ANTIMICROBIAL PEPTIDES OF INNATE IMMUNITY AS PROTOTYPES OF NEW AGENTS TO FIGHT ANTIBIOTIC-RESISTANT BACTERIA

Shamova O. V.[1, 2], Zharkova M. S.[1, 2], Chernov A. N.[1, 2], Vladimirova E. V.[1], Sukhareva M. S.[1], Komlev A. S.[1], Kochenda O. L.[1, 2], Orlov D. S.[2]

[1]World-Class Research Center for Personalized Medicine, Saint Petersburg, Russia
[2]Institute of Experimental Medicine, Saint Petersburg, Russia

Corresponding author:
Shamova Olga V.,
Institute of Experimental Medicine,
Academician Pavlov str. 12, Saint Petersburg, Russia, 197376.
E-mail: shamova@iemspb.ru

Received day 20 September 2021;
accepted 25 October 2021.

ABSTRACT

The review represents the analysis of the literature data on antimicrobial peptides (AMPs) of the innate immune system as promising prototypes of new antibiotic agents for overcoming the antibiotic resistance of microorganisms. Structural and functional properties of these peptides are highlighted, information on the mechanisms of antimicrobial action and, briefly, on their effects on the cells of higher eukaryotes is provided. The advantages of AMPs in comparison with conventional antibiotics and the problems of practical application of AMPs are discussed. Examples of drugs developed based on AMPs that are at the stage of clinical trials are given, the necessity of creating new peptide drugs for medical application in the treatment of infectious diseases caused by antibiotic-resistant microorganisms is substantiated.

Key words: antibacterial action, antimicrobial peptides, clinical trials, infectious diseases, microbial resistance.

For citation: Shamova OV, Zharkova MS, Chernov AN, et al. Antimicrobial peptides of innate immunity as prototypes of new agents to fight antibiotic-resistant bacteria. Russian Journal for Personalized Medicine. 2021;1(1):146-172.

INTRODUCTION

In recent years, the resistance of pathogenic microorganisms to antibiotics used in medicine has been growing rapidly. According to forecasts, by 2050, mortality from infections caused by antibiotic-resistant bacteria will reach 10 million people per year [1]. The problem of fighting hospital infections is particularly acute. Among the most dangerous representatives of such bacteria, assigned by the WHO to the 1st priority category, are multiresistant gram-negative bacteria of the genus *Acinetobacter, Pseudomonas* and various species of Enterobacteriaceae family (including *Klebsiella, E. coli, Serratia* and *Proteus*) resistant to carbopenems and other antibiotics [2]. This list provides guidelines for priority developments for research organizations. According to WHO guidelines, an urgent search for fundamentally new anti-infective medicines is needed, as well as the development of fundamental and applied scientific research related to the decoding of the natural anti-infective defense mechanisms of the body.

Bacteria that form biofilms are a particular problem, which greatly increases their resistance to chemotherapy [3—5]. The search for means to combat such bacteria is an urgent task of experimental and practical medicine.

Analogues of natural antimicrobial peptides (AMP) of the innate immunity system are currently considered as fundamentally new antibiotics due to the difficult formation of the resistance of microorganisms to these compounds and the absence of negative effects on the immune system, characteristic for some conventional antibiotics.

GENERAL CHARACTERISTICS AND STRUCTURAL CLASSIFICATION OF PEPTIDES

AMPs are known as molecules acting as the most important effector link in the system of innate immunity of animals [6—8]. In addition, peptides with antimicrobial activity are found not only in animals, but also in plants, fungi, bacteria [7, 9, 10]. These compounds are positively charged peptide molecules, which include 15-45 amino acid residues. The peptides in question were named antimicrobial due to the discovery of a wide range of antibiotic activity in these substances — these peptides inhibit the growth and development of gram-negative, gram-positive bacteria, fungi (including yeasts), parasites (including planaries and nematodes), and even viruses such as HIV and herpes virus [8, 11—17].

Antimicrobial peptides have a variety of primary structures and different conformations of molecules. One of the classifications of AMPs is based on differences in their secondary structure and divides the known peptides into several main groups [18-20]:

* peptides having an α-helix conformation;
* linear peptides having an increased content of one or another amino acid in the composition of the molecule: peptides enriched with proline, tryptophan, histidine or glycine;
* cystine-containing peptides are peptides having one, two or more disulfide bonds. This group usually includes peptides with a mixed structure, which, in addition to β-layers, also include spiral sections; as well as macrocyclic peptides closed in a ring by a peptide bond (θ- defensins RTD-1, -2, -3).

The vast majority of antimicrobial peptides are cationic molecules. However, several anionic peptides have been described [21, 22], for example, dermaseptin, a peptide found in the secretions of human sweat glands and exhibiting antibacterial and fungicidal activity — maximin H5 from the skin of toad Bombina maxima [23] and others.

MAIN GROUPS OF ANTIMICROBIAL PEPTIDES IN MAMMALS

Mammals have two main groups of antimicrobial peptides: a family of structurally related cystine-containing AMP defensins and a group of peptides with diverse structures that make up the family of cathelicidins [18, 24].

The existence of low molecular weight cationic proteins with antimicrobial action was first shown by American researchers Zeya and Spitznagel in the sixties [25], who discovered them in rabbit and guinea pig neutrophils and named them “lysosomal cationic proteins”. In our country, studies of these polypeptides were initiated at the Research Institute of Experimental Medicine and at the Department of Biochemistry of Leningrad University; their bactericidal and antiviral activity was demonstrated [26-30].

The term “defensins” as a definition of this group of substances was introduced in 1985 [31] with the beginning of a new period in the study of these peptides. The primary structure of defensins in rabbit [32], humans [31, 33], guinea pig [34] and rat [35] was deciphered. It is shown that they have universal antimicrobial activity, inactivating *in vitro* gram-positive, gram-negative bacteria, fungi, and some envelope viruses. Subsequently, these peptides were called α-defensins to emphasize their difference from other AMPs, similar in structure, but different in the nature of the closure of disulfide bonds, which in turn received the name β-defensins.

Four isoforms of α-defensins were isolated from human neutrophils, three of which HNP-1, HNP-2 and

HNP-3 differ from each other only in one N-terminal amino acid. HNP-4 is present in neutrophils in amounts one hundred times less than HNP 1-3 [14]. Peptides of this group were found not only in neutrophils, but also in human lymphocytes, natural killer cells [36], in epithelial cells of the genitourinary tract [37], although in much smaller quantities than in neutrophils. In addition, α-defensins, called HD-5 and HD-6, were found in intestinal crypts in Paneth cells [38].

Six human α-defensins are encoded by five DEFA genes localized on chromosome 8p23.1. Defensin HNP-2 differs from HNP-1 and HNP-3 by the absence of an N-terminal residue (alanine in HNP-1 or aspartic acid in HNP-3); thus, this defensin is a product of the DEFA1 gene encoding HNP -1, or DEFA3 encoding HNP-3, and is formed as a result of proteolytic cleavage of N-terminal residues of these peptides. 1×10^{6} human neutrophils contain approximately 4-5 μg of defensins HNP-1-3, and about 250 mg of these AMPs are produced in the bone marrow every day during hematopoiesis in neutrophils [14].

While α-defensins are found mainly in phagocytes, and in many animal species (cats, dogs, horses, sheep and others) these peptides are completely absent, the peptides of the β-defensin group are more widespread. They are present in the epithelial cells of all studied mammalian species and have been identified in reptiles and birds; in addition, peptides similar in structure have also been found in fungi, plants, and bacteria.

28 genes encoding various β-defensins have been described in humans. Four main isoforms of these peptides are distinguished: HBD-1 is found in epithelial cells of the respiratory and genitourinary tract, keratinocytes, astrocytes, microglia [39, 40] and leukocytes; HbD-2 — in epithelial cells of the skin, respiratory, genitourinary, digestive tracts [41]; HbD-3 in various types of epithelial cells: its highest concentration was found in saliva and genitourinary tract it is also found in the liver, heart, placenta [42, 43]; HBD-4 is found in cells of the genitourinary and digestive tracts [44, 45]. HBd-1 biosynthesis is constitutive, HBd-2 and HBd-3 are inducible: the expression level of HbD2 and HbD3 genes increases when epithelial cells come into contact with microorganisms [46].

Another unusual group of defensins is cyclic θ-defensins. Peptides of this group were found in white blood cells of rhesus macaque [47, 48] and hamadryl baboon [49]. It has been shown that the RTD-1 peptide (rhesus θ-defensin 1) is a crosslinking product of two shortened α-defensins encoded by two different genes. The cyclic structure of θ-defensins makes them relatively insensitive to the presence of sodium chloride in the medium and allows for antimicrobial function at physiological concentrations of salts. Although humans also have genes encoding θ-defensins, they are not expressed due to the presence of a stop codon in the DNA region responsible for the synthesis of the pre-part of these molecules.

Representatives of the family of cathelicidins were found in phagocyte granules, as well as in cells of various barrier epitheliums. Cathelicidins, unlike defensins, exhibit a wide structural diversity. These structurally different peptides are grouped into one family due to the fact that they are all formed from precursor molecules [50], which include a site region, homologous to the protein katelin (i. e., the inhibitor of cathepsin L, a protein with a mass of 11 kDa which was first isolated from pig leukocytes [51]). Precursor molecules do not show antimicrobial effects; a mature active peptide is formed only after cleavage of the prepro part by enzymes of activated neutrophils [52].

Cathelicidins have been found in human protective cells of mammals, birds, reptiles, and fish [52-54].

ANTIMICROBIAL ACTIVITY OF PEPTIDES

The spectrum of antimicrobial activity of AMPs depends on the peptide structure. Some AMPs have a wide spectrum of antibiotic effects and are active against gram-negative gram-positive bacteria, fungi. Other AMPs have a more limited spectrum of antimicrobial activity: for example, peptides enriched with proline inactivate mainly gram-negative bacteria [55]. A number of AMPs has fungicidal activity; it has been demonstrated for rabbit and human α-defensins, human β-defensins, histatins, protegrins and other peptides [8, 12, 14, 56]. Many peptides exhibit pronounced activity against strains of microorganisms resistant to most antibiotic drugs used in medicine [57-60]. These properties of peptides are due to the mechanism of their antimicrobial action, which will be discussed below.

Despite the huge structural diversity of the natural antimicrobial peptides described to date, all of them, as a rule, are cationic and amphipathic molecules in which hydrophilic and hydrophobic groups of amino acid residues are spatially separated. The presence of a positive charge allows them to bind electrostatically to the anionic components of microbial cell membranes (anionic phospholipids, lipopolysaccharides, teichoic acids), and due to their hydrophobic properties, embed in the lipid bilayers of membranes, which can cause irreversible damage to the structure of the bacterial membrane and disruption of its functions, and lead to the death of target cells [8, 18, 20, 61].

Thus, bacterial membranes are the target of the action of most natural AMPs. Currently, there is a large number of works in the literature dedicated to the study

of the action of antimicrobial peptides on artificial lipid membranes (monolayers, bilayers, liposomes), the composition of which is close to the lipid composition of bacterial membranes or eukaryotic cells. Although the mechanism of embedding antimicrobial peptides into the membranes of living cells has not yet been fully understood, experiments on model membranes resulted in data that have been analyzed, making it possible to propose several models of interaction of antibiotic peptides with lipid membranes [62].

The amphipathic nature of antimicrobial peptides is their key physicochemical property, important for the implementation of the process of embedding peptides into lipid membranes: hydrophobic regions are necessary to interact directly with the lipophilic phase of membranes, while hydrophilic regions either interact with negatively charged groups of phospholipids or are directed into the pore cavity.

At the first stage of AMP-membrane contact, peptides preferentially assume an orientation parallel to the membrane, electrostatically binding to negatively charged phosphate groups of phospholipids on the membrane surface [8, 62, 63]. At the same time, many peptides change their conformation during the transition from an aqueous medium to a lipid environment, in particular, many peptides from the α-helical group acquire an ordered α-helical structure precisely during adsorption on the membrane [64, 65].

Depending on the structure of peptides, the mechanism of membrane damage varies. It is also assumed that peptides can influence membranes by combining several different methods of action. According to classical ideas about the mechanism of violation of the structural integrity of membranes, peptides, being sorbed on its surface, reach a certain threshold concentration, after which their embedding into the membrane begins with the formation of a pore formed by peptide molecules (the "barrel assembly" model), or a pore composed of peptide and lipid molecules (a toroidal pore), or with the formation of micellar structures in the membrane (the "carpet" model") [19, 63, 64, 66].

The toroidal pore model assumes that peptide clusters acquire an orientation perpendicular to the membrane, bending it inward to form a pore and form a "passage" lined with hydrophilic groups (including heads of membrane phospholipids) directed into the cavity.

In the "barrel assembly" or "barrel riveting" model, the peptide molecules are reoriented, acting as "boards" ("rivets") forming the walls of the "barrel"-pores, i.e. they form a cluster located perpendicular to the membrane surface, so that the hydrophobic regions of each peptide in the cluster are connected to the lipid core of the membrane, while the hydrophilic regions look into the cavity of the transmembrane pore formed.

In contrast to the models of pore formation, the "carpet" model assumes that peptide molecules located parallel to the lipid bilayer cover entire local areas like a carpet [67] and, when a sufficiently high concentration is reached, exhibit detergent-like activity, causing local violations of membrane integrity. Sections of the membrane can break into micelles, which can lead to the formation of pores. Intermediate compounds composed of lipid molecules bound to a peptide can also be formed.

A decrease in the thickness of the lipid bilayer in the presence of AMPs has also been described [19, 61] and is considered as one of the methods of action leading to disruption of the barrier function of membranes.

The adsorption of peptides on the membrane increases when they come into contact with oxidized phospholipids. In some cases, no significant damage to the membrane is detected when exposed to peptides, but the membrane potential of target cells drops sharply. A model of "electroporation" has also been proposed [19, 68], according to which the accumulation of peptides in the outer sheet of the lipid bilayer of the membrane leads to an increase in the membrane potential above the threshold value, which entails an increase in the permeability of the membrane to various molecules, including the peptides themselves.

Some AMPs at the lowest effective concentration do not cause membrane disintegration, and yet bacteria die. These peptides move through the membrane and accumulate inside cells, where they disrupt many important cellular processes, mediating cell death: inhibit nucleic acid synthesis, protein synthesis, enzymatic activity and cell wall synthesis [18, 66, 69].

For example, the frog antimicrobial peptide buforin penetrates the bacterial membrane without causing its destruction, and binds to DNA and RNA in the *E. coli* cytoplasm [70]. Similarly, some α-helical peptides, such as dermaseptin isolated from frog skin, or pleurocidin derivatives obtained from fish AMPs, cause inhibition of DNA and RNA synthesis without destabilizing the *E. coli* cell membrane [71]. Inhibition of nucleic acid synthesis has also been demonstrated for antimicrobial peptides from various structural classes, such as the human β-structure α-defensin HNP-1 [72] or the linear, tryptophan-enriched peptide of bovine neutrophils indolicidin [73].

In addition, it has been shown that some of these AMPs can affect protein synthesis. A decrease in the level of protein synthesis is observed, including under the action of pleurocidin and dermaseptin, PP-39 and indolicidin. Using the example of proline-rich insect AMP pyrhocorycin, a mechanism for similar peptides has been revealed, according to which the peptide enters the target cell (*E. coli*) and binds to DnaK, a heat

shock protein that is involved in chaperone-dependent protein folding. The peptide inhibits ATP-ase activity of DnaK, disrupting the spatial convolution of protein molecules, which results in the accumulation of proteins with impaired conformation and cell death [74]. This activity was also confirmed for bovine bactenecin 7 and sheep bactenecin 7.5 [75—77]. For a number of proline-rich AMPS, including insect apidaecins and oncocins, as well as bovine bactencins 5 and 7, the possibility of blocking their translation on ribosomes due to binding to the 70S subunit (in the area of the exit tunnel) was also revealed [55, 78-82].

Antimicrobial peptides can also target the formation of structural components, such as the cell wall. The lantibiotic nisin, in addition to its ability to form pores, can bind lipid 2, thus inhibiting cell wall synthesis [83]. Interestingly, the same stages of its biosynthesis process are the target of the action of the antibiotic vancomycin. However, it is assumed that nisin and vancomycin show their effect by interacting with different molecular parts within lipid 2, as a result of which the nisin peptide is also active against vancomycin-resistant bacteria [84].

Many researchers tend to think that the mechanism of action of each peptide may vary slightly, depending on the characteristics of the target cell. In addition, AMP can inactivate bacteria using two or more mechanisms of action, combining the destabilization of the cell membrane and the violation of intracellular processes. It is believed that AMP can act as a "multi-purpose" mechanism [85, 86], namely that peptides with a high positive charge of the molecule, in addition to disrupting bacterial membranes, penetrate microbial cells and bind to anionic compounds in the cytoplasm, such as nucleic acids or enzymes, thus interfering with the processes in which these molecules are involved. Thus, it has been shown that cationic peptides of various structural classes can bind and specifically inhibit the activity of aminoglycoside-modifying enzymes that contain an anion-binding pocket [87]. The high degree of complexity of such a mechanism and the multiplicity of antimicrobial targets are the reasons for the unlikely appearance and selection of mutants resistant to cationic peptides [86, 88].

In addition to the activity associated with the direct inactivation of bacteria, fungi and viruses, AMPs show a number of effects on the body's own cells. Many peptides have cytoxicity against various tumor and normal eukaryotic cells [63, 89-91], act as chemoattractants for macrophages, neutrophils, immature dendritic cells [92-94], increase vascular permeability and stimulate their growth [95-98], cause mast cell degranulation [96, 99-102], affect cytodifferentiation [103-105], inhibit corticosterone production by the cells of the adrenal cortex *in vitro* [106-108].

DRUGS BASED ON ANTIMICROBIAL PEPTIDES

In light of the rapidly developing resistance of pathogenic microorganisms to antibiotics used in the clinic and the increasingly acute problem of finding new effective antimicrobials, one of the attractive properties of AMPs of animal origin as candidates for the role of the latter is the high activity of many of them, also in relation to antibiotic-resistant clinical isolates of bacteria and fungi [109-114]. It has been shown that they are also efficient against biofilms, the formation of which is associated with a significant part of intractable chronic bacterial infections [115-117]. At the same time, the fact that some AMPs have not only antimicrobial, but also immunomodulatory activity mentioned in the previous section, makes these compounds especially promising for their development the basis of antibiotic drugs for the correction of various complicated pathological processes, including those accompanied by immunodeficiency states. In general, the proposed areas of practical use of AMPs are quite diverse and are associated with their use as direct antibiotic agents that cause the death of pathogenic microorganisms or transformed cells; as immunomodulating substances or as carriers of other medicinal compounds through cell membranes [12, 118-120]. At the same time, most of the current developments are related to the first opportunity.

The direct antimicrobial effect of most active AMPs is carried out in a short period of time — a few minutes, as it is associated with damage to the integrity of the membranes of bacteria. The labored development of resistance of microorganisms to AMPs in the wild is largely associated with this circumstance [60, 88, 121]. However, it is AMPs with pronounced membranolytic effects that are more often toxic to the body's own cells, which complicates the development of drugs directly based on these compounds. Therefore, the efforts of scientists are aimed at creating modifications of AMPs with an optimal combination of properties: high antimicrobial activity and low toxicity for the own body's cells.

Unfortunately, despite the progress in analyzing the relationship between the structure and activity of AMP in recent decades, attempts to develop structural analogues of AMP *de novo* using only computer modeling tools have had very limited success. The search for new natural peptides, for example, their isolation from animal leukocytes, remains relevant. Taking into account the long evolutionary selection, the appeal to natural sources often leads to the identification of structures of peptide molecules with promising properties from the point of view of practical application, and further mod-

ification is already under way on this basis.

To date, a number of AMP-based drugs have been developed, most of which are at various stages of clinical and preclinical trials. Many of them are based on natural peptides. For example, on the basis of the short tryptophan-rich cathelicidin, bovine indolicidin, Migenix has proposed the drugs MX-594AN (for the treatment of acne) and MBI-226 (omiganan; initially for use in catheter-associated infections) [122]. To date, omiganan has completed phase III clinical trials as a treatment for rosacea and is undergoing phase II as a drug against acne, atopic dermatitis and vaginal intraepithelial neoplasia [123, 124]. Another drug, P-113 (PAC-113), developed by Demegen on the basis of histatin 5 (one of the group of histidine-rich cationic peptides of saliva), has completed phase II clinical trials as a drug for oral cavity treatment in candidiasis in HIV patients [56, 123]. OctoPlus, a subsidiary of Dr. Reddy's Research has successfully completed phase II clinical trials of the 24-amino acid derivative of cathelicidin LL-37 OP-145 for the treatment of chronic middle ear infections [123, 125], and ProMore Pharma is conducting phase IIb trials of LL-37 itself as a drug against chronic ulcers of the lower extremities [123, 126].

It is also interesting to note the drugs developed by PLANTON GmbH based on human β-defensin 2 (HbD2), which are intended to be used in the treatment of atopic dermatitis; skin damage, burns and complications of infectious diseases, and pulmonary infections. It is noteworthy that recombinant peptide preparations are produced using biotechnological approaches that make it possible to produce a peptide in the tubers of transgenic potatoes, which significantly reduces the cost of drug production compared to the more commonly used production of peptides using cultured bacterial or eukaryotic cells [127].

On the basis of cytokine-like peptides of insects (larvae of the *Calliphoridae* family), the domestic drug Alloferon was developed, which is currently used in medical practice as a drug that stimulates the antiviral, antimicrobial and anticancer activity of the human immune system [128, 129].

Despite the modest success of implementation at the moment, interest in the possibilities of using AMPs does not weaken and the list is being updated with new drugs undergoing preclinical trials. Examples are the drug NZ2114 based on the beta-defensin-like peptide of the fungus *Pseudoplectania nigrella* plectazine, developed by Novozymes for the treatment of infections associated with antibiotic-resistant bacteria [130-132], or the drug A3-ARO, created on the basis of a proline-enriched peptide from insect hemolymph [133-135]. The latter peptide is interesting because, despite the low antibacterial activity *in vitro*, when used *in vivo* (on the model of skin infection, respiratory tract infections in mice) shows high efficacy, exceeding the values of traditionally used antibiotics when administered intramuscularly or used in the form of an aerosol [133].

CONCLUSION

Even the analysis of the trials of drugs in progress makes it obvious that the researchers associate the closest prospects for applying AMPs in medicine with their use as topical agents: for the treatment of infected wounds, including burns, mucocutaneous infections, chronic trophic ulcers, in particular with diabetic foot syndrome, etc. In addition, the possibilities of including AMP in the composition of antibacterial coatings that can be used in the creation of various medical devices: catheters, stents, dental implants, etc. are being considered. [136—138]. Both of these areas allow reprioritizing to some extent a number of existing problems, such as collateral toxicity, targeted delivery issues or limited lifetime of free peptides in biological media [139, 140]. The probable lack of economic advantage in case of equal effectiveness of new peptide antibiotics in comparison with the drugs already in use remains an obstacle as well [16, 140].

Nevertheless, the prospect of using AMP-based drugs to solve more complex and global problems is still undoubtedly attractive. The totality of available data confirms the idea that these components of the innate immunity system in humans and animals exhibit a wide range of biological properties that are realized during various adaptive and protective processes, such as infection, inflammation, and distress. A deeper understanding of the underlying relationships and molecular mechanisms can make it possible to comprehensively realize the potential of AMPs not only as antimicrobial, but also as immunomodulatory agents.

In addition to the actual effectiveness against resistant bacteria, the effects of synergistic antimicrobial action with antibiotics of various nature have been shown for a number of AMP,s in particular in cases where bacteria are resistant directly to antibiotics included in the combination [141-146]. In light of this, the development of combined antibiotic drugs for personalized therapy of infections caused by antibiotic-resistant bacteria is promising.

The choice in favor of potential AMP-based drugs may be appropriate in the case of severe hospital infections, when standard approaches to chemotherapy are ineffective and there is information about the spectrum of antibiotic-resistant pathogens in a particular patient. AMP-based drugs may also have an advantage in cases of complex action: peptides having also angiogenic and reparative effects alongside antimicrobial ones may additionally promote the healing of trophic ulcers, and peptides with additional antitumor properties may be

the optimal choice for the prevention and correction of infectious complications in cancer patients (against the background of a decrease in immune status, for example, during chemotherapy).

Thus, due to the outstanding potential of AMPs, the development of therapeutic drugs based on these compounds does not lose relevance, despite a number of difficult problems facing researchers.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. World Health Organization. No time to wait: Securing the future from drug-resistant infections — Report to the Secretary-General of the United Nations. 2019. https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf (4 October 2021).
2. World Health Organization. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. 2017. https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12 (4 October 2021).
3. Jamal M, Ahmad W, Andleeb S, et al. Bacterial biofilm and associated infections. J Chin Med Assoc. 2018; 81(1):7–11. DOI: 10.1016/j.jcma.2017.07.012.
4. Vestby LK, Grønseth T, Simm R, et al. Bacterial Biofilm and its Role in the Pathogenesis of Disease. Antibiotics (Basel). 2020; 9(2):59. DOI: 10.3390/antibiotics9020059.
5. Bjarnsholt T. The role of bacterial biofilms in chronic infections. APMIS Suppl. 2013; (136):1–51. DOI: 10.1111/apm.12099.
6. Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol. 2009; 30(3):131–141. DOI: 10.1016/j.it.2008.12.003.
7. Riera Romo M, Pérez-Martínez D, Castillo Ferrer C. Innate immunity in vertebrates: an overview. Immunology. 2016; 148(2):125–139. DOI: 10.1111/imm.12597.
8. Kokryakov VN. Essays on innate immunity. Saint Petersburg: Nauka, 2006. 261 p. In Russian [Кокряков В.Н. Очерки о врождённом иммунитете. СПб: Наука, 2006. 261 с.].
9. Li Y, Xiang Q, Zhang Q, et al. Overview on the recent study of antimicrobial peptides: origins, functions, relative mechanisms and application. Peptides. 2012; 37(2):207–215. DOI: 10.1016/j.peptides.2012.07.001.
10. Pasupuleti M, Schmidtchen A, Malmsten M. Antimicrobial peptides: key components of the innate immune system. Crit Rev Biotechnol. 2012; 32(2):143–171. DOI: 10.3109/07388551.2011.594423.
11. Zasloff M. Antimicrobial peptides, innate immunity, and the normally sterile urinary tract. J Am Soc Nephrol. 2007; 18(11):2810–2816. DOI: 10.1681/ASN.2007050611.
12. Nijnik A, Hancock R. Host defence peptides: antimicrobial and immunomodulatory activity and potential applications for tackling antibiotic-resistant infections. Emerg Health Threats J. 2009; 2:e1. DOI: 10.3134/ehtj.09.001.
13. Wiesner J, Vilcinskas A. Antimicrobial peptides: the ancient arm of the human immune system. Virulence. 2010; 1(5):440–464. DOI: 10.4161/viru.1.5.12983.
14. Lehrer RI, Lu W. α-Defensins in human innate immunity. Immunol Rev. 2012; 245(1):84–112. DOI: 10.1111/j.1600-065X.2011.01082.x.
15. Wang G. Antimicrobial peptides: Discovery, design, and novel therapeutic strategies. Wallingford: CABI Publishing, 2010. 230 p.
16. Mookherjee N, Anderson MA, Haagsman HP, et al. Antimicrobial host defence peptides: functions and clinical potential. Nat Rev Drug Discov. 2020; 19(5):311–332. DOI: 10.1038/s41573-019-0058-8.
17. Pachón-Ibáñez ME, Smani Y, Pachón J, et al. Perspectives for clinical use of engineered human host defense antimicrobial peptides. FEMS Microbiol Rev. 2017; 41(3):323–342. DOI: 10.1093/femsre/fux012.
18. Huan Y, Kong Q, Mou H, et al. Antimicrobial Peptides: Classification, Design, Application and Research Progress in Multiple Fields. Front Microbiol. 2020; 11:582779. DOI: 10.3389/fmicb.2020.582779.
19. Nguyen LT, Haney EF, Vogel HJ. The expanding scope of antimicrobial peptide structures and their modes of action. Trends Biotechnol. 2011; 29(9):464–472. DOI: 10.1016/j.tibtech.2011.05.001.
20. Kumar P, Kizhakkedathu JN, Straus SK. Antimicrobial Peptides: Diversity, Mechanism of Action and Strategies to Improve the Activity and Biocompatibility In Vivo. Biomolecules. 2018; 8(1):4. DOI: 10.3390/biom8010004.
21. Harris F, Dennison SR, Phoenix DA. Anionic antimicrobial peptides from eukaryotic organisms. Curr Protein Pept Sci. 2009; 10(6):585–606. DOI: 10.2174/138920309789630589.
22. Phoenix DA, Dennison SR, Harris F. Antimicrobial Peptides. Singapore: Wiley-VCH, 2013. 231 p.
23. Lai R, Liu H, Hui Lee W, et al. An anionic antimicrobial peptide from toad Bombina maxima. Biochem Biophys Res Commun. 2002; 295(4):796–799. DOI: 10.1016/s0006-291x(02)00762-3.
24. Dorin JR, McHugh BJ, Cox SL, et al. Chapter 30—Mammalian Antimicrobial Peptides; Defensins and Cathelicidins. In: Tang Y-W, Sussman M, Liu D, et al. eds. Molecular Medical Microbiology. 2nd ed. Cambridge, MA, USA: Academic Press, 2015:539–565. DOI: 10.1016/B978-0-12-397169-2.00030-5.

25. Zeya HI, Spitznagel JK. Antibacterial and enzymatic basic protein from leukocyte lysosomes: separation and identification. Science. 1963; 142(3595):1085–1087. DOI: 10.1126/science.142.3595.1085.

26. Ashmarin IP, Kokryakov VN, Lyzlova SN, et al. Interaction of cationic proteins of granules and myeloperoxidase of leukocytes. Problems of medicinal chemistry (Biomedical chemistry since 2003). 1977; 3:534–537. In Russian [Ашмарин И.П., Кокряков В.Н., Лызлова С.Н., и др. Взаимодействие катионных белков гранул и миелопероксидазы лейкоцитов. Вопросы медицинской химии (Биомедицинская химия с 2003). 1977; 3:534–537].

27. Kokryakov VN, Ashmarin IP, Pigarevsky VE. On the nature of some fractions of lysosomal cationic proteins of leukocytes. Biochemistry. 1973; 38(6):1276–1280. In Russian [Кокряков В.Н., Ашмарин И.П., Пигаревский В.Е. О природе некоторых фракций лизосомальных катионных белков лейкоцитов. Биохимия. 1973; 38(6):1276–1280].

28. Masing YuA. Neutrophilic granulocytes and the body's defense system. Archive of pathology. 1991; 9:70–73. In Russian [Мазинг Ю.А. Нейтрофильные гранулоциты и система защиты организма. Архив патологии. 1991; 9:70–73].

29. Pigarevsky VE, Ashmarin IP, Tolybekov AS, et al. On the in vitro effect of leukocyte and thymic giton and their fractions on the activity of the causative agent of meningopneumonia. Journal of Microbiology, Epidemiology and Immunobiology. 1975; 10:76–78. In Russian [Пигаревский В.Е., Ашмарин И.П., Толыбеков А.С., и др. О влиянии in vitro лейкоцитарного и тимусного гитона и их фракций на активность возбудителя менингопневмонии. Журнал микробиологии, эпидемиологии и иммунобиологии. 1975; 10:76–78].

30. Pigarevsky VE, Kokryakov VN, Taros LYu, et al. Antiviral properties of defensins in experimental herpes infection. In: Pathomorphology of tumors and background diseases. Leningrad, 1989:122–124. In Russian [Пигаревский В.Е, Кокряков В.Н., Тарос Л.Ю., и др. Антивирусные свойства дефенсинов при экспериментальной герпетической инфекции. В кн.: Патоморфология опухолей и фоновых заболеваний. Л., 1989: 122–124].

31. Ganz T, Selsted ME, Szklarek D, et al. Defensins. Natural peptide antibiotics of human neutrophils. J Clin Invest. 1985; 76(4):1427–1435. DOI: 10.1172/JCI112120.

32. Selsted ME, Brown DM, DeLange RJ, et al. Primary structures of six antimicrobial peptides of rabbit peritoneal neutrophils. J Biol Chem. 1985; 260(8):4579–4584.

33. Selsted ME, Harwig SS, Ganz T, et al. Primary structures of three human neutrophil defensins. J Clin Invest. 1985; 76(4):1436–1439. DOI: 10.1172/JCI112121.

34. Selsted ME, Harwig SS. Purification, primary structure, and antimicrobial activities of a guinea pig neutrophil defensin. Infect Immun. 1987; 55(9):2281–2286. DOI: 10.1128/iai.55.9.2281-2286.1987.

35. Eisenhauer PB, Harwig SS, Szklarek D, et al. Purification and antimicrobial properties of three defensins from rat neutrophils. Infect Immun. 1989; 57(7):2021–2027. DOI: 10.1128/iai.57.7.2021-2027.1989.

36. Agerberth B, Charo J, Werr J, et al. The human antimicrobial and chemotactic peptides LL-37 and alpha-defensins are expressed by specific lymphocyte and monocyte populations. Blood. 2000; 96(9):3086–3093.

37. Selsted ME, Ouellette AJ. Mammalian defensins in the antimicrobial immune response. Nat Immunol. 2005; 6(6):551–557. DOI: 10.1038/ni1206.

38. Jones DE, Bevins CL. Paneth cells of the human small intestine express an antimicrobial peptide gene. J Biol Chem. 1992; 267(32):23216–23225.

39. Valore EV, Park CH, Quayle AJ, et al. Human beta-defensin-1: an antimicrobial peptide of urogenital tissues. J Clin Invest. 1998; 101(8):1633–1642. DOI: 10.1172/JCI1861.

40. Nakayama K, Okamura N, Arai H, et al. Expression of human beta-defensin-1 in the choroid plexus. Ann Neurol. 1999; 45(5):685. DOI: 10.1002/1531-8249(199905)45:5<685::aid-ana25>3.0.co;2-6.

41. McCray PB Jr, Bentley L. Human airway epithelia express a beta-defensin. Am J Respir Cell Mol Biol. 1997; 16(3):343–349. DOI: 10.1165/ajrcmb.16.3.9070620.

42. Harder J, Bartels J, Christophers E, et al. Isolation and characterization of human beta-defensin-3, a novel human inducible peptide antibiotic. J Biol Chem. 2001; 276(8):5707–5713. DOI: 10.1074/jbc.M008557200.

43. Ghosh SK, Gerken TA, Schneider KM, et al. Quantification of human beta-defensin-2 and -3 in body fluids: application for studies of innate immunity. Clin Chem. 2007; 53(4):757–765. DOI: 10.1373/clinchem.2006.081430.

44. Shestakova T, Zhuravel E, Bolgova L, et al. Expression of human beta-defensins-1, 2 and 4 mRNA in human lung tumor tissue: a pilot study. Exp Oncol. 2008; 30(2):153–156.

45. Otte JM, Neumann HM, Brand S, et al. Expression of beta-defensin 4 is increased in human gastritis. Eur J Clin Invest. 2009; 39(2):126–138. DOI: 10.1111/j.1365-2362.2008.02071.x.

46. Pazgier M, Hoover DM, Yang D, et al. Human beta-defensins. Cell Mol Life Sci. 2006; 63(11):1294–1313. DOI: 10.1007/s00018-005-5540-2.

47. Tang YQ, Yuan J, Osapay G, et al. A cyclic antimicrobial peptide produced in primate leukocytes by the ligation of two truncated alpha-defensins. Science. 1999; 286(5439):498–502. DOI: 10.1126/science.286.5439.498.

48. Leonova L, Kokryakov VN, Aleshina G, et al. Circular minidefensins and posttranslational generation of molecular diversity. J Leukoc Biol. 2001; 70(3):461–464.

49. Stegemann C, Tsvetkova EV, Aleshina GM, et al. De novo sequencing of two new cyclic theta-defensins from baboon (Papio hamadryas) leukocytes by matrix-assisted laser desorption/ionization mass spectrometry. Rapid Commun Mass Spectrom. 2010; 24(5):599–604. DOI: 10.1002/rcm.4424.

50. Zanetti M, Gennaro R, Romeo D. Cathelicidins: a novel protein family with a common proregion and a variable C-terminal antimicrobial domain. FEBS Lett. 1995; 374(1):1–5. DOI: 10.1016/0014-5793(95)01050-o.

51. Kopitar M, Ritonja A, Popovic T, et al. A new type of low-molecular mass cysteine proteinase inhibitor from pig leukocytes. Biol Chem Hoppe Seyler. 1989; 370(10):1145–1151. DOI:10.1515/bchm3.1989.370.2.1145.

52. Zanetti M. The role of cathelicidins in the innate host defenses of mammals. Curr Issues Mol Biol. 2005; 7(2):179–196.

53. Kościuczuk EM, Lisowski P, Jarczak J, et al. Cathelicidins: family of antimicrobial peptides. A review. Mol Biol Rep. 2012; 39(12):10957–10970. DOI: 10.1007/s11033-012-1997-x.

54. Wang Y, Wang M, Shan A, et al. Avian host defense cathelicidins: structure, expression, biological functions, and potential therapeutic applications. Poult Sci. 2020; 99(12):6434–6445. DOI: 10.1016/j.psj.2020.09.030.

55. Graf M, Wilson DN. Intracellular Antimicrobial Peptides Targeting the Protein Synthesis Machinery. Adv Exp Med Biol. 2019; 1117:73–89. DOI: 10.1007/978-981-13-3588-4_6.

56. Mercer DK, O'Neil DA. Innate Inspiration: Antifungal Peptides and Other Immunotherapeutics From the Host Immune Response. Front Immunol. 2020; 11:2177. DOI: 10.3389/fimmu.2020.02177.

57. Mechkarska M, Ahmed E, Coquet L, et al. Antimicrobial peptides with therapeutic potential from skin secretions of the Marsabit clawed frog Xenopus borealis (Pipidae). Comp Biochem Physiol C Toxicol Pharmacol. 2010; 152(4):467–472. DOI: 10.1016/j.cbpc.2010.07.007.

58. Wang J, Wong ES, Whitley JC, et al. Ancient antimicrobial peptides kill antibiotic-resistant pathogens: Australian mammals provide new options. PLoS One. 2011; 6(8):e24030. DOI: 10.1371/journal.pone.0024030.

59. Roque-Borda CA, da Silva PB, Rodrigues MC, et al. Challenge in the Discovery of New Drugs: Antimicrobial Peptides against WHO-List of Critical and High-Priority Bacteria. Pharmaceutics. 2021; 13(6):773. DOI: 10.3390/pharmaceutics13060773.

60. León-Buitimea A, Garza-Cárdenas CR, Garza-Cervantes JA, et al. The Demand for New Antibiotics: Antimicrobial Peptides, Nanoparticles, and Combinatorial Therapies as Future Strategies in Antibacterial Agent Design. Front Microbiol. 2020; 11:1669. DOI: 10.3389/fmicb.2020.01669.

61. Lohner K. New strategies for novel antibiotics: peptides targeting bacterial cell membranes. Gen Physiol Biophys. 2009; 28(2):105–116. DOI: 10.4149/gpb_2009_02_105.

62. Hollmann A, Martinez M, Maturana P, et al. Antimicrobial Peptides: Interaction With Model and Biological Membranes and Synergism With Chemical Antibiotics. Front Chem. 2018; 6:204. DOI: 10.3389/fchem.2018.00204.

63. Tornesello AL, Borrelli A, Buonaguro L, et al. Antimicrobial Peptides as Anticancer Agents: Functional Properties and Biological Activities. Molecules. 2020; 25(12):2850. DOI: 10.3390/molecules25122850.

64. Li J, Koh JJ, Liu S, et al. Membrane Active Antimicrobial Peptides: Translating Mechanistic Insights to Design. Front Neurosci. 2017; 11:73. doi: 10.3389/fnins.2017.00073.

65. Tuerkova A, Kabelka I, Králová T, et al. Effect of helical kink in antimicrobial peptides on membrane pore formation. Elife. 2020; 9:e47946. DOI: 10.7554/eLife.47946.

66. Brogden KA. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat Rev Microbiol. 2005; 3(3):238–250. DOI: 10.1038/nrmicro1098.

67. Pouny Y, Rapaport D, Mor A, et al. Interaction of antimicrobial dermaseptin and its fluorescently labeled analogues with phospholipid membranes. Biochemistry. 1992; 31(49):12416–12423. DOI: 10.1021/bi00164a017.

68. Miteva M, Andersson M, Karshikoff A, et al. Molecular electroporation: a unifying concept for the description of membrane pore formation by antibacterial peptides, exemplified with NK-lysin. FEBS Lett. 1999; 462(1–2):155–158. DOI: 10.1016/s0014-5793(99)01520-3.

69. Le CF, Fang CM, Sekaran SD. Intracellular Targeting Mechanisms by Antimicrobial Peptides. Antimicrob Agents Chemother. 2017; 61(4):e02340-16. DOI: 10.1128/AAC.02340-16.

70. Park CB, Kim HS, Kim SC. 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 Commun. 1998; 244(1):253–257. DOI: 10.1006/bbrc.1998.8159.

71. Patrzykat A, Friedrich CL, Zhang L, et al. Sublethal concentrations of pleurocidin-derived antimicrobial peptides inhibit macromolecular synthesis in Escherichia coli. Antimicrob Agents Chemother. 2002; 46(3):605–614. DOI: 10.1128/AAC.46.3.605-614.2002.

72. Lehrer RI, Barton A, Daher KA, et al. Interaction of human defensins with Escherichia coli. Mechanism of bactericidal activity. J Clin Invest. 1989; 84(2):553–561. DOI: 10.1172/JCI114198 .

73. Subbalakshmi C, Sitaram N. Mechanism of antimicrobial action of indolicidin. FEMS Microbiol Lett. 1998; 160(1):91–96. DOI: 10.1111/j.1574-6968.1998.tb12896.x.

74. Kragol G, Lovas S, Varadi G, et al. The antibacterial peptide pyrrhocoricin inhibits the ATPase actions of DnaK and prevents chaperone-assisted protein folding. Biochemistry. 2001; 40(10):3016–3026. DOI: 10.1021/bi002656a.

75. Scocchi M, Lüthy C, Decarli P, et al. The Proline-rich Antibacterial Peptide Bac7 Binds to and Inhibits in vitro the Molecular Chaperone DnaK. Int J Pept Res Therapeut. 2009; 15(2):147–155. DOI: 10.1007/s10989-009-9182-3.

76. Zahn M, Berthold N, Kieslich B, et al. Structural studies on the forward and reverse binding modes of peptides to the chaperone DnaK. J Mol Biol. 2013; 425(14):2463–2479. DOI: 10.1016/j.jmb.2013.03.041.

77. Zahn M, Kieslich B, Berthold N, et al. Structural identification of DnaK binding sites within bovine and sheep bactenecin Bac7. Protein Pept Lett. 2014; 21:407–412. DOI: 10.2174/09298665113206660111.

78. Krizsan A, Prahl C, Goldbach T, et al. Short proline-rich antimicrobial peptides inhibit either the bacterial 70S ribosome or the assembly of its large 50S subunit. Chembiochem. 2015; 16(16):2304–2308. DOI: 10.1002/cbic.201500375.

79. Krizsan A, Volke D, Weinert S, et al. Insect-derived proline-rich antimicrobial peptides kill bacteria by inhibiting bacterial protein translation at the 70S ribosome. Angew Chem Int Ed Engl. 2014; 53:12236–12239. DOI: 10.1002/anie.201407145.

80. Roy RN, Lomakin IB, Gagnon MG, et al. The mechanism of inhibition of protein synthesis by the proline-rich peptide oncocin. Nat Struct Mol Biol. 2015; 22:466–469. DOI: 10.1038/nsmb.3031.

81. Mardirossian M, Grzela R, Giglione C, et al. The host antimicrobial peptide Bac71-35 binds to bacterial ribosomal proteins and inhibits protein synthesis. Chem Biol. 2014; 21:1639–1647. DOI: 10.1016/j.chembiol.2014.10.009.

82. Mardirossian M, Barrière Q, Timchenko T, et al. Fragments of the Nonlytic Proline-Rich Antimicrobial Peptide Bac5 Kill Escherichia coli Cells by Inhibiting Protein Synthesis. Antimicrob Agents Chemother. 2018; 62(8):e00534-18. DOI: 10.1128/AAC.00534-18.

83. Brötz H, Bierbaum G, Reynolds PE, et al. The lantibiotic mersacidin inhibits peptidoglycan biosynthesis at the level of transglycosylation. Eur J Biochem. 1997; 246(1):193-199. DOI: 10.1111/j.1432-1033.1997.t01-1-00193.x.

84. Breukink E, de Kruijff B. Lipid II as a target for antibiotics. Nat Rev Drug Discov. 2006; 5(4):321–332. DOI: 10.1038/nrd2004.

85. Liu SP, Zhou L, Lakshminarayanan R, et al. Multivalent Antimicrobial Peptides as Therapeutics: Design Principles and Structural Diversities. Int J Pept Res Ther. 2010; 16(3):199–213. DOI: 10.1007/s10989-010-9230-z.

86. Guilhelmelli F, Vilela N, Albuquerque P, et al. Antibiotic development challenges: the various mechanisms of action of antimicrobial peptides and of bacterial resistance. Front Microbiol. 2013; 4:353. DOI: 10.3389/fmicb.2013.00353.

87. Boehr DD, Draker KA, Koteva K, et al. Broad-spectrum peptide inhibitors of aminoglycoside antibiotic resistance enzymes. Chem Biol. 2003; 10(2):189–196. DOI: 10.1016/s1074-5521(03)00026-7.

88. Wimley WC, Hristova K. Antimicrobial peptides: successes, challenges and unanswered questions. J Membr Biol. 2011; 239(1–2):27–34. DOI: 10.1007/s00232-011-9343-0.

89. Lichtenstein AK, Ganz T, Nguyen TM, et al. Mechanism of target cytolysis by peptide defensins. Target cell metabolic activities, possibly involving endocytosis, are crucial for expression of cytotoxicity. J Immunol. 1988; 140(8):2686–2694.

90. Lichtenstein A. Mechanism of mammalian cell lysis mediated by peptide defensins. Evidence for an initial alteration of the plasma membrane. J Clin Invest. 1991; 88(1):93–100. DOI: 10.1172/JCI115310.

91. McKeown ST, Lundy FT, Nelson J, et al. The cytotoxic effects of human neutrophil peptide-1 (HNP1) and lactoferrin on oral squamous cell carcinoma (OSCC) in vitro. Oral Oncol. 2006; 42(7):685–690. DOI: 10.1016/j.oraloncology.2005.11.005.

92. Huang HJ, Ross CR, Blecha F. Chemoattractant properties of PR-39, a neutrophil antibacterial peptide. J Leukoc Biol. 1997; 61(5):624–629. DOI: 10.1002/jlb.61.5.624.

93. Biragyn A, Surenhu M, Yang D, et al. Mediators of innate immunity that target immature, but not mature, dendritic cells induce antitumor immunity when genetically fused with nonimmunogenic tumor antigens. J Immunol. 2001; 167(11):6644–6653. DOI: 10.4049/jimmunol.167.11.6644.

94. Dürr M, Peschel A. Chemokines meet defensins: the merging concepts of chemoattractants and antimicrobial peptides in host defense. Infect Immun. 2002; 70(12):6515–6517. DOI: 10.1128/IAI.70.12.6515-6517.2002.

95. Li J, Post M, Volk R, et al. PR39, a peptide regulator of angiogenesis. Nat Med. 2000; 6(1):49–55. DOI: 10.1038/71527.

96. Kanazawa K, Okumura K, Ogawa H, et al. An antimicrobial peptide with angiogenic properties, AG-30/5C, activates human mast cells through the MAPK and NF-βB pathways. Immunol Res. 2016; 64(2):594–603. DOI: 10.1007/s12026-015-8759-5.

97. Koczulla R, Bals R. Cathelicidin antimicrobial peptides modulate angiogenesis. In: E. Deindl and C. Kupatt eds. Therapeutic Neovascularization-Quo Vadis? Netherlands: Springer, 2007:191–196. DOI: 10.1007/1-4020-5955-8_10.

98. Takahashi M, Umehara Y, Yue H, et al. The Antimicrobial Peptide Human β-Defensin-3 Accelerates Wound Healing by Promoting Angiogenesis, Cell Migration, and Proliferation Through the FGFR/JAK2/STAT3 Signaling Pathway. Front Immunol. 2021; 12:712781. DOI: 10.3389/fimmu.2021.712781.

99. Territo MC, Ganz T, Selsted ME, et al. Monocyte-chemotactic activity of defensins from human neutrophils. J Clin Invest. 1989; 84(6):2017–2020. DOI: 10.1172/JCI114394.

100. Niyonsaba F, Someya A, Hirata M, et al. Evaluation of the effects of peptide antibiotics human beta-defensins-1/-2 and LL-37 on histamine release and prostaglandin D(2) production from mast cells. Eur J Immunol. 2001; 31(4):1066–1075. DOI: 10.1002/1521-4141(200104)31:4<1066::aid-immu1066>3.0.co;2-#.

101. Yoshioka M, Fukuishi N, Kubo Y, et al. Human cathelicidin CAP18/LL-37 changes mast cell function toward innate immunity. Biol Pharm Bull. 2008; 31(2):212–216. DOI: 10.1248/bpb.31.212.

102. Gupta K, Kotian A, Subramanian H, et al. Activation of human mast cells by retrocyclin and protegrin highlight their immunomodulatory and antimicrobial properties. Oncotarget. 2015; 6(30):28573–28587. DOI: 10.18632/oncotarget.5611.

103. Davidson DJ, Currie AJ, Reid GS, et al. The cationic antimicrobial peptide LL-37 modulates dendritic cell differentiation and dendritic cell-induced T cell polarization. J Immunol. 2004; 172(2):1146–1156. DOI: 10.4049/jimmunol.172.2.1146.

104. Fu L, Jin P, Hu Y, et al. KR12a6 promotes the osteogenic differentiation of human bone marrow mesenchymal stem cells via BMP/SMAD signaling. Mol Med Rep. 2020; 21(1):61–68. DOI: 10.3892/mmr.2019.10843.

105. van der Does AM, Joosten SA, Vroomans E, et al. The antimicrobial peptide hLF1-11 drives monocyte-dendritic cell differentiation toward dendritic cells that promote antifungal responses and enhance Th17 polarization. J Innate Immun. 2012; 4(3):284–292. DOI: 10.1159/000332941.

106. Zhu QZ, Hu J, Mulay S, et al. Isolation and structure of corticostatin peptides from rabbit fetal and adult lung. Proc Natl Acad Sci U S A. 1988; 85(2):592–596. DOI: 10.1073/pnas.85.2.592.

107. Zhu Q, Solomon S. Isolation and mode of action of rabbit corticostatic (antiadrenocorticotropin) peptides. Endocrinology. 1992; 130(3):1413–1423. DOI: 10.1210/endo.130.3.1311240.

108. Zhu QZ, Singh AV, Bateman A, et al. The corticostatic (anti-ACTH) and cytotoxic activity of peptides isolated from fetal, adult and tumor-bearing lung. J Steroid Biochem. 1987; 27(4–6):1017–1022. DOI: 10.1016/0022-4731(87)90184-1.

109. Cho JH, Kim SC. Non-membrane targets of antimicrobial peptides: novel therapeutic opportunities? In: Wang G, ed. Antimicrobial peptides: discovery, design and novel therapeutic strategies. Wallingford: CABI Publishing, 2010: 128–140.

110. Mangoni ML. Host-defense peptides: from biology to therapeutic strategies. Cell Mol Life Sci. 2011; 68(13):2157–2159. DOI: 10.1007/s00018-011-0709-3.

111. Alba A, López-Abarrategui C, Otero-González AJ. Host defense peptides: an alternative as antiinfective and immunomodulatory therapeutics. Biopolymers. 2012; 98(4):251–267. DOI: 10.1002/bip.22076.

112. Deslouches B, Steckbeck JD, Craigo JK, et al. Rational design of engineered cationic antimicrobial peptides consisting exclusively of arginine and tryptophan, and their activity against multidrug-resistant pathogens. Antimicrob Agents Chemother. 2013; 57(6):2511–2521. DOI: 10.1128/AAC.02218-12.

113. Kang SJ, Park SJ, Mishig-Ochir T, et al. Antimicrobial peptides: therapeutic potentials. Expert Rev Anti Infect Ther. 2014; 12(12):1477–1486. DOI: 10.1586/14787210.2014.976613.

114. Mwangi J, Hao X, Lai R, et al. Antimicrobial peptides: new hope in the war against multidrug resistance. Zool Res. 2019; 40(6):488–505. DOI: 10.24272/j.issn.2095-8137.2019.062.

115. Pletzer D, Hancock RE. Antibiofilm Peptides: Potential as Broad-Spectrum Agents. J Bacteriol. 2016; 198(19):2572–2578. DOI: 10.1128/JB.00017-16.

116. Yasir M, Willcox MDP, Dutta D. Action of Antimicrobial Peptides against Bacterial Biofilms. Materials (Basel). 2018; 11(12):2468. DOI: 10.3390/ma11122468.

117. Shahrour H, Ferrer-Espada R, Dandache I, et al. AMPs as Anti-biofilm Agents for Human Therapy and Prophylaxis. Adv Exp Med Biol. 2019; 1117:257–279. DOI: 10.1007/978-981-13-3588-4_14.

118. Piotrowska U, Sobczak M, Oledzka E. Current state of a dual behaviour of antimicrobial peptides-Therapeutic agents and promising delivery vectors. Chem Biol Drug Des. 2017; 90(6):1079–1093. DOI: 10.1111/cbdd.13031.

119. Mahlapuu M, Håkansson J, Ringstad L, et al. Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. Front Cell Infect Microbiol. 2016; 6:194. DOI: 10.3389/fcimb.2016.00194.

120. Borrelli A, Tornesello AL, Tornesello ML, et al. Cell Penetrating Peptides as Molecular Carriers for Anti-Cancer Agents. Molecules. 2018; 23(2):295. DOI: 10.3390/molecules23020295.

121. Yu G, Baeder DY, Regoes RR, et al. Predicting drug resistance evolution: insights from antimicrobial peptides and antibiotics. Proc Biol Sci. 2018; 285(1874):20172687. DOI: 10.1098/rspb.2017.2687.

122. Midura-Nowaczek K, Markowska A. Antimicrobial peptides and their analogs: searching for new potential therapeutics. Perspect. Medicin. Chem. 2014; 6:73–80. DOI: 10.4137/PMC.S13215.

123. Koo HB, Seo J. Antimicrobial peptides under clinical investigation. Pept. Sci. 2019; 111:e24122. DOI: 10.1002/pep2.24122.

124. Rubinchik E, Dugourd D, Algara T, et al. Antimicrobial and antifungal activities of a novel cationic antimicrobial peptide, omiganan, in experimental skin colonisation models. Int J Antimicrob Agents. 2009; 34(5):457–461. DOI: 10.1016/j.ijantimicag.2009.05.003.

125. Ming L, Huang JA. The Antibacterial Effects of Antimicrobial Peptides OP-145 against Clinically Isolated Multi-Resistant Strains. Jpn J Infect Dis. 2017; 70(6):601–603. DOI: 10.7883/yoken.JJID.2017.090.

126. Butler MS, Blaskovich MA, Cooper MA. Antibiotics in the clinical pipeline in 2013. J Antibiot (Tokyo). 2013; 66(10):571–591. DOI: 10.1038/ja.2013.86.

127. Ma JK, Drake PM, Christou P. The production of recombinant pharmaceutical proteins in plants. Nat Rev Genet. 2003; 4(10):794–805. DOI: 10.1038/nrg1177.

128. Chernysh S, Kim SI, Bekker G, et al. Antiviral and antitumor peptides from insects. Proc Natl Acad Sci U S A. 2002; 99(20):12628–12632. DOI: 10.1073/pnas.192301899.

129. Chernysh SI. Insects defend themselves: molecules and cells of the immune response. St. Petersburg University: Journal. 2000; 20(3543):11–12. In Russian [Черныш С.И. Насекомые защищаются: молекулы и клетки иммунного ответа. Санкт-Петербургский университет : Журнал. 2000; 20(3543):11–12].

130. Xiong YQ, Hady WA, Deslandes A, et al. Efficacy of NZ2114, a novel plectasin-derived cationic antimicrobial peptide antibiotic, in experimental endocarditis due to methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2011; 55(11):5325–5330. DOI: 10.1128/AAC.00453-11.

131. Breidenstein EB, Courvalin P, Meziane-Cherif D. Antimicrobial Activity of Plectasin NZ2114 in Combination with Cell Wall Targeting Antibiotics Against VanA-Type Enterococcus faecalis. Microb Drug Resist. 2015; 21(4):373–379. DOI: 10.1089/mdr.2014.0221.

132. Zheng X, Wang X, Teng D, et al. Mode of action of plectasin-derived peptides against gas gangrene-associated Clostridium perfringens type A. PLoS One. 2017; 12(9):e0185215. DOI: 10.1371/journal.pone.0185215.

133. Ostorhazi E, Holub MC, Rozgonyi F, et al. Broad-spectrum antimicrobial efficacy of peptide A3-APO in mouse models of multidrug-resistant wound and lung infections cannot be explained by in vitro activity against the pathogens involved. Int J Antimicrob Agents. 2011; 37(5):480–484. DOI: 10.1016/j.ijantimicag.2011.01.003.

134. Ostorhazi E, Horvath A, Szabo D, et al. Transdermally administered proline-arginine-rich host defense peptides show systemic efficacy in a lethal mouse bacteremia model. Amino Acids. 2017; 49(9):1647–1651. DOI: 10.1007/s00726-017-2457-7.

135. Ostorhazi E, Voros E, Nemes-Nikodem E, et al. Rapid systemic and local treatments with the antibacterial peptide dimer A3-APO and its monomeric metabolite eliminate bacteria and reduce inflammation in intradermal lesions infected with Propionibacterium acnes and meticillin-resistant Staphylococcus aureus. Int J Antimicrob Agents. 2013; 42(6):537–543. DOI: 10.1016/j.ijantimicag.2013.08.001.

136. Riool M, de Breij A, Drijfhout JW, et al. Antimicrobial Peptides in Biomedical Device Manufacturing. Front Chem. 2017; 5:63. DOI: 10.3389/fchem.2017.00063.

137. Yu K, Alzahrani A, Khoddami S, et al. Rapid Assembly of Infection-Resistant Coatings: Screening and Identification of Antimicrobial Peptides Works in Cooperation with an Antifouling Background. ACS Appl Mater Interfaces. 2021; 13(31):36784–36799. DOI: 10.1021/acsami.1c07515.

138. Shahid A, Aslam B, Muzammil S, et al. The prospects of antimicrobial coated medical implants. J Appl Biomater Funct Mater. 2021; 19:22808000211040304. DOI: 10.1177/22808000211040304.

139. Gordon YJ, Romanowski EG, McDermott AM. A review of antimicrobial peptides and their therapeutic potential as anti-infective drugs. Curr Eye Res. 2005; 30(7):505–515. DOI: 10.1080/02713680590968637.

140. Dijksteel GS, Ulrich MMW, Middelkoop E, et al. Review: Lessons Learned From Clinical Trials Using Antimicrobial Peptides (AMPs). Front Microbiol. 2021; 12:616979. DOI: 10.3389/fmicb.2021.616979.

141. Cassone M, Otvos L Jr. Synergy among antibacterial peptides and between peptides and small-molecule antibiotics. Expert Rev Anti Infect Ther. 2010; 8(6):703–716. DOI: 10.1586/eri.10.38.

142. Ruden S, Rieder A, Chis Ster I, et al. Synergy Pattern of Short Cationic Antimicrobial Peptides Against Multidrug-Resistant Pseudomonas aeruginosa. Front Microbiol. 2019; 10:2740. DOI: 10.3389/fmicb.2019.02740.

143. Duong L., Gross S.P., Siryaporn A. Developing Antimicrobial Synergy With AMPs. Front. Med. Technol. 2021; 3:9. DOI: 10.3389/fmedt.2021.640981.

144. Pollini S, Brunetti J, Sennati S, et al. Synergistic activity profile of an antimicrobial peptide against multidrug-resistant and extensively drug-resistant strains of Gram-negative bacterial pathogens. J Pept Sci. 2017; 23(4):329–333. DOI: 10.1002/psc.2978.

145. Zharkova MS, Orlov DS, Golubeva OY, et al. Application of Antimicrobial Peptides of the Innate Immune System in Combination With Conventional Antibiotics-A Novel Way to Combat Antibiotic Resistance? Front Cell Infect Microbiol. 2019; 9:128. DOI: 10.3389/fcimb.2019.00128.

146. Kopeikin PM, Zharkova MS, Kolobov AA, et al. Caprine Bactenecins as Promising Tools for Developing New Antimicrobial and Antitumor Drugs. Front Cell Infect Microbiol. 2020; 10:552905. DOI: 10.3389/fcimb.2020.552905.

Author information:

Shamova Olga V., PhD, Corr. Member RAS – Deputy Director, Head of the Department of General Pathology and Pathophysiology, Institute of Experimental Medicine, Head of the laboratory of Alternative Antimicrobial Biopreparations, World-Class Research Center for Personalized Medicine;

Zharkova Maria S., PhD, Senior Researcher, Laboratory of Alternative Antimicrobial Biopreparations, World-Class Research Center for Personalized Medicine, Senior Researcher, Department of General Pathology and Pathophysiology, Institute of Experimental Medicine;

Chernov Alexander N., Researcher, Department of Microbial Therapy, World-Class Research for Personalized Medicine, Researcher, Department of General Pathology and Pathophysiology, Institute of Experimental medicine;

Vladimirova Elizaveta V., Junior Researcher, Laboratory of Alternative Antimicrobial Biopreparations, World-Class Research Center for Personalized Medicine;

Sukhareva Maria S., Junior Researcher, Laboratory of Alternative Antimicrobial Biopreparations, World-Class Research Center for Personalized Medicine;

Komlev Aleksey S., Junior Researcher, Laboratory of Alternative Antimicrobial Biopreparations, World-Class Research Center for Personalized Medicine;

Kochenda Olga L., Technician, Department of General Pathology and Pathophysiology FSBSI Institute of Experimental medicine, Research Laboratory Assistant at the Research Laboratory of Alternative Antimicrobial Biologicals, World-Class Research Center for Personalized Medicine;

Orlov Dmitriy S., MD, PhD, Associate Professor, Head of the Laboratory of Immunepathophysiology, Department of General Pathology and Pathophysiology, Institute of Experimental Medicine.