American Journal of Pathology, Vol. 135, No. 6, December 1989

Keratinocyte Intercellular Adhesion Molecule-1 (ICAM-1) Expression Precedes Dermal T Lymphocytic Infiltration in Allergic Contact Dermatitis (*Rhus dermatitis*)

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The ability of small molecules such as urushiol, present as a wax on the poison ivy leaf surface, to cause allergic contact dermatitis (rhus dermatitis) has fascinated immunologists for decades. Current dogma suggests that these epicutaneously applied catechol-containing molecules serve as haptens to conjugate with larger proteins via reactive o-quinone intermediates. These complexes are then recognized as foreign antigens by the immune system and elicit a hypersensitivity reaction. Phorbol ester can directly induce cultured keratinocyte (KC) intercellular adhesion molecule-1 (ICAM-1) expression via a protein kinase C (PK-C)-dependent mechanism. As urushiol is also a known PK-C agonist, we asked if topical application of a poison ivy/oak mixture could directly induce epidermal KC ICAM-1 expression. During the pre-erythematous phase of this reaction (4 to 20 hours), epidermal KCs expressed ICAM-1; this "initiation phase" preceded the appearance of activated memory T lymphocytes in the papillary dermis, and thus appeared to be nonlymphokine mediated. A near-contiguous cellular-adhesion molecular network was identified by ICAM-1 staining of basal KCs, dermal dendrocytes, and endothelial cells. During the second 24-hour period with the onset of erythema and edema, there was an "amplification phase" of more intense KC ICAM-1 expression coupled with relatively weak KC HLA-DR expression that coincided with dermal and epidermal T-cell infiltration. This suggests the presence of lymphokines, such as gamma interferon, during the amplification phase because of KC HLA-DR expression. On cultured KCs, urushiol directly induced ICAM-1 expression but not HLA-DR. Thus, in addition to functioning as an antigenic hapten, urushiol directly induces KC ICAM-1 expression. The KC ICAM-1 expression may then alter the dynamic trafficking of memory T cells in the epidermis, so as to initiate cutaneous inflammation in a nonantigen specific manner. This initiation phase is followed by T-cell infiltration and consequent lymphokine production that significantly amplifies the original stimulus. Thus much can still be learned about the molecular pathophysiology of this common type of cutaneous inflammation. (Am J Pathol 1989, 135:1045–1053)

While it is generally acknowledged that the cellular elements necessary to induce and regulate allergic contact dermatitis (ACD) reside within the skin, the majority of research has focused primarily on the Langerhans cell and T lymphocyte, with minimal regard for the keratinocytes (KCs).[1] Conventional dogma regarding the pathophysiology of ACD[2] emphasizes the formation of a hapten-carrier complex between the epicutaneously applied low-molecular-weight molecules such as pentadecyl catechol (PDC) and urushiol, representing the antigens in poison ivy/rhus dermatitis and unidentified high-molecular-weight structural proteins of the skin. Previous biochemical investigations of the catechol-containing molecules such as urushiol and PDC have focused on the ability of their respective o-quinone intermediates to covalently crosslink to larger proteins.[3] These complexes are then processed by antigen-presenting cells (Langerhans cells) to stimulate T cells in the dermis and draining lymph nodes. Based on several approaches using both *in vitro* and *in vivo* models,

Portions of this work were supported in part by the British Association of Dermatologists Dowling Traveling Fellowship (CEMG) and NIH grants AR35897, AR01823, and AR40065 (BJN).

Accepted for publication July 28, 1989.

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we have recently suggested that KCs, via their expression of intercellular adhesion molecule-1 (ICAM-1), can actively and directly participate in the epidermal trafficking of T lymphocytes.[4] While normal KCs *in vitro* and *in vivo* rarely express ICAM-1, there is rapid and intense ICAM-1 expression[5] after exposure to lymphokines such as gamma interferon (IFN-γ). The KC ICAM-1 expression facilitates binding of lymphocyte function associated antigen-1 (LFA-1)-expressing T cells and monocytes.[4] Furthermore, the spatial colocalization between intraepidermal T cells and KC ICAM-1 expression in a wide variety of skin diseases strongly implies that the cellular trafficking in the epidermis is mediated by a final common molecular pathway involving LFA-1/ICAM-1 interaction.[6]

The provocative finding that served as the basis for this study was that phorbol ester could induce cultured KCs to express ICAM-1, indicating a mechanism that was mediated via protein kinase-C (PK-C) signal transduction.[7] Because urushiol, the active ingredient in poison ivy extract responsible for rhus dermatitis, has been shown to activate PK-C in another system,[8] we asked if urushiol could induce KC ICAM-1 expression that was not initially dependent on IFN-γ production by activated T cells. Could we detect *in vivo* primary nonlymphokine-mediated epidermal KC ICAM-1 expression before dermal infiltration by T cells? The notion that urushiol can initiate primary inflammatory reactions in the skin is supported by the previous clinical observation by Epstein,[9] who demonstrated that 100% of 102 infants and children between the ages of 1 month and 8 years, who were presumably nonsensitized, developed inflammatory skin reactions to topically applied urushiol.

Materials and Methods

Patients

Five volunteers (four men, one woman; age range, 33 to 42 years) with a positive history for poison ivy dermatitis, who were otherwise in good health and taking no medication, were selected for study after obtaining informed consent with the approval of the University of Michigan Human Subjects Committee.

In Vivo *Methods*

A poison ivy/oak mix 1:50 (w:v) in alcohol (Hollister Stier, Elkhart, IN) was applied with a glass applicator rod to six sites (5 mm diameter, 5 cm apart) on the flexor forearm of each volunteer. The patch test sites were left open and examined at regular intervals until a strong positive reaction was observed. Clinical readings of the patch test sites were graded from 0 to 3: 0, no reaction; 1, erythema; 2, erythema and edema; and 3, erythema, edema, and vesiculation.

Table 1.

Antibody	Specificity	Source
RR-1/1	ICAM-1	Dr. T. Springer, Dana Farber Cancer Institute, Boston, MA
L243	HLA-DR	Becton-Dickinson, Mountainview, CA
Leu2a	CD8	Becton Dickinson
T4	CD4	Coulter Immunology, Hialeah, FL
T11	CD3	Coulter Immunology
UCHL-1		Dako-Patts, Denmark
TS1.18	LFA-1β	Dr. C. Clayberger, Stanford University, CA
TS2.9	LFA-3	Dr. C. Clayberger
2H4	CD45R	Coulter Immunology

Sequential 3-mm punch, skin biopsies were taken under local anesthesia at each examination of the patch test sites, including those before the development of erythema when the skin surface still appeared normal and the first positive patch-test reaction with erythema, and subsequently from the most positive patch-test reaction site from that individual.

The skin biopsies were orientated and mounted on gum tragacanth (Sigma Chemical Co., St. Louis, MO), snap frozen in isopentane chilled in liquid nitrogen, and then stored at −70 C until use. Sections measuring 5μ were cut on a cryostat (Reichart Histostat, Cambridge Instruments, Buffalo, NY) and then stained with a panel of monoclonal antibodies (Table 1) using an immunoperoxidase technique as previously described,[6] with 3-amino 9-ethylcarbazole (AEC) as the chromogen and counterstained with 1% hematoxylin. Stained sections were assessed by light microscopy.

In two patients, punch biopsies of actively inflamed reaction sites on days 3 and 4, as well as peripheral blood mononuclear cells, were examined for T-cell antigen-receptor gene rearrangements as previously described.[10]

In Vitro *Method*

Keratinocyte Culture

Normal human skin obtained from patients undergoing cosmetic surgery were processed as previously described.[5] Small, round, viable cells were seeded onto and grown in either 35-mm plastic petri dishes (Corning Glass Works, Corning, NY) or Lab-Tek chamber slides (Miles

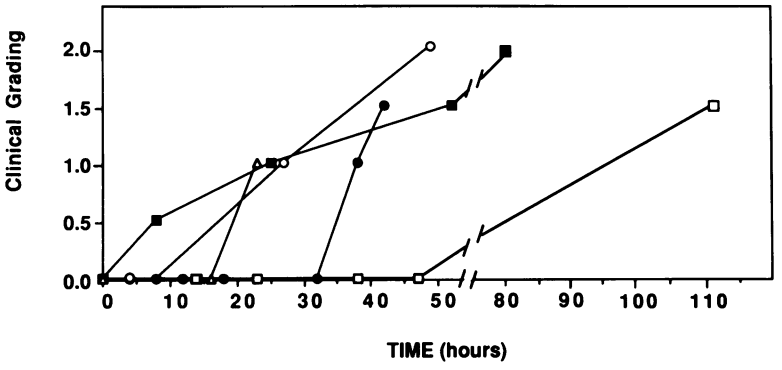


Figure 1. *Time course of clinical features of ACD in five different patients evaluated on a 0- to 3-scale for the presence of erythema, edema, and vesiculation.*

Scientific, Naperville, IL). KCs were grown in a serum-free KC growth medium containing low calcium (KGM, Clonetics, Co., San Diego, CA), maintained in a humidified incubator in 5% CO_2/95% air at 37 C, and used after passage 3.

Highly purified urushiol and pentadecyl catechol (Dr. C. Anderson, Division of Bacterial Products, F.D.A., Bethesda, MD), with or without the calcium ionophore A23187 (Sigma Chemical Co., St. Louis, MO), were added to subconfluent KC monolayers in either Lab-Tek chamber slides or petri dishes, and incubation continued for 2 to 3 days at 37 C. At the end of the requisite incubation period, Lab-Tek chamber slides were fixed in acetone at 4 C and stained with monoclonal antibodies to either ICAM-1 (RR1/1) or HLA-DR (L243) using the immunoperoxidase technique previously described.[6]

KC monolayers in petri dishes were trypsinized using 0.03% trypsin/0.01% EDTA, incubated on ice with 10 μg/ml of monoclonal antibody to either ICAM-1, HLA-DR, with CD8 being used as an IgG isotype control (Table 1). KCs were washed and then stained with 1 μg of fluorescein isothiocyanate-conjugated goat anti-mouse IgG (Tago Inc., Burlingame, CA). The staining intensity and numbers of cells stained were determined using fluorescence-activated cell sorting (EPICS 541, Coulter Co, Hialeah, FL).

Results

KC ICAM-I Expression Preceeds Dermal T-Cell Infiltration

After topical application of the poison ivy/oak mixture, the clinical response comprised erythema and edema without significant epidermal vesiculation. The time course of these clinical parameters is portrayed in Figure 1. It should be noted that there was considerable variability among the patients in the onset and extent of the clinical response. In all patients the biopsies of the earliest pre-erythematous skin stained for ICAM-1 expression revealed focal and solitary basal KC expression involving exclusively the portion of the epidermis between rete pegs in close proximity to the superficial vascular plexus (Figure 2). In between the ICAM-1-expressing basal KC, and the strongly ICAM-1-staining endothelial cells was a relatively constant cell type representing the dermal dendrocyte (Figure 2, arrow), which appeared to cap the top of the papillary dermal capillary loop (Figure 2 and inset). This strategically located dermal dendrocyte had a characteristic elongated nucleus, an undulating nuclear membrane,[11] and ample cytoplasm containing weak reactivity for ICAM-1. The dermal dendrocyte stained positively for Leu M3 (Figure 2, inset) as well as for HLA-DR and Factor XIIIa (data not shown) as previously described.[12] The perivascular location and HLA-DR expression of this cell, which belongs to the monocyte/macrophage lineage,[12] is identical to the dermal macrophage recently described by Sontheimer et al.[13] The spatial distribution in profiles of vertical sections of skin stained with ICAM-1, demonstrated an almost contiguous cellular-adhesion molecule-expressing network consisting of basal KC-dermal dendrocyte-endothelial cell.

During the later pre-erythematous skin biopsies, the epidermal KCs demonstrated increasing ICAM-1 expression manifested by an intercellular "chicken wire" appearance (Figures 3 to 5). There was usually a focal or localized discrete zone of KCs expressing ICAM-1 in which a single cell would be strongly positive with adjacent KCs containing less reactivity. Because the poison ivy/oak mixture had a greenish tinctorial and a granular composition, it was often possible to identify colocalization of the presumably phagocytized urushiol with the same KCs expressing ICAM-1, as defined by the red AEC reaction product under high-power magnification (Figure 5).

It should be emphasized that despite multiple sections of these early pre-erythematous time points and distinctive increased KC ICAM-1 expression, there was no significant dermal infiltration by lymphocytes. The only dermal changes noted during the erythematous phase were increased endothelial-cell ICAM-1 expression and increased ICAM-1 expression by the dermal dendrocytes and sometimes by the perivascular lymphocytes (Figure

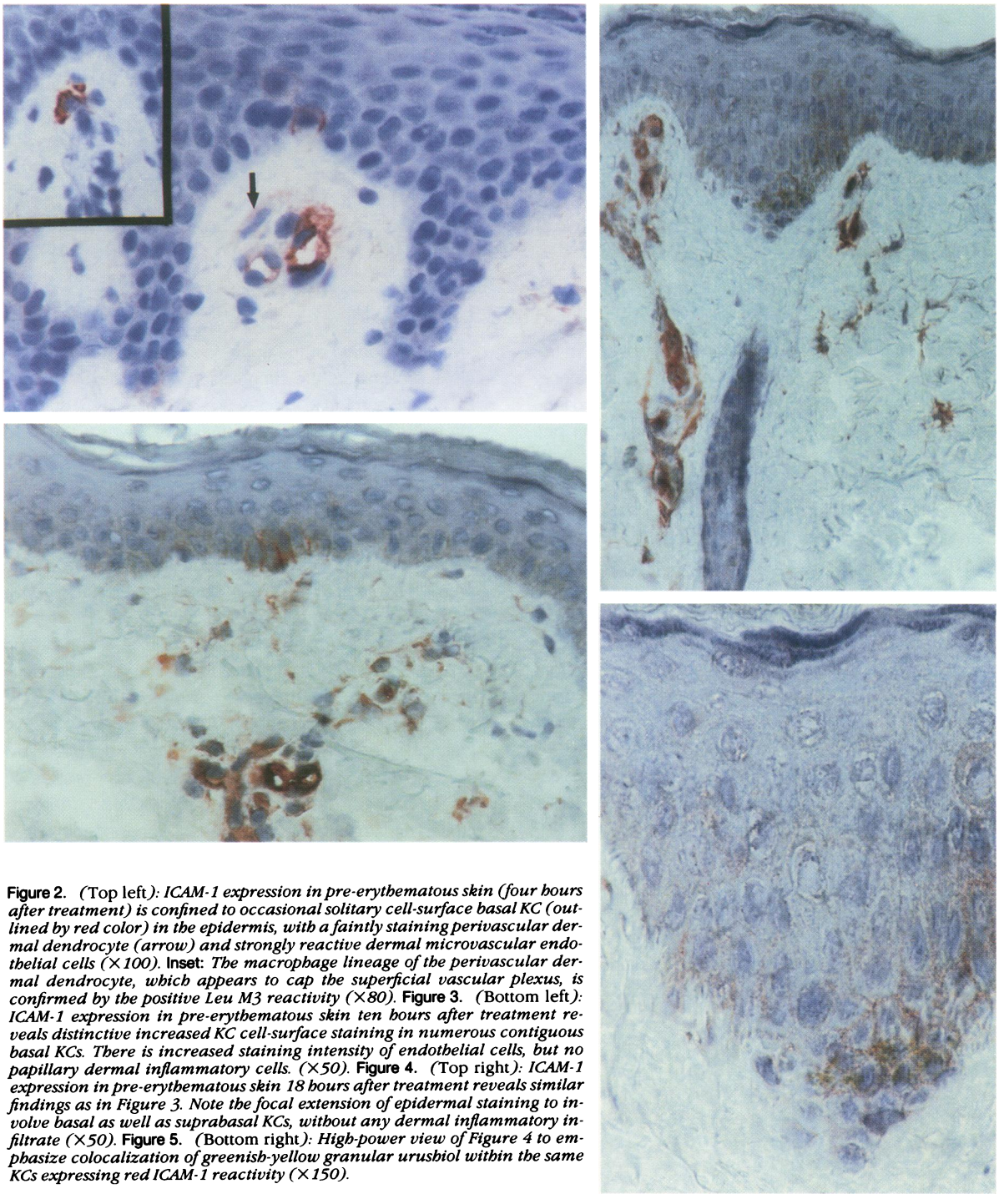


Figure 2. (Top left): *ICAM-1 expression in pre-erythematous skin (four hours after treatment) is confined to occasional solitary cell-surface basal KC (outlined by red color) in the epidermis, with a faintly staining perivascular dermal dendrocyte (arrow) and strongly reactive dermal microvascular endothelial cells (×100).* **Inset:** *The macrophage lineage of the perivascular dermal dendrocyte, which appears to cap the superficial vascular plexus, is confirmed by the positive Leu M3 reactivity (×80).* **Figure 3.** (Bottom left): *ICAM-1 expression in pre-erythematous skin ten hours after treatment reveals distinctive increased KC cell-surface staining in numerous contiguous basal KCs. There is increased staining intensity of endothelial cells, but no papillary dermal inflammatory cells. (×50).* **Figure 4.** (Top right): *ICAM-1 expression in pre-erythematous skin 18 hours after treatment reveals similar findings as in Figure 3. Note the focal extension of epidermal staining to involve basal as well as suprabasal KCs, without any dermal inflammatory infiltrate (×50).* **Figure 5.** (Bottom right): *High-power view of Figure 4 to emphasize colocalization of greenish-yellow granular urushiol within the same KCs expressing red ICAM-1 reactivity (×150).*

4). The early increase in KC ICAM-1 expression was in marked contrast to HLA-DR because only Langerhans cells, and not KCs, reacted positively at these time points (Figure 6).

Characterization of Inflammatory Infiltrate

As mentioned above, during the first 4 to 20 hours after exposure and before the development of erythema, the dermis, including perivascular adventitia, contained no significant increase in inflammatory cells. However, during the next 24 hours, when there was increasing erythema and edema, the dermis contained progressively more mononuclear cells that exhibited a marked proclivity for epidermal infiltration (Figure 7). At the beginning of this inflammatory infiltrate, the mononuclear cells were primarily localized to perivascular adventitial zones, without sig-

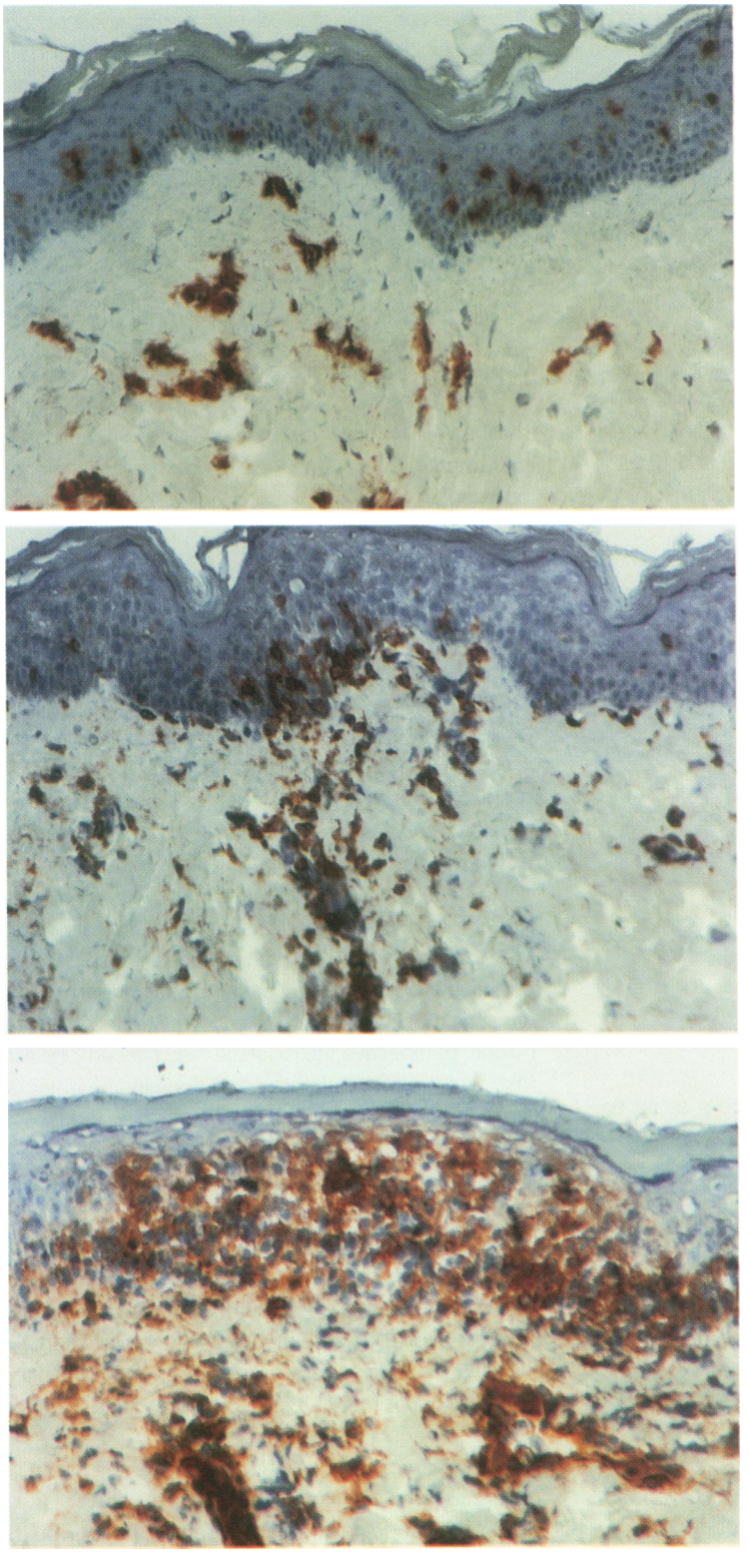


Figure 6. *(*Top*): HLA-DR expression in pre-erythematous skin ten hours after treatment reveals suprabasilar LCs but no KC cell-surface reactivity. The endothelial cells are strongly HLA-DR positive (×50).* **Figure 7.** *(*Middle*): UCHL-1-positive T lymphocytes belonging to the memory subset are identified in this biopsy (34 hours after treatment) of erythematous and edematous skin that displays marked infiltration of the lower epidermis (×75).* **Figure 8.** *(*Bottom*): HLA-DR expression in erythematous and edematous skin 48 hours after treatment reveals positive KC cell-surface staining as well as numerous intraepidermal T cells, perivascular and papillary dermal T cells, and endothelial cells (×80).*

nificant extension into the interstitial dermis. In some cases, there were almost as many mononuclear cells in the epidermis as there were in the papillary dermis. The immunophenotype of these mononuclear cells was more than 90% T cells with an approximately 2 to 4:1 CD4:CD8 ratio, and all of the cells were positive for LFA-1 and HLA-DR. To determine if these early dermal infiltrating T cells belonged to the "memory" subset (see below) rather than the "naive" subset, additional cell-surface molecular expression was studied. The memory T cells of both CD4 and CD8 subsets are characterized by greater cell-surface expression of several adhesion molecules, including LFA-1, LFA-3, and UCHL-1, while lacking 2H4 (CD45R) molecules.[14] In all specimens, the infiltrating T cells strongly expressed (more than 95%) LFA-3 and UCHL-1 (Figure 7) and lacked 2H4, which was consistent with the memory T-cell phenotype.

When both edema and erythema were greater there was a more dense bandlike inflammatory dermal infiltrate with even greater epidermal infiltration than was seen during day 2. The HLA-DR staining pattern (Figure 8) revealed the presence of focal KC HLA-DR expression and also highlighted the increased number of activated-appearing dermal mononuclear cells. Until the introduction of this prominent dermal T-cell inflammatory infiltrate, the KCs had only expressed ICAM-1 alone and not HLA-DR. Parallel with the appearance of HLA-DR by the KCs, there was more prominent and widespread KC ICAM-1 expression at this later time point (data not shown).

Lack of Clonal T-Cell Population in Blood or Skin After Induction of Rhus Dermatitis

To determine if a clonal population of T cells could be detected in the blood or skin of our patients, the T-cell receptor gene-rearrangement analysis was performed three and four days after exposure to the poison ivy/oak mixture. In two patients with actively inflamed lesions, no evidence of a clonal T-cell population was observed (data not shown).

Cultured KCs Express ICAM-1 After Urushiol Exposure

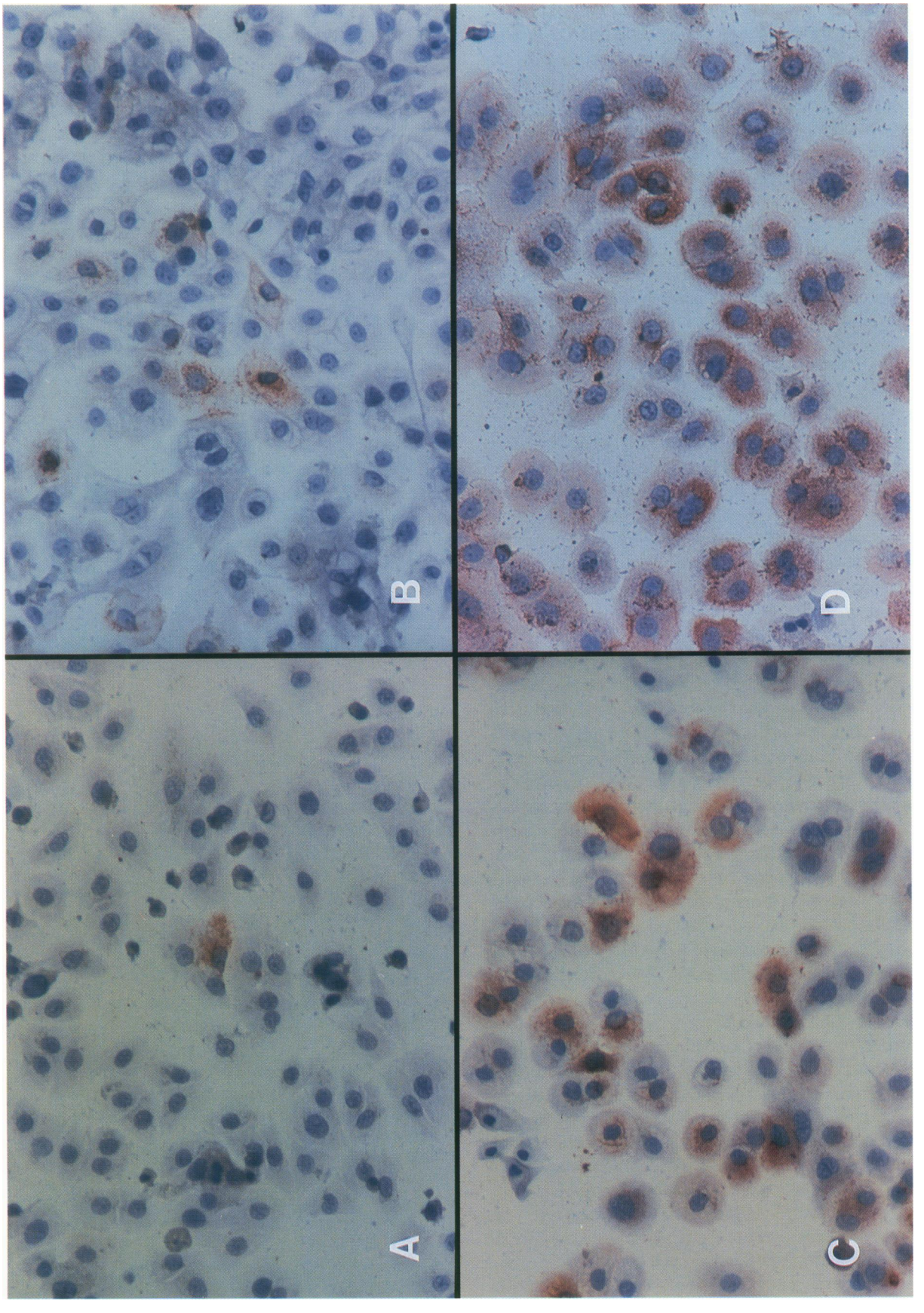
To confirm that urushiol can directly induce KC ICAM-1 expression without the need for IFN-γ-producing activated T cells, the multipassaged cultured KCs were treated with urushiol and examined for ICAM-1. The ICAM-1 expression was studied using immunohistochemical staining, indirect immunofluorescent staining, and FACS analysis. In the absence of treatment, only a rare cultured KC expressed ICAM-1 (Figure 9A). After exposure to either urushiol alone (Figure 9B), or urushiol plus calcium ionophore (Figure 9C), there was increased KC ICAM-1 expression. However, the urushiol plus ionophore-induced expression of ICAM-1 was considerably less than the KC ICAM-1 induced by IFN-γ (Figure 9D).

In KCs grown without treatment, there was no detectable KC ICAM-1 expression by FACS analysis. But after exposure to urushiol there was an increase in the mean channel fluorescence of 12.3 ± 3.5 ($n = 3$) with only minimal HLA-DR expression. By contrast, IFN-γ treatment induced both ICAM-1 and HLA-DR, with mean channel fluorescence values of 94 and 85, respectively, as previously described.[5]

Discussion

The recognition of a primary epidermal KC ICAM-1-expressing state, preceding dermal T-lymphocyte infiltration in the earliest phase of Rhus dermatitis, which can be reproduced *in vitro* using urushiol-treated cultured KCs, is a novel observation. The finding that the urushiol molecule, which had been previously regarded purely for its antigenic hapten properties, can directly interact with KCs to generate immunologically important signals such as ICAM-1 expression, has many important implications for our understanding of the pathophysiology of ACD. Perhaps the most important implication is that from an immunologic perspective the KC itself may play an "initiating" role. While normal untreated skin contains no detectable ICAM-1-expressing KCs,[6] when urushiol induces KC ICAM-1 expression this initiation phase would bring LFA-1-expressing T cells, which are continually trafficking in low numbers through the epidermis of normal skin,[15] into close apposition within the epidermal compartment, thereby facilitating further interaction with Langerhans cells and KCs. The interaction between urushiol, KCs, Langerhans cells, and T cells would then result in T-cell activation and lymphokine production.[16] Lymphokines, such as IFN-γ, produced by intraepidermal and surrounding T cells, could then serve as an "amplification event" and greatly augment the original stimulus by influencing other cell types such as the dermal dendrocyte[12] and microvascular endothelial cell.[17] This amplification would enhance antigen presentation and recruitment of additional mononuclear cells, including both antigen-specific and

Figure 9. *Cultured KC ICAM-1 expression after 48 hours of exposure:* **A:** *No urushiol;* **B:** *urushiol alone;* **C:** *urushiol plus calcium ionophore;* **D:** *100 U/ml of IFN-γ (×100).*


B
D
A
C

antigen nonspecific T-cell clones, into the dermis and epidermis.[18] The activation of endothelial cells by lymphokines *in vitro* has been associated with selective recruitment of memory T cells, thereby explaining the prominence of memory T cells in ACD.[19]

Thus the directional flow of immunologically relevant information involving regulatory molecular interactions for the initiation phase of ACD would direct altered KC-signal transduction,[7] in the absence of lymphokines, from the epidermal KC to the Langerhans cell to the dermal dendrocyte to the T cell to the endothelial cell. The amplification phase would predominantly involve lymphokines and proceed in reverse order. Supportive evidence for the lack of involvement of lymphokines, such as IFN-γ, in the initiation phase is that the KCs expressed only ICAM-1, whereas KC HLA-DR did not appear until a dermal T-cell infiltrate appeared. We have previously demonstrated that IFN-γ induces both ICAM-1 and HLA-DR.[5] Some of the earliest molecular and cellular activation signals involving adhesion molecules would therefore occur in an antigen irrelevant manner,[4] while the latter events would involve hapten-carrier complex formation and antigen specificity, characteristic of ACD. However we could not detect the appearance of a clonal T-cell population in either the skin or blood, suggesting that, if present, they were present at a level less than 1%.[20]

This interpretation of our current results would provide a molecular explanation for the ability of urushiol to produce inflammation in the skin of previously nonsensitized infants and young children[9] because the antigen-irrelevant component of our proposal involving LFA-1/ICAM-1 interaction could result in cutaneous inflammation. Moreover, many other epicutaneously applied molecules that are classically referred to as producing an irritant contact dermatitis,[21] may produce cutaneous inflammation by directly influencing KC signal transduction leading to ICAM-1 expression.[7] Support for this concept comes from the many similarities between ACD and irritant contact dermatitis, including the same cellular kinetics, histologic appearance, close apposition of T cells/LCs, ultrastructural appearance, mononuclear subsets, immunohistochemical localization of HLA-DR, and so on.[22]

Finally, another important observation involves the recognition of the near-contiguous cellular-adhesion molecular network comprising basal KCs-dermal dendrocytes-endothelial cells, which was quite striking, after its initial recognition. This multicellular network became particularly noticeable during the first 10 to 14 hours after urushiol application, suggesting that it may function as an important and rapidly activated signalling complex. In some ways this anatomic, functional unit in the upper layers of the skin is reminiscent of the renal glomerulus in which there are three intimately associated cell types (ie epithelial cells, mesangial macrophagelike cells, and endothelial cells). While we could not establish a direct physical anastomosis between the cellular elements in this multicellular network because the distances separating the basal KC from the angiocentric dermal dendrocyte and endothelial cell are relatively small (20 to 40 microns), it is plausible that cytokines produced by KCs could rapidly diffuse and influence these other cell types and vice versa.[23] This particular zone of skin corresponds to the area between rete pegs as described for serrated-type KCs[24] and could serve as a conduit for the transportation of molecular inflammatory mediators between the epidermis and dermis; whereas the KCs in the rete pegs, which have a nonserrated ultrastructural appearance, are more important in proliferation. For example, it is feasible that the mechanism whereby ultraviolet light inhibits the induction of ACD is not only the reduction of LC numbers[25] but also the suppression of the induction of epidermal KC ICAM-1 production.[26,27] Much more work remains to be performed on this cellular network and the functional diversity of basal KCs. We hope that these new results will stimulate further study of many other aspects of ACD because there is still much to be learned about this common and classical type of inflammatory cutaneous reaction.

Future work should focus particularly on the dermal dendrocyte because these cells are increased dramatically in several cutaneous disorders,[12,28] and have been discovered independently also to play an important role in the induction of contact hypersensitivity in mice.[29]

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Acknowledgment

The authors thank Dr. Curtis Hanson for providing the gene rearrangement evaluations.