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The Role of Cathelicidin in Dermatology Skin

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Abstract

Acne, Atopic Dermatitis, Psoriasis and Rosacea are examples of chronic inflammatory skin conditions. One characteristic of many skin disorders is the dysregulation of innate immunity in the skin. Acne, Atopic Dermatitis, Psoriasis, and Rosacea all have problems with the expression, function, or processing of the key innate immune effector molecule in the skin, cathelicidin LL-37. Cathelicidin induction can be altered to treat Acne and Atopic Dermatitis, which lessens the efficiency of the antimicrobial barrier. However, cathelicidin is overexpressed in Psoriasis and Rosacea. The most recent research on cathelicidin LL-37's involvement in the etiology of inflammatory skin disorders will be included in this review. Since cathelicidin LL-37 may one day be employed as a therapeutic target, many cutting-edge therapy methods for the disease will be discussed.

Keywords: Antimicrobial Peptide, Cathelicidin, Dermatology Skin

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1 Introduction

1.1 AMPs in Skin

The protecting of our body from harmful environmental pressure like microbial infection is one of the skin's most crucial roles [1]. Human skin has a chemical defense system based on the generating microbial lipids and proteins and acting as a physical barrier. Antimicrobial peptides (AMPs) are producted by human skin to protect it from the potentially invasive germ [2]. Antimicrobial peptides (AMPs) serve as the body's first line of defence against bacteria, viruses, and fungi [3] and some of them control the processes of regeneration [4]. The majority of antibacterial AMPs are cationic AMPs that target bacterial cell membranes and break down the lipid bilayer structure, making them the most thoroughly investigated AMPs to date. Most of these AMPs have hydrophilic and hydrophobic domains and are amphipathic as well. AMPs can kill bacteria at low doses without affecting the integrity of the membrane. These AMPs kill bacteria by obstructing critical intracellular activities, including protein synthesis and DNA replication, rather than directly interacting with membrane [5]. Through enzymatic or nonenzymatic disruption, AMPs act as natural antibiotics by concentrating on crucial cell wall or cell membrane structures of microbes's. Additionally, AMPs can act as strong immune regulators by blocking or boosting Toll-like receptor (TLR) signaling and communicating with chemokine receptors [6]. Other actions of AMPs include anti-inflammation, lipopolysaccharide (LPS) or/and lipoteichoic acid (LTA) binding, bacterial agglutination, and so on. These effects are in addition to the well known antibacterial capabilities [7]. While studies have suggested that AMPs may actively contribute to different skin illnesses' etiology, AMPs do protect our skin. There is growing evidence that AMPs play a pathophysiological role in psoriasis, atopic dermatitis (AD), acne vulgaris, rosacea, and wound healing. Due to their unique mechanism of action, AMPs are better able to influence host immune responses than conventional antibiotics they are less likely to result in microbial resistance in the short term. AMPs may be a contender for treating skin conditions related to dermatology [8].

1.2 The Role Cathelicidin in Skin

One Significant family of AMPs in the skin is the cathelisidin [1]. Cathelicidin has been found in various mammals, and the only cathelicidin type found in humans is LL-37 [9]. The gene expression of cathelicidin, primarily expressed by neutrophils and epithelial cells, can be induced by bacterial product and inflammatory stimuli, and it can be controlled by vitamin D3 [10]. These AMP families' main job is to shield the skin from invasion by invading microorganisms. The charge and structure of the AMPs affect how bacteria are killed. Because AMPs are cationic, thet interact with the anionic elements of bacteria, fungi, and viruses to allow the microbial membrane to pass through them. The ion gradient is upset when the membrane becomes permeable, which causes cell lysis [11]. Epidermal barrier components, such AMP cathelicidin and filaggrin barrier protein, significantly control bacterial invasion. By transactivating the epidermal growth factor receptor and causing keratinocyte migration, LL-37 contributes to the healing of wounds, reepithelization, and scarring [12]. In addition to its innate immune action, LL-37 can to create holes in bacterial cell walls [13]. When LL-37 reaches the exterior layer of the bacterial cell wall, it forms complexes with various of molecules, reaching a concentration threshold that allows monomers to be transported to the periplasm and the internal layer's surface. As a result, holes migh develop and cytoplasmic material can seep out into the extracellular environment [14] by interacting with the membrane of certain fungsi and immediately causing reactive oxygen species (ROS), LL-37 also had antimycotic effects. This helps the vesicle membrane separate and quickly disintegrate [15].

Cathelicidin could work in skin as an alarmin, when there are circumstances that lead to skin inflammation, LL-37 expression is quite high. Wuth a particular emphasis on their effects on Toll-Like Receptor (TLR) activation, cathelicidin have been found to be useful for the

detection of damage and microbe associated molecular patterns [16]. Through epidermal growth TLR4 and TLR9 [17], LL-37 triggers biological responses that lead to the activation of proinflammatory cytokines and chemokines, such IL-8 and IL-6, in monocytes, mast cells, and epithelial cells [18]. As a result, cathelicidin peptides regulate inflammatory cascade, and the host cells and tissues that both produce and are impacted by cathelicidin determine the consequances of cathelicidin stimulation [19]. Dermatoses are made worse by danger signals like infection and damage, and the Koebner Phenomenon is the production of new lesions by injury [19]. Through keratinocytes TLR2 activation, anger signals cause the epidermis to generate cathelicidin [20]. Consequently, although the activities and responsibilities of cathelicidin peptides vary depending on the kind of dermatosis, cathelicidin plays a part in the beginning of inflammatory cascade in various disorders [19].

2 Methods

It is a study-related descriptive review, and information was gathered from several website and electronic database sources, including Google Scholar, PubMed, Research Gate amd Scopus. The role of AMP's in the skin has been the subject of studies and other materials from 2005 to 2022. Based on the data entry from that the researcher created, specific information is collected from the literature. Only English-language article and/or research were included in the review search.

3 Results and Discussions

3.1 The Role of Cathelicidin in Acne

Acne is a long-lasting inflammatory condition of the pilosebaceous unit that is marked by scarring and keloids that last the remainder of one's life, as well as seborrhea, comedones, papules, pustules, nodules, and cysts [21]. It is a complex illness brought on by the interaction of genetic and environmental elements [22]. The name of the bacteria that causes ance and causes acne infection on human skin is *Propionibacterium acnes (P.acne). P. acnes* secretes a number of exogenous proteases that can trigger the production of inflammatory mediators like cathelicidin, IL-1a, IL-8, tumor necrosis factor-a, and various matrix metalloproteinases (MMP) by activating the protease-activated receptor-2 on keratinocytes. Cathelicidin play a role in the development of acne in a number of ways. Through preventing *P. acnes* from growing, cathelicidin may help treat acne. When it comes to acne vulgaris, AMPs can either protect the skin by inhibiting *P.acne* or cause inflammation by serving as signaling molecules [23]. AMP with activity against acnes in in vitro settings is cathelicidin LL-37 has been discovered that LL-37 has anti-inflammatory qualities and restricts bacterial development with regard to the pathogenesis of acne. For instance, LL-37 can lessen the synthesis of TNF by macrophages that have been triggered by bacterial components [24]. In addition, cathelicidin has the potential to treat acne vulgaris by directly killing bacteria and preventing NF-B activation caused by Toll-Like Receptor 2 (TLR2) [25]. In 2021, Wu. reported the antimicrobial peptide that Cath-MH was discovered in the frog *Microhyla heymonsivagt's* skin. With a MIC value of roughly 1,56 µM, Cath-MH was discovered to kill *P.acnes* through a membrane disruption mechanism. Additionally, it displayed agglutination capabilities toward *P.acnes* LTA and LPS were both able to bind to Cath-MH, which then prevented LTA/LPS from stimulationg TLR2/4 expression and reduced the inflammatory response in RAW 264,7 cells. As anticipated, Cath-MH reduced the development of edema and the infiltration of inflammatory cells in the acne mice model while also inhibiting *P.acnes* growth and the release of inflammatory cytokines in vivo [25]. With its substantial *P.Acnes* inhibitory action and strong anti-inflammatory properties, Cath-MH has the potential to be a cutting-edge treatment for acne vulgaris. In 2019, Liggins. in response to infection, a subpopulation of dermal fibroblasts quickly differentiate into adipocytes and manufacture the cathelicidin antimicrobial peptide gene Camp. Vitamin A and other retinoids can help treat skin condition including cystic acne while inhibiting adipogenesis [26].

Numoerous studies show that Vitamin D stimulates the expression of the human cathelicidin LL-37 [27]. Vitamin D induces and increases the expression of LL-37 in sebocytes, which has antibacterial properties against *P.acne.* Vitamin D derived LL-37 may be useful for treating acne patients. This would only be

effective, though, if LL-37's antibacterial and anti-inflammatory qualities outweighed their pro-inflammatory counterparts, and Vitamin D also be a treatment option for acne [28]. The bacterial AMP known as bacteriocins is another potential family of antibiotic compounds to treat acne. Numerous investigations found that different bacteriocins had excellent anti *P.acne* action, indicating that they could be an alternate class of antibiotics to inhibit *P.acne* development. In fact, compared to a placebo lotion, a lotion containing an Enterococcus faecalis-derived bacteriocin dramatically decreased the inflammatory acne lesion [29].

Retinoids are helpful for bacterially-exacerbated skin conditions including acne [26]. It is believed that retinoids ability to reduce sebum production and change epidermal function, rather than having an impact on the immune system's ability to defend against bacterial growth, is the mechanism by which they are therapeutically effective in treating acne, a condition that is partially caused by the bacterium acne [30]. In response to bacterial skin infection, dermal fibroblasts of the preadipocyte lineage will rapidly proliferate locally and differentiate [31]. The expression of the cathelicidin gene CAMP, an antimicrobial peptide (AMP) that peaks during this phase as the local adipocytes develop, increase as a result of this process, which is known as reactive aipogenesis, since adipogenic process dysfunction reduces total skin cathelicidin expression and worsens bacterial infection, reactive adipogenesis is cruacial for effective innate immune defence [26],[32].

3.2 The Role of Cathelicidin in Atopic Dermatitis

Atopic Dermatitis (AD) is a common chronic skin condition that often first manifests in childhood and eventually goes away ot gets better with age, however it can occasionally oersist into adulthood with recurring symptoms [33]. The complex and heterogeneous condition known as atopic dermatitis is influenced by a number of variables, including host genetics, aktered skin barrier function anf structure immunological abnormalities, and environmental factors, such as exposure like *Staphylococcus aureus* [34]. Atopic dermatitis (AD) is distinguished by the intricate interaction between breakdown of the skin barrier and immunological dysregulation [35]. Although AMP synthesis in atopic dermatitis skin is higher than in healthy, noninflamed skin, it is insufficient to stop *Staphylococcus aureus* from proliferating. AD skin is more prone to colonization and infection by pathogens such *Staphylococcus aureus* and the herpes virus due to its relative scarcity of AMPs [36]. Additionally, AMP dysregulation in AD alters the microbial makeup of AD skin in comparison to normal skin by erakening the selection pressure on skin microbiota [37]. FLG is a crucial part of the epidermal differentiation complex in the epidermis of human skin. The function of FLG in the barrier-based pathogenesis of AD has been thoroughly studied since the initial publication in 2006, which described a loss-of-function mutation in the gene encoding the filament aggregating protein filaggrin (FLG). Addictionally, FLG mutations raise the probability of AD developing early, which could worsen the condition and make it more persistent [33]. In addition, reduced expression of AMPs such cathelisidin and defensins was seen in lesional skin in atopic dermatitis, leading to the first hypothesis that atopic dermatitis patients had a weak innate antimicrobial barrier [38]. Epidermal barrier components, such as the AMPs Cathelicidin and the filaggrin barrier protein, play a significant role in controlling bacterial entry [39]. In keeping with their function in barrier protection, endogenous antimicrobial peptides (AMPs), such as the human cathelicidin protein, Hcap18 ll-37, are quickly produced in response to injury and infection in human skin. Compared to healthy skin, cathelicidin mRNA transcription induction in response to injury is decreased in atopic dermatitis lesion, because Th2 cythokines including interleukin (IL)-4 and IL-13 which are substantially increased in atopic dermatitis skin, decrease cathelicidin induction in keratinocytes [38]. Since skin wounding from scratching is a defining feature of atopic dermatitis, failing to upregulate cathelicidin in response to injury could reduce the cutaneous antibacterial action in atopic dermatitis skin [40]. The discovery of the vitamin D response element in the cathelicidin promoter and the finding that the conversion of 25-hydroxyvitamin D to the active 1,25 dihydroxyvitamin D by CYP27B1 can take place in keratinocytes and monocytes and is regulated

by Toll-Like Receptor 2 provided significant insight into the mechanism responsible for the production of antimicrobial peptides [41]. Because, increased susceptibility to infection is associated with vitamin D deficiency, and supplementing studie show improved immunity to infection [42]. The expression of CYP27B1 results in the conversion of 25-hydroxyvitamin D to the active 1,25 dihydroxyvitamin D and the consequent induction of cathelicidin when Toll-like Receptor 2 is activated in response to infection or injury [43]. Oral supplementation may give the CTP27B1 enzyme enough substrate to make up for the relative lack and may boost the expression of cathelicidin and defensin in immune cells and tissues, improving barrier performance in atopic dermatitis [42],[44]. Patients who received 4.000 IU/d of oral vitamin D supplementation for 21 days had hinger levels if cathelicidin expression in skin lesions and a marginally higher level in healthy skin [45].

3.3 The Role of Cathelicidin in Psoriasis

Psoriasis is an autoimmune disease of the skin [46]. A chronic immune-mediated inflammatory skin condition known as psoriasis has many phenotypically different subtypes, including plaque, flexural, guttate, pustular, and erythrodermic [47]. The most prevalent from of this condition, psoriasis vulgaris, also known as plaque-like psoriasis, is marked by increased redness, thickness, and scalling of the skin in affected areas [48]. Infection, wounds, obesity, stress, and genetic factors have all been related to an exacerbation of psoriasis, and exposure to specific medicines can cause or exacerbate the condition [49]. The increased synthesis of antimicrobial peptides and protein (AMPs) is one distincitive anomaly of lesional skin in psoriasis [50]. Cathelicidin is highly expressed in psoriasis lesional skin and essential autoinflammatory mediator as well as an antimicrobial peptide in this chronic skin condition [51]. The epidermis of psoriasis plaques contains keratinocytes that are obviously aberrant in many ways and likely impact immunocytes producing inflammatory cytokines and chemokines through influencing or enchancing immune cells, this is trus despite the current focus on T cells in the pathogenesis of psoriasis [17], because peripheral blood and lesional skin have elevated levels of cytokines from the TH1 pathway, such as interferon (IFN), interleukin (IL), and IL-12, psoriasis was initially categorized as a T helper (Th) 1 disease [52]. Antimicrobial peptides and proteins (AMPs) are overproduced by psoriasis keratinocytes, which is one of their irregularities in function [50]. Psoriasis epidermis as well as other inflammatory skin condition, and they hypothesized that this simulation increases the ability of the damaged barrier in the lesions to fligh off microbe [17]. Compared to healthy skin, cathelicidin expression in keratinocytes is higer in psoriasis [53]. This finding could help to partially explain the greater resistance to cutaneous infection that psoriasis patients exhibit. Cathelicidin could work in psoriasis more as an alarmin than an antibacterial [44]. An alarm system in psoriasis, LL-37 stimulates keratinocytes to trigger TLR9 and TLR9 ligand analysis, and plasmacytoid DCs to self indentify DNA through TLR9 [54]. This is how the inflammatory skin condition psoriasis manifest abnormal LL-37 expression. Cathelicidin peptide LL-37 has been discovered as a factor that be in charge of activating cutaneous pDC in the case of psoriasis [53]. It has been proposed that the antimicrobial peptide cathelicidin caises inflammation in psoriasis by enabling plasmacytoid dendritic cells (pDCs) to detect self-DNA through Toll-like receptor 9 (TLR9) [53]. As a result, pDC release IFN- α which triggers the activation of autoimmune T cells and causes skin lesions [55].

The pathogenesis of psoriasis may be influenced by a newly identified subset of Th cells called Th 17 cells, which are identified by the production of IL-17 by CD4+ effector T cells [56], generate the pro-inflammatory cytokines IL-17A and IL-22 as affector molecules. Th 17 cells and cytokines are substantially abundant in skin samples from psoriatic lesions [57]. Cathelicidin are produced in keratinocytes as a result of IL-17A, which is secreted by activated Th 17 cells [58]. Similar to this, neutralizing IL-17A in psoriasis skin T cell supernatants totally prevents the activation of genes that code fot antimicrobial peptide in keratinocytes [59].

Vitamin D has a significant function in this situation [60]. Recent research has shown that vitamin D derivates enhance the clinical state of psoriasis pasient, who have reduced vitamin D levels [61]. Due to its capacity to modulate innate and adaptive immunity as well as its

antiproliferative and prodifferentiative actions on keratinocytes, vitamin D is crucial in the treatment of psoriasis [62]. The epidermal barrier integrity change as a result of a change in vitamin D metabolism, favouring an inflammatory and infectious disease [63]. In addition to preventing changes in immune homeostasis, regulationg the microbial flora, modulating keratinocyte proliferation, and regulating the host's response to infectious disease, vitamin D's role in the pathogenesis of psoriasis is not just a theoretical consideration, it also open up new treatment options [61].

3.4 The Role of Cathelicidin in Rosacea

Rosacea is a persistent, inflammatory skin condition that affects the middle of the face [64]. In terms of phenotypic, rosacea can be divided into four different subtype: popular pustular form, rhinophyma, essential telangiectasia form, and ocular rosacea [65]. New research suggested that Demox spp be a microbe go into remission [66]. Although Demodex mites are frequently found on healthy people's skin, an increasing number is thought to have a pathogenic role in the onset of rosacea [67]. Along with Demodex, various other skin microbes are also crucial in regulating the rosacea related chronic inflammation [65]. By activating a Toll-Like Receptor 2 (TLR2) immune response pathway, the Demodex mite causes angiogenesis and inflammation by increasing the synthesis of the cathelicidin peptide, LL-37 [68].

The keratinocytes, sebocytes, and mast cells secrete antimicrobial peptides (AMP) as part of the innate response. Although it is a crucial line of defense, the expression of these peptides is closy controlled because it can potentially result in tissue damage. There has been research on the dysregulation of the innate immune system in rosacea, including elevated expression of: antimicrobial peptide cathelicidin, toll-like receptor 2 (TLR-2), serine protease kallikrein 5 (KLK5), and matrix metalloproteinases (MMPs) including MMP-2 and MMP-9 [69]. By cleaving KLK5's preproenzyme form, MM-9 activates it, and TLR-2 stimulation on keratinocytes increases KLK5 expression and activity, ehich in turn causes LL-27 to express more strongly. Mast cells be implicated because thay relese both MMP-9 and LL-37 in rosacea sufferers and are elevated in these individuals [70]. Additionally, mast cell are one of the main sources of cathelicidin LL-37, an antimicrobial peptide that has been linked to the etiology of rosacea. The major source of the enzymes that convert cathelicidin to its active form is mast cell, which are one of the main sources of cathelicidin in the skin [71].

Through the Toll-like receptor 2 (TLR-2), various external stimuli, such as ultraviolet rays and microorganisms [72], increase the activity of the enzyme kallikrein-related peptidase 5 (KLK5) in the stratum corneum, which then cleaves the inactive precursor protein cathelicidin to produce tha active LL-37 fragment [73]. As a result, the suppression of kallikrein 5 and cathelicidin production is connected to the machenism of action of various rosacea drug such as invermectin [74], doxycycline [75], the fact that doxycycline, a successful therapy for rosacea symptoms, directly inhibits MMPs supports the idea that MMP-9 is involved in the genesis of the condition, because MMP is involved in rosacea pathogenesis [76], and azelaic acid [69]. In a recent work, we showed that carvedilol inhibited the production of kallikrein 5 and cathelicidin in vitro and decreased TLR2-induced inflammation in macrophages, which are important in the pathogenesis of rosacea in vivo [77]. Treatment for rosacea's flushing and erythema often involves systemic oral beta-adrenergic receptor blokers like carvedilol, whose intial usage was for refractory and chronic symptoms [78]. During the 6 mouth follow-up, oral carvedilol (6.25 mg twice daily) signigicantly reduced the clinical expression of rosacea, as seen by less erythema in red area pictures as judged by VISIA and declining A* value as measured by colorimetry and the IGA score [77]. Carvedilol works in macrophages through the TLR2/KLK5/Cathelicidin pathway to reduce the inflammatory response in rosacea [77],[78].

The disturbance of lipid synthesis and the development of the stratum corneum caused by epidermal inflammation and cathelicidin increased concentration alter the barrier function, favoring the traditional rosacea symptoms including stinging, itching, and burning [79]. These aberrant cathelicidin peptides, which have been linked to

angiogenesis and inflammation, may be part of the pathogenesis of rosacea [64].

Cathelicidin LL-37 expression in rosacea was recently studies because it has pro-inflammatory "alarmin" properties and impacts vascular development [73], because a characteristic of rosacea face dermatitis is an elevated level of the antimicrobial cathelicidin [80]. Cathelicidin LL-27, an antimicrobial peptide that is claved from the 18 KD cathelicidin peptide, is abundantly expressed in the skin of rosacea patients [81].

4 Conclusions

A number of inflammatory skin conditions, including Acne, Atopic Dermatitis, Psoriasis, and Rosacea are characterized bt dysregulated AMP production. Among the significant AMPs discovered in skin is cathelicidin LL-37. As cathelicidin has immunological and antibacterial properties, its expression and processing are dysregulated, which contributes to the development of chronic inflammatory skin disorders. Strategies to affect these processes start to emerge as the regulatory mechanism governing cathelicidin gene control and peptide processing become more understood. Additionally, weel known medicines like topical and systemic medications for dermatology skin by having an influence on cathelicidin. Through their effect on cathelicidin, more studi may uncover new targets and processes that result in creative therapies for dermatology skin condition.

5 Declarations

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5.3 Authors Contributions

The names of the authors listed in this journal contributed to this research.

5.4 Conflict of Interest

The authors declare no conflict of interest

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