Dendritic Cells—A Conductor of T Cell Differentiation—

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ABSTRACT
Induction of different types of adaptive immune responses depending on the nature of antigens and the environmental context is crucial to cope with a variety of pathogens and concurrently to avoid pathological reaction to self antigens. Recent studies have been elucidating that the diversity of immune responses is critically controlled by dendritic cells (DCs). Two DC subsets have been identified in humans: myeloid DCs and plasmacytoid DCs. The DC subsets induce different types of adaptive immune responses depending on environmental factors. Interleukin (IL)-12 from myeloid DCs is a dominant factor for the induction of a Th1 response, whereas OX40 ligand on myeloid DCs is important for the induction of a Th2 response. Furthermore, inducible costimulator (ICOS) ligand on plasmacytoid DCs is critical for the induction of IL-10-producing regulatory T cells. Elucidating cellular and molecular mechanisms by which functions of the two DC subsets are modulated will lead to understanding the pathogenesis of various immune-related diseases and to developing novel immunological therapies.

KEY WORDS
dendritic cells, regulatory T cells, Th1, Th2, Th17

INTRODUCTION

The immune system has evolved to eliminate a variety of microbial pathogens and at the same time to avoid responding to self antigens and innocuous antigens. Elucidating how this demanding task is accomplished is the main theme of immunology. Recent studies have been revealing that dendritic cells (DCs) are deeply involved in the process of differential responses to different types of antigens.[1]

During innate immune responses at the site of infection, immature DCs located in inflamed tissues incorporate pathogens, and become activated in response to pathogens themselves and proinflammatory cytokines. Thereafter, the activated (also called mature) DCs migrate to draining lymph nodes and stimulate naïve T cells to differentiate into functionally competent effector T cells. Importantly, such T cell responses, especially those of CD4+ T helper (Th) cells, are heterogeneous; naïve CD4+ T cells differentiate into effector Th cells that produce different combinations of cytokines. These divergent Th cell responses, the prototypes of which are called Th1 and Th2 responses, induce different types of immune responses appropriate to eliminate given pathogens. Furthermore, recent studies have shown that another type of Th cells, called Th17 cells, develops under the influence of IL-23, transforming growth factor (TGF)-β, and IL-6, and play a key role in promoting autoinflammatory disorders as well as immunity against extracellular bacteria.[2] On the other hand, naïve CD4+ T cells are able to develop into immunosuppressive T cells that inhibit immune responses to self antigens.[3] How these different types of T cell responses are induced after the interaction with DCs is an important issue to understand the pathogenesis of various immune-related disorders and to develop novel immunological therapies.

In humans, DCs are composed of two subsets: myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). Recent studies have revealed that these DC subsets perform different functions in both innate and adaptive immune responses. At the same time, both of the DC subsets have functional plasticity to induce appropriate T cell responses depending on the types of stimuli. In this review, we discuss the diversity of DC

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subsets, mainly in humans, from the perspective of their roles in adaptive immune responses.

HUMAN DC SUBSETS

In human peripheral blood, two DC subsets have been recognized based on the expression of CD11c.[4] The CD11c^{+} cells in blood express myeloid markers such as CD13, CD33, and CD11b,[4] whereas the CD11c^{−} cells do not express significant levels of myeloid markers.[4] Freshly isolated CD11c^{−} cells have plasmacytoid morphology with well developed rough endoplasmic reticulum and Golgi apparatus.[5] The CD11c^{+} DCs are generally called myeloid DCs (mDCs) based on the expression of myeloid markers, whereas CD11c^{−} DCs are called plasmacytoid DCs (pDCs) based on its plasmacytoid morphology at the DC precursor stage.

In addition to these primary DC-committed cells, it is well established that monocytes differentiate into immature DCs in the presence of granulocyte-macrophage colony stimulating-factor (GM-CSF) plus IL-4,[6] or GM-CSF plus interferon (IFN)-α.[7] It has been reported that mDCs in blood develop macrophage morphology as well as the expression of butyrate esterase and CD14 in response to M-CSF,[8] suggesting that at least a subpopulation of mDCs in blood is capable of differentiating into macrophages and is thus related to monocyte-derived DCs in terms of cellular origin. However, the precise relationship between mDCs in blood and monocyte-derived DCs remains to be determined. Here we designate CD11c^{+} mDCs in peripheral blood as "blood mDCs", and blood mDCs and monocyte-derived DCs (as well as mouse myeloid DCs) collectively as "myeloid DCs".

Importantly, pDC precursors exhibit distinct expression profiles of Toll-like receptors (TLRs) compared with monocytes and blood mDCs.[9] Strong expressions of mRNA were found in monocytes for TLR1, TLR2, TLR4, TLR5, and TLR8; in blood mDCs for TLR1, TLR2, TLR3, and TLR5; in pDC precursors for TLR7 and TLR9. Thus, myeloid APCs share several TLRs, whereas pDCs express distinct TLRs. Accordingly, myeloid APCs (monocytes and blood mDCs) mainly recognize bacterial components and produce proinflammatory cytokines TNF-α, IL-6, IL-12, whereas pDC precursors mainly recognize viral components and produce a large amount of type I IFNs.

MYELOID DCS RESPOND TO BROAD RANGE OF MICROBES IN ADAPTIVE IMMUNE RESPONSES

The human immune system has evolved to have two separate mechanisms for protection against different types of microbes. In response to intracellular microbes, such as bacteria, viruses, and intracellular parasites, DCs are induced to produce IL-12 and type I IFNs.[10,11] These activated DCs can then stimulate CD4^{+} Th cells to differentiate into IFN-γ-producing Th1 cells.[12,13] The activated Th1 cells, in turn, help to activate macrophages and CD8^{+} cytotoxic T cells to kill intracellular microbes. In response to extracellular parasites, such as helminthes, CD4^{+} Th cells are activated and induced by activated DCs to differentiate into Th2 cells.[10,14,15] Th2 cells produce proallergic cytokines such as IL-4, IL-5, and IL-13, which trigger IgE production. IgE, in turn, activates mast cells and eosinophils to eradicate the extracellular microbes.

Recent studies have shown that DCs play a critical role in directing different effector T cell responses.[12,16] Myeloid DC subsets have a capacity to produce IL-12 in response to the microbial stimuli and, thereby, to induce Th1 development. Consistent with the paradigm of two types of immune responses (Th1 versus Th2) mentioned above, however, this capacity varies with the type of signals delivered to DCs (Figs. 1A, B). For example, LPS derived from *Escherichia coli*,[17,18] peptidoglycan from gram-positive bacteria,[9,18,19] *Mycobacterium tuberculosis*,[20] *Toxoplasma gondii*,[21,22] *Candida albicans* at the yeast stage,[23] and double-stranded viral RNA,[9,24,25] all activate myeloid DCs to produce IL-12 and to induce Th1 development, whereas LPS from *Porphyromonas gingivalis*,[17,26] *Candida albicans* at the hyphae stage,[23] Der p 1 (house dust mite allergen),[27,28] and *Schistosoma mansoni* egg extract,[24,29,30] all activate myeloid DCs to induce Th2 development, which is associated with a lower capacity of the DCs to induce IL-12. Thus, different microbes and their components induce myeloid DCs to produce different levels of IL-12, which leads to different types of Th responses appropriate to eliminate given pathogens.

Environmentally bioactive substances produced by inflammatory processes that act as a cAMP upregulator, such as prostaglandin (PG) E$_2$[30] and histamine,[31] enhance TNF-α-dependent myeloid DC maturation but suppresses bioactive IL-12 p70 production, resulting in Th2 responses (Fig. 1A).

DCs and mast cells co-localize in peripheral tissues of antigen entry, *i.e.* skin and mucosa. Due to the proximity of these two cell types, activation of mast cells may affect DC functions. Indeed, we showed that IgE-activated mast cells in combination with proinflammatory factors, such as LPS, IFN-γ, and TNF-α, induce Th2-promoting dendritic cells, using human monocyte-derived DCs and cord blood-derived mast cells (Fig. 1A).[32] Activated MCs induced maturation of DCs, and potently suppressed interleukin-12p70 production by the DCs. A combinatorial effect of various MC-derived factors, including histamine and those acting in a cell contact-dependent manner, was required for the optimal induction of Th2-promoting DCs. Thus, the interaction between DCs and IgE-activated mast cells in a proinflammatory environment may be instrumental in
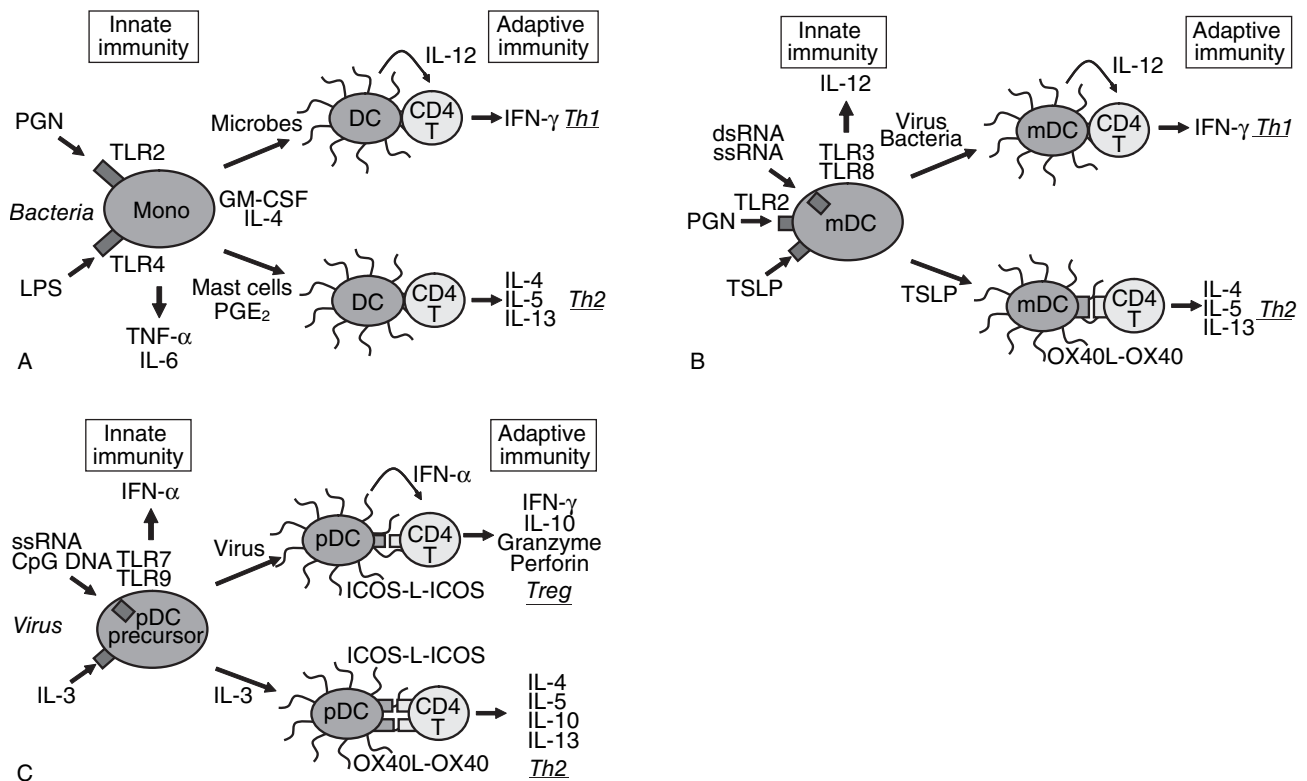
Fig. 1 Human DC subsets induce different types of CD4$^+$ Th cell responses depending on environmental factors. (**A**) During innate immune responses, monocytes produce proinflammatory factors, such as TNF-α and IL-6, in response to bacterial components through TLRs. Thereafter, monocyte-derived DCs induced by GM-CSF and IL-4 produce IL-12 in response to certain microbes, and thus induce a Th1 response. In contrast, monocyte-derived DCs stimulated with mast cells or PGE$_2$ together with proinflammatory factors induce a Th2 response. (**B**) Myeloid DCs produce IL-12 in response to bacterial or viral components through TLRs and thus induce a Th1 response. In contrast, myeloid DCs stimulated with TSLP induce a Th2 response through the interaction between OX40 ligand and OX40. (**C**) During innate immune responses, plasmacytoid DC precursors produce a large amount of IFN-α in response to viral components through TLR7 and TLR9. Thereafter, plasmacytoid DCs stimulated with viruses induce IL-10-producing cytotoxic regulatory T cells, whereas plasmacytoid DCs stimulated with IL-3 induce a Th2 response through the interaction between OX40 ligand and OX40. Moreover, ICOS ligand on plasmacytoid DCs is responsible for the induction of IL-10 by T cells, which is important for an immunoregulatory function of the T cells. PGN: peptidoglycan, LPS: lipopolysaccharides, dsRNA: double-stranded RNA, ssRNA: single-stranded RNA.

maintaining and augmenting Th2 responses in allergy.

Thymic stromal lymphopoietin (TSLP), an IL-7-like cytokine, may be a key physiological mediator that cause allergic inflammation through DCs. TSLP strongly activates human blood mDCs to upregulate costimulatory molecules and to secrete the Th2-attracting chemokines TARC and MDC, but neither IL-12 nor pro-inflammatory cytokines.[33,34] These TSLP-activated DCs in turn induce allogeneic naïve CD4$^+$ T cells to undergo robust proliferation and to differentiate into Th2 cells capable of secreting large amounts of IL-4, IL-5, IL-13, and TNF-α (Fig. 1B). These findings, together with high TSLP expression in keratinocytes from the skin lesions of patients with atopic dermatitis,[34] suggest that TSLP plays a critical role in the initiation of allergic inflammation.

Immunosuppressive cytokines such as IL-10 and TGF-β, as well as steroid, cyclosporin A, and 1-α, 25-dihydoxyvitamin D3, inhibit the maturation of myeloid DCs as well as their IL-12 production.[35-40] These DCs cannot drive DC-mediated Th1/Tc1 responses but rather induce DC-mediated regulatory T cells (or possibly Th2 cells), similar to the immature steady-state DCs.[41,42] Interestingly, a recent study has shown that vitamin D3 activated by skin DCs induces CCR10 on T cells, resulting in their migration to epidermis.[43] Thus, the same factor (vitamin D3) can inhibit or promote T cell responses through the different mode of action.

Taken together, myeloid DCs are capable of inducing naïve CD4$^+$ T cells to differentiate into Th1, Th2, and even regulatory T cells, depending on the stimuli the DCs receive from the environment.

pDC/IPCs REGULATE T CELL RESPONSES UPON VIRAL INFECTION AND IL-3 MILIEU

pDCs, also referred to type I interferon (IFN-α/β/ω)-producing cells (IPCs), are the key effectors in the innate immune system because of their extraordinary capacity to produce type I IFNs upon microbial infection, particularly viral infection.[44,45] Following the innate response phase, pDC/IPCs can switch their functional properties from cytokine producers to mature DCs to directly modulate T cell functions. Signaling through TLR7 and TLR9 by viruses or by synthetic CpG-oligodeoxynucleotide (ODN) can stimulate pDC/IPCs to produce IFN-α/β and rapidly undergo maturation.[46-48] pDC/IPCs possess little phagocytic activity,[5,49] and pDC-derived DCs induced by CpG-ODN can prime CD8+ T cell responses to only endogenous antigens but not to exogenous antigens.[50] These results suggest that pDC-derived DCs may function mainly to present viral or endogenous antigens to T cells. In fact, during influenza viral infection, pDC-derived DCs appear to be capable of priming viral-specific primary and secondary CD4+ and CD8+ T cell immune responses *in vitro* and *in vivo*.[51,52]

Virus-stimulated pDCs induce human naïve CD4+ allogeneic T cells to differentiate into IFN-γ- and IL-10-producing cells,[46] which appear to have an immunoregulatory function (Fig. 1C).[53] In contrast to viral and CpG-ODN stimulation, IL-3 can trigger pDCs to develop into mature DCs in the presence of CD40L but to produce no type I IFNs and then prime naïve CD4+ T cells to produce IL-4, IL-5, and IL-10 (Fig. 1 C).[5,46] The biological significance of pDC differentiation into mature DCs in the presence of IL-3 is unclear. It has been proposed that IL-3 may be produced by basophils, eosinophils, and mast cells during parasite infection, and the pDC-derived DCs may initiate anti-parasite Th2 immune responses.

Several studies have indicated tolerogenic functions of pDCs. The pDCs induced by IL-3 with CD40L prime naïve CD8+ T cells to differentiate into IL-10-producing suppressor T cells, which inhibit bystander proliferation of CD8+ T cells in an IL-10-dependent manner.[54] Recent studies have shown that, in humans, freshly isolated pDC precursors induce CD4+ T cell anergy[55] and pDC-derived DCs activated by CpG-ODN prime naïve CD4+ T cells to differentiate into CD4+CD25+ regulatory T cells characterized as Foxp3+ IL-10-producing suppressor T cells.[56] We have also shown that virus-stimulated pDCs induce naïve CD4+ T cells to differentiate into IFN-γ- and IL-10-producing cytotoxic regulatory T cells that express granzymes and perforin (Fig. 1C).[53] Thus, pDCs that have been stimulated with various stimuli induce IL-10-producing regulatory T cells.

It has been shown that mouse pDCs express CD40 ligand, which activates mDCs to produce IL-12 through CD40 that is induced by IL-15 upon stimulation with CpG DNA.[57] Thus, other than through IFN-α production, pDCs augment immune responses by cross-talking with mDCs with the help of CD40 ligand and IL-15.

DC-DERIVED DECISIVE FACTORS FOR DIFFERENT TYPES OF TH RESPONSES

It is well established that IL-12 represents a dominant inducer of a Th1 response. However, in IL-12-deficient mice infected with *Toxoplasma gondii*, Th1 responses are impaired but still observed to some extent.[58] This indicates that some factors other than IL-12 are responsible for the residual Th1 induction. A recent study has shown that CD70 expressed on mouse DEC-205+ mDCs represents such an IL-12-independent Th1-inducing factor.[59] Also it remains to be clarified how DCs instruct Th2 differentiation, that is, whether Th2 differentiation is caused by a default fate in the absence of IL-12, or requires a positive Th2-instructive signal. IL-4 is an important factor for Th2 differentiation.[14] However, Th2 differentiation can occur without IL-4 produced by non-T cells.[60] In addition, there is no evidence that any DCs produce IL-4. Furthermore, IL-12-deficient mice infected with *Toxoplasma gondii* fail to develop Th2 responses.[58] Accordingly, signals other than IL-4 may presumably instruct Th2 differentiation.

It has been demonstrated in the mouse system that APCs use two types of Notch ligands (Delta and Jagged) to regulate Th cell differentiation. Bone marrow-derived DCs treated with LPS strongly express Notch ligand Delta, which contributes to Th1-inducing activity of the DCs.[61,62] Meanwhile, DCs exposed to cAMP upregulators PGE$_2$ and cholera toxin preferentially express Notch ligand Jagged, which instructs naïve CD4+ T cells to differentiate Th2 cells independently of IL-4.[61]

Several studies have emphasized the role of OX40 ligand (OX40L), a member of the TNF superfamily, in triggering the development and maintenance of Th2 cells in mice and humans.[63-66] *Schistosoma mansoni* egg extract induces human monocyte-derived DCs to express OX40L, which contributes to the priming of Th2 cells.[24] Furthermore, an OX40L-dependent mechanism is functional in pDC-mediated Th2 responses (Fig. 1C). pDC-derived DCs induced by IL-3 or a virus express considerable levels of OX40L, and blockade of OX40L significantly inhibited the ability of DCs to prime naïve CD4+ T cells to produce IL-4, IL-5 and IL-13.[67] OX40L on mDCs activated by TSLP is also responsible for Th2 differentiation of responding CD4+ T cells (Fig. 1B).[68]

It has been shown that ICOS ligand highly expressed on pDCs is responsible for the IL-10 production by T cells (Fig. 1C).[69] This finding indicates that pDCs have an intrinsic ability to induce IL-10-producing regulatory T cells by expressing ICOS

ligand, which discriminates pDCs from mDCs.

Recent studies have revealed the importance of IL-17-producing CD4^{+} T cells, Th17 cells, in autoimmune diseases, such as experimental allergic encephalitis (EAE) and arthritis, as well as in immune responses against extracellular bacteria.[2] Th17 cells are induced by TGF-β and IL-6, and IL-23 promotes the induction of Th17 cells. Human monocyte-derived DCs stimulated with intact *E. coli* together with ATP that binds to purinergic P2 receptors produce IL-23 and thus promote the induction of IL-17-producing CD4^{+} T cells.[70] Mouse CD11b^{+} myeloid DCs in the central nervous system are capable of producing IL-23, TGF-β, and IL-6, and thus induce Th17 cells in an EAE model.[71] Therefore, depending on the environmental factors and possibly on DC subsets, particular types of DCs may preferentially induce Th17 cells. It needs to be further investigated how human and mouse DCs are involved in the differentiation of naïve CD4^{+} T cells into Th17 cells in various pathological conditions.

Collectively, multiple factors, including Th1-, Th2-, and possibly Th17-instructing signals from DC subsets, may dictate the quality of T cell responses in different immunopathological conditions.

CONCLUSION

In host defense, many of the "danger signals" of infection are integrated by DCs and then converted into appropriate immune responses. In this context, not only do different types of DCs have their own potential to initiate innate and adaptive immune responses, but also even the same type of DCs can induce different immune responses depending on the environmental pathogenic stimuli. The molecular events responsible for the crosstalk between DCs and T cells still need to be clarified. The specialized roles of each DC subset in innate and adaptive immune responses have been well characterized in this decade. In the future, further knowledge of the molecular mechanisms that control functional plasticity of the DC system may lead to improvements in the treatment of a wide variety of diseases, such as cancers, infections, allergy, and autoimmune disorders.

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