Although the clinical impact of this work remains to be seen, these observations have moved our understanding of how the hematopoietic system redirects lineage differentiation during infection a step forward and also open the possibility of targeting the IFN-γ pathway to restore neutrophil differentiation during bacterial infections.

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

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Comment on Andersson et al, page 1555

High VWF, low ADAMTS13 puts women at risk

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In this issue of Blood, Andersson and colleagues reveal in a case-control study that high VWF and low ADAMTS13 plasma levels are each a risk factor for ischemic stroke and myocardial infarction, and that the combination of both results in a joint effect.

At sites of vascular injury, platelet adhesion and aggregation on the exposed thrombogenic subendothelial matrix is crucial for normal hemostasis; however, under pathologic conditions it may lead to uncontrolled thrombotic events causing life-threatening disease states such as ischemic stroke and myocardial infarction. One major determinant of platelet adhesion to the injured vessel wall under conditions of elevated shear is the interaction between the platelet transmembrane receptor glycoprotein (GP) Ib and the multimeric plasma protein von Willebrand factor (VWF). VWF is synthesized by megakaryocytes and endothelial cells and stored in platelet α-granules and endothelial Weibel-Palade bodies from where it is released in response to stimulation. Released VWF is rapidly immobilized on the damaged vessel wall, which initiates platelet attachment via GP Ib and provides a substrate for firm adhesion through integrin αIIbβ3 (GP Ib/IIa), thereby starting the process of wound sealing by platelet aggregation and coagulation-dependent fibrin formation. Ultra-large VWF (≥20 million kDa) is the most thrombogenic form of VWF and is cleaved to smaller, less thrombogenic forms by the multidomain structure of 185 kDa metalloprotease a disintegrin-like and metalloprotease with thrombospondin type I repeats–13 (ADAMTS13) in the plasma. In humans, qualitative or quantitative abnormalities of the VWF protein cause the VWF disease, an inherited common bleeding disorder, whereas lack of functional ADAMTS13 results in thrombotic thrombocytopenic purpura, which is characterized by the formation of thrombi in arterioles and capillaries. Studies in mice demonstrated that lack of VWF was highly protective in a model of ischemic stroke and improved the neurologic outcome, whereas ADAMTS13 deficiency aggravated the neurologic damage. Interestingly, these studies also revealed that alterations in the VWF-ADAMTS13 system not only affected thrombotic activity but also modulated immune cell recruitment to the affected brain territory, indicating that GP Ib-VWF interactions contribute to inflammatory responses in this setting by yet undefined mechanisms and lead to the concept of stroke being a “thrombo-inflammatory” disease.

A number of clinical studies assessing the association between VWF or ADAMTS13 levels and the risk of cardiovascular diseases have produced partially controversial results. Here, Andersson and colleagues report a case-control study in which they determined VWF and ADAMTS13 plasma levels in young women with a nonfatal first event of either ischemic stroke or myocardial infarction. The results of this study clearly show that either high VWF or low ADAMTS13 plasma levels—determined after the acute phase—represent risk factors for these diseases (see figure). Interestingly, high VWF levels had a greater impact on the risk to develop ischemic stroke or myocardial infarction than low ADAMTS13 levels but the reason is unknown. Another important finding of this study is that the combination of both high VWF and low ADAMTS13 plasma levels conferred a dramatically increased risk for the development of ischemic stroke (2–3-fold) and myocardial infarction (4–7-fold). This result strongly suggests that individuals with an unfavorable combination of expression levels of these 2 functionally linked proteins may be more prone to develop pathologic thrombotic and/or inflammatory events.

Previously, it was reported in the RATIO case-control study that the intake of oral contraceptives by young women conferred an increased risk of ischemic stroke and myocardial infarction. In a second focus of the present study, Andersson et al made the interesting observation that the use of oral contraceptives considerably increased the risk of both myocardial infarction and ischemic stroke in individuals with high plasma VWF levels whereas it only moderately increased the risk of the latter disease in individuals with low ADAMTS13. How oral contraceptives increase the risk of thrombotic diseases and how this is linked to altered VWF-ADAMTS13 plasma levels is also unexplained. One reason could be...
that these substances increase plasma levels of activated procoagulant proteins as shown by Siegerink et al.10 In that study, the risk of ischemic stroke conferred by a combination of high levels of activated intrinsic coagulation proteins and the use of oral contraceptive was found to be higher than expected based on the single effects.

The results of the current report suggest that it will be important to study VWF and ADAMTS13 plasma levels of young women who want to start using oral contraceptives. If VWF and/or ADAMTS13 turn out to be good indicators, screening of these proteins could decrease the number of young patients suffering from thrombo-inflammatory or thrombotic events such as ischemic stroke and myocardial infarction, respectively.

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Comment on Smith et al, page 1566

Tolerant heaven or mHEL trouble

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In this issue of Blood, Smith and colleagues find that an RBC transfusion can induce tolerance to the foreign antigens on the surface of transfused erythrocytes if the animal has not been given an inflammatory stimulus.1 A risk associated with every RBC transfusion is the development of alloantibodies directed against erythrocyte antigens. While anti-RBC antibodies do not develop after most transfusions, these antibodies can be dangerous for subsequent transfusions and pregnancies. Hence, patients at higher risk for harm from these antibodies are premenopausal females and patients likely to receive multiple RBC transfusions, such as patients with sickle cell disease.

Currently, two approaches are routinely used to minimize the development of anti-RBC antibodies. One approach, minimizing transfusion of foreign antigens, is widely used for a limited number of antigens. Indeed, most
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