The High-Affinity Receptor for IgE Is the Predominant IgE-Binding Structure in Lesional Skin of Atopic Dermatitis Patients

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While the skin of most patients with atopic dermatitis (AD) is known to contain IgE-bearing cells, the contribution of the various IgE-binding structures to this phenomenon is not fully understood. To address this issue, we eluted cell-bound IgE from cryostat sections of lesional AD skin by acid treatment and performed reconstitution experiments with IgE in the absence or presence of reagents directed against the currently known IgE-binding structures. We found that incubation of acid-treated sections, with either chimeric or serum IgE, resulted in the appearance of sizable numbers of anti-IgE-reactive cells. This cellular IgE loading could be entirely prevented by preincubation of the sections with the anti-FceRIα MoAb 15-1 but not with either antibodies against FceRII/CD23 and FcyRII/CD32 or with α-lactose. To exclude the possibility that acid treatment of tissue sections may have adversely influenced the IgE-binding capacity of IgE receptors other than FceRI, we performed an identical series of experiments on AD skin samples that, as an exception, were essentially devoid of anti-IgE-reactive cells. Again, no IgE loading was detected when these sections were preincubated with anti-FcεRIα MoAbs. In contrast, preincubation of the sections with α-lactose and/or MoAbs against FceRII/CD23 or FcγRII/CD32 did not affect IgE loading. Together with the observations that anti-FcεRIα-reactive and IgE-binding cells are largely overlapping populations and include cells of the Langerhans cell/dendritic cell lineage, mast cells, and a few dermal dendrocytes and eosinophils, our results demonstrate that FcεRI is the predominant and, perhaps, the only biologically relevant IgE-binding structure on histogenetically and functionally diverse cell populations of AD skin. Key words: high-affinity receptor for IgE/IgE* antigen-presenting cells.


Although the central role of allergen-specific IgE in the pathogenesis of respiratory allergy is well established, its contribution to the eczematous lesions in cutaneous atopy is still a matter of conjecture and debate. Evidence supporting this involvement comes from the findings (i) that dendritic antigen-presenting cells (APCs) in lesional and, to a lesser extent, in nonlesional skin of atopic dermatitis (AD) patients frequently exhibit surface-bound IgE molecules (Bruynzeel-Koomen et al., 1986; Barker et al., 1988; Bieber et al., 1989a), (ii) that Langerhans cell (LC)-induced allergen-specific T cell activation and proliferation occur more efficiently when the allergen is taken up via these cell surface-bound IgE molecules (Mudde et al., 1990), and (iii) that eczematous reactions to Aeroallergens can be most efficiently induced via skin regions harboring IgE-bearing dendritic cells (DCs) (Mudde et al., 1990). By reasoning that the prevention of IgE-facilitated allergen presentation could be an effective means to stop the cascade of pathogenetic events occurring in AD, we and others aimed to characterize the IgE-binding structure(s) on APCs in AD skin. Candidate molecules include (i) the low-affinity receptor for IgE (FceRII/CD23), a single-chain type-II integral membrane molecule (Sutton and Gould, 1993) whose expression and release can be induced by interleukin 4/interferon-γ on various cell types including LCs (Bieber et al., 1989b); (ii) galectin-3, a β-galactoside-binding protein (Braendes et al., 1994) produced by a variety of cells including keratinocytes (KC) (Wollenberg et al., 1993), and monocytes/macrophages (Liu et al., 1995); and (iii) the high-affinity receptor for IgE (FceRI) expressed as a tetrameric high-affinity receptor on mast cells and basophils (Ravetch and Kiner, 1991; Sutton and Gould, 1993).

Evidence for the participation of FceRI/CD23 in IgE binding to LCs in AD skin came from the findings (i) that the monoclonal antibody (MoAb) BB10, supposedly directed against FceRI/CD23

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Abbreviations: AD, atopic dermatitis; DC, dendritic cell; APC, antigen-presenting cell; KC, keratinocyte; FceRI, high-affinity receptor for IgE; FceRII, low-affinity receptor for IgE/CD23; FcγRII, low-affinity receptor for IgG/CD32; cIgE, monoclonal chimeric IgE; sIgE, AD serum containing high titer of IgE; BIOT, biotinylated.

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Preparation of Tissue Specimens

Biopsies were embedded in TissueTek OCT (Miles Laboratory, Elkhart, IN), frozen in 2-methylbutane (Merck, Darmstadt, Germany), cooled with liquid nitrogen, and stored at −80°C until further use. Cryostat sections (5 μm) were cut, mounted on poly-L-lysine (Sigma, St. Louis, MO)-coated slides, air-dried, and fixed in acetone (4°C) for 10 min.

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Antibodies and Reagents

The following MoAbs were used as blocking reagents: mouse anti-FcεRIα (15-1; 10 μg per ml; Wang et al., 1992), anti-FcεRIα (CD23; 10 μg per ml; Serotec, Oxford, UK), anti-FcγRIIa/CD32 (10 μg per ml; Ortho Diagnostic Systems, Raritan, NJ), and anti-D3 (UCHT1-FTIC; 1 μg per ml; DAKO A/S), and anti-D19 (Leu 12-FTIC; 2.5 μg per ml; Becton Dickinson).

IgE-Binding Assay

After clution of tissue-bound IgE with glycine hydrochloride buffer (0.05 M glycine, 0.085 M NaCl, 0.005 M KCl, 0.01 M ethylenediamine tetraacetic acid, pH 2.5; Ishizaka and Ishizaka, 1974) for 30 min on ice, cryostat skin sections were incubated either overnight at 4°C with monoclonal chimeric (human constant region heavy chain ε/mouse variable region heavy chain/ε light chain) IgE anti-NP (clgE; 2.3–3.6 μg per ml; Serotec) or for 1 h at 37°C with unlabeled sera from AD patients with IgE concentrations from 2.1 to 3.6 μg per ml. In certain experiments, cryostat sections were pre-exposed overnight at 4°C to reagents known to inhibit IgE binding to the various IgE receptors (see "Antibodies and Reagents") prior to their incubation with clgE or human sera. IgE binding was visualized as described below (see "Immunostaining"). Monoclonal chimeric IgE2 anti-NP (2.1–3.6 μg per ml; Serotec) or undiluted serum from non-atopic healthy individuals was used as negative control.

Immunostaining

Slides were washed in Tris(hydroxymethyl)aminomethane-buffered saline (pH 7.6) between incubations. To prevent non-specific binding, sections were "blocked" with 5% sheep serum/3% human AB serum (Serotec/Immuno AG, Vienna, Austria) for 1 h at room temperature prior to incubation with the primary antibody. Antibodies and sera were diluted with staining buffer containing 5% (wt/vol) milk proteins and 0.1% polyoxyethylene sorbitan monolaureate (Tween 20: Bio-Rad).

Immunoperoxidase Single Staining

For the detection of IgE, tissue sections or EBV-transformed B cells immobilized on Adhesion Slides were incubated with Biotin mouse anti-human IgE MoAb followed by peroxidase-conjugated streptavidin complexes (StreptABComplex/HRP; DAKO A/S) and 3-amin-9-ethyl carbazole (Sigma-Aldrich Chemie) in acetate buffer (pH 5.0). For the demonstration of tissue-/cell-expressed FcεRI or FcγRI/CD23, the incubation chain consisted of mouse MoAbs against mouse IgM (5 μg per ml; Becton Dickinson), of Biot-F(ab')2, sheep anti-mouse immunoglobulin (1:800 dilution; Amersham, Little Chalfont, UK), and, finally, of the StreptABComplex/HRP staining kit. Sections were counterstained with hematoxylin (Merck) and mounted in phosphate-buffered saline/ glycerol/Mowiol (Hoechst, Frankfurt am Main, Germany).

Double Immunofluorescence Staining

Cryostat sections were incubated overnight at 4°C with one of the primary MoAbs (anti-human IgE, 5–1, MHM6, or EG1), followed by tetramethylrhodamine isothiocyanate (TRITC)-labeled affinity-purified goat anti-mouse IgG (10 μg per ml; Atlantic Antibodies, Stillwater, MN) for 1 h at room temperature. To increase the detectability of tissue-bound primary antibody, sections were exposed to mouse IgG1 (1 μg per ml; 45 min; room temperature; Sigma-Aldrich Chemie) followed by a second exposure to TRITC-conjugated goat anti-mouse IgG (10 μg per ml). Sections were then stained overnight at 4°C with either (i) one of the FITC-labeled MoAbs (see "Antibodies and Reagents"), (ii) rabbit anti-FcεRIα antibodies followed by FITC-conjugated affinity-purified swine anti-rabbit immunoglobulin (1:100 dilution; DAKO A/S), or (iii) MoAb RFD1 followed by FITC-conjugated rat anti-mouse IgM (10 μg per ml; Southern Biotechnology Associates) and thereafter by FITC-labeled F(ab')2 goat anti-rat immunoglobulin (5 μg per ml; Jackson ImmunoResearch Laboratories, West Grove, PA), (iv) Biot mouse anti-chymase MoAbs followed by FITC-streptavidin (1:100 dilution; Amersham), or (v) rabbit anti-human IgE antibodies followed by FITC-labeled swine anti-rabbit immunoglobulin (1:100 dilution; DAKO A/S). When directly conjugated mouse IgG MoAbs were used for counterstaining, the sections were saturated with unlabeled mouse IgG1 (2.5 μg per ml) or mouse IgG2a MoAbs (1.2 μg per ml; both from Sigma-Aldrich Chemie) of irrelevant specificity. Appropriate (non)labeled isotype-matched antibodies were used as negative controls. All slides were finally embedded in phosphate-buffered saline/glycerol/Mowiol.

Quantification and Lineage Marker Analysis of IgE+ and FcεRIα+ Cells in Epidermis and Dermo

Peroxidase-labeled IgE+ cells, present in five to ten arbitrarily chosen fields (covering an area of ~0.05 mm²) of the epidermis as well as mid and upper dermis, were counted with a semi-automatic image analyzing system (Vidas, Kontron Elektronik, Eching, Germany). For the determination of specific protein binding, sections were double-stained for IgE and human IgE receptors, using a panel of antibodies against specific receptor epitopes (see "Immunostaining"). Results obtained for various experimental groups were compared using the Tukey-Kramer Multiple Comparisons Test and p values of <0.05 were considered to be statistically significant. For immunofluorescence (FITC versus TRITC) double-labeling studies, to determine the proportion of IgE+ or FcεRIα+ cells expressing a given lineage marker, we screened five to seven sequential fields of the epidermis or mid/upper dermis by using an epifluorescence microscope (Nikon, Tokyo, Japan) at a ×400 magnification.

| Table 1. Lesional AD Skin (AD) but not Skin from Non-Atopic Healthy Volunteers (HV) Harbors Numerous IgE-Bearing Cells |
|-------|-------|
|       | HV    | AD |
| (n = 9)|       |    |
| Epidermis | 0 | 120 ± 64 |
| Dermis   | 11 ± 9 | 437 ± 93 |

*"IgE+ cells were visualized by immunoperoxidase staining. Five to 10 arbitrarily chosen microscopic fields (covering an area of ~0.05 mm²) of the epidermis as well as mid and upper dermis were counted with a semi-automatic image analyzing system. Data are expressed as numbers per mm² (mean ± SD)."
tion. The total number of cells labeled with each antibody and of cells that were double-stained was counted and the percentages of the cells expressing both antigens was calculated.

RESULTS

AD Lesions but Not Skin of Nonatopic Persons Harbor Large Numbers of IgE-Bearing Dendritic Cells In accordance with previous reports (Bruynzeel-Koomen et al., 1986; Leung et al., 1987; Barker et al., 1988; Bieber et al., 1989a), anti-IgE immunostaining of lesional AD skin stained numerous cells within both the dermis and the epidermis (Table I). IgE+ cells in the upper skin layers were largely dendritic, frequently associated with the microvasculature, and tended to form clusters (Fig 1a). In sharp contrast, normal-appearing skin of healthy volunteers contained only few IgE+ cells (Table I) localized in the upper and mid dermis (data not shown). Immunofluorescence double labeling of AD sections revealed that virtually all IgE+ cells in the epidermis and the majority of IgE+ cells in the dermis exhibit anti-CD1a and/or RFD1 reactivity (Table II, Experiment a) indicating that these cells belong to the LC/DC family. Other IgE+ cells of the dermis included chymase-containing mast cells, EG1+ eosinophils, and FXIIIa+ dermal dendrocytes (Table II, Experiment a). The lymphocyte population of AD skin, which consists almost exclusively of T lymphocytes, failed to express IgE (data not shown).

Masking the IgE-Binding Site of FcεRIα, but Not the Functional Blockade of Other IgE Receptors, Prevents Blocking of Chimeric and Serum IgE to AD Skin Sections In a first series of experiments, we eluted in vivo-bound IgE by washing lesional AD cryostat skin sections with acid-glycine buffer (Fig 1b) and demonstrated that incubation of these "stripped" sections with either clgE or atopic serum containing a high titer of IgE (3.6 µg per ml) results in an anti-IgE staining pattern that is qualitatively and quantitatively indistinguishable from that of untreated skin (Figs 1, compare a with c, 2a,b). Our further observation that the proportional expression of various lineage markers (CD1a, MoAb RFD1-reactive moieties, chymase, eosinophil cationic protein, FXIIIa) by IgE-bearing cells in vivo (Table II,

Table II. Immunophenotypic Profiles of AD Skin Cells Binding IgE

<table>
<thead>
<tr>
<th></th>
<th>CD1a</th>
<th>RFD1</th>
<th>Chymase</th>
<th>EG1</th>
<th>FXIIIa</th>
<th>HLA-DR</th>
<th>CD45</th>
</tr>
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<tbody>
<tr>
<td>Epidermis (n=7)</td>
<td>77 ± 12</td>
<td>91 ± 6</td>
<td>7 ± 3</td>
<td>3 ± 2</td>
<td>4 ± 3</td>
<td>93 ± 8</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>Dermal (n=7)</td>
<td>27 ± 9</td>
<td>80 ± 12</td>
<td>7 ± 3</td>
<td>3 ± 2</td>
<td>4 ± 3</td>
<td>79 ± 11</td>
<td>92 ± 5</td>
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<tr>
<th></th>
<th>CD1a</th>
<th>RFD1</th>
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<th>CD45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermis (n=7)</td>
<td>85 ± 14</td>
<td>93 ± 5</td>
<td>8 ± 3</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
<td>94 ± 4</td>
<td>89 ± 7</td>
</tr>
<tr>
<td>Dermal (n=7)</td>
<td>21 ± 10</td>
<td>73 ± 9</td>
<td>8 ± 3</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
<td>82 ± 15</td>
<td>93 ± 5</td>
</tr>
</tbody>
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*The proportion of IgE+ cells expressing a given lineage marker was determined by immunofluorescence double-labeling studies. Five to seven sequential fields of the epidermis and mid/upper dermis were screened by using an epiphluorescence microscope. Results are expressed as percentages of IgE+ cells (mean ± SD) bearing a given marker.

*AD cryostat skin sections were subjected to acid treatment followed by incubation with clgE. The proportion of clgE+ cells expressing a given lineage marker was determined as described above. Results are expressed as percentages of clgE+ cells (mean ± SD) bearing a given marker.
or sIgE (Figs 1d; 2b) to the cells of epidermis and dermis. In sharp contrast, the anti-FceRI/CD23 MoAb MHM6 (9–44 μg per ml), α-lactose (0.2–0.5M), or the anti-FceRI/CD32 MoAb IV.3 (10–40 μg per ml) neither visibly nor numerically inhibited clgE and sIgE binding (Fig 1e, 2a,b). The validity of these IgE-binding inhibition studies is further substantiated by our finding that MoAb MHM6, but not 15–1, blocked IgE binding to FceRI/CD23 human EBV-transformed B cells (Fig 3) and tonsillar B lymphocytes (data not shown).

To test the possibility that acid treatment may have altered the IgE-binding capacity of receptors other than FceRI, we carried out an identical series of inhibition experiments on lesional AD skin sections that, as an exception, displayed no detectable in vivo bound IgE and thus allowed us to omit the acid treatment step. As with the situation with AD skin sections expressing in vivo bound IgE, the anti-FceRIα MoAb, but none of the other reagents (MHM6, α-lactose, IV.3), prevented the binding of clgE (Fig 4a) and sIgE (Fig 4b) to these specimens.

An additional argument for the critical importance of FceRI for IgE binding to AD skin cells came from the anti-FceRIα single-color immunolabeling studies on “striped” AD skin sections, which revealed a pattern (Fig 5) closely resembling that of anti-IgE staining of native AD skin sections (Fig 1a). This analogy was furthered by immunofluorescence double-labeling experiments showing that the vast majority of FceRIα+ cells in AD skin are LCs/DCs (Fig 6). The few remaining FceRIα+ cells included virtually the entire population of chymase-containing mast cells, 50–60% of EG1+ eosinophils, and ~5% of FXIIIa+ dermal dendrocytes (data not shown).

**DISCUSSION**

In the skin of AD patients, LCs, dermal dendritic cells, mast cells, and eosinophils frequently bear cell surface-bound IgE molecules (Bruynzeel-Koomen et al., 1986; Leung et al., 1987; Barker et al., 1988; Bieber et al., 1989a, Tanaka et al., 1995; this study). Although these cells apparently express various types of IgE-binding moieties, i.e., FceRI (Bieber et al., 1992; Wang et al., 1992; Gounni et al., 1994; Osterhoff et al., 1994), FcεRI/CD23 (Capron et al., 1986; Bruynzeel-Koomen et al., 1988; Bieber et al., 1989b; Sakamoto et al., 1990; Buckley et al., 1992), and galectin-3/EBP (Truong et al., 1993; Wollenberg et al., 1993; Liu et al., 1995), the contribution of the individual IgE receptors to the in vivo binding of serum IgE by AD skin cells has not been fully clarified. Herein, we provide evidence that, despite the reported presence of different IgE receptors in AD skin, FceRI is selectively responsible for cellular IgE binding. This is substantiated by the findings that an anti-FceRIα MoAb prevented the binding of monoclonal (Bieber and Ring, 1992; Wang et al., 1992; this study) and polyclonal (this study) serum IgE to either acid-treated AD skin sections (i.e., cryostat sections from which in vivo bound IgE was eluted) or sections devoid of detectable in vivo bound IgE. In contrast, reagents known to prevent IgE binding to FceRI/CD23 (Aubry et al., 1986) and galectin-3 (Frigeri and Liu, 1992), as well as antibodies against FcγRI/CD32, an
IgE-binding structure in rodents (Takizawa et al., 1992), failed to interfere with the binding of either of the two IgE preparations (this study). A further argument for the critical and unique role of FcεRI in IgE binding to AD skin cells comes from our finding that the anti-FcεRIα-reactive cells in AD epidermis and dermis display a similar, if not identical, cell morphology, tissue distribution, and immunophenotype as the cells bearing IgE in vivo and binding IgE ex vivo.

Our failure to block IgE binding to AD skin cells with the anti-CD23 MoAb MM6 may be surprising in view of reports describing (i) FcεRI/CD23 expression on various types of AD skin cells (Bruynzee-Koemen et al., 1988; Sakamoto et al., 1990; Buckley et al., 1992; Wollenberg et al., 1996), (ii) cytokine (interleukin 4, interferon γ)-induced up-regulation of FcεRI/CD23 on LCs (Bieber et al., 1989b), and (iii) inhibition of IgE-binding to APC by the "anti-CD23-like" MoAb BB10 (Bruynzee-Koemen et al., 1988). We have also obtained evidence that, in both IgE+ and IgE− lesional AD skin samples, the anti-CD23 MoAb MM6 stains a few cells in the epidermis and dermis (R. Klubal, unpublished observation). Our finding that acid treatment completely removes the anti-CD23 reactivity of AD skin sections (with or without IgE+ cells) but not that of tonsillar sections or EBV-transformed B cells, suggests that FcεRI/CD23 in AD skin is present in its soluble rather than in the acid-resistant transmembrane form. Nevertheless, the possibility exists that, because of limitations in the sensitivity of immunohistochemical methods, minute quantities of transmembrane CD23 may have escaped our detection. Even if this were the case, our blocking and reconstitution studies on acid-treated and untreated sections show that FcεRI/CD23 does not significantly contribute to clgE or slgE binding to lesional AD skin cells.

The β-galactoside-binding lectin, galectin-3, is expressed by KCs (Wollenberg et al., 1993) and mononuclear phagocytes (Liu et al., 1995) and can bind various oligosaccharide-rich structures, including IgE and IgE receptors (Baronde et al., 1994). Recently, Wollenberg et al. (1993) reported that the presence of KC-derived galectin-3 allows the binding of (poorly sialylated) human IgE to LC in vitro. Our results argue against a critical role of galectin-3 in the binding of monoclonal or serum IgE to AD skin cells, because anti-FcεRIα MoAb treatment completely prevented and α-lactose neither positively nor negatively influenced cellular IgE loading.

Data presented in this study further demonstrate that the vast majority (>80%) of AD skin cells capable of FcεRI-dependent IgE binding belong to the lineage of CD1α+/EGI− dermal dendrocytes, whereas mast cells, FXIIIa-expressing dermal dendrocytes, and EGI− eosinophils together account for only 15% of IgE-binding cells in the dermis. Concerning these latter cell populations, our immunofluorescence double-staining protocol allowed for a direct demonstration of FcεRIα on mast cells and certain FXIIIa+ dermal dendrocytes but not on eosinophils. Nevertheless, our recent observation that anti-FcεRI MoAb 15-1 treatment of acid-treated AD skin sections prevented IgE binding to EGI+ dermal cells (R. Klubal, unpublished observation) as well as immunohistologic studies by Gouni et al. (1994) and Tanaka et al. (1995) led us believe that FcεRI is the critical IgE-binding structure also on eosinophils.

Although definitive proof is lacking, it can be assumed that FcεRI, as in its role on peripheral blood APCs (Maurer et al., 1995;
Maurer et al., 1996), serves as an IgE-dependent allergen-focusing receptor on LCs/DCs. If so, FcεRI-bearing LCs may play a critical role in the pathogenesis of AD, because these cells are the first professional APCs to interact with exogenously delivered allergens and/or IgE-reactive epidermal cell-derived autoantigens (Valenta et al., 1996). It is also feasible that allergen-induced activation of FcεRI signaling pathways results in the production and release of mediators by LCs that may disturb the epidermal barrier and/or trigger the emigration of allergen-modified LCs into the dermis. This may allow cell-bound and/or soluble allergens to enter the dermal compartment. The latter event may favor the degranulation of mast cells, which, by the release of endothelial cell activating and chemotactic factors, may initiate the influx of a variety of blood-derived cells including allergen-specific (type 2) T cells (van der Heijden et al., 1991; Müller et al., 1993), as well as FcεRI-expressing eosinophils and APCs (S. Wichlas, unpublished observations). Paralleling these events, LCs/DCs may process the allergens taken up via FcεRI and present the allergen-derived peptides to T lymphocytes in the skin and/or draining lymph nodes. Continuous supply of IgE-reactive exogenous and/or endogenous allergen to FcεRI+ resident and newly attracted APCs will, therefore, lead to a prolonged inflammatory tissue reaction composed of a T cell-dependent as well as a T cell-independent component.

Following this reasoning, interference with the IgE-binding ability and/or functionality of FcεRI should be a promising strategy for early and efficient interruption of the pathogenic circuits operative in atopic tissue inflammation.

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Figure 6. Anti-CD1a- and anti-FcεRIa-reactive cells of an acid-treated cryostat section of AD skin comprise largely overlapping cell populations. An acid-treated cryostat section of AD skin was reacted with the anti-FcεRIa MoAb 15–1 (TRITC) and with MoAb anti-CD1a (FITC) as outlined in Materials and Methods. Photomicrographs resulted from either single [TRITC (a) or FITC (b)] or double [TRITC and FITC (c)] exposure. White dots delineate the dermal–epidermal junction. Scale bar, 30 μm.


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