Hypoxia degradation have been undertaken to target, as evidenced by recent clinical trials in marrow microenvironment.

not specifically studied, increased HIF-2 responsible for familial erythrocytosis.5 Alternatively high levels of HIF-2/H9251 illustrate by Marie Dauenheimer.

incomplete deletion of the transcription factor subunit are sufficient for EPO expression. On the other hand, a recent report by Percy et al5 indicates that EPO synthesis is very sensitive to increased HIF-2α. In a family with a genetic mutation that reduces the degradation of HIF-2α under high oxygen tension, constitutively high levels of HIF-2α were made responsible for familial erythrocytosis.3 Although erythroid progenitor maturation was not specifically studied, increased HIF-2α levels may also have had an effect on the bone marrow microenvironment.

The HIF pathway is a potential therapeutic target, as evidenced by recent clinical trials in which attempts at pharmacologic inhibition of HIF derepression have been undertaken to increase EPO synthesis in patients.4 From the widespread importance of HIF-dependent regulation of gene expression, multiple effects would have been expected. So far, preliminary data indicate that erythropoiesis was preferentially induced through increased EPO synthesis and effects on enzymes involved in iron metabolism that are also under the control of HIF.6 The present study by Yamashita et al may explain why erythropoiesis is particularly sensitive to modulation of HIF-α: because increased EPO falls on “fertile soil,” a bone marrow microenvironment that has been optimized by endothelial-specific, HIF-2α-driven expression of VCAM-1 to provide cell-cell contacts between stromal and hematopoietic progenitors.

**Conflict-of-interest disclosure: The author declares no competing financial interests.**

**REFERENCES**


**GVHD therapy: let there be light!**

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In this issue of Blood, Gatza and colleagues demonstrate in a murine model of GVHD that ECP induces increases in circulating endogenous Tregs.

**Comment on Gatza et al, page 1515**

**Graft-versus-host disease (GVHD) remains one of the most frequent and challenging complications faced by allogeneic stem cell transplantation clinicians.1 While glucocorticoids remain the mainstay of therapy for patients who develop GVHD following the failure of prophylactic immunosuppression, treatment failures are all too common, as are complications associated with the immunologic and systemic effects of steroids.**

**Conflict-of-interest disclosure: The author declares no competing financial interests.**

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were induced by the transfer of ECP-treated splenocytes, and that in vivo purging of Tregs eliminated the benefits of ECP.

Some limitations of this study deserve mention. First, the models used primarily recapitulate acute GVHD, while most of our clinical information about the utility of ECP is derived from studies of patients with chronic GVHD, which is much more difficult to model in mice. Although the authors demonstrate clearly that Tregs were induced by ECP, they do little to demonstrate the mechanism of Treg induction. IFNγ production was shown to be attenuated, yet the authors did not examine TNFα, shown in their own prior studies to be critical in GVHD-associated inflammation, nor did they examine whether ECP induced tolerogenic cytokines, including IL-10 and TGF-β. Finally, while it was shown that ECP-induced apoptosis indirectly induced Tregs, the direct role of cellular intermediaries (especially antigen-presenting cells including dendritic cells) was not examined.

Despite these limitations, this study provides the most convincing evidence to date that the induction of lymphocyte apoptosis by ECP exerts its therapeutic effects through induction of Tregs. This study suggests that altering the ratio of Tregs to alloreactive effectors may effectively reduce GVHD, and provides impetus for other approaches that augment natural levels of Tregs. Better longitudinal studies of GVHD patients, examined before and after ECP therapy, will be required to confirm whether Tregs are similarly induced in humans, and whether other immune functions (eg, virus- and cancer-specific T cells) are relatively spared. It will also be important to utilize this valuable model of ECP therapy to better define the mechanisms of Treg induction. Such knowledge will surely lead us to more effective and/or less invasive approaches to treat GVHD and other human diseases mediated by T-cell dysregulation.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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