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Epicutaneous application of leukotriene B₄ induces patterns of tenascin and a heparan sulfate proteoglycan epitope that are typical for psoriatic lesions

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Abstract Application of leukotriene B₄ (LTB₄) to normal human skin induces changes similar to those found in psoriatic skin, and it has proved to be a useful model for studying the pathogenesis and treatment of psoriasis. We studied the expression patterns of molecules that have recently been shown to be altered in lesional psoriatic skin, including the extracellular matrix protein tenascin (TN) and the basement membrane and cell surface-associated heparan sulfate proteoglycans (HSPGs). During 72-h the expression of these markers was studied immunohistochemically and the expression of TN was correlated with epidermal proliferation and influx of inflammatory cells. Following the peak influx of polymorphonuclear leukocytes, a marked increase in TN expression was noted in the papillary dermis 72 h after LTB₄ application. The expression patterns of basal membrane-associated epitopes of HSPG remained unaltered, whereas the expression of cell surface-associated HSPG disappeared 72 h after LTB₄ application. A significant correlation was found between dermal TN expression and epidermal hyperproliferation, and between TN expression and the presence of dermal T cells. These findings indicate that the model of LTB₄-induced acute cutaneous inflammation displays many characteristics of early psoriatic lesions and could serve as a model to study some of the cell biological changes in this disease.

Key words Tenascin · Heparan sulfate proteoglycans · Extracellular matrix · Psoriasis · Leukotriene B₄

Introduction

Epicutaneous application of the potent chemoattractant leukotriene B₄ (LTB₄) results in a reproducible cutaneous inflammatory response, initially dominated by an accumulation of polymorphonuclear leukocytes (PMN) with a maximum at 24 h, and followed by a dermal T-cell infiltrate which is most pronounced after 72 h. Epidermal hyperproliferation occurs, reaching a maximum after 72–96 h. These phenomena are dose dependent [1, 2]. Although LTB₄ is not likely to be the only or primarily pathogenetic event in psoriasis [3], the morphologic changes in the skin using the LTB₄-model are a useful means of investigating acute inflammation in vivo and partially mimic the hallmarks of psoriatic skin lesions.

The extracellular matrix (ECM) plays an important role in cell growth, differentiation and migration. It provides firmness, elasticity, and resilience to tissues. The ECM is not inert but interacts with keratinocytes, inflammatory cells, cytokines and growth factors. Recently it has been shown that some ECM molecules are altered in lesional skin of psoriatic patients [4, 5], including tenascin and the heparan sulfate proteoglycans (HSPGs).

The expression of the dermal glycoprotein tenascin is limited in normal skin but profoundly increased in chronic and subacute inflammatory disorders such as psoriasis, acne, and alopecia areata [4, 6, 7]. It is also found in increased amounts in epidermal tumors and in wound healing [8]. In acute inflammation, however, the expression of tenascin has never been investigated.

In addition, the basal membrane (BM) and cell surface associated HSPGs have been shown to be changed in psoriasis [5]. HSPGs play an important role in assembly of the BM, bind growth factors and influence charge-dependent transport of molecules. They consist of heparan sulfate (HS) side chains, which are covalently bound to a core protein, and they are present in the BM of the epidermis, cell membranes and blood vessels [9]. In psoriasis, cell surface-associated HSPGs are absent, whereas they are clearly found in the epidermis of normal skin [5].

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Furthermore, the pattern of basal membrane-associated HSPGs are also altered in psoriasis: the high-sulfated domain of the HS side chain is absent in the tips of the dermal papillae [5].

In this study, the expression of the ECM proteins tenascin and basal and cell surface-associated HSPGs was studied immunohistochemically in normal human skin after epicutaneous application of LTB₄ over 72 h. In order to find out whether tenascin expression is most related to proliferation or differentiation in this model of acute inflammation, its expression in relation to epidermal proliferation and influx of inflammatory cells (PMNs and T lymphocytes) was investigated. This study indicated that the application of LTB₄ induced many changes in ECM molecules that can also be found in early psoriatic lesions.

Materials and methods

Volunteers and biopsies

A group of 16 healthy male volunteers (mean age 27 years) without signs or history of skin disorders participated in this study. Before the application of LTB₄, a 4-mm punch biopsy was taken under local anaesthesia, to assess the histology of the unchallenged skin.

Aliquots of 100 ng LTB₄ (Paesel, Frankfurt, Germany) dissolved in 10 µl ethanol were applied to the skin of the upper part of the back of the volunteers through a plastic cylinder (6.5 mm diameter) and the ethanol was evaporated under a stream of nitrogen. The test sites were covered with impermeable dressing (Silver Patch, van der Bend, Brielle, The Netherlands) held in place with Leukosilk tape (Beiersdorf, Hamburg, Germany).

Further 4-mm punch biopsies were taken 24 and 72 h after LTB₄ application under local anaesthesia. The biopsies were washed in phosphate-buffered saline (PBS; NPBI, Emmer-Compascuum, The Netherlands), embedded in Tissue Tek OCT compound (Miles Scientific, Naperville, Ill.), snap-frozen in liquid nitrogen and stored at -80°C. They were sectioned at 7 µm and fixed for 10 min in acetone/ether (60/40 vol%) for MIB-1, or in acetone (0°C) for staining with the other antibodies and again stored at -80°C until use.

Permission to conduct this study was obtained from the local Ethics Committee of the University Hospital Nijmegen. Informed consent was given by all subjects in this study. All volunteers tolerated the applications of LTB₄ well. After 24 h, slight erythema was seen at the application sites.

Antibodies

For immunohistochemical staining of tenascin, the monoclonal antibody (mAb) T2H5 was used (kindly provided by Dr. A. A. Verstraten, The Netherlands Cancer Institute, Amsterdam, The Netherlands). For immunohistochemical staining of HSPGs, three mAbs were used: JM-72, JM-403, and JM-13 (J. vd Born, Department of Nephrology, University Hospital Nijmegen). The production, characterization and demonstration of specificity of these mAbs has been carried out by van den Born et al. [10–13]. The mAb JM-72 is directed against the BM-associated HSPG core protein, JM-13 against the sulfated domains of the HS side chains and JM-403 against the unmodified/low-sulfated domains of the HS side chains. To study inflammation, the mAbs T11, directed against T lymphocytes (anti-CD2; Dakopatts, Copenhagen, Denmark) and antielastase against elastase present in PMN (Dakopatts) were used. The mAb MIB-1 which detects the nuclear antigen Ki-67 present in the late G₁, S and G₂ + M phases of the cell cycle was used as a marker for proliferation (Immunotech, Marseille, France).

Immunohistochemical staining

For staining with the mAbs JM-72 (1 : 250 in PBS), JM-403 (1 : 250), T2H5 (1 : 2000), MIB-1 (1 : 50) and antielastase (1 : 100) and indirect peroxidase technique was used. After thawing at room temperature for 30 min, slides were fixed again in acetone (0°C), or in acetone/ether (60/40 vol%) for MIB staining, for 10 min. They were washed in PBS and incubated for 1 h with the primary antibodies. After washing twice in PBS the slides were incubated for 30 min with a solution of peroxidase-conjugated rabbit antimouse immunoglobulins (RAM-Ig) 1 : 50 (Dakopatts) in phosphate buffer containing 5% human AB serum. After two further washes in PBS, slides were stained in a solution of 3-amino-9-ethyl-carbazole (AEC) in sodium acetate buffer containing 0.01% H₂O₂ for 10 min.

Staining with the mAb JM-13 was carried out using the Vectastain Elite ABC kit (Vector Laboratories, Burlingame, Calif.). Sections were preincubated for 20 min with 20% normal horse serum and after removing the excess serum, sections were incubated with an undiluted culture supernatant of the mAb JM-13 for 60 min. After two washing steps, sections were incubated for 30 min with a solution of horse antimouse immunoglobulins, diluted 1 : 200 in PBS containing 1% bovine serum albumin. This was followed by a washing step and incubation with Vectastain Elite ABC reagent for 30 min. After two further washes in PBS, slides were stained in a solution of AEC in sodium acetate buffer containing 0.01% H₂O₂ for 10 min.

Staining with T11 was carried out using a peroxidase antiperoxidase technique (PAP). Slides were incubated with the primary antibody (1 : 100) for 60 min, washed twice in PBS and then incubated with 1 : 50 RAM-Ig (Dakopatts). After two more washes in PBS, PAP complexes were added (Dakopatts). The incubation with RAM-Ig and PAP was repeated and after two additional washes in PBS and preincubation with sodium acetate buffer, pH 4.9, slides were stained with AEC solution. All slides were counterstained with Mayer's hematoxylin (Sigma, St. Louis, Mo.) mounted in glycerine gelatine (Sigma), and studied by light microscopy.

Histological examination

The distribution of the stainings was assessed by two independent investigators. Tenascin expression in the dermis was assessed using an eight-point scale: 0 = no staining, 1 = sporadic staining in the upper dermis adjacent to the BM of the dermoepidermal junction (DEJ), 2 = a patchy distribution in the upper dermis adjacent to the BM, but not present in all dermal papillae, 3 = a patchy expression in the tips of *all* dermal papillae, but not continuous, 4 = 3 but extending more deeply into the dermis, 5 = a thin but continuous layer adjacent to the BM, 6 = a continuous layer adjacent to the BM and in the papillary dermis, 7 = staining extending into the reticular dermis. Expression of HSPGs (JM-13, JM-403 and JM-72) in the BM of the DEJ and the BM of blood vessels was appraised using a three-point scale: 0 = staining not present, 1 = discontinuous staining, 2 = continuous staining. The expression of cell surface-associated HSPGs (JM-403 in the epidermis) was assessed using a four-point scale: 0 = no staining, 1 = sporadic staining, 2 = pronounced staining, 3 = complete staining. Epidermal proliferation was measured by counting the number of MIB-1-positive nuclei per millimeter length of section. The density of PMN and T lymphocytes was assessed in the epidermis and dermis using seven-point scales: *epidermis* 0 = no positive cells observed, 1 = sporadic staining, 2 = minimal presence, 3 = moderate presence, 4 = moderate/pronounced presence, 5 = pronounced presence, 6 = complete staining; *dermis* 0 = no positive cells, 1 = sporadic staining, 2 = 1–25% of infiltrate cells stained, 3 = 26–50%, 4 = 51–75%, 5 = 76–99%, 6 = 100%. The dermal infiltrate was subdivided into perivascular staining and diffuse dermal staining.

Statistical analysis

For statistical analysis Student's *t*-test was used. The chosen level of significance was $P \leq 0.05$.

Results

Immunohistochemistry

Tenascin

In all specimens of unchallenged skin, tenascin expression was discontinuous, varying from sporadic to patchy, in the papillary dermis (Fig. 1). Continuous staining for tenascin was found adjacent to the BM of blood vessels, eccrine sweat ducts and hair follicles. A slight decrease in tenascin expression was seen 24 h after LTB₄ application, but after 72 h, a marked increase in tenascin was found ($P = 0.089$ and $P = 0.0006$, respectively). All dermal papillae were intensely stained and the staining extended into the papillary and reticular dermis (Fig. 2), and in 10 of 16 specimen this distribution was continuous.

Fig. 1 Tenascin expression in normal human skin (× 200)

Fig. 2 Tenascin expression in normal skin 72 h after topical LTB₄ application (× 200)

Fig. 3 HSPG staining in normal skin using mAb JM-403 directed against the low-sulfated side chains (× 200)

Fig. 4 HSPG staining in normal skin 72 h after LTB₄ application (JM-403, × 200)

HSPGs

In normal skin, staining with JM-403, directed against the low-sulfated domains of the HS side chains, showed a keratinocyte surface-associated pattern (Fig. 3). After 24 h of LTB₄ exposure, however, the staining became less prominent ($P < 0.0001$) and after 72 h the expression varied from sporadic to completely absent ($P < 0.0001$, Fig.

Table 1 Results of immuno-histochemical stainings (means $\pm$ SEM, $n = 16$)

	0 h	24 h	72 h
Tenascin	2.69 ($\pm$ 0.34)	2.25 ($\pm$ 0.30)	4.63 ($\pm$ 0.39)
HSPG core DEJ	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HSPG core blood vessels	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HSPG core epidermis	0.00 ($\pm$ 0.00)	0.00 ($\pm$ 0.00)	0.00 ($\pm$ 0.00)
HS low-sulfated DEJ	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HS low-sulfated blood vessels	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HS low-sulfated epidermis	2.00 ($\pm$ 0.20)	0.88 ($\pm$ 0.13)	0.31 ($\pm$ 0.12)
HS highly sulfated DEJ	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HS highly sulfated blood vessels	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)	2.00 ($\pm$ 0.00)
HS highly sulfated epidermis	0.00 ($\pm$ 0.00)	0.00 ($\pm$ 0.00)	0.00 ($\pm$ 0.00)
Ki-67-positive nuclei	62.1 ($\pm$ 3.99)	23.2 ($\pm$ 3.54)	201 ($\pm$ 33.8)
Elastase, epidermis	0.00 ($\pm$ 0.00)	3.78 ($\pm$ 0.23)	1.63 ($\pm$ 0.21)
Elastase, diffuse dermis	0.00 ($\pm$ 0.00)	4.00 ($\pm$ 0.18)	2.41 ($\pm$ 0.30)
Elastase, perivascular	0.13 ($\pm$ 0.09)	3.19 ($\pm$ 0.19)	1.94 ($\pm$ 0.12)
T lymphocytes, epidermis	0.97 ($\pm$ 0.16)	1.44 ($\pm$ 0.18)	1.50 ($\pm$ 0.13)
T lymphocytes, diffuse dermis	1.06 ($\pm$ 0.11)	1.69 ($\pm$ 0.15)	2.34 ($\pm$ 0.16)
T lymphocytes, perivascular	2.09 ($\pm$ 0.07)	2.66 ($\pm$ 0.20)	3.53 ($\pm$ 0.26)

4). In addition, JM-403 staining was seen in the BM of the epidermis and blood vessels where no differences were seen between challenged and unchallenged skin.

Neither JM-72 (directed against the core protein of HSPG) nor JM-13, (directed against the highly sulfated domains of the HS side chains) showed differences in expression between unchallenged and challenged skin 24 and 72 h after LTB₄ application. The distribution of JM-72 was continuous and restricted to the BM of the DEJ and blood vessels. JM-13 staining of the BM of the DEJ was comparable to JM-72 staining but the BM of blood vessels did not stain before or after application of LTB₄. Semiquantitative data on immunohistochemical stainings are summarized in Table 1.

Correlation of tenascin expression with epidermal proliferation and inflammation

Proliferation

The number of MIB-positive nuclei changed after LTB₄ challenge: following a reduction after 24 h ($P < 0.0001$), a marked increase was observed at 72 h ($P = 0.001$). Figure 5a shows that the changes in the expression of tenascin were correlated significantly with the numbers of MIB-stained nuclei in the epidermis ($r = 0.642$, $P < 0.0001$).

Inflammation

In epidermal and dermal skin compartments a reproducible accumulation of PMNs was seen as assessed by staining for leukocyte elastase. Maximal presence of PMNs was seen 24 h after LTB₄ exposure ($P < 0.0001$) in the dermis in a perivascular and diffuse pattern, as well as in the epidermis. At 72 h there were substantially fewer

PMNs in both compartments ($P < 0.0001$) but they were still present. Only a borderline significant correlation was found between tenascin expression and epidermal PMNs ($r = 0.27$, $P = 0.06$). No correlations were found between the presence of PMNs in the dermis and tenascin expression.

In contrast to the slight increase in epidermal T lymphocytes, dermal diffuse and perivascular T lymphocytes showed a marked increase in number, with a maximum at 72 h ($P < 0.0001$). The expression of dermal T lymphocytes (perivascular and diffuse) correlated significantly with tenascin expression ($r = 0.45$, $P = 0.001$ and $r = 0.48$, $P = 0.0004$, respectively). This is shown in the Figures 5 b, c. No significant correlation was found between epidermal T lymphocytes and tenascin expression.

Discussion

In this study, the expression of the ECM molecules tenascin and HSPG in acutely inflamed skin after topical LTB₄ application was investigated and related to epidermal proliferation and cutaneous inflammation. A significant increase in tenascin expression was found as early as 72 h after LTB₄ challenge. The staining pattern was similar to that found in psoriasis. The increase in tenascin correlated with epidermal proliferation, the presence of T lymphocytes in the dermis and the influx of epidermal PMN.

Tenascin is known to be increased in conditions of increased epidermal proliferation including wound healing, tape stripping and hyperproliferative skin diseases such as psoriasis and skin carcinomas [4, 14, 15]. It is thought that the production of tenascin might be stimulated by the proliferating epidermis [15]. On the other hand, an increased expression of tenascin has been reported in skin disorders characterized by inflammation (alopecia areata, acne), in areas where many inflammatory cells are present. It has been postulated that cytokines derived from inflammatory

Fig. 5a–c Correlations between: **a** numbers of MIB-stained nuclei and tenascin expression ($r = 0.64$), **b** expression of dermal perivascular T lymphocytes and tenascin expression ($r = 0.45$), **c** expression of dermal diffuse T lymphocytes and tenascin expression ($r = 0.48$)

infiltrate may regulate tenascin synthesis [6, 7]. In addition, tenascin inhibits monocyte adhesion to the ECM and alters the adhesion properties of T cells *in vitro*, which may be due to abrogation of an accessory cell function at an early stage of the interaction between antigen-present-

ing cells and T cells [16], and may therefore have anti-inflammatory activity. Furthermore, tenascin is elevated during acute phase responses [17]. In this model, in which acute inflammation can be investigated, tenascin expression correlated best with the expression of MIB-1, a marker for proliferation.

A significant alteration in cell surface-associated HSPG expression was found in normal skin after LTB_4 application. The pattern of cell membrane-associated staining present in normal epidermis after staining with JM-403 disappeared 72 h after LTB_4 application. In psoriasis, this cell membrane-associated staining is also absent, in contrast to uninvolved psoriatic and normal skin, suggesting a comparable mechanism behind the changed JM-403 staining in psoriasis and the LTB_4 skin model. An influx of inflammatory cells in the dermis and epidermis may influence the expression of cell membrane-associated HSPGs. In acute irritant dermatitis, however, an increase in the concentration of HS occurs in normal skin and psoriatic skin [18], as determined using glycosaminoglycans electrophoresis of skin biopsies. Staining with JM-403 showed a continuous staining in the DEJ of normal skin both before and 72 h after LTB_4 application.

Staining of the core protein of HSPG did not show any changes in acute LTB_4 -induced inflammation. Previous studies on LTB_4 -challenged skin have indicated degradation of BM components by neutrophil elastase and ultrastructural damage of the BM [1, 19]. This does not necessarily imply, that the epitope of the large core protein of HSPG, stained by JM-72, disappears. It can be concluded that the core protein of HSPG, one of the major constituents of the BM, remains virtually unaffected.

Staining with JM-13, against the high-sulfated parts of the HSPG side chains, did not change after LTB_4 application. In psoriasis, however, loss of staining of JM-13 has been found in the tips of the dermal papillae [5], where PMNs are moving from the tips of the dermal papillae into the epidermis and are known to release elastase and free radicals. Degradation of the DEJ by proteolytic enzymes from human skin and human PMNs has been described [20–22]. Furthermore, Diamond et al. have described a direct interaction between the leukocyte integrin Mac-1 and HSPGs [23]. Mac-1 is the main integrin involved in adhesion of PMN. It has thus been speculated that in psoriasis the loss of side chain staining of HSPG could be due to cleavage of the JM-13 epitope by proteolytic enzymes. In the LTB_4 model however, migrating PMNs did not cause visible cleavage of the JM-13 epitope during 72 h. In this study, staining of the dermal blood vessels was unaltered, although the loss of HSPGs has been previously reported in endothelial cells caused by PMN-derived proteases [24].

In conclusion, pronounced changes in the dermoepidermal interface were found in acute LTB_4 -induced inflammation. An increased tenascin expression and a reduction in keratinocyte-associated HSPG staining in the epidermis were detected. Correlations with epidermal proliferation as well as cutaneous inflammation were found, but the correlation with proliferation of the epidermis was

most pronounced. The findings indicate that the model of LTB₄-induced acute cutaneous inflammation displays many characteristics of the early psoriatic lesion and could serve as a model for the study of some of the cell biological changes in this disease.

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