Jurnal RSMH Palembang
Journal Homepage: http://jurnalrsmh.com/index.php/JRP

Role of Cathelicidin (Ll-37) and Human B-Defensin In Atopic Dermatitis And Psoriasis

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ARTICLE INFO

Keywords:
AMP
Cathelicidin
Defensin
Atopic Dermatitis
Psoriasis

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/JRP.v1i1.4

ABSTRACT

The Human epithelium, including the epidermis produces *antimicrobial peptide* (AMP) as part of innate immunity. Cathelicidin and human β-defensins are the most AMP found on the skin. This *antimicrobial peptide* has a role in the response of the natural immune system by becoming the front line of the defense system against infection. The discussion of this literature review will focus on cathelicidin and human β-defensin-1 which are the main AMPs that affect atopic dermatitis and psoriasis. *Antimicrobial peptides* are excessively produced in lesional psoriatic scales or rosacea in contrast to the atopic skin that shows lower AMP levels when compared with psoriasis. Despite the impaired skin barrier which facilitates potentially pathogenic microbes to colonize the epidermis, patients with psoriasis surprisingly present a low frequency of skin infections, whereas patients with atopic dermatitis are predominantly susceptible to particular cutaneous bacterial, fungal and viral infections. One possible explanation of the fact is the difference in the expression of AMPs. DA patients have fewer AMP expression characteristics, especially cathelicidins LL-37 and HBD-2. Research on antimicrobial use can help reduce pathogen colonization so that clinical improvement of AD occurs. In the case of psoriasis, AMP expression increases, especially LL-37 and HBD-2, showing synergistic antimicrobial activity that is effective in eradicating microbial colonization, so there is no strong evidence to support antibiotic use in treating psoriasis or in preventing disease.

1. Introduction

The human skin epithelium, including the epidermis, produces *antimicrobial peptide* (AMP) as part of natural immunity. Apart from antibacterial properties, some proteins have antimitotic and possibly antiviral properties[1]

It was found that a range of more than 20 proteins showed antimicrobial activity. *Cathelicidin and human ß-defensins* are the most common AMP found in the skin.[2] In addition to *human ß-defensins*, cathelicidins (LL-37) there are several other AMPs, namely psoriacin, and RNase 7, which are produced in keratinocytes, and dermcidin which is secreted in sweat glands human. This literature review discussion will focus on *cathelicidin and human ß-defensin-1* which are the main AMPs affecting atopic dermatitis and psoriasis.[3]

Differences in AMP expression have a role in patients with chronic inflammatory skin disease complicated by infection. Psoriasis, lupus erythematosus, and contact dermatitis will induce LL-37 in keratinocytes. Likewise, Human *ß-defensin*-2 (HBD-2) and HBD-3 will *upregulate* keratinocytes in psoriasis patients. However, the expression of LL-37 and HBD-2 is not *upregulated* in atopic dermatitis (DA), so that DA patients are very susceptible to bacterial, fungal, and viral infections.[4]

Antimicrobial peptide has the ability to kill

pathogenic microbes, as well as indirectly strengthen the host defense system. Against the backdrop of the rapidly increasing resistance to conventional antibiotics worldwide, efforts to investigate AMP in the clinical setting are also increasing.[5] The aim of this literature review is to broaden and study the role of human AMP, especially in psoriasis and atopic dermatitis and the relationship of AMP in therapeutic aspects of both diseases

2. Human *Antimicrobial Peptide* (Amp)

Cathelicidin and defensin are the most commonly produced AMPs in the skin and have been extensively studied. Cathelicidin and defensin are expressed in keratinocytes and are involved in a variety of skin conditions.

Cathelicidin

Cathelicidin is the first AMP found in mammals. Human cathelicidin is often referred to by its peptide form (LL-37) or by nomenclature assigned to its protein precursor, such as *human cationic antimicrobial peptide-18* (hCAP18). The human hCAP18 protein precursor is produced by skin cells, including keratinocytes, mast cells, neutrophils, and eccrine gland cells. Protein protease, for example *protease* 3, will process hCAP18 into an LL-37 effector molecule (the name LL-37 is derived from the active amino acid 37 AMP released by the C-terminal protein).[6] Then LL-37 interacts with mammalian cells to trigger a host response. These mechanisms include direct interaction of LL-37 with cell surface receptors, such as *formyl-peptide receptor-like* 1 (FPRL-1) or G *protein-coupled receptors,* thereby producing a direct effect on intracellular signaling pathways. 3 These molecules also have broad antibacterial effects on Gram-negative and Gram-positive. This molecule is able to neutralize lipopolysaccharides, and has a synergistic antibacterial effect with defensins, and is a chemotactic agent for neutrophils, monocytes, and T cells using *formyl peptide receptor-like 1 (*FPRL-1) .[7]

Defensin

Mammalian defensins consist of non-glycosylated peptides and arginine is the primary cationic residue. Defensin has a molecular mass of 3.5-6 kDa and contains six cysteine residues which form three intramolecular disulfide bonds. In humans, there are two types of defensins, namely α-defensin and β-defensin[8]

It is known that α-defensin has a chain length of 29-35 amino acids, with a characteristic disulfide chain located between 1-6, 2-4, and 3-5 cysteines. There are four α-defensins in humans that are expressed in neutrophil granules, and are called *human neutrophil peptides* (HNP) -1 to -4. 6 For example, if bacteria are present, defensins 1-3 can increase the expression of *tumor necrosis factor* (TNF) -α and interleukin-1 (IL-1) in human monocytes. It is known that α-defensin can suppress the expression of vascular cell adhesion-1 molecules in umbilical vascular endothelial cells activated by TNF-α. [9]

The β-defensin molecule contains three disulfide chains located at cysteines 1-5, 2-4, 3-6. There are four β-defensins in humans that are best known, namely *human ß-defensin*-1 to -4 (HBD-1, HBD-2, HBD-3, HBD-4), which are found in various cell types, including epithelial cells and mononuclear cells in peripheral blood. The nature of β-defensin has *broad-spectrum* antimicrobial activity and has the added function of cellular immunity. For example, HBD-2 binds to CCR6 and is chemotactic in immature dendritic cells and memory T cells. In addition, HBD-2 also increases histamine release and prostaglandin D2 production in mast cells.[4]

3. Amp In Atopic Dermatitis

Atopic dermatitis (AD) is an inflammatory skin disease characterized by xerosis cutis, pruritus, and erythematous lesions with increased *trans epidermal waterloss*. New insights into the pathophysiology of this disease refer to the role of structural abnormalities of the epidermis in relation to immune dysregulation. Several studies analyzing AMP in the skin lesions of AD patients

showed a contrast to psoriasis, rosacea, and acne vulgaris. In AD patients, the characteristic expression of AMP is less, especially cathelicidins LL-37 and HBD-2.[10]. There is an inverse correlation between the severity of inflammatory skin disease and the level of AMP production. To support this hypothesis many studies have concentrated on AD patients. It is hypothesized that the increased susceptibility of AD patients to S. aureus superinfection arises from impaired AMP expression. The study revealed that the expression of HBD-2, HBD-3, and LL-37 was lower in the skin of AD patients when compared to psoriasis vulgaris.[11] Most of the AD skin infections were dominated by the pathogen *S. aureus*. Nearly 90% of AD patients show *S. aureus* colonization, and only 5-30% colonization of the organism is found in the control population.[12]

The most likely molecular explanation is from studies showing that HBD-2 induction in *cultured human keratinocytes* (keratinocytes HaCaT) is inhibited by the Th2 cytokines IL-4 and IL-13. These findings suggest that AMP deficiency in AD will lead to increased bacterial colonization and infection of DA patients.[13] There is a hypothesis that the Th2 cytokines IL-4 and IL-13 cause low expression, because they inhibit the expression of HBD-2 and HBD-3 on keratinocytes. This observation is important because HBD-3 is an important AMP form of keratinocytes that control the growth of *S. aureus* in the skin.[12] This hypothesis is also supported by another study reporting *microarray* data, showing that gene expression encodes the *innate* immune response to HBD-2, IL-8. and *inducible NO synthetase* (iNOS) decreased in AD patients versus psoriasis. Immunohistochemical and polymerase chain reaction (PCR) studies have shown reduced HBD-3 expression in AD patients compared with psoriasis. Increased levels of IL-13 are associated with decreased levels of HBD-3, and cell culture studies have shown inhibition of TNF-α and IFN-γ induction that induces expression of HBD-2 and HBD-3 genes by Th2 cytokines IL-4 and IL-13 (**Fig. 1**).[13]

Scratching due to itching, which is the main symptom in AD patients, causes skin lesions in AD patients. A decrease in the production of LL-37 expression will occur in the skin lesions of AD patients. On the other hand, the damaged skin defenses will lead to increased immune reactivity of HBD-2 and HBD-3 and secretion of RNase 7. So the conclusion is that damage to skin defenses can trigger AMP in DA skin.[11]

Overall, the role of AMP in DA still needs research and can still be developed. There is evidence that AMP is induced in the skin of AD. Several studies have suggested that the induction, release and movement of some AMP in AD may not reach levels suitable for controlling the microbial colonization of AD skin. In particular, the enhancement of the function of some AMP immunoregulators and the impact on the clinical condition of the skin is unclear. So that further research is needed to clarify the role of AMP in DA.[14]

4. Amp In Psoriasis

Psoriasis vulgaris is an inflammatory skin disease characterized by histological changes including abnormal epidermal proliferation and cellular infiltrates including neutrophils and T cells. Abnormalities in keratinocyte function in psoriasis are the overproduction of AMP. In psoriasis lesions, overexpressed AMPs include cathelicidin, β-defensin.[15]

Although considered an autoimmune disease, the trigger for the induction of inflammation in psoriasis remains uncertain. Recent studies have found that *human cathelicidin peptide* LL-37 allows *self*-DNA response by *plasmacytoid dendritic cells* (pDC), thereby inducing psoriasis activation. In psoriasis skin there are lots of pDCs that express TLR9, which are intercellular receptors that can recognize viral and microbial nucleic acids present in the endosomal. Human

DNA cannot activate pDC, but in psoriasis this tolerance is damaged. Cathelicidin LL-37 converts non-stimulatory *self*-DNA from keratinocyte apoptosis in psoriasis skin, to a potent trigger of pDC activation by forming an LL-37 / DNA complex which is delivered into pDC, to stimulate TLR9 activation. In response, pDC produces IFN-α, thereby initiating autoimmune T cell activation, resulting in skin lesions. These results indicate a basic role of cathelicidin in activating psoriasis skin inflammation.[16,17]

In psoriasis skin almost all AMP is increased, such as β-defensin HBD-2, HBD-3 cathelicidin LL-37, psoriacin, RNase 7. This overexpression of AMP is followed by synergistic interactions which are the important reason for the low susceptibility to infection in psoriasis skin. Although the mechanism of AMP induction in psoriasis skin is not clear, there appears to be a strong association with elevated cytokines IL-1β and IL-6, as well as IFN-α and –γ. This hypothesis was also confirmed by induction of cathelicidin LL37 by IFN-α **(Figure 5)**.[10]

5. Relationship of Amp With Atopic Dermatitis And Psoriasis Therapy

Cells protected by extracellar biofilm are highly resistant to antimicrobials and are a major cause of chronic infection. About 80% of human bacterial infections are related to biofilms. The main obstacle of AMP against biofilms is the possibility of electrostatic interactions between the peptide cations and the negative charge of the biofilm matrix. This relationship will inhibit or stop AMP from reaching the biofilm cells.[18]

Superantigen *S. aureus* activates keratinocytes, induces release of proinflammatory cytokines and exacerbates AD. Due to these damaging effects of *S. aureus*, researchers are looking for ways to suppress bacterial growth, which is important in treating AD. There are several studies reporting the use of topical antibiotics can improve clinical severity. However, several other studies showed no significant effect[14]

The use of antibiotics and antiseptics has been widely applied in the treatment of AD. As one of the functions of the skin defense system, it is known that AMP expression is lacking in AD patients, thus affecting the ability to eradicate pathogens. With the use of antibiotics and / or antiseptics, it is known that they work synergistically so that they can help AMP function in reducing microbial colonization so that there is clinical improvement.[13,17]

The opposite situation occurs in the skin of psoriasis patients. Research shows the production of AMP including LL-37 and HBD-2 in psoriasis lesions is increased resulting in lower skin infection rates when compared to DA skin lesions.[15] Psoriasis skin lesions are rarely complicated by recurrent bacterial, viral, or fungal infections. Only 7% of skin lesions in psoriasis patients had bacterial or viral infections, compared to 30% of skin lesions in AD patients. The combination of LL-37 and HBD-2 exhibits synergistic antimicrobial activity and is therefore effective in eradicating microbial colonization.[16] Several studies have shown an association between psoriasis and *S. aureus* colonization, but no strong evidence has been found to support the use of antibiotics to treat psoriasis or to prevent disease. So that the use of antibiotics is not recommended in psoriasis patients[17]

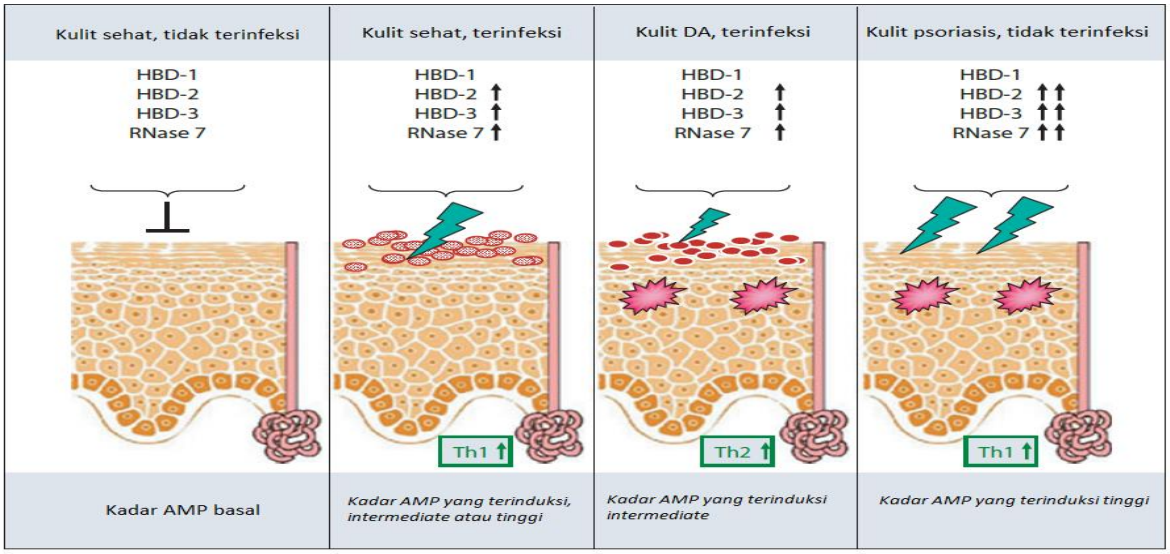

Figure 4. Expression and function of AMP in healthy skin, AD, and psoriasis. In healthy, uninfected skin, the expression of AMP HBD 1-3, RNase 7 in basal levels. After infection of healthy skin by *S. aureus*, the expression of AMP HBD-2, HBD-3, and RNase 7 induction increases with intermediate to high levels, resulting in pathogen destruction. On the DA, AMP HBD-2, HBD-3, and RNase 7 shears were induced with *intermediate* levels. The level of AMP-induced expression on the skin of AD was not able to kill the *S. aureus* pathogen infection. On the other hand, in psoriasis skin, the level of AMP-induced expression was high so that it succeeded in providing protection against pathogenic colonization

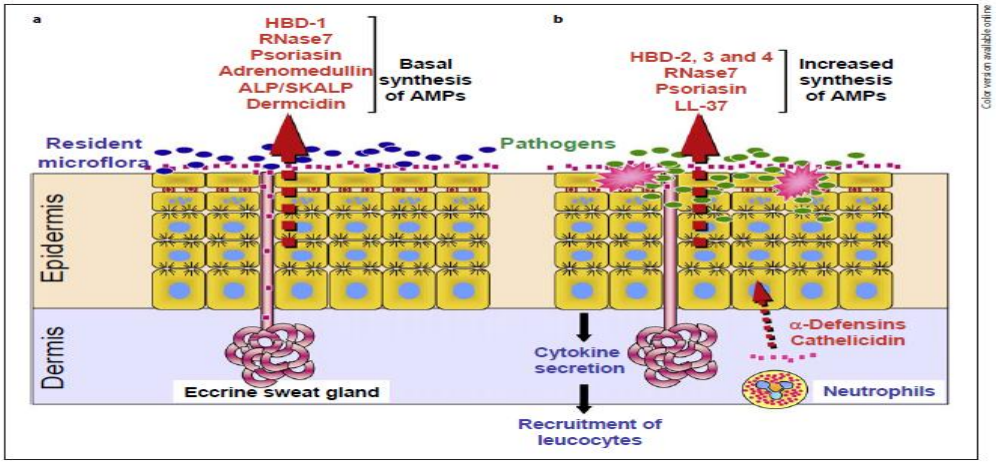

Figure 5. Illustration of the protective function of AMP in normal skin (a), in infectious / inflammatory skin such as psoriasis (b).[10]

6. Summary

Antimicrobial peptide has the ability to kill pathogenic microbes, and also indirectly strengthen the host defense system. Against the backdrop of the rapidly increasing resistance to conventional antibiotics worldwide, efforts to research AMP in the clinical setting are also increasing. The increased susceptibility of AD patients to *S. aureus* superinfection arises from impaired AMP expression. The study revealed that the expression of HBD-2, HBD-3, and LL-37 was lower in the skin of AD patients when compared to psoriasis. Lack of AMP in AD will lead to increased bacterial colonization and infection of AD patients. With the use of antibiotics and / or antiseptics, it is known that they can work synergistically to help AMP in reducing microbial colonization so that there is clinical improvement. The opposite

situation occurs in the skin of psoriasis patients. Research shows the production of AMP including LL-37 and HBD-2 in psoriasis lesions increases resulting in low skin infection rates. There is no strong evidence to support the use of antibiotics to treat psoriasis or to prevent disease. This therapeutic aspect is useful in determining the appropriate topical therapy steps in AD and psoriasis.

REFERENCES

1. Schawrz T. Immunology. In: Bolognia JL, Schaffer J V, Cerroni L, editors. Dermatology. 4th ed. New York: Elsevier Inc; 2018. p. 101.
2. Schauber J, Gallo RL. Update review Antimicrobial peptides and the skin immune defense system. J allergy Clin Immunol. 2008;122(Fig 1):261–6.
3. Robert L. Modlin, Lloyd S. Miller Christine Bangert & GS. Innate and Adaptive Immunity in the Skin. In: Goldsmith SA, Katz SI, Gilchrest BA, Paller SA, Leffell DJ WK, editor. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: McGraw-Hill; 2012. p. 106–8.
4. Braff MH, Bardan A, Nizet V, Gallo RL. Cutaneous defense mechanisms by antimicrobial peptides. J Invest Dermatol. 2005;125(1):9–13.
5. Mahlapuu M, Håkansson J, Ringstad L, Björn C. Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. Front Cell Infect Microbiol
6. Guaní-Guerra E, Santos-Mendoza T, Lugo-Reyes SO, Terán LM. Antimicrobial peptides: General overview and clinical implications in human health and disease. Clin Immunol
7. Kumar P, Kizhakkedathu JN, Straus SK. Antimicrobial peptides: Diversity, mechanism of action and strategies to improve the activity and biocompatibility in vivo. Biomolecules. 2018;8(1).
8. Smet K De, Contreras R. Human antimicrobial peptides : defensins , cathelicidins and histatins. Biotechnol Lett. 2005;27:1337–8.
9. Bardan A, Nizet V, Gallo RL. Antimicrobial peptides and the skin. Expert Opin Biol Ther
10. Schröder J. Antimicrobial Peptides in Healthy Skin and Atopic Dermatitis. Allergol Int
11. Kopfnagel V, Harder J, Werfel T. Expression of antimicrobial peptides in atopic dermatitis and possible immunoregulatory functions. Curr Opin Allergy Clin Immunol. 2013;13(5):531–6.
12. Schittek B. The Antimicrobial Skin Barrier in Patients with Atopic Dermatitis. 2011;41:54–67.
13. Morizane S, Gallo RL. Antimicrobial peptides in the pathogenesis of psoriasis. J Dermatol. 2012;39(3):225–30.
14. Lande R, Chamilos G, Ganguly D, Demaria O, Frasca L et al. Cationic antimicrobial peptides in psoriatic skin cooperate to break innate tolerance to self-DNA. Eur J Immunol. 2014;1–27.
15. Peric M, Koglin S, Kim S-M, Morizane S, Besch R, Prinz JC, et al. IL-17A enhances vitamin D3-induced expression of cathelicidin antimicrobial peptide in human keratinocytes. J Immunol. 2008;181(12):8504–12.
16. Elfatoiki FZ, El Azhari M, El Kettani A, Serhier Z, Othmani MB, Timinouni M, et al. Psoriasis and staphylococcus aureus skin colonization in Moroccan patients. Pan Afr Med J. 2016;23:1–5.
17. Dogan B, Karabudak O, Harmanyeri Y. Clinical trial Antistreptococcal treatment of guttate psoriasis : Int J Derm. 2008;14–6.
18. di Luca M, Maccari G, Nifosí R. Treatment of microbial biofilms in the post-antibiotic era: Prophylactic and therapeutic use of antimicrobial peptides and their design by bioinformatics tools. Pathog Dis. 2014;70(3):257–70.