Members of the matrix metalloproteinase (MMP) family of enzymes participate in matrix remodeling and share a number of structural and functional features. The activity of this family of proteinases is carefully regulated at the level of zymogen activation and by a family of specific inhibitors termed tissue inhibitors of metalloproteinases (TIMP). It is now becoming clear that levels of certain MMPs are modulated by their association with cellular receptors that mediate their rapid internalization and degradation. In the current investigation we report that the amount of MMP-9 in conditioned cell culture medium is significantly increased when mouse embryonic fibroblasts are grown in the presence of the 39-kDa receptor-associated protein (RAP), an antagonist of ligand binding to low density lipoprotein receptor-related protein (LRP). In vitro assays reveal that the MMP-9-TIMP-1 complex binds to LRP with high affinity and that the binding determinant for LRP appears to reside on MMP-9. Cell lines expressing LRP mediate the internalization of 125I-labeled MMP-9-TIMP-1 complexes, whereas cell lines genetically deficient in LRP show a diminished capacity to mediate the cellular catabolism of MMP-9-TIMP-1 complexes. The results demonstrate that LRP is a functional receptor for MMP-9 and suggest a major role for LRP in modulating remodeling of the extracellular matrix by regulating extracellular proteinase activity.

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Members of the matrix metalloproteinase (MMP) family of enzymes participate in matrix remodeling and share a number of structural and functional features. All require zinc and calcium ions for activity and are synthesized as inactive zymogens that need to be cleaved to become active enzymes (1–3). One member of this family, MMP-9, plays an important role in controlling angiogenesis (4, 5) and in extracellular matrix remodeling after myocardial infarction (6). Thus, mice in which the MMP-9 gene has been deleted exhibit an abnormal pattern of skeletal growth plate vascularization and ossification (5). Growth plates from MMP-9-deficient mice in culture show a delayed release of an angiogenic activator. Together, these data establish a role for this proteinase in controlling angiogenesis.Using a transgenic mouse model of multistage carcinogenesis Bergers et al. (4) conclude that MMP-9 triggers an angiogenic “switch” that renders normal pancreatic islets angiogenic by releasing increased amounts of vascular endothelial growth factor. In another transgenic model of epithelial carcinogenesis, Coussens et al. (7) observe that mice lacking MMP-9 show reduced keratinocyte hyperproliferation at all neoplastic stages and a decreased incidence of invasive tumors.

Like most proteinases, the activity of MMP-9 is tightly regulated. MMP activity is modulated by a family of specific inhibitors, termed tissue inhibitors of metalloproteinases (TIMP) (8). TIMPs regulate MMP activity during extracellular matrix turnover, and ablation of TIMP gene expression results in enhanced extracellular matrix proteolysis concomitant with up-regulation of cell invasive activity (9, 10). Recent studies demonstrate a unique role for TIMPs independent of their ability to inhibit MMPs by demonstrating that TIMP-2 can directly regulate tyrosine kinase-type growth factor receptor activation (11).

An additional pathway capable of regulating the levels of MMP-13 was recently discovered when Barmina et al. (12) identified cellular receptors that are able to bind MMP-13. One of these receptors, the low density lipoprotein receptor-related protein (LRP), mediates the internalization and degradation of this proteinase. LRP, a member of the LDL receptor superfamily, also modulates levels of MMP-2 by binding and internalizing MMP-2-thrombospondin 2 (TSP2) complexes (13). In both of these studies, the catabolism of MMPs was inhibited by a 39-kDa receptor-associated protein (RAP). This molecule binds reversibly to LRP (14) and other members of the LDL receptor family such as gp330/megalin (15) and the VLDL receptor (16) and inhibits ligand binding by these receptors (14, 17). RAP is found primarily in the endoplasmic reticulum, where it functions as a molecular chaperone by assisting in receptor folding and processing (18) and preventing the association of newly synthesized receptors with endogenous ligands (19). Due to its high affinity for LRP and ability to antagonize ligand binding, exogenously added RAP constitutes a powerful tool to study LRP-mediated mechanisms. In the current investigation, we report that the levels of MMP-9 in conditioned cell culture media are increased significantly when cells are grown in the...
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presence of RAP. Furthermore, we demonstrate that MMP-9 directly binds with high affinity to LRP and that this receptor mediates the internalization and subsequent degradation of this enzyme. Based on these studies, we propose that clearance of MMP-9 by LRP is an important mechanism for regulating extracellular levels of this proteinase.

**EXPERIMENTAL PROCEDURES**

**Proteins**—Human RAP was expressed in bacteria as a fusion protein with glutathione S-transferase as described previously (14). Cleavage with thrombin and purification of recombinant RAP was carried out as described (14) with modification. After elution from glutathione S-transferase-Sepharose, RAP was placed on a MonoQ column equilibrated with 0.02 M sodium phosphate, pH 5.5, and eluted with a gradient from 0 to 2 M NaCl over 30 min at a flow rate of 1 ml/min. The RAP was then recycled three times over AffinityFak™ Detoxi-Gel™ endotoxin-removing gel (Pierce). LRP was purified by ligand affinity chromatography followed by ion exchange chromatography on MonoQ HR (Amersham Pharmacia Biotech) as described (20). MMP-9-TIMP-1 and MMP-2-TIMP-2 complexes were purchased from Chemicon (Temecula, CA). A fragment containing the eight ligand binding repeats of the human VLDL receptor (VLDLr1–8) was generated as a GST fusion protein as described (21). After purification and digestion with thrombin to release the VLDLr1–8, refolding and purification of the soluble receptor fragment was accomplished as described (21). Anti-MMP-9 and anti-MMP-2 monoclonal antibodies were purchased from Calbiochem. Anti-LRP monoclonal antibody 8G1 (22) was produced and purified as described previously. Goat anti-mouse IgG conjugated to either horse-radish peroxidase or alkaline phosphatase was purchased from Bio-Rad.

**Cell Culture Conditions and RAP Treatment**—Mouse embryonic fibroblasts (PEA-10, LRP(+)); PEA-13, LRP(−/−); mouse embryonic fibroblasts (PEA-13, LRP(+/−)) were plated onto 12-well plates at ~1 × 10⁵ cells/well and grown overnight at 37 °C, 5% CO₂. Cells were then washed twice with assay medium (Dulbecco’s modified Eagle’s medium containing Nutridoma media supplement; 20 mM HEPES, pH 7.4, and 1.5% BSA) and incubated in this medium for 1 h at 37 °C. The cells were then incubated with assay medium containing 5 μM 125I-MMP-9-TIMP-1 for the indicated times at 37 °C. After incubation, the cells were washed three times with assay medium and detached with 0.5 ml of trypsin/protease K (to dissociate LRP115-MMP-9-TIMP-1 complexes from the cell surface) and then pelleted by centrifugation (3000 rpm for 5 min). The amount of internalized 125I-MMP-9-TIMP-1 complex was determined by measuring the radioactivity associated with the cell pellet in a γ counter. Nonspecific uptake was assessed by measuring 125I-MMP-9 in the conditioned media collected from untreated cells.

**Cell Internalization and Degradation Assays**—Mouse embryonic fibroblasts (LRP(+/−)) and LRP-deficient mouse embryonic fibroblasts (PEA-13, LRP(−/−)) were plated onto 12-well plates at ~1 × 10⁵ cells/well and grown overnight at 37 °C, 5% CO₂. Cells were then washed twice with assay medium (Dulbecco’s modified Eagle’s medium containing Nutridoma media supplement; 20 mM HEPES, pH 7.4, and 1.5% BSA) and incubated in this medium for 1 h at 37 °C. The cells were then incubated with assay medium containing 5 μM 125I-MMP-9-TIMP-1 for the indicated times at 37 °C. After incubation, the cells were washed three times with assay medium and detached with 0.5 ml of trypsin/protease K (to dissociate LRP115-MMP-9-TIMP-1 complexes from the cell surface) and then pelleted by centrifugation (3000 rpm for 5 min). The amount of internalized 125I-MMP-9-TIMP-1 complex was determined by measuring the radioactivity associated with the cell pellet in a γ counter. Nonspecific uptake was assessed by measuring 125I-MMP-9 in the conditioned media collected from untreated cells.

**RESULTS**

**MMP-9 Accumulates in the Conditioned Medium Collected from Cells Treated with the LDL Receptor Family Inhibitor, RAP**—Previous reports demonstrated that LRP can directly bind and mediate the cellular catabolism of MMP-13 (12) and regulates levels of MMP-2 as well (13). To further investigate the role of LRP in the catabolism of the MMP gelatinases MMP-2 and MMP-9, LRP(+/−) mouse embryonic fibroblasts were cultured in serum-free medium for varying lengths of time in the absence or presence of RAP. RAP was first identified when it was found to co-purify with LRP (20). Subsequent work (14, 17) revealed that this molecule binds tightly to LRP and prevents binding of all known ligands to this receptor. In the current experiments, the conditioned media were collected and analyzed for the presence of gelatinase activity (Fig. 1). The results indicate that LRP(+/−) cells treated with RAP contained similar amounts of 72-kDa MMP-2 when compared to parallel cultures treated with BSA. However, the RAP-treated cultures contained significantly more of the 105-kDa MMP-9 in their media than the control-treated cells. The increased levels of MMP-9 in the conditioned medium of RAP-treated cells suggest that LRP regulates the levels of MMP-9 present in cell culture media.

In the current experiments, we noted that control levels of MMP-2 were high and that very little change in MMP-2 levels occurred when the cells were cultured in the presence of RAP, whereas in another study using mouse dermal fibroblasts, an increase in MMP-2 levels in the presence of RAP was noted (13). As this accumulation did not occur in dermal fibroblasts isolated from mice in which the TSP2 gene was deleted, we previously concluded that MMP-2 catabolism by LRP is mediated by TSP2. Indeed the embryonic fibroblasts used in the
current study produce barely detectable levels of TSP2, as determined by immunoblot of conditioned media.\(^2\)

**MMP-9 Binds Directly to LRP.**—To investigate the mechanism by which LRP modulates MMP-9 levels, we initiated experiments to determine if MMP-9 can directly bind to LRP. The preparation of MMP-9 used in the current experiments was composed of MMP-9 in complex with its cognate inhibitor TIMP-1. Our initial experiments examined the interaction of the MMP-9-TIMP-1 complex with LRP by ligand-blotting experiments. Purified human LRP and a soluble VLDLr fragment containing the ligand binding region of this receptor (VLDLr1–8) were first subjected to SDS-PAGE under nonreducing conditions, transferred to nitrocellulose, and then incubated with 20 nM recombinant human MMP-9-TIMP-1 complex. The binding of MMP-9-TIMP-1 complex to LRP was then visualized using an anti-MMP-9 IgG. The results demonstrate that MMP-9-TIMP-1 binds to LRP (Fig. 2A) but not to VLDLr1–8 (Fig. 2B). The binding to LRP was blocked when excess RAP was incubated along with MMP-9, confirming the specificity of the interaction.

We next wished to ascertain if the presence of TIMP-1 is required for binding of MMP-9 to LRP. To investigate this, a “receptor blot” was performed. In this experiment, RAP (as a positive control), the MMP-9-TIMP-1 complex, and the MMP-2-TIMP-2 complex were first subjected to SDS-PAGE under nonreducing conditions (Fig. 3, A–C) to separate MMP-9 and MMP-2 from TIMP-1 and TIMP-2, respectively. After electrophoresis, the proteins were transferred to nitrocellulose and incubated with purified LRP, and receptor binding was visualized with an anti-LRP IgG. The results demonstrate that LRP recognized RAP (Fig. 3B, lane 1) and TIMP-free MMP-9 (Fig. 3B, lane 2) but not TIMP-1, MMP-2, or TIMP-2. Binding of LRP to MMP-9 was abolished by the addition of excess RAP (Fig. 3C), confirming the specificity of the interaction. MMP-9 is known to be composed of domains stabilized by disulfide bonds, and consequently we investigated the binding of LRP to MMP-9 subjected to SDS-PAGE under reducing conditions. The results (Fig. 3D, lane 2) indicate that LRP failed to bind to MMP-9 when the enzyme was subjected to reduction before SDS-PAGE. In contrast, when RAP was subjected to SDS-PAGE under reducing conditions, no impact on the ability of LRP to bind RAP was noted (Fig. 3D, lane 1), consistent with the fact that RAP contains no cysteine residues. These results indicate that MMP-9 directly binds to LRP even in the absence of TIMP-1 and that reduction of MMP-9 abolishes its ability to bind LRP.

To measure the affinity of LRP for MMP-9-TIMP-1 complexes, a solid phase assay was employed in which the MMP-9-TIMP-1 complex was first immobilized on microtiter wells. Increasing concentrations of RAP were then incubated with the immobilized MMP-9-TIMP-1 complex, and the extent of LRP binding was measured using the anti-LRP monoclonal antibody 8G1. An apparent $K_D$ of 0.6 nM for the binding of LRP to MMP-9-TIMP-1 was estimated by nonlinear regression analysis of the data (Fig. 4, closed triangles). In contrast, MMP-2-TIMP-2 complexes demonstrated much lower affinity for LRP in the same assay (Fig. 4, closed circles), with an apparent $K_D$ value estimated to be at least 10–100-fold weaker than that of MMP-9. No binding of LRP to microtiter wells coated with BSA was observed (Fig. 4, open squares). In the same experiment, the apparent affinity of LRP for microtiter wells coated with RAP was determined to be 0.07 nM (data not shown).

We also investigated the binding of MMP-9-TIMP-1 to micro-
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To determine the physiological relevance of the interaction between MMP-9 and LRP, LRP(+/) and LRP(−/) cells were incubated with 125I-MMP-9-TIMP-1 complex for 6 h. After incubation, the extent of radioactivity associated with the cell surface (Fig. 6A) or internalized (Fig. 6B) was measured. The results indicate that the 125I-MMP-9-TIMP-1 complex associates with the cell surface and is internalized in LRP-expressing cells, and the amount of 125I-MMP-9-TIMP-1 complex associated with the cell surface or internalized by LRP-deficient cells was greatly reduced when the cells were incubated with excess RAP. In contrast, very little 125I-MMP-9-TIMP-1 complexes were associated with the cell surface or internalized in cells deficient in LRP. Interestingly, a small amount of 125I-MMP-9-TIMP-1 internalization was observed in LRP-deficient cells that were inhibited by RAP (Fig. 6B), suggesting that another as yet unidentified member of the LDL receptor family may also recognize the MMP-9-TIMP-1 complex.

We next examined the time course of internalization and degradation of 125I-MMP-9-TIMP-1 complex in LRP-expressing and LRP-deficient cells (Fig. 7). LRP-expressing cells demonstrated a time-dependent accumulation of radioactivity (Fig. 7A), which was prevented when the cells were incubated with excess RAP. In contrast, LRP-deficient cells only internalized small amounts of 125I-labeled MMP-9-TIMP-1 complexes (Fig. 7B). LRP-mediated internalization of 125I-labeled MMP-9-TIMP-1 complexes was associated with their cellular-mediated degradation (Fig. 7C), as confirmed by blocking with chloro-
orquine, an inhibitor of lysosomal proteases. Virtually all of the cellular-mediated degradation was blocked by RAP, and no degradation was detected in cell lines deficient in LRP (Fig. 7D). These data confirm that LRP mediates the cellular uptake of MMP-9-TIMP-1 complexes, leading to their degradation.

**DISCUSSION**

In the current investigation, we have demonstrated that murine fibroblasts cultured in the presence of RAP accumulate MMP-9 in their media, indicating that a RAP-sensitive receptor contributes to the catabolism of this molecule. In vitro binding studies and cellular uptake experiments confirm that this receptor is LRP. These studies established that LRP binds MMP-9 specifically and with high affinity. MMP-9 is secreted as a complex with its specific inhibitor, TIMP-1, and both the MMP-9-TIMP-1 complex and free MMP-9 bind to LRP, suggesting that a LRP binding determinant is primarily located within the MMP-9 molecule. A role for LRP in mediating the cellular catabolism of MMP-9 was confirmed by demonstrating that murine fibroblasts lacking LRP are inefficient in mediating the cellular internalization and degradation of MMP-9. Together, these data confirm that LRP is a cellular receptor for MMP-9 and functions to regulate the levels of MMP-9.

LRP is a member of the LDL receptor family of endocytic receptors that also includes the LDL receptor, the VLDL receptor, apoE receptor 2, gp330/megalin, and LRP-1b. Deletion of the LRP gene in mice revealed an essential but undefined role for this receptor during development (28). The biological activity of LRP was initially characterized as a clearance receptor for chylomicron remnants (29) and complexes of α₂-macroglobulin with proteinases (22). Subsequent work has revealed that this receptor recognizes several classes of ligands, including serine proteinases (30, 31), proteinase-inhibitor complexes (32, 33), and the matricellular proteins TSP1 (26) and TSP2 (34).

The ability of LRP to bind MMP-9 now reveals that this receptor plays a major role in regulating levels of certain MMP family members as well. Barmina et al. (12) demonstrate that the catabolism of MMP-13 (collagenase-3) was found to involve two receptors: a specific collagenase-3 receptor that acts as a primary binding site on cells, and LRP, which is required for internalization of this enzyme. Yang et al. (35) found an adhesive defect in dermal fibroblasts derived from TSP2-null mice that results from accumulation of MMP-2 in the cell media. Anti-LRP IgG and RAP both inhibited adhesion and increased MMP-2 levels in conditioned media from wild type, but not TSP2-null cells, confirming that LRP is also involved in catabolism of MMP-2 as well (13). Since the clearance of MMP-2 was shown to be TSP2-dependent, it was suggested that clearance of MMP-2-TSP2 complexes by LRP is an important mechanism for the regulation of MMP-2 levels (13). The ability of LRP to modulate three MMPs (MMP-2, MMP-13, and MMP-9) indicates a major role for this receptor in removing excessive extracellular proteolytic activity.

In the case of MMP-9, tight regulation of its activity and levels are likely to be important, since this MMP has important biological properties. Thus, studies using mice deficient in MMP-9 have demonstrated roles for this enzyme in embryonic bone development (5), inflammation (36), and tumor progression and metastasis (37). Interestingly, two recent studies (4, 7) that examine the role of MMP-9 in tumor development implicate secretion of the enzyme by macrophages, which are also rich in LRP. These in vivo models indicate that MMP-9 may function to proteolyze the extracellular matrix, resulting in the release of growth factors such as vascular endothelial growth factor, which are normally thought to be sequestered in this matrix. Additionally, MMP-9 may also function to activate transforming growth factor β (38). Both of these molecules are

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### Fig. 7. Time course of internalization and degradation of 125I-labeled-MMP-9 by LRP(+/+) and LRP(−/−) cells. LRP(+/+) (A and C) and LRP(−/−) mouse embryonic fibroblasts (B and D) were plated into wells (1 × 10⁶ cells/well), and 125I-labeled-MMP-9-TIMP-1 complex (5 nm) was added to each well in the absence (circles) or presence of 1 μM RAP (triangles). At the indicated times, the extent of internalization (A and B) and degradation (C and D) were determined as described under “Experimental Procedures.” In panels C and D, 100 μM chloroquine (squares) was employed to determine cellular-mediated degradation. Each point represents the average of triplicate determinations.
able to promote angiogenesis and tumor progression. Curiously, LRP levels and activity are known to be substantially decreased in tumors (39, 40), which would decrease catabolism of MMP-9, leading to higher levels of this enzyme at the tumor site. Of interest in this regard, Kanca et al. (40) investigated the expression of LRP in invasive and noninvasive subclones derived from tumor cells. They observed a 2–3-fold decrease in LRP activity in invasive subclones compared with noninvasive subclones derived from human prostate PC-3 and DU 145 and melanoma A2058 cells. This study suggested a correlation between invasive phenotype and low LRP expression in different tumor cells.

LRP is known to regulate the levels of another protease system involving urokinase-type plasminogen activator (uPA) and its cellular receptor, the uPA receptor. The ability of LRP to modulate uPA receptor levels (41) and uPA activity (42) has been offered as a mechanistic explanation to account for the role that LRP plays in cellular migration and invasion. For example, in human umbilical vein smooth muscle cells, both RAP (43, 44) and anti-LRP antibodies (43) significantly inhibit their migration. In a different model employing mouse embryonic fibroblasts, Weaver et al. (41) observed that LRP-deficient cells migrated nearly twice as rapidly as the LRP-expressing cells. The migration difference was only noted on culture wells that were pre-coated with serum or vitronectin but not in wells coated with type I collagen or Matrigel. In this study, the contribution of LRP to cellular migration was attributed to its effect on the activity of the uPA/uPA receptor system (41). In light of the findings of the current study that LRP is a receptor for MMP-9 and therefore capable of regulating its extracellular levels, it will be important to reevaluate the mechanism by which LRP impacts cellular migration and invasion.

In summary, the studies presented in this manuscript demonstrate that LRP is a functional receptor for MMP-9 and confirm that LRP is capable of mediating the cellular uptake of at least three MMPs (MMP-2, MMP-13, and MMP-9). These findings implicate a major role for LRP in modulating excessive extracellular protease activity and, by doing so, in regulating remodeling of the extracellular matrix. An investigation of the implications of these interactions in vivo is ongoing.

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The Low Density Lipoprotein Receptor-related Protein Modulates Levels of Matrix Metalloproteinase 9 (MMP-9) by Mediating Its Cellular Catabolism
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