

REVIEW ARTICLE

Role of plasmacytoid dendritic cell subsets in allergic asthma

H. Maazi, J. Lam, V. Lombardi & O. Akbari

Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

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Correspondence

Omid Akbari, PhD, University of Southern California, Keck School of Medicine, Department of Molecular Microbiology and Immunology, NRT 5505, 1450 Biggy St, Los Angeles, CA 90033-9605, USA.
Tel.: +1 323 442 7930
Fax: +1 323 442 7944
E-mail: akbari@usc.edu

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Abstract

Plasmacytoid dendritic cells (pDCs) are major type-I interferon-producing cells that play important roles in antiviral immunity and tolerance induction. These cells share a common DC progenitor with conventional DCs, and Fms-like tyrosine kinase-3 ligand is essential for their development. Several subsets of pDCs have been identified to date including CCR9⁺, CD9⁺, and CD2⁺ pDCs. Recently, three subsets of pDCs were described, namely CD8 α ⁺β⁺, CD8 α ⁺β[−], and CD8 α [−]β⁺ subsets. Interestingly, CD8 α ⁺β[−] and CD8 α [−]β⁺ but not CD8 α [−]β[−] pDCs were shown to have tolerogenic effects in experimentally induced allergic asthma. These tolerogenic effects were shown to be mediated by the generation of FOXP3⁺ regulatory T cells through retinoic acid and the induction of retinaldehyde dehydrogenase enzymes. These newly described subsets of pDCs show high potentials for novel therapeutic approaches for the treatment of allergic diseases. In this review, we will address the new progress in our understanding of pDC biology with respect to allergic disease, in particular allergic asthma.

Plasmacytoid dendritic cells (pDCs) are the major type-I interferon-producing cells that are implicated in antiviral immunity and immunological tolerance (1–6). Since their first discovery in 1958, there has been a substantial improvement in our understanding of these cells (7). In the steady state, pDCs show plasma cell-like morphology and express CD11c, CD45R, PDCA-1, Siglec-H, but not CD11b in mice, and CD4, CD45RA, CD303, and CD123, but not CD11c in humans (1, 8–10). Under inflammatory conditions and upon activation, pDCs show a classical DC morphology with dendrites (11). These cells sense pathogens through Toll-like receptor-7 and -9 leading to their rapid and robust secretion of type-I interferons (IFNs) (12, 13). This unique capacity of pDCs to secrete high levels of IFN- α is crucial for innate antiviral immunity (14–16).

In adaptive immunity, pDCs play major roles in the induction of immunological tolerance. Unlike conventional DCs, pDCs are poor antigen-presenting cells to CD4⁺ T cells mainly due to their less-efficient antigen-processing machinery and low expression of co-stimulatory molecules (1, 11, 17). However, there is evidence suggesting that pDCs can efficiently present antigens to CD8⁺ T cells (18). pDCs contribute to the induction of tolerance through enhancing the generation of regulatory T (Treg) cells (19–26). It has been

shown that a subset of thymic stromal lymphopoietin protein receptor-expressing human pDCs potentiates the generation of naturally occurring T cells in the thymus (27). There is also evidence indicating that pDCs contribute to the induction of Treg cells required for immune tolerance in allergic and autoimmune diseases, cancer, transplant and fetal tolerance (19–26).

pDC ontogeny

Understanding the pDC ontogeny and pDC progenitors is an interesting issue that has attracted the attention of many research groups. It has been shown in human and mouse that hematopoietic stem cells (HSCs) can ultimately give rise to pDCs and conventional DCs in the bone marrow (28). HSCs can differentiate to either common lymphoid progenitors (CLPs) or common myeloid progenitors (CMPs) (29), and it has been well established that both CMPs and CLPs can give rise to pDCs or cDCs (28, 30, 31). It was found that a subpopulation of pDCs transiently expresses recombination activating gene-1 (RAG-1) during development, and it was thought that only CLP-derived pDCs had expressed RAG-1 (32, 33). However, it was recently reported that all CLP-derived pDCs and a subpopulation of CMP-derived pDCs

had expressed RAG-1 during their development and in this respect show similarity to B cells (34).

Monocyte DC progenitors (MDPs) are further differentiated progenitors for both pDCs and cDCs that originate from CMPs (35, 36). Fms-like tyrosine kinase-3 ligand (Flt3-L) is an essential cytokine in DC development, and its receptor Flt3 is broadly expressed by DC progenitors in bone marrow (37, 38). Flt3-L drives the differentiation of common DC progenitors from MDPs and further to either pDCs or pre-DCs (39).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is another important factor in DC development that was initially identified as a requirement for *in vitro* generation of DCs (40). However, the development of DCs is only partially ablated in the absence of GM-CSF or its receptor in mice (41). It was thought that Flt3-L-mediated generation of DCs resembles the generation of DCs *in vivo* in steady state (42), whereas GM-CSF mainly drives inflammatory DCs (43). Nevertheless, a recent report from Merad group suggests that GM-CSF is dispensable for the generation of inflammatory DCs (44).

pDCs in allergic diseases

Several lines of research have shown a role for tolerogenic pDCs in allergic diseases including allergic asthma. In a clinical study, it was found that the number of pDCs in infancy inversely correlates with asthma development during the first 5 years of life (45). A recent study shows that human tonsillar pDCs have the capability to induce functional FOXP3⁺ Treg cells that can suppress effector T cells *in vitro* (46). This study reports that pDCs co-localize with FOXP3⁺ Treg cells in human tonsils *in vivo* (46).

In mice, depletion of pDCs has been shown to cause sensitization and lung inflammation to a harmless antigen (47). Increased number of pDCs due to administration of Flt3-L has been reported to be associated with alleviated asthma-like symptoms in mice, which is reversed after depletion of pDCs (48). Besides allergic asthma, there is evidence suggesting that pDCs play tolerogenic roles in food allergy (49). Flt3-L-mediated expansion of pDCs has been shown to inhibit the development of allergic inflammation in the intestines in a murine model of food allergy (49). Altogether, these studies indicate an important role for pDCs in fine-tuned regulation of immunological tolerance in allergic asthma.

Regulation of tolerance

The tolerogenic role of pDCs is delicately tuned to the circumstances of antigen exposure and whether pathogen-associated molecular patterns are present (50–52). Under steady state, pDCs play a tolerogenic role in allergic asthma; however, this effect is abrogated in the presence of danger signals and infectious agents. Adoptive transfer of pDCs from sensitized donors to sensitized recipient has been shown to inhibit the development of house dust mite-driven allergic asthma in a mouse model (53). This effect was abrogated when the transferred pDCs were infected by respiratory

syncytial virus (RSV) (53). Interestingly, it has been reported that *ex vivo* RSV-infected human pDCs express higher levels of T-cell co-stimulatory molecule, CD86, and pro-inflammatory cytokine IL-8, suggesting that pDCs play a role in eliciting the immune response rather than tolerance in the presence of RSV (50). Another study has shown that while low-dose infection with *Chlamydia pneumoniae* facilitates sensitization and development of allergic asthma, high-dose *C. pneumoniae* infection increases the number of pDCs and Treg cells in the lungs and prevents allergic sensitization in a mouse model (54). Unlike infectious agents, the presence of innocuous gut flora seems to be important for the induction of pDC-mediated allergen tolerance. Germ-free mice have reduced number of pDCs and macrophages in their lungs and show exacerbated airway eosinophilia, IgE production, and Th2 cells compared with specified pathogen-free mice (55). In humans, *Bifidobacterium infantis* feeding was shown to induce peripheral FOXP3⁺ Treg cells as well as induction of IDO in pDCs through TLR-9 stimulation *in vitro*, which suggests a role for IDO-expressing pDCs in the induction of oral tolerance by microbiota (51). Recently, it was shown that Siglec-H that is exclusively expressed by pDCs, and recognizes sialic acid molecules of pathogens, is required for eliciting CD8-mediated immune response as well as for the generation of inducible FOXP3⁺ Treg cells *in vivo* (52). Taken together, evidence suggests that pDCs fine-tune the balance between immune response and tolerance based on the presence or absence of danger signals that stimulate pattern recognition receptors on these cells.

pDC subsets

Based on the expression of cell surface markers, pDCs have been further categorized into different subsets (Table 1). Expression of CCR9 on mouse pDCs was first reported by Wendland and colleagues as an intestine homing receptor (56). Subsequently, Hadeiba and colleagues found that CCR9-expressing pDCs suppress acute graft-vs-host disease in mice (57). Whether the CCR9⁺ pDCs have a human counterpart and can contribute to maintaining tolerance to allergens remains to be elucidated. It has been recently shown that in the steady state, CCR9⁺ pDCs are terminally differentiated subsets present only in the liver and bone marrow, but not in the lungs (58), ruling out that CCR9⁺ pDCs might play a role in allergic asthma.

Recently, the Engleman group reported that mouse CD9⁺ and CD9[−] pDCs have distinct roles in antitumor immunity and tolerance (59). They reported that CD9⁺ Siglec-H^{low} pDCs secrete high level of IFN- α when stimulated with Toll-like receptor (TLR) agonists and promote antitumor immunity. In contrast, CD9[−] Siglec-H^{hi} pDCs were found to secrete low amounts of IFN- α and induce FOXP3⁺ CD4 T cells (59). Nonetheless, it is unknown whether there is a human counterpart for CD9⁺ pDC subsets and whether these cells migrate to the lungs to play a role in the immune regulation in this organ.

It has been reported that CD2^{hi} human pDCs obtained from buffy coat packs secrete higher levels of interleukin (IL)-12p40, show higher expression of co-stimulatory

Table 1 Function of pDC subsets involved in the pathology of various diseases

pDC subsets	Function	Tissue	Species	Reference
CCR9	CCR9 ⁺	Associated with suppressing acute graft-vs-host disease and ulcerative colitis by inducing Treg cells and suppressing antigen-specific immune responses.	Intestine, bone marrow, liver, lung	Mouse (56–58)
	CCR9 [−]	Acts as a precursor for CCR9 ⁺ pDC or conventional DC depending on the tissue.		
CD9Siglec-H	CD9 ⁺ Siglec-H ^(low)	Secretes high levels of IFN- α upon TLR stimulation, induces cytotoxic T lymphocytes and promote antitumor activity.	Bone marrow, liver	Mouse (59)
	CD9 [−] Siglec-H ^(high)	Secretes negligible IFN- α levels, induces Foxp3 ⁺ Treg cells, and fails to promote antitumor immunity. Involved in hepatitis C virus recognition after infection.		
CD8 α β	CD8 α ⁺ β ⁺	Activates FoxP3 ⁺ Treg cells to induce tolerance by increasing retinoic acid production.	Lung	Mouse (61)
	CD8 α ⁺ β [−]	Activates Teff cells to induce airway inflammation and airway hyper-reactivity.		
CD2	CD2 ^(high)	Produces IFN- α , granzyme B, TRAIL, lysozyme, and can recall T-cell responses. Also produces higher levels of IL-12p40, CD80, and more efficiently triggers proliferation of naïve allogeneic T cells than CD2 ^(low) .	Tonsils and tumors	Human (60)
	CD2 ^(low)	CD2 ^(low) pDCs are depleted in HIV subjects.		

molecule CD80, and show higher capacity in priming allo-genic T cells (60). However, it is not currently known whether CD2^{hi} pDCs possess any crucial capacity in the induction of tolerance in allergic diseases.

Newly described CD8 α ⁺ pDC subsets in allergic asthma

Recently, three new subsets of pDCs have been described based on the expression of CD8 α and β chain, which include CD8 α [−] β [−], CD8 α ⁺ β [−], and CD8 α ⁺ β ⁺ (61). The frequency of these cells is reported to be 61%, 22%, and 6% in the lungs of naïve mice, respectively. Besides lungs, these three subsets are also present in peripheral lymph nodes and spleen (61). In the steady state, the three subsets express equal levels of Siglec-H, Ly6c, B220, Ly49Q, programmed cell death ligand-1 (PD-L1), programmed cell death ligand-2 (PD-L2), and inducible co-stimulatory ligand (61). Interestingly, it is found that only CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ subsets have the tolerogenic capacities in allergic asthma and CD8 α [−] β [−] pDCs lack this capacity. In fact, CD8 α [−] β [−] pDCs produce substantially higher levels of IFN- α , IL-6, tumor necrosis factor (TNF)- α , and IL-10 compared with CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ subsets upon stimulation with TLR-7 or TLR-9 agonist (61). Furthermore, CD8 α [−] β [−] pDCs are more efficient in antigen uptake and in priming naïve CD4⁺ T cells *in vitro* than the other two subsets as evident by higher naïve CD4⁺ T-cell proliferation and IL-2 production in pDC–T cell co-culture in the presence of antigen (61).

In vivo, when the three subsets are loaded with ovalbumin (OVA) and transferred to naïve mice, only CD8 α [−] β [−] pDCs

can prime T cells, sensitize the mice, and lead to the induction of asthma-like symptoms upon inhalation challenge with OVA (61). Conversely, CD8 α ⁺ β [−] or CD8 α ⁺ β ⁺ pDC subsets lead to tolerance induction in the recipient mice as shown by the lack of airway hyper-reactivity and airway inflammation in the mice receiving CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ pDC subsets.

In a different experiment, OVA-loaded subsets of DCs were transferred to the naïve mice followed by OVA/alum sensitization (61). After intranasal challenge, these mice showed reduced airway hyper-reactivity, airway inflammation, OVA-specific IgE, and Th2 cytokines IL-4 and IL-13 in CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ pDC subset recipient mice compared with those receiving CD8 α [−] β [−] pDCs (61). These data confirm that only CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ pDC subsets are tolerogenic in experimentally induced allergic asthma.

Interestingly, both CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ are more efficient in inducing FOXP3 expression when co-cultured with naïve OVA-specific CD4⁺ T cells in the presence of OVA compared with CD8 α [−] β [−] pDC subset (61). Furthermore, it was found that CD8 α ⁺ β [−] and CD8 α ⁺ β ⁺ pDCs express retinoic acid aldehyde dehydrogenase (RALDH) genes, and blocking retinoic acid receptor using LE540 abrogated the induction of FOXP3 in T cells (Fig. 1).

Mechanisms of tolerogenic effects of pDCs

pDCs contribute to tolerance induction through diverse mechanisms such as facilitating the generation of Treg cells, direct cytotoxicity effects, induction of T-cell anergy, and clo-

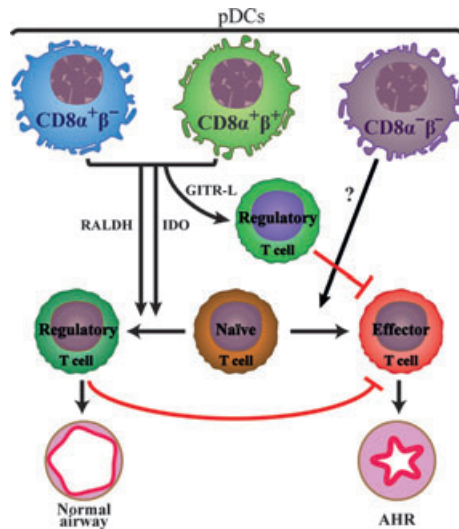


Figure 1 Plasmacytoid dendritic cell (pDC) subsets $CD8\alpha^+\beta^-$, $CD8\alpha^+\beta^+$, and $CD8\alpha^-\beta^-$ activate T-cell-mediated immune responses with opposing effects. $CD8\alpha^+\beta^-$ and $CD8\alpha^+\beta^+$ pDC subsets convert naïve T cells into Foxp3⁺ regulatory T cells (Treg) via several potential mechanisms including expression of retinaldehyde dehydrogenase (RALDH) and indoleamine 2,3-dioxygenase (IDO) to induce tolerance and prevent the induction of airway hyper-reactivity (AHR) and airway inflammation. Moreover, these tolerogenic subsets express high levels of GITR-L that can signal to Treg cells to suppress effector T cells. $CD8\alpha^-\beta^-$ pDCs convert naïve T cells into Teff cells to induce AHR and airway inflammation (61).

nal deletion of T cells (62–67). pDCs can potentiate the generation of Treg cells by several mechanisms: (I) Expression of indoleamine 2,3-dioxygenase (IDO) that is an immunoregulatory tryptophan-degrading enzyme originally found to be constitutively expressed and upregulated by DCs upon stimulation (reviewed in (68)). IDO is shown to be involved in tolerance induction in autoimmune disease, transplantation, and in fetal and cancer tolerance (24, 69–73). Although it was initially thought that the immunoregulatory function of IDO was through tryptophan deprivation and/or generation of kynurenine and its downstream metabolites (reviewed in (74)), it has been recently reported that involvement of IDO in intracellular signaling is important for its immunoregulatory effects, and its enzymatic function is dispensable for the mentioned function (75). (II) Expression of programme cell death ligand-1 (PD-L1). In a mouse model of allergic asthma, it was found that a subpopulation of lung pDCs expresses PD-L1 and adoptive transfer of CpG-stimulated pDCs from mice lacking PD-L1 fails to suppress the asthma-like symptoms in this model (48). (III) Expression of RALDH. There is evidence indicating that retinoic acid stimulates the induction of FOXP3 in T cells *in vitro*. It was recently demonstrated that $CD8\alpha^+\beta^-$ and pDC subsets express high levels of RALDH enzymes which convert retinol to retinoic acid and that blocking RALDH abrogates pDC-mediated induction of FOXP3⁺ Treg cells *in vitro* (61). (IV) Expression of

glucocorticoid-induced TNFR-related protein ligand (GITRL) that is a T-cell co-stimulatory molecule expressed by a variety of antigen-presenting cells including pDCs (76). GITRL on pDCs upon engaging with GITR on Treg cells initiates a bidirectional signal to the Treg cell and to the pDC (77). GITRL/GITR signaling through the pDC has been shown to activate noncanonical NF- κ B pathway and induce IDO in experimentally induced allergy in mice (77).

Another mechanism of pDC-mediated tolerance induction is by directly attacking T cells (62–64). It has been reported that a subset of mouse pDCs and *ex vivo*-cultured human pDCs in the presence of IL-3 express granzyme B (62–64). Interestingly, granzyme B⁺ mouse pDCs were reported to express CD8 α and directly attack and clear tumor cells when stimulated with TLR-7 agonist (63). Granzyme B⁺ human pDCs, however, were shown to have the capacity to directly suppress T cells in the absence of TLR-7 or TLR-9 agonist (64). Therefore, it would be interesting to investigate whether granzyme B⁺ pDCs play a role in maintaining or restoring tolerance to allergens and whether TLR stimulation can change the direction of pDC cytotoxicity effects toward cell types such as T cells.

A recent study showed that liver pDCs exhibit higher tolerogenic capacity and produce significantly higher levels of IL-27 than splenic pDCs (78). This study also showed that IL-27 leads to STAT3-mediated upregulation of B7-H1 only in the liver pDCs that can induce FOXP3⁺ Treg cells (78).

Besides the above-mentioned mechanisms, there is evidence suggesting that pDCs can induce tolerance by anergizing T cells (65, 66). This could be due to low expression of co-stimulatory molecules by pDCs, as antigenic stimulation through the T-cell receptor in the absence of a co-stimulatory signal leads to T-cell anergy (79).

Future directions

Given the important roles of pDCs in antiviral immunity and tolerance induction, a detailed understanding of several aspects of pDCs is required for the translational applications of pDCs in allergic diseases. In this regard, it is very important to identify whether the counterpart of $CD8\alpha^+\beta^-$, $CD8\alpha^+\beta^+$, and $CD8\alpha^-\beta^-$ pDC subsets exists in humans. Furthermore, it is important to identify whether these newly described pDC subsets share a common progenitor and to identify the factors deriving each subset. Finally, it is essential to unravel the mechanisms of tolerogenic effects of $CD8\alpha^+\beta^-$, $CD8\alpha^+\beta^+$, and $CD8\alpha^-\beta^-$ pDC subsets for identifying their potential applications in the treatment of human immune diseases.

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Conflict of interest

Authors declare no conflict of interest.

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