

# Antimicrobial peptides: bridging innate and adaptive immunity in the pathogenesis of psoriasis

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## Abstract

Antimicrobial peptides (AMPs) are small molecules produced by a myriad of cells and play important roles not only in protecting against infections and sustaining skin barrier homeostasis but also in contributing to immune dysregulation under pathological conditions. Recently, increasing evidence has indicated that AMPs, including cathelicidin (LL-37), human  $\beta$ -defensins, S100 proteins, lipocalin 2, and RNase 7, are highly expressed in psoriatic skin lesions. These peptides broadly regulate immunity by interacting with various immune cells and linking innate and adaptive immune responses during the progression of psoriasis. In this review, we summarize the recent findings regarding AMPs in the pathogenesis of psoriasis with a main focus on their immunomodulatory abilities.

**Keywords:** Antimicrobial peptides; Psoriasis; Immune response; Inflammation

## Introduction

Antimicrobial peptides (AMPs) are an integral part of the first-line defense of a host against pathogens. AMPs are mainly amphipathic peptides with  $\alpha$ -helical structures and  $\beta$ -sheets linked by disulfide bridges, extended loops, or cyclic configurations.<sup>[1]</sup> AMPs were initially discovered as substances with bactericidal effects derived from neutrophils and stored in secondary granules<sup>[2]</sup>; immune cells and epithelial cells in the skin, gut, and lungs can also secrete AMPs with various functions.<sup>[3]</sup> The majority of AMPs in human skin are expressed in a steady state and are induced in response to stimuli, including injury, tape stripping, and infections, such that the immune response, chemotaxis, wound healing, apoptosis, and angiogenesis are regulated.<sup>[4-6]</sup> Recently, the immunomodulatory effects of AMPs have been reported to be involved in many autoimmune diseases such as rheumatic arthritis,<sup>[7]</sup> Crohn disease,<sup>[8]</sup> and psoriasis.<sup>[9]</sup>

Psoriasis, a common skin disorder, is an autoimmune condition characterized by aberrant innate and adaptive immune responses, in which T cells, keratinocytes, and dendritic cells (DCs) play a central role.<sup>[10]</sup> Psoriasis can be triggered by injury, infections, and mechanical stimulation, especially in patients with a genetic predisposition.<sup>[11]</sup> In this context, many active immune substances, including

AMPs, rapidly increase in concentration in the local skin and initiate the maturation and activation of DCs and T cells with excessive interleukin (IL)-17 expression, resulting in the infiltration of immune cells and an inflammatory cascade. The expression levels of AMPs, including cathelicidin (LL-37),<sup>[12]</sup> human  $\beta$ -defensins (hBDs),<sup>[13]</sup> S100 proteins,<sup>[14]</sup> lipocalin 2 (LCN2),<sup>[15]</sup> and RNase 7,<sup>[17]</sup> are higher in skin lesions and/or sera of psoriasis patients than in those of healthy participants. Thus, lethal infections are seldom observed in the skin lesions of patients with psoriasis. The immunoregulatory functions of AMPs in psoriasis have been highlighted in recent decades. AMPs activate keratinocytes and innate immune cells, including neutrophils, macrophages, and DCs, mainly in a pattern recognition receptor (PRR)-dependent manner; this activation leads to neutrophil and macrophage recruitment, neutrophil extracellular trap (NET) formation, and DC maturation.<sup>[16]</sup> In addition, AMPs modulate adaptive immune responses in psoriasis by directly interacting with T cells as autoantigens.<sup>[17]</sup> Studies have also reported positive associations between AMP expression and specific symptoms such as itch,<sup>[18]</sup> severity,<sup>[19]</sup> and genetic susceptibility<sup>[20]</sup> of psoriasis. In this review, we summarize the characteristics and pathogenic roles of AMPs in psoriasis [Figure 1] and further discuss their potential as therapeutic agents.

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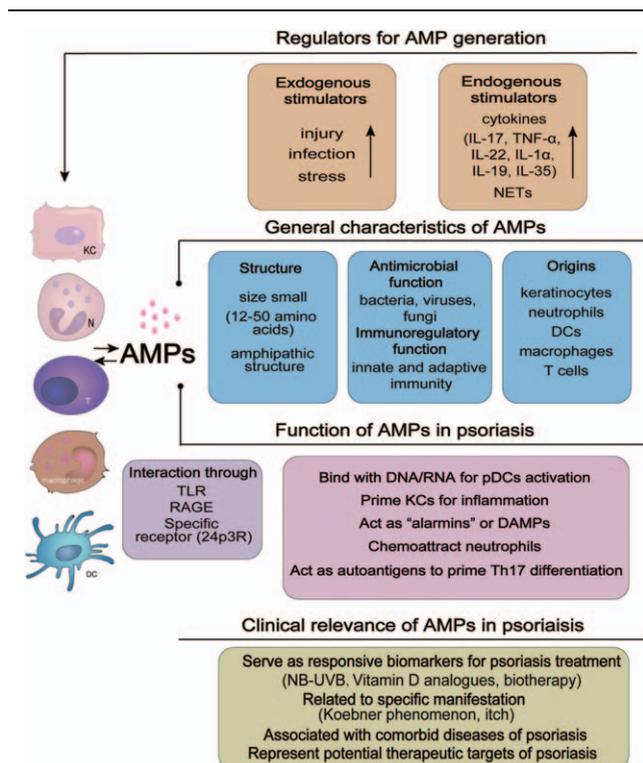
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**Figure 1:** The main characteristics of antimicrobial peptides (AMPs) and their roles in the pathogenesis of psoriasis. AMPs are an integral part of the skin defense generated by keratinocytes and neutrophils. AMPs are induced by exogenous and endogenous stimuli and have antimicrobial functions. AMPs are mostly characterized as small amphipathic cationic peptides. In psoriasis, AMPs regulate both innate and adaptive immune responses. They act as "alarmins" or DAMPs to stimulate plasmacytoid dendritic cells and prime keratinocytes for inflammation through pattern recognition receptors and subsequently initiate the Th17-dominated adaptive immune response. AMPs also have close clinical relevance to psoriasis. DAMPs: Damage-associated molecular patterns; IL: Interleukin; NB-UVB: Narrowband ultraviolet B; NET: Neutrophil extracellular trap; pDCs: Plasmacytoid dendritic cells; RAGE: Receptor for advanced glycation end products; TLR: Toll-like receptor; TNF: Tumor necrosis factor.

## LL-37

LL-37 is an  $\alpha$ -helical amphipathic oligopeptide (37-monomer peptide) released from human cationic antimicrobial protein-18 and is the only human cathelicidin encoded by the gene *CAMP*.<sup>[21]</sup> These characteristics allow LL-37 to form pores on microbial membranes and limit microbial adhesion and proliferation, thus protecting against infections.<sup>[22]</sup> High LL-37 levels in psoriatic skin lesions have been positively correlated with disease activity.<sup>[23]</sup> In psoriasis, the expression of LL-37 in keratinocytes can be promoted by cytokines such as IL-17A and tumor necrosis factor (TNF)- $\alpha$ .<sup>[24]</sup> Given that LL-37 is rapidly induced following skin injury,<sup>[25]</sup> LL-37 may partially contribute to the Koebner phenomenon in which psoriatic lesions appear after physical trauma.

LL-37 binds and forms complexes with DNA and RNA structures released from injured cells.<sup>[26]</sup> The classic LL-37–nucleic acid complex in psoriasis has been widely studied and reported to stimulate plasmacytoid dendritic cells (pDCs) in a toll-like receptor (TLR) 9-dependent manner.<sup>[27]</sup> Stimulated pDCs then secrete a large amount of IFN- $\alpha$  to trigger the activation of myeloid dendritic cells (mDCs) and autoreactive T cells, thus inducing an adaptive

immune cascade.<sup>[28]</sup> Moreover, the LL-37-DNA/RNA complex has been reported to directly activate mDCs<sup>[29]</sup> and keratinocytes<sup>[25]</sup> via TLR9/3 signaling. Recently, the source of the nucleic acids that bind to LL-37 has been further elucidated. In a recent study, it has been reported that complexes formed from LL-37 and RNA derived from NETs trigger the release of cytokines and NETs through the TLR8/TLR13 pathway, in which LL-37 is essential.<sup>[30]</sup> LL-37 can also interact with synthetic RNA oligonucleotides to promote the RNA aptamer internalization by keratinocytes and fibroblasts.<sup>[31]</sup> However, not all self-DNA can bind to LL-37, and it has been reported that LL-37 can bind to cellular DNA CpG sites but not to mitochondrial DNA.<sup>[32]</sup> These findings indicate that the structures of DNA and RNA may affect their binding mechanisms with LL-37 and the priming of inflammation. Notably, LL-37 can also bind to bacterial DNA present during chronic infections<sup>[33]</sup>; this bacterial DNA has not been detected in sterile inflammatory skin diseases. Nonetheless, further investigation that would provide key evidence that skin microbes are involved in psoriasis is warranted.

Apart from the fact that LL-37 forms complexes with nucleic acids, LL-37 also directly regulates keratinocytes and immune cells in psoriasis, for example, LL-37 induces the production of cytokines and chemokines such as IFNs,<sup>[25,34]</sup> IL-36 $\gamma$ ,<sup>[35]</sup> and C-X-C motif chemokine ligands (CXCLs)<sup>[36]</sup> in keratinocytes. Other regulatory effects of LL-37 on keratinocytes include the suppression of apoptosis<sup>[37]</sup> and enhancement of epidermal barrier function<sup>[38]</sup>; these effects indicate the involvement of LL-37 in psoriasis development. In addition, LL-37, as an autoantigen, directly activates T cells that tend to be involved in the maintenance of the IL-23/Th17 axis.<sup>[12]</sup> Moreover, patients with moderate-to-severe plaque psoriasis have been reported to develop LL-37-specific CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells with skin-homing abilities.<sup>[17]</sup> These autoreactive T cells infiltrate either skin lesions or the blood of patients with psoriasis and produce IFN- $\gamma$  and Th17 cytokines. Furthermore, it has been reported that the mouse homolog of LL-37 can serve as an autoantigen that promotes psoriasis-associated atherosclerosis.<sup>[39]</sup> Similarly, LL-37 has been identified as a novel autoantigen in psoriatic arthritis.<sup>[40]</sup> LL-37 can bind to the *PSORS* locus HLA-C\*06:02 allele and thereby form a complex that interacts with T cells via the T cell receptor.<sup>[20]</sup> In addition to T cells, LL-37 also regulates macrophages via TLR9 and induces mast cells to secrete IL-8.<sup>[29,41]</sup> LL-37 drives monocyte polarization toward the CD14<sup>high</sup>CD16<sup>+</sup> subset in psoriasis guttate.<sup>[42]</sup> Thus, we speculate that LL-37 may be a key biomolecule that primes the innate or adaptive immune responses in the pathogenesis of psoriasis.

## hBDs

Defensins are a group of small cationic polypeptides with potent antimicrobial activity. These polypeptides are usually structured as antiparallel  $\beta$ -sheets with abundant arginine and lysine residues stabilized by disulfide bonds.<sup>[43]</sup> Defensins are classified into two subfamilies,  $\alpha$ - and  $\beta$ -defensins, according to their disulfide bond linkages. To date, six hBDs (hBD-1–6) have been identified, among which hBD-2 and hBD-3 have been

extensively studied in psoriasis.<sup>[44]</sup> hBD-2<sup>[45]</sup> and hBD-3<sup>[46]</sup> have been found in most epithelial cells in the skin, respiratory tract, vagina, and gut. In the skin, these factors are expressed in the keratinocytes found in the uppermost layers of the epidermis and can be secreted into the intercellular space.<sup>[47,48]</sup> Many immune factors such as IL-17A, IL-22, and NETs modulate the expression of hBDs in keratinocytes.<sup>[43]</sup> hBD-2 is also found in Langerhans cells (LCs), whose changes are associated with skin aging.<sup>[49]</sup>

HBDs regulate a variety of cell types and facilitate psoriatic inflammation. Both hBD-2 and hBD-3 induce keratinocyte proliferation and the secretion of biomolecules such as IL-6, IL-10, IFN- $\gamma$ -inducible proteins, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-3, and CC chemokine ligand 5.<sup>[50]</sup> hBD-3 has also been reported to induce the expression of IL-37,<sup>[51]</sup> an immunosuppressive cytokine, in human keratinocytes by interacting with CCR6.<sup>[52]</sup> hBD-3 has also been reported to exert a protective effect and improve the function of epithelial tight-junction barrier.<sup>[53]</sup> Therefore, it is worthwhile to elucidate the “double-edged sword” effects of hBD-3 in the pathogenesis of psoriasis. Furthermore, hBDs modulate not only keratinocytes but also immune cells. Similar to LL-37, hBD-2 and hBD-3 promote the uptake of self-DNA or CpG DNA by pDCs and enhance the production of IFN- $\alpha$ .<sup>[54]</sup> hBD-3 also activates mDCs in a TLR1/2-dependent manner.<sup>[55]</sup> In addition, both hBD-3 and its mouse ortholog murine  $\beta$ -defensin-14 induce the production of IL-23 by epidermal LCs and exacerbate psoriasis-like skin inflammation.<sup>[56]</sup> Moreover, hBDs promote type I interferon production in macrophages via different pathways such as hBD-2 through CCR2-mediated Nod2 transduction<sup>[57]</sup> and hBD-3 in a TLR-dependent manner.<sup>[58]</sup> hBD-3 also increases CD86 expression in monocytes by stimulating the ATP-gated channel P2X7<sup>[59]</sup>; as the P2X7 receptor is a key modulator of aerobic glycolysis,<sup>[60]</sup> this finding suggests that hBD-3 may be involved in glycolysis in the pathogenesis of psoriasis. In T cells, hBD-2 has been reported to exhibit a two-way regulatory effect; hBD-2 enhances IFN- $\gamma$  and IL-10 production but suppresses IL-17 production in T cells by suppressing the transcriptional regulator STAT3.<sup>[61]</sup> Therefore, we suggest that hBDs may act as autocrine or paracrine signals in the pathogenesis of psoriasis; nonetheless, this requires further investigation.

Clinically, the high genomic copy number of  $\beta$ -defensin genes has been associated with an increased risk of psoriasis.<sup>[62,63]</sup> Additionally, HBDs can be secreted by commensal bacteria and can affect the homeostasis of the microbiome.<sup>[64]</sup> Hence, it is possible that dysregulated hBD expression also contributes to psoriatic inflammation in a microbiota-associated manner.

### S100 proteins

S100 proteins are a family of calcium-binding molecules with small molecular weights.<sup>[65]</sup> The activation of S100 proteins, especially S100A8/A9 tetramers, requires Ca<sup>2+</sup> binding, protein oligomerization, and the formation of homo- or heterodimers with the help of iron.<sup>[66]</sup> Many members of this family are encoded in the genes within the psoriasis

susceptibility locus on chromosome 1q21; this indicates an association between S100 proteins and psoriasis.<sup>[67,68]</sup> Among these proteins, S100A4,<sup>[69]</sup> S100A7,<sup>[70,71]</sup> S100A8/A9,<sup>[72,73]</sup> S100A12,<sup>[19]</sup> and S100A15<sup>[71]</sup> are highly expressed in both the serum and skin of patients with psoriasis. S100 proteins can be secreted by keratinocytes,<sup>[74]</sup> neutrophils,<sup>[75]</sup> monocytes/macrophages,<sup>[76]</sup> and dermal DCs.<sup>[77]</sup> These proteins are stress-induced molecules and therefore can be rapidly up-regulated by injury,<sup>[78]</sup> proinflammatory cytokines such as IL-1 $\alpha$ , TNF- $\alpha$ , IL-19, and IL-22,<sup>[79-81]</sup> or TLR<sup>[82]</sup> receptor for advanced glycation end products (RAGE) induced<sup>[83]</sup> signaling.

The major role of S100 proteins in psoriasis is their regulation of keratinocytes, for example, the mouse ortholog mS100a7a15 induces the expression of psoriasis-associated cytokines such as IL-1 $\alpha$ , IL-23, and MIP-2 in keratinocytes in a RAGE-dependent manner.<sup>[67]</sup> S100A8/A9 stimulates the expression of IL-8, CXCL1, CXCL2, CCL20,<sup>[84]</sup> and complement component 3 in keratinocytes to mediate psoriatic inflammation.<sup>[85]</sup> Additionally, these proteins also promote the excessive proliferation<sup>[86]</sup> and abnormal differentiation<sup>[73,82]</sup> of keratinocytes that contribute to the development of hyperkeratosis and parakeratosis in psoriasis. Furthermore, S100 proteins can recruit and activate neutrophils<sup>[87,88]</sup>; this characteristic of S100 proteins may accelerate neutrophil infiltration in psoriatic skin lesions. Importantly, S100A8 and S100A9 promote the development of autoreactive CD8<sup>+</sup> T cells, thereby suggesting that S100A8 and S100A9 are linked to inflammation and autoimmunity.<sup>[89]</sup> Intriguingly, S100A8 and S100A9 has been shown to inhibit self-activity by forming the (S100A8/S100A9)<sub>2</sub> tetramer, which inhibits the binding of S100A8/S100A9 with TLR4/MD2 to restrict sterile inflammation.<sup>[90]</sup> The loss of this mechanism may free the binding sites from S100A8/S100A9 heterodimers and subsequently activate TLR4/MD2-mediated local inflammation. As this has not yet been fully elucidated, it requires further study.

S100 proteins have been linked to psoriasis-related comorbidities, including psoriatic arthritis, Crohn disease, metabolic syndrome, and cardiovascular disorders. For example, the concentrations of S100A8/S100A9 and S100A12 are markedly elevated in the serum of patients with psoriatic arthritis; S100A8/S100A9 and S100A12 act as potential biomarkers of disease severity.<sup>[76,91]</sup> Recently, the expression of S100 proteins was reportedly associated with lipid metabolism, which may be involved in metabolic syndrome and cardiovascular disease. Diet-induced obesity has also been demonstrated to induce aberrant S100 protein production and psoriasiform inflammation in clinical and murine model studies.<sup>[92-94]</sup> Additionally, S100A7/S100A15 and S100A8/S100A9 levels in serum are positively correlated with intima-media thickness<sup>[71]</sup> and aortic vascular inflammation,<sup>[95]</sup> respectively, in patients with psoriasis. Interestingly, the activation of the itch-associated genes transient receptor potential vanilloid type 1 (TRPV1)<sup>[96]</sup> and transient receptor potential ankyrin 1 (TRPA1)<sup>[97]</sup> positively regulates S100A8/S100A9 expression and promotes psoriatic inflammation, thereby indicating the potential role of S100 proteins in psoriatic pruritus.

## LCN2

LCN2, also known as neutrophil gelatinase-associated lipocalin, is a glycoprotein encoded in a gene located at chromosome 9q34.11.<sup>[98]</sup> LCN2 is supposed to have two receptors, megalin and 24p3R<sup>[99]</sup>; however, the melanocortin-4 receptor was recently identified as another LCN2 receptor expressed on neurons in the hypothalamus and associated with appetite control.<sup>[100]</sup> LCN2 was originally identified as a component of neutrophil secondary granules with versatile functions in inflammatory processes.<sup>[101]</sup> LCN2 has also been regarded as an AMP that inhibits bacterial iron acquisition<sup>[102]</sup> and as an adipokine involved in obesity, insulin resistance, and metabolic diseases.<sup>[98,101]</sup> In a previous study, we have demonstrated that LCN2 is secreted by keratinocytes stimulated with IL-17A, IL-22, and TNF- $\alpha$  or by infiltrated neutrophils in psoriatic skin lesions.<sup>[15,103]</sup> Consistently, other studies have revealed that TNF- $\alpha$  induces LCN2 production in keratinocytes and granulocytes in hidradenitis suppurativa (HS).<sup>[104]</sup> LCN2 can also originate from CD4<sup>+</sup> T cells,<sup>[105]</sup> macrophages,<sup>[106]</sup> DCs,<sup>[107]</sup> adipose tissues,<sup>[108]</sup> or hepatocytes<sup>[109,110]</sup> and contribute to systemic or local LCN2 levels.

We and others have found that LCN2 is overexpressed not only in the skin lesions of psoriasis vulgaris,<sup>[111]</sup> generalized pustular psoriasis, and palmoplantar pustular psoriasis, but also in imiquimod (IMQ)-induced psoriasis-like lesions in mice.<sup>[15]</sup> We further found that LCN2 induced chemotaxis and cytokine secretion in neutrophils via the 24p3R and downstream p38-MAPK and ERK-1/2 signaling pathways and that the neutralization of LCN2 significantly attenuated disease severity and inflammatory infiltration in IMQ-induced mice.<sup>[15,103]</sup> Although serum LCN2 levels have not been linked to psoriasis area and severity index, it has been positively linked to the degree of itch in patients with psoriasis.<sup>[18,112]</sup> Interestingly, recent studies highlight a mechanism by which LCN2 facilitates chronic itch in inflammatory skin diseases as a downstream effector of astrocytic STAT3 signaling, which directly enhances spinal gastrin-releasing peptide-induced scratching.<sup>[113,114]</sup>

Importantly, LCN2 has been reported to modulate lipid metabolism pathways, and LCN2 deficiency has been reported to protect mice from obesity-induced insulin resistance by inhibiting 12-lipoxygenase and TNF- $\alpha$  levels in adipose tissues.<sup>[115,116]</sup> Similarly, LCN2 also induces insulin resistance and inhibits autophagy in cardiomyocytes.<sup>[117]</sup> In view of these studies, LCN2 may contribute to the comorbid diseases of psoriasis such as metabolic syndrome, cardiovascular disease, Crohn disease, and non-alcoholic fatty liver disease.

## RNase 7

RNase 7 is a member of the RNase A superfamily and a biomolecule with disulfide bonds; it is encoded on chromosome 14q11.2.<sup>[118]</sup> It was first identified as an AMP in healthy human skin in 2002<sup>[119]</sup> as it can protect against infections. In primary keratinocytes in the stratum corneum<sup>[119]</sup> and in bronchial<sup>[120]</sup> and kidney<sup>[121]</sup> epithelial cells, RNase 7 is reportedly abundant. The inflammatory

cytokines IL-17A, IFN- $\gamma$ , and IL-1 $\beta$  are positive regulators of RNase 7 expression.<sup>[122,123]</sup> Notably, RNase 7 has been reported to be more rapidly induced than hBD-2 and hBD-3 by skin injury with increased levels in skin lesions in both psoriasis and atopic dermatitis (AD).<sup>[124]</sup> This finding indicates the functions of RNase 7 in the acute phase of inflammation and refutes that the expression of AMPs in AD is decreased.<sup>[125]</sup> Notably, RNase 7 has been reported to promote the sensing of self-DNA by human pDCs and keratinocytes via TLR regulation<sup>[126,127]</sup>; this suggests that RNase 7 is another psoriasis trigger similar to LL-37 and hBDs. Interestingly, RNase 7 has been reported to suppress the production of Th2 cytokines (IL-13, IL-4, and IL-5) in human CD4<sup>+</sup> T cells, which is independent of its ribonuclease activity.<sup>[128]</sup> Therefore, the functions of RNase 7, especially its regulatory roles in inflammatory skin disease, remain unclear and require further investigation [Table 1].

## Perspectives and discussion

Increasing evidence has indicated that AMPs triggered by local tissue signals are essential for the initiation and development of inflammatory diseases such as psoriasis, rosacea, rheumatic diseases, and HS.<sup>[104,129]</sup> Here, we summarize the potential roles of AMPs in the pathogenesis of psoriasis. (1) AMPs act as chaperones to DNA/RNA and are recognized by pDCs, thereby triggering the activation of psoriatic inflammation. (2) AMPs are natural innate immune components triggered by local signaling that serve as alarmins or damage-associated molecular patterns and interact with PRRs such as TLRs and RAGE to induce uncontrolled inflammatory cascades in psoriasis. (3) AMPs (LL-37), as autoantigens, activate T cells to induce subsequent adaptive immune responses. This response is, in turn, regulated by cytokines and chemokines and establishes vicious feedback loops to maintain psoriatic inflammation.

Discrepancies in AMP production among inflammatory skin diseases should be studied. Studies have indicated that AMP levels are increased in psoriasis but are decreased in AD.<sup>[130,131]</sup> In psoriasis, AMPs mainly exert proinflammatory effects, whereas beneficial effects of AMPs have been observed in AD, such as those relating to skin barrier maintenance and Th2 suppression. The distinct frequency of recurrent skin infections between the two diseases has been accepted to be partially due to this discrepancy. However, AMPs and several cytokines have been identified across the spectrum of these two diseases in recent decades. Harder *et al*<sup>[124]</sup> reported the overexpression of RNase 7, S100A7, and hBD-2 in skin lesions in patients with AD and psoriasis. Concurring, increasing evidence shows overlaps in prominent IL-17 components between specific subtypes of AD (pediatric and Asian-origin AD) and psoriasis.<sup>[132,133]</sup> These results indicate that multiple immune pathways can be observed in one inflammatory milieu and that the imbalance in the interactions between T cell subsets may largely impact skin processes, including AMP production. Hence, continued research is warranted to understand the common and different immune pathways in psoriasis and AD. In recent decades, AMPs were reportedly highly expressed in other autoimmune skin diseases such as systemic lupus erythematosus<sup>[134]</sup> and

**Table 1: The origins and target cells of AMPs in the pathogenesis of psoriasis.**

AMPs	Origins	Target cells	Potential mechanism in the pathogenesis of psoriasis
Cathelicidin (LL-37)	Keratinocytes Neutrophils T cells Monocytes NK-cells Mast cells	Keratinocytes pDCs mDCs Monocytes/ macrophages Neutrophils CD4 <sup>+</sup> T cells CD8 <sup>+</sup> T cells	Forming complex with DNA/RNA to activate pDCs or mDCs through TLR dependent manner <sup>[27-30]</sup> ; Priming keratinocytes for inflammation <sup>[25,34-36]</sup> ; Serving as an autoantigen directly activating CD4 <sup>+</sup> and/or CD8 <sup>+</sup> T cells <sup>[17]</sup> ; Driving monocyte polarization toward the CD14 <sup>high</sup> CD16 <sup>+</sup> subset. <sup>[42]</sup>
Human $\beta$ -defensin 2	Keratinocytes LCs	Keratinocytes pDCs Macrophages	Inducing keratinocyte proliferation and secretion <sup>[50]</sup> ; Promoting the uptake of self-DNA or CpG DNA by pDCs and enhance IFN- $\alpha$ production <sup>[54]</sup> ; Promoting type I IFN production in macrophages. <sup>[57]</sup>
Human $\beta$ -defensin 3	Epithelial cells (keratinocytes)	Keratinocytes pDCs mDCs LCs Monocytes/ macrophages	Inducing keratinocyte proliferation and secretion <sup>[50]</sup> ; Promoting the uptake of self-DNA or CpG DNA by pDCs and enhance IFN- $\alpha$ production <sup>[54]</sup> ; Activating mDCs in via TLR1/2 <sup>[55]</sup> ; Promoting type I IFN production in macrophages <sup>[58]</sup> ; Increasing CD86 expression on monocytes by stimulating the ATP-gated channel P2X7. <sup>[59]</sup>
Psoriasin (S100A7)	Keratinocytes Monocytes/ macrophages	Keratinocytes Monocytes/ macrophages Neutrophils	Inducing cytokines production of keratinocytes <sup>[67]</sup> ; Chemoattractant. <sup>[87]</sup>
S100A8/A9	Keratinocytes Monocytes/ macrophages Neutrophils mDCs Endothelial cells	Keratinocytes Neutrophils CD8 <sup>+</sup> T cells	Priming keratinocytes for inflammation <sup>[85]</sup> ; Promoting excessive proliferation and abnormal differentiation of keratinocytes <sup>[73,82,86]</sup> ; Chemoattracting and activating neutrophils <sup>[87,88]</sup> ; Promoting the development of autoreactive CD8 <sup>+</sup> T cells <sup>[89]</sup> ; Filling to inhibit self-activity by forming the (S100A8/S100A9) <sub>2</sub> tetramer and activating TLR4/MD2-mediated local inflammation. <sup>[90]</sup>
S100A15	Keratinocytes	Keratinocytes	Inducing cytokines production of keratinocytes. <sup>[67]</sup>
Lipocalin 2	Neutrophils Keratinocytes mDCs Monocytes/ macrophages Aortic smooth muscle cells Adipose tissue Hepatocytes	Neutrophils	Inducing chemotaxis and cytokine secretion in neutrophils via the 24p3R and downstream p38-MAPK and ERK-1/2 signaling pathways. <sup>[15,103]</sup>
RNase 7	Keratinocytes	Keratinocytes pDCs	Promoting the sensing of self-DNA by human pDCs and keratinocytes through TLR regulation <sup>[126,127]</sup>

AMPs: Antimicrobial peptides; pDCs: Plasmacytoid dendritic cells; mDCs: Myeloid dendritic cells; LCs: Langerhans cells.

HS.<sup>[75]</sup> It has been reported that S100 protein levels in the serum and urine of patients with systemic lupus erythematosus are higher than those of healthy participants and that the S100 protein may be a potential biomarker for lupus nephritis.<sup>[134,135]</sup>

Importantly, AMPs have clinical relevance to psoriasis [Figure 1] and may serve as biomarkers during treatment. For example, AMPs can be downregulated by psoriasis treatments, including narrowband ultraviolet B (NB-UVB) therapy and use of antipsoriatic vitamin D analogs.<sup>[136-138]</sup> Notably, biotherapies targeting the IL-23/IL-17 axis, including secukinumab, risankizumab, and ustekinumab, down-regulate the production of hBD-2 and LCN2 in psoriatic skin lesions.<sup>[45]</sup> Moreover, tasquinimod (an S100A9 inhibitor) has been successfully used in clinical trials of patients with metastatic castration-resistant prostate cancer, thereby indicating a promising strategy for targeting AMPs for psoriasis treatment.<sup>[139]</sup>

However, many unsolved problems regarding the roles of AMPs in psoriasis remain. LL-37 prevails during the development of psoriasis and has been identified as an autoantigen that amplifies psoriatic inflammation. Whether other AMPs, including LCN2 and S100 proteins, also have these properties, and the underlying distinction of LL-37 in psoriasis development are worth considering. Moreover, the differing effects of LL-37 in psoriasis cannot be overlooked. Whether the proinflammatory or protective effect of LL-37 is dominant in psoriasis and whether the effects of LL-37 are exerted only in the initial stage or throughout the entire process of psoriasis must be determined. Additionally, it is necessary to determine whether the overexpression of LL-37 is a constitutive factor that triggers the relapse of psoriasis. Furthermore, AMPs interact with PRRs or specific receptors to regulate different immune cells. The interplay among these biomolecules also deserves further investigation. Importantly, whether targeting AMPs is as sufficient as targeting TNF- $\alpha$ , IL-23, or IL-17 antagonists for psoriasis treatment is noteworthy to investigate. The dynamic bioactivity of AMPs warrants further elucidation in the context of the safety of clinical applications.

## Conclusions

This review summarizes the roles of AMPs in the pathogenesis of psoriasis [Table 1] and suggests their roles as biomarkers and therapeutic targets in translational medicine. Nonetheless, we should closely observe their antimicrobial properties, which have potent impacts on immune functions. Additional studies that focus on the characteristics and interactions of AMPs may lead to breakthroughs in elucidating the pathogenesis of psoriasis and establishing promising therapeutic interventions.

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## Conflicts of interest

None.

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