blood®
Editorial

Introduction to a review series on nontraditional roles for the hemostatic system in the vessel wall

Until the recent past, the necessary conceptual understanding of the hemostatic system was quite simple, despite the dizzying complexity of the biochemical and cellular pathways involved. This simplicity had to do with the fact that the major and most obvious derangements of this system result in either bleeding or clotting, sometimes life threatening. Thus, the tendency had been to focus on the functions of clotting factors and platelets as they relate to these disorders. Nature, however, is unconstrained by the organizational principles that humans have sought to apply to it, and slowly the involvement of the hemostatic system in a variety of other processes has begun to emerge. A case in point is the role of the vessel wall, in particular the vascular endothelium.

Because of their continuous and intimate contact with the blood, the vascular endothelial cells that comprise the endothelium can be considered to be a specialized form of blood cells, although ones that do not circulate. The normal endothelium in health has an antithrombotic role, producing antiplatelet substances that prevent the always sticky platelets from binding the vessel wall, substances that include nitric oxide, prostacyclin, and the ecto-ADPase, CD39. The endothelium also prevents runaway clotting by converting thrombin, the most potent coagulation protease, into an anticoagulant that suppresses its own production. It does this through the transmembrane protein thrombomodulin (TM), which binds thrombin and changes its substrate specificity such that it can cleave the zymogen protein C into activated protein C (APC), which douses coagulation by proteolytically inactivating the enzyme cofactors factor Va and factor VIIIa.

In pathological states or at sites of vessel injury, the endothelium can also become prothrombotic. TM is shed or otherwise downregulated; the endothelial cells expose phosphatidylserine to allow assembly of coagulation complexes, and they release the contents of storage granules containing the most important platelet adhesion molecule, von Willebrand factor (VWF). In addition, the endothelial cells produce reactive oxygen species that inactivate nitric oxide and alter hemostatic proteins, usually making them more prothrombotic.

However, like other components of the hemostatic system, the roles of hemostatic components in the vessel wall go far beyond their well-accepted roles in bleeding and clotting. This review series summarizes for the reader many of the emerging and exciting "nontraditional" roles of the hemostatic system in the vessel wall and includes 5 reviews on the following topics:

- T. Son Nguyen, Tsvee Lapidot, and Wolfram Ruf, "Extravascular coagulation in hematopoietic stem and progenitor cell regulation"
- Anna M. Randi, Koval E. Smith, and Giancarlo Castaman, "von Willebrand factor regulation of blood vessel formation"
- Junmei Chen and Dominic W. Chung, "Inflammation, von Willebrand factor, and ADAMTS13"
- Houra Loghmani and Edward M. Conway, "Exploring traditional and nontraditional roles for thrombomodulin"
- John H. Griffin, Berislav V. Zlokovic, and Laurent O. Mosnier, "Activated protein C, protease activated receptor 1, and neuroprotection"

Nguyen, Lapidot, and Ruf explore an area of interest to hematologists interested not only in hemostasis but also in hematopoiesis. These authors describe the involvement of numerous hemostatic proteins in the maintenance of hematopoietic stem cells (HSCs) and in influencing their self-renewal and proliferative capacities. An important example is the role of the endothelial protein C receptor, which serves as a marker of HSC dormancy and multilineage reconstitution potential. Other examples abound, and the authors artfully lay out some of the therapeutic implications of this research.

Two disparate roles of the platelet adhesive protein VWF are discussed in this series. Randi, Smith, and Castaman review the extensive literature on the role of VWF in new vessel formation, and how its deficiency or dysfunction can lead to clinically important problems. VWF largely appears to have an antiangiogenic role, as suppression of VWF expression increases endothelial proliferation, migration, and angiogenesis. VWF's involvement is complex because its absence not only removes an endothelial adhesive and signaling molecule but also prevents formation of Weibel-Palade bodies, the endothelial storage granules that, in addition to storing VWF, contain pro- and antiangiogenic factors. The authors discuss molecular pathways at play and thoroughly lay out the relationship between VWF disorders, angiodysplasia, and mucosal bleeding (particularly in the gastrointestinal tract). This is a problem that has become increasingly frequent for the hematology consultant, especially with the expanding use of left-ventricular assist devices and their attendant association with a high frequency of acquired von Willebrand syndrome and intestinal angiodysplasia.

Chen and Chung review an underappreciated aspect of VWF function, its ability to self-associate into long fibers and other structures. This process increases with VWF concentration and is thus important in inflammatory states in which VWF secretion is

Submitted 1 June 2018; accepted 1 June 2018. Prepublished online as *Blood* First Edition paper, 4 June 2018; DOI 10.1182/blood-2018-06-846097.

increased and its adhesive function is enhanced by oxidative stress. VWF self-association occurs both in the fluid phase of the blood and on surfaces. One such surface is the vascular endothelium, on which VWF accumulates when the activity of the VWF-cleaving protease ADAMTS13 is insufficient to efficiently remove adherent, newly secreted VWF, such as occurs in thrombotic thrombocytopenic purpura. This process allows the formation of platelet thrombi in situ, promoting the occlusion of small blood vessels. Self-association of VWF is primarily regulated by ADAMTS13, which cleaves large VWF multimers that unfold easily in the presence of fluid shear stress into smaller, less malleable multimers. Importantly, VWF self-association is also influenced by plasma high-density and low-density lipoproteins and other factors such as thrombospondin-1, thus connecting VWF self-association to pathologies such as atherogenesis, inflammation, and sepsis.

Nontraditional roles for TM are explored in the review by Longhmani and Conway. This type I transmembrane glycoprotein is expressed on the luminal surface of endothelial cells in virtually all blood vessels and lymphatics and is also synthesized by a variety of other cell types. The authors break down TM function based on the involvement of individual structural domains in different processes, a useful approach given that a variety of soluble fragments of the TM ectodomain circulate in the blood and their concentrations can vary based on the activation of different proteases in various pathological states. As an example, the N-terminal C-type lectin-like domain of TM modulates inflammation in a process that is independent of TM's well-known role in generating APC. This region of TM binds proteins released by damaged cells, preventing their activation of innate immune pathways of inflammation. The involvement of TM in various other pathologies is also discussed, including malignancy, atherosclerosis, transplantation-associated vasculopathies, and preeclampsia, among others.

The review by Griffin, Zlokovic, and Mosnier focuses on the nonhemostatic functions of APC. The roles of this protease go far beyond its antithrombotic effects, acting largely through protease-activated receptors (PARs) that are also activated by other coagulation proteases such as thrombin. However, whereas PAR1 cleavage by thrombin is generally proinflammatory, its cleavage by APC is largely anti-inflammatory, a process called PAR1-biased signaling, which results from both differential subcellular localization of the proteolytic complex and cleavage at a different site of the receptor. These authors discuss how these different signaling processes, and those emanating from cleavage of other substrates, account for the anti-inflammatory and neuroprotective actions of APC, in addition to the implications of these actions for the treatment of ischemic stroke and neuroinflammation, and for neurogeneration.

In summary, this review series has something for almost everyone, highlighting new and nonobvious functions of the hemostatic system in a variety of physiologic and pathological processes, and exposing several fertile areas for future research and promising therapies.

José A. López
Associate Editor, *Blood*