MDC-15 (ADAM-15, metargidin), a membrane-anchored metalloprotease/disintegrin/cysteine-rich protein, is expressed on the surface of a wide range of cells and has an RGD tripeptide in its disintegrin-like domain. MDC-15 is potentially involved in cell-cell interactions through its interaction with integrins. We expressed a recombinant MDC-15 disintegrin-like domain as a fusion protein with glutathione S-transferase (designated D-15) in bacteria and examined its binding function to integrins using mammalian cells expressing different recombinant integrins. We found that D-15 specifically interacts with αvβ3 but not with the other integrins tested (α2β1, α3β1, α4β1, α5β1, α6β1, α6β4, αvβ1, αvβ3, and αvβ5). Mutation of the tripeptide RGD to SGA totally blocked binding of D-15 to αvβ3, suggesting that D-15-αvβ3 interaction is RGD-dependent. When the sequence RPRGD is mutated to NWKRGD, D-15 is recognized by both αIIbβ3 and αvβ3, suggesting that the receptor binding specificity is mediated by the sequence flanking the RGD tripeptide, as in snake venom disintegrins. These results indicate that the disintegrin-like domain of MDC-15 functions as an adhesion molecule and may be involved in αvβ3-mediated cell-cell interactions.

**EXPERIMENTAL PROCEDURES**

Metalloprotease/disintegrin/cysteine-rich proteins (MDCs, also called ADAMs) are membrane-anchored proteins with several domains including a metalloprotease domain, a disintegrin-like domain, a cysteine-rich sequence, an epidermal growth factor-like sequence, a transmembrane domain, and a short cytoplasmic domain (1). The biological functions of MDCs are not clear; however, we do know that fertilins (MDC-1 and MDC-3) interact with integrins in cells and may be involved in αvβ3-mediated cell-cell interactions.

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‡ The abbreviations used are: MDC, metalloprotease/disintegrin/cysteine-rich protein; mAb, monoclonal antibody; GST, glutathione S-transferase; CHO, Chinese hamster ovary; FN, fibronectin; FITC, fluorescent isothiocyanate; wt, wild-type; PBS, phosphate-buffered saline.
MDC (ADAM)-15-Integrin α3β3 Interaction

DH5α by adding 0.1 mM isopropyl-1-thio-β-n-galactopyranoside in culture medium as described previously (29). Protein was extracted from the bacterial suspension by sonication and purified using glutathione-agarose (Sigma) affinity chromatography.

A cDNA fragment of about 1100 nucleotides that encodes the 8–11th type III repeats of rat fibronectin (Ala-1356 to Thr-1720) was amplified by polymerase chain reaction with rat fibronectin cDNA (provided by J. Schwarzbauer, Princeton University, NJ) as a template using 5′-CGGTACCCGCTCTCCCTCCTCCAGC-3′ and 5′-CGGATCCTTAGGT-CAC TGCA TCTGGAAC-3′ as primers. The cDNA fragment was cloned into the BamHI site of a pGEX-2T vector. We expressed the GST fusion protein of rat fibronectin (designated GST-FN) in bacteria and purified it as described above. The GST-FN preparation has a major band with a Mr of about 65,000 (approximately 80% of the total) and some minor protein bands (degradation products) (data not shown), which is consistent with the Mr of 65,773 calculated from the primary structure of GST-FN.

Absorbance at 280 nm was measured to determine the concentration of purified proteins using A280 = 1.356 for D-15, A280 = 1.281 for GST-FN, and A280 = 1.567 for wild-type (wt) GST. The extinction coefficient for each protein was calculated from the amino acid sequence by counting the number of Tyr, Trp, and Cys residues and using the following values for molar extinction. For Tyr, ε280 = 14,000; for Trp, ε280 = 5600; and for Cys, ε280 = 127 for each disulfide bond (2 Cys residues) (21, 22).

Development of Chinese Hamster Ovary (CHO) Cells Expressing Different Human Integrins—We developed CHO cells that express different human integrins. The cDNA constructs were transfected into CHO cells, which express the mouse homologue of the mouse membrane-resistance gene. Those cell lines expressing human α2 (α2-CHO) (23), human α3 (α3-CHO) (24), human α4 (α4-CHO) (25, 26), human α5 (α5-CHO) (26, 27), human αLβ2 (αLβ2-CHO) (28), human αV (αV-CHO), human β3 (β3-CHO), both human αv and β3 (αvβ3-CHO) (29), and human αIIβ3 (αIIβ3-CHO) (30) have been described in the cited references. The cDNA constructs for α6 (α6-CHO) and αβ4 (αβ4-CHO) were co-transfected into CHO cells with a neomycin gene. After selection with G-418, cells stably expressing human integrins were cloned by sorting to obtain high expressing lines.2 The α2-, α3-, α4-, α5-, α6-, and αv-CHO cells homogeneously expressed human α2, α3, α4, α5, and αv/hamster β1 hybrids, respectively. The β3-CHO cells expressed human β3/hamster αv hybrid.

Adhesion Assays—Wells of 96-well Immulon-2 microtiter plates (Dynatech Laboratories, Chantilly, VA) were coated with 100 μl of PBS (10 mM phosphate buffer, 0.15 M NaCl, pH 7.4) containing substrates at a concentration of 20 μg/ml and were incubated overnight at 4 °C. The remaining protein binding sites were blocked by incubating with 1% bovine serum albumin (Calbiochem) for 1 h at room temperature. Cells (104 cells/well) in 100 μl of Dulbecco's modified Eagle's medium were added to the wells and incubated at 37 °C for 1 h. After gently rinsing the wells three times with PBS to remove unbound cells, bound cells were quantified by measuring endogenous phosphatase activity (31).

Affinity Chromatography on D-15—Purified D-15 was absorbed to glutathione-agarose (Sigma) after free glutathione was removed by gel filtration on a PD-10 column (Amersham). Cells were harvested with 3.5 mM EDTA in PBS and washed with PBS. Cells (about 5 × 106) were then surface-labeled with 125I using IODO-GEN (Pierce) (32), washed three times with PBS, and solubilized at 4 °C in 1 ml of 10 mM Tris-HCl buffer, pH 7.4, containing 0.15 M NaCl, 100 mM octylglucoside, 2.5 mM MnCl2, and 1 mM phenylmethylsulfonyl fluoride (Sigma). The insoluble materials were removed by centrifugation at 15,000 × g for 10 min. The supernatant was then incubated with a small amount of underivatized agarose at 4 °C for 15 min to remove nonspecific binding material. The supernatant was incubated at 4 °C for 1 h with 200–500 μl of packed D-15-glutathione-agarose that had been equilibrated with 10 mM Tris-HCl buffer, pH 7.4, containing 0.15 M NaCl, 25 mM octylglucoside, 2.5 mM MnCl2, and 1 mM phenylmethylsulfonyl fluoride (washing buffer). The unbound materials were washed with 20 times the column volume of washing buffer, and the bound materials were eluted with 20 mM EDTA instead of 2.5 mM MnCl2 in washing buffer; then, 0.5-ml fractions were collected. Twenty-μl aliquots from each fraction were analyzed by SDS-polyacrylamide gel electrophoresis using 7% polyacrylamide gel under nonreducing conditions followed by autoradiography.

Binding Recombinant GST Fusion Protein and Fibrinogen to CHO Cells—Recombinant GST fusion protein and fibrinogen (Chromogenix, Stockholm, Sweden) were labeled with fluorescein isothiocyanate (FITC) (33). Cells were incubated with mouse IgG or mAb PT25–2 at 10 μg/ml for 30 min at 4 °C in Dulbecco's modified Eagle's medium. Then, FITC-labeled fibrinogen was added at a final concentration of 100 μg/ml and the mixture was further incubated for 30 min at room temperature. After washing the cells once with PBS to remove unbound labeled protein, bound protein was quantified by flow cytometry in FACScan (Beckton-Dickinson).

Other Methods—Site-directed mutagenesis was carried out using the unique site elimination method (34). The presence of mutations was verified by DNA sequencing.

RESULTS

The Recombinant Disintegrin-like Domain of MDC-15—To prove that MDC-15 mediates cell-cell adhesion through interaction with integrins, we expressed the disintegrin-like domain of MDC-15 (Met-420 to Glu-510), a putative integrin binding site (Fig. 1A), as a fusion protein with GST in bacteria (designated D-15). We obtained soluble D-15 and purified it using affinity chromatography on glutathione-agarose. Fig. 1B shows that the purified D-15 migrates as a monomer with a Mr of 36,000 under nonreducing conditions (lane 1), and the control, wt GST protein, migrates as a monomer with a Mr of approximately 26,000. The sizes of these proteins match the values calculated from the primary structures of these proteins (35,930 and 26,968, respectively). Although the D-15 preparation contained some degradation products, we used it for adhesion and binding assays without further purification.

Adhesion to D-15 of CHO Cells Expressing Different Recom-
binant Integrins—We determined whether D-15 supports integrin-mediated cell adhesion using CHO cells expressing different recombinant integrins. Parent CHO cells express α5β1 as a major integrin but do not express β2 or β3 integrins (29, 35). As shown in Fig. 2A, wt GST (the negative control) does not support adhesion to any of the cells used, but GST-FN (the positive control), which contains the central cell binding domain of rat fibronectin (the 8–11th type III repeats), supported all of the cell lines used. D-15 supported adhesion of β3-CHO cells (that express αvβ3) and αIIbβ3-CHO cells (that express both αIIbβ3 and αvβ3) but not parent CHO cells and cells expressing other exogenous integrins (including α2β1, α3β1, α4β1, α5β1, α6β1, αββ4, αvβ1, and αLβ2). These results indicate that D-15 interacts either with αvβ3 or with both αIIbβ3 and αvβ3. Fig. 2B shows that both D-15 and GST-FN support maximum adhesion of β3-CHO cells to D-15 and GST-FN was determined. Adhesion assays were performed as described above (A). A control mAb KH72 (to integrin α5) did not block adhesion of β3-CHO cells to D-15 (data not shown). LM609 and KH72 were used at X250 dilution of ascites.

FIG. 2. Adhesion of cells expressing different integrins to the recombinant disintegrin-like domain of MDC-15. A, wells of 96-well microtiter plates were coated with 20 μg/ml in PBS) D-15 (black column), GST-FN (white column), or wt GST (shaded column). Cells homogeneously expressing different human integrins were incubated in wells at 37 °C for 1 h. After rinsing the wells to remove unbound cells, bound cells were quantified using endogenous phosphatase activity. GST-FN and purified FN (human or bovine) gave almost identical results. B, adhesion of β3-CHO cells to D-15 and GST-FN was determined as a function of the substrate. The data suggest that the D-15 protein used in the above experiment (20 μg/ml in PBS) is a saturating concentration and that D-15 is comparable to GST-FN in supporting cell adhesion. C, the effect of anti-αvβ3 mAb LM609 on adhesion of β3-CHO cells to D-15 and GST-FN was determined. Adhesion assays were performed as described above (A). A control mAb KH72 (to integrin α5) did not block adhesion of β3-CHO cells to D-15 (data not shown). LM609 and KH72 were used at X250 dilution of ascites.
results indicate that D-15 binds to solubilized αvβ3 but not to solubilized αIIbβ3.

αvβ3-D-15 Interaction Is Dependent on the Tripeptide RGD and the Flanking Sequence in the Putative Integrin Binding Site—To determine whether αvβ3-D-15 interaction is RGD-dependent, we mutated the D-15 RGD sequence to SGA. The mutant protein (designated D-15/SGA) was expressed as a soluble monomer (Fig. 1B), purified using affinity chromatography, and used for adhesion assays. The mutation completely blocked adhesion of β3-CHO cells to the fusion protein (Fig. 4). Increasing the coating concentration of the D-15/SGA mutant did not reverse the effects of the mutation. These results indicate that D-15-αvβ3 interaction is dependent on the RGD tripeptide in the putative integrin binding site.

It has been reported that receptor specificity of snake venom disintegrins is defined by the sequence flanking the RGD tripeptide (36–38). To determine whether receptor specificity is determined by the sequence flanking the RGD tripeptide in D-15, we replaced the sequence RPRGD with NWKRGD, which has been reported to support high affinity binding to αIIbβ3 in a phage display system (39). The mutant, designated D-15/NWK, was also expressed as a soluble monomer in bacteria (Fig. 1B), purified by affinity chromatography, and used for adhesion assays. Fig. 5A shows that D-15/NWK supports adhesion of both β3-CHO and αIIbβ3-CHO cells, suggesting that the mutant interacts with αvβ3; however, it is not clear whether the mutant binds to αIIbβ3 (β3-CHO cells express αvβ3, and αIIbβ3-CHO cells express both αvβ3 and αIIbβ3). To clarify this point, we examined binding of FITC-labeled wt D-15 and D-15/NWK mutant to cells expressing recombinant αIIbβ3. Since CHO cells express an inactive form of αIIbβ3, we activated the integrin using the anti-αIIbβ3 mAb PT25–2 (30). As shown in Fig. 5B, D-15/NWK and fibrinogen (a positive control) bound to αIIbβ3-CHO, but wt D-15 did not. These results indicate that the specificity of the recombinant disintegrin-like domain of MDC-15 is dependent on the sequence flanking the RGD tripeptide in the putative integrin binding site and confirm that wt D-15 binds to αvβ3 but not to αIIbβ3.

Interaction between a Natural Human αvβ3 Heterodimer and D-15—Since we used a recombinant hamster αv/human β3 hybrid integrin on CHO cells to study the receptor specificity of D-15, we determined whether the natural human αvβ3 heterodimer recognize wt and mutant D-15. As shown in Fig. 6, M-21 human melanoma cells expressing αvβ3 adhered to wt D-15 and D-15/NWK but not to D-15/SGA. Adhesion of M-21 cells to wt D-15 and D-15/NWK was completely blocked by LM609. These results indicate that the natural human αvβ3 heterodimer, like a hybrid αvβ3 on CHO cells, specifically recognizes D-15 in an RGD-dependent manner.

FIG. 4. Adhesion of β3-CHO cells to wt and mutant D-15 as a function of coating concentration of substrates. Clonal CHO cells expressing αvβ3 (β3-CHO) were incubated for 1 h at 37°C with wt D-15, D-15/SGA mutant (in which the RGD sequence is mutated to SGA), or wt GST immobilized at different concentrations (up to 20 μg/ml coating concentration). Adhesion was measured as described in the legend to Fig. 2. The data suggest that adhesion to D-15 is dependent on the RGD sequence in the disintegrin-like domain.

FIG. 5. Effects of mutating the sequence flanking the RGD tripeptide in the recombinant disintegrin-like domain of MDC-15. A, β3-CHO cells (that express αvβ3) and αIIbβ3-CHO cells (that express both αIIbβ3 and αvβ3) were incubated with wt D-15 (black column) and D-15/NWK (white column) immobilized to wells of a 96-microtiter plate at 20 μg/ml coating concentrations. Adhesion was measured as described in the legend to Fig. 2. The data suggest that the D-15/NWK mutant (in which the PT2RGD sequence has been mutated to NWKRGG) binds to αvβ3, but it is not clear whether it binds to αIIbβ3. B, parent CHO cells and αIIbβ3-CHO cells were first incubated with either mouse IgG (dotted line) or the activating anti-αIIbβ3 mAb PT25–2 (solid) and then with FITC-labeled protein. FITC-labeled protein bound to cells was determined by flow cytometry. The data suggest that the D-15/NWK mutant and fibrinogen bind to αIIbβ3-CHO cells in the presence of PT25–2, but wt D-15 does not. Fbg, fibrinogen.
makes a disulfide link with another Cys residue. The topology of this region of the disintegrin-like domain is probably very different from that of the snake venom class P II disintegrins in that its loop structure is probably less flexible and its conformation more restricted, with an increase in restriction if the Cys residues flanking the RGD tripeptide are involved in a disulfide linkage (in the snake venom class P II disintegrins, the RGD sequence is positioned within an extended, flexible loop structure where there is only limited conformational restriction of the RGD sequence; see Ref. 42 for review). It is possible, therefore, that using short synthetic peptides (cyclic or linear) derived from the RGD and flanking sequences of the disintegrin-like domain of MDC-15 might provide different receptor specificities than those obtained in this study using recombinant or purified disintegrin-like domains.

The interaction of the disintegrin-like domain of MDC-15 with integrin αβ3 may be related to its biological functions. MDC-15 is not expressed in vivo in normal vessels but is up-regulated in lesions of atherosclerosis, where many macrophages are present (14). MDC-15 on cultured endothelial cells undergoes proteolytic processing (14), which appears to be associated with MDC activation (4, 43). It is possible that activated MDC-15 on endothelial cells interacts with αβ3 on leukocytes during atherogenesis through its exposed disintegrin-like domain. αβ3 has been shown to be involved in the progression of melanoma and the induction of neo-vascularization by tumor cells. αβ3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels (44, 45). It is possible that activated MDC-15 and αβ3 on endothelial cells interact with each other, leading to homotypic aggregation of endothelial cells during angiogenesis. Based on the wide distribution of MDC-15, MDC-15-αβ3 interaction may mediate cell-cell interactions in many other instances (e.g. metastasis).

The snake venom metalloprotease/disintegrin jararhagin is known to block collagen-induced aggregation of platelets (46). It has been proposed that the inhibition of platelet response to collagen by jararhagin is mediated through the binding of jararhagin to the platelet α2b-subunit via the disintegrin domain followed by proteolysis of the β1 subunit with loss of the integrin structure (conformation) necessary for the binding of macromolecular ligands (47). It has been hypothesized that a fragment of MDC-15 containing the metalloprotease and disintegrin-like domains is released from cultured endothelial cells (14). It is possible that the proteolytic fragment of MDC-15 containing the metalloprotease and disintegrin-like domains interacts with αβ3, as in the case of jararhagin and αβ1, and either modifies the function of the integrin or promotes degradation of the matrix proteins surrounding the cells that express αβ3. Therefore, the proposed αβ3-MDC-15 interaction may be of wide biological importance.

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Specific Interaction of the Recombinant Disintegrin-like Domain of MDC-15 (Metargidin, ADAM-15) with Integrin αvβ3

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