Review Article

Homing and mobilization of hematopoietic stem cells

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Abstract

Hematopoietic stem and progenitor cells (HSPCs) are non-stop travelers throughout body in both time and space. Understanding the mechanism of HSPCs homing and mobilization is important to enhance the efficacy at bone marrow transplantation and cellular therapy. Mobilized HSPCs has largely replaced than the use of bone marrow as a source of stem cells for both allogeneic and autologous stem cell transplantation. This review describes the specific factors which play a key role in homing and mobilization of HSPCs, includes SDF-1 and its receptor CXCR4, proteases (MMPs and CPM). Moreover, chemokines inducing rapid HPSCs mobilization would be discussed. In this article we showed that many factors such as adhesion molecules and SDF-1/CXCR4 have critical roles in homing hematopoietic stem cells and G.CSF, MMPs, adhesion molecules and ROS involvement in mobilization of stem cells. According to above, we can be rich the peripheral blood of HSPCS using of this factors and antagonist for this receptors on the osteoblastic cells or/and HSPCs to bone marrow transplant.

Keywords: Homing, Mobilization, Transplant, SDF-1

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Introduction

Hematopoietic stem cells (HSPCs) are distinct cells have been identified by their CD34+ markers on their surface and are predominantly located in the BM microenvironment, which is referred to as their niches (1).The existence of a niche in which HSPCs reside within the BM cavity was proposed more than 30 years ago (2). The BM niche is identified as a local microenvironment , containing different population of cells such as stromal cells, osteoblasts, endothelial cells, adipocytes and fibroblasts (3). There are two kinds of niches for long maintaining of HSPCSs in the BM including the endosteal surface (known as the osteoblast niche) and sinusoidal endothelium (the vascular niche). Mounting evidences revealed later that the BM niche provides not only a static structural support but topographical information and the appropriate physiological cues to control the dynamic balance of HSPCs quiescence, self-renewal, differentiation and apoptosis, as well as HSPC localization and migration (4) (5). It is now apparent that rather than randomly distributed in the BM, HSPCs , are localized along the endosteal surface of bone in close proximity to the osteoprogenitors and osteoblasts and around blood vessels (6). Different

HSPCs subsets are distributed to distinct locations according to their stages of differentiations with the most dormant and primitive HSPCs residing in niche characterized by poor blood perfusion (7). Whereas the endosteal zone is thought to favor the maintenance of cells in an undifferentiated state, the centrally located vascular niche in the BM allows for differentiation .Mobilization is accompanied by a suppression of endosteal osteoblasts, leading to a decreased expression of factors required for retention and self-renewal of HSPCs (8). Furthermore, depletion of endosteal macrophages (osteomacs) form a canopy over mature osteoblasts at sites of bone formation and support osteoblast function to elicit robust mobilization of HSPCs. These data suggest critical role of BM macrophages in the maintenance of endosteal HSPC niches (8). Such nestin+ MSCs express genes involving in HSPCs maintenance and their abrogation would significantly reduce in the number of BM-HSPCs, and their mobilization towards extramedullary sites (8). HSPCs are also retained in niche by adhesion molecules directed at both the levels of cell-to-cell interaction and attachment to ECM components.

2. Homing

2-1.HSPCs homing to Bone marrow niche. HSPC homing is a multistep process in which circulating HSPCs are exposed to signals from chemokines secreted to the local milieu that lead to the activation of surface integrins and firm arresting of HSPC on the endothelium. In the following for transendothelia migration directed by chemokine gradient for HSPC homing process, the tissues should be destroyed; for example BM, spleen, bone marrow barrier and even blood; so several cytokines and chemokines are released to repair the destroyed tissues, so both repairing and homing are significant. There have been numerous reviews about HSPCs homing (9-18).Homing is identified as the early event that lodges and firmly retains HSPCs in the BM prior to their proliferation and expansion (16). Homing occurs when HSPCs are intravenously administered to interact with the micro vascular endothelial cells of the BM, adhere to the vessel wall with sufficient strength to overcome the considerable shear stress exerted by the flowing blood. Finally, HSPCs extravagate across the vascular wall along an SDF-1 gradient generated by osteoblasts in the endostel niche (13, 14). Early on, the homing process was graphically described as the "rolling, crawling and resting" of HSPCs into the marrow stromal space (19). Several studies have already identified the significant contributions of a wide variety of adhesion molecules and their receptors in the mediating cell-to-cell and cell-to-matrix interaction (20, 21). Furthermore, the roles of the SDF-1/CXCR4 axis in the retention of HSPCs in the BM niches were established (22-24). Proteolytic enzymes with degrading ECM components play a critical role in HSPCs homing (25). Further, cytokines such as GM-CSF, IL-3 and SCF by activating VLA-4 and VLA-5 increase the adhesiveness of HSPCs, as well as Flt3-ligand, SCF,IL-3,IL-6 and HGF with up regulation the expression of CXCR4 on HSPCs are factors in the homing of HSPCs (26).

2-2. The role of adhesion molecules in tethering and retaining HSPCs in their niches. A number of adhesion molecules like P-selectin, E-selectin, integrin/ receptor pairs, immunoglobulins and other adhesion receptors mediate the anchoring of HSPCs within the BM (19). Novel non-integrin adhesion receptors have also been identified. For instance, HSPCs were shown to express a glycoform of CD44 known as hematopoietic cell E-/L-selectin ligand, a very potent adhesion molecule that allows blood-borne cells to broke, contact and roll along the endothelium (27). New researches approved the participation of the CD34 Ag in adhesion and/or the likely homing of lympho- hematopoietic progenitors. This has been attributed to the presence of a large number of carbohydrate moieties attached within the extracellular region that provide antigenicity and attaining the mucin-like structure of an adhesion molecule (28). Moreover it was reported that adhesion receptor of Sialomucin core protein 24(CD164), with associating to CXCR4 provide condition to interact CXCR4 with integrins VLA-4 and VLA-5 (29) . CD164 itself regulates the adhesion of CD34+ cells to BM stroma and their recruitment into the cycle. In another study, inhibition of the integrinα4 receptor virtually abrogated the homing of HPC to the BM (30). On the other hand, blockade of α6 integrin

enhanced the homing of human BM-derived HSPC and led to significantly improved engraftment (31). Aside from the established role of the α_4 β_1 integrin receptor VCAM-1in the homing of HSPCs to the BM, the importance of MAdCAM-1 and its ligand,α_4 β_7 integrin, in the homing of BM-derived HSPCs to both the spleen and the BM has been recently postulated (32). Additionally, Annexin II, expressed at high levels by osteoblasts and endothelial cells was shown to mediate adhesive interactions, between HSPCs and osteoblasts mainly through its N-terminal (33). Hyaluronan-mediated adhesion of HSPCs to stabilin-2-transfected cells suggests that stabilin-2 also contributes to the adhesion and homing of circulating stem and progenitor cells to BM (34). N-Cadherin-mediated cell adhesion was shown to be required for the establishment of hematopoiesis in the BM niche after transplantation (35).

2-3.The role of SDF-1/CXCR4 axis in migration of HSPC to their niche. SDF-1 is also known as CXCL-12 or pre B cell growth stimulating factor was primary known as a colony growth stimulating factor. SDF-1 is produce by osteoblast cells in endosteum region and increase by HIF-1 in the BM microenvironment, SDF-1α is produced mainly by endothelial cells, fibroblastic cells and osteoblasts. It provides a potent retention signal for HSPCs mediated via its receptor CXCR4 expressed on these cells. The CXCR4 as mentioned previously is a kind of hepta-helical-receptors which is coupled to GTP-binding proteins and also act as HIV-1 virus receptor. SDF-1 mediates HSPC adhesion through activation of lymphocyte function- associated antigen-1(LFA-1), very late antigen-4 and 5. (VLA-4&5). The role of SDF-1/CXCR4 axis in the homing of HSPC has been demonstrated in non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice (22). It has been suggested that for optimal signaling, CXCR4 must be incorporated into membrane lipid rafts (36, 37). Molecules such as fibronectin, fibrinogen fragments, soluble VCAM-1, platelet-derived micro particles (PMPs),C_3aanaphylatoxin and hyaluronic acid(HA) which are present in the supernatants from leukapheresis products of patients mobilized with G-CSF, increase the chemotactic responsiveness of HSPCs to an SDF-1 gradient (38). These molecules do not chemo attract HSPCs but they prime the chemotactic response of HSPCs to a low or threshold dose of SDF-1 and this chemotaxis is dependent on the cell membrane cholesterol content and the incorporation of CXCR4 into membrane lipid rafts (38). In order to access a favorable clinical outcome of HSPCs, the number of HSPCs should be approximately 2-3×106 /_Kgr. Gene expression can be regulated by chromatin remodeling and histone deacetylase (HDAC) that participates in the regulation of chromatin structure (39). Valporicacid (VPA) is a specific and potent short-chain HDAC inhibitor that has been shown to stimulate proliferation and self-renewal of normal HSPCs(40). It is known that HSPCs derived from PB have superior homing and engraftment capabilities compared to those derived from BM(41). Evidence suggest that the improved engraftment of mobilized HSPCs could be attributed to components such as PMPs which are found in the elevated levels in the supernatant of leukapheresis products to which HSPC have been exposed(41). Micro particles were previously regarded as mere cellular debris but they have recently been recognized to play a role in many cellular functions(41). PMPs are released upon activation of platelets and express several functional membrane receptors, including CXCR4. Investigations suggest that pre-treatment of CD34+ cells with PMPs may prove to be a strategy for accelerating engraftment of BM or CB HSPCs (41). CD41 is efficiently transferred by PMPs to hematopoietic precursors, resulting in their increased adhesion to fibrinogen(42). PMPs were also shown to enhance in vitro invasive potential of breast cancer cells lines and induce metastasis in lung cancer by up regulating the expression of the proteolytic enzymes such as MMP-2, MMP-9 and MT1_MMP. Other molecules present in leukapheresis products that could contribute to priming of the chemotactic responses of HSPCs towards SDF-1 are HA and thrombin. Thrombin, through proteolytic activation of its receptor PAR-1, elicits numerous cellular responses in platelets and endothelial cells, such as induction of adhesion molecules, production of chemokines, activation of pro MMP-2, cytoskeletal reorganization and cell migration(43).

2-4.The role of proteases in HSPCs homing. New evidences suggest that Hemagglutinin (HA) and thrombin prime homing-related responses of HSPC towards SDF-1 by up regulating MT1-MMP expression, which in turn leads to pro MMP-2 activation(44). Activated MMP-2 have a negative feedback in cascade of activation of other MMPs(45). It has been demonstrated that intracellular crosstalk and positive feedback loops between phosphatidylinositol3-kinase(PI3K)-AKT(46) and the Rho family GTPases including Rac, Rho and Cdc42 regulate actin cytoskeletal dynamics and F-actin polymerization(47-50). Moreover, Rac-1 GTPse signaling pathways lead to localized signal amplification which in turn results in enhanced F-actin polymerization and chemotaxis(51). In CD34+ cells, both PI3K and Rac-1 GTPase pathways are activated by HA and thrombin(52). Intracellular crosstalk occurs between these signaling pathways since inhibition of PI3K , and Rac-1GTPase attenuate Rac-1 activation, and phosphorylation of AKT, respectively. Moreover, during HSPC homing SDF-1/CXCR4 signaling occurs in the lipid rafts where CXCR4 and Rac-1 assemble together, thus allowing an optimal chemotactic response to SDF_1(52). Hence HA and thrombin corporate with the SDF-1/CXCR4 axis by signal amplification -activating PI3K and Rac-1 in the presence of a weak SDF-1.. This signal functions are proteolysis. Overall, these signals could enhance homing-related responses of HSPCs and potentially speed upengraftment.

3. HSPCs Mobilization

Stem cell mobilization- release of HSPCs in to the peripheral blood of patient in responds to chemotherapy or cytokine stimulation was first described in the late 1970s and early 1980(7). HSPCs transplantation, a clinical procedure has been successfully performed for decades to treat various cancers and diseases of the blood and immune system(1), in which cells with ability to reconstituting normal BM function are administered to a patient, Traditionally, in both autologous and allogenic transplantation, HSPCs were collected by multiple aspiration of BM, but such harvesting procedure has now been almost completely replaced with the collection of PB. Circulated HPSCs have been extensively applied clinical conditions such as restoration of hematopoiesis following radiotherapy and chemotherapy for cancer patients. Many reviews on the biology of HSPCs mobilization (53-61)and strategies to improve HSPC collection have been published recently(8, 58, 62, 63). Table 2

3-2.The role of cytokines and growth factors in mobilization. Under steady state conditions, a small percentage of HSPCs (0.01-0.05%) are in the circulation; however, this number is significantly increased upon administration of hematopoietic growth factors(64, 65).

Granulocyte colony stimulating factor(G-CSF, filgrastim) and GM-CSF(sargramostim) are currently the only cytokines approved by the FDA for HSPC mobilization, with G-CSF being the standard of care for initial mobilization therapy(66). G-CSF- mobilized HPSCs engraft better and have fewer adverse reactions compared to those from BM or umbilical cord blood(CB). G-CSF is a short-lived protein, with a half-life of 3.5 h in humans. Multiple injections are therefore required to achieve the desired therapeutic outcomes in both neutropenia and stem cell mobilization.In fact, G-CSF is the most important mobilizer substance but has not been administered very much due to toxigenic, adverse effects, multiple injections and different individual responds(4, 52, 67, 68). G-CSF induces activation of proteases, inhibition of adhesion molecules and attenuation of CXCR4/CXCL12signalling. G-CSF downregulates the expression of CXCR4 on cells surface so it causes mobilization of HSPCs to the PB.

Following G-CSF administration, the marrow microenvironment would be rich in proteolytic enzymes released by neutrophils, including metalloproteinase-9 (MMP-9), neutrophil elastase, and Cathepsin G (69). MMP-9, neutrophil elastase, and Cathepsin G can cleave and functionally inactivate SDF-1(8, 24, 70). Further, a study in MMP-9–deficient mice detected defective G-CSF–induced mobilization of hematopoietic progenitor cells (71).

G-CSF down-regulates the expression of CXCR4 on BM myeloid cell lines but not on

lymphocytes. One problem with the clinical use of G-CSF as a mobilizing agent is that its unglycosilated recombinant form is rapidly decay and been cleared into the plasma, so needs to be injected daily. To overcome this the polyethylene glycol(PEG) moiety is bound with G-CSF, a masking proteolytic cleavage sites and elevation in the level of G-CSF would be seen which are sustained for up to 14 days after a single injection (72).it has also been shown that G-CSF binds non- covalently but with high affinity and specificity to polyethylene glycated liposomes, which extends its circulation time and results in higher G-CSF levels several hours after both subcutaneous and intravenous injections (73).Alternative regimens have been suggested based on pre-clinical finding for example the cytokine GROβ mobilizes more murine

Scal+-c-kit+-lin-HSPC when used alone and synergizes with G-CSF(74). GROβ mobilizes HSPCs within 15 minutes, suggesting that a readily accessible large pool of HSPCs likely associated with sinusoidal endothelium can be readily mobilized. Combining G-CSF with other growth factors has also been attempted (58). For example recombinant human stem cell factor (SCF ancetim) shows promising synergy when used in combination with G-CSF. Moreover, such synergy provides an alternative option for patients who mobilize poorly or/ and exhibit refractory BM failure(75, 76). In another study co-administration of IL-8 and Flt3-ligand led to a synergistic enhancement of HSPC mobilization on days 3 and 5, compared to either used alone(77). Also there are elevated levels of hepatocyte growth factor (HGF) in the plasma of patients mobilizes with G-CSF. The HGF level positively correlated with the number of CD34+cells and WBCs in the PB, being low in patients who were poor mobilizer (78). There are two kinds of CD34+ stem cells:

Umbilical CD34+ and mobilized CD34+.

The HGF receptor C-met is highly express on circulated CD34+ cells but not express on steady state BM CD34+ cells. It has been suggested that during G-CSF induced mobilization, C-met expression would increase on BM HSPCs and myeloid cells which renders them more responsive to the HGF gradient in the circulating PB(79). Moreover, G-CSF, together with HGF, increased the secretion of MMP 9 and membrane type1-MMP(MT1-MMP) on the surface of BM leukocytes(17, 79).

3-3.The role of SDF-1/CXCR4 axis in HSPCs mobilization. SDF-1, pre B cell growth- stimulating factor,(PBSF) is a kind of CXC chemokines which previously was known as B cell colony stimulating factor. Its receptor is CXCR4 which is a heptad chain helix receptor, binds to GTP binding proteins. CXCR4 acts as a receptor for HIV-1. SDF-1 is the main chemokine involved in HSPC migration(78); in fact, most of the cytokines and growth factors mediate HSPC mobilization via modulation of SDF-1 or its receptor CXCR4(80). It has been demonstrated that neutralizing SDF1/CXCR4 antibodies significantly reduce HSPC mobilization(81). Following G-CSF administration, SDF-1 levels transiently increase in the BM, followed by down regulation at the gene (82) and protein level(83). Moreover, G-CSF downregulates CXCR4 expression in human BM myeloid cells which attenuates their response to an SDF-1 gradient (84). Thus disruption of SDF-1/CXCR4 signaling is a key step in the release of HSPC from the BM to the PB during mobilization. Human SDF-1 is composed of three distinct structural regions: an N terminus, a central core region of three anti parallel β-sheets and a C-terminal helix. Previous studies have demonstrated the essential role of the N-terminus, particularly the first nine residues, as the major site for direct interaction with the CXCR4 receptor and subsequent signal transduction (85). Modulation of this interaction has been harnessed for application in mobilization. AAMD3100 or Plerixafor is an effective alternative for the collection of sufficient numbers of CD34+ cells for autologous transplantation in patients with poor mobilization. A continuous infusion of saturating dose of AMD3100 is also found to be an efficacious mobilization regime (25). The cleavage of SDF-1 at the N-terminus is effected by various enzymes such as MMPs(72) CD26/dipeptidylepeptidaz 4(86), the serine proteases Cathepsin G(87) and elastase (42). Such enzymes generate distinct truncated forms of SDF-1 that are functionally inactivate. In addition, the major bone-responding proteinase, Cathepsin K elevates SDF-1(88). These enzymes are thought to be released

particularly by neutrophils during G-CSF injection in the BM microenvironment(89). The C-terminus of SDF-1 may also have a functional role while its cleavage by serum carboxyl peptidase N(CPN) that rescue the ability of SDF-1 to bind to heparin and to stimulate chemotaxis(89, 90).

The membrane- bound carboxypeptidase M (CPM), which is ideally situated to elicit a more targets activity at local tissue sites than soluble CPN, is also able to cleave the C- terminal of SDF-1. CPM cleaves the C-terminal lysine residue of the α isoform of SDF-1 resulting in a decrease of its chemoattractant activity towards CD34+HSPCs and find that G-CSF strongly upregulates CPM expression at the gene and protein levels in (mononuclear cells) MNCs and PMNs(44). As it has been suggested that the C-terminal lysine of SDF-1α contributes to the tethering of SDF-1 to heparin on the cell surface and preserving its activity(91). Hence, it seems that cleaving of lysine by CPM facilitates the release of SDF-1 from the cell surface, and exposes it to further degradation by other proteases(44). Degrading the CXCR4 receptor is another way by which chemoattraction can be abrogated. Leukocyte elastase is able to cleave the N-terminal of CXCR4(42) that disrupts binging with its ligand SDF-1. HIF-1 concentration is elevated in some particular organs like brain, heart and liver leading to increasing in SDF-1 expression (Fig 1).

3-4.The role of matrix metalloproteinases (MMP) in HSPC mobilization. Matrix metalloproteinases (MMPs) form a family of closely related, zinc-dependent end proteinases. The first report about MMPs dates back to 1962, when Gross and Lapiere, while attempting to establish how a tadpole loses its tail during metamorphosis, discovered the first member of this family(MMP-1). Since then, the family has expanded gradually with a total of23 human MMPs; the latest member discovered is MMP-28 (92). As their name suggests, MMPs were characterized initially as matrix-degrading proteases. Indeed, these enzymes can degrade all components of the extracellular matrix (ECM), which involve in many important processes, such as cell proliferation, differentiation, migration, and death, as well as cell– cell interactions(3). It is therefore not surprising that MMPs can play a crucial role in many physiological processes, e.g., bone morphogenesis, the menstrual cycle, development and also, in many pathological conditions including cancer invasion, arthritis, and atherosclerosis. The story has been made even more complex by their creasing number of studies revealing many non-matrix substrates for MMPs, such as chemokines, growth factors, and receptors, indicating that MMPs influence an even wider array of physiological and pathological processes4. Inflammatory conditions are almost always characterized by increased MMP activities (93). G-CSF-activated neutrophils release proteolytic enzymes degrading various components of the BM microenvironment that are implicated in HSPCs mobilization. One of the enzymes that is abundantly secreted by neutrophils is MMP 9, which substrates extend from the conventional ECM components(eg; collagens, fibronectin, laminin, proteoglycans) to non-mature molecules(46-48). MMPs have been traditionally considered to facilitate cell migration with breaching basement membrane barriers comprised of matrix proteins. Furthermore, , the gelatinizes MMP2 and/ or MMP 9 are expressed by normal mobilized CD34+ HSPC as well as stromal cells, fibroblasts, endothelial cells and long- term marrow culture cells). 50 ,51(However, the steady state BM CD34+ cells, unlike circulating PB CD34+ cells, have no the expression of MMP 2 and MMP 9. Moreover, various cytokines and growth factors, including IL-3,IL-6,G-CSF,M-CSF, SCF and TNFα which are endogenously produced in the BM microenvironment (94), could induce the secretion of MMP 2 and MMP 9 by BM CD34+ cells and up regulate their trans- migration across reconstituted basement membrane by 50% to 150%. Further, the trans- matrigel migration of CD34+ cells is reduce by antibodies against the MMP 2,MMP 9 tissue inhibitors of metalloproteinases (TIMP-1and TIPMP-2) and the synthetic protease inhibitor, o-phenantrolin (25). Furthermore, the cytokines IL-8 and MIP-1α also directly stimulate the secretion of bothMMP 2 MMP 9 in BM CD34+ cells (94). MT1-MMP degrades ECM macromolecules, cytokines, chemokines and adhesion molecules and mediates tumor cell migration. For example, MT1-MMP cleaves CD34+ marker and SDF-1 that is resulted in detachment and reduced

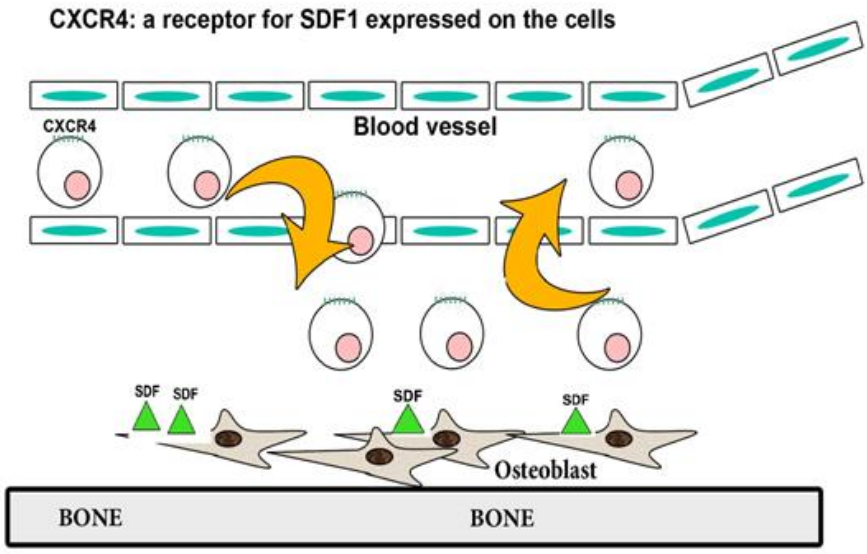

Figure 1. Homing and mobilization HSPC : CXCR4 bind to SDF-1 secreted by osteoblast cells and lead to homing HSPC.

egression of HSPC from the BM (95, 96). Previous investigations suggested that MY1-MMP facilitates the migration of MSC, CB CD34+ cells and exvivo-expanded megakaryocytic progenitors(96, 97). Recent studies approved the role of MT1-MMP in the mobilization of HSPCs from BM(98). CD26 is a membrane-bound extracellular peptidase that cleaves dipeptides from the N-terminus of polypeptide chains after a proline or an alanine(99). The N-terminus of chemokines is known to interact with the extracellular portion of chemokine receptors (100). CD26 affect CXCL12 and CCL22 which are expressed on CB CD34+; hence CD26 is play a crucial role in G-CSF-mobilized HSPCs. In addition to CD26 , which is also expressed by HSPC, has been shown to cleave and inactivate SDF-1 and consequently, mobilization is reduced with CD26 inhibition or CD26 deficient mice(101). Other proteases implicated in HSPCs mobilization include plasminogen activator inhibitor-1 (Pai-1), α2-antiplasmin. Inhibitor Pai-1 and α2-antiplasmin increases HSPCs mobilization in response to G-CSF(101, 102). Moreover, thrombolytic agents enhance HPC mobilization in mice and humans, indicating a possible role for plasmin in augmenting G-CSF-induced HPSC mobilization. Recently, the expression, secretion and function of the cysteine protease Cathepsin X by cells of the human BM has been examined with interesting results. Osteoblasts and stromal cells but not HSPCs secrete Cathepsin X. Activated Cathepsin X enhances mobilization with reducing cellular adhesive interaction between CD34+ HSPC and osteoblast, and digesting SDF-1/ CXL12(103). Moreover, recent data suggest that the destruction of VCAM1/VLA4 axis with a small molecule inhibition of VLA4, BIOS192, results in a 30-fold increase in mobilization of HSPCs, over basal level. Further, 3-fold increase in HSPCs mobilization has been reported when AMD3100, a small molecule inhibitor of theCXCR4/SDF-1 axis, is combine with BIOS192. Furthermore, the combination of G-CSF, BIOS192, and AMD3100 enhance mobilization by 17-fold compare G-CSF alone.

3-5.The role of ROS in HSPCs mobilization. The PBSCs leave their original hypoxic living environment their intracellular reactive oxygen species(ROS) level changes. Some studies also show that the ROS level are increased during in vivo mobilization and in vitro culture, causing the biological functions to change as well(1, 2). ROS are products of cells utilizing oxygen for energy metabolism. The antioxidants of the cells can remove the continually produced ROS and maintain the ROS

at a low level, thereby regulating the proliferation, growth, signal transduction and gene expression of the cells. When the ROS production in the cells increases or antioxidant capacity of the cells weakens, ROS stress occurs. The ROS stress changes the properties and functions of HSPCs, and is caused to cell mitochondrial DNA damage and apoptosis (4). The production of ROS is dependent on oxygen concentration and directly affects the capacity of HSPCs for self-renewal(5). In the view of negative effects of ROS on PBSCs, Haao and et.al, considered the effect of two antioxidants, including GSH and ascorbic Acid 2-phosphat (AA2P) derivate of vit-c in the mobilization process and in vitro amplification of BM HSPCs to eliminate the effects of ROS on HSPCs. The application ofAA2P may become effective methods for protecting the HSPCs reconstitution capacity of PBSCs, and improving the success rate of PBSCT.

3-6.The role of adhesion molecules and other factors in HSPCs mobilization. Integrins are a major family of adhesion molecules that mediate cell-to-cell and cell-to-matrix interactions. The binding of HSPCs through VLA4with VCAM-1 on BM stromal cells was found to be essential for the homeostatic distribution of HSPCs (104) and recently were approved that the alpha cytoplasmic domain plays a critical role(105). The monoclonal anti-VLA-4 antibody (natulizumAb) has been shown in the clinic to mobilize CD34+ HSPC(106). CD44 is the cell-surface glycoprotein receptor for HA and can also interact with other ligands such as osteopontin, collagens and MMPs (107). HPSCs bind to various ECM components and blocking CD44 is resulted in mobilization of murine HSPC(12). In clinical trials, a significant decrease in CD44 expression was observed during G-CSF- induced mobilization(13). Other factors have also been implicated in HSPC mobilization, including hormones and neurotransmitters (108). As mentioned previously, HSPCs are localized in close proximity to osteoblastic cells, lining on the endosteal surface of the bone. Osteoblasts are known to respond to parathyroid hormone(PTH), the endocrine regulator of calcium concentration in extracellular fluid(6). Injecting mice with PTH lead to a significant increase in the SC enriched subpopulation (lin- sca+ C-kit+) in the BM(109). In addition stimulated granulocytes and monocytes via C5a fragment of complement system induce reduction in CXCR4 expression and also chemotaxis towards an SDF-1 gradient which leads to increased secretion of MMP-9 and expression of MT1-MMP and carboxypeptidase M. These findings showed that C5a fragment of complement system as a part of innate immune system play an important role in subsequent mobilization of hematopoietic stem cells towards peripheral blood (110).

Conclusion

The factors such as SDF-1/CXCR4 and other adhesion molecules have the important role in homing HSPCs. Although the essential ligand for SDF-1 is the CXCR4,but it can also attach to CXCR7,thus the CXCR7-expressing cells also can be also homing to HPSC but this is yet unclear. Other adhesion molecules such as LFA1, CD44 and VLA4 can also contribute to homing HSPCs .These adhesion molecules expressed on the HSPCS can bind to their receptors on the osteoblast cells. So any change in the stability of these connections can cause mobilization HSPCs and their egression from BM into the circulation. Many other factors can have role in the mobilization including G-CSF(the key factor), GM.CSF,MMPs especially MMP2 and MMP9 and adhesion molecules. G-CSF is one of the most common factors that by use number of the mechanisms can contribute to HSPCs mobilization such as degranulation of neutrophil granular contents that result in to increase in metalloproteases which break connections between SDF-1/CXCR4 and other adhesion molecules, finally migration HSPCs into the circulation . Metalloproteinase such MMP2, 9 also can break the connection HSPCs to osteoblast cells in the bone marrow. According to above, we can rich the peripheral blood of HSPCS by using of this factors and antagonist for this receptors on the osteoblastic cells or/and HSPCS for bone marrow transplant.

Conflicts of Interest

The authors declare that there is no conflict of interest in this study.

Acknowledgment

None

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