particularly those with low MV-PGC and/or high PAI-1, is exciting.

Finally, Cointe et al analyzed plasma factors from patients with sepsis that affected fibrinolysis. Plasma from patients with sepsis was analyzed using a multiplex array for 23 molecules that are known to modulate the uPA/uPAR system. Levels of NE correlated with Gran-MV-PGC. NE has also been shown to degrade PAI-1.[9] Indeed, addition of NE increases the fibrinolytic activity of Gran-MVs because of degradation of PAI-1 (see figure). Therefore, neutrophils increase fibrinolysis in 2 ways: they release uPAR-expressing MVs that bind uPA and increase plasmin generation, and also via release of NE that degrades PAI-1.

The study has some limitations. Although the data supporting the notion that Gran-MVs improve survival in septic mice by rebalancing the coagulation and fibrinolytic systems is compelling, one cannot exclude the possibility that Gran-MVs have other beneficial activities that increase survival of the septic mice. For instance, neutrophil MVs contain annexin 1, which has anti-inflammatory activity. For the mouse experiments, MVs were derived from unstimulated human granulocytes rather than from murine neutrophils. MVs released from human granulocytes cultured under different conditions may have different fibrinolytic activities. One study prepared 2 types of MVs from stimulated human neutrophils and found that only 1 type of MV protected septic mice.[10] Another study found that neutrophil-derived MVs isolated from the peritoneal cavity of septic mice reduced survival of septic mice.[11] Clearly, further work is needed but the current study suggests that MVs derived from human granulocytes may be useful in treating disorders associated with microvascular thrombosis, such as sepsis and COVID-19.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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DOI 10.1182/blood.2021015280

TRANSPLANTATION

Comment on Docampo et al, page 2392

GPR109A in GVHD: friend or foe?

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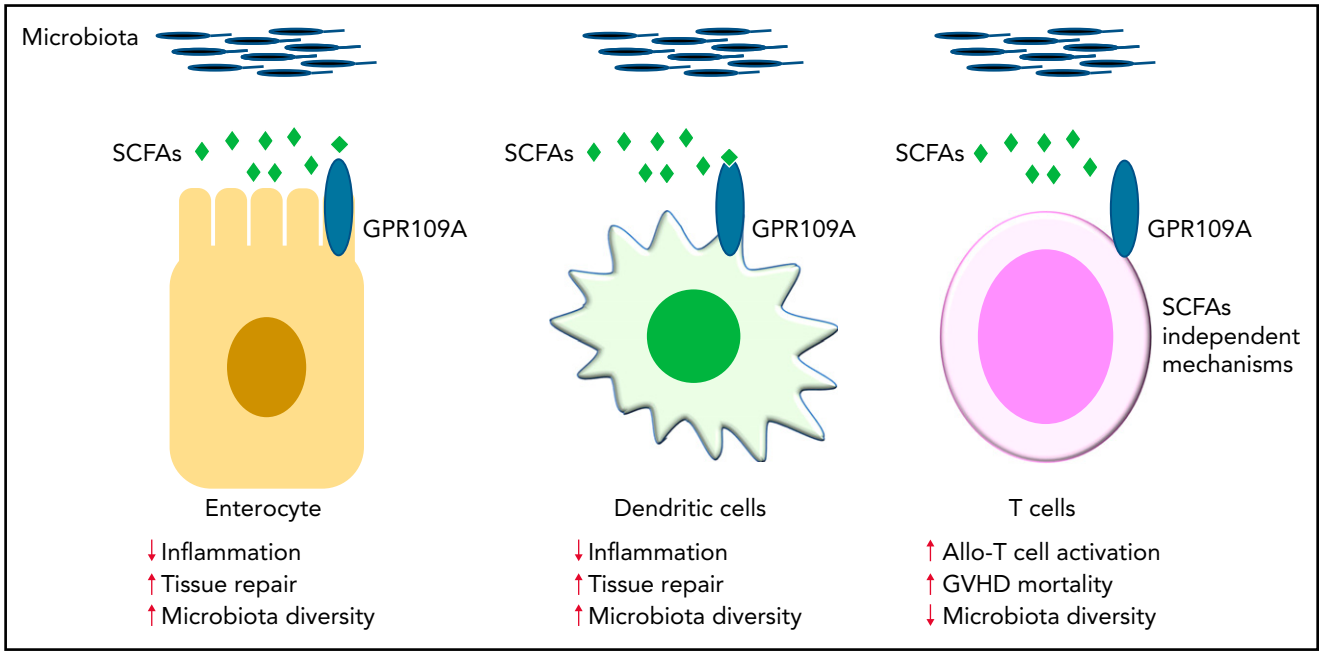
In this issue of *Blood*, Docampo et al[1] explore the role of G protein–coupled receptor (GPR)109A, a receptor for the short chain fatty acid (SCFA) butylate and the B vitamin niacin, in the pathophysiology of experimental graft-versus-host disease (GVHD).

Previous work has demonstrated that activation of GPR109A in colonic antigen-presenting cells (APCs), such as macrophages and dendritic cells (DCs), promotes anti-inflammatory responses by inducing regulatory T cell (Treg) differentiation and interleukin-10 (IL-10) production by T cells.[2] In addition, GPR109A was previously shown to be essential for butyrate-mediated induction of IL-18 and tissue repair in the intestinal epithelium.[2] These data suggested that GPR109A may mitigate GVHD. Docampo et al tested the role of GPR109A in murine models of GVHD and found that its absence in recipients did not alter GVHD severity or mortality. Surprisingly, however, GPR109A-deficient ($GPR109A^{-/-}$) donor T cells caused dramatically less GVHD. Recipients of $GPR109A^{-/-}$ donor T cells had reduced GVHD histopathological scores, decreased proliferation of alloreactive T cells in target organs, and reduced accumulation of alloreactive T cells in target tissues.

Functional analyses demonstrated that $GPR109A^{-/-}$ T cells were more prone to apoptosis and had diminished mitochondrial oxidative phosphorylation capabilities. Hence, alloreactive $GPR109A^{-/-}$ T cells were metabolically dysregulated. However, antioxidant treatment with *N*-acetyl cysteine restored their alloreactivity and ability to drive GVHD. At steady-state, GPR109A deficiency did not alter T-cell subtypes, activation/exhaustion markers, differentiation, or Treg suppressive function, which suggests that GPR109A alters T-cell function under inflammatory conditions. Importantly, the graft-versus-tumor (GVT) and antiviral activities of $GPR109A^{-/-}$ donor T cells were maintained. These data collectively suggest that GPR109A in donor T cells is indispensable for expansion and metabolic homeostasis following allogeneic hematopoietic cell transplantation (allo-HCT). Thus, GPR109A in allogeneic T cells enhances their inflammatory capacity, whereas in gut epithelial



GPR109A is a receptor for the SCFA butylate. Previous work demonstrated that GPR109A is essential for butyrate-mediated induction of IL-18 in the intestinal epithelium, which facilitates repair of damaged tissue and then maintains gut homeostasis and regulates immune responses (left panel).[2,3] In addition, activation of GPR109A in colonic APCs, such as DCs, promotes anti-inflammatory responses (middle panel).[2,3] Docampo and colleagues have now clarified the role of GPR109A in allogeneic T cells, which enhance their inflammatory capacity in a butyrate-independent manner (right panel). Contrary to previous findings[2,3] in gut epithelial cells and APCs, this study demonstrates a novel intrinsic mechanism in allogeneic T cells that is mediated by GPR109A.

cells and APCs it protects against and decreases inflammation (see figure).[2,3] This study demonstrates a novel intrinsic mechanism in allogeneic T cells that is mediated by GPR109A.

GVHD remains a major life-threating complication of allo-HCT. Recent advances demonstrated that the intestinal microbiome and its metabolites play critical roles in the pathogenesis of GVHD.[4,5] In particular, SCFAs, such as butyrate and propionate, play a significant role in promoting and maintaining gut homeostasis and reducing GVHD in murine models.[5,6] SCFAs bind to specific GPRs, such as GPR43 and GPR109A, on gut epithelial cells and immune cells, thereby regulating inflammatory immune responses and mediating tissue-protective functions.[2,3] These functions include inhibiting histone deacetylase activity[5] or the NLRP3 inflammasome.[6] Because mice lacking GPR43 or GPR109A are more susceptible to chemically induced colitis,[2] SCFA-mediated signaling pathways are thought to be indispensable for maintaining gut homeostasis. However, butyrate can also reduce GVHD in a GPR43-independent manner by maintaining enterocyte homeostasis and restoring intestinal epithelial cell (IEC) junction integrity.[6] These data suggest that metabolites and their receptors have intrinsic immune-regulatory functions.

Docampo and colleagues have now clarified the role of GPR109A in allogeneic T cells. Their results suggest that GPR109A has opposing roles in donor T cells, where it increases GVHD, vs IECs, where it likely protects against GVHD. However, in T cells and IECs, GPR109A altered metabolic homeostasis, even in the absence of butyrate. Nevertheless, several outstanding questions remain. First, given GPR109A's opposing influence on the outcome of inflammation in T cells vs APCs or IECs, what factors determine its anti- or proinflammatory immune response? Second, what upstream signaling drives GPR109A expression in alloreactive T cells? Third, what effect do niacin and butyrate have on clinical GVHD? Fourth, because conditioning and GVHD alter the gut microbiome and its metabolites, what is the role of other SCFAs in the absence of GPR109A in allogeneic T cells? Despite these remaining questions, Docampo et al's findings may lead to new strategies for separating GVHD from GVT or antiviral activity by paving the way for research into engineered donor T cells with pre-modified GPR109A expression.

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

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DOI 10.1182/blood.2021014128