The Low-Density Lipoprotein Receptor-Related Protein (LRP) Mediates Clearance of Coagulation Factor Xa In Vivo

By Masaaki Narita, Amy E. Rudolph, Joseph P. Miletich, and Alan L. Schwartz

Blood coagulation factor X plays a pivotal role in the clotting cascade. When administered intravenously to mice, the majority of activated factor X (factor Xa) binds to α2-macroglobulin (α2M) and is rapidly cleared from the circulation into liver. We show here that the low-density lipoprotein receptor-related protein (LRP) is responsible for factor Xa catabolism in vivo. Mice overexpressing a 39-kD receptor-associated protein that binds to LRP and inhibits its ligand binding activity displayed dramatically prolonged plasma clearance of 125I-factor Xa. Preadministration of αM-proteinase complexes (αM*) also diminished the plasma clearance of 125I-factor Xa in a dose-dependent fashion. The clearance of preformed complexes of 125I-factor Xa and αM was similar to that of 125I-factor Xa alone and was also inhibited by mice overexpressing a 39-kD receptor-associated protein. These results thus suggest that, in vivo, factor Xa is metabolized via LRP after complex formation with αM.

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MATERIALS AND METHODS

Reagents. N-Succinimidyl 3-(4-hydroxy-5-[125I] iodosphenyl) propionate (Bolten and Hunter reagent) was purchased from Amersham (Arlington Heights, IL). Human αM was purified and activated (αM*) as described previously.20 BALB/c mice were obtained from Jackson Laboratories (Bar Harbor, ME). AT-III was purchased from Kabi Pharmacia Diagnostics (Piscataway, NJ). Factor VII- and X-deficient plasma and phospholipid (rabbit brain cephalin) were obtained from Sigma (St Louis, MO). Rabbit brain thromboplastin was from Ortho (Raritan, NJ). The chromogenic substrate Spectrozyme FXa (methoxy-carbonyl-D-hexahydrotryosyl-L-alanyl-L-arginine-p-nitroanilide-diacetate) was obtained from American Diagnostica Inc (Greenwich, CT). Factor X-deficient plasma was from George King Bio-Medicals Inc (Overland Park, KS).

Coagulation factors. Recombinant factor X was prepared and purified as described by Miletich et al,21 with minor modifications.22 The cDNA encoding human factor X was obtained by polymerase chain reaction amplification from first-strand cDNA template from a human hepatocyte library, ligated into the mammalian expression vector ZMB3, and stably transfected into human kidney 293 cells. Factor X was isolated from the culture media by absorption to barium citrate, followed by resuspension in 32% saturated (NH4)2SO4 in the presence of 5 mmol/L diisopropyl fluorophosphate and incubation for hour at 4°C. The precipitate was collected by centrifugation and the resulting supernatant was dialyzed into 10 mmol/L HEPES, pH 7.0, 100 mmol/L NaCl, and 1 mmol/L benzamidine. The dialyzed supernatant was concentrated and immunoaffinity purified using antibody 3698.1A8.10, which is a calcium-dependent monoclonal antibody directed against the Gla domain of factor X. Factor X was further purified using a Pharmacia Mono Q FPLC column. Plasma (human)-derived factor X was isolated by the same procedure. In some experiments, factor X was activated using factor X coagulant protein (XCP) from Russell’s viper venom in a factor X: XCP ratio (wt/wt) of 100:1 in 10 mmol/L HEPES, pH 7.4, 100 mmol/L NaCl, 5 mmol/L CaCl2. XCP was purified from crude viper venom as described previously.23 Because native factor X is composed of two polypeptide chains joined by a disulfide bond, the gel pattern in
the presence of β-mercaptoethanol is particularly useful to confirm successful processing from the 1-chain form to the 2-chain native form. On nonreducing sodium dodecyl sulfate (SDS)-gels (Fig 1, lanes 1 and 2), the apparent molecular weight of both plasma-derived and recombinant factor X was approximately 68 kDa (noted by arrow). On the other hand, under reducing conditions (lanes 3 and 4), the apparent molecular weight of both factor Xs was 49 kDa for the heavy chain (solid arrowhead) and 23 kDa for the light chain (open arrowhead). Plasma-derived (lanes 1 and 3) and recombinant (lanes 2 and 4) factor X migrated identically on both reducing and nonreducing conditions, indicating that they have the same apparent molecular size. Furthermore, no difference in functional activity between plasma-derived and recombinant factor X was detected.24

**Mutagenesis of factor X.** The S379A factor X mutant was constructed as follows. The mutation was engineered into the cDNA of factor X using a Transformer Site-Directed Mutagenesis Kit from Clontech (Palo Alto, CA). The codon encoding the active site serine at position 379 was mutated to alanine: (GAC)(AGC)(GGG)/(GAC)(GGT)(GGG). The DNA sequence of the constructs was verified by the dideoxy chain termination technique. Mutated constructs were shuttled into the ZMB3 mammalian expression vector, transfected into the 293 cells for expression, and purified as described above.

**Protein iodination.** Factor X was iodinated using the Bolton and Hunter reagent according to the manufacturer’s instructions. Specific radioactivities were 5 to 10 µCi/µg of protein (0.13 to 0.26 mol 125I/mol protein). Functional activity of recombinant 125I-labeled and unlabeled factor X was evaluated using the modified prothrombin time (PT) as follows. Various dilutions of factor X samples were mixed with factor X-deficient plasma and incubated at 37°C for 5 minutes in a fibrometer. Cloting was initiated by the addition of thromboplastin and 15 mmol/L CaCl2. No difference was seen in the coagulant activity between labeled and unlabeled protein. Enzymatic activity of recombinant 125I-labeled and unlabeled factor X was also determined by measurement of factor Xa activity against the chromogenic peptide substrate, Spectrozyme FXa. No difference was seen in the enzymatic activity between labeled and unlabeled protein. These results show that iodination using Bolton and Hunter reagent does not affect functional and enzymatic activity of factor X and Xa.

**Adenovirus purification.** Recombinant adenovirus containing the full-length 39-kD protein cDNA (Ad-39-kD) or the Escherichia coli β-galactosidase cDNA (Ad-β-Gal) were prepared and titered as described previously.17,18 The virus titer was approximately 100 virus particles/plaque-forming unit.

**In vivo viral delivery.** In vivo viral delivery was performed via intravenous administration as described previously.19 Various viral particle doses were examined. Optimal expression was achieved after the administration of 4 × 1011 particles (4 × 1010 plaque-forming units) of either Ad-39-kD or Ad-β-Gal. All experiments were performed on day 5 after viral delivery, because optimal expression of the 39-kD protein was at day 4 or 5 after virus administration.

**In vivo plasma clearance in mice.** Twelve- to 16-week-old BALB/c mice (weighing 20 to 25 g) were anesthetized with sodium pentobarbital (1 mg/20 g body) during the course of the experiment. The indicated radiolabeled protein (∼10 pmol of factor 125I-X, 125I-Xa, or 125I-S379A Xa) in sterile saline (total volume, 100 µL) was injected into a tail vein over 30 seconds. At the indicated times, 40 to 50 µL of blood was collected by periorbital bleeding. The amount of radiolabeled protein in the plasma samples was determined as described previously.18 After 20 minutes, the animals were killed, and the liver, spleen, kidneys, and lungs were removed and weighed. 125I-radioactivity was determined in a gamma counter from Packard Instrument Co (Meriden, CT). Studies were performed in 2 to 7 animals for each condition described. Recombinant factor Xa was used in all experiments in Figs 2 through 5.

**Reaction of factor Xa with purified plasma proteinase inhibitors.** Complexes of 125I-Xa with human α2M and AT-III were prepared by reacting 125I-Xa with increasing concentrations of each inhibitor. The optimal AT-III:factor Xa binding ratio was determined by quantitation of the residual factor Xa activity against the chromogenic peptide substrate, Spectrozyme FXa. Factor Xa inhibition by α2M could not be determined by this method, because the complex still retains partial activity toward peptide substrates. Therefore, the optimal α2M:factor Xa ratio was determined by the clotting method of Fujikawa et al,25 using factor VII- and X-deficient plasma in the presence of CaCl2 and phospholipid. Inhibition reactions were performed at room temperature for 30 minutes in the buffer containing 10 mmol/L HEPES, 100 mmol/L NaCl, 5 mmol/L CaCl2, 1 mg/mL PEG 8000, 1 mg/mL bovine serum albumin, pH 7.0. The initial factor Xa concentration was kept constant at 1.0 µmol/L, and the concentration of the inhibitors varied to obtain the desired molar ratio. After incubation, aliquots were removed and tested for residual factor Xa activity. Residual factor Xa activity decreased linearly with increasing inhibitor concentration. An AT-III:factor Xa ratio of 1:1.8 yielded complete inhibition of factor Xa. Complete inhibition of factor Xa by α2M was obtained at a 1:1 molar ratio.

**SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and autoradiography.** SDS-PAGE was performed according to Laemmli.26 Dried gels were exposed to Kodak XAR film (Eastman Kodak, Rochester, NY) at −80°C for autoradiography.
RESULTS

125I-factor Xa and 125I-factor Xa clearance in normal mice and Ad-39-kD–injected mice. The plasma clearance of plasma-derived 125I-Xa after intravenous administration of 10 pmol of 125I-Xa in normal mice and Ad-39-kD–injected mice is shown in Fig 2A. The initial plasma half-life of 125I-Xa was approximately 3 minutes, with 10% of the administered dose remaining in the circulation at 20 minutes. Figure 2B shows the plasma clearance of 125I-recombinant Xa. The plasma clearance curves for 125I-plasma-derived Xa and 125I-recombinant Xa are identical. The plasma clearance of 125I-X was substantially slower than that of 125I-Xa, with a half-life of approximately 10 minutes (Fig 2C). The plasma clearance curve for 125I-Xa seen in Fig 2A was similar to that reported earlier by Fuchs and Pizzo. Approximately 60% of the injected 125I-X and 125I-Xa was associated with the liver at 20 minutes (Table 1 and data not shown, see below). These data show rapid hepatic clearance of 125I-X and are consistent with a receptor-mediated endocytosis mechanism. Among those candidate receptors is LRP, which mediates the endocytosis of several protease-protease inhibitor complexes such as α2M-complexes, uPA:PAI-1, t-PA:PAI-1, and protease nexin:uPA. To examine the role of LRP in 125I-Xa and 125I-X clearance in vivo, we took advantage of an adenoviral delivery vector to express an LRP-antagonist, the 39-kD protein, in mouse liver. Overexpression of the 39-kD protein in liver results in plasma accumulation of the 39-kD protein. Previously, we showed that mice receiving 4 x 1011 particles of Ad-39-kD expressed sufficient 39-kD protein in plasma to completely inhibit LRP, and we also showed that viral infection induced no gross or microscopic morphologic changes in the liver.18,19 This dose of Ad-39-kD was administered intravenously to mice via tail vein. Five days after administration, plasma clearance studies of recombinant 125I-Xa and 125I-X were performed. As seen in Fig 2, administration of Ad-39-kD prolonged the plasma clearance of 125I-X significantly (Fig 2A and B), whereas administration of Ad-39-kD did not alter the plasma clearance of 125I-X (Fig 2C). To confirm that the viral infection did not induce adverse effects on the clearance of 125I-Xa, studies were performed in mice after administration of Ad-β-Gal. The plasma clearance of 125I-Xa in Ad-β-Gal-injected mice was essentially the same as that of the noninfected mice (data not shown). These results indicate that the rapid hepatic clearance of 125I-Xa, but not of 125I-X, is mediated by LRP.

In vivo association of 125I-Xa among protease inhibitors. Previous studies have shown that, 2 minutes after the injection of 125I-Xa into mice, 90% of that bound within the plasma was associated with α2M.7 To confirm and extend this observation, plasma samples obtained 30 seconds after the injection of 125I-Xa or the injection of the preformed complex of α2M and 125I-Xa (α2M,125I-Xa) were subjected to SDS-PAGE (Fig 3). Standards containing α2M,125I-Xa, AT-III:125I-Xa, 125I-Xa, and 125I-X were also analyzed. In both plasma samples, complexes of α2M with 125I-Xa were observed at the identical size as the α2M,125I-Xa standard. These results show that the vast majority of exogenously administered 125I-Xa is complexed to α2M.

Effect of preadministration of α2M* or α2M on the clearance of 125I-Xa in mice. Because in vivo the vast majority of factor Xa is bound to α2M (Fuchs and Pizzo7 and Fig 3) and because α2M:protease complexes and activated factor Xa (α2M*) but not free or uncomplexed α2M are metabolized via LRP,11 we next examined whether preadministration of α2M* (which competes for the α2M* binding site on LRP) can influence on the plasma clearance of 125I-Xa. As seen in Fig 4, preinjection of various amount of α2M* (0.5, 1, and 2.5 mg) altered the plasma half-life of 125I-Xa from approximately 3 minutes to >20 minutes in a dose-dependent manner. On the other hand, preinjection of various amount of α2M (which does not bind to LRP) essentially did not change the plasma half-life of 125I-Xa. These results further support the hypothesis that factor Xa complexed to α2M is cleared via LRP.

Clearance of α2M,125I-Xa and AT-III:125I-Xa. To further characterize the protease inhibitor-dependent phase of 125I-Xa clearance, complexes of 125I-Xa with α2M (α2M,125I-Xa) were prepared and examined in clearance studies (Fig 5A). The clearance of α2M,125I-Xa in normal mice was rapid, with a plasma half-life of approximately 5 minutes. On the other hand, the clearance of α2M,125I-Xa in Ad-39-kD–injected mice was extremely slow. The characteristics of these clearance curves are essentially the same as those of 125I-Xa in normal mice and
Ad-39-kD–injected mice, as described above (Fig 2A and B). Next, the role of proteinase inhibitor, AT-III, was examined. Complexes of 125I-Xa with AT-III (AT-III:125I-Xa) were prepared and evaluated in clearance studies (Fig 5B). Plasma clearance of AT-III:125I-Xa was rapid, with a half-life of approximately 5 minutes. Clearance was also prolonged in Ad-39-kD mice but not to the extent observed with a2M:125I-Xa. Fuchs et al27 have previously reported that AT-III:protease complexes are rapidly cleared, with a half-life of approximately 6 minutes, and that this rapid clearance is independent of a2M*. Our data suggest that a2M:125I-Xa is metabolized solely via LRP and, in addition, that LRP plays an important role in the metabolism of AT-III:125I-Xa. This latter conclusion is consistent with recent observations of Kounnas et al28 in studies of AT-III-thrombin and LRP. However, our observation that, after the injection of AT-III:125I-Xa, the clearance of approximately 75% of the 125I-Xa was prolonged, suggests that another clearance receptor may well be involved. Future studies will address this issue further.

Clearance of a factor Xa mutant that cannot bind proteinase inhibitors. Previously, Fuchs and Pizzo7 showed that the clearance of diisopropyl fluorophosphoryl (DFP)-inactivated factor Xa, which cannot bind to the protease inhibitors, was more rapid than factor Xa alone, suggesting that DFP-inactivated factor Xa has a binding site(s) that is distinct from LRP. To further characterize the role of the proteinase inhibitors in factor Xa clearance, we prepared mutant factor Xa in which the active-site serine of factor Xa has been substituted by alanine. The resultant mutant (S379A Xa) cannot bind to the proteinase inhibitors (α2M, AT-III, etc). Plasma samples obtained 30 seconds after intravenous administration of 125I-Xa and 125I-S379A Xa were subjected to SDS-PAGE and autoradiography. The injected 125I-S379A Xa migrated at the same molecular size as the uninjected standard, indicating that S379A Xa does not form SDS-stable complexes with proteinase inhibitors in vivo (data not shown). Clearance studies were then

Table 1. Organ Distribution of 125I-Xa and 125I-S379A Xa

<table>
<thead>
<tr>
<th>Organ</th>
<th>125I-Xa</th>
<th>125I-S379A Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>Spleen</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Blood</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Lung</td>
<td>0.5</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values are the percentage of the injected dose. Mice were injected with approximately 10 pmol of 125I-Xa and 125I-S379A Xa as described in the Materials and Methods. After 20 minutes, the animals were killed, organs and plasma were obtained, and their content of 125I-radioactivity was determined by gamma counting.

<table>
<thead>
<tr>
<th>α2M</th>
<th>AT-III</th>
<th>125I-Xa</th>
<th>125I-Xa injected</th>
<th>α2M</th>
<th>125I-S379A Xa injected</th>
</tr>
</thead>
</table>

Fig 3. Plasma species of 125I-Xa and α2M:125I-Xa after injection to mice. As described in the text, plasma samples (3 µL) obtained 30 seconds after the injection of 125I-Xa or α2M:125I-Xa were subjected to 7.5% SDS-PAGE and autoradiography. Standards containing α2M:125I-Xa, AT-III:125I-Xa, 125I-Xa, and 125I-Xa were also analyzed as indicated. Molecular weight markers in kilodaltons are indicated on the left.

Fig 4. Effect of preadministration of α2M* and α2M on the plasma clearance of 125I-Xa. Various doses (0.5, 1.0, and 2.5 mg) of α2M* (○) or α2M (●) were preadministered 1 minute before injection of 125I-Xa. Plasma 125I-Xa radioactivities were determined at the indicated times, as described in Fig 2.
performed using this mutant. The clearance of $^{125}$I-S379A Xa was extremely rapid, with a plasma half-life of approximately 1 minute, which was essentially the same as that of DFP-inactivated factor Xa (data not shown). Ad-39-kD did not affect the clearance of $^{125}$I-S379A Xa (data not shown). These data suggest that a pathway(s) distinct from LRP is involved in the clearance of $^{125}$I-S379A Xa.

**Organ distribution of $^{125}$I-Xa and $^{125}$I-S379A Xa in normal mice.** The organ distributions of radioactivity at 20 minutes are summarized in Table 1. $^{125}$I-Xa is found primarily in liver (56%). However, recovery of $^{125}$I-S379A Xa in liver (32%) was significantly less than that of $^{125}$I-Xa. Lung distribution was also examined. The distribution of radioactivity was low in the lung for both $^{125}$I-Xa (0.5%) and $^{125}$I-S379A Xa (0.9%).

**DISCUSSION**

The present observations show that (1) inhibition of LRP in vivo by gene transfer of a 39-kD protein prolongs the plasma half-life of $^{125}$I-Xa; (2) the plasma half-life of $^{125}$I-X is slow and unaltered by the 39-kD protein; (3) the vast majority of exogenously administered $^{125}$I-Xa is bound to $\alpha_2$M; (4) preadministration of $\alpha_2$M*, but not $\alpha_2$M, prolongs the plasma half-life of $^{125}$I-Xa; and (5) the clearance of preformed $\alpha_2$M: $^{125}$I-Xa complexes is the same as that of $^{125}$I-Xa. Taken together, these results indicate that, in vivo, LRP mediates the hepatic clearance of $^{125}$I-Xa after complex formation with $\alpha_2$M.

Factor Xa plays a pivotal role in the clotting cascade, because it can be activated by both the intrinsic and the extrinsic pathways. After intravenous administration, $^{125}$I-Xa was rapidly cleared from the circulation into liver, whereas clearance of $^{125}$I-X was much slower. The observation that the expression of the 39-kD protein altered the clearance of $^{125}$I-Xa indicates that the expression of $^{125}$I-Xa, but not $^{125}$I-X, is mediated by LRP. The mechanism(s) responsible for the clearance of $^{125}$I-X is currently unknown. Previously, using adenoviral gene transfer of the 39-kD protein, we showed that LRP mediates the clearance of both t-PA and TFPI in vivo.18,19 TFPI is cleared as the free species, whereas t-PA is cleared as both the free species as well as that complexed to PAI-1.

LRP did not mediate the plasma clearance of $^{125}$I-S379A Xa, an active-site serine factor Xa mutant that cannot bind serine-site proteinase inhibitors, including $\alpha_2$M, AT-III, $\alpha_1$PI, etc. This finding suggests that LRP does not modulate the active coagulation process occurring in the periphery such as the microvascular environment, but once circulating coagulation factors are inactivated by proteinase inhibitors, these may be eliminated from the circulation via LRP.

Regulation of the blood coagulation cascade is a complex, multifactorial process. Several proteinase inhibitors are active participants in this process via inhibition of the activated coagulation factors. In vitro, factor Xa is primarily inactivated by AT-III and $\alpha_1$PI, as has been observed in both purified systems as well as whole plasma.6,8 Although $\alpha_2$M only accounts for 10% to 15% of factor Xa inactivation in vitro, Fuchs and Pizzo7 showed that, 2 minutes after injection of $^{125}$I-Xa into mice, 90% of the radioactivity was associated with $\alpha_2$M. This finding suggested that $\alpha_2$M is a major inhibitor of factor Xa in vivo. Our present observations are consistent with these findings.

The vascular endothelium also plays an important role in the coagulation process. Activation of prothrombin to thrombin by factor Xa and factor Va is believed to occur not only on platelets but also on vascular endothelial cells. Lollar and Owen29 reported that thrombin binds to active site-independent high-affinity binding sites on the endothelial cell surface. This interaction catalyzes the inactivation of thrombin by AT-III. Thereafter, thrombin–AT-III complexes are selectively removed by the liver. Because both thrombin and factor Xa are inactivated by AT-III on the vascular endothelial cell surface, factor Xa inactivation by $\alpha_2$M may also occur on or in proximity to the vascular endothelial cell surface.

Numerous cellular binding sites/receptors have been implicated in the recognition of factor Xa (reviewed in Altieri30). These include those on the surface of platelets,31 endothelial cells,32 alveolar macrophages,33 leukocytes, and hepatoma cells. Specific recognition (inhibitory) molecular candidates include cell-associated AT-III, TFPI,34 protease nexin-1,34 and effector cell protease-1 (EPR-1).35 Each of these binding sites has been implicated in intravascular activation or inhibition of coagulation via interaction with factor Xa. For example, platelets and vascular endothelial cells provide cell surface sites for the generation of prothrombin as described above. Recently, in in vitro studies in the absence of other protease inhibitors, we have identified a new factor Xa cellular binding/uptake pathway that
requires TFPI and is independent of LRP. However, in vivo, LRP appears to play a distinctly different role, because it functions as the major pathway responsible for elimination of inactivated Xa from the circulation.

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