How do platelets prevent bleeding?

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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), in 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 potent 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 platelet plug formation occurs independently of von Willebrand factor, GPIb, GPVI, 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 inhibition of GPIb or GPVI profoundly protects 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.

REFERENCES

JAK2V617F: better diagnostic tool than marrow?

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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 thrombocytosis.

REFERENCES
Comment on Obara et al, page 5223

Where the Epo cells are

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In this issue of Blood, Obara and colleagues report on their use of a GFP transgene to mark kidney Epo-producing cells in mice. These cells in the interstitial space express neuronal markers, and their number correlates with plasma Epo levels and increases with hypoxic induction.

JAK2V617F mutation is present in over 90% of patients with polycythemia vera (PV) but only in 50% to 70% of those with essential thrombocytosis (ET), and thus is not useful for the diagnosis of ET. It is also not a good indicator of prothrombotic risk for patients with these myeloproliferative disorders (MPDs). On the other hand, in splanchnic vein thrombosis (SVT), including Budd-Chiari syndrome (BCS) and portal vein thrombosis (PVT), Ph1-negative MPDs are the major underlying predisposing factors. However, it is often difficult to diagnose MPDs in patients with SVTs due to concur rent hypersplenism, gastrointestinal bleeding, and hemodilution. In this issue of Blood, Kiladjian and colleagues present a retrospective multicenter study of 241 patients, 104 with BCS and 137 with PVT, using diagnostic methods including bone marrow biopsy, endogenous erythroid colony formation (EEC), and red cell mass. These were compared with molecular detection of JAK2V617F, JAK2 exon 12 mutation, and MPL mutations (W515L and W515K) for the diagnosis of an underlying MPD.

JAK2V617F was found in 39% of the 241 patients, and abnormal marrow histology was noted in 30%. No patients in this series had JAK2 exon 12 or MPL mutations. The combination of both JAK2V617F and abnormal marrow histology was noted in 44% of patients, JAK2V617F was present in nearly all those patients with both positive marrow histology and abnormal EEC results, while 25% of BCS patients had JAK2V617F but no abnormal marrow histology or EEC. In other words, in these 25% of BCS patients, the MPD diagnosis could not have been made by marrow histology or EEC. This study confirms the findings of an earlier retrospective study with fewer patients, but additionally shows that combined positive results for JAK2V617F and marrow histology provide a high degree of diagnostic accuracy. Both studies indicate that JAK2V617F is a better diagnostic tool for MPDs in BCS and PVT than the traditional hematologic methods of bone marrow histology, endogenous erythroid colony formation (EEC), and red cell mass.

Abnormal EEC without JAK2V617F was observed in 23% of patients, and 58% had discordant marrow histology and EEC. One may speculate that abnormal EEC represented some occult and yet-unrecognized subset of MPDs.

As both BCS and PVT are serious complications, a good prognostic test is always welcome. In this study, the presence of JAK2V617F was able to discriminate those BCS patients with the worst Child-Pugh scores, Clichy prognostic indices, and Rotterdam BCS scores. This is not the case with PVT, nor did presence of PVT affect long-term survival.

One weakness in the Kiladjian study is the tendency to combine BCS and PVT as one syndrome of SVT. BCS is often a more serious condition. Although the diagnostic value for MPDs using the JAK2V617F mutation applies to both conditions, there are differences between BCS and PVT shown in this study. Also, ET and PV were not analyzed separately. Although JAK2V617F does not predict thrombotic risk in PV, some published studies suggest a positive correlation between JAK2V617F and thromboembolic events in ET.

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

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