A Macrophage Phenotype for a Constitutive, Class II Antigen-Expressing, Human Dermal Perivascular Dendritic Cell

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A previously uncharacterized population of class II antigen-bearing dendritic cells that are intimately associated with the dermal microvasculature was identified in normal human skin using a double-label, indirect immunofluorescence technique. The only other major HLA-DR positive dermal cell type noted in these studies, the dermal microvascular endothelial cell (DMVEC), appeared to express lesser amounts of HLA-DR region gene product than did this dermal perivascular dendritic cell (DPDC). These DPDC were particularly common around small vessels in the superficial vascular plexus of the papillary dermis and were distinct from the mast cell, another cell type normally seen in a similar location. Phenotypic and ultrastructural studies have determined that the DPDC is more closely related to the monocyte/macrophage lineage than the dendritic cell lineage. The perivascular location and phenotype of this cell distinguishes it from other previously described constitutive dermal cell types such as the classic "histiocyte," veiled cell, and dendrocyte. The relatively rich expression of all three major HLA-D region gene products by this dermal perivascular dendritic macrophage would suggest that it could play a significant role in the immunobiology of the dermal microvascular unit. *J. Invest Dermatol 93:154–159, 1989*

While using a double label, indirect immunofluorescence technique to examine the class II histocompatibility antigen-expressing capacity of human dermal microvascular endothelial cells (DMVEC) in situ, we were surprised to find a previously unrecognized population of perivascular dendritic cells that appeared to display greater amounts of HLA-DR antigen than the endothelial cells with which they were intimately associated [1]. Others have commented upon a class II antigen positive, dendritic-appearing cell in normal adult [2] and fetal [3] human dermis; however, such cells have previously been felt to be rather randomly distributed throughout this tissue. In addition, a cell having a veiled morphology has also been noted to surround nonlesional human dermal microvessels [4]. While data regarding this latter cell type's ability to express HLA-D region antigens have not yet been formally presented, very recent observations have suggested that it might be capable of doing so (personal communications, Dr. I.M. Braverman). If this perivascular veil cell is confirmed to constitutively express class II histocompatibility antigens, it would be closely related to the cell that we have observed in the current study. Both the dermal histiocyte and veil cell have been felt by some to be related to the fibroblast lineage [2,4]. Because the dermal perivascular dendritic cell (DPDC) which we have observed in the present study appears to have a macrophage rather than fibroblast phenotype, it was our impression that this cell has not yet been formally studied. Therefore, we initiated a systematic examination of the phenotypic and ultrastructural characteristics of this previously uncharacterized cell type.

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Abbreviations:

DMVEC: dermal microvascular endothelial cell (s)
DPDC: dermal perivascular dendritic cell (s)
DPDM: dermal perivascular dendritic macrophage (s)
FITC: fluorescein isothiocyanate
PBS: phosphate buffered saline
TRITC: tetramethyl rhodamine isothiocyanate

MATERIALS AND METHODS

Tissue Source Normal human skin specimens from three anatomical regions were examined in this study: 1) abdominal wall skin taken from the edge of excised Cesarean section scars removed from healthy adult multiparous females (n = 20), 2) newborn foreskin (n = 12), and 3) normal adult male deltoid skin (n = 6).

Double Label Indirect Immunofluorescence Technique Freshly obtained skin specimens were trimmed, embedded in O.C.T. compound embedding medium ("Tissue-Tek," Miles Scientific, Naperville, IL), and snap frozen in liquid nitrogen. Four micron vertical sections were prepared, applied to a clean glass slide, and fixed by a 5 min immersion in 100% acetone. The sections were then exposed to one of the following three combinations of lectins, monoclonal antibodies, and fluorochrome conjugated antisera: 1) Rabbit anti-human factor VIII antiserum (1:20 dilution) (Dako Co., Santa Barbara, CA) followed by tetramethyl rhodamine isothiocyanate (TRITC)-conjugated goat anti-rabbit IgG antiserum (1:20) (Cappel, Cochranville, PA) followed by murine monoclonal antibody (1:10) (see types and sources in Table I) followed by fluorescein isothiocyanate (FITC)-conjugated goat anti-mouse IgG antiserum (1:20) (Cappel); 2) FITC-conjugated *Ulex europeus* lectin,

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Table I. Immunologic Phenotype of a Human Dermal Perivascular Dendritic Cell

Monoclonal Antibodies and Lectins	Specificity	Cellular Reactivity[a]	Source[b]	Result[c]
Class II Antigens				
L243	HLA-DR		1	+++
FA	HLA-DP		2	+
Leu-10, Tu-22	HLA-DQ		1,2	+
Langerhans cell				
OKT-6	CD1a	ELC, Thym.	3	−
Mast cell				
Avidin		Mast cells	4	−
T cell				
OKT-3	CD3	T cells	3	−
OKT-4	CD4	T subset	3	−
OKT-8	CD8	T subset	3	−
B cell				
B-1	CD20	B cells	5	−
CR2 (C3dR)	CD21	B cells, FDRC	1	−
NK cell				
Leu-7 (HNK-1)		NK	1	−
Leu-11	CD16	Nk, PMN	1	−
Monocyte/macrophage				
OKM-1 (CR3, MAC-1, Mo-1)	CD11b	Mo, Mp, PMN	3	+
Leu-M5 (p150,95)	CD11c	Mo, PMN	1	+
63D3		Mo, Mp	2	+
H7.10		Mo, Mp	2	+
H38.1A		Mo, Mp	2	+
OKM-5		Mo, Mp, Plat.	3	−
Mo-2	CD14	Mo, FDRC	5	−
CR1	CD35	Mo, Mp, PMN	1	−
25F9		tissue Mp	6	−
13 other monocyte-specific monoclonals		Mo, Mp	2	−
Miscellaneous				
HLe-1	CD45	Cells of bone marrow origin	1	+
7C4	CD1b		7	−
7C6	CD1c	B cells, DDC	7	−

[a] ELC: epidermal Langerhans cells; thym: cortical thymocytes; NK: natural killer cells; PMN: polymorphonuclear nuclear leukocytes; Mo: monocytes; Mp: macrophages; FDRC: follicular dendritic reticulum cells; DDC: dermal dendritic cells; Plat: platlets.

[b] 1: Beckton Dickinson (Mountain View, CA); 2: Gift from Dr. Peter Stastny (Dept. of Dermatology, Univ. of Texas Southwestern Medical Center, Dallas, TX); 3: Ortho Diagnostic Systems (Raritan, NJ); 4: Boehringer Mannheim Biochemicals (Indianapolis, IN); 5: Coulter Immunology (Hialeah, FL); 6: Gift from Dr. Bettina Mues and Dr. C. Sorg (Munster, Wester Germany); 7: Prof. Dr. W. Knapp (Third International Workshop on Human Leukocyte Differentiation Antigens), courtesy of Dr. Jack Longley (Department of Dermatology, Yale University School of Medicine).

[c] +++: strong fluorescence intensity; +: weak fluorescence intensity; −: no specific fluorescence.

an endothelial cell marker [5], (100 μg/ml) (Vector Labs, Burlingame, CA) followed by monoclonal antibody (1:10) (Table I) followed by TRITC-conjugated goat anti-mouse IgG antiserum (1:20) (Cappel); 3) FITC-avidin, a mast cell marker [6] (1:100) (Boehringer Mannheim, Indianapolis, IN) followed by murine monoclonal anti-HLA-DR, L243 (1:10) (Beckton Dickinson, Mountain View, CA) followed by TRITC-goat anti-mouse IgG antiserum (1:20) (Cappel).

Each reagent was diluted in phosphate buffered saline (PBS) and applied to the tissue sections for 30 min in a humidified environment. The sections were then washed thoroughly in PBS after each incubation and examined and photographed with a Leitz Orthoplan fluorescence microscope equipped for epi-illumination.

The appropriate controls revealed that there was no cross-reactivity between the goat anti-mouse IgG and the rabbit anti-human factor VIII antisera. In addition, no specific fluorescence was detected in skin sections incubated with any of the fluorochrome conjugated antisera used alone.

Peroxidase-Antiperoxidase Technique for Light and Electron Microscopy Cutaneous tissue was fixed in 2% periodate-lysine-paraformaldehyde for 90 min at 4°C. The tissue was then washed in PBS for 2 h at 4°C and imbedded in OCT mounting medium followed by snap freezing in liquid nitrogen. At this point the tissue was either stored at −70°C or further processed immediately. Four-micron vertical frozen sections were prepared and placed on 1% gelatin coated slides. The slides were then air dried and incubated with a 1:10 dilution of the primary mouse monoclonal antibody (L243) for 30 min at room temperature. They were then washed 3 times in PBS (5 min for each wash) and further incubated in a goat anti-mouse IgG antiserum (1:20) for 30 min at room temperature followed by another wash in PBS 3 times. Mouse peroxidase anti-peroxidase (Jackson Laboratories, Avondale, PA) (1:25 dilution) was then applied to the slides for 30 min at room temperature followed again by washing 3 times. The sections were then covered with 2.5% glutaraldehyde for 1 h at 4°C followed by another wash in PBS 3 times. They were then developed in 0.05% diaminobenzidine for 15 min in the dark followed by another wash in PBS 3 times. The slides were then covered with 1% osmium tetroxide for 1 h at 4°C and then again washed in PBS 3 times. The sections were then dehydrated by sequential 15-min immersions in 70%, 85%, 90%, and 95% ethanol. They were then soaked in 100% ethanol for 1 h, changing the ethanol every 20 min. Liquified Epon-filled cassettes were then inverted over the sections on the slides. The Epon was allowed to harden for 3 d at 60°C. The slides, with the solidified, Epon-filled cassettes attached, were then im-

mersed in liquid nitrogen to facilitate separation of the Epon-embedded sections from the glass surface. Both unstained and lead citrate stained, ultrathin sections were then examined with a Joel 100 CX electron microscope.

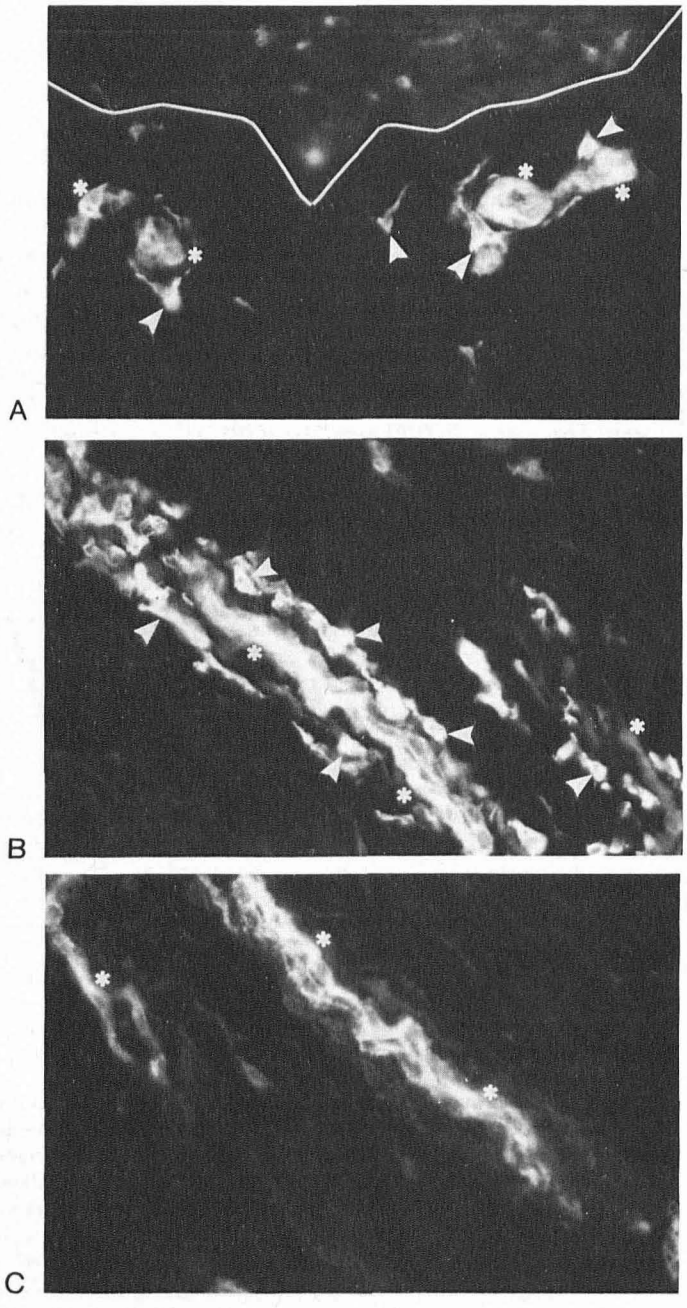

Figure 1. *A:* Immunofluorescence micrograph of normal human abdominal wall skin processed with reagent combination 1 in *Materials and Methods* to simultaneously demonstrate the presence of factor VIII and HLA-DR antigens. This preparation was viewed and photographed under FITC excitation filters. Note the HLA-DR positive dendritic cells (FITC) *(arrowheads)* surrounding the HLA-DR and factor VIII positive endothelial cells of dermal microvessels in cross section (FITC and TRITC) *(asterisks)*. The dermal-epidermal junction is indicated by the *white line.* This single exposure micrograph has the appearance of a double exposure due to the fact that some TRITC fluorescence does occur and "bleeds through" with FITC excitation wavelengths. *B:* Longitudinal section of a papillary dermis microvessel stained, photographed, and labeled as in *A*. Note virtual conduit of HLA-DR expressing perivascular dendritic cells *(arrowheads)* surrounding HLA-DR and factor VIII positive endothelial cells *(asterisks)*. *C:* Same field as in *B* photographed under TRITC excitation filters. Only tubular red fluorescence of the factor VIII positive endothelial cell channel is seen *(asterisks)*.

RESULTS

Phenotype of the DPDC These studies have shown that there are two morphologically distinct, class II antigen positive cells which are normally resident in human dermis: the microvascular endothelial cell and a dendritic cell predominately located in the immediate perivascular space. Figure 1*A,B* illustrates the appearance of this second cell type. These HLA-DR positive cells were seen in greatest density in the upper papillary dermis. Their appearance was the same when either factor VIII or *Ulex europeus* was used to mark the presence of endothelial cells. While Ulex binds to both lymphatic and vascular endothelial cells, factor VIII is expressed predominately by vascular endothelial cells [7]. Because the appearance and density of DPDC around Ulex and anti-factor VIII positive endothelial cells was quite similar, we feel that this cell type is primarily associated with the microvasculature rather than small lymphatic vessels. However, this point needs to be more closely examined.

As seen in Fig 1*B*, the DPDC in some sections appeared to almost form a conduit around the microvessels in this location. However, the bodies of these cells did not appear to be in direct physical contact with the vessel wall, supporting the argument against the possibility that they are pericytes. Direct apposition of HLA-DR positive perivascular cells to endothelial cells was also not observed in the immunoelectron microscopy studies. The possibility that the dendritic processes of these cells might be actually touching the vessel wall cannot be excluded from our studies to date.

The striking perivascular array of these cells was less evident in the reticular dermis and subcutaneous tissue. It is our current impression that much lower densities of DPDC exist in these two areas compared with the papillary dermis. This could relate to lower densities of microvessels in these deeper areas compared with the superficial vascular plexus. We are currently examining these issues with a quantitative, morphometric point-counting technique.

The appearance and density of DPDC did not vary significantly in numerous individual specimens of the three types of normal skin examined in this study, except for the possibility that they could be somewhat more numerous in the pregnancy abdominal wall skin. While serial sections were not systematically examined in this investigation, it was our impression that a large majority of the class II antigen-positive dendritic cells present in the dermis were in fact closely associated with microvessels.

The perivascular location of these cells suggested the possibility that they might be related to mast cells, another cell type normally present in this location. However, examination of skin sections treated with FITC avidin, a mast cell marker [6], followed by a combination of reagents to mark the presence of HLA-DR antigen (combination 3 in *Materials and Methods*), revealed that DPDC and dermal mast cells were completely separate cell populations (data not shown). This experiment also confirmed that at least a majority of dermal mast cells do not express enough HLA-DR antigen in situ to be detected by immunofluorescence microscopy. While we did not attempt to quantitate the density of mast cells in this study, the number of DPDC appeared to be equal to or perhaps even greater than that of mast cells.

Because we initially identified the DPDC by its expression of large amounts of HLA-DR antigen, molecles present in high density on the surface of several cell types involved in the immune response, we chose to further examine this cell for other phenotypic markers displayed by immunocompetent cells. Table I lists the murine monoclonal antibodies and lectins that were used to further probe the identity of this cell type.

The pattern of reactivity observed suggests that these cells are of bone marrow origin but are not fully mature epidermal Langerhans cells because they did not express CD1a (OKT-6). The presence of epidermal dendritic cells in the same section served as a positive control for the OKT-6 monoclonal antibody. The possibility that DPDC might represent dermal Langerhans cells, which have not yet expressed the CD1a determinant, on their way to the epidermis cannot be completely excluded, even though the ultrastructural

appearance of the DPDC (see below) was different from that of the epidermal Langerhans cell. Recent observations by others have suggested that the epidermis and cytokines produced by epidermal keratinocytes such as IL-1 may be able to induce the expression of CD1a on cells that were previously negative for this phenotype [8–9]. In addition, other investigations have suggested that messenger RNA coding for related molecules in this gene family such as CD1c might be expressed on a population of dermal dendritic cells [10]. Likewise, van de Rijn et al [11] have reported that the CD1c determinant is expressed in human skin predominately on perivascular cells in the dermis. However, in our studies, the HLA-DR positive dermal perivascular dendritic cells which expressed several macrophage markers did not react with a different CD1c monoclonal antibody. This specificity (7C6) bound only to scattered cells in the upper dermis just below the dermal-epidermal junction. A related monoclonal antibody specific for CD1b (7C4) did not react with any cutaneous cell type in our studies.

The HLA-DR positive DPDC did not bind T-cell, B-cell, or NK-cell reactive monoclonal antibodies. However, they did react with HLA-DP -DQ specifications, and several monocyte/macrophage reactive antibodies (Leu-M5, 63D3, OKM-1). All DPDC appeared to express HLA-DQ determinants, which are present on only about 50% of circulating monocytes [12]. The fluorescence intensity was quite weak with all antibodies except the HLA-DR specificity, L243. It is thus possible that the failure of the other macrophage-specific monoclonals, such as Mo-2, to bind to DPDC could relate to the relative insensitivity of the immunofluorescence technique used in this study. It is also possible that these perivascular macrophages, like other tissue macrophages, do not express this particular monocyte determinant [13].

Ultrastructural Characteristics of DPDC To further characterize the identity of DPDC, immunoperoxidase electron microscopy was carried out. Figure 2 represents the appearance of normal abdominal wall skin that was reacted with the HLA-DR specific monoclonal antibody L243, followed by a peroxidase-antiperoxidase visualization technique. Several cells having dark peroxidase reaction product on their surfaces can be seen surrounding a microvessel, whose endothelial cells are not associated with the reaction product. This supports our observation, using the indirect immunofluorescence technique, that these perivascular dendritic cells express relatively greater amounts of HLA-DR antigen than DMVEC and raises the possibility that heterogeneity might exist with respect to class II antigen expression by different types of dermal microvessels. Recent studies have suggested that certain activation determinants are expressed on only dermal post capillary venular endothelial cells [14]. Studies which are in progress in our lab have also suggested that significant variation exists in the degree of HLA-D region antigen expression by Ulex positive dermal endothelial cell subpopulations freshly isolated from the same skin specimen (personal unpublished observation).

Figure 3 illustrates the ultrastructural characteristics of DPDC. These cells have a distinctive folded nucleus and a highly ruffled, irregular surface. In the lead citrate counterstained sections, relatively dark cytoplasm containing mitochondria and an occasional lysosome was seen. Birbeck granules were not observed. In the unstained sections, HLA-DR antigen was found predominately on the plasma membrane. The appearance of this cell is highly reminiscent of the classic dermal histiocyte which has been noted to be present in the perivascular space by others [15]. However, most workers have felt that histiocytes are randomly distributed throughout the dermis.

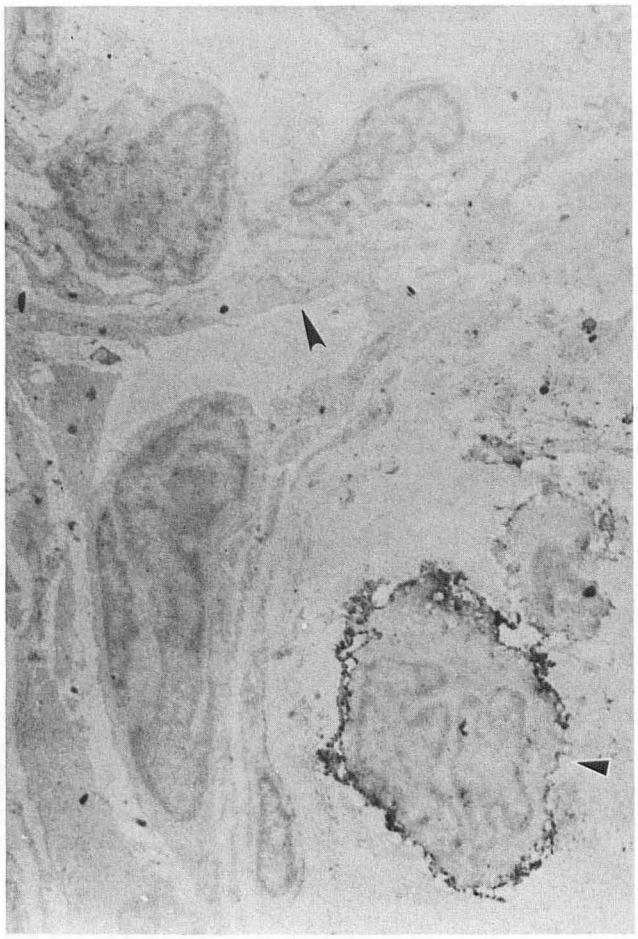

Figure 2. Electron micrograph of periodate/lysine/paraformaldehyde-fixed frozen section of normal skin that had been reacted with HLA-DR antibody (L243) followed by a peroxidase-antiperoxidase visualization technique. Note the two cells with dark reaction product on their surfaces *(white bordered arrowheads)* surrounding a microvessel whose endothelial cells *(unbordered arrowheads)* are not similarly decorated with reaction product. The possibility that the HLA-DR positive perivascular cells in this singly labeled preparation might be activated T cells rather than perivascular macrophages cannot be excluded, because similar cells having somewhat cerebriform nuclei in other preparations were occasionally found to express a human Thy-1 determinant, 309 (data not shown). However, the large majority of HLA-DR positive, perivascular cells seen in this study had the appearance of the cell shown in Fig 3. Magnification: X5000.

DISCUSSION

The concept of the existence of a population of constitutive, randomly-distributed dermal mononuclear cells, variously referred to as histiocytes, dendrocytes, or dendritic cells, is certainly not a new one. There is, however, an ongoing debate regarding the true lineage and function of these cells, with some workers feeling that designations such as "histiocyte" are obsolete [16]. Recent studies have suggested that at least some normally present, dermal, mononuclear, dendritic cells do express class II antigens in situ [2,3]. While the function of such cells has not yet been formally examined, some workers have suggested that they might represent specialized fibroblasts and others have argued in favor of an antigen-presenting cell phenotype. The double label immunofluorescence technique which we have used in the present study has allowed us to determine that many, if not the majority, of the cells of this type are not randomly distributed through the dermis but share a rather intimate relationship with the dermal microvasculature. In addition, our studies suggest that the phenotype and ultrastructural characteristics of this cell are most compatible with a tissue macrophage. The possibility that they could represent a precursor stage of epidermal Langerhans cells has not been fully excluded; however, this seems unlikely.

This dermal perivascular dendritic macrophage (DPDM) appears to be distinct from any previously described constitutive dermal cell type. Its dendritic morphology and rich endowment of HLA-D region antigens would at first glance suggest that it might represent

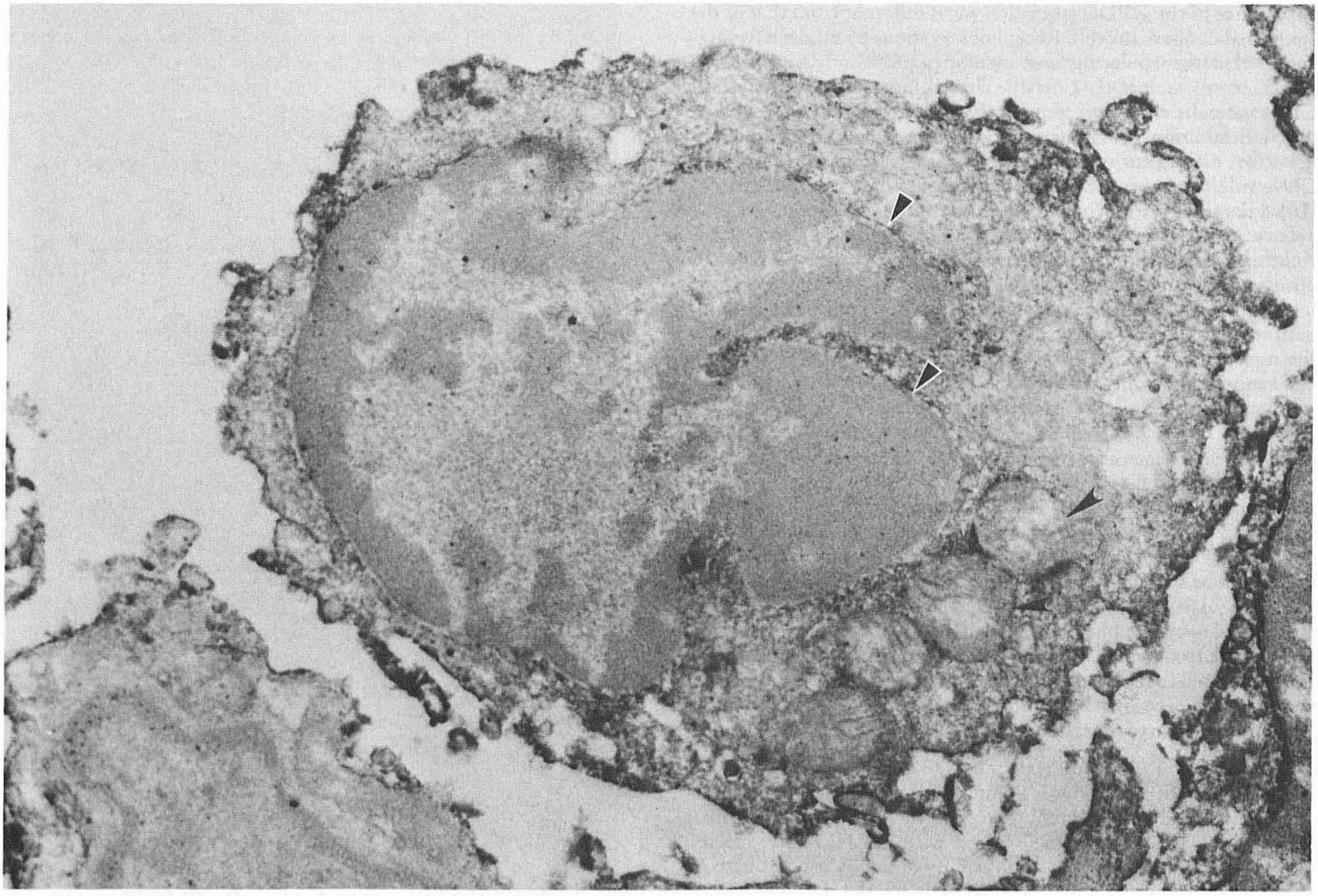

Figure 3. Ultrastructural characteristics of HLA-DR positive dermal perivascular cells in normal human skin. Ultrathin sections were prepared from Epon-embedded frozen sections which had been processed by the technique described in Fig 2 and the *Materials and Methods* section. In addition, this section was counterstained with lead citrate to enhance cytoplasmic structural detail. Note the somewhat folded nucleus *(white bordered arrowheads)* and relatively dark cytoplasm containing several mitochondria *(unbordered arrowheads)*. In other similar sections, an occasional lysosome was observed. Birbeck granules were not seen. The dark peroxidase reaction product in the plasma membrane which marks the presence of HLA-DR antigen is not seen as distinctly here as in Fig 2 because of the lead citrate counterstaining. In other sections that were not stained, HLA-DR antibody binding was limited to the cell surface. Magnification: X26,000.

a dermal precursor of the bone marrow-derived epidermal Langerhans cell. However, its macrophage phenotype, ultrastructural appearance, absence of CD1a (OKT-6) expression, and absence of Birbeck granules all argue against this possibility. The CD1 gene family (CD1a, CD1b, CD1c) is felt to possibly represent the human equivalent of the murine thymus lukemia-like or Qa antigen systems [17]. The CD1a (OKT-6) determinant is expressed predominately on cortical thymocytes and epidermal Langerhans cells. The CD1c gene product was previously thought to have a relatively limited tissue distribution. However, recent human studies employing the M241 monoclonal antibody have found it to be expressed on normal circulating B cells [17] as well as a dendritic cell type normally found within the dermis [11]. This latter report has suggested that CD1c positive dermal dendritic cells are found predominately within the perivascular space. The perivascular dendritic cell that we have characterized does not express the CD1c determinant, as defined by the 7C6 monoclonal antibody. In addition, no dermal or epidermal cells were observed in our studies to express the CD1b determinant identified by monoclonal antibody 7C4. No other studies to date have reported CD1b positive cells within the skin.

The macrophage phenotype and expression of all three major HLA-D region gene products by this cell coupled with its close relationship with the dermal microvasculature suggests the possibility that it might play a role in the immunobiology of the dermal microvascular unit. For the purpose of this discussion, the term "dermal microvascular unit" is used to refer to DMVEC and those other constitutive dermal cell types (e.g., DPDM, mast cells, pericytes, and extravascular T cells), which share an intimate anatomical relationship with the microvessels of normal human skin.

Recent studies by others have documented that T cells, some expressing activation markers, can also be found to surround dermal microvessels in normal skin [18]. If the DPDM has antigen-presenting capabilities, its location would place it in an ideal position to interact with these perivascular T cells to generate protective immune responses against antigens that might be delivered to this area from the circulation (e.g., infectious agents, drugs). In addition, this interaction could serve as a backup system for those antigens from the external environment, especially complex ones that might require endocytic processing, which successfully breach the outer perimeter of the epidermal Langerhans cell network. Cytokines resulting from DPDM-triggered, perivascular T-cell activation could provoke an effector response by another member of the dermal microvascular unit, the mast cell, because this cell is known to be capable of responding to certain lymphokines. Others have re-

cently reported that Ia positive, bone marrow-derived, perivascular microglial cells might serve a similar antigen-presenting cell function within the central nervous system [19].

The expression of HLA-D region antigens by tissue cells does not always correlate positively with antigen-presenting capabilities. While gamma-IF can stimulate dermal fibroblasts to express class II antigens, such cells do not function well in presenting antigen to unprimed T cells [20]. In addition, normal pulmonary alveolar macrophages do express class II antigens; however, these cells have been found to be relatively poor antigen-presenting cells, related in part to their low capacity for IL-1 secretion and inability to effectively bind to T cells [21]. Hepatic Kupffer cells also are relatively deficient in antigen-presenting capabilities [22]. It is thus possible that DPDM might also prove to be relatively inefficient antigen-presenting cells. Studies are currently underway in our laboratory to isolate dermal macrophages in order to address this issue [23]. If this cell is also found to be relatively deficient in antigen-presenting capabilities, what then might be its physiologic significance? Recent studies in our lab have documented that another cellular component of the dermal microvascular unit, the microvascular endothelial cell, does possess some antigen-presenting cell capabilities when stimulated with cytokines such as gamma interferon [24]. At least some of the many substances which are produced by macrophages, such as interleukin-1 and tumor necrosis factor-alpha, are capable of upregulating certain endothelial cell functions [data reviewed in Ref 25]. It is therefore possible that factors produced by DPDM might be capable of influencing the function of the dermal microvascular endothelial cells, including their ability to actively bind and stimulate circulating T cells.

A number of inflammatory skin disorders (e.g., polymorphous light eruption, Jessner's lymphocytic infiltrate, morbilliform drug eruptions, cutaneous lupus erythematosus) have as a prominent component of their histopathology, a vasocentric pattern of infiltrating mononuclear lymphoid cells. A better understanding of the immunologic functional interactions that can occur between the cells of the dermal microvascular unit in normal skin could serve as a framework for further characterizing the pathophysiology of such clinical disorders.

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