Thrombosis down to the vessel wall

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to 20 mg/kg of anti-CD40L administered every 2 to 4 weeks although the responses are rarely durable. These abstracts,[3-5] together with the study reported here, suggest that CD40/CD40L blockade with IDEC-131/E6040 is a potentially effective therapy for refractory ITP through selective suppression of autoreactive T cells to platelet antigens.

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2. Van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukoc Biol. 2000;67:2-17.
3. George J, Raskob G, Lichtin A, et al. Safety and effect on platelet count of single- dose monoclonal antibody to CD40 ligand (ANTOVA™) in patients with chronic ITP [abstract]. Blood. 1998;92:707a.
4. Bussel J, Wissert M, Oates B, et al. Humanized monoclonal anti-CD40 ligand antibody (hu5c8) rescue therapy of 15 adults with severe chronic refractory ITP [abstract]. Blood. 1999;94:646a.
5. George J, Raskob G, Bussel J, et al. Safety and effect on platelet count of repeated doses of monoclonal antibody to CD40 ligand in patients with chronic ITP [abstract]. Blood. 1999;94:19a.

And a final message from antithrombin

Much is now made of the finding that the genome of the human is only somewhat larger than that of the simplest of organisms. Essentially then, all species are composed of a similar array of constituent proteins. What makes us special is not the number of these proteins but the way evolution has adapted them to allow their function to vary from tissue to tissue. As hematologists, we have been able to see exactly how this happens through the advances over the last decade in our understanding of the molecular mechanisms of coagulation. It turns out that thrombin is not just a passive protease but an allosterically controlled protein that changes its function from initiator of coagulation in the arterial circulation to anticoagulant when it binds to the endothelium of the capillaries. Similarly, the plasminogen activator inhibitor PAI-1, which has a prime function in controlling fibrinolysis, has evolved a series of complex interactions that also affect tissue growth and differentiation. PAI-1, as with other serpins, traps its target protease with a springlike movement of its reactive site, which shifts from the exterior to the interior of the molecule. This mechanism normally occurs in serpins following proteolytic cleavage of the reactive site, but with PAI-1 it can also occur spontaneously, without cleavage of the loop, to give an inactive latent form. The maintenance of PAI-1 in its active form is due to its allosteric interaction with a plasma protein vitronectin, but vitronectin also competitively binds to a range of cell surface integrins and activators. This leads to a series of complex molecular and cellular interactions that are well described as cross-talking. An increasingly recognized contributor to such interactions, the mobile phones, so to speak, of cross-talking, are the heparan proteoglycans, epitomized in hematology by the heparins.

Evolution has added yet another layer to this complexity in the utilization of spent coagulation factors as signals for a variety of tissue responses. An example is the adaptation of a fragment of plasminogen to yield endostatin, an inhibitor of angiogenesis. But the most spectacular example of antiangiogenesis came with the finding by O'Reilly and others[1] that spent forms of antithrombin blocked angiogenesis in the mouse, with an accompanying induction of tumor regression. Antithrombin can, like PAI-1, undergo a conformational transition to latent and cleaved forms, but what has puzzled the field is how such minor rearrangements could lead to such a remarkable suppression of angiogenesis. An answer is provided here in the paper of Zhang and colleagues (page 1185). They show that the latent and cleaved, but not the native, forms of antithrombin produce a down-regulation of the gene for the proangiogenic proteoglycan, perlecan. The effect is to decrease the cell surface receptors for the growth factors that stimulate angiogenesis. The importance of this paper is in the completeness and credence it adds to the earlier findings of O'Reilly et al. It opens up intriguing prospects for biochemical, structural, and cellular research. We really are beginning to listen in to, as well as observe, the cross-talk that underlies our biologic complexity.

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1. O'Reilly MS, Pirie-Shepherd S, Lane WS, Folkman J. Antiangiogenic activity of the cleaved conformation of the serpin antithrombin. Science 1999; 285:1926-1928.

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Protein C is the major natural anticoagulant and a complete deficiency leads to a severe thrombotic tendency shortly after birth. It is activated by thrombin when it is bound to thrombomodulin on the endothelial surface. Since thrombin is the central procoagulant, this constitutes a strong regulatory system to keep coagulation limited and localized. Activated protein C (APC) inhibits coagulation, in the presence of its cofactor protein S, by proteolytic cleavage of procoagulant factors Va and VIIIa. Reduced performance of this system, such as in partial (heterozygous) deficiencies of protein C or protein S, or in an amino acid change at one of the cleavage sites of factor V, as in factor V Leiden, results in thrombophilia (ie, an increased risk of venous thrombosis).

The endothelial protein C receptor (EPCR), discovered in 1994, has been reported to enhance the activation of protein C by thrombin bound to thrombomodulin.[1,2] It is logical to postulate that abnormalities in this receptor play a role in the etiology of venous thrombosis. Because the receptor is bound to the endothelial cells of the blood vessels, its function cannot be readily assessed in vivo. However, a soluble form of EPCR (sEPCR) can be measured in plasma, which is probably a degradation product of EPCR, but still has some of the functions of EPCR, such as binding to protein C. Interestingly, levels of sEPCR have a strikingly bimodal distribution in plasma, suggestive of single locus genetic control.[3]

Poor function of EPCR could cause