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Review Article

Advances in Hematopoietic Stem Cell Mobilization and Peripheral Blood Stem Cell Transplantation

Kaveh Tari[1] M.Sc., Arezou Rahimi[2] M.Sc., Amir Atashi[1*] Ph.D., Saeid Abroun[1] Ph.D., Mohammad shahjahani[1] Ph.D., Ali Jalili[3] Ph.D.

[1]Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.
[2]Department of Immunology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Department of Immunology & Hematology, Faculty of Medicine, Kurdistan University of Medical Sciences Sanandaj, Iran.

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Hematopoietic stem/progenitor cells (HSPCs) which give rise to different blood cell types are present within the bone marrow microenvironment, especially in flat bones such as skull, vertebrae, pelvis and chest. Interacting factors such as stromal derived factor-1/CXCR4, very late antigen-4/vascular cell adhesion molecule-1, Lymphocyte function-associated antigen-1/ intercellular adhesion molecule-1 retain the cells in the microenvironment. Any factor affecting these links may lead to migration and mobilization of HSPCs into peripheral blood. Several factors are involved in hematopoietic stem cells (HSC) mobilization such as granulocyte-colony stimulating factor, sphingosine-1-phosphate, hepatocyte growth factor, complement system, plasminogen system and matrix metalloproteinases. In bone marrow transplantation, HSC is transferred to the recipient from bone marrow of the donor, which can be performed in two ways. In the first method, Jamshidi needle is used for aspiration of bone marrow to extract hematopoietic cells usually from the hip. The second method uses mobilizer factors such as granulocyte-colony stimulating factor and granulocyte-macrophage colony-stimulating factor to mobilize the HSC into peripheral blood. Mobilized hematopoietic stem cells are suitable for the bone marrow transplantation in leukemias such as chronic myeloid leukemia, acute myeloid leukemia, chronic lymphocyte leukemia, Hairy cell leukemia, etc.

* **Corresponding Author:** Department of Hematology, Faculty of Medical Sciences, Tarbiat Modarres University, Tehran, Iran. **Email:** Atashia@modares.ac.ir, **P.O.Box**: 14115-331.

Introduction

Bone marrow (BM) is composed of two parts known as osteoblastic and vascular microenvironments. The mobilization of hematopoietic stem and progenitor cells (HSPCs) from bone marrow into the blood circulation has been used for bone marrow transplantation [1]. HSPCs residing in BM are released from their niches and circulate under steady-state conditions at detectable levels in the peripheral blood, and their number increases in response to systemic or local inflammation, strenuous exercise, stress, tissue/organ injury and pharmacological agents. The mobilization process has been postulated to be directed by a number of factors, including a decrease in SDF-1–CXCR4 and very late antigen (VLA)-4-vascular cell adhesion molecule (VCAM)-1 interactions in BM microenvironment due to release of proteolytic enzymes or after molecular blockade by administration of small molecule CXCR4 or VLA-4 antagonists, release of neurotransmitters from synapses of the nerves innervating the BM microenvironment (for example, those involving the dopamine and β2-adrenergic receptors), reversal of the trans-endothelial chemotactic gradient between the BM microenvironment and plasma, activation of the plasminogen system and the complement cascade (ComC) [2-6].

Hematopoietic cells form a small percentage (0.01 to 0.05%) of PB cells, which are increased under the influence of several growth factors. Although the mechanism is not well understood, hematopoietic stem cells are recognized to be released into the bloodstream in response to pharmacological agents, physical and environmental factors such as stress and physiological factors [7]. Today, mobilization of hematopoietic stem cells into the peripheral blood is used for the bone marrow transplantation [8, 9]. granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can be applied to mobilize the hematopoietic cells [10, 11]. Among other factors involved in hematopoietic cell mobilization, chemokines, adhesion molecules such as integrins, and metalloproteinases can be mentioned [12, 13].

Definition of mobilization

The forced migration of HSPC from BM into peripheral blood is called mobilization. Mobilization is considered from a clinical point of view as a procedure that allows for HSPC collection [14]. HSPCs in peripheral blood can be utilized in autologous and heterologous bone marrow transplantation. Traditionally, bone marrow stem cells have been collected and injected into patients for bone marrow transplantation, though this method is regarded painful. However, today in bone marrow transplantation, HSPCs entering into peripheral blood via mobilization process are the first choice, specifically in autologous transplantation. Use of HSPCs in peripheral blood has been shown to be even better than cord blood HSPCs in bone marrow transplantation. Several factors play a role in

mobilization of HSPCs, including G-CSF, GM-CSF, SDF-1/CXCR4 axis, integrins and chemokines (Table 1) [5, 15-16].

Table 1. Agents and their mechanisms in the HPSC mobilization

Agent	Mechanisms
G-CSF	Induces activation of proteases, inhibition of adhesion molecules and attenuation of CXCR4/CXCL12 signaling.
SDF-1/CXCR4	SDF-1 is the major chemokine involved in HSPC migration, HSPC mobilization via modulation of SDF-1 or its receptor CXCR4.
MMPs	MT1-MMP degrades ECM macromolecules, cytokines, chemokines and adhesion molecules and mediates tumor cell migration. MMPs have been shown to cleave and inactivate SDF-1 and consequently, mobilization.
S1P	Increases the mobilization
HGF	Increases the mobilization
Plasminogen	plasmin-mediated proteolytic mechanisms increase the MMP and cleavage of the CXCR4/CXCL12 axis.
complement system	Modulates the CXCR4/CXCL12 axis

The role of G-CSF in mobilization of HSPCs

G-CSF is a short-lived protein with a half-life of approximately 3.5 hours. G-CSF is the most powerful and the most common agent used in this process. The use of G-CSF in bone marrow transplantation, especially in autologous transplantation, has been approved by Food and Drug Administration in US. Although the functional mechanism of G-CSF is not understood, it presumably augments the initial precursors of myeloid lineage and increases their number in the peripheral blood. Upregulation of CXCR1 and CXCR2 on neutrophils is the second stated mechanism of action for G-CSF [15, 16]. Another possibility is induction of protease secretion from myeloid cells leading to loss of communication between HSPCs and BM stroma [17, 18]. In addition, other mechanisms involved in this process consist of inhibition of macrophage stimulation and downregulation of CXCL12 expression, decrease in the number of B-cells in bone marrow, a change in gradient of chemotactic factors such as sphingosine-1-phosphate (S1P) and CXCL12, degranulation of neutrophils as well as breakdown and inactivation of stromal derived factor (SDF)-1 [19-22]. Humanized and glycosylated recombinant form of G-CSF is called lenogratism, and non-glycosylated form of G-CSF is called neopazen or philgrastim. G-CSF not only induces the mobilization of HSPCs, but also induces the mobilization of immature cells such as stromal mesenchymal and endothelial cells. In addition, G-CSF induces increased hepatocyte growth factor (HGF) in plasma (especially in patients) and its receptor of "C-Met" on HSPCs and myeloid cells, and it is conjectured that mobilization occurs via interaction between HGF and C-Met

[23]. It was also demonstrated that increase in HGF is directly correlated with the number of $CD34^+$ cells in the peripheral blood [24]. The combination of G-CSF and HGF leads to increased secretion of matrix metalloproteinases (MMP)-9 [25]. In addition, G-CSF causes an increase in MMP-9 and MT-1MMP in polymorphonuclear leukocytes as well as mononuclear cells, and increases the number of HSPCs in the peripheral blood [26], augmenting the level of HGF more effectively [25].

Role of SDF-1/CXCR4 in stem cell mobilization

SDF-1 is a member of CXC chemokine family initially identified as a growth factor of precursor B-cells. It binds CXCR4, produced by the stromal cells in bone marrow, which is also known as CXCL12 [5, 6]. It also has the ability to bind to CXCR7, that is the most important chemokine involved in the migration of hematopoietic stem cells [24-27]. Moreover, it seems to be essential regarding circulation and homing of hematopoietic stem cells [28]. Research has also shown that SDF-1 plays a key role in migration of primitive hematopoietic cells from fetal liver to the bone marrow. Reduced level of SDF-1 on the stimulated cells, which indicates the relationship between SDF-1 and CXCR4, plays a key role in blood cell migration [6]. Increased levels of SDF-1 in peripheral blood enhances the migration of the hematopoietic cells into the peripheral blood [5, 29]. Many cytokines and factors are involved in mobilization by regulating and modulating the interaction between CXCR4 and SDF-1; for instance, G-CSF breaks down the connection between SDF-1 and CXCR4 [30]. The use of CXCR4 antagonists induces the migration of hematopoietic cells into peripheral blood [31]. Moreover, a decrease in function of SDF-1 protein in bone marrow is sufficient for hematopoietic cell migration [32]. Based on the above facts, it can be concluded that the relationship between SDF-1 and CXCR4 plays an important role in hematopoietic cell mobilization (Fig. 1).

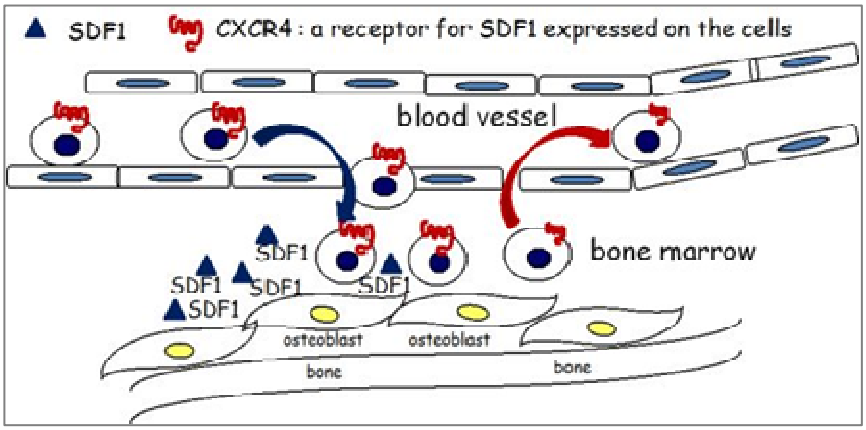

Fig. 1. Role of SDF-1/CXCR4 axis in stem cell mobilization. Stromal derived factor-1 (SDF-1, CXCL12) and its major receptor (CXCR4) play crucial roles in homing and mobilization of hematopoietic stem cells. SDF-1 is expressed on stromal cells in BM niche and binds to its receptor, CXCR4 on hematopoietic stem cells, resulting in homing of the stem cell.

Role of VLA-4 and other adhesion molecules in stem cells mobilization

Integrins are cell adhesion receptors involved in cell-cell and cell-matrix interactions [33], among which VLA-4 can be mentioned which is expressed on hematopoietic cells and bound to its receptor known as VCAM-1, expressed on bone marrow stromal cells. It plays a major role in homeostatic distribution of hematopoietic cells [34]. Homing and mobilization of hematopoietic stem cells depend on the interactions between VLA-4/VCAM and SDF-1/CXCR4. Studies have reported that the use of antibodies against VLA-4 can cause entry of hematopoietic stem cells into peripheral blood [35-37]. Moreover, it has been revealed that mobilized CD34+ cells in the peripheral blood show a lower expression level of VLA-4 compared with the bone marrow $CD34^+$ cells [38, 39]. Hence, VLA-4 on CD34+ hematopoietic cells has a key role in homing and mobilization of hematopoietic stem cells [40, 41]. In addition, it was proposed that applying small molecules against VLA 4 results in approximately 30-fold increase in circulating HSPCs relative to normal hematopoietic cells [42]. CD44 is another adhesion molecule that has effects on stem cell mobilization involved in binding to extracellular components. It is worth mentioning that its defect or use of antibodies against it can lead to stem cell mobilization. Moreover, CD44 is reduced on the mobilized bone marrow cells. Indeed, the use of G-CSF can lead to a decrease in expression of CD44 [43]. Another factor involved in homing and mobilization of stem cells is parathyroid hormone, which increases the calcium concentration in the bone marrow as well as the number of osteoblasts [44].

Role of MMPs in stem cell mobilization

MMPs are a family of over 24 zinc-dependent endopeptidase enzymes responsible for proteolytic processing of ECM structural proteins in various physiological and path-ological processes. MMP-2 and MMP-9 gelatinases preferentially cleave denatured collagens (gelatin), laminin and collagen type IV, which are major constituents of basement membranes [45]. Degradation and functional inactivation of BM extracellular matrix proteins via such proteases as elastase, cathepsin G and MMP-9 are also indicated as a major player in the stem cell mobilization [46]. As their name suggests, MMPs are endoproteinases (matrix-degrading proteases) that actually cause destruction of all components of the extracellular matrix [13]. So far, 24 MMPs have been detected with a similar structure but are different in expression and substrate specificity.

MMPs play an important role in physiological processes such as bone morphogenic determination. They induce mobilization of stem cells to peripheral blood through breakdown of basement membrane in the bone marrow. The most important members are MMP-2 and MMP-9, which are expressed by normal bone cells [26]. Research has shown that $CD34^+$ cells in bone marrow, unlike circulating $CD34^+$ cells, are unable to express MMP-2 and MMP-9; therefore, it can be concluded that increased expression of MMP-2 and MMP-9 on

hematopoietic stem cells results in increased migration of these cells into the peripheral blood [31, 47]. Studies have revealed that one of the CD44 mechanisms in stem cell mobilization is neutrophil degranulation and release of enzymes including MMP-9. MMP-9 destroys SDF-1 as its substrate. In addition, SDF-1 also increases the expression of MMP-9, finally increasing the stem cell mobilization [48]. Furthermore, the use of antibodies against MMP-9 can prevent migration of hematopoietic cells into the peripheral blood; therefore, SDF-1 destruction by MMP-9 is a critical step in stem cells mobilization [23]. It has been demonstrated that MT-1MMP could induce the activation of MMP-2 protein directly leading to the mobilization of hematopoietic cells into peripheral blood [49].

Role of complement system in stem cell mobilization

The complement cascade cleavage fragments, resulted from the activation of complement cascade, seem to be effective on mobilization of HSPCs. complement cascade and innate immunity emerge as important underappreciated modulators of trafficking of HSPC. Research has shown that the complement becomes activated in the bone marrow during G-CSF-induced mobilization by classical immunoglobulin (Ig)-dependent pathway, and C3 cleavage fragments increase the responsiveness of HSPC to an SDF-1 gradient [50].

Evidence has accumulated that the complement system, which is part of innate immunity, may also orchestrate regeneration. Complement becomes activated with the release of C3 cleavage fragments (e.g., C3a, desArgC3a, and iC3b) during tissue/organ injury. Recently, it has been demonstrated that these fragments modulate responsiveness of $CXCR4^+$ stem cells to an SDF-1 gradient. Thus, a high concentration of SDF-1 and C3 cleavage fragments in damaged organs results in the formation of an optimal gradient for chemoattracting the circulating $CXCR4^+$ stem cells [51].

In one study, mobilization was induced with G-CSF in both C3-deficient (C3-/-) and C3a receptor-deficient (C3aR-/-) mice as well as in wild-type mice in the presence or absence of a C3aR antagonist, i.e. SB 290157. The study findings indicated that G-CSF-induced mobilization in C3-/- and C3aR-/- mice was significantly accelerated compared with wild-type mice and enhanced G-CSF-induced mobilization in wild-type but not in C3-/- or C3aR-/-mice treated with SB 290157 as well as deposition of C3b/iC3b fragments onto the viable bone marrow cells of G-CSF-treated animals (52). Jalili et al. have proposed that C5 cleavage fragments are strong chemoattracts for granulocytes, promoting their egress into arrow blood, which is crucial for subsequent mobilization of HSPC. They can induce a highly proteolytic microenvironment in the human BM, which perturbs retention through the CXCR4/SDF-1 axis, as well. [53].

Plasminogen system in regulating stem cell mobilization

Activation of the fibrinolytic system is dependent upon conversion of plasma zymogen, plasminogen (Plg), to serine

protease plasmin (Pm) by physiological activators urokinase-type Plg activator (uPA) or tissue-type plasminogen activator (tPA) [54]. Many studies indicate that the Plg system facilitates HPSC mobilization through plasmin-mediated proteolytic mechanisms, by which plasmin inactivates chemotactic cytokines and degrades ECM in BM compartment. Plg activation via administration of tPA promotes cleavage of KitL mediated by MMP-9 secreted from stromal cells, which subsequently enhances HPSC proliferation, differentiation, and mobilization. These data suggest that Plg regulates HPSC function via MMP-9-mediated KitL release [46]. Genetic loss of PAI-1 or plasmin inhibitor α_2-antiplasmin has been found to enhance plasmin generation, increased HPSC mobilization in response to G-CSF, as well as thrombolytic agents such as tenecteplase and microplasmin enhanced HPSC mobilization in mice and humans [55]. It has been demonstrated that Plg is required for G-CSF-induced stem cell mobilization. A recent study has established the interplay between Plg and SDF-1/CXCR4 signals. Furthermore, the interaction of Plg with its cell surface receptors and plasmin activation result in degradation of matrix proteins as well as activation of cytokines. Plg directly binds to ECM, and upon its conversion to plasmin, degrades multiple ECM proteins including fibrin, laminin and fibronectin. Plasmin can also activate other proteases such as MMP-3, MMP-9, MMP-12 and MMP-13 to degrade other matrix components such as collagens [46]. Recent data elucidated a novel mechanism that is to say Plg regulates MMP-9-dependent CXCR4 expression in order to facilitate HPSC mobilization in response to G-CSF [56].

Role of S1P in stem cell mobilization

The S1P families of G protein-coupled receptors regulate essential cellular processes such as proliferation, migration, cytoskeletal organization, and adherents junction assembly as well as morphogenesis. S1P is a breakdown product of sphingomyelin. Five members of this receptor family include S1P (1), S1P (2), S1P (3), S1P (4) and S1P (5), previously referred to as endothelial differentiation gene (EDG)-1, -5, -3, -6 and -8 [57, 58]. HSPCs also express S1P receptor signaling pathway through which their mobilization from non-lymphoid peripheral tissues to draining lymphatics has been shown to enhance. Steady level of S1P in plasma creates a gradient, which continuously attracts bone marrow HSPCs, and is counteracted by HSC interactions within the BM niche. Mechanisms that either weaken the effect of the niche on HSC retention or those that increase HSC attraction to plasma will lead HSC mobilization to the peripheral blood [59,60].

Role of HGF in stem cell mobilization

Hepatocyte growth factor, initially identified as a potent mitogen for mature hepatocytes, is a kringle-containing polypeptide growth factor possessing structural homology with plasminogen. Takai et al. have stated that human BM stromal cells constitutively produce a significant amount of biologically active HGF, which have both motogenic and mitogenic activities [61]. In addition, HGF enhances the formation of burst-forming unit-erythroid and

colony-forming unit-granulocyte erythroid, macrophage, megakaryocyte by BM mononuclear cells in the presence of GM-CSF and erythropoietin. In fact, HGF and SDF-1 are required in regard with effective HSC mobilization and homing to the liver after hepatic resection [62]. Jalili et al. have suggested that G-CSF-mediated HSPC mobilization occurs in part through HGF/c-Met axis in HSPC and myeloid cells, eliciting increased production of matrix-degrading enzymes and subsequently facilitating egress of HSPC [25].

Peripheral blood stem cell (PBSC) transplantation

In the bone marrow transplantation, BM hematopoietic cells are taken from donor BM that is then transferred to a recipient. It can be carried out in two ways. The first method is performed through the aspiration of bone marrow cells with Jamshidi needle normally taken from hip of another person, which is known as allogeneic hematopoietic stem cell transplantation. In the second method, hematopoietic stem cells are mobilized to the peripheral blood using a mobilizer of stem cells such as G-CSF, GM-CSF or MMPs, which can be either the individual's peripheral blood (autologous) or donor's peripheral blood with human leukocyte antigen similar to recipient (allogeneic). Allogeneic hematopoietic stem cell transplantation is treatment of choice for many hematological malignancies [63]. Due to easy collection, PBSC transplantation is widely used in autologous transplantation [64-66].

Autologous or allogeneic granulocyte colony-stimulating factor-mobilized peripheral blood is regarded as an important source of hematopoietic progenitor cells for subsequent transplantation in various hematologic diseases, but the therapeutic success to mobilize sufficient numbers of $CD34^+$ cells is limited in a number of patients, in part because of their refractoriness or poor response to G-CSF [55]. The first bone marrow transplant was performed in 1980, in which the hematopoietic stem cells were mobilized to peripheral blood using a mobilizing agent. The recent IBMRT data report that since 1990, autologous transplantation has been performed more frequently than allogeneic transplantation, and since 1993, transplants from peripheral blood have increased compared to BM transplantations [14]. The idea that PBSC transplantation is superior to BM transplantations and other methods was studied by many researchers. Robbert et al. proposed that individuals who received autologous transplantation of PBSC had faster recovery in both neutrophil and platelet counts compared to autologous and allogeneic bone marrow transplant recipients [67]. Henon et al. indicated that mortality, hospitalization time and cost of PBSCs transplantation were less than bone marrow transplantation, and recovery time in all lineages in the first group was reported shorter than the second one [68]. Moreover, Kessinger et al. demonstrated that transfer of tumor cells was less likely to occur in PBSC transplantation than BM transplantation [69].

Other advantages of PBSC transplantation over BM transplantation include avoiding the general anesthesia, no requirement for patient

hospitalization and reduced risk of contamination with malignant cells [70]. PBSC transplantation bears a higher risk of graft-versus-host reaction due to the large number of T cells [71]. Thus, by 1989, autologous PBSC transplantation was practiced, and in the same year, the first attempt was performed for human leukocyte antigen-identical allogeneic PBSC transplantation at Nebraska Medical Center in Omaha. In this case, mobilizing factors were not used, graft-versus-host reaction was limited to skin, and the patient died after 34 days [72]. In 1994, the second allogeneic PBSC transplant was failed, and the recipient died after 58 days, albeit the mobilizing factors were not used [73]. Ultimately, in 1995, the first successful clinical trial of allergenic PBSC and BM transplant was performed in Anderson Cancer Center [74].

Conclusion

The present study has reviewed several factors involved in stem cell mobilization to the peripheral blood, which are useful in peripheral blood stem cell transplantation. Furthermore, several novel pathways have been described in HSC mobilization, consisting of SDF-1/CXCR4 axis, S1P, VCAM/VLA-4, MMPs and complement cascade. The use of G-CSF-mobilized PBSC has largely replaced BM as a source of stem cells for both autologous and allogeneic stem cell transplantations. The main advantages of PBSC transplantation are low cost, no need for hospitalization, less pain and faster recovery. It should be noted that graft-versus-host reaction is more prevalent in the transplantation of PBSC than bone marrow transplantation due to presence of more T-cells.

Conflict of Interest

Authors declare no conflict of interest.

Aknowledgements

There is no acknowledgement to declare.

References

[1]. Zhang J, Ren X, Shi W, Wang S, Chen H, Zhang B, et al. Small molecule Me6TREN mobilizes hematopoietic stem/progenitor cells by activating MMP-9 expression and disrupting SDF-1/CXCR4 axis. Blood 2014; 123(3): 428-41.

[2]. Borkowska S, Suszynska M, Wysoczynski M, Ratajczak M. Mobilization studies in C3-deficient mice unravel the involvement of a novel crosstalk between the coagulation and complement cascades in mobilization of hematopoietic stem/progenitor cells. Leukemia 2013; 27(9): 928-30.

[3]. Cottler-Fox MH, Lapidot T, Petit I, Kollet O, DiPersio JF, Link D, et al. Stem cell mobilization. ASH Edu. Program Book 2003; 2003(1): 419-37.

[4]. Shirvaikar N, Marquez-Curtis LA, Janowska-Wieczorek A. Hematopoietic stem cell mobilization and homing after transplantation: The role of MMP-2, MMP-9, and MT1-MMP. Biochem Res Int. 2012 Mar 4; 2012.

[5]. Aiuti A, Webb I, Bleul C, Springer T, Gutierrez-Ramos J. The chemokine SDF-1 is a chemoattractant for human CD34+ hematopoietic progenitor cells and provides a new mechanism to explain the mobilization

of CD34+ progenitors to peripheral blood. J Experiment. Med. 1997; 185(1): 111-20.
[6]. Dar A, Kollet O, Lapidot T. 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. Experiment Hemato. 2006; 34(8): 967-75.
[7]. Ross J, Li L. HSC mobilization: new incites and insights. Blood 2009; 114(7): 1283-284.
[8]. Shichinohe H, Kuroda S ,Yano S, Hida K, Iwasaki Y. Role of SDF-1/CXCR4 system in survival and migration of bone marrow stromal cells after transplantation into mice cerebral infarct. Brain Res. 2007; 1183: 138-47.
[9]. Wang Y, Deng Y, Zhou G-Q. SDF-1α/CXCR4-mediated migrationof systemically transplanted bone marrow stromal cells towards ischemic brain lesion in a rat model. Brain Res. 2008; 1195: 104-12.
[10]. Petit I, Szyper-Kravitz M, Nagler A, Lahav M, Peled A, Habler L, et al. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. Nature Immuno. 2002; 3(7): 687-94.
[11]. Watanabe T, Dave B, Heimann D, Lethaby E, Kessinger A, Talmadge J. GM-CSF-mobilized peripheral blood CD34+ cells differ from steady-state bone marrow CD34+ cells inadhesion molecule expression. Bone Marrow Transplant 1997; 19(12): 1175-181.
[12]. Pelus LM, Horowitz D, Cooper SC, King AG. Peripheral blood stem cell mobilization: A role for CXC chemokines. Critic Rev Oncol Hematol. 2002; 43(3): 257-75.
[13]. Ries C, Egea V, Karow M, Kolb H, Jochum M, Neth P. MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: differential regulation by inflammatory cytokines. Blood 2007; 109(9): 4055-63.
[14]. To LB, Haylock DN ,Simmons PJ, Juttner CA. The biology and clinical uses of blood stem cells. Blood 1997; 89(7): 2233-258.
[15]. Greenbaum A, Link D. Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia. 2010; 25(2): 211-17.
[16]. Morris ES, MacDonald KP, Hill GR. Stem cell mobilization with G-CSF analogs: a rational approach to separate GVHD and GVL? Blood 2006; 107(9): 3430-435.
[17]. Jin F, Zhai Q, Qiu L, Meng H, Zou D, Wang Y, et al. Degradation of BM SDF-1 by MMP-9: the role in G-CSF-induced hematopoietic stem/progenitor cell mobilization. Bone marrow transplant. 2008; 42(9): 581-88.
[18]. Papayannopoulou T, Scadden DT. Stem-cell ecology and stem cells in motion. Blood 2008; 111(8): 3923-930.
[19]. Ratajczak MZ, Serwin K, Schneider G. Innate immunity derived factors as external modulators of the CXCL12-CXCR4 axis and their role in stem cell homing and mobilization. Theranostics 2013; 3(1): 3.
[20]. Ratajczak M, Kim C, Wojakowski W, Janowska-Wieczorek A, Kucia M, Ratajczak J. Innate immunity as orchestrator of stem cell mobilization. Leukemia 2010; 24(10):1667-675.
[21]. Schulz C, von Andrian UH, Massberg S. Hematopoietic stem and progenitor cells: their mobilization and homing to bone marrow and peripheral tissue. Immuno Res. 2009; 44(1-3): 160-68.
[22]. Pelus LM. Peripheral blood stem cell mobilization: new regimens, new cells, where do we stand. Curr Opinion hemato. 2008; 15(4): 285.
[23]. Kollet O, Shivtiel S, Chen Y-Q, Suriawinata J, Thung SN, Dabeva MD, et al. HGF, SDF-1, and MMP-9 are involved in stress-induced human CD34+ stem cell recruitment to the liver. J Clinic Invest. 2003; 112(2): 160-69.
[24]. Kucia M, Reca R, Miekus K, Wanzeck J, Wojakowski W, Janowska-Wieczorek A, et al. Trafficking of Normal Stem Cells and Metastasis of Cancer Stem Cells Involve Similar Mechanisms: Pivotal Role of the SDF-1–CXCR4 Axis. Stem cells 2005; 23(7): 879-94.
[25]. Jalili A, Shirvaikar N, Marquez-Curtis LA, Turner AR, Janowska-Wieczorek A. The HGF/c-Met axis synergizes with G-CSF in the mobilization of hematopoietic stem/progenitor cells. Stem cells dev. 2009; 19(8): 1143-51.
[26]. Pelus LM, Bian H, King AG, Fukuda S. Neutrophil-derived MMP-9 mediates synergistic mobilization of hematopoietic stem and progenitor cells by the combination of G-CSF and the chemokines GROβ/CXCL2 and GROβT/CXCL2δ4. Blood. 2004; 103(1):110-19.
[27]. Pusic I, DiPersio J. The use of growth factors in hematopoietic stem cell transplantation. Curr. pharmaceutic design 2008; 14(20): 1950-61.
[28]. Lévesque J-P, 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 clinic invest. 2003; 111(2): 187-96.
[29]. Gazitt Y, Akay C. Mobilization of Myeloma Cells Involves SDF-1/CXCR4 Signaling and Downregulation of VLA-4. Stem Cells 2004; 22(1): 65-73.
[30]. TÖGel F, Isaac J, Hu Z, Weiss K, Westenfelder C. Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury. Kidney Int. 2005; 67(5): 1772-784.

[31]. Delgado MB, Clark-Lewis I, Loetscher P, Langen H, Thelen M, Baggiolini M, et al. Rapid inactivation of stromal cell-derived factor-1 by cathepsin G associated with lymphocytes. Euro J Immuno. 2001; 31(3): 699-707.

[32]. Nervi B, Link DC, DiPersio JF. Cytokines and hematopoietic stem cell mobilization. J Cell Biochem. 2006; 99(3): 690-705.

[33]. Ramirez P, Rettig MP, Uy GL, Deych E, Holt MS, Ritchey JK, et al. BIO5192, a small molecule inhibitor of VLA-4, mobilizes hematopoietic stem and progenitor cells. Blood 2009; 114(7): 1340-343.

[34]. Vermeulen M, Le Pesteur F, Gagnerault M-C, Mary J-Y, Sainteny F, Lepault F. Role of adhesion molecules in the homing and mobilization of murine hematopoietic stem and progenitor cells. Blood 1998; 92(3): 894-900.

[35]. Lee S, Im SA, Yoo ES, Nam EM, Lee M, Ahn JY, et al. Mobilization Kinetics of CD34+ Cells in Association with Modulation of CD44 and CD31 Expression during Continuous Intravenous Administration of G-CSF in Normal Donors. Stem Cells 2000; 18(4): 281-86.

[36]. Moog R. Management strategies for poor peripheral blood stem cell mobilization. Transfu. Apheresis Sci. 2008; 38(3): 229-36.

[37]. Morabito F, Tomaino A, Cristani M, Martino M, Minciullo P, Saija A, et al. 'In vivo'time course of plasma myeloperoxidase levels after granulocyte colony-stimulating factor-induced stem cell mobilization. Transfu Med. 2005; 15(5): 425-28.

[38]. Vose JM, Ho AD, Coiffier B, Corradini P, Khouri I, Sureda A, et al. Advances in mobilization for the optimization of autologous stem cell transplantation. Leukemia Lymphoma 2009; 50(9): 1412-421.

[39]. Papayannopoulou T. Current mechanistic scenarios in hematopoietic stem/progenitor cell mobilization. Blood 2004; 103(5): 1580-585.

[40]. Xie Y, Yin T, Wiegraebe W, He XC, Miller D, Stark D, et al. Detection of functional haematopoietic stem cell niche using real-time imaging. Nature 2010; 466: 1134.

[41]. Zhang J, Niu C, Ye L, Huang H, He X, Tong W-G,et al. Identification of the haematopoietic stem cell niche and control of the niche size. Nature 2003; 425(6960): 836-41.

[42]. Chute JP. Stem cell homing. Curr Opinion Hemato. 2006; 13(6): 399-406.

[43]. Laird DJ, von Andrian UH, Wagers AJ. Stem cell trafficking in tissue development, growth, and disease. Cell 2008; 132(4): 612-30.

[44]. Méndez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, MacArthur BD, Lira SA, et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature 2010; 466(7308): 829-34.

[45]. Yu Q, Chen L, You Y, Zou C, Zhang Y, Liu Q, et al. Erythropoietin combined with granulocyte colony‐stimulating factor enhances MMP-2 expression in mesenchymal stem cells and promotes cell migration. Molecul Med Reports 2011; 4(1): 31-6.

[46]. Gong Y, Hoover-Plow J. The plasminogen system in regulating stem cell mobilization. BioMed Research International 2012 Oct 14; 2012.

[47]. Pruijt JF, Fibbe WE, Laterveer L, Pieters RA, Lindley IJ, Paemen L, et al. Prevention of interleukin-8-induced mobilization of hematopoietic progenitor cells in rhesus monkeys by inhibitory antibodies against the metalloproteinase gelatinase B (MMP-9). Proceed. Nation Academy Sci. 1999; 96(19): 10863-868.

[48]. Heissig B, Hattori K, Dias S ,Friedrich M, Ferris B, Hackett NR, et al. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. Cell 2002; 109(5): 625-37.

[49]. Poincloux R, Lizárraga F, Chavrier P. Matrix invasion by tumour cells: a focus on MT1-MMP trafficking to invadopodia. J Cell Sci. 2009; 122(17): 3015-24.

[50]. Ratajczak MZ, Wysoczynski M, Reca R, Wan W, Zuba-Surma EK, Kucia M, et al. A pivotal role of activation of complement cascade (CC) in mobilization of hematopoietic stem/progenitor cells (HSPC). Curr. Topics Complement II: Springer; 2008: 45-58.

[51]. Ratajczak MZ, Reca R, Wysoczynski M, Yan J, Ratajczak J. Modulation of the SDF-1–CXCR4 axis by the third complement component (C3)—Implications for trafficking of CXCR4< sup>+</sup> stem cells. Experiment. Hemato. 2006; 34(8): 986-95.

[52]. Ratajczak J, Reca R, Kucia M, Majka M, Allendorf DJ, Baran JT, et al. 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 2004; 103(6): 2071-78.

[53]. Jalili A, Shirvaikar N, Marquez-Curtis L, Qiu Y, Korol C, Lee H, et al. 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. Experiment. Hemato. 2010; 38(4): 321-32.

[54]. Castellino FJ, Ploplis VA. Structure and function of the plasminogen/plasmin system. Thromb Haemost. 2005; 93(4): 647-54.

[55]. Tjwa M, Janssens S, Carmeliet P. Plasmin therapy enhances mobilization of HPCs after G-CSF. Blood 2008; 112(10): 4048-50.

[56]. Gong Y, Fan Y, Hoover-Plow J. Plasminogen Regulates SDF-1/CXCR4-mediated Hematopoietic Stem Cell Mobilization by Activation of Matrix Metalloproteinase-9. Arteriosclerosis, thrombosis, vascular Bio. 2011; 31(9): 2035.

[57]. Sanchez T, Hla T. Structural and functional characteristics of S1P receptors. J Cellul Biochem. 2004; 92(5): 913-22.

[58]. Rosen H, Gonzalez-Cabrera PJ, Sanna MG, Brown S. Sphingosine 1-phosphate receptor signaling. Ann Rev Biochem. 2009; 78: 743-68.

[59]. Motabi IH, DiPersio JF. Advances in stem cell mobilization. Blood Rev. 2012; 26(6): 26-78.

[60]. Hopman RK, DiPersio JF. Advances in stem cell mobilization. Blood Rev. 2014; 28(1): 31-40.

[61]. Takai K, Hara J, Matsumoto K, Hosoi G, Osugi Y, Tawa A, et al. Hepatocyte growth factor is constitutively produced by human bone marrow stromal cells and indirectly promotes hematopoiesis. Blood 1997; 89(5): 1560-565.

[62]. Lehwald N, Duhme C, Wildner M, Kuhn S, Fürst G, Forbes SJ, et al. HGF and SDF-1-mediated mobilization of CD133+ BMSC for hepatic regeneration following extensive liver resection. Liver Int. 2014; 34(1): 89-101.

[63]. Moalic V. Mobilization and collection of peripheral blood stem cells in healthy donors: Risks, adverse events and follow-up. Pathologie Biologie 2013; 61(2): 70-74.

[64]. Bensinger WI, Clift R, Martin P, Appelbaum FR, Demirer T, Gooley T, et al. Allogeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: a retrospective comparison with marrow transplantation. Blood 1996; 88(7): 2794-800.

[65]. Körbling M, Anderlini P. Peripheralblood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood 2001; 98(10): 2900-908.

[66]. Bensinger W, Weaver C, Appelbaum F, Rowley S, Demirer T, Sanders J, et al. Transplantation of allogeneic peripheralblood stem cells mobilized by recombinant human granulocyte colony-stimulating factor [see comments]. Blood 1995; 85(6): 1655-658.

[67]. To L, Roberts M, Haylock D, Dyson P, Branford A, Thorp D, et al. Comparison of haematological recovery times and supportive care requirements of autologous recovery phase peripheral blood stem cell transplants, autologous bone marrow transplants and allogeneic bone marrow transplants. Bone Marrow Transplant 1992; 9(4): 277-84.

[68]. Henon PR, Liang H, Beck-Wirth G, Eisenmann J, Lepers M, Wunder E, et al. Comparison of hematopoietic and immune recovery after autologous bone marrow or blood stem cell transplants. Bone marrow Transplant 1992; 9(4): 285-91.

[69]. Kessinger A, Armitage JO, Smith DM, Landmark JD, Bierman PJ, Weisenburger DD. High-dose therapy and autologous peripheral blood stem cell transplantation for patients with lymphoma. Blood 1989; 74(4): 1260-265.

[70]. Koç ON, Gerson SL, Cooper BW, Dyhouse SM, Haynesworth SE, Caplan AI, et al. Rapid hematopoietic recovery after coinfusion of autologous-blood stem cells and culture-expanded marrow mesenchymal stem cells in advanced breast cancer patients receiving high-dose chemotherapy. J Clinic Onco. 2000; 18(2): 307.

[71]. Besalduchg J, Vivancoslo P, Diazfi M ,Moraledag J, Carreras E, Ojeda E, et al. Allogeneic peripheral blood progenitor cell transplantation: analysis of short-term engraftment and acute GVHD incidence in 33 cases. Bone Marrow Transplant 1996; 18: 35-40.

[72]. Kessinger A, Smith D, Strandjord S, Landmark J, Dooley ic stem cells after myeloablative treatment in a patient with acute lymphoblastic leukemia. Bone Marrow Transplant 1989; 4(6): 643-46.

[73]. Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. Blood 2011; 117(24): 6411-416.

[74]. Korbling M, Przepiorka D, Huh Y, Engel H, Van Besien K, Giralt S, et al. Allogeneic blood stem cell transplantation for refractory leukemia and lymphoma: potential advantage of blood over marrow allografts [see comments]. Blood 1995; 85(6): 1659-665 D, Law P, et al. Allogeneic transplantation of blood-derived, T cell-depleted hemopoiet.