Anniversary Issue Contribution

Von Willebrand factor: Looking back and looking forward

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Summary
Looking back at the last thirty years of studies on von Willebrand factor is a lesson on the importance of combining clinical observations with basic research. Most of what we know today originates from the perceptive evaluation of patients with congenital disorders of haemostasis such as haemophilia and von Willebrand disease. Understanding the causes of these diseases was akin to the current approach of using mutagenesis in animal models to get insights into the function of specific gene products. The information generated to date has been detailed and comprehensive, but looking into the future one sees that much remains to be done to understand how the role of von Willebrand factor and its primary platelet receptor, glycoprotein Ib, is integrated into the complex responses to vascular injury. Many challenges remain, along with the hope of translating the knowledge acquired into new and efficacious treatments for arterial thrombosis.

Keywords
Adhesion molecules, platelets, vascular biology, extracellular matrix, thrombin

Introduction
With advancing age one typically appreciates more the value of historical perspective in relation to all human activities, and scientific research is no exception. We seem to learn that challenging existing concepts and exploring new directions is best done when we fully appreciate the achievements of those who came before us. Their quest was the same we are pursuing today and others will pursue tomorrow; their discoveries are as essential to the progress towards our goals as the meticulous fine-tuning of the tools we use in our experimental work. The golden anniversary of a journal devoted to disseminating scientific information provides the opportunity to reflect on these concepts, looking back to successes and controversies in order to find, or one may dare say provide, inspiration and motivation for the journey forward.

Early years
I initiated my studies in the field of thrombosis and haemostasis in 1968, although the social and political unrest that swept through most universities in the world at the time was a strong competing interest. Judith Pool had described a few years before the method to prepare cryoprecipitate enriched in factor VIII (1, 2), and a young Pier Mannuccio Mannucci, fresh from his training in England with Ingram and Biggs (3), was starting to create the program that so profoundly contributed to improve the lives of haemophiliacs in Italy and elsewhere. Only a few years later Ted Zimmerman provided the definitive demonstration that the protein deficient in von Willebrand disease was normally present in haemophilia A (4), in essence ending – but without fully realizing it, yet – the debate on "one protein, two functions" (more about this later) (5). Insightful patient studies in Sweden – by Nilsson, Holmberg et al. (6–8) – and France – by Larrieu, Meyer and Caen (9–11) – contributed important information on the heterogeneity of von Willebrand disease and the bases for its distinctness from haemophilia A. The quantitative determination of "factor VIII-related antigen" made possible by Ted’s discovery also created the basis for diagnosing the state of haemophilia A carrier in females (12). Thus, the decade between 1964 and 1973 witnessed seminal discoveries that established the foundations for the molecular understanding of haemophilia A and von Willebrand disease in the following 20 years, at the same time initiating the modern era of substitution therapy for these congenital bleeding disorders. Only a few years later, the group lead by Mannucci brought to fruition years of studies (13) with the clinical demonstration that factor VIII and von Willebrand factor (VWF) activities in plasma could be raised to therapeutically useful levels in patients with mild haemophilia and type I von Willebrand disease using a synthetic vasopressin analogue, thus avoiding the risk of transfusion-transmitted infections (14–16).
The field of platelet research was not standing still. In the early 1970s it became evident that abnormalities of platelet membrane glycoproteins resulted in functional defects characterized by excessive bleeding (17–20), and once again careful studies of patients paved the way to basic experimental work aimed at understanding the mechanisms of platelet adhesion. During the same years, a selected group of investigators began studies on the influence of hemodynamic conditions (21-23) and other physical parameters (24), on thrombus formation, and the results of these efforts ultimately blossomed into the initial understanding of key relationships between shear forces and adhesive platelet interactions that were somehow related to von Willebrand disease (25–28). In essence, by the end of the seventies one could sense that the stage was set for new developments to happen that would bring the knowledge on the functions of factor VIII and VWF to new levels.

The molecular era

For somebody with an interest in understanding the function of VWF and the molecular basis of von Willebrand disease, it was natural to want to work with Ted Zimmerman (Fig. 1). For a number of years investigators had been debating whether the activity that controls the bleeding time and is defective in von Willebrand disease (a.k.a. angiohaemophilia), on one side, and the procoagulant function that is defective in haemophilia A, i.e. factor VIII, were two functions of the same molecules. What we now know as VWF was for many years the factor VIII antigen and then the factor VIII-related antigen. Ted had developed the tools to prove that the two activities were the expression of different, albeit associated, molecules, and was interested in studying the structure and function of both in great detail. I began as a fellow in his laboratory in 1978 and was assigned to the VWF project; Carol Fulcher (Fig. 2), who joined the group a few months after me, started working on factor VIII. Her meticulous work would lead to the method to purify factor VIII that in great part contributed to the availability of virus-free concentrates for therapeutic use before recombinant factor VIII became available (29). In those years we devised a method to study the multimeric structure of VWF that became widely used (30, 31). The first application for me was to study the strange variant of von Willebrand disease that had been identified some years before in Italy (32) and made no sense because the patients were paradoxically hyper-responsive to ristocetin when, according to their diagnosis, they should have been hypo-responsive (33).

The major advance that ushered in the new era of molecular studies on VWF and von Willebrand disease was the cloning of the VWF cDNA (34–36). This achievement confirmed the monumental work of Titani et al. who, essentially at the same time, completed the amino acid sequence of the purified VWF protein (37). Of equal importance for most future developments was the elucidation of the complex biosynthesis of VWF by endothelial cells (38, 39) and megakaryocytes (40), with the subsequent demonstration of the regulated secretion of large VWF multimers from storage organelles (41). These basic research results were instrumental in interpreting the pathophysiological role of VWF multimers in thrombotic thrombocytopenic purpura (42) as well as the significance of the proteolytic processing of VWF after release into the circulation (43, 44). All these studies eventually contributed to the identification of ADAMTS-13 (45), the protease that cleaves VWF multimers (46). Of note, the studies on the biosynthesis of VWF also helped clarify the identity of von Willebrand disease antigen II. This was discovered by Bob Montgomery when he was a fellow with Ted Zimmerman (47), and was later demonstrated to be the VWF propeptide released into the circulation after cleavage from the assembled VWF multimers (48).

Selected aspects of current knowledge

Platelets, shear forces and VWF

Platelets are essential for normal haemostasis and particularly to arrest bleeding from arterioles where shear stress is elevated.
In pathological conditions, platelets are a major contributor to arterial thrombosis, which typically occurs at sites of atherosclerosis with stenosis of the vessel lumen where shear stress values are considerably higher than in the normal circulation (50–52). Shear rate and shear stress have different effects on cellular adhesive interactions. The shear rate is directly related to flow velocity, including the velocity of cells in the fluid layer adjacent to the vessel wall, and limits the time of contact between membrane receptors and immobilized substrates on the vessel wall, thus the on-rate of the adhesive interaction. As a consequence, the efficiency of cell recruitment onto the surface decreases with increasing shear rate. Shear stress, in contrast, influences the lifetime of an adhesive bond once formed, thus the off-rate of the interaction, and the consequence is decreased efficiency caused by detachment of adherent cells with increasing shear stress.

Different pathways of platelet adhesion are variably affected by increasing shear force depending on the biomechanical properties of each receptor-ligand pair. Above a threshold shear rate of 500–800 s\(^{-1}\) in human blood (27, 53) and 2,000–5,000 s\(^{-1}\) in mouse blood (54), only the interaction between immobilized VWF A1 domain (VWF-A1) and the glycoprotein (GP) Ib\(\xi\) in the platelet membrane GP Ib-IX-V receptor complex (55) has a sufficiently fast on-rate to initiate platelet adhesion (56). It is important to note that the threshold discussed here is not a minimum shear rate value to engage the function of immobilized VWF-A1, which can mediate platelet tethering even under venous slow flow conditions (56); rather, it is an upper limit for the function of most other platelet adhesive bonds in the absence of VWF.

**Subendothelial and immobilized plasma-derived VWF**

As a constitutive component of the extracellular matrix of endothelial cells, subendothelial VWF can directly support platelet adhesion (28, 57–59). Nonetheless, haemostasis can be normal in the absence of endogenous endothelial VWF if plasma VWF is present (60). Consequently, the interaction of circulating VWF with exposed vascular and perivascular tissues is a key early event in thrombus formation. The main substrate capable of binding VWF is collagen (61), particularly types I and III in deeper layers of the vessel wall and microfibrillar collagen type VI in the subendothelial matrix (62–65). Two of the type A domains in VWF, A1 and A3, can mediate binding to collagens, and their respective roles may vary depending on the type of collagen involved and the fluid dynamic conditions (64, 66). The VWF A1 domain (VWF-A1), comprising residues 497–716 of the mature subunit (add 763 to obtain the corresponding residue number in pre-pro-VWF) (67), was initially shown to interact with collagen types I (68, 69) and III (70), but its main role may be binding to collagen type VI (64, 71). The latter contains VWF type A domains in its non-collagenous regions that may become engaged in homotypic interactions with VWF-A1 (64, 72). The VWF A3 domain (VWF-A3), comprising residues 910–1111, also binds to collagen types I and III (69, 70, 73), and is apparently necessary and sufficient to mediate the interaction with microfibrillar collagens (53, 74). The VWF-A3 residues involved in collagen binding have been mapped (75, 76) and a high-affinity binding site for VWF has been identified in collagen type III (77). Fluid dynamic conditions and mechanical forces may modulate the VWF-collagen interaction, and the interplay of domains A1 and A3 may be necessary to support VWF immobilization onto extracellular matrices containing various collagen types (64). Of note, VWF multimer size directly correlates with the affinity for collagen binding (78).

Contrasting the information on the role played by VWF-A3 in the interaction with fibrillar collagens in vitro, supported by the demonstrated anti-thrombotic activity of a function-blocking anti-VWF A3 antibody (79), stands the evidence that mutations preventing collagen binding (such as Ser968Thr) are compatible with normal haemostasis in vivo (80, 81). This may indicate that collagen type VI in the endothelial cell and fibroblast matrix is the main VWF binding site through an interaction mediated by the A1 domain (82), and/or that VWF-A1 can substitute for VWF-A3 in supporting binding to different fibrillar collagen, in which the sites interacting with the two domains appear to be overlapping (66). In addition, or in alternative, VWF can interact with extracellular matrix components independently of collagen. The A1 domain contains a heparin-binding site (83, 84) that has been localized to the sequence Tyr565-Ala587 (85). A second, lower-affinity heparinbinding sequence exists within the first 272 residues of the mature VWF subunit (86). These heparin-binding sites may reflect the ability to interact with matrix proteoglycans that contain sulfated carbohydrates. For example, the small proteoglycan decorin, which associates with several matrix components and contributes to matrix assembly, has been reported to bind VWF in an interaction mediated by the glycosaminoglycan chain and regulated by the degree of sulfation (87). In addition, VWF binds to sulfated glycosphinolipids (sulfatides) (88, 89) that are present on cellular membranes and may serve an accessory role in promoting localization on wounded tissues. The binding site for sulfatides has been localized within residues 512–673 of the A1 domain, possibly with a more direct involvement of residues 569584 (90) and/or 626–646 (91). Sulfatides can inhibit platelet adhesion to VWF mediated by GP Ib\(\xi\), suggesting an overlap of interacting sites (92). Because VWF is multimeric, sulfatides may contribute to its binding to surfaces and still allow platelet adhesion to different A1 domains in the same immobilized polymer. Similar considerations apply to heparin and its binding site in the A1 domain (93). Another pathway to VWF immobilization involves the interaction with components of a forming clot. Thus, the cross-linking of VWF to the \(\alpha\)-chain of fibrin (94) can contribute to platelet deposition onto altered vascular surfaces (95), and this may become a relevant adhesion mechanism in areas where acute or chronic inflammation causes fibrin deposition (96).

The ability to self-associate represents an additional mechanism for the transition from soluble to immobilized VWF, in which case circulating multimers interact in a reversible manner with matrix-bound and endogenous subendothelial VWF (97). This mechanism was demonstrated by immobilizing a mutant VWF devoid of domain A1 (\(\alpha\)A1-VWF), thus unable to promote platelet adhesion, onto collagen and showing that GP Ib\(\xi\)-mediated tethering was restored by the presence of soluble VWF in plasma. Very large VWF multimers locally released by stimulated endothelial cells (42) may enhance the efficiency of the process, as these molecules form high-strength bonds with GP...
Ibα (98). Self-association of VWF multimers can occur onto the platelet surface (99) under conditions of hydrodynamic shear that favor the binding of soluble VWF (100). The self-association of VWF apparently involves multiple domains (101) and none has been identified as essential, including A1 and A3 (97).

The distinctive functional properties of immobilized and soluble VWF

Platelets have no measurable interaction with soluble VWF in the circulation, but adhere promptly to exposed immobilized VWF. Such a tight regulation is necessary to prevent intravascular platelet aggregation, and has led to the concept that surface-bound VWF must undergo a conformational change to make the interaction with GP Ibα possible and initiate platelet adhesion. Indeed, VWF molecules may change shape depending on hemoodynamic conditions, so that upon binding to the vessel wall under high shear stress they may appear as elongated filaments rather than the loosely coiled structures seen under static or low-shear-stress conditions (102). Such an "uncoiling" may expose the repeating functional sites present in multimeric VWF, allowing a more efficient support of adhesive interactions as a result of multivalent binding. Three-dimensional structural studies (103) have shown that more subtle conformational changes can occur in the GP Ibα-binding A1 domain as a result of amino acid substitutions, such as those causing type 2B von Willebrand disease (33), which overcome the affinity barrier for soluble VWF binding to platelets. These results prove that conformational changes can regulate the interaction between VWF-A1 and GP Ibα, but there is no evidence that the transition from soluble to surface-immobilized VWF induces these or similar conformations. Studies with a specific antibody fragment (104), a "nanobody", support the concept of a common "active" conformation in the VWF A1 domain of surface-bound multimers, soluble ultralarge multimers released by endothelial cells and mutant type 2B plasma VWF, in contrast to the "inactive" conformation of normal plasma VWF. In fact, the "nanobody" appears to bind preferentially to the A1 domain of VWF species with enhanced affinity for GP Ibα, indicating that they may share the same conformation. It remains to be determined whether such a conformation is dynamically transient or reflects one of the known crystallized structures (103, 105, 106). A particularly relevant "active" form of soluble VWF is represented by the ultralarge multimers (98) released from the storage granules of stimulated endothelial cells and platelets (107, 108). Ultralarge VWF multimers function locally, but under normal conditions they do not accumulate in circulating blood (109) because they are processed by a specific protease, ADAMTS-13 (45).

ADAMTS-13 and the regulation of VWF-mediated platelet adhesion and aggregation

VWF in plasma or released by altered endothelial cells and/or activated platelets at sites of vascular injury has a potent prothrombotic effect by promoting both platelet adhesion and aggregation, particularly under high shear stress conditions. The largest multimers of VWF, with the greatest prothrombotic function (98, 109), are present inside cellular storage granules (107, 108) but are not normally found in the circulation. The reason for this is the efficient processing of all secreted VWF (110) by the metalloprotease, ADAMTS-13 (45), which cleaves one single peptide bond in the VWF subunit (43) and in so doing reduces multimer size (44). Absence of ADAMTS-13 results in a thrombotic microangiopathy (111), suggesting that the physiologic function of the protease is to limit the activity of the most active VWF multimers to the sites where they are released from cells (109). Recently, the results of ex-vivo perfusion experiments have added to this concept by showing that ADAMTS-13 can further cleave circulating VWF multimers while they mediate activation-independent interplatelet cohesion induced by elevated shear stress, resulting in a time-dependent dispersion of the aggregates (112). In contrast, the protease appeared to have no effect, at least under the ex-vivo conditions studied, when thrombus formation was induced by blood exposure to a collagen surface.

The latter finding stands in apparent contradiction with the results of in-vivo studies in mouse thrombosis models, which have shown the ability of recombinant ADAMTS-13 to dissolve experimentally-induced thrombi in the arteriolar circulation leading to the conclusion that the protease could be used as an anti-thrombotic agent (113). While the effect of ADAMTS-13 on microarteriolar thrombi is in agreement with the phenotype caused by its deficiency, i.e. microarteriolar thrombosis (111), the situation may be different in larger arteries. In this case, the anti-thrombotic activity of ADAMTS-13 may depend on the extent to which adhesive molecules such as fibrinogen and fibronectin, rather than VWF, contribute to platelet aggregation. Thus, the anti-thrombotic activity of ADAMTS-13 may be selective for platelet aggregation under high shear stress conditions in which VWF is important for platelet cohesion (114, 115). During hemoastosis, ADAMTS-13 activity may be needed to avoid the propagation of platelet aggregates beyond the limits of a vascular wound, which typically involves the microarteriolar circulation with rapidly flowing blood. It remains to be demonstrated whether ADAMTS-13 may limit the potential role of VWF in mediating the occlusion of stenotic arteries where pathologically elevated shear rates develop. In this regard, it is intriguing to observe that a recent study found a positive correlation between ADAMTS-13 levels and the risk of myocardial infarction in men (116), a finding that is in apparent contrast with the suggestion that ADAMTS-13 may act as an anti-thrombotic agent. The mechanism through which increased ADAMTS-13 levels and/or activity might constitute a risk for arterial thrombosis remains to be understood.

Membrane receptors and the mechanism of platelet tethering to VWF

Platelets have two main binding sites for VWF (117, 118), GP Ibα in the GP Ib-IX-V complex (55) and the integrin αIIbβ3 (115). A second β3 integrin, αvβ3, albeit present at much lower density than αIIbβ3 (120), may contribute to the platelet binding of VWF through the ligand Arg-Gly-Asp (RGD) sequence, an interaction shown to occur on endothelial cells (121). Both VWF platelet receptors are promiscuous and bind several ligands that may mediate adhesion to other platelets and cells. In particular, the GP Ib-IX-V complex is a counter-receptor for P-selectin (122) and for the leukocyte integrin Mac-1 (α2βM) (123), supporting two interactions that may contribute more to inflamma-
tory responses (124) than to platelet thrombus formation. The integrin αIβ3, on the other hand, binds several ligands, in addition to VWF, that are key to the process of platelet adhesion and aggregation, primarily fibrinogen (125), fibronectin (126) and CD40 ligand (127).

The primary VWF platelet receptor is GP Ibα and its binding site in the VWF molecule, later shown to interact with heparin and collagen as well, was identified by Yoshihiro Fujimura (who is shown in Fig. 2) in Ted Zimmerman’s laboratory (68, 83, 128). The identification of its boundaries residues 449 and 728 defined its location within the A1 domain (129). The distinguishing feature of the interaction between GP Ibα and VWF-A1 is the ability to support activation-independent platelet tethering to thrombogenic surfaces even when the velocity of blood is elevated. The interaction has a fast dissociation rate, exhibiting the characteristics of a selectin-like bond (130), and the common paradigm is that it cannot support irreversible adhesion (56); thus, platelets tethered to the vessel wall solely through VWF-GP Ibα binding move constantly in the direction of flow. In inflamed tissues, this function may support the initial platelet contact with stimulated endothelial cells (131), a surface onto which membrane-bound VWF and P-selectin, which also mediates transient adhesion and rolling (132), may be the only adhesive substrates. Initial transient interactions between platelets and reactive surfaces may be essential for allowing a modulated response while surveying vessel wall integrity, as commitment to irreversible adhesion after each initial contact could have adverse consequences, including tissue damage. The presence of additional structures signifying a serious lesion may be the required trigger for subsequent steps such as irreversible platelet adhesion and accumulation. The GP Ibα-mediated translocation velocity onto immobilized VWF is typically less than 2% of the free flow velocity of non-interacting platelets at the same distance from the luminal surface.

This slow motion allows the establishment of additional bonds through receptors that belong mostly, but not necessarily, to the integrin superfamily. Such receptors, many of which depend on platelet activation to express function, typically have an intrinsically slower rate of bond formation but are capable of mediating stable interactions that lead to the definitive arrest of individual platelets and subsequent thrombus development. Notable in this regard is the role of the activated integrin αIβ3, which binds to the Arg-Gly-Asp sequence in VWF itself (117, 118), which binds to the Arg-Gly-Asp sequence in VWF itself or to other adhesive substrates in a complex matrix (133, 134), and of collagen and its receptors (135, 136). When VWF is bound to collagen, the transition from rolling to stable adhesion occurs more rapidly than on immobilized VWF alone and thrombus development occurs at higher shear rates than on collagen without VWF (53). Such a consideration highlights the true synergistic function of the VWF-collagen complex, which also leads to multiple activating signals coupled, in part, to the VWF-GP Ibα interaction (137–141).

An integrated view of VWF-mediated platelet adhesion and aggregation

The concept that the VWF-GP Ibα interaction cannot support long-lasting adhesion must be modified in view of the recently demonstrated ability of non-activated platelets to form aggregates that attach firmly to immobilized VWF under extremely high shear stress conditions (Fig. 3) (115). Several unique features characterize this mechanism of platelet adhesion to extracellular surfaces and to one another, marking substantial differences with the process of single platelet rolling. Perhaps the most relevant distinction is that GP Ibα-mediated long-lasting adhesion and aggregation only occurs above a threshold shear rate of ~ 10,000 s⁻¹, a feature that highlights its potential importance for pathological arterial thrombosis. A second key distinction is that platelet adhesion and aggregation at pathologically elevated shear rates depends on soluble as well as surface-bound VWF. Single platelet adhesion and rolling, in contrast, requires only immobilized VWF, even though it is also enhanced by the presence of soluble VWF at the higher shear rates (115) likely as a result of the slow motion allowing the establishment of additional bonds through receptors that belong mostly, but not necessarily, to the integrin superfamily.

Figure 3: Activation-independent platelet adhesion and aggregation at the interface of immobilized and soluble VWF.
A) Blood containing 93 μM D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone dihydrochloride (PPACK) as anticoagulant, the fluorescent dye mepacrine (10 μM), prostaglandin (PG) E₁ (10 μM) to inhibit platelet activation, and EDTA (5 mM) to prevent ligand binding to integrins, was perfused over immobilized VWF (20 μg/ml) coating concentration). The white line delimits VWF-coated (to the left) from uncoated glass. Single platelets adhere when the shear rate is 3,000 s⁻¹ (top); rolling aggregates (some identified by arrowheads) form at 20,000 s⁻¹ (bottom). B) Perfusion over immobilized VWF of washed blood cells suspended in buffer (20 mM Hepes, 150 mM NaCl, pH 7.4). In the absence of soluble VWF, single platelets adhere when the shear rate is 3,000 s⁻¹ (upper left), and fewer single platelets adhere at 24,000 s⁻¹ (upper right). After adding soluble VWF (20 μg/ml), single platelets adhere at 3,000 s⁻¹ (lower left; an arrow points to a single platelet shown for reference), but aggregates form at 24,000 s⁻¹ (lower right; arrows point to a rolling aggregate and an inset highlights a stretched aggregate during stationary adhesion). C) Perfusion over immobilized VWF of washed blood cells with added soluble VWF and anti-VWF A1 domain monoclonal antibody (NMC-4, 20 μg/ml). No platelet adhesion is detected. (Printed with permission from Ruggeri ZM et al., Blood 2006; 108: 1903–1910.)
sult of VWF multimer self-association favored by shear-induced binding to platelets. A third and equally relevant feature is that GP Ibα-mediated and VWF-dependent firm platelet adhesion and aggregation occur without any requirement for platelet activation and integrin function. Such a statement should not be taken to mean that activation has no influence on platelet thrombus formation at pathologically elevated shear rates, as it remains essential for the stability of aggregates and their attachment to the reactive surface. It is intuitive, however, that the ability of platelets to aggregate onto surfaces even before activation takes place greatly favors the establishment of growing thrombi in a high shear rate environment, in which elevated tensile stress limits the efficiency of adhesive bonds and rapid flow reduces the concentration of agonists required for activation. Under challenging hydrodynamic conditions, therefore, platelet interactions with adhesive surfaces and with one another appear to be synergistic. Of note, ADAMTS-13 can cleave circulating VWF multimers while they mediate activation-independent interplatelet cohesion under high shear stress, thus dispersing the aggregates (112).

A look to the future

It is a relatively easy prediction that research on VWF in years to come will focus on its role in platelet thrombus formation. The interaction between GP Ibα and the VWF A1 domain has unique and specific relevance in this regard, and likely will be targeted for evaluating the potential usefulness of its inhibition in anti-thrombotic therapy. GP Ib within the GP Ib-IX-V complex appears to occupy a key position for platelet adhesion and activation, as discussed above through the interaction with VWF but also through other ligands (142), but also as a point of convergence for coagulation (143–146) and, possibly, regulation of blood cell and vascular responses in host-defense mechanisms (122, 123, 147). The integration of these diverse GP Ib functions and their potential bidirectional regulation by and on VWF activities will be explored in the future.

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