our appreciation of the plasmin-bradykinin axis in hemovascular dysfunction. A recent clinical report links cerebrospinal fluid bradykinin levels to increased brain edema and intracranial pressure in patients with traumatic brain injury, corroborating the results in the current paper.9

In addition to further basic mechanistic studies, the work of Marcos-Contreras and coworkers suggests application of plasmin or bradykinin blockade, or the combination, in treatment of clinical scenarios for which current management is inadequate. Trauma care, for example, has been advanced by the CRASH-2 trial in which tranexamic acid reduced the all-cause relative risk of mortality by 9%—an unprecedented result for a pharmaceutical intervention in this patient population.10 Nevertheless, skepticism regarding tranexamic acid’s utility remains because the trial did not demonstrate significant differences in blood transfusion between study arms. Although blood transfusion may not be the optimal measure of bleeding intensity, this observation has prompted calls to study potential alternative beneficial mechanisms of tranexamic acid in trauma. The present study suggests a promising line of inquiry and an opportunity for studying tranexamic acid and icatibant together in trauma, particularly traumatic brain injury, and other indications in which plasmin activation is associated with pathology.

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REFERENCES


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Comment on Stark et al, page 2435

Platelet HMGB1: the venous clot coordinator

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In this issue of Blood, Stark et al report that the platelet-derived high-mobility group box 1 protein (HMGB1) orchestrates an inflammation-induced venous thrombosis.1

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HMGB1 is a ubiquitous nuclear protein present in the majority of eukaryotic cells. It was discovered as a protein that maintains nucleosome structure and regulates gene transcription. It was later discovered that HMGB1 can also be released from cells into the extracellular space. Bioactive HMGB1 can passively diffuse from necrotic but not apoptotic cells. HMGB1 can also undergo acetylation in the nucleus and be actively released by secretory lysosomes from a variety of immune and nonimmune cells. Once secreted, HMGB1 acts as a danger-associated molecular patterns molecule, triggering inflammation and contributing to the pathology of various inflammatory and autoimmune diseases via activation of receptor for advanced glycation end products (RAGE), TLR2, and TLR4 receptors.

In 2000, Rouhiainen and colleagues demonstrated that, although lacking a nucleus, platelets express HMGB1, and upon platelet activation, HMGB1 is both exported to the cell membrane and released from the cells. Later, it was proposed that platelet-derived microparticles loaded with HMGB1 may contribute to the chronic microvascular injury and endothelial activation observed in systemic sclerosis patients. Vogel and colleagues were the first to demonstrate the contribution of platelet HMGB1 to thrombosis. Ferric chloride–induced thrombus formation in mesenteric arteries was attenuated in mice with a platelet-specific deletion of HMGB1, and blood from these mice was less thrombogenic in a collagen-coated flow chamber system. Furthermore, HMGB1 expression on the platelet surface was significantly upregulated in trauma patients, and platelet-specific deletion of HMGB1 reduced platelet aggregation, microvascular thrombosis, and inflammation as well as organ damage in a mouse model of trauma / hemorrhagic shock.

Stark and colleagues identified activated platelets as the main source of HMGB1 in murine venous thrombosis. In a series of elegant experiments, they demonstrated that HMGB1 released from platelets promotes thrombosis in the inferior vena cava stenosis model by coordinating the crosstalk between platelets, monocytes, and neutrophils. HMGB1 is known to undergo extensive posttranslational modifications that modulate its functions. Interestingly, Stark and colleagues showed that the oxidized, disulfide isoform of HMGB1 is the most important for platelet aggregation, monocyte tissue factor...
expression, and neutrophil extracellular trap formation and subsequent development of venous thrombosis (see figure).

Venous thromboembolism, including DVT and pulmonary embolism, is the third leading cause of cardiovascular death in the world after myocardial infarction and stroke. Anticoagulation, using vitamin K antagonists, heparins, or direct oral anticoagulants, is the primary treatment in patients with venous thromboembolism, both to limit existing thrombus growth and to prevent recurrence. Recent studies on the development of new anticoagulants with a reduced risk of bleeding identified novel therapeutic targets, including factors FXIa, FXIIa, and FXIIIa. Can HMGB1 join that list? Given its important role in chemokine and cytokine expression, prolonged inhibition of HMGB1 could affect the innate immune response to infection. Therefore, targeting HMGB1 may be better suited for the short-term treatment of acute venous thrombosis rather than extended prophylaxis. In addition, platelet-specific deletion of HMGB1 significantly prolonged the tail bleeding time in mice, suggesting that HMGB1 might be important for hemostasis. As an added advantage, targeting HMGB1 might have simultaneous anti-inflammatory and anti-thrombotic effects as well as be effective for the treatment of both venous and arterial thrombosis. Indeed, recent clinical trials demonstrated that a low dose of aspirin, conventionally regarded as an agent that prevents arterial thrombosis, reduced the rate of recurrence of venous thromboembolism. It is important to note that salicylic acid, a metabolite of aspirin, was recently shown to inhibit HMGB1, including the disulfide isomer.

In summary, venous thrombosis can be added to the growing list of pathologic conditions modulated by extracellular HMGB1. The current study by Stark and colleagues highlighted the redox isoform-specific contribution of platelet HMGB1 to sterile inflammation-induced venous thrombosis. Future development of isoform-specific inhibitors of HMGB1 may mitigate excessive inflammation and thrombosis without affecting the beneficial effects of HMGB1 in the resolution of inflammation and tissue repair.

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In this issue of Blood, Kim et al demonstrate, in a mouse model of in utero hematopoietic cell transplantation (HCT), a novel approach to enhancing donor hematopoietic stem cell (HSC) engraftment by mobilizing host HSCs from their endogenous niche and then infusing the donor HSCs during the period of maximal mobilization. Much like a game of “musical chairs”—where everyone tries to sit down when the music stops—when the agents causing mobilization wear off, the donor HSCs have many more empty niches to potentially occupy, thereby resulting in enhanced multilineage engraftment.

Comment on Kim et al, page 2457

Musical chairs: in utero HCT via mobilization

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S
ome infants with genetic diseases of HSCs begin to demonstrate clinical sequelae shortly after birth, a classic example being severe combined immunodeficiency (SCID), in which patients are at immediate risk for the development of serious infections. Other infants, such as those with α-thalassemia, begin to manifest symptoms of their disease even before birth. Hence, when there is prenatal knowledge that such a disease exists, in utero HCT holds great promise for very early correction of the defect. Unfortunately, clinical application of in utero HCT has been significantly limited by the inability to administer the traditional bone marrow “space-making” chemotherapeutics used in most postnatal HCT settings. Therefore, the only successful human reports have been in fetuses with SCID, where there is a profound defect in the patient’s ability to reject donor cells. In these infants, only donor T-cell chimerism has been produced, analogous to the standard outcome seen following postnatal nonconditioned HCT for SCID. However, to expand the practical application of this technique to other diseases, donor engraftment resulting in multilineage cell production needs to be achieved.

To accomplish this, Kim et al hypothesized that blocking the pathways that maintain fetal HSCs in their normal niche (the fetal liver) would open sufficient space for donor HSCs to engraft. To accomplish this, they studied both the CXCR4 inhibitor AMD3100 (plerixafor), as well as fiteparin, a small molecule that antagonizes α4β1-integrin. When administered to the pregnant mothers, both agents rapidly crossed the placenta, with the fetal hepatic niche shrinking and the fetal liver temporarily becoming a large fetal HSC pool space. Future development of isoform-specific inhibitors of HMGB1 may mitigate excessive inflammation and thrombosis without affecting the beneficial effects of HMGB1 in the resolution of inflammation and tissue repair.
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