SPECIAL REPORT

Novel view on hematopoietic stem cell mobilization and homing

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While the α -chemokine stromal-derived factor-1 (SDF-1)—CXCR4—and very late antigen-4 (VLA-4)—vascular adhesion molecule-1 (VCAM-1)—axes have an unquestionably important role in the retention of hematopoietic stem/progenitor cells (HSPCs) in bone marrow (BM),^{1–4} new evidence shows that, in addition to SDF-1, the migration of HSPCs is directed by gradients of the bioactive lipids, such as sphingosine-1 phosphate (S1P) and ceramide 1-phosphate (C1P), and certain extracellular nucleotides, including uridine triphosphate (UTP) and adenosine triphosphate (ATP).^{5,6} We reported that S1P if tested at physiological concentrations that are present in biological fluids is more potent chemoattractant for BM-purified HSPCs as compared with physiologically relevant doses of SDF-1.⁶ Therefore, I postulate that retention of HSPCs in BM niches involving SDF-1–CXCR4 axis is an active process that counteracts high S1P gradient present in peripheral blood (PB) and thus prevents egress of HSPCs (Figure 1).

We also noticed that in contrast to BM-residing HSPCs, HSPCs already circulating in PB are desensitized in their responsiveness to S1P.^{6,7} Thus, this supports further that a major homing factor for HSPCs is SDF-1. We also demonstrated that the SDF-1 chemotactic gradient may be positively primed/enhanced by some cationic peptide (C3a anaphylatoxin, LL-37 cathelicidin and α 2-defensin) members of the innate immunity network and HSPCs respond robustly, even to very low SDF-1 gradients in the presence of these priming factors.^{6,7} All these cationic peptides are upregulated in BM microenvironment conditioned by radio/chemotherapy for transplantation. Therefore, this phenomenon has an important role in homing of HSPCs from PB into BM and, as I postulate, could be implemented in hematopoietic transplants to *ex vivo* prime/enhance responsiveness HSPCs to be transplanted to SDF-1 gradient present in BM.⁴

Figure 1. Chemotactic 'tug-of-war' of SDF-1–S1P gradient between BM and PB explains mobilization and homing of HSPCs. Under steady-state conditions, this gradient should be in balance. New evidence indicates that, rather than changes in the SDF-1 gradient across the BM–PB barrier, S1P gradient in PB has an important role in the mobilization of HSPCs. SDF-1 provides the most important retention/homing signal for HSPCs that is supported by priming effect by C3a, LL-37 and β 2-defensin as well as by other chemoattractants for HSPCs such as some bioactive lipids and some extracellular nucleotides.

The role of SDF-1 gradient in homing of HSPCs could be also supported by several other HSPC chemoattractants including bioactive lipids (S1P, C1P and PGE2) and extracellular nucleotides (ATP and UTP).^{6–8} This explains, for example, why CXCR4^{−/−} fetal liver HSPCs may home to BM in an SDF-1-independent manner⁹ as well as why homing of murine HSPCs made refractory to SDF-1 by incubation and co-injection with a CXCR4 receptor antagonist is normal or only mildly reduced.¹⁰

New evidence also accumulates that trafficking of HSPCs is orchestrated by three ancient interacting with each other proteolytic cascades including complement, coagulation and fibrinolytic cascade.¹¹ As all these cascades show circadian rhythm of activation due to drop of pH during late night hours, we envision that they are also responsible in addition to changes in tonus of vegetative system in circadian rhythm of changes in the level of HSPCs in PB.^{12,13}

Overall, although retention of HSPCs in BM niches is an active process mediated by SDF-1–CXCR4 and VCAM-1–VLA-4 axes, S1P emerges as a major chemoattractant for HSPCs in PB.^{5,11,14,15} Moreover, as S1P, C1P, ATP, UTP, C3a, LL-37 and α2-defensin are upregulated in BM after myeloblastic conditioning for transplantation, a more complex picture of homing emerges.⁶ These observations may lead to development of more efficient mobilization and homing-promoting strategies.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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