Maximized Hemostasis

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Plasma procarboxypeptidase-B (1-4), known also as TAFI (thrombin-activatable fibrinolysis inhibitor) (5, 6), links coagulation and fibrinolysis (7, 8). Mediated and facilitated by a complex of thrombin with thrombomodulin (9), TAFI is activated to TAFIa (plasma carboxypeptidase B), which in turn cleaves C-terminal lysine residues from fibrin. Since plasminogen, plasmin and tissue plasminogen activator (TPA) attach to lysine binding sites, the loss of lysine from fibrin limits fibrinolysis. This makes physiologic sense, since an area of hemostatic need, i.e., a vascular penetration, requires immediate and unadulterated clot formation. A clinical condition of decreased coagulation, such as classic hemophilia, not only is deficient in thrombin and fibrin formation, but by virtue of low TAFI formation, also allows fibrinolysis to proceed relatively unimpeded. The combination of less fibrin and more lysis together contributes to the bleeding seen in patients with factor VIII deficiency. Similarly, patients with deficiency of contact-induced coagulation also have decreased TAFI activation (10), perhaps by inadequate completion of clotting after initial extrinsic activation. In further support of the physiologic role of TAFI are reports of hemophilic management with recombinant factor VIIa (11) or TAFI itself (12). In both instances, increased TAFI content and activity are deduced to result in less fibrinolysis, and therefore improved hemostasis. These reports reinforce prior clinical trials that proved the efficacy of the anti-fibrinolytic agent EACA (epsilon aminocaproic acid) in sustaining the hemostatic effect of factor VIII concentrates after dental surgery (13).

Now comes a further connection of coagulation and fibrinolysis, this time as regards thrombolytic treatment. We know that thrombin is present on the surface of fibrin and exerts catalytic activity undisturbed by antithrombin III (AT III) or by heparin anticoagulation (14, 15). With clinical or experimental thrombus formation and especially with the added action of a plasminogen activator (PA) such as TPA or streptokinase (16), the increased thrombin activity results in increased TAFIa levels. The result is a potential for inhibition of PA-induced therapeutic thrombolysis. Prior work shows that experimental thrombolysis with TPA can be potentiated by inhibition of TAFI (17), which prevents loss of lysine binding sites and allows TPA and plasminogen binding. Small molecule AT III-independent thrombin inhibitors also potentiate TPA-induced thrombolysis (18), but it was not known whether this effect was mediated by an effect on TAFI activation. The report by Mattson and colleagues in this issue of Thrombosis and Haemostasis (19) answers this question in the affirmative. Melagatran inhibits clot bound thrombin, thereby blocking TAFI activation; this action would not be anticipated with AT III-dependent anticoagulants such as heparin (15).

Yet, for all the evidence of physiologic relevance, Nagashima and colleagues (20) show that homozygous TAFI-deficient mice, induced by targeted gene disruption, are totally normal as regards survival, development, fertility, bleeding tendency, or protection against thrombin-induced disorders such as DIC. These authors suggest that while “TAFI plays a regulatory role in t-PA-induced thrombolysis, its effect on endogenous fibrinolysis may be more subtle”. Subtlety, redundancy, balanced opposites – these are all part of the homeostasis of hemostasis. Perhaps the most important aspect of TAFI is the most obvious, namely, that hemostasis, when needed, must be effective. Based on studies of tissue factor, we have concluded that animals respond to bleeding with "maximized hemostasis" (21). Starting with an abundance of tissue factor exposed at an injury site, and enhanced by an infinite concentration of clotting factors focussed onto the surface of massed activated platelets, thrombin is generated quickly and then in quantity to perpetuate and amplify the clotting cascade. Thrombin not only clots fibrinogen, but it protects fibrin from premature lysis by endowing it with crosslink sites and by depleting it of lysine binding sites, through the respective actions of factor XIII and TAFI, both activated by thrombin. In this situation, the hemostatic response is total and complete, overwhelming all inhibitors and ceasing only when the substrates for coagulation are locally consumed. TAFI is another piece of the machinery that contributes to “maximized hemostasis” (21).

References

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