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REVIEW

Antimicrobial peptides and proteins in human biological fluids

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ABSTRACT

Antimicrobial peptides and proteins (AMPs) are endogenous compounds that have a direct antimicrobial effect on bacteria (e.g. by disrupting bacterial membranes) as well as on fungi and viruses. AMPs are the main components of the innate immunity of living organisms and are produced by both epithelial cells (skin cells, cells of respiratory tract, intestines, urinary and genital tracts) and cells of the immune system and are secreted into secretory fluids. AMPs can also act as chemoattractants for immunocompetent cells (neutrophils, monocytes, T lymphocytes, dendritic cells) in the inflammation site and affect the antigen presenting cells by modulating adaptive T cell immune responses. The representatives of the main 15 AMP classes, that we describe in this review, are the most studied group of the large pool of these compounds. We discuss their localization, expression, and concentration in various human biofluids under normal and pathological conditions.

Keywords: antimicrobial peptides, hepcidin, histatins, defensins, cathelicidin, dermcidins, adrenomedullin, psoriasin, secretory leukoprotease inhibitor, lysozyme, lipocalin, azurocidin, calprotectin, lactoferrin

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INTRODUCTION

Antimicrobial peptides and proteins (AMPs) are an important part of innate immunity. The most studied and most common human AMPs can be divided into 15 classes. AMPs are expressed by cells of various tissues and are present in human biofluids. Their composition and concentration differ depending on the type of biofluid as well as on the state of human health (normal or pathological conditions).

There are many definitions of AMPs in the literature as well as descriptions of various mechanisms of their action and spectrum of activity against various pathogens: bacteria, fungi, protozoa, and some viruses [1]. Despite differences in terminology, it is generally accepted that antimicrobial peptides are polypeptides or oligopeptides containing a different number of amino acids (from 5 to 100); polypeptides, with a large number of amino acids, are proteins. Usually, AMPs have a cationic charge and act similar against pathogens, the main mechanism of action being the destruction of the microbial membrane. Information on the presence and concentration of different AMPs in the particular biofluid should add to the understanding of their contribution to the protective properties of this biofluid against the pathogenic microorganisms.

The purpose of this review is to systematize the scientific literature data on the presence and concentration of AMPs in the main human biological fluids in healthy individuals as well as in patients with various diseases and pathologies. We describe here AMPs in ascending order of their molecular masses and give a brief description of their main properties. The classification of AMPs that is suggested here is based on both their concentration in biofluids and the type of cells that produce them.

THE MAIN REPRESENTATIVES OF THE AMPs

Hepcidin

Fig. 1. Hepcidin-201 (DBAASP v3.0 Database of antimicrobial activity and structure of peptides https://dbaasp.org/home)
Amino acid sequence: ICIFCCGCCHRSKCGMCCKT

Hepcidin is a peptide with a molecular mass of 2.8 kDa [2], which serves as an antimicrobial peptide and as an iron regulator, and it acts against bacteria and fungi [3]. It has relatively low antimicrobial activity compared to the other AMPs [4]. Hepcidin is synthesized in the liver and excreted in the urine [3]. In addition, hepcidin can be synthesized by adipocytes [5], macrophages [6], and pancreatic β-cells [7].

Hepcidin is best known as a major iron regulator: it downregulates plasma iron levels ("locks" iron in tissues). Hepcidin binds to ferroportin, which is located on the surface of cells that are iron carriers (macrophages, enterocytes, hepatocytes), and does not allow iron to leave the cells [3]. Hepcidin is an acute phase protein; its level correlates with the level of C-reactive protein and ferritin [8]. An increase in the level of hepcidin expression is observed in obesity [5]. Vitamin D reduces the level of hepcidin [9], but during an infection, there is an increase in the level of hepcidin in the blood and urine [10].

Macrophages, in addition to immune functions, play the role of an iron depot and regulate the level of hepcidin. They bind to hepatocytes, regulating the release of hepcidin through various proteins, including regulation through transferrin [11]. Tissue hypoxia prevents the expression of hepcidin in hepatocytes, regardless of iron reserves in the body [12].

Hepcidin is found in various biological fluids (Table 1). The concentration of hepcidin in urine is comparable to its level in the blood; in saliva, it is an order of magnitude lower. Hepcidin is normally present in bile and transudates. Its concentration is higher in exudates. According to some authors, hepcidin is a marker for the separation of transudates and exudates [13]. Hepcidin was not found in vaginal and sweat secretions. The blood level of hepcidin increases in inflammation, myeloma, and chronic kidney diseases [10, 14], while decreasing in iron deficiency anemia and hemochromatosis [14].

Histatins

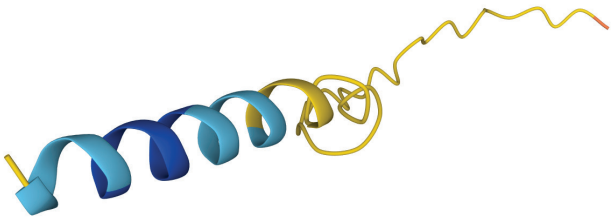

Fig. 2. Histatin-3 (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: MKFFVFALILALMLSMTGADSHAKRHHGYK RKFHEKHHSHRGYRSNYLYDN

Histatins form a separate group of AMPs. The most studied three types of histatins are 1, 3, and 5, with molecular masses of 4.9 kDa, 4.0 kDa, and 3.0 kDa, respectively [15]. Of these, histatin-5 is the most active, and histatin-1 is the least active [16]. Histatins usually have a cationic charge due to the peculiarities of the primary structure, which primarily contains basic amino acids [17].

Histatins have a pronounced antifungal activity (anticandidal activity in particular), which some authors attribute to a high content of the amino acid histidine [17]. Histatins can bind to metal ions, which determines their antimicrobial function [18], but calcium blocks the fungicidal activity of histatin-5 in human saliva [19]. Another function of histatins is wound healing [20, 21]. Histatin is produced by the epithelial cells of the human parotid and submandibular glands [18] as well as in the lacrimal glands [22].

The concentration of histatin in saliva reaches 50,000 ng/ml (Table 1); sometimes it is found in the urine. Histatin-1 is present in the lacrimal fluid, while it is not found in other biological fluids. The concentration of histatin in saliva in human immunodeficiency virus (HIV) patients decreases which leads to an increased susceptibility of these patients to candidiasis [23]. The concentration of histatin in the lacrimal fluid is also reduced in dry eye syndrome [22].

Defensins

Defensins are AMPs with a molecular mass of 2.1- 5.0 kDa [24]. They are small (18-50 amino acids) cationic

Table 1. Concentration of antimicrobial peptides and proteins in the biofluids of healthy individuals.

	Serum	Urine	Saliva	Vaginal secretion	Sweat	Other biofluids	References
	A	B	C	D	E	F	
1. Hepcidin	1. 1.344-280[a] 2. 0.38-0,77 3. 0-31.38 4.29-254 (males), 17-268 (females)	2.156-560	0.6-6.2	n/a	n/a[b]	0-14.77 (bile) 0-31.9 (transudate)	A [108; 10; 13; 14] B [108] C [13] F [13]
2. Histatins	n/a	sometimes present	14300-46900 16600-50000	missing	n/a	absent in nasal secretion, present in lacrimal fluid	B [109] C [110; 111] D [112] F [112; 22]
3. Defensins	4.3-7.1 (HBD-1) 0.019-0.053 (HBD-2) 137-249 (HNP-2)	10-100 (HBD-1)	200-1600 (HNP-1)	20-60 (HBD-1) 440-700 (HBD-2) 280-420 (HNP1-3)	n/a	n/a	A [31; 148] B [113] C [32] D [114]
4. Cathelicidin LL-37	594-903 27.2	0.2-5.9	20-65	65-1000	4500	48700-124300 (seminal fluid)	A [115; 116] B [38] C [39] D [114] E [117] F [118]
5. Dermcidins	2000-2200	n/a	n/a	n/a	1000-20000 (face, cervix, breast) 70000 (front)	n/a	A [45] E [119]
6. Adrenomedullin	1.91	0.00416-0.03644	0.055-0.065	n/a	present	present in milk, amniotic fluid	A [55] B [56] C [50] E [51] F [51]
7. Psoriasin	331	n/a	12700-15300	820-1920	present	n/a	A [62] C [60] D [120] E [121]
8. Secretory leukoprotease inhibitor	25-43	n/a	500-3500 2.3-1919.9	50-200 600-800	n/a	n/a	A [122] C [123; 124] D [125; 114]
9. Lysozyme	2000-3600 9600-16800	<300	2200-5900 10900-49000	400-3000 11000-15000	present	290000-300000 (breast milk) >500000 (tears)	A [126; 127] B [126] C [128; 129] D [125; 114] E [130] F [131; 132]
10. RNase	0 (RNase 7) 1500-5700 (RNase 3) 188-216.2 (RNase 1)	235-3467.2 (RNase 7)	present	present	present	n/a	A [74] B [133] C [133] D [134] E [73]
11. Lipocalin	18.9-46.5 168 57-105	2.1-9.6 34.5	194-462	0.561	n/a	n/a	A [79; 81; 135] B [79; 81] C [135] D [83]
12. Azurocidin	0.4-10.98	4-19	0.041	n/a	present	2.4-8.7 (liquor)	A [89] B [136] C [90] E [137] F [91]
13. Calprotectin	<450 215.8-3770	51 45	3200-40900 2.19 939-4019 290	27000-41000 5000-14000	present	19.9 (coprofiltrate) 25.8 (coprofiltrate)	A [138; 139] B [140; 96] C [141; 142; 143; 144] D [114; 125] E [137] F [95; 145]

Continuation of Table 1. Concentration of antimicrobial peptides and proteins in the biofluids of healthy individuals.

	Serum	Urine	Saliva	Vaginal secretion	Sweat	Other biofluids	References
	A	B	C	D	E	F	
14. Bactericidal/ permeability-increasing protein	4.9-72.1	n/a	77.4-78.9	n/a	present	n/a	A [146] C [147] E [137]
C [147]	400 270	55	8000 245	700-1100 8000	21	8000000 (colostrum), 1500000-4000000 (milk), 2000000 (tears), 112000 (semen), absent in liquor	A [103; 42] B [42] C [103; 42] D [125; 103] E [42] F [103]
E [137]	14 classes	11 classes	14 classes	9 classes	10 classes		

[a] Concentrations are in ng/ml
[b] n/a — no data available

amphiphilic peptides that show activity against bacteria and fungi as well as antiviral activity [25]. Mammalian defensins have beta-sheet structures with three intramolecular disulfide bonds. They can be divided into three main classes according to their structural differences: alpha-defensins, beta-defensins, and theta-defensins [26].

Humans have both alpha-defensins and beta-defensins. Our hominin ancestors lost the ability to produce theta-defensins after the orangutan and hominin lineages diverged. Humans have theta-defensin genes, but they contain a stop codon in the sequence responsible for signal peptide synthesis. It is believed that this mutation made humans more susceptible to HIV infection [27].

Defensins act by non-specific binding to anionic phospholipids in bacterial membranes. Cationic charge, amphipathicity, and the ability to oligomerize are considered the key factors that enable their antibacterial activity [28].

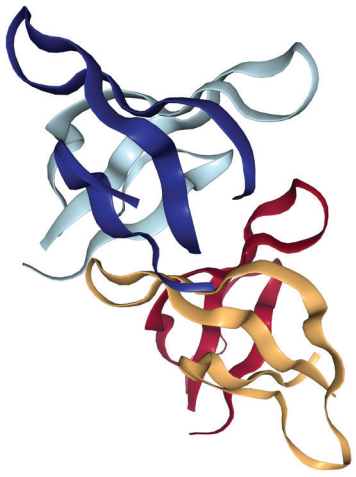

Fig. 3. Human alpha-defensin 5 (HD-5) (DBAASPv3.0 Database of antimicrobial activity and structure of peptides https://dbaasp.org/home)
Amino acid sequence: ATCYCRTGRCATRESLSGVCEISGRLYRLCCR

Defensins are produced by cells of the immune system and epithelial cells. Alpha-defensins (human neutrophil peptides, HNP) are isolated from azurophilic granules of neutrophils and Paneth cells (small intestine). The main producers of beta-defensins (human beta-defensin, HBD) are macrophages, monocytes, dendritic cells, Paneth cells, mucosal epithelial cells, and keratinocytes. The production of beta-defensins by keratinocytes in patients with psoriasis has been observed [26, 29, 30].

Defensins are found in the blood, urine, saliva, and vaginal secretions (Table 1). The concentration of defensins in the blood and urine reaches 100 ng/ml. In saliva and vaginal secretion, their concentration is two orders of magnitude higher. The concentration of defensins in the biological fluids of sick people usually increases. Their concentration in the blood of patients with sepsis reaches 170 μg/ml. High levels of HBD-1 and HBD-2 are found in the blood serum of patients with lung cancer [31] as well as in saliva of patients with diseases of the oral mucosa [32]. The level of alpha-defensins in T lymphocytes is increased in patients with schizophrenia. Therefore, alpha-defensin can be considered as a risk marker for schizophrenia [33].

Cathelicidin

Cathelicidin LL-37 is an AMP with molecular mass of 4.5 kDa that is produced as a precursor hCAP18 (molecular mass 19 kDa) and subsequently converted to LL-37. It is expressed in leukocytes and in various epithelial cells. Approximately 30 cathelicidin genes are known in mammals, while in humans, it is represented by only one gene – CAMP (Cathelicidin Antimicrobial

Peptide) [34]. Cathelicidin is found in different epithelial

Fig. 4. Cathelicidin LL-37 (DBAASPv3.0 Database of antimicrobial activity and structure of peptides https://dbaasp.org/home)
Amino acid sequence: LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLV PRTES

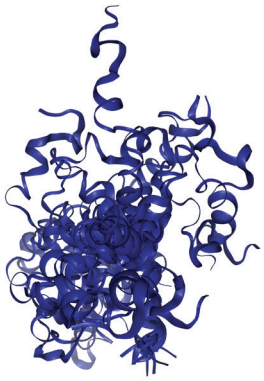

Fig. 5. Dermcidin (DBAASPv3.0 Database of antimicrobial activity and structure of peptide https://dbaasp.org/home)
Amino acid sequence: SSLLEKGLDGAKKAVGGLGKLGKDAVEDLES VGKGAVHDVKDVLDSVL

tissues – epitheliocytes of the skin, gastrointestinal tract (GIT), ovaries, and lungs as well as in the epithelium of the oral cavity, esophagus, tongue, and genitourinary tract [35].

The predominant source of cathelicidins are secretory granules of neutrophils. Cathelicidin is stored in granules as a precursor – hCAP18, which is released from cells upon activation, and is cleaved by neutrophil elastase to form the active peptide LL-37 [36]. In addition, cathelicidin is found in macrophages and monocytes, in B and T lymphocytes, and in natural killer cells. In macrophages, cathelicidin synthesis is stimulated by vitamin D [37]. Cathelicidin is present in the following biological fluids: in the blood, urine, saliva, vaginal secretions, sweat, and semen (Table 1). The concentration of cathelicidins in semen is several orders of magnitude higher than that in other biofluids. In the course of an infection, its concentration increases in the urine in children with cystitis and pyelonephritis (up to 312.5 ng/ml) [38], in the saliva of patients with some erosive diseases in the oral cavity [39] as well as in patients with bacterial vaginosis [40]. In psoriasis, an increase in the concentration of cathelicidin correlates with an increase in the number of T cells [41].

Dermcidin

Dermcidin, an AMP with a molecular mass of 11.28 kDa (precursor) [42], is present in the body in two variants: DCD-1 and DCD-1L that contains leucine at the C-terminus. Unlike most AMPs dermcidin is an anionic peptide: DCD-1L has a net negative charge. DCD-1L exhibits antimicrobial activity against bacteria and fungi, which is maintained over a broad pH range and at high salt concentrations [43].

Dermcidin is expressed in human eccrine (merocrine) sweat glands and excreted in sweat on the skin surface [44]. It was detected in blood at concentrations up to 2200 ng/ mL, and in sweat at concentrations up to 70,000 ng/mL, but it was not found in other biofluids (Table 1). A slight increase in the concentration of dermcidin in the blood is observed in melanoma [45], and a certain amount of this AMP is expressed in tissues in breast cancer [46]. A reduced amount of dermcidin in sweat is observed in atopic dermatitis [44].

Adrenomedullin

Adrenomedullin is a peptide with a molecular mass of 6 kDa [47]. It contains a sequence of 52 amino acids and has parts that are structurally similar to calcitonin; therefore, it belongs to the calcitonin family [48]. It is a hormone with a vasodilating effect being more a local rather than a systemic vasodilator [49]. Adrenomedullin is produced in various tissues [50], although it is believed that it is most common in the cardiovascular system. It is a secretory product of the endothelium [51] and it serves as adipokine – an adipose tissue hormone [52]; it is synthesized by monocytes and macrophages [51].

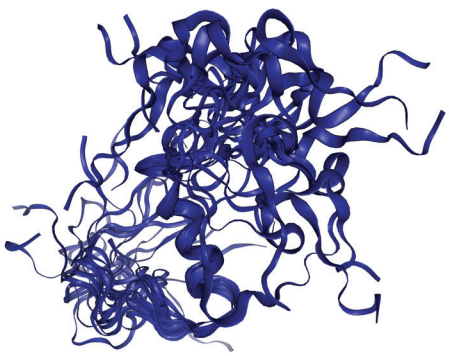

Fig. 6. Adrenomedullin (DBAASPv3.0 Database of antimicrobial activity and structure of peptides https://dbaasp.org/home)
Amino acid sequence: YRQSMNNFQGLRSFGCRFGTCTVQKLAHQI YQFTDKDKDNVAPRSKISPQGY

Adrenomedullin accumulates in epithelial tissues and various biofluids: blood, sweat, milk, saliva, and amniotic fluid. Adrenomedullin as an AMP acts against gram-positive and gram-negative bacteria [51]. The mechanism of the antimicrobial action of adrenomedullin is not known in detail, but there is an assumption that, like most AMPs, it disrupts bacterial membranes [48].

In the blood, its concentration is normally ⩾1.91 ng/ml (Table 1). Increased blood levels of adrenomedullin were detected in patients with arterial hypertension and heart failure [53], in the acute phase of myocardial infarction [54], in patients with pancreatic cancer (4.51 ng/ml) and other diseases (sepsis, type 2 diabetes) [55]. In urine and saliva, its concentrations are low; its concentration increases in the urine of patients with pyelonephritis [56] and in the saliva of patients with periodontitis [57].

Psoriasin

Psoriasin is an AMP with a molecular mass of 11.5 kDa [58]. It is produced in the epidermal keratinocytes and sebaceous glands of human skin, but it is not found in eccrine (merocrine) sweat glands [59]. It was first detected in keratinocytes in psoriasis. It is also found in human fetal tissues. The tissues of the ears, skin, and tongue have the highest content of psoriasin. It is not found in the cells of the immune system, in normal human fibroblasts, lymphocytes, endothelial cells, and transformed epithelial cells of keratinocyte origin in healthy individuals [58]. Psoriasin is a chemoattractant for T cells and is involved in the pathogenesis of acne and psoriasis [60]. It was shown that psoriasin is expressed in bladder carcinoma cells and it was detected in the urine of patients with this disease. Psoriasin expression has also been found in breast cancer. However, it remains unknown whether psoriasin could be considered as a tumor marker in clinical diagnostics [61].

Psoriasin is found in the following biological fluids of healthy individuals: blood, saliva, sweat, and vaginal secretions (Table 1). At the same time, the concentration of psoriasin in saliva is higher than in other biofluids. Psoriasin is not specific for psoriasis; it is also activated in other skin diseases that exhibit hyperproliferation and inflammation [61]. In systemic sclerosis, the concentration of psoriasin in saliva increases up to 25,500 ng/mL [60]. In psoriasis, the level of psoriasin in the blood increases, but decreases with the increasing severity of the disease [62]. Psoriasin is a marker of proliferative skin diseases.

Secretory leukocyte protease inhibitor

The secretory leukocyte protease inhibitor (SLPI) has a molecular mass of 12 kDa [63]. It is a potent inhibitor of granulocyte elastase and cathepsin G as well as an inhibitor of pancreatic enzymes such as trypsin, chymotrypsin, and pancreatic elastase [64].

SLPI is produced by various epithelial cells. It protects tissues of the macroorganism from damage by endogenous proteolytic enzymes. The SLPI gene is expressed by cells on many mucosal surfaces located in the tissues of the lungs, cervix, seminal vesicles, and parotid ducts. SLPI is also one of the dominant proteins in epithelial nasal mucosa and nasal secretions [65]. The expression of SLPI in the beta cells of the islets of Langerhans (pancreas) have been demonstrated by means of immunohistochemical methods [64].

SLPI has a broad spectrum of antibiotic activity, including bactericidal, antifungal [66], and antiretroviral

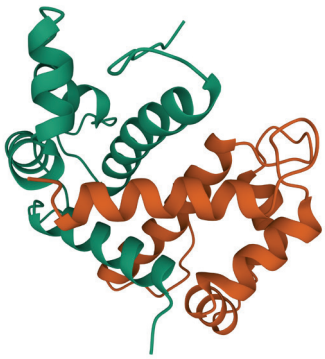

Fig. 7. Psoriasin (RCSB PDB (Protein Data Bank) https://www.rcsb.org/pages/about-us/index)
Amino acid sequence: SNTQAERSIIGMIDMFHKYTRRDDKIDKPSLL TMMKENFPNFLSACDKKGTNYLADVFEKKDKNEDKKIDFSEFLSLLG DIATDYHKQSHGAAPCSGGSQ

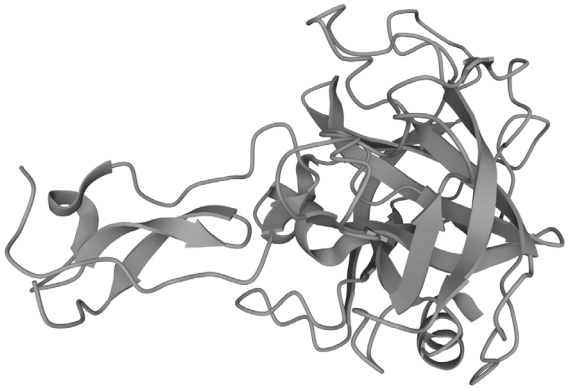

Fig. 8. Secretory leukoprotease inhibitor (SLPI) (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: IVGGRRARPHAWPFMVSLQLRGGHFCGATLI APNFVMSAAHCVANVNVRAVRVVLGAHNLSRREPTRQVFAVQRIFE NGYDPVNLLNDIVILQLNGSATINANVQVAQLPAQGRRLGNGVQCL AMGWGLLGRNRGIASVLQELNVTVVTSLCRRSNVCTLVRGRQAGVC FGDSGSPLVCNGLIHGIASFVRGGCASGLYPDAFAPVAQFVNWIDSIIQ

activity, which is thought to be the reason for the rare oral transmission of HIV [67].

SLPI is found in the blood, urine, and sweat, and its highest concentration was detected in saliva and vaginal secretions (Table 1). Elevated levels of SLPI in saliva and blood may be an indicator of an HIV infection [68]; in the blood, it is observed in ovarian cancer; in the blood and urine, it is found in acute kidney injury and may be considered as a marker of acute kidney injury [69].

Lysozyme

Lysozyme is an antimicrobial protein that destroys the peptidoglycan of bacterial cell walls. Consequently, its action is more pronounced against gram-positive bacteria. The molecular mass of lysozyme is 14.5 kDa [70].

Lysozyme is produced in the cells of the immune system – phagocytes, including macrophages, neutrophils, and dendritic cells [71]. In addition, lysozyme is found in epitheliocytes: in some parts of the rough endoplasmic reticulum of the epithelial cells of the pyloric glands, in the mucinous granules of the stomach, in the cells of the fundic glands, in the epithelial cells of the Brunner glands (duodenal glands), and in Paneth cells [72].

Lysozyme is found in many biological fluids (Table 1). It is found in abundance in saliva and vaginal secretions, in the blood, and it is also present in sweat and urine. It is found in large quantities in the breast milk (up to 0.3 g/l) and tears (over 0.5 g/l). Its concentration increases in infected patients.

RNases (ribonucleases)

RNases (ribonucleases) perform the function of RNA degradation in the body. In addition, RNases act as antimicrobial agents. Along with intracellular RNases, there are also secreted RNases. One of the RNases – RNase 7 – has a molecular mass of 14.5 kDa [73].

The most well-known is RNase A superfamily, which consists of RNase 1 (pancreatic RNase), RNase 2 – eosinophil derived neurotoxin (EDN), RNase 3 – eosinophil cationic protein (ECP), RNase 4, RNase 5 (angiogenin), RNase 6, RNase 7 (skin RNase), and RNase 8 [74].

RNases are secreted by a variety of immune cells, including eosinophils, neutrophils, monocytes, and macrophages [74]. RNase 3 (ECP) is found in the secondary granules of eosinophils [75].

RNases are also secreted by epithelial cells. Pancreatic RNase 1 is expressed in various tissues, including human endothelial cells [76]. RNase 7 was first identified as the most abundant human skin RNase secreted by keratinocytes [73]. RNase 7 is expressed in the epithelial tissues involved in host defense, for example in the respiratory [77] or urinary tract [78].

RNases are present in many biofluids in healthy individuals: blood, urine, saliva, vaginal secretions, and sweat (Table 1). RNases 1, 3, and 7 are secreted into serum under conditions of tissue injury (major surgery or sepsis). RNase 3 (ECP) is used in a blood test to determine the severity of asthma and other allergic diseases. RNase 7 level is significantly higher in patients with renal dysfunction [74].

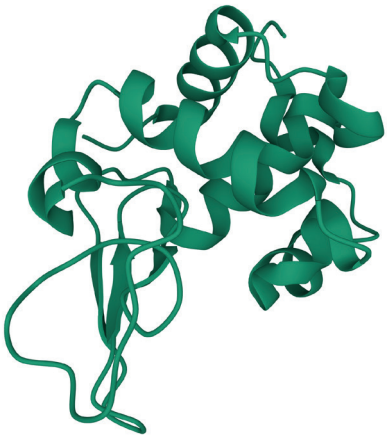

Fig. 9. Lysozyme (RCSB PDB (Protein Data Bank) https://www.rcsb.org/pages/about-us/index)
Amino acid sequence: KVFERCELARTLKRLGMDGYRGISLANWMC LAKWESGYNTRATNYNAGDRSTDYGIFQINSRYWCNDGKTPGAVN ACHLSCSALLQDNIADAVACAKRVVRDPQGIRAWVAWRNRCQNRD VRQYVQGCGV

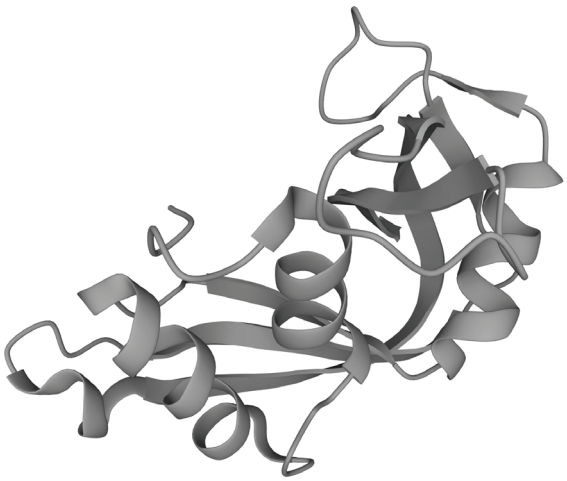

Fig. 10. RNase 2 (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: MKPPQFTWAQWFETQHINMTSQQCTNAM QVINNYQRRCKNQNTFLLTTFANVVNVCGNPNMTCPSNKTRKNCH HSGSQVPLIHCNLTTPSPQNISNCRYAQTPANMFYIVACDNRDQRRD PPQYPVVPVHLDRII

Lipocalin

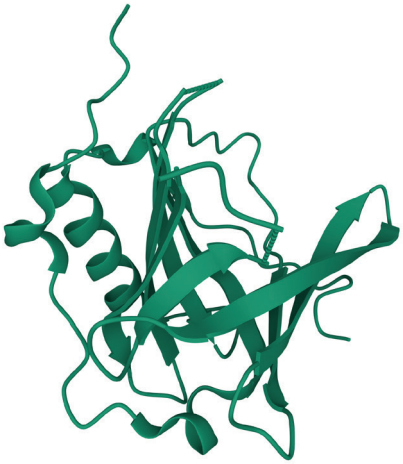

Fig. 11. Lipocalin 2 (RCSB PDB (Protein Data Bank) https://www.rcsb.org/pages/about-us/index)
Amino acid sequence: QDSTSDLIPAPPLSKVPLQQNFQDNQFHGK WYVVGLAGNRILRDDQHPMNMYATIYELKEDKSYNVTSVISSHKKC EYTIATFVPGSQPGEFTLGNIKSYGDKTSYLVRVVSTDYNQYAVVFFK LAEDNAEFFAITIYGRTKELASELKENFIRFSKSLGLPENHIVFPVPID QCIDG

Lipocalin (synonyms: NGAL – neutrophil gelatinase-associated lipocalin, lipocalin 2) is a protein with a molecular mass of 25 kDa [79]. It was first isolated from human neutrophils. Lipocalin enters the plasma from secondary granules of neutrophils, but it has been found that it is synthesized in various organs and tissues. It is expressed and secreted by hepatocytes and the cells of the renal tubules under various pathological conditions [80]. It is also secreted by the cells of the renal tubules after various damaging stimuli [79].

Lipocalin is an acute phase protein, but its concentration does not depend on the number of neutrophils detected in the blood. Lipocalin is a useful early diagnostic biomarker for acute kidney injury [81] and pancreas [82]. Lipocalin prevents iron uptake by microorganisms [83], binds lipophilic substances such as bacterial-derived formyl peptides and lipopolysaccharides, and can act as an inflammation modulator [84].

Lipocalin is present in various biofluids of healthy individuals: blood, urine, and saliva (Table 1). It was found in small quantities in the vaginal secretions. In patients with kidney damage, its blood level increases by 7-16 times and urine level – by 25-1,000 times. The level of lipocalin in urine and bile is also increased in patients with pancreatic cancer and chronic pancreatitis [82].

Azurocidin

Azurocidin (synonyms: cationic antimicrobial protein, CAP37), or heparin-binding protein (HBP) belongs to the serprocidin family. Serprocidins – elastase, proteinase 3, cathepsin G, azurocidin – are present in the azurophilic granules of neutrophils. Only one of them – azurocidin – does not show proteolytic activity [85]. The molecular mass of azurocidin is 37 kDa [86].

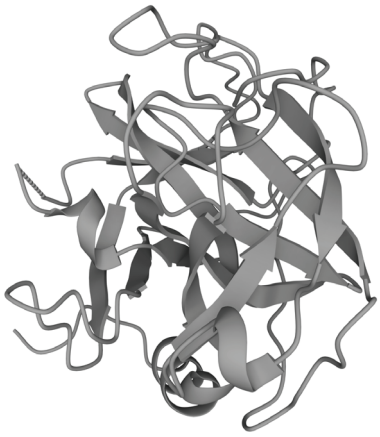

Fig. 12. Azurocidin (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: IVGGRKARPRQFPFLASIQNQGRHFCGGALI HARFVMTAASCFQSQNPGVSTVVLGAYDLRRRERQSRQTFSISSMSE NGYDPQQNLNDLMLLQLDREANLTSSVTILPLPLQNATVEAGTRCQ VAGWGSQRSGGRLSRFPRFVNVTVTPEDQCRPNNVCTGVLTRRGGI CNGDGGTPLVCEGLAHGVASFSLGPCGRGPDFFTRVALFRDWIDGVL NNPGPGPA

It has a wide spectrum of antimicrobial activity, mainly against gram-negative bacteria. Azurocidin serves as a multifunctional inflammatory mediator due to its action on endothelial cells: it causes an increase in vascular permeability, binds endotoxin, and attracts monocytes to inflammation sites [87].

Azurocidin is found in the blood, urine, saliva, sweat, and cerebrospinal fluid (Table 1). High plasma level of azurocidin is a marker for the development of sepsis with circulatory failure [88]. Low maternal serum level of azurocidin in the first trimester is associated with the premature rupture of the fetal membranes [89]. The level of azurocidin in the saliva of patients with the inflammation of the oral cavity increases by 8.8 times [90]. The presence of elevated levels of this heparin-binding protein in the cerebrospinal fluid serves as a marker for acute bacterial meningitis that helps to distinguish patients with this condition from those patients with other infections of the central nervous system [91].

Calprotectin

Calprotectin (synonym: leukocyte protein L1) is a protein with a molecular mass of 36 kDa [92] that is found in high concentrations in neutrophils, monocytes, and some reactive tissue macrophages. In fact, it comprises approx. 60% of the neutrophilic cytosolic protein fraction [93]. In monocytes, it is expressed on the membrane [94].

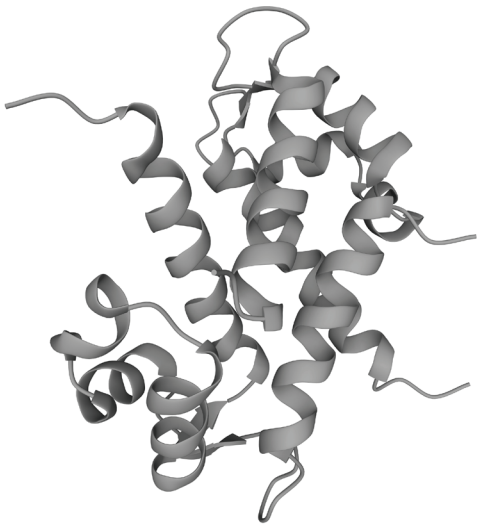

Fig. 13. Calprotectin (UniPort Database. https://www.uniprot.org/peptidesearch/)
Amino acid sequence: MLTELEKALNSIIDVYHKYSLIKGNFHAVYRD DLKKLLETESPQYIRKKGADVWFKELDINTDGAVNFQEFLILVIKMGV AAHKKSHEESHKE

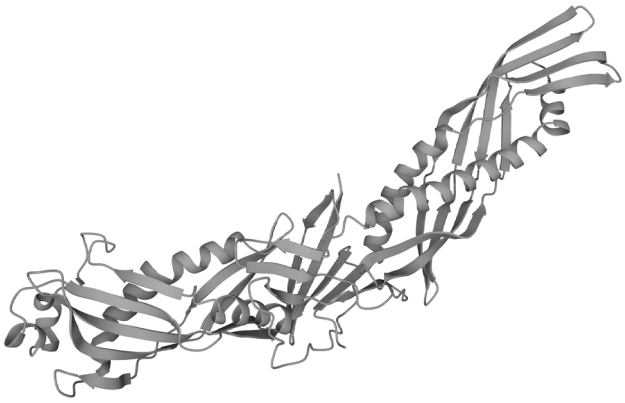

Fig. 14. Bactericidal/permeability-increasing protein (BPI, CAP57) (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: VNPGVVVRISQKGLDYASQQGTAALQKELK RIKIPDYSDSFKIKHLGKGHYSFYSMDIREFQLPSSQISMVPNVGLKF SISNANIKISGKWKAQKRFLKMSGNFDLSIEGMSISADLKLGSNPTSG KPTITCSSCSSHINSVHVHISKSKVGWLIQLFHKKIESALRNKMNSQV CEKVTNSVSSKLQPYFQTLPVMTKIDSVAGINYGLVAPPATTAETLDV QMKGEFYSENHHNPPPFAPPVMEFPAAHDRMVYLGLSDYFFNTAG LVYQEAGVLKMTLRDDMIPKESKFRLTTKFFGTFLPEVAKKFPNMKI QIHVSASTPPHLSVQPTGLTFYPAVDVQAFAVLPNSALASLFLIGMH TTGSMEVSAESNRLVGELKLDRLLLELKHSNIGPFPVELLQDIMNYIV PILVLPRVNEKLQKGFPLPTPARVQLYNVVLQPHQNFLLFGADVVYK

bacterial lipopolysaccharide (LPS). BPI recognizes the highly conserved lipid A region of bacterial LPS through residues clustered at the amino-terminal domain of the BPI molecule [99]. BPI may be present in other tissues, including the epithelial lining of mucous membranes [100]. BPI is found in the blood, saliva, and sweat (Table 1). In patients, its concentration in the blood increases tenfold, while in patients with infectious diseases, its concentration reaches 1,000 ng/ml in ascitic fluid [101].

Calprotectin is released upon the activation of neutrophils or endothelial adhesion of monocytes, and it can be detected in serum or body fluids as a potentially useful clinical marker of inflammation. The soluble form of calprotectin has a bacteriostatic and cytokine-like effect in the local environment [94].

Calprotectin is present in various biological fluids: blood, urine, saliva, vaginal secretions, sweat, and coprofiltrate (Table 1). Its determination in coprofiltrate is of particular importance because calprotectin serves as a marker in the diagnostics of inflammatory bowel disease [95]. In healthy individuals, calprotectin is present in the coprofiltrate at a concentration of 25.8 ng/ml, while in patients with adenoma its concentration reaches 66.3 ng/ml, with intestinal infections –306 ng/ml, and with inflammatory bowel diseases – 797 ng/ml. In the urine of healthy individuals, its content is insignificant, but in patients with acute kidney damage (renal damage), its concentration increases many times, although in patients with prerenal damage to the kidneys, it remains normal. Thus, urinary calprotectin serves as a marker for the differential diagnosis of renal and prerenal kidney damage [96].

Bactericidal/permeability-increasing protein

Bactericidal/permeability-increasing protein (BPI, CAP57), a 55 kDa protein [97] found in the azurophilic granules of mature neutrophils, has a high affinity for lipopolysaccharides and exhibits selective cytotoxic, antiendotoxic, and opsonic activity against gram-negative bacteria [98]. The selective activity of BPI against gram-negative bacteria is explained by its high affinity for the lipid A fragment of

Lactoferrin

Lactoferrin (synonym: lactotransferrin) – an 80 kDa protein [102] – is a glycoprotein capable of binding two ferric ions per molecule [103]. Lactoferrin exhibits an antimicrobial effect by binding iron [104] and shows a direct antimicrobial action, presumably by disrupting the bacterial membrane [105].

Lactoferrin has antimicrobial activity against gram-positive and gram-negative bacteria and fungi. In addition, it has been shown that lactoferrin has an antiviral effect, in particular against HIV [106].

Lactoferrin is localized in the specific granules of neutrophils and is released from the cells at infection and inflammation sites [107]. In addition, lactoferrin is synthesized by exocrine glands [107] and is one of the main proteins of almost all mammalian exocrine secretions.

In healthy individuals, lactoferrin is present in the blood, urine, saliva, vaginal secretions, sweat, seminal

Fig. 15. Lactotransferrin (UniPort Database https://www.uniprot.org/peptidesearch/)
Amino acid sequence: GRRRSVQWCTVSQPEATKCFQWQRNMRK VRGPPVSCIKRDSPIQCIQAIAENRADAVTLDGGFIYEAGLAPYKLRP VAAEVYGTERQPRTHYYAVAVVKKGGSFQLNELQGLKSCHTGLRRT AGWNVPIGTLRPFLNWTGPPEPIEAAVARFFSASCVPGADKGQFPN LCRLCAGTGENKCAFSSQEPYFSYSGAFKCLRDGAGDVAFIRESTVFE DLSDEAERDEYELLCPDNTRKPVDKFKDCHLARVPSHAVVARSVNG KEDAIWNLLRQAQEKFGKDKSPKFQLFGSPSGQKDLLFKDSAIGFSR VPPRIDSGLYLGSGYFTAIQNLRKSEEEVAARRARVVWCAVGEQELR KCNQWSGLSEGSVTCSSASTTEDCIALVLKGEADAMSLDGGYVYTA GKCGLVPVLAENYKSQQSSDPDPNCVDRPVEGYLAVAVVRRSDTSL TWNSVKGKKSCHTAVDRTAGWNIPMGLLFNQTGSCKFDEYFSQSCA PGSDPRSNLCALCIGDEQGENKCVPNSNERYYGYTGAFRCLAENAG DVAFVKDVTVLQNTDGNNNEAWAKDLKLADFALLCLDGKRKPVTE ARSCHLAMAPNHAVVSRMDKVERLKQVLLHQQAKFGRNGSDCPD KFCLFQSETKNLLFNDNTECLARLHGKTTYEKYLGPQYVAGITNLK KCSTSPLLEACEFLRK

fluid, milk, and tears (Table 1), while it is not found in cerebrospinal fluid. The highest concentrations of lactoferrin are found in tears and milk. At the same time, its concentration in mature milk is 2-5 times lower than in colostrum.

DISCUSSION

AMPs are present in the different biofluids of healthy individuals in variable concentrations. Despite the fact that different authors have different, sometimes even conflicting, data on AMPs concentrations in biofluids, it is possible to conditionally divide their concentrations into 3 groups: high (over 10,000 ng/ml), medium (100-9,999 ng/ml), and low (0-99 ng/ml).

Saliva and vaginal secretions are the richest in AMPs among the considered biofluids, while urine is the least rich. Almost all the classes of AMPs except dermcidins are present in saliva, with a prevailing concentration of histatin, and high concentrations of psoriasin, lysozyme, and calprotectin. Nine of the fifteen considered AMP classes are represented in the vaginal secretion, wherein calprotectin and lysozyme have a high concentration. Dermcidin is present in high concentrations in sweat, while cathelicidin is found there in moderate concentrations. Blood serum is a biofluid containing all of the classes of AMPs, except histatins. Their concentrations are distributed fairly evenly: most of AMPs are found in blood serum in medium concentrations. Few AMPs are present in the urine, usually at low concentrations, with lysozyme and RNases (particularly RNase 7) reaching moderate concentrations.

Other biofluids with high levels of AMPs include semen (cathelicidin and lactoferrin), milk and tears (lactoferrin and lysozyme), and colostrum (lactoferrin).

It is possible to correlate the intensity of AMP synthesis with a certain cell type by comparison of AMP-producing cells, their AMP products, and the amount of these products in healthy individuals. The leaders in the AMP production are glandular epithelial cells of exocrine secretion: the mammary gland (lactoferrin), the lacrimal gland (lysozyme), and the salivary glands (histatin). These cells produce AMPs in high and ultra-high concentrations.

AMPs produced by the cells of the immune system (adrenomedullin, azurocidin, BPI, alpha-defensins) usually are present in the corresponding biofluids in lower concentrations. AMPs, which are produced both by cells of the immune system and by various epithelial cells (lysozyme, RNase, cathelicidin, lactoferrin, beta-defensins), have a higher concentration in biofluids if they are produced by the glandular epithelium.

Dermcidins, psoriasin, and a secretory leukoprotease inhibitor are produced by integumentary tissues to protect against pathogens and from their own enzymes.

Some AMPs perform other functions in the body in addition to the antimicrobial action. For example, hepcidin and lipocalin are acute phase proteins: in the acute phase, hepcidin is secreted into the blood and lipocalin is secreted into the urine. Hepcidin and adrenomedullin are hormones that perform regulatory functions. RNase, being a ribonuclease, performs the functions of RNA degradation.

CONCLUSION

All of the AMPs described here can be conditionally divided into several groups based on the data on the AMPs concentrations in biofluids, their main producing cells, and their functions in the body:

a) Secretory AMPs – produced by glandular epithelium (exocrine glands) and may be present at high and ultra-high concentrations in biofluids.

b) Barrier AMPs – produced by integumentary epithelium, secreted in healthy individuals and in patients with pathological conditions; their function is to provide protection against pathogen penetration (barrier).

Their concentrations in biofluids are usually average, but in case of tissue damage or inflammation, they can be present in biofluids at high and ultra-high concentrations.

c) Leukocyte AMPs – localized in the granules or cytosol of immune cells, associated with the immune response and usually present in biofluids at low or moderate concentrations, corresponding to the number of neutrophils or other immune cells.

d) AMPs with other functions – acute phase proteins, immunomodulators, hormones, and enzymes. These AMPs usually have a weak antimicrobial effect and perform other functions in addition to antimicrobial action. Their concentrations in biofluids are usually low compared to other AMPs.

Taking into account the fact that the same AMPs can be synthesized by different groups of cells under different conditions, it is reasonable to study such AMPs separately. For example, lysozymes can be subdivided into leukocyte (located in neutrophil granules), secretory (as a part of lacrimal secretion and breast milk), and barrier (on the surface of epithelial tissues).

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