Psoriatic Epidermal Cells Demonstrate Increased Numbers and Function of Non-Langerhans Antigen-presenting Cells

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The recent findings that the immunosuppressant cyclosporine A (CsA) improves psoriasis raises the possibility that cellular immune processes play a major role in the pathogenesis of psoriasis. We therefore investigated the phenotype and function of cells within psoriatic epidermis that can play a role in cellular immunologic reactivity. Double fluorescence microscopic studies with monoclonal antibodies of epidermal cells in suspension (EC) and of histologic sections demonstrated that involved psoriatic skin contained a significantly increased number of non-Langerhans cell $T6^-DR^+$ EC ($4.9 + 2.1\%$) relative to uninvolved ($0.3 \pm 0.1\%$), $p < 0.01$. This non-Langerhans cell population was comprised of DR^+ monocytes, DR^+ activated T lymphocytes, a few DR^+RFD1^+ antigen-presenting cells (APC), and DR^+ keratinocytes. Langerhans cell (LC) levels in EC suspension were not different between involved and uninvolved psoriatic epidermis. Functional studies demonstrated that involved psoriatic epidermal cells had an increased capacity to induce T-cell activation and proliferation relative to uninvolved EC ($p < 0.04$). This increased APC activity was due to the non-LC $T6^-DR^+HLe1^+$ APC population and not to DR+ keratinocytes. These results demonstrate that involved psoriatic epidermal cells contain both an increased number and function of antigen-presenting cells. The pathogenetic mechanisms in psoriasis may be related to ongoing cellular immune responses in the skin, and the effect of CsA may be mediated through a suppressive effect on the enhanced antigen-presenting cell activity. *J. Invest Dermatol 92:190–195*

Psoriasis is a genetic disease characterized by inflammation and an increased population of hyperproliferative keratinocytes [1]. Active psoriasis is associated with epidermal and dermal infiltration of activated T lymphocytes [2–5]. Activation of T lymphocytes is dependent on antigen-presenting cells (APC) that express class II major histocompatibility (MHC) molecules, such as HLA-DR. In normal human skin $HLA\text{-}DR^+$ APC are represented by Langerhans cells (LC), which also express the T6 antigen ($T6^+DR^+$) [6].

The mechanism of mononuclear cellular infiltration in psoriatic skin is poorly understood, and the role of such cells in the pathogenesis of psoriasis is not yet clear. The recent finding that the immune suppressant cyclosporine A (CsA) is effective in clearing psoriasis [7] raised the possibility that cellular immune processes may play a role in the pathogenesis of psoriasis. The increased number of activated T lymphocytes seen in psoriatic skin may be due to an increased capacity of certain cell types within lesions of psoriasis to activate T cells. Factors released from activated T cells may be important for stimulation of keratinocyte growth [8,9]. We therefore characterized the nature of APC contained within psoriatic epidermis and investigated whether these cells demonstrate an increased capacity to activate T cells. We found that involved psoriatic epidermal cells (EC), relative to uninvolved psoriatic epidermal cells, contain an increased number of $HLA\text{-}DR^+$ antigen-presenting cells and an increased capacity to induce T-cell activation and proliferation.

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Abbreviations:
APC: antigen presenting cells
CsA: cyclosporine A
EC: epidermal cells
FCS: fetal calf serum
LC: Langerhans cells
MHC: major histocompatibility
MNC: mononuclear cells
PBS: phosphate-buffered saline
PMN: polymorphonuclear leukocytes

MATERIALS AND METHODS

Patients Patients with severe, chronic, large plaque-type psoriasis vulgaris participated in the study. Informed consent using a protocol approved by the University of Michigan Human Experimentation Committee was obtained from each individual. Patients were at least 18 years of age, had psoriasis stable in extent and severity for at least two weeks, and had not used systemic, intralesional, or ultraviolet therapy for at least four weeks, or topical therapy except for bland emollients for at least two weeks before the study. Using 1% lidocaine local anesthesia, 6-mm punch biopsy specimens from clinically uninvolved and involved areas were obtained for histology and epidermal cell suspensions.

Preparation of Epidermal Sheets Skin biopsies were placed in 1 molar NaCl for 72 h at 4°C. The NaCl solution was changed every 24 h. After incubation the epidermis was separated from the dermis using fine forceps [10].

Preparation of Cell Suspensions The biopsies were incubated in Dulbecco's phosphate-buffered saline (PBS) containing 0.25% trypsin for 18 h at 4°C. Epidermal sheets were removed from the dermis and transferred to 0.05% DNAse in Dulbecco's PBS, teased

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into a cell suspension, and filtered through a nylon mesh to achieve a single cell suspension as previously described [11]. Fetal calf serum (FCS) was added to inactivate the trypsin and the cells were washed three times in RPMI 1640 containing 10% FCS, 1% penicillin and streptomycin, and 1% glutamine. After washing, the cells were resuspended in RPMI 1640. Cell counts and viability were monitored by trypan blue exclusion in a hemocytometer.

Cell Surface Staining of Epidermal Cells in Suspension Cell suspensions were double stained simultaneously with fluorescein conjugated OKT6 (Orthodiagnostic System, Raritan, NJ) or fluorescein conjugated HLe1 (Becton Dickinson Monoclonal Center, Mountainview, CA) and biotin conjugated HLA-DR (Becton Dickinson Monoclonal Center) antibodies for 45 min at 4°C. Cells were washed three times in Dulbecco's PBS containing 1% Bovine Serum Albumin and 0.01% NaN3. A second incubation was done with streptavidin Texas Red (BRL/Gibco, Bethesda, MD). A Nikon fluorescence microscope with appropriate filters was used for scoring. Results are expressed in mean percent ± SEM of viable positive stained cells compared with total cell count.

Staining of Histologic Sections for In Situ Immunophenotyping Punch biopsies were imbedded in Tissue Tek II O.C.T. compound (Miles Laboratories, Inc. Naperville, IL) and frozen and stored at −70°C. Six-micron sections were cut on a cryostat and air dried. The section was first incubated with the monoclonal antibody for 45 min, followed by three 5-min washes. Second-step staining for 30 min was performed using goat antimouse IgG, heavy and light chain specific, affinity purified, human serum absorbed, and fluorescein conjugated (Kirkegaard and Perry, Gaithersburg, MD). Double staining for simultaneous detection of two separate cell surface antigens was accomplished using a two-step method (one fluorescein conjugated and one biotin-conjugated primary antibody in the first step and Texas Red-conjugated to streptavidin in the second step) or a three-step method [the primary antibody (first step) is visualized with rhodamine-conjugated goat antimouse IgG [second step], followed by a third step using fluoresceinated antibody mixed with normal mouse serum (to block binding of the rhodamine goat antimouse IgG antibody to the third step antibody)].

Monoclonal Antibodies for Phenotypical Characterization OKT6 and anti-Leu6 are monoclonal antibodies directed against an epitope on the CD1 determinant on Langerhans cells and immature thymocytes. Anti-HLA-DR is a monoclonal antibody directed against an epitope on the HLA-DR human class II MHC antigen. Anti-HLe1 is a monoclonal antibody that reacts with an antigen expressed on all bone-marrow derived leukocytes.

Anti-Leu1 (Becton Dickonson) binds the CD5 determinant expressed on all T cells. Anti-Mono1 (BRL/Gibco) is an antibody that detects the majority of blood monocytes and detects the most reproducibly expressed macrophage antigen in human skin diseases (12). RFD1 (kindly donated by Dr. Len Poulter, Royal Free Hospital, London, UK) binds to interdigitating dendritic antigen-presenting cells of peripheral lymph nodes and thymus [13,14].

Functional Assessment of Antigen Presentation Allogeneic peripheral blood mononuclear cells (MNC) were isolated from heparinized venous blood by Ficoll-Hypaque density gradient centrifugation. In vitro allogeneic epidermal cell lymphocyte reactions were performed in round bottom microtitre wells in 0.2 ml RPMI 1640 supplemented with 10% AB serum, 1% glutamine, and 1% penicillin and streptomycin. Gamma-irradiated (2000 RAD) EC were added in varying numbers to 50,000 responder MNC. The cultures were pulsed after 6 d with 1 microcurie of 3H-TdR per well, harvested 18 h later on a PHDTM cell harvester (Cambridge Technology Inc., Cambridge MA), and 3H-TdR incorporation was measured on a Packard scintillation counter (Packard Instrument Co., Downers Grove, IL). Results are expressed as mean ± SEM of triplicate wells.

Depletion of Leukocytes Contained Within Epidermal Cells Complement lysis of leukocytes contained within EC was performed following reaction of EC with either anti-Leu6, or anti-HLA-DR alone, or in combination. The cells were then incubated with rabbit complement (Cedarlane, Ontario, Canada) for 45 min at 37°C in a shaking water bath, washed, and resuspended in RPMI 1640 containing 10% AB serum. In some experiments depletion of HLe1+ and DR+ epidermal cells was performed using magnetic beads. Cells were first incubated with anti-HLe1 (Becton Dickinson) or anti-HLA-DR (Becton Dickinson), and then mixed with magnetic beads coated with antimouse IgG (Dynal Inc., Fort Lee, NJ). After 30 min incubation at 4°C on a rotating rack, cells bound to beads were clumped by exposure to a magnet, and the purified (nonbound) subset isolated by removing the cells remaining in suspension.

Statistical Evaluation For statistical evaluation of the phenotypic data, Wilcoxon's rank sum test for paired comparison was used. A sign test was used for comparing the paired median peak values from the functional data. For comparison of data from normal controls with data from psoriatic patients, Fischer's exact test for unpaired data was used.

RESULTS

Epidermal Sheet Preparations Because of the convoluted architecture of psoriatic epidermis, experiments were performed to determine the optimal method for obtaining epidermal sheets free of dermal contamination. NaBr, NaCl, EDTA, and trypsin were utilized. Among these, only NaCl and trypsin treatments resulted in reproducible epidermal sheet preparations free of dermis. Contamination of the sheets with papillary dermal elements was monitored using fluoresceinated antihuman factor VIII-related antigen to detect endothelial cells, and fluoresceinated anti-HLe1 to detect collections of papillary dermal infiltrating leukocytes. Epidermal sheets free of such dermal elements were obtained only from punch biopsies and not from keratome biopsies.

Epidermal sheets obtained by NaCl were stained as whole mounts to quantitate $T6^+$ and DR^+ cells in the horizontal plane. Although immunocytes in the epidermis overlying papillary tips could be assessed, the extreme thickness of psoriatic epidermal rete pegs precluded quantitation of immunocytes in these areas. For this reason, reliable results could not be obtained from whole mounts of psoriatic epidermal sheets from involved plaques. Thus, quantitations were performed using epidermal cells in suspension after trypsinization of such biopsies.

Involved Psoriatic Epidermis Contains Increased Numbers of $T6^-DR^+$ Epidermal Cells in Suspension No difference was observed in the number of $T6^+DR^+$ epidermal Langerhans cells (LC) between uninvolved (0.8 ± 0.2%) and involved (0.9 ± 0.3%) psoriatic epidermis in suspension (Fig 1). In contrast, clinically in-

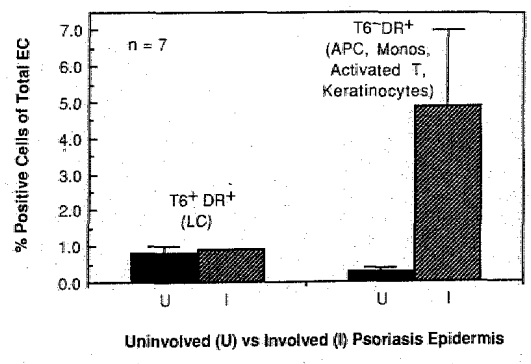


Figure 1. Percentage of $T6^+DR^+$ Langerhans cells and $T6^-DR^+$ epidermal cells in uninvolved *(U)* and *(I)* psoriasis skin. Results are expressed as percentage of total epidermal cells ± SEM.

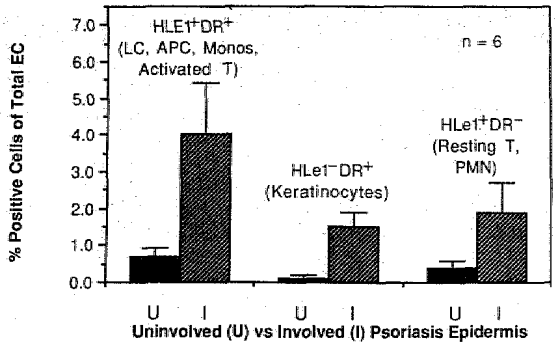


Figure 2. Percentage of HLe1$^+$DR$^+$, HLe1$^-$DR$^+$, and HLe1$^+$DR$^-$ epidermal cells in uninvolved *(U)* and involved *(I)* psoriasis skin. Results are expressed as percentage of total epidermal cells ± SEM.

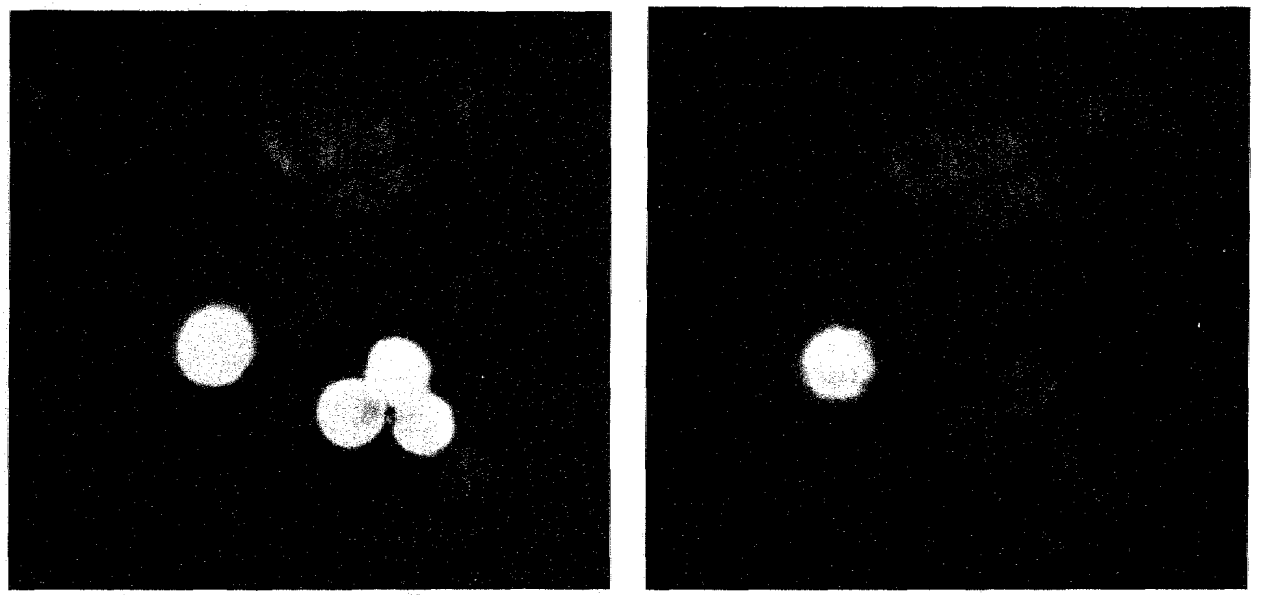
volved psoriatic epidermis contained a large number of T6$^-$DR$^+$ EC (4.9 ± 2.1%) relative to uninvolved psoriatic epidermis (0.3 ± 0.1%, $p < 0.05$) (Fig 1). Interestingly in five of seven patients with psoriasis, uninvolved skin also contained T6$^-$DR$^+$ EC (Fig 1). In contrast, no T6$^-$DR$^+$ EC were detected in the skin of 20 normal volunteers ($p < 0.0003$). Further characterization of the T6$^+$DR$^+$ and T6$^-$DR$^+$ EC populations was performed using double fluorescence microscopy to detect HLe1 and HLA-DR antigen-bearing cells.

Involved Psoriatic EC Suspensions Contain Increased Numbers of DR$^+$ and DR$^-$ Leukocytes as Well as DR$^+$ Keratinocytes Involved psoriatic epidermis contained a significant number of HLe1$^+$DR$^+$ EC (4.0 ± 1.4%) relative to uninvolved skin (0.7 ± 0.2%, $p < 0.05$; Fig 2). In other words, increased numbers of bone-marrow derived leukocytes expressing DR were found in involved psoriatic epidermis. Relative to uninvolved skin (0.1 ± 0.1%) involved psoriatic skin (1.5 ± 0.9) also contained an increased number of HLe1$^-$DR$^+$ EC; that is, DR$^+$ keratinocytes (Fig 2). HLe1$^+$DR$^-$ EC were also significantly increased in involved psoriatic skin (1.9 ± 0.8%) compared to uninvolved (0.4 ± 0.2%, $p < 0.05$; Fig 2). The DR$^+$ epidermal cells from involved psoriatic epidermis can be seen in Fig 3*a*. Figure 3*b* shows the same microscopic field and demonstrates the HLe1$^+$ leukocytes. Thus the three central cells on Fig 3*a* are HLe1$^-$DR$^+$ keratinocytes and the single double-stained cell on Fig 3*a,b* is an HLe1$^+$DR$^+$ leukocyte.

T6$^-$DR$^+$ and HLe1$^+$DR$^+$ EC in Involved Psoriatic Epidermis Contain Both T Cells and Monocytes as Assessed by Fluorescence Microscopy of Vertical Sections of Skin Fluorescence microscopy was performed on vertical sections of involved psoriatic skin 1) to obviate trypsin sensitivity of certain antibody defined determinants, and 2) to assess a larger number of antibodies than is possible using the limited numbers of EC obtainable in suspension from biopsies. In histologic sections using double immunofluorescence microscopy T6$^+$DR$^+$ LC were observed in the suprapapillary plane (Table I*A*). T6$^-$DR$^+$ EC were found throughout the epidermis and were comprised of two distinct subpopulations: 1) HLe1$^+$DR$^+$ leukocytes and 2) HLe1$^-$DR$^+$ keratinocytes (Table I*B*). The HLe1$^+$DR$^+$ population was heterogeneous and consisted of Leu1$^+$DR$^+$ activated T cells, RFD1$^+$DR$^+$ antigen-presenting cells, and MONO1$^+$DR$^+$ monocytes (Table I*C*). Although B cells express DR antigens, no B cells were detected by anti-B1 and anti-human immunoglobulin. The HLe1$^+$DR$^-$ leukocytes were comprised of non-activated T cells and polymorphonuclear leukocytes (PMN)

Table I. Phenotype of Inflammatory Cells in Involved Psoriatic Epidermis

A.	T6$^+$DR$^+$ EC	Langerhans cells
B.	T6$^-$DR$^+$ EC	HLe1$^+$DR$^+$ leukocytes
		HLe1$^-$DR$^+$ keratinocytes
C.	HLe1$^+$DR$^+$ EC	Leu1$^+$DR$^+$ T cells
		RFD1$^+$DR$^+$ APC
		MONO1$^+$DR$^+$ monocytes
D.	HLe1$^+$DR$^-$ EC	Non activated T cells
		Polymorphonuclear leukocytes



A B

Figure 3. Involved psoriasis epidermal cells double stained simultaneously with fluorescein-conjugated anti-HLe1 and biotin-conjugated anti-HLA-DR. Anti-HLA-DR was visualized using Texas red conjugated to streptavidin. *a* demonstrates epidermal cells staining with anti-HLA-DR. *b* shows the same field and demonstrates epidermal cells that stain with anti-HLe1. Note that one of the cells is double stained (HLe1$^+$DR$^+$ leucocyte), whereas three of the cells stain only with anti-HLA$^-$DR (HLe1$^-$DR$^+$ keratinocyte).

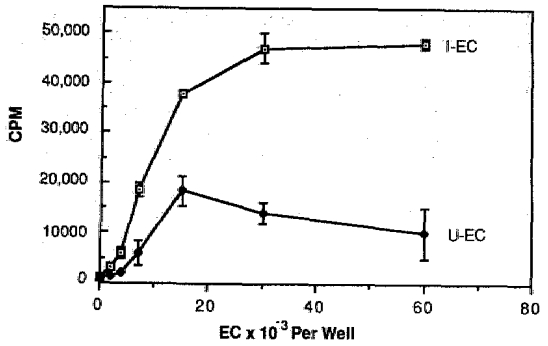


Figure 4. Stimulation of 50,000 allogenic mononuclear cells by varying numbers of uninvolved *(U)* and involved *(I)* psoriasis epidermal cells. Data are expressed as mean ± SEM cpm of triplicate wells from a representative experiment.

as well (Table I*D*). PMN were observed to be present in the epidermis by hematoxylin and eosin staining of vertical sections.

Involved Psoriatic Skin Demonstrates Increased Alloantigen-Presentation Capacity to T Cells Because cellular expression of HLA-DR antigens is associated with antigen-presentation function, we next determined whether the increased level of DR$^+$ cells within involved EC was associated with altered antigen-presentation function of the epidermis. EC in suspension from uninvolved and involved psoriatic skin were incubated with allogeneic mononuclear cells and the resultant T-cell proliferation in response to DR$^+$ antigen-presenting cells was assessed.

Both uninvolved and involved psoriatic epidermal cells could stimulate alloreactive T cells. However, involved psoriatic EC showed an increased capacity to induce activation and proliferation of T cells relative to uninvolved EC (Fig 4). In eight out of nine patients tested, increased alloantigen-presenting capacity of involved psoriatic EC relative to uninvolved was observed. The median peak value of proliferation of T cells stimulated by involved psoriatic EC was 46,903 CPM (range 8,828–77,382) compared to 19,100 cpm (range 2,882–67,326) by uninvolved EC ($p < 0.04$, by sign test for paired data).

The Increased Capacity of Involved Psoriatic Epidermal Cells to Activate T Cells is Dependent on T6$^-$DR$^+$ non-LC APC We next determined whether the increased capacity of involved psoriatic epidermal cells to stimulate T cells was due to the LC population or to the population of T6$^-$DR$^+$ non-LC APC. In uninvolved skin, depletion of either T6$^+$ EC or DR$^+$ EC resulted in comparable levels of depletion of APC activity (data not shown). However, when such cells were depleted from the involved skin from the same individual, a disparity in APC activities was apparent. Complement lysis of T6$^+$ LC of involved EC did not significantly alter the stimulatory capacity of involved EC (Fig 4). This was not due to incomplete lysis of LC because no T6$^+$DR$^+$ EC was detected following complement lysis with Leu 6 (Table II). In contrast, complement lysis of DR$^+$ EC that contained both T6$^-$DR$^+$ EC and T6$^+$ DR$^+$ LC resulted in a significant decrease in antigen-presentation capacity of involved EC. Depletion of both T6$^+$ and DR$^+$ cells did not further decrease the epidermal antigen-presentation capacity over that of DR$^+$ cell removal alone (Fig 5). We then determined

Table II. The Number of T6$^+$DR$^+$ and T6$^-$DR$^+$ Epidermal Cells Before (A) and Following (B) Lysis with Leu6 and Complement

	T6$^+$DR$^+$	T6$^-$DR$^+$
A	1.4%	1.4%
B	0%	1.1%

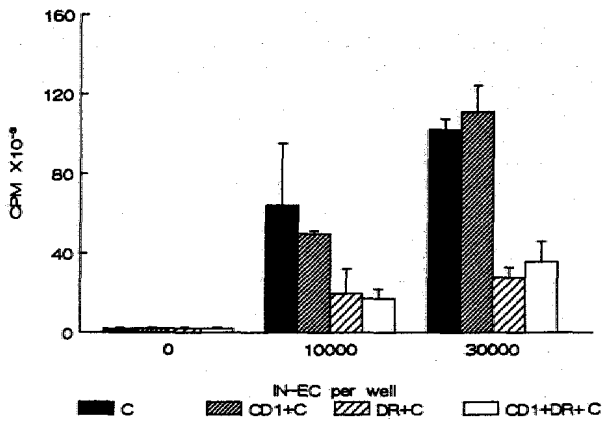


Figure 5. Stimulation of 50,000 allogeneic mononuclear cells by varying numbers of involved psoriatic epidermal cells treated with 1) complement *(C)*, 2) anti-Leu6 and complement *(CD1+C)*, 3) anti-HLA-DR and complement *(DR+C)*, and 4) anti-Leu6, anti-HLA-DR and complement *(CD1+DR+C)*.

whether APC activity in the T6$^-$DR$^+$ EC population was due to DR$^+$ leukocytes or DR$^+$ keratinocytes. Depletion of HLe1$^+$ leukocytes resulted in almost complete abrogation of the APC activity (Fig 6); thus, the remaining DR$^+$ keratinocytes did not appear to participate in the APC activity. Removal of all DR$^+$ EC resulted in a comparable level of decreased antigen-presenting cell activity (Fig 6). Thus, the increased antigen-presentation capacity seems to be due to HLe1$^+$DR$^+$ leukocytes and not HLe1$^-$DR$^+$ keratinocytes.

DISCUSSION

Allogeneic and autologous T-cell activation is dependent on antigen-presenting cells that express MHC Class II molecules such as HLA-DR. The capacity to activate autologous T cells in the absence of exogenous antigens is confined to a minor population of the APC. In contrast, most APC are capable of activating alloreactive T cells; therefore, allogeneic T-cell activation reflects best the total antigen-presentation capacity of EC. Thus, to determine the antigen-presentation capacity of psoriatic skin, epidermal cells from involved and uninvolved psoriatic skin were used to stimulate alloreactive T lymphocytes. Involved psoriatic skin demonstrated an

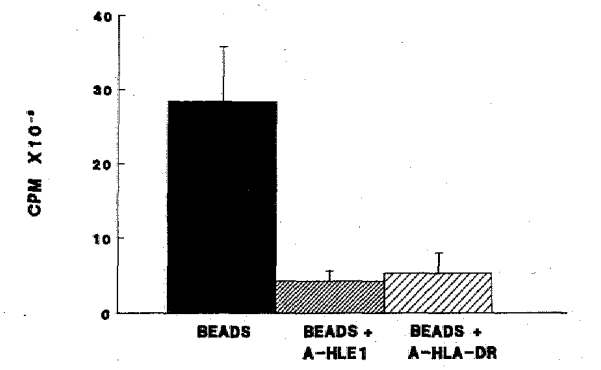


Figure 6. Stimulation of 50,000 allogeneic mononuclear cells by varying numbers of involved psoriatic epidermal cells which have been treated with 1) magnetic beads alone *(beads)*, 2) anti-HLe-1 and magnetic beads *(beads + A-HLe1)*, 3) anti-HLA-DR and magnetic beads *(beads + A-HLA-DR)*. Data are expressed as mean ± SEM cpm of triplicate wells.

enhanced capacity to activate and induce proliferation of allogeneic T lymphocytes. The heightened immune reactivity of psoriatic epidermis may provide a basis for the mechanism by which CsA exerts its beneficial effect in psoriasis.

We have utilized EC in suspension to quantitate the number of $T6^+DR^+$ LC relative to the total EC population. This method best represents the relative proportion of these cells to keratinocytes and correlates well with functional activity of APC [11]. Assessment of the density of LC en face in epidermal sheets is also an excellent quantitative method; however, in agreement with others [15], we found that this approach was not feasible in involved psoriatic skin. In vertical sections of skin, quantitative estimation of LC is problematic in normal skin [16], and in psoriatic skin the results are dependent upon the denominator used (i.e., linear scale, length of basement membrane, or number of basal cells, area, total number of nuclei, etc.). This study supports the findings of Czernielewski [17], who found similar numbers of LC in uninvolved and involved psoriatic skin. In comparing uninvolved and involved psoriatic epidermal sheets with epidermal sheets from healthy normal volunteeers, others have found decreased, and in one study unchanged, numbers of LC [18–20].

Our findings of T cells within involved psoriatic epidermis are in agreement with reports from Baker et al [2–5], but in contrast to Gottlieb et al [21], who found no epidermal reactivity with anti-CD3 (T cells), B1 (B cells), and −63D3 (monocytes). Because we found both DR^+ T cells and DR^+ monocytes, this difference may be due to the use of different antibodies. In agreement with Gottlieb we found no epidermal reactivity with anti-B1.

Depletion of both $T6^+DR^+$ LC and $T6^-DR^+$ EC but not $T6^+DR^+$ LC alone from involved EC resulted in a significantly reduced capacity to activate T cells. This, taken together with our finding that the Langerhans cell levels were not different between involved and uninvolved psoriatic EC, indicates that the increased APC activity of involved EC is due to the non-LC $T6^-DR^+$ EC population. This non-LC population was comprised of DR^+ monocytes, DR^+ T lymphocytes, a few $RFD1^+$ APC's (interdigitating reticulum cells of spleen and lymph nodes), and DR^+ keratinocytes. Blood monocytes and interdigitating reticulum cells ($RFD1^+$) present antigen and strongly support primary alloreactive T-cell proliferation (19–22); in contrast, DR^+ keratinocytes either do not stimulate or are only weak stimulators in this system [23,24]. Among the $T6^-DR^+$ EC, only $HLe1^+DR^+$ antigen-presenting leukocytes and not DR^+ keratinocytes contributed significantly to allogeneic T-cell activation. It is therefore likely that the increased number of monocytes and $RFD1^+$ cells present within psoriatic epidermis are responsible for the increased capacity of involved psoriatic epidermis to activate T cells. The $T6^-DR^+$ EC in psoriasis differ from $T6^-DR^+$ EC that appear following UV exposure in that they are more heterogeneous. Analogies exist, however, in both the phenotype and function of UV-induced $T6^-DR^+$ EC and psoriasis $T6^-DR^+$ EC. Both appear to contain $OKM5^+$ $T6^-DR^+$ EC (data not shown) and both UV-exposed EC and psoriatic EC potently activate autologous immunoregulatory T cells [25–27]. Such autoreactive T cells are thought to be important for the regulation of immune responses and, in particular, autoimmune responses [28–32].

Staining with anti-HLe1 and anti-HLA-DR confirmed that DR^+ keratinocytes are present in involved psoriatic epidermis [21–31]. Although unable to initiate T-cell activation or to process antigens, DR^+ keratinocytes may support proliferation of previously antigen-primed T cells under certain circumstances. DR^+ keratinocytes require protease-digested antigen fragments in order to present antigens to primed T cells (A. Gaspari, M.D., Bethesda, MD, personal communication). Elevated protease activity is found in psoriatic skin and may provide protease activity for digestion of the putative antigen [34]. Keratinocyte expression of HLA-DR is likely related to release of gamma-interferon in the microenvironment of activated lymphokine releasing T cells adjacent to basal keratinocytes [21,35]. In addition to gamma interferon [36], activated T cells also release lymphokines such as IL-2 [37], IL-3 [38–39], IL-4 [40], and GM-CSF [41]. Some of these lymphokines may be growth promoting in psoriasis, and are likely to at least play a role in monocyte/macrophage activation. Activated cells of the monocyte/macrophage series release eicosanoids and IL-1 [42–43], both of which may act to promote keratinocyte proliferation [44–46]. Epidermal cells from the skin of normal volunteers do not contain $T6^-DR^+$ cells. In contrast, 5/7 patients with psoriasis had $T6^-DR^+$ cells in uninvolved psoriatic epidermis. This clearly shows that clinically uninvolved as well as involved psoriatic skin participates in an ongoing immunologic process.

In conclusion, these studies provide support for the hypothesis that psoriatic epidermal cells contain an increased number of antigen-presenting cells that are capable of promoting a heightened level of T-cell activation either as an autoimmune response or in response to an as yet unknown antigen to T cells. Cytokine release from such cells may thereby result in T-cell activation and lymphokine release. Antigen-presenting cell-induced lymphokine release may result in direct effects on keratinocyte growth or indirect growth effects mediated through monocyte macrophage activation and monokine release.

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