Dendritic cells in T- and B-cell proliferation in the skin

DENDRITIC CELLS IN T- AND B-CELL PROLIFERATION IN THE SKIN

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ANATOMY, PHYSIOLOGY, AND DISTRIBUTION OF DENDRITIC CELLS IN NORMAL SKIN

Dendritic cells (DC), otherwise known as *dendritic leukocytes* or *dendrocytes*, represent a relatively homogeneous population of nonlymphocytic cells within lymphoid organs, epithelia, connective tissue, and lymph.[85] The main, common features of DC are their typical dendritic shape (from which their name, although devoid of functional implication, is derived); bone-marrow origin; a constitutive expression of major histocompatibility complex (MHC) class II antigens; usually low phagocytic activity; and high efficiency in stimulating (hence the definition *antigen-presenting cells*, APC) and regulating cell-mediated immune responses.[118] Ultrastructurally, DC share some basic features: a roundish to oval body and variably long, thin cytoplasmic branches (dendrites); an indented nucleus with pale chromatin (excluding a thin peripheral rim); and a cytoplasm containing cytoskeletal filaments (but no fibrils), mitochondria, few stacks of rough endoplasmic reticulum, many smooth vesicles and tubules, a large Golgi apparatus, and few dense bodies (primary lysosomes).[85] This group comprises interdigitating reticulum cells (T-cell areas) and dendritic reticulum cells ([DRC] B-cell areas) of secondary lymphoid organs, so-called *veiled cells* in the afferent lymph, Langerhans cells (LC) and other dendritic leukocytes of squamous and nonsquamous stratified epithelia, and interstitial dendritic leukocytes.

Cutaneous LC[69] are the most well-known and extensively studied DC. Their histogenetic, morphologic, antigenic, and functional features, as well as their alteration by aging and physical-chemical stimuli and their involvement in pathology, have been extensively reviewed elsewhere[19, 24, 95, 100, 105] and will not be the subject of this article. In extreme synthesis, the cardinal features of LC are the presence of typical cytoplasmic inclusions (Birbeck granules, shown by electron microscopy)[17] and the expression of CD1a antigen on their plasma membranes. According to a strict definition, *only cells containing Birbeck granules should be considered LC*. It has been widely demonstrated that LC acquire their complete morphologic features, as judged from the presence and number of Birbeck granules, only following their establishment in the epidermis[10, 23, 81, 91]; for this reason, epidermal and dermal DC not containing Birbeck

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granules have been interpreted as putative precursors of LC and termed *indeterminate cells*, for almost 15 years.[23, 51, 101] Indeed, the apparent lack of Birbeck granules may be related either to a loss of these typical structures following the migration of LC from the epidermis into the dermis or to an absent formation due to the lack of—or minimal—homing in the epidermal microenvironment.[10, 23, 81, 101] The findings of recent reports,[12] however, suggest that the identification of Birbeck granules may also depend on the careful evaluation of many serial ultrathin sections. Consequently, the term *indeterminate cells* seems today a little bit confusing, and many researchers prefer to avoid its use.

In addition to their identificative antigenic marker (i.e., CD1a), LC constitutively express many other membrane molecules that may be related to their functional role in physiology and pathology (e.g., antigen presentation and T-cell activation, cytokine production, adhesion to the extracellular matrix, and migration).[19, 74, 95, 100, 105] The expression of these functionally relevant molecules by LC can be either up regulated or down regulated in specific conditions, with possible clinical consequences. These features support the interpretation of these cells as the "sentinels" of the skin-associated lymphoid tissue (SALT)[119] or skin immune system (SIS).[18]

A novel type of DC has been described in the skin and increasingly investigated in the last years, that is, dermal dendritic cells. Some common, basic features of these dermal DC, variably termed as *dermal dendrocytes* ([DD] the most popular definition),[3, 30, 40, 58, 59] *perivascular veil cells*,[22] or *perivascular dendritic macrophages*,[13] are the expression of class II MHC antigens, a mainly perivascular location (predominantly around the superficial vascular plexus), the lack of expression of CD1a antigen and vascular markers (factor VIII-RA, Ulex Europaeus lectin), and the ultrastructural features of macrophages. The antigenic phenotype of DD, however, is actually a matter of controversy; in fact, despite the substantial agreement concerning their interpretation as a subset of CD68+ dermal macrophages, they have been variably defined as factor XIII+,[3, 30, 40, 58, 59] CD11b−/D11c+/D36−,[113] CD11b+/CD11c+/CD14+/KiM8+/D36−,[129] or CD11b−/CD11c+/CD14+/D36+,[30, 58, 59, 125] Thy-1+[43, 44] (Thy-1 is a human antigen, possibly related to the immunoglobulin supergene family as well as its murine counterpart[77]; however, human Thy-1 is expressed by dermal perivascular DC and not by epidermal DC in both normal and pathologic skin.[43, 44]) The role of these resident dermal DC in murine and human SIS is also controversial: some experimental evidences suggest that they are a further cell type, in addition to LC, capable of initiating delayed-type hypersensitivity responses.[34, 120, 125] Other studies, on the contrary, support the hypothesis that DD may be responsible for the activation of suppressor pathways,[13, 72] similar to a CD36+ subset of blood monocytes.[109] At the present state of our knowledge, it is not possible to hypothesize whether the CD36+ DC identified in normal dermis correspond to those demonstrated in UV-irradiated skin,[4, 5, 32, 33] which are capable of activating suppressor cell responses.

A specific subset of DC, with features closely resembling those of cutaneous DD, has been described in the lamina propria of the oral mucosa.[94] These cells show a typical perivascular location and a CD36+/CD1a−/CD11b−/CD11c− antigenic phenotype; their ultrastructural profile is characterized by the presence of many lysosomes (both primary and secondary, often containing melanin), well-developed rough endoplasmic reticulum, and focal adhesion sites to the extracellular matrix.

CD36+/CD1a+ DC have been found in normal epidermis,[111, 114] although not regularly.[72] It remains to be established whether and how these CD36+ epidermal DC, when present, are related to those found in the dermis. The identification of all CD36 expressing cells as monocyte-derived APC seems at present to be unwise. In fact, CD36+ cells—variably dendritic in shape but not expressing class II MHC antigens or CD45 antigen (the latter indicative of bone marrow origin)—have been found by some authors at the dermoepidermal junction.[129]

THE IMPORTANCE OF STUDYING DENDRITIC CELLS IN LYMPHOPROLIFERATIVE DISORDERS OF THE SKIN

In lymphoproliferative disorders of the skin, lymphocytes are the proliferating cells and DC may be considered their "living room," that is, the framework in which lymphocytes live and proliferate. Therefore, why study DC? This is an obvious, reasonable

question. First of all, DC have a key role in T- and B-cell homing.[85, 118] Second, DC can be the specific target of living and physical and chemical agents, and their alterations may have a pathogenic role in certain cutaneous lymphoproliferative diseases.[50, 74, 75, 110] Third, the morphologic, antigenic, and topographic features of DC may have diagnostic and histogenetic relevance in specific conditions[93] as discussed later on. Finally, DC are crucial for both effector and regulatory immune responses,[118] and might play a role in antitumoral lymphocyte reactions.[57] In addition, investigating the morphologic, antigenic, and functional features and the distribution of DC in different cutaneous pathologic skin models characterized by aberrant lymphoid cell migration and proliferation may greatly contribute to a better understanding of the differentiation and function of SIS and the pathogenesis of SIS-related disorders.[95]

Concerning cutaneous lymphomas, that is, non-Hodgkin's lymphomas primarily presenting in the skin, the significance and possible role of DC in the natural history of the disease have been subjects of investigation for almost 20 years, with no definitive conclusions reached at present.

DENDRITIC CELLS IN T-CELL PROLIFERATIVE DISORDERS

Since 1976,[20, 55, 56] the presence of DC in mycosis fungoides (MF), a classic type of cutaneous T-cell lymphoma (CTCL), has been described by means of electron microscopy and considered the specific expression of lymphocyte homing. This finding has been widely confirmed by numerous immunohistochemical and ultrastructural studies* in MF, Sézary syndrome (SS, which is interpreted as the leukemic variant of MF), and localized pagetoid reticulosis.

In fact, different hypotheses have been proposed concerning the significance and possible role of DC in the pathogenesis of MF. The presence of viruslike particles in the cytoplasm of LC induced some authors to hypothesize a viral infection of these APC, with the consequence of their persistent stimulatory action on CD4+ T cells, eventually leading to the malignant transformation of CD4+ T cells.[50, 74, 75, 110, 122] The report that only intraepidermal T cells are cycling in MF[83] supports the hypothesis of a possible significant role of epidermal LC in the pathophysiology of MF. Other studies, however, have stressed that close contacts between LC and T cells are occasional, even in initial patches, notwithstanding the high numbers of epidermal CD1a− LC[7–11]; these findings raise doubts on this hypothesis of a persistent stimulation of T cells by LC as a crucial event in the pathogenesis of MF. Conversely, a clear-cut correlation between the number, immunoarchitecture, and ultrastructure of dermal CD1a+ DC (indeterminate cells) and the clinical stage-related histoimmunologic modifications has been documented.[9, 10] In early patches of MF (flat lesions, with a scarce, mostly perivascular lymphoid infiltrate), indeterminate cells are relatively few, intermingled with high numbers of CD11c+/CD1a− monocytoid cells (putative precursors ?),[10] and form a rudimentary cellular network, establishing close contacts between each other and with cerebriform lymphocytes: according to our initial paradox, lymphocytes "reclaim their living room." In the plaque stage, indeterminate cells are more numerous, form an extended cellular network, show morphologic signs of enhanced functional activity (abundant cytoplasm with large amounts of mitochondria, multiple Golgi stacks, and numerous cisternae of rough and smooth endoplasmic reticulum), and establish close contacts with CD4+ T cells, often showing blastic morphology and an activated-proliferating phenotype (HLA-DR+/CD25+/CD71+/Ki-67+)[9] (Figs. 1 to 4). In the tumor stage, blastic T cells markedly increase in number and lose their mature CD4+ phenotype, whereas indeterminate cells are sparse and less rich in organelles and show only occasional contacts with T cells.[9] On the basis of these findings, it has been suggested that dermal CD1a+ DC are possibly involved in the homing, proliferation, and neoplastic progression of T cells.[9] On the other hand, CD1a+ DC may differentiate and persist only under the influence of a CD4+ T-cell microenvironment.[9, 10]

If the paucity of close contacts between lymphocytes and epidermal LC seems to speak against a crucial role of epidermal LC in the pathogenesis of MF, how can the constant finding of large numbers of these cells in the epidermis of MF patches and plaques be interpreted? It could be considered an epiphenomenon related to the migration of CD11c+ and CD1a− monocytoid precursors

*References 9–11, 21, 26, 31, 36, 41, 50, 61, 63, 65, 67, 68, 74–76, 99, 110, 112, 123

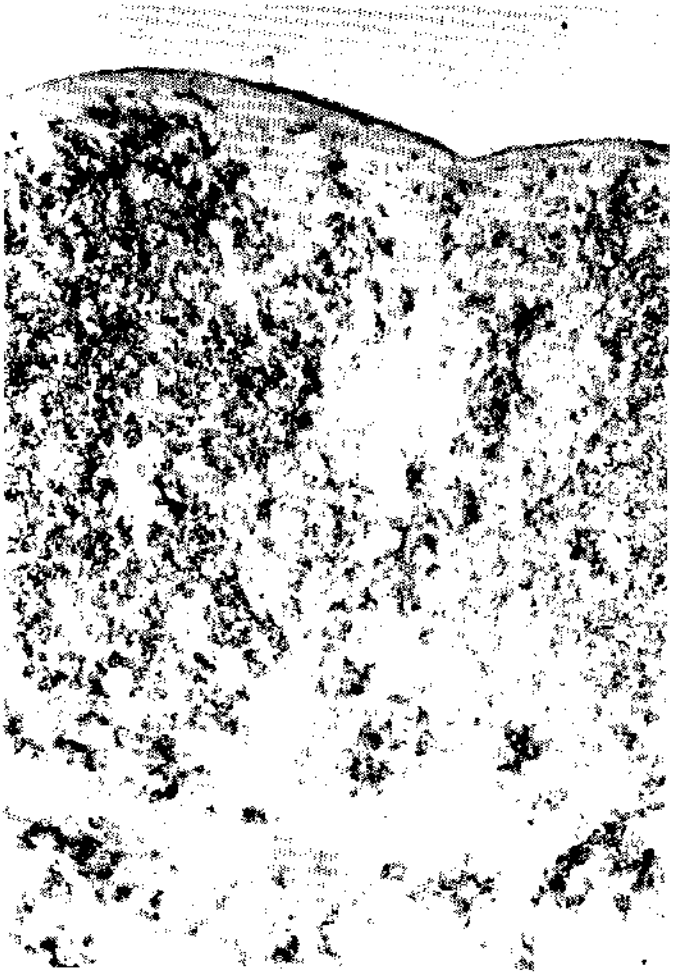

Figure 1. MF (plaque stage). Epidermotropic, bandlike infiltration of CD4 + T cells. The phenotype of these cells is HLA-DR+, CD25+, CD71+, Ki-67+. Immunohistochemical technique used (APAAP) on frozen section (original magnification ×160).

to DC from the dermis into the epidermis,[8, 10] possibly due to the increased relase of cytokines[121] (the role of cytokines is extensively dealt with in the article by Dummer and Schwarz). In the epidermis, these precursor cells eventually acquire the typical antigenic (CD1a expression), morphologic (Birbeck granules), and, probably, functional features of fully mature LC.[8, 10] According to the aforementioned data, the recent report of a positive correlation between higher numbers of epidermal CD1a+ LC and a better prognosis in patients with MF[79] might simply depend on a correlation between the numbers of epidermal LC and the disease stage. The presence of skin tumors, in fact, is accompanied by a paucity of epidermal CD1a+ DC and is related to a poor prognosis. The hypothesis that epidermal LC alterations are a consequence, rather than a cause, of MF lesions is supported by the finding that there are no significant differences in the number and distribution of these cells between the clinically normal skin of MF patients and that of healthy control subjects.

Similar to S100+/CD1a+ DC, factor XIIIa+ DD coexpressing Thy-1 antigen are constantly found in the papillary dermis of MF lesions and progressively increase in numbers from early patches to plaques.[43, 44] The increase of factor XIIIa− and Thy-1+ DC, possibly neodifferentiated from a pool of CD34+ progenitors that have migrated into the papillary dermis from the reticular dermis—where they are usually found in perivascular location[44]—and recruited from the circulation via adhesion to ELAM-1+/ICAM-1+/VCAM-1+ endothelium,[44] seems to counterbalance the increase of CD1a+ DC in MF. This same situation has been observed in some widely studied inflammatory dermatoses, such as lichen planus (LP) or atopic dermatitis.[30] Factor XIIIa +, CD36+ DD could be crucial in the selective activation of sup-

Figure 2. MF (plaque stage). Extended network of CD1a+ dendritic cells. These cells are very numerous in both the epidermis and the dermis. Immunohistochemical technique used (APAAP) on frozen section (original magnification ×160).

pressor-inducer pathways that, if overstimulated, may down regulate host immune responses leading to suppression of antitumor immunity.[43, 72] Factor XIIIa+ and CD1a+ DC[39] and CD36+/CD1a− DC[57, 71] have been found in MF lesional epidermis; no definite hypothesis can be proposed yet on a role of these cells in the disease. The possible significance of DD in the pathogenesis of CTCL is discussed in detail in another article of this issue.

The presence and possible significance of DC in non-MF/S CTCL have not been extensively studied. CD1a+ DC have been observed in low numbers and scattered distribution in both CD30(Ki−1)+[6, 13] andCD30− large T-cell lymphomas[15, 47] primarily presenting in the skin, but no conclusion can be drawn concerning the possible relationship between the characteristics of DC and the clinicobiologic features of these distinctive subtypes of CTCL (e.g., the DC pattern of regressing skin lesions in CD30+ CTCL is presently not known).

Some recent reports specifically address clinical, histologic, and immunohistologic features possibly useful for the differential diagnosis between CTCL and pseudo-CTCL.[98] Specifically concerning dendritic cells, the dermal infiltrate of MF-like pseudo-CTCL (characterized by a bandlike, epidermotropic infiltration of the skin by cerebriform T cells) seems to contain a percentage of CD1a+ DC lower than that commonly found in plaque-stage MF.[98] It should be interesting to compare MF and drug-induced pseudo-MF on electron microscopy to verify whether some differences do exist comparable to those found between MF plaques and well-developed lesions of LP, a classic model of immune cell-mediated, benign dermatosis.[89] In both cases, DC form an extended cellular network

Figure 3. MF (plaque stage). An indeterminate cell (*ic*, dendritic cell of Langerhans lineage, but without identifiable Birbeck granules) is in close contact with a lymphoid cell undergoing clear-cut blastic transformation (*bc*). Electron micrograph (original magnification ×11,000).

in the dermis and establish close appositions with activated, cerebriform T cells. In LP, however, neither DC showing cytomorphologic signs of activation nor lymphocytes with blastic phenotype are found, thus suggesting that a "physiologic" mechanism of lymphocyte activation is operating in LP. A crucial difference between pseudo-CTCL, histologically characterized by a nodular pattern mimicking that found in pleomorphic CTCL, and true pleomorphic CTCL is the abundance of histiocytic cells in the former;[98] no data on the immunophenotype of these cells are currently available.

DENDRITIC CELLS IN B-CELL PROLIFERATIVE DISORDERS

Dendritic Cells in Normal and Neoplastic Lymphoid Tissue

DRC, whose myelomonocytic origin has been only recently demonstrated unequivocally,[45] are DC restricted to the B-cell areas of secondary lymphoid tissue (e.g., lymph nodes, spleen, tonsils, Peyer's patches), namely, primary and secondary follicles.[127] For this reason, they are also commonly known as *follicular dendritic cells*.[88, 116, 127] They are not identifiable in extrafollicular areas of the lymphoid tissue or in normal extranodal tissues (thymus, liver, skin, or kidney).[138] The detection of these cells by conventional light microscopy is extremely difficult and is made possible by enzyme cytochemistry (5-nucleotidase activity[80]), immunohistochemistry[88] (see following), and electron microscopy.[46, 87] The immunophenotype of DRC may be difficult to assess in situ, owing to the close association between them and surrounding B cells.[89] Therefore, immunophenotyping of DRC has been performed in single cell suspensions, giving controversial results that may be related to the heterogeneity of these cells,[88] as discussed further on. In this article, the anatomy and physiology of B-cell areas of

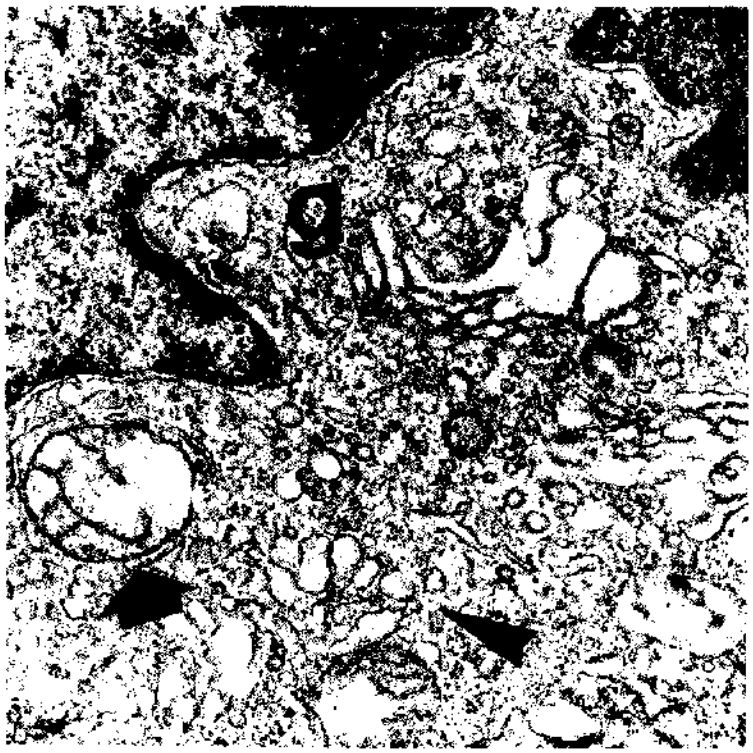

Figure 4. MF (plaque stage). Dermal indeterminate cell showing clear-cut morphologic signs of enhanced functional activity: abundant cytoplasm with large amounts of mitochondria *(arrow)*, multiple Golgi stacks *(g)*, and very high density of tubules and vesicles *(arrowhead)*. Electron micrograph (original magnification ×16,000).

lymphoid tissue cannot be analyzed extensively, and more details can be found in recently published reviews[88]; nevertheless, a simplified description seems necessary to clarify as much as possible the discussion concerning the significance and possible role of DRC in B-cell lymphoproliferative disorders.

In normal lymphoid tissue, DRC form a dendritic network in both primary follicles (in which no antigen-driven processes are taking place) and secondary follicles ("sanctuary" of B-cell differentiation, activation, and proliferation).[73] Concerning their functional significance, a specific role of DRC in B-cell homing is suggested by the expression of VCAM-1 antigen by these cells and of VLA-4 antigen (ligand to VCAM-1) by B lymphocytes.[48, 49] In addition, recent studies[88] suggest that DRC have a significant role in the "trapping" and presentation of antigens (in the form of membrane-bound immune complexes) to antigen-specific B cells, with consequent differentiation, activation, and proliferation.

In primary follicles, DRC form a rudimentary cell network.[73, 88, 127] In secondary follicles, DRC have different features according to their localization. In the germinal center, DRC form a dense, sharply demarcated dendritic web, closely associated with CD10+ B cells (follicular center cells, [FCC]).[73, 88, 116, 127] On electron microscopy, in addition to the aforementioned common features of DC, DRC show characteristic narrow plasma membrane infoldings coated with electron dense material, presumably representing fixed immunocomplexes[46, 87] (see following). The immunophenotype of DRC in the germinal center is fairly constant[88]: DRC-1 (R4/23) +, CD9+, CD11b (C3bi receptor)+, CD14+, CD21 (C3d receptor)+, CD23 (low-affinity receptor for IgE)+, CD35 (C3b receptor)+, CD54 (ICAM-1)+, VCAM-1+, HLA-DR+, acid cysteine-proteinase inhibitor (ACPI) +,[2] nerve growth factor receptor (NGFr)−,[121] and IgG, M, and A+. In non-Hodgkin's lymphomas of FCC origin (known as *FCC lymphoma* or *follicular lymphoma*[70, 88, 116]), showing bcl-2 gene rearrangement[1, 126] related to a chromosomal translocation (t14:18),[132] DRC are a constant finding. They usually retain most of the morphologic and antigenic features found in the normal germinal center, but specifically lack some of them: the electron dense coating of membrane infoldings,[87] membrane-bound immunoglobulins,[88, 116] and ACPI− and NGFr expression.[121] Notwithstanding these morphologic and antigenic aberrations, the capacity to favor B-cell homing and to create an ade-

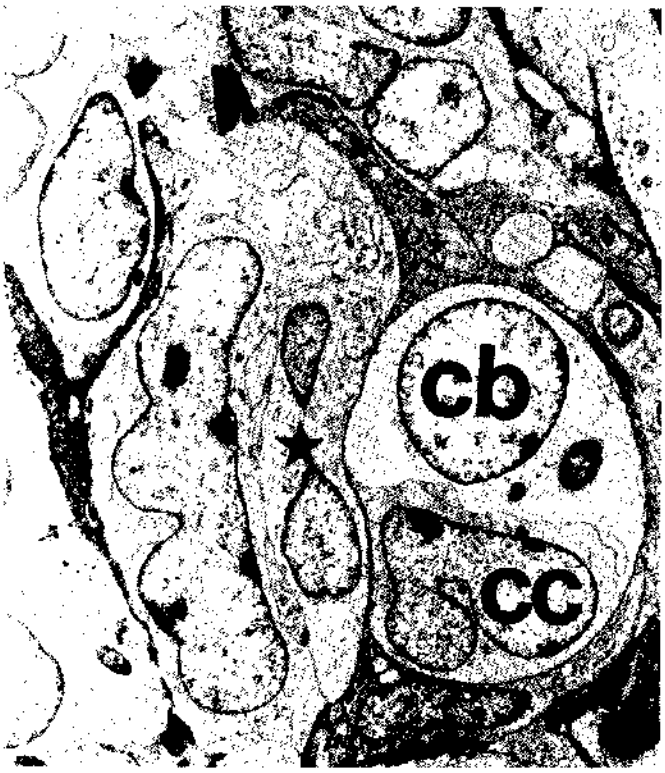

Figure 5. Dermal infiltrate of non-Hodgkin's B-cell lymphoma. Two dendritic reticulum cells *(stars)*, one of which presumably binucleated *(black star)*, establish close contact with blast cells showing a centrocytelike *(cc)* or centroblastlike *(cb)* nuclear morphology. Note the absence of electron dense material between dendritic cells and neoplastic lymphoid cells. Electron micrograph (original magnification ×8,500).

quate microenvironment for the proliferation of B cells seems to be retained in neoplastic conditions, confirming that DRC are a necessary component for B-cell proliferation and suggesting that they can provide a costimulatory signal for neoplastic lymphocytes.[58]

In the follicle mantle (the external portion of secondary follicles), both normal and neoplastic DRC are more loosely arranged[56, 116] and show some significant immunophenotypic differences as compared with those found in the germinal center. In fact, they are CD9−, CD11b+/−, CD14−, CD23−, and IgD+.[29, 29, 54] No lack of specific antigenic markers has been reported so far in lymphomas of follicle mantle origin.[28, 29, 54, 88, 116, 130, 131] In this external portion of secondary follicles, DRC are associated with two main B-cell populations: CD5+/CD10− B cells, and CD5−/CD10− B cells. The former—mantle zone lymphocytes,[130, 131] or mantle cells[70, 88]—may represent the step of B-cell differentiation next to FCC.[73] The CD5− and CD10− cells are particularly well represented in the spleen, where they (*marginal cells*[73]) form a distinct area of the follicle mantle (*marginal zone*), external to that populated by mantle cells (mantle zone). In the lymph node, the CD5−/CD10− B-cell population (parafollicular cells[35, 37, 82]) grow and become clearly evident in some reactive (immature sinus histiocytosis[38, 86, 117]) and neoplastic conditions (known as *parafollicular lymphoma*[35, 37] or *monocytoid B-cell lymphoma*[82, 96, 107, 108]). This parafollicular cell might be interpreted as a B cell that has undergone T-cell–dependent antigen priming and is putatively capable of differentiating into various morphologic subtypes (FCC, mantle cells, plasmacytic cells). This hypothesis is supported by some characteristic features of parafollicular-monocytoid lymphomas. In this peculiar type of lymphoma, typical parafollicular-monocytoid cells are very frequently admixed with other, often monoclonal, cell types: plasmacytic cells (sometimes with transitional forms to typical parafollicular-monocytoid cells) and/or FCC cells and/or mantle cells (often in small clusters), indeed a spectrum of distinct cytologic types originating from one cell, the parafollicular-monocytoid cell.[35, 37, 82, 96, 107, 108] These characteristic features, along with the typical finding of "lymphoepithelial lesions" (clusters of neoplastic B cells infiltrating glandular ducts), have been widely described also in primary extranodal B-cell lymphomas,

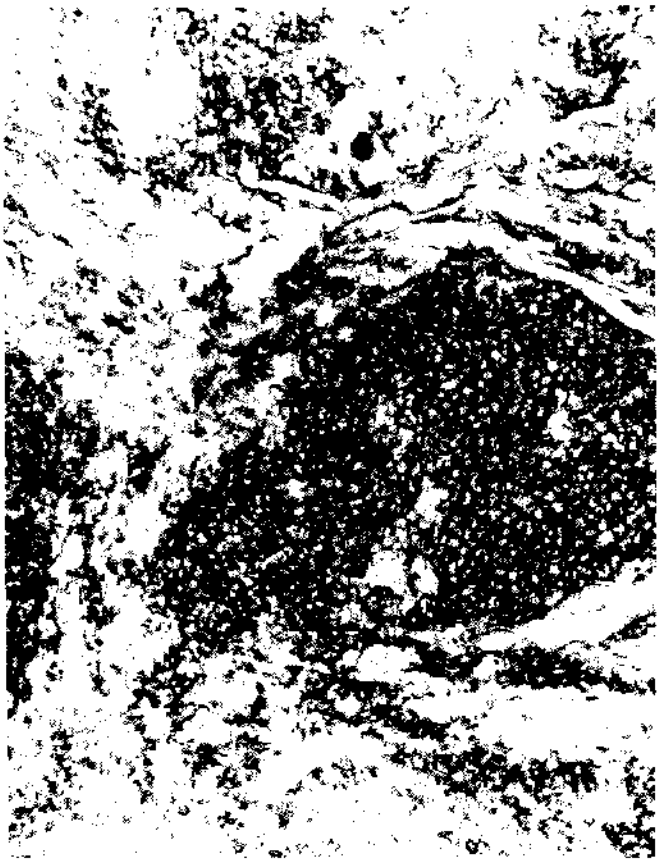

Figure 6. Primary CBCL. Follicielike nodules of CD22+ B cells in the superficial dermis of recently developed lesions. These cells constantly show a CD5 , CD10−, sIg+ (monoclonal) phenotype. Immunohistochemical technique used (APAAP) on frozen section (original magnification ×250).

namely, the so-called MALT lymphoma (lymphoma of the mucosa-associated lymphoid tissue).[66, 84]

Dendritic Cells in Cutaneous B-cell Proliferative Disorders

Since 1981, numerous studies have demonstrated that cutaneous B-cell proliferative disorders are often characterized by the presence of a specialized microenvironment of DRC. The presence of DRC in the skin has been considered specifically related to the FCC homing and, consequently, to the development of "pseudolymphomatous" FCC reactions* or to the localization (primary† or secondary[25, 26, 51, 63, 90, 112, 133]) of neoplastic FCC (FCC lymphoma, follicular lymphoma), independent of the histologic evidence of follicles. According to their ultrastructure, DRC found in the skin infiltrate of FCC lymphomas show a limited degree of morphologic differentiation[90] (Fig. 5), similar to that described in nodal lymphomas.[67]

In a recently published study,[102] we have analyzed—retrospectively and prospectively—a large group of patients with unequivocal diagnosis of primary cutaneous B-cell lymphoma (CBCL). The diagnosis was based on negative staging, positive staining for B-cell restricted antigens CD19/CD20/CD22, and the surface Ig light chain monoclonality of neoplastic B cells, this latter feature being essential for the differentiation from pseudolymphoma.[97] According to our data, CBCL show a constellation of features strikingly similar to those described in parafollicular-monocytoid lymphoma[35, 37, 82, 96, 107, 108] and MALT lymphoma[66, 84]: (1) nonaggressive clinical behavior (preferentially locoregional extension, good response to local treatments, low tendency to spread, and excellent prognosis despite frequent relapses); (2) uniform immunophenotypic (CD5−, CD10−)[14–16, 53, 93, 102, 104] and genotypic features of neoplastic B cells (lack of bcl-2 gene rearrangement),[14, 15, 139] despite the wide variability of cytomorpho-

*References 21, 25, 26, 41, 52, 64, 97, 112, 136, 137, 139
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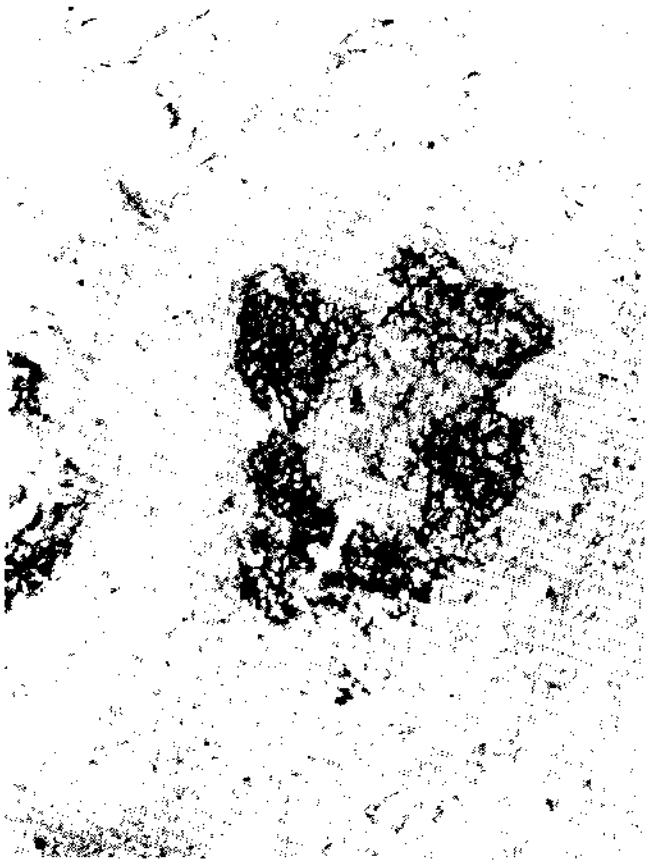

Figure 7. CBCL. DRC-1+ dendritic reticulum cells are clustered with neoplastic B cells (see Figure 6, serial section) in the superficial dermis of recently developed lesions. These cells show an aberrant "centrifugal" pattern and characteristically have a CD14− phenotype. Immunohistochemical technique used (APAAP) on frozen section (original magnification ×250).

logic appearances (the whole spectrum of parafollicular cells, admixed with small lymphocytes, plasma and lymphoplasmacytoid cells); and (3) lymphoepithelial lesions. These features suggest the interpretation of CBCL as the cutaneous counterpart of MALT lymphoma, that is, *skin-associated lymphoid tissue–related B-cell lymphoma*,[53, 93, 102, 104] and lead to hypothesizing their parafollicular origin.[104]

The systematic analysis of biopsies sequentially taken from these patients allows delineation of the histologic and immunohistologic spectrum of CBCL, whose different aspects are largely related to the age and growth rates of skin lesions,[102] without any correlation with clinical course and prognosis (which are good overall). This spectrum ranges from the sometimes inconspicuous "top heavy" infiltrate of intermediate-sized neoplastic B cells (resembling small parafollicular cells[35, 82]) and many reactive T cells observed in early lesions ("low-grade" malignancy picture, classically considered typical of cutaneous pseudolymphomas[21, 25–27, 42, 63, 64, 136, 137]) to the uniformly heavy dermal infiltrate of large neoplastic B cells ("high-grade" malignancy picture) characteristic of late, rapidly growing lesions.

In CBCL, DRC are present in three main fashions[92, 93, 103–104]: (1) associated with CD5− and CD10−, monoclonal, proliferating (Ki-67+ and CD71+) B cells to form follicle-like clusters. These B-cell DRC clusters are mainly found in the superficial dermal infiltrate of recently developed lesions and are irregularly surrounded by reactive T cells and associated CD1a+ DC, thus delineating a quite distinct compartmentalization of the infiltrate not identifiable on histologic grounds alone (Figs. 6 to 8). In this instance, DRC have a DRC-1+/NGFr+/CD14−/CD21(+)−/CD35+ phenotype[102–104] and often show an aberrant "centrifugal" pattern (loosely arranged in ill-defined meshworks with blurred and radiating contours, and skipping the nodule centers)[102] (Fig. 7); (2) scattered among neoplastic B cells, which are intermingled with high numbers of reactive T cells without a clear-cut compartmentalization in the upper and mid-dermis. In this instance, typical of slowly grown, long-standing lesions, DRC

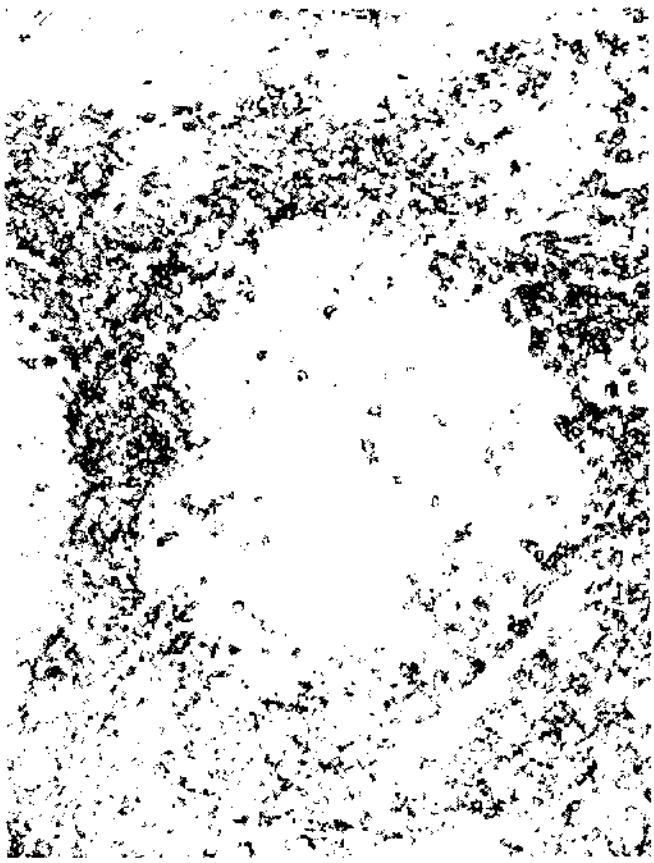

Figure 8. CBCL. CD3+ T cells are abundant and irregularly surround the DRC-B-cell clusters (Figures 6, 7, serial section) in the superficial dermis of recently developed lesions. Immunohistochemical technique used (APAAP) on frozen section (original magnification ×250).

have the same DRC-1+/NGFr+/CD14−/CD21(+)−/CD35+ phenotype; (3) sited in reactive, polyclonal lymphoid follicles, mainly located in the mid-lower reticular dermis of slowly grown, long-standing lesions. These follicles more frequently show a morphologically and immunologically typical organization, that is, a lightly staining germinal center (composed of CD10+ B cells and CD14+ DRC) and a darkly staining mantle (composed of CD5+/CD10− and CD5−/CD10− B cells and CD14− DRC)[102–104] (Fig. 9) and are surrounded by broad strands of neoplastic B cells in a fashion reminiscent of a parafollicular and interfollicular pattern typically observed in parafollicular-monocytoid lymphoma.[102] Parafollicular cells are frequently associated with variable numbers of plasma cells and lymphoplasmacytoid cells, often monoclonal, and a morphologic continuum between parafollicular cells and plasmacytic cells is sometimes evident.[93,102,104] Features resembling lymphoepithelial lesions observed in MALT B-cell lymphoma[66] and other extranodal parafollicular-monocytoid lymphoma,[82, 84] namely, neoplastic cells infiltrating the ductal portion of eccrine sweat glands and the pilosebaceous units, are typically, yet rarely, found.[93, 102] Summarizing, the presence of reactive, polyclonal, typically organized secondary follicles is not necessarily indicative of a reactive, pseudolymphomatous process, and particular attention has to be paid to the features of surrounding B cells: if the latter are virtually all polyclonal, the finding is indicative of pseudolymphoma; on the contrary, if B cells outside the polyclonal follicles are monoclonal (associated or not with sparse polyclonal cells), the finding is definitely suggestive of CBCL.

From a speculative point of view, the evolutionary modifications of skin lesions support the hypothesis that—at the very beginning—DRC favor the homing and proliferation of neoplastic B cells. The neoplastic growth of these B cells is long contrabalanced by a heavy T-cell reaction (also supported by a specific, CD1a+ DC microenvironment) and only late does this control becomes ineffective. Interestingly, however, this neoplastic progression is not accompanied by a parallel worsening of the clinical behavior, which is

Figure 9. CBCL. CD35+ DRC in the germinal center of a reactive, polyclonal follicle in the mid-lower reticular dermis of a slowly grown, long-standing lesion. These follicles more frequently show a morphologically and immunologically typical organization: CD10+ B cells and CD14− DRC in the germinal center, and CD5+/CD10− (mantle cells) or CD5−/CD10− B cells (marginal cells) in the mantle. Immunohistochemical technique used (APAAP) on fixed-embedded material (original magnification ×250).

and remains overall very good. The possible explanation for this discrepancy is given by the putative parafollicular origin of CBCL; in fact, parafollicular-monocytoid nodal lymphoma, MALT lymphoma, and CBCL share nonaggressive clinical behavior and uniform immunophenotype and genotype of neoplastic B cells (CD5−/CD10−; lack of bcl-2 rearrangement).

SUMMARY

In lymphoproliferative diseases of the skin, DC have a key role in T- and B-cell homing. Furthermore, DC alterations may have a pathogenic role in the natural history of specific disorders, either in the neoplastic lymphoid cell progression or in antitumoral lymphocyte reaction. Finally, the morphoantigenic and topographic features of DC may have diagnostic and histogenetic relevance in specific conditions.

In CTCL, dermal CD1a+ DC ("indeterminate cells") seem to play a significant role in the neoplastic progression of MF, whereas the possible pathogenetic role of specific alterations of epidermal LC is yet to be proven. Recently, a possible implication of DD (resident, perivascular factor XIIIa+/CD1a− DC) in the pathogenesis of MF has been also suggested. The presence and possible significance of DC in CTCL non-MF are presently poorly studied. At present, DC number, distribution, and phenotype seem possibly useful in the differential diagnosis between CTCL and pseudo-CTCL, but this hypothesis has to be adequately confirmed.

CBCL has been recently proposed as a unique type of clinically low-grade lymphoma, namely, skin-associated lymphoid tissue (SALT)–related B-cell lymphoma. Both SALT- and mucosa-associated lymphoid tissue (MALT)–related B-cell lymphoma share with a peculiar nodal lymphoma of follicle mantle origin (parafollicular-monocytoid lymphoma) the nonaggressive clinical behavior and the uniform phenotype (CD5−, CD10−) and genotype (lack of bcl-2 gene rearrangement) of neoplastic B cells, despite the wide variability of cytomorphologic appearances. The putative origin of CBCL is further supported by the typical CD14−, nerve growth factor receptor (NGFr)+ immunophenotype of DRC. Moreover, the immunophenotype and architectural fashion of DRC are interesting clues to the differentiation between neoplastic and true reactive folliclelike nodules and may be of help in the differential diagnosis between CBCL and B-cell pseudolymphoma as well as in the correct interpre-

tation of lesions showing monoclonal proliferations of B cells accompanied by polyclonal follicular reactions.

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