Modeling and Functional Analysis of the Interaction between von Willebrand Factor A1 Domain and Glycoprotein Iba*

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Binding of the von Willebrand factor (vWF) A1 domain to the glycoprotein (GP) Ib-IX-V complex mediates platelet adhesion to reactive substrates under high shear stress conditions, a key event in hemostasis and thrombosis. We have now used the known three-dimensional structure of the A1 domain to model the interaction with the GP Ibo sequence 271–279, which has previously been implicated in ligand binding. Docking procedures suggested that A1 domain residues in strand β3 and preceding loop (residues 559–566) as well as in helix α3 (residues 594–603) interact with Asp residues 272, 274, 277 and sulfated Tyr residues 278 and 279 in GP Ibo. To verify this model, 14 mutant A1 domain fragments containing single or multiple side chain substitutions were tested for their ability to mediate platelet adhesion under flow. Each of the vWF residues Tyr565, Glu566, and Lys568 proved to be strictly required for A1 domain function, which, in agreement with previous findings, was also dependent on Gly561. Moreover, an accessory functional role was apparent for a group of positively charged residues, including Arg at positions 629, 632, 636 and Lys at positions 643 and 645, possibly acting in concert. There was, however, no evidence from the model that these residues directly participate in forming the complex with GP Ibo. These results provide a partial model of the vWF-GP Iba interaction linked to the manifestation of functional activity in platelet adhesion.

EXPERIMENTAL PROCEDURES

Modeling of the vWF-GP Iba Interaction—The coordinates of the complex between vWF A1 domain and the monoclonal antibody NMC-4 are deposited in the Protein Data Bank with accession number 1OAK.
The GP Ibα sequence GDTDLYY(DY(SO4)2) was selected for docking onto the vWF A1 domain because of its experimentally proven involvement in ligand binding (25–27). Molecules were constructed and visualized with INSIGHTII (release 95.0 with Builder, Biopolymer, and Discover modules, Biosym/Molecular Simulations Inc.). The presumed conformation of the YDYY portion of the GP Ibα was fixed, whereas all other residues were allowed to vary. The choice of an initial conformation for the calculations, each new peptide unit was treated as completely flexible, was optimized by energy minimization using X-PLOR (28). In these calculations, each new peptide unit was treated as completely flexible, whereas only 2–4 torsion angles at a time were allowed to vary in the YDYY sequence. In subsequent cycles, torsion angles that had been kept fixed were allowed to vary. The choice of an initial conformation for the YDYY portion of the GP Ibα peptide reduced the complexity of calculations, but no portion of the peptide was treated as rigid, thus eliminating or reducing bias. The three Tyr residues in the sequence were constructed both with and without sulfitation. The latter post-translational modification is thought to occur on all three residues in the native protein and to be necessary for normal function (27, 29). The geometry of the modified tyrosine residues was optimized using X-PLOR (28). Docking of the GP Ibα peptide onto vWF was performed with AUTODOCK, release 2.4 (30). This program uses Monte Carlo simulated annealing procedures to explore a wide range of conformational states. In our case, the vWF A1 domain molecule was kept fixed throughout the simulation while the GP Ibα peptide was subjected to random movement in the space around the protein accompanied by changes in its conformation. At each step in the simulation, a small random displacement was applied to each of the internal and external degrees of freedom of the peptide, involving translation of its center of gravity, orientation with respect to the vWF A1 domain, and rotation around each of its flexible dihedral angles. The energy resulting from the new conformation of the peptide and its interaction with the A1 domain was evaluated. This value was accepted as valid if lower than the one obtained in the preceding cycle of the simulation, resulting in a final conformation with the lowest energy of interaction between the GP Ibα peptide and the vWF A1 domain. Intermolecular contacts were generated with CONTACSYM (31) using extended van der Waals radii (32). Cut-off distances of 3.4 Å and 4.33 Å were used for defining hydrogen bonds and van der Waals interactions, respectively. The molecular surface was calculated (33) as described previously using a 1.7 Å probe radius.

Expression and Purification of Recombinant Fragments Containing the vWF A1 Domain—Recombinant polyepitides corresponding to residues 445–733 of the mature vWF subunit, designated rVWF445-733, were expressed in host Ericheria coli BL21-DE3 as described previously in detail (34–36). All vWF fragments used in these studies had Cys mutations at positions 459, 462, 464, 471, and 474 to prevent intrachain disulfide bond (34). They all migrated as a single band with the predicted sequence. All fragments had comparable behavior and were soluble up to a concentration of at least 0.5 mg/ml. The main GP Ibα residues involved in forming a complex with the A1 domain were Asp599 and Lys602 in the A1 domain appeared to play a prominent role in contacting the receptor (Fig. 2). This finding highlights the possible participation of internal β3 and preplatelet αIIbβ3 in the A1 domain.
Functional Analysis of the vWF A1 Domain-GP Ibα Interaction—Recombinant vWF fragments comprising residues 445–733 of the mature subunit and containing the A1 domain were expressed with single or multiple mutations of residues selected among those that appeared to be involved in the modeled interaction with GP Ibα (Table I). Additional residues previously shown to be involved in binding to the function blocking antibody NMC-4 (24) or thought to participate in modulator-induced vWF binding to GP Ibα (24, 41) were also mutated. In total, 14 different mutant fragments in addition to the one with native sequence were individually tested after immobilization onto a glass surface for their ability to interact with platelets when exposed to blood cells flowing in a plasma-free suspension at wall shear rates between 340 and 1500 s\(^{-1}\). After coating onto glass, the presence of all fragments on the surface was confirmed by reactivity with specific monoclonal antibodies detected by enzyme-linked immunoassay (42). In agreement

| A1 domain | GP Ibα | Type of interaction |
|-----------|--------|---------------------|
| Asp\(^{276}\) | Tyr(SO\(_4\))\(^{279}\) | VDW |
| Glu\(^{261}\) | Tyr\(^{278}\) | VDW |
| Ser\(^{292}\) | Tyr\(^{278}\) | H bond |
| Ser\(^{292}\) | Asp\(^{277}\) | H bond |
| Ser\(^{292}\) | Tyr\(^{278}\) | VDW |
| His\(^{363}\) | Asp\(^{277}\) | VDW |
| Ala\(^{364}\) | Asp\(^{277}\) | VDW |
| Ala\(^{364}\) | Asp\(^{274}\) | H bond |
| Tyr\(^{355}\) | Asp\(^{274}\) | H bond |
| Tyr\(^{355}\) | Asp\(^{274}\) | VDW |
| Lys\(^{372}\) | Gly\(^{271}\) | H bond |
| Ileu\(^{380}\) | Asp\(^{272}\) | VDW |
| Glu\(^{396}\) | Tyr(SO\(_4\))\(^{278}\) | H bond |
| Glu\(^{396}\) | Tyr\(^{278}\) | VDW |
| Glu\(^{396}\) | Tyr(SO\(_4\))\(^{278}\) | H bond |
| Lys\(^{399}\) | Tyr\(^{278}\) | H bond |
| Lys\(^{399}\) | Tyr\(^{278}\) | VDW |
| Tyr\(^{400}\) | Tyr\(^{278}\) | VDW |
| Tyr\(^{400}\) | Tyr\(^{278}\) | VDW |
| Tyr\(^{400}\) | Asp\(^{277}\) | VDW |
with previous results, the fragment with native sequence supported a characteristic rolling adhesion of platelets as typically mediated by multimeric vWF with similar shear rate dependence (23). For the purpose of these studies, all platelets in contact with the surface, regardless of velocity of rolling and duration of interaction, were considered as adherent. At shear rates between 1500 and 1210 s\(^{-1}\), 7 of the 14 mutant A1 domain molecules supported platelet adhesion with at least 50% lower efficiency than the native control, and all with the exception of one showed a similar defect at 630–340 s\(^{-1}\) (Fig. 3A). Five of the mutants contained single-residue substitutions, and two had multiple substitutions of positively charged residues. The corresponding side chains are depicted in Fig. 2. Platelet adhesion to the remaining 7 mutant A1 domain fragments was 80% or more of that supported by the native fragment at least at one of the shear rates tested (Fig. 3B). Analysis of variance by both parametric and nonparametric (Kruskal-Wallis) tests indicated that the results obtained with distinct mutant A1 domain fragments were significantly different (p < 0.001 at 1500–1210 s\(^{-1}\); p < 0.002 at 630–340 s\(^{-1}\)). Comparisons between mutants by t test with Bonferroni correction showed that none of the single substitutions R629A, R632A, R636A, K644A, H656A, K660A, and R663A caused significant differences in platelet adhesion at the shear rate of 1500–1210 s\(^{-1}\) (p > 0.05; Fig. 3B). In contrast, each of the single substitutions G561S, Y565A, E596A, and K599A as well as the multiple substitutions R629A,R632A,R636A and K644A,K664A resulted in significantly lower platelet adhesion (p < 0.05; Fig. 3). Moreover, the single substitutions G561S, Y565A, E596A, and K599A caused significantly lower platelet adhesion also at the shear rate of 630–340 s\(^{-1}\). Of note, the four single-residue mutations that essentially caused complete loss of A1 domain function (Fig. 3A) included the substitution of two residues, Glu\(^{596}\) and Lys\(^{599}\), with a putative key role in the modeled interaction with GP Iba (Fig. 2). The other two mutations with such a drastic effect on function were Tyr\(^{565}\) → Ala and Gly\(^{561}\) → Ser, of which the latter is the reported cause of a variant form of von Willebrand disease (43). Single mutations of the three Arg residues at positions 629, 632, and 636 in helix \(\alpha\)d had no relevant effect on platelet adhesion (Fig. 3B), but the concurrent substitution of all three resulted in markedly decreased adhesion (Fig. 3A). In contrast to their apparently negligible participation in GP Iba binding, Arg\(^{632}\) and Arg\(^{536}\) were individually necessary for interacting with the function-blocking monoclonal antibody NMC-4 (Fig. 4), as anticipated on the basis of the solved structure of the latter in complex with the vWF A1 domain (24).

**DISCUSSION**

We have identified a putative GP Iba binding site in vWF using the crystal structure of the A1 domain to model the interaction with the receptor and verifying experimentally the predicted role of specific vWF residues in mediating adhesion of flowing platelets. Previous studies using synthetic peptides (25, 27) and site-directed mutagenesis of recombinant fragments (26, 27, 29) provide evidence that the GP Iba sequence selected for the docking procedure described here contains residues with a role in ligand binding. In this regard, it has already been shown that a peptide corresponding to the GP Iba sequence 251–279 can interfere with vWF binding to platelets.
mediated by ristocetin or botrocetin, whereas a peptide with sequence 271–285 has less inhibitory activity (25). However, only the entire 45-kDa amino-terminal GP Ibo fragment with intact disulfide bonds could block the direct binding of asialo-vWF to platelets (25), indicating that the vWF-GP Ibo interaction in the absence of modulators may depend on conformational attributes that cannot be retained by small synthetic peptides. Such a requirement for function appears to be in addition to sulfation of the Tyr residues at positions 276, 278, and 279, necessary to attain maximal ligand binding efficiency of GP Ibo (27, 29). Thus, we did not attempt to verify whether a synthetic peptide containing the GP Ibo sequence 271–279 modeled here could inhibit platelet adhesion to immobilized vWF under flow. On the other hand, in the absence of information on the three-dimensional structure of GP Ibo, we elected to perform the docking studies with a short sequence to reduce the possibility of bias in the results. As a consequence, we may have obtained only a partial view of the receptor binding site in the A1 domain.

The recombinant vWF fragment used for functional evaluation contains the A1 domain with the intrachain disulfide bond between Cys509 and Cys695 as well as the carboxyl-terminal region of the preceding domain D3 with 5 Cys residues mutated to Ala. We have previously demonstrated (23) that such a fragment exhibits a functional behavior comparable with that of A1 domain in multimeric vWF. Thus, after immobilization onto a surface, it can tether platelets and mediate rolling, but in solution, it fails to inhibit the function of GP Ibo even when present at relatively high concentrations unless an exogenous modulator is added (23). Findings of this type have suggested that the A1 domain undergoes a conformational change upon becoming insolubilized onto a surface, and in addition or in alternative, is modified by shear forces to achieve the functional conformation required for interaction with GP Ibo. There are, however, alternative explanations as to why soluble A1 domain cannot interfere with the function of immobilized A1 domain in the absence of modulators. For example, since the interaction with GP Ibo is rapidly reversible (6), the local high density achieved after binding to a surface may make competition by molecules in solution practically impossible to demonstrate because of limits to the concentrations that can be achieved in blood. Nevertheless, it cannot be excluded that the conformation provided by the known crystal structure of the A1 domain (24, 44), which reflects that of the soluble protein, may not correspond in all details to the functional conformation capable of supporting GP Ibo binding. Even with this caveat, it appears that the docking procedure described here can correctly predict a number of A1 domain residues likely to play a direct role in supporting the interaction with GP Ibo.

Our findings, in agreement with the hypothesis suggested by analysis of the A1 domain crystal structure (24), indicate that the GP Ibo binding interface is centered around a surface groove formed by helix α3 with neighboring strand β3 and helix α4. In this regard, the possible involvement of Glu596 and Lys599 (helix α3) as well as of Tyr637 (helix α4) in GP Ibo binding has already been suggested (24, 41), but the crucial role of Tyr629 (strand β3) has been unknown so far. The latter residue appears to be absolutely required for normal vWF function, since removal of its side chain results in a totally inactive A1 domain. On the other hand, the present results argue against the proposed participation of Lys643 in receptor binding (24). Of note, mutations of two residues predicted by our model to participate in A1 domain function, Gly671 and Glu596, are known to cause decreased vWF binding to platelets in Type 2M von Willebrand disease (3). With respect to GP Ibo, our findings agree with mutagenesis studies (29) and support the participation of sulfate groups on Tyr278 and Tyr279 in vWF binding (27). In the modeled interaction, each of these Tyr residues forms multiple contacts with Glu596, Lys599, and other residues in the A1 domain, perhaps explaining why only the concurrent obliteration of more than one sulfate group causes abnormal GP Ibo function (27). The latter conclusion, however, is based on the results of assays dependent on exogenous modulators and must be verified with the study of platelet adhesion under flow conditions.

An attempt to explain the mechanism of vWF association with GP Ibo has previously been based on alanine-scanning mutagenesis of charged residues in the A1 domain combined with the measurement of soluble ligand binding to platelets in the presence of exogenous modulators (41). The results of those studies correspond at least in part to the findings presented here, notably with respect to the key functional role played by Glu596 and Lys599. In contrast, the suggested participation of Arg632 and possibly Arg629 in receptor binding appears to be contradicted by our observation that single substitutions of these residues have limited effect on the tethering of platelets to the A1 domain. This was certainly true at the higher shear rates tested, although in both instances there was a tendency to partially decreased function at lower shear rates (Fig. 3B). It is possible, therefore, that neither Arg632 nor Arg629 are directly required for the association between immobilized A1 domain and GP Ibo. These residues, however, may participate in interactions dependent on the activity of exogenous modulators (41). Whether the latter have any counterpart in vivo is still questionable; thus, the physiological significance of the finding is uncertain, but it is intriguing to speculate that the results obtained with exogenous modulators may partly reflect vWF and GP Ibo function at lower but not higher shear rates. Such a consideration may be taken to indicate that shear forces directly modulate this ligand-receptor interaction, with possible effects on the conformation of relevant residues in vWF, GP Ibo, or both. We did not evaluate the involvement in GP Ibo binding of charged residues in strand β4 (Arg616) and the preceding loop (Glu613), both of which were indicated as possible participants in modulator-dependent vWF activity (41). The known A1 domain three-dimensional structure (24) shows that the side chains of these residues are oriented away from the receptor binding site defined by our modeling and functional studies. This observation, however, does not exclude the possibility that they may contribute to interactions with residues in GP Ibo other than the ones considered here.

It is of interest that the combined substitution of Arg629, Arg632, and Arg636 with Ala, but not of each individual residue, resulted in markedly reduced platelet adhesion to immobilized A1 domain, as did the combined substitution of Lys643 and Lys645. The side chains of these charged residues, as shown by the three-dimensional structure of the A1 domain (24), are oriented away from the proposed GP Ibo binding site involving mainly strand β3 and helix α3. In the crystal structure, moreover, Lys643 and Lys645 mediate a homodimeric interaction between adjacent A1 domain molecules. These charged residues on the surface of the molecule, therefore, may influence A1 domain conformation and function without participating directly in establishing contact with GP Ibo. Of note, binding to the A1 domain of the function-blocking antibody NMC-4 involves mainly the Arg residues at positions 632 and 636, as shown previously by the solved crystal structure of the complex (24) and confirmed here by functional studies, neither of which is necessary for interaction with GP Ibo. Thus, the inhibitory activity of the antibody may be mainly a consequence of steric hindrance. These considerations are in agreement with the concept that two contiguous but distinct sites in the A1 domain...
are involved in interacting with the antibody and GP Ibα, respectively.

In conclusion, our findings provide three-dimensional modeling and functional data that define a region in the vWF A1 domain necessary for binding to GP Ibα on flowing platelets. These results set the stage for future work aimed at the definitive elucidation of the molecular mechanisms that regulate the association of this ligand-receptor pair and control its key influence on hemostasis and arterial thrombosis.

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