J Mol Med (2011) 89:1167–1174
DOI 10.1007/s00109-011-0792-9

REVIEW

MT1-MMP and RECK: opposite and essential roles in hematopoietic stem and progenitor cell retention and migration

Karin Golan · Yaron Vagima · Polina Goichberg · Shiri Gur-Cohen · Tsvee Lapidot

Received: 15 February 2011 / Revised: 12 July 2011 / Accepted: 26 July 2011 / Published online: 13 August 2011

Abstract Migratory capacity is a fundamental property of hematopoietic stem and progenitor cells (HSPCs). This feature is employed in clinical mobilization of HSPCs to the circulation and constitutes the basis for modern bone marrow (BM) transplantation procedures which are routinely used to treat hematological malignancies. Therefore, characterization of new players in the complex process of HSPC motility in steady-state conditions as well as during stress situations is a major challenge. We report that while the metalloproteinase membrane type 1-metalloprotease (MT1-MMP) has an essential role in human HSPC trafficking during granulocyte colony-stimulating factor (G-CSF)-induced mobilization, its inhibitor reversion-inducing cysteine-rich protein with Kazal motifs (RECK) and the adhesion molecule CD44 are required for HSPC retention to the BM in steady-state conditions. The nervous system via Wnt signaling along with HGF/c-Met signaling and the complement cascade play a major role in regulating MT1-MMP increased activity, CD44 cleavage, and RECK-reduced expression during G-CSF-induced mobilization. This review will elaborate on the opposite roles of MT1-MMP and RECK in HSPC migration and retention and suggest targeting them in order to facilitate HSPC mobilization and engraftment upon BM transplantation in patients.

Keywords Stem cells · Bone marrow · MMP · Retention · Mobilization · SDF-1/CXCR4

K. Golan · Y. Vagima · P. Goichberg · S. Gur-Cohen · T. Lapidot (✉)
Department of Immunology, Weizmann Institute of Science, Rehovot, Israel
e-mail: tsvee.lapidot@weizmann.ac.il

Hematopoietic stem and progenitor cell egress and mobilization by G-CSF

Hematopoietic stem and progenitor cells (HSPCs) as well as maturing leukocytes are typically distinguished by their motility capacity and ability to pave their way out from the bone marrow (BM) reservoir to the circulation, as part of host defense and repair mechanisms. HSPCs and maturing leukocytes are continuously released at low levels from the BM during steady-state homeostasis and at increased rates upon stress, such as bleeding or inflammation [1–4]. Current models of cell egress from the BM imply that HSPCs detach from their supporting stromal niches via adhesion interactions, translocate to the blood vessel, and extravasate through the endothelial barrier into the circulation. This multi-step process is orchestrated by a large number of cytokines, chemokines, proteolytic enzymes, as well as adhesion interactions [5, 6] that are all synchronized in parallel or in a reciprocal manner. These dynamic changes in HSPCs and their microenvironment during trafficking are achieved through a complex interplay between the immune and the nervous systems and bone remodeling (osteoblast and osteoclast activities) [1, 2, 7]. For instance, the sympathetic nervous system regulates the steady-state egress of HSPCs in murine, via circadian rhythms peaking 5 hours after the initiation of light and reaching a nadir 5 hours after darkness [8]. The sympathetic nervous system can directly stimulate human HSPC motility and proliferation [9] in addition to its indirect effect on the murine stroma microenvironment [10, 11]. Once HSPCs are found in the circulation, they may enter the spleen and non-lymphatic tissues or migrate back to the BM in a process called "homing". As evident from the experiments with parabiotic mice, which share blood systems, donor peripheral blood HSPCs are cleared within

minutes from the circulation of intravenously transplanted congeneic recipients [12, 13]. HSPC mobilization can be clinically or experimentally induced by a variety of cytokines and chemokines [5, 6]. At present, granulocyte colony-stimulating factor (G-CSF) is the most commonly used agent [14]. The mechanisms of G-CSF-induced mobilization consist of induction of quiescent HSPC proliferation thus increasing progenitor cell pool, accompanied by a decrease in retention of HSPCs in their BM microenvironment [15]. During the 5-day regimen of G-CSF administration, there is an increased release of proteolytic enzymes from BM neutrophils and other myeloid cells, correlating with the peak in HSPC mobilization [16]. Furthermore, following G-CSF administration, stromal cell-derived factor (SDF-1) (CXCL12, a chemokine able to strongly attract human and murine HSPCs [17–21]) levels in the BM are transiently increased followed by their downregulation at both protein [22, 23] and mRNA [24] levels. Thus, G-CSF administration results in proteolytic degradation of BM SDF-1 with subsequent mobilization of HSPCs. Most HSCs are found in contact with stromal cells that highly express SDF-1 within their specialized niches, which induce stem cell quiescence. Therefore, this chemokine is essential for maintaining a lifelong pool of HSCs by controlling the balance between HSC quiescence and self-renewal [25, 26]. SDF-1 downregulation allows quiescent HSCs to proliferate, differentiate, and to be recruited to the circulation.

MT1-MMP and RECK-mediated regulation of cell motility

Matrix metalloproteinases (MMPs) are a subfamily of zinc- and calcium-dependent enzymes, which all share a conserved methionine residue located C-terminal to the zinc ligands [27]. MMPs are implicated in a variety of physiological processes, including wound healing, uterine involution, and organogenesis, as well as in pathological conditions such as inflammatory, vascular and auto-immune disorders, and carcinogenesis [28–31]. While most MMPs are soluble proteins, six of them are membrane-bound MMPs (MT-MMPs). The proper functioning of membrane type 1-MMP (MT1-MMP) is essential for angiogenesis, wound healing, tissue remodeling [32], as well as tumor growth and metastasis [33, 34]. MT1-MMP-deficient mice develop multiple abnormalities due to defects in the remodeling of connective tissue [35, 36]. In accordance, osteogenic cells from MT1-MMP KO mice cannot degrade collagen and do not form bone when transplanted subcutaneously into host immunodeficient mice [35]. In terms of cell motility, MT1-MMP activates pro-MMP-2, which is involved in the invasion of cancer cells and spread of the metastasis [37]. Accordingly, MT1-MMP accumulates at invadopodia, which are specialized ECM-degrading membrane protrusions of invasive cells and thus facilitates tumor invasiveness [38]. Importantly, MT1-MMP is required during human monocyte migration and endothelial transmigration, thereby revealing a key role for MT1-MMP in monocyte recruitment during inflammation [39]. The induction of MT1-MMP activity in human mesenchymal stem cells by inflammatory cytokines promotes directed cell migration across reconstituted basement membranes [40, 41]. In addition to extracellular matrix degradation, MT1-MMP promotes cell invasion and motility by shedding of cell adhesion molecules, such as CD44 [32] and syndecan-1 [42]. Thus, MT1-MMP is considered a key player in cell trafficking by allowing proper migration of various cell types through mechanical barriers. The catalytic activity of MT1-MMP is regulated at the level of transcription as well as secretion by different endogenous activators and inhibitors such as furin, tissue inhibitor of metalloproteinase-1 (TIMP-1), and TIMP-2 [27]. Another inhibitor is a membranal endogenous glycoprotein, named RECK (reversion-inducing cysteine-rich protein with Kazal motifs) [43]. Homozygous RECK-deficient murine embryos die at E10.5 and are characterized by small body size, reduced structural integrity, and frequent abdominal hemorrhage [44]. It has been previously demonstrated that RECK directly inhibits MT1-MMP via protein–protein interactions, subsequently interfering with the pro-MMP-2 activation cascade [45]. The mutual and reciprocal relationship between MT1-MMP and RECK seems to be necessary for regulation of cell motility.

Regulation of the HSPCs motility by MT1-MMP and RECK

Since MT1-MMP and RECK are essential for the motility and blood vessel intravasation of cancer and inflammatory cells, we and others studied their involvement in the trafficking of HSPCs between the BM and peripheral blood. We have found that both MT1-MMP and RECK are expressed on human and murine hematopoietic progenitor cells. Under steady-state conditions, human CD34+ progenitor cells from the peripheral blood express higher levels of MT1-MMP as compared to their BM counterparts, suggesting its involvement in the egress of these cells [46]. Neutralization of RECK activity in steady-state condition induces mobilization of human CD34+ progenitor cells in chimeric mice, emphasizing its role in retention of these cells in the BM [46]. Interestingly, MT1-MMP in mobilized peripheral blood cells is localized to lipid rafts [47], which are enriched in CXCR4, the major receptor for SDF-1 [48]. Since SDF-1 and lately also sphingosine 1-phosphate [49–51] were shown to be potent

chemoattractants of HSPCs, MT1-MMP activity may affect the CXCR4/SDF-1-regulated trafficking of HSPCs. BM-and cord blood-derived mesenchymal stem cells, responsible for the development of stromal cells, also express MT1-MMP [41]. G-CSF-induced mobilization in clinical BM transplantation protocols is accompanied by an increase in MT1-MMP expression [46, 47] and a parallel decrease in RECK protein level on human and murine HSPCs [46]. The dynamic changes in MT1-MMP expression levels correlate with the numbers of mobilized CD34+ progenitor cells in healthy donors, suggesting a clinical relevant role for this molecule [46]. The reciprocal changes in the expression levels of MT1-MMP and RECK induced by G-CSF in human and murine progenitor cells are dependent on the PI3K/Akt pathway and antagonized by the treatment with rapamycin [an inhibitor of mammalian target of rapamycin (mTOR)] [46, 47]. PI3K/Akt pathway is essential for G-CSF-induced mobilization, since its inhibition by administration of rapamycin diminishes the level of HSPCs in the circulation [46], and abnormal PI3K activation interferes with HSPC retention in the BM [52]. In addition, PI3K/Akt signaling is essential for increased MT1-MMP incorporation into membranal lipid rafts and thus for its localization at the cellular migration front during G-CSF-induced mobilization [47]. Additional regulators implicated in G-CSF-induced mobilization are the cytokine hepatocyte growth factor (HGF) and its receptor c-Met, which were shown to play a crucial role in the motility of cancer cells [53]. HGF is increased in the plasma of mice upon treatment with G-CSF, while its receptor c-Met is upregulated on immature HSPCs [54]. The major regulator of c-Met transcription, HIF-1α was increased as well by G-CSF stimulations, correlating progenitor mobilization with an expansion of hypoxic murine BM areas [55]. HGF activates the mTOR pathway, thus inhibiting FOXO3a expression and leading to an increase in the reactive oxygen species (ROS) production during G-CSF-induced mobilization [54]. Accordingly, direct administration of HGF induces mobilization of HSPCs in humans as well as in mice, albeit at a lower level as compared to G-CSF [54, 56, 57]. Similarly to G-CSF, HGF treatment augments MT1-MMP expression on human CD34+ cells, revealing that activation of the HGF/c-Met pathway may contribute to the increase in MT1-MMP expression by G-CSF [56]. Additionally, HSPC mobilization is orchestrated by elements of the complement cleavage cascade, which is activated in the BM during G-CSF-induced mobilization [58]. As evident from the studies in C5-deficient mice, G-CSF-induced mobilization was significantly suppressed in the absence of functional complement system [58]. Activated C5a fragments (anaphylatoxin) decrease CXCR4 expression and chemotaxis toward an SDF-1 gradient of granulocytes and monocytes and promote proteolysis in the BM microenvironment through increased secretion of MMP-9 and expression of MT1-MMP and carboxypeptidase M in mononuclear and polymorphonuclear cells [58, 59]. Finally, HSPC egress and mobilization are affected by circadian oscillations due to the involvement of sympathetic nervous system in the regulation of hematopoietic cell trafficking [8]. G-CSF activation of peripheral noradrenergic neurons induces mobilization of HSPCs through suppression of endosteal bone-lining osteoblasts and reduction in BM SDF-1 levels [10]. However, our lab showed that this regulation is also through a direct effect on HSPCs since treatment with catecholamine increases the motility of normal and mobilized human progenitor cells, correlating with the increased expression of MT1-MMP and the activity of the metalloproteinase MMP-2 [9]. Interestingly, neurotransmitter stimulation activates the canonical Wnt signaling pathway, which mediates the increase in MT1-MMP activity on human CD34+ HSPCs [9].

How do MT1-MMP and RECK inversely regulate HSPC mobilization?

HSPCs are retained in the BM by adhesion interactions with different types of molecules such as: vascular cell adhesion molecule-1, intercellular adhesion molecule, β1 and β2 integrins, and the CD44 receptor [60]. Homing, as well as adhesion of immature human CD34+ cells to the BM microenvironment, depends on CD44 [61]. During G-CSF-induced mobilization, there is a reduction in CD44 membrane levels on BM HSPCs [61]. CD44-deficient mice display increased frequencies of circulating immature colony-forming cells, suggesting the importance of this adhesion molecule in HSPC retention. In accordance, increased activity of MT1-MMP and inhibition of RECK induces CD44 cleavage in the BM [46], implying that MT1-MMP facilitates progenitor cell release at least partly by antagonizing adhesion interactions, such as CD44-mediated retention. In addition, MT1-MMP affects the trafficking of HSPCs by modulating chemotaxis towards SDF-1 [17, 62, 63]. Blocking of MT1-MMP activity reduces SDF-1-induced chemotactic responses of human G-CSF-mobilized peripheral CD34+ cells [46, 47], whereas neutralization of RECK activity enhanced migration of steady-state human BM CD34+ cells via Matrigel. Accordingly, neutralization of MT1-MMP interferes with homing of human G-CSF-mobilized CD34+ cells to the BM of transplanted NOD/SCID mice, and the engraftment potential of BM progenitor cells from MT1-MMP deficient mice is significantly lower [46]. Interestingly, c-Met silencing on leukocytes obtained from the BM of G-CSF-treated mice impairs their ability of chemotaxis towards SDF-1 [54]. Thus, the emerging picture suggests a functional interaction between c-Met and SDF-1 pathways in BM leukocytes via

MT1-MMP regulation of SDF-1 induced migration. In line with the aforementioned data, C5 and C5a complement cleavage fragments are released to the peripheral blood during mobilization and can directly chemoattract granulocytes and monocytes. These myeloid cells in contrast to stem cells are highly enriched in proteolytic enzymes and activated MT1-MMP and are the first cells that egress during mobilization from BM to pave a way for stem cells to follow [59, 64]. Of note, C3 and C3a complement cleavage fragments are also released in BM microenvironment and increase the responsiveness of HSPCs to SDF-1 [65], which is released from the BM to the blood, leading the way of HSPC [21, 23]. In addition, MT1-MMP can facilitate HSPC mobilization to the circulation by modulating MMP-2 and MMP-9 activity. During G-CSF-induced mobilization, there is an increase in the functional expression of MMP-2 and MMP-9 on circulating CD34+ cells comparing to their BM counterparts [66, 67]. RECK downregulates MMP-2 activation and MMP-9 expression in vivo [43, 44]. Accordingly, the inhibition of RECK activation in mice showed increased levels of secreted MMP-2 and MMP-9 [46]. This activation and secretion of MMP-2 and MMP-9 during G-CSF administration were found to be dependent on MT1-MMP activation [47].

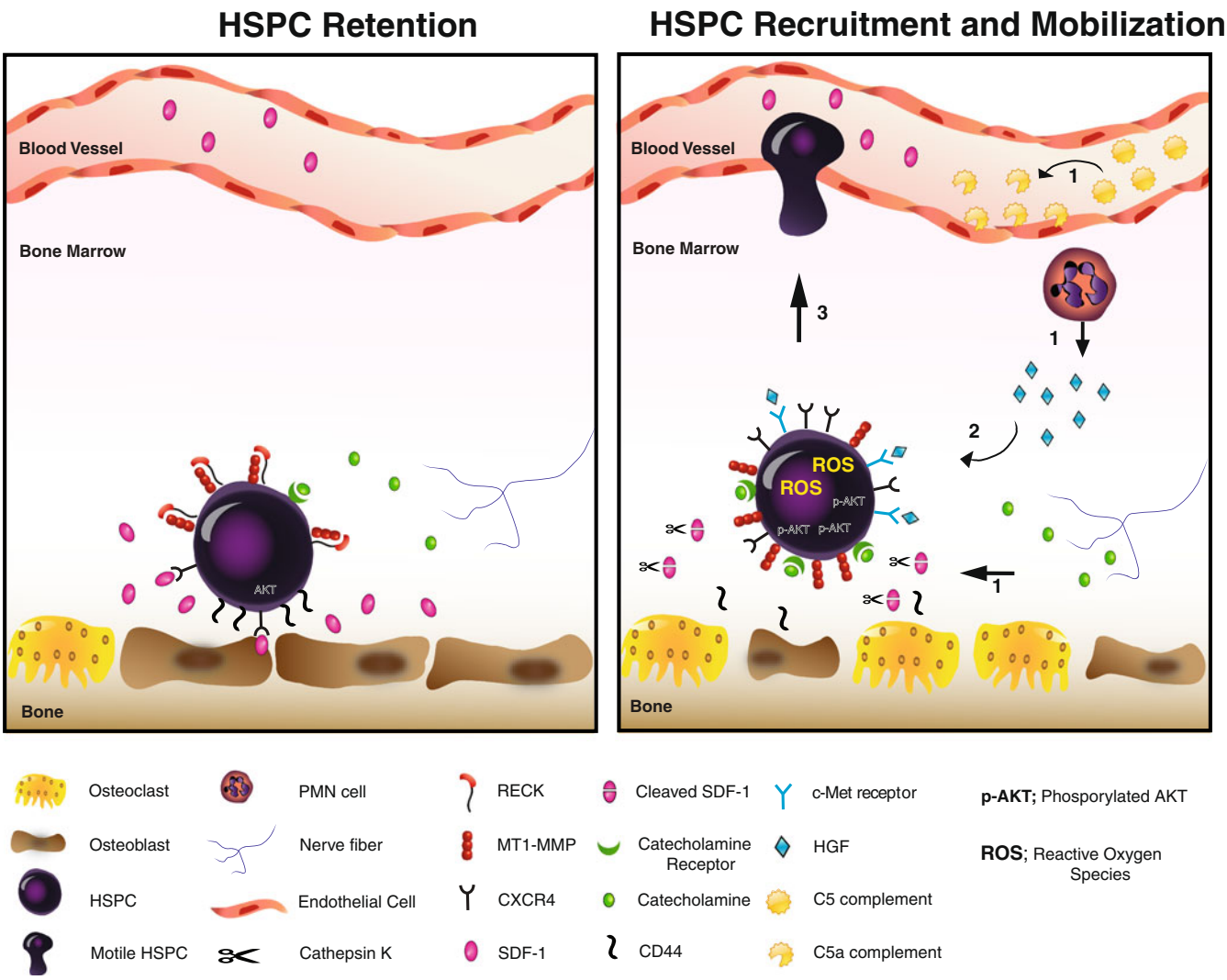

Fig. 1 MT1-MMP and its inhibitor RECK play opposite and essential roles in retention and mobilization of HSPCs. *1* G-CSF administration promote catecholamine secretion from the sympathetic nervous system as well as HGF secretion from PMN cells in the BM and activation of the complement cascade in the blood. *2* HGF binds to its receptor, c-Met, and activates the PI3K/Akt pathway, subsequently leading to ROS production. As a result of *steps 1* and *2*, MT1-MMP activation and RECK inhibition are induced in HSPCs, leading to cleavage of the adhesion molecule CD44 and detachment of HSPCs from stromal cells. *3* In parallel, MT1-MMP activity leads to increased motility of HSPCs towards SDF-1 which leads their way into the blood

Clinical aspects and future directions

The mobilization of HSPCs into the circulation constitutes the basis for modern BM transplantation procedures, which are routinely used to treat patients with hematological malignancies as well as inherited genetic disorders. Therefore, characterization of new regulators of HSPC development and mobilization in homeostasis and during stress became a major focus in the last decades. As MT1-MMP plays an essential role in motility while its inhibitor RECK plays an important role in retention, they both may become prime candidates for future clinical trials aimed at improving HSPC clinical mobilization in patients. Notwithstanding the foregoing, MMPs also play an important role in tumor invasion and metastasis [68, 69] and in particular MT1-MMP was found to have an essential role in the invasive capacity of acute myeloblastic leukemia (AML) cells [70]. The frequency of extramedullary infiltration (EMI) in AML is reported to be up to 40% and is most prevalent in the myelomonoblastic and monoblastic subtypes of AML. EMI patients have lower complete remission rates following induction chemotherapy and a shorter overall survival [71–74]. Therefore, clinical inhibition of MT1-MMP by drugs or neutralizing antibodies in addition to RECK activation in patients with AML or other types of cancer might be an important way to inhibit cancer cell invasiveness and subsequent metastasis formation [75, 76]. In summary, MT1-MMP and RECK are essential for the motility of HSPCs versus retention conditions respectively. During G-CSF-induced mobilization, there is a parallel increase in MT1-MMP and decrease in RECK levels on progenitor cells through the activation of PI3K/Akt pathway. The sympathetic nervous system as well as HGF and its receptor c-Met and also the complement system were all shown to have an important role in the regulation of MT1-MMP and RECK activity (Fig. 1, *step 1*). The HGF/c-Met axis activates PI3K/Akt pathway, leading to increased MT1-MMP activity and decreased RECK levels, both mediating the cleavage of the adhesion molecule CD44 to promote progenitor cell detachment from their BM niches (Fig. 1, *step 2*). Moreover, MT1-MMP and RECK promote the motility of HSPCs and chemotaxis towards SDF-1 thus increasing their migration to the blood (Fig. 1, *step 3*). Future directions in the study of MT1-MMP and RECK role in HSPC egress and mobilization must focus primarily on the molecular aspect of their activation. Though it was previously established by our group that the PI3K/Akt pathway plays an important role in this process, it is still unknown which downstream activators and transducers facilitate MT1-MMP and RECK upregulation both on the transcription and protein levels. In accordance, it is important to find whether MT1-MMP and RECK are both upregulated by the same molecular pathway or by different pathways and whether there is a mutual regulation between those two factors. Since the nervous system has an essential role in the trafficking of HSPCs, the cross talk and regulation of MT1-MMP and RECK by the sympathetic nervous system should be examined. In particular, it would be of great interest to identify a possible circadian oscillation rhythm in the expression of MT1-MMP and RECK on stem and progenitor cells which may correlate to the level of egress as previously described regarding SDF-1 levels in the BM [8]. Nevertheless, the molecular mechanism by which the sympathetic nervous system directly regulates the levels of MT1-MMP and RECK [9] during G-CSF-induced HSPC mobilization would be of great interest for future studies. We conclude by emphasizing that MT1-MMP and its inhibitor RECK play an essential role in HSPC retention versus mobilization from the BM to the peripheral blood.

References

1. Lapidot T, Kollet O (2010) The brain-bone-blood triad: traffic lights for stem-cell homing and mobilization. Hematology Am Soc Hematol Educ Program 2010:1–6
2. Spiegel A, Kalinkovich A, Shivtiel S, Kollet O, Lapidot T (2008) Stem cell regulation via dynamic interactions of the nervous and immune systems with the microenvironment. Cell Stem Cell 3:484–492
3. Hoggatt J, Pelus LM (2011) Many mechanisms mediating mobilization: an alliterative review. Curr Opin Hematol 18:231–238
4. Greenbaum AM, Link DC (2011) Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia 25:211–217
5. Lapidot T, Petit I (2002) Current understanding of stem cell mobilization: the roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. Exp Hematol 30:973–981
6. Nervi B, Link DC, DiPersio JF (2006) Cytokines and hematopoietic stem cell mobilization. J Cell Biochem 99:690–705
7. Kollet O, Dar A, Lapidot T (2007) The multiple roles of osteoclasts in host defense: bone remodeling and hematopoietic stem cell mobilization. Annu Rev Immunol 25:51–69
8. Mendez-Ferrer S, Lucas D, Battista M, Frenette PS (2008) Haematopoietic stem cell release is regulated by circadian oscillations. Nature 452:442–447
9. Spiegel A, Shivtiel S, Kalinkovich A, Ludin A, Netzer N, Goichberg P, Azaria Y, Resnick I, Hardan I, Ben-Hur H, Nagler A, Rubinstein M, Lapidot T (2007) Catecholaminergic neurotransmitters regulate migration and repopulation of immature human CD34+ cells through Wnt signaling. Nat Immunol 8:1123–1131
10. Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA, Frenette PS (2006) Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell 124:407–421
11. Kalinkovich A, Spiegel A, Shivtiel S, Kollet O, Jordaney N, Piacibello W, Lapidot T (2009) Blood-forming stem cells are

nervous: direct and indirect regulation of immature human CD34+ cells by the nervous system. Brain Behav Immun 23:1059–1065
12. Abkowitz JL, Robinson AE, Kale S, Long MW, Chen J (2003) Mobilization of hematopoietic stem cells during homeostasis and after cytokine exposure. Blood 102:1249–1253
13. Wright DE, Wagers AJ, Gulati AP, Johnson FL, Weissman IL (2001) Physiological migration of hematopoietic stem and progenitor cells. Science 294:1933–1936
14. Greenbaum AM, Link DC (2011) Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia 25 (2):211–217
15. Papayannopoulou T, Scadden DT (2008) Stem-cell ecology and stem cells in motion. Blood 111:3923–3930
16. Levesque JP, Takamatsu Y, Nilsson SK, Haylock DN, Simmons PJ (2001) 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 98:1289–1297
17. Peled A, Petit I, Kollet O, Magid M, Ponomaryov T, Byk T, Nagler A, Ben-Hur H, Many A, Shultz L, Lider O, Alon R, Zipori D, Lapidot T (1999) Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4. Science 283:845–848
18. Wright N, Hidalgo A, Rodriguez-Frade JM, Soriano SF, Mellado M, Parmo-Cabanas M, Briskin MJ, Teixido J (2002) The chemokine stromal cell-derived factor-1 alpha modulates alpha 4 beta 7 integrin-mediated lymphocyte adhesion to mucosal addressin cell adhesion molecule-1 and fibronectin. J Immunol 168:5268–5277
19. Dar A, Kollet O, Lapidot T (2006) Mutual, reciprocal SDF-1/CXCR4 interactions between hematopoietic and bone marrow stromal cells regulate human stem cell migration and development in NOD/SCID chimeric mice. Exp Hematol 34:967–975
20. Lapidot T, Kollet O (2002) 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/B2m(null) mice. Leukemia 16:1992–2003
21. Dar A, Schajnovitz A, Lapid K, Kalinkovich A, Itkin T, Ludin A, Kao WM, Battista M, Tesio M, Kollet O, Cohen NN, Margalit R, Buss EC, Baleux F, Oishi S, Fujii N, Larochelle A, Dunbar CE, Broxmeyer HE, Frenette PS, Lapidot T (2011) Rapid mobilization of hematopoietic progenitors by AMD3100 and catecholamines is mediated by CXCR4-dependent SDF-1 release from bone marrow stromal cells. Leukemia doi:10.1038/leu.2011.62
22. Levesque JP, Hendy J, Winkler IG, Takamatsu Y, Simmons PJ (2003) Granulocyte colony-stimulating factor induces the release in the bone marrow of proteases that cleave c-KIT receptor (CD117) from the surface of hematopoietic progenitor cells. Exp Hematol 31:109–117
23. Petit I, Szyper-Kravitz M, Nagler A, Lahav M, Peled A, Habler L, Ponomaryov T, Taichman RS, Arenzana-Seisdedos F, Fujii N, Sandbank J, Zipori D, Lapidot T (2002) G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Nat Immunol 3:687–694
24. Semerad CL, Christopher MJ, Liu F, Short B, Simmons PJ, Winkler I, Levesque JP, Chappel J, Ross FP, Link DC (2005) G-CSF potently inhibits osteoblast activity and CXCL12 mRNA expression in the bone marrow. Blood 106:3020–3027
25. Sugiyama T, Kohara H, Noda M, Nagasawa T (2006) Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 25:977–988
26. Nie YC, Han YC, Zou YR (2008) CXCR4 is required for the quiescence of primitive hematopoietic cells. J Exp Med 205:777–783
27. Hadler-Olsen E, Fadnes B, Sylte I, Uhlin-Hansen L, Winberg JO (2011) Regulation of matrix metalloproteinase activity in health and disease. FEBS J 278:28–45
28. Page-McCaw A, Ewald AJ, Werb Z (2007) Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol 8:221–233
29. Parks WC, Wilson CL, Lopez-Boado YS (2004) Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol 4:617–629
30. Egeblad M, Werb Z (2002) New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2:161–174
31. Nagase H, Visse R, Murphy G (2006) Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 69:562–573
32. Itoh Y, Seiki M (2006) MT1-MMP: a potent modifier of pericellular microenvironment. J Cell Physiol 206:1–8
33. Sato H, Takino T (2010) Coordinate action of membrane-type matrix metalloproteinase-1 (MT1-MMP) and MMP-2 enhances pericellular proteolysis and invasion. Cancer Sci 101:843–847
34. Strongin AY (2010) Proteolytic and non-proteolytic roles of membrane type-1 matrix metalloproteinase in malignancy. Biochim Biophys Acta 1803:133–141
35. Holmbeck K, Bianco P, Caterina J, Yamada S, Kromer M, Kuznetsov SA, Mankani M, Robey PG, Poole AR, Pidoux I, Ward JM, Birkedal-Hansen H (1999) MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. Cell 99:81–92
36. Zhou Z, Apte SS, Soininen R, Cao R, Baaklini GY, Rauser RW, Wang J, Cao Y, Tryggvason K (2000) Impaired endochondral ossification and angiogenesis in mice deficient in membrane-type matrix metalloproteinase I. Proc Natl Acad Sci USA 97:4052–4057
37. Sakr MA, Takino T, Domoto T, Nakano H, Wong RW, Sasaki M, Nakanuma Y, Sato H (2010) GI24 enhances tumor invasiveness by regulating cell surface membrane-type 1 matrix metalloproteinase. Cancer Sci 101:2368–2374
38. Poincloux R, Lizarraga F, Chavrier P (2009) Matrix invasion by tumour cells: a focus on MT1-MMP trafficking to invadopodia. J Cell Sci 122:3015–3024
39. Matias-Roman S, Galvez BG, Genis L, Yanez-Mo M, de la Rosa G, Sanchez-Mateos P, Sanchez-Madrid F, Arroyo AG (2005) Membrane type 1-matrix metalloproteinase is involved in migration of human monocytes and is regulated through their interaction with fibronectin or endothelium. Blood 105:3956–3964
40. Ries C, Egea V, Karow M, Kolb H, Jochum M, Neth P (2007) MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines. Blood 109:4055–4063
41. Son BR, Marquez-Curtis LA, Kucia M, Wysoczynski M, Turner AR, Ratajczak J, Ratajczak MZ, Janowska-Wieczorek A (2006) Migration of bone marrow and cord blood mesenchymal stem cells in vitro is regulated by stromal-derived factor-1-CXCR4 and hepatocyte growth factor-c-met axes and involves matrix metalloproteinases. Stem Cells 24:1254–1264
42. Endo K, Takino T, Miyamori H, Kinsen H, Yoshizaki T, Furukawa M, Sato H (2003) Cleavage of syndecan-1 by membrane type matrix metalloproteinase-1 stimulates cell migration. J Biol Chem 278:40764–40770
43. Takahashi C, Sheng Z, Horan TP, Kitayama H, Maki M, Hitomi K, Kitaura Y, Takai S, Sasahara RM, Horimoto A, Ikawa Y, Ratzkin BJ, Arakawa T, Noda M (1998) Regulation of matrix metalloproteinase-9 and inhibition of tumor invasion by the membrane-anchored glycoprotein RECK. Proc Natl Acad Sci USA 95:13221–13226
44. Oh J, Takahashi R, Kondo S, Mizoguchi A, Adachi E, Sasahara RM, Nishimura S, Imamura Y, Kitayama H, Alexander DB, Ide C, Horan TP, Arakawa T, Yoshida H, Nishikawa S, Itoh Y, Seiki M,

Itohara S, Takahashi C, Noda M (2001) The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis. Cell 107:789–800
45. Noda M, Oh J, Takahashi R, Kondo S, Kitayama H, Takahashi C (2003) RECK: a novel suppressor of malignancy linking oncogenic signaling to extracellular matrix remodeling. Cancer Metastasis Rev 22:167–175
46. Vagima Y, Avigdor A, Goichberg P, Shivtiel S, Tesio M, Kalinkovich A, Golan K, Dar A, Kollet O, Petit I, Perl O, Rosenthal E, Resnick I, Hardan I, Gellman YN, Naor D, Nagler A, Lapidot T (2009) MT1-MMP and RECK are involved in human CD34+ progenitor cell retention, egress, and mobilization. J Clin Invest 119:492–503
47. Shirvaikar N, Marquez-Curtis LA, Shaw AR, Turner AR, Janowska-Wieczorek A (2010) MT1-MMP association with membrane lipid rafts facilitates G-CSF-induced hematopoietic stem/progenitor cell mobilization. Exp Hematol 38:823–835
48. Wysoczynski M, Reca R, Ratajczak J, Kucia M, Shirvaikar N, Honczarenko M, Mills M, Wanzeck J, Janowska-Wieczorek A, Ratajczak MZ (2005) Incorporation of CXCR4 into membrane lipid rafts primes homing-related responses of hematopoietic stem/progenitor cells to an SDF-1 gradient. Blood 105:40–48
49. Ratajczak MZ, Lee H, Wysoczynski M, Wan W, Marlicz W, Laughlin MJ, Kucia M, Janowska-Wieczorek A, Ratajczak J (2010) Novel insight into stem cell mobilization-plasma sphingosine-1-phosphate is a major chemoattractant that directs the egress of hematopoietic stem progenitor cells from the bone marrow and its level in peripheral blood increases during mobilization due to activation of complement cascade/membrane attack complex. Leukemia 24:976–985
50. Golan K VY, Ludin A, Itkin T, Kalinkovich A, Cohen-Gur S, Kollet O, Schajnovitz A, Shivtiel S, Lapidot T (2010) The chemotactic lipid S1P regulates hematopoietic progenitor cell egress and mobilization via its major receptor S1P1 and by SDF-1 inhibition in a p38/Akt/mTOR dependent manner [abstract no. 553]. Blood 116
51. Harun N TM, Juarez JG, Bradstock KF, Bendall LJ (2010) S1P1 Agonists for use as adjunct mobilizing agents [abstract no. 826]. Blood 116
52. Zhang J, Grindley JC, Yin T, Jayasinghe S, He XC, Ross JT, Haug JS, Rupp D, Porter-Westpfahl KS, Wiedemann LM, Wu H, Li L (2006) PTEN maintains haematopoietic stem cells and acts in lineage choice and leukaemia prevention. Nature 441:518–522
53. Trusolino L, Comoglio PM (2002) Scatter-factor and semaphorin receptors: cell signalling for invasive growth. Nat Rev Cancer 2:289–300
54. Tesio M, Golan K, Corso S, Giordano S, Schajnovitz A, Vagima Y, Shivtiel S, Kalinkovich A, Caione L, Gammaitoni L, Laurenti E, Buss EC, Shezen E, Itkin T, Kollet O, Petit I, Trumpp A, Christensen J, Aglietta M, Piacibello W, Lapidot T (2011) Enhanced c-Met activity promotes G-CSF-induced mobilization of hematopoietic progenitor cells via ROS signaling. Blood 117:419–428
55. Levesque JP, Winkler IG, Hendy J, Williams B, Helwani F, Barbier V, Nowlan B, Nilsson SK (2007) Hematopoietic progenitor cell mobilization results in hypoxia with increased hypoxia-inducible transcription factor-1 alpha and vascular endothelial growth factor A in bone marrow. Stem Cells 25:1954–1965
56. Jalili A, Shirvaikar N, Marquez-Curtis LA, Turner AR, Janowska-Wieczorek A (2010) The HGF/c-Met axis synergizes with G-CSF in the mobilization of hematopoietic stem/progenitor cells. Stem Cells Dev 19:1143–1151
57. Kollet O, Dar A, Shivtiel S, Kalinkovich A, Lapid K, Sztainberg Y, Tesio M, Samstein RM, Goichberg P, Spiegel A, Elson A, Lapidot T (2006) Osteoclasts degrade endosteal components and promote mobilization of hematopoietic progenitor cells. Nat Med 12:657–664
58. Reca R, Cramer D, Yan J, Laughlin MJ, Janowska-Wieczorek A, Ratajczak J, Ratajczak MZ (2007) A novel role of complement in mobilization: immunodeficient mice are poor granulocyte-colony stimulating factor mobilizers because they lack complement-activating immunoglobulins. Stem Cells 25:3093–3100
59. Jalili A, Shirvaikar N, Marquez-Curtis L, Qiu Y, Korol C, Lee H, Turner AR, Ratajczak MZ, Janowska-Wieczorek A (2010) Fifth complement cascade protein (C5) cleavage fragments disrupt the SDF-1/CXCR4 axis: further evidence that innate immunity orchestrates the mobilization of hematopoietic stem/progenitor cells. Exp Hematol 38:321–332
60. Prosper F, Verfaillie CM (2001) Regulation of hematopoiesis through adhesion receptors. J Leukoc Biol 69:307–316
61. Avigdor A, Goichberg P, Shivtiel S, Dar A, Peled A, Samira S, Kollet O, Hershkoviz R, Alon R, Hardan I, Ben-Hur H, Naor D, Nagler A, Lapidot T (2004) CD44 and hyaluronic acid cooperate with SDF-1 in the trafficking of human CD34+ stem/progenitor cells to bone marrow. Blood 103:2981–2989
62. Voermans C, Kooi ML, Rodenhuis S, van der Lelie H, van der Schoot CE, Gerritsen WR (2001) In vitro migratory capacity of CD34+ cells is related to hematopoietic recovery after autologous stem cell transplantation. Blood 97:799–804
63. Wright DE, Bowman EP, Wagers AJ, Butcher EC, Weissman IL (2002) Hematopoietic stem cells are uniquely selective in their migratory response to chemokines. J Exp Med 195:1145–1154
64. Lee HM, Wu W, Wysoczynski M, Liu R, Zuba-Surma EK, Kucia M, Ratajczak J, Ratajczak MZ (2009) Impaired mobilization of hematopoietic stem/progenitor cells in C5-deficient mice supports the pivotal involvement of innate immunity in this process and reveals novel promobilization effects of granulocytes. Leukemia 23:2052–2062
65. Ratajczak J, Reca R, Kucia M, Majka M, Allendorf DJ, Baran JT, Janowska-Wieczorek A, Wetsel RA, Ross GD, Ratajczak MZ (2004) Mobilization studies in mice deficient in either C3 or C3a receptor (C3aR) reveal a novel role for complement in retention of hematopoietic stem/progenitor cells in bone marrow. Blood 103:2071–2078
66. Mohle R, Haas R, Hunstein W (1993) Expression of adhesion molecules and c-kit on CD34+ hematopoietic progenitor cells: comparison of cytokine-mobilized blood stem cells with normal bone marrow and peripheral blood. J Hematother 2:483–489
67. Pruijt JFM, Fibbe WE, Laterveer L, Pieters RA, Lindley IJD, Paemen L, Masure S, Willemze R, Opdenakker G (1999) Prevention of interleukin-8-induced mobilization of hematopoietic progenitor cells in rhesus monkeys by inhibitory antibodies against the metalloproteinase gelatinase B (MMP-9). Proc Natl Acad Sci USA 96:10863–10868
68. Choi JH, Han EH, Hwang YP, Choi JM, Choi CY, Chung YC, Seo JK, Jeong HG (2010) Suppression of PMA-induced tumor cell invasion and metastasis by aqueous extract isolated from Prunella vulgaris via the inhibition of NF-kappaB-dependent MMP-9 expression. Food Chem Toxicol 48:564–571
69. Hamsa TP, Kuttan G (2011) Inhibition of invasion and experimental metastasis of murine melanoma cells by Ipomoea obscura (L.) is mediated through the down-regulation of inflammatory mediators and matrix-metalloproteinases. J Exp Ther Oncol 9:139–151
70. Wang C, Chen Z, Li Z, Cen J (2010) The essential roles of matrix metalloproteinase-2, membrane type 1 metalloproteinase and tissue inhibitor of metalloproteinase-2 in the invasive capacity of acute monocytic leukemia SHI-1 cells. Leuk Res 34:1083–1090
71. Creutzig U, Harbott J, Sperling C, Ritter J, Zimmermann M, Loffler H, Riehm H, Schellong G, Ludwig WD (1995) Clinical significance of surface antigen expression in children with acute

myeloid leukemia: results of study AML-BFM-87. Blood 86:3097–3108
72. Ravindranath Y, Steuber CP, Krischer J, Civin CI, Ducore J, Vega R, Pitel P, Inoue S, Bleher E, Sexauer C et al (1991) High-dose cytarabine for intensification of early therapy of childhood acute myeloid leukemia: a Pediatric Oncology Group study. J Clin Oncol 9:572–580
73. Chang H, Brandwein J, Yi QL, Chun K, Patterson B, Brien B (2004) Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. Leuk Res 28:1007–1011
74. Rubnitz JE, Raimondi SC, Halbert AR, Tong X, Srivastava DK, Razzouk BI, Pui CH, Downing JR, Ribeiro RC, Behm FG (2002) Characteristics and outcome of t(8;21)-positive childhood acute myeloid leukemia: a single institution's experience. Leukemia 16:2072–2077
75. Murai R, Yoshida Y, Muraguchi T, Nishimoto E, Morioka Y, Kitayama H, Kondoh S, Kawazoe Y, Hiraoka M, Uesugi M, Noda M (2010) A novel screen using the Reck tumor suppressor gene promoter detects both conventional and metastasis-suppressing anticancer drugs. Oncotarget 1:252–264
76. Suojanen J, Salo T, Koivunen E, Sorsa T, Pirila E (2009) A novel and selective membrane type-1 matrix metalloproteinase (MT1-MMP) inhibitor reduces cancer cell motility and tumor growth. Cancer Biol Ther 8:2362–2370