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Cutaneous Inflammatory Disorder in Integrin $\alpha_E$ (CD103)-Deficient Mice

Michael P. Schön,*† Margarete Schön,† Henry B. Warren,‡ John P. Donohue,* and Christina M. Parker*‡

The integrin $\alpha_E\beta_7$ is thought to play an important role in the localization of mucosal, but not of cutaneous T lymphocytes. Thus, it was surprising that 89% of adult $\alpha_E^{-/-}$ mice on the 129/Sv × BALB/c background developed inflammatory skin lesions without an apparent infectious etiology. Skin inflammation correlated with $\alpha_E$ deficiency in mice with a mixed 129/Sv × BALB/c background, but not in mice further backcrossed to BALB/c and housed in a second animal facility. These studies suggested that $\alpha_E$ deficiency, in combination with other genetic and/or environmental factors, is involved in lesion development. The lesions were infiltrated by CD4$^+$ T cells and neutrophils, and associated with increased expression of inflammatory cytokines. Furthermore, skin inflammation resulted from transfer of unfractonated $\alpha_E^{-/-}$ splenocytes into scid/scid mice, but not from transfer of wild-type splenocytes, suggesting that the lesions resulted from immune dysregulation. We also studied the role of $\alpha_E\beta_7$, in a murine model of hyperproliferative inflammatory skin disorders that is induced by transfer of minor histocompatibility-mismatched CD4$^+$/CD45RB$^+$ T cells into scid/scid mice under specific environmental conditions. Under housing conditions that were permissive for lesion development, transfer of $\alpha_E$-deficient CD4$^+$/CD45RB$^+$ T cells significantly exacerbated the cutaneous lesions as compared with lesions observed in mice reconstituted with wild-type donor cells. These experiments suggested that $\alpha_E$-expressing cells play an important role during the course of cutaneous inflammation. In addition, they suggest that $\alpha_E\beta_7$ deficiency, in combination with other genetic or environmental factors, is a risk factor for inflammatory skin disease. The Journal of Immunology, 2000, 165: 6583–6589.

The integrin $\alpha_E$ (CD103) $\beta_7$ is expressed by T lymphocytes in or adjacent to mucosal epithelia, including 90% of CD8$^+$ intestinal T cells in or adjacent to the small intestinal epithelium, and 40–50% of the CD4$^+$ T cells within the intestinal lamina propria. It binds to E-cadherin (1–3) on epithelial cells and may be important in the localization of diffusely distributed T cells within the intestinal epithelium. Integrin $\alpha_E\beta_7$ also is found on dendritic epidermal T cells, some dendritic cells, some lymphomas and leukemias, and bone marrow-derived mast cells (4–10) cultured in the presence of TGF-$\beta_1$, a cytokine that also induced $\alpha_E\beta_7$ expression on T lymphocytes (1, 11). Like other integrins, the avidity of the interaction between $\alpha_E\beta_7$ and E-cadherin can be regulated through inside-out signaling in response to T cell stimulation with anti-CD3 (1, 11). In addition, $\alpha_E\beta_7$ appears to transmit an outside-in signal, as some anti-$\alpha_E$ mAbs enhance proliferation of T cells in response to suboptimal concentrations of anti-CD3 or induce the lysis of Fc receptor-bearing targets by $\alpha_E\beta_7$-expressing T cells (7, 8). Thus, $\alpha_E\beta_7$ may also function to modulate the response of T lymphocytes to stimulation by epithelial cells, akin to the important accessory role of the integrin CD11a/CD18 (LFA-1) during peripheral T lymphocyte/APC interactions (12–14).

Consistent with the proposed function of $\alpha_E\beta_7$ in intraepithelial retention of mucosal T lymphocytes, we recently reported that integrin $\alpha_E$-deficient mice have reduced numbers of T lymphocytes diffusely distributed within the intestinal and vaginal epithelia (3). However, expression of E-cadherin, the known ligand for $\alpha_E\beta_7$, is not restricted to mucosal epithelial cells, but is also found on epithelial cells in the skin. Furthermore, expression of $\alpha_E\beta_7$ has been observed in some cutaneous disorders, such as T cell lymphomas, lichen planus, or atopic dermatitis (4, 15–17). However, it is unclear whether $\alpha_E\beta_7$ contributes to epidermal localization of T lymphocytes, and a role of integrin $\alpha_E\beta_7$ in the cutaneous immune system and/or the generation of inflammatory skin disorders has not been described.

In this study, we report the surprising observation that nearly all $\alpha_E$ (CD103)-deficient mice spontaneously developed inflammatory ulcerative skin lesions in our initial cohort. This observation prompted further investigations toward a potential function of $\alpha_E\beta_7$ on cutaneous T cells and/or in the pathogenesis of inflammatory skin disorders. Indeed, we found that $\alpha_E\beta_7$ significantly influences the generation of hyperproliferative inflammatory skin alterations in mice. These results suggest that the $\alpha_E\beta_7$ integrin performs a function on T cells localized in the skin and may play a role in hyperproliferative inflammatory skin disorders.

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Materials and Methods

Animals

The generation and genotyping of mice deficient for the αE integrin subunit (CD103) have been described previously (3). In reconstitution experiments, C.B-17/Scid/scid αE-deﬁcient (scid/scid) mice (Taconic Farms, Germantown, NY) of 5–8 wk of age were used as recipients. Mice were kept under specific pathogen-free conditions in microisolator cages. Microbiologic assessment of αE+/− and αE−/− mice included: Gram stain of inflamed skin and eyelids; bacterial and fungal cultures of blood, inflamed and uninflamed skin, and eyelids; and bacterial cultures of nasopharyngeal washes that revealed growth of resident flora including α-streptococcus, Pasteurella aerogenes, Pasteurella multocida, Staphylococcus epidermidis, and Streptococcus acidominimus. Additional evaluation included anal tape test, fecal ﬂotation, and microscopic pelage for metazoan parasites, and serologies for murine viral pathogens including Sendai virus, pneumonia virus of mice, mouse hepatitis virus, minute virus of mice, GD-7 virus, Reo-3 virus, lymphocytic choriomeningitis virus, mouse adenovirus, mouse pusoy virus (ectromelia virus), K-virus, polysoma virus, epizootic disthrea of infant mice, mouse CMV, mouse thymic lymphocyte virus, and Hantaan virus, and for proctaryocytic organisms including cilia-associated respiratory bacillus, Encephalitozoon cuniculi, and Mycoplasma pulmonis.

Antibodies

The following murine Abs were detected by mAbs: CD3ε (500A2; Pharmingen, San Diego, CA), CD4 (RM4-5; Pharmingen), CD8α (53-6.72; American Type Culture Collection (ATCC), Manassas, VA), CD11b (ICR1; α-β2 integrin), Mac-1, M1/70 (α-β2 integrin, 2E6; ATCC), CD25 (IL-2R α-chain, 3C7; Pharmingen), CD45RB (MB23G2, ATCC; 16A, PharMingen), CD49f (α6 integrin, M293; P. Kilshaw (Department of Immunology, AFRC Babraham Institute, Cambridge, U.K.)) (5), or CD122 (IL-2 receptor, 12D7, 1A5; Pharmingen). In addition, rabbit antisera reactive with murine IL-1α and TNF-α (Genzyme, Cambridge, MA) were used. The following mAbs were used as controls: rat IgG1 (R59-40; Pharmingen), rat IgG2a (R35-95; Pharmingen), rat IgG2b (SFK3-DR5; ATCC), and hamster IgG (UC9-B31; Pharmingen). FITC anti-CD45RB (mAb 16A) and PE anti-CD4 (mAb RM4-5) were obtained from Pharmingen; biotinylated goat anti-hamster, mouse-adsorbed rabbit anti-rat and goat anti-rabbit serum were obtained from Vector Laboratories (Burlingame, CA); and goat anti-rat Microbeads were purchased from Miltenyi Biotec (Auburn, CA).

Histopathologic analysis and in vivo 5-bromo-2′-deoxyuridine (BrdU) labeling

For histochemical analysis, tissue samples were fixed, dehydrated, and embedded in JB-4 plastic resin according to the manufacturer’s instructions (Polysciences, Warrington, PA). Sections (3 μm) were stained with hematoxylin-eosin or for chloroacetate esterase reactivity, as described elsewhere (18, 19). Samples were evaluated by an investigator blinded to the error. Samples were evaluated by an investigator blinded to the outcome. Samples were injected i.p. with 5 mg BrdU in 500 μl PBS at both 9 and 6 h before sacrifice. JB-4 plastic-embedded sections were immersed in 0.03% H2O2 in methanol and denatured with 0.4% pepsin (Sigma, St. Louis, MO) in 0.1 N HCl and 0.8 N HCl. Sections then were stained with anti-BrdU (Becton Dickinson, Hamburg, Germany) and the ABC immunoperoxidase method. All immunohistochemical stainings were performed using tissue sections from at least three mice.

Cell proliferation and reconstitution of scid/scid mice

PBMCs from αE+/+ and αE−/− mice were isolated by density gradient centrifugation and H-2 typed, and mice homozygous for the H-2Dα haplotype were used as donors. For adoptive transfer experiments, splenocytes were isolated and passed over a glass wool column to remove debris and to enrich for T cells. To enrich for CD4+ or CD8+ T lymphocytes, negative selection was performed with anti-CD4 or anti-CD8 mAbs using a magnetic cell separation system according to the manufacturer’s instructions (Miltenyi Biotec, Cologne, Germany). The resulting populations were >98% pure. In addition, contamination of the CD4+ population with CD8+ cells or of the CD8+ population with CD4+ cells was <1% in each case, as determined by FACS. C.B-17/Scid/scid αE-deﬁcient recipient mice were injected i.v. with 1.7–2 × 106 of unfractonated splenocytes or with 2 × 105 CD4+ or CD8+ enriched T cells. The cell thicknesses of the recipient scid/scid mice were monitored over 6 wk, and tissues were harvested for histopathologic analysis at the end of the observation period.

For generation of psoriasisform skin lesions by reconstitution of scid/scid mice with CD4+/CD45RB+ T lymphocytes (18), splenocytes from αE+/+ or αE−/− donors that were MHC matched, but minor histocompatibility Ag mismatched, were puriﬁed as described previously (19–21). Briefly, splenocytes were incubated with 20 μg each of anti-B220, anti-αE integrin, anti-CD8α, and anti-MHC class II mAbs/107 cells, followed by 20 μl goat anti-rat microbeads/107 cells and stained cells were depleted using a magnetic cell separation system separation column (type CS; Miltenyi Biotec). The CD4+-enriched population then was incubated for 30 min with 7.5 μg PE-conjugated rat anti-CD4, and 12.5 μg cells FITC-conjugated anti-CD45RB/107 cells. Using a FACSvantage (Becton Dickinson), the 40–45% of cells expressing the highest levels of CD45RB (naive T cells) (22) were selected from the CD4+ population (hereafter referred to as CD4+/CD45RB+ T cells). scid/scid recipient mice were injected with 2–2.5 × 106 cells each. Recipient mice started to develop environmentally modulated psoriasisform skin lesions within 3–4 wk (19, 23). Mice were weighed at weekly intervals. To evaluate the overall skin inflammation, the ear thicknesses were monitored using a skin thickness gauge (Oditest, Dyer, Lancaster, CA), and a clinical score for the psoriasis-like skin disorder was applied as described previously (19). Of note, mice developed lesions in this model when they were fed mouse breeder chow with 9% fat, kept in Pine Soft Wood Chips (100% virgin), and under static air in microisolator cages with weekly airflow. However, lesions did not develop if they were fed Purina RMP3000, kept in Bed-o-cob bedding with continuous air flow in the same animal facility, after transfer was performed at the same time (data not shown).

Statistical analysis

Statistical significance was assessed by the paired two-tailed Student t test, and p < 0.05 was considered to be significant.

Results

Spontaneous inflammatory autoimmune skin lesions in αE--/- mice

To evaluate the impact of αE deficiency on the overall development and life span of mice, wild-type (αE+/+), heterozygous (αE+/−), and homozygous-deficient (αE−/−) mice on the 129/Sv background were monitored at weekly intervals until senescence. Surprisingly, spontaneous inflammatory skin lesions were observed in this cohort of αE−/− mice at ~6 mo after birth, and almost all animals >9 mo old were affected (16/18; 88.9%). Heterozygous mice were affected with an intermediate frequency (4/30; 13.3%), consistent with their expression of reduced αEβ2 levels on T lymphocytes (3), and wild-type mice were not affected (0/8; 0.0%) (Fig. 1a). The inflammatory skin lesions were most commonly seen on the eyelids, but were also observed on trunk and tail, and were manifested by chronic inflammation resulting in ulceration in some cases (Fig. 1a). The course of these lesions was variable, as some lesions spontaneously resolved over time, whereas others worsened. Spontaneous skin lesions developed independently in mice kept in two different animal facilities. When the αE-deficient mice were further backcrossed to the BALB/c strain and housed in the second animal facility, skin lesions also occurred in some wild-type mice and were not clearly correlated with αE genotype. Thus, modifying factors besides αEβ2 contributed to the development of the skin lesions. Indeed, one such factor may be environment.

Histologic analysis revealed normal skin in wild-type mice (Fig. 1b, left panel), but subclinical skin lesions in 100% of αE−/− mice.
FIGURE 1. Spontaneous development of inflammatory skin lesions in αE-deficient mice. 

a, Macroscopic appearance of chronic ulcerative lesions on the trunk and eyelid of two αE-deficient mice. The photographs were taken at 16 (left mouse) and 11 (right) mo of age and are representative of 16 mice. 

b, Histologic analysis of representative eyelids (upper row) and ears (lower row) of wild-type mice (left panels) and αE-deficient mice (right panels) was performed using hematoxylin and eosin-stained tissues. In the bottom row, a subclinical lesion and a manifest ulcer in the skin of αE-deficient mice are shown. Scale bar, 20 μm. The panels are representative of sections from 10 mice. 

c, Sequential sections were prepared from a representative skin lesion from an αE-deficient mouse and stained with hematoxylin and eosin (left panel, neutrophils identified by polymorphonuclear appearance, lymphocytes by dark round nuclei), for chloroacetate esterase reactivity (middle panel to visualize neutrophils as small red cells, and mast cells as large spindle-shaped or round cells containing orange-colored granules), or with methylene blue (right panel to visualize mast cells as large dark purple cells). Scale bar, 20 μm.
organisms, which were similar in eyelids and of nasopharyngeal washes revealed only commensal bacteria in lesions with an intact epidermis from a 50% (mAb 53-6.72), CD4 (mAb RM4-5), CD8 (mAb 53-6.72), and CD25 (mAb 3C7), as indicated. The left three panels represent sequential sections. Scale bar, 20 μm. b, Uninvolved skin (upper row) and inflamed skin (lower row) of an αE−/− mouse were immunostained for the inflammation-associated Ags MHC class II (mAb N22), ICAM-1 (mAb YN1/1.7.4), and integrin α6 (mAb GoH3), as indicated. Scale bar, 20 μm. c, Uninvolved skin (upper row) and inflamed skin (lower row) of an αE−/− mouse were immunostained for the inflamatory cytokines IFN-γ (mAb XM1G1.2), IL-6 (mAb MP5-20F3), GM-CSF (mAb MP1-22E9), and IL-4 (mAb BV6D-24G2), as indicated. Each panel is representative of at least four samples. Scale bar, 20 μm.

Induction of inflammatory skin lesions in scid/scid mice through adoptive transfer of αE-deficient T lymphocytes

To further evaluate the cutaneous lesions resulting from αE deficiency, adoptive lymphocyte transfer studies were performed into MHC-matched scid/scid mice. In these studies, recipient mice that had been reconstituted with 1.7–2 × 10^7 αE±/± splenic leukocytes appeared to be normal and healthy and did not develop cutaneous lesions during the 6-wk observation period. In contrast, 100% of mice reconstituted with splenocytes from αE−/− donors developed inflammatory skin lesions associated with a 50–60% increase in ear thickness (0.438 mm (n = 3, SD = 0.019) in recipients of αE−/−-deficient donor cells vs 0.285 mm (n = 3, SD = 0.005) in recipients of wild-type cells, p = 0.007). This was especially apparent on the ears (data not shown), feet, and surrounding the eyes (Fig. 3). These lesions were characterized by an infiltration of leukocytes, including CD3±/CD4+ T cells (which were presumed to be donor cells, since scid/scid recipients have very few CD3+ T cells) and neutrophils. Epidermal changes included acanthosis and hyperkeratosis (Fig. 3b) and ulcer formation in ~30% of the recipients (one of three animals in each of two independent experiments). Similar to the spontaneous lesions in αE−/−-deficient mice, very few CD8+ T cells were present within the inflammatory lesions in scid/scid recipients reconstituted with αE-deficient splenocytes (Fig. 3b), suggesting a primary pathogenic role of CD4+ αE−/−-deficient T cells. The inflammatory skin lesions in scid/scid mice first were observed 2 wk after adoptive transfer and persisted during the 6-wk observation period (Fig. 3c). Although ulcers did not develop consistently and the skin was more diffusely involved, the cutaneous inflammation in mice reconstituted with αE−/− splenocytes was reminiscent of the spontaneous lesions in aging αE−/− mice. Thus, transfer of spleen-derived leukocytes from αE−/− deficient mice into MHC-matched scid/scid mice initiated skin lesions in immunodeficient recipients appeared to be induced by
cell-mediated mouse model of a psoriasiform skin disorder was used (18). In this system, transfer of MHC-matched but minor histocompatibility-mismatched $\alpha_E^{-/-}$ CD4$^+$/CD45RB$^{high}$ donor cells induced psoriasiform skin inflammation in scid/scid mice in addition to the intestinal inflammation that is known to follow transfer of syngeneic CD4$^+$/CD45RB$^{high}$ donor cells (19, 20). This inflammatory skin disease model is environmentally influenced. Within the murine psoriasiform lesions, epidermal T cells expressed $\alpha_E\beta_7$ (Fig. 4a). To determine whether the $\alpha_E\beta_7$ integrin was involved in the pathogenesis of the murine hyperproliferative inflammatory skin disorder, the development of these lesions was compared in scid/scid mice reconstituted with CD4$^+$/CD45RB$^{high}$ T cells derived from wild-type or $\alpha_E$-deficient mice. In both cases, abundant CD3$^+$ donor T cells infiltrated the skin of the recipients. As expected, there was prominent expression of $\alpha_E\beta_7$ on epidermal T cells in recipients of wild-type CD4$^+$/CD45RB$^{high}$ donor cells, but not in recipients of $\alpha_E$-deficient donor cells (Fig. 4a). Interestingly, the psoriasiform skin inflammation was worsened significantly when $\alpha_E^{-/-}$ donor cells were used, as assessed by both clinical score and ear thickness (Fig. 4, b and c). In addition, in vivo BrdU incorporation in epidermal keratinocytes was 44% higher in recipients of $\alpha_E^{-/-}$ donor cells as compared with recipients of wild-type cells, indicating stronger hyperproliferation (288 BrdU$^+$ cells/mm$^2$ ($\pm$20.89) vs 200.1 ($\pm$23.03), n = 3, Fig. 4d). These findings suggest that $\alpha_E$ deficiency on the donor cells worsened the disorder induced by CD4$^+$/CD45RB$^{high}$ T cells. However, it is also possible that $\alpha_E$ deficiency induced skin changes that were superimposed upon the psoriasiform alterations that result from T cell transfer.

**Discussion**

In this study, we found that aging $\alpha_E$-deficient mice developed inflammatory skin lesions, apparently due to an aberrant immune reaction, as transfer of T cells from $\alpha_E^{-/-}$ mice induced a similar phenotype in scid/scid recipients. Integrin $\alpha_E\beta_7$ expression has been observed on some epidermal T cell malignancies (4, 15, 24) and on T lymphocytes in some benign skin conditions (16, 17). However, it is not generally thought to play an important role in the localization or function of cutaneous T cells. Thus, our observation was surprising and suggests a broader role of the $\alpha_E\beta_7$ integrin than had been previously appreciated. As E-cadherin, the known $\alpha_E\beta_7$ counterreceptor (1, 2), is constitutively expressed within the epidermis (25), it is likely that $\alpha_E\beta_7$ expressed on cutaneous T cells binds to its ligand there. This interaction may serve to enhance the immigration or retention of $\alpha_E\beta_7^+$ cutaneous T cells in the epidermis. This would be consistent with the expression of $\alpha_E\beta_7$ on a greater proportion of the epidermal T cells than of the dermal T cells in cutaneous lesions. The adhesive functions of $\alpha_E\beta_7$ on cutaneous T cells are likely to be mediated in the context of other adhesive molecules. These might include the binding of $\beta_1$ integrins, LFA-1, or as yet unknown molecules on cutaneous T cells with ICAM-1 or the newly identified lymphocyte endothelial epithelial cell adhesion molecule (LEEP-CAM) on keratinocytes (26–30). In addition, it has been suggested that there is another ligand for $\alpha_E\beta_7$ on keratinocytes that has not yet been identified at the molecular level, which could be important in keratinocyte interactions with $\alpha_E\beta_7^+$ leukocytes (31).

The $\alpha_E\beta_7$-E-cadherin interaction could also result in outside-in signaling in response to ligand binding by either $\alpha_E\beta_7$ on T cells or E-cadherin on epithelial cells. Specifically, a role for $\alpha_E\beta_7$ in signaling has been indicated by evidence that anti-$\alpha_E\beta_7$ mAbs enhance the proliferation of T lymphocytes in response to suboptimal concentrations of anti-CD3 (7) and can induce the lysis of target cells in vitro (6, 8). In addition, E-cadherin is known to transmit...
of either cell type. Consistent with this possibility, the presence of $\alpha_E\beta_7$ T lymphocytes adjacent to acinar epithelial cells has been found to correlate with epithelial cell apoptosis in tissue samples derived from Sjögren’s syndrome patients (35).

Interestingly, integrin $\alpha_E$ deficiency also worsened murine psoriasis-like skin lesions induced by CD4$^+$/CD45RB$^{high}$ T lymphocytes in environmental conditions that were permissive for lesion development. This was in contrast to the observation that $\alpha_E$ deficiency alleviated intestinal inflammation that occurred concomitantly in these mice (M.P.S., J.P.D., and C.M.P., unpublished observations). There are several potential mechanisms by which $\alpha_E$ deficiency could modify the phenotypic outcome of partial immune reconstitution in immunodeficient mice. First, the lack of $\alpha_E$ expression might prevent some T cell subsets from localizing to the intestinal epithelium. These cells might then be shunted to the skin, where they would induce inflammation due to their production of inflammatory cytokines (36). In addition, $\alpha_E$ deficiency could result in the loss of a regulatory signal transmitted through the $\alpha_E\beta_7$ integrin that modulates T cell responses. Such signaling might modify the response of cutaneous T cells to stimulation, and thereby result in T cell dysregulation in the skin under conditions in which the T cells become activated.

Overall, our results demonstrate a novel and unexpected function of the $\alpha_E\beta_7$ integrin within the cutaneous immune system. These studies also suggest that $\alpha_E$ deficiency may be a genetic factor predisposing to inflammatory skin disease under some environmental conditions and/or in the context of other genetic factors, based upon the presence of inflammatory skin lesions in $\alpha_E^{-/-}$ mice. This possibility is supported by the observation that hyperproliferative inflammatory skin lesions in a murine model of psoriasis were exacerbated when the transferred T cells lacked $\alpha_E$ expression. Additional genetic studies will be required to determine whether $\alpha_E$ deficiency is associated with an increased risk of inflammatory skin disease in humans, as it appears to be in mice, and to identify the role of $\alpha_E\beta_7$ in cutaneous T lymphocyte responses during antigenic or autoimmune responses.

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