anti-inflammatory effects; rosuvastatin specifically suppressed the expression of the inflammation parameters monocyte chemoattractant protein-1 (MCP-1) and tumor necrosis factor α (TNF-α) in the vessel wall.[4] It has been suggested that the pleiotropic effects of HMG-CoA reductase inhibitors and PPAR-α activators (eg, inhibition of tissue factor and plasminogen activator inhibitor 1 [PAI-1] expression and of endothelin-1 [ET-1] secretion) participate in the capacity of these molecules to reduce coronary heart disease.

Whether the huCRP-lowering capacity of statins and fibrates is secondary to reduced atherogenesis or a direct independent effect has been clarified by recent studies from the Gaubius Laboratory (Leiden, The Netherlands) on the mechanism of action of these agents. It was initially shown that fibrates reduce CRP levels by down-regulation of IL-1–stimulated CRP gene expression via reduction of nuclear p50-NFκB–C/EBPβ (CCAAT/enhancer binding protein β) complex formation.[5]

In this issue of *Blood*, Kleemann and colleagues (page 4188) have shown that atorvastatin and fenofibrate, at doses higher than those required for cholesterol lowering, decrease basal and IL-1β–induced plasma huCRP levels. Since these experiments were performed in nonatherosclerotic huCRP mice, the authors clearly demonstrate that these compounds exert a direct anti-inflammatory action independent of cholesterol lowering and atherogenesis. Furthermore, using human liver slices it was shown that these drugs suppressed the effect of IL-1β at the transcriptional level. The suppression of IL-1–induced huCRP gene transcription appears to involve both an up-regulation of IκBα, an inhibitor of the activity of NFκB, and a reduction of nuclear p50-NFκB-C/EBPβ complexes. It is of note that this direct anti-inflammatory effect was obtained with both the statins and fenofibrate.

Since huCRP may accelerate the progression of atherosclerosis in apolipoprotein E (ApoE)–deficient mice,[2] these results suggest that lowering huCRP with statins or fibrates will regulate the progression of atherosclerosis. However, the possibility that decreasing huCRP concentration may contribute to arrest plaque formation and decrease the likelihood of cardiovascular accidents, as do the cholesterol-lowering doses of statins in humans, remains to be demonstrated. A response will be obtained in this regard from the ongoing low-cholesterol/high-huCRP trial "Justification for the Use of Statins in Primary Prevention: an Interventional Trial Evaluating Rosuvastatin (JUPITER)."[6]

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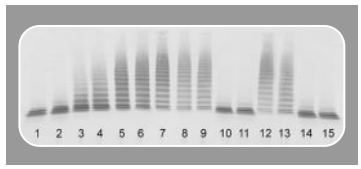
HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

ADAMTS13 and TTP: the clot thickens

Current beliefs are that familial thrombotic thrombocytopenic purpura (TTP) is caused by mutations of the *ADAMTS13* gene and that acquired TTP is caused by autoantibodies that inhibit ADAMTS13 activity. These concepts are consistent with observations on treatment: familial TTP can be effectively treated by plasma infusion to replace ADAMTS13, whereas plasma exchange, presumably performed to remove inhibitory autoantibodies in addition to replacement of ADAMTS13, is more effective treatment for acquired TTP. These observations provide a logical explanation for (1) how TTP occurs in relation to accumulation of unusually large multimers of von Willebrand factor (VWF), and (2) how the treatment works. This is a wonderful example of translational research. However, translation inevitably becomes less clear as more carefully designed clinical observations are reported. Nature speaks many languages with many nuances, subtleties, and surprises.

For example, our assumption about familial TTP is adjusted by the stunning case reports of identical twin sisters who developed TTP at ages 23 years and 24 years by Studt and colleagues (page 4195). Although both sisters had absent ADAMTS13 activity, the presence of immunoglobulin G (IgG) antibodies that inactivated ADAMTS13 and the eventual recovery of normal ADAMTS13 levels demonstrated that the TTP was acquired rather than due to an abnormality of the *ADAMTS13* gene. However, ADAMTS13 levels remained undetectable with persistent inhibitors 5 to 17



months after complete hematologic recovery, demonstrating that severe ADAMTS13 deficiency is not always sufficient to cause TTP.

Another report in this issue by Zheng and colleagues (page 4043) describes 37 consecutive patients with clinically diagnosed TTP. Of 20 patients who had idiopathic TTP, 16 (80%) had severe

ADAMTS13 deficiency, 7 had a demonstrable inhibitor of ADAMTS13 activity, and in 4 patients a high titer of inhibitor predicted a prolonged and severe clinical course. Zheng and colleagues also observed that clinical remissions may occur in spite of continued severe ADAMTS13 deficiency and persistent inhibitor activity.

How can clinicians use this information? Several issues prevent immediate integration of ADAMTS13 assays into routine patient care. Patients with typical TTP may not have severe ADAMTS13 deficiency; therefore, the diagnostic sensitivity of ADAMTS13 deficiency is uncertain. TTP, similar to other thrombotic disorders, may result from multiple risk factors, such as pregnancy, factor V Leiden,[1] obesity, and African American background,[2] in addition to ADAMTS13 deficiency. Furthermore, ADAMTS13 assays are not readily available and their interpretation may often be affected by previous transfusions.

If we learn that one of our patients has severe ADAMTS13 deficiency with a high titer of inhibitory activity, should this influence our management? Zheng and colleagues' observations can support decisions to add immunosuppressive agents to plasma exchange treatment for these patients and escalate immunosuppressive intensity if they do not recover promptly. However, the relation between inhibitor titers and response to plasma exchange is imperfect: patients with strong inhibitors may respond promptly and completely to plasma exchange; others without a demonstrable inhibitor may have a prolonged course.[2]

If we learn that one of our patients has persistent severe ADAMTS13 deficiency while in clinical remission, what should we do? An ominous observation is the description of patients who have recovered from TTP and later had stroke symptoms without thrombocytopenia or anemia.[3,4] In these reports, the documentation of severe ADAMTS13 deficiency and inhibitor activity suggested that TTP was the etiology of the stroke symptoms and the patients responded to rituximab or plasma exchange. However, there is no current role for "maintenance" or "prophylactic" treatment. These observations make the clinical diagnosis of TTP, already often uncertain, even more difficult.

And if we learn that one of our patients with a clinical diagnosis of TTP does not have severe ADAMTS13 deficiency, should this influence our management? Can plasma exchange, with its high risk of complications,[5] be avoided? Not now. Plasma exchange appears to be effective in some patients without severe ADAMTS13 deficiency.[2] Although the rationale for plasma exchange in patients with ADAMTS13 may be clear, the observations of recovery even while severe ADAMTS13 deficiency persists suggest that there are additional reasons why plasma exchange works.

The story of ADAMTS13 is a great milestone in our understanding of TTP. There will be more milestones.

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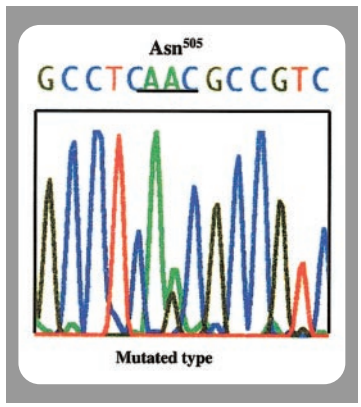
HEMOSTASIS, THROMBOSIS, AND VASCULAR BIOLOGY

Activating mutation in the *c-MPL* gene and FET

Since the identification of the cellular homolog of viral oncogene v-*mpl* (c-MPL) and its ligand thrombopoietin (TPO) as major regulators of megakaryopoiesis and, hence, of circulating platelet numbers, several naturally occurring mutations have been identified in their corresponding genes. Identification of these mutations has come from studies of kindreds diagnosed with familial thrombocythemia or thrombocytopenia. For instance, a germ line mutation in the promoter region of the TPO gene resulting in expression of an unusually stable TPO mRNA transcript has been associated with familial essential thrombocythemia (FET).[1] On the other hand, mutations in the c-MPL receptor gene, including those that lead to amino acid substitutions, have been associated with congenital amegakaryocytic thrombocytopenia.[2]

In a previously reported study, Onishi et al[3] described an experimentally induced substitution from Ser498 to Asn498 (Ser498Asn) in c-MPL, which leads to activation of this receptor. Interestingly, an activating mutation has now been identified in a Japanese pedigree with FET, as described by Ding and colleagues (page 4198). A point mutation was identified in the *c-MPL*



gene segment encoding the transmembrane domain, resulting in a shift from Ser to Asn at amino acid position 505 (Ser505Asn). Importantly, this mutation was detected in all 8 family members with thrombocythemia but in none of 8 other unaffected members in this family or in 19 cases of sporadic ET. These findings were augmented by studies of an interkeukin-3 (IL-3)–dependent cell line that was transfected with either wild-type or mutated (Ser505Asn) *c-MPL* cDNA.