

The Dynamics of Dendritic Cell—Mediated Innate Immune Regulation

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ABSTRACT

After taking up pathogen-derived antigens, dendritic cells (DCs) leave peripheral organs and migrate into sentinel lymph nodes via afferent lymphatic vessels. During this process, they undergo maturation and produce proinflammatory cytokines, which leads to efficient antigen (Ag) presentation and activation of the innate and acquired immune systems. Recent evidence indicates that DC subsets cooperate to activate the innate immune system. It is becoming clear that the total DC population is composed of a network of DC subsets with distinct functions that are critical for sensing pathogens and orchestrating immune responses.

KEY WORDS

cDCs, crosstalk, C-type lectin, IFN- α , pDC

INTRODUCTION

Pathogenic infection-derived immune activation consists of a series of responses, which include Ag uptake by sensor receptors expressed on DCs, Ag processing, DC maturation, chemokine-dependent migration of DCs to the T-cell regions of sentinel lymph nodes (LNs), presentation of processed Ags, and T-cell activation. The maturation stimulus for DCs affects the outcome of the immune response; e.g., the stimulus can promote the differentiation of naive CD4⁺T cells into T helper type 1 (Th1), Th2, Treg, or Th17 cells. In mice, the CD8 α ⁺ and CD8 α ⁻ DC subsets appear to have different properties for secreting IL-12 p70,¹⁻⁴ a critical cytokine for Th1 differentiation. In contrast, in both humans and mice, plasmacytoid dendritic cells (pDCs) are a specialized population of cells that produce interferon (IFN)- α , a critical cytokine for the activation of NK cells and CTLs, and for B-cell differentiation into antibody-producing plasma cells.^{5,6} In this review, following a brief summary of how DCs regulate the activation of the innate immune system, I will concentrate on the cooperative properties of DC subsets in responding to viral infection and in the stimulation of the Toll-like receptor (TLR) ligand.

SENSORS FOR ANTIGEN UPTAKE AND RECOGNITION

The epithelium of the skin and the mucosa physically block pathogens from invading the body, and DCs are positioned as a second line of defense beneath the epithelial layer, without exception. For instance, Langerhans cells (LCs) in the skin lie in the suprabasal layer,⁷ DCs in the intestine are positioned beneath the epithelium and extend their dendrites through epithelial junctions to take up luminal Ags,⁸⁻¹⁰ and in Peyer's patches, tonsils, and nasal-associated lymphoid tissue (NALT), DCs are found just below the antigen-transporting M cells.¹¹⁻¹³ Once infection occurs, DCs take up pathogen-associated Ags through C-type lectin and Fc receptors.^{14,15} The Toll-like receptors (TLRs) are a family of pattern-recognition receptors that detect structural components shared by bacteria, viruses, and fungi.^{16,17} However, in contrast to the C-type lectin and Fc receptors, TLRs do not take up such components; instead, they deliver signals to produce proinflammatory cytokines.

C-type lectins are either produced as transmembrane proteins or secreted as soluble proteins. Some membrane-bound forms of the C-type lectins are expressed on DCs (Fig. 1).^{14,15} The macrophage mannose receptor (MMR/CD206), the prototype of this family, recognizes mannose and fucose not only on a range of bacteria, viruses, and yeast, but also on cer-

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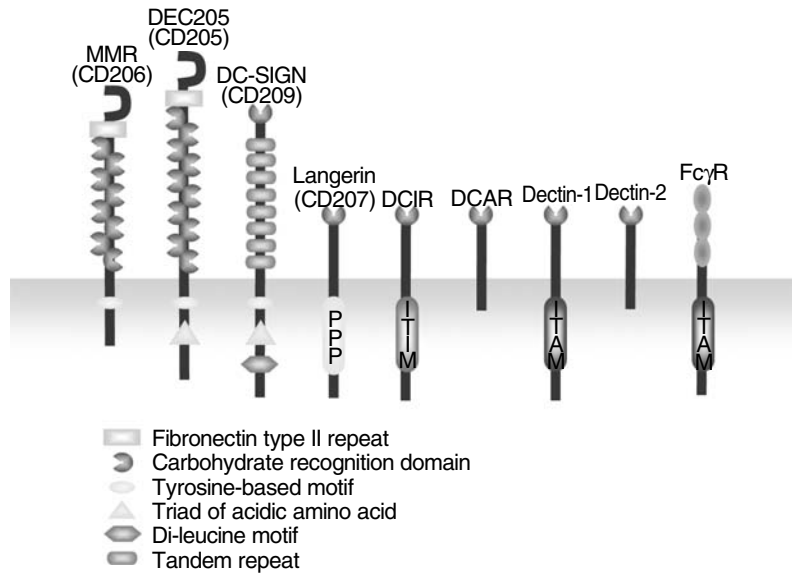


Fig. 1 C-type lectins and Fc γ R on DCs. MMR and DC-SIGN bind mannose and fucose on pathogens, Dectin-1 binds β -glucan, and Fc γ R binds immune complex. Natural ligands for the other C-type lectins remain largely unknown. In addition, DCAR and Dectin-2 form a complex with Fc γ R and deliver signals. P, proline-rich regions; ITIM, immuno-receptor tyrosine based inhibitory motif; ITAM, immuno-receptor tyrosine based activation motif.

tain endogenous glycoproteins, such as lysosomal hydrolases.¹⁸ Similarly, DC-specific ICAM-3-grabbing non-integrin (DC-SIGN/CD209) binds the mannose and fucose on a variety of pathogens, including human immunodeficiency virus (HIV-1).¹⁴ DEC205/CD205 is a DC-specific C-type lectin, and its cytoplasmic tail contains motifs critical for intracellular targeting and for recycling between the cell surface and the endosome, where MHC class II molecules are concentrated.¹⁹ Thus, an anti-DEC205 antibody that is artificially tagged with a certain Ag activates the machinery for MHC class II-dependent Ag presentation and promotes CD4⁺T-cell activation. The natural ligands of the other C-type lectins, including Langerin, DCAR, DCIR, dectin-2, and BDCA-2, remain unknown.^{14,15} Importantly, the TLRs and C-type lectins function cooperatively, which seems to be required for optimal DC activation.^{20,21} In addition to the C-type lectins, DCs express Fc γ R, which takes up immune complexes and presents these antigens on MHC classes I and II.

DC TRAFFICKING TO LYMPH NODES

Upon taking up pathogen-derived foreign antigens, DCs begin to express a lymph node-homing chemokine receptor, CCR7, which enables the DCs to enter afferent lymphatic vessels and migrate into lymph nodes, where CCL19 and CCL21, the ligands for CCR7, are expressed.²² Consistent with this scenario, the transfer of CCR7^{-/-} DCs into wild-type mice severely reduces the number of DCs recovered from

the lymph nodes compared with the transfer of CCR7^{+/+} DCs.²³ Consistent with the idea that CCR7 is important for DC trafficking, in the *plt* mouse, a naturally occurring mutant that lacks the genes for CCL19 and CCL21, DC trafficking to the lymph nodes is impaired.²⁴

REQUIREMENTS FOR T-CELL ACTIVATION

To activate naive T cells in the sentinel lymph nodes efficiently, DCs must mature by the time they arrive there. It is well known that DC maturation is mediated by proinflammatory cytokines such as TNF- α , and by TLR- and CD40L-dependent signals.²⁵⁻²⁸ The definition of mature DCs is closely related to their capacity to activate T cells, which is mediated by signals 1, 2, and 3.²⁹ Signal 1 is delivered through the T-cell receptor (TCR), by its engagement of the MHC/antigenic peptide complex. Signal 2 is referred to as "costimulation," and is typically delivered through CD28 on T cells, by its engagement of CD80/86. Together with signal 1, signal 2 initiates acquired immunity, such as T-cell clonal expansion and differentiation into effector cells. Signal 3 is delivered from DCs to T cells and determines the fate of T cells (Fig. 2). For example, IL-12 is one of the signal 3 mediators and, in cooperation with IFN- α , induces naive T-cell differentiation into Th1 cells and induces cytotoxic activity of and IFN- γ production by NK cells and CTLs.²⁹ Another example is the expression of notch family members on DCs. Delta-1 induces differentiation to Th1, whereas jagged-2 initiates Th2 differen-

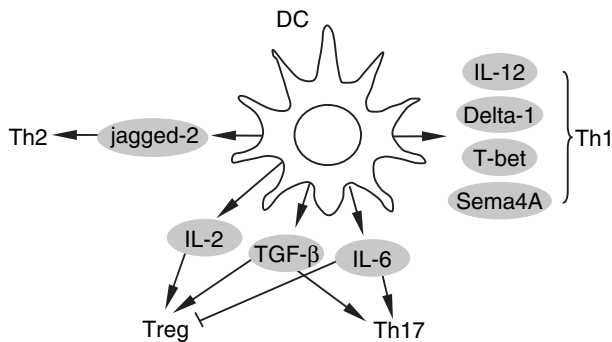


Fig. 2 DC-derived cytokines control the fate of T cells. IL-12, the notch family member Delta-1, T-bet, and semaphorin 4A induce naive T-cell differentiation into Th1 cells, whereas jagged-2 initiates Th2 differentiation. Other DC-derived cytokines, TGF- β and IL-2, induce Treg differentiation, whereas TGF- β and IL-6 are essential for Th17 differentiation. IL-6 suppresses Treg differentiation.

tiation.^{30,31} Other molecules including T-bet and semaphorin 4A are also involved in Th1 differentiation.³²

In addition to Th1 and Th2 cells, it was recently shown that Th17 cells are critically involved in some autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), and experimental autoimmune uveoretinitis (EAU).³³ In contrast, regulatory T cells (Treg) are essential for the maintenance of peripheral immune tolerance. Of note, the DC-derived cytokines TGF- β and IL-2 induce Treg differentiation, whereas TGF- β and IL-6 are essential for Th17 differentiation (Fig. 2). In this context, Treg differentiation is suppressed in the presence of IL-6 (Fig. 2).³⁴

DC SUBSETS AND IMMUNE ACTIVATION

In the lymph nodes, where DCs prime T cells, both blood-derived and tissue-derived DCs are present. The former are derived from bone marrow and are delivered via the peripheral blood, and the latter arrive there by immigration via afferent lymphatic vessels after taking up Ags. The blood-derived DCs can be divided into two subpopulations, conventional DCs (cDCs) and pDCs. Based on the expression pattern of surface markers, including CD4, CD8, CD11b, and DEC205 (CD205), the cDCs can be further divided into multiple subsets.³⁵ CD8 α^+ DCs are CD4-CD8 α^+ CD205 $^+$ CD11b low , whereas CD4 $^+$ DCs are CD4 $^+$ CD8 α -CD205-CD11b high . Another blood-derived DC subset is double-negative (DN) DCs, which are CD4-CD8 α -CD205-CD11b high . The three blood-derived DC subsets appear to develop in lymphoid organs from pre-DC precursors generated in the bone marrow.

On the other hand, the pDCs are specifically responsible for IFN- α production, and are characterized

by the expression of surface markers CD123 (IL-3R), BDCA-2, and BDCA-4 in humans, and Ly6c, B220, 120G8, and mPDCA-1 in mice.^{5,6} A pDC's ability to produce IFN- α depends on its expression of sensor receptors TLR7 and TLR9.³⁶⁻³⁹ TLR7 mediates the recognition of ribonucleotide homologs, including loxoribine, synthetic single stranded (ss) RNA, and RNA viruses, whereas TLR9 is a receptor for CpG, which is prevalent in bacteria and DNA viruses. TLR7/9 ligation in pDCs activates the formation of a complex consisting of MyD88, IRAK4, IRAK-1, TRAF6, IRF-7, TRAF3, I κ B kinase- α , and osteopontin, which leads to IFN- α production.⁴⁰⁻⁴⁶ In cooperation with IL-12, pDC-derived IFN- α induces the cytotoxic activity of and IFN- γ production by NK cells and CTLs, and the differentiation of Th1 cells. In cooperation with IL-6, the IFN- α also affects B-cell differentiation into antibody-producing plasma cells. pDC-derived IFN- α plays a critical role in antiviral immunity by inducing the differentiation of effector lymphocytes, but also participates in the pathogenesis of systemic lupus erythematosus by promoting B-cell differentiation into autoantibody-producing plasma cells (Fig. 3).^{5,6}

CROSSTALK BETWEEN DC SUBSETS

Many *in vitro* and *in vivo* studies have clearly demonstrated distinct functions for each DC subset, as described above. However, these functions alone cannot always explain immune responses, which are actually part of a complex network; rather, the situation may best be described as a "division of labor" among DC subsets. Inter-DC Ag-transfer is one example.^{35,47-49} Upon taking up pathogen-derived foreign Ags, the tissue-derived DCs migrate into lymph nodes and transfer the Ags to the resident CD8 α^+ DCs, termed inter-DC Ag-transfer, rather than directly to CD8 $^+$ T cells. As a result, Ags are mainly cross-presented by the CD8 α^+ DCs to CD8 $^+$ T cells. Several mechanisms for inter-DC Ag-transfer have been proposed, including 1) direct interaction of tissue-derived DCs with CD8 α^+ DCs, 2) secretion of exosomes containing the Ag by tissue-derived DCs, and 3) the incorporation of tissue-derived apoptotic DCs by CD8 α^+ DCs. Another example of DC "division of labor" was shown in a recent study of herpes simplex virus type-1 (HSV-1) infection. The DNA genomes of HSV-1 are detected by Toll-like receptor 9 (TLR9); subsequently, pDCs are recruited to the lymph nodes and generate anti-HSV-1 CTLs in cooperation with cDCs.⁵⁰ Further analysis revealed that the LN cDCs form clusters with T cells only in the presence of pDCs, and induce CTLs. pDCs provide licensing signals to cDCs by expressing CD2 and CD40L, and pDC-derived IFN- α further promotes the differentiation of CD8 $^+$ T cells into HSV-1-specific CTLs (Fig. 4).

We have also shown the importance of collaborative action between cDCs and pDCs for the innate re-

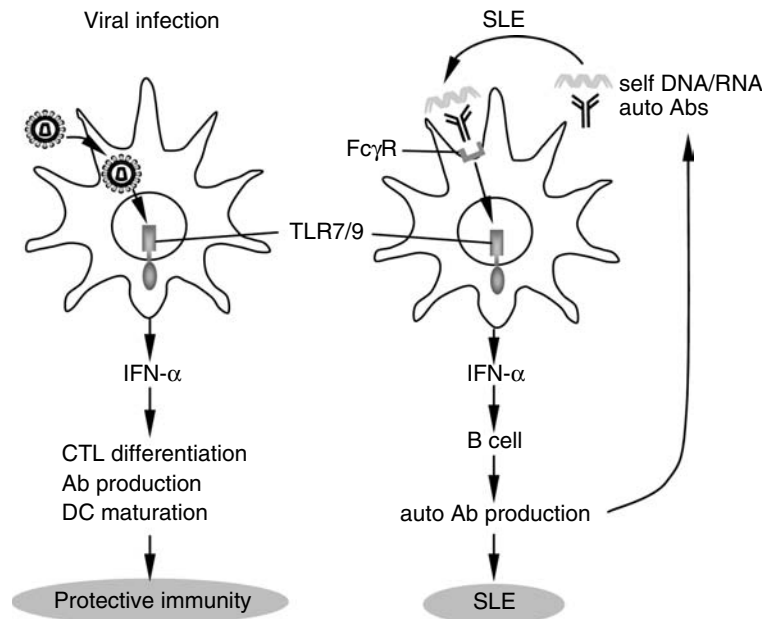


Fig. 3 Roles of pDC-derived IFN- α in infection and autoimmune disease. In viral infections, pDC-derived IFN- α induces the differentiation of CTLs, Ab-producing plasma cells, and the maturation of DCs. IFN- α can also function in the pathogenesis of systemic lupus erythematosus by promoting B-cell differentiation into autoantibody-producing plasma cells.

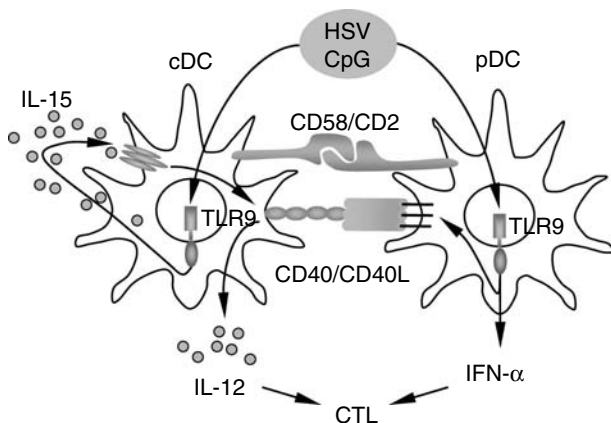


Fig. 4 Crosstalk between DC subsets. CpG binds TLR9 to stimulate DCs to produce IL-15. IL-15 induces CD40 expression on cDCs. CD40 interacts with CD40L expressed on pDCs and leads to IL-12 production. In HSV-1 infection, CD40 and CD58 on cDCs bind CD40L and CD2 on pDCs, respectively. Such interactions, combined with the elaboration of DC-derived IL-12 and IFN- α , are critical for the induction of HSV-1-specific CTL.

sponses to synthetic CpG DNA, a representative TLR ligand.⁵¹ Under physiological conditions, TLR9 is located intracellularly in vesicles, and CpG is transported into these vesicles by endocytosis.⁵²⁻⁵⁴ Inside the vesicles, CpG binds TLR9, and the subsequent re-

cruitment of the myeloid differentiation primary response gene 88 (MyD88)-adaptor protein results in the initiation of the TLR signaling cascade.⁵²⁻⁵⁴ Ultimately, activating protein 1 (AP-1) and NF- κ B transcription factors enter the nucleus and activate a variety of inflammatory genes. The end result is that CpG stimulates DC activation by promoting antigen presentation, co-stimulatory molecule expression, and proinflammatory cytokine production, e.g., large quantities of IL-12, a strong inducer of Th1-mediated immune activation.⁵²⁻⁵⁴

Using an established model of *Listeria monocytogenes* (LM) infection, we initially found that DC-derived IL-15 is essential for the CpG-mediated activation of protective immune responses *in vivo*. To examine whether cDCs and pDCs have distinct roles in CpG-induced IL-15 production and the subsequent immune responses, we selectively depleted pDCs *in vivo* by injecting anti-mPDCA-1. Interestingly, the results clearly showed that cDCs are the major source of both IL-15 and IL-12, and that cDCs fail to produce IL-12 in the absence of pDCs, which suggests crosstalk between cDCs and pDCs. To investigate whether cDC-derived IL-15 acts on cDCs or pDCs, both DC subsets were isolated from WT and *Il15ra*^{-/-} mice 24 h after CpG injection, and were co-cultured *in vitro* in the presence of CpG. WT cDCs co-cultured with WT or *Il15ra*^{-/-} pDCs produced substantial amounts of IL-12, whereas *Il15ra*^{-/-} cDCs co-cultured with WT or *Il15ra*^{-/-} pDCs produced little, if

any, IL-12, indicating that the cDC-derived IL-15 probably acts on the cDCs themselves. These findings imply that cDC-derived IL-15 induces the expression of critical molecule(s) on cDCs that interact with pDCs. In this context, we found that cDC-derived IL-15 induces CD40 expression on cDCs, which interacts with CD40L on pDCs, finally leading to IL-12 p70 production from cDCs (Fig. 4).

CONCLUSIONS

Numerous cooperative interactions are necessary for optimal immune activation. For example, crosstalk between T cells, B cells, and Ag-presenting cells is important for the effective eradication of pathogens. We propose that important crosstalk also occurs between DC subsets. Furthermore, the crosstalk may be critical for the induction, not only of immune activation against foreign Ags, but also of tolerance towards self-Ags. How the DC subsets recognize whether an Ag is derived from non-self or self and how DC crosstalk is involved in these processes remain important issues for future studies.

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