by MRP1 raises anew the possible importance of this Cbl congener in Cbl coenzyme biosynthesis and trafficking.10

Is there any redundancy for Cbl efflux in the form of other transporters, and are there polymorphisms or mutations in the genes encoding such transporters that may disrupt Cbl homeostasis in humans with resulting disease? Future work on the MRP1-dependent Cbl transport pathway conceivably may also have implications with regard to manipulation of resistance to cytotoxic drugs processed through MRP1.

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

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The smaller, the better: VWF in stroke

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In this issue of Blood, Fujioka and colleagues demonstrate that the von Willebrand factor–cleaving protease ADAMTS13 limits brain infarction in a murine model of ischemic stroke.1

Comment on Fujioka et al, page 1650

THROMBOSIS & HEMOSTASIS
Platelet aggregation at sites of vascular injury is essential for normal hemostasis but also causes myocardial infarction and ischemic stroke, the latter representing the second leading cause of death and severe disability worldwide. Acute stroke treatment currently relies on thrombolysis, which is applicable to only a limited portion of patients, as the treatment is safe only when applied within the first 6 hours after the incident. However, it is also recognized that reflow does not guarantee salvage of brain tissue. An attempt to improve the outcome by application of abciximab antibodies directed against the platelet fibrinogen receptor GPIIb/IIIa recently failed due to excess brain hemorrhages and inefficacy. Thus, there is a strong need for novel treatment strategies.

The initial recruitment of platelets to the injured vessel wall is mediated by the reversible interaction between the platelet receptor glycoprotein (GP) Ib and the large multimeric glycoprotein von Willebrand factor (VWF) bound to subendothelial collagen or the surface of activated endothelial cells, followed by cellular activation and aggregation. Recent studies have revealed that inhibition of GPIb or absence of VWF strongly protects mice from ischemic brain infarction without causing intracranial hemorrhage despite a significant prolongation of bleeding times. This indicates that the GPIb-VWF axis may represent a suitable target for stroke prevention and treatment. The most thrombogenic variant of VWF is ultra-large VWF (UL-VWF; >20 million kDa), which is stored in platelet α-granules and Weibel-Palade bodies of endothelial cells from where it is released in response to injury and/or inflammation to facilitate the recruitment of platelets and immune cells. To limit the thrombotic activity to the site of injury, nonoccupied UL-VWF is rapidly cleaved by the metalloprotease ADAMTS13 to less-active VWF multimers that circulate in plasma. The important physiological function of ADAMTS13 becomes most evident in patients suffering from thrombotic thrombocytopenic purpura (TTP), which is in many cases caused by acquired ADAMTS13-inhibiting autoantibodies. In such patients, neurological deficits are frequently observed that are caused by thrombotic events in the cerebral microvasculature, indicating that ADAMTS13 activity might be a major determinant of cerebrovascular thrombosis.

Fujioka et al now provide direct evidence that ADAMTS13 indeed limits thrombotic events and, consequently, neurological damage in a murine stroke model. In this widely used model, transient cerebral ischemia is induced by advancing a thread through the carotid artery into the middle cerebral artery (MCA), thereby markedly reducing regional cerebral blood flow. It is known that in this model thrombus formation continues despite reperfusion after removal of the vessel-occluding thread and that final infarct size depends on the previous occlusion time. The authors demonstrate that the regional cerebral blood flow at early (0.5 hours) and late (24 hours) time points following a 30-minute transient MCA occlusion (tMCAO) was decreased in Adamts13−/− mice compared with wild-type controls. This was accompanied by increased accumulation of immune cells and thrombi in the brain tissue and finally resulted in significantly larger infarctions and stronger neurological deficits in the mutant animals 24 hours after ischemia. These results are in perfect agreement with those very recently reported in an independent study by Zhao and coworkers, who also found increased susceptibility of Adamts13−/− mice to focal cerebral ischemia. In addition, these authors demonstrated that the infusion of a high dose of recombinant human ADAMTS13 into a wild-type mouse immediately before reperfusion reduced infarct volume but did not cause intracerebral hemorrhage. These findings confirm and extend the concept that the GPIb-VWF axis is of paramount importance for (experimental) stroke development and that interference with this early step of platelet–vessel wall and platelet–platelet interaction represents an attractive therapeutic approach (see figure).

We hope that the compelling evidence provided by these independent investigations will encourage preclinical studies to translate this promising approach from animals to patients.

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