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Dendritic Cell Regulation of T Helper Cells

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Abstract

As the professional antigen-presenting cells of the immune system, dendritic cells (DCs) sense the microenvironment and shape the ensuing adaptive immune response. DCs can induce both immune activation and immune tolerance according to the peripheral cues. Recent work has established that DCs comprise several phenotypically and functionally heterogeneous subsets that differentially regulate T lymphocyte differentiation. This review summarizes both mouse and human DC subset phenotypes, development, diversification, and function. We focus on advances in our understanding of how different DC subsets regulate distinct $CD4^+$ T helper (Th) cell differentiation outcomes, including Th1, Th2, Th17, T follicular helper, and T regulatory cells. We review DC subset intrinsic properties, local tissue microenvironments, and other immune cells that together determine Th cell differentiation during homeostasis and inflammation.

INTRODUCTION

Dendritic cells (DCs) are the quintessential antigen-presenting cells (APCs). DCs are located in both peripheral and lymphatic tissues and function as sentinels for immunological insults. DCs maintain homeostasis by inducing immune tolerance in the steady state and are uniquely programmed to respond to perturbations of homeostasis, typically signaled through innate immune triggering, by activating naive T cells circulating through the draining lymph nodes (LNs) (1). Thus, DCs are the translators between innate and adaptive immunity. Both DCs and T cells are heterogeneous and include subsets with different developmental pathways, phenotypes, transcriptomes, functions, and tissue locations. Conventional DCs (cDCs), whose development and heterogeneity are reviewed by Cabeza-Cabrerizo et al. (2), are the major DC subset that migrates into LNs and induces naive T cell proliferation. We provide a concise introduction to DC subsets and the nomenclature used in this review (**Supplemental Table 1**). We then focus on how different DC subsets instruct $CD4^+$ T helper (Th) cell differentiation in both mice and humans (**Figure 1**).

Supplemental Material >

$CD4^+$ Th cells include Th1, Th2, Th17, T follicular helper (Tfh), and T regulatory (Treg) cell subsets (3). DCs play a primary role in regulating naive $CD4^+$ T cell proliferation; DCs in conjunction with accessory cells also instruct polarization into these different subsets, according to the nature of the perturbation. A coordinated series of signals must occur to achieve activation of naive $CD4^+$ T lymphocytes: (*a*) antigen presentation on major histocompatibility complex (MHC) molecules (HLA in humans), (*b*) costimulatory signals, and (*c*) instructive cell surface and cytokine signals. The first two signals establish a threshold that must be crossed to prime a T cell and thereby help ensure tolerance to self or other innocuous molecules. Although the ability to present antigens on MHC along with costimulatory molecules is not a property unique to DCs, DCs are often necessary and sufficient in vivo for T cell priming due to their unique ability to migrate from tissues to LNs or within the spleen (4). The third signal instructs T cell differentiation; as we discuss, these signals come from both DCs as well as other cells in the LN microenvironment. DCs are plastic and can respond to environmental cues, again often provided through innate immune pathways, to provide context-dependent third signals to induce different T cell subsets; however, different types of DCs also have intrinsic functional specificities resulting in preferential induction of particular T cell subsets.

HETEROGENEITY OF HUMAN AND MOUSE DCs

DCs have significant functional and phenotypic heterogeneity. The nomenclature used to describe these different subsets has changed over the years. More recently, uniformity in assigning subsets has been adopted by many groups, based primarily on ontogeny (5). Both mice and humans have equivalent populations for each subset (6, 7). This nomenclature will be used in our review, although certain populations are still difficult to define. We briefly define the basic characteristics of DC subsets, including cDCs, plasmacytoid DCs (pDCs), and the related monocyte-derived DCs (mo-DCs) and Langerhans cells (LCs).

Conventional DCs

cDCs populate almost every lymphoid and nonlymphoid tissue and have been separated into two subsets, cDC1s and cDC2s (5). Developmentally, both cDC1s and cDC2s develop from common DC progenitors in the bone marrow, which further differentiate into cDC-restricted progenitors, pre-cDCs, in both mice and humans (8–10). Pre-cDCs committed to either the cDC1 or cDC2 fate then migrate to tissues and lymph organs through the blood and finalize differentiation into

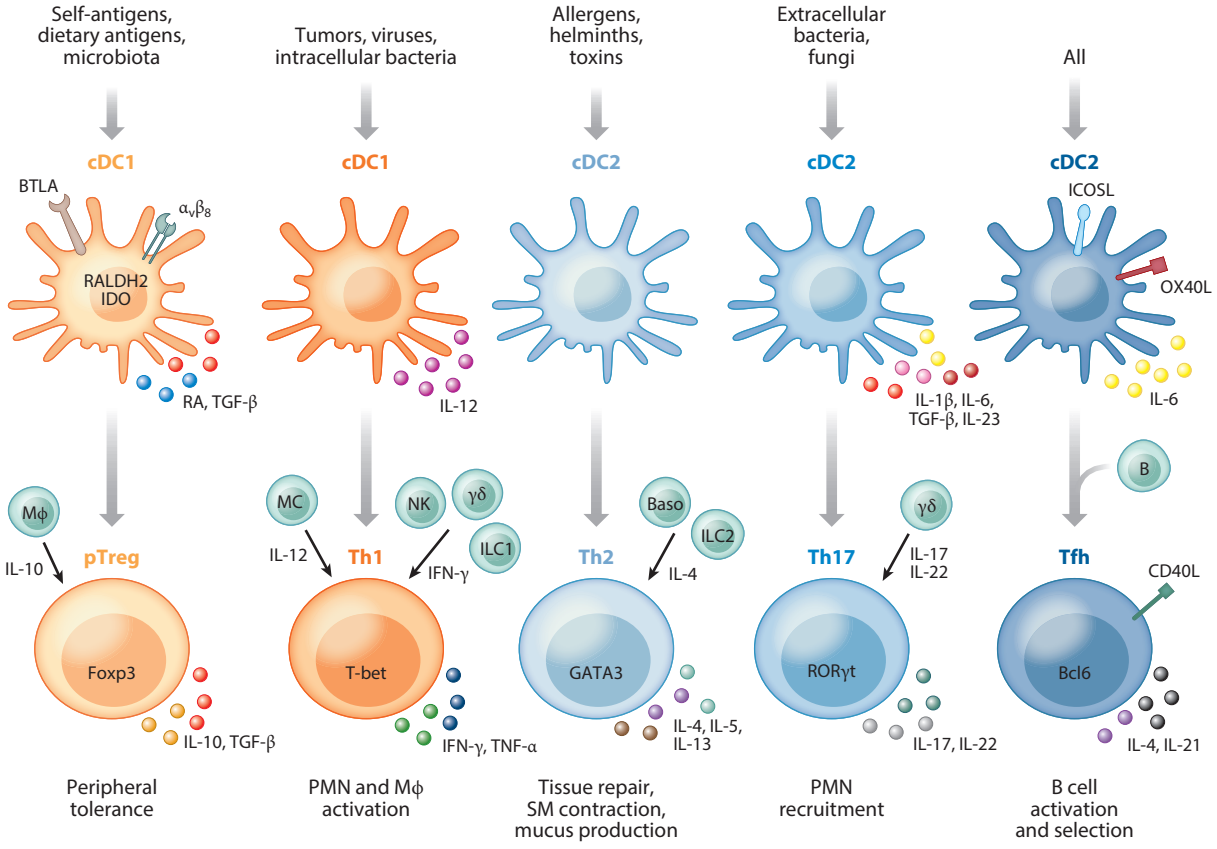


Figure 1

cDC subsets determine CD4$^+$ Th cell differentiation in adaptive immunity. Specific cDC subsets induce distinct T cell activation and differentiation pathways that are determined by the type of antigen, inflammatory cues, and intrinsic properties of each DC subset. The integrated MHC-peptide, costimulatory molecules, cytokines, and metabolites from the DC and local microenvironment, including accessory cells as shown, determine CD4$^+$ T cell activation and differentiation. This illustration focuses on the major cDC subsets that drive regulatory T, Th1, Th2, Th17, or Tfh differentiation based on a majority of reports. Under certain immunization conditions, different types of DCs can also induce the indicated T cell differentiation. Abbreviations: B, B cell; baso, basophil; Bcl6, B cell lymphoma 6; BTLA, B and T lymphocyte attenuator; cDC, conventional DC; DC, dendritic cell; Foxp3, forkhead box P3; γδ, γδ T cell; ICOSL, inducible T cell costimulator ligand; IDO, indoleamine 2,3-dioxygenase; ILC1, group 1 innate lymphoid cell; MC, monocyte-derived cell; Mφ, macrophage; NK, natural killer cell; PMN, polymorphonuclear leukocyte; pTreg, peripheral regulatory T cell; RA, retinoic acid; RALDH2, retinaldehyde dehydrogenase 2; SM, smooth muscle; Tfh, T follicular helper cell; Th, T helper cell.

cDC1s and cDC2s (11–13). FLT3L is indispensable for cDC1 and cDC2 development in both mice and humans (1). The identification of Zbtb46 as a cDC-specific transcription factor helps differentiate cDCs from monocyte-derived cells, especially when combined with Mafb-lineage tracing (14–16).

In the LN, cDCs can be divided into resident cDCs and migratory cDCs according to their initial seeding location from blood-derived precursors. Migratory DCs reside in tissues and migrate during both steady state and states of inflammation to draining LNs via lymphatics. Conversely, the entire life of a resident DC occurs within lymph nodes; despite the name, resident DCs are still motile (4). Lymph tissue without lymphatics, such as that of the spleen, Peyer patches, and tonsils, lacks emigrating DCs; however, migration of particular DC subsets within these tissues

still occurs, and so the migratory and resident distinction may still be applied (17). Both resident and migratory DCs are subdivided into cDC1s and cDC2s (17).

cDC1 phenotype, development, and function. Murine cDC1s are typically characterized as $Lin^{-}MHC\text{-}II^{+}CD11c^{+}CD8^{+}$ (resident cDC1s) or $CD103^{+}$ (migratory cDC1s) (18). Human cDC1s are characterized as $Lin^{-}CD64^{-}HLA\text{-}DR^{+}CD141^{+}$ cells. Almost all human and mouse cDC1s express XCR1, Clec9A, and CADM1 (19–22). Developmentally, cDC1s depend on transcription factors IRF8, Batf3, ID2, and Nfil3 (23).

The most notable function of cDC1s derives from their superior ability to cross present cell-associated antigen to prime $CD8^{+}$ T cells, which makes cDC1s pivotal in antiviral and antitumor immune responses (24, 25). In humans, although earlier studies showed that activated cDC1s were superior to other DC subsets in cross presenting soluble or cell-associated antigen (20, 22, 26–28), subsequent studies have shown that many DC subsets, especially those from lymphoid tissues, are able to cross present in vitro (29, 30). Whether all human DCs can cross present antigen and induce $CD8^{+}$ T cells in vivo is unknown. The detailed mechanism promoting their cross presentation has been extensively reviewed (31) and will not be a focus of this review. cDC1s also present antigen to $CD4^{+}$ T cells and regulate Th cell differentiation, as discussed below, in particular for Treg cell induction during steady state and Th1 cell induction during inflammation.

cDC2 phenotype, development, and function. Murine cDC2s are characterized as Lin^{-} $MHC\text{-}II^{+}CD11c^{+}CD11b^{+}SIRP\alpha^{+}$. cDC2s in intestinal tissue also express CD103 (1). Human cDC2s are identified as Lin^{-} $HLA\text{-}DR^{+}CD1c^{+}SIRP\alpha^{+}$ DCs. However, there appear to be at least two subsets of cDC2s in both mice and humans, with distinct markers and transcriptional profiles depending on the state of inflammation (32–34). One subset aligns closely with the traditional definition of cDC2s and in humans has been identified as $CD1c^{+}CD5^{+}CD14^{-}$ $CD163^{-}$ and in mice as $CD11b^{+}CD64^{-}$ $CCR2^{-}$ $Ly6C^{-}$ $Tbet^{+}$ and $ESAM^{+}$ depending on the tissue (33, 40–43). The second subset has many names, and because of its overlap in marker expression, transcriptional profile, and inflammatory properties, it is difficult to distinguish from mo-DCs, which are discussed in the next section. In human samples, this population, which has been referred to as inflammatory cDC2s or DC3s, is marked by $CD1c^{+}CD5^{-}$ $CD14^{variable}CD163^{+}$, and although this population is not derived from monocytes, the exact cell precursor remains unclear (38–42). In mice this population is most often called inflammatory DCs (inf-DCs), but its relationship to cDCs has only been elucidated in a few studies that demonstrated derivation from cDCs, not monocytes (36, 37). Yet CCR2 supports inf-cDC2 expansion, and inf-cDC2s upregulate mo-DC markers, including CD64, MAR-1, and Ly6C in mice and CD14 in humans, in particular with type I interferon stimulation (36, 37, 44). Although FLT3 is required for both cDC2 subsets, granulocyte-macrophage colony-stimulating factor (GM-CSF) can help drive the inf-cDC2 phenotype; accordingly, inf-cDC2s are expanded in inflamed tissues in both mice and humans (36–39, 41, 42). These phenotypic DC changes in select studies have been correlated with functional differences in terms of $CD4^{+}$ T cell differentiation as discussed below. Future work will need to clarify how these different cDC2 subsets across different tissues, inflammatory states, and species relate to each other. In this review we refer to the two subsets, when identification is possible, as cDC2s and inf-cDC2s.

IRF4 is a key transcription factor for the development, survival, and function of a majority of, but not all, cDC2s. $CD11b^{+}$ cDC2s are reduced in lung, spleen, and intestine but not skin with conditional deletion of *Irf4* with Itgax-Cre, due to developmental and/or survival defects (45–48). IRF4 also affects the migration of $CD11b^{+}$ cDC2s (45, 49). Other transcription factors, such as Notch2 and Klf4, also affect the development of subsets of cDC2s with distinct $CD4^{+}$ T cell

effector functions (43, 50, 51). The function of cDC2s includes activating naive $CD4^+$ T cells and polarizing them into Th2, Th17, Treg, and Tfh cells according to the subset of cDC2s and the inflammatory conditions, as discussed in detail below.

Monocyte-Derived DC Phenotype, Development, and Function

A variety of $CD11c^+CD11b^+$ monocyte-derived cells with phenotypes or functions similar to those of DCs have been described, especially those found during inflammatory states. They have been assigned a number of different names, including inf-DCs, mo-DCs, TNF-α/iNOS-producing (TIP) DCs in the spleen, and $lysozyme^+$ DCs in the gut (37, 52–60); accordingly, the markers to identify these cells, their ontogeny, and their function vary between studies. Both human and mouse blood or bone marrow monocytes can also differentiate in vitro into cells that have the central characteristics of DCs after culture with GM-CSF and/or IL-4 (14, 61–64). Many of the markers used to identify these cells in vivo or in vitro are also expressed by activated monocytes, some macrophages, and cDC2s, making discrimination of different populations difficult.

We use the term mo-DCs to refer to cells derived from CCR2-dependent, FLT3-independent monocytes with the following phenotypes: $MHC\text{-}II^+CD11c^+CD11b^+CD64^{int}Ly6C^{int}CCR2^+CD209^+$ in mice (57, 65) and $HLA\text{-}DR^+CD11c^+CD14^{int}CD206^+CD1c^+$ in humans (58, 66). As discussed in the previous section, cDC2s in both mice and humans adopt many features of monocytes during inflammatory states (36, 37, 39, 42), making differentiation with surface markers difficult. Yet inf-cDC2s derive from cDCs, whereas mo-DCs arise from monocyte precursors; further, macrophage colony-stimulating factor (M-CSF) rather than GM-CSF is required for mo-DC generation in vivo (59). Based on ontogeny, we refer to either cDC-derived inf-cDC2s or mo-DCs when possible to distinguish these two phenotypically similar cell types.

PU.1, IRF4, aryl hydrocarbon receptor, NR4A3, and NCOR2 are critical regulators of monocyte differentiation into mo-DCs both in vitro and in vivo (52, 57, 62–64, 67). CCR2 is required for both monocyte emigration from bone marrow and monocyte accumulation in inflamed tissues (68, 69). Some mo-DCs have been shown to migrate to LNs and act more like cDCs (70), but these mo-DCs likely arrive in LNs via a CCR7-independent mechanism from the blood (60, 71). Accordingly, mo-DCs are typically not required for naive T cell priming but rather help shape differentiation of $CD4^+$ T cell subsets, primarily through the production of cytokines (58, 72–74). Therefore, inf-cDC2s and mo-DCs are functionally distinct. Furthermore, mo-DCs are present in tissues, in particular during states of inflammation, where they can reactivate primed $CD4^+$ T cells.

Plasmacytoid DC Phenotype, Development, and Function

Murine pDCs are identified as $MHC\text{-}II^{int}CD11c^{int}B220^+Ly6C^+BST2^+SiglecH^+$ cells (75). Their development is also dependent on FLT3L, but they can originate from both lymphoid and myeloid progenitors (76). TCF4 is a key transcription factor that plays an important role for the development and maintenance of the phenotype of pDCs (77–79). Other transcription factors, including IRF8, B cell lymphoma 11a (Bcl11a), Zeb2, and SpiB, also contribute to the development of pDCs (76). Human pDCs are identified as $HLA\text{-}DR^+CD11c^-CD4^+BDCA2^+BDCA4^+CD123^+$ cells (80). Patients with a mutation of TCF4 or IRF8 also have a defect in pDCs (1, 77).

Although pDCs have less antigen presentation ability than cDCs at steady state, they can, depending on the subset, induce T cell proliferation after stimulation (7, 75, 80–83). Moreover, pDCs express higher levels of TLR7 and TLR9 in their endosomes and make type I interferon upon recognition of nucleic acids. This makes pDCs an important participant in antiviral and

antitumor immune responses (75, 80) but also in autoimmune diseases such as systemic lupus erythematosus (SLE) (84). Through type I interferon, pDCs can regulate both innate and adaptive immune responses; for example, they regulate natural killer (NK) cell, DC, and macrophage survival and expand $CD4^+$ T cells and $CD8^+$ T cells (85, 86).

pDCs are also heterogeneous. A subpopulation expressing both pDC and cDC markers has been identified in both mice and humans (7, 41, 81–83, 87–89). $CD8^+CX3CR1^+$ DCs were identified that resemble splenic cDC2s according to gene expression profiling but express pDC-specific SiglecH and PDCA1 and depend on TCF4 for development (89). Human $CD123^+BDCA2^+$ cells include a subset with a similar phenotype and function as mouse $CD8^+CX3CR1^+$ DCs, characterized by the expression of CD81, CD5, Axl, and Siglec6; these have been named $Axl^+Siglec6^+$ DCs (7, 32, 41, 81, 88). Another study identified murine and human DCs with features of both pDCs and cDC2s; the authors called them transitional DCs (7). One group suggested these cells are pre-DCs (88), although others have disputed this conclusion. Recent studies showed that in fact pDCs can convert to cDC2-like cells after stimulation (82, 83), suggesting this population might represent a unique activation state. Despite the overlap in phenotype with pDCs, these noncanonical DCs do not produce type I interferon but can induce allogeneic naive T cell proliferation (7, 32, 41, 57, 81, 88) and induce T cell differentiation into Treg cells (81). More work needs to be done to clarify the relationship of this hybrid DC phenotype with other subsets, as well as to define whether it has a distinct role in directing $CD4^+$ T cell responses.

Langerhans Cell Phenotype, Development, and Function

LCs are the only APCs that populate the epidermis. Both murine and human LCs express EpCAM and Langerin (CD207), which forms LC-specific Birbeck granules (1, 90). Different from other DC subsets, LC precursors first originate from hematopoietic precursors in the yolk sac and fetal liver, but they can, upon inflammation, be repopulated from bone marrow–derived precursors in both mice and humans (91–93). In the steady state, LCs are maintained through local self-renewal. LCs develop independently of FLT3L but require IL-34, M-CSF, and TGF-β for their development and maintenance. RUNX3, PU.1, and ID2 are implicated in LC development (90). LCs play a pivotal role in maintaining skin homeostasis by inducing immune tolerance in steady state and initiating adaptive immunity in response to infection.

FUNCTION OF DC SUBSETS IN Th CELL DIFFERENTIATION

Th1 Cell Induction

Th1 cellular responses predominate during many types of antipathogen responses, including responses to intracellular bacteria and viruses (**Figure 1**). They also are a part of antitumor immune responses as well as the self-reactive inflammatory response in many autoimmune diseases. The classic cytokines characteristic of Th1 cellular immunity include IFN-γ and TNF-α. IFN-γ is a potent inflammatory cytokine that activates macrophage destruction of phagocytosed materials, helps induce an antiviral state, and aids cytotoxic $CD8^+$ T cell responses. T-bet is the subset-defining transcription factor essential for Th1 differentiation and function and is induced by IL-12 as well as IFN-γ signaling; however, other signals also promote Th1 differentiation. These include strong T cell receptor (TCR) engagement (long dwell time, high antigen dose, high TCR affinity), strong costimulatory signaling resulting in PI3K signaling and mTORC-induced glycolysis, IL-18, type I interferon–induced STAT1 signaling, IL-2-induced B lymphocyte–induced maturation protein 1 (Blimp-1) upregulation and mTORC1 activity (94), and APC expression of Delta rather than Jagged ligands for Notch (95, 96). Most of these

pro-Th1 differentiation signals can be produced by DCs, but only some of them are known to differ between different DC subsets, as we now discuss.

Almost as soon as subsets of DCs were identified, it was reported that different types of DCs preferentially induce Th1 rather than Th2 polarization (97, 98). Now with an expanded list of DC and T cell subsets, these associations still hold but with more granularity, and more uniformity of the relevant DC subsets across different tissues. A majority of mouse studies support that cDC2s are the primary cDCs that induce $CD4^+$ T cell priming, whereas cDC1s are the primary subset for cross priming $CD8^+$ T cells (24). One exception to this division of labor is the priming of Th1 cells by cDC1s; impaired cDC1 development in Batf3- or IRF8-deficient mice is associated with attenuated Th1 responses to immunization or infection that is systemic or in the gut or skin, whereas impaired cDC2 function has little impact on Th1 induction (99–106). However, not all studies support an absolute requirement for cDC1s in Th1 induction. Deletion of cDC1s using XCR1-DTR mice following footpad immunization with ovalbumin (OVA) and a TLR3 agonist did not impair $CD4^+$ T cell IFN-γ responses, although $CD8^+$ T cell induction was significantly impaired (107). In the human gut, a subset of $SIRP\alpha^+$ monocyte–related DCs was shown to induce Th1 cells in vitro (108). In the lung, both cDC1s and cDC2s have been implicated in Th1 induction, depending on the immunologic insult, although many of these studies used ex vivo DC coculture with T cells to assess $CD4^+$ T cell skewing (109, 110). Multiple groups have observed two subsets within the cDC2 population in a variety of tissues including the lung (32–43, 50). A recent study of lung cDC2s showed that one of these two subsets, marked by MAR-1 and intermediate levels of CD64, can indeed induce Th1 cells in vitro after exposure to viral infection; however, this inf-cDC2 subset was found to upregulate a genetic program that partially overlaps with cDC1s in a type I interferon–dependent manner (36). In sum, cDC1s are the primary APCs for Th1 induction, although cDC2s can, under particular inflammatory conditions, also drive Th1 responses (**Figure 2*a***).

Given that $CD8^+$ T cells and Th1 cells are often induced by similar immune challenges (e.g., intracellular pathogens, tumors), a single niche within the LN that engenders both types of T cell responses might be expected. Indeed, $CD8^+$ T cells and Th1 cells are often observed to be concentrated within the central T cell zone (TCZ) of LNs, colocalized with migratory $CCR7^{hi}CXCR5^{lo}$ cDC1s (104, 111–113). In contrast, $CCR7^{lo}CXCR5^{hi}$ cDC2s and other $CD4^+$ T cell subsets are often found in the outer TCZ, in the T-B border, or directly adjacent to B cell follicles (for a review see 17). The niche created in the TCZ also promotes Th1 cell differentiation.

First, both mouse and human cDC1s produce more IL-12—the primary Th1 differentiation cytokine—than any other DC subsets, although this difference is less pronounced in human DC subsets, depending on the nature of the activation stimulus (27, 29, 98, 101, 103–105, 114–116). Numerous mechanistic explanations exist for the preferential production of IL-12 by cDC1s rather than cDC2s. IRF4, which is expressed by cDC2s but not cDC1s, inhibits IL-12 production (117). Similarly, higher CD5 expression by a subset of human cDC2s correlated with production of IL-12 and Th1 induction (40, 118). Human and mouse cDC1s also selectively produce type III interferons, which are associated with enhanced levels of IL-12 and IFN-γ in solid tumors (119, 120). cDC1s also express a set of pattern recognition receptors (PRRs) that is distinct from that of cDC2s and that is relevant for sensing pathogens such as viruses and inducing IL-12 production. In particular, TLR3, TLR7, TLR9, TLR11, and the C-type lectins CD205 and Langerin are more highly expressed on murine cDC1s than cDC2s (121–124). Human cDC1s also express more TLR3 than human cDC2s and respond to TLR3 ligands with IL-12 production that, in vitro, drives Th1 polarization (27, 125). Yet human mo-DCs and cDC2s can also produce IL-12 or IL-23, depending on the combination of PRRs stimulated (116, 126). How differential PRR

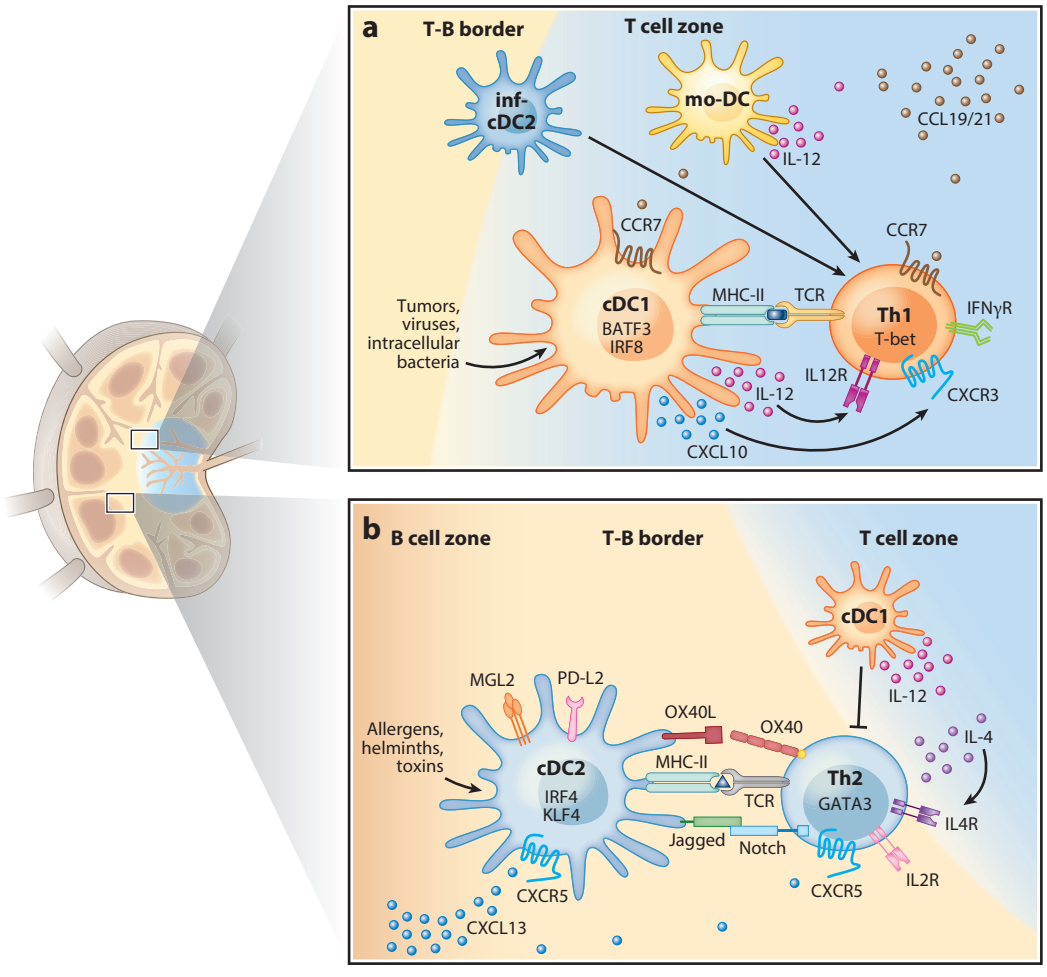


Figure 2

Mechanisms of DC subset induction of Th1 and Th2 differentiation. DC subsets that contribute to Th1 and Th2 differentiation are shown with corresponding microanatomical locations in lymph nodes. The dominant DC subsets that have been shown to prime Th1 and Th2 are drawn as large cells, whereas other DC subsets that, under particular immunization conditions, can also contribute to or block differentiation are shown as small cells. (*a*) In response to tumors, viruses, or intracellular bacteria, cDC1s migrate to the TCZ through the CCR7-CCL19/21 axis, where they prime $CD4^+$ T cells and induce Th1 differentiation via IL-12 and promote a pro-Th1 niche through CXCL10 production. inf-cDC2s and mo-DCs also promote Th1 differentiation. (*b*) The differentiation of Th2 cells happens at the T-B border. CXCL13 produced in the BCZ attracts CXCR5-expressing $CD4^+$ T cells and cDC2s away from the TCZ. Weak TCR (*gray*) signaling favors Th2 differentiation. IRF4- and KLF4-dependent $MGL2^+$ $PD\text{-}L2^+$ cDC2s are the major DC subset that drives Th2 differentiation. Jagged and OX40L expressed by cDC2s may promote Th2 differentiation, but results are controversial. cDC1s inhibit Th2 differentiation through production of IL-12. Abbreviations: cDC1, conventional type 1 DC; DC, dendritic cell; inf-cDC2, inflammatory cDC2; mo-DC, monocyte-derived DC; PD-L2, programmed death ligand 2; TCR, T cell receptor; Th1, T helper 1 cell.

expression on different DC subsets results in the induction of different T cell fates is still incompletely understood (reviewed in 127).

Second, DC-derived CXCL10 production favors development of Th1 cell foci in the LN (112, 128). This may be both a direct effect on retaining developing Th1 cells in the TCZ and favoring prolonged DC–T cell contact time and an indirect effect on recruiting other important

cellular constituents to the niche such as CXCR3$^+$ NK cells (128, 129). NK cells and γδ T cells produce early IFN-γ, which can promote Th1 differentiation; in contrast, NK cell–mediated inflammation appears to have little impact on the CD4$^+$ T cell response during a type 2 immune response (17, 129–131). This early IFN-γ also promotes human and mouse monocyte recruitment and activation. Monocyte-derived cells, including mo-DCs as well as macrophages, can produce more IL-12 than other DCs, along with CXCL10, and they partner with DCs in the LN following viral or bacterial infection or immunization with a type 1 adjuvant to induce Th1 differentiation (60, 73, 131–133). These inflammatory monocytes enter the LN primarily from the blood rather than migrating from the tissue and use CCR2 rather than CCR7 homing signals (60, 133). Accordingly, these blood-derived cells have little influence on CD4$^+$ T cell priming to antigens originating in a tissue, but they are crucial for shaping the differentiation of DC-primed T cells (72, 132). Both monocyte-derived cells and NK cells not only influence the activated T cells but also promote human and mouse cDC1 survival, antigen presentation, and cytokine production, thereby providing a positive-feedback loop in the developing Th1 niche (17).

TCR signal strength, as determined by the TCR affinity for the peptide:MHC-II as well as the quantity of the target and duration of TCR stimulation, is a central determinant of CD4$^+$ T cell differentiation (reviewed in 134). Strong and sustained TCR activation favors Th1 over Th2 differentiation. However, it is not yet clear how to integrate an antigen dose into cDC1-mediated Th1 differentiation. cDC2s express higher levels of MHC-II than cDC1s (24, 135). Therefore, it seems likely that both DC subsets have sufficient MHC-II for Th1 differentiation. This is consistent with Th1- and Th2-promoting adjuvants inducing similar levels of peptide-loaded MHC-II on in vitro stimulated DCs (136). Increased T cell dwell time on DCs appears to promote the upregulation of the IL-12 receptor and Th1 differentiation (136, 137). Different levels of costimulatory molecules, including ligands for CD28, have been implicated in prolonging MHC-II:TCR interactions and thereby favoring Th1 differentiation (136). Increased TCR affinity and DC-derived chemokines, as previously discussed, also promote long dwell times and Th1 differentiation (128, 137). However, it is not clear whether different types of DCs cooperate during different phases of CD4$^+$ T cell activation and differentiation. In line with this, studies have identified roles for pDCs in facilitating Th1 responses to systemic viral infection through type I interferon production, but not antigen presentation (86), and cDC2s were recently found to be necessary but not sufficient for Th1 induction in response to solid tumors (138). Therefore, cooperative models of different APC subsets and cytokine-producing innate immune cells along with T cell–intrinsic and DC-intrinsic properties likely explain the early differentiation signals that polarize naive T cells.

Th2 Cell Induction

Th2 cells mediate the protective immune response to helminth infection and venoms and promote wound healing, while undesired Th2 activity is associated with the pathogenesis of asthma and allergy (139) (**Figure 1**). Th2 cells produce type 2 cytokines IL-4, IL-5, and IL-13, which coordinate the accumulation of eosinophils and production of IgE by B cells and mucus by epithelial cells (139). The signals from APCs that drive Th2 differentiation are still incompletely defined. Low-affinity peptide-TCR interactions or the presence of low amounts of antigen promotes Th2 differentiation (134, 136). IL-4 and IL-2 activate STAT6 and STAT5 in T cells, respectively, which further induce the expression of *GATA3*, the master regulator of the Th2 transcriptional program (139). IL-4 is sufficient to induce in vitro Th2 differentiation (140). However, the in vivo source of IL-4 that initiates Th2 differentiation is unclear (139). There is no evidence that DCs produce IL-4 (139). Instead, basophils, NK T cells, γδ T cells, and ILC2s secrete IL-4, but it is controversial whether they are indispensable for Th2 differentiation (141–144). T cell–intrinsic

IL-4 production is sufficient to induce type 2 immune responses in a peanut allergy mouse model (142); therefore, autocrine cytokine signals may be an important step in Th2 differentiation.

Notch signaling acts as an amplifier of most $CD4^+$ T cell subset differentiation, including Th2 differentiation (96). Whether DCs use different Notch ligands to induce Th2 differentiation remains a subject of debate. Type 2 adjuvants (like PGE2 and cholera toxin) and allergens drive the expression of Jagged family ligands, while bacterial products stimulate Delta family ligand expression in BMDCs (145–148). Although overexpression of Jagged ligands can induce Th2 responses, the in vivo loss of either Jagged1 or Jagged 2 or both on DCs fails to impair Th2 responses (145, 147, 148), suggesting other signals can compensate for the loss of DC-intrinsic Notch ligands in Th2 differentiation.

The requirement for DCs in Th2 differentiation has been shown in models of food allergy, allergic airway inflammation and chronic helminth infection (149–152). Deletion of $CD11c^+$ cells in CD11c-DTR mice inhibits the generation of Th2 cells and type 2 immune responses (149–152). In the lung, both DCs and alveolar macrophages express high levels of CD11c. However, reconstitution of DCs, but not macrophages, restores the type 2 immune responses in DT-treated CD11c-DTR mice (149). Whether mo-DCs could also, under certain inflammatory states, promote Th2 responses has been unclear. Initial work from different groups using house dust mite (HDM) versus *Blomia tropicalis* dust mite supported versus refuted a role for mo-DCs, respectively (70, 153). However, subsequent work from the same group using HDM clarified this finding to indicate that a subset of cDCs with a monocyte-like phenotype, rather than mo-DCs, drove Th2 lung inflammation (36).

cDC2s are the major DC subset implicated in Th2 differentiation in both mouse models and human in vitro cultures (**Figure 2*b***). Disruption of cDC2s via CD11c-Cre IRF4-floxed mice results in decreased frequency of Th2 cells in papain immunization, helminth infection and allergic airway inflammation (153–157). IRF4, a transcription factor required for cDC2 development and survival, also regulates pro-Th2 genes in bone marrow–derived DCs (BMDCs), such as the *Il33* gene (156). Migratory cDC2s express more CXCR5 than cDC1s and accordingly are found at the T-B border in LNs (104, 113, 158). Deletion of CXCR5 in DCs disrupts the localization of DCs at the T-B border and leads to a significant reduction of IL-4-producing T cells in the draining LN after *Heligmosomoides polygyrus* infection, suggesting that the location of DC–T cell interactions may influence Th2 differentiation (111).

Several types of cDC2s promote type 2 responses. $PD\text{-}L2^+$ cDC2s derived from bone marrow or isolated from skin draining LNs induce Th2 differentiation in vitro (154). $Mgl2/CD301b^+$ cDC2s promote Th2 differentiation in the popliteal LN after immunization with OVA and papain (159). KLF4-dependent cDC2s also promote the type 2 response in response to HDM challenge and helminth infection. Deletion of KLF4-dependent cDC2s also impairs Th2 differentiation (51). cAMP signaling, which is required for cholera toxin–induced Th17 differentiation, inhibits the expression of IRF4 and KLF4 in cDC2s and suppresses Th2 differentiation (160). There is potential overlap of the above three cDC2 subsets. $CD301b^+$ cDC2s express PD-L2 in skin draining LNs (161). In lung, deletion of KLF4-dependent cDC2s eliminates all $CD301b^+$ DCs (51). Therefore, it is likely that a KLF4-dependent $CD301b^+PD\text{-}L2^+$ cDC2 subset is responsible for Th2 differentiation in multiple type 2 immune responses, although the molecular mechanism by which it promotes differentiation remains unclear.

Both mouse and human cDC1s have been shown in select studies to induce Th2 differentiation in vitro (110, 162), although other studies using similar in vitro culture systems with mouse cDC1s did not find an ability to induce Th2 differentiation (163). In vivo, most studies found that cDC1s inhibit the differentiation of Th2 cells via production of IL-12 using Batf3-deficient or Langerin-DTR mice (114, 115, 153); however, using BXH2 mice with a mutation in IRF8,

another group suggested cDC1s induce Th2 cells in a lung allergy model (110). As IRF8 has also recently been implicated in skewing cDC2 subsets, it is possible that a non-cDC1 population was also affected in this mouse strain or that another mutation with unknown function affected the response (36). The roles of other DC subsets are similarly varied between studies. Human pDCs stimulated with IL-3 or Sendai virus induce Th2 differentiation in vitro (164), while in vivo, pDCs suppress type 2 immune responses by expanding Tregs or inhibiting the activation of cDCs (165, 166). Human LCs can also support Th2 differentiation in vitro (167), although the in vivo role of LCs is less clear. Different studies found no role, a pro-Th2 role, or an inhibitory role for LCs in mice (157, 159, 168). However, deletion of Langerin$^+$ cells in some of these studies also affected cDC1s due to shared expression of Langerin, making interpretation difficult (157).

Reduced expression of IL-12 by cDC2s is one mechanism that favors Th2 differentiation, yet the identity of specific positive regulators of Th2 differentiation by cDC2s remains elusive. Epithelium-derived cytokines, thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 promote Th2 responses during helminth or allergen exposure. Multiple cell types can produce these pro-Th2 cytokines, including DCs, basophils, mast cells, eosinophils, alveolar macrophages, and Th2 cells. And the receptors of these cytokines are expressed by a wide range of cells, including DCs, basophils, ILC2s, and CD4$^+$ T cells (169). Accordingly, TSLP, IL-33, and IL-25 can promote type 2 immunity through a number of cellular combinations. We focus on the effect of these cytokines on DC–Th2 cell interactions.

Loss of TSLP receptor signaling on mouse DCs impairs Th2 responses to food antigens in vivo (170). TSLP-stimulated human blood DCs upregulate the costimulatory molecule OX40L without inducing IL-12; these in vitro systems, in particular when using human cDC2s, promote Th2 or type 2 Tfh cells in vitro (171, 172). IL-33 also increases the expression of OX40L and other costimulatory molecules, like CD80 and CD86, in DCs (173). In mice lacking the IL-33 receptor, the expression of costimulatory molecules and the migration of DCs, as well as Th2 differentiation, are impaired (173). Impaired OX40/OX40L reduces the frequency of Th2 cells in helminth infection, allergic lung inflammation, and peanut allergy models (142, 174). Human mo-DCs stimulated with soluble egg antigen also promote Th2 polarization in an OX40L-dependent manner in vitro (171, 175). However, OX40L is important for multiple types of CD4$^+$ T cell responses and has been proposed to act as a costimulatory signal for priming rather than a Th2 differentiation signal (176). Similarly, CD28 signaling enhances the production of type 2 cytokines from T cells, but loss of CD28 signaling also inhibits the proliferation of T cells and the production of the type 1 cytokine IFN-γ. Therefore, specific costimulatory or cell surface ligands on DCs that selectively induce Th2 differentiation have not been identified.

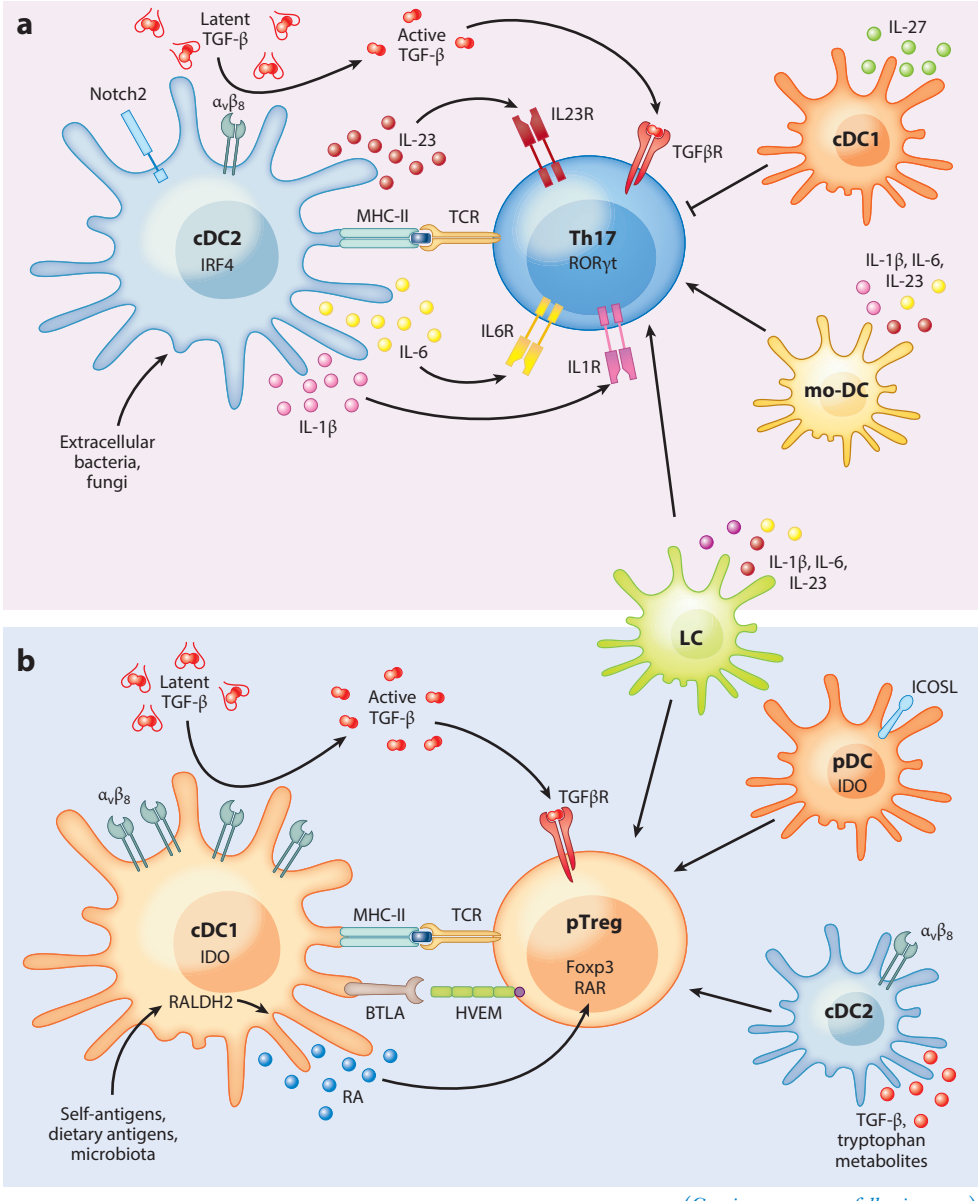
In summary, cDC2s, specifically IRF4- and KLF4-dependent CD301b$^+$PD-L2$^+$ cDC2s, are the primary subset that drives differentiation of Th2 cells. LCs can support Th2 differentiation under certain circumstances, while cDC1s and pDCs mainly inhibit Th2 differentiation. Aside from the preferential production of IL-12 by cDC1s over cDC2s and the positioning of cDC2s at the T-B border, a clear mechanistic explanation of how cDC2s drive Th2 polarization is lacking. It is possible that, as in Th1 differentiation, the niche at the T-B border provides a Th2-promoting environment through the cytokines produced by accessory cells (**Figure 1**), although this model still requires further testing (17).

Th17 Cell Induction

Th17 cells are a CD4$^+$ T cell subset characterized by secretion of IL-17 family cytokines. They can protect against extracellular bacteria and fungi and also can be pathogenic in autoimmune disorders (177) (**Figure 1**). Nuclear receptor RORγt together with other transcription factors, such as IRF4 and STAT3, is required for the differentiation of Th17 cells (178). Cytokines

TGF-β, IL-6, IL-1β, and IL-21 promote the polarization of naive $CD4^+$ T cells into Th17 cells (177). IL-23 is essential for complete and sustained differentiation of Th17 cells (179). Strong TCR stimulation also promotes Th17 differentiation in part by enhancing T cell CD40L expression, which in turn augments IL-6 production by DCs (180). Multiple DC subsets play a pivotal role in Th17 cell induction by activating latent TGF-β and producing IL-6, IL-23, and IL-1β (**Figure 3*a***).

LCs are necessary for Th17 cell differentiation during skin infection with the yeast *Candida albicans* or the bacterium *Staphylococcus aureus* due to both antigen presentation and cytokine production (105, 181, 182). Engagement of Dectin-1 (C-type lectin receptor) on LCs induces



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Mechanisms of DC subset induction of Th17 and Treg cell differentiation. (*a*) With extracellular bacterial or fungal infection, Notch2-dependent cDC2s (found only in spleen and intestine) produce Th17 polarizing cytokines, including IL-6, IL-23, TGF-β, and IL-1β, whereas cDC1s can inhibit Th17 differentiation. mo-DCs can also produce IL-6, IL-23, and IL-1β and support Th17 differentiation in collaboration with cDCs. During skin infection, LCs are necessary for Th17 cell differentiation. (*b*) In the steady state, cDC1s are the major cDC subset that induces pTreg cell differentiation by activating latent TGF-β, producing RA, or expressing cell surface molecules as indicated. Other DC subsets, including cDC2s, LCs, and pDCs, can also promote pTreg cells under context-dependent conditions. Abbreviations: BTLA, B and T lymphocyte attenuator; cDC1, conventional type 1 DC; DC, dendritic cell; Foxp3, forkhead box P3; ICOSL, inducible T cell costimulator ligand; IDO, indoleamine 2,3-dioxygenase; LC, Langerhans cell; mo-DC, monocyte-derived DC; pDC, plasmacytoid DC; pTreg, peripheral Treg; RA, retinoic acid; RALDH2, retinaldehyde dehydrogenase 2; RAR, RA receptor; TCR, T cell receptor; Th17, T helper 17; Treg, regulatory T.

expression of IL-6 (105, 182). MyD88 signaling in LCs is required for expression of IL-1β, IL-6, and IL-23 and Th17 cell differentiation (183). Human skin LCs also induce more Th17 cells than dermal DCs through IL-15 and IL-6 production (184). Conversely, dermal Langerin$^+$ cDC1s inhibit Th17 cell differentiation, possibly through the production of IL-27 (105, 182).

Several models indicate that at mucosal surfaces including the gut and lung, cDC2s are crucial for Th17 induction. Defective Th17 polarization during steady state or gut infections occurs in Cd11c-Cre Irf4$^{fl/fl}$ (46, 47), Cd11c-Cre Notch2$^{fl/fl}$ (43, 50), Cd11c-Cre Tgfβr1$^{fl/fl}$ (185), or SIRPα (186) mutant mice, as well as human Langerin-DTA (187) mice, with loss of intestinal CD103$^+$CD11b$^+$ cDC2s. However, human intestinal cDC1s and cDC2s can induce IL-17-producing T cells in vitro (108). Intestinal cDC2s are an important source of IL-6 (46) and IL-23 (47). Mouse cDC2s in the lamina propria (LP) preferentially express TLR5 and produce IL-6 upon flagellin stimulation, which is required for optimal Th17 responses (188, 189). Integrin $\alpha_V\beta_8$ on DCs (not cDC2 specific) can activate latent TGF-β, and Th17 cells are defective in the colons of mice lacking $\alpha_V\beta_8$ expression on DCs (190). However, deletion of MHC-II on intestinal cDC2s in human Langerin-Cre I-Aβ$^{fl/fl}$ mice does not impair Th17 cell induction (187). Human lung cDC2s also produce more IL-23 than cDC1s and promote Th17 cells in vitro with *Aspergillus fumigatus* challenge (47). Mgl2/CD301b$^+$ cDC2s in the cervical LNs produce IL-6 and induce Th17 responses to *Streptococcus pyogenes* in a TGF-β-dependent manner (191). Therefore, mucosal cDC2s are a crucial source of pro-Th17 differentiation cytokines but may not be essential for antigen presentation.

inf-cDC2s and mo-DCs have also been described to promote Th17 cell differentiation in both humans and mice. In human inflammatory environments, such as synovial fluid from rheumatoid arthritis patients and tumor ascites, CD11c$^+$HLA-DR$^+$CD14$^+$BDCA1$^+$FcεRI$^+$CD206$^+$ mo-DCs promote Th17 cell differentiation in vitro via secretion of cytokines, including IL-1β, IL-6, and IL-23 (58). In the murine gut, intestinal CD103$^-$ CD11b$^+$CCR2$^+$CX3CR1$^+$ inf-cDC2s promote IL-17A production by CD4$^+$ T cells in vitro yet appear to be redundant in vivo (44, 46, 192).

Like other CD4$^+$ T cell subsets, accessory cells in the LN promote Th17 differentiation, although the anatomical LN location for such a niche has not yet been identified. γδ T cells activated by IL-1β and IL-23 amplify Th17 cell responses, possibly by acting as an early source of IL-17 and IL-21 (193, 194). mo-DC cytokine production, in concert with cDC antigen presentation, is necessary for Th17 differentiation ex vivo or in vivo in autoimmunity, alloimmunization, or infection models (72, 74, 195). Some of the observed differences in the requirement for mo-DCs at these various sites in vivo may have to do with the nature of the Th17 cells generated, with induction of pathogenic, rather than homeostatic, Th17 cells showing the strongest requirements for mo-DCs.

Tfh Cell Induction

Tfh cells are located in B cell follicles and direct humoral immunity by promoting the germinal center (GC) reaction and differentiation of memory B cells and plasma cells (196) (**Figure 1**). Tfh cells express the stimulatory molecule CD40L and cytokines IL-4 and IL-21, which provide GC B cells with survival and proliferation signals (197). Tfh cells highly express the transcription factor Bcl6, costimulatory molecules inducible T cell costimulator (ICOS) and PD-1, and the chemokine receptor CXCR5. Blimp-1 antagonizes Bcl6 and therefore favors differentiation toward other effector T cell subsets (198). In addition, transcription factors TCF1, LEF1, and ASCL2 promote Tfh cell differentiation, while FOXP1 (forkhead box P1) and KLF2 inhibit Tfh cell differentiation (199). Loss of Tfh cells impairs high-affinity antibody production, resulting in susceptibility to infectious diseases, while increased Tfh cell frequency is associated with autoimmune diseases like SLE (197).

The differentiation of Tfh cells is a multistep process in which both DCs and B cells are essential (196) (**Figure 4**). DCs are necessary and sufficient for the early development of Tfh cells (three to four days after immunization), but they are insufficient to license completely functional Tfh cells or maintain Tfh cell populations at late time points (one week after immunization) (200, 201). Early Tfh cells activated by DCs upregulate CXCR5 and enter follicles, where they encounter B cells (197). B cells are dispensable for early Tfh differentiation but are required for final Tfh cell differentiation and maintenance at late time points (202–204), in part due to their ability to persist in antigen presentation (205). However, exceptions to this paradigm exist. The requirement for DCs in Tfh cell differentiation can be bypassed by B cells during *Plasmodium* infection or immunization with high-antigen doses, although isolated B cell priming of Tfh cells induces poorly functional Tfh cells with lymphocytic choriomeningitis virus (206–208).

Strong and prolonged TCR-peptide-MHC interactions favor the generation of Tfh cells over other Th effector cell fates (137, 200, 202, 209, 210). Costimulatory signaling through ICOS is required for the induction and maintenance of Tfh cell differentiation via dampening KLF2 expression (202, 204, 211). OX40 signaling also promotes Tfh cell differentiation (212, 213). B cells express ICOS ligand (ICOSL), and DCs express both ICOSL and OX40L. Expression of these ligands can be enhanced by CD40 signaling in DCs and B cells (199, 213, 214), and blocking CD40-CD40L can inhibit Tfh cell maintenance (202, 204, 213, 215) but is not required during early DC–Tfh cell interactions (204, 216, 217). Costimulatory signaling through SAP promotes T cell–B cell interactions and maintenance of Tfh cells, but when SAP is deleted from T cells, they interact with DCs normally and have mild to no defects in early Tfh cell induction (204, 218, 219).

DCs and B cells provide complementary cell surface and cytokine signals to induce Tfh cells (**Figure 4**). Both produce IL-6, which in combination with IL-21 from activated T cells activates STAT3 to promote Tfh cell differentiation (196, 220, 221). However, deletion of either IL-6 or IL-21 does not impair Tfh cell development, indicating redundancy of IL-6 and IL-21 in Tfh cell differentiation (203, 222). In contrast, STAT5-driven signals activated by IL-2 inhibit the generation of Tfh cells (223). Although Tfh cells produce IL-2 (210), they have dampened responsiveness through the IL-2 receptor, possibly in part due to PTEN inhibition of signaling induced by strong TCR activation (134). IL-6 also inhibits IL-2 signaling in developing Tfh cells by reducing IL2Rβ expression (224). In mice and humans, IL-12 promotes the generation of Tfh cells in vitro in part through STAT4-induced Bcl6 and IL-21 induction (225–228). However, Bcl6 expression is also repressed by IL-12-induced T-bet; therefore, IL-12 activation must be transient in order for Tfh rather than Th1 cells to develop (226). Consistent with the role of IL-12 in inducing Th1 differentiation, the Tfh cells induced by IL-12 possess some Th1 features, such as IFN-γ production.

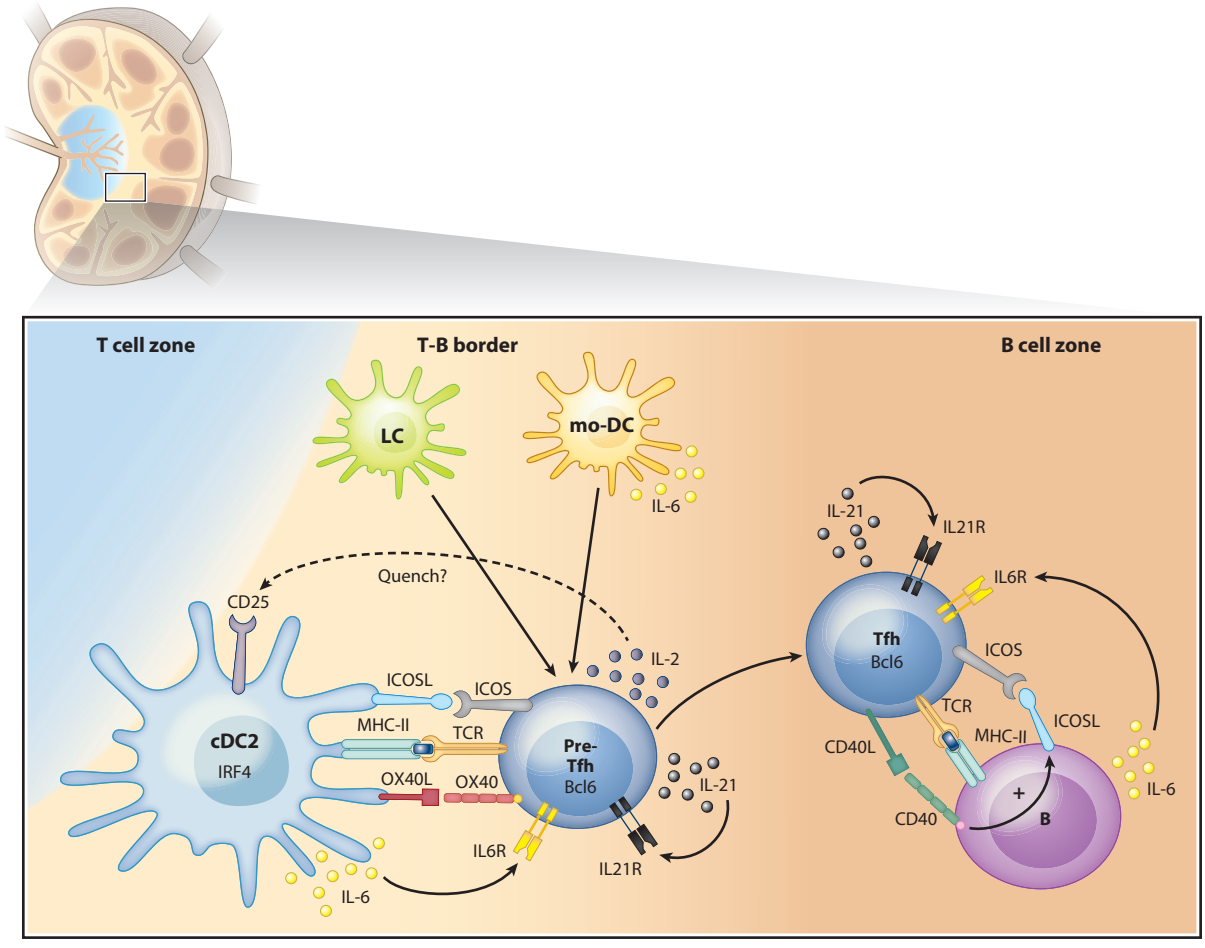


Figure 4

Mechanisms of DC subset induction of Tfh differentiation. Tfh differentiation involves two steps. cDC2s are the major DC subset that induces early Tfh (pre-Tfh) differentiation in the T-B border. The expression of ICOSL and OX40L and the secretion of IL-6 from cDC2s promote early Tfh differentiation. Strong TCR signaling promotes Tfh differentiation. The expression of CD25 in cDC2s has been proposed to quench the inhibitory effect of IL-2 (*dashed arrow*), but consensus on this point has not been established. LCs and mo-DCs can also contribute to Tfh differentiation. Pre-Tfh cells further enter the BCZ, where they interact with B cells through ICOS-ICOSL and CD40L-CD40 interactions, and differentiate into completely functional Tfh cells. Under certain immunization conditions, B cells alone can accomplish both Tfh differentiation phases. Abbreviations: Bcl6, B cell lymphoma 6; cDC2, conventional type 2 DC; DC, dendritic cell; ICOS, inducible T cell costimulator; ICOSL, ICOS ligand; LC, Langerhans cell; mo-DC, monocyte-derived DC; TCR, T cell receptor; Tfh, T follicular helper cell.

TGF-β enhances Tfh cell differentiation in human $CD4^+$ T cells in the presence of IL-12 or IL-23 (229). Type I interferon also promotes Tfh differentiation by either directly acting on T cells (230–232) or indirectly promoting IL-6 production from DCs (233, 234). However, type I interferon also negatively regulates Tfh differentiation by promoting IL-2 and IL-10 production (235, 236). Although many of these cytokines are made by DCs, data for DC- or DC subset–restricted cytokine signals directing Tfh cell differentiation are limited.

Evidence from both mouse models and human studies suggests that cDC2s are the dominant DC subset responsible for the first phase of Tfh cell differentiation. Deletion of cDC2s or

blockade of cDC2 migration to LNs inhibits the generation of Tfh cells and humoral responses against systemic and mucosal antigens (104, 158, 237). Impaired cDC2 activation in both aged mice and older humans is associated with poor Tfh responses to influenza vaccination (238). cDC2s are located in the outer TCZ, interfollicular region, and T-B border (104, 113, 158), the site of Tfh cell induction. cDC2s also highly express cell surface molecules that favor Tfh cell differentiation, including ICOSL, OX40L, and CD25. Quenching of IL-2 by CD25 has been proposed as one cDC2-specific mechanism that favors Tfh cell differentiation, although consensus on this point does not exist (104, 158, 214, 237). Human cDC2s isolated from tonsils or blood, which express Tfh-favoring molecules like OX40L, IL-12, activin A, and TGF-β, also induce the differentiation of Tfh cells in vitro (172, 239). Detailed categorization of cDC2 subsets revealed that Notch2-dependent cDC2s are required for Tfh cell differentiation, while KLF4-dependent cDC2s are dispensable (237). $CD301b^+$ cDC2s can even inhibit the generation of Tfh cells during immunization with weak immunogens, suggesting a division of labor among cDC2 subsets (161).

In contrast to antigen-based immunization, antibody-based DC targeting reveals that multiple DC subsets can participate in Tfh cell induction, although for most of these subsets, loss of the particular DC subsets does not impair Tfh or antibody responses to antigen using nontargeted immunization approaches. Antigen targeting to cDC1s via anti-CLEC9A antibodies, but not anti-DEC205 antibodies, induces the generation of Tfh cells and a humoral response (214, 240, 241). The stronger Tfh-inducing ability of anti-CLEC9A antibodies may result from their long persistence. In addition, antigen targeting to cDC1s via anti-Langerin antibodies induces Tfh cell development but weak humoral responses (242, 243). Therefore, cDC1s can induce the differentiation of at least partially functional Tfh cells. However, deletion of cDC1s does not affect Tfh cell differentiation in response to systemic or mucosal antigens (35, 104, 158, 237), indicating that cDC1s are not required for Tfh cell differentiation in response to untargeted antigens.

Antigen targeting to LCs in mice can also induce Tfh cell differentiation and antibody production (242, 243). Human naive $CD4^+$ T cells can differentiate into Tfh cells when cocultured with in vitro–derived autologous LCs (242). And deletion of LCs using a Langerin-DTR system impairs Tfh cell and GC formation (244, 245). However, in an immunization model using OVA and papain, mice in which LCs are deleted show Tfh cell frequency comparable to that of wild-type mice (161). Antibody-based antigen targeting to cDC2s via DCIR2 also induces Tfh cell differentiation (214), and as described in the prior paragraph, deletion of particular cDC2s impairs Tfh cell induction in vivo in response to a wide variety of immunizations.

Some adjuvants, including cyclic di-GMP and CpG-B, can promote Tfh cell differentiation by activating mo-DCs, which can produce Tfh-skewing cytokines, such as IL-6 (35, 246). However, in the absence of migratory DCs, mo-DCs seem to be insufficient to induce Tfh cell differentiation (161, 232, 244).

In summary, most DC subsets have the potential to induce Tfh cell differentiation using antigen-targeting methods; however, without DC targeting, in vivo Tfh cell induction mainly requires a subset of cDC2s and, in some models, LCs. The reasons for the discrepancy between immunization with antigens in adjuvant- versus antibody-based antigen targeting are not yet clear. The amount of antigen that can be acquired and presented by each DC subset differs based on antigen delivery, and the ability of different DC subsets to home to the relevant perifollicular niche in the LN for Tfh induction also differs (17). DCs can also transfer targeted antigen to other DC subsets (247). But another possible reason for these discrepant findings was suggested by a recent elegant study using antibody-based delivery methods; targeting antigen to cDC1s led to T cell–independent enhanced B cell activation via provision of antigen by cDC1s directly to B cells (248).

Peripheral Treg Cell Induction

Treg cells maintain tolerance and prevent autoimmunity (**Figure 1**). In Treg cells, both cell surface molecules and cytokines, such as CD25, CLTA-4, TIGIT, IL-10, TGF-β, and IL-35, mediate immune response suppression mechanisms (249). Treg cells include thymus-derived Treg (tTreg) cells generated in the thymus and peripheral Treg (pTreg) cells induced at extrathymic sites. Foxp3 is the key transcription factor of Treg cells (250). The differentiation of tTreg cells is promoted by increased-affinity interactions with self-peptide-MHC complexes, whereas differentiation of pTreg cells likely occurs in response to unexposed self-antigens or non-self-antigens. The development of tTreg cells and the role of DCs are reviewed elsewhere (249, 250). Here we focus on the differentiation of pTreg cells, for which DCs play a pivotal role.

Mechanisms by which DCs induce pTreg cells include producing retinoic acid (RA), indoleamine 2,3-dioxygenase (IDO), IL-10, and TGF-β and expressing PD-L1/L2, B and T lymphocyte attenuator (BTLA), and ICOSL (251). Ablation of cDCs in Zbtb46-DTR mice results in reduction of pTreg cells and lack of oral tolerance (252). Migratory DCs constitutively present self or innocuous antigens and are required for expanding pTreg cells (253–255). Ablation of steady-state nonlymphoid tissue cDC accumulation in the cutaneous LNs with CD11c-Cre IKKβ$^{fl/fl}$ mice results in reduction of pTreg cells and spontaneous autoimmunity (256). Transcriptomic analysis demonstrated that migratory cDCs in the steady state, but also in the tumor microenvironment, express genes encoding PD-L1; CD200; the enzyme that metabolizes retinol to RA, retinaldehyde dehydrogenase 2 (RALDH2); and Fas, all of which contribute to Treg cell induction (256–259).

The pathways used by different DC subsets to induce pTreg cells vary and also differ based on the microenvironment (**Figure 3*b***). In response to oral antigens, intestinal migratory CD103$^+$CD11b$^-$ cDC1s induce pTreg cells in mesenteric LNs by promoting RA production (192, 252, 260, 261) or activating TGF-β by means of the integrin $\alpha_v\beta_8$ (252, 262–266). RA synergizes with TGF-β to induce a tolerogenic DC phenotype and pTreg cell production (261, 267, 268). TGF-β itself, along with RA and TLR signaling, can drive high levels of β_8 expression in cDC1s, which might form a positive-feedback loop to strengthen tolerogenic functions of cDC1s (269). Murine lung CD103$^+$ cDC1s similarly upregulate RALDH2 with inhaled antigen and promote Foxp3 expression in T cells and airway tolerance (270). And splenic CD8$^+$DEC-205$^+$ cDC1s induce functional Foxp3$^+$ Treg cells in the presence of low doses of antigen through TGF-β (271). Both human and mouse CD103$^+$ cDC1s express IDO, an enzyme involved in tryptophan catabolism. The immunosuppressive effects of IDO are linked to the reduction of local tryptophan concentration and to the production of immunomodulatory tryptophan metabolites (272, 273). cDC1s also express a higher level of BTLA, which engages with its receptor HVEM and promotes Foxp3 expression in T cells through upregulation of CD5 (257, 274). Therefore, cDC1s across multiple tissues have been shown, through multiple mechanisms, to promote pTreg cells and tolerance.

cDC2s can also promote pTreg cells using similar mechanisms. Human intestinal CD1c$^+$ cDC2s express RALDH2 and $\alpha_V\beta_8$ and potently induce Treg cells in vitro (108, 275). CD103$^-$ CD11b$^+$ cDC2s are the primary DC population to respond to allergy immunotherapy in a murine model and induce pTreg cells by providing active TGF-β and RA (276). Mouse skin draining LNs contain dermis-derived CD103$^-$ CD11b$^+$ cDC2s that cluster with Treg cells, produce RA, and induce Foxp3$^+$ T cells (277, 278). In neonatal mice, cDC2s facilitate immune tolerance via induction of antigen-specific pTreg cells to commensal bacteria, in part through TGF-β-independent signals (279, 280). Lung IFNAR1^{hi}TNFR2$^+$ cDC2s also promote pTreg cell induction in the steady state by an IFN-β–IFNAR1–TGF-β signaling axis (34).

Both mouse and human LCs contribute to immune tolerance. In vivo, targeting self-antigens to LCs or transferring antigen-loaded LCs induces Treg cell differentiation (254, 281). In vitro human epidermal LCs selectively induce the activation and proliferation of autologous memory Treg cells from the skin in an antigen-dependent manner (282).

Murine pDCs can effectively take up inhaled antigen in the lung and induce immune tolerance. In OVA-alum sensitization, adoptive transfer of antigen-pulsed pDCs prevents development of allergic airway inflammation (283). TGF-β-treated mouse pDCs or activated human pDCs can increase the expression of IDO and induce the generation of Treg cells (284, 285). Human pDCs can upregulate the expression of ICOSL, inducing the differentiation of naive $CD4^+$ T cells to IL-10-producing Treg cells in vitro (286). Human pDC expansion of $ICOS^+$ Treg cells is associated with immunosuppression in ovarian cancer and breast cancer and poor prognosis (287, 288).

The redundancy of DC subsets that can promote pTreg cells and immune tolerance is likely useful for preventing autoimmune disease and other inappropriate inflammatory states. One notable but logical exception exists: mo-DCs induced during states of inflammation have not been associated with pTreg cell induction. Although both cDC1s and cDC2s can induce pTreg cells, specific ablation of one of these two subsets usually does not affect Treg cell number (18, 43, 46, 187). However, deletion of both subsets in the gut results in a significant reduction in the number of $FoxP3^+$ Treg cells in the LP (187). Similarly, ablation of all cDCs in Zbtb46-DTR mice, but not isolated loss of $CD103^+CD11b^-$ cDC1s in $Zbtb46^{Cre}IRF8^{fl/fl}$ mice, impaired oral tolerance (187, 252). Therefore, it is likely a response to the microenvironment rather than a specific DC subset that programs a tolerogenic response. Accordingly, even if one subset is impaired, others can compensate to induce immune tolerance. A good example is in the intestine, which is home to microbes and nonself dietary antigens: Here the immune system must balance protection from invasion and tolerance to self and innocuous elements (90, 260). In the steady state, multiple elements constrain the immunogenicity of gut antigens and deliver tolerogenic signals to DCs for pTreg cell induction. The local conditioning includes luminal bacteria and their metabolites, dietary constituents, intestinal epithelial cells, and mucus, which imprint tolerogenic functions on cDCs (260, 289–291). Recent studies have demonstrated that gut draining LNs exhibit differences in their DC composition and their ability to induce pTreg cells according to their anatomical location; proximal gut draining LNs induce more Treg cells than distal gut draining LNs (292). Altogether, these microenvironmental factors influence the function of DC subsets to promote tolerogenic, rather than immunogenic, programs.

CONCLUSION

Multiple types of DCs exist, each with unique, but also overlapping, functions and molecular mechanisms to induce different types of $CD4^+$ T cell responses. Ultimately, induction of the appropriate T helper cell fate is important to recruiting and activating the most effective immune pathway to deal with an insult. As a field, we are starting to identify these different molecular pathways while also recognizing the unity of a wide variety of phenotypically different DCs in different tissues during different types of inflammatory states. cDC2s with developmental and functional differences have recently been recognized, and much work remains to understand the tailored nature of their differential responses. During chronic inflammation, mo-DCs and other DCs with overlapping phenotypes arise, and we are beginning to understand how they are related to and how they complement cDCs. How different DCs induce some $CD4^+$ T cell fates is clear, but others, such as Th2 differentiation, remain ambiguous. Further clarification is needed to identify the similarities of DC subsets across tissues and inflammatory states, but this work will also bring a greater understanding of how Th cell responses are curated according to the nature of the immunogen by rare but powerful immune cells.

DISCLOSURE STATEMENT

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