Thrombin is a multifunctional protein that has both proteinase and growth factor-like activities. Its regulation is largely mediated by interaction with a host of inhibitors including antithrombin III (ATIII), heparin cofactor II (HCII), α₂-macroglobulin (α₂-M), protease nexin I, and plasminogen activator inhibitor-1 (PAI-1). ATIII, HCII, and α₂-M are all abundant in blood and can inactivate blood-borne thrombin leading to rapid hepatic clearance of the thrombin-inhibitor complex. PAI-1 alone, a poor solution phase inhibitor of thrombin, can efficiently inhibit thrombin in the presence of native vitronectin (VN). In this study, active thrombin was found to be efficiently endocytosed and degraded by cultured pre-type II pneumocyte cells, and both processes could be blocked by polyclonal antibodies to PAI-1. When the relative efficiency of cellular endocytosis of thrombin in complex with a number of inhibitors was examined, ¹²⁵I-thrombin-PAI-1 complexes were most efficiently cleared compared to ¹²⁵I-thrombin in complex with the serpins ATIII, HCII, α₂-proteinase inhibitor, or o-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone. Low density lipoprotein receptor-related proteins 1 (LRP) and 2 (gp330/megalin) mediate the endocytosis of thrombin-PAI-1, since antagonists of receptor function such as LRP-1 and LRP-2 antibodies and the 39-kDa receptor-associated protein blocked ¹²⁵I-thrombin-PAI-1 endocytosis and degradation. The LRP-mediated clearance of exogenously added ¹²⁵I-thrombin by cultured cells was found to be enhanced 5-fold by inclusion of wild-type PAI-1 but by only 2-fold when a mutant form of PAI-1 that is unable to bind VN was included. This wild-type PAI-1 enhancement of ¹²⁵I-thrombin clearance was found to occur only in the presence of native VN and not with its conformationally altered form. The results highlight a novel mechanism for cellular clearance of thrombin involving native VN promoting the interaction of thrombin and PAI-1 and the subsequent endocytosis of the complex by LRP-1 or LRP-2. This pathway is potentially important for the regulation of the potent biological activities of thrombin, particularly at sites of vascular injury.

The enzymatic activity of thrombin is responsible for the conversion of soluble fibrinogen to insoluble fibrin, activation of blood coagulation proteins V, VIII, and XIII (1, 2), and activation of platelets via limited hydrolysis of the thrombin receptor (3). Thrombin also negatively controls blood coagulation through activation of protein C, which inactivates factors Va and VIIIa. In addition, thrombin has mitogenic effects on a variety of cells including fibroblasts, endothelial cells, and macrophages (4–7) and chemotactic effects on neutrophils, fibroblasts, and monocytes (8–10). Considering that thrombin can also promote adhesion of polymorphonuclear cells and monocytes to endothelial cells (11, 12), as well as increase the permeability of endothelial cell monolayers and pulmonary vessels (13), it may be an important mediator of inflammatory and vascular wound healing events. The catalytic activity of thrombin is required for its mitogenic effects on fibroblasts (14) and endothelial cells (15), as well as inhibition of neurite outgrowth (16); however, proteolytically active thrombin is not required for its chemotactic effects on neutrophils and monocytes (9, 8) or its ability to increase the permeability of endothelial cell monolayers and pulmonary vasculature (13).

The multitude of biological actions of thrombin necessitates that strict controls be placed on its expression, activity, and halflife. In blood, the inhibition of proteolytic active thrombin is mediated by interaction with a host of inhibitors including ATIII, HCII, and α₂-M. Upon interaction of blood borne thrombin with these inhibitors, the complexes are rapidly cleared by the liver via a receptor-mediated process (17–19). However, little is known about the mechanism of inactivation and clearance of extravascular thrombin, such as that detected on the surface of tissue macrophage or sequestered within thrombi away from the blood flow and the action of circulating inhibitors (20–22). It is likely that in these contexts thrombin exerts its greatest effects on inflammation and vascular wound healing. Given that plasminogen activator inhibitor-1 (PAI-1) is known to be expressed at sites of inflammation and released from platelet granules upon activation (23, 24), it may under these conditions be a relevant inhibitor of thrombin. While PAI-1 alone is a rather poor inhibitor of thrombin, complex formation with VN has been shown to greatly augment its ability to inhibit thrombin (25, 26). VN is known to be present in connective tissue extracellular matrices and released from platelets upon their activation (24, 27). Ehrlich et al. (28) have demonstrated that complexes of thrombin and PAI-1 form on endothelial cell extracellular matrices and the complex formation can be inhibited with antibodies to VN. While they spec-
ulated that the thrombin-PAI-1 interaction might promote plasminogen activator activity by neutralizing PAI-1, this interaction may also mediate cellular clearance of thrombin. The latter would be similar to two other proteinases, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), whose endocytosis and degradation via several members of the low density lipoprotein receptor (LDLR) family are promoted after complex formation with PAI-1 (29–33). The focus of this study was to evaluate cell-mediated endocytosis as a potential mechanism for regulating levels of extravascular thrombin and to determine whether PAI-1, VN, and receptors of the LDLR family have roles in the process.

MATERIALS AND METHODS

Proteins—Human α-thrombin was obtained from Dr. F. Church (University of North Carolina, Chapel Hill, NC) or purchased from Enzyme Research Laboratories (South Bend, IN). Human ATIII was obtained from Dr. F. Church. Human ATIII was obtained from Dr. K. Ingham (American Red Cross, Rockville, MD). Human α2-PI was purchased from Sigma. Human fibrinogen was purchased from Enzyme Research Laboratories (South Bend, IN). α2-Plasminogen-α2-PLG-α2-Arginine-α2-Chloromethyl ketone (PPACK) was purchased from Calbiochem. Human 93-KDa receptor-associated protein (RAP) was expressed and purified as described (34). Low density lipoprotein receptor-related protein (LRP-1) was purified as described (35). Glycoprotein 330/LRP-2 was purified as described previously (36). Native human VN was provided by Dr. T. J. Podor ( McMaster University, Hamilton, Ontario, Canada). Human uPA was provided by Dr. J. Henkin (Abbott Laboratories, Abbott Park, IL). Bacterially expressed human PAI-1 was purchased from Molecular Innovations (Royal Oak, MI). A mutant form of PAI-1 having a Gln123 → Lys substitution that makes it unable to bind to VN (37) was prepared as described (38).

Radioiodination of proteins was performed by IODO-GEN (Pierce). Complexes of thrombin and various inhibitors were prepared by incubating the 125I-thrombin with each inhibitor at a 2:1 molar ratio for 30 min at 25 °C, followed by absorption of free thrombin by chromatography on a column of ATIII-Sepharose (2 mg of ATIII/ml of resin). To prepare active site-inhibited thrombin, 125I-thrombin (100 nM) was incubated with PPACK (5 mM) for 30 min at 25 °C in Tris-buffered saline. The complexes were tested for thrombin activity by incubation with a fibrinogen solution (1 mg of fibrinogen/ml in Tris-buffered saline, 5 mM CaCl2) at 25 °C for 30 min and assaying for fibrin formation.

Antibodies—The rabbit antiserum against LRP-1 (rCl777 and rB810), LRP-2 (rB239 or rB784), and a synthetic peptide corresponding to the last 11 residues of the cytoplasmic domain of LRP-1 (rCl784) have each been described previously (36, 39, 40). Receptor-specific IgG was selected from the LRP-1 and LRP-2 sera by chromatography on columns of either LRP-1 or LRP-2-Sepharose (1–2 mg of receptor/ml of resin). Control rabbit IgG was purified from non-immune sera. IgG from each preparation was purified by affinity chromatography on protein G-Sepharose and absorbed on a column of RAP-Sepharose (2 mg of RAP/ml of resin). Rabbit anti-murine PAI-1 serum was from Molecular Innovations (Royal Oak, MI).

Cells—Rat pre-type II pneumocytes (41) were from Dr. R. K. Mallampani (University of Iowa College of Medicine, Iowa City, IA) and grown in Waymouth’s media (Life Technologies, Inc.) supplemented with 10% bovine calf serum (HyClone Laboratories, Logan, UT), penicillin, and streptomycin.

Solid Phase Binding Assays—Solid phase binding assays were performed as described (34). 125I-Thrombin-PAI-1 complexes (1 nM) in the presence of increasing concentrations of unlabeled complex or RAP were incubated with microtiter wells coated with LRP-1, LRP-2, or bovine serum albumin (3 μg/ml). The program LIGAND (42) was used to analyze the competition data and to determine dissociation constants (Kd, Kd) for receptor-ligand interactions.

Cellular Endocytosis and Degradation of Thrombin and uPA—Type II pneumocytes were seeded into wells of 12-well plates (1–2.5 × 105 cells/well) and grown 18 h at 37 °C in 5% CO2 in Waymouth’s medium containing 10% bovine calf serum. Before addition of 125I-thrombin-inhibitor complexes, the cells were washed twice in serum-free Waymouth’s medium and incubated for 30 min in medium containing 1.5% bovine serum albumin, 20 mM Hepes, pH 7.4, Nutristore serum substitute, penicillin, and streptomycin (assay medium). 125I-Labeled complexes in assay medium were added to cell layers and incubated for 4–6 h at 37 °C.

RESULTS

The Efficient Endocytosis and Degradation of Active Thrombin Is Dependent on PAI-1—When the endocytosis and degradation of exogenously added active versus active-site-inhibited 125I-thrombin was compared, the active thrombin was more efficiently endocytosed and degraded (Fig. 1). Considering that the clearance of two other proteinases (tPA and uPA) has been shown to be augmented by complex formation with PAI-1 (29, 30, 33), we investigated the possibility that PAI-1 was mediating the clearance of the active thrombin in the cultured pre-

FIG. 1. Endocytosis and degradation of active and active site-inhibited thrombin and effects of PAI-1 antibodies. A, 125I-Thrombin-PAI-1 complexes (125I-Th:PPACK) and active 125I-thrombin (125I-Th) each at 20 nM. Also shown in each panel are the effects of rabbit anti-mouse PAI-1 IgG (0.6 mg/ml) or normal rabbit IgG (Control IgG, 0.6 mg/ml) on the endocytosis and degradation of active 125I-thrombin. The data presented are representative of three experiments, each performed in duplicate. Each plotted value represents the average of duplicate determinations with the range indicated by bars.
LRP antibodies to inhibit endocytosis and degradation to the inhibited the endocytosis and degradation of 125I-thrombin-39-kDa RAP, and antibodies to either LRP-1 or LRP-2 each of the LDLR family, LRP-1 and LRP-2 (33). As shown in a cell line has been shown previously to express two members of the LDLR family, LRP-1 and LRP-2 (33). Considering that PAI-1 facilitates the cell-mediated clearance of active 125I-thrombin, whereas control rabbit IgG had a negligible effect on either process (Fig. 1). These data show that active thrombin is endocytosed and degraded and suggest that PAI-1 is involved.

Thrombin in Complex with PAI-1 Is More Efficiently Endocytosed and Degraded as Compared to Complexes with ATIII, HCII, or α2-PI—We next investigated the relative efficiency of cell-mediated clearance of 125I-thrombin in complex with various serpins using the pre-type II pneumocyte cell line. As shown in Fig. 2, 125I-thrombin-PAI-1 complexes were endocytosed (panel A) and degraded (panel B) at levels 6-fold greater (n = 2) than complexes of thrombin and the serpins ATIII, HCII, and α2-PI or of thrombin and the synthetic peptide inhibitor PPACK.

Members of the Low Density Lipoprotein Receptor Family Mediate the Endocytosis and Degradation of Thrombin-PAI-1 Complex—Considering that PAI-1 facilitates the cellular clearance of active uPA (43–45) via members of the LDLR family, we were interested to determine whether such a mechanism was involved in the pre-type II pneumocyte cell line. As shown in Fig. 3, antagonists of LRP-1 and LRP-2 function, namely the 39-kDa RAP, and antibodies to either LRP-1 or LRP-2 each inhibited the endocytosis and degradation of 125I-thrombin-PAI-1 complex. The extent of RAP inhibition was similar to that using excess unlabeled thrombin-PAI-1 complex, suggesting that members of the LDLR family were mediating the endocytosis and degradation of thrombin-PAI-1. While both LRP antibodies blocked 125I-thrombin-PAI-1 endocytosis and degradation, LRP-1 antibodies were more effective than LRP-2 antibodies. This differential effect most likely reflects higher affinity of wild-type PAI-1 (25, 26) and LRP-1 (27, 29) compared to mutant PAI-1 and LRP-2, respectively. RAP was found to compete for the binding of 125I-labeled complex to both receptors (Fig. 4). Thrombin or PAI-1 alone did not compete efficiently for 125I-thrombin-PAI-1 binding to either receptor (Kd > 700 nM). The results indicate that thrombin-PAI-1 complex binds with high affinity to LRP-1 and LRP-2. The fact that PAI-1 is known to bind to both receptors (33, 47), yet is unable to compete for thrombin-PAI-1 binding, may indicate that the complex possesses an additional receptor binding site not present on either thrombin or PAI-1 alone.

The Ability of PAI-1 to Bind VN Facilitates the Efficient Clearance of Thrombin—Considering that VN has been shown to promote the inhibition of thrombin by PAI-1 (25, 26), we were interested to determine whether such a mechanism was involved in the pre-type II pneumocyte cell line. As shown in Fig. 5, panels A and C, inclusion of wild-type PAI-1 produced a greater level of endocytosis and degradation of 125I-thrombin compared to mutant PAI-1. In contrast, the endocytosis of 125I-uPA was enhanced to the same degree by either wild-type or mutant PAI-1 (Fig. 5, panels B and C).
frequency for VN, it is clear from Fig. 5, since PAI-1 binds uPA with high affinity and without a re-
culture acted to accelerate complex formation in lieu of VN. Since PAI-1 binds uPA with high affinity and without a re-
culture acted to accelerate complex formation in lieu of VN. Given that heparin has also been shown to stimulate complex formation although less efficiently than VN (48), it is possible that proteoglycans present in the cell
and deglucan may have contributed the low level of thrombin clear-
ance observed with PAI-1 alone or PAI-1 plus conformationally altered VN. By comparison, 125I-uPA clearance mediated by
LRP receptors. Therefore, when free 125I-thrombin was presented to the cells as in Fig. 5, the formation of a complex with PAI-1-VN was required for the effi-
cient complex formation between thrombin and PAI-1, which leads to rapid LRP-mediated endocytosis and degradation.

PAI-1-promoted Endocytosis and Degradation of Thrombin Is Augmented by Native but Not Conformationally Altered VN—It has been established previously that native VN accelerates the formation of the thrombin-PAI-1 complex, whereas conformationally altered VN does not (26). To determine whether the conformational state of VN influenced PAI-1-mediated cellular clearance of thrombin, we examined the clearance of 125I-thrombin in the presence of PAI-1 and either native or conformationally altered VN. As shown in Fig. 7 (panels A and C), using cells grown in the absence of serum to eliminate exposure to serum VN, exogenously added native VN enhanced 125I-thrombin clearance. Conformationally altered VN was no more effective in promoting the clearance of 125I-thrombin than was PAI-1 alone. Given that glycosaminoglycans have been shown to promote inhibition of thrombin by PAI-1 (48), proteoglycans may have contributed the low level of thrombin clearance observed with PAI-1 alone or PAI-1 plus conformationally altered VN. By comparison, 125I-uPA clearance mediated by complex formation with PAI-1 was not influenced by the pres-

and D). RAP treatment blocked the wild-type PAI-1-promoted endocytosis of both thrombin and uPA. The results suggest that PAI-1 binding to VN derived from serum is important for the clearance of thrombin. We speculate that the clearance of free thrombin requires complex formation with PAI-1, a process that is known to be greatly accelerated by VN. The low level of thrombin clearance promoted by mutant PAI-1 was likely due to its ability to form a complex with thrombin, albeit inefficiently, in the absence of VN. Given that heparin has also been shown to stimulate complex formation although less efficiently than VN (48), it is possible that proteoglycans present in the cell
culture acted to accelerate complex formation in lieu of VN. Since PAI-1 binds uPA with high affinity and without a re-
requirement for VN, its clearance (Fig. 5, panels B and D) was, as expected, not dependent on the ability of PAI-1 to complex with VN.

To show that the PAI-1 mutation did not affect the ability of its complex with thrombin to bind to LRPCs, complexes of 125I-thrombin with either wild-type PAI-1 or mutant PAI-1 were formed in vitro. As shown in Fig. 6, complexes containing either form of PAI-1 were readily endocytosed (panel A) and degraded (panel B) by the pre-type II pneumocyte cells. Both the endo-
cytosis and degradation of the complexes were inhibited by including RAP in the assay. These results indicate that complexes of thrombin and either wild-type or mutant PAI-1 are recognized equally well by LRP receptors. Therefore, when free 125I-thrombin was presented to the cells as in Fig. 5, the formation of a complex with PAI-1-VN was required for the effi-
cient complex formation between thrombin and PAI-1, which leads to rapid LRP-mediated endocytosis and degradation.

**Fig. 4.** Binding of 125I-thrombin-PAI-1 complex to LRP-1 and LRP-2. The binding of 125I-thrombin-PAI-1 (1 nM) to microtiter wells coated with LRP-1 (panel A) or LRP-2 (panel B) was measured in the presence of increasing concentrations of unlabeled thrombin-PAI-1, thrombin, or PAI-1. The curves represent the best fit of the data to a single class of sites. The data presented are representative of four experiments, each performed in duplicate. Each plotted value represents the average of duplicate determinations with the range indicated by bars.

**Fig. 5.** Effect of wild-type PAI-1, or a mutant of PAI-1 that is unable to bind VN, on the endocytosis and degradation of 125I-thrombin or 125I-uPA. Pre-type II pneumocyte cells were incubated with either wild-type PAI-1 (wtPAI-1, 10 nM) or a mutant form of PAI-1 (mPAI-1, 10 nM) that is unable to bind to VN. Either 125I-thrombin (10 nM) or 125I-uPA (10 nM) were added to the cells and incubated for 4–6 h in the presence or absence of RAP (1 μM). The amount of endocytosis and degradation of 125I-thrombin is shown in panels A and C, respectively. The amount of endocytosis and degradation of 125I-uPA is shown in panels B and D, respectively. The data presented are representative of four experiments, each performed in duplicate. Each plotted value represents the average of duplicate determinations with the range indicated by bars.

**Fig. 6.** Endocytosis and degradation of 125I-thrombin that has been pre-complexed to either wild-type PAI-1 or mutant PAI-1. Pre-type II pneumocyte cells were incubated with 125I-thrombin pre-complexed with either wild-type PAI-1 (125I-Th:wtPAI-1) or mutant PAI-1 (125I-Th:mPAI-1) that is unable to bind to VN. 125I-Labeled complex concentration was 10 nM. Where indicated, RAP (1 μM) was added along with the 125I-labeled complex. The amount of endocytosis and degradation of each type of 125I-labeled complexes are shown in panels A and B, respectively. The data presented are representative of two experiments. Each plotted value represents the average of duplicate determinations with the range indicated by bars.
LRP Endocytosis of Thrombin-PAI-1 Complexes

Fig. 7. The effect of native or conformationally altered VN on endocytosis and degradation of $^{125}$I-thrombin and $^{125}$I-uPA in the presence of wtPAI-1. Pre-type II pneumocyte cells grown in serum-free conditions were incubated with either native VN (nVN, 50 nM) or conformationally altered (denatured) VN (dVN, 50 nM). After washing the cells were incubated with wild-type PAI-1 (10 nM), followed by addition of either $^{125}$I-thrombin (10 nM) or $^{125}$I-uPA (10 nM). The amount of endocytosis and degradation of $^{125}$I-thrombin is shown in panels A and C, respectively. The amount of endocytosis and degradation of $^{125}$I-uPA is shown in panels B and D, respectively. The data presented are representative of three experiments. Each plotted value represents the average of duplicate determinations with the range indicated by bars.

Thrombin interaction with some endogenous inhibitor facilitated native VN clearance. This is consistent with our findings showing that active thrombin is cleared much more efficiently than is inactivated thrombin and that PAI-1 antibodies inhibit the clearance of active thrombin. The results taken together point to the possibility that a ternary complex of thrombin-PAI-1 and VN may be cleared, but this remains to be established. The fact that RAP blocks thrombin clearance to the same extent as excess unlabeled thrombin indicates that LRP receptors are primarily responsible for mediating the clearance process.

A major concept to emerge from this work is that PAI-1 can serve to mediate thrombin catabolism, but it raises the issue of when and where such a process might occur in vivo. While PAI-1 inhibits uPA and tPA with a second-order rate constant of $10^7$ M$^{-1}$ s$^{-1}$ (58), by comparison the second-order rate constant for inhibition of thrombin is $\sim$10,000-fold less (26). The physiological relevance of PAI-1 inhibition of thrombin therefore may not be immediately obvious, until one considers that cofactors such as heparin and VN can dramatically enhance the ability of PAI-1 to inhibit thrombin. For example, in the presence of VN the second-order rate constant for the inhibition of thrombin by PAI-1 is increased by more than 2 orders of magnitude (26). This effect makes PAI-1-VN a 10–20-fold better inhibitor of thrombin than ATIII in the absence of heparin. In blood, where the concentration of ATIII is 10,000-fold higher than PAI-1, the relevance of PAI-1 as an inhibitor of blood borne thrombin is unlikely. However, in extravascular sites such as in the recesses of a fibrin-containing thrombus, we speculate that it may be a physiologically relevant inhibitor of thrombin. Fibrin is thought to sequester thrombin, protecting it from circulating inhibitors (22, 59, 60) until lysis of the clot by plasmin (59). The thrombin thereby released would be available to drive post-clotting events such as mediating mitogenesis and chemotaxis of cells involved in clot remodeling and tissue repair. PAI-1, either derived from platelets or synthesized by cells invading a clot or on the boundaries of the clot, and VN, derived either from platelets or synthesized by cells invading a clot or on the boundaries of the clot, and VN, derived either from platelets (24) or blood, could mediate inactivation of thrombin and its clearance by LRP-expressing cells (e.g. smooth muscle cells, macrophage, and fibroblasts). In this way the post-clotting effects of thrombin could be negatively regulated.

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