Psoriasis is Mediated by a Cutaneous Defect Triggered by Activated Immunocytes: Induction of Psoriasis by Cells with Natural Killer Receptors

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This study was performed to ask whether psoriasis is a unique pathologic response of epidermis of psoriatic patients, or cells with natural killer receptors can induce psoriatic changes in skin from nonpsoriatic donors. Human nonlesional skin from five psoriatics, as well as from seven nonpsoriatics was grafted on to beige-SCID mice. Lymphocyte lines with natural killer activity, and mixed natural killer, natural killer T cell phenotype, were generated by culture of peripheral blood mononuclear cells from both psoriatic, and normal donors, in 100 U interleukin-2 per ml for 14 d. Natural killer cells were injected into the human skin grafts, and the grafts were harvested after 4 wk. Injection of natural killer cells from psoriatic donors into autologous nonlesional psoriatic skin resulted in classic psoriasis histology with a significant increase in epidermal thickness, and proliferation, as well as expression of epidermal human leukocyte antigen DR, intercellular adhesion molecule-1, CD1d, and K-16. Superantigen stimulation was not necessary. In contrast, injection of natural killer cells from normal donors into autologous normal skin did not induce the histology of psoriasis, but that of psoriasiform dermatitis. This is a nonspecific reaction pattern. These grafts also exhibited a significant increase in epidermal thickness, and proliferation. Differences from psoriasis included mild epidermal edema (spongiosis), hypergranulosis, irregular elongation of rete ridges, and lack of thinning of the suprapapillary plate. Injection of allogeneic natural killer cells into grafts also resulted in psoriasiform dermatitis, regardless of the source of natural killer cells, or skin. Psoriasis induction by cells with natural killer receptors appears to be dependent upon the source of skin. This suggests that psoriasis results from a cutaneous defect that is triggered by an autoimmune activation. ***Key words: human/natural killer lymphocytes/psoriasis/SCID mice/skin. J Invest Dermatol 119:384–391, 2002***

There is now considerable evidence that psoriasis is triggered by lymphocytes. This evidence includes the ability to clear psoriasis with a fusion protein targeted to interleukin (IL)-2 receptors (Gottlieb *et al*, 1995), as well as the ability to induce (Boehncke *et al*, 1996; Wrone-Smith and Nickoloff, 1996; Boehncke *et al*, 1997), and maintain (Gilhar *et al*, 1997) psoriasis in human skin grafted to SCID mice, by the injection of activated lymphocytes. Features of psoriatic epidermis that have been induced, or maintained in the above studies include, epidermal thickness, labeling index, abnormal differentiation, and keratinocyte expression of intercellular adhesion molecule (ICAM-1), and HLA-DR. Inhibitors of T cell activation and costimulation are also able to clear psoriasis, further supporting the link between lymphocyte activation and psoriasis (Gottlieb *et al*, 2000a, b). Previous experimental work with psoriasis has focused on the function of T lymphocytes, activated with bacterial superantigens.

The potential role of natural killer cells in psoriasis was first suggested by Nickoloff *et al* (1999). Using the human skin explant/SCID mouse system, they found that injection of allogeneic natural killer cells from psoriatic donors induced changes similar to psoriasis in normal skin from nonpsoriatic donors. The suggested role for natural killer cells does not conflict with the previous SCID mouse data, as superantigen and IL-2 stimulation of T cells induces natural killer activity. Nickoloff *et al* subsequently characterized one such $CD94^+/CD161^+$ natural killer T cell line that was generated by stimulation of lymphocytes of a psoriatic patient with IL-2 plus superantigen. This natural killer line induced psoriasis-like histology upon injection into nonlesional skin of psoriasis patients (Nickoloff *et al*, 2000). The interaction of natural killer T cells with epidermis may be mediated by keratinocyte CD1d expression (reviewed in Nickoloff, 2000b). Psoriatic epidermis expresses high levels of CD1d, and the natural killer T cells produce interferon (IFN)-γ upon incubation with CD1d-positive keratinocytes, which is inhibited by anti-CD1d.

This study was performed to ask whether psoriasis is a unique pathologic response of epidermis of psoriatic patients, or whether

Manuscript received July 5, 2001; revised February 26, 2002; accepted for publication February 28, 2002.

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Table I. Distribution of markers (%) of PBMC and lines with natural killer cell activity after culture with IL-2[a]

	Control donors		Psoriatic donors	
Markers	Initial	Final	Initial	Final
CD3	70 ± 9	33 ± 17	65 ± 9	35 ± 16
CD4	35 ± 10	10 ± 10	37 ± 4	11 ± 7
CD8	30 ± 11	56 ± 22	28 ± 4	53 ± 22
CD16	10 ± 8	31 ± 17	11 ± 9	20 ± 11
CD56	14 ± 5	50 ± 21	18 ± 9	45 ± 17
CD94	15 ± 8	54 ± 15	15 ± 6	49 ± 18
CD158a	6 ± 3	9 ± 9	5 ± 4	12 ± 14
CD158b	8 ± 3	15 ± 5	8 ± 7	16 ± 13
CD161	17 ± 8	35 ± 8	15 ± 4	9 ± 6

[a]PBMC from psoriatic, and nonpsoriatic donors cultured with 100 U IL-2 per ml. Phenotypes were determined by cytofluorograph both prior to, and after culture.

autologous natural killer cells can induce psoriatic changes in skin from nonpsoriatic donors. The activity of autologous natural killer cells also needed to be tested, as the Nickoloff studies (Nickoloff *et al*, 1999) made use of allogeneic lines, which raises the possibility of a graft versus host response. An additional aim of this study was to determine whether induction of psoriasis is a general property of natural killer cells.

It was found that autologous natural killer cells (natural killer cells plus natural killer T cells) were able to induce psoriasis in noninvolved skin of psoriasis donors. In contrast, autologous natural killer cells induced psoriasiform dermatitis-like changes in the skin of nonpsoriatic donors. Psoriasiform dermatitis differs from true psoriasis, and is a common reaction pattern of skin to multiple insults ranging from atopic dermatitis, to fungal infection. The data suggest that psoriasis is dependent upon a primary cutaneous defect that is triggered by immunocytes.

MATERIALS AND METHODS

Animals C.B-17/IcrHsd-scid-bg (beige-SCID) mice (Harlan Laboratories Ltd, Jerusalem, Israel), 2–3 mo of age, were used in this study. The mice were raised in the pathogen-free animal facility of the B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology. Animal care and research protocols were in accordance with institutional guidelines, and approved by the institutional committee on animal use.

Patients After receiving approval of the institutional ethics committee, seven healthy nonpsoriatic donors, and five psoriatic patients were included in this study. All patients had classic plaque psoriasis. None of the patients were treated. Non-lesional psoriatic skin was obtained from the thighs of each patient by electrical dermatome (Brown 666). Normal skin obtained from seven nonpsoriatic subjects who underwent surgical procedures at the Plastic Department of the Rambam Medical Center, Haifa, served as a control group.

Culture of cells with natural killer activity and receptors Peripheral blood mononuclear cells (PBMC) were isolated from both psoriatic and nonpsoriatic donors by centrifugation on Ficoll/Hypaque (Pharmacia, Amersham Pharmacia Biotech, Uppsala, Sweden). The PBMC were then cultured with 100 U IL-2 per ml (Pepro Tech Inc, Rocky Hill, NJ) in medium composed of RPMI 1640, 10% human AB serum (Sigma, St. Louis, MO), 1% glutamine, 1% antibiotics (media components; Biological Industries, Kibbutz Beit Haemeck, Israel). Medium was changed as needed. After 21 d the cells were characterized and injected into human skin explants on beige-SCID mice. Cultured cells were phenotyped by cytofluorograph (Becton Dickinson, San Jose, CA) with the following antibodies: anti-CD3, anti-CD4, anti-CD8 (Becton Dickinson), as well as natural killer markers anti-CD56 (Becton Dickinson), CD94, CD158a, CD158d (Serotec, Oxford, U.K.), and CD161 (Pharmingen, San Diego, CA). Murine IgG was used as a control.

Natural killer cytotoxicity assay Cultured cells were assayed for natural killer activity by cytotoxicity on K562 targets using a standard ^{51}Cr release assay (Kalish *et al*, 1988).

Skin transplantation and injection of lymphocytes Skin transplantation was performed as described previously (Gilhar *et al*, 1993; 1995). Skin from psoriasis and non-psoriasis donors was transplanted onto four mice, which were divided into four groups (one mouse each) and injected with T-cells 4 wk following skin engraftment. Mice were divided as follows: (i) not injected control; (ii) autologous natural killer cells; (iii) allogeneic natural killer cells from psoriatic donors; (iv) allogeneic natural killer cells from normal donors. Four weeks after lymphocyte injection (8 wk after engraftment) the grafts were harvested. Grafts were analyzed by histology and immunohistochemistry. Mice were divided as follows: (i) psoriatic skin not injected control; (ii) psoriatic skin, autologous psoriatic natural killer cells; (iii) psoriatic skin, allogeneic natural killer cells; (iv) psoriatic skin, allogeneic normal natural killer cells; (v) normal skin not injected control; (vi) normal skin, autologous normal natural killer cells; (vii) normal skin, allogeneic psoriatic natural killer cells; and (viii) normal skin, allogeneic normal natural killer cells. Natural killer cells were suspended in complete medium (RPMI 1640, 10 human AB serum, 1% glutamine, 1% antibiotics, 100 U IL-2 per ml), at 10×10^6 cells per ml. Natural killer cells were injected intradermally in 0.7 ml (700,000 cells).

Determination of epidermal thickness Histologic assessment of the grafts was performed by light microscopy both before and after transplantation. Evaluation was performed by two blinded observers, one who was not aware of the design of the study. Epidermal thickness was determined with an ocular micrometer, at a minimum of 50 points along the epidermis selected to represent points of maximal and minimal thickness. Thickness of the suprapapillary plate was similarly measured at 50 points for each sample.

Immunohistochemical staining and IFN-γ enzyme-linked immunosorbent assay Monoclonal antibodies to human antigens used were as follows for immunohistochemistry: anti-cytokeratin 16 (Sigma), anti-HLA-DR (Becton Dickinson), anti-CD54 (ICAM-1) (Biodesign, ME, USA), and Ki-67 (Zymed Laboratories, San Francisco, CA). Purified murine IgG was used as a control for the above antibodies. Rat anti-mouse neutrophil antibody obtained from Serotec. Purified rat IgG was used as the control for the above antibody. Immunohistochemistry was performed on OCT embedded specimens with a biotin–avidin system (Vectostain, Vector Laboratories, Burlingame, CA). The human IFN-γ enzyme-linked immunosorbent assay kit was obtained from Endogen (Woburn, MA).

Statistical analysis All statistical comparisons were performed using ANOVA, Tukey–Kramer multiple comparison tests. $p < 0.05$ was considered statistically significant.

RESULTS

Properties of natural killer, and natural killer T cells generated by culture of PBMC with IL-2 Culture of PBMC with 100 U IL-2 per ml generated natural killer activity as manifest both by cytotoxicity against K562 targets, and phenotype. Cytotoxicity for K562 cells was 76%, 73%, and 66% at effector–target ratios of 1:50, 1:25, and 1:12.5, respectively (SD of 11, 13, and 15). IL-2-stimulated lymphocytes also expressed a mixed natural killer, and natural killer T cell phenotype as demonstrated by increased expression of CD56, CD94, CD158a, and CD158b (**Table I**).

IFN-γ levels in culture supernatant of natural killer cells were assayed by enzyme-linked immunosorbent assay for both psoriatic and normal natural killer cell lines. The level of IFN-γ production was equivalent between normal natural killer cell lines (mean 3.1 ng per ml, SD 2.2), and psoriatic natural killer cell lines (mean 2.2 ng per ml, SD 1.2).

Injection of autologous natural killer cell lines into nonlesional psoriatic skin induces histology of a psoriatic plaque Nonlesional skin grafts from five psoriasis patients were injected with autologous natural killer cell lines. The grafted nonlesional skin developed histologic changes classic for a psoriasis plaque (**Fig 1**). These changes included parakeratosis with absence of granular layer, hyperkeratosis, epidermal thickening (acanthosis)

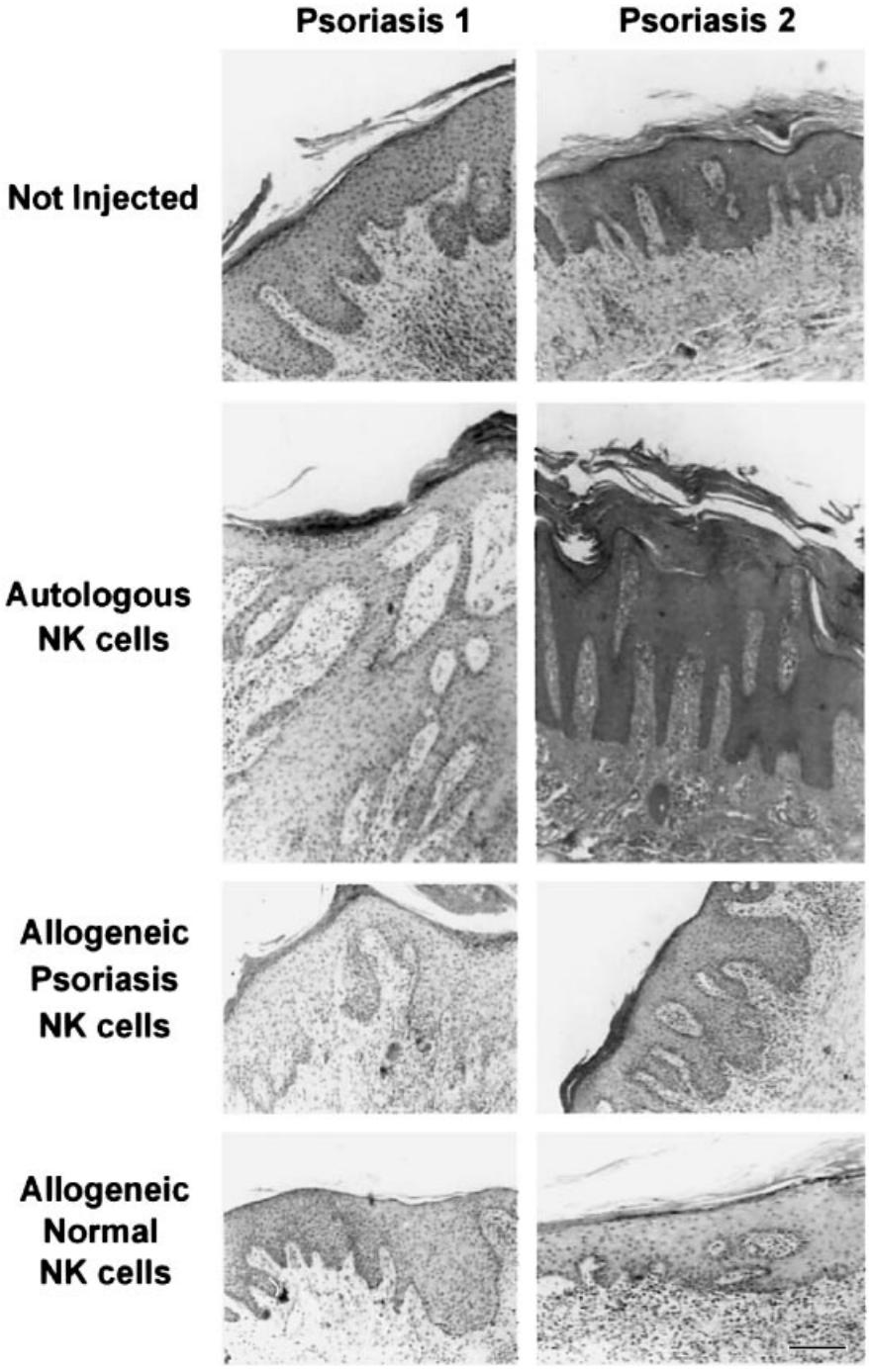

Figure 1. Psoriasis patient nonlesional skin grafted to beige-SCID mice and injected with natural killer cells. Results are shown for two donors, not injected, injected with autologous (psoriasis) natural killer cells, allogeneic psoriasis natural killer cells, and allogeneic normal (nonpsoriasis) natural killer cells. *Scale bar*: 50 μm.

with regular elongation of rete ridges, suprapapillary epidermal thinning, Munro's microabcesses, and minimal or no intraepidermal edema (spongiosis). Munro's microabcesses were observed in the human epidermis, with neutrophils of mouse origin. Murine derivation of the neutrophils was confirmed by immunohistochemistry staining (**Fig 2**). Vascular dilatation associated with a perivascular lymphocytic infiltrate was noted in the papillary dermis. Histologic features of the grafts are listed in **Table II**.

There was a significant increase in epidermal thickness ($p < 0.05$ by Tukey–Kramer multiple comparison test) of injected nonpsoriatic skin compared with control skin (**Fig 3**). This was associated with a significant increase ($p < 0.05$ by ANOVA) in the epidermal proliferation index as measured by Ki-67 staining (**Fig 4**).

Immune activation of the epidermis was evidenced by diffuse expression of HLA-DR (**Fig 2**), and ICAM-1. This was accompanied by loss of proper epidermal differentiation, with expression of K-16 cytokeratin, and Ki-67 as is observed in psoriasis (**Fig 2**). The above antigens were strongly expressed with diffuse staining over at least 50% of the epidermis in grafts from three of three donors. Control, noninjected grafts expressed focal HLA-DR, and ICAM-1 in grafts from one of three donors.

Injection of autologous natural killer cell lines into skin from nonpsoriatic normal donors induces psoriasiform dermatitis, which is not psoriasis The changes seen in skin from seven normal donors injected with autologous natural killer cells included significant epidermal thickening (acanthosis),

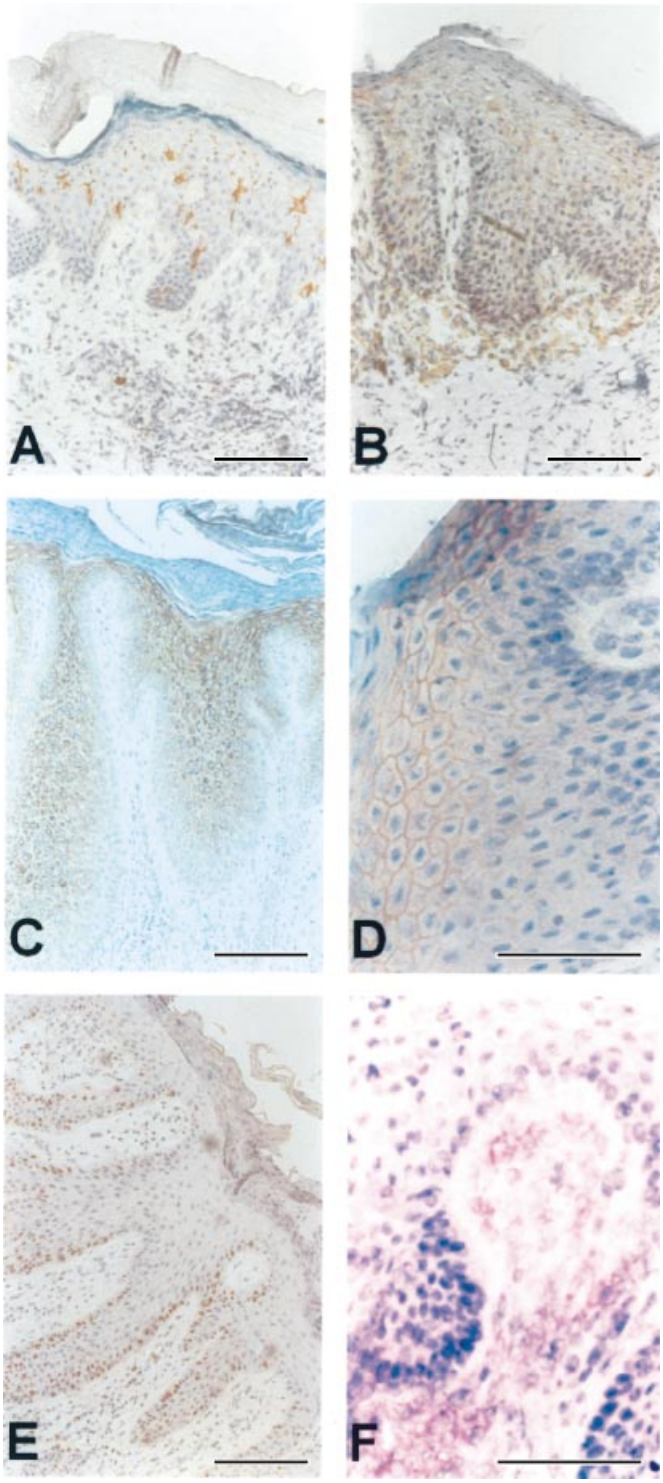

Figure 2. Immunohistochemistry staining. (*A*) Control, noninjected psoriasis skin graft stained for HLA-DR, demonstrating staining only on Langerhans dendritic cells. The remaining figures are of psoriatic skin grafts injected with autologous natural killer cells, and stained for (*B*) HLA-DR, (*C*) K-16, (*D*) CD1d, (*E*) Ki-67, and (*F*) anti-murine neutrophil antibody *Scale bars*: (*A*, *B*, *C*, *E*) 20 μm, (*D*, *E*) 10 μm.

hyperkeratosis, parakeratosis, along with a dermal lymphocytic infiltrate; however, the histology differed from psoriasis because of the presence of mild intraepidermal edema (spongiosis), irregular acanthosis, retention of the granular layer, and lack of thinning of the suprapapillary plate (**Figs 5 and 6**, and **Table II**). Many of the grafts also exhibited hypergranulosis, in contrast to the loss of the granular layer observed in psoriasis. The above data are listed in **Table II**. Injected grafts exhibited significant increases in epidermal thickness (**Fig 3**) and the proliferative index (**Fig 4**), as was observed with psoriasis grafts; however, in contrast to the psoriasis grafts injected with autologous natural killer cells, there was no thinning of the suprapapillary plate (**Table III**).

Immunohistology of the psoriasiform dermatitis was similar to that of psoriasis with expression of HLA-DR, ICAM-1, and cytokeratin 16 (**Fig 2**). These changes were those of psoriasiform dermatitis, a common reaction pattern exhibited in a wide variety of inflammatory skin diseases ranging from atopic dermatitis, to fungal infections.

Injection of allogeneic natural killer cells from normal or psoriatic donors resulted in psoriasiform dermatitis, not psoriasis Skin from normal controls, and nonlesional psoriasis skin was injected with allogeneic natural killer cells derived both from normal and psoriasis donors (**Figs 1 and 5**). Regardless of the source of skin, or natural killer cells, psoriasiform changes were observed similar to those described above for natural killer cells from normal donors (**Figs 5 and 6**); however, the findings were distinct from psoriasis. Features differing from psoriasis included irregular acanthosis (epidermal thickening), hypergranulosis (increased granular layer), and mild spongiosis (epidermal edema) (**Table II**). These grafts also lacked thinning of the suprapapillary plate (**Table III**).

Epidermal expression of CD1d Psoriatic noninvolved skin had diffuse expression of CD1d prior to injection of natural killer cells (three of three), and maintained this expression following their injection (**Fig 2**), confirming the findings of Nickoloff *et al* (1999, 2000). Skin from nonpsoriatic donors either did not express CD1d, or showed weak diffuse staining (three of six). Injection of natural killer cells from autologous, or allogeneic donors resulted in strong diffuse expression of CD1d in six of six grafts.

DISCUSSION

The histologic changes of psoriasis were induced by injection of lymphocytes with natural killer receptors into autologous non-involved skin from psoriatic donors grafted on to beige-SCID mice. This effect of natural killer cells was not dependent upon stimulation with superantigen. In contrast, injection of natural killer cells from seven control nonpsoriatic donors into autologous control skin grafts resulted in the changes of psoriasiform dermatitis, which differed significantly from psoriasis. Psoriasiform dermatitis is a common, nonspecific reaction pattern, which is shared by many conditions as varied as atopic dermatitis and fungal infections. The distinction from true psoriasis is important, because this model has been widely promoted as a model for psoriasis. The principal finding is that skin from psoriatic patients reacts differently in response to natural killer cells. It is proposed that psoriasis results from a cutaneous defect that is triggered by lymphocyte activation.

A primary cutaneous defect in psoriasis was suggested by the athymic nude mouse grafting studies of Krueger *et al* (1981). Involved and noninvolved psoriatic skin was grafted on to nude mice, and compared with grafts of skin from normal donors. Initially, the DNA labeling index of involved psoriatic skin was grossly elevated compared with either uninvolved skin of psoriatic donors, or normal skin from normal donors. After grafting to nude mice, the labeling index of involved psoriatic skin decreased, whereas the labeling index of noninvolved psoriatic skin increased, until they were equivalent, but significantly higher than that of grafted normal skin. This suggests that there is a primary defect in psoriatic skin. As epidermis and dermis interact, it is not possible from these experiments to conclude whether the defect is primary in epidermis or dermis.

The initial finding that natural killer cells can induce psoriasis was made by Nickoloff *et al* (1999, 2000), who reported on a single natural killer line that induced psoriasis-like changes in an allogeneic human skin explant/SCID mouse transfer system. Our

Table II. Histologic features of psoriasis explants

Source of skin	Source of natural killer cells	Granular layer present	Munro's microabscess present	Spongiosis present
Psoriatic	Autologous psoriatic	0/5[a]	3/5[a]	0/5[a]
Psoriatic	Allogeneic normal	4/5	0/5	5/5
Normal	Autologous normal	7/7	0/7	7/7
Normal	Allogeneic normal	7/7	0/7	3/7

[a]$p < 0.05$ in comparison with normal skin, autologous natural killer cells, by χ^2.

Table III. Thickness of suprapapillary plate[a]

Source skin explant	Source of natural killer cells	Thickness suprapapillary plate	(p) by ANOVA
Psoriasis skin	Autologous psoriasis natural killer	17 ± 1 μm	Reference
Psoriasis skin	no natural killer cells injected	33 ± 5 μm	$p < 0.01$
Psoriasis skin	Allogeneic psoriasis natural killer	30 ± 1 μm	$p < 0.001$ by t-test (n = 2)
Psoriasis skin	Allogeneic normal natural killer	31 ± 9 μm	$p < 0.01$
Normal skin	no natural killer cells injected	23 ± 2 μm	$p < 0.001$ by t-test
Normal skin	Allogeneic psoriasis natural killer	29 ± 2 μm	$p < 0.05$
Normal skin	Allogeneic normal natural killer	27 ± 7 μm	$p < 0.05$
Normal skin	Autologous normal natural killer	30 ± 5 μm	$p < 0.01$

[a]For psoriasis skin, n = 5 donors. For normal skin, n = 7 donors.

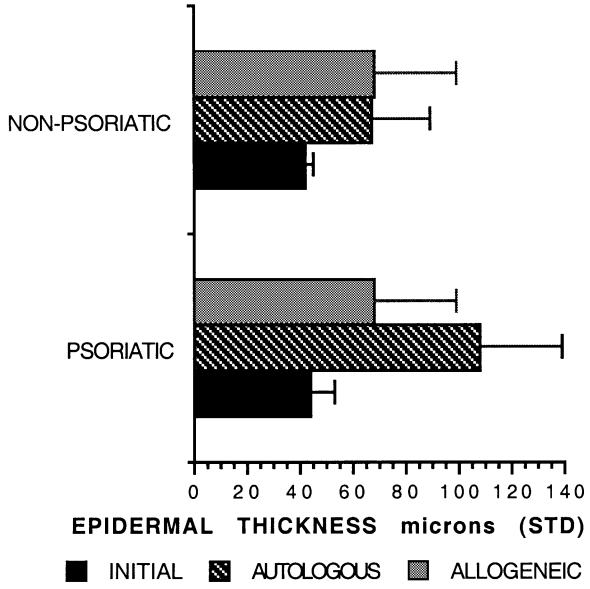

Figure 3. Epidermal thickness of grafts injected with natural killer cells from autologous, or allogeneic donors. Grafts were obtained from both psoriatic, and nonpsoriatic donors.

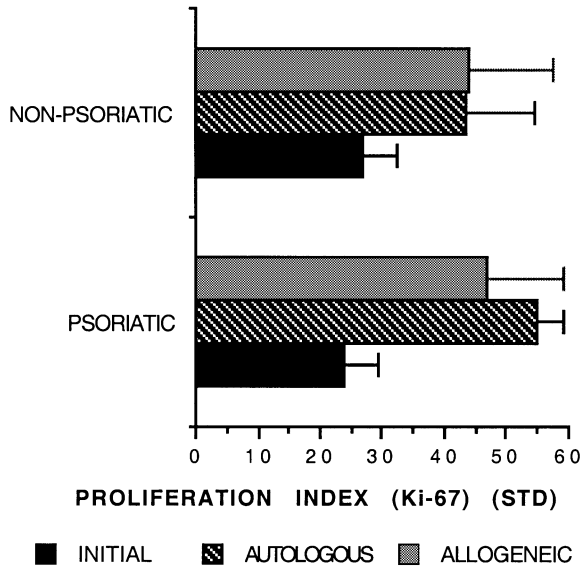

Figure 4. Ki-67 staining index (proliferation marker) of grafts injected with natural killer cells from autologous, or allogeneic donors. Grafts were obtained from both psoriatic, and nonpsoriatic donors.

findings, however, differ from those of Nickoloff *et al*, who reported that natural killer cells induce psoriasis in skin from normal, nonpsoriatic donors. In contrast, we have found that natural killer cells induce psoriasis in nonlesional skin from psoriatic donors, and psoriasiform dermatitis in skin from normal donors. Furthermore, injection of allogeneic natural killer cells from either psoriatic, or normal donors, induced psoriasiform dermatitis. One difference between the experimental systems used is that our mice were beige-SCID, and Nickoloff *et al* used SCID mice. The beige-SCID mice have less natural killer activity. Furthermore, this report demonstrates that bacterial superantigens do not play any unique part in the activation of natural killer cells to induce psoriasis, as we generated natural killer cells with IL-2 alone. We have previously reported that lymphocytes with natural killer activity, activated by the same protocol used for this study, are nonspecifically cytotoxic for keratinocytes, suggesting natural killer recognition of keratinocytes (Kalish, 1989). Our model differs from the Nickoloff model (Nickoloff *et al*, 1999, 2000; Nickoloff, 2000a,b) in that the

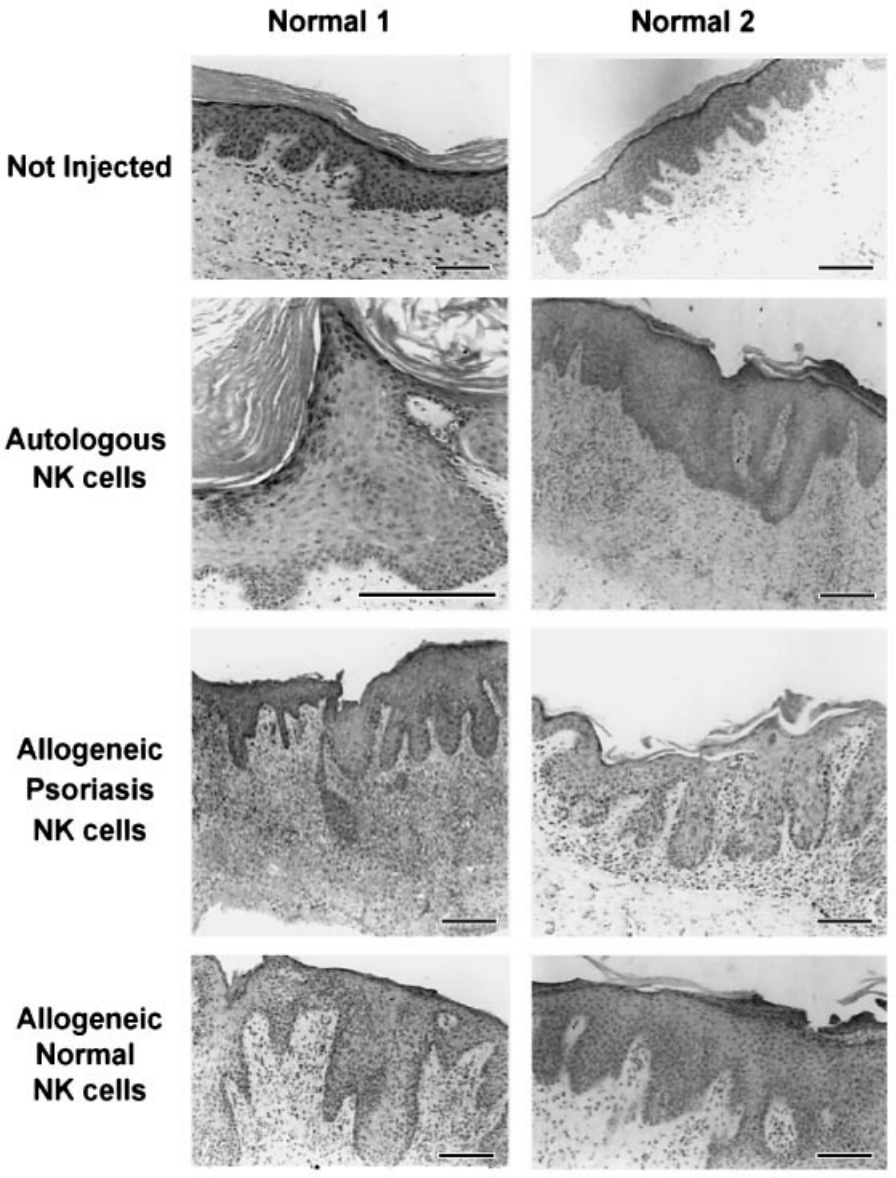

Figure 5. Normal (nonpsoriasis) donor skin grafted to beige-SCID mice and injected with natural killer cells. Results are shown for two donors, not injected, injected with autologous (normal) natural killer cells, allogeneic psoriasis natural killer cells, and allogeneic normal (nonpsoriasis) natural killer cells. *Scale bar*: 50 μm.

lymphocytes with natural killer receptors were generated by IL-2 alone, in the absence of bacterial superantigen. In the absence of superantigen stimulation, cells with natural killer receptors were unable to induce psoriasis in skin from nonpsoriatic donors.

In addition to pure natural killer cells, natural killer receptors are present on subsets of T cells (natural killer T). Natural killer T cells expressing CD161 tend to have T cell receptor expression restricted to Vα16, and recognize the glycolipid, α-galactosylceramide presented by CD1d (Matsuda *et al*, 2000). These $CD161^{+}$ natural killer T cells produce IFN-γ on triggering (Takahashi *et al*, 2000). Keratinocytes in psoriatic skin lesions express high levels of CD1d, and keratinocyte CD1d is capable of inducing natural killer cells to aggregate, and secrete IFN-γ (Bonish *et al*, 2000). Expression of CD1d by psoriatic skin has been confirmed in our study. In contrast, CD1d is expressed at low levels in noninvolved skin. IFN-γ production by natural killer or natural killer T cells may have direct relevance to the induction of psoriasis.

Psoriasis has an association with HLA-Cw6 (Bhalerao and Bowcock, 1998; Brazzelli *et al*, 2000). There are two subclasses of natural killer cell KIR receptors (KIR2D) with specificity for HLA-C. KIR2DL1 recognizes HLA-Cw2, 4, 5, and 6, and KIR2DL2 recognizes HLA-Cw1, 3, 7, and 8 (Winter and Long, 1997; Boyington *et al*, 2000; Fan *et al*, 2000). Both classes of KIR receptor have an inhibitory form with a long cytoplasmic tail (KIR2DL), as well as an activating form with a short cytoplasmic tail (KIR2DS). This raises the possibility that HLA-C associations of psoriasis may be mediated by activating natural killer cell receptors.

IFN-γ may mediate the induction of psoriasis by either natural killer cells, or T lymphocytes (Nickoloff, 2000a). IFN-γ injection induces psoriasis at injection sites (Fierlbeck *et al*, 1990), and both IFN-γ mRNA (Barker *et al*, 1991), and IFN-γ inducible protein 10 are present in psoriatic plaques (Gottlieb *et al*, 1988; Smoller *et al*, 1990). Skin infiltrating T cells produce IFN-γ both following *in vitro* stimulation (Nielsen *et al*, 1998; Austin *et al*, 1999; Brown *et al*, 2000), and when freshly isolated from skin lesions (Szabo *et al*, 1998). Keratinocytes may play a part in promoting IFN-γ production by lymphocytes. Human keratinocytes are capable of secreting IL-18 following activation (Naik *et al*, 1999). IL-12 is present at increased levels in psoriatic lesional skin (Yawalkar *et al*, 1998), and IL-18 synergizes with IL-12 to induce IFN-γ production by T cells (Tominaga *et al*, 2000). Both normal and psoriatic epidermis express IFN-γ receptors, with possibly increased suprabasal expression of IFN-γ receptors in psoriatic skin (van den Oord *et al*, 1995). Furthermore, IFN-γ treatment of human skin explants *in vitro* induces a proliferative epidermal phenotype with expression of K16, similar to the changes of psoriasis (Wei *et al*, 1999). Natural killer cell lines from normal and psoriatic patients, used in this study, produced similar levels of IFN-γ,

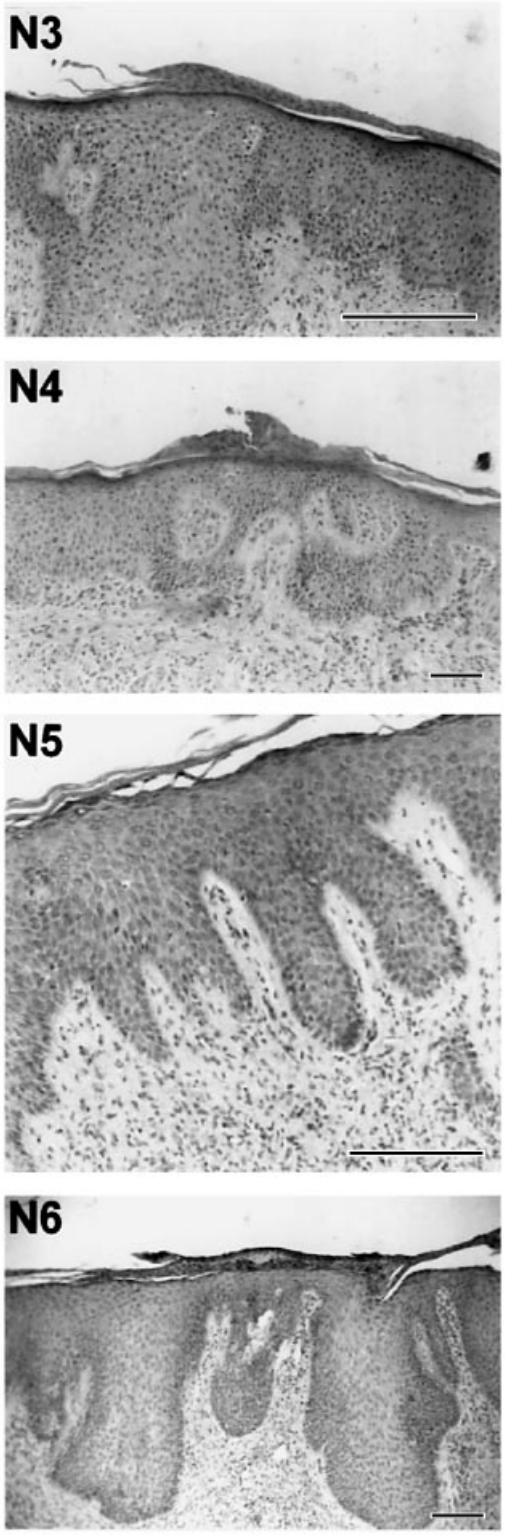

Figure 6. Normal (nonpsoriasis) skin from an additional four donors grafted to beige-SCID mice and injected with autologous normal natural killer cells. *Scale bar*: 50 μm.

suggesting that the tissue response is the critical factor in the generation of psoriasis.

Psoriasiform epidermal changes are seen in many conditions, including the response to dermatophyte infection. Resistance to dermatophyte infection is partially mediated by cellular immunity (Green *et al*, 1983; Calderon and Hay, 1984; MacCarthy *et al*, 1994), but the mechanism has not been delineated. It is possible that increased epidermal proliferation, as seen in psoriasiform epidermal hyperplasia, is a lymphocyte-mediated defense mechanism whereby the epidermis proliferates faster than the dermatophyte can invade, thereby shedding the dermatophyte. Psoriasis may represent an alteration of this normal physiologic response.

Psoriasis induction by lymphocytes with natural killer receptors appears to be dependent upon the source of skin. Natural killer cells from nonpsoriatic control donors induced psoriasiform dermatitis changes rather than true psoriasis. This suggests psoriasis results from a cutaneous defect that is triggered by an autoimmune activation. Superantigen was not necessary for the induction of psoriatic lesions with natural killer cells.

R.S.K. is supported by National Institutes of Health grant 1PO1NS3409201A2. We wish to thank David Colflesh, and the University 1maging Center, SUNY at Stony Brook for expert assistance.

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