TRANSPLANTATION

Normal conditions suit HSCs

Haematopoietic stem cells (HSCs) that are located in specific niches in the bone marrow maintain haematopoiesis for the lifetime of an individual. Because of this unique function, transplantation of HSCs is used to treat individuals with conditions such as primary immunodeficiencies and malignancies. In many cases, patients receive non-specific cytoreductive conditioning before transplantation to ensure that not all HSC niches in the bone marrow are occupied by endogenous HSCs and to decrease the risk of HSC rejection. However, new research published in *The Journal of Experimental Medicine* shows that purified HSCs can engraft histocompatible mice without cytoreductive conditioning.

Recent data indicate that HSC–niche interactions are dynamic and that HSCs are constantly exiting and re-entering the niche. So, Bhattacharya *et al.* reasoned that a small number of HSC niches in the bone marrow should be available for engraftment at any given time. Indeed, they found that HSCs expressing CD45.1 engrafted normal mice expressing CD45.1 and CD45.2 such that ~0.1% of HSCs were of donor origin. By contrast, HSCs expressing CD45.1 could not engraft normal mice expressing only CD45.2, indicating that the minor histocompatibility differences between these congenic strains of mice are sufficient to prevent HSC engraftment. Further analysis showed that $CD4^+$ T cells were essential for preventing the engraftment of donor HSCs with minor histocompatibility mismatches, and transient depletion of $CD4^+$ T cells was sufficient to enable short-term engraftment of minor-histocompatibility-mismatched HSCs.

> “HSC–niche interactions are dynamic and … HSCs are constantly exiting and re-entering the niche”

Purified HSCs were also shown to engraft unconditioned mice lacking recombination-activating gene 2 (RAG2) and the common cytokine-receptor γ-chain (γ_c) — which lack B cells, T cells and natural killer (NK) cells — such that ~0.8% of long-term HSCs were of donor origin. Importantly, this low level of HSC chimerism led to marked reconstitution of B-cell, T-cell and NK-cell numbers, and the reconstituted mice were able to mount a T-helper-2-cell-dependent antibody response comparable to that generated by wild-type mice.

The level of HSC engraftment was not increased from ~0.1%–1% if a higher number of purified HSCs were initially transplanted, but it could be increased by additional rounds of transplantation. Therefore, it seems that endogenous HSCs cannot be displaced from their niches in the bone marrow. Taken together, the data in this report indicate that a small number (~0.1%–1%) of HSC niches in the bone marrow of unconditioned mice are available for engraftment by transplanted HSCs at a given time if host $CD4^+$ T cells are absent or unreactive to the transplanted HSCs. The authors therefore suggest that individuals with lymphoid deficiencies could be treated by HSC transplantation in combination with highly specific lymphoablation rather than with the highly toxic cytoreductive conditioning approaches that are currently used.

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ORIGINAL RESEARCH PAPER
Bhattacharya, D., Rossi, D. J., Bryder, D. & Weissman, I. L. Purified hematopoietic stem cell engraftment of rare niches corrects severe lymphoid deficiencies without host conditioning. *J. Exp. Med.* 27 Dec 2005 (doi:10.1084/jem.20051714)
FURTHER READING Wilson, A. & Trumpp, A. Bone-marrow haematopoietic-stem-cell niches. *Nature Rev. Immunol.* **6**, 93–106 (2006)