colonic stem cells form adjacent to the podoplanin-positive stromal cells, and that podoplanin promotes megakaryocyte growth and proplatelet formation in vitro by interacting with CLEC-2. In addition, they revealed that the binding of megakaryocyte CLEC-2 to podoplanin results in chemokine (C-C motif) ligand 5 (CCL5) secretion from bone marrow stromal cells, which is associated with increased proplatelet formation (see figure).

Megakaryopoiesis and thrombopoiesis are complex and hierarchically processes. Tamura et al’s newly discovered function of CLEC-2 on megakaryocytes interacting with podoplanin on fibroblastic reticular cell-like stromal cells provides an important insight into a regulatory process for platelet production in the bone marrow. Although there are likely differences between humans and mice with regard to the fine details of the system, which require further studies, this new understanding of megakaryopoiesis and platelet production may bring us a step closer to manufacturing platelets in vitro for clinical applications.

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Long-awaited news for hepatic veno-occlusive disease

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In this issue of Blood, Palomo et al1 provide new insight into the mechanism of action of defibrotide as an endothelial protective agent, while Richardson et al2 present the encouraging final results of the phase 3 clinical study of defibrotide for the treatment of severe hepatic veno-occlusive disease (VOD), showing a 23% improvement in day +100 survival after hematopoietic cell transplantation (HCT) compared with historical control.

Hepatic VOD, also called sinusoidal obstruction syndrome (SOS), is an early complication in patients undergoing HCT, with an estimated incidence of 13.7% (range, 0% to 62.3%), depending on criteria used to make the diagnosis (Seattle vs Baltimore criteria).3 Clinically, VOD/SOS is characterized by jaundice, painful hepatomegaly, weight gain or fluid retention, and ascites. In its severe form, VOD/SOS can be life-threatening and is associated with multiorgan failure (MOF); historical literature reports a mortality rate >80% on day +100 for patients with severe VOD.3

Although VOD/SOS pathophysiology is not completely understood, endothelial cell damage triggered by cytotoxic chemotherapy and a prothrombotic-hypofibrinolytic state are key features in the pathway. Historically, management of VOD/SOS involved primarily supportive care (diuretics, dialysis, and oxygen) and use of anticoagulants or antifibrinolytics, with limited efficacy and significant adverse effects, such as fatal bleeding with heparin or tissue plasminogen activator.4

In the European Union, defibrotide was approved for the treatment of severe VOD/SOS following HCT in October 2013, based on several studies carried out over the last 15 years, including those of the current authors.5,6 In the United States, there are no approved therapies for VOD/SOS; however, the phase 3 study results by Richardson et al2 in this issue are being provided to the US Food and Drug Administration as part of a New Drug Application in 2015.

Defibrotide is a first-in-class drug, a sodium salt of complex single-stranded oligodeoxyribonucleotides derived from porcine intestinal mucosal DNA. Its mechanism of action is complex and has not been completely elucidated but thought to involve endothelial protection and restoration of the thrombo fibrinolytic balance.

Palomo et al2,3 and others7 have promoted the primary role of endothelial cell activation in the vascular bed as the common pathogenic mechanism in early HCT complications, such as VOD/SOS, thrombotic microangiopathy, capillary leak syndrome, and acute graft-versus-host disease. Defibrotide is thus a candidate drug for study for such conditions with its proposed protective effects on endothelium. Previous studies from Palomo et al5,7 using endothelial cells (ECs) in culture have demonstrated that there is release of soluble factors after HCT to the circulation that contribute to the activation and damage of ECs of macrovascular (human umbilical vein endothelial cell) and microvascular (human mammary epithelial cell) origin and that defibrotide shows a protective effect on both cell lines by preventing the development of the proinflammatory and prothrombotic phenotypes.8

In the current study, Palomo et al1 deepen the investigation into the mechanisms through which defibrotide interacts with endothelial cells. In a series of well-designed experiments using an endothelial cell line of hepatic origin (SK-HEP1), the investigators demonstrate that defibrotide interacts with ECs by attaching to the external cell membrane and then becoming internalized by the cells, mainly through macropinocytic mechanisms. Further, the study gives direct evidence that the interaction of defibrotide with the cell...
membrane is sufficient to perform its anti-inflammatory and antioxidant effects on the endothelium.

This long-awaited understanding of the precise mechanism of action of defibrotide as a therapeutic endothelial protective agent pairs well with the clinical paper by Richardson et al by strengthening the rationale for the drug as a more targeted agent.

As such, we can be encouraged by the final results of the phase 3 trial of defibrotide for severe VOD and MOF, showing an improved day +100 survival and complete response compared with a historical control. The estimated between-group difference in day +100 survival was 23.0% (95% confidence interval [CI], 5.25% to 40.8%; \( P = .0109 \)), using the propensity-adjusted analysis, which was chosen as the method of analysis due to the use of a nonrandomized control group. Similarly, the estimated difference in complete response by day +180 survival was 19% by propensity score (95% CI, 3.5% to 34.6%; \( P = .0160 \)). The day +180 survival is also reported, but the study was not powered for this end point.

A concerning limitation of this study has been the lack of a randomized control design. The propensity analysis is appropriately applied and allows at least the best estimate, given lack of randomization, and thus we may still draw a meaningful conclusion as to trend.

The authors provide the components of the propensity score, which show an equal distribution between the defibrotide arm and historical control of the 4 prespecified factors that would be prognostic of day +100 survival. Note should be made of the disparity in number of patients in the treatment arm (\( n = 102 \)) vs historical control (\( n = 32 \)) and that ~40% of the patients were age \( \leq 16 \) years, making this a fairly young population result in a limited number comparison.

With the defibrotide mechanism of action better defined, we may look forward to the drug’s broader application as an endothelial protectant in the high-risk early post-HCT period and beyond.

S.A. is a coinvestigator in the Jazz Pharmaceuticals defibrotide clinical trial.

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Long-awaited news for hepatic veno-occlusive disease

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