Invited Review

Epidermal Langerhans cells in infectious diseases

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Introduction

Paul Langerhans was one of the most brilliant scientific observers of his time, contributing considerably not only to medicine but also to zoology by describing new species of invertebrates (De Panfilis, 1988). He was a medical student at the Berlin Pathological Institute when he discovered in 1868 the epidermal cells that bear his name. He believed that these gold chloride-positive midepidermis dendritic cells were intra-epidermal receptors for extracutaneous signals to the nervous system (Langerhans, 1868). This neural hypothesis prevailed for almost a century. Not until 1965, when the morphological identity between Langerhans cells (LC) and histiocytes X cells was described, was a possible mesenchymal derivation for LC postulated (Basset and Turiaf, 1965). In 1966, Campo-Aasen and Pearse demonstrated cytochemically that epidermal LC share specific enzymes with macrophages. Further accumulated evidence supported the striking similarities between LC and macrophage/monocytes, including the expression of Fc and C3 receptors (Stingl et al., 1977), expression of Major Histocompatibility Complex class II (Ia) molecules (Klarskov et al., 1977; Rowden et al., 1977), ability to migrate (Silberberg, 1973) and the in vitro ability to stimulate allogeneic T-cells (Stingl et al., 1978). LC also produce interleukin-1 (IL-1), previously denoted in the skin as epidermal cell-derived thymocyte-activating factor (ETAF) (Sauder et al., 1984). The IL-1 serves as the second signal in triggering the production of interleukin-2 (IL-2) by T-helper cells, thus amplifying ongoing T-cell responses.

Morphology and specific cell markers

Birbeck et al. (1961) observed at the electron microscope level a unique cytoplasmic granule within LC. This distinctive and characteristic structure, the Birbeck granule, is usually a cup-shaped organelle that at one end contains a small vesicle, which in cross sections appears as the characteristic rod or racket structure.

At the light microscopic level LC cannot be identified using conventional histological stains. However, various histochemical or immunocytochemical markers have been used for LC characterization. For many years, membrane-bound ATPase has been widely used in the characterization of LC. However, this cytochemical staining is also present in other cells of the monocyte-macrophage series and interpretation is difficult when the number of cells is high, as in the case of many pathological conditions (Wolff, 1972; Tapia et al., 1988). Other cytochemical procedures such as zinc iodide, cobalt chloride and paraphenylenediamine, have had some applications in the characterization of LC (Niebauer, 1968; Juhlin and Shelley, 1977; Rodriguez and Caorsi, 1978).

The use of monoclonal antibodies and immunocytochemical procedures has allowed the precise characterization of the different cell subsets involved in immune mechanisms. Under normal conditions LC are the only Ia-positive cells in the epidermis (Rowden et al., 1977; Klarskov et al., 1977). However, under certain pathological conditions the keratinocytes can also express these antigens on their surface (De Panfilis and Allegra, 1979; Auböck et al., 1986; Gross et al., 1988). Fithian et al. (1981) were the first to develop a monoclonal antibody directed to a membrane-associated antigen present in human LC and in about 70% of thymocytes. This antigen, referred to as the CD1 molecule (formerly known as T6), can be recognized by various monoclonal antibodies. The availability of anti-CD1 antibodies has contributed to understanding the role of LC in the generation of immune responses involving the skin.
After the Second International Workshop on Human Leucocyte Differentiation Antigens (Haynes, 1986), the CD1 complex was divided into 3 different molecular forms based on differences in molecular weight, cell distribution and specific monoclonal antibodies (Table 1). The CD1a (gp49), CD1b (gp45) and CD1c (gp43) are universally coexpressed in cortical thymocytes (McMichael et al., 1979; Olive et al., 1984; Amiot et al., 1986). In the skin, the three CD1 antigens are coexpressed in dermal indeterminate cells under pathological conditions; in contrast, epidermal LC only coexpressed CD1a and CD1c molecules (Murphy, 1985; Schmitt et al., 1987; Berri et al., 1988; Dezutter-Dambuyant, 1988). It has also been demonstrated that a subgroup of B lymphocytes expressed the CD1c molecule (Small et al., 1987).

Table 1. General characteristics of the CD1 molecules.

<table>
<thead>
<tr>
<th>Molecular form</th>
<th>Mw</th>
<th>Monoclonal antibodies</th>
<th>Cells recognized</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1a</td>
<td>49 kd</td>
<td>OKT6, Leu-6, Na134, BL-6</td>
<td>thymocytes, Langerhans cells, indeterminate cells.</td>
</tr>
<tr>
<td>CD1b</td>
<td>45 kd</td>
<td>NuT2, 4A7,8, WM25</td>
<td>thymocytes, indeterminate cells.</td>
</tr>
<tr>
<td>CD1c</td>
<td>43 kd</td>
<td>M241, L161</td>
<td>thymocytes Langerhans cells B-cell subset indeterminate cells</td>
</tr>
</tbody>
</table>

Human CD1 molecules are MHC class I antigens encoded by a new family of MHC-related genes located in chromosome 1 (Martin et al., 1986, 1987). The CD1a antigen may be part of a receptor since they are internalized throughout organelles which are characteristic of receptor-mediated endocytosis (Hanau et al., 1987).

Other LC markers include the mesenchymal intermediate filament vimentin (Fig. 1) (Löning et al., 1982; De Waal et al., 1984) and the S-100 protein (Cocchia et al., 1981; Nakajima et al., 1982), which have been used for the identification of LC or at least a subgroup of them in various animals.

Recently, Kraal et al. (1986) have developed a monoclonal antibody, the NLDC-145, which can recognize epidermal LC, veiled cells and interdigitating cells in mice, providing further evidence for a close relationship between these cell types.

**Ontogeny of epidermal Langerhans cells**

For many years the origin of LC was a matter of debate. Based on their dendritic form and gold chloride positivity many people believed they were part of the nervous system (Ferreira-Márques, 1951). Others thought LC were degenerated melanocytes (Billingham and Medawar, 1953). The work of Basset and Turiaf (1965) showing that histiocytes X cells were histiocytologically indistinguishable from epidermal LC provided the first suggestive evidence for a mesenchymal origin of the LC. Further works (Katz et al., 1979; Frelinger et al., 1979) showed that murine LC originate from a mobile pool of bone marrow-derived precursor cells. Recently, the bone marrow origin has been shown unequivocally for human LC (Pelletier et al., 1984).

Goordyal and Isaacson (1985) demonstrated the presence of cells with the phenotype characteristics of LC in culture monocyte colonies derived from human bone marrow. These cells were positive to peanut agglutinin (PNA) and also coexpressed the CD1a (LC and thymocytes), CD11 (mature monocytes) and CD14 (mielomonocytes) differentiation antigens. Gothelf et al. (1986) considered these cells as LC precursors, even though they lacked Birbeck granules.

CD1a-positive cells have also been found in normal peripheral blood suggesting that LC precursors migrate from the bone marrow to the epidermis via the blood vessels (Dezutter-Dambuyant et al., 1984; Wood et al., 1984). Recent findings demonstrated that the number of CD1a-positive cells increases in the peripheral blood of burn and trauma patients (Wood et al., 1984; Gohelf et al., 1988). These cells, which possess most of the morphological characteristics of LC, lack Birbeck granules, suggesting that they may appear after exposure to the epidermal microenvironment.

Several studies have shown that LC do divide in the epidermis, thus ending the general belief that they were cells in transit through the epidermis. The first investigations based on 3H-thymidine incorporation demonstrated that murine, human and guinea pig LC entered S-phase in the epidermis (Giacometti and Montagna, 1967; MacKenzie, 1975; Gschnait and Brenner, 1979). More recently, Czernielewski et al. (1985, 1987), using immunocytochemical procedures, have shown that CD1a-positive LC in the epidermis are actively cycling and self-reproducing. These investigators estimated that the cell cycle time was 16.13 days.

![Fig. 1. Epidermal dendritic cells immunoreactive to the intermediate filament vimentin (arrow) in the skin of the armadillo Dasypus novemcinctus. Bar = 10 μm.](image-url)
indicating that LC are a slow cycling cell population. Miyauchi and Hashimoto (1989) have been able to match LC morphological changes to cell cycle stages by using conventional ATPase staining, providing a new tool for the in vivo analysis of LC dynamics.

Functions of Langerhans cells

The skin immune system

Streilein (1978) used the term «skin-associated lymphoid tissues» (SALT) to describe the LC, skin T-lymphocytes, immunocompetent keratinocytes and the skin-draining peripheral lymph nodes, which included vascular high endothelial cells. This concept has been revised recently by Bos and Kapsenberg (1986) suggesting the term «skin immune system» (SIS) as a more appropriate. The SIS includes the dendritic antigen-presenting cells (LC, Granstein cells, indeterminate cells, veiled cells, and interdigitating cells), keratinocytes, tissue macrophages, neutrophilic granulocytes, mast cells, vascular endothelial cells, lymphatic endothelial cells and «homing» T-cells, but excludes the lymph node tissue. The SIS also includes other cell types such as fibroblasts, pericytes, eccrine and apocrine gland cells which may participate in the immune response to a given pathogen.

Antigen-presenting cells of the skin

Macrophages were the first cells to be shown to act as antigen-presenting cells (Unanue, 1972, 1981). This ability for antigen presentation has also been described in LC, indeterminate cells, veiled cells, interdigitating and dendritic follicular reticulum cells (Silberberg-Sinakin et al., 1976; Klaus et al., 1980; Balfour et al., 1981; Faure et al., 1984).

Stingl et al. (1978) clearly demonstrated in guinea pigs that LC were necessary to induce a T-cell proliferative response to soluble protein antigens and chemical haptens. In human beings, LC are efficient antigen-presenting cells in lympho-proliferative assays using PPD, antigens, tricophytin and nickel sulfate as antigens, and T-cells from sensitized donors (Berle et al., 1982; Braathen and Thorsby, 1982). In addition, the use of the Mixed Skin Lymphocyte Reaction (MSLR) in which T-cells proliferate in vitro in response to allogeneic epidermal cells, has also demonstrated the importance of LC as antigen-presenting cells (Braathen and Thorsby, 1980; Czernecki et al., 1983).

Recently, a new antigen-presenting cell has also been described in murine epidermis (Granstein et al., 1984). This cell type, denominated the Granstein cell, is resistant to ultraviolet irradiation, and is I-J restricted. These cells, which may be a subgroup of I-C, are essential for the activation of suppression, particularly inducing the proliferation of the so-called T-suppressor 3 effector cells.

Another skin cell group with a dendritic morphology can be identified by the presence on its surface of the Thy-1 molecule (Bergstresser et al., 1983; Tschachler et al., 1983). Some investigators believe that the Thy-1 positive dendritic epidermal cells are immature T-cells, thus emphasizing the importance of the epidermis as a site for extrathymic T-cell differentiation (Stingl et al., 1987). Others propose that Thy-1-positive dendritic epidermal cells are related to natural killer (NK) cells (Caughman et al., 1986). Sullivan et al. (1986) have recently shown that hapten-coupled Thy-1-positive dendritic epidermal cells, when injected intravenously, cause hapten-specific unresponsiveness to subsequent epicutaneous challenge with contact sensitizers.

The Granstein cell and the Thy-1-positive dendritic epidermal cell are two distinct cell groups involved in down-regulatory immune processes, unlike LC which are associated with the up-regulatory circuit. The participation of these new cell types in different pathological conditions has still to be defined.

Langerhans cells and infectious diseases

1. Delayed-type hypersensitivity and Langerhans cells

Recent evidence has shown that the delayed-type hypersensitivity (DTH) response is the result of a sequence of cell interactions rather than a T-cell-mediated event. Most cell types involved in SIS participate in the DTH response, but its main features are LC hyperplasia, Ia-positive keratinocytes, epidermal T-cell accumulation, and a high T-helper-inducer/T-suppressor-cytotoxic 

CD4/CD8 ratio, with elevated numbers of IL-2-positive T-lymphocytes within the infiltrates (Pouiller et al., 1982; Scheynius et al., 1983; Fullmer et al., 1984).

The lack of LC in the cornea has permitted its use as a model to study the participation of these cells in DTH response. Central corneal allografts fail to elicit graft rejection across a MHC II barrier (Streilein et al., 1979). Similarly, central corneal allografts fail to induce a DTH response in allogeneic hosts (Peeler et al., 1985). The latter can be reconstituted after the addition in the graft of donor-derived LC (Peeler and Niederkorn, 1986). Moreover, the epicutaneous application of 2, 4-dinitrofluorobenzene to LC-depleted skin has led to the development of specific immunological tolerance (Toews et al., 1980).

All these findings indicate that LC are required for the induction of DTH responsiveness to various antigens.

In mammals, a considerable number of chronic diseases which manifest DTH are caused by infectious agents such as viruses, mycobacteria, protozoa, and fungi. In all these diseases the association between DTH and protective immunity, and in consequence the participation of LC, have yet to be established.

2. Langerhans cells and viral infections

Cell-mediated immunity plays an important role in resistance to viruses which spread in a cell-to-cell fashion such as herpes, poxvirus, papilloma and HIV (Hatke, 1988).
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*Herpes simplex virus type 1 (HSV-1) infection*

Sprecher and Becker (1986) demonstrated an increase in LC density after infection of the footpad skin with a pathogenic strain of HSV-1. They also showed that a depletion of LC in the footpad skin produced an enhancement of the virulence in pathogenic and non-pathogenic strains. Further work using steroids to deplete epidermal LC showed that HSV-1 virulence in the murine model depended on the pathogenicity of the virus strain, genetic strain and age of mice, and LC density (Sprecher and Becker, 1987).

*Human papilloma virus (HPV) infection*

HPV induces epithelial proliferation of the skin and mucosa, causing various types of disorders which in general are benign although some may progress to squamous cell carcinoma (Gissman, 1984). In HPV infection, the density of LC is always decreased in the epidermal lesions, suggesting that this may be the result of virus-specific cytopathic effect (Chardonnet et al., 1986). The results show correlation between the density reduction in LC and the extent of the cytopathic changes independent of the virus types.

*Human immunodeficiency virus (HIV) infection*

The expression of CD4 molecules on the surface of LC implies that they may be possible targets of HIV infection. Belsito et al. demonstrated that AIDS/ARC patients have decreased numbers of epidermal LC (Belsito et al., 1984). This decrease in LC density in AIDS patients could be correlated with the clinical stage and the absolute numbers of peripheral blood T-helper cells (Dréno et al., 1988). Tscharckler et al. (1987) were the first to demonstrate cytopathic changes and HIV-like particles in most LC from AIDS patients. In the same study, LC were the only epidermal cells to react with a monoclonal antibody specific to HIV core protein p17. Recent evidence suggests that LC are the primary targets for HIV infection and an important virus reservoir (Niedecken et al., 1987; Tscharckler et al., 1987).

3. **Langerhans cells in mycobacterial and parasitic diseases. Langerhans cells in leprosy**

The clinical-pathological spectrum of leprosy in its diverse forms is the expression of the immunological response of the human host to infection by *Mycobacterium leprae* (Convit et al., 1983). The two polar forms of the spectrum are lepromatous leprosy (LL), in which patients do not develop cell-mediated response to *M. leprae* antigens, and tuberculoid leprosy (TL), in which patients do develop cell-mediated immune response to the bacillus (Bullock and Fasal, 1971; Convit et al., 1983).

Epidermal LC appeared to be increased in TL (Modlin et al., 1983a,b; Mathur et al., 1984) (Fig. 2). In dermis, CD1a-positive dendritic cells are usually located at the borders of the granulomas, especially in the papillary dermis. In erythema nodosum leprosum, a reactional state, the density of LC is found within normal skin values; however, most LC are located in the periphery of the granulomas as in TL. Most studies have shown that the density of LC in LL and borderline lepromatous specimens varies considerably (Modlin et al., 1983b; Liu et al., 1984; Alvarenga et al., 1985). Many cases of LL have decreased numbers of LC with some evidence of morphological cell damage, maybe as the result of LC being the targets of *M. leprae*.

Fig. 2. Numerous epidermal Langerhans cells in a lesion of tuberculoid leprosy. Avidin-biotin immunoperoxidase using an anti-CD1a. Bar = 20 μm.

Dugan et al. (1985) carried out an *in situ* leukocyte characterization of the Mitsuda reaction, the intradermal skin test for assessing the immunological status and the prognosis of leprosy patients. They found a LC hyperplasia which compromises 5% of the total epidermal cell count in both tuberculoid and reversal reaction lesions. CD1a-positive cells were also seen within the dermis in areas of the granulomatous response. Besides the LC hyperplasia, other features include a selective accumulation of T-cells in the epidermis, and a high T-helper-inducer/T-suppressor-cytotoxic CD4/CD8 ratio. These results are similar to those found for tuberculin reactions, the classical DTH response (Poulter et al., 1982; Scheunius et al., 1983; Modlin et al., 1983b; Fullmer et al., 1984).

Recently, Gross et al. (1988) have studied the granulomatous response produced after the inoculation of a mixture of *M. leprae* and BCG in LL patients. They found an increase in the numbers of LC CD1a-positive in the epidermis. In dermis, these cells were mainly localized in the mantle surrounding the granuloma, as described for TL and tuberculin DTH responses (Fig. 3). These findings confirm Convit's observations that the injection of heat-killed *M. leprae* and BCG in LL patients induced an immune granuloma with elimination of both mycobacteria (Convit et al., 1972). These results provided the experimental basis for the use of the mixture of two mycobacteria, one providing the necessary specific antigens and the other triggering macrophage digestion, in studies of immunotherapy and immunoprophylaxis in leprosy (Convit et al., 1979, 1982).
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Fig. 3. Langerhans cells (CD1a-positive) distributed around the granulomas of a tuberculous leprosy patient. Bar = 20 μm.

American cutaneous leishmaniasis

Cutaneous leishmaniasis results from infection by *Leishmania* species, which are obligatory intracellular parasites of macrophages and monocytes. The parasite is transmitted by *Phlebotomus* sandflies. The sandfly bites are superficial and it is likely that the first targets of *Leishmania* are the LC. The first evidence that LC can be infected by *Leishmania* has recently been shown in vitro. (Dompmartin et al., 1988).

Based on these findings, cutaneous leishmaniasis constitutes an excellent model to study the involvement of LC in an infectious disease. American cutaneous leishmaniasis is characterized by a spectrum of host response similar to the one described for leprosy (Convit, 1974). Localized cutaneous leishmaniasis (LCL) is characterized by limited and ulcerated skin lesions which either heal spontaneously or after treatment with pentavalent antimonial salts. In contrast, diffuse cutaneous leishmaniasis (DCL) occurs very rarely and is characterized by the presence of progressive nonulcerated nodules, rich in parasites, which are resistant to treatment (Convit et al., 1972).

Modlin et al. (1985) have shown an increase in the number of epidermal LC and numerous large CD1a-positive cells in the dermis of LCL lesions. The density of LC in DCL was higher than in normal skin but lower than LCL values (Tapia et al., 1988).

The murine models of cutaneous leishmaniasis have been widely used, since they are very useful in understanding many of the immunoregulatory mechanisms associated with the disease. Depending on the *Leishmania* strain, inoculum size and mouse strain, it has been possible to reproduce the distinct clinical forms observed in human beings. Thus, BALB/c mice reproduce lesions similar to DCL, C57BL/6 mice are resistant, reproducing LCL-like lesions, and DBA mice can show intermediate forms of the disease (Preston et al., 1972; Howard et al., 1981; Pérez, 1982).

Results in our laboratory using the NLDC-145 antibody have shown differences in the numbers of LC in *L. mexicana amazonensis* infected BALB/c and C57BL/6 mice (Tapia et al., 1988). Normal density values for BALB/c mice are 1400 LC/mm², whereas C57BL/6 have about 500 LC/mm², values which are similar to those found in normal human epidermis. The high density of LC in BALB/c mice may contribute to the failure to eliminate the parasite, probably due to an excess of possible target cells or to a hyperfunction of the LC. This study showed an exponential increase of LC during the fifteenth week, and a 40% decrease during the sixteenth week of infection. Susceptible *Leishmania*-infected BALB/c mice also showed an increase in the numbers of epidermal LC (Fig. 4) starting with values similar to those found in normal mice (1300 LC/mm²), a decrease during the first week (903 LC/mm²) and peak value (2054 LC/mm²) during the fourth week. An important observation in dermis of infected C57BL/6 mice is the number of NLDC-145 positive cells in close contact with T-helper L3T4 (Ly4, CD4)-positive cells. This type of association may be necessary for lymphokine release, since, as has been described for tuberculoid leprosy, these T-helper cells are also Interleukin-2-positive cells (Modlin et al., 1984). This study shows an association between epidermal LC and the leishmanial infection in murine cutaneous leishmaniasis. This association was made evident through changes in LC density observed during the course of infection. The relevance of these results is being evaluated in our laboratory.
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Langerhans cells and their ultimate role in the immune response

When an infectious agent invades a particular site, polymorphonuclear leukocytes or granulocytes leave the circulating blood and adhere to endothelial cells of the blood vessels. The endothelial cells separate with the help of vasodilator substances, such as serotonin, produced by mast cells, or regulatory peptides such as vasoactive intestinal polypeptide produced by cutaneous nerves or lymphocytes (O'Shaughnessy et al., 1981; O'Dorisio et al., 1985). This vasodilation allows the granulocytes to pass into the infected area where they ingest and destroy the pathogens. Next, antigen-presenting cells, such as LC and macrophages, appear as the predominant cell type, phagocytizing and destroying the foreign agent.

In the skin, the LC processes the antigen and presents it on its surface in conjunction with MHC class II molecules to a T cell, which in most of the cases is a T-helper cell in capable of producing IL-2 (Th1 cell) or IL-4 (Th2 cell). The cellular association induces the LC to produce and express in its membrane IL-1, and possibly, other monokines such as tumor necrosis factor (TNF). Keratinocytes may also produce IL-1 and function as accessory cells (Gahring et al., 1985). This event, in association with antigen stimulation, induces the release of IL-2 or IL-4 and the expression of IL-2 or IL-4 receptors, driving antigen-activated T-cells into proliferation (Fig. 5). Th1 cells mediate DTH reaction whereas Th2 mediate immediate hypersensitivity responses (Mosmann and Coffman, 1987). The T-cell proliferation leads to the formation of a granuloma, which could be of various types: a lympho-histiocytic infiltrate or tuberculin-type reaction composed generally of lymphocytes and monocytes, a tuberculoid granuloma composed of lymphocytes, differentiated macrophages, epithelioid cells and multinucleated giant cells, and macrophagic granulomas composed of undifferentiated macrophages and very few lymphocytes. The latter is the result of the presence of persistent agents within the macrophages, which the cell is unable to destroy. Recent evidence (Modlin et al., 1983a; Gross et al., 1988) has shown that the tuberculoid granuloma is structurally organized with T-suppressor-cytotoxic cells and LC distributed towards the periphery and T-helper-inducer cells distributed throughout the granuloma. T-helper cells are often seen in close association with LC. Macrophagic granulomas formed by undifferentiated cells, in contrast, are more disorganized with no particular cell distribution.

LC are considered terminally differentiated cells, although Schuler and Steinmann (1985) have recently proposed that epidermal LC constitute a pool of immature dendritic cells. They showed that the antigen-presenting capacity of LC is considerably increased upon in vitro cultivation, thus suggesting that LC need to leave the epithelial micro-environment in order to mature into functional immunological cells. Some basis for this hypothesis are the findings of Czernielewski et al. (1985, 1987) showing that LC actually divide within the epidermis.

Recent investigations by Romani et al. (1989) suggest that LC function involves two sequential events: antigen presentation and a sensitization step in which the LC acquires the capacity to induce a T-cell response. The first event occurs in the epidermis whereas the second may occur as the dendritic cells migrate to the draining lymph node or spleen.

Skin cells with potential accessory function include dermal and epidermal macrophages, Thy-1-positive dendritic epidermal cells, LC, and keratinocytes under certain pathological conditions. If the skin is the largest defensive organ it is understandable why accessory cells are so heterogeneous. Some investigators suggest that macrophages are the true phagocytic cells of the skin, whereas LC are only capable of phagocytosis of degraded antigens, previously processed by macrophages or keratinocytes (Hamilos, 1988).

The significance of the increase of LC in different dermatological disorders has still to be elucidated, but it has been suggested that LC may be involved in the initial skin pathology. This may be the case in leishmaniasis where LC are a potential target for the parasites (Dompmartin et al., 1988) or as in pigmentary disorders where LC hyperplasia always precedes the formation of the T-lymphocyte infiltrate (De Panfilis and Rowden, 1985; Gross et al., 1987).

LC are certainly the most important antigen-presenting cells of the skin and their ultimate role has still to be clarified. Further studies should concentrate on the association between LC and other cell types involved in the up-regulatory and down-regulatory circuits.
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