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Dendritic cells in allergy

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Introduction

Evolution has provided two distinct and highly sophisticated defense mechanisms to human beings for survival in a hostile environment. The innate immune system is aimed to react rapidly (from within minutes to a few hours) and in a rather simple way with little variation to attacks of pathogens. In contrast, the acquired immune system provides a more adaptive and highly specific defense response to foreign structures. In addition, it has the unique ability to induce tolerance of self-structures. The mechanisms of acquired immunity involve several steps of recognition and reactions in which various different cell types are engaged. Among antigen-presenting cells (APC), dendritic cells (DC) fulfill a pivotal function by providing information about invading pathogens under optimal conditions to other partners (e.g., effector cells) of the immune system. Thus, after having been neglected for years, DC research is experiencing a revival due to the central role of these cells in the complex machinery of the adaptive immune response. Moreover, understanding the role DC play in pathophysiologic conditions may be a key step in developing treatment strategies for several disease entities.

Since many different DC types have been identified during the last years, including follicular DC and thymic DC, the present review will focus on the "classical" DC as they have been described initially by Steinman and Cohn.

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Dendritic cells 130 years after Paul Langerhans

The first member of the DC system was described more than 100 years ago by Paul Langerhans (1868) and was originally thought to be a type of cutaneous nerve cell. After it had then been considered for a time to be an immature melanocyte, Birbeck (1) described the unique ultrastructural feature of the Langerhans cell (LC), which was named after him. Birbeck granules (BG) are rod-shaped structures with a central, periodically striated lamella and, depending on the section viewed, are tennis-racket shaped. BG are found exclusively in LC from man and other mammals, but not in other DC. They are considered the primary marker of epidermal LC. Nowadays, LC are best recognized in the skin by their CD1a expression.

In the 1970s, Steinman & Cohn first described the structure and function of DC from mouse spleen suspensions (2). Morphologically, DC are characterized by their numerous thin, elongate cytoplasmic processes, which give them a veil-like appearance. They exhibit features of metabolically active cells with scattered mitochondria; a recognizable Golgi apparatus; some lysosomes, phagolysosomes, and lipid droplets; and a well-developed endoplasmic reticulum. They have large and often indented nuclei with heterochromatin preferentially deposited at the nuclear membrane (3). DC have been found in virtually all types of epithelia (skin, mucous membranes, lung) and as interstitial DC in the heart and kidney as well as in other organs. In addition, various subtypes of DC were also discovered in blood and in the lymphatic system (4). These represent different stages of maturation and are connected by circulatory pathways. Beside their typical dendritic structure in tissue and in suspension, DC were initially characterized mainly by their high expression of major histocompatibility complex (MHC) class II HLA-DR and their high stimulatory activity toward allogeneic T cells.

Dendritic cells: “nature’s adjuvant”

Although they ultimately act as highly specialized APC, DC have to undergo four main stages of differentiation and maturation before they fulfill their main function in the lymphoid organs.

Ontogenesis

Since the first demonstration that epidermal LC are derived from bone-marrow cells by Katz et al. (5), many efforts have been made to characterize the precursor cells of DC and LC in bone marrow and blood (Fig. 1). Thus, the ontogenesis and the development of techniques for *in vitro* generation of DC have been the focus in this field of research, especially considering possible therapeutic implications (see below).

Although it is well established that DC derive from bone-marrow CD34⁺ stem cells, two main strategies have been followed over the past years. First, in 1992, Caux et al. described a system that generates CD1a⁺ LC-like DC from CD34⁺ stem cells by supplementing granulocyte/macrophage colony stimulating factor (GM-CSF) and tumor-necrosis factor alpha (TNF- α) (6). The generation of LC/DC was optimized later by adding stem cell factor (SCF) and/or FLT-3 ligand, resulting in a higher yield of CD1a⁺ cells, with a typical dendritic structure, strong expression of MHC class II antigens, CD4, CD40, CD54, CD58, CD80, CD83, and CD86, and the presence of BG in 10–20% of the cells. Most importantly, these cells exhibit a potent capacity to stimulate the proliferation of naive T cells and to present soluble antigens to clones of CD4⁺ T cells.

On the other hand, in 1994, Sallusto & Lanzavecchia (7) were able to generate CD1a⁺ DC corresponding to interstitial DC in their phenotype by culturing monocytes with GM-CSF and interleukin (IL)-4. CD14⁺ monocytes undergo maturation into CD1a⁺ DC, which, however, lack BG and are therefore not considered LC but are more similar to dermal DC since they express CD11b, CD68, and the coagulation factor XIIIa. Typically, after 7 days of culture with GM-CSF and IL-4, monocytes give rise to immature DC which need further stimulation with CD40 ligand, endotoxin, or TNF- α to reach the full maturation stage of highly stimulatory DC.

However, if monocytes are cultured with macrophage colony stimulating factor (M-CSF) alone, they differentiate into macrophage-like cells (CD14⁺, CD1a[−], CD83[−]) and synthesize IL-10 (8).

While these DC are now classified as myeloid DC because they are known to derive from myeloid precursors (see below), more recently, a novel type of so-called lymphoid DC has been described. These lymphoid DC derive from CD4⁺/CD3[−]/CD11c[−] plasmacytoid cells from the blood and the tonsils (9, 10). These precursors do not differentiate into macrophages with GM-CSF or M-CSF. Lymphoid DC are dependent on IL-3, but not on GM-CSF, and are less active in phagocytosis.

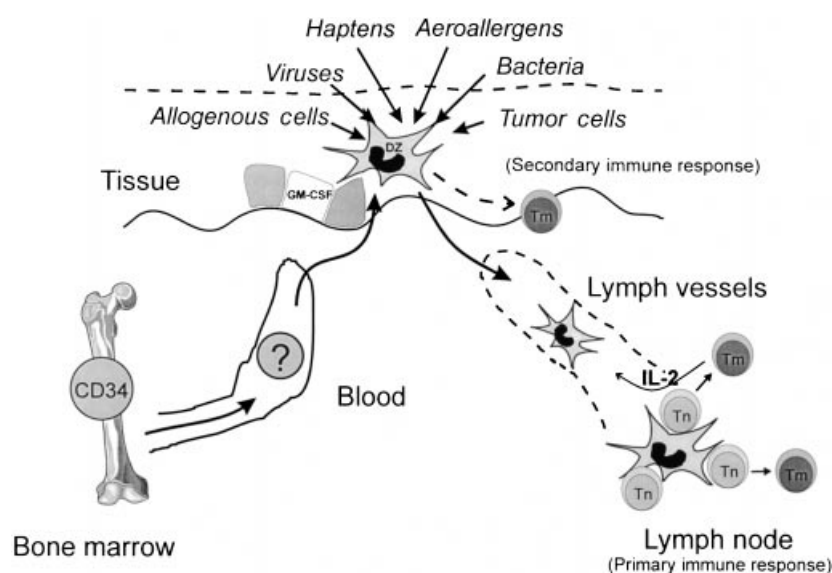


Figure 1. Ontogenesis of dendritic cells (DC). Before being able to activate naive T cells (Tn) (primary immune response), DC must undergo profound maturation step which occurs during their migration to regional lymph nodes. In peripheral tissue, DC may also trigger secondary immune response when encountering memory T cells (Tm) in transit through tissue.

Antigen uptake

When localized in peripheral blood or in nonlymphoid tissue, DC are considered to be functionally immature. This refers to the fact that DC in tissues are highly specialized for capturing and processing foreign or autologous protein antigens or haptens. Uptake of high-molecular-weight antigens by DC may occur through macropinocytosis or more specifically through a number of membrane receptors such as $\text{Fc}\gamma\text{RII}$ and $\text{Fc}\epsilon\text{RI}$ loaded with the adequate antibodies. DC also express membrane receptors bearing multiple lectin domains such as the mannose receptor and the DEC-205 molecule (11). These structures enable DC to internalize antigens by receptor-mediated endocytosis, a pathway which leads to antigen uptake into specialized compartments inside DC and allows efficient processing and subsequent loading of these antigens on MHC class II molecules. In contrast, uptake of low-molecular-weight haptens, e.g., DNCB or oxazolone (12, 13), mostly occurs via binding to surface glycoproteins and subsequent internalization. Experiments with MHC knockout mice suggest that presentation of such haptens is achieved through MHC class I molecules to CD8^+ T cells rather than via MHC class II. A further characteristic of DC is the high stability of MHC class I or class II molecules on their cell surface, allowing them to be loaded for a long time with defined antigens. At this stage of maturation, DC are able to stimulate memory T cells trafficking through the tissue, initiating a secondary immune response at the site of contact with the captured antigen. However, since macrophages and other cells are as efficient as DC in this type of stimulatory activity, it is

assumed that triggering a secondary immune response is not the primary task of DC under normal conditions.

Migration and maturation

In recent years, it has become clear that the migration of many cell types including DC is tightly regulated by chemokines. The expression of chemokines at different anatomic sites and in different pathologic states in combination with the differential expression of chemokine receptors on cells during different maturation stages is the basis of a complex signaling network that orchestrates cell migration and cell interaction in the immune response (14). Specifically for DC, it has been shown that the chemokine receptor profile expressed on immature DC (CCR1 , CCR2 , CCR5 , and CCR6) mainly recognizes chemokines that are released during inflammatory processes. This allows the accumulation of DC that are geared toward antigen uptake at sites of inflammation. Release of cytokines such as IL-1 and $\text{TNF-}\alpha$ further perpetuates this process by inducing immature DC to release even more inflammatory chemokines. Conversely, mature DC downregulate their receptors for inflammatory chemokines and express different chemokine receptors (CCR4 , CCR7 , CXCR4 , SLC , and ELC). These allow them to receive signals which will attract them to the regional lymphatics and eventually to the T-cell-rich areas of the lymph node.

Thus, after antigen uptake, tissue DC migrate to the regional lymph nodes. For example, LC seem to be able to migrate quite fast; i.e., several millimeters within 30 min (15). On their way to the lymph node, DC begin a profound

metamorphosis, leading to significant changes in their structure and phenotype. In the afferent lymphatic vessels, DC have been described as so-called veiled cells and as interdigitating cells in the T-cell-rich paracortical zones of secondary lymphoid tissues. As DC mature, they lose their antigen uptake capacity and their function shifts toward antigen presentation. One of the hallmarks of this development is the upregulation of peptide-loaded MHC class II and costimulatory molecules (CD80, CD86) on the surface of these cells. In the meantime, DC rapidly downregulate and sometimes completely abolish the expression of Fc receptors. Migration and maturation of DC seem to be linked processes *in vivo* since factors such as lipopolysaccharides (LPS), TNF- α , and IL-1 induce both processes (16). *In vitro*, TNF- α has been shown to induce maturation of monocyte-derived DC, also leading to upregulation of CD80, CD86, CD83, and MHC class II. All these molecules are crucial for efficient antigen presentation to resting naive T cells.

Antigen presentation

Priming of naive T cells is one of the crucial tasks that DC have to fulfill. To do so, DC and naive T cells have to colocalize in the paracortical zone of the lymph nodes. An interesting finding was the fact that naive T cells express chemokine receptors (e.g., CCR7) that allow them to receive the signals sent by mature DC which release ELC and DC-specific chemokines (DC-CK1). After having reached the T-cell area, a single DC can prime hundreds of naive T cells. In this process, peptides bound to MHC class II or MHC class I on DC are presented to T cells via the T-cell receptor complex (TCR). Recently, it became clear that, in addition to the signals received via the TCR, costimulatory signals are of key importance in initiating and directing a T-cell response. Interaction of the costimulatory molecules CD80 and CD86 with their counterparts on T cells, i.e., CD28 or CTLA-4, determines whether this stimulation will result in an antigen-specific proliferation of T cells or tolerance. Indeed, additional factors present at the site of DC-T-cell interaction such as IL-10 may modify CD80/CD28 signaling by blocking downstream events in signal transduction, thereby leading to antigen-specific tolerance (17).

An important observation was that DC can release IL-12. This cytokine is involved in the induction of a Th1 T-cell response. Likewise, other cytokines such as IFN- γ may induce a Th1 response, whereas IL-4 has been shown to direct the T-cell response toward Th2. This capacity to influence the type of T-cell response may explain why some antigens induce an allergic reaction and others do not. It is

interesting that the cytokines and factors released during T-cell priming also induce a different chemokine receptor repertoire on stimulated T cells. Whereas Th1 cells express CCR1, CCR2, CCR5, CXCR3, and CXCR5, Th2 cells are characterized by the expression of CCR2, CCR3, CCR4, and CXCR5 (14). The differential expression pattern may recruit these cells to specific types of inflammation (allergic vs nonallergic) and determine which other cell types may be involved in a particular inflammatory response. As far as allergic reactions are concerned, it is noteworthy that Th2 cells, eosinophils, and basophils share the expression of the chemokine receptor CCR3, whereas Th1 cells and monocytes, which can differentiate into DC, share CCR1 and CCR5.

Once antigen presentation has been achieved, DC are not supposed to recirculate in peripheral blood or lymphatic vessels. Indeed, it is assumed that DC will be killed by T cells or will die by apoptosis on site (18, 19).

Dendritic cells and allergy

As mentioned above, the primary task of DC is to inform the immune system about the invasion of foreign and potentially harmful proteins. Much interest has been focused over the last 25 years on the possible pathophysiologic role of DC in a variety of conditions, especially in allergic inflammatory diseases.

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is the archetype of cell-mediated hypersensitivity reactions in which DC play a pivotal role in the sensitization process. While the contact of irritant compounds on the skin leads to the secretion of TNF- α and GM-CSF by keratinocytes, low-molecular-weight haptens (e.g., nickel, DNCB, or oxazolone) stimulate the additional release of IL-1 α , IP-10, and MIP-2. These chemokines activate DC and endothelial cells, leading to an accumulation of even more DC at the site of antigen contact. Moreover, application of hapten induces the release of IL-1 β by epidermal LC and thereby promotes their egress from the epithelium.

After the uptake of the antigen, DC process it while migrating to the regional lymph nodes where it will be presented to antigen-specific naive T cells. Little is known about the mechanisms which enable DC to be highly efficient in priming naive T cells. Another remarkable property of DC is their ability to present exogenous antigens

on MHC class I and II molecules. This leads to the activation of both CD4⁺ and CD8⁺ hapten-specific T cells (20, 21). Whereas classical delayed-type hypersensitivity reactions are mediated by CD4⁺ effector cells, contact dermatitis is mediated by CD8⁺ effector cells (22–24). Other cytokines released during the sensitization process have been implicated in directing the type of immune response mounted by T cells. It has been shown that IL-10 converts LC/DC from potent inducers of a primary immune response to hapten-specific tolerizing cells. A significant decrease in mRNA signals for IL-1 α , IL-1 β , and TNF- α confirms the immunomodulatory role of this cytokine in contact hypersensitivity reactions (25, 26). On the other hand, IL-12 which is released by keratinocytes and by DC themselves (25, 27), is known as a strong inducer of the Th1 response.

After a second contact with a contact allergen, antigen-specific memory T cells can be stimulated either by DC or by APC less potent than DC (e.g., macrophages or monocytes) and, due to their specific homing molecules, elicit an immune response at the appropriate anatomic site.

Atopic diseases

Atopic diathesis is characterized by three major diseases, i.e., allergic rhinoconjunctivitis, allergic asthma, and atopic dermatitis, and is usually associated with elevated serum IgE. Thus, it is assumed that mechanisms regulating IgE synthesis, e.g., secretion of IL-4 and IFN- γ , are of crucial importance in atopic diseases. Consequently, specific IgE may play a role in the initiation of these conditions.

Myeloid DC (DC1) are responsible for Th1 and lymphoid DC (DC2) for Th2 outcome in T-cell stimulation

Since most of the allergens atopic patients react to, do not have direct access to B cells in the blood or in lymphoid tissue, allergen capture, processing, and presentation to T cells must be performed by APC localized in tissues at the interface with the environment; i.e., in the lung, the skin, nasal mucosa, gut, and other epithelia. Thus, as they build up the first line of defense in these peripheral tissues, DC are considered the best candidates for priming naive T cells toward environmental allergens. In the context of the Th1/Th2 dichotomy concept which has dominated immunologic research during the last decade, it was intensively discussed how resting T cells are directed into Th1 or Th2 cells during antigen presentation. While it became clear that IL-12 secreted by DC is mainly responsible for the shift to Th1 (28), it was still a matter of debate which cells may be the source of IL-4, which shifts T-cell response to the Th2 type.

Kalinski et al. gave some evidence that prostaglandin E₂ (PGE₂) may be the critical signal which directs Th0 cells to the Th2 type (29, 30). Very recently, Rissoan et al. have shown that myeloid DC are responsible for driving T cells into Th1 (now referred to as DC1), while lymphoid DC direct T cells into Th2 in an IL-4-independent way (now referred to as DC2) (Fig. 2) (31). Moreover, cross-feedback mechanisms are acting between these DC and T cells. Elucidation of the mechanisms of selective Th2 stimulation by lymphoid DC2 (PGE₂ or other mediators/cytokines and/or costimulatory molecules) certainly will dramatically modify our understanding of how nature has tuned the immune system to maintain an appropriate homeostatic balance of Th1/Th2 immune responses.

Are Fc ϵ RI-expressing DC1 involved in the regulation of IgE response?

It has been reported that LC, monocytes, and myeloid DC1 express the high-affinity receptor for IgE, Fc ϵ RI. Whether lymphoid DC2 bear this structure has not yet been explored. The Fc ϵ RI on LC and DC1 shows several important differences from this receptor on effector cells of anaphylaxis; i.e., mast cells and basophils. Indeed, it is not constitutively expressed on these cells but seems to be regulated by signals of the inflammatory microenvironment surrounding the cells. Thus, the highest Fc ϵ RI expression is displayed on LC and a recently described inflammatory dendritic epidermal cell (IDEC; presumably DC1) from lesional skin of atopic dermatitis (32–37). However, the lack or the low surface expression of the receptor complex is due to the low expression of the signal-transducing γ -chain which is mandatory for the surface expression of the heterotrimeric structure, while the IgE-binding α -chain is present in a preformed manner inside the cells (34). Furthermore, the Fc ϵ RI on LC and DC1, as well as on monocytes, lacks the four-transmembrane domain β -chain (33, 38). This has dramatic functional consequences; in contrast to LC and DC1 from atopic individuals, normal LC (with low receptor expression) are not fully activated upon receptor ligation (33, 37, 39–41).

There is evidence of a role of Fc ϵ RI in antigen focusing by monocytes, LC, and blood DC (37, 38, 42–44). Multimeric ligands that have been taken up by Fc ϵ RI receptor-mediated endocytosis are channeled efficiently into MHC class II compartments such as organelles in which cathepsin-S-dependent processing and peptide loading of newly synthesized MHC class II molecules occur (45). This in turn leads to an optimal antigen presentation to CD4⁺ T cells, as a first-line mechanism for antigen recognition. In this context, one

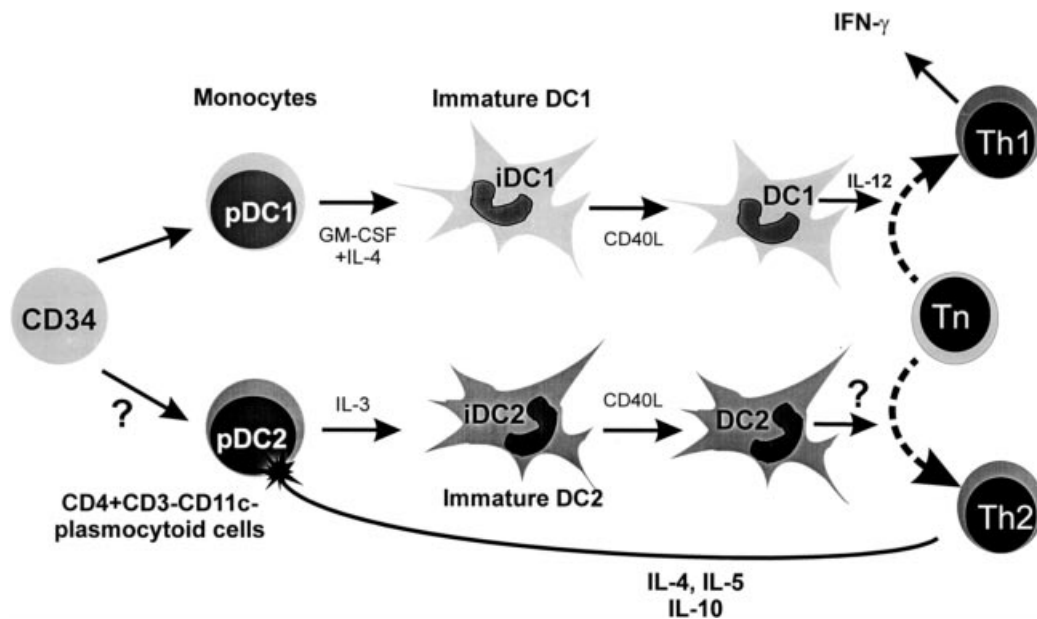


Figure 2. Two types of dendritic cells (DC1 and DC2). Both DC types seem to derive from different lineages and are committed to drive Th1 and Th2 responses, respectively.

may speculate about the putative role of $Fc\epsilon RI$ -expressing DC in the regulation of IgE synthesis.

It is well accepted that IgE molecules and effector cells such as basophils, mast cells, or eosinophils are the evolutionary result of an efficient antiparasitic defense system. It has been proposed that this system has been redirected toward benign environmental allergens because of the lack of its physiologic/pathologic partners. Enough data have been accumulated to clarify the role of $Fc\epsilon RI$ -expressing DC in the network of IgE-mediated immunity and allergic reactions.

As mentioned above, antigen uptake, processing, and presentation are the main functions of DC. Among the ways of antigen capture, which classically include nonspecific adsorption, fluid-phase pinocytosis, and cell-surface receptor endocytosis, the last provides the most efficient and specific pathway. This seems to be the case for $Fc\epsilon RI$. Indeed, the expression of high $Fc\epsilon RI$ density on DC of atopic patients implies several important features. First, DC extend their ability to react to allergens by binding large amounts of IgE molecules with various specificities. This significantly enhances the probability of cross-linking $Fc\epsilon RI$ by a defined allergen at the cell surface. Secondly, the IgE/ $Fc\epsilon RI$ complexes allow the capture of rather large allergens which, under normal circumstances, are not engulfed via the usual pathway; i.e., by pinocytosis. Thirdly, aggregation of $Fc\epsilon RI$ on DC is followed by its internalization via receptor-mediated endocytosis via coated pits, coated vesicles, and endosomes. However, in analogy to the B-cell receptor (BCR)

where $Ig\alpha$ and $Ig\beta$ target different endosomal compartments [46], this route used for antigen uptake by DC, i.e., specifically via IgE and $Fc\epsilon RI$, may dictate whether the foreign structure will be efficiently processed and targeted to MHC class II-rich compartments, ultimately leading to a higher density of specific peptides in the grooves of surface MHC class II molecules. Finally, DC expressing high receptor densities will display full cell activation upon $Fc\epsilon RI$ ligation, most probably inducing the synthesis and release of yet-to-be defined mediators. Such mediators may help to enhance/influence the subsequent antigen presentation.

One may speculate that $Fc\epsilon RI$ -expressing DC armed with specific IgE can boost the secondary immune response and further trigger the IgE synthesis by recruiting and activating more antigen-specific Th2 cells. DC are the most potent stimulators of naive T cells; i.e., they are committed to initiate a primary immune response. At first glance, $Fc\epsilon RI$ -mediated antigen uptake and subsequent presentation seem rather unlikely in the primary reaction since specific IgE should be present at the very beginning. However, it cannot be excluded that complex allergenic structures efficiently captured via $Fc\epsilon RI$ on DC are processed by these cells in a way leading to, among others, the unmasking and presentation of cryptic peptides/epitopes the T cell never met before. This would then initiate a primary reaction against these unhidden antigens, thereby helping to increase the variety of the IgE specificities. It is a very seductive hypothesis that, as suggested above, simultaneous antigen uptake and $Fc\epsilon RI$

aggregation on DC lead to the *de novo* synthesis and release of mediators capable of directing T cells toward a defined phenotype and/or function; i.e., Th1 or Th2 cells. This most striking concept in the study of Fc ϵ RI-expressing DC remains to be verified, especially considering recent findings suggesting an important role of DC-derived IL-12 and PGE $_2$ in driving T cells toward either Th2 or Th1, respectively (47, 48).

Rhinitis

The role and function of APC in allergic respiratory disease still remains unclear. Relatively high numbers of both CD1a- and HLA-DR-expressing DC were found in the columnar respiratory epithelium and the lamina propria of the nasal mucosa of patients suffering from grass-pollen allergy. Some DC of the respiratory epithelium contain BG (nearly 20%), a feature which classifies them as LC. Whether the latter represent LC at a different maturation stage or DC of a different origin remains to be clarified (48–50).

The number of airway DC is highest in the upper airways (600–800 per mm ^{2}) and decreases rapidly further down the respiratory tree (51, 52), suggesting that higher numbers are necessary in the upper airways to cope with the increased antigen exposure. Indeed, it has been demonstrated in patients after allergen provocation testing that the number of DC increases after antigen exposure.

At the beginning of the provocation period, CD1a $^+$ DC were observed in the subepithelial layer and around vessels, redistributing to the epithelium. In the second week of provocation, these cells were found throughout the whole depth of the epithelium (53, 54). As there is little evidence that DC are able to proliferate within the airway mucosa, these changes are likely to reflect alterations in their recruitment and/or egress.

The pivotal role of airway DC for antigen processing is further demonstrated by their rapid steady-state turnover rate with a half-life of only 2 days. This strongly contrasts with the situation encountered in keratinized epithelia such as the normal human skin, where the corresponding DC population, e.g., LC, are replaced with a half-life of 15 days or longer (55).

The interaction of nasal DC with other cell types such as mast cells that can be identified in the nasal mucosa remains to be elucidated (56–60).

Asthma

The cause of asthma is still unknown. Although most asthmatic patients are atopic, only certain atopic subjects

develop this disease. Asthma is a complex clinical entity that is characterized by acute and chronic phases. Whereas the acute phase is characterized by histamine release from airway mast cells, the chronic phase is induced by an inflammatory infiltrate in the airway mucosa. Ultimately, the chronic inflammation leads to permanent injury to the airways. Asthma is a prototypic allergic disease associated with a Th2-type response and elevated serum IgE (61, 62). Lately, it has been speculated that the increasing incidence of asthma and other atopic diseases might be due to a higher level of hygienic standards. Thus, neonates encounter fewer pathogens that prime for a Th1 immune response. In addition, early postnatal stimulation of the weakly primed immune system with allergens predisposes to positive selection for Th2 skewed memory and thereby favors the type of immune response associated with atopic diseases (63). The maturation of airway DC function in the postnatal period is an important factor in the outcome of the Th1/Th2 memory cell selection. Variations in the efficiency of this maturation process may be a key determinant of the genetic risk of asthma (64). Recently, it has been demonstrated by Rissoan et al. (31) that different subpopulations of DC may exert a direct control over Th1 vs Th2 differentiation of naive T cells (65–67).

The first requirement for the induction of an immune response to allergens is that these molecules gain access to immunocompetent cells. Although the airway epithelium represents a highly regulated and tight barrier, transepithelial permeability is increased in asthma. Even the bronchial epithelium becomes increasingly permeable to macromolecules after allergen deposition (68). In addition, allergen exposure induces asthmatic epithelial cells to express GM-CSF, which attracts DC to the site of antigen contact (69).

As far as antigen uptake by airway DC is concerned, the earliest detectable cellular response within the tracheal tissue is the recruitment of putative MHC class II complex-bearing DC precursors. The small, round, intensely class II $^+$ cells remain within the epithelium, reaching a maximum within 1 h after antigen exposure. Then the DC alter their round shape and change to a more pleomorphic form reminiscent of veiled cells. Active DC surveillance within the epithelium is amplified and consequently results in an increase in the traffic of these cells from the epithelium to the lymph nodes. Another mechanism that may contribute to an increased response of asthma patients to inhaled allergens may be that in the inflammatory process “new” DC are recruited from monocytes. It is known that monocyte-derived DC from allergic asthma patients show phenotypic differences in the expression of HLA-DR, CD

11b, and the high-affinity receptor for IgE and even an upregulation of B7-2 (CD86), and develop into more potent accessory cells than those from normal subjects (70–72).

Whereas airway DC are critical in priming the immune system to inhaled allergens, other APC subsets may play a crucial role in the secondary immune response to “known” allergens. In this way, they may contribute to the chronicity of asthma. The major APC subsets in the airways consist of the pulmonary alveolar macrophages (PAM), the intra-epithelial and subepithelial DC, the intraluminal specific B cells, type II alveolar epithelial cells, and, presumably to a lesser extent, bronchial epithelial cells. The interaction of DC with other APC as well as with other effector cells of the immune system remains an active field of research.

Atopic dermatitis

Receptor ligation on DC in the skin putatively triggers the synthesis and release of mediators which may initiate a local inflammatory reaction, as has been demonstrated for mast cells. Thus, from a pathophysiologic point of view, Fc ϵ RI-expressing DC, and particularly LC and related DC in the epidermis, have been suspected to play a crucial role in atopic dermatitis (AD) since they may represent the missing link between aeroallergens penetrating the epidermis and antigen-specific cells infiltrating the skin lesions. This concept is strongly supported by the observation that the presence of Fc ϵ RI-expressing LC bearing IgE molecules is a prerequisite to provoke eczematous lesions by application of aeroallergens on the skin of atopic patients. Consequently, AD may represent the paradigm of an IgE/Fc ϵ RI-mediated delayed-type hypersensitivity reaction (reviewed in Refs. 73 and 74).

The initiation phase of AD may be driven by cytokines derived from activated, allergen-specific Th2-type cells. The expression of ICAM-1, VCAM-1, E-selectin, and luminal P-selectin on endothelial cells is increased (75, 76), leading to the extravasation and invasion of other cells, such as macrophages or eosinophils attracted and activated by Th2-type cytokines (IL-4, IL-5). Eosinophils as well as DC $_1$ have been shown to produce IL-12, leading to an activation of allergen-specific and nonspecific Th1 and Th0 cells. Thus, IL-12 may account for the termination of the Th2-type cytokine pattern and the switch from a Th2 to a Th1 response with the subsequent release of IFN- γ . This cytokine is responsible for the characteristics and chronicity of AD lesions and determines the severity of the disease (77). Indeed, the observation that IFN- γ mRNA in such lesions was preceded by a peak of IL-12 expression indicates the

relevance of the Th2 to Th1 switch in the early phase of AD lesions.

Dendritic cells as targets or vectors for new therapeutic strategies

As a natural adjuvant, DC have a crucial role in the immunologic surveillance of various tissues, especially those in direct contact with the environment. Their pathophysiologic role in allergic contact eczema, as well as in other allergic diseases, is now well documented. Moreover, they seem to have a central role in the recognition, processing, and presentation of tumoral antigens. Hence, strategies have now been developed to target DC in the context of hypersensitivity reactions and, on the other hand, to use these cells as a tool to silence unwanted immunologic reactions. Recently, concepts have evolved that utilize the unique function of DC to boost antitumoral immunity.

Dendritic cells as therapeutic targets

In view of their localization at interface tissues such as the skin and nasal or lung mucosa, DC should be easily accessible for therapeutic targeting. In the skin, UV radiation (especially UVB) is known to alter profoundly the biology of LC/DC (as well as that of surrounding epithelial cells) and is routinely used in the treatment of chronic inflammatory skin diseases. Similarly, glucocorticoids (GC) strongly affect the capacity of DC to induce an immune response, although the exact mechanisms are far from clear. Indeed, DC seem to increase their expression of several functionally relevant molecules such as HLA-DR or CD86, but they clearly suppress their stimulatory activity (78, 79). More recently, it has been shown that a new generation of immunosuppressive macrolides, i.e., tacrolimus and ascomycin, which, in contrast to cyclosporin A, can be used topically, display interesting properties with regard to DC (80–82). They suppress the expression of costimulatory molecules, inhibit the appearance of distinct DC in inflammatory tissue reactions, and decrease the stimulatory activity of DC *in vitro*, as well as *in vivo*, after local application.

Finally, local application of molecules interfering with the binding of IgE to its receptor or compounds inhibiting defined activation mechanisms initiated by Fc ϵ RI-expressing DC *in situ* could represent valuable alternatives in the future management of atopic conditions.

Dendritic cells as therapeutic vectors: the future of immunotherapy?

Recent progress made in understanding the ontogenesis of DC and the techniques developed for their generation *in vitro* have led to an immunologic revolution and opened new therapeutic options. Such *in vitro* generated DC may be used either to silence hypersensitivity reactions or, in contrast, to boost the immune response in a given way, as for antitumoral vaccination.

DC as a tool to silence hypersensitivity reactions

A number of pathologic conditions are known to be induced by distinct forms of hypersensitivity reactions. Among them, organ transplantation, autoimmune diseases, and allergic diseases are the most representative examples. DC with appropriate phenotypic and functional modulation by cytokines such as IL-10 or TGF- β may be suitable to silence auto- and alloreactive, as well as allergen-specific, T cells. Hopes have been raised because immunization with UV-irradiated, hapten-modified LC results in a state of hapten-specific tolerance (83–87).

Another interesting approach is the topical use of the immunomodulatory properties of neuropeptides such as α -MSH. This proopiomelanocortin-derived peptide seems directly to affect the phenotype and the function of DC. It downregulates the expression of the costimulatory molecules CD86 and CD40, and decreases the synthesis and release of IL-1 and IL-12, but increases the production of IL-10 (88). Thus, α -MSH may represent a promising and natural compound able to target DC and to switch them from potent stimulators to putative silencers.

DC as a tool to boost an immune response

The first therapeutic protocols for the treatment of malignant melanoma by vaccination with DC have been established (89). Thus, DC may serve as ideal vehicles for vaccination, as the quality and quantity of an immune response is regulated at the level of DC. Techniques are available to channel selected tumor antigens or peptides to particular presentation pathways (MHC class II vs class I) within DC. Increasingly effective gene delivery systems are becoming available, and DC can apparently induce primary and secondary immune responses of all qualities.

Concluding remarks

About 130 years after the original description of the DC in the skin by Paul Langerhans, our knowledge of the immunobiology of these fascinating cells and especially the progress made in the last decade may be considered milestones in the understanding of crucial pathophysiologic phenomena in immunoallergic diseases. Most importantly, this knowledge is about to revolutionize our vision of future therapeutic strategies, and the use of *in vitro* generated DC in patients has opened a new era in immunotherapy.

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