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Review

Potential Role of the Epidermal Differentiation Complex in the Pathogenesis of Psoriasis

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Abstract

The skin is the largest barrier organ of the human body and serves to protect the internal structure of the body from the harmful environment. The epidermis forms the outermost layer and is exposed to the environment. Keratinocytes are important constituent cells of the epidermis and alter their morphology and structural integrity through a highly complex differentiation process referred to as cornification. Abnormalities in the process of epidermal cornification can lead to skin barrier dysfunction. The epidermal differentiation complex (EDC) is a gene cluster located within a 2 Mb region of human chromosome 1q21. EDC is responsible for epithelial tissue development and for properties of the stratum corneum. One of the most important features of psoriasis is the abnormal terminal differentiation of keratinocytes. However, the relationship between EDC and the occurrence of psoriasis is still unclear. In this review, we summarize current knowledge regarding the physiological functions of EDC and discuss its possible contributions to the pathogenesis of psoriasis.

Keywords: psoriasis; epidermal differentiation complex; filaggrin; late-cornified envelope; involucrin; loricrin; S100

1. Introduction

The outermost layer of the skin, or epidermis, provides a tight barrier for the human body. The cellular composition of the epidermis consists mainly of keratinocytes, melanocytes, Langerhans cells and Merkel cells. Upon leaving the basal layer, keratinocytes begin a complex mechanism of terminal differentiation that culminates in formation of the stratum corneum. This process is known as epidermal differentiation. The epidermal differentiation complex (EDC) is a cassette of genes present in a 2 Mb region of human chromosome 1q21. It is comprised of 62 coding genes present within four gene families, namely: filaggrin (FLG) and FLG-like, late cornified envelope genes (LCEs), small proline-rich regions (SPRRs), and S100 genes (Fig. 1). EDC encodes structural and functional proteins that have a profound effect on terminal differentiation of the human epidermis [1–5].

Epidermal cells undergo a set of programmed proliferation /differentiation events and express specific proteins during an ordered and sequential process (Fig. 2a). Following formation of the spinous layer, the cells acquire keratohyaline granules containing mostly profilaggrin. Profilaggrin is cleaved into filaggrin monomers of approximately 37 kDa which can cause keratin filaments to aggregate into tight bundles. Other structural proteins including loricrin (LOR), involucrin (IVL), small proline-rich proteins (SPRRs), and late cornified envelope proteins (LCEs), are expressed later in the process. Subsequently, the epidermal proteins are cross-linked by transglutaminases to form a cornified envelope. However, abnormalities of this process may lead to barrier dysfunction, resulting in skin disorders such as ichthyosis vulgaris, atopic dermatitis (AD), psoriasis, and skin-related neoplasia [6–10]. The turnover time of normal skin cells is approximately one month, whereas in psoriasis the epidermal cells are replaced in just 4 days [11]. The keratinocyte is the main building block of the epidermis and is the target cell for the major cytokines involved in the psoriatic inflammatory process. The onset and development of the psoriatic phenotype occurs because of increased proliferation and impaired differentiation of keratinocytes (Fig. 2b) [12,13].

2. Filaggrin

Human filaggrin (FLG) is a filament aggregation protein derived from profilaggrin and containing more than 10 filaggrin-repeat units. FLG plays a critical role in the formation of the skin barrier [14]. Based on its cDNA sequence, human profilaggrin contains 25% serine, 15% glycine, 12% histidine, and 10% arginine residues. The profilaggrin precursor mRNA is transcribed as the keratinocytes differentiate into cornecytes [15]. The protein is then synthesized and phosphorylated in the epidermal granular layer. It is subsequently dephosphorylated and cleaved into monomeric filaggrin by a complex group of proteases during the keratinocyte differentiation process from granules to cornified cells [16]. Filaggrin monomers bind to keratin and aggregate the intermediate filaments, thus causing cytoplasmic collapse and the flattening of keratinocytes. Fi-

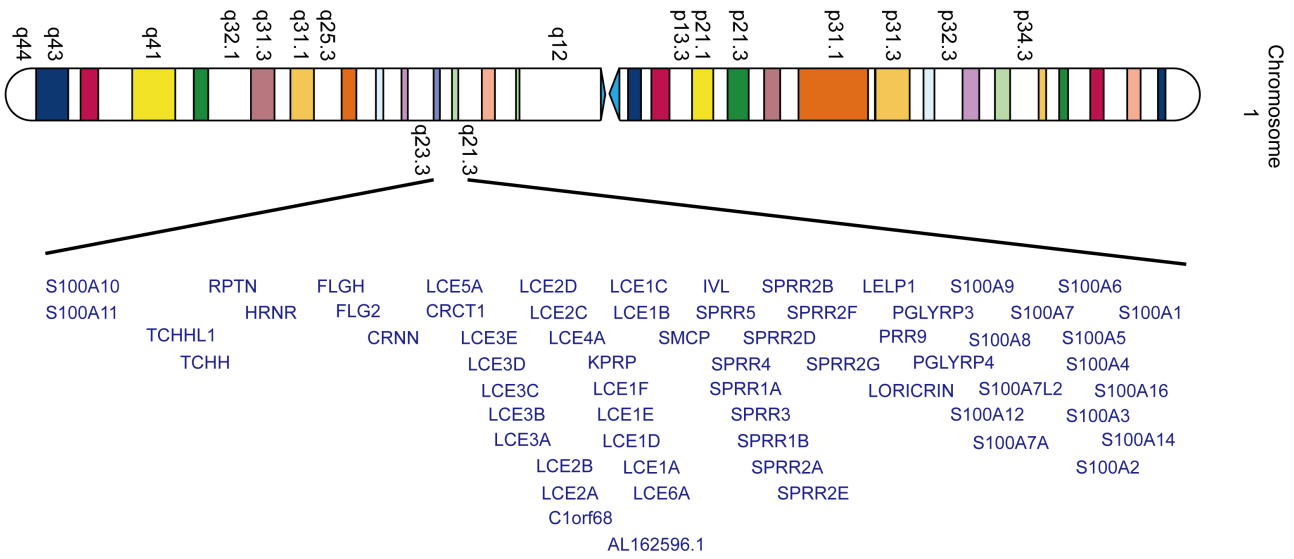

Fig. 1. Schematic representation of human EDC genes on chromosome 1q21.

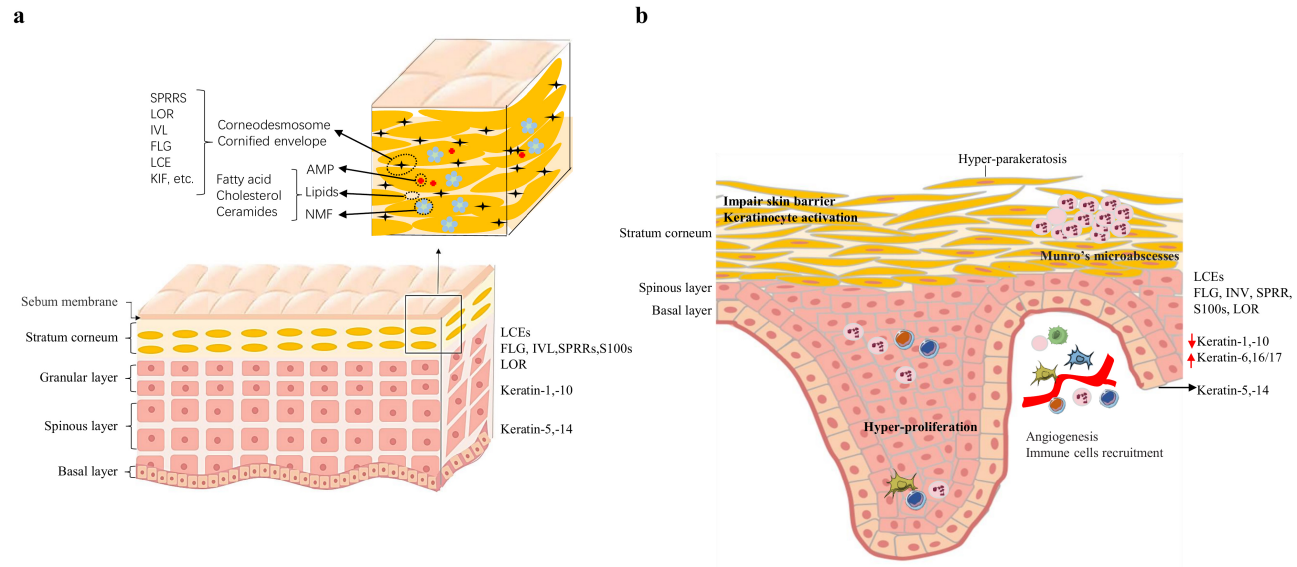

Fig. 2. The normal and psoriatic epidermic structure. (a) Epidermal structure and establishment of the epidermal barrier. During the different stages of epidermal differentiation, epidermal cells express different proteins. (b) Altered epidemic structure present in psoriasis. AMP, antimicrobial peptides; NMF, natural moisturing factor; KIF, keratin intermediate filament; IL, interleukin.

laggrin is then degraded into free amino acids as the corneocytes move outward through the inner layers of the cornified layer. Although filaggrin exists only transiently, it maintains hydration of the stratum corneum and provides a solid barrier for the skin [17].

Filaggrin expression in psoriatic lesions is significantly reduced compared with normal skin [18]. In addition, several studies have shown that inflammatory axis-related cytokines, such as IL-17a, TNF-α, Oncostatin M and IL-36γ, also induce down-regulation of *FLG* expression in psoriasis mouse models and in HaCaT cells. The level of filaggrin mRNA synthesis in keratinocytes derived from healthy doners decreased significantly in response to T_H-1- and T_H-2-associated cytokines [19–22]. Interestingly, after treatment for psoriasis, increased expression of *FLG* occurs following the down-regulation of proinflammatory factors, thereby improving the skin barrier and resulting in remission [23]. Many variants have been identified in *FLG* genes over the last two decades. These mutations include nucleotide base substitutions, out of frame insertions or deletions, and noncoding mutations in exon 3 of the profilaggrin gene. Loss-of-function mutations in *FLG* genes can cause ichthyosis vulgaris, atopic dermatitis, atopic asthma, as well as several other allergic or immune diseases [24].

Table 1. The association between *FLG* mutations and psoriasis in different populations.

Population	Variant	Study group	Result	Reference number
Ireland and UK	R501X (rs61816761)	Ps (n = 691) Controls (n = 2117)	no significant association (p = 0.075)	[27]
	2282del4 (rs558269137)	Ps (n = 691) Controls (n = 2117)	no significant association (p = 0.932)	
Germany	R501X (rs61816761)	PsV (n = 737) Controls (n = 721)	no significant association (p = 0.398)	[18]
		PsA (n = 720) Controls (n = 721)	no significant association (p = 0.675)	
	2282del4 (rs558269137)	PsV (n = 702) Controls (n = 704)	no significant association (p = 0.386)	
		PsA (n = 703) Controls (n = 704)	no significant association (p = 0.291)	
China (Taiwan)	P478S (rs11584340)	Ps (n = 314) Controls (n = 611)	a significant association (p = 0.020)	[25]
China (Mainland)	p.K4022X (rs146466242)	Ps (n = 414) Controls (n = 500)	a significant association (p = 0.011)	[26]

Ps means psoriasis, PsA means Psoriatic arthritis, PsV means Psoriasis vulgaris.

A number of studies have been performed to determine whether *FLG* deficiency is involved in the pathogenesis of psoriasis (Table 1, Ref. [18,25–27]). Hüffmeier and colleagues reported that the expression of *FLG* genes was downregulated in psoriatic skin. However, mutations linked to filaggrin deficiency showed no obvious associations with psoriasis vulgaris or psoriatic arthritis in a genetic analysis of German populations [18]. A case-control study described a significant difference in *FLG* P478S (rs11584340) genotype frequencies between psoriasis patients and controls in Taiwan, suggesting this polymorphism plays an important role in genetic susceptibility to psoriasis [25]. A novel nonsense mutation in *FLG*, p.K4022X, was reported in a Chinese family with psoriasis coexisting with ichthyosis vulgaris, as well as a significant association with the occurrence of psoriasis in the Chinese population [26]. However, parallel studies conducted by other researchers reported inconsistent results for this mutation. A case-control study conducted to investigate the R510X and 2282del4 mutations in profilaggrin found no significant association with psoriasis in the Irish and UK populations [27]. Similar results were obtained from a general population study and from a meta-analysis [28], indicating these profilaggrin null mutations are not associated with the occurrence of psoriasis. Moreover, loss-of-function mutations in *FLG* do not appear to play a major role in childhood psoriasis [29].

Genetic mutations in *FLG* and changes in gene expression may therefore be involved in the susceptibility to psoriasis, but these associations have yet to be fully elucidated. More research is thus required to better understand the role of *FLG* mutations in the pathogenesis of psoriasis.

3. Late-Cornified Envelope (LCE)

Since 2008, the *LCE* gene cluster on chromosome 1q21 has been recognized as a predisposing site for psoriasis (Table 2, Ref. [30–35]) [30,31]. This cluster is further divided into six groups, *LCE1-LCE6*, based on their relevant amino acid sequence, genomic organization and expression pattern [36]. Most *LCE* genes are expressed in granular keratinocytes during keratinocyte differentiation and are amongst the final cornified cell envelope (CE) components to be cross-linked to this structure. The expression of *LCE2* is upregulated by calcium, while that of *LCE1 and LCE2* is induced by UV light [37]. Differential regulation of *LCE* gene expression occurs in the epidermis of psoriatic skin. Quantitative PCR showed that the expression level of all members of *LCE3* was too low to be detectable in normal skin, but was significantly upregulated in psoriatic lesions. In contrast to *LCE3,* expression levels for the *LCE-1, -2, -5* and *-6* groups were significantly downregulated in psoriasis [38]. Similar results were observed for the expression of *LCE* genes after tape stripping [39]. Using immunohistochemistry, LCE3 proteins were detected in the stratum spinosum (SS) and stratum granulosum (SG), but not in the stratum corneum (SC) [40]. Interestingly, Climbazole can also induce the expression of *LCE2* and *LCE3* genes in keratinocytes when used to treat dandruff and where the skin barrier is thought to be dysfunctional [41,42].

Real-time quantitative polymerase chain reaction (qPCR) analysis has shown that human *LCE1* and *LCE2* genes, especially *LCE1C, LCE2A* and *LCE2B,* are mainly expressed in the epidermis [37]. The *LCE1* group can be trans-activated by p53 and is thought to have tumor suppressor functions by regulating the activity of PRMT5 [25]. A GWAS analysis of European and American populations

Table 2. The association between *LCE* mutations and psoriasis in different populations.

Population	Variant	Study group	Result	Reference number
Europe/America	LCE1C (rs6701216)	Ps (n = 233) Controls (n = 519)	a significant association ($p = 6.2 \times 10^{-5}$)	[32]
Mongolia	LCE1C (rs6701216) LCE1B (rs12023196) LCE3A (rs4845454) LCE3D (rs512208) LCE3D (rs4112788) LCE3D (rs4085613) LCE3A (rs1886734)	PsV (n = 305) Controls (n = 383)	a significant association ($p < 0.05$) no significant association ($p > 0.05$)	[31]
China	LCE3A (rs4845454) LCE3A (rs1886734) LCE3D (rs4112788) LCE3D (rs4085613) LCE1B (rs12023196) LCE3C_LCE3B-del LCE3D (rs512208)	Ps (n = 1139) Controls (n = 1132)	a significant association ($p < 0.05$)	[30] [35]
Germany	LCE3C_LCE3B-del	PsA (n = 650) Controls (n = 937)	no significant association ($p = 0.088$)	[33]
Italy	LCE3C_LCE3B-del	PsA (n = 424) Controls (n = 450)	a significant association ($p = 0.03$)	[34]

Ps means psoriasis, PsA means Psoriatic arthritis, PsV means Psoriasis vulgaris.

published in 2008 reported that *LCE1C* (rs6701216) was a potential susceptibility site for psoriasis [32]. The *LCE1C* (rs6701216) and *LCE1B* (rs12023196) genes were later also found to have a strong association with psoriasis vulgaris in a population from Inner Mongolia [31].

The *LCE3* gene cluster can be further divided into five subgroups (*LCE3A, LCE3B, LCE3C, LCE3D* and *LCE3E*) with different structures and functions. Their expression is barely detectable in normal skin and in non-psoriatic lesions [37]. However, *LCE3* expression is induced in the epidermal layer of psoriasis lesions and after superficial skin injury. It has been speculated that *LCE3* may play an important role in repair of the skin barrier after superficial injury, whereas other *LCE* members may play significant roles in the maintenance of normal skin barrier function [2,38]. Several cytokines associated with psoriasis, including TNF-α, IL-1, and IL-6, significantly upregulate the expression of *LCE3*, whereas these cytokines plus the Th17 cytokine and IL-22 significantly downregulate the expression of *LCE1B*. However, IL-17 and IL-22 have no obvious effect on the expression of *LCE3* [38].

GWAS analysis has revealed that *LCE3A* gene mutations (rs4845454 and rs1886734) in the Chinese Han population were associated with the occurrence of psoriasis, suggesting this gene may be a predisposing factor for psoriasis [30]. Both *LCE3B* and *LCE3C* have been associated with the development of psoriasis in different ethnicities [33,43]. In several different populations, the frequency of *LCE3C_LCE3B*-del is much higher in psoriasis patients compared to controls [44,45]. Analysis of 2,831 samples from several European countries demonstrated an association between the *LCE3C_LCE3B*-del variant and psoriasis, consistent with a large family-based study published in 2009 [33]. Meanwhile, it was also confirmed that *LCE3C_LCE3B*-del is associated with psoriasis in the Chinese population [30]. A multicenter meta-analysis has confirmed that *LCE3C-LCE3B*-del is a susceptibility site for psoriasis in multiple European and Asian populations [45].

A possible association between *LCE3C_LCE3B*-del and arthritic psoriasis (PsA) remains uncertain due to insufficient data. No significant associations were observed between *LCE3C_LCE3B*-del frequency and PsA in German and Tunisian populations [33,44,46]. However, other studies have reported that *LCE3C_LCE3B*-del was associated with PsA in Italian and Spanish populations [34,47]. Although *LCE3C_LCE3B*-del is a well-established risk factor for psoriasis, it is not associated with the Koebner Phenomenon in psoriasis [48]. Other studies have shown that *LCE3C* and *LCE3B* are associated with certain immune diseases, such as rheumatoid arthritis and systemic lupus erythematosus [49,50].

With regards to *LCE3D*, the *LCE* gene cluster on 1q21 (rs4112788 and rs4085613) was found to have a close association with psoriasis in a large GWAS study of the Chinese population [30]. Based on the analysis of clinically relevant psoriasis vulgaris subtypes, significant associations were observed between the severity of cutaneous manifestations and LCE3D variants [51]. A novel missense vari-

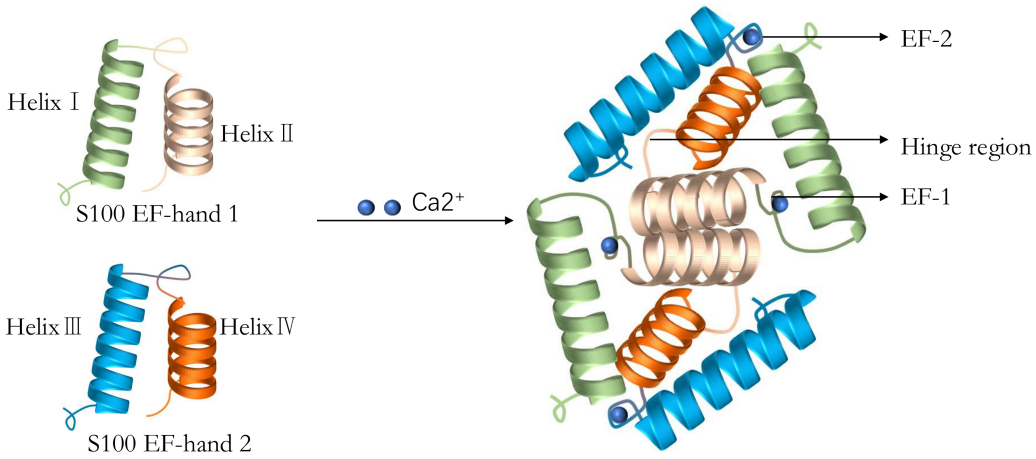

Fig. 3. The typical structure of S100 proteins including two EF-hands, four α-helical segments, a central hinge region connects these structures.

ant in *LCE3D* (rs512208) was reported in the Chinese Han population through a large-scale sequencing study of psoriasis patients [35]. A missense variant in the *LCE3D* locus (rs512208) was also reported to be the most important risk factor for psoriasis patients from Inner Mongolia [31]. Interestingly, proteins from the *LCE3* family show broad-spectrum antimicrobial activity, with *LCE3A* being the most potent [52,53].

The expression of *LCE4A* and *LCE5A* is barely detectable in human tissues, whereas *LCE6A* genes are upregulated during keratinocyte differentiation [37]. However, there is still a lack of evidence to link these three genes with the pathogenesis of psoriasis.

4. S100s

At least 24 different *S100* gene members have been identified to date, most of which are part of the EDC located on human chromosome 1q21 [54,55]. These proteins belong to the Ca^{2+}-binding protein family and have similar important structural features (Fig. 3) [56]. The S100 protein has been associated with several human diseases including cardiomyopathy, cancer and some skin diseases [57,58].

Epigenetic reprogramming is known to be an important factor in the development of psoriasis, with epigenetic regulation of S100 in particular having received a lot of attention. Recent results indicate that S100 protein expression may be correlated with the extent of DNA methylation in *S100* gene regulatory regions, generally presenting as a negative correlation. Differentially methylated CpGs in S100 were reproducibly identified between psoriatic and normal skin tissues, including S100A5, S100A9 and S100A12. Several studies have also reported that the abnormal methylation of S100 protein returns to a normal level after anti-TNF-α therapy [59–62].

No consensus has been reached on the relationship between S100B and psoriasis. S100B protein is overexpressed in psoriatic patients and shows a significant association with disease severity according to the Psoriasis Area and Severity Index (PASI) score [63]. However, another study found no significant association between S100B protein levels in the serum and the PASI score of psoriatic patients [64].

S100 protein A2 is expressed at high levels in psoriasis and has a protective effect against UV light [65,66]. The S100 proteins A4 and A6 are expressed in both the hair follicle bulge and during hair follicle germination. They are significantly associated with the activation of hair follicle stem cells, suggesting they play a crucial role in epidermal renewal [67].

The S100 proteins A7, A12 and A15 are highly expressed in psoriatic skin and blood. Serum levels of S100A7 and S100A12 are significantly associated with psoriasis activity [68]. There are some inconsistent results, however. For example, Borsky and colleagues did not find any association between S100A7/A12 levels and disease severity [69]. Furthermore, S100A7 protein can increase the levels of stress-induced, psoriasis-related angiogenic factors, which in turn act on dermal endothelial cells to promote angiogenesis [70]. The interaction between overexpressed S100A7 and Jab1 may contribute to p27Kip1-dependent proliferative dysfunction in psoriasis [71]. The S100A7 serum level is also correlated with the occurrence of subclinical atherosclerosis in psoriasis [72]. The S100 A15 protein is highly homologous with S100A7. Th17 cytokines play an important role in the pathogenesis of psoriasis by inducing the expression of pro-inflammatory S100A15 through the IL-17AR in keratinocytes. This process can be suppressed by the vitamin D analog calcipotriol, or by narrow-band UVB. Therefore, S100 A15 protein may be a promising marker for the treatment response in psoriasis [73,74].

Several studies have investigated the association between the S100 proteins A8/A9 and psoriasis. Both S100A8 and S100A9 are expressed and released by keratinocytes and activated leukocytes during skin inflammation and wound healing, including psoriatic lesions [75–77]. The tetramerization of S100A8/S100A9 induced by calcium can inhibit the pro-inflammatory function of S100A8/S100A9 dimers [78]. The expression of S100A8 and S100A9 is increased in imiquimod-induced, psoriasis-like skin inflammation and can be stimulated by several of the psoriasis-associated cytokines or chemokines, in particular IL-17A and IL-1α [75,76]. The significantly increased expression levels of S100 A8 and A9 in psoriasis patients not only reflect the abnormal differentiation of keratinocytes, but also correlate with disease activity [75]. The S100A8/S100A9 complex exerts functional activity in psoriasis by modulating the expression of complement factor C3 [79]. S100 A8 and A9 are also considered to be damage-modulating proteins [77].

In conclusion, several studies have suggested that S100 proteins play an important role in psoriasis because of their contribution to the severity and progression of disease, although the mechanisms remain mostly unclear.

5. Loricrin and Involucrin

Loricrin (LOR) and Involucrin (IVL) are structurally similar and highly homologous proteins. They have unique internal domains that are cross-linked by glutamine transaminase to bind different glutamine, proline, and serine-rich repeats [3]. There is evidence that LOR and IVL have important roles in terminal epidermal differentiation, while also being involved in the maintenance of epidermal homeostasis.

LOR is the major structural protein of the epidermal keratinocyte envelope (CE) and is mainly expressed in the granular layers and superior spinous layer [3]. Patients with *LOR* mutations share some common features, including diffuse palmoplantar hyperkeratosis [78,80,81]. However, Loricrin knockout (LKO) mice show only mild and transient erythema in the neonatal period, which then improves in adult mice. This may be explained by compensatory mechanisms that upregulate the expression of other barrier proteins such as SPRRP2D, SPRRP2H, and Lce1 to make up for the loss of LOR expression [82,83]. Psoriasis-associated cytokines such as IL17A and IL22 are known to downregulate the expression of LOR, which then damages the skin barrier function in psoriasis [84,85]. Currently however, there is still a lack of evidence regarding the possible mechanism of action of LOR [86].

Another important CE protein, IVL, is only expressed in the granular and supra-spinous layers in normal epidermitis. IVL is one of the main components of CE and is a marker of the early differentiation of keratinocytes [87]. Several studies have suggested a trend for increased IVL expression in patients with psoriasis [88]. Moreover, it is known that some cytokines related to psoriasis (IL-1, IFN-γ, IL17A etc.) as well as PKC (protein kinase C associated with psoriasis) can induce the expression of IVL [89–92]. However, Boniface *et al.* [84] demonstrated that IVL expression could be downregulated by IL22.

In brief, LOR and IVL may have important roles in maintaining skin barrier function and homeostasis. It is reasonable to speculate these proteins may also have different roles in the initial and maintenance phases of psoriasis. More research is needed to reveal the mechanisms by which LOR and IVL contribute to psoriasis through their effects on terminal differentiation of the epidermis.

6. Non-Coding RNAs that Control Gene Expression of the Epidermal Differentiation Complex

Although past research has mostly focused on genes that code for proteins, it is now clear that non-coding RNAs play an important part in the regulation of many biological processes. This has led to several new research fields, and in particular the roles of microRNAs (miRNA) and lncRNAs. RNA-seq technology has identified many differentially expressed lncRNAs between normal and psoriatic skin. Interestingly, the EDC is one of the highest lncrna density regions and was significantly enriched for at least 28 lncRNAs [93–95]. These results suggest not only a distinct role for lncRNAs in the development of psoriasis, but also provide further evidence for an important role of the EDC in the pathogenesis of psoriasis. Although several studies have found that miRNAs can regulate the proliferation and differentiation of keratinocytes, regulation of gene expression in the EDC complex of psoriasis patients requires further exploration [96]. Due to their specific expression and function, further research on both miRNA and lncRNA could lead to the discovery of new biomarkers for the diagnosis, prognosis and monitoring of therapeutic effects in psoriasis.

7. Summary and Conclusions

The EDC is composed of four gene families: filaggrin/FLG-like, LCE genes, S100 genes, and small proline-rich region (SPRRs, including LOR and IVL). EDC genes encode structural and functional proteins that have a profound impact on terminal differentiation in the human epidermis leading to the formation of a solid physical and chemical barrier of skin. Psoriasis is a common chronic inflammatory skin disease that can be triggered by multiple risk factors. This disease involves a number of processes including antigen presentation, transcriptional regulation, immune cell activation, inflammatory cytokine networks, and cell signaling. Abnormalities in the proliferation and differentiation of keratinocytes are the main pathophysiological manifestations of psoriasis. Traditionally, psoriasis has been considered as a Th1/17 cell-mediated and IL-23/IL-17 inflammatory axis-dependent systemic disease that is based

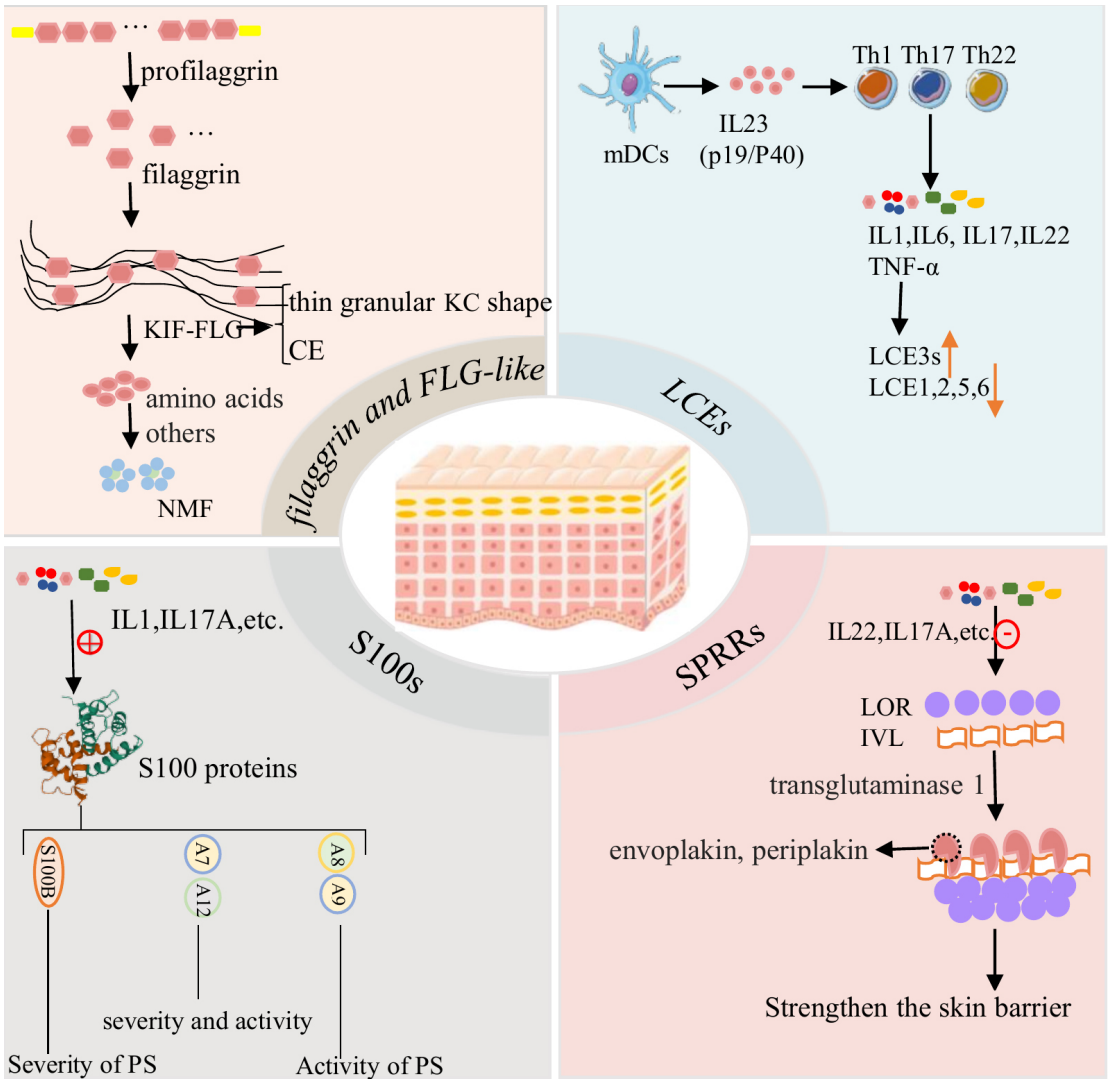

Fig. 4. The possible mechanisms of the expression of EDC genes in the occurrence and development of psoriasis.

on a complex genetic disorder and modulated by environmental factors.

Over the past few decades, considerable progress has been made in our understanding of the role of the EDC in the pathogenesis of psoriasis. However, much more remains to be learned about the pathogenesis of this disease.

Several studies have shown that mutations in *EDC* genes can not only trigger the development of psoriasis, but are also associated with the progression and severity of disease. Although some genetic risk loci for psoriasis have been identified by GWAS analyses, further studies are needed to determine the mechanisms by which EDC gene products affect keratinocyte differentiation and proliferation. In theory, a single or combination of EDC gene variants could affect differentiation of the epidermidis and its integrity. Once the keratinocyte differentiation process from granules to cornified cells is interrupted, the cornified envelope loses its normal physical function. As a consequence, skin barrier damage will be exacerbated in the presence of external mechanical stimulation, resulting in disruption of skin microbiota homeostasis, invasion of pathogens, activation of innate or adaptive immune responses, infiltration of inflammatory cells into the epidermis and dermis, and abnormal proliferation of keratinocytes. Meanwhile, destruction of the skin barrier may also initiate the repair process to upregulate the expression of other EDC genes such as *LCE3* and *IVL* [37,89]. Increased expression of S100-related genes is correlated with the severity of psoriasis [76]. Overexpression of the EDC family of genes may promote the secretion of more inflammatory factors by keratinocytes, rather than inducing the denuclearization process. Nevertheless, several EDC genes are downregulated, including FLG. Both innate and adaptive immunity lead to the activation of keratinocytes, resulting in the production of Th1/17-related cytokines which further influences the expression of EDC-related genes and damages the epidermal barrier. This process can lead to a cascading inflammatory response loop and to abnormal proliferation of keratinocytes (Fig. 4).

There is currently a lack of suitable animal models that accurately reflect the clinical features of human psoriasis. These could serve as a useful preclinical research tool for testing new candidate therapeutics and for exploring the pathogenesis of psoriasis. What occurs when a specific EDC gene is silenced or overexpressed in mice? In particular, do keratinocyte abnormalities caused by the absence or overexpression of EDC genes contribute to the occurrence and development of psoriatic-like inflammation in mice? Large cohort studies of EDC gene variants in patients with different stages of psoriasis and from various worldwide populations may reveal additional genetic risk factors for psoriasis. The development of suitable animal models might also lead to the discovery of novel candidate drugs for the future treatment of psoriasis.

Author Contributions

DQ and LM prepared the initial draft of the review. LQ reviewed and ensured that the descriptions are accurate. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Hoffjan S, Stemmler S. On the role of the epidermal differentiation complex in ichthyosis vulgaris, atopic dermatitis and psoriasis. British Journal of Dermatology. 2007; 157: 441–449.

[2] Henry J, Toulza E, Hsu CY, Pellerin L, Balica S, Mazereeuw-Hautier J, *et al*. Update on the epidermal differentiation complex. Frontiers in Bioscience (Landmark edition). 2012; 17: 1517–1532.

[3] Kypriotou M, Huber M, Hohl D. The human epidermal differentiation complex: cornified envelope precursors, S100 proteins and the 'fused genes' family. Experimental Dermatology. 2012; 21: 643–649.

[4] Sobiak B, Graczyk-Jarzynka A, Leśniak W. Comparison of DNA Methylation and Expression Pattern of S100 and other Epidermal Differentiation Complex Genes in Differentiating Keratinocytes. Journal of Cellular Biochemistry. 2016; 117: 1092–1098.

[5] Połeć A, Rowe AD, Blicher P, Suganthan R, Bjørås M, Bøe SO. PML Regulates the Epidermal Differentiation Complex and Skin Morphogenesis during Mouse Embryogenesis. Genes. 2020; 11: 1130.

[6] Baroni A, Buommino E, De Gregorio V, Ruocco E, Ruocco V, Wolf R. Structure and function of the epidermis related to barrier properties. Clinics In Dermatology. 2012; 30: 257–262.

[7] Natsuga K. Epidermal barriers. Cold Spring Harbor Perspectives in Medicine. 2014; 4: a018218.

[8] Vogel O. Redetermination of the molecular weights of the components of the pyruvate dehydrogenase complex from E. coli Kl2+. Biochemical and Biophysical Research Communications. 1977; 74: 1235–1241.

[9] Marshall D, Hardman MJ, Nield KM, Byrne C. Differentially expressed late constituents of the epidermal cornified envelope. Proceedings of the National Academy of Sciences of the United States of America. 2001; 98: 13031–13036.

[10] Stawczyk-Macieja M, Szczerkowska-Dobosz A, Rębała K, Purzycka-Bohdan D. Genetic background of skin barrier dysfunction in the pathogenesis of psoriasis vulgaris. Advances in Dermatology and Allergology. 2015; 2: 123–126.

[11] Feldman SR, Clark AR. PSORIASIS. Medical Clinics of North America. 1998; 82: 1135–1144.

[12] Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. The Lancet. 2021; 397: 1301–1315.

[13] Kamiya K, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk Factors for the Development of Psoriasis. International Journal of Molecular Sciences. 2019; 20: 4347.

[14] McKinley-Grant LJ, Idler WW, Bernstein IA, Parry DA, Cannizzaro L, Croce CM, *et al.* Characterization of a cDNA clone encoding human filaggrin and localization of the gene to chromosome region 1q21. Proceedings of the National Academy of Sciences of the United States of America. 1989; 86: 4848–4852.

[15] Rothnagel JA, Mehrel T, Idler WW, Roop DR, Steinert PM. The gene for mouse epidermal filaggrin precursor. its partial characterization, expression, and sequence of a repeating filaggrin unit. Journal of Biological Chemistry. 1987; 262: 15643–15648.

[16] Steinert PM, Cantieri JS, Teller DC, Lonsdale-Eccles JD, Dale BA. Characterization of a class of cationic proteins that specifically interact with intermediate filaments. Proceedings of the National Academy of Sciences of the United States of America. 1981; 78: 4097–4101.

[17] Hoober JK, Eggink LL. The Discovery and Function of Filaggrin. International Journal of Molecular Sciences. 2022; 23: 1455.

[18] Hüffmeier U, Traupe H, Oji V, Lascorz J, Ständer M, Lohmann J, *et al*. Loss-of-Function Variants of the Filaggrin Gene are not Major Susceptibility Factors for Psoriasis Vulgaris or Psoriatic Arthritis in German Patients. Journal of Investigative Dermatology. 2007; 127: 1367–1370.

[19] Pohin M, Guesdon W, Mekouo AAT, Rabeony H, Paris I, Atanassov H, *et al*. Oncostatin M overexpression induces skin inflammation but is not required in the mouse model of imiquimod-induced psoriasis-like inflammation. European Journal of Immunology. 2016; 46: 1737–1751.

[20] Kim BE, Howell MD, Guttman E, Gilleaudeau PM, Cardinale IR, Boguniewicz M, *et al*. TNF-α Downregulates Filaggrin and Loricrin through c-Jun N-terminal Kinase: Role for TNF-α Antagonists to Improve Skin Barrier. Journal of Investigative Dermatology. 2011; 131: 1272–1279.

[21] Gutowska-Owsiak D, Schaupp AL, Salimi M, Selvakumar TA, McPherson T, Taylor S, *et al.* IL-17 downregulates filaggrin and affects keratinocyte expression of genes associated with cellular adhesion. Experimental Dermatology. 2012; 21: 104–110.

[22] Wang W, Yu X, Wu C, Jin H. IL-36γ inhibits differentiation and induces inflammation of keratinocyte via Wnt signaling pathway in psoriasis. International Journal of Medical Sciences. 2017; 14: 1002–1007.

[23] Varma SR, Sivaprakasam TO, Mishra A, Prabhu S, M R, P R. Imiquimod-induced psoriasis-like inflammation in differentiated Human keratinocytes: its evaluation using curcumin. European Journal of Pharmacology. 2017; 813: 33–41.

[24] Hoppe T, Winge MCG, Bradley M, Nordenskjöld M, Vahlquist A, Törmä H, *et al*. Moisturizing treatment of patients with atopic dermatitis and ichthyosis vulgaris improves dry skin, but has a modest effect on gene expression regardless of FLG genotype. Journal of the European Academy of Dermatology and Venereology. 2015; 29: 174–177.
[25] Chang Y, Wu W, Chen C, Hu C, Hsu L. Association between P478S polymorphism of the filaggrin gene and risk of psoriasis in a Chinese population in Taiwan. Archives of Dermatological Research. 2008; 300: 133–137.
[26] Hu Z, Xiong Z, Xu X, Li F, Lu L, Li W, *et al*. Loss-of-function mutations in filaggrin gene associate with psoriasis vulgaris in Chinese population. Human Genetics. 2012; 131: 1269–1274.
[27] Zhao Y, Terron-Kwiatkowski A, Liao H, Lee SP, Allen MH, Hull PR, *et al.* Filaggrin null alleles are not associated with psoriasis. Journal of Investigative Dermatology. 2007; 127: 1878–1882.
[28] Thyssen JP, Johansen JD, Carlsen BC, Linneberg A, Meldgaard M, Szecsi PB, *et al*. The filaggrin null genotypes R501X and 2282del4 seem not to be associated with psoriasis: results from general population study and meta-analysis. Journal of the European Academy of Dermatology and Venereology. 2012; 26: 782–784.
[29] Winge MC, Suneson J, Lysell J, Nikamo P, Liedén A, Nordenskjöld M, *et al*. Lack of association between filaggrin gene mutations and onset of psoriasis in childhood. Journal of the European Academy of Dermatology and Venereology. 2013; 27: e124–e127.
[30] Zhang X, Huang W, Yang S, Sun L, Zhang F, Zhu Q, *et al*. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nature Genetics. 2009; 41: 205–210.
[31] Sun L, Cao Y, He N, Han J, Hai R, Arlud S, *et al.* Association between LCE gene polymorphisms and psoriasis vulgaris among Mongolians from Inner Mongolia. Archives of Dermatological Research. 2018; 310: 321–327.
[32] Liu Y, Helms C, Liao W, Zaba LC, Duan S, Gardner J, *et al*. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genetics. 2008; 4: e1000041.
[33] Hüffmeier U, Estivill X, Riveira-Munoz E, Traupe H, Wendler J, Lohmann J, *et al*. Deletion of LCE3C and LCE3B genes at PSORS4 does not contribute to susceptibility to psoriatic arthritis in German patients. Annals Of The Rheumatic Diseases. 2010; 69: 876–878.
[34] Docampo E, Giardina E, Riveira-Muñoz E, de Cid R, Escaramís G, Perricone C, *et al*. Deletion of LCE3C and LCE3B is a susceptibility factor for psoriatic arthritis: a study in Spanish and Italian populations and meta-analysis. Arthritis & Rheumatism. 2011; 63: 1860–1865.
[35] Tang H, Jin X, Li Y, Jiang H, Tang X, Yang X, *et al.* A large-scale screen for coding variants predisposing to psoriasis. Nature Genetics. 2014; 46: 45–50.
[36] Bergboer JGM, Zeeuwen PLJM, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. Journal of Investigative Dermatology. 2012; 132: 2320–2331.
[37] Jackson B, Tilli CMLJ, Hardman MJ, Avilion AA, MacLeod MC, Ashcroft GS, *et al*. Late Cornified Envelope Family in Differentiating Epithelia—Response to Calcium and Ultraviolet Irradiation. Journal of Investigative Dermatology. 2005; 124: 1062–1070.
[38] Bergboer JGM, Tjabringa GS, Kamsteeg M, van Vlijmen-Willems IMJJ, Rodijk-Olthuis D, Jansen PAM, *et al*. Psoriasis Risk Genes of the Late Cornified Envelope-3 Group are Distinctly Expressed Compared with Genes of other LCE Groups. The American Journal of Pathology. 2011; 178: 1470–1477.
[39] He H, Bissonnette R, Wu J, Diaz A, Saint-Cyr Proulx E, Maari C, *et al*. Tape strips detect distinct immune and barrier profiles in atopic dermatitis and psoriasis. Journal of Allergy and Clinical Immunology. 2021; 147: 199–212.
[40] Niehues H, van Vlijmen-Willems IMJJ, Bergboer JGM, Kersten FFJ, Narita M, Hendriks WJAJ, *et al*. Late cornified envelope (LCE) proteins: distinct expression patterns of LCE2 and LCE3 members suggest nonredundant roles in human epidermis and other epithelia. British Journal of Dermatology. 2016; 174: 795–802.
[41] Turner GA, Hoptroff M, Harding CR. Stratum corneum dysfunction in dandruff. International Journal of Cosmetic Science. 2012; 34: 298–306.
[42] Pople JE, Moore AE, Talbot DCS, Barrett KE, Jones DA, Lim FL. Climbazole increases expression of cornified envelope proteins in primary keratinocytes. International Journal of Cosmetic Science. 2014; 36: 419–426.
[43] Coto E, Santos-Juanes J, Coto-Segura P, Díaz M, Soto J, Queiro R, *et al*. Mutation analysis of the LCE3B/LCE3C genes in Psoriasis. BMC Medical Genetics. 2010; 11: 45.
[44] Hüffmeier U, Bergboer JGM, Becker T, Armour JA, Traupe H, Estivill X, *et al*. Replication of LCE3C–LCE3B CNV as a Risk Factor for Psoriasis and Analysis of Interaction with other Genetic Risk Factors. Journal of Investigative Dermatology. 2010; 130: 979–984.
[45] Riveira-Munoz E, He S, Escaramís G, Stuart PE, Hüffmeier U, Lee C, *et al*. Meta-Analysis Confirms the LCE3C_LCE3B Deletion as a Risk Factor for Psoriasis in several Ethnic Groups and Finds Interaction with HLA-Cw6. Journal of Investigative Dermatology. 2011; 131: 1105–1109.
[46] Chiraz BS, Myriam A, Ines Z, Catherine J, Fatma B, Ilhem C, *et al*. Deletion of late cornified envelope genes, LCE3C_LCE3B-del, is not associated with psoriatic arthritis in Tunisian patients. Molecular Biology Reports. 2014; 41: 4141–4146.
[47] Docampo E, Rabionet R, Riveira-Muñoz E, Escaramís G, Julià A, Marsal S, *et al*. Deletion of the late cornified envelope genes, LCE3C and LCE3B, is associated with rheumatoid arthritis. Arthritis & Rheumatism. 2010; 62: 1246–1251.
[48] Bergboer JGM, Oostveen AM, de Jager MEA, Zeeuwen PLJM, Joosten I, Seyger MMB, *et al*. Koebner Phenomenon in Psoriasis is not Associated with Deletion of Late Cornified Envelope Genes LCE3B and LCE3C. Journal of Investigative Dermatology. 2012; 132: 475–476.
[49] Lu X, Guo J, Zhou X, Li R, Liu X, Zhao Y, *et al*. Deletion of LCE3C_LCE3B is associated with rheumatoid arthritis and systemic lupus erythematosus in the Chinese Han population. Annals of the Rheumatic Diseases. 2011; 70: 1648–1651.
[50] Bergboer JG, Umićević-Mirkov M, Fransen J, den Heijer M, Franke B, van Riel PL, *et al.* A replication study of the association between rheumatoid arthritis and deletion of the late cornified envelope genes LCE3B and LCE3C. PLoS ONE. 2012; 7: e32045.
[51] Julià A, Tortosa R, Hernanz JM, Cañete JD, Fonseca E, Ferrándiz C, *et al*. Risk variants for psoriasis vulgaris in a large case–control collection and association with clinical subphenotypes. Human Molecular Genetics. 2012; 21: 4549–4557.
[52] Niehues H, Tsoi LC, van der Krieken DA, Jansen PAM, Oortveld MAW, Rodijk-Olthuis D, *et al*. Psoriasis-Associated Late Cornified Envelope (LCE) Proteins have Antibacterial Activity. Journal of Investigative Dermatology. 2017; 137: 2380–2388.
[53] Archer NK, Dilolli MN, Miller LS. Pushing the Envelope in Psoriasis: Late Cornified Envelope Proteins Possess Antimicrobial Activity. Journal of Investigative Dermatology. 2017; 137: 2257–2259.
[54] Sreejit G, Flynn MC, Patil M, Krishnamurthy P, Murphy AJ, Nagareddy PR. S100 family proteins in inflammation and beyond.

Advances in Clinical Chemistry. 2020; 41: 173–231.
[55] Schäfer BW, Wicki R, Engelkamp D, Mattei M, Heizmann CW. Isolation of a YAC clone covering a cluster of nine S100 genes on human chromosome 1q21: rationale for a new nomenclature of the S100 calcium-binding protein family. Genomics. 1995; 25: 638–643.
[56] Heizmann CW. S100 proteins structure functions and pathology. Frontiers in Bioscience. 2002; 7: d1356–d1368.
[57] De Heller-Milev M, Huber M, Panizzon R, Hohl D. Expression of small proline rich proteins in neoplastic and inflammatory skin diseases. British Journal of Dermatology. 2000; 143: 733–740.
[58] Tyszkiewicz T, Jarzab M, Szymczyk C, Kowal M, Krajewska J, Jaworska M, *et al.* Epidermal differentiation complex (locus 1q21) gene expression in head and neck cancer and normal mucosa. Folia Histochemica Et Cytobiologica. 2014; 52: 79–89.
[59] Leśniak W. Epigenetic regulation of S100 protein expression. Clinical Epigenetics. 2011; 2: 77–83.
[60] Sobiak B, Graczyk-Jarzynka A, Leśniak W. Comparison of DNA Methylation and Expression Pattern of S100 and other Epidermal Differentiation Complex Genes in Differentiating Keratinocytes. Journal of Cellular Biochemistry. 2016; 117: 1092–1098.
[61] Dopytalska K, Ciechanowicz P, Wiszniewski K, Szymańska E, Walecka I. The Role of Epigenetic Factors in Psoriasis. International Journal of Molecular Sciences. 2021; 22: 9294.
[62] Luo Y, Qu K, Kuai L, Ru Y, Huang K, Yan X, *et al*. Epigenetics in psoriasis: perspective of DNA methylation. Molecular Genetics and Genomics. 2021; 296: 1027–1040.
[63] Paradisi A, Guidi B, Diociaiuti A, Forni F, Scribano D, Sisto T, *et al*. Increased S100B protein serum levels in psoriasis. Journal of Dermatological Science. 2007; 48: 148–150.
[64] Salem SAM, El-Khateeb EA, Harvy M, Emam HME, Abdelaal W, Nemr RE, *et al*. Study of serum levels and skin expression of S100B protein in psoriasis. Anais Brasileiros De Dermatologia. 2017; 92: 323–328.
[65] Li Y, Gudjonsson JE, Woods TL, Zhang T, Johnston A, Stoll SW, *et al*. Transgenic expression of S100a2 in hairless mouse skin enhances Cxcl13 mRNA in response to solar-simulated radiation. Archives of Dermatological Research. 2009; 301: 205–217.
[66] Leśniak W, Graczyk-Jarzynka A. The S100 proteins in epidermis: Topology and function. Biochimica Et Biophysica Acta (BBA) - General Subjects. 2015; 1850: 2563–2572.
[67] Ito M, Kizawa K. Expression of Calcium-Binding S100 Proteins a4 and a6 in Regions of the Epithelial Sac Associated with the Onset of Hair Follicle Regeneration. Journal of Investigative Dermatology. 2001; 116: 956–963.
[68] Wilsmann-Theis D, Wagenpfeil J, Holzinger D, Roth J, Koch S, Schnautz S, *et al*. Among the S100 proteins, S100a12 is the most significant marker for psoriasis disease activity. Journal of the European Academy of Dermatology and Venereology. 2016; 30: 1165–1170.
[69] Borsky P, Fiala Z, Andrys C, Beranek M, Hamakova K, Malkova A, *et al*. Alarmins HMGB1, IL-33, S100a7, and S100a12 in Psoriasis Vulgaris. Mediators of Inflammation. 2020; 2020: 1–7.
[70] Vegfors J, Ekman AK, Stoll SW, Bivik Eding C, Enerbäck C. Psoriasin (S100a7) promotes stress-induced angiogenesis. British Journal of Dermatology. 2016; 175: 1263–1273.
[71] Granata M, Skarmoutsou E, Gangemi P, Mazzarino MC, D'Amico F. S100A7, Jab1, and p27kip1 expression in psoriasis and S100A7 CRISPR-activated human keratinocyte cell line. Journal of Cellular Biochemistry. 2019; 120: 3384–3392.
[72] Awad SM, Attallah DA, Salama RH, Mahran AM, Abu El-Hamed E. Serum levels of psoriasin (S100a7) and koebnerisin (S100a15) as potential markers of atherosclerosis in patients with psoriasis. Clinical and Experimental Dermatology. 2018; 43: 262–267.
[73] Batycka-Baran A, Hattinger E, Zwicker S, Summer B, Zack Howard OM, Thomas P, *et al*. Leukocyte-derived koebnerisin (S100a15) and psoriasin (S100a7) are systemic mediators of inflammation in psoriasis. Journal of Dermatological Science. 2015; 79: 214–221.
[74] Hegyi Z, Zwicker S, Bureik D, Peric M, Koglin S, Batycka-Baran A, *et al*. Vitamin D Analog Calcipotriol Suppresses the Th17 Cytokine–Induced Proinflammatory S100 "Alarmins" Psoriasin (S100a7) and Koebnerisin (S100a15) in Psoriasis. Journal of Investigative Dermatology. 2012; 132: 1416–1424.
[75] Nukui T, Ehama R, Sakaguchi M, Sonegawa H, Katagiri C, Hibino T, *et al.* S100A8/A9, a key mediator for positive feedback growth stimulation of normal human keratinocytes. Journal of Cellular Biochemistry. 2008; 104: 453–464.
[76] Christmann C, Zenker S, Martens L, Hübner J, Loser K, Vogl T, *et al.* Interleukin 17 Promotes Expression of Alarmins S100A8 and S100A9 During the Inflammatory Response of Keratinocytes. Frontiers in Immunology. 2020; 11: 599947.
[77] Thorey IS, Roth J, Regenbogen J, Halle J, Bittner M, Vogl T, *et al*. The Ca2+-binding Proteins S100a8 and S100a9 are Encoded by Novel Injury-regulated Genes. Journal of Biological Chemistry. 2001; 276: 35818–35825.
[78] Hohl D, Huber M. Ichthyosen. The ichthyoses. Pathophysiological models of epidermal differentiation. Hautarzt. 2013; 64: 12–21. (in German)
[79] Schonthaler H, Guinea-Viniegra J, Wculek S, Ruppen I, Ximénez-Embún P, Guío-Carrión A, *et al*. S100a8-S100a9 Protein Complex Mediates Psoriasis by Regulating the Expression of Complement Factor C3. Immunity. 2013; 39: 1171–1181.
[80] Catunda R, Rekhi U, Clark D, Levin L, Febbraio M. Loricrin downregulation and epithelial-related disorders: a systematic review. JDDG: Journal Der Deutschen Dermatologischen Gesellschaft. 2019; 17: 1227–1238.
[81] Maestrini E, Monaco AP, McGrath JA, Ishida-Yamamoto A, Camisa C, Hovnanian A, *et al*. A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. Nature Genetics. 1996; 13: 70–77.
[82] Koch PJ, de Viragh PA, Scharer E, Bundman D, Longley MA, Bickenbach J, *et al*. Lessons from Loricrin-Deficient Mice. Journal of Cell Biology. 2000; 151: 389–400.
[83] Ishitsuka Y, Huebner AJ, Rice RH, Koch PJ, Speransky VV, Steven AC, *et al*. Lce1 Family Members are Nrf2-Target Genes that are Induced to Compensate for the Loss of Loricrin. Journal of Investigative Dermatology. 2016; 136: 1656–1663.
[84] Boniface K, Bernard F, Garcia M, Gurney AL, Lecron J, Morel F. IL-22 Inhibits Epidermal Differentiation and Induces Proinflammatory Gene Expression and Migration of Human Keratinocytes. The Journal of Immunology. 2005; 174: 3695–3702.
[85] Nograles KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, *et al*. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. British Journal of Dermatology. 2008; 159: 1092–1102.
[86] Ogawa T, Ishitsuka Y, Nakamura Y, Watanabe R, Okiyama N, Fujisawa Y, *et al*. Loricrin Protects against Chemical Carcinogenesis. Journal of Investigative Dermatology. 2022; 142: 2023–2026.e1.
[87] Eckert RL, Yaffe MB, Crish JF, Murthy S, Rorke EA, Welter JF. Involucrin—Structure and Role in Envelope Assembly. Journal of Investigative Dermatology. 1993; 100: 613–617.
[88] Peng J, Sun S, Yang P, Fan Y. Is Ki-67, keratin 16, involucrin, and filaggrin immunostaining sufficient to diagnose inflammatory linear verrucous epidermal nevus? A report of eight cases

and a comparison with psoriasis vulgaris. Anais Brasileiros De Dermatologia. 2017; 92: 682–685.
[89] Yano S, Banno T, Walsh R, Blumenberg M. Transcriptional responses of human epidermal keratinocytes to cytokine interleukin-1. Journal of Cellular Physiology. 2008; 214: 1–13.
[90] Takahashi H, Asano K, Nakamura S, Ishida-Yamamoto A, Iizuka H. Interferon-gamma-dependent stimulation of human involucrin gene expression: STAT1 (signal transduction and activators of transcription 1) protein activates involucrin promoter activity. Biochemical Journal. 1999; 344: 797–802.
[91] Iizuka H, Takahashi H. Psoriasis, involucrin, and protein kinase C. International Journal of Dermatology. 1993; 32: 333–338.
[92] Chen J, Man X, Li W, Zhou J, Landeck L, Cai S, *et al*. Regulation of Involucrin in Psoriatic Epidermal Keratinocytes: the Roles of ERK1/2 and GSK-3β. Cell Biochemistry and Biophysics. 2013; 66: 523–528.
[93] Tsoi LC, Iyer MK, Stuart PE, Swindell WR, Gudjonsson JE, Tejasvi T, *et al*. Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. Genome Biology. 2015; 16: 24.
[94] Song J, Yin S, Li W, Li X, Luo Y, Luo Y, *et al*. An update on the role of long non-coding RNAs in psoriasis. Chinese Medical Journal. 2021; 134: 379–389.
[95] Moltrasio C, Romagnuolo M, Marzano AV. Epigenetic Mechanisms of Epidermal Differentiation. International Journal of Molecular Sciences. 2022; 23: 4874.
[96] Herter EK, Xu Landén N. Non-Coding RNAs: New Players in Skin Wound Healing. Advances In Wound Care. 2017; 6: 93–107.