



Regulation of allergic inflammation by dendritic cells

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Purpose of review

Dendritic cells are critical in directing inflammatory versus tolerogenic responses. As the burden of allergic disease rises worldwide, increased understanding of mechanisms underlying these diseases is needed. This review highlights research demonstrating how dendritic cells influence allergic disease development, providing important mechanistic insights into current clinical management strategies as well as potential areas of focus for future development of novel therapeutic strategies.

Recent findings

Recent studies continue to elucidate dendritic cell-associated pathways which can either promote or prevent allergic inflammation. Mechanisms involved include various aspects of dendritic cell activity, from antigen sampling and dendritic cell migration to complex dendritic cell interactions with other immune cells, infectious agents and allergens. A deeper understanding of these mechanisms and how dendritic cells promote tolerance provides insight into potential strategies to therapeutically target dendritic cells in the management of allergic disease.

Summary

Recent discoveries illustrate crucial roles of dendritic cells as regulators of inflammatory versus tolerant cascades. Building on lessons from oncologic strategies for harnessing dendritic cells to promote antitumor responses, several novel pathways could also be targeted to promote dendritic cell-mediated tolerogenesis in the context of allergy. Additional studies are needed to further define the roles and potential effects of dendritic cells in these potential strategies to reduce allergic inflammation.

Keywords

allergic inflammation, dendritic cells, IL-10, T-regulatory cells, tolerance

INTRODUCTION

Dendritic cells are professional antigen-presenting cells possessing a diverse range of functions, dictated by their particular subset, location, and context. Dendritic cells function as key mediators at the interface of the innate and adaptive immune system, coordinating signals from innate immune responses to present processed antigen from peripheral tissue to guide T-cell differentiation. Dendritic cells thus promote immunity to foreign antigens and tolerance to self-antigens. Dendritic cells contribute to the promotion or prevention of allergic inflammation through mechanisms involving various aspects of dendritic cell activity, ranging from antigen sampling and dendritic cell migration to complex interactions with other cells, infectious agents and allergens. The growing body of evidence has further elucidated core mechanistic roles of dendritic cells in tolerogenesis and has also identified possible therapeutic targets. This review provides an update on the most recent discoveries

related to the role of dendritic cells in allergic inflammation.

TEXT OF REVIEW

Dendritic cell sampling and migration

Based on ontogeny, dendritic cells can be classified into the following subsets: conventional dendritic cell (cDC), plasmacytoid dendritic cell (pDC), monocyte-derived dendritic cell (moDC), and Langerhans

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KEY POINTS

- Dendritic cells are critical regulators of the adaptive immune system, directing responses toward either inflammatory or tolerant cascades.
- Dendritic cells regulate allergic inflammation and tolerogenesis at multiple functional stages, including antigen sampling, migration, cytokine secretion, and through interactions with other immune cells, infectious agents, and allergens.
- Potential future therapeutic strategies to target dendritic cells in allergic disease include antigen-primed dendritic cell vaccines, promotion of IL-10 or interferon (IFN) α expression by dendritic cells, and the use of allergen-adjuvant complexes to condition dendritic cells to stimulate antigen-specific Treg expansion.

cells [1,2]. cDCs can be further subdivided into type one and type two cDC, based on both surface markers and function. A significant function of type one cDC (cDC1) is to cross-prime CD8⁺ T cells, whereas type two cDC (cDC2) cross-prime CD4⁺ T cells. Although many of the subsets participate in both antigen presentation to T cells and signaling to coordinate immune responses, differences exist in their predominant functions, recently reviewed here [2], which will be discussed when pertinent throughout this review. Dendritic cell migration, reviewed previously [3], broadly includes the immigration of dendritic cell precursors to peripheral tissues, entry to initial lymphatic vessels upon activation, transport via afferent lymphatic vessels to draining lymph nodes, and the homing of dendritic cells from blood circulation to secondary lymphoid organs (SLOs) and their migration within. Migration plays a critical role in dendritic cell function, as the physical positioning of dendritic cell subsets in SLOs creates specific niches that dictate T-cell activation and differentiation, recently reviewed here [4]. As such, dendritic cell presentation of antigen to stimulate specific T-cell responses leading to allergic inflammation is predicated on the process of migration and organization of physical context.

Trafficking of antigen-primed dendritic cells to draining lymph nodes via the initial and afferent lymphatic vessels is mediated by numerous chemotactic factors, including conserved cysteine (CC)-chemokine receptor seven (CCR7) and others [3,5]. Regulatory T cells (Tregs) can limit dendritic cell migration to the draining lymph nodes by targeting CCR7. Hanakawa *et al.* [6[•]] found that skin-resident Tregs release IL-10 which inhibits CCR7 upregulation in dendritic cells, thus limiting cutaneous dendritic cell migration and subsequent

percutaneous sensitization. Intracellular targets that attenuate dendritic cell migration continue to be investigated. In ovalbumin (OVA) and Th2-skewing Nod2 agonist muramyl dipeptide-primed mice subsequently exposed to OVA challenge, inhibition of STAT6 reduced dendritic cell migration to mediastinal lymph nodes (MLN) which was associated with phenotypic decreases in airway hyperresponsiveness (AHR) and lower OVA-specific IgE [7]. Similarly, targeting an intracellular p21-activated kinases one, a regulator of cytoskeleton remodeling, decreased dendritic cell trafficking from the lungs to the MLN, serum IL-4, IL-5, and IL-13 levels, as well as phenotypic airway inflammation and AHR in a systemic OVA-sensitized mouse model of asthma [8].

Dendritic cell interactions with other cells also regulate dendritic cell migration and signaling. Mast cells provide an intriguing example. Mast cells promote dendritic cell migration to skin draining lymph nodes after IgE-mediated activation, with peripheral tumor necrosis factor (TNF) release by mast cells playing an important role in efficient migration [9]. Building on these findings, Dudeck *et al.* demonstrated that mast cells promote mast cell granule (MCG) uptake by dendritic cells via mast cell-produced TNF, which significantly increases MCG uptake [10[•]]. Furthermore, MCG uptake subsequently increases surface expression of CCR7, promoting migration of MCG-containing dendritic cells to lymph nodes. Once in the lymph node, MCG-containing dendritic cells displayed enhanced ability to prime IL-4 and IL-17 producing CD4⁺ T cells compared with non-MCG-containing dendritic cells [10[•]]. Dendritic cells also play a critical role in blood-borne antigen sampling that mediates anaphylaxis. Although mast cells can probe the blood for antigen directly, Choi *et al.* demonstrated that the more dominant mechanism of antigen presentation to perivascular mast cells occurs through perivascular CD301b⁺ cDC2, a key dendritic cell subset that acts as sentinels in the periphery and SLOs and crosses prime CD4⁺ T cells. CD301b⁺ cDC2 rapidly uptake blood-borne antigens and present antigen to nearby perivascular IgE-sensitized mast cell leading to cross-linking and degranulation of MCG [11^{••}]. These cDC2 cells discharge microvesicles with surface-bound allergen in a constitutive fashion which in turn activates mast cell leading to rapid degranulation. In a mouse model of anaphylaxis, depletion of CD301b⁺ cDC2 resulted in elimination of a clinical anaphylactic response when exposed to antigen [11^{••}].

Dendritic cells also interact with B cells to promote signaling to naïve T cells, especially in the case of dendritic cell presentation of IgE-immune complexes (IgE-IC). Engeroff *et al.* reported that both B

cells and moDCs bind IgE-IC in a CD23-dependent manner [12[¶]]. Direct binding of IgE-IC to CD23+ moDC led to internalization and degradation while binding to B cells resulted in subsequent recycling to the cell surface. This B-cell IgE-IC recycling allowed IgE-IC uptake by CD23+ moDC via B cell transfer in a contact-dependent fashion, and these activated moDCs subsequently stimulated antigen-specific CD4+ T-cell proliferation [12[¶]]. These findings broaden our understanding of the role of dendritic cells at the interface of innate and adaptive immunity, where dendritic cells go beyond antigen presentation to naïve T cells to serve as mediators through which both innate and other adaptive immune components additionally influence T-cell differentiation.

Dendritic cell activation of Th2 (eosinophilic) versus Th17 (neutrophilic) inflammation

Dendritic cells also regulate allergic inflammation via their capacity to recruit Th2 and Th17-associated innate immune cells to various sites. In the lung, the cDC2 subset is predominantly involved in promoting eosinophil recruitment during primary allergic airway responses. Yi *et al.* recently demonstrated that interactions between several murine lung dendritic cell subsets regulate eosinophil recruitment during the memory phase of chronic allergic asthma [13]. Although both cDC1 and cDC2 subsets participated in initial eosinophil recruitment via dendritic cell-secreted CCL17/CCL22 (known eosinophil chemoattractants) and nitric oxide, a different lung cDC2 subset conversely inhibited eosinophil recruitment later after allergen challenge, through secretion of TGFβ1 [13]. Data from a house dust mite (HDM)-driven murine asthma model revealed one potential mechanism by which dendritic cells regulate the development of Th2-mediated eosinophilic versus Th17-mediated neutrophilic asthma. Although wild-type mice developed Th2-mediated eosinophilic inflammation in both acute and chronic HDM-driven models, mice with reduced dendritic cell expression of TNF-α-induced protein three (TNFAIP3), a negative regulator of nuclear factor κB activation, developed Th17-mediated neutrophilic inflammation [14]. Other models of allergic airway disease, including OVA/flagellin and HDM-sensitized mice, confirm the role of dendritic cells in regulating neutrophilic inflammation and provide evidence that *Myd88* is involved. Compared with wild type, mice lacking *Myd88* in CD11c+ dendritic cells had significantly diminished neutrophil inflammatory responses upon OVA or HDM challenge, respectively [15^{¶¶}]. Results from a repeated exposure OVA and house dust extract

mouse model revealed reduced Th17-inflammatory responses in mice lacking cDCs and also in those selectively lacking Toll-like receptor (TLR) *Tlr4* in CD11c+ cells, providing evidence that TLR4-mediated activation of cDCs plays a role in sustaining Th17 and subsequent neutrophilic inflammation [16].

Dendritic cells have also been shown to activate Th17 inflammatory responses in a model of contact dermatitis, via IL-25-induced production of IL-1β by dermal dendritic cells [17]. In the context of atopic dermatitis, Nakahara *et al.* examined how endothelin-1, a pruritogenic mediator increased in the skin and plasma of atopic dermatitis patients, impacted dendritic cells and subsequent immune responses [18]. Dendritic cells exposed to endothelin-1 primed Th17, but not Th2 responses, that dendritic cells regulate Th17-mediated inflammatory responses in allergic skin disease [18].

A critical role for dendritic cell metabolism and mechanistic target of rapamycin (mTOR)-dependent metabolic adaptation in dendritic cell-driven allergic inflammation was recently demonstrated in a landmark study by Sinclair *et al.* [19^{¶¶}]. In this study, mTOR was essential in regulating cellular metabolism and accumulation of CD103+ lung dendritic cells in an HDM-sensitized mouse model. In addition, mTOR-deficient lung CD11b+ dendritic cells were metabolically reprogrammed to skew allergic inflammatory responses toward a neutrophilic Th17 phenotype. These novel findings provide evidence that mTOR mediates metabolic adaptation of dendritic cells in specific tissues as a mechanism to regulate allergic inflammation, and suggest that metabolic reprogramming of such dendritic cells may represent another potential future therapeutic direction in allergic disease research [19^{¶¶}].

Infectious agents and allergens: impact on dendritic cell regulation of allergic responses

Interactions with a variety of pathogens and antigens have been shown to influence dendritic cell-driven allergic responses. In the context of allergic asthma, combined effects of respiratory virus and allergen exposure have long been recognized to synergistically promote allergic airway disease, reviewed in [20]; several recent studies shed light on potential roles of dendritic cells in this process. In a study of children with severe allergic asthma, IgE-mediated disruption of ex-vivo dendritic cell antiviral responses to rhinovirus and influenza was observed; these antiviral responses were restored among those treated with anti-IgE therapy (omalizumab) [21[¶]]. This posttreatment change in dendritic cell antiviral function was associated with

improved clinical outcomes (fewer exacerbations in the group with the greatest change in ex-vivo antiviral responses), suggesting that dendritic cells may regulate allergic responses in vivo. One mechanism by which this may occur is through pDC suppression of proliferation and cytokine production of type two innate lymphoid cells mediated by IFN α [22[■]]. Conversely, evidence that viral activation of dendritic cells may enable sensitization to airway antigens was recently demonstrated by Reuter *et al* [23]. In this study, airway coexposure to low-potency allergen (OVA) and another respiratory virus, cytomegalovirus (CMV), resulted in enhanced OVA uptake by CMV-activated migratory airway dendritic cells during the sensitization phase and increased recruitment of these airway dendritic cells to tracheal lymph nodes. These data indicate that viral-exposed dendritic cells can mediate sensitization even to antigens with poor intrinsic allergenic potential and contribute to the development of allergic airway disease [23]. In a different murine model utilizing *Blomia tropicalis* extract (BTE) aero-allergen and influenza virus infection, prior exposure to low-dose allergen resulted in less severe influenza infection, with reduced influenza-associated lung disease and faster clearance of the virus. This was attributed to increased numbers of CD11b⁺ dendritic cells in the lung draining lymph nodes observed in BTE-sensitized mice and enhanced dendritic cell-mediated CD8⁺ T-cell priming [24]. Taken together, these data highlight the complexity of IgE/allergen and viral-associated dendritic cell responses and provide evidence that each can potentially promote or reduce dendritic cell-mediated allergic airway responses.

In the context of atopic dermatitis, a recent study suggests a role for dendritic cells in eczema herpeticum, a common viral-associated atopic dermatitis complication. Herpes simplex virus type 1 (HSV-1) induction of *ANKRD1*, a proposed biomarker of eczema herpeticum risk, was reduced in dendritic cells and other APCs in atopic dermatitis patients with a history of eczema herpeticum [25]. The investigators also demonstrated that silencing of *ANKRD1* disrupted interferon transcription upon TLR9 agonist stimulation, suggesting a role for *ANKRD1* in host responses to DNA virus infection and pointing to a potential defect in dendritic cell antiviral responses that could contribute to the pathogenesis of eczema herpeticum [25].

Dendritic cell role in tolerance

The role of dendritic cells in immune homeostasis and induction of tolerance continues to be investigated. Dendritic cells may participate in central

tolerance, influencing thymic clonal deletion of self-reactive T cells, as well as peripheral tolerance via influencing Tregs and clonal deletion of antigen-specific T cells. FOXP3⁺ Treg cells play a crucial role in this process. Akkaya *et al.* describe a novel pathway through which dendritic cell–Treg interactions mediate antigen-specific suppression of T-cell proliferation via a dual-pronged mechanism [26[■]]. In this study, communication with antigen-primed dendritic cells induced significant morphologic changes in antigen-specific Tregs, resulting in wider membrane fusion sites and longer contact duration compared with dendritic cell interactions with naïve T cells. These findings suggest that expansive interactions between dendritic cell–Tregs could effectively prevent access of naïve T cells to dendritic cell major histocompatibility complex class II (MHCII) antigen presentation, resulting in suppression of naïve T-cell proliferation upon antigen exposure. Furthermore, antigen-specific dendritic cell-induced Tregs were shown to remove their cognate-specific MHCII complexes from the dendritic cell surface in a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-independent fashion, with no effect on unrelated antigen MHCII complex expression on dendritic cells [26[■]].

The context of antigen exposure influences specific interactions in which dendritic cells participate. For oral tolerance, antigen-specific Treg differentiation depends on dendritic cell-mediated transport of oral antigen from lamina propria to the draining mesenteric lymph nodes, reviewed here [27]. CD103⁺ cDCs migrate from the lamina propria to the mesenteric lymph nodes in a TLR4-dependent manner [28], producing TGF β and retinoic acid to stimulate antigen-specific Treg [27]. The mechanism of peptide-based immunotherapy for desensitization may intervene at this point; a recent study demonstrated that hydrolysate of OVA with pepsin induced the expression of retinaldehyde dehydrogenase, also promoting the production of retinoic acid [29]. Mucosal pDCs also impact Treg differentiation and were recently shown to mediate de-novo differentiation of FOXP3[–] T cells to FOXP3⁺ Treg cells through TGF β autocrine loops. In this study, significantly fewer GALT tissue antigen-specific Tregs after oral antigenic feeding were observed in pDC-depleted mice compared with controls, highlighting a role for pDCs in oral tolerance. CD103⁺ pDCs in mesenteric lymph nodes exhibited a more tolerogenic phenotype compared with splenic pDC, with lower ability to present antigen to CD4⁺ T cells and greater ability to stimulate FOXP3⁺ Treg differentiation [30[■]].

Similar data exist for cutaneous antigen exposure, providing additional insights into dendritic cell-related mechanisms underlying immunotherapy responses. Dioszeghy *et al.* demonstrated a critical

role for Langerhans cells in inducing CD62L⁺ Tregs during epicutaneous immunotherapy (EPIT), with Langerhans cell-depleted mice displaying diminished Treg differentiation in response to EPIT [31]. Similarly, subcutaneous immunotherapy (SCIT) in *dermatophagoides pteronyssinus*-sensitive allergic patients resulted in reduced cDC2 and pDC FcεRI expression with parallel changes in IgE [32]. Decreased numbers of pDCs with increased IFNα expression were observed in recipients of SCIT compared with non-SCIT treated allergic controls [33] suggesting both quantitative and qualitative effects of immunotherapy on dendritic cell populations.

Dendritic cells can also induce T-cell anergy. Silva-Vilches *et al.* reported a role for dendritic cell-produced extracellular adenosine in promoting T-cell anergy, a process mediated by dendritic cell expression of the ATP-degrading ectoenzyme CD73 [34]. Knockout CD73^{-/-} mice were unable to stimulate the same anergic response when challenged with antigen; anergy induction was rescued with adenosine supplementation [34]. Furthermore, certain dendritic cell subsets have increased expression of adenosine receptor, that when activated results in IL-10 production and its subsequent suppressive actions [35]. IL-10 is a key regulatory cytokine; production by dendritic cells suppresses Th2 responses, recently reviewed here [36]. Although T cells and B cells also express IL-10R, IL-10 interaction with dendritic cells seems more significant in mediating tolerogenesis [37]. In a murine asthma model, IL-10 secreting dendritic cells profoundly impacted allergic inflammation, suppressing Th2-cell proliferation, inducing Treg differentiation, and even suppressing allergen-specific B-cell IgG1 and IgA secretion. Dendritic cells influenced this via both direct dendritic cell presentation of intact allergen to IgG1-secreting B cells and through IL-10 secretion [38].

Direct targeting of dendritic cells represents a potential therapeutic strategy for allergic disease. Sun *et al.* demonstrated that allergen-stimulated moDC promoted differentiation and expansion of Tregs *in vitro* [39]. Furthermore, adoptive transfer of these moDCs to OVA-sensitized mice led to reduced allergic nasal symptoms and airway inflammatory cell profiles, highlighting that allergen-activated dendritic cells can drive potentially beneficial immunoregulatory responses *in vivo* [39]. Multiple adjuvants to promote dendritic cell secretion of IL-10 have been investigated, recently reviewed [36,40]. Mechanistically, mTOR has been identified as a key transcriptional mediator of dendritic cell IL-10 secretion. Investigating fusion proteins with the TLR5 ligand flagellin and birch pollen allergen Bet v 1, Th2 responses were suppressed through activation

of mTOR in moDC and subsequent promotion of IL-10 secretion. Blockade of mTOR resulted in a loss of IL-10 secretion by moDC but did not inhibit proinflammatory cytokine secretion [41].

CONCLUSION/FUTURE DIRECTIONS

Ralph Steinman, who received the Nobel Prize for his discovery of the dendritic cell and its role in adaptive immunity, posed a series of critical questions regarding the role of dendritic cells in the induction of tolerance [42]. Can dendritic cells be harnessed as a therapeutic target to induce permanent tolerance? Years later, this question has profound implications for the field of allergy. The novel findings discussed herein suggest numerous possible targets that could be evaluated in answering this question, building on foundational work beyond the scope of this review. Table 1 summarizes potential mechanistic strategies that could be considered in targeting dendritic cells to suppress allergic inflammation and provides the context of significant studies upon which the current discoveries are built.

Recent discoveries highlight several key mechanisms that target dendritic cells in the differentiation and expansion of antigen-specific Tregs to mediate tolerance. As Akkaya *et al.* demonstrated [26], antigen-primed dendritic cell influences the development and expansion of antigen-specific Tregs via multiple mechanistic pathways; can these pathways be activated through an antigen-primed dendritic cell vaccine to produce tolerogenesis? Interestingly, dendritic cell vaccines have been studied in the context of cancer with the opposite goal of triggering an inflammatory antigen-specific T-cell response against tumor cells, highlighting the critical role dendritic cells play in directing inflammatory versus tolerant cascades. Examining strategies evaluated in such cancer studies provides an opportunity to glean important shared lessons; for example, the efficacy of dendritic cell antitumor vaccines is dependent on the distinct dendritic cell subsets utilized, and this would likely be an important factor in potential development of dendritic cell tolerogenic vaccine approaches for allergy. A recent review of dendritic cells in cancer immunology and immunotherapy highlights other common thematic elements when targeting dendritic cells, including the use of adjuvants or cytokine signaling to drive specific dendritic cell responses [56]. In this vein, there has been significant interest in promoting dendritic cell IL-10 expression and modifying allergens with adjuvants to condition dendritic cells toward a tolerogenic program. Recent findings described in this review present promising signs that these targets

Table 1. Potential strategies for targeting dendritic cells for the treatment of allergic inflammation

Strategy	Recent findings and their foundational context	Reference(s)
Dendritic cells and IL-10	Mature pulmonary dendritic cells that produce IL-10 are essential to the induction of CD4 ⁺ T-cell anergy after respiratory exposure to antigen	[43]
	Similar to above, IL-10 treated dendritic cells induced antigen-specific T-cell anergy. It was also demonstrated that these anergic T cells suppressed proliferation of cocultured T cells of the same antigen specificity without suppressing other T-cell lines	[44]
	In-vitro IL-10-treated dendritic cells expressed higher levels of IL-10 and lower levels of IL-12. Transfer of these IL-10 treated dendritic cells into an in-vivo antigen-sensitized mouse model, resulted in decreased airway hyperresponsiveness and Th2-cytokine production when the mice were exposed to antigen challenge. This suggests that IL-10 acts to regulate dendritic cell function toward attenuating allergic inflammation and that in-vitro modifications can be transferred to produce in-vivo effects	[45]
	Gregori <i>et al.</i> further characterized IL-10 producing dendritic cells from healthy donors, identifying them as a unique subset of dendritic cells that mediate their suppressive actions through the Immunoglobulin-like Transcript 4–human leukocyte antigen G pathway	[46]
	One critical effect of IL-10 signaling is the induction of Treg differentiation. Pacciani <i>et al.</i> demonstrated that human dendritic cells differentiated in the presence of IL-10 and pulsed with Der p 2, induced Der p 2-Treg cells <i>in vitro</i> . Pelliren <i>et al.</i> found that tolerogenic dendritic cells incubated in IL-10 and pulsed with Ara h one and Ara h two induced Ara h1 and Ara h two specific Tregs in peanut-allergic and healthy individuals. Interestingly, upon secondary stimulation with antigen, anergy was induced in healthy controls but not those with peanut allergy despite the presence of antigen-specific Tregs, suggesting that there is an underlying deficit in peanut-allergic patients that abrogates the functional suppressive actions of Tregs	[47,48]
	OVA-specific tolerance was induced in mice with specific deletion of IL-10R α in T cells, B cells, macrophages, and neutrophils, but not in mice with IL-10R α deletion in dendritic cells, suggesting that dendritic cells are the requisite main target of IL-10 in tolerance induction	[37]
	In a murine asthma model, IL-10 secreting dendritic cells suppress allergen-specific B-cell IgG1 and IgA secretion via both direct dendritic cell presentation of intact allergen to IgG1-secreting B cells and through IL-10 secretion	[38]
Induction of Treg differentiation	Numerous studies have demonstrated that certain dendritic cell subsets are required for the induction of antigen-specific Tregs and tolerance. Ochando <i>et al.</i> reported that pDCs present allo-antigen acquired from transplant allografts, migrate to lymph nodes and mediate alloantigen-specific Treg development and allograft tolerance, a process abrogated in a pDC depleted model. Uto <i>et al.</i> similarly demonstrated the critical role pDCs play in the induction of oral tolerance, with abrogation of Treg-mediated oral tolerance in a pDC-ablated model. Esterhazy <i>et al.</i> demonstrated that cDCs were critical for Treg induction and oral tolerance to OVA antigen in a mouse model of delayed hypersensitivity whereas moDCs were not	[30 [■] ,49,50]
	As above, IL-10 plays an important role in dendritic cell induction of Tregs. Akkaya <i>et al.</i> demonstrated a novel pathway through which dendritic cells suppress antigen-specific T cell proliferation. This dual-pronged mechanism involves both Treg competition for contact with dendritic cells as well as removal of antigen-specific MHCII complexes from the surface of dendritic cells	[26 [■]]
Dendritic cells and IFN	Duerr <i>et al.</i> demonstrated that deficient signaling through the type I IFN receptor resulted in deregulated activation of ILC2, which was associated with type two immune responses. Type I IFN regulated both mouse and human ILC2 directly leading to decreased cytokine production, decreased ILC2 proliferation and increased ILC2 cell death. Moro <i>et al.</i> demonstrated that both type I and type II IFN suppress ILC2 function, suggesting that IFNs contribute to an important negative feedback mechanism for ILC2 function and their mediated type two immune responses	[51,52]
	Maazi <i>et al.</i> found that pDCs restrain the cytokine production and survival of ILC2 cells, which was abrogated in a pDC-depleted model. Furthermore, IFN α was the primary mechanism through which pDCs regulated ILC2	[22 [■]]
	Antiviral pDC IFN α responses were enhanced in allergic asthmatic children treated with omalizumab. This enhanced IFN α response was associated with improved clinical outcomes (i.e., fewer exacerbations of asthma in the outcome period), suggesting that targeting dendritic cells to increase IFN α secretion may provide potential clinical benefit in allergic disease	[21 [■]]
	Similarly, Sousa <i>et al.</i> found that patients undergoing subcutaneous immunotherapy had pDCs with increased IFN α secretion compared with controls, suggesting that immunotherapy may also play a role in improving IFN signaling in allergic patients	[33]

Table 1 (Continued)

Strategy	Recent findings and their foundational context	Reference(s)
Modifying antigen to condition dendritic cell responses	There is evidence that manipulation of antigen presentation through methods of coculturing or conjugation can influence dendritic cells immune response. Pochard <i>et al.</i> demonstrated that in-vitro costimulation of dendritic cell TLR signaling by microbial products during exposure to peanut antigen led to subsequent suppression of T-cell proliferation and Th2 cytokine production. Zhou <i>et al.</i> demonstrated that mannose-conjugated antigen had a protective effect from antigen-induced anaphylaxis in vivo. Mannose-conjugate antigen selectively targeted dendritic cells expressing specific intercellular adhesion molecule-grabbing nonintegrin receptor 1, resulting in increased IL-10 expression, induction of Treg differentiation and subsequent tolerance Sirvent <i>et al.</i> created glutaraldehyde-polymerized allergoids from phleum pratense grass allergen and coupled this allergoid to nonoxidized mannan. They found that the conjugated allergoid-mannan compound had increased uptake by human dendritic cells, and subsequent induction of Tregs compared with the allergoids and native antigen	[53,54] [55]
Metabolic regulation of dendritic cell tolerogenesis	Sinclair <i>et al.</i> demonstrated that mTOR was essential in regulating cellular metabolism and accumulation of CD103+ lung dendritic cells in an HDM-sensitized mouse model; mTOR-deficient lung CD11b+ dendritic cells were metabolically reprogrammed to skew allergic inflammatory responses toward a neutrophilic Th17 phenotype. This was also reported by Schulke <i>et al.</i> who found that birch pollen-flagellin fusion proteins activated mTOR in moDC and promoted subsequent expression of IL-10. Taken together, mTOR mediation of metabolic adaptation of dendritic cells in specific tissues offers a possible mechanism to regulate allergic inflammation	[19 [■] ,41 [■]]
Dendritic cell migration	Dendritic cell migration to lymph nodes is essential whether the result of their antigen presentation induces Tregs and tolerance or drives antigen-sensitization and allergic inflammation. Thus, targeting dendritic cell migration in the absence of tolerogenic conditions which would result in allergic sensitization represents a possible therapeutic target. Hanakawa <i>et al.</i> found that skin-resident Tregs release IL-10 which inhibits CCR7 upregulation in dendritic cells, thus limiting cutaneous dendritic cell migration and subsequent percutaneous sensitization. Interestingly, decreasing dendritic cell trafficking through inhibiting intracellular components such as PAK1 and STAT6 resulted in decreased Th2 cytokine production and end-organ airway hyperresponsiveness when exposed to antigen in sensitized mice	[6 [■] ,7,8]

CCR7, CC-chemokine receptor seven; HDM, house dust mite; IFN, interferon; ILC2, innate lymphoid type two cells; mTOR, mechanistic target of rapamycin; OVA, ovalbumin; PAK1, p21-activated kinases one; TLR, Toll-like receptor.

may be of clinical benefit to patients, but more work needs to be done. Future research is needed to further define the mechanisms through which distinct dendritic cell subsets achieve Treg differentiation in response to the above-targeted strategies and to rigorously evaluate potential efficacy of such dendritic cell-focused strategies, an approach that the field of oncology has already been exploring.

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Conflicts of interest

There are no conflicts of interest.

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