Immunol Res (2009) 44:160–168
DOI 10.1007/s12026-009-8109-6

Hematopoietic stem and progenitor cells: their mobilization and homing to bone marrow and peripheral tissue

Christian Schulz · Ulrich H. von Andrian · Steffen Massberg

Published online: 2 April 2009

Abstract Hematopoietic stem and progenitor cells (HSPCs) are a rare population of precursor cells that possess the capacity for self-renewal and multilineage differentiation. In the bone marrow (BM), HSPCs warrant blood cell homeostasis. In addition, they may also replenish tissue-resident myeloid cells and directly participate in innate immune responses once they home to peripheral tissues. In this review, we summarize recent data on the signaling molecules that modulate the mobilization of HSPCs from BM and their migration to peripheral tissues.

Keywords Hematopoietic stem cells · Progenitor cells · Migration · Homing · Bone marrow · Peripheral tissue

Introduction

Hematopoietic stem cells (HSCs) are a subset of bone marrow (BM) cells with self-renewing capacity that form all types of blood cells [1]. The precise mechanisms that control hematopoietic stem and progenitor cell (HSPC) function still remain largely unknown. In this review, we will give an overview on more recent data that provide further insight into the processes that regulate HSPC differentiation, mobilization from BM and migration to secondary organ sites and back to the BM compartment.

C. Schulz · S. Massberg (✉)
Deutsches Herzzentrum, Technische Universität München, Lazarettstraße 36, 80636 Munich, Germany
e-mail: massberg@dhm.mhn.de

U. H. von Andrian · S. Massberg
Immune Disease Institute and Department of Pathology, Harvard Medical School, Boston, MA 02115, USA

HSPC maintenance

Hematopoietic stem and progenitor cells require distinct local microenvironments, so-called 'niches', for their maintenance. In adult BM, these niches are thought to be located in sinusoidal perivascular areas (vascular niche) or in the trabecular endosteum (osteoblastic niche) [2]. Interestingly, formation of osteoblastic niches requires local endochondral ossification as well as the presence of osteoblastic cells, a process closely related to bone formation [3, 4]. Notably, niches not only exist in the BM, but have also been identified in extramedullary tissues [5]. Rather than comprising a static compartment, niches act as a dynamic environment and, thus, may support rapid increases in hematopoietic cell production depending on the physiological requirements [6]. Distinct cells, such as osteoblastic cells, regulate the HSC niche and HSPC proliferation and survival [4, 7]. In addition, growth factors and cytokines, including stromal cell-derived factor (SDF)-1α and transforming growth factor (TGF)-β, modulate HSPC proliferation within BM niches [8, 9]. For example, TGF-β, which is known to exert various effects on cells including proliferation, differentiation, and also apoptosis [10], regulates the cell cycle entry of HSPCs and by this means modulates their quiescence [8, 11]. TGF-β may act directly on HSPCs or indirectly through modification of the niche [10]. Of note, TGF-β receptors stimulate the phosphorylation of receptor-regulated Smad proteins which control gene transcription and, thus, have evolved as important effectors following TGF-β stimulation [12, 13].

In addition to TGF-β, particularly SDF-1α (CXCL-12) regulates HSPC function and maintains HSPCs in a quiescent (or dormant) state, which is pivotal to sustain a pool of highly regenerative stem cells [8, 9, 14]. Interestingly, the majority of long-term HSPC activity is retained in a low number (<1,000) of dormant stem cells [15]. Recent evidence suggests that activated HSPCs return to their quiescent state within niches once they have re-established homeostasis (e.g., following regeneration of the blood system) [15]. A detailed overview on the regulation of HSPC function in niches is given by Kiel et al. [16].

Mobilization from bone marrow

Hematopoietic stem and progenitor cell mobilization from BM enables migration to peripheral blood and homing to peripheral tissues. This process is tightly controlled by specialized signals [17, 18]. Chemo-attractant cytokines, growth factors, and hormones are modulators that control the egress of HSPCs from BM. Particularly, the SDF-1α(CXCL-12)/CXCR4 axis plays a pivotal role for HSPC positioning in the BM compartment. Abrogation of SDF-1α/CXCR4-mediated cell signaling results in rapid mobilization of HSPCs from BM niches [19, 20]. SDF-1α also mediates a variety of other cellular functions such as engraftment in peripheral tissues. Binding of GROβ to its receptor CXCR2 also induces mobilization of HSPCs [21]. In contrast, other chemokines such as monocyte chemoattractant protein (MCP)-1 and its receptor CCR2, may exert myelosuppressant effects and, thus, limit HSPC proliferation within BM [22].

Activation of the parathyroid hormone (PTH) receptor also increases the number of HSPCs mobilized into the bloodstream [23, 24]. The PTH receptor (PTHR) has recently been identified on osteoblasts, which represent an important cellular component of the adult HSPC niche. Thus, activation of PTHR may be of therapeutic use to mobilize HSPCs into peripheral blood [23, 24].

The role of proteolytic enzymes for HSPC mobilization from BM is largely unknown. However, the serine proteases neutrophil elastase and cathepsin G have been identified in BM niches following G-CSF stimulation [25], and it was therefore hypothesized that these enzymes might modulate HSPC mobilization. Indeed, both proteases are capable of disrupting interaction of SDF-1α with its cognate receptor CXCR4 through proteolytic cleavage [26]. Further, proteolytic enzymes may reduce surface-expression of cellular adhesion molecules (i.e., VCAM-1) on BM cells [25]; an effect was also seen following G-CSF stimulation of the HSC niche. However, HSPC mobilization by G-CSF was found to be normal in mice lacking functional neutrophil serine proteases [27]. This indicates that both protease-dependent and protease-independent pathways contribute to HSPC mobilization [27].

Although there are a number of factors that, in either way, influence HSPC mobilization from BM, specific 'flavors' of growth factors and chemokines seem to mobilize distinct subsets of stem and progenitor cells in a highly selective manner in mice [18].

Other signaling molecules involved in HSPC migration

Nitric oxide (NO), a well-known signaling molecule that controls the vascular tone and inhibits platelet function, has recently been implicated in the mobilization of hematopoietic progenitor cells from BM. Correspondingly, mice deficient in endothelial NO synthase (eNOS) showed reduced mobilization of CD34+/Flk-1+ progenitor cells from BM when compared with wildtype mice [28]. However, NO did not alter mobilization of less-differentiated HSPCs [29, 30].

Bone marrow cell homeostasis is also closely controlled by changes of local oxygen tensions. For example, low oxygen levels modulate SDF-1α expression in hypoxic BM compartments via the transcription factor hypoxia-inducible factor (HIF)-1α [31]. Similar mechanisms seem to occur in ischemic peripheral tissue. Here, local hypoxia leads to upregulation of SDF-1α expression on endothelial cells, which mediates recruitment of HSPCs to sites of vascular injury [31, 32]. Hence, the local microenvironment found not only in niches in the BM but also in peripheral tissues plays a critical role for recruitment and function of HSPCs.

Homing to bone marrow and peripheral tissues

Hematopoietic stem and progenitor cells exit the BM by migration through the BM–blood barrier, and then become disseminated in the circulation. Once blood-borne, HSPCs may home back to the BM compartment with high efficiency [33]. Within the BM vascular bed, HSPCs become firmly adherent to microvascular endothelial cells. This process involves a multistep adhesion cascade that closely resembles homing of mature blood leukocytes in peripheral tissues [34–38]. BM homing is the prerequisite for consecutive HSPC proliferation and it is of pivotal importance during fetal development and for HSC homeostasis in adulthood.

Murine progenitors transplanted intravenously are rapidly cleared from circulation in the recipient mice [39]. Hence, HSPC homing is an efficient and prompt process that occurs within minutes or few hours rather than days [39]. The molecular mechanisms that control HSPC trafficking to the BM are not entirely clear. However, several candidate adhesion molecules expressed on the surface of HSPCs have been indentified in recent

years. For example, the $\alpha 4\beta 1$ integrin (VLA-4) is expressed on most HSPC [40]. While VLA-4 binds to several ligands in the BM microenvironment, the vascular cell adhesion molecule 1 (VCAM-1), expressed on stromal cells and endothelium, probably is the most prominent ligand [41, 42]. Importantly, interference with VCAM-1/VLA-4 by antibody treatment resulted in reduced homing and increased HSPC mobilization [41, 43]. The role of VCAM-1/VLA-4 for HSPC migration seems well-conserved across different species including humans [44]. Interestingly, the VCAM-1/VLA-4 pathway alone is capable of providing effective capture of cells within the BM, but other adhesive pathways, particularly selectins and potentially also $\beta 2$-integrins seem to synergistically contribute to BM homing of HSPCs [45–47].

It is commonly assumed that the BM is the exclusive physiological source and destination of blood-borne HSPCs. However, our sparse knowledge of HSPC trafficking does not rule out that circulating HSPCs migrate also to extramedullary sites. In fact, we have recently shown that the BM is not the only compartment that HSPCs home to. We established that BM-derived HSPCs traffic constitutively to multiple extramedullary tissues where they reside for several days until entering draining lymphatics to return to the blood [48]. Correspondingly, clonogenic HSPCs are detectable in many murine tissues, including the lung, liver, and kidneys. Virtually all tissue HSPCs are BM-derived, since they uniformly expressed GFP in chimeric wildtype recipients of GFP^+ BM. Tissue HSPCs are constitutively replenished by the pool of HSPCs that circulates in the blood, as predicted from our parabiosis experiments. Most of these blood-derived tissue HSPCs are not permanently retained in extramedullary organs, but recirculate freely via lymph and blood compartments, because we also detected partner-derived HSPC chimerism in the lymph (and blood) of parabiotic mice. While we are beginning to understand the mechanisms underlying HSPCs homing to the BM compartment, the adhesive cascades involved in HSPC homing to peripheral tissues are as yet unclear.

Sphingosine-1-phosphate regulates recirculation of tissue-resident HSPCs

Whereas future studies will have to address the mechanisms that regulate the homing of HSPCs into peripheral tissues, our previous own work has identified sphingosine-1-phosphate (S1P) as a critical signal that controls the egress of tissue HSPCs into the draining lymphatics.

S1P is a bioactive phospholipid that has recently been identified as a key regulator of cell trafficking. Steep gradients of S1P, maintained by the enzyme S1P lyase, exist in various tissues between interstitium and the blood and lymph fluids. Among others, S1P lyase maintains low tissue levels of S1P [49], while high S1P levels are found in blood and lymph [50, 51]. It is widely accepted that such S1P gradients regulate the egress of mature lymphocytes from the thymus, spleen, and lymph nodes [49, 52, 53] (for review see [54]). Correspondingly, modulation of S1P receptors by the immunosuppressant FTY720 induces lymphocyte sequestration in secondary lymphoid organs, causing profound lymphopenia in blood and lymph [55].

We have shown that a comparable mechanism also controls the exit of HSPCs from peripheral tissues into the draining lymph [48]. We observed that murine HSPCs, like resting lymphocytes and human HSPCs [56], express S1P receptors, particularly S1P1. Interestingly, murine HSPCs were found to migrate towards steep gradients of S1P in a predominantly S1P1 receptor-dependent manner [48]. Modulation of S1P receptors with FTY720 or the S1P1 binding agent SEW2871 blunts the egress of tissue-resident HSPCs

into lymphatics and, thus, inhibits their recirculation from extramedullary tissues [48]. It is important to note that mature lymphocytes get access to the lymphatic vasculature by homing to lymphoid organs. In contrast, HSPCs enter the lymphatic system mostly in non-lymphoid tissues via lymphatic vasculature [48]. This indicates that S1P acts as a regulator of leukocytes migration in both lymphoid and non-lymphoid tissues. Notably, G-CSF-induced mobilization of HSPCs from BM was not influenced by S1P receptor modulation.

As outlined earlier, S1P lyase is essential to maintain physiological S1P gradients between tissues, blood, and lymph and hence regulates immune cell migration. Correspondingly, pharmacological blockade of S1P lyase abrogates lymphocyte egress from lymphoid tissues and results in significant lymphopenia. In parallel, the number of lymph-borne HSPCs is markedly reduced, indicating that S1P lyase is also required for HSPC passage through tissues [48]. Therefore, S1P gradients established by S1P lyase are essential for HSPC trafficking by regulating their egress from peripheral tissues.

Biological significance of HSPC recirculation between BM and peripheral tissues

Together, work from our lab suggests that there is a constitutive recirculation of HSPCs between BM, blood, extramedullary tissues, and lymph compartment [48]. But, what is the purpose of constitutive HSPC recirculation across peripheral tissues?

In humans, an abrupt change in HSC proliferative activity occurs between 2 and 4 years after birth [57]. In mice, all HSPCs are cycling until 3 and 4 weeks after birth. Then, within 1 week, most HSPCs become quiescent and are maintained in hematopoietic niches such as the BM cavity [58]. Within the BM, HSPC clones produce mature blood cells to replenish the pool of circulating cells [59]. As delineated earlier, HSPCs may reversibly switch between dormancy and self-renewal as needed to preserve homeostasis. Since we and others have previously shown that some HSPCs recirculate constantly between BM and peripheral blood [33] and lymph [48], it was tempting to speculate, that a pool of circulating HSPCs might help to locally replenish tissue-resident subsets of specialized myeloid cells, including several subsets of monocytes, macrophages, and dendritic cells (DCs) (reviewed in [60]). Indeed, our previous work indicates that circulating HSPCs divide locally and give rise to mature myeloid cells once they have entered extramedullary tissues [48]. Migratory HSPCs, in addition to more committed myeloid precursors, the MDPs [60], might therefore help to constitutively replenish specialized tissue-resident myeloid cells under steady-state conditions.

In addition to the constitutive replenishment of tissue-resident myeloid cells under steady-state conditions, circulating HSPCs might also directly participate in innate immune responses during tissue injury and/or infection. Recently, HSCs and lineage-specified progenitors have been shown to express functional Toll-like receptors (TLRs) [17, 61], which recognize foreign molecules such as the bacterial outer membrane component LPS [62]. Binding of LPS to TLRs promotes entry of quiescent HSPCs into the cell cycle and triggers myeloid differentiation [17, 61]. Initially, it was proposed that HSPCs that reside in BM could be stimulated by circulating pathogen products. However, our own work indicates that HSPCs can also address the threat of infection at the point of entry within peripheral tissues. We reported that once HSPCs enter peripheral tissues and sense microbial danger signals through TLRs, they start to proliferate vigorously and boost the local supply of innate effector cells. Hence, migratory HSPCs possess the ability to survey peripheral tissues and respond rapidly to situations, such as tissue damage and infections that require the prompt influx of large numbers of innate immune cells. However, we found

that even in the absence of inflammation recirculating HSPCs divide locally in peripheral tissues and differentiate into mature myeloid cells. Under steady-state conditions, homed HSPCs may therefore help to constitutively replenish the diverse population of tissue-resident leukocytes that perform multiple essential functions in peripheral organs, including removal of dead cells and debris. Notably, TLR ligands not only amplified local proliferation of HSPCs in extramedullary tissues, but also prevented the exit of HSPCs out of peripheral tissues. This was, at least in part, due to interference with S1P-S1P1 receptor signaling in recirculating HSPCs. Hence, recognition of TLR ligands not only triggers local proliferation and differentiation, but also disrupts the normal S1P-dependent signaling cascade and leads to retention of HSPCs within extramedullary tissues.

Together, these results indicate that extramedullary tissues are continuously surveyed by circulating hematopoietic progenitors, which may respond rapidly to invading pathogens before this information reaches the BM. Although the exact in vivo significance of HSPC migration across tissues to date is largely unknown, it is tempting to speculate that constitutively recirculating HSPCs replenish tissue-resident myeloid cells under steady-state conditions and provide a rapidly recruitable source for the local production of inflammatory effector cells (for review see [63]).

Conclusions

Hematopoietic stem cells possess the unique capacity for self-renewal and differentiation. Besides their role in the production of mature blood cells necessary to replenish the pool of circulating cells, recent publications have indicated immunological functions of HSPCs. Various signaling molecules and guidance factors control mobilization and targeted migration of HSPCs from BM to peripheral tissues, as well as their recirculation to BM. Understanding of these mechanisms will be critical to target HSPC trafficking for future therapies.

References

1. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. Science. 1988;241(4861):58–62.
2. Morrison SJ, Spradling AC. Stem cells and niches: mechanisms that promote stem cell maintenance throughout life. Cell. 2008;132(4):598–611.
3. Chan CK, Chen CC, Luppen CA, Kim JB, DeBoer AT, Wei K, et al. Endochondral ossification is required for haematopoietic stem-cell niche formation. Nature. 2009;457(7228):490–4.
4. Mayack SR, Wagers AJ. Osteolineage niche cells initiate hematopoietic stem cell mobilization. Blood. 2008;112(3):519–31.
5. Majka SM, Jackson KA, Kienstra KA, Majesky MW, Goodell MA, Hirschi KK. Distinct progenitor populations in skeletal muscle are bone marrow derived and exhibit different cell fates during vascular regeneration. J Clin Invest. 2003;111(1):71–9.
6. Avecilla ST, Hattori K, Heissig B, Tejada R, Liao F, Shido K, et al. Chemokine-mediated interaction of hematopoietic progenitors with the bone marrow vascular niche is required for thrombopoiesis. Nat Med. 2004;10(1):64–71.
7. Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature. 2003;425(6960):841–6.
8. Fortunel NO, Hatzfeld JA, Monier MN, Hatzfeld A. Control of hematopoietic stem/progenitor cell fate by transforming growth factor-beta. Oncol Res. 2003;13(6–10):445–53.
9. Nie Y, Han YC, Zou YR. CXCR4 is required for the quiescence of primitive hematopoietic cells. J Exp Med. 2008;205(4):777–83.

10. Ruscetti FW, Akel S, Bartelmez SH. Autocrine transforming growth factor-beta regulation of hematopoiesis: many outcomes that depend on the context. Oncogene. 2005;24(37):5751–63.
11. Yamazaki S, Iwama A, Takayanagi S, Eto K, Ema H, Nakauchi H. TGF-beta as a candidate bone marrow niche signal to induce hematopoietic stem cell hibernation. Blood. 2009;113(6):1250–6.
12. He W, Dorn DC, Erdjument-Bromage H, Tempst P, Moore MA, Massague J. Hematopoiesis controlled by distinct TIF1gamma and Smad4 branches of the TGFbeta pathway. Cell. 2006;125(5):929–41.
13. Derynck R, Zhang Y, Feng XH. Smads: transcriptional activators of TGF-beta responses. Cell. 1998;95(6):737–40.
14. Sugiyama T, Kohara H, Noda M, Nagasawa T. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity. 2006;25(6): 977–88.
15. Wilson A, Laurenti E, Oser G, van der Wath RC, Blanco-Bose W, Jaworski M, et al. Hematopoietic stem cells reversibly switch from dormancy to self-renewal during homeostasis and repair. Cell. 2008;135(6):1118–29.
16. Kiel MJ, Morrison SJ. Uncertainty in the niches that maintain haematopoietic stem cells. Nat Rev Immunol. 2008;8(4):290–301.
17. Welner RS, Kincade PW. Stem cells on patrol. Cell. 2007;131(5):842–4.
18. Pitchford SC, Furze RC, Jones CP, Wengner AM, Rankin SM. Differential mobilization of subsets of progenitor cells from the bone marrow. Cell Stem Cell. 2009;4(1):62–72.
19. Lapidot T, Kollet O. The essential roles of the chemokine SDF-1 and its receptor CXCR4 in human stem cell homing and repopulation of transplanted immune-deficient NOD/SCID and NOD/SCID/B2 m(null) mice. Leukemia. 2002;16(10):1992–2003.
20. Broxmeyer HE, Orschell CM, Clapp DW, Hangoc G, Cooper S, Plett PA, et al. Rapid mobilization of murine and human hematopoietic stem and progenitor cells with AMD3100, a CXCR4 antagonist. J Exp Med. 2005;201(8):1307–18.
21. Pelus LM, Fukuda S. Peripheral blood stem cell mobilization: the CXCR2 ligand GRObeta rapidly mobilizes hematopoietic stem cells with enhanced engraftment properties. Exp Hematol. 2006;34(8):1010–20.
22. Reid S, Ritchie A, Boring L, Gosling J, Cooper S, Hangoc G, et al. Enhanced myeloid progenitor cell cycling and apoptosis in mice lacking the chemokine receptor, CCR2. Blood. 1999;93(5):1524–33.
23. Adams GB, Chabner KT, Alley IR, Olson DP, Szczepiorkowski ZM, Poznansky MC, et al. Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. Nature. 2006; 439(7076):599–603.
24. Adams GB, Martin RP, Alley IR, Chabner KT, Cohen KS, Calvi LM, et al. Therapeutic targeting of a stem cell niche. Nat Biotechnol. 2007;25(2):238–43.
25. Levesque JP, Takamatsu Y, Nilsson SK, Haylock DN, Simmons PJ. Vascular cell adhesion molecule-1 (CD106) is cleaved by neutrophil proteases in the bone marrow following hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor. Blood. 2001;98(5):1289–97.
26. Levesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. J Clin Invest. 2003;111(2):187–96.
27. Levesque JP, Liu F, Simmons PJ, Betsuyaku T, Senior RM, Pham C, et al. Characterization of hematopoietic progenitor mobilization in protease-deficient mice. Blood. 2004;104(1):65–72.
28. Aicher A, Heeschen C, Mildner-Rihm C, Urbich C, Ihling C, Technau-Ihling K, et al. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. Nat Med. 2003;9(11):1370–6.
29. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. Nature. 2004;428(6983):668–73.
30. Ozuyaman B, Ebner P, Niesler U, Ziemann J, Kleinbongard P, Jax T, et al. Nitric oxide differentially regulates proliferation and mobilization of endothelial progenitor cells but not of hematopoietic stem cells. Thromb Haemost. 2005;94(4):770–2.
31. Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, Kleinman ME, et al. Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med. 2004;10(8):858–64.
32. Ceradini DJ, Gurtner GC. Homing to hypoxia: HIF-1 as a mediator of progenitor cell recruitment to injured tissue. Trends Cardiovasc Med. 2005;15(2):57–63.
33. Wright DE, Wagers AJ, Gulati AP, Johnson FL, Weissman IL. Physiological migration of hematopoietic stem and progenitor cells. Science. 2001;294(5548):1933–6.
34. Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell. 1994;76(2):301–14.

35. Bonig H, Priestley GV, Papayannopoulou T. Hierarchy of molecular-pathway usage in bone marrow homing and its shift by cytokines. Blood. 2006;107(1):79–86.
36. Lapidot T, Dar A, Kollet O. How do stem cells find their way home? Blood. 2005;106(6):1901–10.
37. Mazo IB, von Andrian UH. Adhesion and homing of blood-borne cells in bone marrow microvessels. J Leukoc Biol. 1999;66(1):25–32.
38. Bonig H, Priestley GV, Nilsson LM, Jiang Y, Papayannopoulou T. PTX-sensitive signals in bone marrow homing of fetal and adult hematopoietic progenitor cells. Blood. 2004;104(8):2299–306.
39. Papayannopoulou T. Bone marrow homing: the players, the playfield, and their evolving roles. Curr Opin Hematol. 2003;10(3):214–9.
40. Chan JY, Watt SM. Adhesion receptors on haematopoietic progenitor cells. Br J Haematol. 2001; 112(3):541–57.
41. Papayannopoulou T, Craddock C, Nakamoto B, Priestley GV, Wolf NS. The VLA4/VCAM-1 adhesion pathway defines contrasting mechanisms of lodgement of transplanted murine hemopoietic progenitors between bone marrow and spleen. Proc Natl Acad Sci USA. 1995;92(21):9647–51.
42. Potocnik AJ, Brakebusch C, Fassler R. Fetal and adult hematopoietic stem cells require beta1 integrin function for colonizing fetal liver, spleen, and bone marrow. Immunity. 2000;12(6):653–63.
43. Papayannopoulou T, Nakamoto B. Peripheralization of hemopoietic progenitors in primates treated with anti-VLA4 integrin. Proc Natl Acad Sci USA. 1993;90(20):9374–8.
44. Zanjani ED, Flake AW, Almeida-Porada G, Tran N, Papayannopoulou T. Homing of human cells in the fetal sheep model: modulation by antibodies activating or inhibiting very late activation antigen-4-dependent function. Blood. 1999;94(7):2515–22.
45. Papayannopoulou T, Priestley GV, Nakamoto B, Zafiropoulos V, Scott LM. Molecular pathways in bone marrow homing: dominant role of alpha(4)beta(1) over beta(2)-integrins and selectins. Blood. 2001;98(8):2403–11.
46. Bonig H, Priestley GV, Oehler V, Papayannopoulou T. Hematopoietic progenitor cells (HPC) from mobilized peripheral blood display enhanced migration and marrow homing compared to steady-state bone marrow HPC. Exp Hematol. 2007;35(2):326–34.
47. Katayama Y, Hidalgo A, Furie BC, Vestweber D, Furie B, Frenette PS. PSGL-1 participates in E-selectin-mediated progenitor homing to bone marrow: evidence for cooperation between E-selectin ligands and alpha4 integrin. Blood. 2003;102(6):2060–7.
48. Massberg S, Schaerli P, Knezevic-Maramica I, Kollnberger M, Tubo N, Moseman EA, et al. Immunosurveillance by hematopoietic progenitor cells trafficking through blood, lymph, and peripheral tissues. Cell. 2007;131(5):994–1008.
49. Schwab SR, Pereira JP, Matloubian M, Xu Y, Huang Y, Cyster JG. Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. Science. 2005;309(5741):1735–9.
50. Yatomi Y, Igarashi Y, Yang L, Hisano N, Qi R, Asazuma N, et al. Sphingosine 1-phosphate, a bioactive sphingolipid abundantly stored in platelets, is a normal constituent of human plasma and serum. J Biochem. 1997;121(5):969–73.
51. Hla T, Venkataraman K, Michaud J. The vascular S1P gradient-cellular sources and biological significance. Biochim Biophys Acta. 2008;1781(9):477–82.
52. Rosen H, Goetzl EJ. Sphingosine 1-phosphate and its receptors: an autocrine and paracrine network. Nat Rev Immunol. 2005;5(7):560–70.
53. Pappu R, Schwab SR, Cornelissen I, Pereira JP, Regard JB, Xu Y, et al. Promotion of lymphocyte egress into blood and lymph by distinct sources of sphingosine-1-phosphate. Science. 2007;316(5822): 295–8.
54. Rosen H, Gonzalez-Cabrera P, Marsolais D, Cahalan S, Don AS, Sanna MG. Modulating tone: the overture of S1P receptor immunotherapeutics. Immunol Rev. 2008;223:221–35.
55. Massberg S, von Andrian UH. Fingolimod and sphingosine-1-phosphate–modifiers of lymphocyte migration. N Engl J Med. 2006;355(11):1088–91.
56. Kimura T, Boehmler AM, Seitz G, Kuci S, Wiesner T, Brinkmann V, et al. The sphingosine 1-phosphate receptor agonist FTY720 supports CXCR4-dependent migration and bone marrow homing of human CD34+ progenitor cells. Blood. 2004;103(12):4478–86.
57. Rufer N, Brummendorf TH, Kolvraa S, Bischoff C, Christensen K, Wadsworth L, et al. Telomere fluorescence measurements in granulocytes and T lymphocyte subsets point to a high turnover of hematopoietic stem cells and memory T cells in early childhood. J Exp Med. 1999;190(2):157–67.
58. Bowie MB, McKnight KD, Kent DG, McCaffrey L, Hoodless PA, Eaves CJ. Hematopoietic stem cells proliferate until after birth and show a reversible phase-specific engraftment defect. J Clin Invest. 2006;116(10):2808–16.
59. Orkin SH, Zon LI. Hematopoiesis: an evolving paradigm for stem cell biology. Cell. 2008;132(4): 631–44.

60. Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol. 2009. doi:10.1146/annurev.immunol.021908.132557.
61. Nagai Y, Garrett KP, Ohta S, Bahrun U, Kouro T, Akira S, et al. Toll-like receptors on hematopoietic progenitor cells stimulate innate immune system replenishment. Immunity. 2006;24(6):801–12.
62. Hoshino K, Takeuchi O, Kawai T, Sanjo H, Ogawa T, Takeda Y, et al. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. J Immunol. 1999;162(7):3749–52.
63. Laird DJ, von Andrian UH, Wagers AJ. Stem cell trafficking in tissue development, growth, and disease. Cell. 2008;132(4):612–30.