Adhesion and homing of blood-borne cells in bone marrow microvessels

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Abstract: After birth, the bone marrow (BM) is the principal site of hematopoiesis in mammals. Thus, a large number of newly formed blood cells must penetrate the wall of BM microvessels to enter the circulation. In addition, the BM appears to function as a lymphoid organ and is also part of the macrophagal system. Subsets of circulating lymphocytes and other cells of the immune system continuously home to the BM. However, neither the mechanisms of blood cell migration to and from the BM nor its precise role in the immune system are well understood. One reason for the relative paucity of data on BM physiology is the fact that normal BM is surrounded by thick cortical bone that impedes direct observation and experimental manipulation. One notable exception is the calvaria of the murine skull where hematopoietically active BM is only covered by a thin lamella of bone that is sufficiently translucent to allow a detailed in situ analysis of the BM microcirculation by epi-fluorescence microscopy. Here, we review our current knowledge of the anatomic, hemodynamic, and endothelial properties of the specialized microvascular bed within murine skull BM. In addition, we summarize recent studies on the molecular mechanisms that mediate the homing of circulating hematopoietic progenitor cells to the BM, an event that is critical for the success of BM transplantations. J. Leukoc. Biol. 66: 25–32; 1999.

Key Words: hematopoiesis · lymphocytes · mouse

INTRODUCTION

The existence of the bone marrow (BM) has been noted since ancient times when it was believed to be either a source of nourishment or a waste product (excrementum ossium) from the bones [reviewed in ref. 1]. Evidence of a hematopoietic function of the BM was discovered in 1868 when it was proposed to be a site of erythropoiesis [2]. In 1877, Paul Ehrlich published a staining technique that allowed different types of marrow cells to be distinguished [3]. This technique stimulated extensive research on the anatomy and physiology of the BM. Subsequent work by many investigators throughout this century has led to the classification of BM as a tissue that has many other functions in addition to its pivotal role in hematopoiesis. Aside from generating nearly all cellular constituents of both the innate and acquired immune system, the BM has been identified as a key organ that regulates several immune functions. For instance, the BM is considered to be the principal site of B cell development [4]. This is likely to require the presence of complex selection mechanisms that may involve the activity of professional antigen-presenting cells (APC), which may regulate the survival, elimination, or differentiation of cells with diverse antigen receptors. It is interesting in this regard that the BM is also considered to be a part of the macrophagal system and contains an abundance of phagocytes. However, although there is detailed knowledge of the initial regulatory events in the ontogeny of the T cell system in the thymus, relatively little is known about the control of B cell development in the BM. The BM is also an important site of antibody production and harbors about half of all plasma cells in the body [5]. Plasma cells arise from activated B cells in the periphery and must subsequently enter and leave the bloodstream to reach the BM [6]. In addition, the BM also has the capacity to recruit circulating T cells [7]. The adhesive, signaling, and migration events that control immune cell trafficking into and out of the BM are unknown.

HISTOLOGY, MORPHOLOGY, AND CELLULAR COMPOSITION OF THE BM IN MAMMALS

In addition to mature and immature blood cells, the BM also contains at least seven types of stromal cells (osteoblasts, osteoclasts, fat cells, mast cells, fibroblasts, endothelial cells, and smooth muscle cells) that are thought to undergo complex interactions with hematopoietic cells [8]. This cellular composition can change quickly in response to various physiological and pathological stimuli. For instance, bleeding enhances the hematopoietic activity of hypoplastic BM by rapidly increasing its cellularity and vascularity [9], whereas a lethal dose of ionizing radiation causes a rapid and complete loss of hematopoiesis [10].

Due to its anatomic localization, BM develops in close contact with bone. Indeed, studies have shown a correlation between the distribution of blood flow to the skeleton and the...
distribution of marrow within the skeleton. Thus, it has been suggested that BM develops better when it is supplied by blood that has just passed through bone, indicating that bone and BM are a functional unit [11]. Consistent with this concept, experiments have shown that transplantation of erythropoietic marrow to a non-osseous site causes either degeneration or inertia of the BM tissue until a surrounding shell of new bone has formed [12, 13]. Furthermore, endosteal trauma induces reactions in the surrounding bone that appear to provide a growth stimulus for hematopoietic marrow [14].

The major arterial supply of the BM in long bones is a nutrient artery that runs in the central longitudinal axis of the diaphysis. It gives off several branches that extend throughout the marrow. Arterial capillaries in the periphery of the BM cavity feed a branching network of venules and sinusoids. These vessels carry blood to the central vein in the center of the medullary cavity, branching network of venules and sinusoids. These vessels carry blood to the central vein in the center of the medullary cavity, which in adults is filled with fatty tissue (yellow BM) [15]. Hematopoietically active (red) BM in adult long bones lies within porous chambers of spongy bone (diploë) in the epiphysis. Flat bones also contain red marrow in their diploë, which is sandwiched between the compact bone. Studies on corrosion casts from rats have shown that flat bones that are thicker than 0.4 mm contain BM within a dense microvascular network that is anatomically and structurally distinct from the cortical and periosteal microcirculation [16]. These observations are in good agreement with our own studies in murine skull [17].

Electron microscopic observations have contributed significantly to our understanding of the histological organization of the BM microvasculature. Doan, studying pigeon BM, introduced the term venous sinusoid for the extensively distributed wide venous capillaries that form much of the microvascular bed of the marrow [18]. The walls of sinusoids in mature BM are trilaminar [15, 19, 20]. The luminal layer consists of so-called lining or littoral cells, a type of endothelium. Sites of attachment between adjacent lining cells often overlap or interdigitate. The putative function of these cells is to provide a selective barrier between BM and blood. The basement membrane is the medial layer in the sinus wall. It is an irregular, discontinuous membrane that may be absent for long stretches. This and the absence of tight junctions between endothelial cells are thought to facilitate sinusoidal dilatation in highly active BM [1]. The outer surface of the sinusoidal wall is formed by a discontinuous layer of adventitial cells that have more phagocytic properties than lining cells and can accumulate a substantial amount of fat. Migration of hematopoietic cells through the sinusoidal wall is a two-way process that was described to occur not only through intercellular junctions, but through intracellular pores as well [15, 19].

There is considerable knowledge about BM morphology and histology, but much less is known about the dynamics of the BM. Interpreting BM physiology or pathology merely on the basis of histological examination of smears or sections is often tentative. Some insights have been gleaned from long-term BM cultures [21], which allow direct examination of hematopoietic BM cells in close physical association with a heterogeneous adherent stromal layer. However, the extent to which this in vitro assay is representative of the many functions of the BM in situ remains to be defined. For instance, in vitro culture assays lack a functional microvasculature. Thus, these assays provide few insights into the mechanisms of cellular migration from the BM into the circulation and vice versa.

THE BM AS A TARGET FOR CIRCULATING HEMATOPOIEITIC PROGENITOR CELLS (HPC)

In particular, the mechanisms that guide circulating HPC into the BM are clinically significant because the success of stem cell transplantation depends on efficient seeding of grafted cells in a recipient's BM. It is due to this homing of transplanted cells that BM transplantsations can be performed by simple intravenous infusion, rather than requiring invasive surgery, as is the case with the transplantation of any other organ. Homing of HPC can be defined as the set of molecular interactions that allows circulating HPC to recognize, adhere to, and migrate across BM endothelial cells and results in the accumulation of HPC in the unique hematopoiesis-promoting microenvironment of the BM. Homing of progenitor cells can be conceived as a multi-step phenomenon. HPC arriving in the BM must first interact with the luminal surface of BM endothelium. This interaction must occur within seconds after the HPC has entered the BM microvasculature and provide sufficient mechanical strength to permit the adherent cell to withstand the shear force exerted by the flowing blood. Adherent HPC must then pass through the endothelial layer to enter the hematopoietic compartment. After extravasation, HPC encounter specialized stromal cells whose juxtaposition supports lineage-specific HPC differentiation, proliferation, and maturation, a process that involves stroma-derived cytokines and other growth signals [8]. These processes are strictly regulated in the hematopoietic microenvironment. Some of the molecular mechanisms of HPC-stromal cell interaction have been examined in detail. However, due to the anatomical inaccessibility of BM microvessels in most species little has been known until recently about the actual homing process that occurs at the interface between the extra- and intravascular compartments.

INTRAVITAL MICROSCOPY OF BM TISSUE

It would thus appear that microscopic examination of the living BM in situ might be a useful tool in the investigation of the relationship between blood-borne cells and the vessel wall. Early attempts date back to the period between 1959 and 1971 when several techniques for intravitral microscopy of regenerating BM in situ were devised in rabbits [1, 22, 23]. These methods generate a narrow BM window by removing parts of the periosteum and bone from a rabbit fibula and/or tibia [1]. A metallic chamber is then implanted that permits chronic microscopic examination of living BM in situ [23]. These methods are associated with considerable trauma to the bone and BM. Secondary events such as changes in cytokine production and/or expression of endothelial surface adhesion molecules or toxic effects from metallic implants could be triggered by these procedures. Thus, it is unclear whether the
observations obtained by these techniques represent the normal state of affairs. Moreover, each of these models has been described in rabbits, and the limited availability of neutralizing antibodies and other molecular tools in this species constrains the extent of experimental manipulations.

Recently, we have developed a new method that allows the direct microscopic observation and quantitative analysis of blood cell adhesion in physiologically perfused BM of anesthetized mice [17]. We exploited the fact that the thin flat bones that form the skull’s calvaria are sufficiently transparent to allow the visualization of hematopoietic tissue. The scalp of anesthetized young adult mice was incised in the midline and the frontoparietal skull was exposed while carefully avoiding damage to the bone tissue. The head was fixed in a stereotactic holder and a plastic ring was inserted in the skin incision to spread the skin and allow application of physiological saline solution to avoid drying of the tissue (Fig. 1). Areas in the skull that contain BM could be macroscopically identified by their red color. They contain a branching microvascular network, localized primarily in the parasagittal region. Fluorescent circulating cells in these vessels can be visualized by stroboscopic epifluorescence microscopy. For injection of fluorescent cells, a catheter was inserted into the right common carotid artery and advanced to allow injections into the aortic arch. This route reduces the number of cells needed for experiments because it avoids trapping of fluorescent cells in the pulmonary circulation (which would be inevitable with intravenous injections) and permits microscopic observation of cells during their first passage through the left cranium.

MICROVASCULAR ORGANIZATION AND HEMODYNAMICS OF THE MURINE SKULL BM

To enhance the visibility of the BM microcirculation, we intravenously injected fluorescein isothiocyanate (FITC)-dextran, an inert plasma marker that remains strictly confined to the intravascular compartment and facilitates measurements of luminal dimensions [24] (Fig. 2). The organization of the vasculature in murine skull BM has some parallels to that of long bones [15]. The most prominent vessel is a macroscopically detectable large collecting venule (BMCV, equivalent to the central longitudinal vein in long bones). This venule collects blood from the postransverse venules (BMPS), intermediate venules (BMIT), and sinusoids. In most preparations, the BMCV drains into the superior sagittal sinus, but blood flow in this vessel can occasionally be directed toward the temporal region. In contrast to venules and sinusoids, arterioles are rarely detectable in this preparation. Most arterioles appear to originate from deeper vessels close to the sagittal suture or the temporal bone.

The space lying between and around these venules and sinusoids is occupied by hematopoietic tissue that contains HPC at a similar frequency as the femoral BM [17]. On injection of the low-molecular-weight fluorophores rhodamine 6G or rhodamine 123, a marked accumulation of these nuclear dyes can be seen in the parasagittal regions of the frontoparietal bones around some, but not all, vessels (Fig. 3). This rhodamine distribution indicates anatomically confined conglomerations of metabolically active cells (both reagents preferentially stain mitochondria) and are unique to the skull. Bone venules (BV) do not acquire such a halo of extravasated rhodamine. BV are also distinct from BM microvessels in several other aspects: they have relatively few branches and are typically longer and more regularly shaped.

To assess BM microhemodynamics, fluorescently labeled murine erythrocytes were injected intra-arterially and their velocity in BM and BV was determined by off-line video analysis as previously described [24]. The basic hemodynamic parameters are presented in Table 1. The calculated values (i.e., \(V_{\text{blood}}, \text{wall shear rate}, \text{and blood flow}\)) given in Table 1 are approximations based on idealized formulas that are likely to slightly underestimate the actual hemodynamic conditions encountered by circulating cells. Nevertheless, our results indicate that the average hydrodynamic shear in BM microvessels in the skull is lower than in most other organs (Table 2). Using the same measurement technique in other murine tissues, we have shown previously that the average wall shear rate is higher in the cremaster muscle (5.6-fold), subiliac lymph node (3.3-fold), skin (3.9-fold), and Peyer's patch (13.5-fold). Similarly, published data from rabbit BM [1] confirm the presence of low wall shear rates in BM microvessels compared with postcapillary vessels in other rabbit tissues such as the mesentery [25].

MOLECULAR MECHANISMS OF HPC ADHESION IN BM MICROVESSELS

Although the low shear rates in the BM are likely to facilitate HPC adhesion, the frequency of interactions between circulating cells and the vessel wall depends not as much on hemodynamic properties of these vessels as on endothelial adhesiveness. This was evident when we tested the adhesive behavior of FDCP-mix cells, a murine cell line with HPC-like properties [26]. Only BM venules and sinusoids, but not BV,
supported FDCP-mix cell rolling despite comparable hemodynamic conditions (Table 1).

Studies on mature leukocytes in the microcirculation of a number of other organs have demonstrated that cells must undergo a sequence of distinct adhesion steps to accumulate in a tissue. In most vascular beds, one (or more) of the three members of the selectin family (CD62) and their counter-receptors allow flowing cells to tether and subsequently roll along the vessel wall [27]. This first step mediates close contact with chemoattractants that may diffuse into the vessel lumen from the extravascular space or may be generated by and displayed on the surface of the endothelium. Chemoattractants then induce an intracellular signaling cascade, which leads to activation of integrin adhesiveness. Activated integrins bind to their counter-receptors on endothelial cells and mediate firm adhesion of the rolling cell [28, 29]. Using the aforementioned new approach, neutralizing antibodies and genetically manipulated mice, we showed that HPCs undergo a similar process to adhere to microvessels in the BM [17].

Rolling of FDCP-mix cells and murine HPC does not involve L-selectin (which is expressed on most circulating leukocytes and some HPC), but is partially reduced in wild-type mice treated with antibodies to P- and E-selectin and in mice that are deficient in these two selectins. Remarkably, a significant fraction of HPC can undergo rolling interactions in BM in a selectin-independent fashion [17]. This is almost completely mediated by the $\alpha_4\beta_1$-VCAM-1 pathway. Indeed, several studies have shown that VCAM-1 is constitutively expressed on BM endothelial cells [17, 30, 31]. Others have demonstrated the presence of E-selectin on resting BM endothelial cells [31, 32]. Our data strongly suggest that P-selectin is constitutively expressed in BM venules and sinusoids as well [17]. These molecules are rarely expressed on endothelial cells in the absence of inflammatory stimulation in other organs. Constitutive expression of VCAM-1 in rat peripheral lymph node high endothelial venules [33] and of E- and P-selectin in murine skin vessels [34, and L. H. Ulfman, G. Cheng, J. B. Lowe, and U. H. von Andrian, unpublished results] have been described. However, the BM is the only known organ where these three adhesion molecules are simultaneously expressed and functional in the same non-inflamed vascular bed. This tissue-restricted combination of constitutively expressed adhesion molecules may be a critical feature for the selective recruitment of distinct subsets of circulating cells to the BM (Fig. 4). Thus, the combination of the two endothelial selectins and VCAM-1 is analogous to the vascular addressins, MAdCAM-1 and peripheral node addressins (PNAd), which are critical for the tissue-specific homing of lymphocytes to gut-associated lymphatic tissues and lymph nodes, respectively [35].

We noticed that even in mice that were genetically deficient
in both endothelial selectins rolling was not completely abolished after administration of anti-VCAM-1 or anti-α4 mAb, indicating that other adhesion pathway(s) could make a minor contribution. It is interesting that a recent study indicates that CD44 contributes to homing of some HPC to the BM [36]. CD44 on activated T cells has been shown to mediate rolling on immobilized hyaluronate [37]. However, it is not known whether hyaluronate is expressed in BM vessels or whether CD44 on HPC can mediate rolling on hyaluronate. Also, the homing experiments that have identified a role for CD44 do not allow a distinction between intra- and extravascular events. Thus, it remains to be determined whether CD44 binding to BM endothelial cells constitutes a fourth rolling pathway. Alternatively, CD44 could be important during HPC migration, proliferation, or survival. Other proteins have been reported to participate in homing. HPCs have been shown to express a lectin-like membrane protein with specificity to galactosyl and mannosyl moieties, which mediates recognition of stromal cells by HPC [38]. Histological staining has also defined a subset of HPC that express binding sites for ubiquitin. It has been suggested that ubiquitin may be involved in homing of HPC to spleen and in vitro assays indicate that ubiquitin can mediate HPC adhesion to BM stromal cell cultures [39].

**PHYSIOLOGICAL SIGNIFICANCE OF BM-SPECIFIC ENDOTHELIAL ADHESION PATHWAYS**

Homing of circulating blood cells to the BM is a key event not only in BM transplantation, but also for seeding of the BM during fetal development. Studies in sheep and mice have shown that hematopoiesis in the BM occurs only after birth, whereas fetal blood is generated in the yolk sac, fetal liver (FL), and aorta-gonads-mesonephros region [40–42]. In the mouse, pluripotent circulating HPC begin to colonize the nascent BM before day 14 of gestation [42]. In embryos as well as in adults constitutively expressed endothelial selectins and VCAM-1 may function as a safeguard to provide continuous access for circulating HPC to the BM. This abundance of adhesion pathways could explain why hematopoiesis is successfully established in mice genetically deficient in P- and/or E-selectin or their fucosylated ligands, in animals that express a hypomorphic VCAM-1 mutant, and in chimeric mice that lack α4 integrins on hematopoietic cell subsets [32, 43–45].

It seems possible (but remains to be demonstrated) that other circulating cells such as the mature lymphocyte subsets that home to the BM can make use of the same adhesion pathways as HPC. Indeed, functional selectin ligands and/or α4 integrins can be found on many lymphoid and myeloid cells [27, 29]. However, not all cells that possess this composition of adhesion

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**TABLE 1.** Dimensions and Hemodynamic Parameters of BM and Bone Microvessels

<table>
<thead>
<tr>
<th>Parameters</th>
<th>BM CV</th>
<th>BM sin.</th>
<th>BM PSV</th>
<th>BM IV</th>
<th>BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n of venules</td>
<td>16</td>
<td>14</td>
<td>5</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Diameter (µm)</td>
<td>51.7 ± 22.9 (27.4–99.7)</td>
<td>41.9 ± 10.8 (21.9–60.2)</td>
<td>56.2 ± 11.9 (47.6–74.8)</td>
<td>28.8 ± 9.1 (17.0–50.4)</td>
<td>21.6 ± 7.9 (13.7–36.8)</td>
</tr>
<tr>
<td>VRBC (µm/s)</td>
<td>525 ± 293 (120–1220)</td>
<td>418 ± 126 (255–731)</td>
<td>508 ± 190 (385–842)</td>
<td>196 ± 153 (88–750)</td>
<td>222 ± 124 (75–385)</td>
</tr>
<tr>
<td>VBlood (µm/s)</td>
<td>573 ± 357 (149–1585)</td>
<td>455 ± 158 (227–834)</td>
<td>540 ± 192 (351–847)</td>
<td>197 ± 150 (85–741)</td>
<td>266 ± 108 (91–384)</td>
</tr>
<tr>
<td>WSR (s⁻¹)</td>
<td>91.7 ± 43.6 (23.7–167.9)</td>
<td>91.4 ± 36.9 (50.5–164.8)</td>
<td>76.9 ± 19.9 (54.5–98.1)</td>
<td>56.9 ± 33.6 (15.2–130.6)</td>
<td>98.6 ± 38.5 (53.3–144.9)</td>
</tr>
<tr>
<td>Blood flow (nL/s)</td>
<td>1.03 ± 1.2 (0.08–4.44)</td>
<td>0.43 ± 0.27 (0.08–1.14)</td>
<td>0.94 ± 0.78 (0.42–2.32)</td>
<td>0.12 ± 0.21 (0.02–0.92)</td>
<td>0.08 ± 0.08 (0.008–0.25)</td>
</tr>
<tr>
<td>RFDCP (%)</td>
<td>14.1 ± 11.6 (1.6–64.0)</td>
<td>23.4 ± 17.7 (0–80)</td>
<td>12.0 ± 11.2 (0–42.9)</td>
<td>36.2 ± 17.0 (10.9–64.3)</td>
<td>1.4 ± 3.3 (0–10.3)</td>
</tr>
</tbody>
</table>

The predominant direction of blood flow in these vessels is shown in Figure 2 (left panel). VRBC, mean red blood cell velocity; VBlood, mean blood flow velocity; WSR, wall shear rate; RF, rolling fraction of FDCP-mix cells, i.e. the percentage of interacting cells in the total flux of interacting and non-interacting cells passing through individual vessels. Numbers shown are arithmetic mean ± so; ranges are shown in parentheses.
molecules appear to accumulate in the BM, indicating that additional factors play a role. This is not surprising because it has been well documented that a cell’s ability to undergo rolling interactions alone is not sufficient for homing [24, 25]. The rolling cell must encounter an activating stimulus that triggers the rapid activation of integrins that can provide sufficient mechanical stability to arrest the cell, even in the presence of high shear flow. The selectivity in subset recruitment to the BM could be explained if organ-specific chemoattractant/activation signals were generated within the BM microenvironment. These signals could provide the optimal conditions for high-affinity interactions of HPC with BM endothelium, and for their subsequent extravasation and lodging within lineage-specific stromal niches. Chemokines are promising candidates to provide such signals. For instance, a chemokine secreted by BM stromal cells has been described [46]. This stromal-derived factor (SDF-1α) has activity not only on mature T and B lymphocytes and monocytes [46], but also promotes migration of CD34+ HPC in vitro and in vivo [47, 48]. It is interesting to note that mice that are genetically deficient in SDF-1α or its receptor, CXCR4, have severe defects in FL and BM hematopoiesis [49–51]. This does not exclude the possibility that other chemokine(s) also contribute to the homing or interstitial migration of HPC or other blood cells in the BM.

ROLE OF ENDOTHELIAL SELECTINS AND VCAM-1 IN BM TRANSPLANTATION

As discussed above, the homing of transfused HPC to the BM of lethally irradiated patients is critical for the success of BM transplantation. The experimental conditions that have uncovered a role for P/E-selectins and VCAM-1 in HPC rolling did not include prior irradiation of experimental animals [17]. Therefore, it remains to be determined whether conditioning with chemotherapy or irradiation before BM transplantation changes the molecular mechanisms of HPC seeding of the BM. Irradiation has been shown to up-regulate the expression of VCAM-1 on BM endothelial cells [30] and to induce release of Weibel-Palade bodies containing P-selectin from endothelial cells in culture [52]. Recent studies have shown increased leukocyte rolling in irradiated rat mesenteric venules [53] and up-regulation of E-selectin expression on human umbilical vein endothelial cells [54] shortly after irradiation but there is no
published evidence that irradiation induces increased surface expression of endothelial selectins in the BM. Although the effects of ionizing radiation on endothelial adhesiveness in the BM remain uncertain, it should be noted that the up-regulation of adhesion molecules above the constitutively expressed levels in non-irradiated BM is probably not necessary to allow HPC homing. Indeed, one study has reported a decrease in the accumulation of HPC in the BM shortly after lethal irradiation [55].

It was shown recently that lethally irradiated recipient mice deficient in P- and E-selectin survived poorly compared with wild-type littermates when transplanted with a limited number of BM cells. This high mortality of P-/E-selectin-deficient mice after BM transplantation was due to decreased homing of HPC into the BM, but not due to differences in hematopoiesis per se. Homing to the BM of P-/E-selectin-deficient mice was even more compromised after administration of function-blocking VCAM-1 antibody [56]. These data are in good agreement with our intravital microscopy studies [18] and with a recent report of increased numbers of transplanted progenitor cells in the circulation of lethally irradiated mice after injection of anti-VCAM-1 mAb [57]. However, it is unclear whether irradiation promotes HPC seeding of the BM because of enhanced HPC recruitment from the blood or because of other effects such as an increased accessibility of extravascular sites (niches) that promote HPC survival and hematopoiesis.

CONCLUDING REMARKS

Many factors contribute to the migration of stem and progenitor cells to the BM. A detailed knowledge of these events is important because the kinetics of hematopoietic recovery after HPC transplantation correlate with the efficacy of HPC homing to the BM, particularly when the number of available HPCs is limited. This could be especially important for therapeutic approaches that require highly purified autologous HPCs or transfected HPCs as a treatment for cancer or genetic deficiencies. A thorough understanding of the regulation of key adhesion molecules, cytokines, and chemoattractants that mediate HPC homing may be useful to enhance the success of BM transplantations. Specific conditioning of donor HPCs or a recipient’s BM endothelial cells might further reduce the number of cells necessary for successful engraftment and hematopoietic recovery. Here, we have reviewed recent advances in our ability to dissect the molecular mechanisms of HPC homing to the BM owing to the availability of a novel method that allows intravital microscopy studies of murine BM. This new approach may not only be useful for the analysis of HPC trafficking, but could also serve as a powerful tool to study the migration of the multitude of other cell types that are known to target this enigmatic tissue.

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