

The Langerhans' cells^{*}

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The morphological, enzymatical, immunocytochemical and functional properties of Langerhans' cells are briefly reviewed. Langerhans' cells are located mainly in the squamous stratified epithelia, but are also present in the thymus and in superficial lymphnodes. At the ultrastructural level, they are characterized by unique cytoplasmic organelles, the Birbeck granules, whose function is still unknown. Langerhans' cells possess strong ATPase activity and are weakly positive for alpha-naphtyl acetate esterase and for acid phosphatase; they are immunoreactive for CD1a (T6), class II MHC antigens and S-100 protein. In some pathological conditions, like dermatopathic lymphadenopathy and Langerhans' cell histiocytosis, Langerhans' cells also are characterized by the expression of monocyte-macrophage antigens. Langerhans' cells act as antigen-presenting cells to T lymphocytes; their functional capacity is strictly dependent on the levels of expression of class II MHC antigens. Langerhans' cells are of bone marrow origin and are derived from a circulating precursor which is probably related to the monocyte.

In 1868, the medical student, Paul Langerhans, discovered a population of dendritic cells in the suprabasal layer of the epidermis by impregnating human skin with gold salts (1). Since the gold chloride stain has particular affinity for nerve tissue, it was originally proposed that Langerhans' cells were part of the nervous system. During the 1950's and the 1960's, the general opinion was that Langerhans' cells were closely related to melanocytes. This view was shared by Birbeck and coworkers who in 1961 discovered that Langerhans' cells contain unique cytoplasmic organelles, the Birbeck or LC granules (2). The description of LC granules provided a useful marker to identify Langerhans' cells and locate them in a variety of stratified squamous epithelia, and in some lymphoid organs as well (3). In the late 1960's, the observation that LC granules were present in some pathological histiocytic cells provided circumstantial evidence for a mesenchymal origin of Langerhans' cells (4, 5). In the late 1970's,

the antigen-presenting function of Langerhans' cells and their central role in the immune response of the skin-associated lymphoid tissue (SALT) were recognized definitively (6).

Morphological features of Langerhans' cells

Langerhans' cells are regularly spaced in the suprabasal layer of the epidermis, with a density of about 800 to 1200 per mm (7). Using light microscopy, they appear as large cells, about 12 µm in diameter, with clear or weakly eosinophilic cytoplasm and with an irregularly shaped nucleus. Using electron microscopy, Langerhans' cells have a clear cytoplasm devoid of tonofilaments, desmosomes and melanosomes; the nucleus is frequently convoluted and contains one to three nucleoli. The cytoplasmic organelles include a moderate amount of endoplasmic reticulum, a considerable number of mitochondria, centrioles, lysosomes, and a well-developed Golgi system. As mentioned above, Langerhans' cells are characterized by the presence of unique intracytoplas-

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Table 1
Enzyme histochemical reactions in Langerhans' cells and macrophages

Enzyme	Langerhans' cells	Macrophages
ATPase	+ + +	+
ANAE*	+	+ + +
ANBE**	+	+ + +
Acid phosphatase	+	+ + +
Beta-glucuronidase	-	+

*Alpha-naphtyl acetate esterase.
**Alpha-naphtyl butirate esterase.

mic organelles, the LC or Birbeck granules. LC granules are rod-shaped organelles with a variable length (190–360 nm) and a consistent width (33 nm). They have a central striated line and an occasional terminal vesicular dilatation (tennis racket-shape appearance). Some of the granules are close to and directly continuous with the cell membrane. Although the function of the granules is unknown, it has been suggested that they might shuttle ligand-receptor complexes between the cell membrane and the Golgi system (8).

Enzymatic and antigenic properties of Langerhans' cells

The enzymatic and immunophenotypic properties of Langerhans' cells have been investigated extensively (9, 10). Langerhans' cells are weakly positive for non-specific acetate esterase (ANAE), show dot-reactivity for acid phosphatase (AP) in the Golgi area, and intense membrane reactivity for ATPase (Table 1). The enzyme content of Langerhans' cells is profoundly different from that of macrophages; the latter are markedly ANAE + /AP + , and are weakly ATPase + . A major contribution to our understanding of Langerhans' cells came from the demonstration that Langerhans' cells are CD1a + (Table 2) (11, 12). The CD1a antigen is a glycoprotein, structurally related to the class I major histocompatibility complex (MHC) antigens, which was first recognized on cortical thymocytes (13). In extra-thymic tissues, CD1a is a reliable marker for Langer-

hans' cells and seems to be as specific as the TEM demonstration of LC granules. On paraffin-embedded material, Langerhans' cells can be recognized by their immunoreactivity for S-100 protein (14). Unlike CD1a, S-100 protein has a wide distribution in tissues and has been detected in a variety of different cell types (15). Epidermal Langerhans' cells do not express monocyte-macrophage antigens and do not contain enzyme activities, like lysozyme, alpha-1-antitrypsin and alpha-1-antichymotrypsin, which are typical of macrophages. Langerhans' cells express CD45 antigen, a macromolecular complex which is selectively present on bone marrow-derived cells. Langerhans' cells are faintly positive for CD4 (16) and markedly positive for class II MHC antigens (17). Both these molecules are probably involved in the antigen presenting function of Langerhans' cells.

Immunological functions of Langerhans' cells

Langerhans' cells possess surface receptors for a variety of molecules of the immune system. In fact, they have receptors for complement, for the Fc fragment of IgG (18), and for IL-2 (19). In addition, Langerhans' cells are able to produce and release IL-1 (20), and to form aggregates with T lymphocytes (21). All these features support the concept that Langerhans' cells

Table 2
Immunocytochemical properties of Langerhans' cells and macrophages

Antigen	Langerhans' cells	Macrophages
CD45 (T200)	+	+
CD4 (T4)	+/-	+
CD1a (T6)	+ + +	-
Anti-Mac mAB*	-**	+ + +
S-100 protein	+ +	-
Lysozyme	-	+
Alpha-1-antitrypsin	-	+
Alpha-1-antichymotrypsin	-	+
HLA-DR	+ + +	+ + +

*mAB = monoclonal antibody.
**A weak reactivity with F4/80 has been described in murine epidermal Langerhans' cells.

play a major role in the skin-associated lymphoid tissue (SALT) (22). The first evidence for a possible role of Langerhans' cells in contact hypersensitivity reactions came from the work of Silberberg et al. (For review, see 21) who noted that lymphocyte-like cells were apposed to Langerhans' cells in the skin of allergic subjects a few hours after a specific patch test. In subsequent studies from the same authors, it was shown that Langerhans' cells were able to bind foreign antigens and, in some instances, to carry antigen particles to the regional nodes via the afferent lymph. These observations were further developed in *in vitro* systems where it was shown that Langerhans' cells are able to induce T lymphocyte proliferation through active antigen presentation. It has been suggested that IL-1 and foreign antigen molecules, complexed with class II MHC antigens, represent effective signals to activate T lymphocyte proliferation. This view has received further support by the recent demonstration that the antigen-presenting capacity of Langerhans' cells is strictly paralleled by the levels of class II MHC antigen expression (23).

Origin and traffic of Langerhans' cells

Several lines of evidence indicate that Langerhans' cells are derived from a bone marrow precursor (For review, see 6). In fact, murine skin allografts are populated by Langerhans' cells of recipient origin. Moreover, patients receiving lethal irradiation and allogeneic bone-marrow reconstitution possess epidermal Langerhans' cells of donor origin (24). Finally, Langerhans' cells express the macromolecular complex T200 or CD45 which is generally present on cells of bone marrow origin. The differentiation pathway of Langerhans' cells is much less clear. Nevertheless, there is strong evidence that they are related to the monocyte-macrophage lineage. In fact, Langerhans' cells have been detected within blood-derived monocyte colonies (25). In irradiated patients, skin repopulation by Langerhans' cells is preceded by the appearance of intra-epidermal macrophages which have a faint expression of CD1a antigen (26). In addition, in pathological conditions like

the dermatopathic lymphadenitis and the Langerhans' cell histiocytosis (histiocytosis-X), Langerhans' cells are often positive for monocyte-macrophage antigens (9, 27).

The tissue traffic and the phenotypic properties of LC circulating precursors are still poorly understood. In the normal peripheral blood, CD1a+ cells are usually absent; circulating CD1+ LC-related cells have been described in particular conditions like the cord blood of newborns (28) and the peripheral blood of patients with extensive burns (29). Thus, it may be speculated that in normal conditions the circulating LC-related cells have no distinctive trait allowing their recognition; alternatively, their frequency might be so low to be barely detectable.

The "veiled" cells, first described in the afferent lymph from the skin by Spry (30), are CD1a+/HLA-DR+ cells with extremely rough membranes. It was proposed that the "veiled" cells are circulating epidermal Langerhans' cells carrying the antigen from the skin to the regional lymph node.

Finally, the interdigitating reticulum cells (IDRCs) of the T-dependent areas are probably closely related to the cells of the Langerhans' lineage. The IDRCs have most of the enzymatic and antigenic properties of Langerhans' cells, but lack CD1a and Birbeck granules. The relation, if any, of Langerhans' cells to IDRCs has not yet been clarified. It has been suggested that IDRCs derive from Langerhans' cells migrated into the lymph node. Alternatively, Langerhans' cells and IDRCs might represent distinct differentiation products arising from the same circulating precursor. The absence of reliable markers has left unsolved many crucial questions concerning the properties of the circulating precursor. Perhaps one of the most interesting suggestions is the possibility that Langerhans' cells and other dendritic cells with antigen-presenting functions derive from a special subset of circulating cells which is closely related but not identical to monocytes.

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