

ADAM, a Novel Family of Membrane Proteins Containing A Disintegrin And Metalloprotease Domain: Multipotential Functions in Cell–Cell and Cell–Matrix Interactions

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CELL–cell and cell–matrix adhesion, as well as proteolysis of the extracellular matrix, are vital for normal processes such as tissue morphogenesis and wound healing, as well as for pathologies such as tumor cell invasion and metastasis. A variety of cell surface adhesion proteins and proteases are important players in these events. Families of membrane-anchored cell surface adhesion molecules include cadherins, immunoglobulin superfamily members, selectins, integrins, and syndecans (7). Membrane-anchored cell surface proteases include membrane-type matrix metalloprotease (4) and mepripin (9). In this review we describe the ADAMs, a recently discovered gene family encoding membrane proteins with A Disintegrin And Metalloprotease domain. ADAMs¹ are unique among cell surface proteins in possessing both a potential adhesion domain as well as a potential protease domain. ADAM cDNAs have been found in a wide array of mammalian tissues as well as in lower eukaryotes (Tables I and II). The eleven full-length members described to date encode proteins of 750–800 amino acids which contain pro-, metalloprotease-like, disintegrin-like, cysteine-rich, EGF-like, transmembrane, and cytoplasmic domains (Table I, legend). Although these domains are not similar in sequence to those of other membrane-anchored adhesion molecules or proteases, they are related to domains found in a family of soluble snake venom proteins, the snake venom metalloproteases (SVMPs) (5). SVMPs are encoded by three cDNA classes. N-I encodes pro and metalloprotease domains, N-II encodes pro, metalloprotease, and disintegrin domains, and N-III encodes pro, metalloprotease, disintegrin-like, and cysteine-rich domains. We will refer to the primary translation products as P-I, P-II, and P-III, respectively. In a snake bite victim, snake venom metalloproteases and disintegrins promote hemorrhage. Soluble metalloproteases degrade capillary basement

membranes (5), and soluble disintegrins bind to platelet integrins, thereby inhibiting platelet aggregation (12).

We refer to the cDNAs encoding members of this recently discovered family of cell surface proteins as ADAMs, for proteins containing A Disintegrin And Metalloprotease domain (21). This name reflects the key structural domains of these proteins and alludes to the initial characterization of these domains in the fields of snakes and fertility; the first ADAMs described, fertilin α and β , are expressed in spermatogenic cells (3, 20, 21). Proteins encoded by members of this gene family are known by many names including fertilins (11) and MDCs (15). For ease of comparison, we will refer to the eleven full-length cDNAs as ADAMs 1–11, numbered as in Table I. By analogy to the SVMPs, we expect that some ADAM metalloprotease-like domains degrade extracellular matrix components, and that some or all ADAM disintegrin-like domains are involved in integrin-mediated interactions. In fact, one ADAM, ADAM 10, is a known metalloprotease (see GenBank entry Z21961), and another, fertilin β , has been implicated in integrin-mediated sperm-egg binding (1).

Description of the ADAMs

The eleven unique full-length ADAMs (Table I) have a median identity of 28%. ADAMs 1–6 have been implicated in spermatogenesis, in sperm-egg binding and fusion, and in adhesive and proteolytic reactions in nonreproductive tissues (1–3, 6, 11, 13, 15, 20, 21, and references therein). All six mRNAs are expressed in spermatogenic cells, but at different times. RNAs encoding ADAMs 2 and 3 are found only in testis, but RNAs encoding ADAMs 1, 4, and 5 are present in other tissues as well. The proteins encoded by ADAMs 1 and 2, fertilin α and β , are found as a sperm surface heterodimer. Both proteins are synthesized in the testis as precursors and are proteolytically processed during sperm development. The fertilin α/β heterodimer is implicated in sperm-egg binding and fusion since an antibody against fertilin β inhibits sperm-egg fusion, the α/β complex shares features with certain viral fusion proteins, and peptide analogues of the fertilin β disintegrin domain inhibit sperm-egg binding and fusion. EAPI, the protein encoded by the cDNA we refer to as ADAM 7, is

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1. *Abbreviations used in this paper:* ADAM, A Disintegrin And Metalloprotease; SVMP, snake venom metalloprotease.

Table I. Full-length ADAMs

cDNA	Designation	Organism	Acc.
ADAM 1	PH-30 α	G.P.	Z11719
	Fertilin α	Mouse	U22056
	Fertilin α I*	Monk	X79808
	Fertilin α II*	Monk	X79809
ADAM 2	PH-30 β	G.P.	Z11720
	Fertilin β	Mouse	U22057
	Fertilin β	Monk	X77653
ADAM 3	Cyristestin	Mouse	X64227
	tMDC I	Monk	X76637
ADAM 4	ADAM 4	Mouse	U22058
ADAM 5	ADAM 5	G.P.	U22060
	ADAM 5	Mouse	U22059
	tMDC II	Monk	X77619
ADAM 6	ADAM 6	G.P.	U22061
ADAM 7	EAP I	Monk	X66139
	EAP I	Rat	X66140
ADAM 8	MS2	Mouse	X13335
ADAM 9 [†]	Hum. ORF 09	Hum	D14665
ADAM 10 [§]	MP cDNA	Bov	Z21961
		Rat	Z48444
		Hum	Z48579
ADAM 11	MDC	Hum	D31872

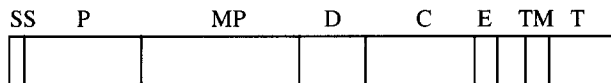
Acc., GenBank accession number; G.P., Guinea pig; Monk, Monkey; Hum, Human; Bov, Bovine.

* Fertilin α I and α II are isoforms of monkey fertilin α .

[†] ADAM 9 contains an insertion in its cysteine-rich domain between nucleotides 1343 and 1489.

[§] ADAM 10 is a distantly related member of the ADAM Family.

SS, signal sequence; P, prodomain; MP, metalloprotease-like domain; D, disintegrin-like domain; C, cysteine-rich domain; E, EGF-like repeat; TM, transmembrane domain; T, cytoplasmic tail.



found on the apical surface of epithelial cells in the caput region of the epididymis (14). This androgen-regulated protein does not appear to be proteolytically processed. MS2, the protein encoded by the cDNA we refer to as ADAM 8, is a macrophage surface antigen (22). Its mRNA is upregulated by macrophage stimulators, and its protein does not appear to be proteolytically processed. ADAM 9 is a cDNA cloned from human myeloblasts. ADAM 10 encodes a bovine brain metalloprotease. ADAM 11 (MDC) was reported as a candidate human breast cancer tumor suppressor. The translation product of the major transcript shares domain organization with the other ADAMs. A minor transcript is reported to encode a protein that terminates in the cysteine-rich domain (8).

Expressed sequence tags representing fragments likely derived from ADAMs have been generated from a variety of tissues and organisms (Table II). Eight cDNA fragments have been amplified from mouse cDNA (18); five likely represent novel ADAMs. Of the twenty-five fragments of human ADAMs which have been amplified, ten appear to be unique and represent four to ten novel human ADAMs. Some of these human sequence tags are expressed in fetal or infant brain and may be important in

cell-cell interactions in the developing nervous system. Others are expressed in skeletal muscle or placenta, tissues which, like sperm and egg, undergo cell-cell fusion. Nine fragments of *C. elegans* ADAMs have been sequenced. Two are pieces of *C. elegans* ADAM 10, six are portions of *C. elegans adm-1* (Podbilewicz, B., personal communication), and one appears to be unique. Thus, there are at least three *C. elegans* ADAMs. Based on considerations of sequence overlap among these sequence tags, our estimate, based on the published cDNAs listed in Tables I and II, is that at present count the ADAM gene family includes minimally between nineteen and twenty-eight unique members.

The Metalloprotease-like Domain

All full-length ADAMs encode a metalloprotease-like domain which is similar in sequence to SVMP zinc-dependent metalloproteases. However, sequence analysis predicts that, unlike the SVMPs, only some ADAMs are proteolytically active (Fig. 1 a). The metalloprotease domains of all SVMPs contain the consensus active site sequence HEXGHNLGXXHD (5). Structural analysis suggests that the three histidines (*underlined*) bind zinc, the glycine (*italicized*) allows a turn, and the glutamic acid (*bold*) is the catalytic residue. The metalloprotease-like domains of ADAMs 1, 8, 9, and 10 contain SVMP-like active site residues (Fig. 1 a), and are likely catalytically active. Indeed, bovine ADAM 10 is a functional metalloprotease (see GenBank entry Z21961). ADAMs 2-7 and 11 encode different sequences at the location of the active site (Fig. 1 a). Thus, although their metalloprotease-like domains are structurally similar to those of the proteolytically active ADAMs, they are not likely active proteases.

The Disintegrin-like Domain

The disintegrin-like domains of some or all ADAMs are likely to be ligands for integrins or other receptors. Soluble snake venom disintegrins formed by proteolytic processing of P-II SVMPs are known integrin ligands of ~50-80 amino acids (12). These disintegrins interact with integrins through their disintegrin loop, a thirteen amino acid motif which contains an integrin-binding sequence (e.g., RGD) at its tip (12). The disintegrin-like domains of ADAMs and P-III SVMPs have a different tripeptide at the corresponding position (Fig. 1 b, *asterisks*), and also contain an additional adjacent cysteine (3, 20, 21).

Although all ADAMs share certain disintegrin loop residues, most notably cysteines, many residues are not conserved (Fig. 1 b). About half of the ADAMs, but all of the SVMP disintegrins, contain a negatively charged residue at the position of the RGD aspartic acid. A negatively charged residue at this position may be critical for function as an integrin ligand. In addition, not all ADAMs have the same number of residues in their disintegrin loops. This diversity of sequences suggests at least three hypotheses. First, different ADAMs may interact with different integrins and/or other receptors. Work with P-II SVMP disintegrins implies that the specificity of integrin binding may depend on the sequence within (12), as well as outside of (16), the disintegrin loop. Second, different ADAMs might

Table II. ADAM Expressed Sequence Tags

Acc.	Organism	Tissue
D37404	<i>C. elegans</i>	Whole animal
U06146	Mouse	Testis
U06147	Mouse	
U06148	Mouse	
U06149	Mouse	
U06151	Mouse	
R52569	Human	Infant brain
R73970	Human	Placenta
X85598	Human	Testis
Z20936	Human	Fetal brain
H12627	Human	Placenta
H26225	Human	Breast
R69500	Human	Breast
T05706	Human	Fetal brain
R53746	Human	Placenta
T54209	Human	Placenta

Acc., GenBank accession number.

Additional sequences from various tissues are portions of previously identified ADAMS. M79534 and D36654: *C. elegans* ADAM10; D34813, D35574, D27380, D37413, D35941, and M89068: *C. elegans adm-1* (Podbilewicz, B., personal communication); U06144: mouse ADAM 1; U06145: mouse ADAM 9; U06150: mouse ADAM 5; T19196, H11999, R31348, T29061, D45617, and R71267: human ADAM 9; T79341, T79769, Z19226, and R72402: human ADAM 10; F08148 and R15038: R52569; T48605 and T49942: R73970; X85599: X85598.

interact with the same or highly related receptors, as all disintegrin-like domains may adopt a similar structure. Finally, only a subset of ADAMs may be functional adhesion molecules.

The disintegrin loops of all ADAMs and P-III SVMPs contain an extra cysteine as compared to those of P-II SVMPs. This cysteine, which provides the disintegrin-like domain with an odd number of cysteines, may be free, or it may form a disulfide bond with a cysteine in the cysteine-rich domain, which also contains an odd number of cysteines (17). Recent evidence suggests that disintegrin-like domains which contain this extra cysteine are functional adhesion molecules. For one, a P-III SVMP inhibits platelet aggregation (17). In addition, since peptide analogues of the guinea pig and mouse fertilin β disintegrin loops prevent interactions between sperm and egg plasma membranes (1, 11), and since the mouse egg integrin $\alpha 6\beta 1$ is involved in sperm-egg binding (1), the disintegrin-like domain of fertilin β likely interacts with egg integrins.

The Potential Fusogenic Domain

In its cysteine-rich domain, guinea pig fertilin α contains a putative fusion peptide, which, like viral fusion peptides, may promote membrane fusion (3, 19). A peptide analogue of the fertilin α fusion peptide interacts with membranes and induces fusion (10). To date, candidate fusion peptides have been identified by their overall hydrophobicity and their ability to model as an α helix with one very hydrophobic face. Monkey and mouse fertilin α , mouse ADAM 5, and ADAMs 9 and 11 also have potential fusion peptides at the sequence location corresponding to that of guinea pig fertilin α . However, many proteins contain amphipathic helices, and extensive mutagenic and biochemical analyses are needed before one can ascribe a definitive role to the potential fusion peptide sequences (19).

The Cytoplasmic Tails

ADAMs have unusual cytoplasmic tails, many rich in proline, serine, glutamic acid, and/or lysine (e.g., Fig. 1 in [21]). None of the tails show obvious sequence similarity to other proteins. Given the roles of the cytoplasmic domains of other plasma membrane proteins, the tails of the ADAMs could be involved in oligomerization or, perhaps, in signaling.

Regulation of ADAM Activities

Regulation of the activity of the ADAMs is likely a complex process. At the primary structure level, only some ADAMs encode potentially active metalloproteases or fusogenic molecules, and it is not yet known if all encode active adhesion proteins. Furthermore, in mouse, more than one gene encodes fertilin α (Cho, C., P. Primakoff, and D. G. Myles, unpublished). Transcription of ADAM mRNA is modulated both positionally and temporally. For example, although some ADAM mRNAs are testis-specific, others are found in a variety of tissues (21). In addition, transcription of ADAMs 1-6 in the testis is developmentally regulated (21). Splicing of ADAM transcripts could also be regulated. Many ADAMs are composed of multiple small exons (8, 22) (Cho, C., P. Primakoff, and D. G. Myles, unpublished), and alternatively spliced forms of ADAM 11 have been proposed (8). The two isoforms of monkey ADAM 1 could be due either to alternative splicing or to multiple genes (13).

ADAMs may also be regulated at the protein level. The only known complex of ADAM proteins is that of the fertilin α/β heterodimer present on sperm (2) (Waters, S., and J. M. White, unpublished). However, it is possible that ADAMs may form other combinations of dimers or oligomers. For example, as ADAMs 1 and 4 show identical patterns of tissue distribution (21), there may be ADAM 1/4 complexes in some cell types. Proteolytic cleavage between domains may regulate certain functions, as many SVMPs (5), and possibly guinea pig fertilin β (2, 20), are proteolyzed at interdomain boundaries. Many ADAMs and SVMPs contain di- or tetrabasic residues between domains (e.g., Fig. 1 in [20, 21]) which could be recognized by subtilisin-like proteases. As in the case of viral fusion proteins, proteolytic processing may be necessary to render fusion competence (19). Guinea pig fertilin α and β are processed during sperm maturation (2), but EAPI (ADAM 7) (14) and MS2 (ADAM 8) (22) have been reported only as unprocessed proteins. By analogy to the SVMP metalloproteases, regulation of ADAM metalloprotease activity may occur by a cysteine-switch mechanism, in which a prodomain cysteine ligands the active site zinc and maintains it in an inactive state (5). ADAMs which encode the metalloprotease active site residues (Fig. 1 a) contain a cysteine in their prodomain which is not present in ADAMs which lack the zinc-liganding histidines. It is not yet known with certainty whether any mammalian ADAMs, like the SVMPs, lack EGF-like, transmembrane, and cytoplasmic domains are therefore secreted proteins (8).

Conclusions

A large, novel family of membrane-spanning cell-cell and cell-matrix interactive proteins, the ADAMs, has been

a) Metalloprotease Active-Site										b) Disintegrin Loop																		
Mus. ADAM 1	H	E	L	G	H	N	L	G	I	Q	H	D	Mus. ADAM 1	C	R	P	A	E	D	V	C	D	L	P	E	Y	C	
GP ADAM 1	H	E	L	G	H	N	L	G	I	R	H	D	GP ADAM 1	C	R	P	S	V	G	P	C	D	L	P	E	Y	C	
Monk. ADAM L1	H	E	L	G	H	N	L	G	I	Q	H	D	Monk. ADAM L1	C	R	P	T	Q	D	E	C	D	L	P	E	Y	C	
Monk. ADAM L2	H	E	L	G	H	N	L	G	I	Q	H	D	Monk. ADAM L2	C	R	P	T	Q	D	E	C	D	L	P	E	Y	C	
Mus. ADAM 2	Q	L	L	S	L	S	M	G	L	A	Y	D	Mus. ADAM 2	C	R	L	A	Q	D	E	C	D	V	T	E	Y	C	
GP ADAM 2	Q	L	L	S	V	S	M	G	L	A	Y	D	GP ADAM 2	C	R	E	S	T	D	E	C	D	L	P	E	Y	C	
Monk. ADAM 2	Q	L	L	S	L	S	M	G	L	P	Y	D	Monk. ADAM 2	C	R	P	S	F	D	E	C	D	L	P	E	Y	C	
Mus. ADAM 3	Q	L	L	G	I	N	L	G	L	A	Y	D	Mus. ADAM 3	C	R	K	S	K	D	Q	C	D	F	P	E	Y	C	
Monk. ADAM 3	Q	L	L	G	I	N	L	G	L	T	Y	D	Monk. ADAM 3	C	R	K	S	I	D	M	C	D	F	P	E	Y	C	
Mus. ADAM 4	H	A	V	G	H	L	L	D	V	S	H	D	Mus. ADAM 4	C	R	D	K	N	G	I	C	D	L	P	E	Y	C	
Mus. ADAM 5	Q	L	L	S	I	G	M	G	L	T	Y	D	Mus. ADAM 5	C	R	K	S	V	D	E	C	D	L	E	Y	C		
GP ADAM 5	Q	L	L	S	L	S	A	G	V	M	Y	D	GP ADAM 5	C	R	K	S	V	D	K	D	C	D	F	D	E	Y	C
Monk. ADAM 5	Q	L	L	G	L	N	L	G	L	T	Y	D	Monk. ADAM 5	C	R	K	S	V	D	E	C	D	F	T	E	Y	C	
GP ADAM 6	H	Q	L	G	R	A	F	G	L	F	Y	D	GP ADAM 6	C	R	P	I	R	N	I	C	D	L	P	E	Y	C	
Rat ADAM 7	H	Q	L	G	H	S	L	G	M	R	H	D	Rat ADAM 7	C	R	P	A	K	N	E	C	D	I	S	E	Y	C	
Monk. ADAM 7	H	Q	L	G	H	N	L	G	M	Q	H	D	Monk. ADAM 7	C	R	P	A	E	D	E	C	D	F	P	E	M	C	
Mus. ADAM 8	H	E	L	G	H	N	L	G	M	S	H	D	Mus. ADAM 8	C	R	L	S	K	D	K	C	D	L	E	F	E	C	
Hum. ADAM 9	H	E	L	G	H	N	L	G	M	N	H	D	Hum. ADAM 9	C	R	G	K	T	S	E	C	D	V	P	E	Y	C	
Bov. ADAM 10	H	E	V	G	H	N	F	G	S	P	H	D	Bov. ADAM 10	C	R	D	D	S	D	C	A	K	E	G	I	C		
Rat ADAM 10	H	E	V	G	H	N	F	G	S	P	H	D	Rat ADAM 10	C	R	D	D	S	D	C	A	K	E	G	I	C		
Hum. ADAM 10	H	E	V	G	H	N	F	G	S	P	H	D	Hum. ADAM 10	C	R	D	D	S	D	C	A	R	E	G	I	C		
Hum. ADAM 11	Q	T	L	G	Q	N	L	G	M	M	W	N	Hum. ADAM 11	C	R	E	A	V	N	E	C	D	I	A	E	T	C	
Ht-a	H	E	L	G	H	N	L	G	M	V	H	D	Ht-a	C	R	P	A	R	S	E	C	D	I	A	E	S	C	

Figure 1. Selected regions of full-length mammalian ADAMs and Ht-a, a P-III SVMP. (a) Residues which align with the consensus SVMP metalloprotease active site sequence, HEXGH-NXGXXHD, are shown. Postulated functional amino acids are shaded. Boxes indicate identical residues conserved between ADAMs which encode the consensus active site sequence. (b) Residues which align with those of the SVMP P-II disintegrin loop are shown. Asterisks indicate the region which corresponds in location to the SVMP P-II integrin-binding RGD tripeptide. Residues are boxed at positions of greater than 50% identity.

identified. This family has clearly expanded beyond its origins in the male reproductive tract, as investigators studying a variety of cellular events have cloned ADAMs. ADAM mRNAs are expressed in a variety of mammalian tissues, and ADAMs have been discovered in the nematode *C. elegans*. In addition to the cDNAs listed in Tables I and II, other members of this gene family have been cloned from monkey (15). Some ADAMs contain a metalloprotease active site consensus sequence and could be active in degradation of cell matrix components. All are potential integrin ligands which could bind integrins or other receptors on cells or in the extracellular matrix. Some may also function in membrane fusion. We expect that the nineteen to twenty-eight ADAMs described here are but a subset of a large, widely expressed, and developmentally regulated family of proteins. We anticipate that, through their proteolytic, adhesive, and/or fusogenic functions, ADAMs will be implicated in a variety of important physiological and pathogenic processes.

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