Inhibition of Platelet Adhesion to Fibronectin, Fibrinogen, and von Willebrand Factor Substrates by a Synthetic Tetrapeptide Derived From the Cell-Binding Domain of Fibronectin

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The role in platelet function of the cell-binding region of fibronectin was explored by the use of synthetic peptides. The prototypical peptide gly-arg-gly-asp-ser was capable of inhibiting thrombin-induced platelet aggregation without altering the degree of platelet activation as judged by the secretion of ¹⁴C-serotonin. The peptide also effectively inhibited, in a concentration-dependent manner, the binding of radiolabeled fibronectin to platelets and the adhesion of platelets to fibronectin substrates. The smallest peptide from the cell-binding region of fibronectin which retained full activity was arg-gly-asp-ser. Transposition of amino acids or conservative substitutions of amino acids within this short sequence resulted in inactive peptides. Peptides containing the arg-gly-asp-ser sequence were also capable of inhibiting the adhesion of platelets to fibronectin and von Willebrand factor substrates. Examination of the entire panel of synthetic peptides for ability to inhibit adhesion to fibronectin or von Willebrand factor substrates revealed the same structure–function relationships that had been determined in the studies with fibronectin. 1985 by Grune & Stratton, Inc.

FIBRONECTIN (FN) is a disulfide-linked glycoprotein which is synthesized by a variety of cells and is found on cell surfaces, in the extracellular matrix, in plasma, and in other body fluids. Each of the similar, but not necessarily identical, peptide chains is composed of a series of relatively protease-resistant domains which contain binding sites for macromolecules such as collagen (gelatin), glycosaminoglycans, fibrin, and a cell surface receptor that mediates the adhesion and spreading of cells on FN-containing substrates. Recent studies have revealed that a synthetic peptide with an amino acid sequence contained within the cell-binding domain of FN retains the cell attachment promoting activity associated with the larger proteolytic fragments of FN containing the cell-binding domain. This sequence of amino acids is located about two thirds of the length of the molecule from the amino terminus.

The role of FN in platelet function remains to be clarified. Following the identification of FN as one of the proteins remaining associated with collagen following collagen-induced platelet aggregation and subsequent lysis of platelets by sonication and detergent treatment, Bensusan et al proposed that FN served as the collagen receptor on platelets. The observation by Santoro and Cunningham that denatured collagen, which has a higher affinity for FN than does native collagen, failed to inhibit the adhesion of platelets to collagen or to inhibit collagen-induced aggregation indicated that FN was unlikely to serve as the collagen receptor.

Subsequent studies revealed that FN is located within the alpha granules of platelets and is secreted upon platelet activation. FN is not expressed on the surface of unactivated platelets, but does become platelet surface-associated following activation. This association is presumably mediated by the expression of specific FN receptors on platelets following activation as demonstrated by Plow and Ginsberg.

These observations are all consistent with the concept that FN plays a role in platelet function. This concept is supported by the report of a patient exhibiting abnormal platelet aggregation in response to collagen and adenosine diphosphate (ADP), which was partially corrected by the addition of purified FN by the demonstration that high concentrations of FN can inhibit platelet aggregation, and by the description of a monoclonal antibody against FN which inhibits platelet aggregation.

The studies described in this report were designed to investigate the role of the cell-binding domain of FN in the interactions of FN with platelets. The structure–function relationships required for these interactions were explored by the use of a series of related synthetic peptides. The specifically ordered sequence arg-gly-asp-ser was found to contain the minimal structural requirements for binding to the platelet surface FN receptor.

MATERIALS AND METHODS

Materials. FN was purified from human plasma by affinity chromatography on gelatin-Sepharose as described. von Willebrand factor (vWF) was purified from the cryoprecipitate fraction of plasma as described earlier. Fibrinogen (FGN) was obtained from Kabi, Stockholm (grade L). FGN was undetectable in the vWF preparations by a sensitive competitive enzyme-linked immunosorbent assay (ELISA). By the same technique, FN was found to represent a contaminant in the vWF preparations of 0.015% ± 0.003% by weight. FN was initially present in the FGN preparation at a level of 2%, but this was reduced to undetectable levels following chromatography on gelatin-Sepharose. No differences in the adhesive properties of substrates prepared from FGN before or after removal of contaminating FN were observed.

The synthetic peptides were obtained from Peninsula Laboratory (Belmont, Calif) and Vega Biotechnologies (Tucson, Ariz). They were characterized as described. Purified human α-thrombin was generously provided by Dr Joseph P. Miletich, Washington University. Radiochemicals were from New England Nuclear, Bos-
ton (carrier-free Na\(^{251}\)I, \(^{14}\)C-serotonin) and ICN, Inc, Irvine, Calif (Na\(^{35}\)CrO\(_4\)).

**Platelet preparation.** Human platelets were isolated from freshly drawn whole blood anticoagulated with a 1/10 volume of acid-citrate-dextrose ([ACD]) 39 mmol/L citric acid, 75 mmol/L sodium citrate, 135 mmol/L glucose, pH 4.5. After centrifugation at 160 g for 15 minutes, the platelet-rich plasma was removed, an additional 1/10 volume of ACD was added, and the platelets were pelleted by centrifugation at 1,300 g for ten minutes. The platelet pellet was resuspended and subjected to gel filtration over a Sepharose 2B column as described by Plow and Ginsberg. The columns were equilibrated with buffers described below.

**Aggregation studies.** For aggregation studies, platelets were suspended in 0.14 mol/L NaCl, 2.7 mmol/L KCl, 12 mmol/L NaHCO\(_3\), 0.42 mmol/L Na\(_2\)HPO\(_4\), 0.55 mmol/L glucose, and 5 mmol/L Hepes, pH 7.35, at 5 \times 10\(^8\) platelets per milliliter. Aggregation was measured in a Payton dual-channel aggregometer (Buffalo, N.Y.). The reaction mixture consisted of 200 \(\mu\)L of platelet suspension and 200 \(\mu\)L of buffer containing various concentrations of synthetic peptides. CaCl\(_2\) and MgCl\(_2\) were added to final concentrations of 2 mmol/L. Thrombin (1 U/mL) was added and the activated platelets were preincubated with l-mL aliquots of TBS containing 5 mmol/L glucose and incubated for ten minutes (data not shown). For the data presented here, 2.5 \times 10\(^8\) platelets were preincubated at 37 \(^\circ\)C with 10 \(\mu\)g/mL of \(^{251}\)FN and thrombin was added. At ten minutes, 50 \(\mu\)L of the 100-\(\mu\)L reaction mixture was removed and the platelet-rich plasma was removed, and the platelet pellet was resuspended in approximately 2 mL of Tris-buffered saline (TBS), supplemented with 5 mmol/L glucose and incubated for 30 minutes at room temperature with 100 \(\mu\)Ci Na\(^{35}\)CrO\(_4\). The platelet suspension was then washed by gel filtration on a Sepharose 2B column as described by Plow and Ginsberg. The columns were equilibrated with buffers described above, the platelet pellet was resuspended in approximately 2 mL of Tris-buffered saline (TBS), supplemented with 5 mmol/L glucose and incubated for 30 minutes each. The extracts were pooled and the \(^{35}\)Cr content was determined. The extent of adhesion is expressed as a percentage of the platelets initially added to the dish. Precautions to minimize platelet aggregation included performance of the adhesion assay at 25 \(^\circ\)C rather than at 37 \(^\circ\)C, avoidance of shaking during the adhesion assay, and the use of Tris buffers. The platelets were fully activated under the conditions of the assay as judged by the secretion of \(^{14}\)C-serotonin. Examination of the plates by phase contrast and scanning electron microscopy confirmed that the platelets adhere primarily as single cells and not as platelet aggregates.

**Fibronectin binding.** Platelets were prepared and binding experiments were conducted exactly as described by Plow and Ginsberg. FN was labeled to a specific activity of 2 to 4 \(\mu\)Ci/\(\mu\)g using iodobeads (Pierce Chemicals, Rockford, Ill.). In preliminary experiments, binding of \(^{125}\)I-FN at 37 \(^\circ\)C reached a maximum at seven to ten minutes (data not shown). For the data presented here, 2.5 \times 10\(^7\) platelets were preincubated at 37 \(^\circ\)C with 10 \(\mu\)g/mL of \(^{125}\)I-FN and the synthetic peptides used in this study and their abbreviations based upon the single-letter amino acid code are given in Table 1.

The binding of FN to unactivated platelets is assigned a value of 100%. The binding of FN to platelets in the absence of any inhibitory peptide is expressed as a percentage of the binding observed with activated platelets.

### RESULTS

**Effects of the cell-binding region of FN on platelet aggregation.** Previously reported studies which have indicated that a monoclonal antibody directed against FN can inhibit platelet aggregation and that an excess of exogenously added FN can inhibit platelet aggregation implicate FN in the mechanism of platelet aggregation. A similar observation that excess FN can inhibit the adhesion of fibroblasts to FN substrates has recently been reported. The inhibitory activity was localized to a small polypeptide derived from the cell-binding region of FN. To initiate studies into the role, if any, of this cell-binding domain of FN in platelet function, a synthetic peptide containing the active amino acid sequence of the cell-binding region of FN was examined for its effect on platelet aggregation. The synthetic peptides used in this study and their abbreviations based upon the single-letter amino acid code are given in Table 1.

The synthetic peptide gly-arg-gly-asp-ser (GRGDS) was found to inhibit thrombin-induced platelet aggregation in a concentration-dependent manner (Fig 1). Other synthetic peptides not containing the GRGDS sequence had no effect on aggregation. Platelet activation by thrombin was not affected by the presence of GRGDS as \(^{14}\)C-serotonin secretion (70\% ± 2\%) was comparable for all concentrations of the peptide tested. These results suggested that the cell-binding domain of FN may play a role in platelet aggregation.

### Table 1.

<table>
<thead>
<tr>
<th>Peptide No.</th>
<th>Peptide</th>
<th>Single-Letter Abbreviation</th>
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<tr>
<td>1</td>
<td>gly-arg-gly-asp-ser-pro-cys</td>
<td>GRGDSPC</td>
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<tr>
<td>2</td>
<td>gly-arg-gly-asp-ser</td>
<td>GRGDS</td>
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<tr>
<td>3</td>
<td>gly-arg-gly-asp</td>
<td>GRGD</td>
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<td>4</td>
<td>arg-gly-asp-ser-pro-ala-asa-lys-pro</td>
<td>RDGSSPKP</td>
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<tr>
<td>5</td>
<td>arg-gly-asp-ser</td>
<td>RGDS</td>
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<tr>
<td>6</td>
<td>ser-asp-gly-arg</td>
<td>SDGR</td>
</tr>
<tr>
<td>7</td>
<td>asp-val-gly-asp-as-phe-leu-arg</td>
<td>DVSRESSFLR</td>
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<tr>
<td>8</td>
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</tr>
<tr>
<td>12</td>
<td>cys-gln-asp-ser-glu-thr-thr-phe-tyr</td>
<td>CODSETRTFY</td>
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</table>
also abolished inhibitory activity. An unrelated peptide from glutamic acid for aspartic acid (GRGES, peptide 10) and aspartic acid, respectively (KGES, peptide 11), or such as lysine and glutamic acid for arginine substitutions (GDGRS, peptide 9) resulted in peptides or transposition of the two charged residues arginine and serine (GRGD, peptide 3) resulted in a peptide that retained a small degree of inhibitory activity. The structure–function relationships within the sequence in terms of ability to inhibit the binding of FN to the cell-binding domain mediates FN binding to the activation-dependent receptors and that the synthetic peptide GRGDS inhibits this binding. In order to directly assess this possibility, the binding of 125I-labeled FN was determined in the presence or absence of 50 μg/mL of the synthetic peptides listed in Table I. Peptides containing the RGDS sequence with varying aminoterminal and carboxyterminal extensions of the sequence from the cell-binding domain of FN were examined. Structure–function relationships within the RGDS sequence were examined through the use of peptides containing amino acid substitutions and transpositions within the RGDS sequence.

As shown in Fig 2, only those peptides (peptides 1, 2, 4, and 5) containing the sequence RGDS were effective inhibitors of the binding of 125I-FN to thrombin-activated platelets. RGDS appeared to be the shortest sequence that retained maximal inhibitory activity. Deletion of the carboxyterminal serine (GRGD, peptide 3) resulted in a peptide that retained only a small degree of inhibitory activity.

The high degree of specificity manifest by the RGDS sequence in terms of ability to inhibit the binding of FN to platelets is clearly evident from the results obtained with peptides containing permutations of the RGDS sequence. Neither of the two peptides in which this sequence is reversed, SDGR (peptide 6) and DVGSDGRFLR (peptide 7), had any detectable inhibitory activity. Transposition of the glycine and aspartic acid residues (GRDGS, peptide 8) or transposition of the two charged residues arginine and aspartic acid (GDGRS, peptide 9) resulted in peptides unable to inhibit the binding of FN. Conservative amino acid substitutions such as lysine and glutamic acid for arginine and aspartic acid, respectively (KGES, peptide 11), or simply glutamic acid for aspartic acid (GRGES, peptide 10) also abolished inhibitory activity. An unrelated peptide from elsewhere in FN (CQDSETRTFY, peptide 12) was also devoid of any effect on FN binding. In these experiments, the binding of FN to thrombin-activated platelets in the absence of any peptide was 1,720 ± 60 ng FN per 10^8 platelets. The binding of FN to unactivated platelets was <90 ng FN per 10^8 platelets.

The relative effectiveness of the synthetic peptides was more carefully examined by testing the binding of FN to platelets over a wide range of peptide concentrations. The results are shown in Fig 3. There were no marked differences in the abilities of the four peptides containing the RGDS sequence (GRGDS, GRGD, RGDSPASSKP, and RGDS) to inhibit the binding of FN to platelets when they were compared on a molar basis. Inhibition of FN binding by 50% resulted when the peptides were present at approximately 10^{-12} mol/L. As shown in Fig 3, the reduced effectiveness of the peptide GRGD is very apparent. The concentration of this peptide required to achieve 50% inhibition of binding was nearly two orders of magnitude greater than that required for similar extents of inhibition by peptides containing the RGDS sequence (10^{-12} mol/L as compared to 10^{-14} mol/L).

Effects of the cell-binding region of FN on platelet adhesion. We next sought to determine whether or not the RGDS sequence, shown above to mediate the fluid phase binding of FN to platelets, was also capable of mediating the adhesion of platelets to FN substrates and, if it was, whether the same structure–function relationships exist within the peptide. The adhesion of thrombin-activated platelets and unactivated platelets to FN-coated Petri dishes was examined. As shown in Fig 4A (control), the adhesion was...
Fig 3. Concentration-dependent inhibition of FN binding by synthetic peptides. The binding of $^{125}$I-FN to thrombin-activated platelets was determined as in Fig 2 in the presence of the indicated concentrations of the different synthetic peptides. Peptides 1 (III), 2 (O), 3 (A), 4 (C), 5 (□), 6 (Δ), 7 (■), 8 (○), 9 (△), 10 (×), 11 (▲), and 12 (+). Peptides are numbered according to the system outlined in Table 1.

Fig 4. Inhibition of thrombin-enhanced platelet adhesion by synthetic peptides. The adhesion of thrombin-activated platelets to Petri dishes coated with FN (A), FGN (B), or vWF (C) in the presence of each of the 12 different synthetic peptides (20 μg/mL) was determined as described under Materials and Methods. The bar labeled “control” represents the extent of adhesion to the substrate in the presence of thrombin. The crosshatched region of the bar represents the extent of adhesion by unactivated platelets. The bar labeled “BSA” gives the extent of adhesion to a BSA substrate. The peptides are numbered as in Table 1.

Activation-dependent (20.7% adhesion in the presence of thrombin as compared to 4.5% in the absence of thrombin). The low extent of adhesion (1.0% to 1.5%) to BSA substrates was not altered by activation with thrombin. Microscopic examination revealed that under the conditions of these experiments, the platelets adhere as single cells and not as aggregates.

Initial studies into the possible role of the cell-binding domain as a mediator of platelet substrate interactions were conducted using the prototype peptide GRGDS. Platelets were activated with thrombin in the presence of increasing concentrations of GRGDS and then allowed to adhere to FN-coated dishes. As shown in Fig 5A, GRGDS effectively inhibited the adhesion of activated platelets to FN substrates in a concentration-dependent manner. The concentration of peptide required to attain 50% inhibition in the solid-phase adhesion assay was somewhat higher than that required to achieve a similar extent of inhibition in the fluid-phase binding assay ($4 \times 10^{-5} \text{ mol/L}$ as compared to $10^{-3} \text{ mol/L}$).

In order to assess the structure–function relationships within the GRGDS peptide in the adhesion assay, the same panel of peptides used in the fluid-phase assay (Table 1) was examined for effect in the solid-phase adhesion assay. The results (Fig 4A) reveal essentially the same pattern of inhibitory activity that was observed in the fluid-phase binding assay (Fig 2). Only those peptides containing the specifically ordered RGDS sequence were effective inhibitors of platelet adhesion to the FN substrate. The peptide GRGD (peptide 3) again retained only slight inhibitory activity. The remainder of the peptides tested were ineffective. The identical patterns of inhibitory activity suggest that the interactions of platelets with solid-phase FN are in fact identical to the interactions of platelets with soluble FN and that the adhesion assay is a suitable method by which to study these interactions.

The adhesion assay was also used to examine the interactions of platelets with FGN and vWF substrates. As shown in Fig 4B and C, platelets also adhere to these substrates in an activation-dependent manner. The presence of GRGDS during the adhesion assay resulted in a concentration-dependent
inhibition of adhesion to both the FGN and vWF substrates, which was very similar to the concentration-dependent inhibition of platelet adhesion to the FN substrate produced by this peptide (Fig 5). Furthermore, examination of the entire panel of synthetic peptides for effects on adhesion to FGN and vWF substrates (Fig 4) revealed the same structure-function relationships determined from studies of the binding of FN to platelets (Fig 2) and the adhesion of platelets to FN substrates (Fig 4A).

**DISCUSSION**

The ability of FN to support the adhesion and spreading of cells has been well established. Recent studies have demonstrated that this activity can be localized to a very short sequence of four to five amino acids contained within the larger proteolytic fragments of FN previously shown to retain the ability to promote cell attachment. Application to FN of the methods used to predict the secondary structure of proteins suggests that the very hydrophilic sequence of amino acids that constitute the cell-binding region may be located at a β-turn which probably forms a hydrophilic loop at the surface of the molecule and would thus be well suited to interact with a cell surface.

Several lines of evidence suggest that FN may play an important role in platelet function. These include the localization of FN to the α-granules of platelets and its secretion upon platelet activation, the development of specific platelet surface receptors for FN upon activation, the ability of excess FN to inhibit platelet aggregation, and the ability of a monoclonal antibody against FN to inhibit platelet aggregation.

The series of experiments described in this report was performed to examine the role of the previously characterized cell-binding region of FN in platelet function. The results indicate that small peptides containing the RGDS sequence can effectively inhibit thrombin-induced platelet aggregation, the thrombin-induced binding of FN to platelets, and the adhesion of platelets to FN substrates. Alteration of the sequence of amino acids within this small peptide by transposition or conservative substitution of amino acids eliminated activity. The peptide GRGD, in which the carboxyterminal serine was deleted, retained some activity, although a nearly 100-fold higher concentration of this peptide was required to inhibit by 50% the binding of FN to platelets.

Platelets, therefore, appear to recognize the same small region of FN as do fibroblasts. Two interesting differences are apparent, however, in the way fibroblasts and platelets view this sequence. Whereas GRGD was significantly more active than RGDS in the fibroblast system, the two peptides did not differ significantly in the platelet system. Second, with fibroblasts, the peptide in which the entire RGDS sequence was reversed, SDGR, was active. This peptide lacked the ability to inhibit the binding of FN to platelets, or to inhibit the adhesion of platelets to FN substrates.

The receptor for FN on fibroblasts also appears to differ from that present on platelets. Pytela et al. have recently isolated a 140,000-dalton single-chain glycoprotein from human osteosarcoma cells, which appears to be the FN receptor. The glycoprotein IIb-IIIa complex on platelets, which is composed of three polypeptide chains, two of which are linked by disulfide bonds (IIb and IIb), and which associate noncovalently with the third component (IIIa), has been implicated as the FN receptor on platelets.

Several lines of evidence suggest that FN and two other platelet-adhesive proteins, FGN and vWF, share a common receptor. The thrombin-induced binding of FN, FGN, and vWF to platelets is markedly reduced in individuals with Glanzmann’s thrombasthenia, in which platelet membrane glycoproteins IIb and IIIa are deficient. Unlabeled FGN or a specific dodecapeptide derived from the carboxy-terminal region of the gamma chain of FGN can effectively inhibit the binding of radiolabeled FN, FGN, or vWF to platelets.

Since identical structure–function relationships within the RGDS sequence were detected by use of either the fluid-phase binding assay or the solid-phase adhesion assay, the latter assay appears to represent a valid approach to the study of the interaction of platelets with FN. The same panel of synthetic peptides was also examined for effects on the adhesion of platelets to FGN and vWF substrates. Adhesion to both of these substrates, like adhesion to FN substrates, was activation-dependent. Adhesion to the three different substrates is unlikely to result from cross-contamination, since the three preparations are homogeneous by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and the extents of platelet adhesion as a function of substrate concentration are similar for the three substrates (data not shown). The trace levels of contaminants could not, therefore, give rise to the extents of adhesion which were observed. Peptides containing the RGDS sequence not only inhibited platelet adhesion to FN substrates but also effectively inhibited adhesion of platelets to FGN and vWF substrates. The same structure–function relationships derived from the studies...
with FN were found in the studies with FGN and vWF. Hence, the inhibition of platelet aggregation by GRGDS cannot be attributed solely to its ability to inhibit the binding of FN to platelets. These observations appear to support the concept of shared receptors. They also complicate it.

Although the RGDS sequence is present within the α-chain of FGN, it is not contained within the region of FGN thought to mediate the binding of FGN to platelets.18 Since fibroblastic cells do not adhere to solid-phase FGN, it seems likely that in FGN, the RGDS sequence is structurally constrained or otherwise not accessible to cell surfaces. On the other hand, evidence has appeared which suggests that the α-chains of FGN can and do interact with the platelet surface.23,24 It remains to be established whether or not this interaction is mediated by the RGDS sequence present within the FGN α-chain. Recent evidence obtained from studies of the nucleotide sequence of a vWF cDNA and the amino acid sequence of the vWF polypeptide indicates that an RGDS sequence is, in fact, present within the vWF molecule approximately 300 amino acid residues from the carboxyterminus (E. Sadler, Washington University, personal communication, March 1985). This sequence is, therefore, a likely mediator of the thrombin-induced association of vWF with the platelet surface.

Bearing in mind the tight structural constraints we find required for activity of the RGDS-containing peptides and the sequence of the active dodecapeptide from FGN thought to represent the major platelet-binding site on FGN, it seems unlikely that both small peptides bind to identical regions of the glycoprotein IIb–IIIa complex. Perhaps several, at least two, distinct binding sites are present on the glycoprotein IIb–IIIa complex. One site recognizes the RGDS sequence of FN or vWF whereas the other recognizes the dodecapeptide derived from the γ-chain of FGN. The two sites may be overlapping or conformationally linked such that occupancy of one site precludes binding to the second site. The inhibition would then appear to be competitive. This concept of somewhat different binding sites is consistent with the observation that, whereas the binding sites for FGN and vWF are inducible by thrombin and ADP, only thrombin can induce the binding sites for FN.21

Although the binding of FN to platelets is mediated by the cell-binding region of FN, the function of FN in platelet aggregation appears to be more complex than simply forming bridges between platelets via the cell-binding domains present on each of the two polypeptide chains of FN. We have previously described a monoclonal antibody directed against FN which does not interfere with the function of the cell-binding region of FN. The ability of this monoclonal antibody to inhibit platelet aggregation suggests that an additional region of FN must also interact with a second site on the platelet surface or with another platelet-adhesive protein to form a complex adhesive matrix between aggregating platelets.

ACKNOWLEDGMENT

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Inhibition of platelet adhesion to fibronectin, fibrinogen, and von Willebrand factor substrates by a synthetic tetrapeptide derived from the cell-binding domain of fibronectin

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