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A polygenic mouse model of psoriasiform skin disease in CD18-deficient mice

(psoriasis/inflammation)

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ABSTRACT **Previously, a hypomorphic mutation in CD18 was generated by gene targeting, with homozygous mice displaying increased circulating neutrophil counts, defects in the response to chemically induced peritonitis, and delays in transplantation rejection. When this mutation was backcrossed onto the PL/J inbred strain, virtually all homozygous mice developed a chronic inflammatory skin disease with a mean age of onset of 11 weeks after birth. The disease was characterized by erythema, hair loss, and the development of scales and crusts. The histopathology revealed hyperplasia of the epidermis, subcorneal microabscesses, orthohyperkeratosis, parakeratosis, and lymphocyte exocytosis, which are features in common with human psoriasis and other hyperproliferative inflammatory skin disorders. Repetitive cultures failed to demonstrate bacterial or fungal organisms potentially involved in the pathogenesis of this disease, and the dermatitis resolved rapidly after subcutaneous administration of dexamethasone. Homozygous mutant mice on a (PL/J × C57BL/6J)F_1 background did not develop the disease and backcross experiments suggest that a small number of genes (perhaps as few as one), in addition to CD18, determine susceptibility to the disorder. This phenotype provides a model for inflammatory skin disorders, may have general relevance to polygenic human inflammatory diseases, and should help to identify genes that interact with the β_2 integrins in inflammatory processes.**

A large number of leukocyte and endothelial cell adhesion molecules are known to play a role in inflammatory processes, leukocyte trafficking, and immune responses (1). The molecules include immunoglobulin family members such as intercellular adhesion molecule 1 (ICAM-1), the selectins, selectin ligands, and leukocyte integrins (1). The β_2 leukocyte integrins are heterodimers of CD18 with one of three CD11 subunits: LFA-1 (CD18/CD11a), Mac-1 (CD18/CD11b), and p150/95 (CD18/CD11c). Mutations in CD18 have been reported in humans (2, 3) and in cattle (4, 5) and result in the life-threatening disorder termed leukocyte adhesion deficiency type I. CD18-deficient patients suffer from recurrent microbial infections, leukocytosis, impaired wound healing, failure of granulocyte emigration, and lack of pus formation (2, 3). Severe and moderate phenotypes have been described in humans, and the severity of the phenotype appears to correlate with the presence of null or hypomorphic mutations, respectively (3, 6).

Previously, a hypomorphic mutation for CD18 was introduced into mice with homozygotes displaying mild leukocytosis, an impaired response to chemically induced peritonitis, and delays in transplantation rejection (7). These mice express a low level of normal CD18 on leukocytes with 2–16% of wild-type levels of CD18 expression on resting or activated leukocytes, respectively (7). We have now observed the development of an inflammatory skin disorder when this CD18 mutation was crossed onto the PL/J strain of mice. This is notable since no comparable skin disease has been reported in humans or cattle with leukocyte adhesion deficiency type I and since this disorder did not occur in mice when the mutation was studied on a C57BL/6 or 129/Sv background. This inflammatory skin disorder represents a model of dermatitis with similarities to human psoriasis and autoimmune skin disease.

MATERIALS AND METHODS

Mice. CD18-deficient 129/Sv mice were backcrossed onto the PL/J strain (The Jackson Laboratory); fourth (N_4), seventh (N_7), and eighth (N_8) generation homozygous mutants were used for analyses. CD18 heterozygotes, their wild-type littermates, and inbred PL/J mice were studied as specified; all mice were more than 6 weeks old.

Histopathology. Seven affected and five control mice were sacrificed for histological analysis, and selected tissues were fixed in 10% (vol/vol) neutral-buffered formalin supplemented with zinc chloride. Paraffin-embedded sections were stained with hematoxylin/eosin. Peripheral blood was collected into dry EDTA tubes prior to sacrifice by cardiac puncture under anesthesia. Total white blood cell and differential leukocyte analyses were performed by using a Technicon H.1 analyzer (Miles) calibrated for analysis of murine samples.

Microbiological Analyses. Six homozygous mutant and six littermate control mice were anesthetized, and the hair of the back was cleansed with 70% alcohol to remove surface contaminants. For bacterial culture, sterile swabs were moistened in phosphate-buffered saline containing 0.1% Triton X-100 and used to scrub the area for inoculation onto Columbia sheep blood agar plates. Hair was removed from the same area with sterile scalpel blades and inoculated onto Mycosel agar and incubated at 25°C for 1 month for culture of fungi. After 2 weeks, this procedure was repeated on the same mice and an additional four homozygous mutants. Hair was also inoculated on Lowenstein Jensen's agar and incubated at 30°C for 2 months for isolation of *Mycobacteria.* In addition, hair was examined microscopically.

Dexamethasone Treatment. Three CD18 homozygous mice displaying severe dermatitis and three nonmutant littermate controls were given daily subcutaneous injections of 20 μg of dexamethasone for at least 6 weeks. Dexamethasone was then withdrawn completely or the concentration was lowered over a period of several weeks. Improvement and exacerbation of the dermatitis was clinically assessed on a daily basis.

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Abbreviation: mAb, monoclonal antibody.
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Immunohistochemistry. Skin samples were embedded in O.T.C. compound and snap frozen. For localization of granulocytes or CD18-positive cells, frozen sections were labeled with monoclonal antibodies (mAbs) including a rat anti-murine granulocyte antigen Gr-1 (RB6-8C5) at 1.56 μg/ml, a rat anti-murine CD18 (C71/16) at 6.25 μg/ml, a control rat IgG_{2a} (R35-95) at 6.25 μg/ml, or blocking buffer; all mAbs were from PharMingen. The primary antibody was detected with peroxidase-conjugated $F(ab')_2$ fragment mouse anti-rat IgG (heavy and light chain specific; Jackson ImmunoResearch) and detected by 3,3′-diaminobenzidine tetrahydrochloride tablets. The sections were counterstained with Mayer's hematoxylin solution.

CD18 and Mac-1 Expression on Granulocytes. Peripheral blood was collected from homozygous mutant or PL/J inbred mice from the retroorbital plexus with EDTA anticoagulation. Expression of CD18 and Mac-1 was determined by immunostaining with either a fluorescein isothiocyanate-conjugated CD18 mAb (C71/16) or a fluorescein isothiocyanate-conjugated Mac-1 mAb (M1/70) and analyzed by a cytofluorograph.

Backcross Experiments. CD18 homozygous mutant PL/J N_7 and C57BL/6 N_7 homozygous mutant mice were crossed to produce F_1 mice. These mice were then bred with CD18 mutant PL/J N_7 mice to produce N_2 mice for study. Both F_1 and N_2 mice were visually inspected for at least 6 months for skin and hair abnormalities. For H-2 analyses, peripheral blood was collected from 14 diseased and 14 nondiseased N_2 backcross mice. Expression of the $H\text{-}2^b$ allele was determined by immunostaining with a R-phycoerythrin-conjugated anti-$H\text{-}2K^b$ mAb (AF6-88.5) and analyzed by a cytofluorograph. For analysis of the CD11 genotypes, a fragment of the mouse CD11a cDNA was used to identify *Pst* I and *Xba* I DNA variants in the PL/J vs. C57BL/6 alleles (8). Southern blots containing *Xba* I or *Pst* I-digested DNA from 12 diseased and 12 nondiseased N_2 backcross mice were hybridized with the cDNA fragment and each mouse was scored for the PL/J- and C57BL/6-specific DNA fragments.

RESULTS

Inbred CD18-deficient 129/Sv mice were backcrossed onto the PL/J strain with the original intent to study the effects of this mutation on the pathogenesis of experimental allergic encephalomyelitis, an autoimmune process that occurs after immunization with myelin basic protein. After four backcross generations, heterozygotes were mated to produce homozygous mutant mice. Unexpectedly, adult CD18 homozygous mice developed a progressive dermatitis, characterized by erythema, alopecia, and scale and crust formation (Fig. 1 *A* and *B*). Visible signs of the disease first appeared as red scaly skin on the ears, paws, tail, and facial area. As the disease progressed, mice developed alopecia in the facial region and/or base of the tail. In severely affected mice, the dorsum of the trunk developed scales and crusts; some severely affected mice also displayed these manifestations on the abdomen and neck. We observed a high penetrance of this dermatitis with ≈91% (57 of 63) of N_4 generation homozygotes and 100% (25 of 25) of the N_7 and N_8 homozygotes developing disease. The average age of onset for N_7/N_8 mice was ≈11 weeks (Fig. 2), with all mice progressing to severe disease by 18 weeks. These manifestations were not observed in CD18 homozygous mutant mice on the 129/Sv or C57BL/6 strain backgrounds (7).

Skin histopathology from affected mice revealed an irregular psoriasiform hyperplasia of the epidermis, subcorneal microabscesses, orthohyperkeratosis, parakeratosis, and lymphocyte exocytosis (Fig. 1 *D–F*). In the more acute stages, focal spongiosis and erosion of the epidermis were occasionally observed, the latter most likely due to scratching. The dermal infiltrate consisted of granulocytes, lymphocytes, histiocytes, and scattered mast cells; skin sections stained for Gr-1 antigen, a marker for granulocytes, showed both dermal and epidermal infiltration (Fig. 3*A*). Both $CD4^+$ and $CD8^+$ T cells were observed in skin lesions (data not shown). Dermal collagen appeared disorganized, and vessels within the dermal papillae were dilated.

Affected mice also displayed a general reactive lymphadenopathy with enlarged lymph nodes and myeloid hyperplasia in spleen and bone marrow. Numbers of circulating leukocytes in homozygous mice were significantly increased compared to littermates as shown in Table 1. This increase was largely due to elevated numbers of circulating neutrophils, but lymphocyte and monocyte numbers were also increased. In addition, circulating eosinophils, basophils, and platelets were significantly increased in diseased mice (data not shown). Numbers of neutrophils in the peripheral blood of CD18 homozygous mice on the 129/Sv background were elevated but were considerably lower than that observed in the PL/J mutant mice (7).

To search for an infectious agent that might be involved in this skin disease, we performed the following studies. Gram, acid fast, periodic acid-Schiff, and Grocott staining of skin sections failed to detect organisms. In addition, sentinel mice housed in the same rooms as the CD18-deficient mice repeatedly tested negative for common mouse viruses. Multiple skin samples from affected and control mice were cultured for bacteria and fungi and did not reveal pathogens, although *Staphylococcus epidermidis* was isolated from one culture.

The response of the dermatitis to corticosteroids was assessed by daily subcutaneous injections of 20 μg of dexamethasone. Improvement was seen within 1 week in all three affected mice; dramatic improvement with disappearance of scales, crusts, and erythema occurred after 2 weeks and was accompanied by regrowth of hair. Hair regrowth was almost complete by 6 weeks (Fig. 4). Acute withdrawal of the dexamethasone dose or reduction of the dose to 10 μg/day resulted in a severe exacerbation of the dermatitis (data not shown). These results support the interpretation that an infectious organism is not the primary cause of this dermatitis and suggest the involvement of an autoimmune or other inflammatory process.

The CD18 mutation described herein is a hypomorphic allele; in 129/Sv mice, resting levels of CD18 and Mac-1 on granulocytes as measured by a cytofluorograph were found to be ≈2% and 8% of wild-type levels, respectively (7). This raises the question of whether the presence or absence of the dermatitis in various strains of mice might be related to the level of expression from the hypomorphic allele. Lower levels of CD18 expression could be a susceptibility factor for the development of the disease. For this reason, CD18 expression was measured on the surface of granulocytes in PL/J homozygotes and was found to be 3–4% of wild-type levels, while Mac-1 expression was 2–3% of wild-type levels (data not shown). Serial sections of inflamed skin from mutant mice revealed only weak staining for CD18 on a small fraction of Gr-1-positive granulocytes in the dermis and epidermis (Fig. 3). In contrast, normal mouse skin contained very few extravascular leukocytes, whereas skin from normal mice with carrageenan-induced inflammation (9) showed intense staining of CD18 on the majority of extravascular granulocytes (data not shown). These data show that CD18 expression in 129/Sv and PL/J mice is comparable and that the dermatitis is not the result of a more severe deficiency of CD18 in PL/J mice.

Our data show that the development of the dermatitis requires homozygosity for the CD18 mutation and is strain-dependent. To assess the role of other genetic loci, homozygous mutant mice on the susceptible PL/J and resistant C57BL/6 backgrounds were intercrossed. None of the F_1 mice developed dermatitis, but 50% of mice developed dermatitis

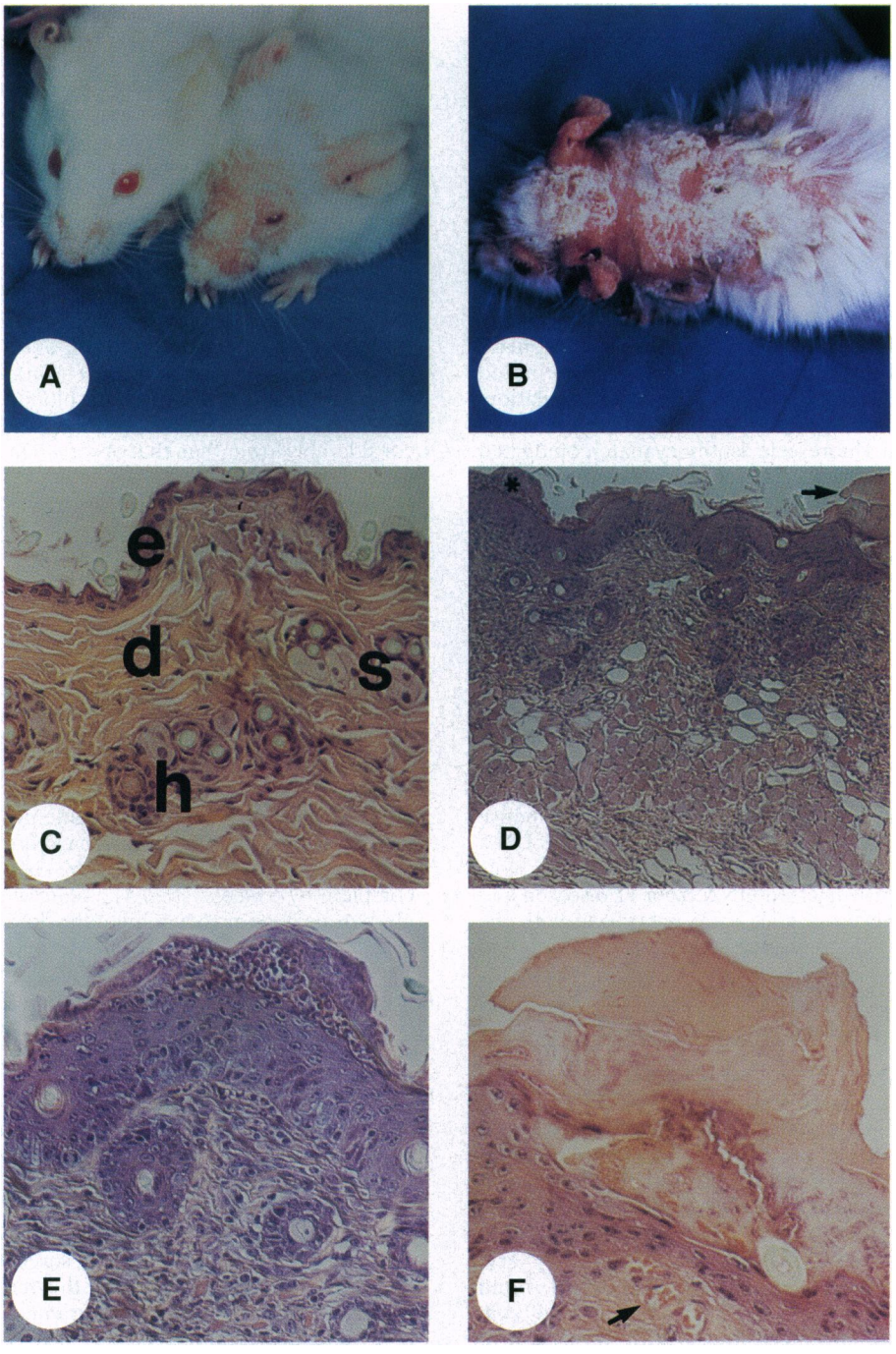

FIG. 1. Clinical features and histopathology of skin disease. (*A*) Homozygous CD18 PL/J animal (mouse on the right) showing mild erythema and alopecia in the facial area; a heterozygote littermate is shown on the left. (*B*) Severe dermatitis with progressive alopecia, severe erythema, scales, and crusts. (*C*) Histology of normal skin from PL/J mouse. Note that the epidermis (e) consists of two or three cell layers. Embedded in the dermis (d) are hair follicles (h) and sebaceous glands (s). (*D*) Histology of CD18 PL/J diseased skin showing hyperplasia of the epidermis, subcorneal microabscesses (*), and hyperorthokeratosis (arrow). In the dermis, a diffuse inflammatory cell infiltrate is observed. (*E*) Higher magnification of *D* showing granulocytes within a microabscess. (*F*) Higher magnification of *D*. Note the hyperorthokeratosis and dilated capillaries in the dermis (arrow). (*C* and *D*, ×100; *E* and *F*, ×400).

when the F_1 mice were backcrossed with CD18-deficient mice on the susceptible PL/J strain (Table 2). These data suggest that a single locus determines the development of dermatitis in this backcross. The lack of dermatitis in F_1 mice indicates that the C57BL/6 allele for this putative locus is dominant to the PL/J allele. The analysis of F_2 mice (not yet undertaken) may reveal the influence of other loci.

Two candidate loci evaluated for possible modifier effects were the H-2 region and the CD11 gene cluster. The major histocompatibility complex in mice (H-2) and humans (HLA) are involved in genetic susceptibility to many inflammatory disease processes (10–12). The CD11 genes are candidate modifier loci because of their known subunit interaction with CD18, and in humans the CD11 genes map to a small region of chromosome 16 (13). Although only the mouse CD11a gene has been mapped (chromosome 7), it is likely that the other CD11 genes will also map to this region (14, 15). If either locus was the primary modifier, we would predict that all diseased mice would be homozygous for the PL/J genotype and all nondiseased mice would be heterozygous for the PL/J and

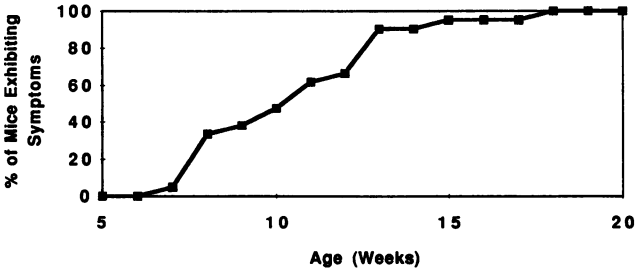

FIG. 2. Age of onset of skin disease. Twenty-one CD18 homozygous mutant N_7 or N_8 PL/J mice were observed weekly for disease symptoms.

C57BL/6 alleles. The genotypes for the N_2 backcross mice suggest that neither the H-2 region nor the CD11 gene cluster show the expected segregation pattern for a major modifier locus (Table 2).

DISCUSSION

We have observed an inflammatory skin disease in mice associated with homozygosity for a mutation in CD18. This disease is strain-dependent with the disease occurring in PL/J mice but not in C57BL/6 or 129/Sv mice. There was no evidence for microbial infection, and the disease improved rapidly with corticosteroid treatment. This is in contrast to CD18 deficiency in humans or cattle where cutaneous manifestations are thought to be entirely related to chronic microbial infection (3, 16).

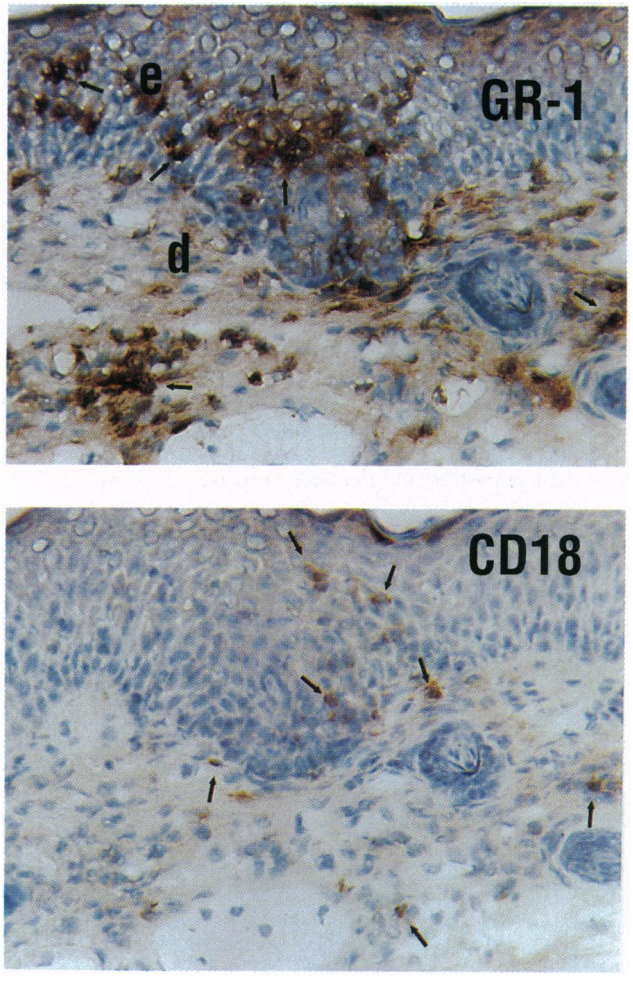

FIG. 3. Serial sections of diseased skin stained for granulocyte antigen Gr-1 (*A*) and CD18 (*B*). Both dermal (d) and epidermal (e) infiltration of granulocytes are observed (arrows). Note the paucity of CD18 labeling on granulocytes (arrows) in both dermis and epidermis. (Immunoperoxidase labeling, brown deposit; hemotoxylin counterstain. ×400.)

Table 1. Peripheral blood leukocyte counts

Animals	Neutrophils*	Lymphocytes*	Monocytes*
Littermates†	0.89 ± 0.15 (0.34–1.75)	3.62 ± 0.64 (1.57–8.93)	0.11 ± 0.02 (0.05–0.25)
Homozygotes	18.05 ± 4.25‡ (1.61–70.9)	9.86 ± 0.85‡ (3.61–18.31)	0.81 ± 0.16‡ (0.18–3.30)

*Mean values are presented as no. × 10^6 cells per ml (±SEM) from 10 littermates and 19 homozygous mutant mice; ranges are shown in parentheses.
†Includes wild type and heterozygotes.
‡Significant differences between the two groups of mice shown by Welch's *t* test for unequal variances at $P < 0.001$.

This murine model of inflammatory skin disease is particularly attractive for further study because there is strong evidence for polygenic inheritance with the involvement of only one or a few modifier genes as judged by the incidence of disease in F_1 and backcross mice. Because of the known association of CD18 and CD11 subunits and because there is evidence that the CD11 genes map within a single cluster (13), this region would be a candidate modifier locus. However, when F_1 mice are backcrossed to the PL/J strain, genotype analysis of the progeny indicated that homozygosity for the PL/J alleles at this locus did not determine the presence of skin disease. Likewise, the H-2 region was considered a candidate modifier, but our data suggest that the H-2 genotype does not determine the disease susceptibility in backcross mice. It will be appropriate to undertake a search of the entire mouse genome to identify modifier loci by using the backcross mice for linkage analysis (17, 18).

As for many inflammatory skin diseases in humans, the pathogenesis of this mouse model is not yet completely understood. Although CD18 deficiency is a major genetic determinant, it is not clear whether deficiency of LFA-1, Mac-1, or p150,95 expression, alone or in combination, determines susceptibility to the skin inflammation. Our data show that the level of expression of CD18 in disease-susceptible PL/J mutants was comparable to the expression in resistant CD18 mutant strains, indicating that susceptibility was not caused by a more extreme deficiency of CD18. In addition, we have now generated a null mutation for CD18, and homozygous mice on a mixed 129/Sv and C57BL/6 background do not develop this skin disease (K.S.-K., unpublished data). Interestingly, the disease does not develop in ICAM-1-deficient mice (19) backcrossed for four generations onto the PL/J strain (D.C.B., unpublished data). ICAM-1 serves as one of the major counter receptors for both LFA-1 and Mac-1, and the interaction of both proteins is thought to be crucial for many CD18-related functions (20).

A recent report that mice lacking interleukin 2 receptor β show deregulation of T-cell activation provides an interesting precedent indicating that the skin disease could involve dysregulation of immune and/or inflammatory processes. A general reactive lymphadenopathy and enlarged lymph nodes were noted in affected PL/J mice, but preliminary studies of T cells and B cells in peripheral blood and spleen have not revealed major changes in cell populations (Nigel D. Staite, personal communication). Myeloid hyperplasia in spleen and bone marrow were also observed, but this is a feature of CD18 deficiency in humans and cattle. A milder hyperplasia was also noted in nonsusceptible 129/Sv CD18 homozygotes (7), suggesting that it may be a feature of CD18 deficiency and not a predisposing factor for the development of skin inflammation.

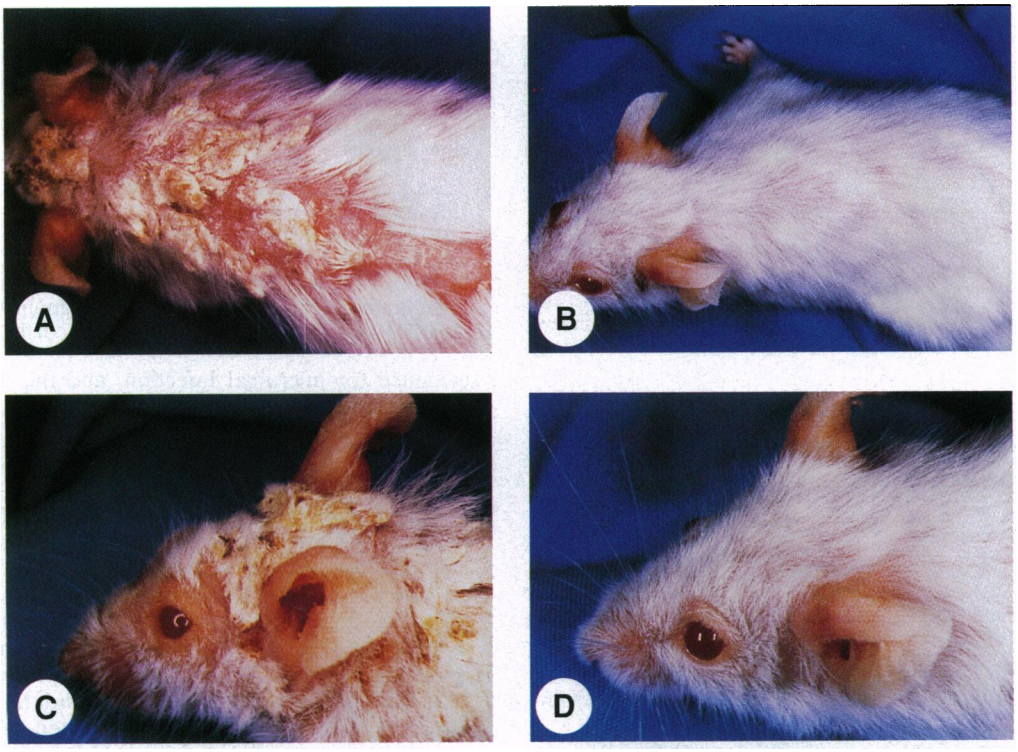

FIG. 4. Dexamethasone treatment of skin disease. An untreated mouse (*A* and *C*) displaying severe disease compared to the same mouse after 6 weeks of daily dexamethasone injections (*B* and *D*). Erythema, scales, and crusts have disappeared and extensive hair growth has occurred.

The skin disease in PL/J mice shows several histological and clinical similarities to human hyperproliferative inflammatory skin disorders, such as psoriasis (21). These include epidermal hyperplasia, hyperkeratosis, parakeratosis, subcorneal microabscesses, lymphocyte exocytosis, and dilation of dermal capillaries. The gross morphology, anatomical distribution, disease course, and response to dexamethasone treatment are all features with similarity to human psoriasis and other inflammatory skin disorders. Other animal models showing some similarity to psoriasiform dermatitis have been described and include the mouse mutations flaky skin (*fsn*) and chronic proliferative dermatitis (*cpd*) and transgenic HLA-B27 rats (12, 22). Histopathologically, the skin disease in CD18-deficient PL/J mice shows several similarities to both *fsn* and *cpd*; however, this disease differs from *fsn* and *cpd* in the age of onset and several clinical features. Unlike the skin disease reported here, skin manifestations are observed when both the *fsn* and *cpd* mutations are backcrossed onto the C57BL/6 strain background. The disease model described here is of particular interest in that one relevant mutation is known, and it is feasible to identify major modifier genes. The association of CD18 deficiency with skin disease in the mouse suggests that analysis of genetic polymorphisms for CD18 and related genes should be examined in humans with psoriasis and other dermatoses in an attempt to gain additional insights into the pathogenesis of these diseases.

Table 2. Backcross analysis including genotypes for H-2 and CD11a

	No. of mice with disease	No. of mice without disease
Backcross		
F_1	0	13
N_2	31	31
H-2 genotype of N_2 mice		
$H\text{-}2^u/H\text{-}2^u$	8	6
$H\text{-}2^u/H\text{-}2^b$	6	8
CD11a genotype of N_2 mice		
(PL/J)/(PL/J)	7	11
(PL/J)/(C57BL/6)	5	1

(PL/J × C57BL/6)F_1 and (F_1 × PL/J)N_2 animals were all homozygous CD18-deficient. F_1 and N_2 backcross mice were visibly inspected for manifestations of skin inflammation for a period of 6 months. After this time period, the H-2 and CD11a genotype was determined for a representative group of both diseased and nondiseased mice.

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