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Recruitment of cycling epidermal cells and expression of filaggrin, involucrin and tenascin in the margin of the active psoriatic plaque, in the uninvolved skin of psoriatic patients and in the normal healthy skin

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Abstract

The peripheral changes in the uninvolved skin adjacent to the extending psoriatic lesions may represent early events. The sequence of these events remains controversial. In the present study we evaluated epidermal and dermal aspects of the margin of the progressive psoriatic plaque, the distant uninvolved skin and normal healthy skin, using immunohistochemistry with markers for keratinization, proliferation and connective tissue: filaggrin, involucrin, Ki-67 and tenascin. The results showed that: (i) processes in distant uninvolved skin were comparable with the observations in normal skin; (ii) in the margin zone of the spreading psoriatic lesion, following the increased appearance of tenascin, the transition into parakeratosis, abnormal expression of filaggrin, involucrin and recruitment of cycling epidermal cells, happened simultaneously. The simultaneous normalization of these epidermal processes might be a consequence of a signal which is simultaneously transduced to the basal and suprabasal cell layers of the epidermis. Based on the present results and earlier findings, we would like to propose a triple stage model for the development of the psoriatic lesion: Stage 1, involvement of the stroma; stage II, inflammatory infiltrate formation and penetration into the upper layers of the epidermis, with suprabasal expression of keratin 16; stage III, recruitment of cycling epidermal cells and abnormal terminal differentiation. Further studies are required on the regulation of tenascin expression, focusing on factors derived from the stroma affecting both recruitment of cycling epidermal cells, involucrin and filaggrin expression. An intermediate step in the dermo-epithelial interrelation is the inflammatory infiltrate, penetrating into the most superficial zone of the epidermis, and the suprabasal expression of keratin 16. © 1997 Elsevier Science Ireland Ltd. All rights reserved

Keywords: Margin zone psoriatic skin; Uninvolved skin; Filaggrin; Involucrin; Ki-67; Tenascin

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1. Introduction

Initial changes in psoriasis differ from those in the fully developed psoriatic plaque.

At the cellular level, the established psoriatic lesion is characterized by epidermal changes consisting of an increased proliferation and incomplete keratinization, and dermal changes such as inflammation and an increased expression of the extracellular matrix glycoprotein tenascin. In contrast to the histological changes found in the mature psoriatic plaque, the pin-point papules show only slight epidermal proliferation, whereas the changes in the corium, consisting of inflammatory infiltrates, are more pronounced [1-14]. The sequence of events however remains controversial. An experimental approach to this problem is the investigation of the margin of the spreading psoriatic lesion [15-18]. In this experimental model, van de Kerkhof et al. reported that changes in the capillary may precede those in the epidermis during the centrifugal expansion of the psoriatic lesions [15]. Using laser-Doppler flowmetry and immunocytochemical techniques, Hull et al. postulated that the earliest change in the developing psoriatic plaque is an increased blood flow, possibly associated with a diffusible humoral initiating factor that accumulates at the active edge, stimulating transformation of normal skin to psoriatic plaques [16]. De Mare et al. reported that the suprabasal K8.12 binding (keratin 16 expression) was the earliest change in the epidermis [17]. De Jong et al. found evidence that the dermal compartment is involved early in the pathogenesis of psoriasis [18].

In the present study, we compared and contrasted the immunohistological findings in the normal human adult skin of healthy volunteers, the uninvolved skin of psoriatic patients and the margin of spreading psoriatic lesions.

In the dermis we studied the expression of the extracellular matrix glycoprotein tenascin [14,29,30].

2. Material and methods

2.1. Patients

Fifteen patients (eight male and seven female; mean age 49.4 (28-69 years)) suffering from plaque psoriasis participated in this study. They did not receive any topical treatment for at least 2 weeks and no systemic treatment for at least 1 month. In all patients the total body extent varied between 5-10%. In 10 patients suffering from unstable progressive plaque psoriasis, 6-mm punch biopsies were taken across the margin of a spreading lesion. In five of these patients a 3-mm punch biopsy was also taken from the uninvolved skin at exactly 10 cm from the psoriatic lesions. In the other five psoriatic patients with stable disease we only took 3-mm punch biopsies from the uninvolved skin, also at exactly 10 cm from a psoriatic lesion.

From eight healthy volunteers (three female and five male; mean age 26.1 (23-33 years)) 3-mm punch biopsies were taken.

All biopsies of the uninvolved skin of psoriatic patients and normal human adult skin of the healthy volunteers were take from the skin of the upper arm.

2.2. Monoclonal antibodies

To approximate the number of cycling cells we used the monoclonal anybody Ki-67, which recognizes a nuclear antigen present in cycling cells (1:10, Ki-67, Dakopatts, Copenhagen, Denmark) [25-28]. To assess epidermal differentiation a monoclonal antibody against filaggrin (1:500, antifilaggrin, BTI, BT576) [31] and a monoclonal antibody against involucrin (Mon-150, 1:25) [32] were used.

A monoclonal antibody against tenascin (T2H5, 1:2000) was obtained from AA Verstraeten, The Netherlands Cancer Institute, Amsterdam, The Netherlands.
Table 1
Histological results from the normal healthy and from the distant uninvolved skin of psoriatic patients (mean ± SEM) and the p-values

<table>
<thead>
<tr>
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<th>Healthy skin (n = 8)</th>
<th>Uninvolved skin (n = 10)</th>
<th>p-value</th>
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<tr>
<td>Filaggrin str. corneum (%)</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>1.00</td>
</tr>
<tr>
<td>Filaggrin str. granulosum (%)</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>1.00</td>
</tr>
<tr>
<td>Ki-67 positive nuclei</td>
<td>10.5 ± 2.5</td>
<td>9.2 ± 2.6</td>
<td>0.69</td>
</tr>
<tr>
<td>Involucrin interpapillar (%)</td>
<td>20.9 ± 2.7</td>
<td>17.4 ± 1.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Involucrin tip (%)</td>
<td>25.4 ± 1.2</td>
<td>26.1 ± 1.3</td>
<td>0.23</td>
</tr>
<tr>
<td>Tenascin</td>
<td>1.3 ± 0.2</td>
<td>1.2 ± 0.1</td>
<td>0.78</td>
</tr>
</tbody>
</table>

2.3. Staining procedure

Every biopsy was embedded in Tissue Tek OCT Compound (Miles Scientific, Naperville, USA), snap-frozen in liquid nitrogen and stored at −80°C until use. From each biopsy consecutive sections were cut (6 μm), air-dried and fixed in acetone/ether (60:40%) in case of Ki-67 staining and in acetone for the staining with the other monoclonal antibodies. An indirect immunoperoxidase technique was used. For 10 minutes the slides were fixed in acetone/ether (60:40 vol%) (Ki-67/ filaggrin staining) or acetone (involucrin and tenascin). After these slides were air-dried they were put in a phosphate-buffered stock solution (PBS solution: 360 ml Na₂HPO₄ (7.9 g Na₂HPO₄, Merck in 500 ml demineralized water) plus 70 ml NaH₂PO₄ (13.8 g NaH₂PO₄, Merck, in 500 ml demineralized water) plus 70 ml demineralized water. For 60 min, the slides were incubated with the monoclonal antibodies. After washing in phosphate buffer, the slides were incubated with rabbit anti-mouse immunoglobulin conjugated with peroxidase (1:50, RAMPO). After washing in the phosphate-buffered stock solution and pre-incubation with sodium-acetate buffer (pH 4.9), a solution of 3 amino-9-ethylcarbazole (AEC) in sodium-acetate buffer containing 0.01% H₂O₂ was added for 10 min.

All slides were counterstained with Mayer’s Haematoxylin (Sigma, St. Louis, MO) and mounted in glycerol gelatin.

2.4. Histological examination

Epidermal proliferation was measured by counting the number of Ki-67 positive nuclei per mm length of the section. In exactly the same area

Fig. 1. Filaggrin and Ki-67 expression in the distant uninvolved skin of a psoriatic patient. The filaggrin expression shows a continuous staining pattern in the stratum granulosum and stratum corneum. A minimal expression of nuclear Ki-67 is seen in the basal layer.

Fig. 2. Involucrin expression in the normal healthy skin. A continuous staining pattern in the upper epidermis can be seen.
the filaggrin expression was assessed by measuring the percentage of the length of the stratum corneum and stratum granulosum which was stained [34].

The involucrin expression was assessed by calculating the ratio positive cell layers/total cell layers of the living epidermis. This was done on two sites: at the tip of a dermal papila and between two dermal papillae [34].

The distribution of tenascin in the papillary dermis was assessed using the following grading system:

1. Continuous expression adjacent to the basal lamina (C) versus discontinuous expression adjacent to the basal lamina (D);
2. Staining intensity (0–3) [35].

The immunohistochemical findings in the biopsies taken from the margin of an active psoriatic lesion were compared with the localization of parakeratosis to assess the transition point into uninvolved skin. The orientation of these biopsies was from their clinically involved edge to their symptomless edge. These biopsies were examined on four spots: on 20% and 40% (involved part), 60% and 80% (uninvolved part) of the length of the sections.

2.5. Statistical evaluation

We used the Mann-Whitney test for statistical analysis of the results from the biopsies of the distant uninvolved skin of psoriatic patients and from the normal human adult skin. For statistical analysis of the results from the biopsies of the margin zone, we used the Wilcoxon test for matched pairs.

3. Results

3.1. Normal healthy adult skin and distant uninvolved skin of psoriatic patients

We did not observe a statistically significant difference between the results from the normal skin of healthy volunteers and the uninvolved skin of the psoriatic patients (Table 1). The filaggrin expression in the stratum granulosum and its expression in the stratum corneum was 100 ± 0% (p = 1.00) in the normal healthy skin as in the uninvolved skin (Fig. 1). The involucrin expression at the interpapillar region and above the tip of a dermal papilla in the uninvolved skin and in the healthy skin were within the same range (p_inter-papillar ≥ 0.75 and p_tip ≥ 0.2) (Fig. 2). Seven of eight biopsies of normal skin showed a discontinuous tenascin expression immediately beneath the basal lamina, compared to eight of 10 biopsies of uninvolved skin. The staining intensity of the tenascin expression in the normal healthy skin and the uninvolved skin did not show a significant difference (p ≥ 0.78) (Fig. 3).

3.2. Margin of spreading psoriatic plaques

In eight out of 10 biopsies taken from the margin of a spreading psoriatic lesion, the transition of the parakeratotic horny layer into an orthokeratotic stratum corneum was abrupt. In the involved areas of these biopsies a marked acanthosis was observed, whereas in the uninvolved parts the acanthosis disappeared. In the remaining two biopsies we did not observe parakeratosis. In one of these biopsies however, we observed acanthosis.

The histological examination in the biopsies of the margin zone was performed at 20%, 40%, 60% and 80% of the length of the sections (Tables 2–5), 20 and 40% representing the involved part.
and 60 and 80% representing the uninvolved area of the biopsy.

At 20% of the sections the filaggrin expression in the stratum corneum and stratum granulosum was discontinuous or absent. Compared to the uninvolved part of the margin zone at 80%, filaggrin expression was significantly different \( (\rho_{\text{corneum}} \leq 0.01, \rho_{\text{granulosum}} \leq 0.02) \) and comparable with the filaggrin staining as can be observed in normal healthy skin.

The number of Ki-67 positive nuclei in the involved areas of the sections (areas with evident parakeratosis) was markedly elevated and different from the number we found in the uninvolved part of the sections \( (p \leq 0.005) \). In the two sections without parakeratosis the number of Ki-67 positive nuclei did show a minor increase. Fig. 4 demonstrates the Ki-67/filaggrin staining in the 40–60% zone.

In the involved parts (at 20 and 40%) the involucrin expression was seen in more layers of the stratum spinosum, whereas the expression in the uninvolved areas was observed exclusively in the granular layer and the upper part of the stratum spinosum. The difference between the involucrin expression at 20% and the expression at 80% of the length of the section was significant \( (\rho_{\text{interpapillar}} \leq 0.04; \rho_{\text{tip}} \leq 0.01) \). Fig. 5 demonstrates the involucrin expression in the 40–60% zone.

In eight biopsies, a pronounced parakeratosis was observed in the involved areas. A transition point between ortho- and parakeratosis was seen at about 40–60% of the length of the sections. These biopsies also showed a transition point for filaggrin and involucrin expression from involved to normal pattern at 40–60%.

Tenascin is an extracellular matrix glycoprotein. In vitro studies suggest that proliferating epithelium induces the production of tenascin by mesenchymal cells [33]. In the involved areas, tenascin expression was observed as a continuous and intense staining pattern in the dermis immediately adjacent to the basal lamina. Compared to the tenascin expression in the normal healthy skin, its staining in the involved areas extended to the upper dermis (Fig. 6). In six out of nine sections we also observed a continuous but a substantially less pronounced staining pattern in the uninvolved parts. The other three sections showed a transition into a more discontinuous pattern in the uninvolved areas. The intensity of the anti-tenascin staining in the involved skin and its intensity in the uninvolved areas did not show a statistically significant difference \( (p = 0.67) \), while the staining intensities of the uninvolved areas in the margin zone did show a substantial difference with the expression observed in the normal healthy skin and the uninvolved skin at 10 cm distance from a lesion \( (p = 0.02 \text{ and } p = 0.005, \text{ respectively}) \).

4. Discussion

Margins of spreading psoriatic lesions permit the investigation of the sequence of events during the development of psoriasis. The peripheral changes in the uninvolved skin adjacent to the extending lesions may represent early changes. In
the present study we confirm that changes in dermal expression of tenascin precede epidermal changes. Tenascin was the only parameter which did not show a statistically significant difference between the involved and the uninvolved areas of the margins of progressive psoriatic lesions. These findings confirm the observations of de Jong et al. [18]. In the uninvolved skin at 10 cm distance from a psoriatic lesion, the tenascin expression was within the same range as the staining pattern we observed in the normal healthy skin, whereas the staining intensity of tenascin in the uninvolved part of the margins (at 80%) was statistically significantly different from the expression we observed in the normal healthy skin and the distant uninvolved skin.

In the epidermis the transition point between parakeratosis and orthokeratosis was observed between 40 and 60% of the length of the section. In the same region we observed a transition point with regard to the number of Ki-67 positive nuclei, filaggrin and involucrin expression from an involved into a no-involved pattern. These parameters were expressed differently in the involved and in the uninvolved parts of the margin zone. In the uninvolved parts the number of Ki-67 positive nuclei, the filaggrin and involucrin expression were not significantly different from the values which we observed in the normal healthy and in the distant uninvolved skin.

The early expression of tenascin in the dermal compartment of the uninvolved skin adjacent to the spreading psoriatic lesion together with the normal staining pattern of Ki-67, filaggrin and involucrin in the uninvolved areas of the marginal zone suggest that the dermis is involved in an early stage of the evolution of psoriasis. Several observations suggest that activated epithelium, wound healing and hyperproliferative skin diseases (cancer, psoriasis) induce tenascin expression in the human dermis. Mackie et al. suggested that the migrating, proliferating epidermis induces the expression of tenascin [33]. The present results suggest that tenascin expression is an earlier event than the recruitment of cycling cells.

The present investigation reveals that the expression of the epidermal proteins filaggrin and involucrin in psoriatic epidermis differs from their expression in the uninvolved parts (60 and 80%), in the normal healthy skin and in the uninvolved skin at 10 cm distance from a psoriatic lesion. These observations indicate that an abnormal keratinization process is secondary to other changes. The fact that the transition points between uninvolved and involved psoriatic skin, with respect to parakeratosis, recruitment of cycling epidermal cells, filaggrin and involucrin expression between uninvolved and involved psoriatic skin were observed between 40 and 60% of the length of the section strongly suggest a close relationship between epidermal hyperproliferation and abnormal keratinization. Our observations confirm the results of van de Kerkhof et al. [15]. They observed a simultaneous change of enzyme markers for proliferation and keratinization in the margin zone of a spreading psoriatic lesion. The simultaneous normalization of these epidermal processes might be a consequence of a signal which is simultaneously transduced to the basal and suprabasal cell layers of the epidermis.

Table 3
The histological results from the 40% zone of the margin of spreading psoriatic plaques (the involved part). Numbers 1–10 represent the 10 biopsies taken from the margin of a spreading psoriatic lesion

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<td>100</td>
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<td>20</td>
<td>0</td>
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<td>Filagg. str. gran. (%)</td>
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<td>40</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Ki-67 positive nuclei</td>
<td>40</td>
<td>52</td>
<td>204</td>
<td>16</td>
<td>60</td>
<td>28</td>
<td>96</td>
<td>48</td>
<td>120</td>
<td>140</td>
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<tr>
<td>Involucrin interpap. (%)</td>
<td>32</td>
<td>30</td>
<td>nd</td>
<td>29</td>
<td>32</td>
<td>48</td>
<td>53</td>
<td>nd</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Involucrin tip (%)</td>
<td>60</td>
<td>30</td>
<td>nd</td>
<td>56</td>
<td>53</td>
<td>70</td>
<td>62</td>
<td>nd</td>
<td>33</td>
<td>83</td>
</tr>
<tr>
<td>Tenascin</td>
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<td>C/3</td>
<td>C/2</td>
<td>C/3</td>
<td>C/3</td>
<td>C/3</td>
<td>C/2</td>
<td>C/2</td>
<td>C/3</td>
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nd, not done; C, continuous expression.
TABLE 4
The histological results from the 60% zone of the margin of spreading psoriatic plaques (the uninvolved part). Numbers 1–10 represent the 10 biopsies taken from the margin of a spreading psoriatic lesion.

<table>
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<tr>
<td>Filagg. str. corneum (%)</td>
<td>100</td>
<td>100</td>
<td>60</td>
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<tr>
<td>Filagg. str. gran. (%)</td>
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<td>100</td>
<td>100</td>
<td>100</td>
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<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Ki-67 positive nuclei</td>
<td>16</td>
<td>12</td>
<td>128</td>
<td>16</td>
<td>44</td>
<td>8</td>
<td>32</td>
<td>40</td>
<td>40</td>
<td>12</td>
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<tr>
<td>Involutrin interpap. (%)</td>
<td>26</td>
<td>18</td>
<td>nd</td>
<td>38</td>
<td>29</td>
<td>21</td>
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<td>29</td>
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<tr>
<td>Involutrin tip (%)</td>
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<td>25</td>
<td>nd</td>
<td>56</td>
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<td>33</td>
<td>38</td>
<td>nd</td>
<td>50</td>
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</tr>
<tr>
<td>Tenascin</td>
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<td>D/1</td>
<td>C/2</td>
<td>C/3</td>
<td>C/3</td>
<td>C/2</td>
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<td>C/3</td>
<td>nd</td>
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nd, not done; C, continuous expression; D, discontinuous expression.

Based on the present results and earlier findings [18], we would like to propose a triple stage model for the development of the psoriatic lesion: Stage I, involvement of the stroma; stage II, inflammatory infiltrate formation, penetration into the upper layers of the epidermis, with suprabasal expression of keratin 16; stage III, recruitment of cycling epidermal cells and abnormal terminal differentiation.

The changes of the stroma in Stage I could well be the result of mediators, diffusing from the psoriatic lesion into the clinically uninvolved skin. Possible candidates include: TGFβ, a mediator which is capable of inducing tenascin; [36] and arachidonic acid derivatives which have a potent effect on endothelial cells. A remarkable feature, however, is the relatively large interval between stage I and stage II (the infiltrate formation and keratin 16 expression). Some degree of tachyphylaxis to respond to mediators of inflammation might be of relevance in this respect. A reduced responsiveness of the clinically uninvolved psoriatic skin to epicutaneous application of the eicosanoid leukotriene B4 has been demonstrated in previous experiments [37,38]. Such a defense system against pro-inflammatory events could be interpreted as an attempt of the skin to keep psoriatic plaques restricted to sharply demarcated plaques. It is attractive to speculate that this process prevents overt inflammatory events in the symptomless skin and during stage I of the inter-phase.

Stage II represents the expression of keratin 16 in the suprabasal compartment and the appearance of the inflammatory infiltrate. In a previous experiment, an association between keratin 16 expression and cutaneous inflammation was shown [18]. Following tape stripping of the normal human skin, keratin 16 expression had already appeared after 24 h, well before overt epidermal hyperproliferation, whilst the inflammatory infiltrate was present 24 h post-stripping. Several other observations further strengthen the supposition that the expression of keratin 16 is not the result of epidermal proliferation but rather might be independent from proliferation of the epidermis. In lupus erythematoses, a skin disorder characterized by atrophy of the skin, the expression of keratin 16 is prominent above the inflamed skin [39]. In monogenic disorders of keratinization, the expression of keratin 16 appeared to be associated with the inflammatory conditions, but to our surprise did not always occur in hyperproliferative diseases [40]. Therefore, not only in psoriasis but in many skin conditions keratin 16 expression should be regarded as part of an inflammatory response. Controversy remains with respect to the question which inflammatory cell can be identified as 'le premier'. According to some authors the polymorphonuclear leukocyte is the first invader, according to others the mast cell, the monocyte, or the T lymphocyte [3,12,18,41]. So far, the communis opinio is that there is no single cell type involved as the 'on-switcher' of psoriatic inflammation.

Stage III comprises a process of recruitment of cycling epidermal cells and a change in the cell layers containing involucrin and filaggrin. Although the molecular regulation of these changes is by no means totally understood, the observa-
Table 5
The histological results from the 80% zone of the margin of spreading psoriatic plaques (the uninvolved part). Numbers 1–10 represent the 10 biopsies taken from the margin of a spreading psoriatic lesion

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<tbody>
<tr>
<td>Filagg. str. corneum (%)</td>
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<td>100</td>
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<td>100</td>
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<tr>
<td>Filagg. str. gran. (%)</td>
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<td>Involucrin interpap. (%)</td>
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<td>11</td>
<td>nd</td>
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<td>14</td>
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<td>23</td>
</tr>
<tr>
<td>Involucrin tip (%)</td>
<td>40</td>
<td>11</td>
<td>nd</td>
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<td>D/1</td>
<td>C/2</td>
<td>C/3</td>
<td>C/3</td>
<td>D/2</td>
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nd, not done; C, continuous expression; D, discontinuous expression.

dition of a simultaneous transition of these processes is most likely caused by a common regulating process. It has been shown, in vitro, that activation of the EGF receptor and an enhanced transcription of TGFα can be induced by TNFα, IL8 and γ-interferone [42]. Activation of the EGF receptor and increased transcription of TGFα is associated with activation of phospholipase C, yielding an increased intracellular Ca²⁺ concentration, and activation of protein kinase C. An increased intracellular concentration of calcium leads to activation of transglutaminase. Phosphorylation of the sodium hydrogen antiport by protein kinases will elicit the recruitment process of cycling epidermal cells. It has been shown that activation of protein kinase C will induce keratinization [43]. Therefore the induction of epidermal growth and altered keratinization following the infiltrate formation can be controlled by joint molecular pathways. However, further investigations are required to identify the exact mechanisms involved.

Fig. 4. Filaggrin and Ki-67 expression in the 40-60% zone of the margin of a spreading psoriatic lesion. The 40% zone (left, the involved part of the biopsy) shows a markedly decreased filaggrin expression in the granular layer and stratum corneum and an increased number of Ki-67 positive nuclei in the lower region of the epidermis. In the 60% zone (right, the uninvolved part of the biopsy) a normal filaggrin expression can be seen, while the number of Ki-67 positive nuclei has markedly decreased, compared with the 40% zone.

Fig. 5. Involucrin expression in the 40-60% zone of the margin of a spreading psoriatic lesion. On the right (40% zone, involved part) the involucrin expression is extended to the lower part of the epidermis, whereas in the 60% zone (left, the uninvolved part) the involucrin expression is seen in less cell layers of the epidermis.
shows an intense and continuous distribution adjacent to the dermis, whereas in the 60% zone (left) the tenascin expression of a spreading psoriatic lesion. On the right (40% zone, Fig. 6, Tenascin expression in the 40-60% zone of the margin basal lamina.

References


