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Review Article

Hematopoietic stem cell mobilization

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Abstract

Hematopoietic stem cell (HSC) transplantation has been used to treat hematopoietic diseases for over 50 years. HSCs can be isolated from bone marrow (BM), umbilical cord blood, or peripheral blood. Because of lower costs, shorter hospitalization, and faster engraftment, peripheral blood has become the predominant source of HSCs for transplantation. The major factors determining the rate of successful HSC transplantation include the degree of human leukocyte antigen matching between the donor and recipient and the number of HSCs for transplantation. Administration of granulocyte colony-stimulating factor (G-CSF) alone or combined with plerixafor (AMD3100) are clinical used methods to promote HSC mobilization from BM to the peripheral blood for HSC transplantations. However, a significant portion of healthy donors or patients may be poor mobilizers of G-CSF, resulting in an insufficient number of HSCs for the transplantation and necessitating alternative strategies to increase the apheresis yield. The detailed mechanisms underlying G-CSF-mediated HSC mobilization remain to be elucidated. This review summarizes the current research on deciphering the mechanism of HSC mobilization.

Keywords: *Granulocyte colony-stimulating factor, Hematopoietic stem cell transplantation, Mobilization*

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Introduction

Hematopoietic stem cells (HSCs) reside in the bone marrow (BM) niche. "Niche" was first proposed as a medical term by Schofield in 1978. The niche comprises various cells that support the microenvironment to prevent stem cell differentiation and maintain self-renewal capabilities [1]. Many cell types in BM, including nonhematopoietic and hematopoietic cells, form the niche network to regulate and retain HSCs in BM [2,3]. Autologous or allogeneic HSC transplantation has become a primary treatment for many hematopoietic diseases, such as sickle cell anemia, thalassemia, and hematological malignancies [4-10]. Sources of HSCs are BM, mobilized peripheral blood, and umbilical cord blood. Because of lower costs, a less invasive harvesting procedure, faster engraftment, higher HSC yields, and shorter hospitalization, mobilized peripheral blood has replaced BM as the routinely used source for HSC transplantation [11]. Successful HSC transplantation requires good matching of the human leukocyte antigen between the donor and recipient and a sufficient number of HSCs. After 4–5 days of treatment with granulocyte colony-stimulating factor (G-CSF), the number of HSCs in the peripheral blood increases by an average of 50–100 times [12,13]; thus, G-CSF represents the gold standard agent for mobilized peripheral blood HSC transplantation [14]. Nevertheless, approximately 5%–10% of healthy donors and up to 40% of patients requiring autologous transplant are poor mobilizers of G-CSF [15-19]. However, it is challenging to identify such poor mobilizers [15]. To obtain a sufficient number of HSCs for transplantation, alternative strategies (such as larger volume leukapheresis, re-mobilization, the use of other mobilization agents, chemotherapy plus G-CSF, and BM harvesting) can be used [20]. A better understanding of how HSCs are mobilized from BM to peripheral blood can help in developing a more effective regimen for HSC transplantation. In this review, we discuss some known mechanisms of HSC mobilization.

Proteases released by neutrophils change hematopoietic stem cell retention in bone marrow

On G-CSF administration, neutrophils are activated and degranulated, releasing the serine proteases neutrophil elastase, cathepsin G (CG), dipeptidyl peptidase I (DPPI), and matrix metalloprotease 9. These proteases accumulate in BM and

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allow for the degradation of molecules (vascular cell adhesion molecule 1 [VCAM-1], stromal-derived factor-1 [SDF-1, also called CXCL12], and c-Kit [CD117]), thus disrupting the interaction with very late antigen-4 (VLA-4), CXC chemokine receptor-4 (CXCR4), and stem cell factor, respectively. This disruption interaction between HSCs and niche cells leads to HSC mobilization [21-26] [Figure 1a and b]. The mobilization drug plerixafor (AMD3100) has a similar mechanism, plerixafor combined with G-CSF can enhance HSC mobilization by 2–3 times compared with G-CSF alone. Thus, plerixafor serves as a mobilization-enhancing agent when used together with other agents, especially in patients with lymphoma or myeloma who have been heavily pretreated with G-CSF [27,28]. Plerixafor binds to CXCR4 expressed on the HSCs, blocks the adhesion between HSCs and niche cells, and then mobilizes HSCs [28,29]. Compared with G-CSF, plerixafor-triggered HSC mobilization has clear mechanism. The interaction between Notch2 and its ligand also maintains HSC niche retention; Notch2-blocking antibodies sensitize HSCs to the mobilizing stimuli of G-CSF and plerixafor, resulting in a 3–4-fold increase in mobilization [30-32].

Reduction of stromal-derived factor-1 expression in niche cells promotes hematopoietic stem cell mobilization

G-CSF activates the sympathetic neurons innervating BM by binding to the G-CSF receptors and then

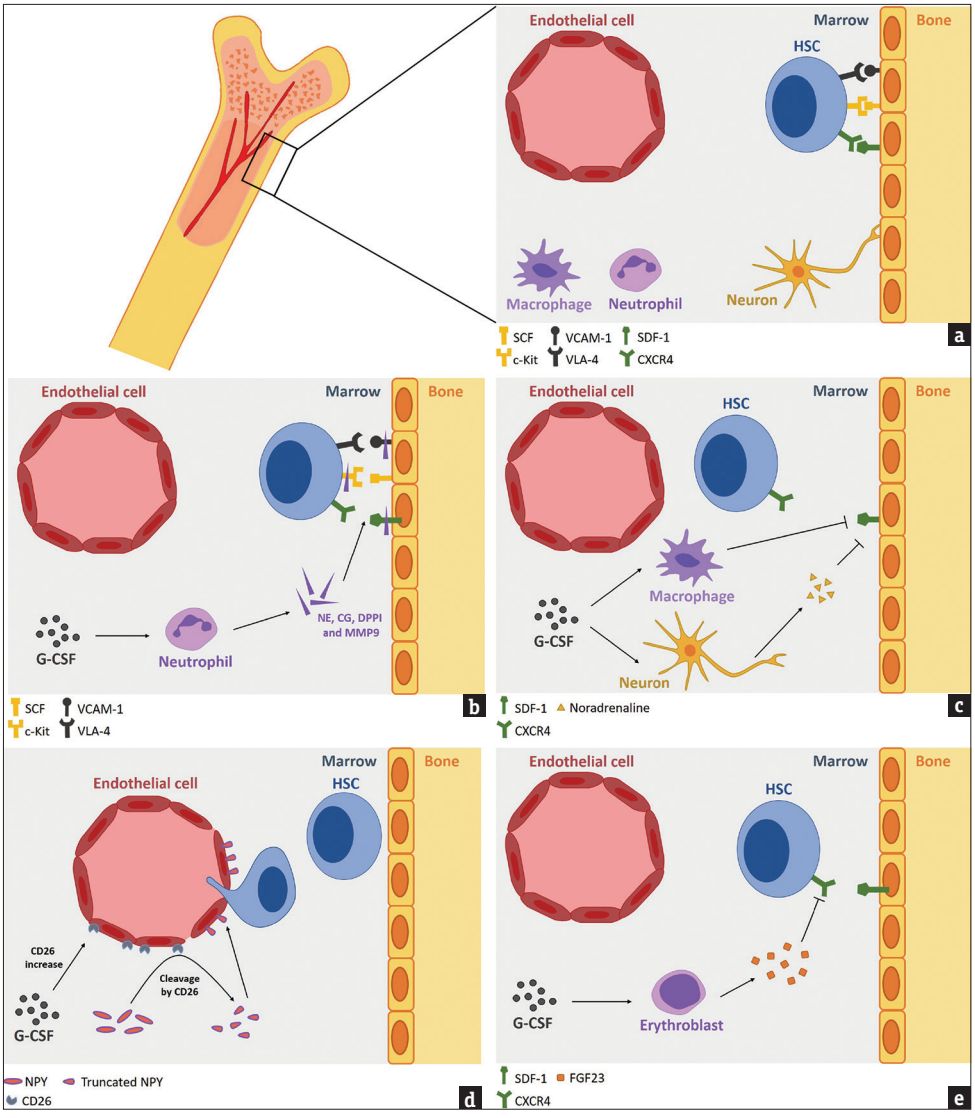

Figure 1: Granulocyte colony-stimulating factor stimulates hematopoietic stem cell mobilization by cleaving the retention axes, downregulating stromal-derived factor-1 expression, opening the endothelial boundaries, and counteracting the function of CXC chemokine receptor-4 through erythroblasts-derived fibroblast growth factor 23. In the steady state, hematopoietic stem cells are located and retained in bone marrow through several retention axes, such as SCF/c-kit, vascular cell adhesion molecule 1/VLA-4, and stromal-derived factor-1/CXC chemokine receptor-4 between hematopoietic stem cells and niche cells (a). Upon granulocyte colony-stimulating factor treatment, neutrophils secrete proteases, such as neutrophil elastase, cathepsin G, dipeptidyl peptidase I, and matrix metalloprotease 9, to cleave the retention axes (b). Granulocyte colony-stimulating factor induces sympathetic neurons to secrete noradrenaline and macrophages to secrete unknown factors to suppress stromal-derived factor-1 expression on the surface of niche cells (c). Granulocyte colony-stimulating factor increases CD26 on the surface of endothelial cells and then cleaves the N-terminal of NPY. Truncated NPY then binds the receptors on the surface of endothelial cells, downregulates VE-cadherin, and opens endothelial boundaries (d). Granulocyte colony-stimulating factor triggers erythroblasts to secrete fibroblast growth factor 23 and then counteract the function of CXC chemokine receptor-4 (e).

releases noradrenaline to reduce SDF-1 expression (which binds to CXCR4 on the HSCs) on the osteoblasts and nestin^{+} mesenchymal stem cells through β2-and β3-adrenergic receptors, respectively [33-35]. G-CSF can also activate the macrophages in BM to release some unknown factors to suppress SDF-1 expression on the surface of osteoblasts and then promote HSC mobilization [33,36-38]. The SDF-1/CXCR4 axis retains HSCs in BM; downregulation of SDF-1 expression disrupts the retention axis and promotes the exit of HSCs from BM [Figure 1c].

Perturbation of the endothelial cell junctions results in increased permeability and hematopoietic stem cell mobilization

Following G-CSF administration, CD26 (also known as dipeptidylpeptidase-4) is increased on the sinusoidal endothelial cells, which become the gatekeepers at BM–peripheral blood interface and regulate hematopoietic cell trafficking [39]. CD26, a serine exopeptidase, cleaves N-terminal dipeptides of the full length of neuropeptide Y (NPY) to form NPY_{3-36}. The truncated NPY preferentially binds to NPYR2 and NPYR5 instead of NPYR1. After binding, the tight junction element vascular endothelial cadherin (VE-cadherin) [40,41] is internalized and degraded, thus enhancing HSC transendothelial migration [42,43] [Figure 1d].

Fibroblast growth factor 23 secreted by erythroblasts promotes hematopoietic stem cell mobilization

The hormone fibroblast growth factor 23 (FGF-23), mainly secreted by osteoblasts and osteocytes, regulates phosphate homeostasis in the kidney[44] and suppresses erythropoiesis [45,46]. G-CSF can trigger erythroblasts in BM to release FGF-23 within the first 24 h of G-CSF administration. FGF-23 can counteract the function of CXCR4 and then mobilize HSCs [47,48] [Figure 1e].

Coupling of purinergic signaling, NOD-like receptor family pyrin domain-containing 3 inflammasome, and the complement cascade promotes hematopoietic stem cell mobilization

Accumulated studies have revealed that G-CSF can activate innate immune cells, including granulocytes and monocytes, to release extracellular adenosine triphosphate (eATP) in a pannexin-1 channel-dependent manner [49,50]. eATP subsequently activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes through P2X4 and P2X7 purinergic receptors on the surface of HSCs or innate immune cells [51-54]. Inflammasomes are caspase-1-containing protein complexes that promote inflammation [55-57]. The NLRP3 inflammasome is among the most widely studied inflammasome members; it comprises NLRP3, an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and pro-caspase-1 [58-60]. After its activation, pro-caspase-1 becomes activated and cleaves pro-interleukin-1β (IL-1β) and pro-IL-18 to form IL-1β and IL-18 [60-63]. Activated caspase-1 can also cleave the gasdermin-D (GSDMD) protein; the N-terminal mature form of GSDMD (N-gasdermin) is oligomerized and inserted into the cell membrane to form pores for the release of IL-1β, IL-18 [64,65], and other danger-associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1) protein and S100 calcium-binding protein A9 (S100A9) [66-70]. IL-1β or IL-18 may aid HSC mobilization because of the injection of the NLRP3 inflammasome activation mediators IL-1β- or IL-18-induced HSC mobilization in mice [49,50,71,72]. Other DAMPs (HMGB1 and S100A9) are recognized by mannan-binding lectin, which then activates the complement system through mannan-binding lectin–associated serine proteinase. The activated complement C5a then lyses the erythrocytes and releases sphingosine-1-phosphate (S1P) into the peripheral blood to attract the HSCs mobilized from BM [3,66,67,73-77] [Figure 2].

Pain-sensing nerve cells (nociceptors) control hematopoietic stem cell mobilization

Nociceptors belonging to sensory neurons can sense pain. These neurons have been well investigated in barrier tissues, such as the skin and gut [78]; however, their biological role in nonbarrier tissues, such as BM remains unknown. Recently, a study demonstrated that BM nociceptors can be stimulated by G-CSF to release the neurotransmitter

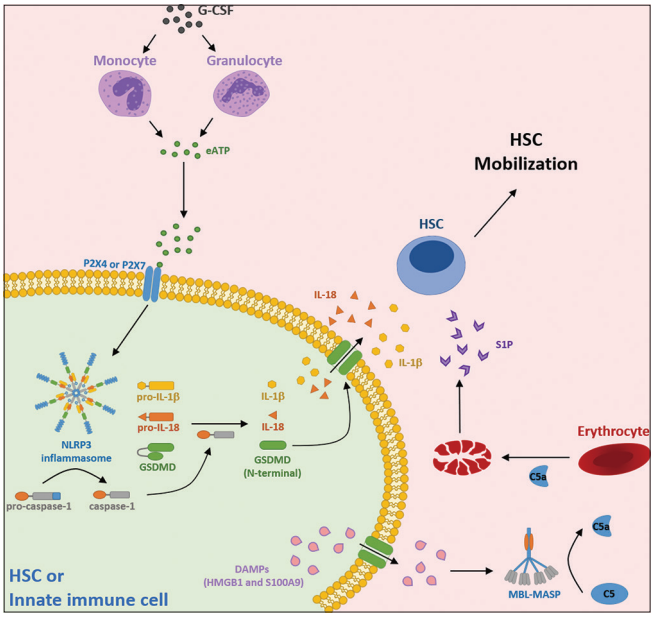

Figure 2: Granulocyte colony-stimulating factor induces hematopoietic stem cell mobilization by activating inflammasome and complement systems. Granulocyte colony-stimulating factor triggers monocytes and granulocytes to release eATP, which binds P2X4 or P2X7 on the surface of hematopoietic stem cells or innate immune cells to activate the NLRP3 inflammasome. Interleukin-1β, interleukin-18, and danger-associated molecular patterns are released through the pores formed by GSDMD. Danger-associated molecular patterns activate complement C5, releasing S1P from mature erythrocytes. Interleukin-1β, interleukin-18, and S1P together promote hematopoietic stem cell mobilization.

molecule calcitonin-gene-related peptide (CGRP) [78]. The administration of CGRP combined with G-CSF greatly improved HSC mobilization. CGRP binds directly to HSCs through a receptor dimer comprising the calcitonin receptor-like receptor (CALCRL) and receptor activity modifying protein 1 (RAMP1) and then mobilizes HSCs by activating downstream $G\alpha_s$–adenylyl cyclase–cAMP signaling [79,80] [Figure 3]. Notably, feeding mice with capsaicin can stimulate the nociceptors to release CGRP and mobilize HSCs [79,80] [Figure 3].

Conclusions

G-CSF–triggered HSC mobilization is a complex process involving many mechanisms and niche cells, such as neutrophils, macrophages, sympathetic neurons, mesenchymal stem cells, osteoblasts, sinusoidal endothelial cells, granulocytes, monocytes, nociceptors, and erythroblasts. Other mechanisms remain to be discovered. For individuals who are poor mobilizers of G-CSF, a comprehensive understanding of the mechanisms underlying HSC mobilization is crucial to minimize HSC transplantation failure due to insufficient HSC mobilization. Researchers must attempt to develop a fast, accurate, sensitive, and simple screening method for identifying poor mobilizers and establish a new regimen for HSC mobilization.

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Conflicts of interest

Prof. Hsin-Hou Chang, an editorial board member at *Tzu Chi Med J*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

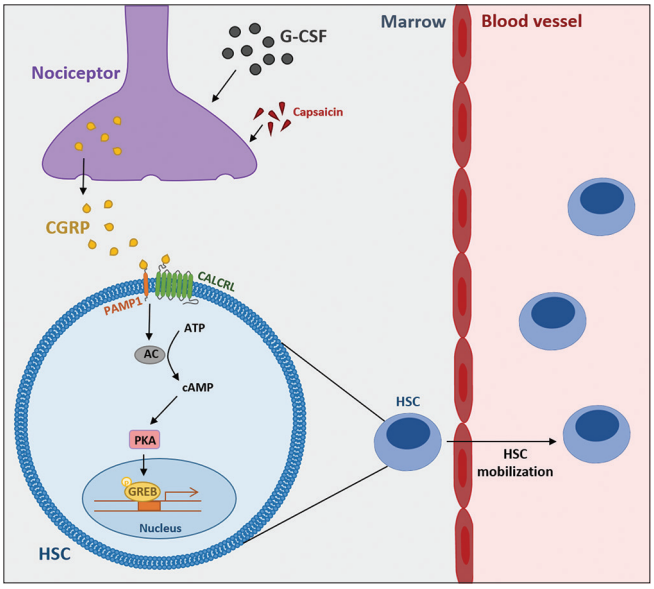

Figure 3: Granulocyte colony-stimulating factor and capsaicin mobilize hematopoietic stem cells by activating nociceptors in bone marrow. Granulocyte colony-stimulating factor and capsaicin stimulate nociceptors to release calcitonin-gene-related peptide and activates the downstream $G\alpha_s$–adenylyl cyclase–cAMP signaling through receptor (RAMP1/CALCRL) to promote hematopoietic stem cell mobilization.

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