28 Inflammatory Dendritic Epidermal Cells

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Many chronic inflammatory skin diseases share distinct clinical and histological features such as a lymphohistiocytic infiltrate [1, 2]. Specific clinical and therapeutic considerations have formed the scientific basis for subdivision of this heterogeneous disease group long before our understanding of their individual pathophysiology increased within time. Our current understanding of chronic inflammatory skin diseases implies that the cellular infiltrate mainly composed of T cells has to be initiated or sustained by antigen-presenting cells (APC). As a rule, T cells require efficient stimulation by these cells in order to become effector cells and to be implicated in a pathophysiological process. Consequently, it is assumed that APC play a key role in driving the inflammatory reaction in atopic eczema (AE) lesions [3–5]. APC are a functionally defined, heterogeneous group of cells including macrophages, B cells, and dendritic cells (DC). The latter are a morphologically and functionally defined, growing cell family, which are found in small percentages in most organs of the human body [6, 7] and may be further divided into a myeloid and a lymphoid type of DC. DC are the most efficient of all APC and are capable of the initiation of both primary and secondary immune responses.

28.1 Langerhans Cells

Langerhans cells (LC) are the DC of the normal epidermis and probably the best-characterized DC population of the human body. When the medical student Paul Langerhans (1847–1888) described in his thesis a novel, dendritically shaped cell type of the epidermis, he assumed these to be cutaneous outposts of the nervous system [8]. During the last century, a number of most relevant findings have changed our understanding of this cell type. In 1961, the LC granule (Birbeck granule) was shown to be the most specific ultrastructural characteristic of the LC [9]. The antigen-presenting capacity of these cells was clearly demonstrated by a number of experiments [10, 11], leading to a functional reclassification of the LC to the APC of the immune system. The intraepidermal network of the LC and their dendrites is nowadays regarded as a first barrier of the immune system towards the environment. LC are the exclusive DC population of the normal, uninflamed human epidermis and may initiate primary and secondary immune responses. Surface expression of the nonclassical MHC molecule CD1a on LC was demonstrated in 1981 [12] and is still regarded as the most specific immunohistological marker of LC in normal human skin. Routine light microscopic examination shows the LC as a clear cell in the suprabasal layer of the epidermis. LC and their dendrites may be identified by immunohistological staining of their surface molecules HLA-DR and CD1a. Today, LC are defined as bone marrow-derived, epidermally located, dendritically shaped APC, which contain Birbeck granules and express CD1a and MHC-class II molecules [13].

28.2 Inflammatory Dendritic Epidermal Cells

During the last years, accumulating data indicates the presence of a second epidermal dendritic cell type which is exclusively present in inflammatory skin lesions. These inflammatory dendritic epidermal cells (IDEC) have been defined as epidermally located, dendritically shaped cells, which do not contain Birbeck granules and express CD1a, CD11b, and class II mole-

cules [14]. As a rule, all inflammatory skin diseases associated with a lymphohistiocytic skin infiltrate are associated with the occurrence of IDEC in the epidermis. AE, psoriasis vulgaris, allergic contact eczema, mycosis fungoides, lichen planus as well as the more uncommon diseases Dorfman-Chanarin syndrome, Netherton syndrome, Oid-Oid disease, and others are bearing variable percentages of IDEC within the epidermis [15 – 17]. This article summarizes the published data and current understanding of these IDEC with respect to immunophenotype, ultrastructure and function.

28.3 Delineation of Inflammatory Dendritic Epidermal Cells from Langerhans Cells

When the term IDEC was introduced by us in 1996 [14], earlier work from different research groups had already demonstrated either some epidermally located, dendritically shaped cells lacking Birbeck granules or some immunophenotypically defined subpopulations of epidermally located, MHCII positive cells [18 – 20]. In addition, the expression of the high-affinity-IgE-receptor FcεRI on epidermal DC of normal human skin had been demonstrated by us and others a few years ago [21 – 23].

In combining flow cytometric and immunoelectron microscopic techniques to study epidermal DC isolated from lesional skin of AE and other inflammatory skin diseases, we were able to link the two immunophenotypically distinct epidermal cell populations with the two ultrastructurally different cell types [14]. The classic LC were ultrastructurally characterized by a clear cytoplasm, a lobulated nucleus, the lack of desmosomes, melanosomes or Merkel cell granules and, most importantly, by the presence of the highly specific, tennis racket-shaped, cytoplasmic Birbeck granules. In contrast, IDEC showed a relatively invariable CD1a+++, FcεRI+, FcγRII++, HLA-DR+++, CD11b- immunophenotype. The ultrastructure of IDEC resembled that of LC because of their clear cytoplasm, lobulated nucleus and lack of desmosomes, melanosomes, and Merkel cell granules, but IDEC did not contain any Birbeck granules; their immunophenotype was constantly CD1a++, HLA-DR++++, CD11b- and FcγRII++, but the high-affinity IgE-receptor expression varied strongly according to the diagnosis from FcεRI+ to FcεRI+++ (Fig. 28.1). The

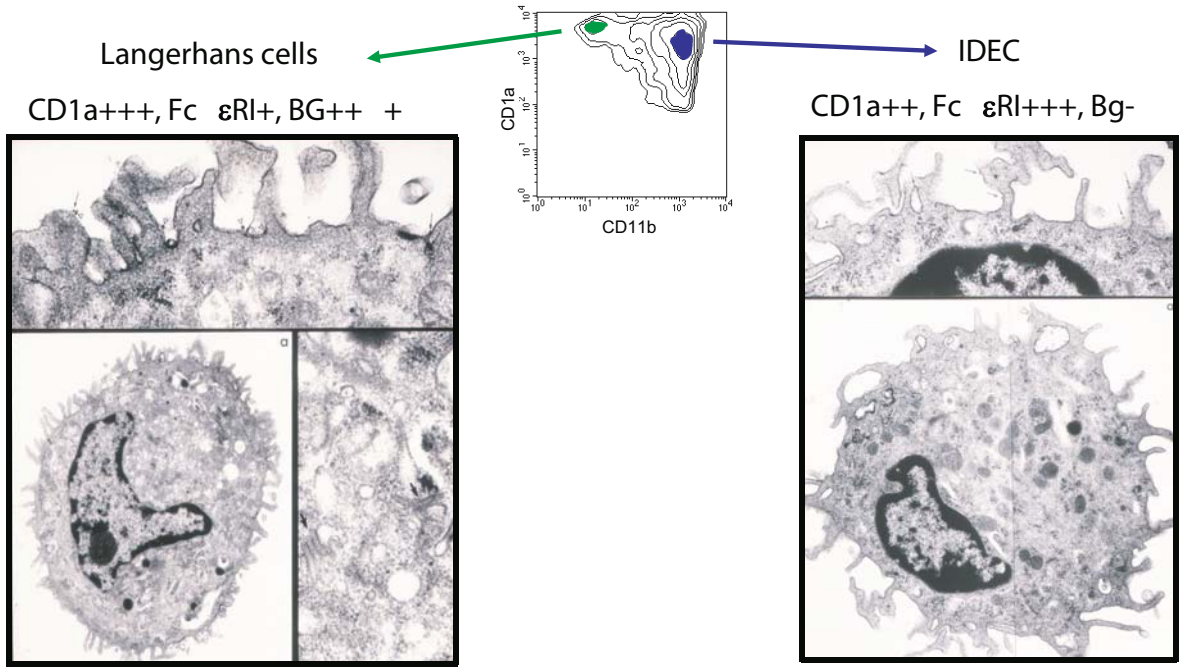

Fig. 28.1. Phenotypic and ultrastructural characteristics of Langerhans cells and IDEC

identity of the two ultrastructurally different cell types with the two immunophenotypically different cell populations was formally shown by a combination of double immunoelectron microscopy and the flow cytometric detection of the Birbeck granule-specific LAG antigen CD207 [14].

28.4 Ontogenesis of Inflammatory Dendritic Epidermal Cells

The ontogenesis of IDEC has not been resolved yet, but unpublished (Moderer et al., in preparation) as well as published data [24, 25] show that IDEC and immature MoDC share many phenotypic and functional similarities. As the cytokines GM-CSF and IL-4/IL13 are known constituents of the inflammatory microenvironment of AE lesions [26 – 29], it is assumed that IDEC may derive from monocytic cells which have invaded the skin lesions and have matured into myeloid dendritic cells in response to the inflammatory environment.

28.5 Inflammatory Dendritic Epidermal Cells Are Present in Early Atopic Eczema Lesions

Since IDEC had only been demonstrated in untreated chronic inflammatory skin diseases, a novel series of experiments was performed to elucidate the role of IDEC in early, developing lesions of AE. This series of experiments involved the recently standardized atopy patch test [30], which is an epicutaneous application of intact protein allergens relevant to AE in an otherwise classical patch test setting, as a model for early lesions of AE. It turned out that the influx of IDEC is an early event in formation of the IgE-associated „extrinsic“ as well as the non-IgE-associated „intrinsic“ AE lesions [31]. In contrast, the characteristic phenotype of the IDEC, providing the basis for diagnostic immunophenotyping [17], takes a few days to develop [31].

28.6 Inflammatory Dendritic Epidermal Cells Are Present in Extrinsic and Intrinsic Atopic Eczema

Evidence from different research groups has supported the concept of two different subtypes of AE: the „extrinsic“ or „allergic“ form (occurring in the context of sensitization towards environmental allergens) and the „intrinsic“ or „nonallergic“ form (occurring in the absence of an atopic background) [32, 33]. Based on our current understanding of AE, APC should be involved in both forms of this disease [34].

Skin lesions from extrinsic and intrinsic AE patients were recently analyzed by epidermal dendritic cell phenotyping (EDCP) and showed a comparably high expression of the thrombospondin receptor CD36, indicating a similar disease activity in both subgroups of the disease [35]. Furthermore, no significant differences in the presence of LC and IDEC were detected. However, epidermal DC of extrinsic AE showed a significantly higher FcεRI expression than IDEC from intrinsic AE. In addition, the diagnostic FcεRI/FcγRII expression ratio was significantly elevated in extrinsic but not intrinsic AE, indicating immunodermatological differences between these two subtypes of disease [35].

28.7 IgE-Receptor Expression of Inflammatory Dendritic Epidermal Cells

With the delineation of IDEC from LC in inflamed skin, a number of features previously attributed to LC needed to be re-evaluated if they were actually LC-based or IDEC-based findings. Although earlier work had claimed that LC were the IgE-binding and FcεRI-expressing epidermal DC population in AE lesions [36 – 38], we could actually show that IDEC and not LC are the relevant IgE-binding and FcεRI-expressing epidermal dendritic cell population, [14, 17] and that their immunophenotype varies with the inflammatory microenvironment of the underlying skin disease. This FcεRI expression correlated significantly to the total serum IgE level, suggesting an IgE-dependent regulation of the FcεRI expression or an at least in part common regulation of both molecules [14]. Atopy patch test reactions were recently investigated as a model for

early AE lesions, identifying the ultra high FcεRI expression on IDEC as a late event during formation of the lesion, whereas the influx of IDEC is an early event [31]. The addition of reducing agents such as beta-mercapto-ethanol or di-thio-threitol to monocyte cultures increases the expression of FcεRI in the monocyte-derived dendritic cells (MoDC), which can be used as a model for IDEC [24]

Since the expression of the low affinity IgE receptor CD23 had remained a matter of debate, we readdressed this issue in different inflammatory skin diseases [39]. It was the IDEC population and not the LC which stained positive with two different CD23-specific antibodies, but acid stripping control experiments revealed that this CD23 was the soluble form of CD23 passively attached to the cell surface and not the membrane-bound form known to be expressed on B-lymphocytes [39].

28.8 In Situ Expression of Costimulatory Molecules on Inflammatory Dendritic Epidermal Cells

Costimulatory molecule expression by APC is a prerequisite for the successful initiation of an immune response. Expression of CD86 (B7-2) and CD80 (B7-1) had been demonstrated on CD1a expressing epidermal DC in AE lesions by immunohistological and functional analysis in 1997 [40, 41], but the authors did not differentiate between LC and IDEC.

We demonstrated CD80 as well as CD86 positive, dendritically shaped cells within the lesional epidermis and dermis of AE by immunohistological technique, suggesting them to be either LC or IDEC [42]. Double immunofluorescence staining of isolated epidermal cells showed only minute amounts of both CD80 and CD86 on freshly isolated LC from normal human skin. In contrast, LC from inflammatory skin expressed higher amounts of both structures. In all biopsies investigated, IDEC showed a significantly higher expression of both CD80 and CD86 than the corresponding LC and AE lesions and showed a higher expression as compared to psoriasis or contact dermatitis [42]. Upon short-term culture, both LC and IDEC showed an almost identical strong upregulation of CD80 and CD86. Finally, a functional role of the CD86 expression was shown by thymidine incorporation assays and a blocking monoclonal antibody [42]. Keeping in mind the hyperstimulatory capacity of the epidermal DC suspensions in AE [43], our findings support the concept of a role for the IDEC in the presentation of antigens in AE skin.

28.9 Pinocytosis and Receptor-Mediated Endocytosis of Epidermal Dendritic Cells

As many fungal antigens from *Pityrosporon* species are mannosylated, we were interested in the expression and function of the human mannose receptor CD206 on epidermal DC from AE lesions. This 175-kD transmembrane glycoprotein is characterized by 8 N-linked glycosylation sites and 8 C-type lectin carbohydrate recognition domains [44]. Controversial data had been obtained about the expression of CD206 on LC from normal human skin [45–47], and there was no published data on inflamed skin.

We detected a membranous staining pattern of CD206 expressing DC in the dermal and epidermal compartment of inflamed skin by immunohistochemistry [25]. Flow cytometric analysis revealed CD206 expression on monocyte-derived dendritic cells (MoDC), whereas freshly isolated monocytes and LC from normal and inflamed human skin were CD206 negative. A high CD206 expression was found on IDEC in AD and psoriasis [25].

CD206-mediated endocytosis was demonstrated by Dextran-FITC uptake time course studies in MoDC and could be blocked by the addition of mannan, whereas CD206-independent pinocytosis was assessed with the fluorescent dye Lucifer yellow. Similar to MoDC, freshly isolated IDEC showed a significant uptake of dextran-FITC in a time dependent manner. By preincubation with mannan, only half of the CD206-mediated dextran-FITC uptake could be blocked. This argued for a second, CD206-independent pathway of uptake, which might be based on the pinocytotic activity of IDEC demonstrated by Lucifer yellow uptake [25].

Electron microscopy of IDEC revealed ultrastructural signs of receptor-mediated endocytosis: Numerous clathrin-coated pits and vesicles were observed in 50 % – 100 % of all IDEC close to their cell membrane. The coated vesicles made contact with larger endosome-like structures, suggesting a fusion of the coated vesicles with the larger endosome-like structures and a high endocytotic activity of the IDEC [25]. Immuno-

gold staining of IDEC for CD206 showed gold particles both on the cell surface and intracellularly, thus confirming the results obtained by immunophenotyping [25].

Thus, CD206 on IDEC is functional in terms of antigen uptake of mannosylated antigens by means of mannose-receptor mediated endocytosis. This mechanism may play a role in *Pityrosporon ovale*-associated head and neck dermatitis, a clinical subtype of AE.

28.10 Diagnostic Epidermal Dendritic Cell Phenotyping

The immunophenotype of IDEC has been investigated by us in epidermal single cell suspensions from more than 950 inflammatory skin lesions using a standardized, quantitative flow cytometric technique. It is based on an indirect triple staining for unfixed, vital epidermal cell suspensions and allows a separate analysis of the LC and IDEC immunophenotype on a single laser equipped flow cytometer in one single vial [17]. The immunophenotype of IDEC has been thoroughly investigated and includes Fc-receptors, MHC molecules, adhesion molecules, chemokine receptors, the costimulatory molecules CD80 and CD86, the thrombospondin receptor CD36, and the mannose receptor CD206. Soon it became clear that a number of IDEC surface receptors show a variable expression, whereas others follow a quite stable expression pattern (see Table 28.1). Based on our initial findings of a disease-specific upregulation of FcεRI in AE, we proposed epidermal DC phenotyping as a diagnostic tool for differential diagnosis of inflammatory skin diseases. We were able to identify AE lesions with a high sensitivity and specificity from all other skin diseases by calculation of an expression ratio of FcεRI and FcγRII/CD32 and a threshold value of 1.5 [48]. In addition, the high expression of the two Fc-receptors for IgG, CD32, and CD64 is a diagnostic hallmark of psoriasis vulgaris [49]. In contrast to skin prick tests and in vitro IgE tests, this technique allows the individual analysis of different skin lesions in a single patient.

Table 28.1. Expression of surface molecules on epidermal dendritic cells in the inflamed epidermis, shown for LC and IDEC. While some surface markers are showing a rather stable expression, others are subjected to strong regulatory signals from the epidermal micromilieu

	LC	IDEC
CD1a	+++	+/++
CD1b	ø	+/++
CD9	++	++
CD11a	ø	++
CD11b	ø/±	+++
CD11c	+	+++
VLA4/D49d	+	+/++
FcεRI	ø/++	+/+++
FcεRII/CD23	ø/+	ø/++
FcγRI/CD64	ø/+	++
FcγRII/CD32	++	++/+++
CD36	ø/+	++/+++
MR/CD206	ø	++
LAG/CD207	++	ø

28.11 Epidermal Dendritic Cells in Skin Lesions Under Topical Therapy

Though topical glucocorticosteroids are still considered the mainstay of AE therapy, the recently licensed topical immunomodulators (TIM) tacrolimus and pimecrolimus are an increasingly used therapeutic alternative for AE [50]. Lymphocytes are well-known target cells, and there is also evidence for an effect on mast cells, endothelial cells, and eosinophils, but little was known about its mode of action on epidermal DC. Therefore, a first study of the effects of tacrolimus ointment on epidermal DC was performed, which included immunohistological analysis, EDCP and skin mixed lymphocyte reactions on skin biopsies from treated and untreated lesional skin of 10 AE patients participating in a clinical trial with tacrolimus ointment [51].

Untreated AE lesions were characterized by a high proportion of CD1a+ cells, which was largely due to a high proportion of IgE-bearing IDEC strongly expressing FcεRI [52]. Epidermal cell suspensions from untreated AE lesions exhibited a high stimulatory activity towards their autologous T cells, which was strongly reduced as clinical improvement was seen with tacrolimus therapy [52]. Concomitantly, a decreased FcεRI expression was observed in both LC and IDEC. Finally, tacrolimus ointment led to a progressive decrease in the IDEC population within the pool of CD1a+ epidermal DC and also to a decrease in their CD36 expression, which is indicative of lower local inflammation [52].

In a next step, ex vivo studies were performed in AE patients treated with either hydrocortisone butyrate or tacrolimus ointment in a phase III study [53]. At this time, cell suspensions were prepared for EDCP from AE lesions before and after 1 week of therapy. Epidermal DC numbers decreased markedly during treatment with tacrolimus and hydrocortisone ointment. Thereby, only a slight decrease of LC was seen, in contrast to a highly significant, 75% reduction in the cell number of IDEC [54]. Topical treatment with tacrolimus and hydrocortisone led to a clinical improvement of the skin lesions, which was accompanied by a reduced expression of the costimulatory molecules CD80 and CD86 on epidermal DC. Consequently, the diagnostic FcεRI/CD32 ratio fell below the threshold value of 1.5 [54]. Apoptosis of LC and IDEC was assessed by annexin V and TUNEL technique. The rate of early apoptotic DC in situ was increased in hydrocortisone-treated AE lesions, whereas tacrolimus treatment did not increase the percentage of apoptotic epidermal DC [54. In summary, tacrolimus ointment treatment of AE changes the immunophenotype of epidermal DC and leads to a depletion of IDEC from the epidermis, but does not seem to induce apoptosis of epidermal DC in vivo.

28.12 Outlook

During the last years, many phenotypic and ultrastructural features of IDEC have been identified, and there is considerable evidence for a monocyte-derived origin of IDEC and their active role in the pathogenesis of chronic inflammatory skin diseases, and especially in AE. Further investigations of IDEC are in progress by us and others, and will hopefully increase our understanding of the skin immune system in general and the role of epidermal dendritic cells in the pathogenesis of allergic skin diseases.

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