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Antimicrobial Peptides in Atopic Dermatitis: Review Article

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ABSTRACT

Background: Atopic dermatitis (AD) is a common chronic inflammatory skin disease. Skin-produced antimicrobial peptides (AMPs) have a central function in the defense against microbes. Human β-defensins (HBD) are found mostly in epithelial surfaces, such as skin. Recent studies demonstrated that AD cases displayed minimal levels of human β-defensin-2 (HBD-2) in their skin biopsies.

Objective: This article aimed to throw the light on antimicrobial peptides in atopic dermatitis.

Methods: Data were obtained from online papers, review articles, and studies on PubMed, Google Scholar, and Science Direct. We searched for Atopic dermatitis, Erythema, Excoriation, Anti-microbial peptides, β-defensins. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from October 2002 to August 2023 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: There is a possible relation between B-defensin and pathogenesis of atopic dermatitis. Also, there is a significant relationship between B-defensin and disease severity (SCORAD). So, B-defensin can be utilized as a promising marker in the context of AD severity.

Keyword: Atopic dermatitis, Erythema, Excoriation, Anti-microbial peptides, β-defensins, Severity Scoring of Atopic Dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a frequent chronic inflammatory skin lesion. It usually affects children, however adults may also be affected [(1)].

AD could be detected in about 20% of children and 6% of adults in developed nations [(2)]. Its pathogenesis is complicated and includes several mechanisms such as defective epidermal barrier, genetic background, altered microbiota, and environmental triggers [(3, 4)].

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are a main element of innate immunity and have a central function in the body's defense against microbes, such as bacteria, viruses, and fungi [(5, 6)].

Relationship between AMPs and AD pathogenesis

Much research has suggested that alterations in the expression and function of AMPs may contribute to AD pathogenesis. Here are some key points regarding the association between AMPs and atopic dermatitis [(7-11)]:

- **Deficiency of AMPs:** People with atopic dermatitis often exhibit diminished concentrations of AMPs, which include cathelicidins and β-defensins, in their skin. This deficiency may compromise the skin's barrier functions, making it more susceptible to colonization and infection by pathogenic microorganisms.
- **Skin microbiome dysbiosis:** Atopic dermatitis is associated with alterations in the skin microbes, featured by an overgrowth of pathogenic bacteria and a decrease in beneficial bacteria. AMPs help keeping the equilibrium of the skin microbiome by controlling the growth of microorganisms. Reduced levels of AMPs in AD might participate in dysbiosis and the persistence of pathogenic bacteria.
- **Impaired barrier function:** AMPs possess direct antimicrobial activity and have a central function in keeping normal skin barrier functions. They help regulate epidermal differentiation, the wound healing process, and the formation of lipids that participate in the skin's barrier integrity. Deficiencies in AMPs can disrupt the barrier functions, causing an increase in transepidermal water loss (TWL) and increased susceptibility to allergic and irritant agents.
- **Inflammatory response:** AMPs have immunomodulatory properties and can regulate the inflammatory response. Reduced concentrations of AMPs in AD may lead to exaggerated inflammatory responses, characterized by the discharge of proinflammatory cytokines and chemokines that contribute to the chronic inflammation seen in AD.
- **Genetic factors:** Genetic variations in genes encoding AMPs, which include the cathelicidin gene (CAMP) and β-defensin genes (DEFB1 and DEFB4), have been accompanied by an increased risk of developing AD. These genetic variations can affect the expression, structure, or function of AMPs, potentially influencing the susceptibility to AD.

(1) Defensins

Preceding research has demonstrated a reduction in both HBD-2 and HBD-3 concentrations in

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the skin biopsies of AD cases in comparison with psoriasis vulgaris (PV) cases [12, 13].

(2) Cathelicidins

With regard to AD cases, AD lesions were accompanied by a significant reduction in cathelicidin concentration. In addition, cathelicidin level is accompanied by exacerbation of AD infection and linked to the resistance to skin infections caused by staphylococcus aureus [12].

(3) Psoriasin

It is well-identified that psoriasis formation could be reinforced after affection of the skin barrier functions [14].

(4) Dermcidin

Atopic dermatitis (AD) cases were associated with a significant reduction in dermcidin concentration in the sweat, making them more liable for skin infections, and altered colonization in such cases could be accompanied by a reduction in AMPs in the sweat.[15].

(5) Ribonuclease 7(RNase 7)

There was upregulation of RNase7 expression among AD cases as demonstrated in their skin biopsies compared to both normal and PV subjects [14].

Effect of atopic dermatitis treatment on AMPs

Preceding research recorded that AMP expression could be adjusted by ceramide-dominant emollient application in AD cases [16]. As a result, the application of a ceramide-dominant emollient restores skin barrier and improves the AMP barrier in AD cases and is recommended by a lot of treatment protocols in terms of AD management [17-19].

DEFENSINS

Definition: Defensins are broadly distributed in both humans and animals involved in host defense or AMPs and have antimicrobial activity and/or immune signalling activities. In addition, they have antibacterial, antifungal, and antiviral activities [20, 21].

Structure: Defensins are a category of cationic and Cysteine-rich proteins with eighteen–forty five amino acids (two–five kilodalton) with preserved 3D structures: Evident beta-sheets stabilized by three disulphide bonds [22].

Classification: According to disulphide topology, defensins present in mammals are categorized into three families, alpha, beta, and theta. In terms of human beings, they contain alpha and beta-defensins. On the other hand, theta-defensin, with a distinctive circular configuration stabilised by 3 parallel disulphide bonds, are only demonstrated in white blood cells (WBCs) of rhesus macaques [23].

Types of human defensins

Human organism:

The human body has seventeen peptides belonging to the defensin family, which have been identified as elements of innate immunity, viz. six alpha-defensins (DEFA-1–4, DEFA-5 and DEFA-6) and eleven beta-defensins (DEFB-1–6 and DEFB-25–29). The primary function of such peptides was mostly reliant on their antimicrobial activities against pathogens [24].

Table (1): The names of human defensin genes and peptides, together with their expression sites and functions [24]

Gene	Protein	Expression site	Functions
DEFA1B	HNP-1	a-Defensin Neutrophils, Paneth cells (specialized secretory epithelial cells in the gut), tracheal epithelium, saliva, gum, tongue, buccal mucosa, and submandibular gland (SMG)	Antimicrobial activity against Gram-negative (GNB) and Gram-positive bacteria (GPB) and fungicidal and antiviral activities
DEFA2		Neutrophils, Paneth cells, tracheal epithelial lining, saliva, gums, tongue, buccal mucosa, and SMG	Antimicrobial activity against GNB and GPB. Antifungal and antiviral activities
DEFA3	HNP-3	Neutrophils, Paneth cells, saliva, gums, tongue, buccal mucosa, and SMG	Antibiotic, fungicidal and antiviral activities, antimicrobial activity against GNB and GPB
DEFA4	HNP-4	Neutrophils, Paneth cells, tracheal epithelial lining, saliva, gum, tongue, buccal mucosa, and SMG	Antimicrobial activity towards GNB, and to a minor degree (partially) towards GPB and fungi. Potential protection against the development of HIV-I infection
DEFA5	Defensin-5	Vagina, cervical mucosa, saliva, gums, tongue, buccal mucosa, SMG neutrophils, Paneth cells of the small intestine (SI), and nasal and bronchial, and tracheal epithelial cells	Antimicrobial activity towards GNB and GPB. Killing microbes by interfering with the permeability of their plasma membranes
DEFA6 (DEF6)	Defensin-6 (a-defensin6)	Saliva, gums, tongue, buccal mucosa, SMG, neutrophils, Paneth cells, and tracheal epithelial lining	Minimal antimicrobial activity towards GNB and GPB. Could carry potential defense against HIV-1 infection
DEFB1	b-Defensin 1	SI, colonic, pancreatic and renal tissues, prostate, vagina, the ectocervix, endocervical mucosa, uterus, placenta, thymus, bronchi, breast, parotid gland, buccal mucosa, tongue or gum, macrophages acquired from cases with bronchopneumonia, and plasma	Has bactericidal effect
DEFB4A	b-Defensin 4A	Epithelium of trachea, kidneys (in addition foetal kidneys), bladder, uterus, prostate, stomach, SI, hepatic and pancreatic tissues, thymus, bone marrow (BM), WBCs, keratin producing cells, and the skin	Antibacterial action
DEFB103A	b-Defensin 103	Keratinocytes, tonsils, skin, oesophagus, placenta, trachea, uterus, kidney, thymus, adenoid, pharynx, tongue, myocardium, foetal thymus, skeletal muscles, gums, tongue, buccal mucosa, dental cells	Antimicrobial activity against GPB and GNB and some fungal infections. Killing vancomycin-resistant E. fecium and multi-resistant S. aureus.
DEFB104A (DEFB104, DEFB4)	b-Defensin 104	Neutrophils, epithelium of kidneys, lungs, uterus and thyroid, gastric antrum, uterus, neutrophils, , and kidneys	Antimicrobial action. Synergistic action with lysozymes
DEFB105A	b-Defensin 105	Testis	Antibacterial action
DEFB106A	b-Defensin 106	Epididymis and lungs	Antibacterial action
DEFB127	b-Defensin 127	None	Antibacterial action
DEFB125	b-Defensin 125	None	Antibacterial action
DEFB128	b-Defensin 128	None	Antibacterial action
DEFB129	b-Defensin 129	Testis	Antibacterial action

Functions of defensins:

The most common function of defensins is their antibacterial action, as they have antiviral and antifungal properties. In addition, they have immunomodulatory action in the inflammation and cancer development [25, 26].

Being positively charged peptides, they could attack the microbe and suppress bacterial growth by several mechanisms, such as producing holes in the negatively charged bacterial membrane [27], and suppressing bacterial wall synthesis [28].

In addition, they could neutralise bacterial discharged toxins to decrease bacterial infection [29]. The antibacterial activity of defensins mostly involves three stages: (I) through electrostatic attraction, the positively charged defensins attach to the negatively charged bacterial membrane; (II) defensin molecules interact with phospholipid heads and water molecules on the bacterial plasma membrane, forming a channel, which considerably raises the biological membrane permeability; and (III) bacterial inner cell content leaking happens [22, 30].

With regard to the antiviral effect of defensins, they could directly suppress the viral infection, and this antiviral activity is mainly reliant on both defensin concentration and the tightness of disulphide bonds. Of note, time, pH, ionic strength, and temperature are also factors that could affect the antiviral activity. The optimum defensin activity could be reached in neutral and low ionic strength situations [31].

Regulation of defensin expression:

The pattern recognition receptors present on the surface of defensin-expressing cells are responsible for defensin formation after their stimulation by microbial products (such as protein, lipid, DNA, and RNA) [32]. The TLR, NOD-like receptors, RIG-I-like receptors, and C-type lectin receptors are examples of the pattern recognition receptors [33].

Applications:

Till now, the prevalent distribution of antibiotic resistance needs the emerging of novel antimicrobials. Therefore, defensins could play a promising role in this context. Additionally, it has been demonstrated that defensins have prominent antibacterial activity towards a broad spectrum of microbes. Moreover, defensins could improve the efficacy of traditional antibiotics [34].

Defensin mimetics, fully synthetic, non-peptide, minor molecules, simulate defensins in shape and action. Comparable compounds, which include brilacidin, are emerging as antibiotics [35].

CONCLUSION

There is a possible relation between B-defensin and pathogenesis of atopic dermatitis. Also, there is a significant relationship between B-defensin and disease severity (SCORAD). So, B-defensin can be utilized as a promising marker in the context of AD severity.

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