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Pathogenesis of Atopic Dermatitis and Psoriasis: Focus on the Epidermal Differentiation Complex

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Abstract: Loss-of-function mutations in the FLG gene (encoding the epidermis-specific protein filaggrin) were recently shown to be associated with atopic dermatitis in several populations. These findings have challenged the dogma that atopic dermatitis is primarily an immune-mediated disease, and suggest skin barrier deficiency as a major cause. Similarly, psoriasis was until recently regarded as a T-cell driven disease caused by (auto)immune mechanisms. This view is supported by clinical data, and several genetic studies have identified risk factors associated with a function in adaptive immunity such as HLA-Cw6. Analysis of the PSORS4 region on chromosome 1q, however, has recently identified the deletion of late cornified envelope (LCE) genes LCE3B/C as novel psoriasis genes with a considerable population attributable risk. Because these genes are expressed in epithelial cells and not by the immunocytes, these findings have changed our view on psoriasis. The mechanism by which loss of LCE3B/C genes predisposes to psoriasis is unclear as both genes are not expressed in normal skin but appear to be induced upon skin barrier disruption or inflammation. We hypothesize that psoriasis could be the result of an interplay of immunological mechanisms and deficient repair of skin barrier integrity. Altogether, these findings demonstrate that in addition to immune mechanisms, genetic variation of skin barrier genes contribute to major skin diseases such as atopic dermatitis and psoriasis.

Keywords: Atopic dermatitis, epidermal differentiation complex, filaggrin, late cornified envelope, LCE3B/C deletion, psoriasis.

GENETIC STUDIES ON SKIN DISEASES: INVOLVEMENT OF THE EPIDERMAL DIFFERENTIATION COMPLEX

Atopic dermatitis and psoriasis are clinically distinct, chronic inflammatory skin diseases with a strong genetic basis, and are extensively reviewed [1-5]. Several genomewide analyses have been performed to discover genetic factors contributing to atopic dermatitis and psoriasis. These analyses have revealed chromosomal regions harboring possible susceptibility loci for both diseases on chromosomal regions 1q21, 3q21, 17q25 and 20p12. In this review we will focus on the overlapping locus on 1q21, for psoriasis the so-called psoriasis susceptibility (PSORS) 4 locus. This shared locus overlies the epidermal differentiation complex (EDC) (see Fig. 1), a cluster of genes encoding proteins found in the uppermost layers of the epidermis, which are of great importance for keratinocyte differentiation and skin barrier maintenance [6]. Genes located in the EDC include loricrin (LOR), involucrin (IVL), filaggrin (FLG), the small proline rich protein (SPRR) genes and the late cornified envelope (LCE) genes. This last cluster, with a total of 18 members, is divided into six families, LCE1-6, based on related amino acid sequences, genomic organization and expression patterns [7]. The focus on genes involved in skin barrier function as susceptibility factors for atopic dermatitis and psoriasis is not entirely new. Studies on permeability, barrier function and morphological examinations of patients’ epidermis demonstrated an impaired barrier function for both diseases [8, 9]. Already in 1999, it was proposed that a genetic predisposition to a defective skin barrier was a primary event in the development of atopic dermatitis, allowing allergen penetration and enhanced Th2 responses [10].

THE FILAGGRIN ATOPIC DERMATITIS CONNECTION: A CHANGE OF PARADIGM

In atopic dermatitis, until recently regarded as a primarily immune-mediated condition, the disrupted barrier function of the skin is now considered as a major cause of the disease. Loss-of-function mutations in FLG were shown to be associated with atopic dermatitis in several populations [11, 12]. Large population based studies show a population attributable risk (PAR) of 13.5%. As the FLG gene is located in or near PSORS4, FLG mutations were also studied in psoriasis patients, however no associations were found [13].

Filaggrin is specifically expressed in the epidermis, where it has a function in the aggregation of keratin filaments, which is necessary for the formation of the stratum corneum [14]. Subsequently, within the stratum corneum, filaggrin is degraded into a pool of hydrophilic amino acids, which make up the natural moisturizing factor (NMF). These molecules play a central role in maintaining the hydration of the stratum corneum. NMF levels have been shown to correlate with FLG null allele status, and may therefore directly contribute to the dry skin phenotype seen in atopic dermatitis [15]. In addition to the structural properties of filaggrin, a filaggrin breakdown product,
urocanic acid, is a UV-absorbing molecule [16] and the cis-isomer has local and systemic immunosuppressive effects, which is demonstrated in murine models and in human keratinocytes and leukocytes in vitro [17].

Interestingly, also the cytokine environment associated with atopic dermatitis appears to contribute to compromised skin barrier function, as interleukin-4 and interleukin-13 suppress filaggrin gene expression [18]. Studies on flaky tail mice, harboring a mutation analogous to the common human FLG mutation, demonstrated that topical application of allergens resulted in cutaneous infiltration and an allergen-specific antibody response. These data demonstrate that antigen transfer through a defective epidermal barrier could be a key mechanism in atopic diseases [19].

IDENTIFICATION OF THE LCE3B/C DELETION AS THE PSORIASIS ASSOCIATED RISK FACTOR IN THE PSORS4 LOCUS

The question if psoriasis is an epithelial disease or an immune-mediated disease has generated considerable debate over the last decades, but remains essentially unresolved. Until the early eighties psoriasis was primarily regarded as an immune mediated disease, but the advent of cyclosporin A as an effective mechanism-based treatment has changed this [20]. Many studies have even assumed an autoimmune basis of psoriasis. This was, however, largely founded on circumstantial evidence, as autoantibodies or autoreactive T-cells have never been demonstrated. For the last three decades psoriasis was primarily regarded as an immune-mediated disease although this view is changing rapidly [21, 22]. Independent genetic studies have shown that PSORS1 is the strongest and invariably reproduced psoriasis susceptibility locus. This locus contains several genes including HLA-Cw6, involved in adaptive immunity, and corneodesmosin (CDSN), encoding a skin barrier protein expressed in differentiated keratinocytes. However, due to linkage disequilibrium (LD), the tendency of two genes to be inherited together more often than would be predicted by chance, it is difficult to identify the true causative susceptibility gene of the PSORS1 locus [23-25].

Although most of the available genetic and clinical data supported a role for T-cell driven processes, the importance of epidermis-expressed genes could not be ruled out completely. In addition to the genetic association with PSORS4 and the possible role of CDSN, cell biological studies implied that keratinocytes of psoriatic patients are intrinsically different from keratinocytes of healthy controls or atopic dermatitis patients. Cultured keratinocytes from patients were found to react differently to stimuli like cytokines, most likely due to genetically programmed differences [26, 27].

A hallmark of lesional psoriatic skin is premature keratinocyte differentiation and disturbed keratinization, including altered formation of the cornified envelope. In psoriatic skin the components of the cornified envelope are differentially expressed as compared to normal skin. The expression of the early differentiation markers like involucrin, corneodesmosin, the small proline-rich proteins, cystatin A and transglutaminase 1 is upregulated, while the expression of the late differentiation markers like loricrin and filaggrin is downregulated [28, 29]. The defective formation of the cornified envelope influences the barrier capacity of the skin in psoriasis patients. Several independent studies demonstrated that the transepidermal water loss (TEWL) of lesional psoriatic skin is higher compared to the TEWL of normal and uninvolved psoriatic skin. Furthermore, the level of the TEWL is related to the clinical severity of the lesion, suggesting that the barrier function of lesional psoriatic skin is weaker than in normal skin [30, 31]. Another indication for the involvement of the physical barrier function of the skin is the Koebner phenomenon, i.e. the appearance of psoriatic lesions in uninvolved skin of psoriatic patients as a consequence of superficial trauma [32].

Until recently, no genetic association of specific EDC genes, e.g FLG and LOR, with psoriasis was found. De Cid et al. [33], however, demonstrated an association of the deletion of LCE3B and LCE3C with psoriasis in populations from Spain, Italy, The Netherlands and the USA. This

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**Fig. (1). Overview of the EDC region on chromosome 1.** The EDC region is shown in the top half of the diagram, with the genes LOR, the SPRR family, IVL and FLG highlighted. Loss-of-function mutations in FLG are associated with atopic dermatitis. In the lower half of the diagram a part of the LCE cluster, which consists of a total of 18 genes, is present. The deletion of LCE3B and LCE3C (highlighted) is associated with psoriasis. Adapted by permission from Macmillan Publishers Ltd: J Invest Dermatol [7], copyright 2005.
common deletion was found with a higher frequency in psoriasis patients (68%) compared to controls (59%) with a corresponding PAR of 23%. These results have been replicated in a German cohort [34]. In addition, in an independent genome wide association study of a large Chinese cohort, single nucleotide polymorphisms (SNPs) in strong LD with the LCE3B/C deletion were identified as risk factors for psoriasis [35]. Interestingly, the LCE3B/C deletion was not found to be associated with psoriatic arthritis [36].

In order to investigate the putative function of the LCE3B and LCE3C proteins, De Cid et al. [37] investigated the expression of the LCE3C (located in the deletion, and therefore absent in some individuals) and LCE3E genes (not located in the deletion and therefore used as a reference) in epidermal sheets of normal and psoriatic skin. The expression of LCE3C and LCE3E was hardly detectable in normal and uninvolved psoriatic skin. Though, in lesional psoriatic skin, both LCE3C (when at least one intact LCE3C allele was present) and LCE3E were highly induced. To examine if skin barrier disruption might be a pathophysiological stimulus for LCE3 expression, LCE3C and LCE3E expression was analysed in healthy individuals following minor skin injury by tape stripping. Indeed, in normal skin both genes were induced upon tape stripping, suggesting that induction of these genes is a repair response.

The LCE genes have not been extensively studied. In mice, Marshall and colleagues [37] showed that members of the LCE family of proteins are incorporated into the cornified envelope via crosslinking by transglutaminases rather late in the process of epidermal differentiation, and it was proposed that these proteins modulate barrier activity on the skin surface. Jackson et al. [7] demonstrated that LCE1 and 2 family members are primarily expressed in skin, and that they are barely expressed in internal epithelia. The LCE3 family members are variably expressed at low levels in epithelia, and they show varying expression between tissue types. LCE4 and LCE5 expression was hardly detected in the investigated tissues. LCE6 expression was not analysed. In cultured keratinocytes, Jackson et al. [7] revealed that the LCE2 expression is induced by calcium, and UV induces the expression of the LCE1 and LCE2 families and of the LCE3E gene.

CONCLUDING REMARKS

Genetic studies on inflammatory skin diseases, and on complex diseases in general, have proven to be useful tools to provide new insight into their pathophysiology. For atopic dermatitis, mutations found in FLG have challenged the dogma that atopic dermatitis is primarily an immune-mediated disease, and suggest skin barrier deficiency as a major cause. The association of the deletion of LCE3B and LCE3C with psoriasis is the first replicated susceptibility factor in the EDC, for this disease. We can only hypothesize about the role of the LCE3B/C deletion in the pathogenesis of psoriasis. Since the expression of LCE3C is induced after barrier disruption, we propose that incomplete barrier repair after minor injury might lead to penetration of environmental antigens or stimuli through the skin. These could trigger an inflammatory process that leads to psoriasis. Clearly, the molecular details of such a scenario need to be elucidated.

The nature of the environmental stimuli is at present unclear but microbial components e.g. from *Streptococcus* spp. would be excellent candidates. In general, components from the commensal flora or transient infection of throat and gut could very well trigger skin inflammation. The recently initiated human microbiome project is likely to contribute to novel insights in the pathogenesis of inflammatory skin diseases [38, 39]. Analysis of the skin microbiome in psoriasis patients and controls has already revealed differences in microbial community structure [40].

Altogether, these findings demonstrate that in addition to immune mechanisms, genetic variation of skin barrier genes contribute to major skin diseases such as atopic dermatitis and psoriasis.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>CDSN</th>
<th>Corneodesmosin</th>
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<tr>
<td>EDC</td>
<td>Epidermal differentiation complex</td>
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<td>FLG</td>
<td>Filaggrin</td>
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<td>IVL</td>
<td>Involucrin</td>
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<td>LCE</td>
<td>Late cornified envelope</td>
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<td>LD</td>
<td>Linkage disequilibrium</td>
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<td>LOR</td>
<td>Loricrin</td>
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<tr>
<td>NMF</td>
<td>Natural moisturizing factor</td>
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<td>PAR</td>
<td>Population attributable risk</td>
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<td>PSORS</td>
<td>Psoriasis susceptibility locus</td>
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<td>SNPs</td>
<td>Single nucleotide polymorphisms</td>
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<td>SPRR</td>
<td>Small proline rich protein genes</td>
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<td>TEWL</td>
<td>Transepidermal water loss</td>
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**REFERENCES**


