inside blood commentary

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Comment on Xu et al, page 11

Angiogenesis and the ADAMTS13-VWF balance

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In this issue of *Blood*, Xu et al describe a new function for the metalloprotease ADAMTS13 in blood vessel formation following brain ischemia. Using multiple approaches in mice, they show that ADAMTS13 is required for neovascularization and vascular repair following ischemic stroke. Not only was neovascularization reduced in ADAMTS13-deficient mice, but injection of recombinant ADAMTS13 in wild-type mice also improved vascularization and functional recovery 14 days after ischemia.[1]

The authors also show that these effects are mediated by the only known target of ADAMTS13, namely von Willebrand factor (VWF), a hemostatic protein that mediates platelet adhesion and acts to stabilize coagulation factor VIII.

ADAMTS13 controls the hemostatic function of VWF by cleaving the more active, higher-molecular-weight (HMW) VWF multimers, thus controlling its interaction with platelets.[2] The processes of hemostasis and angiogenesis are key biological functions coordinated by blood vessels, often colocalized in time and space. It is therefore logical that proteins that control hemostasis may also influence the formation, maturation, and stability of blood vessels during the complex process of angiogenesis. Both VWF and ADAMTS13 have already been shown to influence blood vessel formation and angiogenesis in different settings,[3,4] as modulators rather than essential drivers of the process. Here, Xu et al carry out a detailed in vivo analysis of vascular repair in mice postischemic damage in the brain, and find that the effect of ADAMTS13 in promoting vascular repair is entirely linked to VWF because the decreased vascularization in ADAMTS13 knock out (ko) mice is normalized by anti-VWF antibodies or by genetic VWF deletion in the double ADAMTS13/VWF ko mice.

Previous studies have shown that loss of VWF results in enhanced vascularization in models of physiological angiogenesis and vascular development, possibly by promoting maturation of new vessels[3,5]; this study identifies a role for VWF in ischemic angiogenesis in the brain. Given that the overall effect of VWF is to limit blood vessel formation, it seems logical that lack of ADAMTS13, which in this mouse model causes an increase in circulating VWF HMW multimers, results in decreased angiogenesis, which can be normalized by blocking VWF. This study highlights for the first time the importance of maintaining the correct balance of VWF activity through removal of its most active HMW multimers, within the context of angiogenesis. This is an intriguing and important finding, which may be relevant to the clinical observation that loss of HMW VWF multimers in a subset of patients with congenital or acquired von Willebrand disease (VWD) can be associated with vascular malformations in the gastrointestinal tract called angiodysplasia, which is often responsible for severe intractable bleeding in these patients.[6] Angiodysplasia has been linked to dysfunctional angiogenesis, and the finding that VWF and its protease ADAMTS13 control blood vessel formation and maturation has opened a new direction of research that will hopefully deliver novel treatments for these patients.

The pathways through which VWF and ADAMTS13 regulate blood vessel formation still need to be fully characterized. Given the numerous properties of VWF, as a regulator of endothelial storage and as a binding partner to multiple angiogenesis regulators,[7] a complex network of pathways is likely to be implicated, possibly with different relative importance depending on the microenvironment and tissue. Interestingly, the same mediators appear to be implicated in ADAMTS13- and VWF-dependent control of blood vessel formation: proangiogenic mediators angiopoietin-2 (Ang-2) and galectin-3 (Gal-3) are reciprocally regulated by VWF and ADAMTS13, in line with their roles in blood vessel formation and stability. Surprisingly, overexpression of either Ang-2 or Gal-3 alone was found to correct postischemic angiogenesis in the brain of ADAMTS13 mice. These pathways converge on the regulation of the master angiogenic pathway, namely vascular endothelial growth factor receptor-2 (VEGFR-2), and both VWF- and ADAMTS13-dependent angiogenic phenotypes are normalized by inhibition of VEGFR-2 activation.[1,3] It is possible that forcing a single pathway may override the system and/or normalize VEGFR-2 signaling; ultimately, these findings confirm that maintaining the balance of activators and inhibitors of angiogenesis is critical for effective angiogenesis.

The study by Xu et al provides important validation of the role of ADAMTS13-VWF balance in regulating blood vessel formation; however, several questions remain to be

addressed. For example, VWF is essential for formation of storage organelles called Weibel-Palade bodies (WPBs), which also store Ang-2; loss of VWF has been shown to cause a tissue-specific increase of Ang-2 release and, intriguingly, synthesis in vitro and in vivo.[3,8] This study, conversely, shows that ADAMTS13 deficiency results in decreased Ang-2 synthesis.[1] How does ADAMTS13 regulate Ang-2 expression, given that its effect on VWF is not known to affect WPB formation? These findings suggest that VWF may regulate Ang-2 levels not only through an intracellular WPB-dependent pathway, but also through extracellular signals that depend on the presence of HMW VWF multimers. This would open an entirely new chapter on the relationship between extracellular VWF and the function of the vascular endothelium. Also, regulation of Ang-2 by VWF appears to be context-specific, active in the heart but not in the lung[8]; does the same apply to ADAMTS13? This may have important implications for the possible therapeutic potential suggested by the authors, which will have to be addressed in specific disease settings.

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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Rasche et al, page 30

Toward a GEP-based PET in myeloma

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In this issue of *Blood*, Rasche et al provide the first evidence of the biological basis underlying the occurrence of false-negative scans with use of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in newly diagnosed transplant-eligible multiple myeloma (MM) patients.[1]

According to the updated diagnostic criteria for MM,[2] the novel imaging techniques, including whole-body low-dose CT, magnetic resonance imaging (MRI), and PET/CT, are now considered a valuable tool for the diagnostic workup of MM because of their higher sensitivity and ability to detect bone damage at an earlier phase than whole-body radiograph. Several studies have demonstrated the usefulness of FDG-PET/CT at diagnosis, reporting a sensitivity and specificity for detection of bone lesions in the range between 80% and 100%. Moreover, functional imaging techniques, such as PET and MRI, are able to distinguish between metabolically active and inactive sites of clonal proliferating plasma cells (PCs), thus allowing us to evaluate metabolic response to therapy.

The unprecedented rates of high-quality responses afforded by more effective classes of novel agents and the association between the depth of response and long-term outcomes[3] have recently led to refinement of the response criteria by using more sensitive techniques for assessment of minimal residual disease (MRD), both inside and outside the bone marrow (BM).[4] More specifically, owing to the patchy pattern of bone marrow plasma cell (BMPC) infiltration and the existence of extramedullary sites of clonal PCs, a new response category of imaging-MRD negativity has been identified, based on the disappearance of every area of increased tumor metabolism assessed with functional imaging techniques.

Almost 10 years ago, the Little Rock group first evaluated the role of FDG PET/CT in the context of the Total Therapy 3, demonstrating that PET-positive lesions at diagnosis and during/after the completion of therapy were predictive of prognosis.[5] Several other independent studies confirmed the improved outcomes of patients achieving PET negativity after transplant, including those in conventionally defined complete remission.[6] On the basis of these results, FDG PET/CT is actually considered the preferred imaging technique for evaluating and monitoring metabolic response to therapy.[7] However, it is important to emphasize that both false-negative and false-positive results may occur with use of FDG PET/CT. In particular, false-negative scans can be related to hyperglycemia or recent administration of high-dose steroids, leading to a transient metabolic suppression. Moreover, it has been reported that, in a variable though not yet well-defined rate of patients, PCs may not be FDG avid.

In addition to FDG, new PET/CT tracers targeting different metabolic pathways or receptors expressed by MM cells, and acting as molecular imaging biomarkers, potentially more sensitive, have been preliminarily investigated in limited series of MM patients; however, their lower availability, the lack of direct comparisons with FDG, and the interpatient tumor heterogeneity regarding specific targets prevent any definite conclusion from being drawn.[8,9]

Initial experience with functional MRI approaches, such as diffusion weighted imaging (DWI), enabling quantitative assessment of disease burden by quantifying the molecular diffusion of body water and the microcirculation of blood in the capillary network, showed a high sensitivity of the technique, in particular for detection of diffuse BMPC infiltration, a higher correlation with BM trephine samples in comparison with PET/CT, and the capability to identify