Development of Dendritic-Cell Lineages

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DOI 10.1016/j.immuni.2007.06.006

Dendritic cells (DCs) are a heterogenous population of bone-marrow-derived immune cells. Although all DCs share a common ability to process and present antigen to naive T cells for the initiation of an immune response, they differ in surface markers, migratory patterns, localization, and cytokine production. DCs were originally considered to be myeloid cells, but recent findings have demonstrated that DCs can develop not only from myeloid- but also from lymphoid-committed progenitors. The common feature of the progenitors capable of developing into DCs is the surface expression of Flt3 receptor. The development of different populations of DCs is differentially regulated by various transcription factors and cytokines. This review summarizes the recent advances made in the field of DC development.

Introduction

Dendritic cells (DCs) are antigen-presenting cells crucial for the innate and adaptive immune response to infections and for maintaining immune tolerance to self-tissues (Banchereau and Steinman, 1998). DCs represent a sparsely distributed population of bone-marrow-derived cells. Although they share many common features, multiple subtypes of DCs with distinct life span and immune functions have been identified (Shortman and Liu, 2002; Shortman and Naik, 2007). The DC subtypes found in a steady-state mouse and in human include type-1 interferon-producing plasmacytoid DCs (pDCs) and the conventional DCs (cDCs) in the nonlymphoid tissues, in the circulation, and in lymphoid tissues. The resident cDCs in lymphoid tissues include cDCs present in the thymus, spleen, and lymph nodes and consist of phenotypically different subtypes.

cDCs can also be divided into subsets according to their tissue localizations, such as skin DCs including Langerhan’s cells (LCs) in epidermis and dermal DCs in dermal areas; mucosal tissue-associated DCs; lymphoid tissue-associated DCs including splenic marginal zone DCs, T cell zone-associated interdigitating cells, germinal center DCs, and thymic DCs; and interstitial tissue DCs including liver DCs and lung DCs. Tissue microenvironments appear to have major impact on the function of the residential DCs. In addition, DCs that are not found in the steady state but develop after infection or inflammation include the monocyte-derived DC and the tumor necrosis factor (TNF)-producing and inducible nitric oxide synthase (iNOS)-expressing DCs (Geissmann et al., 1998; Naik et al., 2006; Randolph et al., 1999; Serbina et al., 2003). Here we review the recent progress on the development of DC subsets.

Ontogeny of DCs

In mice, DCs can be detected in the thymus as early as at embryonic day 17, coinciding with the emergence of CD4+CD8+ thymocytes and the beginning of thymocyte selection processes. Thereafter, the number of DCs and thymocytes increases rapidly in parallel. The majority of DCs at this early stage are CD8+ with the emergence of CD8+ DC observed at 1 week after birth. The CD8+ population becomes the major population by 2 weeks of age, with the relative proportions of each subset similar to those found in the adult thymus (Dakic et al., 2004). The pDCs appear at the same time as cDCs in the thymus, and their numbers increase with age and in parallel with the increase in the number of cDCs.

A substantial number of DCs can be detected in mouse spleen on day 1 after birth (Dakic et al., 2004; Sun et al., 2003). The absolute numbers and proportion of both cDC and pDC do not reach adult amounts until 5 weeks of age. During this period, the composition of the cDC populations changed markedly. In contrast to the cDCs found in an adult spleen that contains the CD8+CD205+ (~25%) and CD8+CD205− (~75%) populations, in the spleen of a day 1 newborn mouse, the CD8+CD205− cells represent a minor cDC population, whereas the dominant cDC population is CD8− that also express CD205 (CD8−CD205+). Moreover, this CD8−CD205+ cDC subset has the capacity to produce IL-12p70, a cytokine normally produced by the CD8+CD205+ cDC in adult spleen (Dakic et al., 2004; Sun et al., 2003). Interestingly, at 3 weeks of age, the CD8+CD205+ cDC population becomes undetectable and the CD8+CD205+ cDCs become the major cDC population with the capacity to produce IL-12p70, although at a relatively lower amount than their adult counterpart, whereas the CD8+CD205− cDCs remain as a minor population.

At the young adult stage (6 weeks), the ratio of the CD8+CD205+ and CD8+CD205− cDCs changes substantially, with the CD8+CD205+ cDCs becoming the dominant population. These phenotypic and functional changes suggest that the neonatal CD8+CD205+ DCs represent an immature stage of the CD8+CD205+ cDC population found in adult mouse spleen and that different DC populations have different developmental kinetics during ontogeny.
Consistent with the developmental kinetics of DC during mouse ontogeny, functional analysis of neonatal DC have shown that they are immature in a number of different functions including cytokine production and antigen presentation (Dakic et al., 2004; Muthukkumar et al., 2000; Ridge et al., 1996; Sun et al., 2003; Vollstedt et al., 2003).

In humans, MHC class II-expressing DC-like cells can be detected in the yolk sac and mesenchyme as early as 4–6 weeks of gestation, which preceded the formation of liver, bone marrow, and thymus (Janossy et al., 1986). These MHC class II-expressing DC-like cells appear in the thymic medulla and paracoritcal area of mesentery lymph nodes at 11–14 weeks, nonlymphoid tissues except brain at 12 weeks, bone marrow at 14–17 weeks, the T zone of spleen at 16 weeks, and fetal skin and tonsillar crypts at 23 weeks of gestation (Janossy et al., 1986; Hofman et al., 1984). Little is known on the ontogeny of human pDCs, although pDCs can be detected in fetal thymus and liver (Y.-J.L., unpublished observation).

**Myeloid Origin of DC**

DCs were originally considered to have a myeloid origin. Early studies demonstrated that mouse BM myeloid precursors had a capacity to produce macrophages, granulocytes, and DCs in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) (Inaba et al., 1993). Similar development was found in the studies of human cells where a CD34+ BM-derived precursor differentiated into CD1a− monocytes, a granulocyte-precursor population, and a bipotential precursor population with the ability to produce mature DC when cultured in the presence of GM-CSF and TNF-α or macrophages when cultured in the presence of M-CSF (Reid et al., 1992; Szabolcs et al., 1996; Caux et al., 1996). Further evidence for a myeloid origin of DC came from the finding that monocytes differentiate into DCs in the presence of GM-CSF and IL-4, in vitro (Romani et al., 1994; Sallusto and Lanzavecchia, 1994; Akagawa et al., 1996; Kiertscher and Roth, 1996; Pickl et al., 1996; Zhou and Tedder, 1996; Chapuis et al., 1997). This differentiation process also occurs in vitro when monocytes reverse transmigrate in an ablumenal-to-lumenal direction across endothelial cells (Randolph et al., 1999). A similar phenomenon has been observed in vivo with subcutaneous tissue monocytes (Figure 1; Randolph et al., 1999).

Direct evidence for a myeloid origin of DC came from studies demonstrating that the transplantation of mouse BM common myeloid progenitors (CMPs) into irradiated recipients led to the reconstitution of the cDCs and pDCs in the spleen and thymus (Traver et al., 2000; Wu et al., 2001; Manz et al., 2001a). Further studies demonstrate that the CMPs are heterogenous in Flt3 expression, and it is the Flt3+ fraction of CMPs that is able to produce all cDC and pDC subsets found in the mouse spleen and thymus (Figure 1; D’Amico and Wu, 2003). In addition, a CX3CR1+CD117+ clonogenic progenitor that can give rise to macrophages and splenic-resident cDCs but not pDC has been identified from mouse BM (Fogg et al., 2006). This progenitor may represent a common precursor for macrophage and cDCs downstream of the CMP and the branch point of pDC differentiation.

**Lymphoid Origin of DC**

Early studies on the lymphoid tissue-resident DCs demonstrate that thymic cDCs and subpopulations of cDC in mouse spleen and LNs express markers associated with lymphoid cells, including CD8α, CD4, CD2, BP1, and CD25 (Vremec et al., 1992). This finding suggests that some DCs may have a lymphoid origin. The first direct evidence for a lymphoid origin was provided by studies showing that the transfer of intrathymic lymphoid-restricted precursors...
expressing low CD4 into the thymus of irradiated recipients give rise to both T cells and CD8+ thymic cDCs (Figure 1; Wu et al., 1995; Ardavin et al., 1993). This precursor was also shown to have the potential to produce both CD8+ and CD8− splenic cDC when injected intravenously and to be devoid of myeloid potential (Wu et al., 1996, 2001; Martin et al., 2000). Subsequent studies of the mouse BM common lymphoid progenitor (CLP) also demonstrate the potential of these progenitors to differentiate into DCs both in vitro and in vivo (Wu et al., 2001; Manz et al., 2001b; Izon et al., 2001). Although a bias toward producing the CD8+ DC population was observed, the CLP displayed the capacity to give rise to all splenic and thymic DC subsets (Wu et al., 2001; Dakic and Wu, 2003). Thus, evidence for a lymphoid origin of DCs has been firmly established.

The fact that both the CMP and CLP are capable of giving rise to all DC subtypes of the spleen and thymus not only demonstrates that DCs can be of either myeloid or lymphoid origin, but also indicates that the phenotype of the DCs is not a reflection of its lineage origin.

**Origin of pDCs**

It was initially suggested that pDC (also known as interferon-producing cell, IPC) is of lymphoid origin, based on the finding that human pDCs express many lymphoid markers, including germline IgK and pre-T cell receptor (Grouard et al., 1997; Rissoan et al., 1999) but do not express myeloid markers. In addition, mouse pDCs were found to express the Rag gene and harbor IgH D-J rearrangement (Corcoran et al., 2003; Shigematsu et al., 2004; Pelayo et al., 2005). Two separate studies further support the lymphoid origin of pDC in human and mice. First, over-expression of the dominant-negative transcription factors Id2 or Id3 in human CD34+ hematopoietic progenitor blocks development of pDC, T cells, and B cells, but not myeloid DC (Spits et al., 2000). Second, knockdown of Spi-B, a hematopoietic-specific Ets family transcription factor that is expressed exclusively in lymphoid cells, in human CD34+ hematopoietic progenitor progenitors strongly inhibits their potential to differentiate into pDC (Schotte et al., 2004). However, more recent studies revealed that Flt3+ cells within either CLPs or CMPs could differentiate into both cDC and pDC in cultures and in vivo (D’Amico and Wu, 2003; Chicha et al., 2004; Shigematsu et al., 2004). An interesting observation from the study of Shigematsu et al. was that although Rag expression and IgH D-J rearrangements were not detectable in CMPs, CMP-derived pDCs express both Rag and IgH D-J rearrangement. The authors suggest that the expression of Rag and IgH D-J rearrangement does not necessarily reflect pDC lineage origin but is a result from the “ectopic expression” or “reactivation” of Rag and IgH D-J rearrangement during CMP differentiation into pDCs. Alternatively, because CMPs contain the Flt3+ progenitor population that is capable of differentiating into pDC, cDCs, and more interestingly B cells (D’Amico and Wu 2003), the pDCs derived from the Flt3+ fraction of CMPs could be the progeny of the precursors with potential for both pDC and B cell differentiation. If this is indeed the case, the question will be where pDC, cDC, and B cells branch out from the Flt3+ progenitors, and what regulates this divergence.

**Development of DC from the Immediate Precursors**

A precursor that is at a developmental stage just before the formation of a phenotypically identifiable DC is termed immediate DC precursor. These precursors can be identified and isolated from mouse blood and have a capacity to differentiate into mature subsets of DCs in vitro. Two populations of DC precursors in mouse blood have been described (O’Keeffe et al., 2003). The CD45RA+CD11crCD11b− population represents immature cDC that acquires the morphology of mature cDCs in the presence of TNF-α and the ability to stimulate T cells and to produce IL-12 in response to microbial stimuli. The CD45RA+CD11crCD11b− population represents the pDCs. These cells mature into cDC-like cells only in the presence of stimuli such as CpG and GM-CSF, weakly stimulate T cells in this matured state, and produce large quantities of type I interferon (Nakano et al., 2001; Martin et al., 2002; Asselin-Paturel et al., 2001). Thus, although this precursor DC population is able to differentiate into a cDC-like population of cells, their poor antigen-presenting capabilities make them distinct from the mature cDCs (Krug et al., 2003).

The DCs in peripheral lymphoid organs are continually replaced by blood-borne precursors. A recent study reported that DCs in mouse spleen and LNs underwent a limited number of cell divisions in situ and could be entirely replaced within 10–14 days (Liu et al., 2007). Consistent with this finding, in situ cDC precursors (pre-DCs) with limited proliferation potential have been identified in mouse spleen and lymph nodes (Naik et al., 2006; Diao et al., 2006). These precursors were identified in mouse spleen as CD11c+CD45RA+CD43+Sirp-α+CD4−CD8− and comprised 0.05% of splenocytes (Naik et al., 2006). When transferred into nonirradiated recipient mice, they differentiated into all splenic cDC populations with limited proliferation within 3–5 days, representing the most immediate cDC precursors identified to date. These pre-DCs are distinct from monocytes, because transfer of purified monocytes into a steady-state mouse did not generate significant number of cDC in the spleen. Monocytes can differentiate into splenic cDC only under a GM-CSF-mediated inflammatory condition (Naik et al., 2006). There are two major monocyte subsets that vary in chemokine receptor (CCR) and adhesion molecule expression and in migratory and differentiation properties. In humans, “classical” CD14+CD16− monocytes express CCR2, CD64, and CD62L, whereas “nonclassical” CD14+CD16+ monocytes lack CCR2. Their counterparts in mice are CCR2+Gr-1+ and CCR2+Gr-1+ monocytes, respectively. Gr-1+ (Ly6C+) monocytes are recruited to inflammatory sites, e.g., inflamed skin or acutely inflamed peritoneum, and give rise to macrophages and DCs in inflammatory or infectious disease models and to epidermal LCs after skin inflammation. Gr-1+ monocytes have been proposed as precursors for steady-state DCs, but experimental evidence is as of yet limited (Tacke and Randolph, 2006).
Table 1. Differential Requirement for Transcription Factors in DC Development

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The requirement of transcription factor for the development of each DC populations is presented as follows: +, required; –, not required; +/–, partially required; and nd, not determined.

<sup>a</sup>A. Dakic, S. Nutt, and L.W., unpublished observations.

Transcription-Factor Regulation of DC Development

Given that both myeloid and lymphoid precursors have the capacity to generate all lymphoid-resident DC subsets, the following questions still remain: how are the individual subsets delineated, and at what point in DC development is the commitment made to a subpopulation of DC? These questions have been partially addressed by studies on the roles of transcription factors in DC development. Growing evidence indicates that distinct DC subpopulations require different transcription factors during ontogeny (Table 1). The zinc finger transcriptional regulator Ikaros has been shown to play an essential role in DC development. Although a dominant-negative mutation in the Ikaros gene in mice led to the ablation of all DC subsets, a null mutation in the Ikaros gene showed an absence of CD8<sup>-</sup> cDC and pDC and residual CD8<sup>+</sup> cDC development (Wu et al., 1998; L.W., unpublished data). These studies demonstrate a requirement for Ikaros for the development of most cDC and pDC, which is consistent with the observation that Ikaros is required for the normal development of the early hematopoietic progenitors (Nichogiannopoulou et al., 1999).

The first transcription factor identified as being important in subset delineation was RelB. RelB is a member of the NF-κB (Rel) family and was found to be expressed at higher amounts in CD8<sup>-</sup> cDC compared to CD8<sup>+</sup> cDC in the spleen. Disruption of RelB gene resulted in the defective development of cDCs, especially the splenic CD4<sup>−</sup>CD8<sup>−</sup> DC subset, but not the CD4<sup>+</sup>CD8<sup>+</sup> and CD4<sup>−</sup>CD8<sup>−</sup> DCs (Weih et al., 1995; Burkly et al., 1995; Wu et al., 1998; L.W., unpublished data). Consistent with these observations, mice lacking the TRAF6 transcription factor, believed to act upstream of the same signaling cascade of RelB, also show defects in CD4<sup>+</sup>CD8<sup>-</sup>-cDC development (Kobayashi et al., 2003).

The three interferon regulatory factors (IRF), namely IRF-2, IRF-4, and IRF-8 (also known as ICSBP), also play important roles in the development of different DC populations. Mice lacking a functional IRF-2 or IRF-4 gene showed defects in the development of CD4<sup>+</sup>CD8<sup>-</sup> cDC, and IRF-4-deficient mice also showed defect in pDC subsets in the spleen (Suzuki et al., 2004; Ichikawa et al., 2004; Honda et al., 2004). In contrast, IRF-8 plays crucial roles in the development and function of CD4<sup>−</sup>CD8<sup>+</sup> cDCs, pDCs, and LCs (Schiavoni et al., 2002, 2004). Further studies on mice with double deficiencies of IRF-4 and IRF-8 show defects in the development of all DC populations, suggesting a nonredundant role of each of the factors in the development of specific DC subsets (Tamura et al., 2005). Although these studies demonstrate the importance of these IRFs in DC development, further investigation is required to elucidate the molecular mechanisms.

Id2, a member of the inhibitory helix-loop-helix (HLH) transcription factor family, is upregulated during DC development and is required for the development of CD4<sup>+</sup>CD8<sup>-</sup> cDCs and LCs (Hacker et al., 2003). In contrast, overexpression of Id2 in hematopoietic stem cells inhibited the development of pDCs, indicating that Id2 acts as an inhibitor of pDC development (Spits et al., 2000). This inhibitory effect of Id2 in pDC development may be mediated by antagonizing the functions of activating HLH factors HEB and E2A, as indicated by the fact that overexpression of these factors in hematopoietic progenitors stimulated pDC development (Schotte et al., 2004). The ETS transcription factor Spi-B is expressed by pDCs, B cells, and CD34<sup>+</sup> hematopoietic progenitors, but not by cDCs. The knockdown of Spi-B mRNA expression in human hematopoietic progenitors led to the defective development of pDCs, but stimulated the development of B cells and myeloid cells. These findings demonstrated that Spi-B functions as a key regulator of pDC development (Schotte et al., 2004). The transcription factor PU.1, another member of the ETS family that interacts with Spi-B, IRF-4, and IRF-8, is also required for the development of both cDCs and pDCs, as shown by the fact that impaired development of cDCs from the hematopoietic
progenitors in the embryo or in neonatal PU.1-deficient mice (Guerriero et al., 2000; Anderson et al., 2000) and defective development of both cDCs and pDCs in the adult mice with induced deletion of PU.1 have been observed (A. Dakic, S. Nutt, and L.W., unpublished data).

Distinct molecular-signaling pathways for the development of steady-state DC and the inflammation-induced DC differentiation have recently been distinguished. The transcription factor STAT3 is required for Flt3L-dependent steady-state DC development. Deletion of STAT3 in hematopoietic cells abolished the effects of Flt3L on DC development and led to a profound deficiency in the DC compartment in lymphoid tissues. In contrast, deletion of STAT3 did not affect DC development in vitro in the presence of GM-CSF, indicating that STAT3 is not required for GM-CSF-dependent inflammatory DC differentiation (Laouar et al., 2003). Moreover, the transcriptional repressor Gfi1 has been shown to control DC development through regulating STAT3 activation. Gfi1-deficient mice showed a global reduction of myeloid- and lymphoid-derived DCs in all lymphoid organs, whereas epidermal LCs were enhanced in number (Rathinam et al., 2005). Gfi1 also functions as a critical modulator of DC versus macrophage development (Rathinam et al., 2005).

Cytokine Regulation of DC Development

In addition to the transcription factors that differentially regulate the development of distinct DC subsets via different signaling pathways, several cytokines have been shown to differentially promote the growth and differentiation of different DC subsets. As mentioned above, Flt3L is a crucial factor in both human and mouse for promoting the development of both cDC and pDC in vivo and in vitro. However, a bias toward the generation of CD8+ cDC and pDC in the spleen has been observed in mice treated with murine Flt3L (O’Keefe et al., 2002b; Bjorkc, 2001). In contrast, treatment of mice with GM-CSF, a cytokine that promotes the differentiation of myeloid DC from the early hematopoietic progenitors and monocytes, promoted the development of the splenic CD8- cDC (O’Keefe et al., 2002b). Studies have also shown that although GM-CSF and Flt3L both play a critical role in the development of cDC, only Flt3L is critical for the development of pDCs. In addition, GM-CSF promotes cDC development at the expense of pDC development mediated by Flt3L in vivo and in vitro (Maraskovsky et al., 1996; Pulendran et al., 2001; Blom et al., 2000; Gilliet et al., 2002; Naik et al., 2006). GM-CSF requires STAT5 to suppress Flt3L-driven pDC development from the lin Flt3+ bone-marrow progenitor population. In vivo, STAT5-deficient hematopoietic progenitors repopulate the pDC lineage preferentially relative to STAT5-sufficient progenitors. In contrast, STAT5 is necessary for maximal reconstitution of cDCs. STAT5 activation by GM-CSF rapidly attenuates the expression of critical pDC-related genes in lin Flt3+ bone-marrow progenitor cells cultured in Flt3L. GM-CSF therefore controls pDC development through a STAT5-dependent pathway that impinges upon the pDC transcriptional network, influencing the production of DC subsets from the progenitor compartment (E. Esashi, Y.-H. Wang, O. Perrn, X.-F. Qin, Y.-J- L., and S.S. Watowich, unpublished data).

The cytokine TGF-β1 plays a critical role in LC development as demonstrated by the fact that the in vitro generation of LCs from CD34+ progenitors can be greatly enhanced by TGF-β1 (Caux et al., 1999). The TGF-β1-deficient mice lacked LCs (Borkowski et al., 1996), but BM cells from TGF-β1-deficient mice could give rise to LC after transfer into lethally irradiated recipients. Thus, the LC defect in TGF-β1-deficient mice is not a result of deficiency in BM LC precursors; instead, TGF-β1 produced by non-BM-derived cells is required for the differentiation of LCs (Borkowski et al., 1997). It has been suggested that TGF-β1 exerts its effect through regulating the expression of its downstream transcription factor Id2, which is required for the normal development of LCs (Zenze and Hieronymus, 2006).

Organ-Specific DC Populations in the Thymus

The thymus is a primary lymphoid tissue where T cell differentiation and selection occurs and leads to the generation of naïve CD4+ and CD8+ T cells with a diverse TCR repertoire, naturally occurring CD4+CD25+ regulatory T cells (Apostolou et al., 2002; Jordan et al., 2001; Watanabe et al., 2005), as well as some of the double-negative invariant T cell subsets, such as NK T cells (Benlagha et al., 2005; Tilloy et al., 1999) or mucosa-associated invariant T (MAIT) cells (Treiner et al., 2003). Thymus is also the site for central immune tolerance induction. Mouse thymus contains CD11c+CD45RA+ pDCs and two CD11c+CD45RA- cDC subsets that can be segregated on the basis of CD8 and the signal regulatory protein-α (Sirp-α) expression, as CD8-Sirp-α and CD8-LoSirp-α cDC subsets (Laohud et al., 2006). The CD8-Sirp-α subset representing ~70% of thymic cDC is generated within the thymus from the earliest intrathymic progenitors, whereas the minor CD8-LoSirp-α cDC subset is originated from the peripheral migratory DCs (Donskoy and Goldschneider, 2003; A. Proietto and L.W., unpublished data). Similarly, human thymus also contains pDCs and two subsets of mature CD11c+ cDC: CD11b+CD45ROhi DCs that lack myeloid markers and a minority of CD11b+CD45ROim DCs expressing many myeloid markers (Bendriess-Vermare et al., 2001; Vandenabeele et al., 2001). Thymic pDCs were shown to produce type I IFN in HIV-1-infected thymus, which exerts antiviral effects (Gurney et al., 2004) and upregulates MHC class I expression on thymocytes (Keir et al., 2002). Whether thymic pDC play a role in the differentiation and/or selection of T cell subsets is unclear.

Thymic cDC, although sharing many common features, differ from other peripheral DC subsets in that the majority of thymic cDCs in mouse is derived from an intrathymic precursor, suggesting a nonmigratory behavior (Ardavin et al., 1993; Wu et al., 1995, 1996), and they mostly present self-Ag rather than foreign Ag (Steinman et al., 2003). Thymic cDCs play important roles in the induction of central tolerance through the process of negative selection (Gao et al., 1990; Brocker et al., 1997; Goldschneider 2007 Elsevier Inc.)
Organ-Specific DC Populations in the Spleen

The spleen is a rich source of lymphoid tissue-resident DCs. The DC populations in mouse spleen have been well characterized. Three cDC subsets have been identified in the mouse spleen based on the surface expression of CD8α and CD4, in addition to high levels of CD11c expression on all cDCs. These cDC subsets are CD4+CD8α−, CD4−CD8α+, and CD4−CD8α− (Vremec et al., 2000). The CD4+CD8α− cDCs also express CD205, but not SIRPα. In contrast, the CD4−CD8α− and CD4−CD8α+ cDCs do not express CD205−, but are SIRPα+ (Vremec et al., 2000; Lahoud et al., 2006). The CD8−CD205+ cDCs are located in the marginal zone, whereas the CD8−CD205− cDCs are in T cell areas (De Smedt et al., 1996). Marginal-zone DC can rapidly migrate into the T cell zone after LPS stimulation (De Smedt et al., 1996). Cell kinetic study via BrdU can rapidly migrate into the T cell zone after LPS stimulation (Naik et al., 2006; Diao et al., 2007). It is therefore suggested that IKDC may arise from NK cells, the development of IKDC requires Id2, but the major precursor population for IKDC appears to be the Lin−Sca−1−c−KitTHy−1.1+L-selectin− lymphoid progenitors (LSP) rather than CLPs (Welner et al., 2007). It is therefore suggested that IKDC may arise from a unique differentiation pathway that diverges early from those responsible for NK, pDC, T, and B cells.

The studies of splenic DC populations in human have been hampered by the limited tissue sources. One study reported that human splenic DCs were located in marginal zone, T cell, and B cell areas with a phenotype of CD11c+HLA-DQ−CD1a−CD4+CD11b−CD16−CD54+ (McIlroy et al., 2001). However, it is not clear how these DC correlate functionally with mouse splenic DC subsets or with the human blood DC subsets.

Organ-Specific DC Populations in Lymph Nodes

The DC populations found in mouse LNs are more complex. In addition to the three phenotypically and functionally equivalent cDC populations found in mouse spleen, three additional subpopulations have been described (Henri et al., 2001; Hochrein et al., 2001). They correspond to the mature CD8−CD205+ and CD8−CD205− cDC that migrate from the dermis and epidermis, respectively, to the LNs. Subcutaneous LNs contain a higher percentage of the CD8−CD205+ LC-like cells than the mesenteric LNs (Henri et al., 2001). The migratory LC-derived DCs are responsible for carrying antigens picked up from periphery to the draining LNs.

Organ-Specific DC Populations in Skin

Human CD34+ hematopoietic progenitors differentiate into both LCs and dermal DCs in culture with GM-CSF and TNF-α (Caux et al., 1992). CD34+ progenitors differentiate into common lymphoid progenitors (CLPs) and common myeloid progenitors (CMPs). CMPs appear to differentiate into CLA+ (cutaneous lymphocyte antigen) and CLA− populations, which subsequently differentiate into CD11c+CD1a+ and CD11c+CD1a− DC, respectively (Strunk et al., 1997). Whereas CD11c+CD1a+ DCs migrate into the skin epidermis and become LCs, CD11c+CD1a− DCs migrate into the skin dermis and other tissues and become interstitial DCs (ito et al., 1999). As described above, TGF-β plays a critical role in LC development as demonstrated by the fact that the in vitro generation of LCs from CD34+ progenitors can be greatly enhanced by TGF-β (Caux et al., 1999), TGF-β-deficient mice lack LCs (Borkowski et al., 1996, 1997). More recent studies further demonstrated that Fct+ CMPs as well as monocytes could all give rise to LCs in vivo (Mende et al., 2006; Ginhoux et al., 2006). These studies suggest that both LCs and dermal DCs belong to the myeloid DC lineage.

DC Populations in Blood

Human DC subsets in the blood are well characterized because of tissue accessibility. Human blood contains two types of DC precursors, monocytes and pDC, which can be induced to differentiate into DCs after ex vivo culture (Grouard et al., 1997; Rissoan et al., 1999; Sallusto and Lanzavecchia, 1994). In addition, human blood contains a subset of immature CD11c+ myeloid DC (O’Doherty et al., 1994). Blood DC11c+ mDC subsets are considered “naïve” cells that are migrating from the bone marrow to the peripheral tissue. This assumption is based on their
immature phenotype and on the fact that DCs do not recirculate from peripheral tissue to blood, as suggested by mouse studies (Austyn et al., 1988; Kupiec-Weglinski et al., 1988). It is currently believed that blood CD11c+ mDCs locate to the secondary lymphoid organs and peripheral tissues as resting interstitial DCs and that they are related to the in vitro generated monocyte-derived or CD34-derived interstitial DCs (Shortman and Liu, 2002). mDC lineage-CD4+CD11c+ or CD4-CD11c+ cells express CD45RO, myeloid markers, such as CD13 and CD33, and the MHC-like molecule CD1c. These phenotypic markers allow clear distinction of blood mDCs from blood pDCs (which lack CD11c but express CD123 and BDCA2) and can be used to purify the two subsets for in vitro studies (Duramad et al., 2003; Rissoan et al., 1999; Soumelis et al., 2002). Blood pDCs express L-selectin and migrate to the secondary lymphoid organs through the high endothelial venules (Yoneyama et al., 2004).

Mouse blood also contains two populations of precursor DCs. Cells with the surface phenotype CD11c+CD11b+CD45RA- closely resemble the human immature CD11c+ precursor DCs and rapidly transform into DC8+ CDCs after TNF-α stimulation. A second population of cells with the surface phenotype CD11c+CD11b-CD45RA- closely resemble human pDCs by morphology and function. On stimulation with CpG, these cells make large amounts of type-1 IFNs and rapidly develop into DCs that bear CD8 (O’Keeffe et al., 2003).

Concluding Remarks

DCs represent a cell system consisting of several phenotypic and functionally distinct subsets. Although the ultimate origin of all cDCs and pDCs is the BM HSCs, DCs, unlike other hematopoietic cell lineages, can develop through either the myeloid or lymphoid pathways from a Flt3-expressing progenitor (Figure 1). Different transcription factors and cytokines play important roles in controlling the development of different DC populations with distinct functional potentials. Although the intrinsic property of each DC subset may dictate their functional specialty, their final maturation and the functional capacities are also influenced by the tissue environments and the cell types they interacted. A better understanding of the detailed processes governing the development and function of these DC subsets is essential for future application of DCs in immune modulation, vaccine design, and immune therapies.

REFERENCES


