Review Article

Role of dendritic cells in Th1/Th2 balance: A novel therapeutic target of allergic diseases

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ABSTRACT

Considerable evidence supports the role of dendritic cells (DC) in the pathogenesis of allergic diseases. Dendritic cells, as the most potent antigen-presenting cells (APC) for the induction of primary immune response to antigen, are deeply involved in the differentiation of naïve T cells into Th2 cells, thereby developing the development of allergic sensitization. After sensitization, DC may also function as a major APC to control the activation and clonal expansion of memory Th2 cells. In addition, DC are able to produce chemokines to recruit Th2 cells into inflammatory sites, indicating DC are important agents in various phases of allergic inflammation. Recently, we have demonstrated that monocyte chemotactic protein-1 not only regulates the homing of DC, but also modulates DC function. The present paper reviews the role of DC in the regulation of the Th2 response in allergic diseases and discusses the possibility of a new therapeutic strategy targeting chemokine-mediated regulation of DC function.

Key words: dendritic cell, monocyte chemotactic protein-1, OX40 ligand, regulatory T cells, Th2.

INTRODUCTION

Numerous experimental and clinical studies support the concept that $CD4^+$ T cells that produce a Th2 cytokine profile (e.g. interleukin (IL)-4, IL-5, IL-13 and IL-9) are responsible for pathophysiological manifestations of allergic diseases.[1] Antigen-derived stimulation

from antigen-presenting cells (APC) is essential for the generation and activation of antigen-specific Th2 cells. However, the role of APC in the pathogenesis of allergic disease has been disregarded. Dendritic cells (DC) are the most potent APC: their unique ability to stimulate a primary T cell response places them in a pivotal role with regard to immune responses.[2] Precursors of DC migrate from peripheral blood into peripheral tissues and are distributed as immature DC. The immature DC take up antigens and move to the draining lymph nodes while maturing into efficient APC by processing antigen to form an antigen–peptide–major histocompatibility complex (MHC) complex and upregulating costimulatory molecules. Matured DC present antigen-derived peptide to naïve T cells in the T cell zone of the draining lymph nodes. Thereby, DC initiate acquired immune responses.

In human nasal mucosa, $CD1a^+$ DC and $CD123^{high}$ plasmacytoid DC are identified in the epithelia and lamina propria, respectively.[3] Accumulation of DC into the nasal mucosa of patients with allergic rhinitis occurs after topical allergen challenge. In contrast, human leukocyte antigen (HLA)-DR^+CD1a^+ myeloid DC, but not $CD123^{high}$ plasmacytoid DC, are identified in human bronchial mucosa.[4] The frequency of DC in the bronchial mucosa of asthmatic patients is higher than in healthy individuals. Moreover, the frequency increases after allergen exposure. Inhaled corticosteroid treatment diminishes the number of DC in the airways of patients with asthma and allergic rhinitis, suggesting that DC play an important role in the allergic reaction of the airways.[4,5]

DENDRITIC CELLS ORCHESTRATE ANTIGEN-SENSITIZATION: IMMUNOGENIC OR TOLEROGENIC RESPONSE

Soluble protein antigen delivered through an intact mucosal surface does not provoke strong immune

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responses under normal circumstances. Instead, it induces a state of antigen-specific hyporesponsiveness.[6] In the absence of ongoing inflammation and an immune response, DC located in peripheral tissues, including the bronchial mucosa, are immature, lack costimulatory molecules and present antigen inefficiently.[2] Naïve T cells are thought to fail to respond or become anergic to the antigen when the immature DC present antigen to naïve T cells because of the requirement of both an antigen-derived signal and costimulatory signals to activate naïve T cells. This failure leads to peripheral tolerance.[7] In contrast, the antigen-specific T cell response and the subsequent sensitization to antigen occur either under a state of coincident respiratory virus infection or in the presence of locally overexpressed granulocyte–macrophage colony stimulating factor (GM-CSF) or when antigen is delivered with lipopolysaccharide (LPS).[8,9] It is presumed that signals from pathogens and pro-inflammatory cytokines, often referred to as 'danger signals', induce the maturation of DC into efficient APC, resulting in an immunogenic response.[2,10] Therefore, the maturation state of DC, which depends on the nature of antigen and the local environment, determines whether sensitization to antigens is induced or not.

Akbari et al.[11] reported that tolerogenic DC and IL-10-producing regulatory T cells (Tr1 cells) in bronchial lymph nodes play an important role in the tolerance induced by antigen inhalation. The tolerogenic DC that produce large amounts of IL-10 and express inducible costimulator (ICOS) ligand regulate Tr1 differentiation. In contrast, DC in mesenteric lymph nodes have been shown to produce transforming growth factor (TGF)-β and to induce Th3 cells,[11] which are essential players in oral tolerance and produce mainly TGF-β. These observations support the concept that certain types of DC actively induce tolerance as tolerogenic DC.

INSTRUCTIVE ROLE OF DC IN THE DIFFERENTIATION OF NAÏVE T CELLS INTO TH1/TH2

Several factors regulate Th subset development, including: (i) the nature and intensity of T cell receptor-mediated signals; (ii) the cytokine and humoral milieu in which naive T cells are primed; (iii) the strength and nature of costimulatory signals; (iv) the type of APC; and (v) the ratio of T cell to APC.[12,13] The integration of these signals according to the genetic background of T cells dictates Th subset differentiation (Fig. 1). Among all

factors, IL-12 and IL-4 play critical roles in the differentiation of naïve T cells into Th1 and Th2 effectors, respectively. In addition to the role of primary APC for naïve T cells, DC are a main source of IL-12. Thus, they are able to induce differentiation of Th1 cells. It has been demonstrated that naïve T cells are themselves capable of producing IL-4 and that endogenous IL-4 leads to Th2 differentiation under the shortage of a Th1 driving force by IL-12.[13] Moreover, costimulatory signals delivered through CD86 and OX40 ligand (OX40L) and cytokines secreted by DC, such as IL-6 and monocyte chemotactic protein (MCP)-1, reinforce endogenous IL-4 production of naïve T cells, resulting in commitment to Th2 cells.[14–16] Therefore, DC are inferred to be deeply involved in the differentiation into Th2 cells.

Initially, the lineage of DC was proven to determine differentiation of Th subsets (e.g. myeloid DC induce Th1 and plasmacytoid DC induce Th2).[2] However, DC have functional plasticity, by which DC show different effector functions, including cytokine-producing ability and surface costimulatory molecule expression, depending on the conditions during their initial activation as sentinel cells.[17] Myeloid DC matured in the presence of prostaglandin (PG) E_2 acquired the capability of inducing Th2 cells by decreasing IL-12-producing ability and enhancing OX40L expression, whereas DC matured in the presence of interferon (IFN)-γ produce high amounts of IL-12 upon subsequent engagement of naïve T cells, leading to the development of Th1 cells. Moreover, upon microbial infection, different microbial compounds polarize the maturation of human myeloid DC into stably committed Th1 cell-promoting (DC1) or Th2 cell-promoting effector DC (DC2); they polarize Th cells via different mechanisms.[18] Notably, heterogeneity exists within DC1 and DC2 subsets in terms of the expression and use of Th-polarizing molecules, even though the DC1 and DC2 induce similar Th1 and Th2 cell subsets, respectively. Within DC2, the DC primed with soluble egg antigens of *Schistosoma mansoni* use OX40L to promote the development of Th2 cells, whereas DC primed with cholera toxin or PGE_2 promote Th2 cells via one or more unidentified soluble factores.[18]

More recently, human myeloid DC stimulated with thymic stromal lymphopoietin (TSLP) *in vitro* acquired an ability to induce helper T cells producing IL-5 and IL-13. Keratinocytes in the skin lesions of atopic dermatitis expressed TSLP; its mRNA is detected in bronchial epithelia and fibroblasts.[19] It is possible that TSLP expressed by bronchial epithelia of asthma patients allows DC to

Phenotype of DC

Lineage   Plasmacytoid DC
                 CD1a- myeloid DC

Localization mucosal DC

Adjuvant factors
  CpG
  Cholera toxin

TCR signals
  Ag dose: low
  Affinity: low
  Duration: sustained

Costimulatory molecules
  CD86   OX40L
  ICAM-1   ICOSL
                T1/ST2

Cytokines
  IL-4   IL-12
  IL-6   IL-18
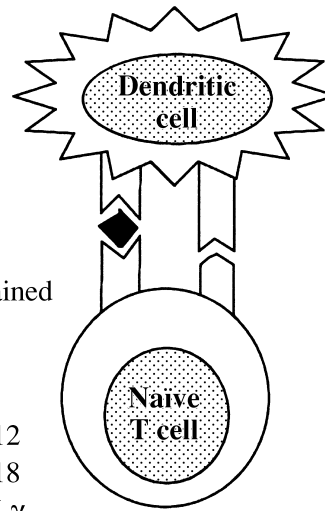 MCP-1   IFN-γ

DC:T ratio: low

Hormone
  progesterone

PGE$_2$

Genetic background

Fig. 1 Differentiation of Th cells induced by dendritic cells (DC). CpG, unmethylated CpG dinucleotides motif; TCR, T cell receptor; Ag, antigen; IL, interleukin; MCP-1, monocyte chemotactic protein-1; IFN-γ, interferon-γ; PGE$_2$, prostaglandin E$_2$; ICAM-1, intercellular adhesion molecule-1; ICOSL, inducible costimulator ligand; OX40L, OX40 ligand.

induce differentiation of effector T cells involved in allergic inflammation.

EXPANSION OF ALLERGIC INFLAMMATION BY DENDRITIC CELLS

Harris *et al.*[20] reported that, after adoptive transfer of *in vitro*-activated T cells, effector memory T cells that migrated into the airway produced substantial cytokines upon antigen challenge, but were incapable of proliferating or migrating back to the lymph nodes. In contrast, central memory T cells homing into the lymph nodes could be stimulated by antigen to proliferate, produce effector cytokines and migrate to peripheral tissues. The DC are capable of capturing antigens at airways and transferring processed antigen into the lymph nodes, where clonal expansion of antigen-specific T cells occurs (Fig. 2). Eosinophils also accumulate in the draining lymph nodes during eosinophilic airway inflammation and are capable of inducing some proliferation in effector T cells, but not as vigorous as that induced by DC.[21] These findings suggest that clonal expansion of Th2 cells is controlled mainly by DC. An allergic inflammation model has revealed that a unique subset of airway CD11c⁺CD11b⁺ DC expressing high levels of costimulatory molecules retain and present antigen for a prolonged period after exposure to the antigen, suggesting the involvement of airway DC in chronic infiltration of Th2 and chronic eosinophilic airway inflammation.[22]

In an allergic airway inflammation model, depletion of DC by ganciclovir treatment from antigen-sensitized thymidine kinase-transgenic mice led to failure to develop eosinophilic infiltration and goblet cell hyperplasia upon re-exposure to inhaled antigen.[23] These results indicate that DC are extremely important for presenting inhaled antigen to T cells in the lung, even after sensitization to the antigen.

Histamine affects the maturation of DC upregulating CD86 and MHC class II expression and suppressing IL-12 production.[24] Freshly isolated DC from allergic patients express FcεRI and take up antigens efficiently through IgE immobilized on FcεRI.[25] These data suggest that, once antigen-specific IgE is produced, IgE-mediated antigen uptake and histamine released from mast cells allow DC to effectively induce differentiation of Th2 cells. Engagement of FcεRI stimulates DC to produce IL-16, a chemoattractant of helper T cells and eosinophils.[26] Furthermore, TSLP-activated DC produce thymus and
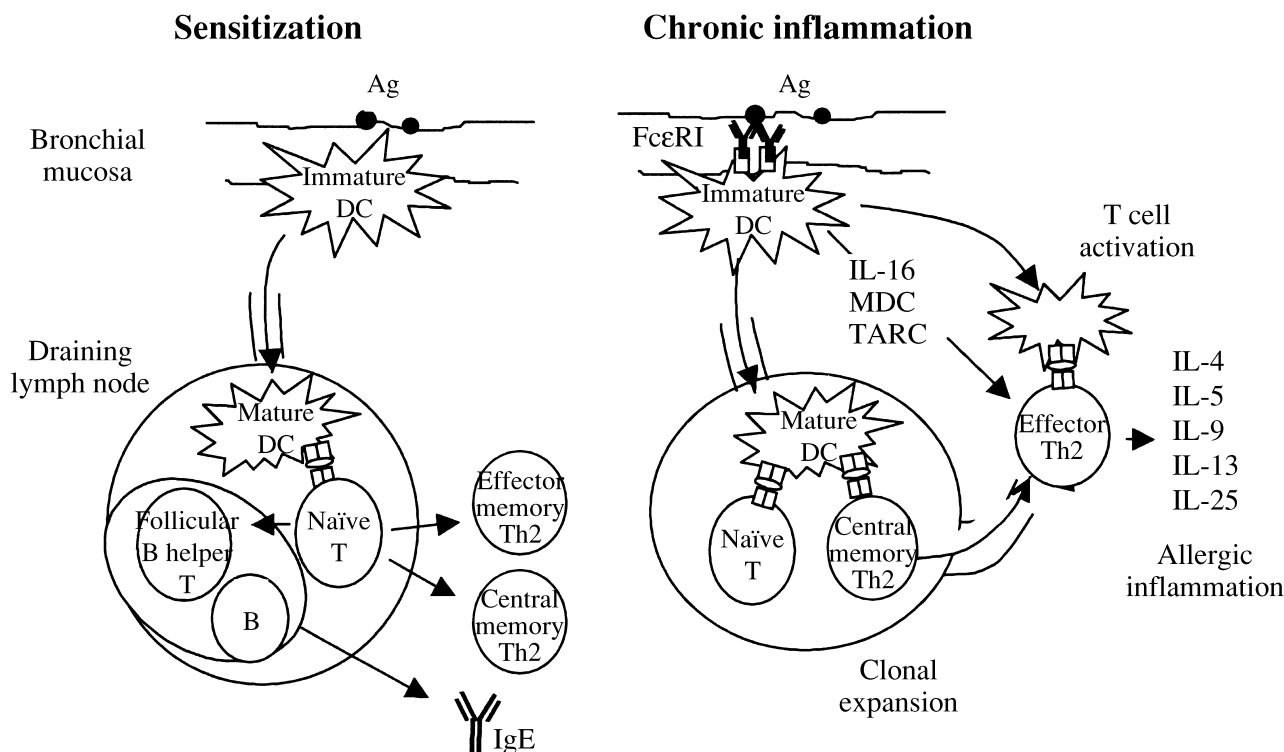
Fig. 2   Roles of dendritic cells (DC) during the sensitization to antigen (Ag) and subsequent allergic inflammation. IL, interleukin; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine.

activation-regulated chemokine (TARC) and macrophage-derived chemokine (MDC), which selectively attract Th2 cells.[19] The Th2 cell-derived IL-4 and IL-13 augment MDC production by DC.[27] Thereby, DC are involved in the amplification of allergic inflammation by regulating the recruitment of Th2 cells and eosinophils into inflammatory sites, as well as the clonal expansion of Th2 cells.

DENDRITIC CELLS AS A NOVEL THERAPEUTIC TARGET OF ALLERGIC DISEASES

Because DC play important roles in several steps of allergic inflammation (including the generation of antigen-specific Th2 cells and amplification) and in the maintenance of allergic inflammation, elucidating the function of DC could be a novel therapeutic target of allergic diseases. Some current asthma treatments putatively function through their effects on DC. The regular use of inhaled corticosteroid, which is the most effective controller in asthma treatment, is associated with a marked reduction in the number of CD1a^{+} DC in the bronchial mucosa of asthma patients.[4] The inhibitory effect of inhaled corticosteroid on the number of DC

may occur through suppression of the production of chemokines and cytokines that regulate the accumulation and maturation of DC. Alternatively, the steroid could induce apoptosis of immature DC in the airway and suppress differentiation of monocytes into DC. More recently, humanized anti-IgE therapy has been shown to be an effective asthma treatment.[28] Anti-IgE inhibits free IgE from binding to FcεR. Thereby, it attenuates the activation of mast cells and basophils. Because DC of allergic patients also express functional FcεR, anti-IgE may prevent them from producing IL-16 and taking up antigen through FcεR, resulting in diminished accumulation and activation of Th2 cells.

Molecules involved in the Th2 cell-polarizing activity of DC depend on the nature of the antigens and the maturing conditions.[18] Studies with knockout animals have demonstrated an important contribution of an OX40/OX40L interaction to the development of Th2-mediated pulmonary inflammation,[29] suggesting that OX40L is the important Th2-polarizing molecule of DC in the pathogenesis of atopic asthma and the most efficient therapeutic target molecule to block DC function. In a murine model of asthma, administration of neutralizing

anti-OX40L monoclonal antibody (mAb) during the antigen-sensitization period abolished the induction of asthmatic responses characterized by airway hypersensitivity, accumulation of eosinophils, increased mucus production and high levels of Th2 cytokines in the lung.[29] However, the administration of anti-OX40L mAb during airway challenge with antigen failed to inhibit asthmatic responses. These results indicate that blocking of OX40L could be an effective treatment when started prior to, but not after, the development of asthma. Further studies are required to confirm the clinical usefulness of OX40L blockade because the differentiation of naïve T cells into Th2 cells in asthma patients presumably occurs even after manifestation of asthma symptoms.

MODULATION OF DC FUNCTION BY CHEMOKINES

The recruitment of DC and their precursors into peripheral tissues and the migration of maturing DC into draining lymph nodes are regulated by various chemokines.[30] The biological activities of chemokines encompass effects on the activation of immunocompetent cells in addition to those on the recruitment of inflammatory cells.[31] Concurrent with that observation, we found that monocyte-derived DC generated in the presence of MCP-1 displayed a markedly reduced production of IL-12 in response to CD40 ligand.[32] Although MCP-1 affected neither the surface phenotype nor the T cell-stimulating activity of DC, naïve T cells stimulated with MCP-1-primed DC produced much less IFN-γ

and favored differentiation into Th2 effector cells[32] (Y Ohshima *et al.*, unpubl. data, 2002). Neither macrophage inflammatory protein (MIP)-1α nor eotaxin, the receptor of which is also expressed on monocyte-derived DC, affected DC function. Therefore, it is conceivable that MCP-1 modulates the differentiation of monocytes into DC and thereby shifts the Th1/Th2 balance to Th2 (Fig. 3). More recently, monocytes expressing CCR2, a functional receptor for MCP-1, were shown to be recruited preferentially to inflammatory lesions and to differentiate into DC.[33] It was reported that, depending on the state and nature of the inflammation, the attraction of DC precursors into the airway may be governed by a different set of chemokine receptors and their ligands; alternatively, different subsets of DC may be recruited.[34] Neutralization of MCP-1 to modulate DC function and to inhibit the accumulation of DC into the airway is inferred to be a feasible therapeutic strategy for asthma because increased levels of MCP-1 have been detected in bronchoalveolar lavage fluids and bronchial tissue from asthma patients.[35] Supporting this possibility, it has been reported that, in murine models of asthma, the administration of anti-MCP-1 antibodies during allergic airway response diminishes airway hyperreactivity and the inflammation that is associated with a decrease in leukotrienes and Th2-derived cytokines.[36,37] In addition, viral CC chemokine inhibitor (vCCI; a poxvirus-derived protein) and the cyclic retro-inverso analog constructed of D-amino acids in the reverse sequence (termed NR58-3.14.3), which are broad-spectrum chemokine inhibitors, were shown to be highly

Fig. 3 Monocyte chemotactic protein (MCP)-1 may influence the differentiation and effector function of Th2 cells by modulating the function of dendritic cells (DC). Monocyte chemotactic protein-1 is involved in the recruitment of DC precursors into inflammatory sites and in the functional maturation of DC in terms of Th-polarizing activity. IL, interleukin; HEV, high endothelial venules.
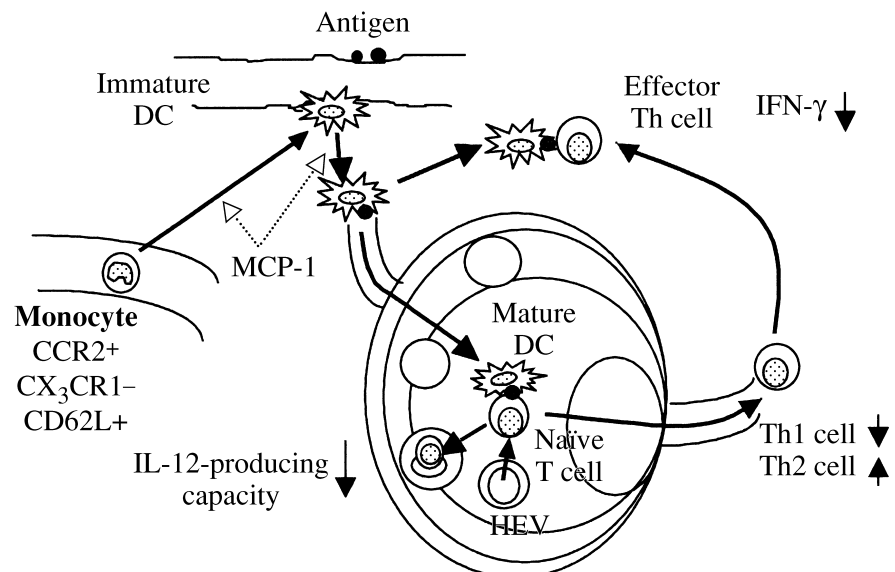
effective in inhibiting allergen-induced asthma in mice.[38,39] These chemokine inhibitors may present alternative procedures to regulate the recruitment and function of DC instead of neutralizing antibody.

ADJUVANT ROLE OF DC IN ANTI-ATOPY VACCINE

The application of counterbalance by Th1 cells or the inhibitory effects of regulatory T cells on Th2-dominant immune responses could be another DC-based therapeutic strategy because certain types of DC may be capable of inducing Th1 and regulatory T cells.[2,7] Antigen-pulsed Th1-promoting DC that become able to produce high levels of IL-12 by in vitro modification could be used as an anti-atopy vaccine similar to an antitumor vaccine. Moreover, the application of various reagents has been reported for the induction of antigen-specific Th1 responses. Such reagents include live or heat-killed bacteria like Bacillus Calmette–Guérin and Lactobacillus, detoxified derivative of lipopolysaccharide and CpG-oligodeoxynucleotide.[40] Although precise mechanisms underlying the Th1-promoting effects of these reagents remain unclear, it is presumed that signals through a pattern-recognition receptor, such as Toll-like receptors, activate DC, leading to acquisition of Th1-promoting activity. Controversy surrounds the functional impairment of DC from atopic patients in terms of IL-12 production and the expression of costimulatory molecules.[41–43] It remains to be clarified whether antigen-pulsed DC from individuals with an atopic predisposition show sufficient Th1-promoting activity in vivo, but not Th2-promoting activity. In contrast, Toll-like receptor-mediated signals may induce the secretion of large amounts of pro-inflammatory cytokines from DC, resulting in toxic shock. In experimental models of asthma, adaptive transfer of allergen-specific Th1 cells per se are reported to be capable of causing inflammatory responses with lung neutrophilia.[44] In addition, coadministration of allergen-specific Th1 cells enhances infiltration of Th2 cells into the lung, engendering deterioration of the allergic inflammatory response.[44] Moreover, enhanced allergic airway inflammation and IgE production were observed when LPS was given after sensitization with allergen. In this context, an anti-atopy vaccine using the Th1-promoting activity of DC seems to have potentially harmful side-effects. Even if it was available, its administration would preferably be commenced prior to the development of allergic diseases.

The term 'regulatory T cells' refers to those cells that actively control or suppress the function of other cells, generally in an inhibitory fashion.[45] Currently described candidates of regulatory T cells are Th3, Tr1, $CD4^+CD25^+$ Tr and anergic T cells. Certain types of regulatory T cells, termed Th3 and Tr1, preferentially induced by intestinal and respiratory exposure to antigen, respectively, are inferred to play an important role in the maintenance of tolerance.[45] In addition, DC are involved in the induction of regulatory T cells.[11] Adoptive transfer of IL-10-producing pulmonary DC has been shown to block subsequent antigen sensitization by inducing Tr1 cells.[11] Furthermore, it has been reported that DC generated by treatment with a combination of steroid and vitamin D_3, cholera toxin or pertussis filamentous hemagglutinin are able to generate allergen-specific regulatory T cells in vitro.[46,47] The administration of antigen-pulsed regulatory T cell-promoting DC or in vitro-generated IL-10-producing regulatory T cells per se may help suppress the Th2 response.

Specific mechanisms for the development and function of regulatory T cells remain unclear. Although Th3 cells and Tr1 cells seem to be involved primarily in regulating gastrointestinal and respiratory diseases, respectively, it remains uncertain which regulatory T cells effectively control allergic diseases. It is possible that regulatory T cells induce infectious tolerance in which T cells that are anergized by regulatory T cells inhibit DC maturation. Thereby, the immature DC anergize other T cells.[40] Thus, immunosuppression by regulatory T cells may engender increased susceptibility to infection and cancer.

CONCLUDING REMARKS

Taken together, experimental evidence from animal models and clinical evidence of the roles of DC in allergic diseases suggest that DC are effective targets for the development of therapeutic interventions. At least two different DC-based therapeutic strategies exist: (i) cellular adjuvant of anti-atopy vaccine using the APC function of DC; and (ii) a blocking target located upstream of the allergic inflammation cascade. Blockade of chemokines may be applicable to the latter DC-based therapeutic strategy of allergic diseases.

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