The Glycoprotein Ib-IX-V Complex Mediates Localization of Factor XI to Lipid Rafts on the Platelet Membrane*

Received for publication, December 19, 2002, and in revised form, January 3, 2003
Published, JBC Papers in Press, January 6, 2003, DOI 10.1074/jbc.M212991200

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Factor XI binds to activated platelets where it is efficiently activated by thrombin. The factor XI receptor is the platelet membrane glycoprotein (GP) Ib-IX-V complex (Baglia, F. A., Badellino, K. O., Li, C. Q., Lopez, J. A., and Walsh, P. N. (2002) J. Biol. Chem. 277, 1662–1668), a significant fraction of which exists within lipid rafts on stimulated platelets (Shrimpton, C. N., Borthakur, G., Larrucea, S., Cruz, M. A., Dong, J. F., and Lopez, J. A. (2002) J. Exp. Med. 196, 1057–1066). Lipid rafts are membrane microdomains enriched in cholesterol and sphingolipids implicated in localizing membrane ligands and in cellular signaling. We now show that factor XI was localized to lipid rafts in activated platelets (~8% of total bound) but not in resting platelets. Optimal binding of factor XI to membrane rafts required prothrombin (and Ca2+) or high molecular weight kinogen (and Zn2+), which are required for factor XI binding to activated platelets. An antibody to GPIb (SZ-2) that disrupts the binding to the GPIb-IX-V complex (and Ca2+) or high molecular weight kinogen (and Zn2+), which are required for factor XI binding to activated platelets. An antibody to GPIb (SZ-2) that disrupts the binding to the GPIb-IX-V complex (and Ca2+) or high molecular weight kinogen (and Zn2+) thereby promote FXI activation by thrombin (8, 10). We have previously demonstrated that the Apple 3 (A3) domain of FXI mediates the binding of FXI to platelets (11, 12). FXI binds to the glycoprotein Ib-IX-V (GPIb-IX-V) complex since 1) Bernard-Soulier platelets lack the GPIb complex and are deficient in binding FXI; 2) a monoclonal antibody against GP Ibα (SZ-2) inhibits the binding of FXI to platelet surface; 3) bovine von Willebrand protein, which binds GP Ibα, also inhibits the binding of FXI (13); and 4) FXI binds to glycoprotein Ibα in the presence of HK and Zn2+. We determined by analyzing fractions of Triton X-100 platelet lysates that a significant fraction of the GPIb-IX-V complex (and Ca2+) or high molecular weight kinogen (and Zn2+) is localized to GPIb in membrane rafts and that this association is important for FXI activation by thrombin.

This study was supported by National Institutes of Health Grants HL64796 (to J. A. L.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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The abbreviations used are: FXI, factor XI; GP, glycoprotein; HK, high molecular weight kinogen; A3, Apple 3; TRAP, thrombin receptor agonist peptide; MβCD, methyl-β-cyclodextrin; MES, 4-morpholineethanesulfonic acid.

EXPERIMENTAL PROCEDURES

Materials—All reagents were obtained from Sigma unless stated otherwise. Human FXI, human prothrombin, human FXIa, and human HK were purchased from Hematologic Technologies Inc. (Essex Junction, VT). Human α-thrombin (2,800 NIH units/mg) was purchased from Enzyme Research Laboratories (South Bend, IN). Methyl silicon oil (1 DC-200) and Hi phenyl silicon oil (125 DC-550) were purchased from Cadmus Professional Communications, on October 7, 2011.
from William F. Nye Inc. (Fairhaven, MA). Carrier-free Na\(^{125}\)I was from Amersham Biosciences. The chromogenic substrate for measurement of FXIa activity (S2366) was obtained from Chromogenix (Molndal, Sweden). The thrombin receptor agonist peptide (TRAP), SFLLRN-amide, was synthesized at the Protein Chemistry Facility of the University of Pennsylvania on the Applied Biosystems 430A Synthesizer, and reverse-phase high performance liquid chromatography was used to purify it to >99% homogeneity. A monoclonal antibody (SE-2), which recognizes the NH\(_2\)-terminal extracellular globular domain of GPIbα, blocks thrombin binding to platelets at low concentration, and inhibits thrombin-induced platelet aggregation, was used in experiments examining FXI binding to platelets. An isotype-specific mouse IgG2a κ chain control antibody was purchased from Sigma.

Radio-labeling of FXI—Purified FXI was radio-labeled with \(^{125}\)I by a minor modification (8) of the Iodogen method to a specific activity of \(5 \times 10^{6}\) cpm/μg. The radiolabeled FXI retained >98% of its biological activity.

Preparation of Washed Platelets—Platelets were prepared from normal donors as described in Refs. 9, 11, and 12. Platelet-rich plasma obtained from citrated human blood was centrifuged, and the platelets were resuspended in calcium-free Hepes-Tyrode's buffer (126 mM NaCl, 2.7 mM KCl, 1 mM MgCl\(_2\), 0.38 mM Na\(_2\)HPO\(_4\), 5.6 mM dextrose, 6.2 mM sodium Hepes, 8.8 mM Hepes free acid, 0.1% bovine serum albumin), pH 7.3. The platelets were pelleted and filtered on a column of Sepharose 2B equilibrated in calcium-free Hepes-Tyrode's buffer, pH 7.2. Platelets were counted electronically (Coulter Electronics, Hialeah, FL).

Platelet Binding Experiments—Platelets were prewarmed to 37 °C and incubated at a concentration of \(1 \times 10^{10}\) cells/ml in calcium-free Hepes-Tyrode's buffer, pH 7.3, in a 1.5-ml Eppendorf plastic centrifuge tube with a mixture of radiolabeled FXI, divalent cations, a thrombin receptor agonist (PAR-1) activation peptide (SFLLRN-amide) as a platelet agonist (11), and HK or antibodies or other proteins as designated in the legends. All incubations were performed at 37 °C without agitation, with an initial mixing of the reaction mixture. At various time points, aliquots were removed (100 μl) and centrifuged onto a continuous sucrose gradient of 10% sucrose by addition of an equivalent volume of sucrose. Four milliliters of 30% sucrose was layered on top of the 40% sucrose by gentle layering over the 40% sucrose in the ultracentrifuge tube. The samples were then centrifuged at 100,000 g for 30 min in a SW40 Rotor (Beckman Instruments) and collected from the top of the gradient. Protein concentrations were determined using the Micro BCA Protein Assay kit (Pierce) according to the manufacturer's instructions. Dot blot analysis was performed using a Bio-Dot Microfiltration Apparatus (Bio-Rad). The manufacturer's instructions and probes (6) were used with horseradish peroxidase-conjugated cholera toxin B-subunit (10 μg/ml).

Cholesterol Depletion of Platelets—To specifically deplete the platelet membrane of cholesterol, platelet-rich plasma was incubated with methyl-\(^{14}\)C-cycloexidrin (M\(_{\text{BCD}}\)) at a final concentration of 20 μg for 30 min at 37 °C. Cells were repleted with cholesterol by incubating them in the presence of a cholesterol/M\(_{\text{BCD}}\) mixture at 37 °C for 30 min at 37 °C. A stock solution of 0.4 mg/ml cholesterol and 10% cycloexidrin was prepared by vortexing at 24 °C in 10 ml of 10% M\(_{\text{BCD}}\) with 200 μl of cholesterol (20 mg/ml in ethanol solution).

Assay of FXI Activation—Activation of FXI (60 nm) by thrombin (1.25 nm) was measured by chromogenic assay as described previously (8, 10). Briefly, incubations were carried out at 37 °C in 200 μl of Tris-buffered saline (50 mM Tris, 150 mM NaCl, pH 7.3) and 1% bovine serum albumin. Gel-filtered platelets were activated by incubation at 37 °C for 1 min with thrombin receptor activation peptide (SFLLRN-amide, 2 μM). After dilution to a final volume of 1 ml with Tris-buffered saline with 1% bovine serum albumin containing 600 μM S2366 (EPR-para-nitroanilide, Chromogenix), the amount of free para-nitroanilide was determined by measuring the absorbance at 405 nm (λ\(_{\text{max}}\)). The amount of FXIa generated was assayed by reference to a standard curve constructed using purified FXIa.
The presence of 42 nM HK, 25 mM CaCl2 for 30 min at 37 °C and washed, pelleted, and lysed with various concentrations of TRAP (25 μM) in MBS (0.025–0.1%) and 2 mM CaCl2 for 30 min at 37 °C and washed, pelleted, and lysed with various concentrations of prothrombin (1.2 mM). Lysates were subjected to discontinuous sucrose gradient centrifugation as described under “Experimental Procedures.” Percentage of raft-associated receptors indicates the percentage of 125I-FXI in fractions 1–4 containing lipid rafts. The experiment shown is representative of six independent experiments.

**Fig. 2.** Detergent-sensitive association of factor XI with membrane rafts. TRAP (25 μM)-activated platelets were incubated with 22 nM 125I-FXI (in the presence of 42 nM HK, 25 μM ZnCl2, and 2 mM CaCl2) for 30 min at 37 °C and washed, pelleted, and lysed with various concentrations of TRAP (25 μM) and CaCl2 for 30 min at 37 °C and washed, pelleted, and lysed with various concentrations of prothrombin (1.2 mM). Lysates were subjected to discontinuous sucrose gradient centrifugation as described under “Experimental Procedures.” Percentage of raft-associated receptors indicates the percentage of 125I-FXI in fractions 1–4 containing lipid rafts. The experiment shown is representative of six independent experiments.

**Cofactor Requirements for Binding of Factor XI to Lipid Rafts in TRAP-activated and Unactivated Platelets—**We have previously determined the optimal cofactor requirements for FXI binding to the platelet surface. It was shown that HK, Ca2+, and Zn2+ ions or prothrombin and Ca2+ ions are required as cofactors for optimal binding of FXI to the activated platelet surface (8, 27). The presence of 125I-FXI in sucrose density fractions of lysates from both stimulated and unactivated platelets, respectively, using the various cofactors necessary to bind FXI to the platelet surface. The data show that the presence of prothrombin (1.2 mM) and CaCl2 (2 mM) or HK (42 mM), ZnCl2 (25 μM), and CaCl2 (2 mM) are required not only for binding of FXI to the activated platelets but also for FXI association with the membrane raft fraction. The amount of FXI associated with the raft fraction (5–8%) was the same for both cofactors. Platelets that were not activated did not bind FXI, and thus FXI was not associated with membrane rafts. A lesser amount of FXI was bound to membrane rafts (3–4% of total binding) in the presence of ZnCl2 (25 μM) without added HK. FXI binding was observed in the presence of HK and added prothrombin. Thus, the optimal conditions for FXI binding to activated platelets are identical with membrane rafts.

**Fig. 3.** The Effects of an Antibody to Glycoprotein Ib and the Recombinant Apple 3 Domain on the Binding of Factor XI to Membrane Rafts—FXI binds activated platelets specifically and reversibly, and this interaction is mediated by amino acids within the A3 domain of FXI (11, 12, 27). The A3 domain of FXI (11, 12, 27). Fig. 6A demonstrates that the recombinant A3 domain abolishes the binding of FXI to membrane rafts as well as the non-raft fractions in the sucrose gradient. In a study demonstrating that the platelet receptor for FXI is the GPIb-IX-V complex, an antibody (SZ-2) that recognizes the NH2-terminal extracellular globular domain was shown to block FXI binding to activated platelets. Fig. 6B demonstrates that the antibody SZ-2 also abolishes binding of FXI to lipid rafts as well as non-raft fractions in the sucrose gradient. These experiments are consistent with the conclusion that FXI binds through its A3 domain to GPIbα and that the FXI-GPIbα complex is compartmentalized within membrane raft structures.

**The Activation of Factor XI by Thrombin Occurs in Lipid Rafts—**Activated gel-filtered platelets as well as glycolicin promote FXI activation by thrombin in the presence of HK or...
prothrombin at optimal rates, thereby initiating intrinsic coagulation independent of contact proteins (13). Initial rates of FXI activation by thrombin were significantly decreased compared with normal platelets when activated Bernard-Soulier platelets (deficient in GPIb complex) were used as a surface (13). These observations suggest that the GPIb-IX-V complex serves as a receptor for facilitating thrombin-catalyzed FXI activation. To investigate the physiological relevance of FXI-GPIb-IX-V complex-raft association, we disrupted the structural integrity of lipid rafts by cholesterol depletion with methyl-β-cyclodextrin (MβCD) (8, 9) as a sequen of amino acids (Ser248–Val271) in the A3 domain (11, 12, 27), FXI binds reversibly and specifically to high affinity sites on the activated platelets in the presence of methyl-β-cyclodextrin (5). The effect of MβCD (from 5 to 40 mM) was examined on the binding of 125I-FXI (in the presence of 42 mM HK, 25 mM ZnCl₂, and 2 mM CaCl₂) to THP-1 cells (from 37°C as described under Experimental Procedures. Each point is an average of three determinations, and the maximum variation of counts/min bound was <3% of total counts/min bound. One hundred percent binding of FXI represents an average of 110,600 cpm bound.

DISCUSSION

Utilizing a sequence of amino acids (Ser248–Val271) in the A3 domain (11, 12, 27), FXI binds reversibly and specifically to high affinity sites on the activated platelets in the presence of HK (and Zn²⁺ ions) or prothrombin (and Ca²⁺ ions) (8, 9) as a consequence of which the rate of FXI activation by thrombin is
accelerated >5,000-fold (8, 10). FXI interacts with the GPIb-IX-V complex on the platelet surface, and this interaction promotes thrombin-catalyzed FXI activation (13). The GPIb-IX-V complex is a large plasma membrane complex comprising four polypeptide chains, GPIba, GPIbβ, GPIX, and GPV, arranged in stoichiometry of 2:2:2:1 (28). Approximately 25,000 copies of the first three peptides are constitutively expressed on the unactivated platelet surface along with half as many copies of GPV (29–31). The complex also binds thrombin and von Willebrand factor with high affinity (32). However, platelet activation results in a ~65% decrease of GPIb from the platelet surface (33) and a redistribution to the surface canalicul system (34). Therefore, how do we account for the fact that platelet activation is required for the binding of FXI to platelet GPIb-IX-V complex and its activation by thrombin? Recently it has been reported that specialized membrane microdomains (lipid rafts) are involved in GPIb-IX-V-mediated signaling (14).

At high concentra-
Platelet Membrane Rafts Bind FXI and GPIb-IX-V

FXI binding to platelet rafts appears to be activation-dependent. Although FXI is present (8% of total) in lipid rafts of resting platelets, FXI binding to GPIb-IX-V and/or the association of the FXI-GPIb-IX-V complex with lipid rafts is activation-dependent. Although GPIb-IX-V is present in lipid rafts of resting platelets, GPIb-IX-V is not able to bind to resting platelet lipid rafts. The stoichiometry of interaction between GPIb-IX-V and FXI in the lipid fraction is not an artifact of Triton X-100 solubilization (data not shown).

Three different conditions were utilized in the present study to characterize FXI interactions with membrane rafts on platelets: i.e. in the presence of HK and Zn$^{2+}$ ions, prothrombin and Ca$^{2+}$ ions, or Zn$^{2+}$ alone. The interaction of FXI with activated platelets is optimal in the presence of either prothrombin and Ca$^{2+}$ ions or HK and Zn$^{2+}$ ions, with 1,500 sites per platelet and $K_{d(app)}$ ~ 10–15 mM (8, 9). However, in the presence of Zn$^{2+}$ ions alone (25 µM), FXI interacts with half the number of platelet sites (~800 sites per platelet and $K_{d(app)}$ ~ 12 mM) (13). We determined that ~8% of FXI bound to activated platelets appears in lipid rafts in the presence of HK and Zn$^{2+}$ ions or prothrombin and Ca$^{2+}$ ions (Fig. 3, A and B) and ~4% of FXI bound to activated platelets in the presence of Zn$^{2+}$ alone appears in lipid rafts. Thus FXI binding to membrane rafts appears to occur even in the absence of added protein cofactors provided Zn$^{2+}$ ions are present. A possible mechanism to account for this binding in the absence of added HK or prothrombin is the presence of HK in platelet α-granules and its secretion and surface membrane binding after platelet activation (37).

Several reports have implicated platelet membrane lipid rafts in signaling events mediated by von Willebrand factor (VWF) and von Willebrand factor (VWF) (23, 25). We examined both TRAP-activated and resting platelets and determined that association of FXI with membrane lipid rafts is activation-dependent. Although FXI binding to membrane rafts of resting platelets is not able to bind to resting platelet lipid rafts, the capacity of FXI to bind to activated platelet lipid rafts remains to be determined. Thus, FXI binding to platelet lipid rafts is activation-dependent. Whether some biochemical modification of FXI may occur (i.e. palmitoylation) to direct it to the lipid rafts is unknown but possible since enzymatic acylation and deacylation of the GPIb-IX-V complex may regulate its association with rafts (14).

To investigate the physiological significance of the partitioning of FXI into lipid rafts, we selectively depleted platelet membrane cholesterol using the cholesterol-binding agent MβCD. It has been determined that 10 mM MβCD efficiently removes cholesterol from [H]cholesterol-labeled platelets as a function of time with ~75% of incorporated cholesterol released in 30 min (14). We therefore utilized 20 mM MβCD in our experiments. Cell viability was not affected by this treatment. In platelets treated with MβCD for 30 min, FXI was completely removed from the lipid raft fractions, and replenishment of cholesterol to depleted platelets restored the binding of FXI to the lipid raft fractions (Fig. 4). To exclude the possibility that the loss of FXI interaction with rafts following cholesterol depletion was due to a failure to activate cholesterol-depleted platelets, we assessed receptor levels in FXI binding studies (Fig. 5). FXI binding to the activated platelets remained unchanged following a 30-min treatment of up to 40 mM MβCD when compared with untreated platelets. Thus, it is important to emphasize that cholesterol depletion does not prevent the exposure of FXI receptor upon TRAP-mediated PAR-1 activation but does prevent FXI association with lipid rafts.

We also carried out experiments to determine whether the 35% loss of FXI binding to membrane rafts of cholesterol-depleted, MβCD-treated platelets is not due to a loss of FXI receptor(s) on platelets. Initial rates of FXI binding at 1,500 sites per platelet and 85% by cholesterol depletion of the capacity of FXI binding to platelets were inhibited by MβCD. FXI binding to activated platelets in the presence of Zn$^{2+}$ ions is not saturated with FXI, which may occupy only 4% of the available raft-associated GPIb-IX-V complexes. The stoichiometry of interaction between GPIb-IX-V and FXI and the manner in which the GPIb-IX-V complex and FXI are partitioned into lipid rafts remains to be determined. Thus, 1,600 copies of GPIb-IX-V per platelet, 8% (~2,000 molecules per platelet) is partitioned into lipid rafts in resting platelets, and 26% (~6,500 copies per platelet) is partitioned into lipid rafts in von Willebrand factor-activated platelets (14). In contrast, the 1,500–2,000 FXI molecules bound per platelet, ~8% (~130–160 molecules per platelet) is partitioned into rafts of TRAP-activated platelets. This suggests that the GPIb-IX-V complex is not saturated with FXI, which may occupy only ~10% of the available raft-associated GPIb-IX-V complexes. Another ligand known to bind to and signal through the GPIb-IX-V complex is thrombin (32). The present studies strongly suggest the possibility that the FXI-thrombin-GPIb-IX-V complex is partitioned within membrane lipid microdomains for efficient thrombin-catalyzed FXI activation. Consistent with this possibility is our observation that disruption of lipid rafts by cholesterol depletion with MβCD does not prevent platelet activation leading to FXI binding to platelets but does prevent FXI localization within lipid rafts and FXI activation by thrombin.

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J. Biol. Chem. 2003, 278:21744-21750.
doi: 10.1074/jbc.M212991200 originally published online January 6, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M212991200

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ADDITIONS AND CORRECTIONS

VOLUME 277 (2002) PAGES 1662–1668

Factor XI binding to the platelet glycoprotein Ib-IX-V complex promotes factor XI activation by thrombin.
Frank A. Baglia, Karen O. Badellino, Chester Q. Li, José A. López, and Peter N. Walsh

RETRACTION

PAGES 1665–1667:
Figs. 4 and 5 and Table 1 have been retracted by the authors for the following reasons.

All of the authors with the exception of F. A. Baglia retract the specific data listed above because recent experiments conducted by Dipali Sinha, Sergei Shikov, Wenman Wu, and Syed Ahmad in the laboratory of Peter N. Walsh failed to confirm the conclusion that activated platelets promote the activation of factor XI by thrombin. All of the other results reported in the paper are valid. A detailed explanation of the chronology of events leading to this retraction and the retraction of a paper from Biochemistry (Baglia, F. A., and Walsh, P. N. (1998) Pro-thrombin is a cofactor for the binding of factor XI to the platelet surface and for platelet-mediated factor XI activation by thrombin. Biochemistry 37, 2271–2281) has been published in the journal Biochemistry (manuscript bi-2007-01501k, accepted July 27, 2007). We apologize to the readers, reviewers, and editors of the Journal of Biological Chemistry for publishing these erroneous data.

VOLUME 278 (2003) PAGES 21744 –21750

The glycoprotein Ib-IX-V complex mediates localization of factor XI to lipid rafts on the platelet membrane.
Frank A. Baglia, Corie N. Shrimpton, José A. López, and Peter N. Walsh

RETRACTION

PAGE 21748:
Fig. 7 has been retracted by the authors for the following reasons.
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VOLUME 278 (2003) PAGES 48112–48119

Thrombin activation of factor XI on activated platelets requires the interaction of factor XI and platelet glycoprotein Ibα with thrombin anion-binding exosites I and II, respectively.
Thomas H. Yun, Frank A. Baglia, Timothy Myles, Duraiswamy Navaneetham, José A. López, Peter N. Walsh, and Lawrence L. K. Leung

RETRACTION

PAGE 48116:
Table 1 has been retracted by the authors for the following reasons.
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