Psoriasiform Dermatitis Susceptibility in *Itgb2*^{tm1Bay} PL/J Mice Requires Low-Level CD18 Expression and at Least Two Additional Loci for Progression to Severe Disease

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***Itgb2*^{tm1Bay} PL/J mice express low levels of the β_2 integrins and, unlike *Itgb2*^{tm1Bay} C57BL/6J mice, spontaneously develop psoriasiform dermatitis with several similarities to human psoriasis. To define the genetic requirements for skin disease susceptibility we analyzed more than 500 F2 progeny from an *Itgb2*^{tm1Bay} (PL/J $\times$ C57BL/6J) intercross. We found that 23.5% developed chronic inflammatory skin disease, although significant differences in severity were observed. Another CD18 mutation, *Itgb2*^{tm2Bay}, has now been generated that completely eliminates CD18 expression. Surprisingly, of 10 *Itgb2*^{tm2Bay} homozygote PL/J N4 mice generated, none showed clinical or histopathological evidence of disease. However, *Itgb2*^{tm1Bay}/*Itgb2*^{tm2Bay} PL/J mice developed dermatitis indistinguishable from *Itgb2*^{tm1Bay} PL/J mice. In addition, approximately half of *Itgb2*^{tm1Bay}/*Itgb2*^{tm2Bay} (C57BL/6J $\times$ PL/J)F1 mice were found to develop mild psoriasiform dermatitis identical to the early stages of disease seen in *Itgb2*^{tm1Bay} PL/J mice. Collectively, these results suggest a complex inheritance pattern of psoriasiform dermatitis in this model that involves lowered, but not absent, CD18 expression and at least two additional PL/J loci for the development of severe disease. The susceptibility allele can act in either a heterozygous or homozygous state, dependent on the level of CD18 expression. (Am J Pathol 2003, 163:197–202)**

involve both genetic and environmental components. Histologically, psoriasis is characterized by epidermal proliferation, dilation of dermal blood vessels, and a mixed inflammatory cell infiltrate including CD4⁺ and CD8⁺ T cells. Although it is now clear that T lymphocytes are crucial for the initiation and progression of this disease,¹ defects in epidermal proliferation may also contribute. Epidemiological studies have shown an increased incidence of psoriasis in relatives of psoriatic patients.^{2,3} Many loci have been implicated as susceptibility traits for psoriasis; however, there is no consensus on which loci are critical for disease development and progression. The most investigated loci to date, including PSORS1, are on the short arm of chromosome 6,^{4–12} Other implicated loci include PSORS2 on the short arm of chromosome 17,^{4,8} PSORS3 on chromosome 4,^{8,13} PSORS4 on chromosome 1,¹⁴ and many others.^{4,6,8,9,15,16}

Currently, there are no spontaneous animal models that completely reproduce all of the different manifestations of psoriasis. However, several mouse models with a psoriasiform phenotype have been reported and can be used to study both the cellular mechanisms and genetic pathways that lead to the development of human inflammatory skin diseases. We have previously reported a model of psoriasiform dermatitis that develops in homozygous *Itgb2*^{tm1Bay} PL/J mice.¹⁷ *Itgb2* encodes CD18, the β_2 subunit of the β_2 integrins, a family of four heterodimeric proteins expressed only on leukocytes.¹⁸ The β_2 integrins mediate many immune and inflammatory processes through interactions with a diverse set of ligands including ICAM-1. The *Itgb2*^{tm1Bay} mutation is hypomorphic in that it results in low level, but not null expression of CD18. *Itgb2*^{tm1Bay} PL/J mice, unlike *Itgb2*^{tm1Bay} C57BL/6J or 129/Sv mice, spontaneously develop dermatitis characterized clinically by erythema, alopecia, and scale and crust formation and histologically by lymphocyte infiltration of the superficial dermis and deep epidermis, epidermal proliferation with hyperkeratosis and parakeratosis, and accumulation of neutrophils in affected epidermis with formation of subcorneal pustules.

Psoriasis is a common disease characterized by the development of inflammatory plaques on the skin. The pathogenesis of this disease is poorly understood, but appears to

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Such dermatitis has not been reported in cattle or humans with spontaneous CD18 deficiency resulting in the disease leukocyte adhesion deficiency-1.

The phenotype of these mice is surprising considering the severe anti-inflammatory effects generally associated with inhibition or loss of CD18 expression. The chronic dermatitis observed in *Itgb2^{tm1Bay}* PL/J mice shows high penetrance, with 91% of fourth generation backcross (N4) and 100% of N6-N8 mice developing disease. Previous genetic analyses of *Itgb2^{tm1Bay}* PL/J (susceptible) and *Itgb2^{tm1Bay}* C57BL/6J (resistant) mice suggested that there may be a single recessive PL/J allele in addition to *Itgb2^{tm1Bay}* that is responsible for the disease susceptibility.¹⁷ This hypothesis was based on observations that *Itgb2^{tm1Bay}* (C57BL/6J × PL/J)F1 mice were phenotypically normal whereas 50% of N2 progeny generated from backcrossing these F1 mice to *Itgb2^{tm1Bay}* PL/J mice developed psoriasiform dermatitis.

Here we report the results of additional studies designed to further elucidate the genetics of psoriasiform dermatitis in *Itgb2^{tm1Bay}* PL/J mice. Analysis of a large cohort of F2 intercross progeny generated from *Itgb2^{tm1Bay}* PL/J and *Itgb2^{tm1Bay}* C57BL/6J mice showed that 23.5% of mice developed chronic skin inflammation with highly variable severity. This finding suggests that skin disease susceptibility in CD18-deficient mice requires a single recessive PL/J allele. We also studied the effects of lowered CD18 expression on skin disease development using another mutation, *Itgb2^{tm2Bay}*, which completely eliminates CD18 expression.¹⁹ Surprisingly, we observed that *Itgb2^{tm2Bay}* PL/J mice did not develop any clinical or histological evidence of psoriasiform dermatitis, whereas *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* compound heterozygous PL/J mice developed dermatitis indistinguishable from *Itgb2^{tm1Bay}* PL/J mice. In addition, nearly half of *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* (PL/J × C57BL/6J)F1 mice developed mild psoriasiform dermatitis, in contrast to our previously reported finding that *Itgb2^{tm1Bay}* (PL/J × C57BL/6J)F1 mice are completely resistant to inflammatory skin disease.¹⁷ These findings indicate a crucial role for CD18 expression as well as other PL/J loci in the pathogenesis of psoriasiform dermatitis in this model.

Materials and Methods

Generation of *Itgb2^{tm1Bay}* (PL/J × C57BL/6J)F2 Mice

Itgb2^{tm1Bay} 129/Sv mice were backcrossed onto the PL/J and C57BL/6J mouse strains (The Jackson Laboratory, Bar Harbor, ME) for seven generations. F1 mice were generated by intercrossing homozygous *Itgb2^{tm1Bay}* N7 PL/J mice (susceptible) with homozygous *Itgb2^{tm1Bay}* N7 C57BL/6J mice (resistant). These F1 mice were bred together to produce an F2 population. Homozygous *Itgb2^{tm1Bay}* mice were observed for 6 months. Animals were evaluated every 2 to 3 weeks for 6 months and assigned a score based on the clinical severity of psoriasiform dermatitis. Disease was scored by the following scale: 1, red or dry skin in obvious areas with no hair loss;

2, red, dry skin with alopecia on the head, ears may or may not show signs of necrosis; and 3, hair loss extends to areas other than head, scale and crust formation. Animals were categorized based on the highest score they received throughout the 6-month study period.

Additional Crosses

The *Itgb2^{tm2Bay}* mutation (The Jackson Laboratory) was backcrossed four generations onto the PL/J strain background and homozygous *Itgb2^{tm2Bay}* mice were generated. *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* PL/J compound heterozygote mice were produced by intercrossing *Itgb2^{tm1Bay}* N6 PL/J mice with *Itgb2^{tm2Bay}* N5 PL/J mice. *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* (PL/J × C57BL/6J)F1 mice were generated by intercrossing *Itgb2^{tm1Bay}* N8 PL/J with *Itgb2^{tm2Bay}* N7 C57BL/6J. *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* C57BL/6J mice were made by intercrossing *Itgb2^{tm1Bay}* N10 C57BL/6J with *Itgb2^{tm2Bay}* N8 C57BL/6J. All animals were observed for age of onset and severity disease for a period of 6 to 9 months.

Preparation of Histology Sections

Samples of muzzle, ear, dorsum, and tail were fixed by immersion in alcoholic formalin (10 ml 40% formalin:70 ml absolute ethanol:20 ml distilled water); routinely trimmed, processed, and embedded in paraffin; sectioned at 5 μ m; and stained with hematoxylin and eosin. Sections were evaluated with the identity of the experimental groups unknown to the examiner.

DNA Sequencing

Primers were generated from the *Itgb2* genomic sequence obtained from the Celera and public databases. Primers were designed using Primer3 software (Massachusetts Institute of Technology, Cambridge, MA) in the intron sequence surrounding each of the 15 *Itgb2* exons listed by Celera, an additional exon listed in NCBI (but not in Celera), the duplicated exon 3 with the neomycin resistance cassette-disrupted intron-exon boundary, and a part of exon 16 that was listed as exon sequence by NCBI and intron sequence by Celera. Primer sequences were as follows: exon 1 forward primer: ggcgctgacttagaacagga, exon 1 reverse primer: gccactctgaggtgtttc, exon 2 forward primer: ctg-gagtcacactgctcctc, exon 2 reverse primer: gccactgtcaaggatgtc, exon 3 forward primer: agtcagccctgtctgtctcc, exon 3 reverse primer: ggaagggcagcttagactctg, exon 3/neo forward primer: ggattgggaagacaatagcag, exon 3/neo reverse primer: ggaagggcagcttagactctg, cryptic exon 1 forward primer: caagtcagaggtggcgaaac, cryptic exon 1 reverse primer: agtggcgataagtcgtgtct, cryptic exon 2 forward primer: ggcacctatctcagcgatct, cryptic exon 2 reverse primer: cgttgcgcaaactattaactg, exon 4 forward primer: ttctagcctatgccctctgc, exon 4 reverse primer: aca-cattccaaccaggttcc, exon 5 forward primer: gctcagagtgtc-ccttgctt, exon 5 reverse primer: tcccaaggttgaaggagtg, exon 6 forward primer: tctgctctgtctgtctgc, exon 6 reverse primer: gccctgagttgagggaagt, exon 7 forward primer: gg-

gaaaccaaggcaggaac, exon 7 reverse primer: aggcaggcagcactcac, exon 8 forward primer: gtcctggaaggctgtctga, exon 8 reverse primer: attgcacaaggttccgctta, exon 9 forward primer: cctgcgctagcttgatcttc, exon 9 reverse primer: cagcttgctggagactcac, exon 10 forward primer: cagccactcctgtctctct, exon 10 reverse primer: gcaccctgctatagaacca, exon 11 forward primer: acccacagttggaactgaa, exon 11 reverse primer: cctttccatgaactgatgc, exon 12 forward primer: cccaagggcacacctaagta, exon 12 reverse primer: cctggtacaatggacaaggaa, exon 13 forward primer: cctgcaggaagttagtcat, exon 13 reverse primer: ctcccagtagtcacagcagt, exon 14 forward primer: cctgactcctcctcctc, exon 14 reverse primer: aggtaccaccagcctcac, exon 15 forward primer: ctgacattttggtgtgtgc, exon 15 reverse primer: accacaagggttcccaaag, exon 16.1 forward primer: acctccctgcactgacaaga, exon 16.1 reverse primer: aagattgtgcaggtcggaag, exon 16.2 forward primer: cagggtttccaggacttgt, exon 16.2 reverse primer: cagcatggatgaagcttta. The exons were amplified from genomic DNA isolated from *Itgb2^{tm1Bay}* PL/J and *Itgb2^{tm1Bay}* C57BL/6 mice in 25- μ l reactions in a Perkin-Elmer (Norwalk, CT) 9600 Thermal Cycler. The polymerase chain reaction products were electrophoresed in a 2% agarose gel and purified from excised gel slices using the QIAquick Gel Extraction Kit (Qiagen, Chatsworth, CA). DNA sequencing was performed using the ABI PRISM BigDye Terminator and Dye Primer Cycle Sequencing Ready Reaction Kits (Applied Biosystems, Foster City, CA) followed by electrophoresis on the ABI 377 automated sequencer.

Results

Previous crosses designed to estimate the number of loci contributing to the psoriasiform phenotype in this model showed that ~50% of backcross progeny developed disease with varying degrees of severity.¹⁷ This analysis suggested that a small number of loci, perhaps a single recessive PL/J allele, are required in addition to CD18 deficiency for susceptibility. However, this cross did not allow evaluation of the suppressive or other modifying effects of C57BL/6J homozygosity at these loci.

To further characterize the genetic requirements of psoriasiform dermatitis in this model, we intercrossed *Itgb2^{tm1Bay}* C57BL/6J and *Itgb2^{tm1Bay}* PL/J mice to produce F2 progeny. We observed 23.5% (116 of 494) incidence of disease in the homozygous *Itgb2^{tm1Bay}* offspring. For a single gene autosomal recessive trait in this cross, 25% incidence of disease would be expected, because all mice are homozygous for the *Itgb2^{tm1Bay}* mutation. Analyses by Z-test with Yates correction factor showed that there is no significant difference between our results and the expected incidences for a single recessive allele ($P = 0.542$). These data support our earlier backcross results and further suggests that susceptibility to this skin disease is controlled by two loci, *Itgb2^{tm1Bay}* and a recessive PL/J allele.

Approximately half of the affected F2 mice developed only mild disease with erythema and/or dry skin with correspondingly mild histological changes. In the remaining F2 mice, the disease progressed to a severe form

Figure 1. Maximum score obtained by *Itgb2^{tm1Bay}*(C57BL/6J $\times$ PL/J)F2 mice that developed skin disease throughout the 6-month study period. All mice were scored on a 0 to 3 scale of increasing severity of psoriasiform dermatitis (see Materials and Methods).

with various degrees of alopecia (Figures 1 and 2). Areas of alopecia are characterized by extension of the epithelial and inflammatory changes into the infundibulum of the follicle, progressive destruction and loss of affected follicles, and scarring. However, the features of the early stages of the severe form are clinically and histologically identical to those of the mild, nonprogressive form. Previously we reported that highly backcrossed *Itgb2^{tm1Bay}* PL/J mice always progress to the severe psoriasiform phenotype.¹⁷ Thus, these data suggest that the severity of skin disease is determined by PL/J loci other than the susceptibility locus.

The disease frequencies observed in these crosses suggested that susceptibility to psoriasiform dermatitis was controlled by a single genetic locus. We think it is possible, but unlikely, that sequence variations exist between the C57BL/6 and PL/J *Itgb2^{tm1Bay}* alleles, and that these are responsible for the skin disease phenotype. The *Itgb2^{tm1Bay}* mutation was originally backcrossed onto PL/J and C57BL/6 from the same 129/Sv strain background, and a spontaneous mutation could have occurred in this gene during one of the backcross generations. To rule out this possibility, we sequenced regions of the *Itgb2^{tm1Bay}* gene in both strains. We found no polymorphisms in any of the exons, including the duplicated exon 3 region. Although this approach cannot detect the presence of splice variants, the absence of polymorphisms in coding regions between susceptible and resistant strains suggests that a locus distinct from the *Itgb2^{tm1Bay}* mutation mediates susceptibility to this disease.

Previous studies showed that the level of *Itgb2* expression on peripheral blood leukocytes in both *Itgb2^{tm1Bay}* 129/Sv and *Itgb2^{tm1Bay}* PL/J was less than 10% of control animals.²⁰ Because psoriasiform dermatitis does not develop in heterozygous PL/J *Itgb2^{tm1Bay}* mice, one requirement for disease susceptibility appears to be substantially reduced *Itgb2* expression. To determine the effect of complete loss of *Itgb2* expression on disease development, we backcrossed the *Itgb2^{tm2Bay}* mutation onto the PL/J strain background. Surprisingly, of 10 homozygous

Figure 2. **A:** Normal skin of a wild-type PL/J mouse. **B:** Normal skin of a *Itgb2^{tm2Bay}* PL/J mouse. *Itgb2^{tm2Bay}* homozygotes do not express CD18. **C:** Dermatitis in *Itgb2^{tm1Bay}* PL/J mouse expressing low levels of CD18. The epidermis is acanthotic and there is orthokeratotic hyperkeratosis with focal accumulation of neutrophils. In the dermis there is infiltration of neutrophils and lesser numbers of lymphocytes, and the superficial dermal vessels are dilated. **D:** Dermatitis in a PL/J *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* heterozygote mouse, showing changes similar to those in *Itgb2^{tm1Bay}* PL/J mice. **E:** Mild dermatitis in a *Itgb2^{tm1Bay}* PL/J mouse. The epidermis is acanthotic and hyperkeratotic, but there are few neutrophils in the epidermis or dermis. The predominant inflammatory cells are lymphocytes, which are located primarily in the superficial dermis, the basal layer of the epidermis, and around hair follicles. **F:** Mild dermatitis in an *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* (C57BL/6J × PL/J)F1 mouse. Changes are similar to those in **E**, with lymphocytes prominent in the basal layers of the epidermis of the hair follicles.

Itgb2^{tm2Bay} PL/J N4 mice generated, none showed clinical or histopathological evidence of disease (Figure 2, A and B), nor did heterozygous *Itgb2^{tm2Bay}* PL/J mice develop psoriasiform dermatitis. We then bred these

Itgb2^{tm2Bay} PL/J mice with *Itgb2^{tm1Bay}* PL/J mice to produce *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* PL/J compound heterozygotes. In this study we found that all compound heterozygote *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* PL/J mice developed

disease that was clinically and histologically indistinguishable from that in *Itgb2^{tm1Bay}* PL/J mice (Figure 2, C and D). In these mice, dermatitis was moderate to severe. Although the lesions tended to be multifocal or patchy, and not all changes were present in all sections from each mouse, the typical pattern included epidermal acanthosis and both orthokeratotic and parakeratotic hyperkeratosis. In the most severely affected areas, the epidermis contained infiltrates of neutrophils, with sparse focal intraepidermal neutrophil accumulations, or microabscesses. Neutrophils, with lesser numbers of lymphocytes, also were present in the superficial dermis, and the superficial dermal vessels were dilated. In a few sections, these changes tended to be particularly prominent in and around hair follicles.

Next, we generated *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* (PL/J × C57BL/6J)F1 compound heterozygous mice and found that 40% (4 of 10) developed mild psoriasiform dermatitis (Figure 2, E and F). The lesions were closely similar to early lesions in *Itgb2^{tm1Bay}* PL/J mice, with epidermal acanthosis and hyperkeratosis, and a mild, predominantly lymphocytic inflammatory cell response located primarily in the superficial dermis and the basal layer of the epidermis. Neutrophils were sparse or absent. In some areas, lymphocytes were most numerous in and around hair follicles. In contrast, homozygous *Itgb2^{tm1Bay}* (PL/J × C57BL/6J)F1 mice are completely resistant to the psoriasiform dermatitis.¹⁷ As a control we bred *Itgb2^{tm1Bay}* C57BL/6J mice to *Itgb2^{tm2Bay}* C57BL/6J mice to generate *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* C57BL/6J compound heterozygotes. These mice showed no clinical or histological evidence of skin disease (0 of 20).

Discussion

Psoriasis is a common inflammatory skin disease. Its etiology is unknown, but probably involves both genetic and environmental factors. Even in a single patient there can be highly variable manifestations of the disease, suggesting that multiple mechanisms are involved in the pathogenesis of psoriasis. Unfortunately, there are few available animal models amenable to genetic analysis. The *Itgb2^{tm1Bay}* mouse serves as an excellent model for genetic studies of psoriasiform dermatitis, because both susceptible (PL/J) and resistant (C57BL/6J and 129/Sv) mouse strains have been described. Similar to human psoriasis, the *Itgb2^{tm1Bay}* PL/J phenotype is polygenic but has the advantage that one involved gene, *Itgb2*, is already known. The disease is 100% penetrant in highly backcrossed mice and offspring are viable and fertile, thus large numbers of animals can be generated. The dermatitis is also spontaneous and requires no surgical manipulation. Finally, we have recently observed that the skin disease in *Itgb2^{tm1Bay}* PL/J mice, like human psoriasis, is immunologically driven. Using T-cell depletion strategies, we found that the skin inflammation in this model was mediated by CD4⁺ and CD8⁺ T lymphocytes (SC Barlow et al, submitted).

In these studies, we wanted to further characterize the inheritance of psoriasiform dermatitis and evaluate the

requirements for CD18 expression in this model. Our previous report suggested that only a few loci (possibly one) in addition to *Itgb2^{tm1Bay}* were responsible for the inflammatory skin disease observed in *Itgb2^{tm1Bay}* PL/J mice.¹⁷ This was based on the observation that 50% of the N2 offspring generated by breeding *Itgb2^{tm1Bay}* (C57BL/6J × PL/J)F1 mice to *Itgb2^{tm1Bay}* PL/J mice developed clinical signs of skin disease. Our finding that 23.5% of homozygous *Itgb2^{tm1Bay}* F2 mice developed psoriasiform dermatitis, combined with this previous result, strongly suggests that susceptibility to psoriasiform dermatitis in *Itgb2^{tm1Bay}* mice requires only the influence of a single recessive PL/J allele. Analysis of the genomic DNA sequence from dermatitis-susceptible and -resistant strains demonstrates that susceptibility to the disease is not mediated by polymorphisms in the *Itgb2^{tm1Bay}* mutation itself.

In these mice we observed highly variable severity of disease (Figure 1). In highly backcrossed *Itgb2^{tm1Bay}* PL/J mice, the disease develops as erythema and/or dry skin on the ears and tail and then progresses over the body and involves significant alopecia in the advanced stages. Interestingly, in the F2 mice we observed some mice that developed the early manifestations of psoriasiform dermatitis, erythema and/or dry skin on ear and tail, but did not progress to the more severe phenotype involving alopecia. The highly variable severity observed in these F2 mice suggest that other PL/J loci control the extent to which disease develops, although at this time it is difficult to estimate the exact number of modifying loci.

Another CD18 mutation, *Itgb2^{tm2Bay}*, has now been reported that completely eliminates expression of CD18, and thus all β_2 integrins.¹⁹ This mutation on a mixed 129/Sv and C57BL/6J background did show a phenotype of spontaneous skin ulcerations, but unlike CD18-deficient (*Itgb2^{tm1Bay}*) PL/J mice, this trait was associated with bacterial infection and the mice did not develop psoriasiform lesions. We backcrossed this mutation onto the PL/J strain background to evaluate whether the complete absence of CD18 would alter the pathogenesis of psoriasiform dermatitis. This mutation on other strain backgrounds, such as C57BL/6J and 129/Sv, results in a phenotype characterized by the increased susceptibility to infection.¹⁹ In our analysis, we observed no clinical or histological signs of psoriasiform dermatitis in homozygous *Itgb2^{tm2Bay}* mice backcrossed four generations onto PL/J. This is in contrast to *Itgb2^{tm1Bay}* N4 mice, in which more than 90% incidence of disease was observed.¹⁷ These data suggest that lowered, but not absent, expression of CD18 is required for the development of inflammatory skin disease in this model.

One possible explanation of these observations is that the initiation of psoriasiform dermatitis in these mice involves reduced β_2 integrin expression and that complete elimination of these adhesion molecules prevents the onset of disease. Low- β_2 integrin expression, resulting from this *Itgb2^{tm1Bay}* mutation, may result in reduced cellular interactions and/or alterations in intracellular signaling and lead to the development of psoriasiform dermatitis in PL/J mice. From our data we would thus predict that these altered events may not occur in wild-

type, *Itgb2^{tm1Bay}* heterozygous, and *Itgb2^{tm2Bay}* PL/J mice. Another possible explanation is that the initiating events mediating skin inflammation occur in *Itgb2^{tm2Bay}* mice, but the total absence of the β_2 integrin expression inhibits leukocyte emigration into the skin, thus preventing the disease. However, previous studies have shown that there is significant overlap of function among the β_2 integrin and other leukocyte adhesion molecules.²¹ Therefore, we think it is unlikely that the *Itgb2^{tm2Bay}* mutation prevents the disease from developing by blocking leukocyte emigration. Our data further suggests that the genetic requirements for the development of psoriasiform dermatitis in PL/J mice vary dependent on the level of CD18 expression. This is evident from our findings that approximately half of *Itgb2^{tm1Bay}/Itgb2^{tm2Bay}* (C57BL/6J $\times$ PL/J)F1 mice develop dermatitis, unlike *Itgb2^{tm1Bay}* (C57BL/6J $\times$ PL/J)F1 mice. This suggests that the PL/J susceptibility locus can sometimes act in either a heterozygous or homozygous state, dependent on the level of CD18 expression. However, the progression to the more severe psoriasiform phenotype requires PL/J homozygosity at another locus or loci.

In summary, our findings indicate that the psoriasiform phenotype in *Itgb2^{tm1Bay}* PL/J mice has a complex inheritance pattern. The development of this disease requires lowered CD18 expression and multiple PL/J alleles for progression to severe disease. Our ongoing efforts to localize and identify the PL/J loci that mediate skin disease susceptibility and severity will allow characterization of this complex inheritance and may have relevance to the genetics of human psoriasis and other chronic inflammatory diseases.

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