To the editor:

Increased susceptibility of von Willebrand factor to proteolysis by ADAMTS13: should the multimer profile be normal or type 2A?

The size of von Willebrand factor (VWF) is a major determinant of its biologic activity, the largest multimers being the most efficacious in supporting platelet adhesion and aggregation during primary hemostasis. In the dynamic situation at the time of hemostatic challenge, if VWF possesses a normal size distribution but is more fragile through increased susceptibility to proteolysis, the efficiency of primary hemostasis may be compromised.

However, is increased susceptibility of VWF to proteolysis compatible with a normal multimer profile in the circulation? Information to date suggests the answer should be “no”: group 2 type 2A von Willebrand disease (VWD) variants show increased susceptibility to proteolysis, and this appears to be the underlying explanation for the characteristic loss of large and intermediate multimers from the plasma.

Recent findings in type 1 VWD (in which the multimer profile is normal but the quantity of VWF decreased) may therefore appear paradoxical: the cysteine allele of the VWF amino acid polymorphism Tyr1584Cys has been shown to be enriched in a cohort of patients with type 1 VWD and also has been shown to correlate with increased susceptibility of VWF to proteolysis by ADAMTS13.

Can increased susceptibility of VWF to proteolysis be reconciled with a normal multimer profile? Several potential explanations exist, but perhaps the most plausible comes from a comparison of 2 independent data sets in the literature. In 1997, Tsai et al investigated the proteolysis of recombinant type 2A VWF mutants R1597W and R1597Q. For both mutations, the expressed mutant VWF showed increased proteolysis compared with wild-type VWF. For the R1597W mutant, the increased proteolysis was formally measured and found to be approximately 4 times that for wild-type VWF. This contrasts with a mere 13% to 23% increase in VWF proteolysis, associated with the Tyr1584Cys polymorphism. Additionally, Tsai et al found that R1597W and R1597Q exist in susceptible conformations and are cleaved under conditions that cause little cleavage of normal VWF, whereas for the Tyr1584Cys variation, as for wild-type VWF, mild denaturation was required for proteolysis to occur.

Together, these observations indicate that there is an 18- to 30-fold difference in the susceptibility to proteolysis of the type 2A VWF variants compared with VWF possessing C1584, and in vivo the former are likely to be overtly susceptible to proteolysis, while the latter may require shear stress.

The available data therefore take us some way toward answering the question posed at the outset of this letter: our first instincts would lead us to predict a type 2A profile, but VWF appears to enjoy the element of surprise and has clearly presented us with a normal profile in the case of the Tyr1584Cys variation. It appears that increased susceptibility to proteolysis can masquerade in different forms according, at least in part, to its extent or dependence on shear forces.

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References

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