

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Illuminating Immune Privilege — A Role for Regulatory T Cells in Preventing Rejection

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Bone marrow transplantation has had a substantive therapeutic impact on survival, but its usefulness can be limited by the lack of matched donors, as well as by the risks of graft rejection and graft-versus-host disease (GVHD). Current strategies attempt to address these issues with conditioning regimens that often include radiation, chemotherapy, and the sustained use of immunosuppressive drugs. These preparative regimens are undertaken in an effort to block the immune response in both host cells and donor cells and are thought to facilitate engraftment by creating space in the microenvironment. Unfortunately, they are by nature toxic and exact a high toll: a significant percentage of bone marrow recipients either succumb to transplant-related death or live with chronic and often debilitating autoimmune diseases triggered by the immune system of the original graft. Thus, there is a substantial need for new therapies that circumvent these problems by exerting better control over the immune system during and after transplantation. An understanding of immune privilege and of the way certain anatomical sites offer protection from an immune response could provide clues about how best to design the next generation of immunosuppressive therapies — ones that, it is hoped, will be less toxic and more effective.

Fujisaki et al.¹ recently reported their use of *in vivo* imaging technology to identify the bone marrow as a potential site of immune privilege. They modeled an allogeneic graft by transplanting dye-labeled hematopoietic stem and progenitor cells (HSPCs) into strain-mismatched host mice. Using intravital microscopy, they were able to detect these hematopoietic precursors up to 30 days after the cells were transplanted into unconditioned hosts, and they observed that these cells were usually located close to the endosteal surface within the mar-

row cavity. Because regulatory T cells are immunosuppressive, the authors searched for these cells in the vicinity of the residual hematopoietic precursors. Using mice with fluorescent dye-labeled regulatory T cells as recipients, the authors found regulatory T cells in close proximity to the hematopoietic precursors (Fig. 1). In contrast, the transplantation of more differentiated allogeneic cells resulted in no detectable cells after 7 days; before their apparent disappearance, these cells were located farther away from the endosteum and from regulatory T cells. Ablation of endogenous regulatory T cells by two different approaches before transplantation resulted in far fewer surviving allogeneic HSPCs, as compared with the numbers of transplanted allogeneic HSPCs in mice with normal numbers of regulatory T cells.

The idea that an allogeneic transplant of stem and progenitor cells can survive without conditioning or immunosuppression may seem surprising. However, the knowledge that transplants fail without suppression is based primarily on studies of chimerism of differentiated cells. The current study is important in part because the authors used imaging technology to look directly into the bone marrow niche, thus permitting insight into the inherent physiological differences in the ability of immature and differentiated cells to survive in an allogeneic environment.

This work is exciting because it raises the possibility that allogeneic transplants in unconditioned hosts could be protected from immune rejection by the coinfusion of regulatory T cells. For long-term successful transplantation, however, protecting HSPCs alone is not enough. Thus, in the future, gaining a better understanding of why immature cells preferentially reside at a potential site of immune privilege and are associated with T regulatory cells, as

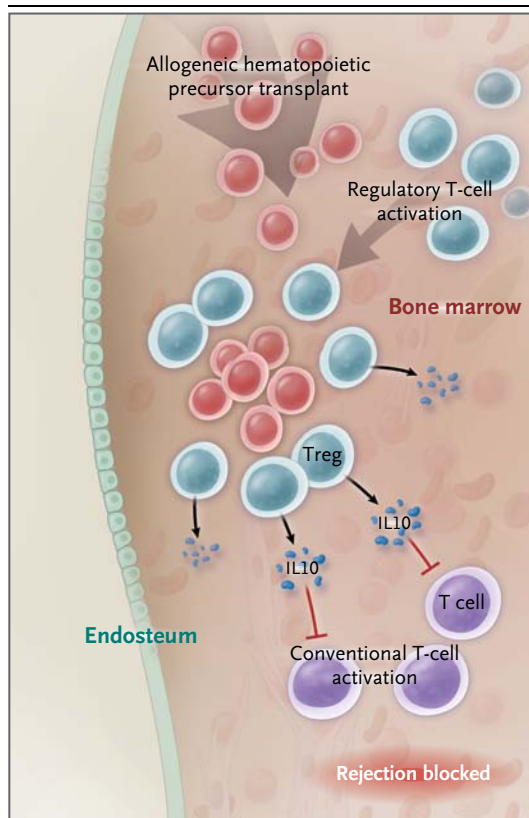


Figure 1. Model of the Bone Marrow as a Possible Site of Immune Privilege.

A recent study by Fujisaki and colleagues¹ supports a model of immune privilege in the bone marrow niche. They transplanted allogeneic hematopoietic stem and progenitor cells into nonirradiated hosts and used in vivo imaging to detect these cells 30 days later. The cells were found close to the endosteal surface and adjacent to regulatory T cells. With the ablation of regulatory T cells (Treg) or the inhibition of interleukin-10 (IL10), protection for transplanted allogeneic cells was lost, suggesting a possible model in which the activation of regulatory T cells and the release of interleukin-10 by these cells repress the activation of conventional T cells and thereby block rejection.

well as finding out whether more differentiated hematopoietic cells could also be protected by these regulatory cells, will be important goals. Part of this task will involve efforts to identify the pathways taken by immature cells to attain

immune privilege. A step in this direction was the finding by Fujisaki et al. that the production of interleukin-10 by regulatory T cells is critical to the survival of the hematopoietic precursor cells in bone marrow.

The possibility that regulatory T cells may be useful in controlling the immune system in the setting of bone marrow transplantation has already been considered. Ongoing clinical trials, informed by a study in mouse models,² involve the use of regulatory T cells to target GVHD. The effects of the coinfusion of induced or enriched natural regulatory T cells derived from the umbilical cord have been tested, and early results suggest that the delivery of such cells may protect against GVHD^{3,4} even in the absence of immunosuppression.³ If the promise of these studies is borne out, it would be worth testing if the delivery of regulatory T cells might provide an alternate strategy to prevent graft rejection. This could pave the way for less toxic transplant-preparatory regimens that could benefit a larger patient pool and might also allow access to the more readily available but more mismatched donor population. By using imaging to illuminate the architecture of a bone marrow transplant, the authors highlight how a more physiological understanding of immune privilege may offer new insight into how to protect graft from an unwanted immune response.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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1. Fujisaki J, Wu J, Carlson AL, et al. In vivo imaging of Treg cells providing immune privilege to the hematopoietic stem cell niche. *Nature* 2011;474:216-9.
2. Hoffmann P, Emann J, Edinger M, Fathman CG, Strober S. Donor type CD4(+)CD25(+) regulatory T cell suppress lethal acute graft versus host disease after bone marrow allogeneic transplantation. *J Exp Med* 2002;196:389-99.
3. Di Ianni M, Falzetti F, Carotti A, et al. Tregs prevent GVHD and promote immune reconstitution in HLA haploidentical transplantation. *Blood* 2011;117:3921-8.
4. Brunstein C, Miller JS, Cao Q, et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. *Blood* 2011;117:1061-70.

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