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RESEARCH ARTICLE

THE ANTIMICROBIAL PEPTIDES AS IMMUNE BOOSTERS

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ABSTRACT

Antimicrobial peptides (AMPs) are widely present in nature and play the role of self-protection of a living organism from the presence of foreign presenters. They are amphipathic, i.e. contain both charged and hydrophobic domains, however, they are divided into cationic and anionic, depending on the presence of positively or negatively charged amino acids in the active domains, which allows them to easily bind to the surface of the bacterial membrane, which has an advantage of phosphatidylserines different from eukaryotic cells on the outer surface of the plasma membrane, as well as with the surface of fungi and tumor cells. The mechanism of the killer action of AMPs is based on their ability to form pores according to the principle of a toroidal, mosaic and barrel model. But the mechanism of the immunomodulatory action of AMP does not end there. Along with the above action, which ensures the leakage of vital intracellular components into the external environment, AMPs act on DNA transcription, RNA and protein synthesis, sharply inhibiting their formation in a virulent cell, preventing colony development. Of course, a diet depleted in protein and antibiotics are undesirably introduced into the process of self-regulation of immune reactions in the body under the influence of AMP, which is the reason for the deterioration of the condition of patients after taking chemotherapy drugs. Simultaneously, the emergence of multidrug resistance cannot be ignored. On the contrary, increased AMP production due to thediet enriched by essensial, especially widely presented in AMPs hydrophobic amino acids has a beneficial effect on the outcome of an infectious disease. It has been shown that the supplementation of such essential nutrients as tryptophan and branched amino acids, as well as vitamins D and A, increases the host defense by increasing the expression of genes responsible for AMP synthesis.

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INTRODUCTION

Antimicrobial peptides as a decisive disease outcome tool in the multidrug resistance era: All living things in nature: soil bacteria, insects, amphibians, mammals and plants produce antimicrobial peptides (AMPs) as indispensable part of host defense system. AMPs differ in peptide structure, charge, solubility and mechanism of action. AMPs are known to be active against viruses, bacteria, fungi, and protozoa. These peptides are considered as an alternative source of treatment to traditional antibiotics in cases where therapists are faced with Multidrug resistance (MDR), such as nisin AMP is used for infection with methicillin-resistant Staphylococcus aureus. They are used in combo with antibiotics against parasites (nisin Z with ampicillin), which also helps more effectively in the fight against Pseudomonas fluorescens than with the use of one antibiotic (1). To date, 3425 antimicrobial peptides from six life kingdoms with leading antibacterial activity followed by antifungals, peptides against candida and endotoxins and HIV, antiviral, antiparasitic, anticancer, antidiabetic, hemotactic etc. have been recognized.

There are even antioxidant, anti-inflammatory, wound healing peptides, ion channel and protease inhibitors, as well as AMPs with other activities (2). More than 2000 AMPs are produced in animals, among which leading defensins, cathelicidin, followed by lysozyme, lysine of natural killer cells, a family of regenerating proteins, hepcidin, chemokines, and some RNA enzymes (3). In the past few years, the use of antibiotics as feed additives has led to the emergence of antimicrobial resistance, resulting in increased morbidity and mortality from diseases previously treatable with antibiotics. AMPs as part of host defense system used in nature have come to the rescue, since microorganisms do not develop resistance to them, so the use of AMPs is seen as a strong candidate to replace conventional antibiotics (4). Lehrer and c-workers obtained from macrophages AMPs with interlinked cysteines termed defensins (5). AMPs are also a link between innate and adaptive host defense immunity. AMP genes are expressed in phagocytic and mucosal epithelial cells under induction of pathogens and cytokines.

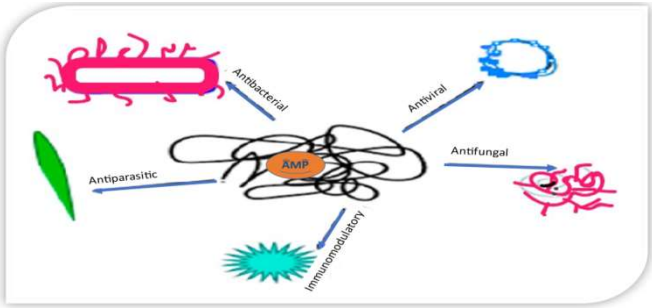

Fig.1.The main effects of Antimicrobial peptides

Bacterial factors can suppress the production of AMP (6). Multidrug resistance (MDR) to antibiotics and anticancer drugs is a major public health problem. For this reason, antimicrobial membrane disrupting peptides (AMPs) have recently attracted particular attention. Due to their high selectivity and negligible side effects, which can be neglected due to the huge benefits of their impact on an infected and malignant organism. To reduce even this slightly pronounced negative effect, it is important to develop methods for their effective selective delivery to the desired lesion. Nanoparticles are proposed as potential containers for improving the therapy strategy, the most promising among which are cationic nanoparticles that can fight the occurrence of MDR both in bacteria and in cancer cells (7).

Structural features and action mechanism of AMPs: AMPs usually have an amphipathic structure with separate clusters of hydrophobic and hydrophilic amino acids (8). Scientists have found a direct correlation between the content of α-helices in the host defense system's AMP structure and its antimicrobial activity(**9**). It was also revealed that cationic α-helical AMPs, such as cecropins (10), magainin (11), pleurocidin from winter flounder (12), and melittin from bee venom acquire an α-helical structure upon contact with membranes. Due to the cationic charge, these AMPs are attached to the bilayers of the plasma membrane, penetrate deeper due to their amphipathicity, and are embedded in the structure of the lipid bilayer forming pores. Three main mechanisms of AMP pore formation are distinquished: "barrel", "carpet", and "toroidal pores". However, transmembrane pores are not the only mechanism of microbial killing, because in addition to initiating membrane entry, AMPs alter the formation of the cytoplasmic membrane septum, up to inhibition of cell wall synthesis, as well asinhibition ofnucleic acids, protein, and/or enzymes formation (13). AMPs that destroy pathogens by a non-membrane method (14) and damage the cellular processes of microorganisms have also been found. They can disrupt the synthesis of macromolecules (for example, RNA and/or DNA) in them (15) and wash out ATP (16). The lantibioticmersacidin (an AMP of gram-positive bacteria containing the thioether amino acid lanthionine) binds to lipid II, disrupting the formation of polymeric peptidoglycan, causing inhibition of cell wall formation and the death of pathogens. Changes in the properties of E. coli DNA and RNA occur after its binding to buforin II. PR-39 does not form traditional pores in the target cell, however, after passive absorption, this AMP stops protein and DNA synthesis in the cell (17). The proline hinge of buforin II helps it enter cells (14). The cationic charge of AMPs is due to lysine, tryptophan, and arginine residues, while the abundance of hydrophobic amino acids makes them amphipathic. Cationic peptides more effectively disrupt the effect of LPS in the membrane of Gram-negative bacteria than Mg2+ and Ca2+ cations (18).

AMPsactivity spectrum (ya da: distinguished by charge): A new AMP, pleurocidin, from the skin secretions of the flounder (Pleuronectes americanus) showed antimicrobial activity against Escherichia coli (12). AMPs P9A and P9B from Hyalophora cecropia exhibit potent antibacterial activity against Escherichia coli and other Gram-negative bacteria. Unlike the AMP of bee venom, melittin, cecropin A, which lyses both bacteria and eukaryotic cells, is specific for bacteria (10). The family of amphiphilic peptides from the skin of the Xenopus laevis frog has a broad spectrum of antimicrobial activity without a non-hemolytic effect. These AMPs are active against many types of bacteria and fungi, as well as protozoa (11). The amphipathic structure and positive charge allow AMPs to interact with membrane lipids. Cationic residues are electrostatically attracted to negatively charged phospholipids, lipopolysaccharides on the outer surface of the bacterial plasma membrane, leading to adhesion of AMP to the membrane; when the concentration reaches a threshold value, the membrane exfoliates with the formation of pores in it. Anionic peptides of extracts of surfactant and epithelial cells of the respiratory tract (13), human dermcidin from sweat glandare active against gram-positive and gram-negative bacteria, (19), amphibian maximin H5 (ILGPVLGLVSDTLDDVLGIL-NH2)is active against Gram-positive strain of Staphylococcus aureus (20). The third group includes AMPs rich in certain amino acids. These include the almost half proline abaecin of bees, bactenecins and PR-39, also consisting of 30% arginine; tryptophan-rich indolicidin; the absence of cysteine in these AMPs makes them extremely flexible (13). The fourth group of AMPs is represented by fragments obtained by cleavage of larger peptides. For example, lactoferricin (21) is formed by hydrolysis of the N-terminal part of lactoferrin, and cathelicidins are the degradation product of cathelin serine protease from the C-terminus (22). Lactoferricin B, which inhibits the growth of a number of gram-positive and gram-negative bacteria, is formed in the body of mammals during the breakdown of lactoferrin under the action of pepsin. It was revealed that this AMP has a rapid effect, causing the loss of the ability to form colonies from Escherichia coli, Salmonella enteritidis, Klebsiella pneumoniae, Proteus vulgaris, Yersinia enterocolitica, Pseudomonas aeruginosa, Campylobacter jejuni, Staphylococcus aureus, Streptococcus mutans, Corynebacterium diphtheriae, Listeria monocytogenes and Clostridium monocytogenes perfringens (21).

In the cytoplasmic granules of mammalian neutrophilic leukocytes, a family of AMPs with the properties of cysteine proteinase inhibitors - cathelicidins, which are released upon activation of the immune response, has been identified. Cathelicidins, along with the destruction of bacteria, neutralize the bacterial lipopolysaccharide, preventing its binding to the host cell and stimulating wound healing (22). The fifth group is represented by defensins of plants, arthropods, and β-defensins of higher animals, including birds, reptiles, and mammals (23);(24); θ-defensins are found only in rhesus monkeys. The most common human AMPs are defensins and cathelicidins formed from a precursor after partial hydrolysis. AMP-encoding genes in mammals are expressed in circulating cells and in the epithelium. So, the cationic peptides defensin and cathelicidin are present in the covering respiratory epithelium fluid. Human beta-defensin-1 is constitutively present in the airways, while human beta-defensin 2 and -3 are induced in response to bacterial invasion after ligand binding to a Toll-like receptor. These peptides enhance the chemotaxis of the innate and adaptive immune system cells. Inhibition of antimicrobial peptide activity by a protein-poor diet or gene expression by antibiotics results in increased susceptibility to infections. Virulent strains along with air pollution can also inhibit the expression of the defensin gene and increase the body susceptibility to pathogens (25). In humans, α-defensins are found primarily in neutrophils and named HNP 1-4; transcription of HNP1-4 stops with the maturation of neutrophils (26). They are used for oxygen-independent antibacterial action. There are also intestinal α-defensins; removal of the signal peptide from the precursor secreted into the lumen of the small intestine under the action of trypsin (27) leads to its activation. As for β-defensins, they are found mainly in the epithelial cells of the oral cavity, respiratory tract, and skin (7). In epithelial cells, human β-defensin 1, 2, and 3 are usually transcribed at a low level, but microbes and cytokines such as inflammatory mediators TNF-α, interleukin (IL)-1β, and IL-17 (28), as well as Toll-similar receptors (TLRs), such as LPS, dramatically increase their expression (7). More recently, three cytokines, IL-12, 23, and 27, have been shown to enhance IL-1β-mediated hBD2 induction (29).

Plant AMPs: Antimicrobial peptides are also widely present in roots, seeds, flowers, stems and leaves of a wide variety of species and are active against plant pathogens, humans, viruses, bacteria, fungi, protozoa, parasites and tumor cells (Montesinos). 2007). Plant AMPs

include defensins, thionins, lipid carrier proteins, cyclotides, snakins, and hevein-like proteins; some plant species have hundreds of different AMPs(30).Differences in the mechanism of antifungal and antibacterial activity of plant AMPs are associated with different structures of target membranes. Thus, in the fungal membrane, γ-thionins bind to glucosylceramides and sphingolipids, while in the bacterial cell their targets are phospholipids (31). However, many AMPs are active on both; both bacteria and fungi. Plant AMPs are typically rich in cysteine and/or glycine and have disulfide bridges that help them maintain structural stability. About 20% of their amino acids are positively (due to arginine and/or lysine) or negatively (due to aspartic acid and glutamic acid) charged, which increases their affinity for pathogenic bacteria. The formation of membrane pores in pathogens leads to the leakage of their ions and metabolites, membrane depolarization, and disruption of respiratory processes, which ends in cell death (32).Thioninsof plants are positively charged at physiological pH values of AMP rich in arginine, lysine and cysteine residues. Their structure includes two antiparallel α-helices and an antiparallel double-stranded β-sheet with three or four disulfide bonds. Pyulariapubera γ-thionine, a 47-residue peptide with four internal disulfide bonds, was found to contain an aspartic acid residue at position 32 instead of arginine commonly found in other γ-thionines. Asp32 is essential for in vitro activity against various Gram-negative bacteria (Rhizobium melioti and Xanthomonas campestris), as well as fungi Fusarium oxysporum, Plectosphaerellacucumerina and Botritis cinerea (33).

Dietary products as enhancers of AMP synthesis in the body: In recent years, several nutrients such as branched chain amino acids, certain fatty acids, lactose, zinc, and cholecalciferol have been shown to significantly increase the body's AMP production. Proper nutrition and the supply of essential amino acids as immune boosters is seen as a promising defense against pathogenic infections (34). Tryptophan is an essential aromatic hydrophobic amino acid required for incorporation into AMP lipophilic motifs and may be used to regulate mucosal immune functions (35).Thus, an activated mammalian target of rapamycin (mTOR) can promote AMP expression (36), while tryptophan can directly activate the mTOR pathway, independently of the phosphatidylinositol-3-kinase-AKT pathway. ACE2 regulates innate immunity, gut microbial ecology, and is responsible for susceptibility to colitis, while tryptophan directly regulates ACE2-dependent changes in epithelial immunity and intestinal microbiota (37). So a balanced addition of tryptophan to the diet enhances AMP induction in intestinal tissue. Retinoic acid (the active form of Vitamin A) increases the activity of the human cathelicidin antimicrobial protein 18 promoter in bone marrow cells (38). In addition, retinoic acid activates the expression of the α-defensin 1 gene by binding to the proximal and distal elements of the minimal promoter (39). Moreover, some regions of the AMP promoter contain an element responsible for retinoic acid (40). By binding to the nuclear receptor and causing histone acetylation, dihydroxycholecalciferol enhances AMP expression in the intestine (41);(42).

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