In this issue of Neurology®, Giwa et al.¹ report robust expression of thrombomodulin (TM) in small vessel disease, i.e., in small brain arteries or arterioles that exhibit the typical hyalinized thickening characteristic of chronic hypertensive changes. Using immunohistochemistry of postmortem brain tissue, the authors demonstrate extensive presence of TM in these small arterial vessels, with substantial association between extent of vessel sclerosis and TM expression. Not only was small vessel TM expression significantly less in age-matched controls, but younger subjects with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy also exhibited increased TM expression in small caliber arterial vessels. Enhanced expression of TM thus appears to be characteristic of cerebral small vessel disease, and the authors suggest that the TM in this setting may be both compensatory and protective.

It would be an understatement to say that TM is not commonly discussed within neurologic circles. Within the field of vascular biology, however, TM remains an intense focus of attention, with a recent review article even referring to this molecule as the “protectorate God of the vasculature.”² TM is an integral membrane protein routinely found in vascular endothelium of systemic blood vessels. TM’s function, as its name implies, is to modulate the powerful prothrombotic molecule thrombin (figure). In the presence of TM, thrombin not only becomes incapable of generating fibrin clot from fibrinogen, but the TM-thrombin complex also activates circulating protein C. Activated protein C, in turn, has an important anticoagulant function including inactivation of clotting factors Va and VIIIa.² TM thus appears to have a crucial role in maintaining vessel patency and blood fluidity, at least in systemic vessels.

TM became a topic of neuroscientific interest with the observation suggesting that TM is absent in brain microvessels.³ Further immunohistochemical study demonstrated that TM, while difficult to demonstrate, was indeed present in brain capillaries and had a regional variation consisting of particularly low abundance in brain areas where small vessel infarction is common.⁴ Consistent with the restricted expression observed in fixed tissue, cell culture studies showed transcriptional regulation of TM by astrocytes in a blood–brain barrier model, with approximately 20-fold reduction of TM mRNA in presence of the blood–brain barrier phenotype.⁵ Restricted expression of TM by brain capillaries represents one of the first examples of organ-specific regulation of thrombosis and hemostasis.⁶

The function of TM in normal brain has received limited attention. Despite its restricted expression in brain capillaries, TM appears to be functionally active in brain as demonstrated by protein C activation in brain vasculature, when measured during transient surgical carotid occlusion.⁷ Nevertheless, a major role for TM as protector against human brain thrombosis remains to be demonstrated, particularly given the apparent absence of contribution to stroke risk by TM polymorphisms.⁸

Clues to the function of brain TM may come from observations in transgenic and knockout mice. Studies of TM-deficient mice have demonstrated extensive increased fibrin deposition (as much as 10- to 30-fold) in lung, heart, spleen, and liver; however, the brain was spared an increase in fibrin deposition.⁹ This observation was later expanded upon by studies of mice deficient in both TM and tissue factor pathway inhibitor (TFPI), another endothelial anticoagulant molecule. TFPI inhibits the tissue factor-VIIa complex, and TFPI heterozygosity combined with TM deficiency results in relatively selective albeit limited fibrin deposition in brain.¹⁰ Thus, TFPI may help compensate for the relative paucity of brain TM, and contribute to brain vascular patency under normal conditions.

These clinical and basic science findings have largely pointed to a relatively limited role for brain TM under physiologic conditions. The novelty of
the findings of Giwa et al.\textsuperscript{1} relate to a suggested role for TM in the pathogenesis of cerebral small vessel disease. Despite its high prevalence, pathophysiology of small vessel infarction is not well understood. This is due to the fact that while small vessel stroke is an important cause of morbidity, it is not a fatal disease and thus postmortem studies of small vessel stroke are typically conducted well after the acute infarction.

It is tempting to speculate that the robust TM observed in small vessel disease is compensatory for the relative paucity of TM in downstream capillaries. Is small vessel disease TM really protective? That question will require careful comparative analysis of small vessel infarction and small vessel TM expression, a topic not addressed by the current article. Nevertheless, these observations of Giwa et al. are likely to awaken interest in TM by stroke neurologists. The report of protective benefit of recombinant human soluble TM in patients with disseminated intravascular coagulation\textsuperscript{7} may help generate attention for a clinical trial of this compound in acute ischemic stroke. A recent trial of activated protein C in acute stroke was unfortunately terminated due to poor enrollment. However, recombinant soluble TM has a theoretical advantage over activated protein C in that the former may have a thrombin-specific effect and thereby target ongoing thrombus in acute ischemic stroke. It hardly seems farfetched to envision a future in which TM and the brain are prominently linked in the minds of stroke neurologists.

**DISCLOSURE**

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**REFERENCES**