

platelet surface through tumor necrosis factor- $\alpha$ -converting enzyme (TACE/ADAM17) and how this affects stored platelet function and survival. Using mice that express a non-functional form of TACE, they confirm that TACE is responsible for the cleavage of GPIb $\alpha$  and GPV, as previously reported.<sup>3-5</sup> Canault et al show that inhibition of TACE is important in posttransfusion clearance of platelets.<sup>1</sup> Shedding of both glycoproteins by TACE is not mediated through PKC, MEK/ERK, or caspases, as demonstrated by pharmacologic inhibitor work.<sup>1</sup> Instead, inhibition of p38 MAPK significantly reduces the shedding of GPIb $\alpha$  and GPV from the platelet surface.<sup>1</sup> Inhibition of p38 MAPK does not affect platelet function but does affect increased platelet recovery and improved platelet function after transfusion.<sup>1</sup>

The work presented by Canault et al<sup>1</sup> suggests that treating all stored platelets with a p38 MAPK inhibitor would increase the efficacy of platelet transfusions. However, questions arise over whether or not this is possible in humans. Posttransfusional function of platelets and survival of transfused mice suggest that the addition of a p38 MAPK inhibitor will not have any adverse effects. Importantly, this is inconsistent with previous data using human platelets in which inhibition of p38 MAPK resulted in the loss of platelet aggregation induced by collagen<sup>6,7</sup> or by low-dose thrombin,<sup>7</sup> although some recovery occurred at higher concentrations of the agonists.<sup>6,7</sup> Is it possible that the differences can be attributed to the model being studied, that is, human platelets versus mouse platelets? Clearly, further experimentation is needed to clarify the clinical effects of long-term storage with a p38 MAPK inhibitor on platelet function, survival, and patient-specific platelet reactivity.

Another issue with this approach is that inhibition of MAP kinase as a means of preventing platelet storage disease is nonspecific. It is well established that this pathway regulates many parts of platelet activation (not just shedding) and many functions in the vasculature. Animal studies looking at the inhibition p38 MAPK in high-salt, high-fat diets have shown a reduction in blood pressure, and improved endothelial-dependent and -independent vasorelaxation.<sup>8</sup> Hypoxia-induced endothelial dysfunction can be reversed with inhibition of p38 MAPK by improving vasorelaxation, increasing NO production, and reducing superoxide levels.<sup>9</sup>

Although these properties, that is, vasodilation, may be beneficial in the setting of elevated blood pressure, vessel dilation can be dangerous in the setting of hemorrhage. Clearly, the global effect of p38 MAP kinase inhibition on the vasculature relevant to bleeding would need to be examined.

Can MAP kinase inhibition be used to maintain the integrity and functionality of platelets stored for transfusion? Whereas this article presents some exciting mechanistic data, more questions are raised concerning the clinical relevance of this approach. As there are many other factors that can affect platelet function during storage, such as bacterial contamination and activation by plasma products, that are independent of p38 MAPK signaling, these interesting data stress the importance of taking a broad view of the problems involved with platelet transfusion.

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

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## ● ● ● TRANSPLANTATION

Comment on Cai et al, page 1669

# Separation of GVHD and GVL

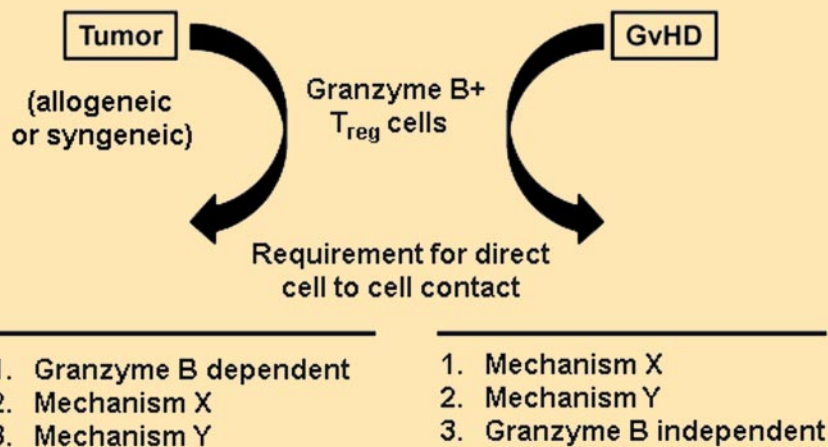
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CD4<sup>+</sup>Foxp3<sup>+</sup>T<sub>regs</sub> suppress antitumor responses using a granzyme B–dependent mechanism while the regulatory control of GVHD by T<sub>regs</sub> exploits a distinct mechanism that is granzyme B–independent.

**A**llogeneic bone marrow transplantation (BMT) is a viable therapeutic option for the treatment of a variety of hematologic malignancies. A major complication of allogeneic BMT is graft-versus-host disease (GVHD), in which the alloreactive T cells transferred along with the bone marrow graft respond to antigenic differences expressed on host tissues. Although this posttransplantation complication is a significant cause of morbidity and mortality after allogeneic BMT, GVHD does appear to have a significant antitumor benefit, often termed a graft-versus-leukemia (GVL) effect. Relapse rates in patients who develop GVHD are considerably lower compared with rates

in patients who do not develop this complication after transplantation. Over the past several decades, attempts to identify and separate specific immune effector mechanisms that mediate GVHD and GVL have been largely unsuccessful. Sometimes the best way to make progress in a field is not to keep trying to get further down the same road, but to take the road less traveled. In this issue of *Blood*, Cai and colleagues have uncovered the fact that suppression of GVHD and GVL appear to function by different mechanisms.<sup>1</sup> If these differences in the regulation of GVHD and GVL effector mechanisms can be exploited, the potential for therapeutic enhancement of allogeneic

## Differential susceptibility of anti-tumor and GVHD effector cells to regulatory T cell suppressive mechanisms



Distinct pathways of CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cell-mediated suppression of GVHD and GVL.

BMT for the treatment of hematologic malignancies is great.

Cai et al evaluated the potential role and underlying mechanisms of CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells (T<sub>regs</sub>) in regulating GVHD after allogeneic BMT. These T<sub>regs</sub> are known to play a critical role in maintaining peripheral tolerance to self-antigens by suppressing autoreactive immune effector functions. T<sub>regs</sub> can also suppress the development of antitumor immunity, which, in fact, may be a consequence of maintaining peripheral tolerance. T<sub>regs</sub> appear to function through a number of different mechanisms to suppress or control an immune re-

sponse. can release immunoregulatory cytokines (IL-10, TGFβ) that can modify activated T cells and suppress the function of antigen-presenting cells. Another mechanism used by T<sub>regs</sub> requires direct cell contact and engagement of CTLA-4 with CD80/86 costimulatory cell-surface receptors. Engagement of these receptors can inactivate the responding T cells and alter dendritic cell function. Regulatory T cells can also eliminate effector cells through a granzyme B/perforin-dependent cytolytic mechanism. Previous studies by this group led by Dr Timothy Ley revealed that CD4<sup>+</sup>Foxp3<sup>+</sup>T<sub>reg</sub> suppression of antitumor

responses was granzyme B-dependent. In this setting, the antitumor immune effector T cells were eliminated through a cytolytic mechanism. In contrast, the present studies by Cai et al indicate that regulation of GVHD by T<sub>regs</sub> was independent of granzyme B. The alloreactive T cells that mediate GVHD were suppressed by an alternate mechanism(s) used by the CD4<sup>+</sup>Foxp3<sup>+</sup>T<sub>reg</sub> compartment (see figure). Interestingly, suppression of both GVL and GVHD immune responses required direct contact between regulatory and effector T cells.

The studies by Cai et al reveal that CD4<sup>+</sup>Foxp3<sup>+</sup>T<sub>regs</sub> appear to use distinct non-overlapping mechanisms to suppress GVHD and the antitumor response (GVL effect) after allogeneic BMT. Differential mechanisms of suppression may allow for the segregation of GVHD and GVL and provide the foundation to specifically modify different allotumor, autotumor, and antitumor immune responses by targeting distinct pathways of T<sub>reg</sub>-mediated suppression. Exploitation of these differential functional mechanisms holds great therapeutic promise. The decades-long struggle to enhance the antitumor response of allogeneic BMT while suppressing the graft-versus-host response finally may be in sight by exploring the road less traveled.

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

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