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PSORIASIS (J WU, SECTION EDITOR)

Autoimmunity in Psoriasis: Evidence for Specific Autoantigens

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Abstract
Purpose of Review The pathophysiology of psoriasis is highly complex, and the role of autoantigens in psoriasis has been debated for decades. In this article, we examine the evidence in support of psoriasis autoantigens and their contribution to the development of this chronic, inflammatory condition. We also provide an overview of the known biological functions of these psoriasis autoantigens and their potential role in the pathogenesis of psoriatic disease.
Recent Findings Since 2014, three potential psoriasis autoantigens (LL-37, ADAMTSL5, and PLA2G4D) have been described in the scientific literature.
Summary Current evidence lends support for the role of autoantigens in psoriasis and offers insights into the underlying mechanisms enabling the breakdown of immune tolerance in the skin. A systematic approach to identify novel psoriasis autoantigens is needed and has the potential to lead to the development of novel interventions and/or treatment strategies, including a possible cure for this condition.

Keywords Psoriasis · Autoimmunity · Autoantigens · LL-37 · ADAMTSL5 · PLA2G4D

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Introduction

Psoriasis vulgaris is a heterogeneous, chronic, inflammatory skin condition affecting approximately 2–3% of the US population [1]. Most commonly characterized by well-demarcated, erythematous plaques, psoriasis is associated with systemic inflammation and multiple disease comorbidities, such as cardiovascular disease, ischemic heart disease, stroke, joint disease, metabolic syndrome, diabetes, pulmonary disease, depression, and sleep disorders [2–7]. The economic burden of psoriasis and its co-occurring conditions is significant, estimated at more than $35 billion annually [8, 9]. The persistent, life-long nature of this condition also represents a substantial psychosocial burden for patients and their families.

The etiology of psoriasis is multifaceted and involves a complex interplay between the skin, the innate and adaptive immune responses, genes, and environmental stimuli such as trauma and infections. Despite tremendous scientific advances which have led to improved treatments and an increased understanding of psoriasis pathogenesis, major research gaps exist concerning the molecular mechanisms of psoriasis and the initial immune events triggering its onset. Additionally, current treatment strategies have significant limitations due to their inability to induce long-term disease remission.

Whether psoriasis represents a true autoimmune disease has been a topic of debate among clinicians and scientists. The role of autoantigens as plausible triggers of psoriatic disease is a research question of fundamental importance. The purpose of this article is to provide a brief overview of the immunologic basis of psoriasis, as well as an in-depth review of the current evidence for the role of autoantigens in the development of this chronic inflammatory condition. The identification and characterization of psoriasis autoantigens offer valuable insights into the natural history of psoriasis and may, ultimately, lead to the development of novel therapeutic targets and/or treatment strategies.

The Evolution of Psoriasis Pathogenesis: a Historical Perspective

For hundreds of years, papulosquamous skin conditions were misclassified and mistaken for other skin diseases such as leprosy. It was only after the detailed clinical observations of Robert Willan and Ferdinand von Hebra in the nineteenth century that psoriasis became recognized as a distinct clinical entity [10]. For the next century, clinicians continued to document additional clinical features of psoriasis and described multiple disease variants. Little was known about the pathogenesis of psoriasis at that time and treatments were, therefore, largely ineffective and anecdotal.

Evidence supporting the role of the immune system in the pathogenesis of psoriasis began accumulating in the 1980s. This evidence included early observations that patients with severe psoriasis responded favorably to non-specific inhibitors of the immune system and antimetabolic medications such as cyclosporine [11, 12] and methotrexate [13], respectively. Psoriatic skin was also noted to have increased numbers of inflammatory cellular infiltrates [14, 15], and psoriasis patients undergoing bone marrow transplants were observed to have complete resolution of their disease [16]. The requirement of the immune system for the development of active psoriatic lesions was further confirmed in vivo by the assessment of transplanted psoriasis skin onto congenitally athymic (nude) mice [17]. The authors of this study also noted the inherent propensity of psoriatic keratinocytes for increased proliferation compared to the skin of healthy controls, providing a framework wherein psoriasis started to be viewed as a complex disease resulting from the interaction between the skin and the immune system.

As researchers began to dissect out the various immune cells involved in the aberrant skin response observed in psoriasis patients, the central role of the T lymphocyte became readily apparent. The infiltration of activated $CD4^+$ and $CD8^+$ T cells in the skin was shown to be a consistent hallmark of psoriatic disease [14, 18], and this lymphocytic infiltrate positively correlated with disease activity measurements [19–21]. However, definitive proof for the predominant role of pathogenic T cells in psoriasis was shown by selective inhibition of activated T lymphocytes in psoriasis patients via a novel fusion protein made of diphtheria toxin fragments and human interleukin-2 (DAB_{389}IL-2) [22•]. The efficacy of T cell targeted therapies was further shown in several proof-of-concept psoriasis studies: abatacept [23], alefacept [24], and efalizumab [25]. These studies formed the principal foundation for subsequent studies investigating the immune basis of psoriasis pathogenesis and, ultimately, led to the discovery of other pathogenic immune cells and cell signaling pathways such as tumor necrosis factor-alpha (TNF-α) and the IL-23/T17 axis. We are now witnessing unparalleled advances in the treatment of psoriasis due to the development of novel medications including the IL-17 antagonists.

Psoriasis as an Autoimmune Disease: Weighing the Evidence

The vital importance of the T lymphocyte to the development of psoriasis and its strong association with the human leukocyte antigen (HLA) locus (i.e., *HLA-C*06:02*) have led many to consider psoriasis as an autoimmune disease. This autoimmune concept is reinforced by the finding that skin from healthy controls contains few T lymphocytes with no evidence of expanded T cell receptor (TCR) clones, whereas the T cell repertoire in psoriatic skin is strikingly expanded with varying TCR clonality [18, 26–28]. The expansion of these select T lymphocyte clones suggests the possibility that foreign and/or self-antigens (i.e., autoantigens) may trigger the onset of this chronic disease, including keratinocyte-derived proteins (e.g., keratin 17) [29, 30] and proteins associated with group A ß-hemolytic streptococcal infections [31]. However, the notion that psoriasis represents an autoimmune disorder remained controversial due to the fact that no specific autoantigens had ever been identified or characterized. Since 2014, three potential psoriasis autoantigens (Table 1) have been reported in the scientific literature. Here, we summarize the known biological functions of these psoriasis-related autoantigens and provide an overview of their role in the pathogenesis of psoriatic disease (Fig. 1).

LL-37

LL-37 (also known as cathelicidin, CAMP or hCAP18) is a cationic antimicrobial peptide (AMP) from the human cathelicidin family [32]. It is produced by multiple cell types (e.g., keratinocytes, antigen presenting cells (APCs), neutrophils, and mast cells) in response to skin injury or bacterial/viral infections (Table 1) [33, 34, 35•, 36•]. Like other AMPs, LL-37 is a key mediator of the innate immune system and has direct antimicrobial properties [37]. The cationic structure of LL-37 allows it to form complexes with the anionic phosphate backbone of DNA and RNA fragments [36•]. The dysregulation of AMPs and the identification of LL-37 nucleic acid complexes in the tissues of patients with classic autoimmune conditions, such as systemic lupus erythematosus (SLE) [38, 39] and rheumatoid arthritis (RA) [40], suggested a possible link between AMPs and the development of autoimmunity. This led investigators to study the role of AMPs in chronic inflammatory conditions of the skin, such as psoriasis [36•], atopic dermatitis [41], and rosacea [42], which were also found to have increased levels of LL-37. However, it was unclear if LL-37 was directly contributing to the development of autoimmunity.

The study of specific dendritic cell (DC) populations and their central function in the immune response established a clear link between LL-37 and autoimmunity. DCs are a heterogeneous group of highly specialized cells that form a

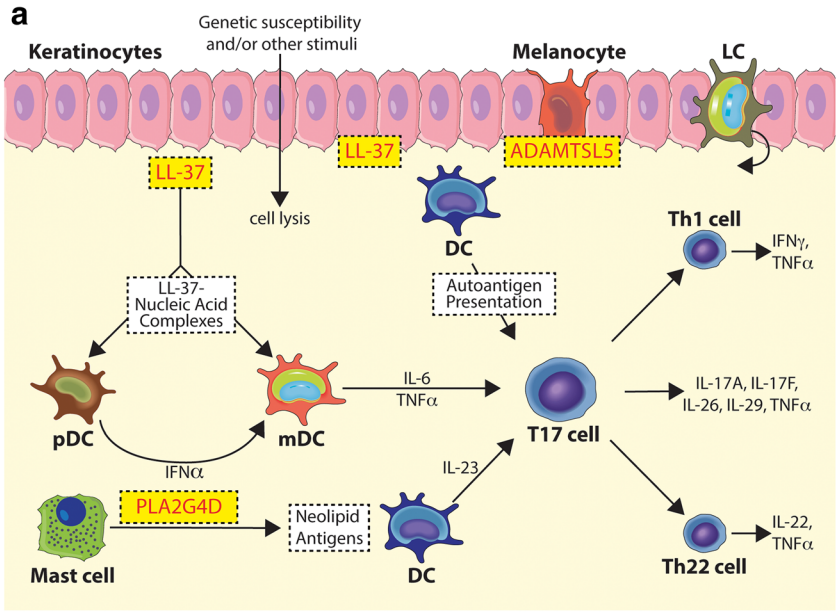
Table 1 General characteristics of psoriasis autoantigens and their role in psoriasis pathogenesis

Antigen	Alternate name(s)	Locus	Cellular source	Biological functions	Expression in psoriasis	Role in psoriasis
LL-37	Cathelicidin, CAMP, hCAP18	3p21.31	Keratinocyte, macrophage, monocyte, DC, PMN, and mast cells	A cationic peptide with inherent antimicrobial activity and the ability to form aggregates with extracellular DNA or RNA leading to the activation of endosomal or cytosolic TLRs of immune cells	Increased	Upregulation of LL-37 contributes to the loss of immune tolerance through 1) the stimulation of TLRs and activation of APCs, such as pDCs and mDCs; 2) promoting the expansion of T cells that produce IFNγ and T17 cytokines; and 3) serving as an autoantigen on target cells, such as keratinocytes
ADAMTSL5	A disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5, ADAMTS-like protein 5	19p13.3	Melanocyte, keratinocyte, and discrete dermal cells	Binds to fibrillin-1,2 and promotes microfibril formation and regulation of the extracellular matrix; specific functions are also tissue dependent	Increased	Upregulation of ADAMTSL5 in melanocytes from *HLA-C*06:02*-positive individuals results in the stimulation of $CD8^+$ T cells and increased IFNγ and T17 cytokines compared to controls
PLA2G4D	Phospholipase A_2 group IVD, $cPLA_2\delta$	15q15.1	Keratinocyte, and dermal mast cells	Catalyzes hydrolysis and release of free fatty acids and lysophospholipids	Increased	PLA2G4D generates neolipid autoantigens recognized by $CD1a^+$-restricted Langerhans cells to produce increased Th1 and T17 cytokines; transfer of neolipid autoantigens to neighboring APCs also occurs via the transfer of small, secreted multivesicular bodies called exosomes

DC dendritic cell, *pDC* plasmacytoid dendritic cell, *mDC* myeloid dendritic cell, *PMN* polymorphonuclear leukocyte, *TLR* toll-like receptor, *APC* antigen presenting cell

bridge between the innate and adaptive arms of the immune response. Like LL-37, plasmacytoid dendritic cells (pDCs) are capable of mounting a rapid immune response when activated by viral infections or tissue injury. pDC activation occurs primarily through toll-like receptors (TLRs) via the detection of nucleic acids [43]. Activated pDCs represent an important effector cell of the innate immune response and are the predominant source of type I interferons (IFNα and IFNβ), the primary cytokines driving autoimmunity [44]. Increased pDCs and elevated levels of type I IFNs are observed in multiple autoimmune conditions. Their primary function in autoimmune disease is the recognition and binding of self DNA or self RNA, which leads to increased IFNα and the subsequent activation of myeloid dendritic cells (mDCs) [36•]. Mature mDCs sustain autoimmunity through the secretion of pro-inflammatory cytokines (e.g., IL-23) and the stimulation of autoreactive T lymphocytes [44, 45•]. In line with these observations, psoriasis patients have increased numbers of pDCs in psoriatic plaques [45•], and IFNα produced by these cells represent an early cytokine signal driving the development of their skin lesions. Similarly, monocytes co-cultured with LL-37 and M-CSF induced a pro-inflammatory differentiation of macrophages following exposure to lipopolysaccharides [46]; internalization of LL-37 into the macrophage was mediated by the $P2X_7$ receptor and directed to the endosome via clathrin-mediated endocytosis [47•].

The exact mechanism by which DCs are activated in psoriasis and lose their ability to discriminate between self and foreign nucleic acids is complex. Noting that cutaneous trauma results in activation of pDCs, upregulation of LL-37, and the development of psoriatic plaques (i.e., Koebner phenomenon), Lande et al. [36•] sought out to determine whether LL-37 could mediate the activation of pDCs in psoriasis. The authors found that fractions of skin extracts from psoriasis patients containing LL-37 resulted in pDC activation and marked increases in IFNα [36•]. This pDC activation appears to be LL-37-specific since stimulation with other dysregulated AMPs in psoriasis, such as S100A7 and human beta-defensin 2 (hBD2), did not result in upregulation of IFNα. Importantly, they also uncovered a novel function of LL-37 by demonstrating how this AMP is capable of binding self DNA and activating pDCs in patients with psoriasis—a surprising finding since pDCs from healthy controls do not typically respond to self-nucleic acids due to multiple biological safeguards. These safeguards include distinct differences in the structure and content of bacterial/viral DNA and RNA (e.g., unmethylated CpG motifs, single-stranded RNA, U- or GU-rich nucleotide sequences), abundant nucleases in the extracellular space, and the intracellular compartmentalization of TLRs which favors DC activation by endocytosed bacterial/viral contents [48, 49]. Nevertheless, one recent study indicates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and/or other stimuli
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TNFα
LL-37-
Nucleic Acid
Complexes
Autoantigen
Presentation
IL-6
TNFα
IL-17A, IL-17F,
IL-26, IL-29, TNFα
pDC
mDC
T17 cell
IFNα
IL-23
PLA2G4D
Neolipid
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IL-22,
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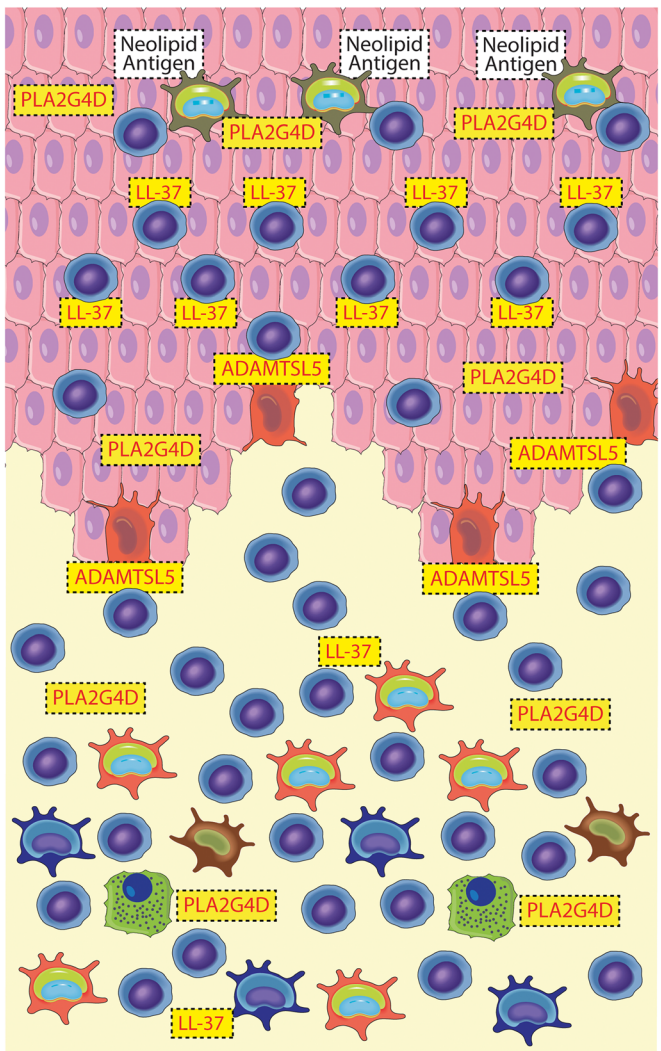
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◀ **Fig. 1** Working model for the potential role of autoantigens in psoriasis. **a** Development of an early stage psoriasis plaque—an initial stimulus (e.g., infection or skin trauma) in genetically susceptible individuals results in cell damage and the release of self-nucleic acids. Extracellular LL-37 complexes with and protects these nucleic acids from degradation, allowing uptake of this complex by pDCs and mDCs via endocytosis. Transportation of LL-37 to intracellular endosomes activates TLRs. Immature dendritic cell subtypes (pDC, mDC) are then activated and lead to the activation of T17 cells. Alternatively, mast cells from psoriasis patients uniquely express PLA2G4D, a novel phospholipase A_2 enzyme capable of generating neolipid antigens recognized by $CD1a^+$-restricted Langerhans cells. Finally, upregulation of ADAMTSL5 in melanocytes results in the activation of $CD8^+$ T cells and increased amounts of IFNγ and T17 cytokines compared to controls. All three psoriasis autoantigens can be presented by DCs leading to activation of the IL-23/T17 and Th1 pathways, which are central to the development of psoriasis. **b** Maintenance of a mature psoriatic plaque—propagation of the autoantigen-driven inflammatory process leads to epidermal hyperplasia, increased numbers of melanocytes, and infiltration of the epidermis by T17 cells, which further sustains the inflammatory response within psoriatic plaques by producing pathogenic cytokines and through surrounding autoantigen-target cell interactions. *ADAMTSL5* a disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5, *DC* mature dendritic cell, *IFN* interferon, *IL* interleukin, *LC* Langerhans cell, *mDC* myeloid dendritic cell, *pDC* plasmacytoid dendritic cell, *PLA2G4D* phospholipase A_2 group IVD

that the transport of extracellular nucleic acids into the cytosol of specific immune cells may occur in a TLR-independent manner [50•] highlighting the need for additional studies in this area.

Lande et al. [36•] showed that high levels of LL-37 in the presence of self-DNA led to the spontaneous formation of multimeric LL-37 DNA aggregates which were highly resistant to nuclease degradation and able to readily enter and activate pDCs. These aggregates were retained within the endosomal compartment of activated pDCs where they mediated the production of IFNα in a TLR-9-restricted manner without resulting in cell maturation; neither LL-37 nor DNA alone resulted in the activation of pDCs or increased IFNα. A nearly identical mechanism was subsequently described for the activation of pDCs by LL-37 RNA aggregates via TLR-7. The LL-37 RNA complex triggers mDC activation via TLR-8, which results in the over-production of TNF-α and IL-6 as well as mDC maturation [51]. mDC maturation results in the activation of naïve T cells and is simultaneously enhanced by IFNα made by activated pDCs (Fig. 1) [45•, 51]. Together, these findings provide a mechanism wherein LL-37 cooperates with pDCs and mDCs to break immune tolerance and promote autoimmunity in psoriasis via the binding of extracellular self-nucleic acids resulting from cell death or Koebnerized skin.

LL-37 also has the ability to directly induce the proliferation of autoreactive T cells in psoriasis. In a study [35•] evaluating the peripheral blood from 56 psoriasis patients, 46% of patients were noted to have LL-37-specific $CD4^+$ or $CD8^+$ T cells; this percentage approached 75% in patients with moderate-to-severe psoriasis which they defined by a Psoriasis Area and Severity Index (PASI) score >10. The cytokine profile of these T cells showed a strong Th1 (IFNγ) and T17 (IL-17, IL-21, IL-22) phenotype. The LL-37-specific T cells isolated from these patients were also found to express increased levels of skin-homing receptors, such as CCR6, CCR10, and CLA, and were frequently found in lesional psoriatic skin implicating their direct role in the inflammatory process [35•]. These findings are consistent with previous clinical and histologic studies demonstrating a pathogenic role for $CD4^+$ or $CD8^+$ T cells in human psoriasis. Interestingly, Lande et al. [35•] identified several LL-37 fragments were bound by a variety of HLA alleles (e.g., *HLA-DR* and *HLA-C*06:02*) demonstrating the immunogenicity of LL-37 and the potential role for psoriasis susceptibility loci in determining which antigens trigger autoimmunity in patients [52]. Additional genetic studies and the systematic screening of psoriasis patients for LL-37-specific T cells are necessary in order to tease out this relationship between inherited psoriasis-associated genes and LL-37.

ADAMTSL5

ADAMTSL5 (also known as a disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 or ADAMTS-like protein 5) is a protein related to the ADAMTS superfamily of secreted zinc metalloproteases [53]. Though its biological function is poorly understood, ADAMTSL5 has an affinity for fibrillin-1 and fibrillin-2 and may play an important role in the formation of microfibrils and the regulation of components of the extracellular matrix (Table 1) [54]. In 2015, ADAMTSL5 became the focus of psoriasis research after a study by Arakawa et al. [55•] indicating that this protein is upregulated in melanocytes and may be the target of clonal $CD8^+$ T lymphocytes isolated from psoriatic skin lesions.

Previous studies had established the pathogenic role of $CD8^+$ T cells and their preferential rearrangement of the Vβ13S1 TCR in psoriasis [18, 56]. Based on this information, Arakawa et al. [55•] established a T cell hybridoma cell line from a reconstituted $CD8^+$ T cell clone (Vα3S1/Vβ13S1) collected from a *HLA-C*06:02*-positive psoriasis patient. Using this model, the authors were able to assess TCR activation under multiple experimental conditions, such as pre-incubation and co-culturing with melanocytes and keratinocytes. Their work revealed that only melanocytes from *HLA-C*06:02*-positive individuals (regardless of psoriasis status) activated the Vα3S1/Vβ13S1 TCR hybridoma. This activation was further enhanced by the upregulation of HLA-C via incubation with IFNγ. TCR activation was not observed during co-culturing with keratinocytes or skin fibroblasts from *HLA-C*06:02*-positive individuals or melanocytes from *HLA-C*06:02*-negative individuals.

Immunostaining for CD8 and several melanocyte markers in psoriatic lesions also revealed a close spatial association between $CD8^+$ T cells and melanocytes compared to inflamed, non-psoriatic skin suggestive of a melanocyte-directed autoimmune immune response. Importantly, ADAMTSL5 stimulation of T cells isolated from the peripheral blood of psoriasis patients revealed increased expression of IL-17A and IFNγ in approximately two-thirds of patients compared to healthy controls, and these T cells do not appear to induce melanocyte destruction upon infiltration of the skin.

The identification of ADAMTSL5 in melanocytes as a potential psoriasis autoantigen is of interest for several reasons. First, melanocyte expansion occurs in psoriatic skin along with increases in epidermal thickness. This places melanocytes and the ADAMTSL5 antigen at the primary site of T cell infiltration in lesional psoriatic plaques. Further, a recent immunohistochemical analysis of untreated, lesional psoriasis plaques revealed that the melanocytes within psoriasis lesions displayed features of activation, such as dilatation and the presence of long, prominent dendrites [57]. These observations suggest that the expansion of melanocytes in the lesional skin of psoriasis patients has the ability to directly activate IL-17-producing T cells that are restricted by *HLA-C*06:02* via ADAMTSL5, thereby perpetuating the central inflammatory signaling pathway in this condition (Fig. 1). Whether this process is restricted to melanocytes is not entirely clear. A recent study from our laboratory showed strong expression of ADAMTSL5 in keratinocytes, and discrete dermal cells, suggesting that the likelihood of ADAMTSL5-induced T cell activation may not be unique to melanocytes [58].

PLA2G4D

PLA2G4D (also known as phospholipase A_2 group IVD or $cPLA_2\delta$) is a calcium-dependent member of the phospholipase A_2 (PLA_2) enzyme family known to catalyze the production of lysophospholipids and pro-inflammatory free fatty acids, such as arachidonic acid [59]. Increased PLA_2 activity has been associated with a variety of inflammatory conditions, including acute pancreatitis, bacterial sepsis, malignancy, acute respiratory distress syndrome, and rheumatoid arthritis [60]. PLA_2 activity has also been linked to T cell-specific responses involved in a number of inflammatory disorders involving the skin, such as reactions to bee and wasp venom [61]. The presentation of bee and wasp antigens to T cells is dependent on CD1a-expressing APCs, such as macrophages, Langerhans cells (LC), and mDCs [61, 62]. Furthermore, transgenic mice overexpressing human group II PLA_2 exhibited phenotypic features of psoriasis, such as epidermal thickening, hyperkeratosis, and alopecia [63]. Increased expression of PLA2G4D in the epidermis of lesional skin from patients with psoriasis, atopic dermatitis, and mycosis fungoides has also been described [59]. Collectively, these observations suggested that the dysregulation of PLA_2 activity and/or the increased expression of PLA2G4D in psoriatic tissues could lead to the formation of autoreactive T cells in a $CD1a^+$-dependent manner.

The role of PLA2G4D in the development of autoreactive T cells in psoriasis is significant for several reasons. First, PLA2G4D is a novel psoriasis-associated PLA_2 enzyme [59], and increased PLA_2 activity is observed in psoriasis plaques [64]. Second, PLA2G4D expression is increased in keratinocytes and mast cells and results in the generation of non-peptide, neolipid antigens. These lipid antigens are then prepared for antigen presentation and recognition by $CD1a^+$-reactive T cells, which produce high amounts of Th1 and T17 cytokines [65•]. Finally, mast cell-derived lipid autoantigens can be transferred to neighboring APCs via small, secreted multivesicular bodies (i.e., exosomes) and may, therefore, contribute to psoriasis pathogenesis by facilitating the activation of autoreactive T cells in this disease. These findings provide evidence for the immunogenicity of non-peptide antigens in psoriasis, which could explain why subsets of psoriasis patients lack LL-37 or ADAMTSL5-specific T cells [65•]. Unfortunately, these non-peptide, lipid antigens are more difficult to characterize since they cannot be stained using traditional immunohistochemical antibodies.

Future Directions

The overexpression of LL-37, ADAMTSL5, and PLA2G4D in psoriatic skin coupled with the identification of AMP-specific T cells provides direct evidence for the role of autoantigens in the pathophysiology of psoriasis. The studies outlined above also provide insights into the possible factors contributing to the breakdown of immune tolerance in the skin and the development of autoimmunity in this condition. Furthermore, the relationship between AMPs and the activation of specific immune cells (e.g., pDCs and mDCs) following trauma provides a possible mechanism for the Koebner phenomenon seen in many patients with psoriasis. There are a number of important questions, however, that remain unanswered and need to be carefully explored in subsequent psoriasis studies.

Additional information about the specific mechanisms leading to the breakdown of immune tolerance in the skin is of the utmost importance. Like many autoimmune conditions, very little is known about the event(s) leading to the initiation of psoriatic disease in susceptible individuals. While the identification of autoantigens in actively, inflamed psoriatic skin is an important association, a causal relationship has not yet been shown. Rather, the specific factors which trigger disease onset are currently unknown. The potential contribution of bacterial infections, such as streptococcal pharyngitis, and the skin microbiome to the breakdown of cutaneous tolerance via

mimicry or T cell cross-reactivity should be explored. It is also interesting to note that the primary mechanism of autoimmunity in plaque psoriasis appears to be distinctly different than other autoimmune conditions, such as rheumatoid arthritis or insulin-dependent diabetes mellitus, in that the pathogenic immune response in psoriasis does not lead to permanent damage of the skin. Elucidating the immune mechanisms that account for this difference is important and can advance our understanding of autoimmunity.

A thorough, systematic evaluation of psoriatic tissues aimed at identifying additional autoantigens and their expression in various skin compartments is also necessary. This need is highlighted by the fact that LL-37, ADAMTSL5, and neolipid-specific T cells are not present in all patients diagnosed with psoriasis. It is reasonable to assume that the etiology of psoriasis, like many other autoimmune conditions, may be sustained by the continuous stimulation of T cells specific for multiple peptide or non-peptide autoantigens. The identification of additional psoriasis autoantigens would add to our understanding of the natural history of psoriasis and may even lead to the development of a psoriasis-specific panel of biomarkers to be used for the screening of patients with uncertain cutaneous lesions. Whether the autoantigens found in other subtypes of psoriasis (e.g., psoriatic arthritis, pustular, inverse, or guttate) are similar or completely different than those found in plaque psoriasis is not yet known. It will also be interesting to explore the relationship between these autoantigens and other clinical parameters, such as disease severity and age of onset (e.g., early versus late disease onset).

Finally, the relationship between psoriasis autoantigens and known psoriasis susceptibility loci (e.g. *HLA-C*06:02*) has not been carefully studied. While several studies have suggested the importance of specific HLA or other class I alleles in the development of autoimmunity in psoriasis, other studies have found that autoantigen-specific T cell reactivity was independent of a patient's HLA status [35•]. Whether specific susceptibility loci correlate with the cutaneous expression of autoantigens in psoriatic skin or a patient's risk for developing disease will require further study. Lastly, further details about the internal processing, trafficking to specific cellular compartments, and presentation of autoantigens in immune cells are needed. One fundamental question is whether APCs found in psoriatic skin are able to process autoantigens and present these antigens via specific major histocompatibility complex (MHC) class II molecules. Similarly, can specific target cells (e.g., keratinocytes) within psoriatic skin present autoantigens and directly stimulate infiltrating T cells within the epidermis?

Conclusion

Psoriasis is a common, chronic inflammatory disorder primarily mediated by T cells. The pathophysiology of this condition is due to the complex interchange between the skin, immune system, environment, and psoriasis-associated susceptibility loci such as *HLA-C*06:02*. The recent identification of three psoriasis autoantigens, some presented by *HLA-C*06:02*, lends support for the role of autoimmunity in this disease and suggests that these antigens may trigger the onset of psoriasis in susceptible individuals with specific environmental exposures. A comprehensive evaluation and search for psoriasis autoantigens is warranted and may reveal novel immune mechanisms related to disease pathogenesis. Ultimately, the uncovering of these immune mechanisms may lead to the development of novel treatments or therapeutic strategies, bringing us one step closer to finding a cure for this chronic inflammatory condition.

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Compliance with Ethical Standards

Conflict of Interest Jason E. Hawkes and Jose A. Gonzalez declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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