Comment on Goerge et al, page 4958
How do platelets prevent bleeding?

Bernhard Nieswandt

A new study presented by Goerge and colleagues in this issue of Blood demonstrates that platelets preserve vascular integrity in inflamed tissue independently of classic adhesion mechanisms.

At sites of vascular injury, platelets adhere and aggregate on the exposed subendothelial matrix to form a platelet plug, which, in combination with the coagulation system, seals the vessel and limits blood loss. The importance of platelets for hemostasis becomes most evident in clinical situations such as idiopathic thrombocytopenic purpura (ITP), during which platelet counts drop. Many patients in these situations develop spontaneous bleeding that may become life-threatening, particularly if it occurs in the brain. However, other patients with equally low platelet counts do not show signs of hemorrhage, suggesting that additional factors may determine the occurrence of bleeding in ITP. The causes have remained elusive probably because in most cases, thrombocytopenia is considered a sufficient explanation of the bleeding diathesis and further studies are not performed.

Goerge et al now provide experimental evidence that inflammation is a potenter trigger of hemorrhage in thrombocytopenia. In a series of elegant experiments, they show that severe thrombocytopenia (platelet counts < 2.5% of control), despite dramatically increasing tail bleeding times, does not cause detectable spontaneous bleeding in mice. This finding confirms that there is no clear correlation between bleeding time and bleeding risk. However, when the animals were subjected to a localized inflammatory stimulus, hemorrhage was noted in the inflamed tissue, but not in noninflamed areas. In vivo fluorescence microscopy revealed the onset of bleeding in the cutaneous Arthus reaction as soon as 20 minutes after the inflammatory challenge. Similar effects were also observed in models of endotoxin-induced lung inflammation and, notably, a model of ischemic brain infarction. This intriguing observation directly demonstrates for the first time that platelets are required for the maintenance of vascular integrity in inflammation, and also shows that thrombocytopenia alone is not sufficient to cause spontaneous hemorrhage.

A second novel and important aspect of this study is that platelet-mediated protection of vascular integrity only requires transient platelet/vessel-wall interactions and that it occurs independently of von Willebrand factor, GPIIb, GPIV, or integrin αIIbβ3, molecules known to be crucial for platelet plug formation. Thus, maintenance of vascular integrity in inflammation and platelet plug formation appear to be mechanistically distinct processes. Based on this hypothesis, one might speculate that inhibitors of firm platelet adhesion and aggregation could efficiently prevent occlusive thrombus formation without increasing the risk of spontaneous bleeding. This sounds like wishful thinking, but indeed, recent studies have shown that inhibitors of GPIIb or GPIV profoundly protect mice from ischemic stroke without increasing the risk of intracranial hemorrhage. Therefore, the work by Goerge et al could have major implications for our understanding of how platelets support vascular integrity and how antithrombotic agents influence hemostasis and/or the risk of spontaneous bleeding.

The study does not clarify how platelets contribute to the maintenance of vascular integrity, but the authors propose an involvement of locally delivered vasoactive mediators released from storage granules during transient interaction with the inflamed vessel wall. It can be anticipated that the current work will stimulate intense research to test this hypothesis.

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

REFERENCES

Comment on Kiladjian et al, page 4922
JAK2V617F: better diagnostic tool than marrow?

Hau C. Kwan

In patients with Budd-Chiari syndrome and with portal vein thrombosis, Kiladjian et al observed that JAK2V617F positivity is indicative of the diagnosis of an underlying Ph1-negative myeloproliferative disorder, that is, polycythemia vera or essential thrombocythosis.
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