

● ● ● HEMOSTASIS

Comment on Haberichter et al, page 3344

VWF propeptide: a useful marker in VWD

Augusto B. Federici AUGUSTO B. FEDERICI IRCCS FOUNDATION, MAGGIORE HOSPITAL OF MILAN

Haberichter and colleagues describe a specific subset of patients with type 1 von Willebrand disease in 4 different families and suggest that an increased ratio between the von Willebrand propeptide and von Willebrand factor antigen may indicate a true genetic defect and decreased VWF survival.

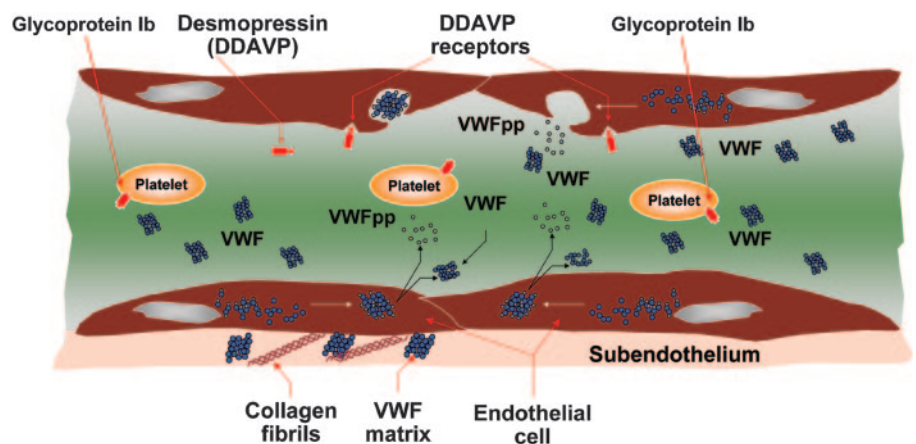
Von Willebrand factor (VWF) is a large adhesive multimeric glycoprotein that plays major roles in hemostasis by mediating platelet adhesion and aggregation at the sites of vessel wall injury and serving as the carrier of factor VIII. The primary product of the VWF gene, located at chromosome 12p13.2, is a 2813–amino acid protein made of a signal peptide of 22 amino acids, a large propeptide of 741 amino acids, and a mature VWF molecule of 2050 amino acids. The pre–pro VWF, synthesized in endothelial cells (ECs) and megakaryocytes (MKs), undergoes intracellular modifications including signal peptide cleavage, C-terminal dimerization, glycosylation, sulfation, and aminoterminal multimerization. Then proteolysis occurs in the trans–Golgi where the VWF propeptide (VWFpp) is cleaved but remains stored together with mature VWF in alpha–granules (MKs) and Weibel–Palade bodies (ECs). After secretion into plasma, VWFpp dissociates from VWF and can be measured with specific antibodies. VWFpp circulates at a concentration of about 1 µg/mL with a half-life of 2 to 3 hours, whereas mature VWF circulates at about 10 µg/mL with a half-life of 8 to 12 hours.^{1,2} Several physiologic or pathologic stimuli can release VWF and VWFpp from ECs: desmopressin (DDAVP) is the first-choice treatment of mild forms of von Willebrand disease (VWD) because it can increase plasma VWF levels by releasing it from ECs.³ These events

are summarized in figure (see below). Type 1 VWD is characterized by partial quantitative deficiency of VWF with autosomal dominant inheritance and a high variable phenotype.³ Most patients with type 1 VWD show good biologic responses to DDAVP; however, heterogeneous half-lives of VWF activities can be found (see figure on the next page). Recently, a novel mechanism for type 1 VWD has been linked to increased clearance of VWF from plasma.⁴ VWFpp has also been recommended to identify patients with acquired von Willebrand syndrome who might have increased clearance of VWF because of autoantibodies to VWF.⁵

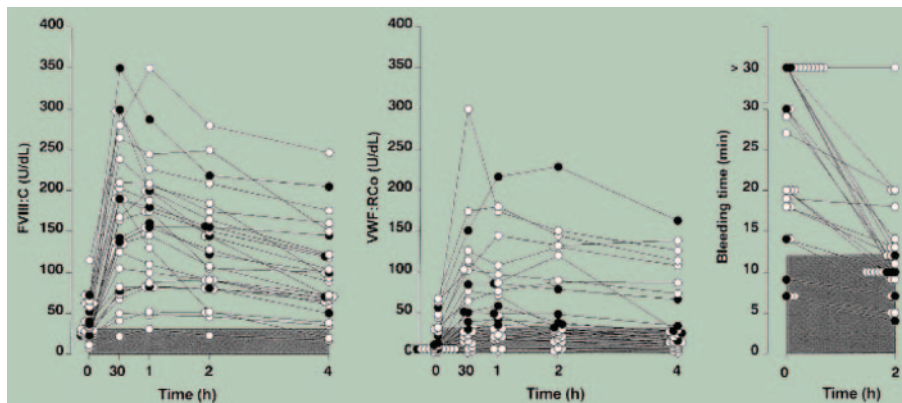
Haberichter and colleagues report a peculiar decreased survival of VWF in 4 families with moderately severe inherited type 1 VWD. In fact, VWF half-lives were significantly shorter (1–3 hours) than in healthy individuals, whereas the half-life of VWFpp was normal. Affected individuals of these 4 families were characterized by low plasma VWF antigen (VWF:Ag) and factor VIII levels, proportionately low ristocetin cofactor activity, and dominant inheritance. Single novel heterozygous mutations were found in affected members: S2179F in 2 families and W1144G in 2 families.

In conclusion, data by Haberichter et al suggest that plasma VWFpp can be a useful additional marker for identifying inherited type 1 VWD patients with a shortened VWF half-life and open new insights in the field of VWD management. However, since this VWFpp assay has not been standardized yet, more patients with inherited and acquired defects of VWF should be evaluated in controlled multicenter laboratory studies.

Dr. Federici is associate professor of hematology at the University of Milan School of Medicine. ■



Pictorial representation of the events related to VWF biosynthesis and release induced by desmopressin (DDAVP).



Biologic responses to DDAVP in 26 patients with type 1 VWD. Changes of factor VIII (FVIII:C), ristocetin cofactor (VWF:RCo), and bleeding time (BT) before and following DDAVP.³

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● ● ● PHAGOCYTES

Comment on Vidarsson et al, page 3573

Tickle my innards

Gregory P. Downey UNIVERSITY OF TORONTO

The manuscript by Vidarsson and colleagues is the first description of a role for the neonatal Fc receptor (FcRn) in promoting phagocytosis of microorganisms by neutrophils. The primary site of action of FcRn is apparently not on the cell surface (as for other classical phagocytic receptors) but rather within the acidic milieu of the phagosome after ingestion. The mechanism by which FcRn mediates these important effects remains to be clarified.

Vidarsson and colleagues have identified a novel role for the neonatal Fc receptor (FcRn) in promoting ingestion (phagocytosis) of IgG-opsonized bacteria by neutrophils. In these professional phagocytes, FcRn is not expressed on the cell surface, in contrast to the classic phagocytic receptors such as Fcγ receptors and complement receptor 3 (CR3). Rather, FcRn is expressed within primary (azurophilic) and secondary (specific) granules in neutrophils and is transported to the developing phagosome along with the granules during phagocytosis, when the granules fuse with the phagosome. What then is FcRn doing in an intracellular (granular) compartment of mature phagocytes, and how does it modulate

phagocytosis from this distant and relatively isolated refuge?

FcRn is a structurally distinct receptor for IgG that is composed of a unique α-chain coupled to β2-microglobulin. Intriguingly, the latter also couples with the major histocompatibility complex (MHC) class I protein that serves a vital function in antigen presentation. The function of FcRn has been best studied in nonphagocytic cells where it is expressed on the plasma membrane and functions in the internalization and transcellular uptake of IgG. For example, in syncytiotrophoblasts of the placenta, FcRn functions in maternal-fetal transport of IgG. In epithelial cells, FcRn functions in the transport of IgG

across mucosal surfaces. In the vasculature, FcRn is expressed on the surface of endothelial cells where it is postulated to regulate the circulating levels of IgG. However in neutrophils, this IgG transport function of FcRn does not appear to be involved in promotion of phagocytosis.

The current manuscript illuminates some of these issues and provides compelling data for a role for FcRn in the phagocytosis of bacterial pathogens. The authors propose a model whereby the CH2 region of the heavy chain of IgG bound to microbial pathogens ligates FcRn on the phagosomal membrane and triggers a signaling cascade through domains within its cytosolic tail. FcRn efficiently binds IgG at low pH, a property that is ideally suited to ligand-receptor interactions in the acidic milieu of phagosomes and phagolysosomes. However, this property also raises some potential problems with the proposed model (see next paragraph). The physiologic importance of this receptor is highlighted by a phagocytic deficiency in neutrophils from mice that are deficient in either β2-microglobulin or in the α-chain of FcRn (both lack expression of FcRn). Further, opsonization of bacteria with mutant IgG (H435A) that binds to classic Fcγ receptors but not FcRn fails to support phagocytosis.

Taken together, these observations contribute to a novel paradigm in regulation of phagocytosis, a process of fundamental importance in innate immunity. They suggest the somewhat heretical notion that classic Fcγ receptors such as FcγRIIa and FcγRIIIb function in particle recognition and binding, whereas FcRn directs somewhat later stages of phagocytosis. At first consideration, this notion is at odds with experiments where non-professional phagocytic cells such as the simian kidney fibroblast cell line COS or Chinese hamster ovary (CHO) cells (that presumably do not express FcRn) are rendered efficiently phagocytic by expression of classic Fcγ receptors.¹ Additionally, the current manuscript does not identify the precise function of FcRn in the complex process of phagocytosis. Finally, there are some glaring inconsistencies in the proposed model that need to be reconciled. For example, if FcRn is not expressed on the cell surface and can only bind IgG at low pH as occurs in a more mature phagosome (the phagosome cannot acidify if it is not a closed vacuole), how can it sense and contribute to internalization of phagocytic prey? During