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Maintaining What Is Already There: Strategies to Rectify HSC Transplantation Dilemmas

Claudia Waskow[1,*]
[1]Regeneration in Hematopoiesis and Animal Models in Hematopoiesis, Institute for Immunology, Faculty of Medicine, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany
*Correspondence: claudia.waskow@tu-dresden.de
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Hematopoietic stem cell (HSC) transplantation remains the only cure for various hematological diseases, but low HSC numbers in many donor samples are a critical problem preventing their clinical use. Now in *Nature* and *Cell*, two creative strategies to rescue and improve pre-existing engraftment potential are presented.

HSCs are the only adult stem cells that are routinely used in the clinic for the replacement of diseased blood tissues including cell-based therapies and gene therapeutic approaches. Further, bone marrow transplantation from healthy individuals into patients still remains the only cure for numerous hematological disorders, such as primary immune deficiencies, and also acquired states of bone marrow failure, including certain leukemias and anemias. For this reason HSCs have been studied intensely, and a better understanding of their biology and function is required in order to improve and develop novel, less invasive therapies in the future. The only available donor cell sources are cord blood, primary bone marrow, and mobilized peripheral blood. The success of a clinical bone marrow transplantation correlates with the number of donor HSCs infused (Danby and Rocha, 2014). Thus, a key limiting factor for clinically successful HSC transplantation is often the number of histocompatible donor HSCs that are available for a specific patient from those sources (Li and Sykes, 2012). Despite rapid progress in understanding the precise phenotype of HSCs that can contribute to long-term hematopoiesis in transplantation recipients, the inability to obtain or generate donor cell numbers in sufficiently large numbers for robust repopulation remains a significant challenge for clinicians. In fact, low numbers of donor HSCs make the majority of stored donor samples—mainly cord blood—unusable (Danby and Rocha, 2014).

Approaches to improve HSC transplantation have traditionally focused on increasing numbers of donor HSCs. Instead, two recent publications now show that HSC transplantation can be much improved by maintaining pre-existing stem cell potential (Mantel et al., 2015) and by increasing homing efficiencies (Li et al., 2015), providing previously unrecognized or "under-investigated" strategies that may lead to the use of many more donor samples (Figure 1).

To understand whether current isolation procedures are compatible with maximal recovery of stem cell potential, Broxmeyer and colleagues focused on the preparation of bone marrow cells under hypoxic conditions to mimic the oxygen concentration in situ (Mantel et al., 2015). Recovery of mouse and human HSCs under hypoxic conditions led to increased numbers of phenotypic HSCs and correspondingly to improved repopulation potential. HSC numbers were increased because the low oxygen concentration protected them from undergoing an extraphysiologic oxygen shock/stress response (EPHOSS), which leads to elevated differentiation when HSCs are harvested in air. Careful dissection of the involved pathways showed that harvest of HSCs in hypoxia prevents the accumulation of reactive oxygen species by increasing the activity of mitochondrial permeability transition pores (MPTP) that are regulated by cyclophilin D (CypD) and p53. Consistently, CypD knockout mice have increased numbers of HSCs and p53 deficiency prevents air-exposure-induced EPHOSS. EPHOSS can also be prevented by using cyclosporine A (CSA), an FDA-approved small-molecule inhibitor that mimics the protective cell physiological effects of bone marrow harvest under hypoxic conditions in murine and human cells, supporting the immense translational potential of the study. Protection of human HSCs from EPHOSS by CSA may improve the outcome of clinical bone marrow transplantation.

Zon and colleagues applied a different approach to address the same problem in HSC transplantation by harnessing the quantitative power of chemical screens performed in zebrafish (Li et al., 2015). Using competitive transplantation of chemically treated, labeled HSCs combined with in vivo imaging, the authors identified a new lipid mediator important for HSC specification during development and for enhanced HSC engraftment upon transplantation. During development, treatment of the embryo with 11,12-epoxyeicosatrienoic acid (11,12-EET) results in increased numbers of HSCs emerging at the regular site of hematopoiesis but also ectopically in a non-hematopoietic region of the tail, suggesting that 11,12-EET is a strong inductor of HSC fate. Gene expression, knockdown studies, and a chemical suppressor screen in zebrafish embryos showed that increased HSC specification mediated by 11,12-EET depends on PI(3)K-mediated induction of *runx1* expression via the transcription factor AP-1. In adult mice, 11,12-EET treatment of purified HSCs also results in increased engraftment, largely owing to an advantage during homing. Finally, bridging the study to potential clinical use, the authors show that human cord blood cells upregulate the expression of AP-1 family members after brief exposure to 11,12-EET in vitro, evidencing that this eicosanoid pathway for hematopoiesis is conserved between zebrafish, mice, and humans.

In summary, both studies uncover innovative strategies to improve the outcome of HSC transplantation and explore in great detail the involved pathways to identify compounds that can be used for clinical transplantation in the future. Recent approaches to improve transplantation outcomes have focused mainly on in vitro expansion and the generation of HSCs from pluripotent cells. Both scenarios harbor tremendous potential but are to date not advanced enough to be used in experimental or clinical settings (Danby and Rocha, 2014; Vo and Daley, 2015). Instead, Mantel et al. (2015) show that CSA treatment preserves HSC function that is already present but frequently lost due to the isolation procedure and may result in novel approaches to obtain donor samples for clinical HSC transplantation. Similarly, Li et al. (2015) uncover an eicosanoid pathway that improves the natural homing capacity of HSCs. It will be interesting to find out whether this effect is conserved in human HSCs and whether this strategy will allow the use of cord blood samples that have already been obtained and are currently in storage. Such studies in combination with the use of much improved recipient mouse strains that allow the engraftment of low donor HSC numbers in the absence of inflammation (Cosgun et al., 2014; Goyama et al., 2015; Waskow et al., 2009) may present the next step toward clinical translation. Finally, both studies exemplarily link basic research on cell biological functions to clinically highly relevant questions.

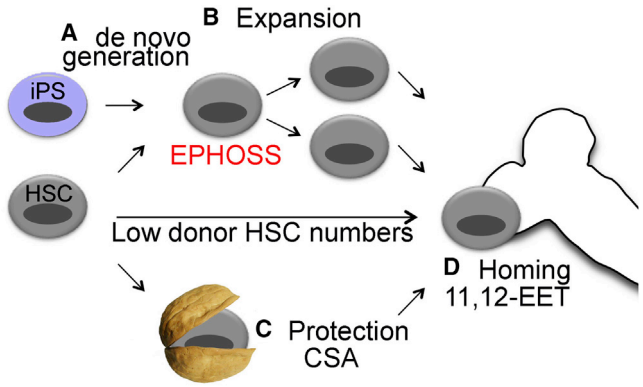

Figure 1. Strategies to Improve the Outcome of Bone Marrow Transplantation by Enhancing HSC Function

Low donor HSC numbers strictly correlate with a poor success rate in bone marrow transplantation. Current methods to increase donor HSCs by de novo generation from pluripotent cells (A) or by in vitro expansion (B) have not proven sufficiently successful to be a viable clinical option yet. Mantel et al. (2015) rescue pre-existing stem cell potential by using CSA that protects HSCs from EPHOSS that is induced by exposure to air (C). Li et al. (2015) present improvements at the other end—the homing of donor HSCs to bone marrow niches that provides a significant advantage for the engraftment efficiency in the long-term (D).

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