Structure and Function of von Willebrand Factor

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Introduction

The reader will find here a concise summary of established notions on the structure and function of von Willebrand factor (vWF), followed by a brief discussion of selected recent advances that illustrate how this molecule supports platelet function in hemostasis and thrombosis. A comprehensive review of the topic is beyond the scope of this chapter and may be found elsewhere.\textsuperscript{1-3}

Multimeric Structure of von Willebrand Factor

The glycoprotein (GP) known as von Willebrand factor (vWF), identified by Zimmerman and collaborators in 1971,\textsuperscript{4} is present in plasma, in the α-granules of platelets and in subendothelial matrices. It has two essential functions required for the normal arrest of bleeding at wound sites (hemostasis): it promotes platelet adhesion to thrombogenic surfaces and platelet-to-platelet cohesion during thrombus growth, and it serves as the carrier for factor VIII in plasma, greatly prolonging the lifetime of this coagulation coenzyme in the circulation and making its function possible in the generation of α-thrombin.

The vWF found in plasma and platelets and, presumably, the protein in subendothelial matrices, consists of a series of polymers of progressively increasing size, as shown by analysis in large pore acrylamide or agarose gels containing sodium dodecyl sulfate (SDS) and under conditions preserving intact disulfide bonds.\textsuperscript{5-7} The smallest secreted species is a dimer of identical disulfide-linked subunits.\textsuperscript{5-10} The mature vWF subunit contains 2,050 amino acid residues, 169 of which are Cys clustered in domains located at the amino- and carboxyl-terminal ends.\textsuperscript{11} The estimated carbohydrate content varies between 10% and 12% of the total mass, with up to 22 chains, 10 α-linked to Ser or Thr residues and 12 N-linked to Asn residues.\textsuperscript{11} Subunit dimers are building blocks, or protomers, that are assembled intracellularly into larger multimers by disulfide linkage.\textsuperscript{12,13} The maximum number of subunits in the largest multimers is estimated to be on the order of 50 to 100. The molecular mass ranges from approximately 540 kDa for the dimer to several thousand kDa for the largest molecule. Analysis by SDS-polyacrylamide gel electrophoresis of plasma-derived vWF with reduced disulfide bonds reveals a predominant band with mobility corresponding to an apparent molecular mass of 225 kDa. This value reflects an aberrant electrophoretic mobility in SDS-containing gels, since the molecular mass of the vWF subunit is approximately 270 kDa on the basis of chemical composition. In addition to the main species, reduced plasma vWF of all normal individuals reproducibly contains two smaller bands of apparent molecular mass 176 kDa and 140 kDa, respectively, as well as a minor band of apparently 189 kDa.\textsuperscript{14} In contrast, vWF in platelet α-granules is composed exclusively of 225 kDa subunits.\textsuperscript{10} This observation implies that the smaller species are generated at the time of or after secretion from endothelial cells into the circulation.

The two predominant fragments seen after reduction of plasma vWF multimers, representing approximately 5% to 10% of the total subunit content, originate from cleavage of the peptide bond between residues Tyr842 and Met843.\textsuperscript{15} Because there are no intrachain or interchain disulfide bonds across the bond, this single event can separate a vWF multimer into two smaller species, each having a different cleaved subunit at the amino or carboxyl terminal end of the polymeric chain.\textsuperscript{10} On the basis of the model explaining their origin, which has been confirmed by chemical analysis,\textsuperscript{10} the 146 kDa fragment corresponds to residues 1 to 842 of the vWF subunit and that of 176 kDa corresponds to residues 843 to 2,050. The fact that these two fragments have a combined apparent molecular mass greater than that of the intact subunit must reflect distinctly aberrant individual patterns of electrophoretic mobility. Moreover, no explanation has been found, to date, for the origin of the minor subunit fragment of 189 kDa. This may possibly be a reflection of heterogeneity resulting from glycosylation or other post-translational processing. Models have been proposed to explain how cleavage of the single peptide bond between Tyr842 and Met843 may result in the heterogeneity of species seen upon high-resolution analysis of plasma vWF by electrophoresis\textsuperscript{10} or electron microscopy.\textsuperscript{13}

The degree of polymerization, thus, the size, of mature vWF multimers appears to vary depending on the anatomical location of the molecule. The largest species with the greatest thrombogenic potential are present in cellular compartments—endothelial cell and platelet storage sites—and not in plasma, where they may be secreted at sites of vascular lesion.\textsuperscript{16,17} With respect to physiological conditions at rest, therefore, some of the vWF molecules present in platelets or endothelial cells may appro-
Pritely be defined as "unusually large."\textsuperscript{18} Proteolytic cleavage of the subunit is the main, if not only, physiologic process responsible for reducing the size of the largest vWF multimers in plasma, directly generating smaller species from larger ones. Two independent studies have provided strong evidence that normal plasma contains a metalloproteinase acting specifically on vWF multimers and cleaving the subunit at the bond between Tyr842 and Met843.\textsuperscript{19,20} The action of this enzyme in vitro was found to be greatly facilitated by partial denaturation of vWF. In vivo, a similar effect may result from the action of shear forces changing the three-dimensional structure of vWF\textsuperscript{21} and exposing the susceptible peptide bond.\textsuperscript{20}

**Biochemistry, Storage, and Secretion of von Willebrand Factor**

The large vWF gene, approximately 180 kb in length, reflects the complex structure of the corresponding protein. The gene contains 52 exons\textsuperscript{22} and is located at the tip of the short arm of chromosome 12, region 12p12-12pter.\textsuperscript{23} An unprocessed pseudogene that partially duplicates exons 23 through 34 has been identified on chromosome 22.\textsuperscript{24} Expression of the vWF gene is restricted to endothelial cells and megakaryocytes. Endothelial cell expression is dependent on at least two positive regulatory domains, the first approximately 200 nucleotides upstream of the transcription start site, and the second located within the first untranslated exon of the gene.\textsuperscript{25,26} Expression of vWF is not homogenous in all vascular beds. In mice, for example, the 487 nucleotides 5' to the transcription start site direct restricted expression to a subpopulation of endothelial cells in the yolk sac and adult brain.\textsuperscript{27} It appears, therefore, that the heterogeneity in vWF expression depends on specific genetic elements within the vWF promoter, possibly contributing to the vascular diversity documented in this regard by immunohistochemical and mRNA analyses.\textsuperscript{28,29}

The vWF cDNA translation product is a 2,813-residue precursor polypeptide referred to as pre-pro-vWF.\textsuperscript{30,31} The unusually large 741-residue propeptide, released from the parent molecule during biosynthesis,\textsuperscript{12,32} is identical to a previously characterized protein, von Willebrand antigen II (vWAII).\textsuperscript{33} This antigen is found in plasma and platelets as a species immunologically distinct from mature vWF, but similarly decreased in patients with von Willebrand disease.\textsuperscript{35} The propeptide and mature subunit of vWF, together representing pro-vWF, are almost entirely composed of four types of repeating domains, designated A through D, arranged from amino- to carboxy-terminal in the order D1-D2-D'-D3-A1-A2-A3-D4-B1-B2-B3-C1-C2.\textsuperscript{36} The four D domains are approximately 360 residues in length, and each contains between 32 and 36 cysteine residues. The three homologous A domains, the presence of which identifies a superfamily of proteins,\textsuperscript{37} altogether span residues 497 to 1,111 of the mature vWF subunit. The C domains of vWF have sequence similarity to thrombospondin and \( \alpha \)-procollagen types I and III.\textsuperscript{38} Domain C1 in vWF contains the sequence Arg-Gly-Asp, considered the signature recognition site for adhesion receptors of the integrin superfamily.\textsuperscript{39,40}

Following translation of the mRNA, removal of the signal peptide, and initial glycosylation, pro-vWF undergoes extensive post-translational processing to produce multimeric vWF. This is initiated by the association of pro-vWF monomers into dimers through intermolecular disulfide bridges within their carboxyl terminal regions.\textsuperscript{41} It appears that the last 151 residues in the vWF subunit, following the C2 domain and without any other obvious internal homologous sequence, are the only structure required for dimerization.\textsuperscript{42,43} Concurrent with, or soon after, carbohydrate processing in the Golgi apparatus, the propeptide drives the association of pro-vWF dimers into higher order structures linked through Cys residues in the amino terminal domain of each mature subunit. Multimer formation requires domains D1 and D2, forming the propeptide sequence, as well as domains D' and D3 at the amino-terminal of the mature subunit.\textsuperscript{44} The vWF propeptide may possess endogenous disulfide isomerase-like activity that promotes interdimer disulfide bond formation between pairs of D3 domains.\textsuperscript{45}

The complexity of vWF multimer biosynthesis is not fully explained by schematic representations, as illustrated by the recognition of the dominant negative effect exerted on the process by the single amino acid substitution Cys2010→Arg.\textsuperscript{43} This mutation, in heterozygous patients, is responsible for type IID von Willebrand disease, a variant characterized by abnormal vWF structure with the absence of the largest multimers.\textsuperscript{14,46} Introduction of the mutation in the isolated carboxy-terminal vWF fragment Glu1366-Lys2050 prevents the spontaneous dimerization seen with the wild-type counterpart.\textsuperscript{43} In heterozygous patients who have both normal and abnormal subunits, large multimer formation is impaired, but assembly can still progress to polymeric chains composed of several subunits. The dominant negative nature of the phenotype caused by the Cys2010→Arg mutation suggests that subunits unable to dimerize at their C-termini may still be incorporated into nascent polymers as individual species. A possible explanation for this effect is that pro-vWF, mutated at Cys2010, even without dimerizing, can form intermolecular bonds with the reactive N-termini of normal subunits in multimers being assembled. When this happens, the presence of a dysfunctional carboxy-terminal domain at one of the growing ends of the polymeric chain blocks further addition of protomers on that side. If the same process occurs at both ends of the molecule, multimerization is arrested. This event can take place at any moment during the random incorporation of protomers into polymers and makes the synthesis of large multimers virtually impossible in these patients. The pathogenesis of von Willebrand disease type IID appears to indicate that, perhaps only when abnormal conditions occur, individual subunits may become part of multimers independently of prior dimerization at carboxyl termini.\textsuperscript{44}

Unlike most other proteins, vWF can follow more than one pathway of secretion from endothelial cells,\textsuperscript{47} namely, a constitutive pathway directly linked to synthesis (i.e., molecules are released as soon as their synthesis is completed) and a regulated pathway involving storage of mature molecules in appropriate granules for release after stimulation by secretagogues.\textsuperscript{48} Secretion by the regulated pathway yields multimers of higher molecular mass than originating from constitutive secretion,\textsuperscript{49} a fact that may have biological relevance since larger multimers are
hemostatically more effective. The vWF released either constitutively or from storage in the Weibel-Palade bodies is directed toward both the lumen (apical secretion) and the subendothelial matrix (basolateral secretion). The modality of constitutive and regulated vWF release in vivo remains essentially unknown, and whether the polarity of secretion varies in a different district of the vasculature or under the influence of various stimuli affecting the endothelium has yet to be established. For example, an immunohistological survey of the human body has led to the conclusion that subendothelial deposition of vWF occurs only in arteries, arterioles, and large veins, and another study has shown that secretion of vWF towards the basal membrane of capillary endothelial cells in vivo occurs only after stimulation. The initially proposed concept that regulated secretion occurs predominantly in the basolateral direction has been subsequently challenged with the evidence that up to 80% of vWF released from storage organelles is directed toward the apical side of the cell. These different results imply that the polarity of vWF secretion from both constitutive and regulated pathways is more complex than presently understood from in vitro studies, and it may be influenced in vivo by the nature of the release-inducing stimulus.

The synthesis of vWF by megakaryocytes has not been studied in great detail because of problems with culturing these platelet progenitors in vitro. Although secretion of vWF into a culture medium has been demonstrated in vitro, experiments involving bone marrow transplantation from normal pigs into pigs with severe von Willebrand disease argue against the existence of a significant physiological mechanism of vWF release from megakaryocytes. There is no doubt, however, that all of the vWF stored in platelet α-granules derives from synthesis in megakaryocytes and, unlike other α-granule proteins such as fibrinogen, is not derived from plasma. Indeed, platelet α-granules represent an isolated compartment that becomes available for hemostasis only when platelets are activated and the release reaction takes place. Platelet-derived vWF is structurally similar to that stored within Weibel-Palade bodies in endothelial cells and is composed of the largest multimeric species.

Domain Structure of the von Willebrand Factor Subunit

The vWF subunit contains several discrete sites mediating interactions with other molecules. These domains exist in each subunit with conformation and function independent of multimer assembly, as indicated by the fact that isolated monomeric fragments generated by proteolysis or expressed recombinantly retain substrate recognition specificity. The location of the main functional sites in the vWF subunit has been identified, and some of the corresponding biochemical and structural characteristics have been delineated.

Domains Interacting with Extracellular Matrix Components: A1 and A3

The collagen-binding function of vWF appears to be expressed in two of the three type A domains of the molecule, A1 and A3. Evidence obtained with various approaches, including recombinant fragments, initially suggested that domain A3 is necessary and sufficient to support vWF binding to fibril-forming collagens, while the function of domain A1 in this regard was considered either expendable or nonexistent. A more varied situation is now emerging, with experimental findings indicating that domains A1 and A3 may play diverse roles in supporting interaction with different types of collagen. For example, domain A1 appears to be uniquely involved in mediating binding to collagen type VI, while domain A3 is necessary for binding to types I and III. Ongoing studies appear to indicate that fluid dynamic conditions and mechanical forces may further modulate the situation, with a complex interplay of domains A1 and A3 in effecting vWF immobilization onto various collagen types. In addition to the collagen-binding site, the A1 domain of vWF also contains apparently distinct sequences that support interactions with other molecules capable of mediating immobilization onto exposed tissue matrices. A heparin-binding site is presumably located in the loop region between residues Cys509 and Cys695. A second heparin-binding sequence, albeit of lower affinity, exists within the first 272 residues of the mature subunit, in the region that also supports formation of the complex with factor VIII. These sites may reflect the ability of vWF to interact with proteoglycans that contain sulfated sugars similar to heparin.

A1 Domain and the Interaction with Platelet Glycoprotein Ibα

Initial information on the location of the platelet GP Ibα binding site in vWF was obtained in 1986 and 1987, but defining the residues directly involved in the interaction has proven difficult and remains to be accomplished. Results of inhibition studies with synthetic peptides originally suggested that residues 474 to 488 (at the boundary between D3 and A1 domains) and 694 to 708 (within the A1 domain loop) were possibly involved in this function. It is now believed that those results largely reflected the effect of synthetic peptides rich in Pro residues on the action of ristocetin, the modulator used to induce vWF binding to platelets. Other studies with synthetic peptides suggested that residues 514 to 542 form an essential site for GP Ibα binding, but no direct proof has demonstrated the role of this sequence in biologically-relevant mechanisms, as opposed to selected experimental conditions in vitro. The results of alanine-scanning mutagenesis studies, on the other hand, suggest that a number of A1 domain residues in discontinuous sequence location may contribute to support the interaction with GP Ibα.

Crystal Structure of Domains A1 and A3

The crystal structure of the two homologous vWF domains, A1 and A3, has been solved. Both domains have a typical α/β fold, consisting of a central hydrophobic parallel β-sheet flanked by amphipathic α-helices on each side, a type of fold also identified in the homologous I domains of integrin subunits and α and α. Notable in both vWF domains is the absence of the typical metal ion-dependent adhesion site (MIDAS) motif and, consequently, of metal binding. This contrasts with the fact that integrin I domains interact with their respective ligands in a divalent cation-dependent manner.
involving the MIDAS motif. Evidence obtained with site-directed mutagenesis studies has confirmed this mechanism for collagen binding to the α2 integrin subunit I domain, but mutation of homologous residues in the vWF A3 domain had no effect on collagen binding. A comparison between the structure of the α2 subunit I domain and the vWF A3 domain has not revealed, in spite of the similar folding, obvious shared features that could be suggestive of a common mechanism for binding to collagen. Thus, the exact location of the residues forming the contact surface between collagen and vWF A3 domain remains to be elucidated.

The A1 domain has been crystallized in complex with the Fab fragment of the function-blocking antibody NMC-4. The solved structure, at 2.2-Å resolution (Fig. 1), provides information, not only on the vWF residues interacting with the antibody, but also on the possible location of the GP Ibα binding site. NMC-4 interacts with the A1 domain bridging to helix α4, formed by vWF residues 627 to 643. Helix α4 is part of an extended surface that includes strand β3 and helix α3. The N-terminal portion of helix α3 forms a depression in this surface, suggestive of a binding pocket, delimited on one side by the N-terminal portion of helix α4 and on the other by the amino-terminal portion of strand β3. This surface may constitute the site where binding of GP Ibα occurs, presumably with a role for residues whose side chains point upward from the groove formed by helix α3, notably Glu596 and Lys599 (Fig. 2). Indeed, substitution of the latter two with Ala has previously been shown to inhibit GP Ibα binding. The vWF A1 domain has also been crystallized separately, confirming the structure described above.

Interaction with Integrin Receptors αIIbβ3 and αvβ3
Arg-Gly-Asp Sequence in Domain C1

The sequence Arg-Gly-Asp was initially identified as sufficient to express the cell adhesive properties of fibronectin but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, the Arg-Gly-Asp sequence corresponding to residues 1744 to 1746 in the carboxyl terminal C1 domain of the subunit represents the essential, if not unique, αIIbβ3-binding site. Another β3 integrin, αvβ3, can interact with the RGD sequence in vWF. Endothelial cells can adhere to immobilized vWF through the latter receptor, but the biological significance of the interaction remains to be proven.

Interaction with Factor VIII

The region of vWF that binds factor VIII lies between amino acids 1 and 272. This region is the RGD sequence, but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, there are intrachain disulfide bonds that appear essential for factor VIII-binding. The region of vWF that binds factor VIII lies between amino acids 1 and 272. This region is the RGD sequence, but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, there are intrachain disulfide bonds that appear essential for factor VIII-binding. The region of vWF that binds factor VIII lies between amino acids 1 and 272. This region is the RGD sequence, but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, there are intrachain disulfide bonds that appear essential for factor VIII-binding. The region of vWF that binds factor VIII lies between amino acids 1 and 272. This region is the RGD sequence, but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, there are intrachain disulfide bonds that appear essential for factor VIII-binding. The region of vWF that binds factor VIII lies between amino acids 1 and 272. This region is the RGD sequence, but was later found to exhibit a similar function in several other proteins involved in interaction with integrin receptors. In vWF, there are intrachain disulfide bonds that appear essential for factor VIII-binding.

Figure 1. Ribbon diagram of the complex between vWF A1 domain (the molecule on top) and NMC-4 Fab (the molecule on the bottom). The light (L) and heavy (H) chains in the Fab are depicted in blue and green, respectively. The A1 domain is depicted in purple, except for helix α4, shown in red, interacting with the Fab L and H chain loops. Reprinted from Celikel et al with permission.

Figure 2. Stereo view of a ribbon representation of the vWF A1 domain, formed by six α-helices surrounding a central β-sheet with five parallel and one antiparallel β-strands. Four of the α-helices are shown in purple, 5 of the β-strands in green, and all loops in yellow. Helices α3 and α4 and strand β3, forming the proposed GP Ibα binding site, are shown in red. Mutations of three residues in this region, Gly561 (filled blue circle), Glu596 (red, near the beginning of helix α3), and Lys599 (blue, in the middle of helix α3), have been associated with loss of the GP Ibα binding function. The side chains of Tyr637 (light blue, in close proximity to Lys599) and Lys644 (blue, in the loop following helix α4) that may contribute to GP Ibα binding are also shown. The side chains of Cys509 and Cys695, linked in an intrachain disulfide bond, appear in dark red near the bottom of the molecule. Reprinted from Celikel et al with permission.
Interactions with Other Ligands

The binding of vWF to sulfated glycolipids present on cellular membranes may serve an accessory role in promoting platelet interactions with vWF. The binding site for sulfatides is apparently located within residues 512 to 673 in the A1 domain loop between Cys509 and Cys695, presumably, directly involving residues 569 to 584. This location is in close proximity to other key sites supporting vWF activities, but the possible existence of structural or functional interplay involving the residues that participate in these different interactions remains to be established. The binding of vWF to fibrin may have important implications for platelet adhesion at a site of vascular injury. It seems clear that vWF can become crosslinked to the α-chain of fibrin, but there is no information as to the residues involved in this process.

Function of von Willebrand Factor in Platelet Thrombus Formation

The main biological activity of vWF is to support adhesive interactions that are key to the participation of platelets in thrombus formation. This function is essential in vessels in which rapid blood flow tends to oppose the establishment of hemostatic thrombi firmly attached to areas of vascular lesion. The requirement for vWF in thrombus formation decreases or ceases in vessels with relatively slow blood flow, a situation in which other adhesive molecules may support platelet function. Establishing a threshold shear rate value to discriminate the function of vWF from that of other adhesion substrates is difficult, since fluid forces on the surfaces of growing thrombi may vary significantly from those present in a normal vessel with unperturbed blood flow. Certainly, vWF is required for platelet adhesion and aggregation in the segments of the vascular tree where efficient primary hemostasis is key to arresting bleeding, such as small arterioles and arterial capillaries in which median wall shear rate estimates are on the order of 1,700 s⁻¹.

Upon exposure of rapidly flowing blood to extracellular matrix components, initial platelet tethering to the wounded tissue is mediated by immobilized vWF interaction with GP Ibα. This process depends on bonds that form with fast forward rate but support slow translocation, rather than arrest at the site of first contact, owing to an inherently high dissociation rate and short half-life. Nevertheless, coupling of GP Ibα to the vWF A1 domain substantially reduces the velocity of tethered platelets, compared to those flowing freely in the boundary layer, enabling relatively slow integrin-mediated interactions that are required for irreversible adhesion to occur. It is interesting to note that, regardless of whether vWF is immobilized onto glass or adsorbed onto collagen, GP Ibα-mediated tethering results in similar velocity of translocation, implying no difference in the association and dissociation rates of the interaction. This observation suggests that the mechanism of vWF binding to GP Ibα is not likely to involve specific conformational changes dependent on binding to matrix components, a commonly stated hypothesis never proven experimentally. Indeed, the general assumption that plasma vWF has a “nonfunctional” (“nonadhesive”) conformation that must switch to “functional” to initiate platelet adhesion, in turn supporting the concept of a required conformational change, may not be true. Published evidence suggests the possibility of a different scenario, since it is clear that the A1 domain function in platelet adhesion does not require the ability to form stable bonds with GP Ibα. Thus, the native A1 domain conformation may be set for receptor binding with high association and dissociation rates, allowing vWF immobilized at wound sites to mediate rapid platelet tethering and, at the same time, soluble vWF in blood to be nonreactive, owing to the fact that any interaction with platelets is short-lived in the absence of other thrombogenic stimuli.

At shear rates relevant for hemostasis in arterioles and thrombosis in atherosclerotic arteries, the most prominent integrins mediating stable platelet adhesion and aggregation are αIIbβ₃ and αIbβ₂. The role of αIbβ₂, as a key receptor for adhesive proteins involved in linking platelets to one another, notably, fibrinogen and vWF, is well-established. The uniquely relevant function of αIbβ₂, in turn, is expressed by its ability to act in concert with GP Ibα-vWF and αIβ₂, to promote stable platelet adhesion as well as activation. It is apparent from experiments on subendothelial matrix that both attributes are important, since selective αIbβ₂ blockade causes a relatively modest inhibition of surface coverage but a pronounced decrease in thrombus volume. Such an effect on the formation of large aggregates cannot depend on direct participation in interplatelet bonding. Rather, it may reflect the role of αIbβ₂ in platelet activation following adhesion, a function possibly crucial when thrombin activity is limited. The occurrence of bleeding in patients with congenital defects of αIβ₂ is in agreement with these concepts.

Once firm platelet adhesion is established at sites of vascular injury, homotypic platelet aggregation leads to thrombus development. The long-held contention that fibrinogen and αIβ₂ have an exclusive role in linking platelets to one another appears to be applicable only to fluid dynamic environments characterized by low shear stress, for example, in veins, in which this process, however, may be less directly relevant for hemostasis. Recent evidence also questions the validity of two additional concepts still held as valid, namely, that vWF may have a role in platelet aggregation, but is limited to pathologically extreme shear rates, and that the functional involvement of fibrinogen decreases as that of vWF becomes manifest. On the contrary, the two adhesive proteins may be complementary and synergistic, and both may be needed to support thrombus development at all levels of arterial flow (Fig. 3). The adhesive potential of platelets, therefore, appears to result from the sum of distinct pathways supported by coordinated receptor–ligand interactions specifically adapted to respond to different environmental conditions. In particular, the functional integration of the receptors GP Ibα, αIbβ₂, and αIβ₂ with their respective ligands and the coordinated function of vWF and fibrinogen as adhesive molecules bridging across platelets, may have direct physiopathological relevance.

Conclusions

Progress is rapidly being made toward further understanding the structure and function of vWF. Knowledge of the
three-dimensional structure of isolated domains is supporting renewed efforts aimed at defining, in detail, the molecular basis of von Willebrand disease—a constant source of new information critical to defining, in detail, the structure and function of vWF and the genetic regulation of its biosynthesis. The next few years should be exciting for investigators interested in these topics.

References

4. Zimmerman TS, Ratnoff OD, Powell AE. Immunologic differentiation of classic hemophilia (Factor VIII deficiency) and von Willebrand’s disease. With observations on combined deficiencies of antithemophilic factor and procoagulant (Factor V) and on an acquired circulating anticoagulant against antithemophilic factor. J Clin Invest. 1971;50:244-254.
17. Lopez-Fernandez MF, Ginsberg MH, Ruggeri ZM, Batlle J, Zimmerman TS. Multimeric structure of platelet factor VIII/von Willebrand factor. The presence of larger multimers and their...


