MFps/Fes displayed numerous aberrant vascular structures in the yolk sac and defects in cardiovascular and craniofacial development. These and other results suggest that constitutive MFps/Fes activity in the absence of normal Flk1 signaling leads to exuberant vasculogenesis/angiogenesis. Finally, Haigh and colleagues demonstrate that MFps/Fes expression in *Flk1* null or heterozygous ES cells results in an increase in migratory behavior of mesodermal cells in vivo and a 5- to 10-fold increase in hemangioblast development in vitro. Though no direct interaction between Flk1 and Fps/Fes was demonstrated, the results of the study suggest that Fps/Fes may play a role downstream of VEGF-A/Flk1 signaling and/or complement a parallel signaling pathway.

One surprising result was that MFps/Fes expression failed to rescue hematopoietic development in the *Flk1* null ES cells. The authors suggest that a more detailed evaluation may indicate some level of rescue that was missed in the current study. As vascular smooth muscle cells are also derived from Flk1-expressing cells, future studies may also wish to address whether MFps/Fes rescues this lineage in *Flk1* null ES cells.

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von Willebrand factor: polymorphism predicts prompt polypeptide proteolysis

von Willebrand factor (VWF) has at least 3 important hemostatic roles: (1) bound to collagen, it captures platelets from rapidly flowing blood at sites of vessel wall injury; (2) it is able to cross-link platelets during aggregation, particularly at sites of high fluid shear stress; and (3) it serves as a carrier for coagulation factor VIII, which it delivers to the sites of enzyme complex assembly when it binds platelets. VWF is synthesized in only 2 tissues, endothelial cells and megakaryocytes, and in both it is either secreted constitutively or stored in specialized granules, the Weibel-Palade bodies or α-granules, respectively, from which it is released when the cells are stimulated. This large polypeptide (2791 residues before cleavage of the 741-residue propolypeptide) first forms dimers in the endoplasmic reticulum through a C-terminal disulfide bond. In the Golgi, the dimers attach to each other through disulfide bonds near their N-termini, forming concatamers of potentially enormous length. These large multimers, called ultra-large VWF (ULVWF), are abnormally reactive by all measures of VWF activity, including their ability to bind platelets and collagen.[1,2] When released into the plasma, however, ULVWF multimers are rapidly processed to smaller, less-reactive forms through the action of the plasma protease ADAMTS-13, a reaction that somehow stops short of completely degrading VWF. ADAMTS-13 cleaves a site within the VWF A2 domain, 1 of 3 tandem A domains. The other 2, A1 and A3, bind platelet glycoprotein Ibα and collagen, respectively. Unlike A1 and A3, however, A2 is not enclosed within a disulfide loop, which may allow access to the cleavage site to be regulated by shear stress, thereby providing a mechanism to limit the extent of VWF proteolysis. Failure of VWF proteolysis due to congenital or acquired ADAMTS-13 deficiency underlies a severe and potentially catastrophic disorder, thrombotic thrombocytopenic purpura (TTP).[3]

In this issue of *Blood,* Bowen and Collins (page 941) describe a polymorphism within the A2 domain that increases VWF's susceptibility to proteolysis in plasma, with all evidence pointing to ADAMTS-13 as the responsible protease. It is curious that these investigators found the polymorphism while investigating a patient with type I von Willebrand disease (VWD), a disorder caused by global reduction in VWF levels, affecting multimers of all sizes. This patient had a normal pattern of VWF multimers in her plasma but displayed accelerated VWF proteolysis when her cryoprecipitate was incubated with cryo-poor plasma, a source of ADAMTS-13. The single nucleotide change (A to G) converts Tyr1584 to Cys at a site 21–amino acids N-terminal to the ADAMTS-13 cleavage site, and appears responsible for the enhanced susceptibility to proteolysis. The gain of a Cys residue within A2 is of interest and may explain the association of the variant with increased VWF proteolysis, given the recent finding that plasma disulfide reductase activity, in addition to proteolysis, may reduce the size of VWF by reduction and may enhance its proteolysis.[4]

The clinical consequences of this polymorphism are unclear. It is yet not determined whether the polymorphism is widespread or ethnically restricted. Nevertheless, its association with a more severe bleeding phenotype in a patient with type I VWD suggests that it can enhance the tendency to bleed when in the setting of other hemostatic defects. It is also possible that the polymorphism could ameliorate the effects of ADAMTS-13 deficiency, with carriers being spared the full spectrum of TTP. Finally, polymorphisms that moderately increase the susceptibility of VWF to proteolysis may modulate the tendency to thrombosis in other instances in which platelet thrombi are major contributors—in myocardial infarction and stroke, for example.

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1. Furlan M. Von Willebrand factor: molecular size and functional activity. Ann Hematol. 1996;72:341-348.
2. Fischer BE, Kramer G, Mitterer A, et al. Effect of multimerization of human and recombinant von Willebrand factor on platelet aggregation, binding to collagen and binding of coagulation factor VIII. Thromb Res. 1996;84:55-66.
3. Moake JL. Thrombotic microangiopathies. N Engl J Med. 2002;347:589-600.
4. Xie L, Chesterman CN, Hogg PJ. Control of von Willebrand factor multimer size by thrombospondin-1. J Exp Med. 2001;193:1341-1349.

NF-κB activation in atherosclerosis: a friend or a foe?

Atherosclerosis is an inflammatory disease of the arterial wall that carries an important socioeconomic burden. The severe clinical manifestations of atherosclerosis (myocardial infarction, stroke) are mainly due to the