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Mast cells of psoriatic and atopic dermatitis skin are positive for TNF-α and their degranulation is associated with expression of ICAM-1 in the epidermis

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Abstract **The release of cytokines from cutaneous cells may be of major importance in the initiation and development of many inflammatory skin disorders. For example, tumor necrosis factor-alpha (TNF-α), which in healthy skin is found preformed only in mast cells, is able to induce the expression of several adhesion molecules including intercellular adhesion molecule-1 (ICAM-1). Increased expression of ICAM-1 occurs in keratinocytes in lesional skin of psoriasis and atopic dermatitis (AD) and it is considered to be an important initiator of leucocyte/keratinocyte interactions in skin inflammation. We counted the mast cells showing TNF-α immunoreactivity using a double-staining method in nonlesional and lesional skin sections from 12 patients with AD and 12 patients with psoriasis. The percentage of TNF-α$^+$ mast cells in lesional and nonlesional AD skin was 36 ± 22% and 21 ± 15% (P < 0.018, paired t-test), respectively, and in psoriatic skin was 16 ± 25% and 15 ± 15%, respectively (P < 0.89, paired t-test). We also cultured whole skin biopsies taken from the healthy-looking skin of psoriatic and AD patients in the presence of mast cell degranulator compound 48/80, which resulted in focal expression of ICAM-1 in the epidermis. In cultured keratinocytes, both histamine and an extract of a human mast-cell line (HMC-1) induced ICAM-1 immunostaining only in occasional cells, but the combination of histamine and the HMC-1 extract resulted in intense ICAM-1 staining in numerous cells. This enhancement of ICAM-1 staining was abolished by preincubation of the HMC-1 extract with anti-TNF-α antibody. These results suggest that the degranulation of mast cells induces the expression of ICAM-1 in keratinocytes probably via TNF-α and histamine.**

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Introduction

Mast cells are mononuclear, granule-containing secretory cells that reside mostly in the skin, and also in the respiratory and gastrointestinal tracts. After activation by immunological or nonimmunological stimuli, mast cells release various preformed mediators including histamine, proteases (tryptase, chymase, cathepsin G and carboxypeptidase), adenosine, acid hydrolases and proteoglycans. Mast cells also contain preformed cytokines, such as tumor necrosis factor-alpha (TNF-α) [36] and interleukin-4 (IL-4) [1]. After stimulation, rapidly synthesized mediators include the metabolic products of arachidonic acid, e.g. prostaglandin D_2, leukotriene C_4, and platelet-activating factor. Human mast cells have also been shown to produce various other cytokines besides TNF-α and IL-4 including IL-1 [30], IL-3 [25], IL-5 [15], IL-6 [17], IL-8 [23], IL-13 [3], granulocyte macrophage-colony stimulating factor [25] and interferon-gamma (IFN-γ) [12].

The release of cytokines in diseased skin may be of major importance in the development of many inflammatory skin disorders. Particular interest has focused on TNF-α, which is confined to mast cells in normal skin [36], but following stimulation may be produced by a variety of cutaneous cells, including Langerhans cells [19], dermal dendritic cells [24] and keratinocytes [16]. In human volunteers, a single intradermal injection of TNF-α leads to rapid accumulation of neutrophils, and multiple injections of TNF-α lead to the formation of inflammatory cell infiltrate consisting of mostly CD4$^+$ lymphocytes [8]. In several investigations it has been found that increased levels of this cytokine are present in psoriatic skin, which is a chronic dermatosis characterized by a T-helper type 1 lymphocyte infiltrate [34]. One of the mechanisms by which TNF-α influences the development of skin inflammation is the induction of adhesion molecules including endothelial E-selectin (ELAM-1), intercellular

adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) expression [26, 27]. Other known effects of TNF-α include increased expression of class 1 major histocompatibility complex antigens [28].

Induction of ICAM-1 expression in the epidermis is considered to be an important initiator of leucocyte/keratinocyte interactions in many inflammatory skin diseases. ICAM-1 is the ligand for the β2 integrin leucocyte function-associated antigen-1 found on most leucocytes [20]. In addition of TNF-α, IFN-γ [5], ultraviolet radiation [18] and staphylococcal enterotoxin B [35] have also been shown to induce ICAM-1 expression in keratinocytes. Also histamine alone has been shown to induce only weak ICAM-1 expression in keratinocytes via the H2 receptor, but interestingly, when histamine is combined with TNF-α, a significant augmentation of ICAM-1 expression in keratinocytes is observed [22]. In uninvolved skin of patients with psoriasis and atopic dermatitis (AD) and in normal skin there is no expression of ICAM-1 in keratinocytes in contrast to endothelial cells, but increased expression of ICAM-1 occurs in keratinocytes in lesional skin of psoriasis and AD [7].

The increased number and degranulation of mast cells is a typical feature of both psoriasis and AD [31–33], indicating the participation of mast cells and their mediators in the pathogenesis of both dermatoses. In this study we investigated the percentage of TNF-α^+ mast cells in psoriasis and AD. Also the effect of degranulation of mast cells on the expression of ICAM-1 in keratinocytes was studied in cultured whole-skin biopsies taken from the healthy-looking skin of psoriatic and AD patients. Finally, a human mast-cell line (HMC-1) extract was used together with histamine to stimulate cultured keratinocytes and the expression of ICAM-1 was studied. Blocking experiments with anti-TNF-α were performed.

Materials and methods

Patients and biopsies for sequential double-staining of TNF-α in mast cells

Punch biopsies (4 mm) were taken from lesional and nonlesional skin of 12 patients with chronic psoriasis (6 males and 6 females; mean age 52 years, range 24–70 years), and 12 patients with acute or subacute AD (5 males and 7 females; mean age 31 years, range 16–62 years), under local anaesthesia with 1% lidocaine and adrenaline. Nonlesional skin samples were taken at least 3 cm away from lesional skin. The diagnosis of AD was made according to the criteria of Hanifin and Rajka [10]. The patients had not received any systemic or local treatment for at least 2 weeks before entering the study. After removal, the biopsies were immediately embedded in OCT compound (Miles Scientific, Naperville, Ill.), and frozen in isopentane cooled with a mixture of absolute ethanol and dry ice.

The methods of this study were approved by the Ethics Committee of the Kuopio University Hospital, Kuopio, Finland. All volunteers gave informed consent prior to inclusion in the study.

Skin biopsy cultures and mast cell degranulation

Punch biopsies (4 mm) were taken from healthy-looking skin of three patients with psoriasis (three males; mean age 46 years, range 36–54 years), and three patients with AD (one male, two females; mean age 36 years, range 22–57 years), under local anaesthesia with 1% lidocaine and adrenaline. Two biopsies were taken from each patient. The patients had not received any systemic or local treatment for at least 2 weeks before entering the study. For studies of mast cell degranulation and the induction of ICAM-1 expression in keratinocytes, one of the biopsies of each patient was cultured for 24 h in 1 ml RPMI-1640 (Gibco Brl, Life Technologies, Roskilde, Denmark) supplemented with 10% fetal calf serum, 100 U/ml penicillin and 100 μg/ml streptomycin in the presence of 10 μg/ml compound 48/80 (Sigma, St. Louis, Mo.) to elicit mast cell degranulation. The other biopsy was cultured without compound 48/80 as the negative control. Stimulation for 24 h with compound 48/80 was shown to elicit maximal degranulation of mast cells in skin biopsies (data not shown). After stimulation, the biopsies were washed twice with cold phosphate-buffered saline (PBS) and cultured in supplemented RPMI-1640 for a further 24 h.

Preparing the HMC-1 cell extracts

The human mast cell line HMC-1 [4] was cultured in Iscove's modified DMEM with glutamax-1 (Gibco Brl, Life Technologies, Roskilde, Denmark) supplemented with 10% fetal calf serum, 100 U/ml penicillin, 100 μg/ml streptomycin and 1.2 m*M* monothioglycerol (Sigma) at 37° C in an atmosphere containing 5% CO_2. The cell line was passaged every 3–4 days. The viability of the cells was over 95%. The cells were washed twice with cold PBS, counted, and 5×10^6 cells were resuspended in 1 ml PBS. The cells were sonicated to release the formed mediators from the cells and the cell extract was stored at –20° C before use.

Keratinocyte cultures and stimulation

Human foreskin keratinocytes were cultured in keratinocyte-SFM serum-free medium (Gibco, Grand Island Biological Company, Grand Island, N.Y.) supplemented with 5 ng/ml epidermal growth factor, 50 μg/ml bovine pituitary extract, 100 U/ml penicillin and 100 μg/ml streptomycin at 37° C in an atmosphere containing 5% CO_2. Cell cultures were used at the third to eighth passage and studied at 70–80% confluence. Viability of the cells was > 95% in all the experiments. The keratinocytes were grown in 16-well Lab-Tek slide tissue culture chambers (Nunc, Naperville, Ill.) and stimulated with 0.1, 0.5 and 2 m*M* histamine (Fluka, Buchs, Switzerland) with and without HMC-1 cell extract corresponding to 5×10^4 cells/well for 2 days. A blocking experiment was also performed by preincubating the HMC-1 extract with 500 μg/ml rabbit polyclonal antihuman TNF-α antibody (Sera-Lab, Crawley Down, UK) or control for 1 h at room temperature. This antibody-blocked extract was also used with 0.5 m*M* histamine to stimulate the keratinocytes. After stimulation. the keratinocytes were washed twice with cold PBS and fixed in cold methanol for 10 min. Also, as controls for previous experiments keratinocytes were cultured with 10 μg/ml compound 48/80 and anti-TNF-α.

Enzyme histochemical staining methods

For the staining of mast cell tryptase, 5 μm cryosections were cut on poly-L-lysine-coated slides. The sections were fixed in cold acetone for 10 min. Enzyme activity of mast-cell tryptase was demonstrated with 1 m*M* carbobenzoxy-Gly-Pro-Arg-4-methoxy-2-naphthylamide (Z-Gly-Pro-Arg-MNA; Bachem, Bubendorf, Switzerland) as the substrate, and 0.5 mg/ml Fast Garnet GBC or Fast black K salt (Sigma) as the chromogens, each dissolved in 100 m*M* Tris-HCl buffer, pH 7.5. We have previously found that this enzyme histochemical method selectively and sensitively stains mast cells only [11].

Immunohistochemical staining methods

Immunohistochemical staining was carried out by first fixing the skin sections in cold acetone for 10 min. TNF-α was stained with 50 μg/ml rabbit polyclonal antihuman-TNF-α IgG antibody (Sera-

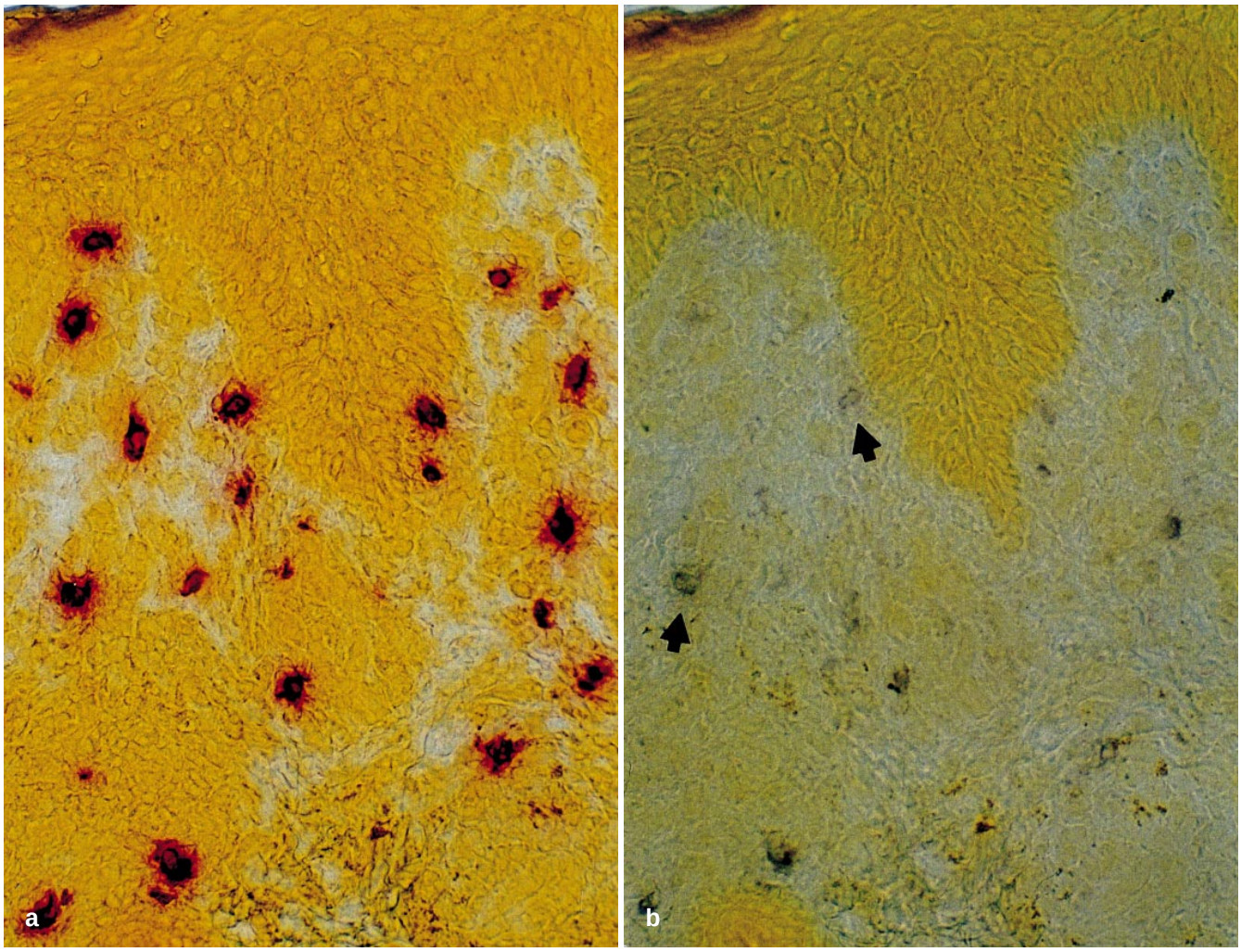

Fig. 1 **a** A section of lesional skin of AD stained with Z-Gly-Pro-Arg-MNA as the substrate, and Fast Garnet GBC as the chromogen. **b** After photographing, the dye was removed with Tween 20, and the section was stained with polyclonal anti-TNF-α antibody. Mast cells *(arrows)* are the only cell type staining positively for TNF-α (× 270)

Lab) dissolved in PBS containing 1% bovine serum albumin. The bound polyclonal antibody on skin sections was visualized using the Vectastain Elite ABC Kit (Vector, Burlingame, Calif.) together with 0.05% 3,3′-diaminobenzidine tetrahydrochloride, 0.04% nickel chloride, and 0.03% hydrogen peroxide. Control slides were similarly treated, either with the primary antibody replaced by PBS, rabbit serum (1:500) or an unrelated rabbit polyclonal IgG antibody at the same concentration as the TNF-α antibody. An immunohistochemical method has previously been used by another group for staining of TNF-α in mast cells of human skin [36]. Immunohistochemical stainings using mouse monoclonal antihuman ICAM-1 IgG antibody (1:100) (Immunotech SA, Marseille Cedex, France) were also performed in the same way.

Sequential double-staining method

To confirm that TNF-α is located in mast cells, the skin sections were first stained using the enzyme histochemical staining method to identify the mast cells. The sections were then photographed using 66 × magnification. Nine adjacent photographs along the epidermis, and extending approximately 0.4 mm into the dermis, were taken of each skin section. After removal of the azo dye by overnight treatment with 15% Tween 20, the same sections were stained immunohistochemically for TNF-α, and photographed at exactly the same sites as the previous pictures. This method has been used for the immunohistochemical staining of tryptase, chymase, $alpha_1$-antitrypsin, $alpha_1$-antichymotrypsin [11] and IL-4 [13] in mast cells.

Counting of mast cells

The number of TNF-α^+ mast cells was counted in all the adjacent photographs, and the percentage of TNF-α^+ mast cells was then calculated. The total number of tryptase-positive cells was counted on separate skin sections, using a 0.2 × 0.2 mm ocular grid (Ella Graticules, Tonbridge, UK). The area of the papillary dermis was measured with the Quantimet image analysis system (Leica, Nussloch, Germany) and the mast cells in the papillary dermis were then counted separately.

Results

TNF-α in mast cells

In all the lesional and nonlesional skin sections of psoriasis and AD, mast cells with immunoreactivity for TNF-α were present (Fig. 1). The antibody against TNF-α used in

Table 1 Total number of mast cells and the percentage of TNF-α⁺ mast cells in lesional and nonlesional skin of patients with psoriasis and AD. The values are means ± SD

* $P < 0.0018$ (paired *t*-test);
** $P < 0.01$ (unpaired *t*-test)

	Lesional skin		Nonlesional skin	
	Mast cells/mm²	TNF-α⁺ (%)	Mast cells/mm²	TNF-α⁺ (%)
AD ($n = 12$)	142 ± 69	36 ± 22*,**	120 ± 55	21 ± 15*
Psoriasis ($n = 12$)	293 ± 100	16 ± 25**	96 ± 27	15 ± 15

this study was specific, because no immunostaining was detected either in the absence of any specific primary antibody or in the prsence of rabbit serum or an unrelated antibody used at the same concentration as the specific antibody.

The percentage of TNF-α⁺ mast cells in the upper dermis (extending approximately 0.4 mm down from the epidermis) was 36 ± 22% in lesional AD skin and 21 ± 15% in nonlesional AD skin ($P < 0.018$, paired *t*-test). Furthermore, the total number of mast cells was increased by an average of 18% in lesional AD skin compared with nonlesional AD skin (Table 1). In psoriasis, the percentage of TNF-α⁺ mast cells was 16 ± 25% in lesional and 15 ± 15% in nonlesional skin ($P < 0.89$, paired *t*-test). However, in psoriasis the total number of mast cells was increased by 305% (Table 1) and therefore there was also an increase in the TNF-α⁺ mast-cell count. In addition, a statistically significant difference was found between lesional skin of AD and of psoriasis with regard to the percentage of TNF-α⁺ mast cells (36% vs 16%, $P < 0.01$, unpaired *t*-test).

Most of the TNF-α⁺ cells in the nonlesional AD and psoriatic skin appeared to be mast cells, with only a few other cells showing TNF-α immunoreactivity. These results are in accordance with those of previous experiments which also show that TNF-α is already preformed in mast cells of normal skin, with very little immunoreactivity of TNF-α in other cell types [36].

Degranulation of mast cells in skin biopsies induces ICAM-1 expression in keratinocytes

Degranulation of mast cells following treatment with 10 μg/ml compound 48/80 induced a clear multifocal expression of ICAM-1 in basal and suprabasal keratinocytes in two out of three skin biopsies from the healthy-looking skin of psoriatic patients. In the control biopsies from the same patients, no immunoreactivity for ICAM-1 in keratinocytes could be seen (Fig. 2). Also, in two out of three skin biopsies from the healthy-looking skin of AD patients, a slight induction of ICAM-1 in the epidermis was seen in the biopsies incubated with compound 48/80, but only occasional individual keratinocytes became ICAM-1⁺. In control biopsies from the same patients, no keratinocytes positive for ICAM-1 were seen. To study the possibility that the induction of ICAM-1 expression in keratinocytes was a direct effect of compound 48/80, we cultured keratinocytes in the presence of 10 μg/ml compound 48/80 for 2 days. No induction of ICAM-1 expression was observed.

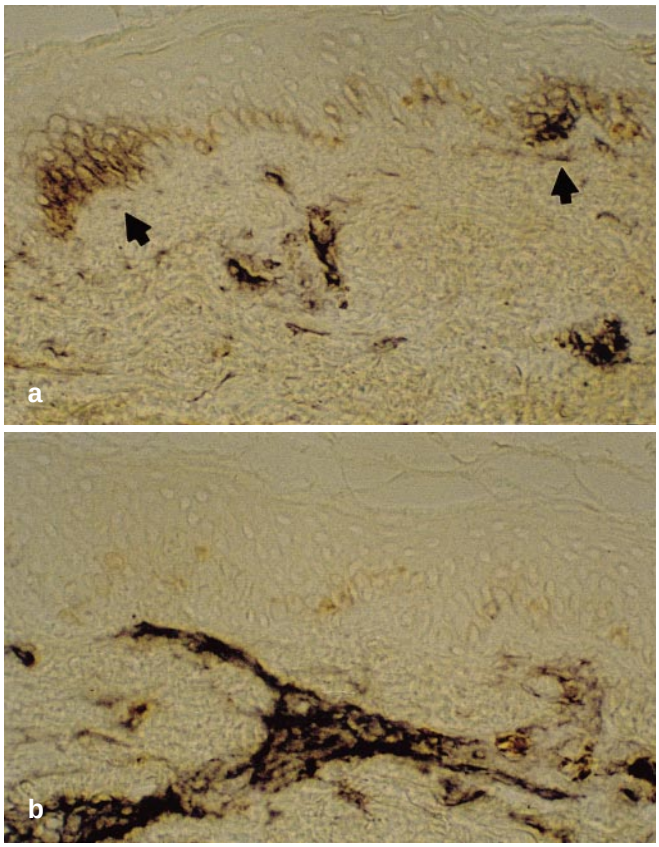

Fig. 2 a, b Two punch biopsies were taken from the healthy-looking skin of a patient with psoriasis. **a** One of the biopsies was cultured in the presence of 10 μg/ml compound 48/80 to elicit mast cell degranulation and afterwards a section of the biopsy was stained with monoclonal anti-ICAM-1 antibody. There is focal expression of ICAM-1 in the epidermis *(arrows)*. **b** The other biopsy was cultured without compound 48/80 and stained with monoclonal anti-ICAM-1 antibody. No ICAM-1 positivity can be seen in the epidermis (× 270)

HMC-1 extract together with histamine induces ICAM-1 expression in cultured keratinocytes, which is blocked by an antibody against TNF-α

Histamine (0.1, 0.5, 2 m*M*) induced a dose-dependent increase in the number of ICAM-1⁺ keratinocytes in the absence and presence of HMC-1 extract. However, a clear increase in the number of ICAM-1⁺ keratinocytes was observed when histamine and HMC-1 extract were present simultaneously. HMC-1 extract together with 0.5 m*M* histamine gave about the same number of positively stained cells as 2 m*M* histamine alone (Fig. 3). To determine whether TNF-α was the component in HMC-1 cell extract

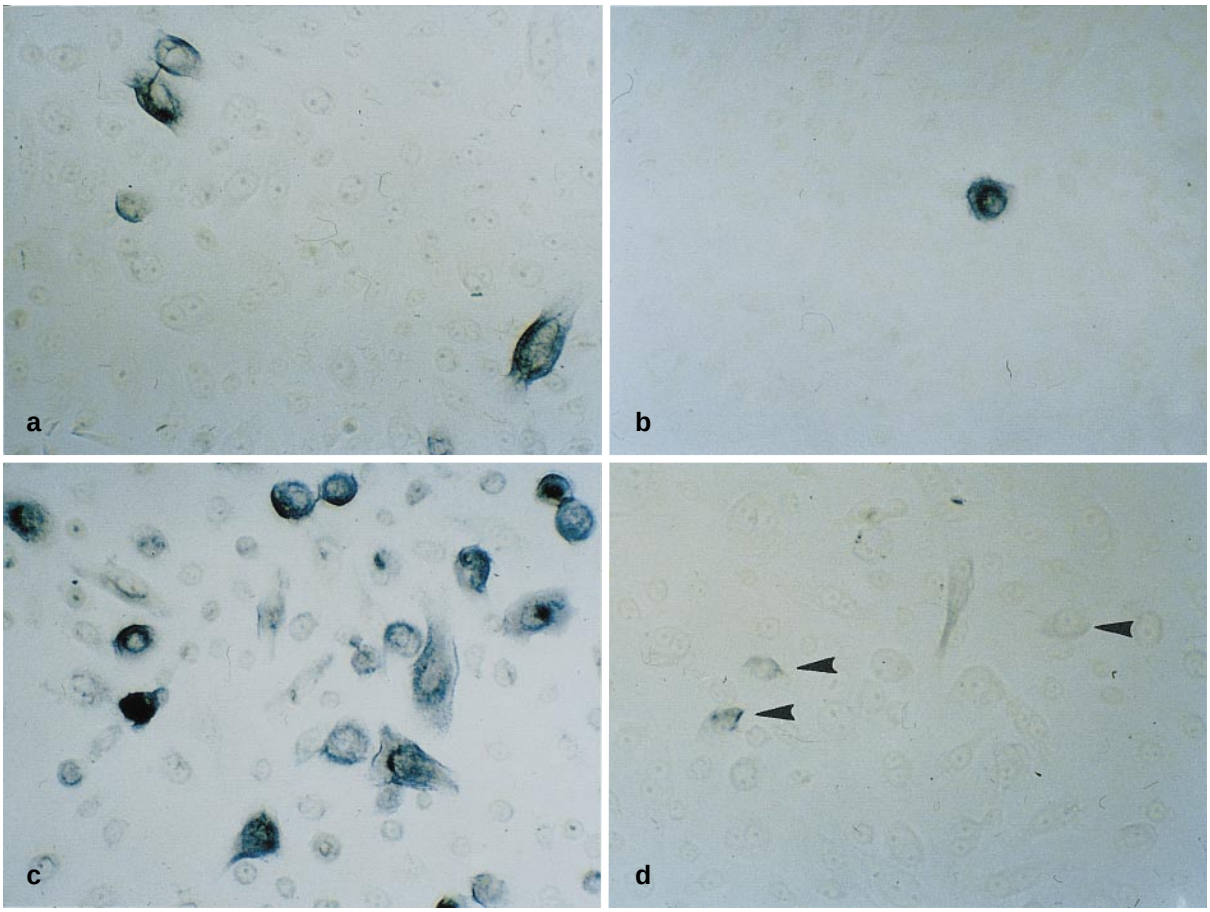

Fig. 3 a–d Cultured foreskin keratinocytes were fixed in cold methanol and stained with a monoclonal anti-ICAM-1 antibody. **a** Keratinocytes incubated with 0.5 m*M* histamine alone display only occasional ICAM-1$^+$ cells and the majority of the keratinocytes show hardly observable or no ICAM-1 positivity. **b** Keratinocytes incubated with HMC-1 extract show only rare ICAM-1$^+$ cells. **c** Keratinocytes incubated with HMC-1 extract together with 0.5 m*M* histamine and stained with anti-ICAM-1 antibody show a significantly increased number of ICAM-1$^+$ keratinocytes. **d** Keratinocytes incubated with 0.5 m*M* histamine and HMC-1 extract pretreated with anti-TNF-α antibody and were stained with anti-ICAM-1 antibody show only faint ICAM-1 positivity in occasional cells *(arrowheads)* (× 270)

enhancing this histamine-induced ICAM-1 expression, blocking experiments were performed. Only occasional ICAM-1$^+$ cells were observed after 0.5 m*M* histamine treatment (Fig. 3 a) and rarely after incubation with HMC-1 cell extract (Fig. 3 b). However, stimulation of the keratinocytes with HMC-1 cell extract together with 0.5 m*M* histamine clearly increased the number of ICAM-1$^+$ cells (Fig. 3 c). Preincubation of the HMC-1 cell extract with anti-TNF-α antibody markedly reduced the number of ICAM-1$^+$ cells when keratinocytes were stimulated with 0.5 m*M* histamine together with this antibody-blocked extract (Fig. 3 d).

Discussion

This study shows that the activation of mast cells in healthy-looking skin of patients with psoriasis and AD induces the expression of ICAM-1 in keratinocytes. ICAM-1 is an important adhesion molecule that initiates cellular interactions in the immune response and is upregulated in keratinocytes in chronic inflammatory skin diseases such as AD and psoriasis [7]. In both AD and psoriasis, mast cells are degranulated in the early stages of disease development and later they also increase in number [29, 31–33]. Particularly in psoriasis, mast cells are most numerous just beneath the epidermis [33] enabling these cells to communicate with keratinocytes. Previously it has been shown that TNF-α [27], IFN-γ [5], ultraviolet radiation [18] and staphylococcal enterotoxin B [35] are capable of inducing ICAM-1 in keratinocytes. Because our pilot blocking experiments with neutralizing antibodies failed to prevent ICAM-1 expression in the whole skin biopsies, most likely because the large antibodies could not penetrate the skin biopsy to a sufficient depth to reach their target, cultured keratinocytes were used.

As the HMC-1 cell extract induced only weak ICAM-1 expression in cultured keratinocytes, 0.5 m*M* histamine was added to this extract, as in previous studies histamine had been shown to significantly enhance TNF-α induction of ICAM-1 expression in keratinocytes [22]. Under the

experimental conditions in this study the concentration of histamine derived from HMC-1 cells was only 0.6 μ*M* (Huttunen et al., unpublished results). This concentration is far too low to induce ICAM-1 expression and for this reason additional histamine was included in the medium. Histamine and HMC-1 cell extract each induced only weak expression of ICAM-1 in keratinocytes, but when combined they clearly stimulated ICAM-1 expression. This effect was abrogated with anti-TNF-α, indicating that TNF-α was the cytokine responsible for this effect.

However, the human mast cell line HMC-1 may differ from cutaneous mast cells in regard to its mediators, so it is possible that other mediators also released by cutaneous mast cells are responsible for the induction of ICAM-1 in keratinocytes in skin biopsies. However, it is also possible that the degranulation of mast cells activates other cell types as well as keratinocytes, and these cells release their mediators resulting in induction of ICAM-1 in keratinocytes. It is also possible that the in vivo upregulation of ICAM-1 in keratinocytes of lesional atopic skin results from IFN-γ derived from T cells in particular since in situ expression of IFN-γ has been shown in one study to be linked to the clinical course of AD [6]. However, upregulation of IFN-γ has only been shown in chronic lesions of AD [6], whereas in acute lesions of AD usually very low levels of IFN-γ are found [9]. So, as TNF-α together with histamine are already preformed in mast cells of normal skin, they seem more likely candidates than IFN-γ for ICAM-1 upregulation in keratinocytes.

The percentage of TNF-α^+ mast cells was higher in lesional than in healthy-looking skin of AD patients. Bradding et al. have reported that there is also a sevenfold increase in the number of mast cells stained for TNF-α in the bronchial mucosa of atopic patients with asthma [2]. In patients with psoriasis, no differences were seen in the percentage of TNF-α^+ mast cells between lesional and healthy-looking skin. However, the total number of mast cells was increased by 305% in the lesional psoriatic skin compared with healthy-looking skin, so the total number of TNF-α^+ mast cells was increased. No significant difference was observed between healthy-looking skin of AD and of psoriatic patients, but in both diseases many of the mast cells of normal-looking skin contained preformed TNF-α.

TNF-α is produced by many cell types, especially those of monocyte/macrophage and T-cell lineages. In contrast to mast cells, T cells have little capacity for mediator storage and they secrete their cytokines once produced. However, the observation in this study and in previous studies [2, 36] that TNF-α is localized predominantly in mast cells suggests that mast cells may function as an important storage and source of this cytokine. It is possible that during the early stages of both psoriasis and AD, mast cells are activated by an unknown mechanism and this can be seen as degranulation of these cells. Preformed TNF-α, released in the early stages of development of skin lesions, could induce the expression of ICAM-1, ELAM-1 and VCAM-1 in keratinocytes, endothelial cells and dendritic cells, initiating cellular interactions in the immune response. Later, activated mast cells could also produce other cytokines in addition to TNF-α, which could contribute to the pathogenesis of these skin diseases.

Previously, it has been shown that TNF-α released from mast cells is capable of inducing the expression of ELAM-1 on both cultured endothelial cells in vitro and dermal postcapillary venules in vivo [36] and of ICAM-1 in cultured fibroblasts in vitro [21]. Degranulation of mast cells and the release of TNF-α have also been shown to upregulate alpha-6 integrins on epidermal Langerhans cells [14]. Meng et al. have also shown that the degranulation of mast cells by treatment with calcium ionophore induces an upregulation of ICAM-1 in keratinocytes in a skin-equivalent model [21], and they suggest that the mediator responsible for the effect is TNF-α. Our results give further evidence that TNF-α and histamine released from mast cells are capable of inducing the expression of ICAM-1 in keratinocytes.

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