunomodulators.

Types of antimicrobial peptides

The diversity of AMPs makes their classification difficult to achieve; but based on their properties [3], AMPs can be grouped into several main classes, depending on their degree of preferential action, namely:

i. nonspecific AMPs, which do not have specificity in terms of their action on microbial membranes (Melitina – *Apis mellifera*).

ii. AMPs that destabilize eukaryotic cell membrane:

   a. tumor cells (Magainin 2 – *Xenopus laevis*);

   b. fungi (Lactofericin B – *Bos taurus*); fungi are susceptible to the action of AMPs due to their ergosterol content (which is not found in human cells);

   c. viruses (Lactofericin B – *Bos taurus*).

iii. AMPs that affect the membrane of prokaryotic cells, bacteria (β defensin 3 *Homo sapiens*):

   a. Gram-positive bacteria (Nisin A-*Lactococcus lactis*);

   b. Gram-negative bacteria (Polymyxin E-*Bacillus colistinus*);

iv. Biological source - AMPs from bacteria, plants or animals, each with its own subcategories [4-6]

Biological functions - AMPs can have antibacterial, antiviral, antifungal, antiparasitic, insecticidal, chemotactic effect, can be involved in processes such as wound healing or growth induction; The biological characteristics of these molecules justify the interest in innovative and alternative therapeutic agents in the scientific community, especially in infections caused by antibiotic-resistant microorganisms [7].

Some characteristics of AMPs make them particularly attractive as potential therapeutic tools: a wide range of activities: they are active against viruses, bacteria, fungi and protozoa; rapid bactericidal activity (99.9% kill bacteria on exposure for 20 minutes); are able to interact synergistically with conventional antibiotics; are effective against bacteria that have developed resistance to antibiotics in that they have different mechanisms of action compared to certain antimicrobials. The latter has stimulated the attention of researchers, especially those dealing with cystic fibrosis (CF), when repeated antibiotic treatments to resolve pulmonary infectious events selected several resistant or pan-resistant bacterial strains that are resistant. To all antimicrobials used in clinical practice [8].

Molecular topology suggested by AA sequences - from the point of view of the interactions between the component AAs, the PPs can be classified into linear, loop or circular PPs [9].

Three-dimensional structure - from this point of view, PPs can be classified into: α-helix; β – folded; α – β conformations; non α – β conformations; Mechanism of action - AMPs affecting the cell membrane and AMPs affecting internal components of the cell, both of which can be subclassified according to the specific mode of action [10].

A number of insect PPs and their synthetic derivatives with antifungal and antibacterial activity (abacin, bactericidal, bombolitin, moricin, defensin, etc.) are known.

Among the PPs with antimicrobial functions in invertebrates, the prototypical ones are:

- Cecropsins are α-helical PPs found in the hemolymph of flies;
- Melitine has the same α-helix structure and is found in bee venom;
- Tachyplesin and polyphemusin have β-hairpin structures and are isolated from the horseshoe crab;
- Defensins - are the most abundant immunologically active PPs in invertebrates. They have an open PP structure with three or four disulfide bridges. They are classified according to their main activity: anti-bacterial or anti-fungal [11].

PPs with antimicrobial action can be classified into:

1) Linear PPs with alpha helix (spirals) without cysteine content;

2) cysteine-rich PPs with beta-stratified structure, which contain from 4 to 8 cysteine residues between which 2 to 4 bridges are formed (S = S);

3) Cyclic PPs containing 2 cysteine residues with the formation of a disulfide bridge and a ring structure (loop-structure);

4) PPs rich in certain AAs - proline, arginine, tryptophan, histidine, glycine - which do not form any secondary structures and have an extensive form in the hydric environment and in the hydrophobic phase of the membrane [12].

AMPs, according to the mechanism of the appearance of the mature PP, can be subdivided into those with: encoding on the individual mRNA in the form of a predecessor that undergoes proteolysis upon maturation; proteolysis of a larger protein with the formation of PAM that ensures the specific function. Although proteolysis is found in both cases, they differ in maturation processes and regulatory mechanisms [13].

The protection of the body from viral infection is achieved by non-specific factors (kills / blocks viruses, bacteria, infected cells) and specific (forms the immune response to the specific virus, including memory cells). Specific protection factors are cytotoxic T lymphocytes (CD8 +) and B lymphocytes (produce specific antibodies), and nonspecific ones are represented by the natural kiler system, mononuclear phagocytes (monocytes, tissue macrophages), granulocytes (neutrophils, eosinophils, basophils), beta, gamma, some interleukins (TNFalpha, IL – 6, etc.) and some plasma proteins (complement system) [14-16].

The natural kiler system is the group of cellular factors with an important role in the mechanism of natural (innate) immunity represented by cells: NK – natural kiler cells; K – kiler cells; LAK – activated lymphocyte kiler cells; NK / T – lymphocytes – intermediate link between innate and acquired immunity. NK cells are a population of lymphocytes that come from the hematopoietic stem cell and mature in the bone marrow [17].

They have an immune surveillance function by: lysis of cells infected with viruses and other intracellular microorganisms, as well as tumor cells; production and secretion of immunoregulatory cytokines (INF alpha, gamma, IL-1, lymphotoxin) [18].

In NK-virus infection, cells migrate to infected tissue under the influence of INF type 1, recognizing and lysing target cells that lack markers or are altered as markers of healthy cells. On the surface of NK cells are the receptors kiling activators and kiling inhibitors. Infected cells are recognized by kiling receptor activators, whose expression increases under the action of cytokines. As a result of NK recognition, the cells secrete perforin and granules. Perforins infiltrate the membrane of the target cell with the formation of pores, and the granules penetrate the target cell with its lysis [19, 20].

NK cells do not require proliferation, transcription, or protein synthesis (do not require time to mature) or the involvement of antibodies and complement. Such cytolysis is called cell-mediated cytotoxicity [21].

NK-cell activity has no immunological specificity and is manifested until the inclusion of specific immune protection factors. NK / T lymphocytes are an intermediate link between innate and acquired immunity and are characterized by the presence of NK-cell markers (CD56 and CD16) and T-lymphocytes - a receptor that recognizes the antigen, a natural receptor formed to identify lipid antigens [22].

These cells not only function as kilers, but also transmit the signal for Th1 and Th2 with the production of cytokines. Thus, it amplifies the regulation of the immune response by including the mechanisms of specific immunity (protection against viruses, bacteria, parasites, antitumor immunity, preventing the development of autoimmune pathology) [23].

NK / T lymphocytes are resistant to apoptosis which allows them to survive after activation and maintain their amount at a normal level. LAK cells are common lymphocytes that have been activated by IL-2 and have acquired the ability to achieve the kiling effect. K cells have on their receptor surface the Fc-IgG fragment and are capable of antibody-dependent cell-mediated cytotoxicity [24].

The interaction between these elements is a key mechanism of the cytolytic process, in which a K cell can lyse several target cells. The role of cytokines in the body is reduced to: inhibiting viral genome transcription and viral mRNA translation with decreasing time and increasing the elimination process; contributes to the proper immune response to the infiltration of the infectious agent into the body (initiates the cascade of immune reactions).

In the 1980s, Russian scientists investigated biologically active substances in insects, including antibacterial PPs isolated from several species. The studies focused on surgical larvae, used by I. Pirogov as early as the 19th century in the Russo-Turkish war to heal wounds and ulcers. Finally, several families of protein compounds capable of directing the immune system to fight viral infections have been separated from insect hemolymph [25].

Experimental research on cellular and humoral immunity in the larvae of *Callophora vicina* has elucidated the presence of three groups of pharmacologically active substances of prospective medicine - allopherones, allostats and AMPs. PPs isolated from surgical larvae (which damage bacteria) or from the hemolymph of the *C. vicina* fly have a long history of use in medicine. *C. vicina* is also known for its ability to produce, after experimental modeling, a number of substances with potential antimicrobial effect with a primary structure similar to those described in other insects such as defensins, cecropins, diptericins and proline-rich proteins [26].

The experiments, which preceded the discovery of allopherones, noted that the primary (fresh) hemolymph of *Calliphora* contains a factor capable of stimulating antiviral and antitumor resistance in mice. In this case, an increase in the spleen of NK-cells was found, key elements in the innate antiviral and antitumor immunity in vertebrates and some invertebrates. It has been suggested that *C. hemolymph* may contain cytokine-like material, which interacts with NK – mouse cells that protect against viral infection or tumor modification. After extraction and purification of the hemolymph, 2 PPs with 13 and 12 AA residues were obtained [27].

The 13-residue PP was named alloferon 1, which was subsequently synthesized and studied for biological activity.

Alloferon 2 (residues of 12 AAs) and alloferon 3 and 4 were synthesized with a shorter chain of AAs but which showed a similar biological action, determined by the sequence Ser – Gly – His – Gly – Gln – His – Gly – Val corresponding to alloferon 4.

The structure of alloferon 1 (HGVSGHQHGVHG) and alloferon 2 (GVSGHGQHGVHG) have common sequences with those of hemagglutinin influenza B virus, antifungal protein from *Sarcophaga peregrina* (meat fly), bovine kininogen and human endothelial collagen [28].

Allopherones - PPs of the immune system, similar to cytokines, which regulate specific antiviral and antitumor immunity. These are linear PPs of 12–13 L – AAs that interact with human immunocompetent cells (neutrophils, lymphocytes, and monocytes) to increase cytotoxic activity and stimulate interferon production. Alloferrons are PPs that selectively stimulate the cytotoxic activity of natural kilers with an important role in the antiviral and antitumor immunity of vertebrates. Due to its small size, it was possible to synthesize allophones without impurities [29].

Allopherones have been used to synthesize a range of substances, including alpha allopheron, registered in Russia in 2003 as an antiviral drug.

Allopheron alfa is a linear oligoPP of 13 L-AAs (His – Gly – Val – Ser – Gly – His – Gly – Gln – His – Gly – Val – His – Gly), representing a new class of selective stimulators of innate immunity factors. with antiviral and antitumor properties [30].

The preparation is the representative of a new group of antivirals (called - preparations that prevent the avoidance of cytokines), based on the ability of the oligoPPs of the insect's immune system to include cytokines in the fight against viruses. High efficacy in the treatment of viral infections (hepatitis, herpes, papillomavirus infections) and the possibility of using them as monotherapy has been demonstrated [31].

The study of allopherones made it possible to target the synthesis and to obtain allostatin-oligoPPs from 10-15 AAs. Allostatins are synthetic PPs that combine structural features for allopherones and some immunologically active vertebrate proteins. These, like allopherones, have a stimulating effect on the cytotoxic activity of natural kilers and the production of interferons, and some of them have adjuvant properties - the ability to increase the immune recognition of antigens [32].

These PPs have antiviral and antitumor effect. The latter is based on the direct inhibition of cancer cell proliferation and the activation of immune mechanisms to reject the tumor. Allostatin combines the properties of immunomodulator (mobilization of cytotoxic lymphocytes, interferons and possibly other mechanisms of antitumor and antiviral immunity) and cytostatic (direct inhibition of cancer cell proliferation) [33].

Currently, these substances are effective in increasing the resistance of the skin and mucous membranes to viral infections, and in the near future they will find their use in immunotherapy for cancer and other diseases. Experimental studies have shown that allopherones are non-toxic (in acute and chronic toxicity) and do not show sensitizing, allergenic, embryotoxic, teratogenic and mutagenic action. It undergoes rapid and complete biodegradation through extra and intracellular proteases [34].

Alloferon is a cytokine-like PP and can be considered an interferonomimetic because the pharmacological activity is similar to that of interferon alfa in influencing the natural kilter system and resistance to viral infection. The action of allopherone is achieved in very low concentrations –0.05–0.5 ng / ml. Alloferon is considered an inducer of interferon synthesis, an effect characterized by 2 peaks (6 and 24 hours), especially at 24 hours unlike other interferon inducers (cyclopherone). The interferonomimetic and interferon-inducing properties are important for the treatment of deficiencies in the system of natural kilers and interferon encountered in viral, fungal and oncological diseases [35].

Alloferon (intranasally and subcutaneously) has been shown to be effective in treating viral infections in mice caused by influenza A and B virus at much lower doses compared to the reference preparations, remantadine and ribavirin, respectively [36].

The study of antitumor activity noted the property of alloferon to potentiate the ability of lymphocytes in the peripheral blood of healthy people to lyse tumor cells, an action that does not yield to interferon alfa. At the same time, the drug stimulated the lysis of tumor cells by cytotoxic lymphocytes of cancer patients. The effect was more pronounced on NK cells and more marked in patients with acute and chronic leukosis, but less in those with lymphomas (37). The stimulatory action of allopherone and interferon alfa correlates with reduced or no lymphocyte cytotoxicity. Alloferon 1 and its analogues 3 and 4, similar to interferon alfa, stimulated the cytotoxic activity of lymphocytes in healthy people and patients with cancer. Allochin alfa is an antiviral drug that selectively simulates natural immunity factors [38]. The active substance of the preparation is

alloferon, a synthetic oligoPP based on insect PP, the main link in antiviral protection.

Concluding Remarks and Future Perspectives

The possibility of bacteria developing different bacterial resistance strategies (surface charge changes) against the activity of natural PPs suggests the need for new approaches in the design of new AMPs. Increasing the safety and efficacy of new drugs is essential for new PPs (extracted from protein fragments and PP libraries or designed sequentially). Research approaches to AMPs can be classified into 3 categories: template-based (PPs are treated as AA sequences, limited to their individual properties, such as hydrophobicity, electrical charge / charge, etc.), quantitative structural relationship models. activity, QSAR (numerical analyzes describing the relationships between the properties of PPs as inputs and biological activity as output, limited by the function used) and biophysical studies (molecular modeling based on free energy, molecular dynamics, etc., limited scale, membrane models). Another aspect to consider is the cost of production, as its chemical synthesis is expensive. In the future, biotechnological production with transgenic microorganisms, tissue cultures, animals or plants could probably lead to an economical production of AMPs. Also, the effective dose of these PPs that can replace antibiotics in the diet of pigs has not yet been determined. Finally, the development of antimicrobial PP-resistant microbial strains is still unknown, although some studies have shown that certain genes may confer resistance to AMPs, and studies have been conducted to determine whether such genes can be transferred between bacteria.

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