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+48 226 0 227 03
editorial_office@rsglobal.pl

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THE BACTERICIDAL PROTEINS OF THE EPIDERMIS

Kamil Kania *(Corresponding Author, Email: kania.kamil.lek@gmail.com)*
Medical University of Silesia, Katowice, Poland
ORCID ID: 0000-0002-7660-2505

Marcel Bobiński
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0007-8351-5884

Aleksandra Bubnowska
Independent Public Healthcare Institution in Szamotuły, Poland
ORCID ID: 0009-0006-2690-1343

Wiktoria Skowron
Independent Public Healthcare Institution of the Ministry of Interior and Administration in Katowice, Katowice, Poland
ORCID ID: 0009-0008-2494-837X

Rozalia Kujawa
Prof. S. T. Dąbrowski Hospital, Puszczykowo, Poland

Anna Rogala
Independent Public Healthcare Institution of the Ministry of the Interior and Administration named after Prof. Ludwik Bierkowski in Poznań, Poland
ORCID ID: 0009-0005-5465-6771

Bartosz Frańczak
J. Strus City Multispecialty Hospital, Poznań, Poland

Konrad Rzymski
Monument of the Baptism of Poland Hospital in Gniezno, Poland

Klaudia Romejko
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0003-6452-1323

Justyna Bartol
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0007-8635-9418

ABSTRACT

The skin is the biggest human's organ. It is concerned with plenty of functions, such as: providing protection against harmful factors of the external environment, both chemical and physical, or regulating temperature and the amount of evaporating water. It is responsible for receiving sensory stimuli and vitamin D3 synthesis. However, this review focuses on an underestimated role of the skin as a barrier against bacteria, maintained thanks to the human's natural antibiotics – the antimicrobial proteins of the epidermis.

KEYWORDS

Epidermis, Bactericidal Proteins, Dermicidin, Psoriasin, Defensins, Chemerin, Kathelicidin

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1. Introduction

1.1 The skinstructure

The skin is composed of three distinct layers: epidermis, dermis and hypodermis. Their structures and functionsdiffer significantly.

The most superficial part, the epidermis is primarily built up of keratinocytes and consists of 5 layers: the stratum basale (also known as stratum germinativum), stratum spinosum, stratum granulosum, stratum lucidumand stratum corneum [1].

Stratum basale is the single cell, proliferative layer where keratinocytes divisions and differentiation take place. It also contains melanocytes and Merkel cells. Melanocytes have neuroectodermal origin and produce melanin, responsible for the pigmentation of the skin and providing protection against UV radiation. Merkel cells interact with free nerve endings due to receiving light touch stimuli, therefore they are mostly accumulated in palms and soles [1].

When keratinocytes stop dividing, they lose connection with the basement membrane and move on to the next level, which is the stratum spinosum. It has 8-10 cell layers and is composed of characteristic, irregular cells with outgrowths, resembling spines. Langerhan's cells can be found in this epidermal layer. These are dendritic, antigen presenting cells, containing tennis racket shaped Birbeck granules (BGs). Despite many studies BGs still remain enigmatic, specifically considering their derivation and function. The exocytosis theory assumes an intracellular origin from Golgi apparatus, whereas the endocytosis theory suggests, that BGs are formed from the cell membrane. Stratum spinosum is the zone, where production of the involucrin begins. This is a protein, that takes part in creating a cornified envelope [1-3].

Afterwards, keratinocytes migrate to the stratum granulosum, composed of 3-5 cell layers. In this zone occur different kinds of granules, containing keratohyalin (a precursor of filaggrin, responsible for keratin bonding), loricin and cornifin (components of a cornified envelope). The lamellar granules include glycolipids. As they are excreted, they caulk intercellular space creating water impermeable barrier [1,3].

Stratum lucidum, 2-3 cell layered occurs only in thick skin, located in the palms and soles. It is cells comprise transparent protein – eleidin. They are devoid of the nucleus thus they pass to the non-living state to form corneocytes [1].

The supreme zone of the epidermis, the stratum corneum has 20-30 cell layers. It only consists of corneocytes. Corneocytes create an envelope of cross-linked proteins (involucrin, loricrin and cornifin), that surround a network of keratin filament.This is where the process of cornification (keratinization) ends [1,3].

Although the epidermis is permanently remodelling, extremely dynamic tissue, it is well organised. Cells' firm integration is provided by intermediate filaments that depend on connections to intercellular desmosomes [4].

The dermis is inferior to the epidermis. The predominant cells of the dermis are fibroblasts, but there are also macrophages, dendritic cells and lymphocytes. The dermis is composed of two layers – the papillary and reticular layer. The papillary layer is below the epidermis and is separated from it by the basement membrane. In the upper part it is organised into dermal papillae including nerve endings and microvascular vessels. Papillary dermis is denser than the reticular one and contains more proteoglycans. The two zones of the dermis are separated by the vascular plexus. The reticular layer is made up of a network created by bunches of collagen and elastic filaments. In the elderly the papillary dermis becomes replaced by the reticular [5].

The most profound part of the skin is the hypodermis. It is built up of loose connective tissue, containing adipose tissue. The large content of proteoglycan and glycosaminoglycans result in accumulation of water thus the tissue is mucous. Besides adipose cells in the hypodermis occurs also fibroblasts and macrophages. The main function of the hypodermis is thermal and mechanical isolation [6].

1.2 The phylogenesis

If it comes to the defensins, based on the matrix sequence analysis, it was shown that all vertebral defensins probably evolved from a common ancestor - primary β-defensin. During evolution, the group of these genes expanded to include more protein families. As indicated by the phylogeny of α-defensins, they are evolutionarily younger, which is explained by the fact that they occur only in mammals and their higher level of homology as a group. As a result of the divergence, in humans on the chromosome 8p23 contiguous clusters were created separately for α- and β-defensin genes [7].

Cathelicidins are highly heterogeneous having different structures and length among species but they are all called cathelicidins because of highly conserved N-terminal cathelin domain containing 100 residues. In all species, they exhibit the same antimicrobial properties. The number of cathelicidins among species are different. When horse, pig, sheep seem to have 7 different cathelicidins, human have only one. Similar situation is in mouse or rhesus monkey where also single cathelicidin was found. What is more, cathelicidin domain turns out to be 70-80% identity in human and mice. These species are phylogenetically more closely related than those having more than one cathelicidin. Research showed that cathelicidins were found even in the ancient species like hagfish thereby it is believed that cathelicidin genes developed 300 million years ago and may be present in most vertebrates [8,9].

It is believed that chemerin belong to the structural cathelicidin/cystain family of proteins consisted of antibacterial polypeptide cathelicidins and inhibitors of cysteine proteinases (cystatins). However, chemerin does not inhibit human cysteine proteases, it is more likely to be a substrate for cathepsin K and L. Chemerin is cleaved by cathepsin K and L, which indicate migration of human blood-derived pDC ex vivo [10].

Regarding to dermicidin and psoriasin, their sequences of amino acids haven't been identified as a similar to any other protein.

2. Antimicrobial Peptides – Amp

2.1 Dermicidin

A protein, which represents AMP class is Dermcidin (DCD). It presents close activity to other AMPs. However, it has been proven, that there is no homology between DCD and any published AMP gene sequence [11].

According to research, theDCD gene (cDNA) consist of 458 bp which stand for 110 amino acids. It is expressed exclusively in human skin inside eccrine sweat glands (dark mucous cells of the secretory coil). Constitutively secreted by eccrine sweat glands DCD into skin is not active. It is proteolytically processed by cathepsin D, 1,10-phenanthroline-sensitive carboxypeptidase, that results mainly in active 47 amino acid DCD (DCD-1) comparing to 63-109 original translated peptide, DCD-1L, SSL-25, SSL-29, SSL-46, LEK 45 and Y-P30, which consists of 30 aa. The amount of these peptides and dominant types is different among individuals [7,8,9]. The modification might take place in human sweat as it is abundant in various proteases, but direct processing in eccrine sweat gland cells should also be considered [13,14,15].

DCD-1 and other dermcidin derived peptides have revealed antimicrobial activity. Due to performing in skin environment, which is acidic, because of sweat, DCD continues to protect host in low pH and high concentration of sodium and chloride, which makes it salt- and pH- insensitive (in physiological range) – atypical for AMP [11]. The active form of DCD was found in 7 days sweat stains on clothes, which indicates it's great stability on human skin and resistance to bacterial proteases [11,12]. Furthermore, research shows,

that the protein is able to switch its structure between α-helical and β-sheet depending on buffer condition, which might be essential for its antimicrobial properties [16,17].

As contrast to other AMP family proteins, DCD derived peptides present mainly negative charge. Although, few are cationic ex. SSL-25. Irrespectively of their charge, all of tested (DCD-1L, Lek-45, SSL-29,SSL-23) proved to be effective against large spectrum of hostile microbes (E. coli, S. aureus MSSA and MRSA, and S. epidermidis). However, there is distinction in success rate between several peptides in killing different bacteria [18]. Other susceptible pathogens are Enterococcus faecalis, Listeria monocytogenes, Pseudomonas putida, Salmonella typhimurium and Candida albicans [11,18,19].

The mechanism, in which DCD attacks bacteria is based on changing its membrane and its properties. It binds to bacterial cell envelope, connects to phospholipids: phosphatidylcholine (DOPC) and phosphatidylglycerol (DOPG) – DOPC-DOPG membranes. Interestingly it exhibits only weak binding to bacterial components such as lipopolysaccharide (LPS) obtained from Gram-negative bacteria or peptidoglycan, lipoteichoic acid (LTA), wall teichoic acid (WTA) obtained from S. aureus [20]. The modified cell envelope, present in mutant specimens has an impact on susceptibility to DCD activity. It can be increased or decreased comparing to normal microbes. The S.aureus mutants mprF and dltA were more sensitive to DCD derived peptides. On the other hand, the mutant seemed to be less sensitive to DCD peptides than the wild-type S. epidermidis strain [18]. Binding to bacteria surface is predated by changing secondary structure (from random coil to alpha helical conformation) and oligomerization of monomeric DCD-1L, which is supported by Zn^{2+}. Afterwards, the cationic N terminus gets attracted electrostatically to negatively charged bacterial membrane. Furthermore, presence of Zn^{2+} and low pH enhances protein's ability to interact with cell envelope. This process is followed by inserting DCD-1L into membrane and creating ion channels, which destabilize internal environment of bacteria and leads to cell death [21].

DCD-1L properties also include modulating human keratinocytes. It stimulates production of cytokines and chemokines such as tumour necrosis factor-a, interleukin-8 (CXCL8), interferon-inducible protein 10 (CXCL10) and macrophage inflammatory protein-3a (CCL20), that indicates important role of dermcidin in regulating inflammatory responses of skin [22]. However, DCD is secreted rather continuously as a part of constitutive defense and it doesn't react to inflammation or injury [23].

In addition, significant decrease in expression of dermcidin on human skin is present during skin afflictions such as Acne Vulgaris [24], Sweat of Tinea Pedis [25] and Atopic Dermatitis, which makes patients more vulnerable to skin colonization by other microbes [26]. This information proves crucial role of dermcidin in innate skin defence and brings out the importance of further research in order to improve skin disease therapy.

2.2 Psoriasin

Psoriasin was first found in 1991, in the keratocytes of patients with psoriasis. Further research enabled to include it in a family of the S100 protein, which has been shown to bind calcium. Therefore, psoriasin gained its other name – the S100A7 protein [27]. This protein is found in stratum corneum of the epidermis [28].

Psoriasin is made up of 101 amino acids and its molecular mass is 11,457 Da [29]. Psoriasin protein occurs as a dimer with an acetylated N-terminal end. Monomer of psoriasin comprises five α helices and one calcium-binding EF-hand. Besides the ability to bind calcium, psoriasin can also bind zinc ions. What is more, research has proven, that binding of zinc result in the change of the protein structure [27].

The ability to bind zinc is an important element of its antimicrobial activity. The mechanism affects bacteria directly and includes deprivation of zinc ions, which are necessary for bacterial metabolism. There's evidence that psoriasin leads to the increase of pore formation in bacterial membrane in acidic pH under 6,0. In lower concentrations psoriasin acts mainly against Escherichia coli, whereas higher doses affect Pseudomonas aeruginosa and Staphylococcus aureus. The importance of the antimicrobial function of psoriasin has been shown by an experiment, which proved that colonisation of the skin by Escherichia coli bacteria can be possible only after using psoriasin inhibitors [27].

Expression of psoriasin in the healthy skin of an adult is low, however concentration of this protein increases in sites of higher risk of bacterial colonisation, such as the anogenital region, the forehead, palms, soles and armpits. Furthermore, it was detected that level of psoriasin expression in the newborns skin is higher [23,26].

Besides its direct influence on the bacteria, psoriasin has other functions in the immune response. Studies have shown, that psoriasin manifests a chemotactic activity towards neutrophils and CD4+ T lymphocytes. In addition, it can alternate other functions of neutrophils – higher psoriasin levels enhance the production of cytokines and chemokines including interleukin-6, interleukin-8, tumour necrosis factor α and macrophage inflammatory proteins (MIP-1α, MIP-1β, MIP-3α). It was proven that psoriasin also intensifies the secretion

of reactive oxygen species. Moreover, psoriasin induces the expression of mRNA of α-defensins, leading to the increase of their extracellular levels [30].

Due to its functions, alternation of psoriasin expression in keratocytes is observed among different skin conditions, often associated with inflammation and hyperproliferation. Therefore, it can be considered as a marker of keratocyte function. As said before, the increase of secretion of psoriasin protein was first observed in psoriatic lesions, but its upregulation was also detected in the edges of wounds. What is more, acute wounds trigger a significant induction of psoriasin secretion, whereas in chronic wounds the amount of psoriasin isn't remarkably raised. Therefore, it was suggested, that chronic wounds may be related to the decrease in psoriasin expression. It was also proven that psoriasin expression elevates noticeably in patients with bladder and breast cancer. Furthermore, similar increase was observed in precancerous skin lesions and carcinomas. This suggest, that overexpression of psoriasin may be a relevant indicator of cancer progression [31].

2.3 Defensins

The defensins are a family of small positively charged peptides with a molecular weight of 3-4 kDa. All defesins contain in their structure three intramolecular disulfide bridges formed by six invariant cysteines that stabilize β-sheet structures [32]. According to their structural differences the defesins are classified in three main subfamilies: α-, β- and θ-defensin. The division into α- and β-defensin is based on the position of three disulfide bridges in the molecule [33]. It has been shown that the modification or removal of cysteine sulphide bridges in the defensin molecule causes a reduction or complete disappearance of their antimicrobial properties [34]. Humans α-defensins are represented by six molecules - HNP-1, HNP-2, HNP-3, HNP-4 (human neutrophil peptides) predominantly present within azurophilic granules of neutrophils and defensins synthesized in Paneth cells of the human intestine, such as HD-5, HD-6. They are peptides with three S-S bonds formed between cysteines at positions 1-6, 2-4 and 3-5. Up to now they are not discovered in human keratinocytes or cells derived from skin appendages [35]. In β-defensins linkages occur at positions 1-5, 2-4 and 3-6. To date six types of ß-defensins (hBD – 1 to – 6) have been identified from human body and their function and expression have been well known. The place of production of hBD-1 to hBD-4 in the human body is primarily epithelia - skin keratinocytes, epithelium lining the respiratory and urogenital tract, but expression of HBD-3 has been also demonstrated in other tissues such as skeletal muscle and heart. The other two human defensins (hBD-5 and hBD-6) are expressed inter alia in the epididymis [36]. θ-defensins have not been detected in humans so far. They are cyclic and their presence has been confirmed in non-human primate neutrophils [37].

The genes encoding the defensins are composed of two exons and one intron. The effect of their expression is a propeptide containing the N-terminal signal peptide and the C-terminal mature peptide. There is a relationship between the number of defensin gene copies and the amount of the resulting mRNA transcript [35]. hBD-1 is constitutively produced in various human epithelia including epidermal cells, sweat gland ducts and sebaceous glands. The basal layer of the epidermis has a lower level of hBD-1 than in differentiated keratinocytes. In addition, the level of expression of hBD-1 in the epithelium increases as a result of stimulation by bacterial lipopolysaccharides and peptidoglycan [38]. On the other hand, the expression of HBD-2, HBD-3 and HBD-4 is primarily dependent on the induction. The synthesis of hBD-2 and hBD-3 is intensified by cytokines like interleukin (IL)-1α and -1β, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, also by lipopolysaccharide and cell differentiation [7]. hBD-3 can be induced in epidermis by epidermal growth factors. It happens in case of a sterile wounds, which results in increases resistance to possible infection. It is believed that the contribution of hBD-4 in keratinocytes is limited to mRNA synthesis [36].

Both α- and β-defensins have a broad spectrum of antibacterial activity against gram-positive and gram-negative bacteria. Their bactericidal activity has been confirmed, among others, against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa [38]. Due to the electropositivity, defensin bind to negatively charged elements of bacterial membranes and increase membrane permeability, which is believed to be the main defensin-destroying mechanism [33]. There are also reports of their action against fungi, viruses and parasites [35]. Furthermore, defensins initiate the host response after exposure to microbe-derived molecules which is manifested by cellular response, an increase in the expression of cytokines, chemokines and inflammation. The hBD-2 ~ 4 induce production of IL-6, IL-10 interferon-inducible protein 10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-3a (MIP3-α), in human keratinocytes. Overmore, hBDs stimulate keratinocytes to migrate and proliferate by phosphorylation EGFR and STAT proteins [39] hBDs also show chemotactic activity for many cell types, including immature dendritic cells and memory T-cells through CCR6 and accelerate angiogenesis and wound healing [35]. hBD-3 is also

involved in mast cell degranulation. Interestingly, the salt has an inhibitory effect on the bactericidal activity of hBD-1, -2 and -4, while it does not affect the action of hBD-3 [40]. Beside to antimicrobial properties that contribute to innate immunity, defensins also take part in adaptive immunity due to their regulatory and effector activity as confirmed by current evidence.

2.4 Chemerin

Chemerin is a protein, which has multifunctional impact on the body. Chemerin takes part in adipogenesis, angiogenesis, osteoblastogenesis, glucose homeostasis, immune cell migration and myogenesis. Concentration of chemerin might be changed in various diseases such as chronic kidneys disease, psoriasis, obesity, non-inflammatory bowel disease, chronic pancreatitis and liver failure. Chemerin is an adipokine which is involved in adipocyte differentiation. Primarily, the protein combines metabolic and immune function [38-40].

Chemerin is a ligand to CMKLR1 (chemokine-like receptor 1 also known as ChemR23 or DEZ), GPR1 (G protein-coupled receptor 1) and CCLR2 (CC motif chemokine likereceptor 2) [43]. CMKLR1 is a G protein-coupled receptor located on plasmacytoid dendritic cells (pDCs), macrophages and NK cells causing cell migration [41]. CMKLR1 gives rise to intracellular calcium mobilization, inhibition of cAMP accumulation, launch the mitogen-activated protein kinase (MAPK) cascade, recruit β-arrestin and receptors internalization [38,41]. GPR1 takes part in β-arrestin2 association and receptors internalization. CCLR2 is atypical chemerin receptor, which also regulates concentration of this protein [45].

TIG2 (tazarotene induced gene 2) also called RARRES2 (retinoic acid receptor responder gene 2) encodes chemerin. Liver and fat tissue are the main source of the protein [41], but it is also presented in many tissues among others pancreas, placenta, skin, and lung [46]. Plasma contains nanomolar range of chemerin (~4 nM) [47]. Structure and evolutionary origin of chemerin is similar to cathelicidin (factors which has antibacterial function), cystatins (cysteine protease inhibitors) and kininogens [44]. Firstly, chemerin is produced as a preprochemerin. Subsequently, it is removed 20 amino acid N-terminal signal peptide. Prochemerin is inactive form of chemerin secreted from a cell. Serine and cysteine proteases, fibrinolytic and inflammatory cascade enzymes including neutrophil elastase and cathepsin G, mast cell tryptase, plasma-derived factor XIIa, VIIa and plasmin cleavage carboxyl-terminus of the protein causing activation. Due to that, chemerin can be presented in variety of isoforms [42,45]. Skin chemerin can form high molecular weight protein complex through covalent binding to other proteins [47,48,49]. F149-S157 domain, which corresponds to the C-terminus, is responsible for chemotactic activity through CMKLR, that is why chemerin 157S has the greatest chemotactic activity. However, chemerin 157S as well as chemerin 125R, which is non-chemotactic protein, inhibit growth of bacteria equally. It proves that in chemotactic and antibacterial function are arranged different protein domain. The most important region of chemerin responsible for antibacterial function is peptide 4 (p4) Val66-Pro85 domain. Optimum of activity of peptide 4 has at neutral pH and in low salt conditions, which corresponds to healthy epidermis habitat [10,46].

Expression of mice TIG2 in the skin is at least 6 times lower than in the liver and fat tissue. However, contraction of chemerin in tissue lysates is only 2 or 3 times lower in the skin than in the liver and fat tissue. Moreover, in the skin epidermis-keratinocytes are the major source of chemerin and produces similar values as the liver. In epidermis basal and suprabasal layers mostly express chemerin. This location of chemerin proves that it has substantial role in skin interruption such as burns [41].

Bacteria such as E. coli and S. aureus provoke keratinocytes to produce chemerin. However, each bacteria trigger different process. Live bacteria stimulate skin to produce chemerin in greater degree than the dead ones. That might suggest that vita-PAMPs (viability associated pathogen-associated molecular patterns) could have an impact. Furthermore, it is proved that not only bacteria suspensions stimulate expression of chemerin. That ability has released factors into the cultured fluid by bacteria [38,47]. S. aureus secrets staphopain B- cysteine protease causing activation of prochemerin, leading to generates chemerin 157S variant [50].

Tazarotene, which induces chemerin synthesis, is used for treatment of hyperproliferative skin diseases. It points that manipulation of bioactivity chemerin and chemerin-divided peptides can be found to be useful to treat skin infections [45].

2.5 Cathelicidin (LL-37)

Cathelicidins are cationic peptides that are known for their antimicrobial action, they are called natural antibiotics [51]. As it was mentioned before, in the human body there is only one known cathelicidin, it is LL-37, which is 37 amino acid long peptide [52]. LL-37 stands for first two N-terminal's amino acids, which are leucines and the length of peptide. LL-37 has hydrophobic and hydrophilic side and forms α-helix structure, which due to the fact that it is cationic peptide, can easily bind to the anionic lipid-rich membrane causing disruption membrane integrity [53]. In the skin, major source of LL-37 are keratinocytes, however, it can also be provided by immune cells like neutrophils [52], mast cells or T cells [54]. LL-37 production in the healthy person's skin is on low level or undetectable whereas it is considerably increased in association with inflammation, infection or injury of the skin [52].

As recent study showed, in the human genome, exons 1-4 for LL-37 are located on chromosome 3 p21 having an information about gene CAMP, strongly induced in keratinocytes [53], which encodes a sequence of inactive propeptide hCAP-18 (human cationic antimicrobial protein 18kDa) build of N-terminal cathelin domain and C-terminal cationic domain. Each domain has its own abilities. For example, N-terminal domain has the capacity to inhibit cathepsine L cysteine protease activity [55] whereas C-terminal domain encodes the mature active antimicrobial peptide [52]. The final step of generating this active form happens when hCAP-18, stored in lamellar bodies in keratinocytes, is secreted on the skin surface, then C-terminal domain is cleaved from hCAP-18 by serine protease. After the cleavage, LL-37 gains fully antimicrobial activity [52,53]. The expression of LL-37 can be disturbed in some diseases.

LL-37 is excessively produced in psoriasis and it contributes to psoriasis pathogenesis by activating dendritic cells and T cells which thought to be main cause. On the other hand, the expression of LL-37 is insufficient in atopic dermatitis leading to more susceptibility to infections of the wounded skin [51,52].

LL-37 presents its antimicrobial properties in two major ways. First of all, electrostatic forces interaction of positively charged protein LL-37 with negatively charged lipids in the membrane of microorganisms allow LL-37 to cling into the membrane or neutralize the charge of microbe's membrane. Subsequently, the structure of the protein changes giving the opportunity to incorporate into the membrane and that leads to forming pores, which are direct cause of microbe's cell's death [56]. Besides that, LL-37 has an ability to binding and neutralizing LPS, endotoxin occurred on the outer membrane of gram-negative bacteria [57]. What is more, research shows that LL-37 has an antiviral and antifungal effect as well [52].

However, antimicrobial activity is not the only feature of LL-37 in fighting against pathogenic microbes. It is known that LL-37 stimulates immune cells like neutrophils, mast cells but also keratinocytes to secretion [52] of cytokines like IL-18 [58], IL-6 and IL-10 [54] or IL-1β, which is activated by interacting with G protein coupled receptor, P2X7 [53] and chemokines like interferon inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 3α having chemotactic activities on immune cells, which are expressed by gathering these cells in the place of infected skin thus it is consider to be not only antimicrobial but also an alarmin peptide [52,54]. On a molecular level, LL-37 activates another G protein coupled receptor, FPRL-1 (formyl peptide receptor like 1), which attracts immune cells and allows to induce angiogenesis [53]. Finally, LL-37 appears to be vital aspect in repair of damaged tissue and wound healing by activating epidermal growth factor receptor (EGFR) and as a result, producing new epithelial cells and neovascularization, leading to closing the wound [53,57,59].

Interesting fact is that, turns out, vitamin D has an important role in regulation of secretion of LL-37 in human cells [60]. On the promoter region of CAMP there are number of regulatory elements such as e.g vitamin D receptor (VDR) or Toll-like receptor (TLR), which have direct or indirect effect on LL-37 synthesis [61]. Vitamin D attached to VDR activates a pathway which leads to increase CAMP expression in immune cells but also epithelial cells. Hence, it might be an interesting subject of research in the future therapies against diseases with deficient synthesis of LL-37 like atopic dermatitis [60]. Moreover, TLR activation by recognizing structurally conserved molecules derived from microbes, increases CYP27 expression, which has an impact on hydroxylation and creation of vitamin D3, the main ligand of VDR thereby inducing CAMP production [60,62,63]. CYP27 has two forms, CYP27A1 expressed mainly in the liver and CYP27B1 expressed in the kidney whereas both of these forms are expressed independently in keratinocytes of the skin [60].

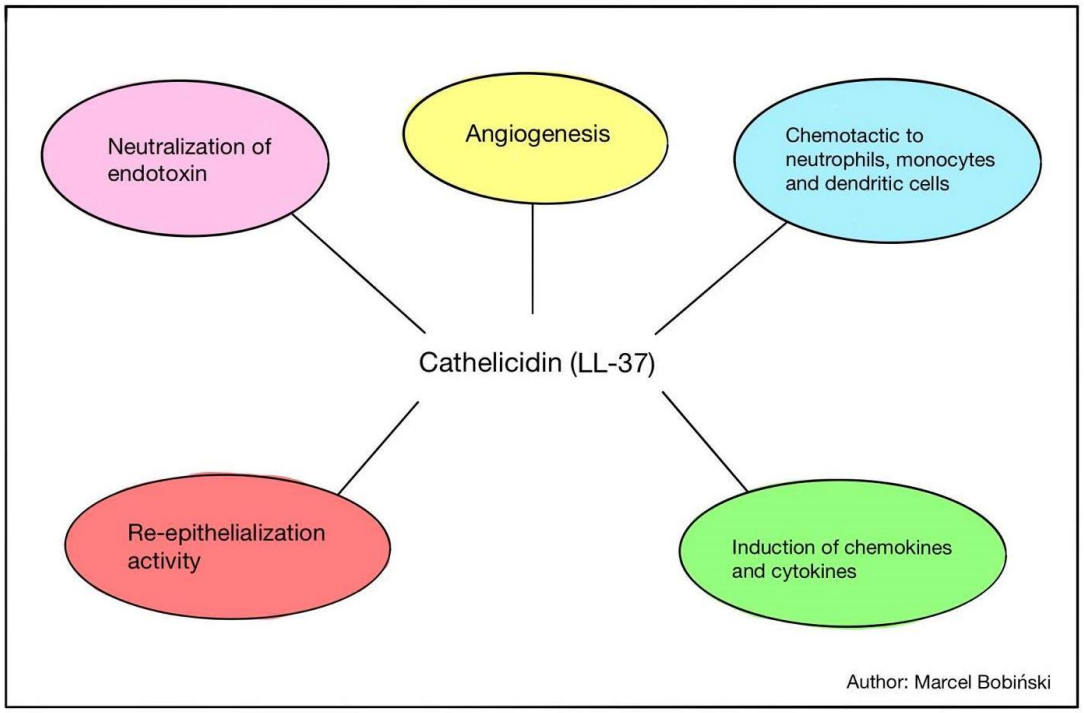

Fig. 1 Schematic representation of the functions of LL-37

3. Conclusions

We opened this paper by noting, that the role of the skin as a shield against bacteria has still remained underestimated as it is antimicrobial proteins haven't been well known. To sum up, here we present some essential facts about them.

Dermicidin has no homology to any AMP. It is expressed exclusively in human skin. DCD is secreted rather continuously as a part of constitutive defense and it doesn't react to inflammation or injury. DCD derived peptides present mainly negative charge. The mechanism, in which DCD attacks bacteria is based on changing its membrane and its properties - creating ion channels, which destabilize internal environment of bacteria and leads to cell death.

Psoriasin, also known as S100A7 protein is a significant antibacterial factor in the human skin. It affects bacteria both directly - in the mechanism of deprivation of zinc ions, and in the indirect way, stimulating the cells of host defense system. The main target of psoriasin protein is Escherichia coli, however in higher concentration psoriasin affects also Pseudomonas aeruginosa and Staphylococcus aureus.

Defensins as a salient group of antimicrobial peptides display broad range antibacterial activity against gram-positive and negative bacteria, against fungi, and also have antiviral properties against enveloped and nonenveloped viruses. They exhibit immune modulatory activities including cell signaling, pro-inflammatory functions, toxic functions, and enzyme inhibition. All of it makes them one of the major effectors of the innate immunity.

Chemerin, which is encoded by gene TIG2, has several specific roles, but most importantly this protein combines metabolic and immune function. The protein can be presented in diversity of isoforms, which differ in chemotactic and antibacterial action. The main source of the protein are liver and fat tissue, but it is also presented in many tissues including epidermis.

Members of the cathelicidin family of antimicrobial polypeptides are characterized by a highly conserved region (cathelin domain) and a highly variable cathelicidin peptide domain. Their main biological function is located on C-terminal domain. Cathelicidins exhibit broad-spectrum antimicrobial activities. They are inflammatory mediators having influence on migration of various immune cells in association with inflammation or injury of the skin. The fact, that their level is increased or decreased in some serious diseases like psoriasis or atopic dermatitis, can be used in the future therapies.

All authors have read and approved the manuscript. The authors declare no conflict of interest.

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