Review

Immunology and Cell Biology

Hematopoiesis leading to a diversity of dendritic antigen presenting cell types

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Abstract

Hematopoietic stem cells (HSC) undergo expansion and differentiation giving rise to all terminally differentiated blood cells throughout life. HSC are found in distinct anatomical sites during development, and in adults, hematopoiesis occurs predominantly on the luminal side of the bone cavity in bone marrow. Millions of newly formed blood cells are generated per second to accommodate the short half-life of hematopoietic cells. In order for this to happen, HSC must sustain their self-renewal capacity as well as their capability to commit and differentiate towards multiple cell lineages. Development of the hematopoietic system is finely regulated as the animal ages, so that it does not become exhausted or misdirected. This review covers aspects of hematopoietic development from the embryonic period through adult life in relation to development of dendritic cells (DC). It also considers a role for HSC in extramedullary sites and their possible role in myelopoiesis with formation of tissue-specific antigen presenting cells (APC).

Keywords: hematopoiesis, hematopoietic stem cells, dendritic cells, myelopoiesis

EARLY HEMATOPOIESIS

The hematopoietic and cardiovascular organ systems are the first to emerge during embryogenesis because the embryo requires a functional heart, vascular system, and blood for survival and growth in the early post-implantation period. Blood cell development in the embryo depends on gastrulation and mesoderm formation. Mesodermal cells contribute to the heart, the aorta in the embryo proper, formation of hematopoietic cells in yolk sac and vascular interconnection in the embryo.[1] Embryonic hematopoiesis in mice begins after gastrulation at embryonic day 6 (E6), when mesodermal cells commit to becoming hematopoietic cells.[2] The sequential sites for hematopoiesis during embryonic development then include yolk sac, the aorta-gonad-mesonephros (AGM) region, placenta, fetal liver, spleen, and finally bone marrow.[3]

Yolk sac, a bilayer structure of mesoderm and endoderm-derived cell layers, is the initial site for blood cell formation. The first hematopoietic precursors derive from mesoderm that gives rise to the hemangioblast, a bipotential precursor for blood and endothelium that enters the yolk sac to initiate primitive hematopoiesis across E7-E7.5. Blood cells produced at this time are primitive hematopoietic cells consisting mainly of large nucleated red blood cells.[4] The presence of definitive hematopoietic progenitors then marks the start of a second wave of blood cell production on day E8.5.[5] However, the microenvironment in the yolk sac does not support the differentiation of definitive hematopoietic progenitors. These therefore exit the yolk sac via the vitelline veins. Following transient appearance in the AGM region, HSC are seen to colonize fetal liver passing through umbilical cord vessels of the placenta where they contribute to robust expansion and definitive hematopoiesis.

HSC then appear in the fetal liver at E11.5 where they undergo proliferation and differentiation, with maximum expansion of HSC across E15.5-E16.5, followed by a decline in cell numbers.[6] CFU-E and proerythroblasts prevail in early fetal liver, whereas myeloid

and lymphoid progenitors accumulate at later stages. Modification of the liver microenvironment during fetal development occurs in preparation for HSC expansion and lineage differentiation[7], consistent with phenotypic changes in HSC across different developmental stages.[8]

Bone development begins at E12.5 as mesenchymal condensations are observed. Briefly, mesenchymal progenitor cells first give rise to chondrocytes that create a cartilaginous framework for bone. Chondrocytes are later replaced by osteoblastic cells that build up calcified bone through endochondral ossification to form the bone marrow cavity.[9] Vascular invasion into the bone then facilitates the circulation and seeding of HSC. Clonogenic hematopoietic activity in bone marrow can be found at ~E17.5 and persists throughout postnatal life.[10]

Hematopoiesis in fetal spleen occurs from E13 until the first weeks of the postnatal period. Hematopoietic progenitors from fetal liver migrate to fetal spleen at E13-E14 and undergo proliferation and differentiation to give mature blood cells. In contrast to fetal liver, fetal spleen does not have significant hematopoietic activity.[11] Hematopoiesis in fetal liver depends on expansion of progenitors, while hematopoiesis in fetal spleen relies on immediate hematopoietic precursors derived from fetal liver which home directly to spleen. Special microenvironments or niches in fetal spleen appear to restrict or favor the development of particular blood cell lineages.[12]

PROPERTIES OF HEMATOPOIETIC STEM CELLS

In adult humans, bone marrow is the major hematopoietic organ producing more than 10^9 mature blood cells per day. Due to the short half-life of mature cells, continuous production of cells depends on the ability of HSC to self-renew and differentiate to give all blood cell types.[13] In the steady-state, specialized niches in bone marrow provide an optimal

microenvironment for maintenance of HSC by regulation of their self-renewal and differentiative capacity, and conservation of their multipotency throughout cell division.[14]

Self-renewal is driven intrinsically by gene expression and modulated through HSC interaction with extrinsic cues in the environment. HSC niches are crucial regulators which determine whether symmetric or asymmetric cell division occurs.[15] During asymmetric division, HSC form a daughter cell and another HSC. Asymmetric division has been described for several tissue-specific stem cells, and several cell fate regulators including Notch, HoxB4, and Sonic hedgehog have been shown to play a role in the self-renewal process.[16-19] Wnt signaling is important for self-renewal because induced expression of a frizzled ligand-binding domain, an inhibitor of the Wnt signaling pathway, leads to inhibition of HSC growth *in vitro*.[20]

Lineage commitment is the process by which HSC become restricted in their differentiation and develop into a fully committed progenitor of a single blood cell lineage.[21] All murine adult hematopoietic cells derive from the multipotential HSC. This single cell type can restore the mature peripheral population of hematopoietic or blood cells in lethally irradiated recipient mice via bone marrow transplantation. Murine HSC were first characterized by their lack of lineage (Lin) specific antigens, their expression of Sca-1 (stem cell associated antigen) and c-Kit, and low expression of Thy-1.[22] This subset was later classified as the $Lin^{-}Sca\text{-}1^{+}c\text{-}Kit^{+}$ compartment (LSK). Within the HSC hierarchy, LSK represent a diverse group which can be classified as long-term self-renewing HSC (LT-HSC), shortterm, or transiently, self-renewing HSC (ST-HSC), and multipotential progenitors (MPP).[23, 24]

LT-HSC have capacity for life long reconstitution of the hematopoietic system. In mice, they are highly enriched in the LSK-$Thy1.1^{lo}$ cell fraction that can be further purified as $Flk\text{-}2^{-}$ cells.[25] The CD150, CD244 and CD48 signaling lymphocyte activation molecules have

recently been found to discriminate HSC subpopulations such that, LSKCD150^{+}CD48^{-} CD244^{-}CD34^{-} cells are defined as HSC, LSKCD150^{-}CD48^{-}CD244^{+}CD34^{-} as MPP, and LSKCD150^{-}CD48^{+}CD244^{+} as more committed progenitors.[26-28]

A hierarchy of hematopoietic cell differentiation continues to be established using both cell surface marker analysis and *in vitro* colony forming and functional assays. HSC, as multipotent progenitors, sit at the top of the hierarchy and possess high capacity for self-renewal and differentiation. Downstream on the hierarchy, HSC lose their self-renewing ability and develop into MPP that give rise to several lineages of blood cells.[25] MPP represent a heterogeneous population of stem/progenitor cells, and remain under investigation in terms of their subsets and their differentiative potential.[26, 29-31]

In terms of differentiation to give a diversity of APC, the myeloid pathway is of particular interest. HSC give rise to common myeloid progenitors (CMP) and common lymphoid progenitors (CLP) through a multipotential progenitor (MPP).[31, 32] CMP then differentiate to give granulocyte-macrophage progenitors (GMP) and megakaryocyte-erythroid progenitors (MEP). GMP are the progenitors of granulocytic and macrophage/monocytic cells including neutrophils, eosinophils, basophils, and monocytes. MEP give rise to red blood cells and megakaryocytes. CLP give rise to lymphoid and NK cell progenitors, followed by generation of mature T cells, B cells and NK cells. The Flt3^{+} subset of CMP and CLP give rise to dendritic cells (DC).[33] Two further progenitors have recently been defined in relation to DC development (Figure 1). The earliest is the MDP, a myeloid dendritic progenitor which overlaps with the CMP and CLP, but not the GMP population.[34, 35] A downstream common dendritic progenitor (CDP) which responds to Flt3L has been identified as a specific progenitor of conventional (c)DC and plasmacytoid (p)DC.[36, 37] The relationship between CDP and the previously defined CLP, CMP and MDP populations is still under investigation.

HSC ARE DISTRIBUTED AND NOT RESTRICTED TO BONE MARROW

Bone marrow primarily provides niches for HSC seeding and contributes the microenvironment which supports self-renewal and differentiation. In the adult, HSC migration from BM into the bloodstream in the steady-state is important for maintaining homeostasis. Collection of stem cells for transplantation in a clinical setting takes advantage of this natural migratory phenomenon by enforcing the release, or by 'mobilising' HSC, from bone marrow by infusion of chemotherapeutic drugs or cytokines like granulocyte-colony stimulating factor (G-CSF). HSC can then be collected from blood for stem cell transplantation. Adoptive transfer then leads to reconstitution of all hematopoietic cells after HSC home to and infiltrate bone marrow. One enigma is that HSC introduced into the peripheral blood circulation can traffic back into lymphatic circulation and into bone marrow, and so find their niches in this tissue (Figure 2).[38] It is also clear that following intravenous infusion, HSC localize in spleen and other extramedullary tissue niches (Figure 2).[38]

Several mechanisms are known to regulate HSC homing into niches. CXCL12 or stroma-derived factor-1 (SDF-1) and its receptor CXCR4 are master regulators of HSC migration through blood during embryonic development, consistent with reduction of myeloid progenitors in $CXCR4^{-/-}$ and $CXCL12^{-/-}$ mice.[39, 40] HSC also use VLA-4 (integrin $\alpha4\beta1$) to localise themselves in contact with blood vessels in bone marrow via binding to VCAM-1 expressed on bone marrow stromal or endothelial cells (Figure 2).[41] Migration of HSC into extramedullary hematopoietic organs such as spleen and liver is also mediated via interaction of VLA-4 with VCAM-1, ahead of returning to the appropriate niche that secretes SDF-1 (CXCL12) (Figure 2).[41]

Studies now show that HSC can enter and circulate through the lymphatic system. The egress of HSC from bone marrow into extramedullary tissues depends on sphingosine-1-phosphate receptor ($S1P_1$) (Figure 2). HSC also use $S1P_1$, to migrate across lymphatic

vessels and so restore specialized myeloid cells in peripheral tissues.[42] HSC express toll-like receptors (TLR), and their co-receptors MD-2 and CD14, required for recognition of pathogen associated molecular patterns such as bacterial lipopolysaccharide (LPS).[43] Interaction of TLR with LPS signals myeloid differentiation in migratory HSC localized in peripheral tissues. LPS was found to amplify the differentiation of HSC in local tissues, and to reduce the expression of $S1P_1$ on HSC, so leading to retention of HSC within tissue sites.[42]

During inflammatory responses, the phagocytic activity of sinusdoidal-lining macrophages is dramatically increased in order to remove invading pathogens. During inflammation, HSC protect themselves from macrophage uptake by upregulating CD47, an immunoglobulin-like protein which interacts with integrins and thrombospondins to protect HSC from reactive phagocytosis.[44-46] CD47 interacts with its receptor, SIRPα on macrophages and dendritic cells, to prevent phagocytosis, so ensuring survival of HSC during inflammation.[44, 45]

NICHES FOR HEMATOPOIESIS ARE DISTRIBUTED

Several niches have been described as sites for HSC maintenance, including endosteum of bone and vascular niches in bone marrow and spleen.[47, 48] In adult mice, the majority of HSC reside within osteoblastic and vascular niches in bone marrow where most hematopoietic activity occurs, whilst smaller numbers reside in vascular niches in other tissues.

Bone marrow niches contain specialized cells that provide membrane-bound and secreted growth factors to support HSC growth.[49, 50] Many studies have focused on the role of endosteal cells lining the inner surface of bone at the interface with bone marrow, in HSC maintenance.[14, 51-54] Endosteal cells differentiate into osteoblasts which support cell-to-cell contact with HSC, mediated through multiple adhesive interactions including homotypic interactions involving N-cadherin (Figure 2). Osteopontin (OPN) induces HSC retention and

quiescence in the bone marrow by binding to several integrins or to CD44, resulting in downregulation of Jagged1 expression on stromal cells and Notch1 expression on HSC.[55] Endosteal cells produce growth factors like stem cell factor (SCF) which support HSC function and survival (Figure 2). Angiopoietin (Ang-1) and thrombopoietin (TPO) promote quiescence of HSC, while SDF-1 (CXCL12) regulates migration of HSC within the bone marrow.[56-58] The endosteum also comprises the bone resorbing osteoclasts and a balance between osteoblastic and osteoclastic activities in the bone marrow is important for development of HSC.[59]

The highly vascularised nature of the endosteum is also consistent with endothelial cells having a critical role in regulation of HSC development in bone marrow.[50] Vascular niches are considered alternate sites for HSC maintenance. During embyogenesis, HSC arise from progenitors located in perivascular sites, and HSC in extramedullary tissues like liver and spleen are located in sinusoidal or vascular areas in the absence of osteoblastic cells.

Lifelong maintenance of the HSC pool depends on protecting HSC from premature exhaustion under conditions of stress. Quiescence in terms of cell cycle is a common property of niche-associated HSC. Although HSC divide infrequently, the entire HSC pool turns over every few weeks. In mice, dormant HSC divide every 145 days or 5 times per lifetime.[28] These multilineage long-term self-renewing cells create a silent reservoir of HSC during homeostasis. Upon stimulation with G-CSF, dormant HSC enter cell cycle, and then switch back to dormancy. HSC can reversibly undergo self-renewal under conditions of stress.[28] Quiescence is maintained by signaling within the niche, which induces the Tie-2 tyrosine kinase receptor on HSC which interacts with angiopoietin-1 (Ang-1) on osteoblasts[57], as well as the TPO/Mpl and Wnt/β-catenin signaling interactions, also important for HSC quiescence (Figure 2).[60]

Vascular conduits are the major highways by which hematopoietic cells and hematopoietic progenitors traffic to liver and spleen in adults.[61-63] It is generally accepted that a small number of hematopoietic progenitors circulate through peripheral sites and then home back to the bone marrow.[64, 65] Consistent with HSC migration, several studies have identified hematopoietic progenitors in heart.[66-68] Indeed, c-kit$^+$ cells isolated in the heart after myocardial infarction have been reported to have a bone marrow origin[69-71]. Hematopoietic progenitors from bone marrow can give rise to microglia following transplantation into brain.[72, 73] After brain injury it is possible that HSC or other hematopoietic progenitors from bone marrow may enter the brain and differentiate to become APC. There are also reports of the presence of hematopoietic progenitors in peripheral tissue sites like kidney[74], skin[75], and intestinal tract.[76] Such progenitors can give rise to hematopoietic cells specific to each tissue site. Similarly, Langerhans cells in skin derive from self-renewing hematopoietic progenitors which colonise the epidermis during embryonic development.[77]

HEMATOPOIESIS LEADING TO A DISTRIBUTED PATTERN OF MYELOID AND DENDRITIC CELLS IN MULTIPLE TISSUES

Hematopoiesis leading to APC formation now appears to reflect a complex set of developmental pathways originating from progenitors in bone marrow, leading to a diverse range of cells in different states of development within tissue sites such as bone marrow, liver, spleen and other lymphoid and non-lymphoid organs.[78] DC emerge from bone marrow progenitors, but the exact progenitors that give rise to DC and how they relate to known progenitors of lymphoid and myeloid cells *in vivo* is still under investigation (Figure 1). Recent developmental studies show that DC subsets and monocytes/macrophages are generated along a myeloid pathway.[34, 79] Data from parabiotic mice also support the hypothesis that lymphoid tissue DC and monocytes share a common bone marrow-derived

macrophage/dendritic progenitor (MDP), identified as a $Lin^{-}Sca1^{-}c\text{-}Kit^{hi}CD115^{+}CX3CR1^{+}Flt3^{+}$ subset also expressing CD34 and CD16/32.[35, 80] A more committed, distinct bone marrow progenitor called the common DC progenitor (CDP) has been identified as a Lin^{-} $Sca1^{+}c\text{-}Kit^{lo}CD115^{+}Flt3^{+}$ subset which gives rise cDC and pDC (Figure 1).[35, 37] Data such as these supports the concept that development of monocytes and macrophages is separated from that of DC before these cell types migrate into peripheral lymphoid tissues.

Multiple DC subsets have now been identified in tissues around the body. Their immune capacity varies in terms of ability to take up antigen and presence of inflammatory stimuli. In thymus, DC derive from an intrathymic lymphoid progenitor and represent a specialized subset important in creating a self-tolerant T cell repertoire[78]. In murine spleen, several subsets are recognized including cDC and pDC (Figure 1), each phenotypically and functionally distinct. Conventional DC are small, non-granular cells comprising two subsets of $CD8\alpha^{+}$ and $CD8\alpha^{-}$ cDC.[81] Counterpart cells can also be found in humans, free of infection and inflammation.[82] The majority of DC in spleen are $CD8\alpha^{-}$ cDC with only ~20% cDC of $CD8\alpha^{+}$ phenotype.[83] The $CD8\alpha^{+}$ cDC are localised in the T-cell rich areas or periarteriolar lymphatic sheath (PALS) of spleen, while the $CD8\alpha^{-}$ cDC are found in the marginal zone. $CD8\alpha^{-}$ cDC can migrate into the T-cell zone upon activation with bacterial lipopolysaccharides (LPS).[84, 85] Plasmacytoid DC have strong capacity to secrete type-1 interferon (IFN-α) upon viral or bacterial infection, and express CD11c, B220, CD36, CD4, CD68, and MHC-II on their cell surface. The function of pDC is linked to their expression of TLR-7 and TLR-9 which detect viral nucleic acid in early endosomes.[86]

Monocytes can also be induced to differentiate *in vitro* under the influence of inflammatory cytokines like GM-CSF and TNF-α to give monocyte-derived DC (mo-DC). These have been commonly studied as a model DC type and used in intervention or

immunotherapy against malignancies. However, DC produced by this protocol represent inflammatory DC, and are distinct from steady-state cDC. It is not yet clear whether mo-DC correspond to any DC subsets in steady-state lymphoid organs.[87] Other myeloid subsets described in spleen include TNF/iNOS-producing (Tip) DC[88] and inflammatory monocytes.[89]

In general, DC exist in peripheral tissues in an immature state and possess high capability for capturing and processing antigens from the local environment. After endocytosis of foreign antigens, these immature DC in peripheral tissues migrate to lymphoid organs where they undergo antigen processing and cell maturation, whereby DC upregulate co-stimulatory molecules like CD40, CD69, CD80, and CD86. Mature DC possess high capacity for presentation of antigen to naïve T lymphocytes[90, 91], and have high capability for cross presentation of endocytosed antigen for subsequent $CD8^+$ T cell activation.[92] Presentation of antigenic peptides by DC expressing appropriate co-stimulatory molecules results in activation of T cells for immunogenic responses, while antigen presentation without co-stimulation leads to T cell activation for tolerogenic responses.[93, 94] A wide range of DC subsets are therefore formed which act as extremely important central controllers of tolerance and immunity.

EXTRAMEDULLARY SITES FOR MYELOPOIESIS OF DC

DC can also develop within peripheral tissue sites and this has clearly been demonstrated for Langerhans cells. Cells of host origin were found several months after bone marrow transplantation[77], indicating that skin Langerhans cells are derived from tissue-restricted myeloid progenitors. Thus, DC development from progenitors within peripheral tissue sites might be possible given the distribution of HSC within tissues, and the potential for hematopoietic niches in multiple tissue sites. However, the extent to which this happens is not yet fully understood. In particular, spleen appears to support extramedullary

hematopoiesis for development of tissue-specific APC. In humans and mice, steady state-spleen contains cDC and pDC which are maintained by the replenishment of pre-DC, or precursors of cDC and pDC which derive from progenitors in bone marrow. We now present evidence that distinct dendritic-like cells appear to arise in spleen from endogenous self-renewing progenitors (Figure 1).[95]

In vitro studies from this lab showed that continuous long-term stromal cultures (LTC) of spleen support production of distinct dendritic-like cells which are large cells expressing CD11c, CD11b, and MHC-I, but not MHC-II.[96] Since these cells resembled immature myeloid DC, they were named LTC-DC.[96-100] The phenotype of cells produced has remained stable over years of culture with characteristic expression of CD11c, CD11b, CD80, CD86, MHC-I, CD205 but not MHC-II CD8α or B220.[96, 100] Gene expression studies have shown that LTC-DC express genes encoding several cell surface molecules expressed by DC.[101, 102] LTC are distinct from other *in vitro* cultures for DC production in that stromal cells support DC production without addition of exogenous inflammatory cytokines, reflecting the capacity of the spleen stromal cells to support DC haematopoiesis.[103] The continual production of immature myeloid DC in LTC led to the hypothesis that hematopoietic stem or progenitor cells are maintained within LTC.[104, 105] Ongoing investigations have now supported that hypothesis.

Recently it was shown that LTC-DC have an *in vivo* counterpart cell, distinguishable from other DC subtypes on the basis of marker expression.[106] These cells are distinct from cDC by their higher endocytic activity, absence of MHC-II expression, and their RelB-independent development.[107, 108] They are also phenotypically and functionally distinct from monocytes.[106] The *in vivo* counterpart of LTC-DC, termed 'L-DC' has now been identified in both adult and neonatal spleen, and these cells possess highly endocytic activity, and can cross-present antigens to $CD8^+$ T cells, with very limited ability to stimulate $CD4^+$ T cell

responses.[106] The inability of L-DC to induce a helper T cell response is likely due to the absence or low MHC-II expression on these cells.[100] LTC-DC and L-DC are readily distinguished from monocytes which cannot cross-present antigen to $CD8^+$ T cells.[105, 106]

Hematopoietic progenitors in LTC and their counterparts *in vivo* have been investigated in order to substantiate the development of L-DC as a distinct APC in the context of the spleen microenvironment. Based on the finding that a population of small cells is maintained in LTC, which reflect $Lin^-c\text{-}kit^+Sca\text{-}1^+$ progenitors[109], the question was raised as to whether HSC or MPP could serve the role as L-DC progenitors in spleen.[95] HSC derived from spleen[104] and bone marrow[105] have now been shown to act as progenitors of L-DC in LTC. When these same subsets of HSC from spleen or bone marrow were adoptively transferred into lethally irradiated mice there was a bias favouring production of L-DC over other DC subsets in spleen.[104, 105] These data raise the possibility that APC can develop in spleen from endogenous self-renewing HSC and have tissue-specific function perhaps related to blood-borne antigens. Further studies are underway to gain complete understanding of the development of this putative novel DC subset in the splenic context.

CONCLUSION

Indeed, there is much to be learned about tissue niches for HSC and about tissue-specific hematopoiesis for production of APC, before their importance in tissue-specific inflammation and immunity can be interpreted and considered in terms of immunotherapy. Indeed, a role for self-renewing tissue-specific progenitors in production of tissue-specific APC during the steady-state and during inflammation can be justified in terms of tissue-specific immunity reflecting some level of diversification and compartmentalisation of the immune response.

ACKNOWLEDGEMENTS

This work was supported by project grant 585443 from the National Health and Medical Research Council of Australia to HO. SP was supported by a postgraduate scholarship from the Royal Thai Government.

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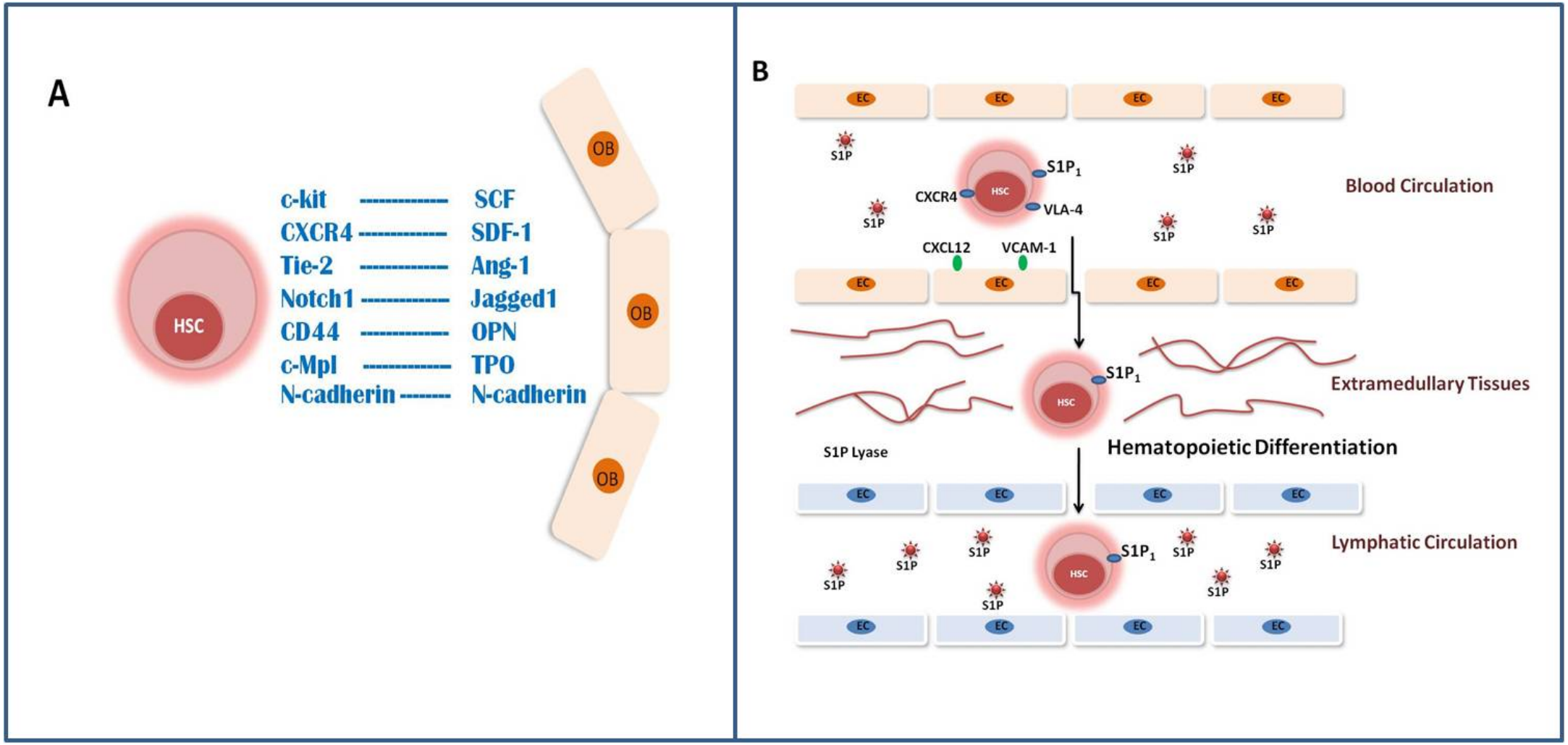
Figure Legends

Figure 1 Myelopoiesis leading to dendritic cell development. The bone marrow maintains hematopoietic stem cells (HSC). Myeloid cells are produced from a downstream common myeloid progenitor (CMP). These further differentiate to give macrophage/dendritic progenitors (MDP) which are precursors of monocytes, macrophages and dendritic cells. Recently a common dendritic progenitor (CDP) was shown to give restricted development of splenic DC via a precursor detectable in both blood and spleen. A novel antigen presenting cell type has been characterized in murine spleen. These dendritic-like cells have been named 'L-DC' and appear to derive by direct differentiation from HSC in bone marrow and spleen.

Figure 2 The bone marrow microenvironment provides signals which control HSC self-renewal, migration, and quiescence. **(A)** HSC migrate within the niche by interaction of SDF-1 (CXCL12) produced by osteoblasts (OB) with CXCR4 on HSC. HSC are maintained on the endosteal surface of bone through cell-cell interactions, including homotypic interactions involving N-cadherin, and osteopontin (OPN) interaction with CD44 or integrins. Osteopontin supports retention of HSC in the niche by down regulation of Jagged-1 expression which interacts with Notch-1 on HSC. These interactions allow Tie-2 on HSC to interact with angiopoietin (Ang-1), and cKit to interact with stem cell factor (SCF) on the surface of osteoblasts. Angiopoietin (Ang-1) and thrombopoietin (TPO) interactions with their receptors on HSC supports HSC quiescence. **(B)** HSC migrate from blood into extramedullary tissues via a sphingosine-1-phosphate (S1P) gradient. The interaction of S1P with its receptor ($S1P_1$), in combination with other molecules such as CXCR4 and VLA-4 which interact with ligands on endothelial cells (EC) (CXCL12 and VCAM-1), facilitates HSC migration into extramedullary tissues. The S1P level in tissues is lower due to

S1P lyase activity. This results in localization of HSC within tissue niches for differentiation. HSC can also enter lymphatic tissues including bone marrow through the guidance of S1P.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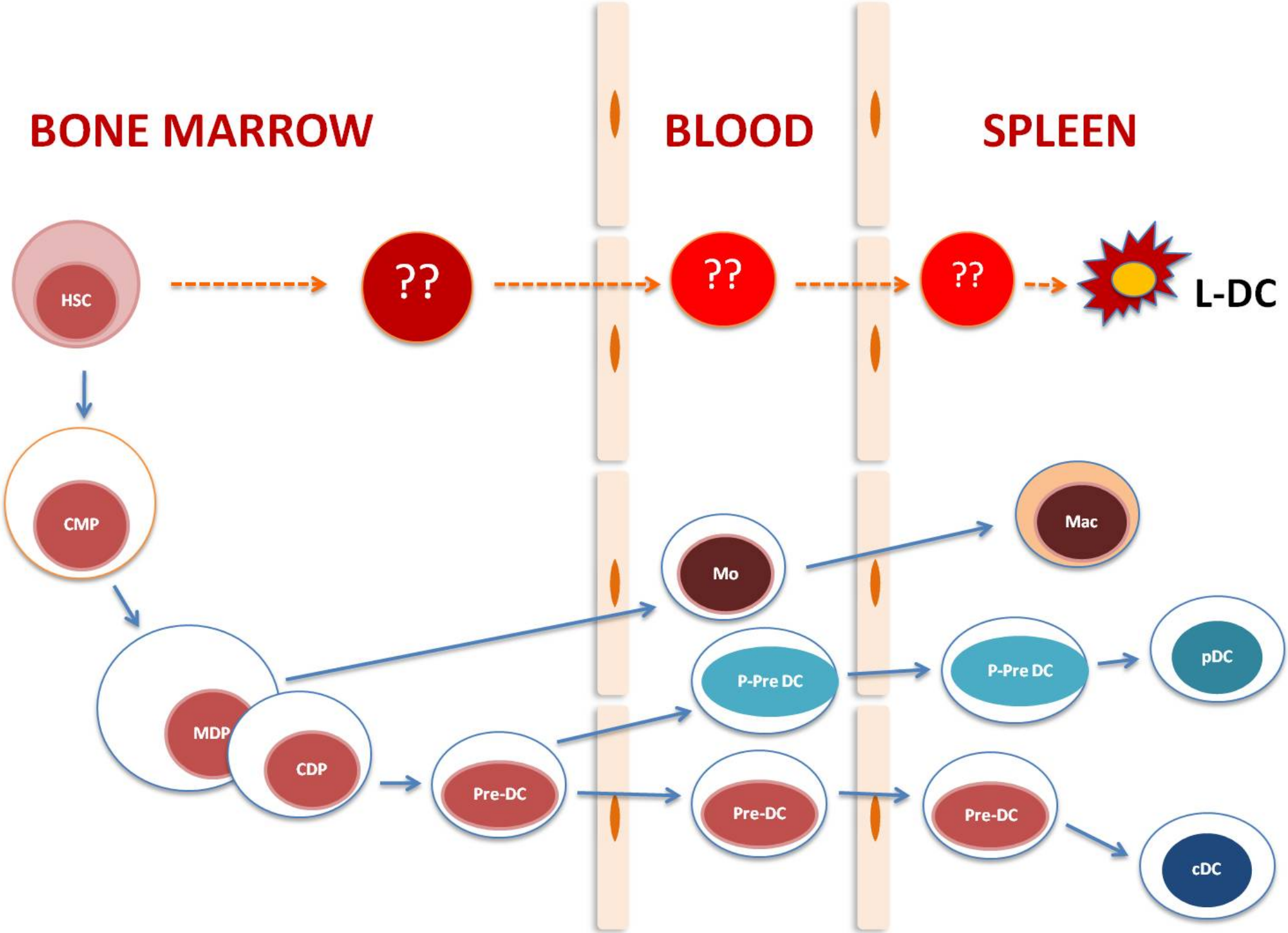
S1P Lyase
Hematopoietic Differentiation
Lymphatic Circulation


BONE MARROW
BLOOD
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L-DC
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