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Distinct dendritic cell subsets actively induce Th2 polarization

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Abstract

The mechanisms by which dendritic cells induce Th2 polarization (DC^{Th2} cells) have been controversial. Many have argued that DC^{Th2} cells are not a distinct functional DC subset, but rather, DC-induced polarization of Th2 cells is a default pathway that occurs in the absence of inflammatory signals leading to DC-induced polarization of Th1/Th17 cells. However, recent studies demonstrate that distinct subsets of tissue DCs actively polarize Th2 cells after stimulation with type-2 inducing stimuli. DC^{Th2} cells development is marked by the upregulation of specific transcription factors, cell surface molecules, and cytokines. These findings counter previous hypotheses that Th2 skewing by DCs is a passive response and support a model in which DCs are actively programmed to induce Th2 differentiation.

The mechanisms by which dendritic cells induce Th2 polarization (DC^{Th2} cells) have been controversial. Recent studies have provided new evidence that distinct DC subsets in the tissue mediate development of Th2 responses through upregulation of specific genetic programs driven by Th2 stimuli [1]. It is well known that DCs polarize Th1 and Th17 through the production of IL-12 or IL-23/IL-6 respectively [2], but the lack of Th2-skewing IL-4 production by DCs has lead researchers to investigate how DCs impact Th2 differentiation. Indeed, over the years, many have suggested that DC polarization of Th2 differentiation is not an active process but rather a passive pathway of Th polarization that occurs in the absence of active DC-induced polarization of T cells into Th1 cells [3–8]. Another prevailing hypothesis has been that in the absence of an inflammatory signal, immature DCs preferentially stimulate Th2 responses due to decreased TCR signaling and low co-stimulatory signals [9–13]. While many of these studies used *in vitro*, *ex vivo*, or adoptive transfer experiments, recent advances have allowed more detailed investigations concerning the function and specificity of DCs *in vivo* at both the steady state and during inflammatory responses. In this article, we review the latest studies that demonstrate how distinct subsets of tissue DCs are involved in the induction of Type-2 immunity. Moreover, these DC^{Th2} cells actively polarize Th2 cells in response to specific signals through the

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upregulation of specific transcription factors [14–16], cell surface molecules [17,18], and cytokines [11,13,19,20]. These findings counter previous hypotheses that Th2 skewing by DCs is a passive response, and support a model in which DCs are actively programmed to induce Th2 differentiation.

Lung and skin Th2 responses are mediated by distinct DC subsets

Development of Type-2 immune responses during helminth infections, allergic airway inflammation, or atopic dermatitis has been most frequently associated with both CD11b⁺ conventional DCs (cDCs) and CD11b⁺ monocyte-derived DCs (moDCs) [5,13,16,21–23]. At steady state, CD11b⁺ cDCs are located primarily below the basement membrane, but after antigen challenge they accumulate around the airways allowing antigen uptake [16,17,21,24–31]. Upon activation, CD11b⁺ cDCs can upregulate CCR7 and CD47 to promote migration to the mediastinal lymph node [32–34] where they preferentially activate CD4⁺ T cells [35,36]. During inflammatory responses, production of the chemokine CCL2 recruits CCR2^{hi} monocytes to the lungs where they can differentiate into CD11b⁺ moDCs [24,37,38]. Using a house dust mite (HDM)-mediated model of asthma, Plantinga *et al* found that both CD11b⁺ cDCs (CD64[−]FcεRI[−]) and CD11b⁺ moDCs (CD64⁺FcεRI⁺) were sufficient to induce Th2 responses in the lungs [24]. However, while CD11b⁺ cDCs were responsible for migrating to the draining lymph node and initiating Th2 differentiation, the primary function of the CD11b⁺ moDCs was to produce significant amounts of chemokines to attract monocytes and granulocytes [24]. Previously, CD11b⁺ moDCs were thought to participate in priming naïve CD4⁺ T cells [30,39–41]. However, many recent studies support a model in which CD11b⁺ cDCs and CD11b⁺ moDCs exhibit distinct but complementary functions in driving Th2 immunity [16,24,29,37,42,43].

Interestingly, the CD11b⁺ subset was also shown to play a critical role in promoting Th2-mediated skin inflammation [17,31]. Using a murine model of atopic dermatitis, it was found that only CCL17⁺CD11b^{hi} DCs could drive Th2 differentiation in the skin draining lymph nodes. This model was dependent on thymic stromal lymphopoietin (TSLP) responsive DCs, indicating that the TSLP receptor (TSLPR) could be another marker used to identify DCs specialized to induce Th2 responses [17,31]. More recently, CD207[−] dermal DCs, expressing CD301b and PDL2, were identified as the mediators of Th2 responses in an OVA-mediated and papain-mediated skin inflammation model [16,29]. Using *Mgl2*(CD301b)-DTR mice it was demonstrated that CD301b⁺ DCs were the primary transporters of soluble antigens from the skin to the draining lymph node where they facilitated CD4⁺ T cell accumulation and Th2 priming [29]. Overall, specific subsets of DCs responsible for promoting Th2 responses can be identified *in vivo*; however, the relationship between lung cDCs and moDCs with skin CD301b⁺PDL2⁺ DCs and CCL17⁺CD11b^{hi}TSLPR⁺ DCs remains unclear.

The confusion regarding the specific roles CD11b⁺ cDCs and CD11b⁺ moDCs play in mediating Type-2 responses, is due in part, to the lack of markers that distinctly identifies these subsets (Table 1). One of the first markers identified, Ly6C, was utilized as the primary marker to separate CD11b⁺ cDCs and CD11b⁺ moDCs [22]. However, Ly6C is lost upon differentiation of monocytes into macrophages or dendritic cells and is a temporal

marker that changes depending on the timing of an experiment [24]. Other groups have tried to identify more accurate panels of markers using FcγRI (CD64) and FcεRI [24,30,44], CD301b and PDL2 [16,29], CD24 [45], Ly6G [18], CCR2 [30,37], MERTK [36], CCL17 and TSLP receptor (TSLPR) [17,31], and CX3CR1 [46], but there is currently no standard panel. Moreover, there is a continuum of expression on DC subsets for many of these markers making it difficult to identify distinct populations of cells. An additional layer of complexity is the fact that the different markers were identified in various anatomical locations. There appears to be a greater degree of similarity between DCs in the skin and lung as FcγRI (CD64), CD301b, PDL2, CCR2, and MERTK were found to be expressed on CD11b⁺ cDCs and CD11b⁺ moDCs in both tissues [16,21,24,30,36,37]. In contrast, although transcriptional regulation of DC ontogeny has demonstrated that CD11b⁺ DCs from lung and small intestine cluster closer to each other than to CD103⁺ DCs and macrophages, they exhibit significantly variable expression of a defined core cDC signature that includes Flt3L and CSF-1R highlighting the heterogeneity of CD11b⁺ DCs from different tissues [23]. Thus, using a specific genetic program to identify DC^{Th2} cells may be a more accurate way to recognize which cells are driving Th2 immunity rather than relying on historically defined surface markers.

Given the significant genetic overlap between monocytes, macrophages, and DCs, it has been difficult to create mouse strains that specifically delete one subset of antigen presenting cells without affecting the other populations. For instance, although most studies have implicated a role for CD11b⁺ cDCs and CD11b⁺ moDCs, Th2-mediated allergic airway inflammation was found to be impaired in BXH2^{-/-} mice which specifically lack CD103⁺ cDCs implicating this subset in type-2 inflammatory responses [47]. However, BXH2^{-/-} mice also have impaired monocyte development, particularly of Ly6C⁺ monocytes that have the ability to transport antigen to lymph nodes [36], and can differentiate into CD11b⁺ moDCs during inflammation [48]. A different CD103⁺ cDC deficient strain, BATF3^{-/-} mice (that lack both CD103⁺ and CD8α⁺ DC subsets), responded normally to OVA sensitization and challenge [49]. In fact, recent findings have suggested that the CD103⁺ DC subset is essential for the development of tolerance to inhaled antigens [50] and for the inhibitory effects of *Helicobacter pylori* intestinal infection on type-2 immunity [49]. Identification of more specific markers for DC^{Th2} cells so that they can be specifically deleted is critical to understanding their function in the initiation and development of Th2 responses.

DC^{Th2} cells upregulate a specific genetic program

Substantial progress has been made in the recent years to identify distinct genetic signatures specific to DC subsets [23]. The transcription factors STAT5, IRF4, PU.1, RelB, SpiB, IRF8, NFκB, and C/EBPα have all been implicated in DC subsets development [51]. Two of these transcription factors, IRF4 and STAT5, play a critical role in mediating the functionality of DCs to promote Th2 responses. STAT5 is a downstream target of TSLP [52], a cytokine that promotes DC^{Th2} differentiation *in vitro* [53] as well as DC migration to the draining lymph node and initiation of Th2 differentiation *in vivo* [17,53,54]. Specific deletion of STAT5 in DCs impairs DC responsiveness to TSLP, and diminishes Th2-mediated inflammation due to decreased DC upregulation of co-stimulatory molecules (i.e. CD80, CD86, and OX40L) and decreased differentiation of Th2 cells [55]. Interestingly, this

defect was found to be specific for CD11b⁺ DCs [55] further supporting the hypothesis that this DC subset has a genetic predisposition towards driving Th2 immunity. It is important to note that TSLP and subsequent upregulation of STAT5 does not appear to be necessary to maintain a Th2 response during helminth infections [56] and late stage allergic inflammation [57]. Therefore, STAT5 signaling in DCs plays a critical role during early Th2 polarization and sensitization.

The transcription factor IRF4 has emerged as a key regulator of DC^{Th2} cell development [14–16]. Multiple mechanisms by which IRF4 promotes the development and function of DC^{Th2} cells have been suggested. IRF4-deficient DCs were found to have a decreased ability to present antigen to CD4⁺ T cells [14], and demonstrate defects in production of Th2 skewing cytokines, specifically IL-10 and IL-33 [15], which have been implicated in Th2 differentiation [15,58,59]. Within the skin, IRF4 deficiency prevented CD11b⁺ DCs from upregulating chemokine receptors and migrating from the dermis to cutaneous lymph nodes [60]. While it is possible that defect in migration may indirectly lead to decreased Th2 immunity, Williams et al and Gao et al both showed that in vitro stimulation of T cells with IRF4-deficient DCs failed to induce Th2 differentiation [15,16]. Thus, IRF4 expression is key to the ability of DCs to induce Th2 polarization. These studies are partly confounded by the different mouse strains that were created for each study. At baseline, there were significant differences in what DC populations were present between the IRF4-deficient mice [14–16,45,61], and it was suggested that this result was dependent on when IRF4 was deleted during development. A better understanding of when IRF4 is turned on or off during DC subset differentiation would help clarify its role in the development of DC^{Th2} cells. Furthermore, a comprehensive understanding of DC^{Th2} differentiation should include investigating whether or not other binding partners of STAT5 and IRF4 are involved in this process including PU.1, SpiB, IRF8, and others [51]. Together, the identification of STAT5 and IRF4 expression in DC^{Th2} cells further supports the emerging model that a distinct genetic signature is upregulated in DCs to promote Th2 responses.

Activation of specific receptors on DCs can promote Th2 responses

Clarification of the transcriptional regulation of DC^{Th2} cells has led to significant interest in determining what receptors allergens are signaling through to promote DC^{Th2} cells. Allergic responses can be generated against functionally and structurally distinct allergens, and one of the unresolved questions in the field is how different allergens are able to lead to a similar outcome of Th2-mediated inflammation. Allergens have been classified based on their enzymatic activity: Class I allergens (i.e. dust mite and cockroach) have allergenic components that can act as enzymes, while Class II allergens (i.e. animal dander) do not exhibit enzymatic activity [62]. Several receptors on DCs that bind to Th2 stimuli and lead to DC^{Th2} cells have been identified including house dust mite (HDM) and *Aspergillus fumigatus* binding to Dectin-2 [63], IgG-immune complexes (IgG-ICs) binding to FcγRIII [64], IgE-ICs binding to FcεRI [27], and glycosylated allergens binding to the mannose receptor [65]. Recently, we identified FcRγ-associated receptors as a common pathway used by both Class I (HDM) and Class II (IgG-ICs) allergen to promote DC^{Th2} cells [66]. FcRγ is a signaling chain associated with multiple receptors including Dectin-2, FcγRI (CD64), FcγRIII (CD16), and FcεRI [67,68]. Signaling CD11b⁺ DCs through either Dectin-2 or

Fc γ RIII, in conjunction with a TLR4 signal, led to the induction of IRF4- and IL-33 dependent Th2 responses in the lungs (Figure 1) [15,64,66,69]. Interestingly, antigen uptake of ICs and HDM was shown to preferentially occur in both CD11b⁺ cDCs and CD11b⁺ moDCs further supporting their role as DC^{Th2} cells [24,64]. Thus, differential expression of FcR γ -associated receptors on CD11b⁺ DCs may be one mechanism to explain why specific DC subsets are more likely to skew towards a Th2 phenotype.

Conclusion

In the past several years, there have been significant advances in our understanding of the requirements for the development of DC^{Th2} cells. It is now clear that distinct DC subsets can upregulate specific transcriptional programs to promote Th2 responses. Studies have clearly demonstrated that DC^{Th2} cells upregulate a specific genetic signature including STAT5 and IRF4, and thus, DC polarization of Th2 differentiation is an active process similar to the DCs that promote of Th1 or Th17 responses and should no longer be thought of as a default pathway. Although our understanding of DC^{Th2} cells has significantly increased in the past few years, there are still questions that remain unanswered. Standardization of identification of DC^{Th2} cells in the tissues needs to be established; conclusions about DC^{Th2} cells activation, genetic signature, and function *in vivo* is limited by the lack of consistent markers for these cells. Future investigations into the ontogeny of DC^{Th2} cells will create a more complete understanding of the transcriptional regulation that drives DC^{Th2} differentiation. Lastly, although our study identified one pathway through FcR γ -associated receptors on DC^{Th2} cells utilized by Th2 stimuli, other pathways allergens may activate in DCs to initiate a Th2 inflammatory response remains unknown. Allergens which do not bind to FcR γ -associated receptors including lipocalins, diesel particles, chemicals and dyes, amines, indicates that other pathways are playing a role in mediating the development of DC^{Th2} cells. Understanding the mechanisms by which DC^{Th2} cells develop and function will provide essential information on how Type-2 responses *in vivo* are instigated, and how they may be effectively regulated therapeutically to reduce the pathology of Type-2 diseases such as asthma, atopic dermatitis, and allergies.

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Figure 1.

Signaling through FcR γ -associated receptors on dendritic cells drives IL-33-dependent Th2-type responses. Class I allergens (i.e. pollen, house dust mite, and pollen) have allergenic components that can act as enzymes, while Class II allergens (i.e. animal dander) do not exhibit enzymatic activity. Class I allergens contain glycans that can bind directly to Dectin-2 whereas more homogenous protein allergens like animal dander must form antigen-specific IgG immune complexes that can activate Fc γ RIII. Ligation of these receptors on DCs leads to signaling through FcR γ , which upregulates the transcription factor IRF4 as well as IL-33 and IL-10 to promote development of DC^{Th2} cells and allergic airway inflammation.

Table 1

Summary of markers used to identify and separate CD11b⁺ cDCs and CD11b⁺ moDCs.

Markers	CD11b ⁺ cDCs	CD11b ⁺ moDCs	References
CD11c	+	+	
MHCII	+	+	
Ly6C	–	+	[22]
CD64 and FcεRI	–	+	[24,30,44]
CD301b	+	–	[16,29]
PDL2	+	–	[16]
CD24	+	–	[45]
CCR2	–	+	[30,37]
CCL17 and TSLPR	+	–	[17,31]
CX3CR1	–	+	[46]