mutations are associated with high HbF levels.\textsuperscript{9,10} The role of BCL11A in SAR1-mediated HbF expression remains unclear, as BCL11A mRNA but not protein levels was affected by experimental manipulation of SAR1. Relationships between these and other known γ-globin modifiers may be sensitive to cellular context, requiring animal-based rather than cell-based assays to decipher.

This report suggests that hydroxyurea induces HbF through cellular pathways that overlap with those of other HbF-inducing agents, especially if DNA damage or modification is involved. Zhu et al bring the signaling mechanisms of hydroxyurea-mediated induction of HbF into sharper focus. These findings suggest that SAR1 and/or its signaling partners may provide targets for designing clinically useful HbF-stimulating agents. Identification of specific components of a pathway to γ-globin induction also raises the possibility that screening for such agents may even be adaptable for in vitro assays.

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

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Comment on Taur et al, page 1174

Less (bacterial diversity) is more (deaths)

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In this issue of \textit{Blood}, Taur et al demonstrate that a lack of intestinal microbial diversity independently predicts nonrelapse mortality (NRM) in allogeneic hematopoietic cell transplant recipients.\textsuperscript{1} At the time of engraftment, patients with low microbial diversity were at fivefold higher risk for NRM than patients with high microbial diversity, primarily because of graft-versus-host disease (GVHD).

GVHD remains the major cause of morbidity and mortality following allogeneic hematopoietic cell transplant and limits its use as a curative therapy for malignant and nonmalignant hematologic diseases. The gastrointestinal (GI) tract is affected in nearly all cases of severe GVHD,\textsuperscript{2} and thus better prevention and control of GI GVHD is essential to reducing NRM. Recent studies show that the GI microbiome plays a role in orchestrating the immune responses that culminate in both experimental and human GVHD.\textsuperscript{3,4} The detection of specific microbes by Toll-like receptors on intestinal epithelial cells triggers an inflammatory response that leads to both the recruitment of T cells to the GI tract and activation of the antigen-presenting cells that drive the adaptive immune response.\textsuperscript{5} Damage to the intestinal epithelial barrier, either by pathogens or the pretransplant conditioning regimen, results in translocation of bacteria and their byproducts that can further damage to the intestinal epithelium.\textsuperscript{6} The intestinal mucosal barrier protects itself from such damage by the secretion of antimicrobial peptides, which are primarily produced by Paneth cells and which regulate the composition of the microbiome and maintain intestinal health. When these peptides are in short supply, intestinal homeostasis is disrupted and pathogenic bacterial species can predominate. The role of these antimicrobial peptides in clinical GVHD was confirmed when Reg3α was validated as a GI GVHD biomarker.\textsuperscript{7} The important role played by regulators of bacterial composition in GVHD is further supported by the observation that Paneth cell loss correlates with higher NRM in both experimental and clinical allogeneic hematopoietic cell transplantation.\textsuperscript{3,8}

If regulation of commensal bacteria is important to GI GVHD control, then one would predict that the loss of regulation and the subsequent bacterial species overgrowth and loss of diversity would increase the risk of lethal GVHD. It is in this context that the present
study is particularly significant because it correlates loss of diversity with lack of GVHD control and death. It is likely that overgrowth of specific bacterial pathogens overwhelms the defenses of the intestinal mucosal barrier, resulting in apoptosis of intestinal epithelial cells and permitting gaps for the translocation of the bacterial products that activate the adaptive immune system and promote GVHD (see figure). It is also possible that the bacterial metabolites play an important role in modulating GI mucosal immunity. For example, short chain fatty acids such as butyrate, which are generated by anaerobic bacteria in the intestine, are known to increase the number of regulatory T cells. Regulatory T cells can reduce GVHD. Thus, the overall composition of the intestinal microbiome may modulate GI epithelial health through a variety of mechanisms.

This work has important clinical implications. It suggests that maintenance or restoration of intestinal bacterial homeostasis may prevent or control GI GVHD. The correlation of low bacterial diversity at a single assessment, the period surrounding engraftment, with transplant-related deaths that occurred months later is notable and raises the question as to whether an intervention early after transplant would be effective. One might explore the more selective use of antibiotics, administration of probiotics, or even fecal transplants as strategies to achieve higher rates of intestinal bacterial diversity. In that regard, the finding that bacterial diversity was lowest during active GI GVHD but reverted to normal when symptoms improved supports examining such strategies.

We do not yet know why bacterial diversity is so variable in allogeneic hematopoietic cell transplant recipients. Taur et al report that patients who received intensive conditioning regimens were more likely to have lower bacterial diversity, but their study population was not sufficiently large to identify other risk factors. The variation may therefore be due, in part, to the intensity of therapy prior to transplantation; intensive regimens are more likely to induce febrile neutropenia and subsequent use of broad spectrum antibiotics, which can profoundly reduce intestinal diversity. A better understanding of the risk factors for low bacterial diversity is still needed to design the best clinical trials.

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Less (bacterial diversity) is more (deaths)

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