

Molecular mechanisms in allergy and clinical immunology

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Antigen-presenting cells in allergy

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The complex interaction of the innate and adaptive immune system requires flexibility and cooperation among various cell types. In this regard, antigen-presenting-cells (APCs) play a pivotal role in transferring information from the periphery of the organism to lymphoid organs, where they initiate the activation of naive T cells. Dendritic cells, Langerhans' cells (LCs), and macrophages are also critical in the induction of allergic inflammation by presenting allergens to T lymphocytes and by contributing to the local recruitment of effector cells. Because of a complex genetic background, atopic individuals exhibit a dysregulation of T cell-mediated immune mechanisms. Attempts to understand the role APCs play in these patho-physiologic conditions are in progress and may allow development of new treatment strategies. In this review we will focus on the biology of APCs and their unique role in the induction and control of allergic inflammation. (*J Allergy Clin Immunol* 2001;108:329-39.)

Key words: Dendritic cell, atopic dermatitis, FcεRI

In Western societies the prevalence of atopic diseases, such as allergic bronchial asthma, allergic rhinitis, and atopic dermatitis (AD), increased significantly over the last 2 decades and accounts for one of the most common causes of chronic disease. Atopic individuals bear a complex hereditary constitution, leading to an increased production of specific IgE toward common environmental allergens. Thus by means of gene-gene interactions, this inherited genetic background ultimately leads to alterations of the immune system. For example, recent genetic studies have suggested the association of atopy with a polymorphism of the gene for the β-chain of the high-affinity receptor for IgE (FcεRIβ) and/or a variation in the α-chain of the IL-4 receptor, which may lead to altered IL-4 signaling.^{1,2} On the other hand, gene-environment

Abbreviations used

ACD:	Allergic contact dermatitis
AD:	Atopic dermatitis
APC:	Antigen-presenting cell
BG:	Birbeck granule
DC:	Dendritic cell
HPC:	Hematopoietic progenitor cell
IDEC:	Inflammatory dendritic epidermal cell
LC:	Langerhans' cell
MCP:	Monocyte chemoattractant protein
MIP:	Macrophage inflammatory protein
OVA:	Ovalbumin

interactions are suspected to play a pivotal role in triggering mechanisms, leading to allergic inflammation in a particular genetic background. In this respect it is well accepted that antigen-presenting cells (APCs) are mandatory for initiating and controlling the immune response to antigens present at the interface with the environment.^{3,4} APCs form a morphologically heterogeneous group of cells with the common task of presenting antigens in the context of the MHC. Among professional APCs, dendritic cells (DCs) and Langerhans' cells (LCs) are unique in their ability to prime naive T cells and are thus responsible for the primary immune response (ie, the sensitization phase of allergy).

Hence studying the role of APCs in allergy will unravel the very first events in the humoral and cellular cascades leading to allergic inflammation and hopefully provide new concepts for specifically targeting these crucial players in the complex atopic game.

ORIGIN AND CHARACTERISTICS OF APCs

Professional APCs are mainly divided into 2 systems: the DCs, including blood and tissue DCs and epidermal LCs, and the monocyte-macrophage system. All these cell types originate from pluripotent bone marrow CD34⁺ hematopoietic progenitor cells (HPCs). During their maturation process, DCs are characterized by different phenotypes and functions. In the immature state DCs have excellent skills for the surveillance of peripheral tissues. The capacity to take up and process antigens is high, whereas these cells are weak in priming T cells. Pheno-

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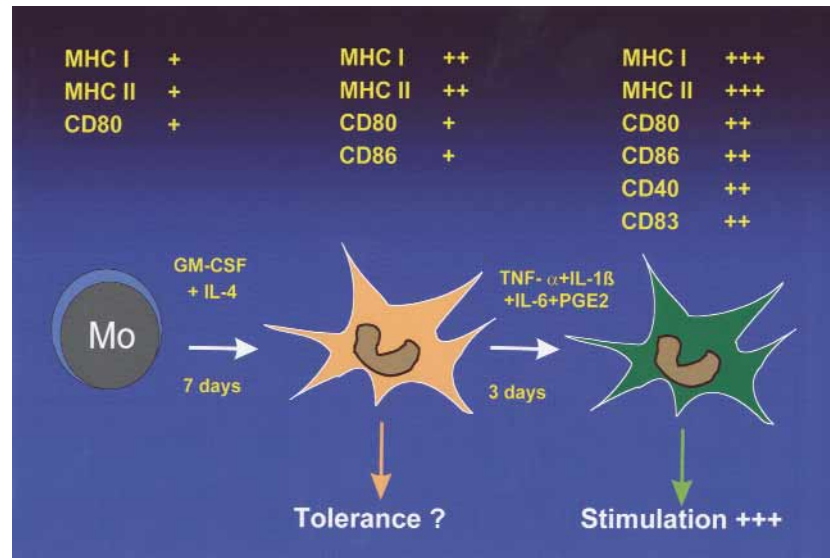


FIG 1. Phenotypical and functional alterations of monocyte-derived DCs. Mo, Monocytes.

typically, they show low or absent expression of costimulatory and maturation molecules, such as CD80, CD83, or CD86, as well as low expression of MHC class II. It is assumed that immature DCs are involved in peripheral self-tolerance induction because they capture apoptotic bodies from the periphery and transfer cell-associated self antigens to tolerogenic DCs in the lymph nodes. During maturation with, for example, TNF- α , they lose their capacity to take up and process antigens, and there is upregulation of costimulatory molecules and a translocation of MHC II to the cell surface. At this stage, DCs appear as cells with long dendrites. The most important changes are of functional relevance: mature DCs acquire the ability to prime T cells and are indeed the most potent inducers of primary T-cell responses (Fig 1).^{5,6}

Importantly, under certain conditions, DCs may present exogenous peptides instead of endogenous, newly synthesized peptides, together with MHC class I. This phenomenon has been termed *cross-priming* and allows the activation of CD8⁺ T cells. Cross-priming has been shown to be important in initiating MHC class I-restricted responses to tumors and peripheral self, viral, and bacterial antigens.

DCs may, under defined circumstances, express receptors for IgA,⁷ IgG (Fc γ RII),⁸ and IgE (Fc ϵ RI and Fc ϵ RII)⁹⁻¹¹ and produce various cytokines on activation (TNF- α , IL-6, and IL-8).^{12,13}

Regarding the DC system, at least 2 distinct DC precursor cells have been identified in the blood (Fig 2): the so-called DC1 subset carries the myeloid surface antigen CD11c, and the CD11c⁻ subset forms the plasmacytoid precursors of lymphoid DCs (ie, pDC2).^{14,15} Each subset represents only about 0.3% of mononuclear cells from the peripheral blood.¹⁶

Plasmacytoid precursor cells (pDC2) give rise to lymphoid DCs (DC2) and are characterized by a unique surface phenotype: CD4⁺CD3⁻IL-3R α ⁺⁺HLA-DR⁺.^{17,18} Recently, the developmental pathway from CD34⁺ HPCs

to pDC2 was dissected by characterizing 4 distinct cell populations in vivo.¹⁹ In culture, pDC2s differentiate into DC2s with IL-3 and CD40 ligand.

Myeloid DCs differentiate from CD34⁺ HPCs or from myeloid blood precursors, such as monocytes, in vitro. Culture of CD34⁺ stem cells with GM-CSF and TNF- α leads to LC-like DC1s.^{20,21} The addition of stem cell factor, FLT-3 ligand, or both results in a higher proliferation rate of the CD1a⁺ LC-like DCs. These cells display surface antigens characteristic of dermal DCs (MHC class II⁺⁺ CD4⁺ CD40⁺ CD54⁺ CD58⁺ CD80⁺ CD86⁺), display dendrites, and contain Birbeck granules (BGs) in 10% to 20% of cells. Peripheral blood monocyte precursors of immature DC1s have been designated pDC1s. They give rise to myeloid DC1s after culture with GM-CSF and IL-4 for 5 days.²² After maturation with CD40 ligand or endotoxin, the cells produce large amounts of IL-12. The surface markers of DC1s mirror their origin from myeloid precursors: CD11c⁺CD33^{+/+}CD1a⁺ MHC class II⁺CD80⁺CD86⁺.

Among DCs, epidermal LCs have a particular place. They are highly specialized DCs located in the basal and suprabasal layers of the epidermis and contain typical cytoplasmic granules (ie, the BGs). In vitro LCs are generated by culture of CD34⁺ HPCs in the presence of GM-CSF, FLT3-L, stem cell factor, TNF- α , and transforming growth factor β , which seems to be mandatory for the generation of LCs. Recently, the selective chemotactic recruitment of CD1a⁺ LC precursors into the epidermis on macrophage inflammatory protein 3 α (MIP-3 α) exposure was demonstrated.²³

As already mentioned, myeloid DCs and LCs are thought to share common precursors with monocytes and macrophages. Monoblasts are the first recognized cells for these myeloid-derived peripheral cells in the bone marrow. Monoblasts differentiate into promonocytes that constitute the storage pool for the monocytic lineage in the bone marrow. Promonocytes mature into monocytes and are

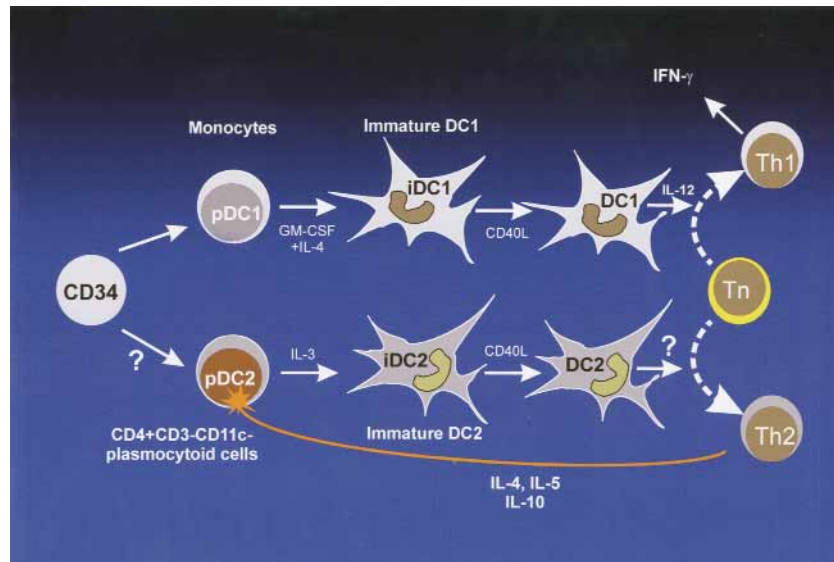


FIG 2. Two types of DC precursors in the blood (pDC1 and pDC2) that originate from different cell lineages. They seem to drive Th1 and Th2 responses, respectively. Tn, Naive T cells.

released into the blood within 2 days. These monocytes are transformed into distinct tissue macrophages, depending on local factors. In vitro monocytes cultured in macrophage colony-stimulating factor differentiate into macrophage-like cells (CD14+CD1a-CD83-). Monocytes and macrophages are much weaker in their T-cell stimulatory capacity than DCs or LCs, and as APCs, they play a major role in secondary immune responses because they do not prime naive T cells. Macrophages are highly phagocytic cells; their role in specific T-cell mediated immune responses could be well established in the last years. Some macrophages are inducers of T-cell responses (inductive or antigen-presenting macrophage subset), whereas others suppress T-cell responses (suppressive macrophage subset). These groups can be distinguished by a set of mAbs: stimulatory cells (D1+) are RFD1+RFD7-, phagocytes (D7+) are RFD1-RFD7+, and suppressive cells (D1+D7+) are RFD1+RFD7+. Functions of the subsets are not entirely exclusive to a given population.²⁴

APCs IN ALLERGIES

Atopy and receptors for IgE

Atopy defines a genetically determined predisposition for the development of diseases, such as allergic asthma, allergic rhinoconjunctivitis, or AD, and the display of increased serum IgE levels against common environmental allergens. The high-affinity receptor for IgE (FcεRI) is expressed on 2 distinct groups of cells: (1) constitutively on effector cells of anaphylaxis (ie, mast cells, basophils, and rarely eosinophils) and (2) variably on professional APCs. Although absent or present in very low amounts on LCs from normal skin of nonatopic individuals, the expression density of FcεRI is highest on LCs and related DCs, such as inflammatory dendritic epidermal cells (IDECS), in lesional skin of AD and, interestingly, on

LCs and DCs from normal oral mucosa (Bieber et al, unpublished data). Unlike the classical receptor on effector cells of patients with anaphylaxis, FcεRI on APCs differs in structure by lacking the β-chain.²⁵

The pathophysiologic role of the low-affinity receptor for IgE, FcεRII (CD23), on APCs in allergy remains to be determined. Although FcεRI is the principal IgE-binding structure in atopic subjects, it cannot be ruled out that FcεRII is involved in antigen trapping and presentation. However, because of its low affinity for monomeric IgE, one would assume that this receptor instead binds IgE-antigen complexes. Whether this leads to activation of APCs in vivo is unknown.

Phases of allergic reactions

On encountering an allergen, 2 distinct phases should be distinguished. First is the sensitization phase, in which APCs take up the allergen for the first time and migrate to regional lymph nodes. There they prime naive T cells, which develop into effector cells and T memory cells. Allergen-specific immunoglobulins (eg, IgE) are subsequently produced and may contribute to the increased efficacy of allergen defense on re-exposure. This phase is clinically silent and takes between 8 and 15 days.

The second phase is the elicitation phase, which means the induction of inflammatory reactions on a second encounter of the allergen. Memory T cells and specific immunoglobulins (eg, IgE) bound to the cell surface of tissue APCs rapidly respond to known antigenic structures of the allergen and initiate a cascade, eventually leading to a chronic inflammatory reaction. The delay of clinical appearance of a given allergic reaction is highly variable and depends mainly on the type of tissue and the cells involved: the duration ranges from a few minutes (immediate-type hypersensitivity) to about 48 hours (delayed-type hypersensitivity).

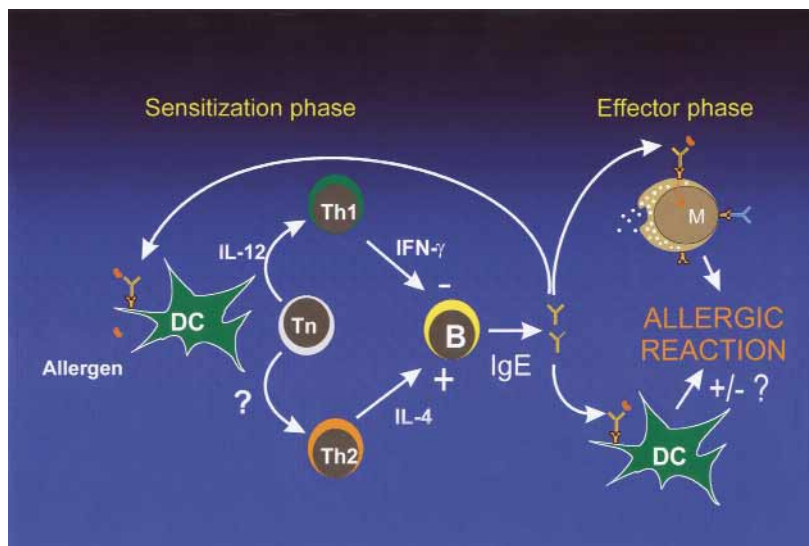


FIG 3. Scenario of the contribution of DCs in allergy. During the sensitization phase and in the absence of specific IgE, DCs capture allergens by means of unspecific pathways and present the peptides thereof to prime naive T cells, predominantly into T_H2 effector responses. Subsequently, IgE production occurs and binds to FcεRI on APCs and mast cells. In the effector phase, on the one hand, IgE bound to FcεRI on DCs allows them to capture and present antigens in a more efficient way to T cells. This could lead to an amplification of the IgE synthesis. On the other hand, binding of IgE on mast cells enables them to trigger immediate hypersensitivity reactions (eg, rhinitis). Furthermore, IgE bound to APCs in target organs of allergic reactions may contribute to trigger, modulate, or both IgE-dependent delayed-type hypersensitivity reactions (eg, AD). *Tn*, Naive T cells; *B*, B cells; *M*, mast cells.

The sensitization phase

The mechanisms used to internalize an allergen and the nature of the allergen determines the type of allergic reaction induced.

Receptor-mediated endocytosis is used mainly for high-molecular-weight molecules, such as pollens or dust mites. Binding of allergens at the cell surface may occur rather unspecifically through lectin structures or more specifically through immunoglobulins fixed on Fc receptors.

Passive absorption and pinocytosis is the usual way to take up rather low-molecular-weight products (ie, haptens), which must bind to cell-surface proteins of the cellular matrix to become immunogenic.²⁶ The prototype of immune reaction that follows the ingestion of low-molecular-weight molecules is the cell-mediated contact hypersensitivity reaction (eg, ACD). Frequent haptens that elicit an allergic response are dinitrochlorobenzol and metallic ions like nickel or cobalt.

Antigen uptake by APCs

The first contact of unknown high-molecular-weight molecules with APCs in the periphery (eg, in the skin or the lung) probably leads to either unspecific macropinocytosis, receptor-mediated endocytosis, or both through yet-to-be-defined receptors of the allergen. Besides its role in the effector phase of IgE-mediated hypersensitivity reactions, FcεRI may play an important role during the sensitization phase (Fig 3). A given allergen-specific IgE is fixed on FcεRI on APCs and recog-

nizes and internalizes its allergen. This complex is directed into cathepsin S-sensitive compartments for efficient processing, with subsequent unmasking of hidden epitopes of this allergen giving rise to a large variety of peptides. In the case of molecular homology of some peptides to peptides from other unrelated allergens (molecular mimicry), one would expect that the APCs could activate naive T cells with a different T-cell receptor repertoire. This could ultimately lead to a widening of the IgE spectrum because of homology of epitopes or cross-reactivity of IgE toward different allergens.

In ACD, epithelial LCs play a pivotal role during sensitization. Passive absorption and pinocytosis are mainly used to ingest haptens that have previously bound to cellular matrix proteins to become full antigens. On activation, LCs release IL-1β, thereby promoting their egress from the epithelium.

Migration of APCs

Migration of DCs, LCs, or both from tissues to the regional lymph nodes and spleen or inversely to the site of inflammation is regulated at 2 levels: the endothelial cell level and the chemokine-chemokine receptor system level.^{27,28} For example, in the skin, on allergen uptake and activation of APCs, inflammatory chemokines are released from these cells and from surrounding keratinocytes, followed by dramatic upregulation of migration. Monocyte chemoattractant protein 1 to 5 (MCP 1-5) or MIP-1α and MIP-1β are chemokines that act strongly on the recruitment of monocytes-macrophages. Inflam-

matory chemokines increase the expression of adhesion molecules, such as P- and E-selectins, on vascular endothelial cells. Blood DCs express a glycosylated form of P-selectin glycoprotein ligand 1, which mediates firm adhesion of DCs to endothelial cells by binding to P- and E-selectins.²⁹ This adherence to endothelial cells is a prerequisite for consequent extravasation to sites of inflammation. Immature DCs express a chemokine receptor profile (CCR1, CCR2, CCR5, and CCR6) that reacts with chemokines released at inflammatory sites. Maturing DCs that captured antigen navigating from inflamed tissue to T-cell areas of the lymphatics undergo profound changes of their chemokine receptor repertoire. There is upregulation of constitutively expressed chemokine receptors, such as CXCR4, CCR4, and CCR7, and concomitant downregulation of cognate receptors.³⁰ In lymphatic tissue secondary lymphoid tissue chemokine and Epstein-Barr virus-induced molecule 1 ligand chemokine are produced, and these chemokines are particularly recognized by CCR7. This receptor is therefore regarded as a key molecule in the second-step navigation from tissues to T-cell areas. As a third step of navigation, mature DCs in lymph nodes produce further chemokines, such as thymus and activation-regulated chemokine, macrophage-derived chemokine, and Epstein-Barr virus-induced molecule 1 ligand chemokine, that act on other mature DCs, as well as on naive and memory T cells.³¹

Antigen presentation by APCs

During activation and migration of APCs, there is strong upregulation of MHC class I and II molecules and accessory molecules (eg, CD40, CD80, and CD86) and downregulation of Fc receptors. This maturation process transforms APCs into particularly potent T cell-stimulating cells. Cross-talk between APCs and T cells in their immunologic synapse ultimately leads to T-cell activation. It is still unclear what kind of signal is specifically delivered by matured DCs that enables them to potentially activate naive T cells.

Role of DCs in the T_H1/T_H2 switch

The most potent differentiation stimuli known for developing T_H1 or T_H2 effector functions of CD4⁺ T cells are cytokines.³² IL-12 is the key cytokine that switches naive T_H cells into T_H1 effector cells and is secreted by APCs. IFN- γ promotes T_H1 development, mainly by enhancing IL-12 secretion and partly by stabilizing functional IL-12 receptors on CD4⁺ T cells. The development of T_H2 cells is largely dependent on IL-4 being produced by probably naive T cells. Data indicate that at the moment of priming, naive T cells receive an initial T_H1 or T_H2 polarizing signal. Because DCs are the major APCs localized at the interface with the environment, it is thought that these cells carry the signal for the differentiation of T cells into T_H1 and T_H2 in addition to signals concerning the antigenicity of the pathogen.

Until today, 2 different concepts of how DCs achieve this polarization have existed. Rissoan et al³³ have shown that DC1s are responsible for inducing T_H1 cells, where-

as DC2s induce T_H2 differentiation. Furthermore, this group showed a negative feedback regulation among these 2 effector reaction patterns. The T_H2 cytokine IL-4 enhances the maturation of DC1s and leads to apoptosis of pDC2s. IFN- γ from T_H1 cells protects pDC2s against IL-4- and IL-10-induced killing and promotes DC2 differentiation. On the other hand, Kalinski et al³⁴ claim that DC1s are responsible for directing naive T cells into T_H1 and T_H2 subsets because these are the only cells that pick up foreign antigen, travel to the lymph nodes, and stimulate naive T cells. Some in vitro and in vivo studies indicate that DC1s are inducers of both T_H1 and T_H2 cells.³⁵ The critical factor for the polarizing mechanism seems to be the level of IL-12 produced by DC1s. The IL-12-producing capacity can be influenced and modulated directly by the pathogen, by microenvironmental factors, and by affecting DC1 maturation at different stages. For instance, it has been suggested that PGE₂, a common inflammatory product of fibroblasts and epithelial cells, causes early development of immature DC1s into T_H2-promoting cells.

Atopic individuals show a kind of inherited dominance of T_H2 responses. Blood T cells of these patients respond to allergens, such as birch pollen allergen, with the production of IL-4, IL-5, and IL-13 rather than IFN- γ from T_H1 cells, as in healthy individuals.^{36,37} IL-4 and IL-13 are principal mediators for B-cell antibody class switching toward IgE and therefore are key initiators of IgE-dependent reactions. Allergen-specific IgE binds to Fc ϵ RI on effector cells of anaphylaxis and on APCs in the epidermis-dermis and airway mucosa. IL-5 acts mainly on eosinophils as an activating cytokine. These mediators of the same T-cell subset account for the frequently observed high serum levels of IgE and activated eosinophils seen in T_H2-dominant diseases.

The elicitation phase

The binding of an allergen to the complex of IgE-Fc ϵ RI on mast cells and basophils leads to the rapid activation and degranulation of preformed granules. Histamine, leukotrienes, prostaglandins, serotonin, and tryptase are released and account for the immediate symptoms, such as smooth muscle contraction, vasodilatation, and increased vascular permeability. Clinically, these mechanisms lead to anaphylaxis, rhinoconjunctivitis, and urticaria. As shown for epidermal LCs, binding of an allergen to Fc ϵ RI on APCs from an atopic individual with high levels of Fc ϵ RI expression leads to fully activated cells on receptor cross-linking.³⁸ This is not the case when the receptor is only expressed at low levels (ie, in nonatopic subjects). Mediators and cytokines like MCP-1 and MIP-1 are released and attract more APCs to the site of inflammation. MCP-1, together with IL-8, triggers the firm adhesion of monocytes to vascular endothelium and promotes transendothelial migration.³⁹

The cutaneous late-phase reaction is characterized by specific cell infiltrates and depends largely on the amount and nature of the allergen. In patients with AD, LCs, IDECs, eosinophils, and T cells infiltrate the site.

Late-phase reactions can be triggered in the absence of immediate hypersensitivity involving cells of anaphylaxis. In patients with asthma who were allergic to cats, these reactions were provoked by an intradermal injection of a cat allergen.⁴⁰ These experiments were crucial in demonstrating antigen presentation in an MHC-restricted way, followed by T-cell activation, which evoked the symptoms. Thus APCs are critical in the late phase by controlling and perpetuating allergic infiltration. Here the presence and activation through FcεRI takes place for special reasons: FcεRI-IgE-allergen complexes facilitate antigen uptake and antigen presentation.⁴¹ These receptors extend their antigen-focusing ability toward a defined protein by expressing IgE molecules with several specificities of the allergen, thereby increasing the probability of FcεRI cross-linking. IgE-FcεRI-mediated endocytosis allows large molecules, which are normally not engulfed through the normal pathway by pinocytosis, to be internalized. These complexes are efficiently directed into distinctive MHC class II-rich compartments, where processing and assembly of newly synthesized MHC class II molecules occur.⁴² This results consequently in a higher density of MHC class II molecules with peptides on the cell surface of an APC and thus increases the stimulatory capacity of DCs. Clearly, the strong upregulation of the high-affinity receptor for IgE in atopic diseases acts as a link between aeroallergens and antigen-specific T-cell immunity.

ALLERGIC DISEASES

Allergic bronchial asthma

Allergic asthma is a chronic inflammatory lung disease displaying clinical symptoms of airflow obstruction and bronchial hyperresponsiveness. DCs, macrophages, mast cells, neutrophils, eosinophils, and allergen-specific T_H2 lymphocytes play a major role in the development and maintenance of this condition. Most cases (95%) of childhood asthma are associated with atopy.⁴³

In the lung the DC network is located above the basement membrane of the airway epithelium, where it has access to inhaled antigen. In asthmatic subjects the number of CD1a⁺ and MHC class II⁺ DCs is higher in the bronchial mucosa than numbers found in control subjects.⁴⁴ APCs play an essential role in initiating inflammatory responses because T cells cannot respond to allergens without the help of APCs. In mouse asthma models it has been demonstrated that ovalbumin (OVA)-pulsed myeloid DCs injected into the airways of naive mice were responsible for the T_H2 inflammation on rechallenge with an aerosol of OVA.⁴⁵ Moreover, by comparing airway DC-depleted and DC-undepleted mice and exposure of these animals for a second time to OVA after 2 weeks of primary sensitization, the pivotal role of lung DCs for presenting allergens to previously primed T_H2 memory cells was explored.⁴⁶ These results clearly demonstrate a key role for DCs not only in the induction of primary immune responses but also in secondary immune responses and in the perpetuation of chronic airway disease.

Previous studies addressed the role of macrophages in immune regulation of the lung because they are normally present in relatively large numbers within the mucosa.⁴⁷ Aerosol-induced inflammatory lung lesions develop to a greater extent and IgE production is higher in animals depleted of alveolar macrophages.⁴⁸ This reveals airway macrophages to be poor APCs. Instead, these cells may play an important role in maintaining local homeostasis by suppressing local immune activation. Indeed, in the state of chronic asthma, an imbalance of macrophage subsets has been stated. The study of frozen biopsy specimens from normal and asthmatic subjects revealed elevated numbers of inductive, antigen-presenting macrophage subsets (D1⁺) in asthmatic subjects, whereas the suppressive subset (D1⁺D7⁺) was diminished.⁴⁹ Thus overstimulation of the immune system in asthma is at least in part caused by the absence of appropriate regulator function of macrophages.

In dual asthmatic reactions (asthma with early-phase and late-phase components) the interaction of mast cells and leukocytes could be shown to play an important role in peribronchial inflammatory events. Initially, mast cell mediators directly act on bronchial tissue and indirectly recruit and activate neutrophils and monocytes, which contribute to the late-phase response. Infiltrating leukocytes provoke a second release of mast cell-associated mediators in the late phase, which may contribute to non-specific bronchial hyperreactivity in chronic asthma.⁵⁰

Exposure of the airway with allergen increases local IL-5 concentrations and correlates with the amount of airway eosinophilia. In particular, major basic protein from eosinophilic granules, but also other inflammatory substances from these cells, can directly damage airway epithelium and cause degranulation of mast cells.⁵¹

In atopic asthma T_H2 lymphocytes are the predominant lymphocyte population present in bronchial biopsy specimens and in bronchoalveolar lavage fluid.⁵² As mentioned above, the cytokine pattern of this lymphocyte subset promotes allergy, and the degree of T_H2 activation in allergic asthma directly correlates with the severity of the symptoms.

Allergic rhinitis

Allergic rhinitis is one of the major diseases in industrial countries and the most common atopic manifestation. There are little data concerning the role and function of APCs in allergic rhinitis. Most of the information comes from quantitative comparison studies of nasal biopsy specimens taken from allergic and nonallergic patients. Under nonallergic conditions, CD1a⁺ MHC class II⁺ cells are distributed throughout the nasal epithelium and the lamina propria. Most of the intraepithelial DCs contain BGs, which classifies these cells as LCs.⁵³ In contrast, only few DCs in the lamina propria contain BGs. The highest number of mucosal DCs are found in the upper airway (600-800/mm²), and the number decreases rapidly further down the respiratory tree.⁵⁴ This might reflect the primary function of these cells to sample incoming allergens, which may then be processed

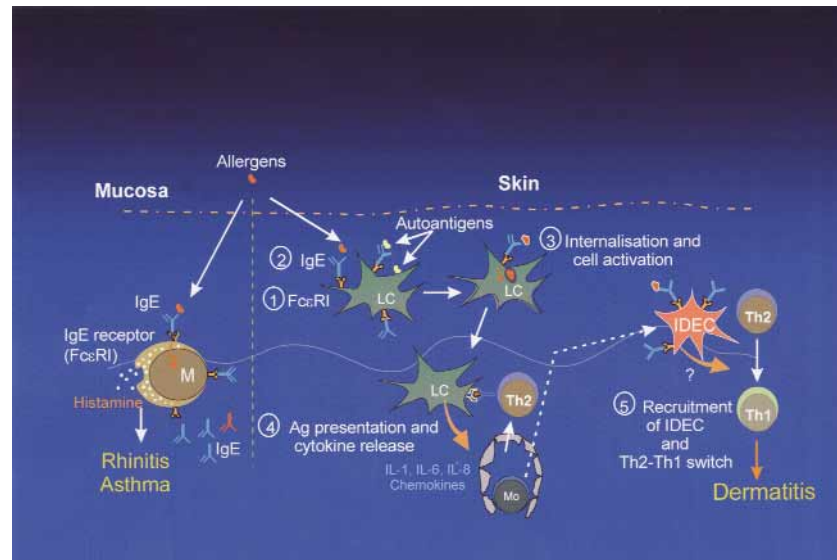


FIG 4. The possible role of FcεRI⁺ LCs and IDECs in the pathogenesis of AD. In rhinitis and asthma IgE-FcεRI cross-linking leads to the degranulation of mast cells, which may initiate immediate and late-phase events. In contrast, in the skin of patients with AD, specific IgE binds to FcεRI on LCs and activates trafficking or resident T cells. Activation of T cells will lead to an inflammatory cascade contributing to a rapid recruitment of IDECs that is known to be highly efficient in stimulating autologous T cells. Furthermore, IDECs may lead to the switch of T_H2 to T_H1 cell responses and putatively contribute to the chronicity of AD. *M*, Mast cell; *Mo*, monocyte.

and presented to regional lymph node T cells. In patients with grass pollen allergy, high numbers of CD1a⁺ MHC class II⁺ LCs in the columnar epithelium of the nasal mucosa have been found. From provocation studies, it became clear that on allergen exposure there is rapid redistribution of DCs from subbasal epithelial layers and around vessels of the lamina propria to the whole depth of the epithelium. The constant delivery of potentially harmful pollutants into the airway necessitates continuous and rapid response of the immune system. Indeed, the steady-state turnover rate of DCs in nasal mucosa has been determined to be a half-life of only 2 days, whereas in keratinized epithelium, such as skin, the half-life of the corresponding DCs (eg, LCs) is 15 days or longer.

Atopic dermatitis

Lesional skin of patients with AD is histologically characterized by increased numbers of LCs, IDECs, and T cells. IDECs constitute a distinct DC population that is mainly found in AD but is also seen in other inflammatory skin diseases, such as psoriasis or ACD.⁵⁵ Ultrastructurally, these cells resemble LCs, but they lack BGs. The presence of FcεRI⁺ LCs bearing IgE molecules is a prerequisite to provoke eczematous lesions by means of application of aeroallergens on the skin of atopic patients.^{56,57} It has long been proposed that T_H2 cells play a key pathogenic role in AD. T_H2 cells have been found at an increased frequency in lesional skin of atopic patients and in skin where an inhalant allergen to which the patient was sensitized was applied. In contrast, recent studies of biopsy specimens from patients with chronic atopic eczema showed a predominant

expression of the T_H1 cytokine IFN-γ on a messenger RNA and protein level in over 80% of patients with AD. From that, it has been suggested that AD is a multistep disease in which T_H2-type cells are activated predominantly at the beginning and T_H1-type cells account for chronicity.⁵⁸ A new and interesting concept involves FcεRI⁺ LCs as the pivotal cells in the sensitization phase of AD because they are present in higher numbers in the skin of atopic persons compared with healthy individuals.^{59,60} LCs migrate to regional lymph nodes and prime naive T cells. The following activation of T cells attracts more IDECs into the epidermis. Because LCs produce only small amounts of cytokines and IDECs are able to secrete a substantial amount of inflammatory mediators, IDECs might be the principal cells of the elicitation phase (Fig 4). Moreover, on a single cell level, FcεRI expression is higher on IDECs than on LCs, which might lead to full cell activation and IgE-mediated trapping of the allergen.⁵⁵

Allergic contact dermatitis

ACD is a delayed-type hypersensitivity reaction in which LCs are the main APCs for the primary immune response. In the elicitation phase, however, other APCs, such as macrophages, dermal DCs, or even MHC class II-expressing endothelial cells, may contribute to the local inflammation.^{61,62} The chemical reactivity, lipid solubility, or both of the haptens (eg, nickel or dinitrochlorobenzol) facilitate the entrance through the stratum corneum into the epidermis. In most cases they bind to cell substances in the epidermis to become full antigens, a process that is called haptination. In the sec-

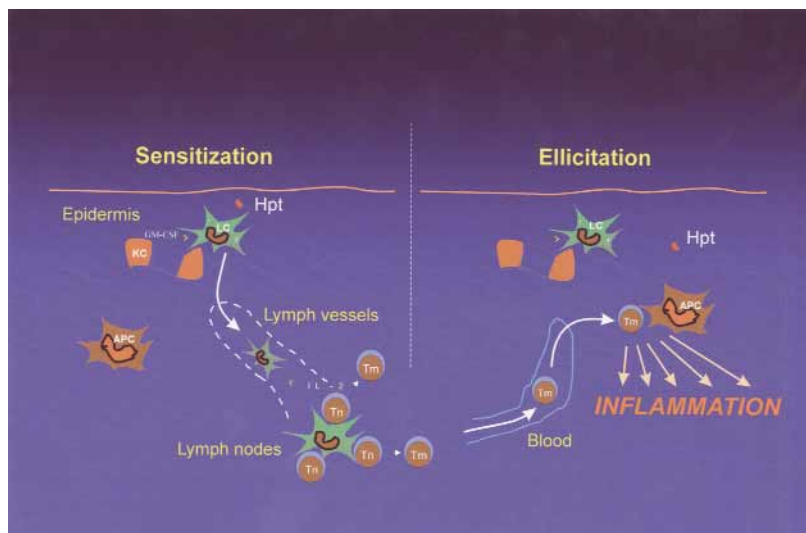


FIG 5. In ACD, LCs are the pivotal DCs in the sensitization phase. They take up low-molecular-weight haptens that have previously bound to cell substances on keratinocytes or LCs themselves to become full antigens. LCs will leave the epidermis and migrate to the regional lymph nodes, where they present the peptides to naive T cells, thus initiating sensitization. On a second encounter of the hapten in the skin, antigen presentation most probably occurs through different resident MHC class I or II⁺ APCs (eg, macrophages, dermal DCs, or endothelial cells), which activate trafficking memory T cells and trigger the allergic inflammatory reaction, ultimately leading to the clinical dermatitis lesion. *Hpt*, Hapten; *KC*, keratinocyte; *Tn*, naive T cells; *Tm*, memory T cells.

ondary immune response the site of antigen presentation is not exactly known. Because of the relatively short time of eczema development (24-48 hours), it is assumed that in the elicitation phase of ACD, APCs do not migrate into regional lymph nodes, and the activation of memory T cells takes place in the skin (Fig 5). More likely, memory T cells passing by in blood vessels of the dermis are activated through skin APCs. In addition, allergens directly stimulate the release of cytokines from keratinocytes, such as $\text{TNF-}\alpha$, GM-CSF, and $\text{IL-1}\alpha$.^{63,64} These chemokines further attract DCs at the site of antigen contact. Because DCs are able to present exogenous antigens together with MHC class I or MHC class II, activation of both CD4^+ and CD8^+ T cells ensues. It should be emphasized that unlike classical delayed-type hypersensitivity reactions, which involve CD4^+ cells, contact hypersensitivity reactions are carried out mainly by CD8^+ T cells.⁶⁵

THERAPEUTIC IMPLICATIONS

Allergic bronchial asthma

For the relief of symptoms, quick-acting and long-acting aerosolized β -agonists in combination with inhalative corticosteroids are most widely used. To minimize potential side effects of corticosteroids, such as growth suppression in children, concomitant treatment with theophylline or leukotriene antagonists is used.⁶⁶ In children with AD and a positive atopic family background, the Early Treatment of the Atopic Child study could demonstrate the decreasing incidence of asthma by means of early treatment with the H_1 -antihistamine ceti-

rizine. Thus prophylactic therapy of 1- to 2-year-old atopic children with this drug for 6 months or longer may abrogate asthma development in later life.⁶⁷

New approaches use recombinant anti-human IgE antibody (rhUmAb-E25), which forms complexes with free IgE, thereby blocking the attachment of the immunoglobulin to APCs, mast cells, and basophils.⁶⁸ Clinical studies revealed that this antibody can inhibit not only the early bronchoconstriction after allergen exposure but also the late-phase response. Recently, the application of DNA vaccines that contain repeated CpG motifs has been a promising treatment for allergic diseases.⁶⁹ These motifs can bind to receptors on APCs, thereby evoking IL-12 , which drives $\text{T}_\text{H}1$ -mediated responses.

Allergic rhinitis

The treatment of allergic rhinitis is based on a combination of allergen avoidance, antiallergic medication, and specific immunotherapy if possible. Antihistamines and anticholinergic agents are drugs that relieve symptoms, and topical nasal corticosteroids suppress allergic inflammation. Another treatment strategy is specific immunotherapy, which shows long-lasting remission and, importantly, seems to alter the immunologic reactivity toward local $\text{T}_\text{H}1$ or so-called modified $\text{T}_\text{H}2$ responses.⁷⁰ It is suspected that APCs are a primary target in the induction of tolerance in the context of immunotherapy. However, the exact mechanisms are far from being clear, especially in the case of sublingual immunotherapy, in which high doses of allergens are in direct contact with $\text{Fc}\epsilon\text{R1}$ -expressing LCs in the oral mucosa of such patients.

Atopic dermatitis

Chronic dermatitis and eczema might be treated with topical application of corticosteroids of class I or class II. Severe exacerbation and superinfection requires topical corticosteroids of class III and systemic antibiotics. Superantigens derived from *Staphylococcus aureus* may maintain chronic inflammation by means of polyclonal T-cell activation. H₁-receptor antagonists may relieve the symptoms of itching and should be given continually at early ages (see above). Generalized eczema responds well to UV light radiation of a particular wavelength: UVA₁ with a spectrum of 340 to 400 nm is able to penetrate into the dermis. Repeated exposure to UV light over a period of several months results in longer remission periods. Severe and nonresponding AD may be treated with methotrexate or low-dose oral cyclosporine.

Recent studies reported the benefit of topical tacrolimus (FK506) in AD.^{71,72} Tacrolimus, a carbocyclic lactone-lactam isolated from *Streptomyces tsukubaensis*, is used to prevent graft rejection after organ transplantation in human patients. Although tacrolimus is known to act at the level of T cells, it could be shown that CD1a⁺ APCs in the epidermis are important targets: topical tacrolimus leads to the depletion of IDECs from atopic skin, a decrease in the expression of FcεRI on IDECs and LCs, and a dramatic reduction in the stimulatory capacity of epidermal DCs toward T cells.^{73,74} From a clinical point of view, tacrolimus leads to rapid improvement of eczema and, unlike steroids, lacks atrophogenic activity.

Allergic contact dermatitis

The conventional therapy for contact dermatitis consists of allergen avoidance, topical or systemic application of corticosteroids, and systemic application of antibiotics for superinfection.

New approaches in the treatment of ACD may consist of the blocking of LC emigration from the epidermis to the lymph nodes on activation with a peptide that abrogates the function of hyaluronan. Hyaluronan serves as an important substrate for LC migration. Another new technology may be the inhibition of LC maturation or the introduction of CD95L (Fas ligand) cDNA into LCs. On antigen encounter and maturation, these cells will kill Fas⁺ T cells.⁷⁵

CONCLUSION

APCs are a heterogeneous group of cells with a crucial effect on the initiation and chronicity of atopic allergic diseases and contact allergy. They critically control T cell-mediated immune responses, thus directing the outcome of the encountered allergen toward silent elimination, allergy, or tolerance. Important progress is made by understanding the ontogenesis of APCs, which allows cultivation and delineation of subgroups of APCs with different functions under special conditions in vitro. Consideration of recent developments in chemokine reg-

ulation of APCs and T-cell activity adds much to an overall view of the tight link between innate and adaptive immunity. Strategies for the treatment of allergic diseases involve the education of appropriate DC subsets that either deliver signals to amplify natural anti-inflammatory signals or induce tolerance.

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