Comment on Deppermann et al, page 1702

Platelet granules in vascular integrity

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In this issue of Blood, Deppermann et al dissect the role of platelet granule secretion in maintaining vascular integrity during inflammation.1 The authors show that mice lacking platelet granule secretion do not bleed in skin or lung inflammation models. Lack of platelet release however resulted in increased brain hemorrhage after experimental stroke. The latter finding is of clinical importance when designing novel therapies to improve stroke outcome.

It is well known that platelets are crucial for stopping bleeding. Platelets prevent excessive posttraumatic blood loss at sites of vascular injury by forming a platelet plug. Upon exposure of the subendothelial extracellular matrix, platelets are recruited to the site of injury and become activated, resulting in firm adhesion and subsequent platelet aggregation. The molecular mechanisms underlying the formation of a hemostatic platelet plug are relatively well understood: upon exposure of the subendothelial matrix, platelets either interact directly with matrix proteins (eg, via glycoprotein VI [GPVI] and α2β1 to collagen) or bind to von Willebrand factor (VWF) that is deposited at the site of injury. Transient interactions between platelet GP Ib and VWF support platelet tethering at sites of high shear stress. Firm adhesion and subsequent aggregation is mediated by activated integrin receptors such as αIIbβ3. G-protein–coupled receptors mediate activation signals after being triggered by soluble agonists such as thrombin, thromboxane A2, and adenosine 5‘-diphosphate, which reinforce thrombus propagation.

Interestingly, newer insights reveal that platelets also safeguard a different form of hemostasis by maintaining vascular integrity during acute inflammation.7 It was recently shown that single platelets seal vascular breaches caused by neutrophils.3 In contrast to our understanding of vascular injury–induced thrombus formation, much less is known about the mechanisms used by platelets to prevent inflammation–induced hemorrhage. Intriguingly, the process by which platelets maintain vascular integrity at the site of inflammation is independent from the ability of platelets to form a hemostatic platelet plug. Indeed, neither the adhesion receptors GP Ib and αIIbβ3, nor signaling via G-protein–coupled receptors are necessary to maintain vascular integrity in inflamed organs.4,5 The immunoreceptor tyrosine-based activation motif receptors GPVI and CLEC2 on platelets have been identified as crucial mediators supporting vascular integrity.3,5 However, the exact triggers that induce platelet signaling and the downstream effector mechanisms involved in the prevention of inflammatory bleeding remain unclear. Platelet components released from intracellular storage granules have been suggested to be implicated in this process.6

To address the role of platelet granule content in maintaining vascular integrity in inflammation, Deppermann et al generated Unc13d+/−/Nbeal2+/− mice.1 Platelets from these mice are unable to secrete their α- or dense-granule content. The authors used these mice in models of lung inflammation, skin inflammation, and brain infarction. Similar to previous studies, intradermal hemorrhage was observed in platelet-depleted wild-type (WT) mice at the site of inflammation. Strikingly, no bleeding was observed in the inflamed skin of Unc13d+/−/Nbeal2+/− mice. Analogous results were observed in lung inflammation. These experiments show that release of α or dense granules is not necessary to maintain vascular integrity at sites of acute inflammation in skin and lung. Much different results were however obtained in the stroke model used by the authors. Indeed, when subjected to transient middle cerebral artery occlusion, Unc13d+/−/Nbeal2+/− mice were prone to intracranial bleeding in the infarcted areas. Cerebral hemorrhage in these mice resulted in a significantly increased mortality compared with WT animals. In an elegant approach using platelet transfusion experiments, the authors showed that the observed effects of combined Muncl3−/− and Nbeal2−/− mice were related to the platelet-specific secretion effects and not to potential defects in other cells.

The results from Deppermann et al are important in 2 ways. First, this study shows that platelets use different pathways to ensure hemostasis in different inflammatory settings and vascular beds. Second, the results demonstrate that platelet granule release is important to safeguard hemostasis during stroke injury. The latter insight might become particularly relevant for the development of novel treatment of ischemic stroke. Maintaining cerebral hemostasis during a stroke is of high clinical relevance because intracranial bleeding often leads to aggravation of the disease state and increase of mortality. Strategies to prevent or treat acute ischemic stroke should not increase the risk of cerebral bleeding. In this context, anti–thromboinflammatory therapeutics have shown promising preclinical results.7 Thromboinflammation causes progressive ischemic brain damage via complex pathways that include early platelet adhesion and activation but not platelet aggregation.7 Importantly, the release of α or dense granules also contributes to thromboinflammatory brain injury.8,9 Correspondingly, in the current study, Deppermann et al observed reduced infarct volumes and fewer neurological deficits in those Unc13d+/−/Nbeal2+/− mice that did not die of intracranial hemorrhage. Hence, although preventing platelet granule release might seem an attractive strategy to reduce
thromboinflammatory injury, the novel results by Deppermann et al indicate that total abrogation of both α and dense granules would not be ideal due to an increased risk of intracranial bleeding. Of note, previous studies from this group showed that defective secretion from either α or dense granules alone did not affect intracerebral hemostasis during stroke, although it still reduced brain infarct sizes.8,9 Molecules from both α and dense granules thus contribute to cerebral hemostasis in stroke, and release of either type could maintain cerebral vascular integrity. The latter might be the case when blocking initial platelet adhesion, for example by inhibiting the GPIb-VWF interaction, given that this strategy reduces brain damage.10

Several issues remain unanswered. Although Deppermann et al clearly showed the contribution of platelet granules in supporting vascular integrity in the brain, the exact underlying mechanisms remain elusive. Future research is necessary to further identify granular mediators from both α and dense granules that prevent bleeding in the ischemic brain. In addition, the differences between tissue-specific platelet responses to prevent inflammatory bleeding need further investigation. Better elucidation of the intricate interplay between platelets, neutrophils, and the inflamed vessel wall will be key to better understanding the vessel-stabilizing effect of platelets in inflammation.

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REFERENCES
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