Functional Classification of ADAMs Based on a Conserved Motif for Binding to Integrin α9β1

IMPLICATIONS FOR SPERM-EGG BINDING AND OTHER CELL INTERACTIONS*

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ADAMs (a disintegrin and metalloproteases) are members of the metzincin superfAMILY of metalloproteases. Among integrins binding to disintegrin domains of ADAMs are α9β1 and α9β3, and they bind in an RGD-independent and an RGD-dependent manner, respectively. Human ADAM15 is the only ADAM with the RGD motif in the disintegrin domain. Thus, both integrin α9β1 and α9β3 recognize the ADAM15 disintegrin domain. We determined how these integrins recognize the ADAM15 disintegrin domain by mutational analysis. We found that the Arg481 and the Asp-Leu-Pro-Glu-Phe residues (residues 488–492) were critical for α9β1 binding, but the RGD motif (residues 484–486) was not. In contrast, the RGD motif was critical for α9β3 binding, but the other residues flanking the RGD motif were not. As the RX4DLPEF α9β3 recognition motif (residues 481–492) is conserved among ADAMs, except for ADAM10 and 17, we hypothesized that α9β1 may recognize disintegrin domains in all ADAMs except ADAM10 and 17. Indeed we found that α9β1 bound avidly to the disintegrin domains of ADAM1, 2, 3, and 9 but not to the disintegrin domains of ADAM10 and 17. As several ADAMs have been implicated in sperm-oocyte interaction, we tested whether the functional classification of ADAMs, based on specificity for integrin α9β1, applies to sperm-egg binding. We found that the ADAM2 and 15 disintegrin domains bound to oocytes, but the ADAM17 disintegrin domain did not. Furthermore, the ADAM2 and 15 disintegrin domains effectively blocked binding of sperm to oocytes, but the ADAM17 disintegrin domain did not. These results suggest that oocytes and α9β1 have similar binding specificities for ADAMs and that α9β1, or a receptor with similar specificity, may be involved in sperm-egg interaction during fertilization. As α9β1 is a receptor for many ADAM disintegrins and α9β3 and ADAMs are widely expressed, α9β1-ADAM interaction may be of a broad biological importance.

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ADAMs (a disintegrin and metalloproteases) or MDC (metalloprotease/disintegrin/cysteine-rich) proteins are a family of transmembrane glycoproteins of more than 30 members (see www.people.virginia.edu/~jaggin/Table_of_the_ADAMs.html and www.gene.ucl.ac.uk/nomenclature/genefamily/metallo.html). ADAMs have a prodomain, a metalloprotease domain, a disintegrin domain, a cysteine-rich region, an EGF-like domain, a transmembrane domain, and a cytoplasmic tail (1–3). Several ADAMs are involved in crucial biological processes such as fertilization (ADAM1, 2, and 3) (4–6) and muscle cell differentiation (meltrin-α, ADAM12) (7, 8). Most, but not all, ADAMs have a catalytically active metalloprotease domain, which processes several biologically important cell surface proteins including tumor necrosis factor-α (tumor necrosis factor converting enzyme (TACE), ADAM17) (for reviews, see Refs. 9 and 10), Alzheimer protein precursor (ADAM10 and 17) (11, 12), Delta (ADAM10) (9, 13, 14), and heparin-binding EGF (ADAM9) (15).

The ADAM disintegrin domains are homologous to snake venom disintegrins and are potential integrin ligands. Snake venom disintegrins bind to the platelet integrin α9β1 in an RGD-dependent manner. Of all known ADAMs, ADAM15 is the only one that has the RGD motif in the disintegrin domain. Indeed, as we have reported, the ADAM15 disintegrin domain binds to integrin α9β1 in an RGD-dependent manner. However, ADAM15 binds also to α9β1 in an RGD-independent manner (16). Moreover, ADAM15 binds also to α9β1 in an RGD-independent manner (17) and to integrin α9β3 (18). Several laboratories, including ours, have reported that the non-RGD ADAM disintegrin domains interact with several integrins such as ADAM2 and 9 with α9β1 (5, 19), ADAM12 with α9β1 (17), ADAM23 with α9β3 (20), and ADAM28 with α9β1 (21).

At least three ADAMs have been shown to participate in fertilization (ADAM1, 2, and 3) (Refs. 5 and 22, and for review, see Ref. 23). The ADAMs on the sperm surface are processed and lack the pro- and metalloprotease domains; thus the disintegrin domains of ADAMs may be the most important in sperm-egg binding. Recent reports showed that several amino acid residues within the putative integrin-binding loop of the ADAM disintegrin domain are critical for sperm-egg interaction (24–26). The identity of the integrin(s) to which the disintegrin domains bind has not been fully established. As antibodies to integrin α9 were shown to block sperm-egg binding, it has...
been proposed that integrin αβ2 recognizes the ADAM15 disintegrin domain by mutating amino acid residues in the putative integrin-binding site of the disintegrin domain. We found that αβ2 and αβ1 recognize distinct motifs in the disintegrin domain, the RGD (residues 484–486) and the RX_{DL}PEF (residues 481–492) motifs, respectively. The RX_{DL}PEF αβ1 recognition motif is conserved among ADAMs, except for ADAM10 and 17, and we provide evidence that αβ1 recognizes several, perhaps all, ADAM disintegrins with this motif. We also found that oocytes and αβ1 have similar binding specificities for ADAM disintegrin domains and propose that αβ1, or a receptor with similar specificity, may be involved in sperm-oocyte interaction during fertilization. Considering that αβ2 and ADAMs are widely expressed, αβ1-ADAM interactions may have a broad significance in many biological and pathological processes such as fertilization, development, and tissue remodeling.

**MATERIALS AND METHODS**

**Production of Recombinant Disintegrin Domains as Glutathione S-Transferase (GST) Fusion Proteins**—Complementary DNA fragments encoding the disintegrin domain of ADAMs were amplified by polymerase chain reaction and cloned in a pGEX-2T vector (Amersham Biosciences) as described previously (16). The disintegrin domains were derived from mouse ADAM1 (Arg^{499}–Gln^{504}), mouse ADAM2 (Lys–Pro^{179}–Glu^{185}), mouse ADAM3 (Gly^{294}–Glu^{308}), human ADAM5 (Ser^{232}–Glu^{238}–Thr^{243}), mouse ADAM9 (Glu^{447}–Thr^{452}), human ADAM15 (Met^{420}–Glu^{425}–Lys^{426}–Thr^{431}), mouse ADAM15 (Met^{421}–Glu^{426}), and mouse ADAM17 (Ser^{474}–Thr^{480}). GST fusion proteins were produced and purified as described previously (16). Absorbance at 280 nm was measured to determine the concentration of purified proteins, and the amount of proteins was calculated as described previously (16). In some experiments, because GST controls for egg plasma membrane (24) disintegrin domain used for bead coating (see below) were released from the GST by incubating with thrombin (1 unit/mg of protein) for 6 h at room temperature, and the free GST was removed by glutathione-agarose affinity chromatography.

**Chinese Hamster Ovary (CHO) Cell Adhesion Assays**—CHO cells expressing αβ1, human αv, or human αvβ3 (designated β3C, αvβ3, or αvβ3-CHO cells, respectively) have been described elsewhere (17). Adhesion assays were performed as described previously (16). Briefly, wells of 96-well Immulon-2 microtiter plates (DYNATECH Laboratories, Chantilly, VA) were coated with substrates in 100 μl of PBS (10 mM phosphate buffer, 0.15 M NaCl, pH 7.4) overnight at 4 °C. Remaining protein-binding sites were blocked by incubating with 1% bovine serum albumin (BSA) (Calbiochem) for 1 h at room temperature. After washing with PBS, CHO cells (10^5 cells/well) in 100 μl of Dulbecco’s modified Eagle’s medium supplemented with 1% BSA were added to the wells and incubated at 37 °C for 1 h. After unbound cells were removed by rinsing the wells with Dulbecco’s modified Eagle’s medium, bound cells were quantified by measuring endogenous phospahatase activity (29).

**Gamete Preparation for in Vitro Binding Assays**—Three-week-old B6129PF1/J female mice (Jackson Laboratory) were superovulated using standard hormonal treatment. Oocytes were collected 12–13 h after administration of human chorionic gonadotrophin, and cumulus cells were removed by incubation with hyaluronidase in flushing and Holding medium (Specialty Media) for 5 min at 37 °C. The zona pellucida were softened in Flushing and Holding medium containing 10 μg/ml α-chymotrypsin (Sigma) and then removed by passing the eggs through a narrow pipette as described previously (5). Zona pellucida-free eggs were allowed to recover in fertilization medium composed of Human Tubal Fluid medium (Irvin Scientific) supplemented with 5 mg/ml BSA fraction V (Sigma) for 1–2 h at 37 °C under mineral oil in a 5% CO_2 atmosphere.

Sperms were collected from 3–6-month-old B6129F1 male mice (Taconic Farms) by placing the cauda of the epididymis and the vas deferens in 1 ml of fertilization medium under mineral oil. Each tissue was slit open with the edge of an injection needle. Sperms were allowed to swim out for 20 min at 37 °C in an atmosphere of 5% CO_2. Tissues were removed from the medium, and spermatzoa were capacitated for 2–3 h under the same conditions. The sperm concentration was estimated with a hemocytometer.

**Binding of Disintegrin-coated Beads to Eggs**—Fluorescent beads (0.2-μm yellow-green sulfate microspheres, Molecular Probes, Inc.) were coated overnight at 4 °C with purified GST-free disintegrin domains (0.3 mg/ml), washed with PBS, quenched for 1 h at 4 °C in fertilization medium containing 3% BSA, and resuspended by sonication with a water bath sonicator just before use. Zona pellucida-free eggs were incubated in 25-μl drops of 0.1% (w/v) coated beads in 2% BSA fertilization medium under mineral oil for 30 min at 37 °C in a 5% CO_2 atmosphere. Eggs were then washed three times with fertilization medium, fixed in 0.5% glutaraldehyde, and analyzed by confocal microscopy (Bio-Rad, MRC 1024). To confirm that beads were coated with equal amounts of recombinant protein, aliquots of coated beads were boiled in Laemmli SDS sample buffer and subjected to SDS-polyacrylamide gel electrophoresis followed by staining with Coomassie Blue.

**Sperm-Egg Binding Assay**—Zona pellucida-free eggs were preincubated with GST fusion proteins in 100-μl drops of fertilization medium under mineral oil for 20 min at 37 °C in a 5% CO_2 atmosphere. The concentration of GST elution buffer (100 mM Tris, 5 mM reduced glutathione) was adjusted to 10% (v/v) final concentration. Sperm was then added into the drops (2.5 × 10^6 sperm/ml final concentration) and incubated for 1 h. Eggs were washed by removing medium from the dish, adding fresh Flushing and Holding medium containing 3% BSA, and 3% BSA. Finally eggs were fixed by adding glutaraldehyde to the drops to a final concentration of 0.5%. The number of spermatozoa bound to each egg was counted immediately under a microscope. Aliquots of the GST fusion proteins used were subjected to SDS-PAGE under reducing conditions, transferred onto nitrocellulose membrane, and stained with Ponceau S to confirm the amount and the quality of recombinant proteins at the end of the incubation. Control in vitro fertilization was routinely performed at ~50 × 10^6 sperm/ml to ascertain the quality of gametes and to verify that more than 90% of the eggs could be fertilized.

**RESULTS**

**Integrins αβ1 and αβ3 Bind to Distinct Motifs in the Disintegrin Domain of ADAM15**—Human ADAM15 is the only ADAM with the RGD motif within the putative integrin-binding sites of disintegrin domains (Fig. 1a). We have reported that αβ2 and αβ1 recognize the ADAM15 disintegrin domain in an RGD-dependent and an RGD-independent manner, respectively (17). To identify how different integrins recognize the ADAM15 disintegrin domain, we introduced mutations around the RGD motif. The mutant ADAM15 disintegrin domains were synthesized in bacteria as GST fusion proteins. The ability of the mutant disintegrin domains to bind to αβ1 and αβ3 was determined in cell adhesion assays with CHO cells expressing recombinant αβ1 or αβ3 (designated β3C-CHO cells and αv-CHO cells, respectively). CHO cells transfected with expression vector (designated mock-CHO cells) were used as controls. CHO cells express endogenous αβ1, αβ3, and αβ3 (30), but these integrins do not bind to ADAM15 (16). Fig. 1b shows that mutating the RGD motif to SGA completely blocked the binding of αβ3 but had no detectable effect on the binding of αβ1 to the ADAM15 disintegrin domain, consistent with the previous report (17). We found that the R481A, C487A, D488A, L489A, E491, and F492A mutations negatively affected adhesion of αv-CHO cells to the ADAM15 disintegrin domain (Fig. 1, c and d). In contrast, the same mutations flanking the RGD motif did not significantly affect adhesion of β3C-CHO cells to the ADAM15 disintegrin domain (Fig. 1, c and f). Mutating the Asp^{489} and Glu^{491} simultaneously did not further affect the adhesion of αv or β3C-CHO cells to the ADAM15 disintegrin domain (Fig. 1, d and f). Altogether these results show that the αβ2-ADAM15 interaction requires the RGD motif but not the surrounding residues. Thus, αβ2 and αβ3 recognize ADAM15 in distinct manners.
Interestingly, the residues critical for \( \alpha_9 \beta_1 \) binding in the disintegrin domain, including Asp488, have also been identified as critical for sperm-egg binding in ADAM2 and 3 (24–26). The sperm-egg binding studies were performed without reference to any specific integrin, but the results are compatible with \( \alpha_9 \beta_1 \) being the oocyte receptor.

The \( \alpha_9 \beta_1 \) binding motif in ADAM15 is conserved in many ADAMs. The alignment of the sequences of the putative integrin-binding motif in ADAM15 is shown in Fig. 1a. A mutant disintegrin-GST fusion protein was generated in bacteria, and the disintegrin domain was cleaved and purified as described under "Materials and Methods." Adhesion of \( \alpha_9 \) and \( \beta_3 \)-CHO cells was tested as a function of the coating concentration of the disintegrin domain. TM, transmembrane.

**Fig. 1.** Effect of point mutations on binding of cells expressing \( \alpha_9 \beta_1 \) (b–d) or \( \alpha_9 \beta_3 \) (b, e, and f) to the disintegrin domain of human ADAM15. a shows the position of the RGD motif in the putative integrin-binding region in the disintegrin domain of human ADAM15. Mutant disintegrin-GST fusion protein was generated in bacteria, and the disintegrin domain was cleaved and purified as described under "Materials and Methods." Adhesion of \( \alpha_9 \) and \( \beta_3 \)-CHO cells was tested as a function of the coating concentration of the disintegrin domain. TM, transmembrane.
grin-binding regions of several ADAM disintegrin domains is shown in Fig. 2a. The Arg 481, Asp 488, Leu 489, Pro 490, Glu 491, and Phe 492 residues that are critical for H9251/H9252 binding in ADAM15 (designated the RX6DLPEF motif) are conserved among the disintegrin domains of all mammalian ADAMs except for ADAM10, which has the sequence RX5AREGI, and ADAM17, which has the sequence QX7KGVSY, in this region. We thus hypothesized that H9251/H9252 is a common receptor for many, if not all, ADAM disintegrin domains with this motif. To address this hypothesis, we tested the disintegrin domains of several ADAMs for interaction with H9251/H9252 in cell attachment assays (Fig. 2, b and c). We found that H9251/H9252-CHO cells adhered to the disintegrin domains from ADAM1, 2, 3, and 9 as well as 15 used as a positive control. H9251/H9252-CHO cells do not spread very well on these disintegrins. The H9251/H9252-CHO cells did not significantly adhere to the disintegrin domains from ADAM10 or 17. Control mock-transfected CHO cells did not significantly adhere to any of the ADAMs tested. We further found that adhesion of H9251/H9252-CHO cells to the ADAMs was completely blocked by anti-H9251/H9252 monoclonal antibody Y9A2 (data not shown), showing that the adhesion was H9251/H9252-specific. These results indicate that H9251/H9252 may be a common receptor for ADAM disintegrin domains with the RX6DLPEF-like motif.

Since H9251/H9252 has been implicated in ADAM2 and ADAM3 binding (26), we tested whether H9251/H9252 expressed in CHO cells bound to the ADAM2 and 3 disintegrin domains. We found that H9251/H9252 did not mediate adhesion of H9251/H9252-CHO cells to ADAM2 and 3 under the conditions in which H9251/H9252-CHO cells adhered to these ligands (data not shown).

**Interaction of Oocytes with Disintegrin Domains of ADAMs—** Several residues in the putative integrin-binding region of ADAM1, 2, and 3 have been identified as critical for sperm-egg binding (24–26), but it has not been established which receptor(s) may be involved. Since ADAM1, 2, and 3 disintegrins bind avidly to H9251/H9252, we wanted to test whether the binding of sperm to the oocyte may have a specificity similar to disintegrin binding to H9251/H9252. To address this hypothesis, we first studied whether the recombinant ADAM disintegrin domains interact with oocytes. Although ADAM15 and 17 have not been shown to be present on sperm, they were used to test specificity.

We tested whether fluorescent beads coated with disintegrin domains of ADAM2, 15, and 17 bind to zona pellucida-free eggs. As GST alone binds to such eggs (24), the GST portion of the recombinant fusion proteins was cleaved off, and the recombinant GST-free disintegrin domains were purified prior to coating of the beads. Fig. 3 shows that the beads coated with the ADAM15 disintegrin domain bound efficiently to the oocytes.
the binding being largely concentrated to the microvillar region of the egg (Fig. 3b, inset). ADAM2 disintegrin domain-coated beads also bound to the egg microvillar region (Fig. 3c) but to a lesser extent than ADAM15-coated beads. Beads coated with the ADAM17 disintegrin domain (Fig. 3c) and BSA-coated beads (not shown) did not bind to eggs.

We next tested whether recombinant disintegrin domains, used as GST fusion proteins, would inhibit the binding of sperm to oocytes. The disintegrin domains from ADAM2 and ADAM15 inhibited the binding of sperm to mouse eggs in a dose-dependent manner, whereas that from ADAM17 did not affect sperm-egg binding (Fig. 4). The ADAM15 disintegrin domain was a more potent inhibitor than the ADAM2 disintegrin domain, blocking sperm-egg binding completely at 3 μM. Consistent with previous reports, the ADAM2 disintegrin domain at 3 μM inhibited sperm-egg binding to about 50%. Altogether, these results indicate that the binding specificity of sperm for the oocyte is similar to that of ADAM disintegrin for integrin α3β1.

**DISCUSSION**

We have shown here that the conserved RX6DLPEF motif flanking the RGD motif in the ADAM15 disintegrin domain, but not the RGD motif itself, is important for binding of ADAM15 to α3β1. The ADAM disintegrin domains with this motif, e.g., those of ADAM1, 2, 3, 9, 12, and 15, bind avidly to α3β1, but those lacking this motif, ADAM10 and 17, do not. The RX6DLPEF motif is conserved among all ADAM disintegrin domains except ADAM10 and 17 (Fig. 2a), suggesting that α3β1 is a receptor for all ADAMs with this recognition motif and that binding of ADAM disintegrin domains to α3β1, through this motif, may have critical biological functions. ADAM10 and 17 represent a subfamily within the ADAM family with several distinct structural (and functional) features. The disintegrin domains of ADAM10 and 17 contain only 13 of the 15 cysteine residues characteristic of a typical type III snake venom disintegrin domain, indicating that the disintegrin function of ADAM10 and 17 may be different from those of ADAMs with the conserved RX6DLPEF motif as well as from that of snake venom disintegrins and may not bind to any integrin at all.

The RGD motif is not important for α3β1 binding to ADAM15. Thus, α3β1 recognizes ADAM15 in a manner distinct from that of α3β3. Human ADAM15 is the only ADAM with the RGD motif in the disintegrin domain, and the RGD motif is not conserved among ADAM disintegrin domains (even mouse ADAM 15 does not have this motif), suggesting that RGD-dependent interaction of ADAM15 with integrins may have only limited importance. This is in stark contrast to many snake venom disintegrins in which the RGD motif is highly conserved. Snake venom disintegrins bind to α6β1 or α6β3 integrins and block thrombosis and hemostasis (for reviews, see Refs. 2 and 31).

The three-dimensional structures of the snake venom disintegrins echistatin (Protein Data Bank code 2ECH) and kistrin (1KST) are available. The “disintegrin loops” of echistatin and kistrin are protruding loops (approximately 15 Å long and 4 Å wide) with the RGD motif at the tip of the loops. The three-dimensional structure of the ADAM disintegrin is not available. We generated a molecular model of the “disintegrin loop region” of the ADAM15 disintegrin domain based on the echistatin structure (2ECH) using the SWISS-MODEL protein modeling server (Fig. 5) assuming that the ADAM disintegrin and snake venom disintegrins are similar in structure. In this model oppositely charged residues (Arg481 and Glu491, Arg484 and Asp488) and hydrophobic residues (Pro482 and Pro490) are close to each other, stabilizing the loop. This model predicts that the Arg481 and the DLPEF motif in the α3β1 binding motif are located on the opposite side of the loop and that Arg481 and Glu491 are close to each other in space, although they are distant from each other in the primary structure. The RGD motif is present at the tip of the loop. It is likely that the entire loop sequence may be required for synthetic peptides of the ADAM disintegrins to be properly folded and effectively bind to α3β1. α3β1 has been shown to mediate cell adhesion and migration but not cell spreading in vitro. The association of an adhesion receptor, such as α3β1, with a metalloprotease such as an ADAM, would be expected to facilitate cell migration in vivo in that the protease may digest and modify extracellular matrices and other tissue barriers in the immediate area of adhesion.

**FIG. 3.** Binding of disintegrin domains to the egg microvillar region. Fluorescent microspheres were coated with 0.3 mg/ml GST-free recombinant disintegrin domains of mouse ADAM2 (a), ADAM15 (b), and ADAM17 (c) and incubated with zona pellucida-free eggs. Bead binding was analyzed by confocal microscopy after washing. Left panel, phase contrast image. Right panel, projection of fluorescence images in a single plane. Pictures show results from one representative experiment of three. ADAM15- and to a lesser extent ADAM2-coated beads bound to the microvillar region (b, inset) of all eggs, while ADAM17-coated beads did not bind significantly. Scale bar, 100 μm.

**FIG. 4.** The disintegrin domain of ADAM15 inhibits the binding of sperm to the egg plasma membrane. The disintegrin domains produced as GST fusion proteins were tested for their ability to interfere with the in vitro binding of capacitated sperm to zona pellucida-free eggs. Data represent means ± S.E. (n = 18–21) from one representative experiment of three.
The association between αβ1 and ADAM would further be expected to occur between molecules on the same cell, i.e. in cis, as cell-cell interaction is not normally a feature of cell migration. In contrast, it has been proposed that shedding of growth factors occurs with the growth factor and including tumor necrosis factor-α and the Alzheimer precursor protein. Few ADAMs other than ADAM10 and 17 have been tested for capacity to process the proteins they target, including tumor necrosis factor-α and the Alzheimer precursor protein. The digestion may then occur either in cis or in trans depend-
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