

Comment on Norona et al, page 1442

# I have a gut feeling...

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**Overcoming graft-versus-host disease (GVHD) remains the holy grail in allogeneic hematopoietic cell transplantation (HCT). In this issue of *Blood*, Norona et al uncover another novel pathway that is critical in this disease, which offers more hope that we will get there.<sup>1</sup>**

In contrast to other autoimmune rheumatologic diseases, GVHD differs in that we have an exact timeline for the onset of disease, namely the infusion of the allogeneic donor cells setting up a T-cell immunologic response of donor against an immunosuppressed host that cannot reject the donor graft. On the side of the donor graft, the numbers of naïve, effector, and memory T cells, regulatory T and B cells, dendritic cells, natural killer cells, myeloid-derived suppressor cells (MDSCs) to name a few, have all been shown to contribute to the disease.<sup>2</sup> Yet there is a plethora of responses in the host that have a profound impact on the level of T-cell response and tissue damage. If the host immune system is not suppressed sufficiently, the host will reject the graft. Conversely, if the host is too damaged (eg, doses of radiation in the 1500 cGy range), there is a higher incidence of acute GVHD (aGVHD).

Many of the elements that are involved in this process have been recently elucidated. The most important has been the involvement of the gastrointestinal (GI) tract. This is not surprising, given that many of our conditioning regimens are toxic to the gut as evidenced by mucositis and diarrhea. Experiments with in vivo imaging demonstrated that the donor cells traffic to the gut first, and from there, they went on to other target tissues, which suggests that a research focus on the GI tract would be fruitful.<sup>3</sup> One specific area of research that has flourished has been the interaction of the gut microbiome with the immune system.<sup>4</sup> Several studies have demonstrated that the composition and loss of diversity of the gut microbiome drives GVHD perhaps through signaling by short chain fatty acids.<sup>5</sup> Another area is the actual gut cells themselves. The epithelial cells that comprise the villi of the GI tract turn over every few days. Thus, the ability to return to homeostasis after the preparatory regimen is heavily influenced by the ability of the intestinal stem

cells to repopulate and give rise to normal villi. Efforts to promote healing of the gut have included keratinocyte growth factor, interleukin-22 (IL-22), and R-spondin, among others. The interaction of intestinal stem cells (ISCs), goblet cells, and Paneth cells (PCs) have been shown to influence the onset of GVHD.<sup>6</sup> The GI tract is also the largest neuroendocrine organ with different cells (eg, K, L, I, G, N, S, D, and M cells) that secrete a variety of hormones involved in absorption, metabolism, motility, inflammation, microbiome regulation, and healing.

In their article, Norona et al demonstrate that protection of the ISCs and PCs (which support the ISCs) results in improvement in GVHD. Specifically, the authors demonstrate that glucagon-like peptide 2 (GLP-2), an enteroendocrine hormone produced by L cells, is antiapoptotic and necessary for the regeneration of PCs and ISCs. This regeneration leads to enhanced production of antimicrobial peptides that cause microbiome changes and improve GVHD. They show that GVHD leads to loss of L cells (being targets of the donor T cells) and that intestinal GLP-2 levels were reduced in both mice and patients with GVHD. By using a clinical grade GLP-2 agonist, teduglutide (approved to treat short bowel syndrome), they were able to show reduced de novo aGVHD and steroid-refractory GVHD in mice through rescue of ISCs and PCs without the loss of the graft-versus-leukemia effect. Teduglutide induced changes in the gut microbiota likely through rescue of PCs that produce antimicrobial peptides, although it did not have an impact on microbial diversity. Moreover, the use of this drug decreased proinflammatory cytokines and increased Claudin-4, an important tight junction protein that perhaps decreases the loss of barrier function. Interestingly, circulatory levels of GLP-2 were elevated in patients with GVHD. Because the function of endogenous GLP-2 is regulated by

dipeptidyl peptidase-4 (DDP4), which is expressed on absorptive and crypt-based enterocytes alongside inflammatory myeloid cells, the presence of DDP4-positive cells in the gut might thus impact bioavailability of GLP-2 and may explain the lack of gut regeneration in the presence of elevated levels of GLP-2 in aGVHD patients.

As with all good studies, there are still many questions to be answered. For example, since L cells make both GLP-1 and GLP-2, what is the contribution of GLP-1, which has significant anti-inflammatory activity? Does the effect of GLP-2 work through insulin-like growth factor-1 (IGF1) and its receptor? Will this drug work in established GVHD in patients? Are there other enteroendocrine cells targeted by the donor T cells or through cytokines that contribute to GVHD pathology? Will there be synergy with other methods to promote ISCs or PCs? Can one deliver exogenous donor L cells grown from gut organoids? There is also the possibility of using stable GLP-2 receptor agonists such as teduglutide to modify microbiota in other disorders (obesity, aging-associated inflammation, cancer), and it may be an interesting perspective that might foster future studies. There are many more questions, but the data from the Norona et al study do support a clinical trial of teduglutide in HCT patients.

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

## REFERENCES

- Norona J, Apostolova P, Schmidt D, et al. Glucagon-like peptide 2 for intestinal stem cell and Paneth cell repair during graft-versus-host disease in mice and humans. *Blood*. 2020; 136(12):1442-1455.
- Chen BJ, Cui X, Sempowski GD, Liu C, Chao NJ. Transfer of allogeneic CD62L<sup>+</sup> memory T cells without graft-versus-host disease. *Blood*. 2004;103(4):1534-1541.
- Negrin RS, Contag CH. In vivo imaging using bioluminescence: a tool for probing graft-versus-host disease. *Nat Rev Immunol*. 2006;6(6):484-490.
- Peled JU, Gomes ALC, Devlin SM, et al. Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2020;382(9):822-834.
- Mathewson ND, Jenq R, Mathew AV, et al. Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. *Nat Immunol*. 2016;17(5):505-513.
- Levine JE, Huber E, Hammer STG, et al. Low Paneth cell numbers at onset of gastrointestinal graft-versus-host disease identify patients at high risk for nonrelapse mortality. *Blood*. 2013; 122(8):1505-1509.

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