Grudlewska Katarzyna, Sysakiewicz Martyna, Buda Kamil, Sobecka Monika, Alska Ewa, Zukow Walery, Sokołowski Remigiusz, Ciesielska Natalia. Possibility of using defensins in medicine = Możliwość wykorzystania defensyn w medycynie. Journal of Health Sciences. 2014;04(07):011-017. ISSN 1429-9623 / 2300-665X. DOI: 10.13140/2.1.2753.3449 http://dx.doi.org/10.13140/2.1.2753.3449

The journal has had 5 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 1107. (17.12.2013).

Conflict of interest: None declared. Received: 10.06.2014. Revised 15.07.2014. Accepted: 24.07.2014.

Possibility of using defensins in medicine

Możliwość wykorzystania defensyn w medycynie

Katarzyna Grudlewska[1], Martyna Sysakiewicz[1], Kamil Buda[1], Monika Sobecka[1], Ewa Alska[1,2], Walery Żukow[3], Remigiusz Sokołowski[1], Natalia Ciesielska[1]

[1]Department and Clinic of Geriatrics, Nicolaus Copernicus University Collegium Medicum, Bydgoszcz, Poland
[2]Department of Allergy, Clinical Immunology and Internal Medicine, Nicolaus Copernicus University Collegium Medicum, Bydgoszcz, Poland
[3]Department Physical Culture, Health and Tourism, Kazimierz Wielki University, Bydgoszcz, Poland

Key words: antibiotics, antimicrobial peptides, defensins, treatment of infections, HIV
Słowa kluczowe: antybiotyki, peptydy antydrobnoustrojowe, defensyny, leczenie zakażeń, HIV

Abstract

Introduction. Antimicrobial proteins (antimicrobial peptides - AMP) probably belong to one of the oldest and most primitive defense mechanisms of the body. It is now known about 800 types of AMP present in plants, insects and animals. Two main types of AMP is likely to occur in mammalian defensins and cathelicidin antimicrobial activity showing. Defensins are small cationic proteins that are part of the innate immunity, humoral immunity. Among of mammalian defensins can be distinguished: defensin α, β defensins and θ defensins. Human defensins are located in various tissues, mainly synthesized in neutrophils and other immune cells.
Purpose. Provide an overview of the literature on the construction, function and possible use of defensins in the treatment of infections
Materials and methods. Using the key words: antibiotics, Antimicrobial peptides, defensins, treatment of infections, HIV searched bibliographic databases: Medline, Science Direct, Ebsco, Springer Link, Wiley Online Library.
Results. Selected articles were used to describe the structure and function of defensins. Discusses the latest news on the possible use of defensins in the treatment of infections and the state of knowledge about their function in the course of infection with human immunodeficiency virus (HIV) and infections involving multidrug-resistant bacteria.
Conclusions. The literature review shows the important function of defensins they play in the course of infection. Defensins through a variety of properties are an attractive alternative to traditional methods of treating infections caused by pathogenic microorganisms. It is necessary to better understand the mechanism of action of these substances in vivo models.

Streszczenie

Wstęp. Białka antydrobnoustrojowe (antimicrobial peptides – AMP) prawdopodobnie należą do jednych z najstarszych i najbardziej prymitywnych mechanizmów obronnych organizmu. Obecnie jest znanych około 800 rodzajów AMP występujących u roślin, owadów oraz zwierząt. Dwa główne rodzaje AMP występujące u ssaków to katelicydyny oraz defensyny wykazujące działanie przeciwdrobnoustrojowe. Defensyny to małe białka kationowe, które są elementem odporności nieswoistej, humoralnej. Wśród defensyn występujących u ssaków można wyróżnić: defensyny α, defensyny β oraz defensyny θ. Ludzkie defensyny zlokalizowane są w różnorodnych tkankach, głównie syntetyzowane w neutrofilach i innych komórkach układu odpornościowego.
Cel. Przedstawienie przeglądu literatury na temat budowy, funkcji oraz możliwości wykorzystania defensyn w leczeniu zakażeń
Materiały i metody. Posługując się kluczowymi słowami: *antybiotyki, peptydy antydrobnoustrojowe, defensyny, leczenie zakażeń, HIV* przeszukano bazy bibliograficzne: *Medline, ScienceDirect, Ebsco, SpringerLink, Wiley Online Library*.
Wyniki. Wybrane artykuły wykorzystano do opisu budowy oraz funkcji defensyn. Omówiono najnowsze doniesienia na temat możliwości wykorzystania defensyn w leczeniu zakażeń oraz stan wiedzy na temat ich funkcji w przebiegu zakażenia ludzkim wirusem niedoboru odporności (HIV) oraz zakażeń z udziałem wielolekoopornych bakterii.
Wnioski. Przegląd literatury ukazuje ważną funkcję defensyn jaką pełnią w przebiegu zakażeń. Defensyny dzięki różnorodnym właściwościom stanowią atrakcyjną alternatywę dla tradycyjnych metod leczenia zakażeń wywołanych patogennymi mikroorganizmami. Konieczne jest lepsze poznanie mechanizmu działania tych substancji w modelach in vivo.

Introduction

Irrational use of antibiotics has led to the emergence of multi-drug resistant microorganisms are increasingly resistant to the majority of drugs available in medicine. Hence, the growing interest of researchers bonds of antimicrobial.

Antimicrobial proteins (antimicrobial peptides - AMP) also known as peptide antibiotics, probably belong to one of the oldest and most primitive defense mechanisms of the body. [1] Although the first reports of the existence of AMP derived from the sixties of the twentieth century is just Zasloff [2] in the early eighties isolated from frogs and toads wounded substances that inhibit

the growth of microorganisms and called them magains. It is now known about 800 types of AMP present in both plants, insects and animals. [3,4] AMP classification is extremely difficult because this group comprise all oligo-and polypeptides capable of killing microorganisms or inhibiting their growth. Two main types of AMP is likely to occur in mammalian defensins and cathelicidin that kill or inhibit the growth of bacteria (Gram-positive and Gram-negative), fungi, parasites and certain viruses, which was confirmed in in vitro and in vivo. [1,3,5,6,7,8]

Defensins are one of the oldest evolutionary defense mechanisms of the immune system, more specifically, they are part of innate immunity, humoral immunity. They belong to a group of small cationic proteins composed of 30-40 amino acids having a molecular weight of 3-4 kDa β-structured harmonica. [7,9,10]

Classification, structure and spatial structure of defensins

Among of mammalian defensins can be distinguished: defensin α, β defensins and θ defensins. [4, 9,11] This division is based on the differences in the positions of cysteines forming disulfide bridges (Schneider) Loss of disulfide bridges can disrupt the effectiveness of defensins in killing microorganisms.[9] Defensins α occurring in humans are represented by the HNP 1-4 (human neutrophil peptides 1-4), HD5 and HD6 protein (human defensin 5-6) and protein NP5 (neutrophil peptide 5). Antymicrobe proteins belonging to a group are β defensin HBD 1-3 (human beta-defensin). [3,7, 10,12,13] The following table (Table 1) presents a brief description of defensins and their place of synthesis.

Genes encoding human α defensin all located on chromosome 8p23.Genes encoding HNP-1, HNP-2, HNP-3 have a length of about 3 kb and is composed of three exons, while the HD-5 and HD-6 are composed of the two exons encoding the functional protein. Genes encoding β-defensins known occurring in mammals are made up of two exons and in many of the animals is highly homologous sequence. Both of the genes encoding β-defensins in humans to chromosome 8. [9, 11,14]

Θ defensins are the result of two defensins cyclization in the process of post-translational α synthesized by monocytes and leukocytes monkeys. This group includes RTD1 protein-3 (θ-defensin rhesus), which are unique to monkeys and retrocyklinę 1 and 2, which are present in most mammals. In humans there is a gene that could be responsible for the synthesis of defensins of this group, however, appears prematurely codon in the nucleotide sequence "stop" inhibits the translation process.Θ defensin structure is also stabilized by three disulfide bridges between the cysteine residues at positions 1-6, 2-5, 3-4. [3,9,10,13, 15]

Table 1. Breakdown and synthesis of human defensins

Defensin	Example:	Positions of cysteines and disulfide bridges	Source
α	HNP1 HNP-2 HNP-3 HNP-4 HD5 HD6 NP5	three SS bridges between cysteines at positions 1-6, 2-4 and 3-5	Neutrophils Monocytes Macrophages NK cells The epithelial cells of the reproductive tract of women, urinary tract cells Paneth cells
β	HBD1 HBD-2 HBD-3 HBD-4	three SS bridges between cysteines at positions 1-5, 2-4 and 3-6	Epithelial cells Keratinocytes

Place the presence of defensins

Summarized in Table 2 indicate defensin locus of the large variety of the lock in the human body. These proteins are present both on the skin, which are secreted by the sebaceous glands, are produced by the Paneth cells in the gastrointestinal tract where they regulate the amount and type of bacteria commensal and pathogenic microorganisms detected. In presents also in epithelial cells of

the genitourinary tract and oral mucosa. In addition, an important component of proteins and protein neutrophil azurophilic grains.[11,14,16,17]

Table 2. The locus in the human defensins

------	HNP 1-4	HBD 1-3
Place of occurrence	Bearing, intestinal mucosa, cervix, neutrophils, spleen, thymus, lungs	Bearing, intestinal mucosa, cervix, spleen, thymus, lungs, mucous membrane of the mouth and nose, plasma, salivary glands, gastrointestinal tract, mammary gland, urinary tract and urine, tonsils, skin, eyes, lung epithelial cells, placenta, kidney, pancreas, trachea and prostate, saliva, vaginal secretions, stomach

Mechanisms of action of defensins to cover bacterial cell

Defensins are capable of destroying bacteria, because they have a positive charge, which allows them to bond to the negatively charged cell membrane, which is damaged. It has been shown that the antimicrobial activity discloses multistage after about 3-4 hours after binding of the defensins of the targeted cell membrane. There are three ways to transfer defensins across the cytoplasmic membrane. [8,17]

Model "staves" lies in the fact that the peptides are incorporated in the cell membrane perpendicular to its plane in such a way that the parts interact with non-polar lipids, and the hydrophilic portion of the peptide forming a gap through which the leaking components of the cytoplasm. [1,9,17]

The second mechanism is the destruction of the membrane model "ring", wherein the peptides penetrate between two layers of the membrane which creates a gap in the head which contains phospholipids and peptides. [1,9,17]

Another mechanism is the model "carpet" characterized in that the peptides do not incorporate in the cell membrane of the microorganism. The hydrophobic portion of the defensin amino acid chain is combined with the negatively charged membrane phospholipids heads. As a result of electrostatic interactions of protein molecules pass through the membrane chambers gathering inside her in a form resembling a carpet. This causes the tension of the film, changing the arrangement of defensins in the membrane and formation of pores therein through which flow into the cytoplasmic components of the cell. [1,9,17]

Functions of defensins

Defensins exhibit antimicrobial activity (Both on Gram-positive and Gram-negative). In the case of gram-positive bacteria interact teichoiov acid and a thick layer of peptidoglycan, while the gram negative bacteria interacts with amino phospholipids and lipopolysaccharide. [3,13]

Defensins vary in effectiveness against the same microbial species.
Ericksen et al observed that against the bacteria *Staphylococcus aureus* strongest bactericidal activity shows defensin HNP-2, and the weakest HNP-4.While in the case *of Escherichia coli* and *Enterobacter aerogenes* most active proved to be HNP-4.Defensin HD-5 show high activity against Gram-negative bacteria and similar to HNP-2 against *Staphylococcus aureus.* In contrast, β-defensins are more active against aerobic to anaerobic than. [10,18]

Defensins also act antiviral (mainly enveloped viruses such as HIV and influenza viruses. A-defensins virus to inhibit the adhesion of cells, and defensin HNP-1 can directly inactivate the virus by destroying the viral envelope. Moreover, this group of peptides exhibit antimicrobial activity against fungi and parasites. [17,19]

These proteins exhibit chemotactic activity, as they can cause the attraction of other cells of the immune system in lieu of an ongoing inflammatory response. β-defensins exhibit a chemotactic for immature dendritic cells that have CCR6 receptor and T-cell memory. -3 HBD shows chemotactic activity for monocytes. Defensins such action suggests that the connecting element are innate and acquired immunity. [4,12,20] α-defensins also exhibit chemotactic activity for native CD4 + T cell, CD8 + cell, and immature dendritic cells. In addition, HNP1-4 may have immunomodulatory effects and boost the immune system against specific antigens, as demonstrated in a study on mice. [3,15,21]

Due to the fact that they are immune system proteins, regulate the production of cytokines, chemokines and their receptors. HBD-defensin HBD-2 and 4 are synthesized in response to pro-inflammatory activity of substances such as interleukin 1 (IL-1), tumor necrosis factor (TNF-α) and lipopolysaccharide (LPS). [3,7,12,21] In vitro and in vivo carried out on HBD-3 shows that this protein also exhibits an immunosuppressive effect, as inhibit the production of TNF-α and IL-6.This new feature suggests HBD-3 part in silencing of inflammation in the body, it is necessary that the inflamed tissue was not damaged by proinflammatory cytokines. [15,20]

In addition, activators of complement, macrophages and mast cells.
Although they are non-specific response element affect specific immune responses, the antibodies acting to enhance the maturation of cells, and initiating dendritic. [7,21]

Examples of the use of defensins in the treatment of bacterial infections

Natural antibiotics such as defensins, in the near future may be used to treat infections involving microbes resistant to antibiotics.

It is possible to use β-defensins in the treatment of diseases of the oral epithelium, because of their broad spectrum of activity. The purpose of the therapy may be ulcerative lesions in the oral cavity, as well as mouth ulcers and chronic inflammation often difficult to treat (e.g., periodontal disease).The methods developed skin tissue engineering, wherein the defensin HBD-3 was added to a keratinocyte cell line. Bred epidermis was applied to rats showed antimicrobial activity. Gene introduction defensin HBD-3 into somatic cells, it may be a new way to treat damage to the membranes of the oral cavity. [22,23]

Chronic periodontal disease is a complex process, in which are involved the development of anaerobic oral bacteria *Porphyromonas gingivalis,* such as, *Tannerella Fusobacterium nucleatum* or *forsythiensis.* [24,25] Pereira et al in their studies observed a higher level of HBD-2 in the saliva of patients suffering from chronic periodontal disease than in healthy subjects and patients treated. This points to a share of the protein substance in the immune response to the ongoing inflammation in the body. [25] Other studies have also demonstrated the presence of α defensins (HNP 1-3) in both the saliva and serum of healthy individuals as well as with periodontal disease. The higher concentration of defensins in the saliva was observed only in those patients compared with controls, which may be related to the local immune system rip. [24] The above studies show that defensins may be a useful tool in the diagnosis of chronic periodontal disease.

In the near future, defensins can be used to treat infections as an alternative to treatment with antibiotics.In vitro studies demonstrated the ability of HBD-2 and HBD-3 for the killing of *Klebsiella* spp producing ESBL (called Extended-Spectrum Beta-Lactamases), which belong to the group of opportunistic bacteria, which are one of the most common causes of sepsis. [26] Also shown HBD-3 activity against multi-drug resistant strains of *Staphylococcus aureus, Enterococcus faecium, Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and *Acinetobacter baumannii* isolated from the hospital environment.[27]

Although several in vitro antimicrobial activity, there is evidence of little tests to determine their function in the living body during infection. An analysis of the occurrence HBD1-4 an abscess around the tonsils, where it has been shown that infection by the expression of β-defensin in epithelial crypts, and the surface is higher than in the same tonsil lymphoid tissue. Defensins are in direct contact with the bacteria, so they can not easily penetrate into the interior of the tonsils.

Production of antimicrobial peptides may help to reduce the adhesion and invasion of pathogenic bacteria and commensal during such infections as peritonsillar abscess. [28]

Use of defensins in the treatment of HIV infection

Human immunodeficiency virus, HIV (human immunodeficiency virus) is responsible for the slow weakening of the host's immune system which results in increased susceptibility to infection and the development of acquired immunodeficiency syndrome, AIDS (called Acquired Immune Deficiency Syndrome).Treatment of HIV-infected individuals is based on antiretroviral therapy, which is not a cure, but with n total, slows the progression of the disease. [19,29]

Antiviral activity of defensins described much later than bactericidal properties, but there are many studies proving their interaction with the viral envelope and with the same virus which can be used in the treatment of HIV infection. [19,29]

Defensins in vitro study is made difficult due to the fact that they lose their immunomodulatory, antibacterial and antiviral agents in the presence of serum. Physiologically defensins are secreted outside the cell, occur mainly on the surface of the mucous membranes, and it is practically free from the environment serum. [19] Furci et al conducted a study in vitro, in protein-free and serum demonstrated that α-defensin HD5 inhibits the replication of HIV-1 in CD4 + lymphocytes pristine, and inhibits the fusion of the viral envelope of HIV-1 to the cell membrane through interaction with the major glycoprotein shell-HIV-1 gp120. HD-5 activity oval ham isolates of HIV-1, which showed an affinity for the cellular chemokine co-receptors, both CXCR4 and CCR5. Furthermore, HD-activity was observed not only against 5 strains of laboratory HIV-1, but also the clinical isolates of HIV-1. These results suggest that the defensin HD-5 is involved in the control of HIV-1 infection at an early stage, preventing the virus from entering cells.[30] The antiviral activity was also observed in the case of β-defensins, HBD-3.It has been observed that it is able to induce monocyte-derived chemokine and induces the expression of RANTES protein (called Regulated on Activation Normal T-cell Expressed and secreted) which is a monocyte chemotactic factor m.in monocytes and T cells isolated from HIV + patients were characterized by a higher level of expression of certain chemokines (monocyte, chemoattractant protein 1, MPC-1, macrophage proteins Inflammatory MIP-1 α and MIP-1 β) than monocytes derived from healthy individuals. It is also noted that HBD-3 induce the expression of costimulatory molecules such as CD80 and CD86, which are present on antigen presenting cells. At the same time the level of expression of other molecules (monocyte-macrophage-derived MDC, Gro-α oncogene and vascular endothelial growth factor, VEGF) is lowered HIV + patients. The study suggests that people with HIV cell migration to the inflamed tissue is different than in healthy subjects, and HBD-3 may play an important role in the induction of chemokine production in monocytes and immune response to infection.[31] Another group of researchers assessed the impact of the protein Tat of HIV-1 on the expression of β-defensin in the B cells of HIV-1 Tat is one of the products genes necessary for viral replication and expression of the viral genome. After stimulation of B cells of HIV-1 protein. So there was a significant increase in expression of mRNA, and the protein concentration HBD-2. The emergence of high levels of HBD-2 can induce resistance to infection caused operate or slower progression of the disease. [32]

Inhibitory activity against HIV-1 has also been shown in studies in mice. Defensins from groups α and β efficiently induced cellular immune response (production of cytokines by Th1/Th2 cells, the secretion of IFN-γ and perforins by CD4 + T cells / CD8 +) in mice that have been immunized with a fragment of p24 protein, and defensins synthesized peptide chains. This shows that defensins may be used as an adjuvant responsible for the induction of a cellular response in mice infected with HIV-1. [33]

Although anti-viral activity of defensins has been shown in many in vitro studies that in vivo studies are inconclusive. Jiang et al analyzed the concentration of β-defensins (HBD-2 and HBD-3) in the secretions coming from the vagina of women infected with HIV and healthy women. The level of β-defensins were comparable among the study group and the control group. [34] In

contrast, examining Nittayananta et al. HBD-2 concentration in saliva showed that it was significantly higher in HIV-infected patients than in healthy subjects, although there has been a significantly higher level HBD-2 mRNA, indicating that a local increase in the level of these proteins in the oral cavity of infected individuals.[35] Other scientists studying the concentration of HNP 1-3 in the serum of individuals infected with HIV-1 also observed significantly higher levels of these proteins in patients compared to the control group, which accounted for a healthy person. Interestingly, the highest concentrations were observed in the initial phase of infection, which may be associated with participation defensins primarily during the invasion of the virus into cells, and also decreasing the level of granulocytes (which are an important source of defensins) with the infection. [36]

Conclusions

Defensins through a variety of therapeutic properties are an attractive alternative to traditional methods of treating infections caused by pathogenic microorganisms. Despite many advantages such as low molecular weight and a broad range of activities, should solve some problems such as the stability and efficiency of defensins. It is necessary to further improvement of these substances, in terms of obtaining and mode of administration.

References

1. Guaní-Guerra E., Santos-Mendoza T., Lugo-Reyes S.O., Terán L.M. Antimicrobial peptides: General overview and clinical implications in human health and disease. Clinical Immunology. 2010; 135:1–11
2. Zasloff M. Magainins, a class of antimicrobial peptides from Xenopus skin: isolation, characterization of two active forms, and partial cDNA sequence of a precursor. Proc Natl Acad Sci USA. Aug 1987; 84(15): 5449–5453.
3. Yang D., Chertov O., Oppenheim J.J. Participation of mammalian defensins and cathelicidins in antimicrobial immunity: receptors and activities of human defensins and cathelicidin (LL-37). J. Leukoc. Biol. 2001; 69: 691–697.
4. Wiechuła B.E., Tustanowski J.P., Martirosian G. Peptydy antydrobnoustrojowe. Wiad Lek 2006; 59(7–8): 542–547.
5. Gordon Y.J., Romanowski E.G. A review of antimicrobial peptides and their therapeutic potential as anti-infective drugs. Curr Eye Res. 2005; 30(7): 505–515.
6. Silva P.M., Gonçalves S., Santos N.C. Defensins: antifungal lessons from eukaryotes. Front.Microbiol. 2014; 5(97). doi:10.3389/fmicb.2014.00097
7. Steinstraesser L., Kraneburg U., Jacobsen F., Al-Benna S. Host defense peptides and their antimicrobial-immunomodulatory duality. Immunobiology 2011; 216: 322–333
8. Schneider J.J., Angela Unholzer A., Schaller M., Schäfer-Korting M., Korting H.C. Human defensins. J Mol Med. 2005 83: 587–595
9. Ganz T. Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol. 2003; 3(9):710-720
10. Żyłowska M., Wyszyńska A., Jagusztyn-Krynicka E.K. Defensyny–peptydy o aktywnosci przeciwbakteryjnej.
11. Jarczak J., Kościuczuk E.M., Lisowski P., Strzałkowska N., Jóźwik A., Horbańczuk J., Krzyżewski J., Zwierzchowski L., Bagnicka E. Defensins: Natural component of human innate immunity. Human Immunology 2013; 74:1069–1079
12. Oppenheim J.J., Biragyn A., Kwak L.W., Yang D. Roles of antimicrobial peptides such as defensins in innate and adaptive immunity. Ann Rheum Dis 2003;62(Suppl II):ii17–ii21
13. Niedźwiedzka-Rystwej P., Deptuła W. Defensyny–ważny wrodzony element układu odpornościowego u ssaków. Postepy Hig Med Dosw. 2008; 62: 524-529
14. Ganz T. Defensins: antimicrobial peptides of vertebrates. C. R. Biologies 2004; 327:539–549
15. Vordenbäumen S., Schneider M. Defensins: Potential effectors in autoimmune rheumatic disorders. polymers 2011; 3: 1268-1281
16. De Smet K., Contreras R. Human antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnology Letters. 2005; 27: 1337-1347
17. Witkowska D., Bartyś A., Gamian A. Defensyny i katelicydyny jako naturalne antybiotyki peptydowe. Postepy Hig Med Dosw. 2008; 62: 694-707
18. Ericksen B., Wu Z., Lu W., Lehrer R.I. Antibacterial activity and specificity of the six human α-defensins. Antimicrob. Agents Chemother. 2005; 49(1) 269–275
19. Wilson S.S., Wiens M.E., Smith J.G. Antiviral mechanisms of human defensins. J. Mol. Biol. 2013; 425: 4965–4980
20. Semple F., Webb S., Li H., Patel H.B., Perretti M., Jackson I.J., Gray., Davidson D.J., Dorin J.R. Human β-defensin 3 has immunosuppressive activity in vitro and in vivo. Eur. J. Immunol. 2010; 40: 1073–1078

21. Menendez A., Finlay B.B. Defensins in the immunology of bacterial infections. Current Opinion in Immunology. 2007; 19: 385–391
22. Abiko Y.,Saitoh M., Nishimura M., Yamazaki M., Sawamura D., Kaku T. Role of β-defensins in oral epithelial health and disease. Med Mol Morphol 2007; 182: 179–184
23. Sawamura D., Goto M., Shibaki A., Akiyama M., McMillan J.R., Abiko Y., Shimizu H. Beta- defensin-3 engineered epidermis shows highly protective effect for bacterial infection
24. Hofman J., Szkaradkiewicz A.K., Karpiński T.M. Ocena występowania defensyn (HNP 1-3) w ślinie i surowicy osób z przewlekłym zapaleniem przyzębia. Czas. Stomatol., 2008; 61(12): 881-885
25. Pereira A.L., Holzhausen M., Franco G., Cortelli S.C., Cortelli J.R. Human β-defensin 2 and protease activated receptor-2 expression in patients with chronic periodontitis. Archives of oral biology 2012; 57: 1609 – 1614
26. Sahly H., Schubert S., Harder J., Kleine M., Sandvang D.,Ullmann U., Schroder J.M., Podschun R. Activity of human β-defensins 2 and 3 against ESBL-producing Klebsiella strains. Journal of Antimicrobial Chemotherapy. 2006; 57: 562–565
27. Maisetta G., Batoni G., Esin S., Florio W., Bottai D., Favilli F., Campa M. In vitro bactericidal activity of human β-defensin 3 against multidrug-resistant nosocomial strains. Antimicrobial agents and chemotherapy 2006; 50(2): 806–809
28. Schwaab M., Hansen S., Pearson M. D., Shagdarsuren S., Dazert S. Human β-defensins—at the front line of the peritonsillar abscess. Eur J Clin Microbiol Infect Dis. 2009;28(7): 745-755
29. Zwolińska K. Czynniki genetyczne związane z podatnością na zakażenie HIV oraz z progresją zakażenia. Postepy Hig Med Dosw. 2009; 63: 73-91
30. Furci L., Tolazzi M., Sironi F., Vassena L., Lusso P. Inhibition of HIV-1 infection by human α-defensin-5, a natural antimicrobial peptide expressed in the genital and intestinal mucosae PLoS ONE 2012; 7(9): e45208
31. Petrov V., Funderburg N.,Weinberg A., Sieg S. Human β-defensin-3 induces chemokines from monocytes and macrophages: diminished activity in cells from HIV-infected persons. Immunology 2013; 140: 413–420
32. Ju S.M., Goh A.R., Kwon D.J., Youn G.S., Kwon H.J., Bae Y.S., Choi S.Y., Park J. Extracellular HIV-1 Tat induces human beta-defensin-2 production via NF-kappaB/AP-1 dependent pathways in human B cells. Mol Cells. 2012;33(4):335-341
33. Mohan T. , Sharma C., Bhat A.A, Rao D.N. Modulation of HIV peptide antigen specific cellular immune response by synthetic α- and β defensin peptides. Vaccine 2013; 31: 1707– 1716
34. Jiang W., Ghosh S.K., Flyckt R., Kalinowska M., Starks D., Jurevic R., Weinberg A., Lederman M.M., Rodriguez B. Bacterial colonization and beta defensins in the female genital tract in hiv infection. Curr HIV Res. 2012;10(6): 504–512
35. Nittayananta W. Kemapunmanus M., Amornthatree K., Talungchit S., Sriplung H. Oral human β-defensin 2 in HIV-infected subjects with long-term use of antiretroviral therapy. J Oral Pathol Med. 2013; 42(1): 53–60
36. Wiercińska-Drapało A., Jaroszewicz J., Parfieniuk A., Dąbrowska M., Siwak E. Serum concentrations of α-defensins in patients with different stages of HIV-infection. HIV&AIDS 2007; 6(4): 20-22