Maintenance of Donor Phenotype After Full-Thickness Skin Transplantation from Mice with Chronic Proliferative Dermatitis (*cpdm/cpdm*) to C57BL/Ka and Nude Mice and Vice Versa

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Chronic proliferative dermatitis is a spontaneous mutation in C57BL/Ka mice (*cpdm/cpdm*) and is characterized by epithelial hyperproliferation, infiltration by eosinophils and macrophages, and vascular dilatation. To elucidate whether these pathologic features are the result of a local (skin) process or a consequence of a systemic disorder, transplantations were performed of full-thickness grafts of affected skin from *cpdm/cpdm* mice and normal skin from control (C57BL/Ka) mice on the back of *cpdm/cpdm*, C57BL/Ka and athymic nude mice. After 3 months, the grafts maintained the histologic phenotype of the donor animal. Intercellular adhesion molecule-1 continued to be expressed by basal keratinocytes of the *cpdm/cpdm* grafts after transplantation. In contrast, the basal keratinocytes of the C57BL/Ka grafts onto *cpdm/cpdm* mice remained negative for intercellular adhesion molecule-1 3 months after transplantation. An increased number of proliferating keratinocytes was present in the *cpdm/cpdm* skin-graft transplanted to nudes or to C57BL/Ka mice based on short-term bromodeoxyuridine labeling. The bromodeoxyuridine incorporation in the keratinocytes of the control C57BL/Ka skin grafts transplanted to *cpdm/cpdm*, nude, or C57BL/Ka mice was the same as in the keratinocytes of normal C57BL/Ka mice. This study demonstrates that the pathologic features found in the *cpdm/cpdm* mice are the result of a disorder in the epidermis or dermis and not due to a systemic defect.

Key words:* *dermatitis/mouse model/transplantation/skin.

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We have recently described a mouse mutant with chronic proliferative dermatitis (gene symbol *cpdm*) on a C57BL/Ka background [1,2]. The skin lesions in this *cpdm/cpdm* mouse are macroscopically characterized by erythema, severe hair loss, and mild scaling. Microscopically, the lesions are characterized by hyper- and parakeratosis, acanthosis, apoptosis of keratinocytes, vascular proliferation, and infiltration of dermis and epidermis by mast cells, macrophages, and granulocytes (mainly eosinophils). Only a small percentage of the inflammatory infiltrate are T cells. Based on these characteristics, this mouse mutant may serve as a useful model to study chronic proliferative dermatitis. Similar lesions as found in the skin were also observed in the esophagus and forestomach, which, in the mouse, are lined by orthokeratinizing epithelium.

Two other mouse mutants, the asebia (*ab/ab*) and the flaky skin (*fsn/fsn*) mouse, also have skin lesions characterized by epidermal hyperproliferation and scaling. The inflammatory reaction in the asebia mouse is different from that of the *cpdm/cpdm* mouse because the infiltrating cells in the dermis and epidermis are mostly mononuclear cells. The cause of the inflammatory reaction in the asebia mouse is thought to be rupture of the lipid-laden macrophages that have infiltrated the dermis [3]. So far, this mouse mutant has not yet been proved to be a representative model for chronic dermatitis in humans [4]. The flaky skin mouse mutation superficially resembles the *cpdm/cpdm* mouse mutation, but apoptosis and follicular keratosis are absent and the mice develop anemia [5]. Certain transgenic mice also develop proliferative skin lesions. However, the distribution and light microscopy of these lesions do not resemble the skin lesions of the *cpdm/cpdm* mouse [6–10]. Another attempt to study chronic proliferative dermatitis in an animal model has been the transplantation of human allografts of diseased skin onto *nu/nu* mice [11–13]. A disadvantage of these models is that the systemic character of the disease is difficult to study.

Although the skin lesions of the *cpdm/cpdm* mice are the most apparent, inflammatory foci were also present in the lungs, liver, and joint-associated tissues. These lesions suggest that the dermatitis is part of a systemic condition, but they could also result from massive cytokine release of keratinocytes. Failure to transfer the *cpdm/cpdm* lesions to syngeneic control animals using hemopoietic cells from spleen or bone marrow from affected mice suggests that such cells do not play a primary role in its pathogenesis [1].

To further elucidate whether the pathologic features observed in the *cpdm/cpdm* mouse originate in the skin or result from a systemic

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Abbreviations: *cpdm*, chronic proliferative dermatitis mouse mutation; *nu*, nude mouse mutation; *fsn*, flaky skin mouse mutation; BrdU, bromodeoxyuridine.

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disorder, we performed transplantations of full-thickness skin grafts from affected *cpdm/cpdm* mice and control (C57BL/Ka) mice to *cpdm/cpdm*, C57BL/Ka and athymic nude (*nu/nu*) mice. Here we report that after transplantation the donor phenotype was maintained in the recipients.

MATERIALS AND METHODS

Animals Skin graft donor mice consisted of female *cpdm/cpdm* mice and C57BL/KaLawRij control mice 6–8 weeks old. Recipients consisted of 8–12-week-old C57BL/KaLawRij control mice, *cpdm/cpdm* mice and BALB/c *nu/nu* mice. Mice were individually housed in Macrolon cages and were provided autoclaved pelleted food and acidified, sterilized bottled drinking water *ad libitum*.

Transplantation The grafts were performed according to the methods described earlier [14]. Briefly, donor mice were sacrificed by CO_2 inhalation, dorsal skin (dermis and epidermis) was removed, and excess fat and blood vessels were stripped off. The recipient mice were anesthetized with Hypnorm (1:20, 120 μl/mouse; Janssen Pharmaceutica, Tilburg, The Netherlands). Two circular pieces of dorsal skin (dermis and epidermis), approximately 1 cm in diameter, were aseptically removed down to the pannus carnosus. The donor skin was cut to fit the transplant bed and held in place using six sutures. The transplant was covered with Op-Site (Smith & Nephew, Hull, England) and protected by gauze held in place with 3M surgical foam tape. The tape was kept on for at least 2 weeks. *Nu/nu* recipients (4) were each transplanted with two skin grafts: one from a *cpdm/cpdm* mouse and one from a C57BL/Ka control mouse. C57BL/Ka recipients (3) were similarly transplanted with skin grafts from a *cpdm/cpdm* mouse and a C57BL/Ka control mouse. One *nu/nu* mouse and two C57BL/Ka mice received two skin grafts from a *cpdm/cpdm* mouse. Three *cpdm/cpdm* donor mice received only one graft for transplantation from a C57BL/Ka mouse. The direction of the hairs of the C57BL/Ka graft on the C57BL/Ka recipient was turned 90° to allow the graft to be distinguished from the donor skin by the orientation of the hairs.

Bromodeoxyuridine (BrdU) Labeling and Histology Three months after transplantation, the recipient mice were administered 0.625 mg BrdU (Sigma) intraperitoneally to determine the rate of cell proliferation. Thirty minutes after injection, the mice were sacrificed by ether inhalation. The transplanted and peripheral skin of the donor mice were removed and trimmed into three pieces. One part was immediately frozen and stored in liquid nitrogen. The other parts were fixed for 18 h in neutral-buffered formalin, stored in 70% alcohol, and later embedded in paraffin. Paraffin-embedded sections were deparaffinized, rehydrated, and incubated with monoclonal anti-BrdU antibody (Dakopatts, Copenhagen, Denmark) or stained with hematoxilin-phloxine-saffron or with toluidine blue. The labeled nuclei of the slides incubated with anti-BrdU were visualized by peroxidase-labeled rabbit anti-mouse Ig (Dakopatts), followed by diaminobenzidine in combination with 1% cobalt-chloride to enhance staining intensity.

Immunohistochemistry Cryostat sections of the transplanted skin were stained using the indirect peroxidase method. Sections were fixed in acetone, washed in phosphate-buffered saline, and incubated overnight at 4°C with the monoclonal antibody against anti–intercellular adhesion molecule-1 (ICAM-1) purified as described earlier [1]. Thereafter, sections were incubated with mouse anti-rat peroxidase (Jackson Immunoresearch Laboratories, West-Grove, PA) for 60 min at room temperature followed by staining with diaminobenzidine and hydrogen peroxide. The sections were counterstained with Mayer's hematoxylin (Merck, Darmstadt, FRG)

Morphometry and Statistical Analysis BrdU-labeled nuclei were counted per centimeter of epidermal basement membrane. The density of dermal mast cells was determined in toluidine blue sections as cells/mm^2 dermis. The area of the dermis was determined by subtracting the area occupied by pilosebaceous units and blood vessels from the total area of the dermis. The measurements were performed with computer-aided morphometry (Kontron-Videoplan, Zeiss, Germany). All data are expressed as mean ± SD. Statistical analysis was performed using the Student t test.

RESULTS

Maintenance of Donor Phenotype After Transplantation Transplantation of the 10 C57BL/Ka grafts to the *nu/nu*, *cpdm/cpdm*, and C57BL/Ka mice was macroscopically characterized by a thin graft and normal fur with the exception of the development of long, white hairs in some C57BL/Ka grafts transplanted to the *nu/nu* mouse. At the time of transplantation, the *cpdm/cpdm* fur was normal but the skin was slightly thickened. In the 3 months after transplantation, the 11 *cpdm/cpdm* grafts transplanted to the *nu/nu* and C57BL/Ka mice lost their hair, became thicker, and developed fine scale. **Figure 1** gives a representative photograph of a *nu/nu* host mouse with a full-thickness skin graft from a *cpdm/cpdm* and a C57BL/Ka mouse. One *cpdm/cpdm* skin transplantation onto a *nu/nu* and onto a C57BL/Ka mouse was not succesful.

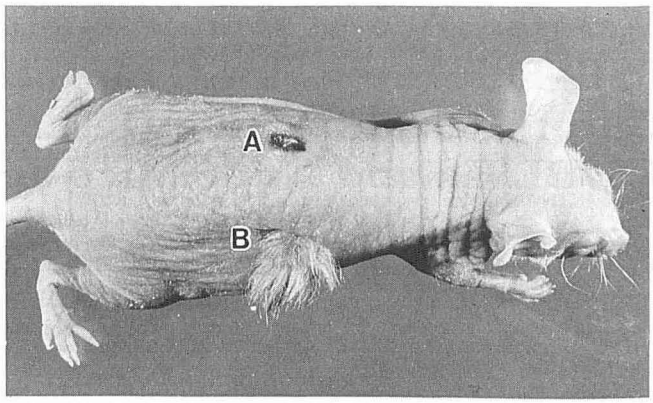

Figure 1. The macroscopic appearance of *cpdm/cpdm* and C57BL/Ka skin is maintained 3 months after transplantation onto *nu/nu* mice. Full-thickness skin from a *cpdm/cpdm* (*A*) and a C57BL/Ka mouse (*B*) was transplanted to a *nu/nu* host mouse. The *cpdm/cpdm* skin graft showed fine scaling.

Microscopically, the C57BL/Ka grafts could be distinguished from the *nu/nu* recipient mouse by differences in hair follicles and epithelial thickness. The hair shafts of the *nu/nu* mice were distorted and malacic [15], and the epidermis was about five cell layers thick. The epidermis of the C57BL/Ka grafts was three cell layers thick. The C57BL/Ka grafts could be distinguished from the C57BL/Ka recipient mice by the different orientation of the hair shafts **(Fig 2)**.

All 10 normal C57BL/Ka grafts onto *cpdm/cpdm*, C57BL/Ka, and *nu/nu* mice showed no differences compared with C57BL/Ka control skin except for variable loss of melanin pigment from hair bulbs and occasionally scattered dermal macrophages and granulocytes **(Fig 2)**, probably a result of the surgical procedure. In contrast, all 11 *cpdm/cpdm* skin grafted on C57BL/Ka and *nu/nu* mice showed marked acanthosis **(Fig 3)**. Ten of 11 *cpdm/cpdm* grafts showed spongiosis **(Fig 4)**, and in five of 11 *cpdm/cpdm* grafts eosinophils were observed in the epidermis. Only two *cpdm/cpdm*

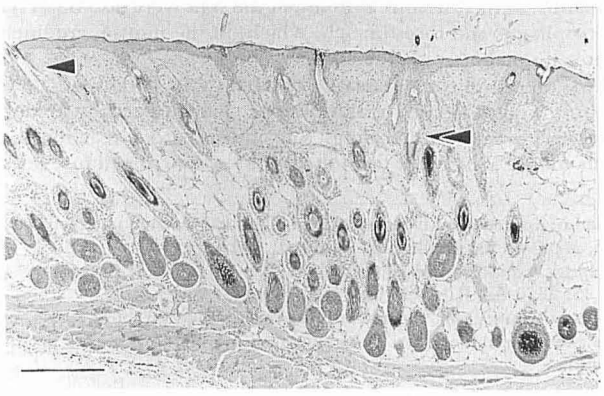

Figure 2. The phenotype of C57BL/Ka skin grafted onto a C57BL/Ka recipient is maintained 3 months after transplantation. Sections were stained with hematoxylin-phloxine-saffron. Note the different orientation of the hair shafts between the graft (*arrowhead*) and the recipient (*double arrowhead*). No lesions were observed in the graft, except for the occasional scattered dermal infiltrate (*bar*, 0.3 mm).

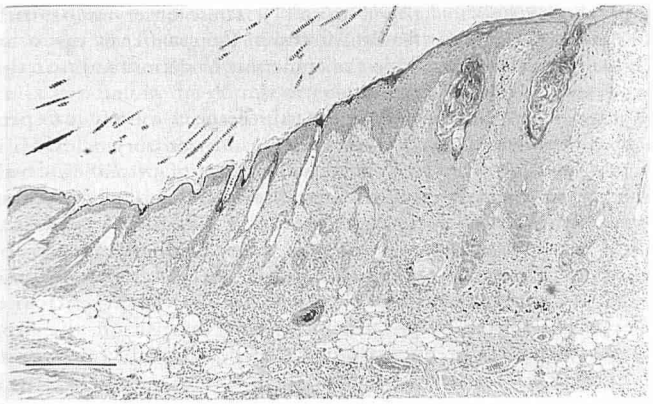

Figure 3. The phenotype of *cpdm/cpdm* skin grafted onto a C57BL/Ka recipient is maintained 3 months after transplantation. Full-thickness skin of a *cpdm/cpdm* mouse (*right*) was transplanted to a C57BL/Ka mouse (*left*). Sections were stained with hematoxylin-phloxine-saffron. The *cpdm/cpdm* skin graft showed marked acanthosis (*bar*, 0.3 mm).

grafts showed hyperkeratosis, eight showed parakeratosis, and in four *cpdm/cpdm* grafts apoptosis of keratinocytes was observed **(Fig 4)**. The dermis of all 11 grafts was infiltrated by a mixed population of inflammatory cells, predominantly eosinophils, mast cells, and macrophages. There were significantly more mast cells present in the dermis of the *cpdm/cpdm* grafts (532 ± 108 and 527 ± 31, respectively) than in the surrounding dermis of the *nu/nu* (170 ± 64) recipients ($p < 0.025$) and C57BL/Ka (115 ± 44) recipients ($p < 0.001$). Ten *cpdm/cpdm* grafts showed tortuous, dilated capillaries in the superficial dermis. **Table I** summarizes the results of the *cpdm/cpdm* transplantation to *nu/nu* and C57BL/Ka mice. Only a few lymphocytes were observed in the epidermis and dermis of the *cpdm/cpdm* grafts. These characteristics of the *cpdm/cpdm* grafts were similar to the *cpdm/cpdm* donor skin **(Table I)**. Neutrophils were occasionally present in the subepidermal adventitial dermis as a consequence of the grafting procedure. There were only minor differences between the *cpdm/cpdm* grafts transplanted to the C57BL/Ka and to the *nu/nu* mice **(Table I)**.

No gross lesions were observed in the other organs of the recipient mice.

BrdU Labeling Remains High After Grafting **Table II** summarizes the results of the BrdU-labeling studies. The grafts from the *cpdm/cpdm* to the C57BL/Ka and *nu/nu* mice had signif-

Table I. Microscopical Lesions of *cpdm/cpdm* Skin Remain After Grafting to *nu/nu* and C57BL/Ka Mice

	Grafts (Skin) with Lesion/Total Examined Grafts (Skin)			
	Graft			Donor
Lesion	*cpdm/cpdm* on *nu/nu*	*cpdm/cpdm* on C57BL/Ka	Total	*cpdm/cpdm*
Acanthosis	5/5	6/6	11/11	6/6
Inflammatory cells in epidermis	4/5	1/6	5/11	1/6
Apoptosis	2/5	2/6	4/11	6/6
Spongiosis	5/5	5/6	10/11	5/6
Parakeratosis	3/5	5/6	8/11	3/6
Hyperkeratosis	3/5	0/6	3/11	6/6
Dilated capillaries	4/5	6/6	10/11	6/6
Inflammatory cells in dermis	5/5	6/6	11/11	6/6

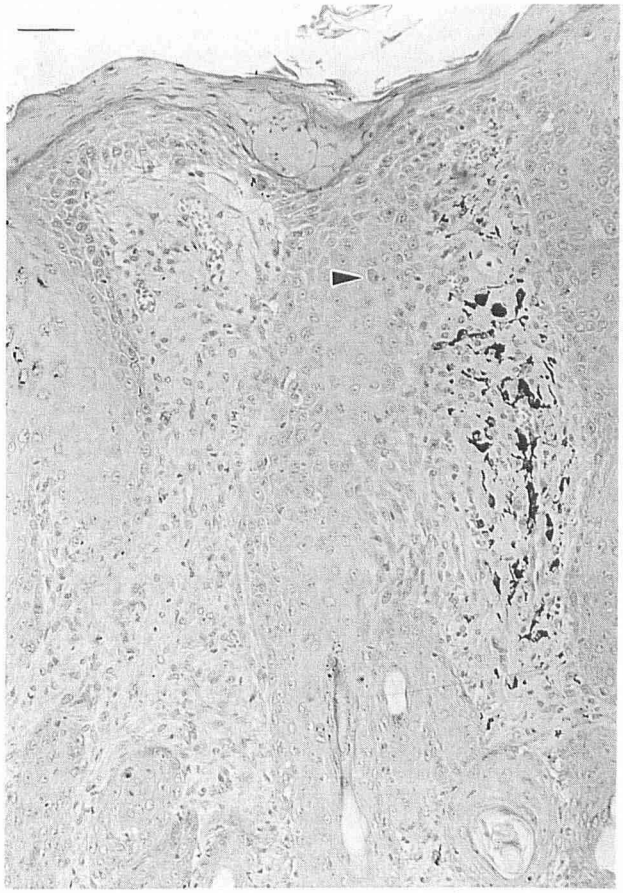

Figure 4. The characteristics of *cpdm/cpdm* grafts are similar to those of untransplanted *cpdm/cpdm* donor skin. Full-thickness skin of a *cpdm/cpdm* mouse was transplanted to a *nu/nu* mouse. Sections were stained with hematoxylin-phloxine-saffron. Note spongiosis, parakeratosis, and apoptosis (*arrowhead*) of keratinocytes, and blood vessel dilatation and inflammatory infiltration in the dermis of a *cpdm/cpdm* skin graft (*bar*, 50 μm).

icantly more BrdU-positive nuclei than C57BL/Ka control grafts ($p < 0.025$) **(Fig 5*a,b*)** and the number of BrdU-positive cells was comparable with the number of BrdU-positive cells in the epidermis of *cpdm/cpdm*. The grafts from C57BL/Ka to *cpdm/cpdm* did not show an increase of the BrdU-positive nuclei compared with the number of BrdU-positive nuclei of the normal C57BL/Ka epidermis. There was no difference in BrdU incorporation in the nuclei of the C57BL/Ka grafts transplanted to the *nu/nu* or to the C57BL/Ka mice. The number of positive nuclei in the epidermis of the

Table II. BrdU Incorporation in Nuclei of Grafts and Recipients Remains Comparable to Donor Skin

	BrdU Incorporation in Nuclei[a]	
	Graft	Recipient
cpdm/cpdm graft on *nu/nu* recipient	286 ± 62[b,c]	89 ± 36
C57BL graft on *nu/nu* recipient	47 ± 21	165 ± 45
cpdm/cpdm graft on C57BL recipient	365 ± 118[d]	40 ± 18
C57BL graft on C57BL recipient	36 ± 4	34 ± 15
C57BL graft on *cpdm/cpdm* recipient	56 ± 9	338 ± 84

[a] BrdU-labeled cells per cm basement membrane length.
[b] Standard deviation.
[c] $p < 0.025$ *cpdm/cpdm* graft versus C57BL/Ka graft on *nu/nu* recipient.
[d] $p < 0.001$ *cpdm/cpdm* graft versus C57BL/Ka graft on C57BL/Ka recipient.

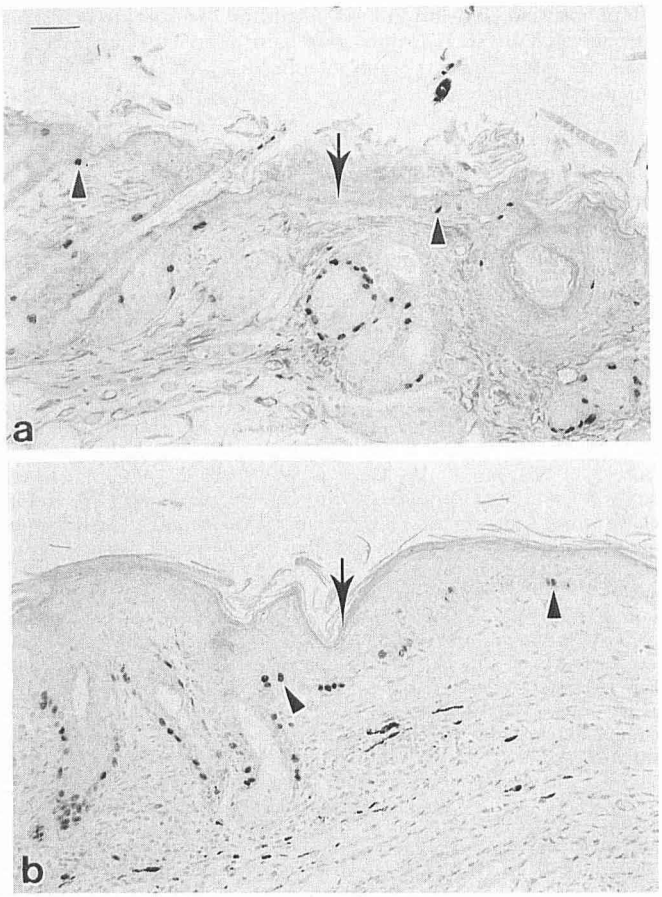

Figure 5. BrdU labeling of *cpdm/cpdm* and C57BL/Ka skin grafted onto *nu/nu* recipients is unaltered 3 months after transplantation. The recipient mice were injected intraperitoneally with 0.625 mg BrdU 30 min before sacrificing. Paraffin-embedded sections were stained immunohistochemically using an anti-BrdU antibody. BrdU-positive nuclei (*arrowheads*) in a C57BL/Ka (*a*) and a *cpdm/cpdm* (*b*) skin graft on a *nu/nu* recipient. Skin grafts are left of the *arrow* (*bar*, 0.1 mm).

recipient BALB/c *nu/nu* was relatively high when compared with that of recipient normal skin.

ICAM-1 Remains Present in *cpdm/cpdm* Skin Grafts The ICAM-1–staining pattern of the keratinocytes of the grafts was similar to the staining-pattern observed in the keratinocytes of the normal C57BL/Ka and *cpdm/cpdm* skin. ICAM-1 was weakly expressed on endothelial cells of blood vessels in the deep dermis of skin of C57BL/Ka mice. In *cpdm/cpdm* mice, ICAM-1 was expressed on basal keratinocytes and on endothelial cells of dermal blood vessels. The basal keratinocytes of the *cpdm/cpdm* grafts also stained for ICAM-1 whereas the basal keratinocytes of the C57BL/Ka recipient did not. The keratinocytes of the C57BL/Ka grafts did not stain, whereas the *cpdm/cpdm* recipient keratinocytes remained reactive. The endothelial cells in *cpdm/cpdm* and C57BL/Ka grafts also stained. As expected, the endothelial cells in *cpdm/cpdm* recipient skin surrounding the graft stained for ICAM-1, but the endothelial cells in the skin of the C57BL/Ka and *nu/nu* recipient surrounding the transplant also stained.

DISCUSSION

Transplanted *cpdm/cpdm* full-thickness skin grafts onto *nu/nu* or C57BL/Ka control mice maintained the *cpdm/cpdm* phenotype. Only apoptosis and hyperkeratosis were observed in a limited number of *cpdm/cpdm* grafts, probably due to the restricted size of the graft. Based on BrdU incorporation, we found a comparable proliferation rate of the *cpdm/cpdm* keratinocytes in the grafts and the keratinocytes of *cpdm/cpdm* mice [1]. These observations indicate that the pathologic features found in the *cpdm/cpdm* mice are the result of a disorder within the epidermis or dermis and not due to a systemic defect.

Keratinocytes can be triggered to secrete a variety of proinflammatory cytokines and thus elicit an inflammatory reaction in the underlying dermis [16]. Persistent release of cytokines could result in a chronic dermatitis. Alternatively, subepithelial mesenchymal components, such as fibroblasts or endothelial cells, can release factors that induce proliferation and differentiation of epithelia [17]. We have transplanted full-thickness grafts to *nu/nu* and C57BL/Ka mice, and it is not clear whether the vascularization of the graft is achieved by penetration of new vessels from the host into the transplant or by anastomosis of host blood vessels with pre-existing graft vessels. Data from the literature are conflicting in this respect [18–20]. Endothelial cells may cause or contribute to chronic inflammation by persistent expression of adhesion molecules.

The endothelial cells in the *cpdm/cpdm* grafts and *cpdm/cpdm* recipients stained for ICAM-1, consistent with previous observations on the *cpdm/cpdm* mice [1]. However, the endothelial cells in the C57BL/Ka grafts and in the skin of C57BL/Ka and *nu/nu* recipients were also ICAM-1 positive in contrast to earlier studies in which we could not detect ICAM-1 staining on dermal endothelium of C57BL/Ka mice [1]. The expression of ICAM-1 is rapidly increased upon endothelial activation [21]. Thus, the endothelial cells of the C57BL/Ka and *nu/nu* recipients and grafts in this transplantation study are activated, presumably as a result of the injury inflicted by the transplantation.

This study shows that the inflammatory cells found in the dermis and epidermis of the *cpdm/cpdm* mouse do not play a primary role in its pathogenesis. The eosinophils infiltrated in the *cpdm/cpdm* graft should originate from the host because of the estimated short survival time of these cells (approximately 14 d) in the skin [22,23]. Transplantation of human psoriatic skin onto nude mice showed that psoriatic epidermis did not contain polymorphonuclear cells [13]. This could indicate that the *cpdm/cpdm* skin, in contrast to the psoriatic skin, produces cytokines that are responsible for the mobilization or attraction of eosinophils. A role for T cells in the development and maintenance of the *cpdm/cpdm* lesion seems improbable. Transplantation of skin from human proliferative diseases such as psoriasis to *nu/nu* mice has suggested that natural killer cells or immature T lymphocytes of nude mice might infiltrate the human skin grafts and release mediators that stimulate proliferation of potentially hyperreactive epidermal cells from psoriatic patients [24]. However, C57BL/Ka skin grafted onto *nu/nu* mice did not show any increase in BrdU labeling indicating that, if there was a low-level graft rejection reaction in these animals, it was too limited to affect epidermal proliferation and unlikely to play a role in the *cpdm/cpdm* lesion. Similarly, human breast skin transplanted onto *nu/nu* mice shows no increase in proliferative index up to 3 months after transplantation (G. Elliott, personal communication). Moreover, only a few T lymphocytes are present in the dermis and epidermis of the *cpdm/cpdm* mouse and transplantation of the *cpdm/cpdm* skin to the athymic *nu/nu* mouse implies that these T lymphocytes are not required for maintenance of the lesion. In addition, transfer of hemopoietic cells from *cpdm/cpdm* mice failed to cause *cpdm/cpdm* lesions in the recipient, indicating that hemopoietic cells are unlikely to play a primary role in the pathogenesis [1].

Full-thickness skin transplantation from *fsn/fsn* and littermate control mice to *nu/nu* mice resulted in maintenance of the mutant phenotype [25]. These authors previously found that bone marrow grafted from *fsn/fsn* mice to severe combined immunodeficiency (*scid/scid*) mice resulted in the development of a proliferative skin disease in the recipients [26]. Double mutants (*fsn/fsn, scid/scid*) were created specifically to remove parts of the immune system, and these mice still developed a psoriasiform dermatitis. Apparently, the difference between the *cpdm/cpdm* and *fsn/fsn* mice is situated in the hemopoietic progenitor cells. In the *fsn/fsn* mouse,

these cells are necessary for production of the *fsn* phenotype, whereas the functional lymphoid cells are not required for development of the skin lesions. However, the bone-marrow–derived cells residing in the dermis or epidermis in the full-thickness grafts are sufficient to maintain the *fsn* phenotype.

We have demonstrated that *cpdm/cpdm* skin grafted onto *nu/nu* and C57BL/Ka mice maintain the *cpdm/cpdm* phenotype in the recipient as measured by histopathology, proliferation rate, and ICAM-1 expression. The *cpdm/cpdm* mouse should therefore be a useful model for screening potential therapy strategies for psoriasiform and other chronic inflammatory skin disorders.

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