Review

The ADAM metalloproteinases

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ABSTRACT

The ADAMs (a disintegrin and metalloproteinase) are a fascinating family of transmembrane and secreted proteins with important roles in regulating cell phenotype via their effects on cell adhesion, migration, proteolysis and signalling. Though all ADAMs contain metalloproteinase domains, in humans only 13 of the 21 genes in the family encode functional proteases, indicating that at least for the other eight members, protein–protein interactions are critical aspects of their biological functions. The functional ADAM metalloproteinases are involved in "ectodomain shedding" of diverse growth factors, cytokines, receptors and adhesion molecules. The archetypal activity is shown by ADAM-17 (tumour necrosis factor-α convertase, TACE), which is the principal protease involved in the activation of pro-TNF-α, but whose sheddase functions cover a broad range of cell surface molecules. In particular, ADAM-17 is required for generation of the active forms of Epidermal Growth Factor Receptor (EGFR) ligands, and its function is essential for the development of epithelial tissues. Several other ADAMs have important sheddase functions in particular tissue contexts. Another major family member, ADAM-10, is a principal player in signalling via the Notch and Eph/ephrin pathways. For a growing number of substrates, foremost among them being Notch, cleavage by ADAM sheddases is essential for their subsequent "regulated intramembrane proteolysis" (RIP), which generates cleaved intracellular domains that translocate to the nucleus and regulate gene transcription. Several ADAMs play roles in spermatogenesis and sperm function, potentially by effecting maturation of sperm and their adhesion and migration in the uterus. Other non-catalytic ADAMs function in the CNS via effects on guidance mechanisms. The ADAM family are thus fundamental to many control processes in development and homeostasis, and unsurprisingly they are also linked to pathological states when their functions are dysregulated, including cancer, cardiovascular disease, asthma, Alzheimer's disease. This review will provide an overview of current knowledge of the human ADAMs, discussing their structure, function, regulation and disease involvement.

Contents

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1. Introduction

The ADAMs (a disintegrin and metalloproteinase) are a family of transmembrane and secreted proteins of approximately 750 amino acids in length, with functions in cell adhesion and proteolytic processing of the ectodomains of diverse cell surface receptors and signalling molecules. Their name derives from their modular construction and makes an entertaining allusion to the initial characterization of members of the family in snake venom and as sperm proteins associated with fertility (Wolfsberg et al., 1995). They have been identified in many species, from the nematode *Caenorhabditis elegans* through to the expanded family found in vertebrates (Huxley-Jones et al., 2007). ADAM-like sequences have been found in the fission yeast *Schizosaccharomyces pombe* but are absent from *Saccharomyces cerevisiae* and plants. The biological processes to which ADAMs have been linked functionally include sperm–egg interactions, cell fate determination in the nervous system, cell migration, axon guidance, muscle development and diverse aspects of immunity. In humans, ADAM-17 (otherwise known as tumour necrosis factor-α converting enzyme, TACE) orchestrates immune and inflammatory responses via activation of pro-TNF-α, but is also essential during development for activation of membrane-associated ligands of the epidermal growth factor receptor (EGFR) (Blobel, 2005). Ectodomain shedding of several substrates is coupled to their subsequent cleavage by "regulated intramembrane proteolysis" (RIP) generating nucleus-targeted signals, foremost among these being Notch (Saftig and Hartmann, 2005). ADAM-10 is the principal sheddase involved in Notch signalling and it has also emerged as a key player in fate specification and guidance mechanisms via Eph tyrosine kinases and their ligands, ephrins (Janes et al., 2005). The ADAMs play a potentially protective role in the pathogenesis of Alzheimer's disease by participating in non-amyloidogenic processing of amyloid-β precursor protein (APP). However, in cancer several ADAMs enhance the malignant aspects of tumour behaviour by stimulating cell proliferation via EGFR Receptor activation (Borrell-Pages et al., 2003; Kenny and Bissell, 2007) and by induction of epithelial–mesenchymal transition via cleavage of E-cadherin (Maretzky et al., 2005a). Thus, particular ADAMs are attractive targets for drug development (Moss et al., 2008a), though it is clearly essential to understand the complex repertoire of physiological roles of these important and multifaceted molecules in order to avoid the disappointments that attended clinical use of broad spectrum matrix metalloproteinase inhibitors (Coussens et al., 2002).

This chapter reviews current knowledge of the ADAM metalloproteinases, with a major focus on the human ADAMs and their pathophysiological roles. Attention will be concentrated on the ADAMs proper, and we exclude from this survey detailed discussion of the related and fascinating ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, since there have been several excellent recent reviews of this group, whose roles are fundamentally distinct from those of the ADAMs (Apte, 2004; Jones and Riley, 2005; Porter et al., 2005).

The reader is directed to a number of other valuable sources of information on the ADAMs, including the book "The ADAM Family of Proteases", edited by Hooper and Lendeckel (2005, Springer, The Netherlands) (White et al., 2005), and important recent reviews (Arribas et al., 2006; Blobel, 2005; Garton et al., 2006; Mochizuki and Okada, 2007; Rocks et al., 2008; Seals and Courtneidge, 2003; Tousseyn et al., 2006; White, 2003; Murphy et al., 2008).

1.1. Overview of the ADAM family: modular proteins with proteolytic and non-proteolytic functions

The ADAMs belong to the M12B adamalysin protease subfamily in the MEROPS classification (http://merops.sanger.ac.uk/; Rawlings et al., 2008), which includes the closely related class PIII snake venom reprolysins and the ADAMTSs. They have also in the past been referred to as the MDC (metalloproteinase disintegrin cysteine-rich) family (Blobel, 1997), but the ADAM nomenclature is now established in common use, though their MDC alternative names are also provided for the examples listed in Table 1. The typical modular layout of the ADAMs is shown in Fig. 1, which also contrasts their structure with those of their closest relatives.

The ADAMs, matrix metalloproteinases (MMPs), ADAMTSs and snake venom metalloproteinases (SVMPs) all possess signal sequences at their N-termini, which direct the proteins to the secretory pathway. This is followed in all by a pro-domain,

Table 1
The human ADAMs

Gene	Other aliases	Accession number	Location	Proteolytic activity?	Present in *Mus musculus*	Inhibition by TIMPs	Major sites of expression in human tissues
ADAM1	Fertilin alpha, FTNAP, Ftna, PH-30a	NG_001216	12q24.13	Pseudogene	Yes (NM_172126, NM_172125)	–	–
ADAM2	Fertilin beta, CRYN1, CRYN2, FTNB, PH-30b, PH30	NM_001464	8p11.2	No	Yes (NM_009618)	No study	Testis
ADAM3	CYRN1, tMDCI	NR_001569	8p21-p12	Pseudogene	Yes (NM_009619)	–	–
ADAM5	TMDCII	NR_001448	8p11.23	Pseudogene	Yes (NM_007401)	–	–
ADAM6	t MDCIV; C14orf96	NR_002224	14q32.33	Probably pseudogene	Yes (NM_174885)	–	–
ADAM7	EAPI, GP-83	NM_003817	8p21.2	No	Yes (NM_007402)	–	Testis, erythrocytes
ADAM8	CD156, MGC134985, MS2	NM_001109	10q26.3	Yes	Yes (NM_007403)	None	Bone marrow lymphoid/ myeloid cells, lymphatic system, haematopoietic stem cells, peripheral blood lymphoid/myeloid cells
ADAM9	KIAA0021, MCMP, MDC9, Mltng, meltrin gamma	v1 NM_003816 v2 NM_001005845	8p11.23	Yes	Yes (NM_007404)	None	Mesenchymal stem cells, placenta, pancreas, adult stem cells, adipose tissue
ADAM10	CD156c, HsT18717, MADM, kuz	NM_001110	15q22	Yes	Yes (NM_007399)	TIMP-1 TIMP-3	Mesenchymal stem cells, placenta, blood myeloid cells, bladder, bone marrow myeloid cells
ADAM11	MDC	NM_002390	17q21.3	No	Yes (NM_009613, NM_001110778)	–	Erythrocytes, central and peripheral nervous systems, liver and biliary system, salivary gland
ADAM12	RP11-295J3.5, MCMP, MCMPMltna, MLTN, MLTNA, Meltrin alpha	v1 NM_003474 v2 NM_021641	10q26.3	Yes	Yes (NM_007400)	TIMP-2 TIMP-3	Placenta, mesenchymal stem cells, adult stem cells
ADAM15	MDC15, Metargidin	v1 NM_207191 v2 NM_003815 v3 NM_207194 v4 NM_207195 v5 NM_207196 v6 NM_207197 v6a AB209157 v6b AY560599 v7a AY560600 v7b AY560601 v8 AY576417	1q21.3	Yes	Yes (NM_001037722, NM_009614)	No study	Widespread (highest in mesenchymal stem cells and urogenital system)

ADAM17	CD156b, MGC71942, TACE, cSVP	NM_003183	2p25	Yes	Yes (NM_009615)	TIMP-3	Widespread (highest in lymphatic)
ADAM18	ADAM27, MGC41836, MGC88272, tMDCIII	NM_014237	8p11.22	No	Yes (NM_010084)	–	Testis, erythrocytes, bone marrow, pancreas)
ADAM19	FKSG34, MADDAM, MLTNB	v1 NM_023038 v2 NM_033274	5q32–q33	Yes	Yes (NM_009616)	None	Widespread (highest in placenta, mesenchymal stem cells, lymphatic system, heart)
ADAM20		NM_003814	14q24.1	Yes	No	No study	Testis, erythrocytes, bone marrow
ADAM21	ADAM31, MGC125389	NM_003813	14q24.1	Yes	Yes (NM_020330)	No study	Testis, erythrocytes, central and peripheral nervous systems
ADAM 22	MDC2, MGC149832	v1 NM_021723 v2 NM_021722 v3 NM_016351 v4 NM_004194 v5 NM_021721	7q21	No	Yes (NM_001007220, NM_001007221, NM_001098225)	–	Peripheral and central nervous systems
ADAM23	MDC3	NM_003812	2q33	No	Yes (NM_011780)		Peripheral and central nervous systems, heart
ADAM28	ADAM23, MDC-Lm, MDC-Ls, MDCL, eMDC	v1 NM_014265 v3 NM_021777	8p21.2	Yes	Yes (NM_010082, NM_183366)	TIMP-3 TIMP-4	Haematopoietic stem cells, pancreas, gastrointestinal system, bone marrow myeloid cells, lymphatic system, respiratory system, bladder
ADAM29	svph1	NM_014269	4q34	No	Yes (NM_175939)	–	Testis
ADAM30	svph4	NM_021794	1p13-p11	Yes	Yes (NM_027665)	No study	Testis
ADAM32	FLJ26299, FLJ29004	NM_145004	8p11.23	No	Yes (NM_153397)	–	Blood lymphoid cells
ADAM33	RP5-964F7.2, DJ964F7.1, DKFZp434K0521, FLJ35308, FLJ36751, MGC149823, MGC71889	v1 NM_025220 v2 NM_153202	20p13	Yes	Yes (NM_033615)	TIMP-3 TIMP-4	Uterus, other urogenital system, respiratory system, gastrointestinal system, tongue, endocrine system
ADAMDEC1 (ADAM-like, decysin 1)	M12.219	NM_014479	8p21.2	Yes	Yes (NM_021475)	No study	Lymphatic system, bladder, gastrointestinal system

Records for ADAM4 and ADAM25 have been discontinued by NCBI.

Also present in Mus musculus Adam4 (NM_009620), Adam4b (EG214321 – predicted gene), Adam24 (NM_010086), Adam25 (NM_011781), Adam26 (NM_010085), Adam31 (AF251559), Adam34 (NM_145745), Adam36 (BN000114), Adam37 (BN000115), Adam38 (NM_001009548), Adam39 (NM_001025380).
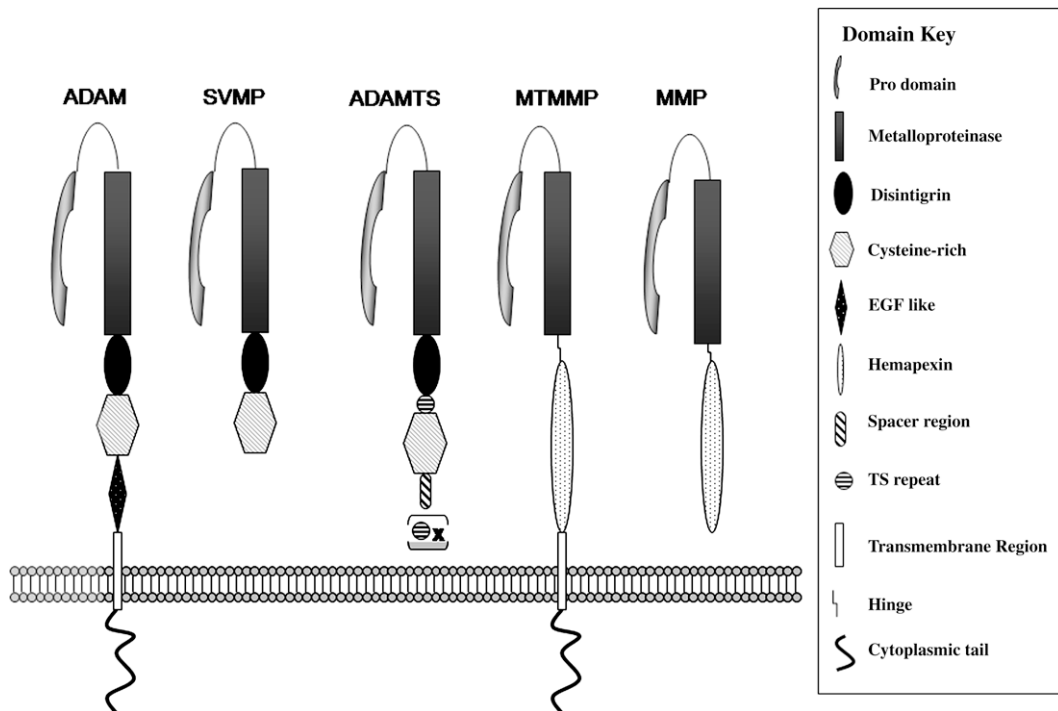
Fig. 1. Comparison of the domain structures of the ADAM, MMP, SVMP and ADAMTS metalloproteinases. The domain organization of the proteases is compared, and their membrane or secreted location is indicated. Domains are not drawn to scale.

which acts as an intramolecular chaperone to ensure correct protein folding (Roghani et al., 1999) and functions via a cysteine-switch mechanism to maintain enzyme latency. The pro-domain is generally removed intracellularly during transit through the Golgi system by pro-protein convertases (Lum et al., 1998), though for ADAM-8 and -28 there is evidence that this can involve an autocatalytic mechanism (Howard et al., 2000; Schlomann et al., 2002). The metalloproteinase (MP) domain is immediately C-terminal to the pro-domain, and at this point the structural organization begins to diverge dramatically in different MP families. In the ADAMs, ADAMTSs and SVMPs, the MP domain is followed by a disintegrin-like domain, so-called for the ability of small proteins found in hemorrhagic snake venoms to bind platelet integrin αIIbβIIIa thereby blocking platelet aggregation (Niewiarowski et al., 1994). The disintegrin domain contains a 14-amino acid stretch known as the "disintegrin loop" that is implicated in interactions between ADAMs and integrins (White, 2003). [An exception to this is ADAMDEC-1, which is unusual in being truncated part way through the disintegrin domain through the introduction of a stop codon (Bates et al., 2002)]. The disintegrin domain is followed in the ADAMs by the cysteine-rich domain, which is also seen in the SVMPs and ADAMTSs, though in the latter the first of a series of C-terminal thrombospondin-like repeats is interposed (Porter et al., 2005). Most ADAMs then have an EGF-like domain [though this is absent in ADAM-10 and -17 (Janes et al., 2005)], adjacent to a membrane-spanning region, which is followed by a cytoplasmic tail that varies extensively in length and sequence between different ADAM family members. ADAM cytoplasmic domains have been shown to interact with proteins involved in intracellular signalling, trafficking and cytoarchitecture, and several display proline-rich motifs that can act as ligands for SH3 (Src homology region-3)-domain containing proteins, which will be discussed more extensively in Section 2.5.

Several *ADAM* genes display alternatively spliced transcripts that give rise to variant proteins. In particular, *ADAM12* encodes both a long form (ADAM-12L) that has the typical transmembrane modular structure, and also ADAM-12S which is a secreted form that lacks the transmembrane and cytoplasmic domains (Wewer et al., 2006). A similar situation occurs for *ADAM9* (Mazzocca et al., 2005), *ADAM11* (Katagiri et al., 1995) and *ADAM28* (Fourie et al., 2003; Roberts et al., 1999), while *ADAM15* gives rise to as many as 13 different splice variants, all of which affect exons encoding the cytoplasmic domain (Kleino et al., 2007). The pattern of splice variants of *ADAM15* is conserved between mouse and humans (Kleino et al., 2007), and this also applies for *ADAM22,* where again the alternative splicing affects only the cytoplasmic domain (Sagane et al., 2005). Alternative splicing of *ADAM19* gives rise to a short form that lacks the pro-, metalloproteinase and disintegrin domains, and is found exclusively intracellularly (Kurisaki et al., 2002).

Thirty-eight members of the ADAM family have been catalogued from various species (http://people.virginia.edu/~jw7g/Table_of_the_ADAMs.html; http://www.uniovi.es/degradome/tables/table_met.htm). There is considerable variation in the *ADAM* genes between rodents and humans (Puente and Lopez-Otin, 2004; Puente et al., 2003). The human genome contains 25 *ADAM* genes of which 4 appear to be pseudogenes (see Table 1). In contrast, mouse and rat have 37 and 34 *Adam* genes,

Table 2
ADAM substrates

ADAM	Substrate	References
ADAM-8	ADAM8 (pro-domain cleavage)	Schlomann et al. (2002))
	CD23	Fourie et al. (2003) and Moss and Rasmussen (2007a)
	CD30-Ligand (CD153)	Fourie et al. (2003) and Moss and Rasmussen (2007a)
	CHL-1	Naus et al. (2004)
	L-selectin	Gomez-Gaviro et al. (2007)
ADAM-9	Pro-HB-EGF	Izumi et al. (1998)
	Amyloid precursor protein (APP)	Koike et al. (1999)
	Kit-ligand	Koike et al. (1999)
	p75 neurotrophin receptor	Koike et al. (1999)
	Insulin B chain	Roghani et al. (1999)
	Delta-like ligand-1 (Dll1)	Dyczynska et al. (2007)
	IGFBP-5	Mohan et al. (2002)
	ADAM-10	Cisse et al. (2005)
	Collagen XVII	Franzke et al. (2004)
	Laminin	Mazzocca et al. (2005)
	Pro-EGF	Peduto et al. (2005)
	FGF Receptor 2 iiib	Peduto et al. (2005)
ADAM-10	Notch	Pan and Rubin (1997)
	Amyloid precursor protein (APP)	Slack et al. (2001), Allinson et al. (2003), and Postina et al. (2004)
	N-cadherin	Reiss et al. (2005)
	E-cadherin	Maretzky et al. (2005a)
	Proto-cadherin-γ C3 and B4	Reiss et al. (2006)
	VE-cadherin	Schulz et al. (2008)
	CD23	Moss and Rasmussen (2007a), Weskamp et al. (2006), and Lemieux et al. (2007)
	Delta-like ligand-1 (Dll1)	Qi et al. (1999) and Six et al. (2003)
	Pro-EGF	Sahin et al. (2004)
	Pro-betacellulin	Sahin et al. (2004)
	Ephrin A5	Janes et al. (2005)
	c-Met	Kopitz et al. (2007)
	Fas-ligand	Kirkin et al. (2007) and Schulte et al. (2007a)
	HER2/neu (ERBB2)	Liu et al. (2006)
	CD30	Eichenauer et al. (2007)
	CD44	Nagano et al. (2004)
	Collagen XVII	Franzke et al. (2004)
	TRANCE/RANKL	Hikita et al. (2006)
	L1-CAM	Mechtersheimer et al. (2001), Maretzky et al. (2005b) and Gavert et al. (2007)
	CX3CL1/Fractalkine	Schulte et al. (2007b) and Hundhausen et al. (2007)
	CXCL16	Scholz et al. (2007) and Schulte et al. (2007b)
	LAG-3	Li et al. (2007)
	Desmoglein-2	Bech-Serra et al. (2006)
	Klotho	Chen et al. (2007)
	Cellular prion protein PrP^c	Cisse et al. (2005)
	Thyrotopin Receptor (TSHR)	Kaczur et al. (2007)
	Axl	Budagian et al. (2005)
ADAM-12	Delta-like ligand-1 (Dll1)	Dyczynska et al. (2007)
	Gelatin	Roy et al. (2004)
	Type IV collagen	Roy et al. (2004)
	Fibronectin	Roy et al. (2004)
	IGF-BP-3, IGF-BP-5	Loechel et al. (2000) and Okada et al., 2008
	HB-EGF	Asakura et al. (2002)
	S-Carboxymethylated transferrin	Jacobsen et al. (2008)
ADAM-15	CD23	Fourie et al. (2003)
	Pro-amphiregulin	Schafer et al. (2004a)
	Pro-HB-EGF	Hart et al. (2005)
	E-cadherin	Najy et al. (2008a)
ADAM-17	Pro-TNF-α	Black et al. (1997) and Moss et al. (1997)
	Pro-TGF-α	Althoff et al. (2001), Borrell-Pages et al. (2003), Kenny and Bissell (2007), Peschon et al. (1998), and Sahin et al. (2004)
	Pro-Amphiregulin	Gschwind et al. (2003) and Sahin et al. (2004)
	Pro-HB-EGF	Sahin et al. (2004) and Schafer et al. (2004a)
	Pro-epiregulin	Sahin et al. (2004)
	Neuregulin	Yokozeki et al. (2007)
	Epigen	Sahin and Blobel (2007)
	P75 TNF Receptor	Peschon et al. (1998) and Reddy et al. (2000)
	P55 TNF Receptor	Reddy et al. (2000)
	IL-1 Receptor-II	Reddy et al. (2000)
	Amyloid precursor protein (APP)	Buxbaum et al. (1998) and Slack et al. (2001)

Table 2 (continued)

ADAM	Substrate	References
	Delta-like ligand-1 (Dll1)	Dyczynska et al. (2007)
	Notch1	Brou et al. (2000)
	TRANCE/RANKL	Lum et al. (1999) and Mohan et al. (2002)
	Kit ligand-1 and -2	Kawaguchi et al. (2007)
	L-selectin	Peschon et al. (1998)
	Neurotrophin receptor p75NTR	Weskamp et al. (2004)
	TrkA neurotrophin receptor	Diaz-Rodriguez et al. (2002)
	ErbB4/HER4	Maatta et al. (2006) and Rio et al. (2000)
	CD44	Nagano et al. (2004)
	CD40	Contin et al. (2003)
	CD30	Hansen et al. (2004)
	Growth hormone receptor	Schantl et al. (2004) and Zhang et al. (2004)
	L1-CAM	Maretzky et al. (2005b)
	VCAM-1	Garton et al. (2003) and Singh et al. (2005)
	IL6 Receptor	Chalaris et al. (2007)
	Cellular prion protein (PrPᶜ)	Alfa Cisse et al. (2007)
	CX3CL1/Fractalkine	Schulte et al. (2007b)
	LAG-3	Li et al. (2007)
	Colony stimulating factor-1 CSF-1	Horiuchi et al. (2007a)
	Nectin-4	Fabre-Lafay et al. (2005)
	ALCAM	Bech-Serra et al. (2006)
	Desmoglein-2	Bech-Serra et al. (2006)
	Klotho	Chen et al. (2007)
	Vacuolar protein sorting Vps10-p	Hermey et al. (2006)
	N-CAM	Kalus et al. (2006)
	PTP-LAR	Ruhe et al. (2006)
	Collagen XVII	Franzke et al. (2004)
	Pre-adipocyte factor-1 (Pref-1)	Wang and Sul (2006)
	ACE2/ SARS-CoV Receptor	Haga et al. (2008), Lambert et al. (2008) and Lambert et al. (2005)
	Semaphorin 4D	Zhu et al. (2007)
	NPR (neuronal pentraxin receptor)	Cho et al. (2008)
	MICA/MICB (MHC-class I-related chain A/B	Boutet et al. (submitted for publication)
ADAM-19	Neuregulin	Yokozeki et al. (2007)
	TRANCE/RANKL	Chesneau et al. (2003)
	Pro-TNF-α	Zheng et al. (2004)
	ADAM-19 (in Cys-rich domain)	Kang et al. (2002)
ADAM-28	CD23	Fourie et al. (2003)
	IGFBP-3	Mitsui et al. (2006) and Mochizuki et al. (2004)
ADAM-33	Kit-ligand-1	Zou et al. (2004)
	CD23	Meng et al. (2007)

many of which are specifically expressed in testis (Puente and Lopez-Otin, 2004). Of the 21 presumed functional human *ADAMs*, 13 encode proteins that possess the characteristic reprolysin-type active site (HEXGHXXGXXHD) in the metalloproteinase domain followed downstream by the "Met turn" that is the signature of the Metzincin enzymes (Bode et al., 1993), indicating functional proteolytic capability. Although it is not included in other surveys of the ADAMs, we have chosen to include ADAMDEC-1 (also known as decysin), since we feel it has a legitimate claim for ADAM status. ADAMDEC-1 has the third of the histidines in the Zn-binding site replaced by an aspartate residue (HELGHVLGMP**D**V), a feature that is also seen in M6 and M7 family metzincins that are active metalloproteinases, and thus ADAMDEC-1 is likely also to be an active endopeptidase (Bates et al., 2002). The catalytically active human ADAM proteases are thus: ADAMDEC-1, ADAM-8, -9, 10, -12, -15, -17, -19, -20, -21, -28, -30 and -33. In contrast, ADAM-2, -7, -11, -18, -22, -23, -29 and -32 lack one or more critical features in the Zn-binding active site, suggesting that the metalloproteinase domain in these proteins may play roles in protein folding and protein–protein interactions rather than catalysis. However, based on studies with gene knockout mice which will be discussed in Section 1.3, it is clear that there are important developmental roles for individual ADAMs of both the active and proteolytically inactive groupings. Table 2 provides an overview of the substrates that have been identified for the catalytically active ADAMs, many of which will be considered in more detail when ADAM functions are explored in Section 3.

In humans and other vertebrates, *ADAM2, 7, 18, 20, 21, 29* and *30* are expressed primarily in the testis, consistent with their involvement in spermatogenesis and sperm function (Fig. 2). Of the remaining genes, *ADAM9, 10, 12, 15, 17* and *19* are expressed quite broadly in somatic tissues, while *ADAM28* and *33* show a more restricted tissue range and *ADAM8* is primarily active in hematopoietic cell types. Table 1 highlights the profound differences in tissue expression of the family members, based on In Silico Transcriptomic Datamining studies (K. Iljin and O. Kallioniemi, personal communication).

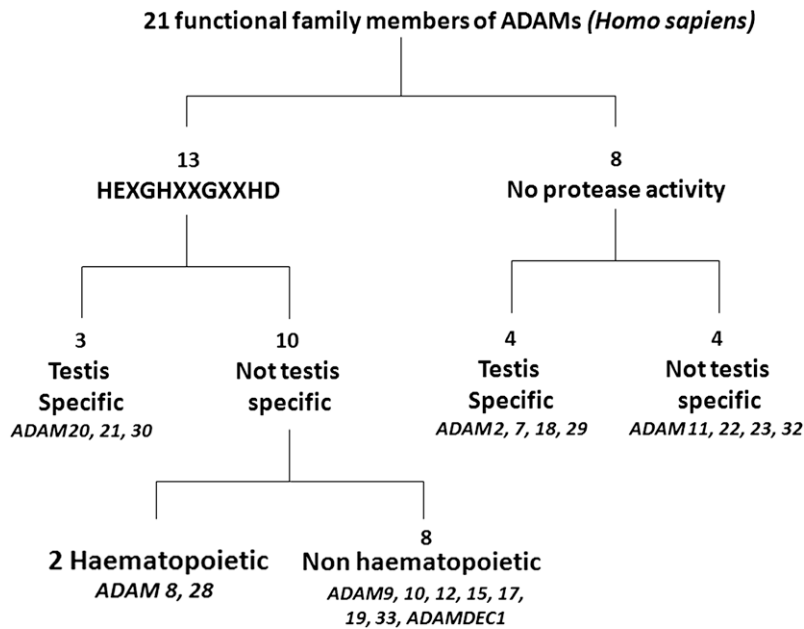## 21 functional family members of ADAMs *(Homo sapiens)*

Fig. 2. The 21 members of the human ADAM family, in relation to their metalloproteinase activity and sites of expression.

Noteworthy is the expression of *ADAM11*, *ADAM22* and *ADAM23* predominantly in the central and peripheral nervous systems, and *ADAM12* in placenta and mesenchymal or adult stem cell populations.

For the MMPs, a major level of control occurs via their interaction with specific tissue inhibitors of metalloproteinases (TIMPs), of which there are four in mammals (Baker et al., 2002). TIMPs inhibit MMPs by forming 1:1 tight, non-covalent complexes with active enzymes. With a few notable exceptions, TIMPs are broadly interchangeable in their ability to inhibit the MMPs, an exception being TIMP-1, which is inactive against MT1-MMP/MMP-14 and certain other MMPs (Baker et al., 2002). However, the TIMPs show much greater specificity towards the ADAM proteinases (see Table 1). In general, TIMP-3 is a functional inhibitor of the majority of proteolytically active ADAMs, and individual ADAMs display characteristic susceptibilities to the other TIMPs. The catalytic domain of ADAM-10 is inhibited by both TIMP-1 and TIMP-3 (Amour et al., 2000), whereas ADAM-8, -9 and -19 defy any pattern and are insensitive to TIMP inhibition (Amour et al., 2002; Chesneau et al., 2003). In contrast, ADAM-12S has recently been shown to be inhibited by TIMP-3 and TIMP-2 in preference to TIMP-1 (Jacobsen et al., 2008). ADAM-33 is moderately inhibited by TIMP-3 and TIMP-4, but weakly by TIMP-2 and is insensitive to TIMP-1 (Zou et al., 2004). These highly divergent characteristics reflect the importance of not only the MP domain in binding of TIMPs to active metalloproteinases, and this aspect will be discussed further in a following section. In addition to TIMPs, REversion-inducing Cysteine-rich protein with Kazal motifs (RECK), an unrelated protein that also displays MMP inhibitory capability (Baker et al., 2002) has been shown to be a physiological inhibitor of ADAM-10 in development of the nervous system (Muraguchi et al., 2007).

ADAM activity is also regulated by diverse stimuli. We will discuss this in more depth in Section 3.2 on ectodomain shedding, but suffice here to point out that ADAM-mediated shedding is both constitutive and inducible by agents such as G-protein coupled receptor (GPCR) activators, PKC activators, Ca ionophores, and other experimental or natural stimuli. The mechanisms are poorly understood, though involvement of the cytoplasmic domain is an obvious possibility. Phosphorylation or other modifications of the cytoplasmic domain may influence the interactions of ADAMs with adapter or trafficking proteins that direct substrate interactions or location in membrane sub-domains or other specific cellular locations. However, the cytoplasmic domain may be necessary only for particular functions, since the membrane localization and stimulus-induced shedding elicited by ADAM-17 and -19 has been shown, at least in some model systems, to occur in the absence of their cytoplasmic domains, and is dependent only on a membrane-spanning region (Reddy et al., 2000; Wakatsuki et al., 2004). Following stimulation, ADAM-17 rapidly disappears from the cell surface via endocytosis (Doedens and Black, 2000) which represents another potential control point for regulation of ADAM function.

1.2. Evolution of the ADAM genes

Insights into the evolutionary origins of human *ADAM* genes is emerging from comparison with other sequenced genomes, including rodents (Puente and Lopez-Otin, 2004), the primitive chordate *Ciona intestinalis* and the zebrafish *Danio rerio* (Huxley-Jones et al., 2007), and sea urchin (Angerer et al., 2006). The *C. intestinalis* genome is particularly insightful because *Ciona* is one of the closest invertebrate relatives of vertebrates. Its genome contains 4 *ADAM* genes: ADAMa and ADAMb are

orthologous to *ADAM17* and *ADAM10*, respectively, and define an A sub-group, while ADAMc1 and c2 genes define a separate B sub-group that corresponds to human *ADAM2, 7–9, 11, 12, 15, 18, 19, 22, 23, 28, 32, and 33*. The remaining human *ADAMs* are specific to the vertebrate lineage, though as the authors point out, it is possible that invertebrate orthologs of these genes may have been lost during evolution. Like *Ciona*, *Drosophila melanogaster* contains orthologs of *ADAM17* and *ADAM10*. Indeed there are two *Drosophila* genes that are highly similar to *ADAM10* – kuzbanian (kuz) and kul (Huxley-Jones et al., 2007). *Drosophila* also has two genes corresponding to the B subgroup seen in *Ciona*. The sea urchin *Strongylocentrus purpuratus* contains only 2 *ADAM* genes, and does not seem to have an ortholog of *ADAM10*, though an ortholog exists in the nematode *Caenorhabditis elegans* (Angerer et al., 2006). The two sea urchin genes appear to be most closely related to *ADAM17* and one of the B subgroup *Ciona* ADAMs (described as *ADAM12/15/19/33*-like) (Angerer et al., 2006). The absence of an *ADAM10* ortholog in sea urchin is perhaps surprising, given the central role of this protease in signalling via the Notch pathway.

Based on the sequence of the metalloproteinase domain, the human *ADAMs* can be arranged in the family tree shown in Fig. 3, which emphasizes the separation of *ADAM10* and *17* from the other ADAMs, and draws attention to particular sub-groups such as a proteolytically active cluster encompassing *ADAMDEC1, ADAM8, 12, 15, 19, 28* and *33*. Some of these relationships are borne out by chromosomal locations: for instance, *ADAMDEC1, ADAM7* and *ADAM28* are clustered together on chromosome 8p12, suggesting a common origin from an ancestral gene by duplication (Bates et al., 2002). Other sub-groups of non-proteolytically active ADAMs are also apparent, such as the *ADAM11, 22, 23* set and *ADAM2, 18* and *32*. A broadly similar subgroup analysis has been reported recently based on comparison of the full protein coding sequences of the ADAMs, and also on gene exon–intron organization (Kleino et al., 2007).

Further discussion on the evolution of *ADAMs* can be found in Section 3.1 on the role of ADAMs in fertility. Comparative analysis of the sequences of mammalian *ADAM* genes has revealed that the testis-specific genes are evolving at the fastest rate, with positive selection (as opposed to purifying selection) of codons in the disintegrin/cysteine-rich domains, which
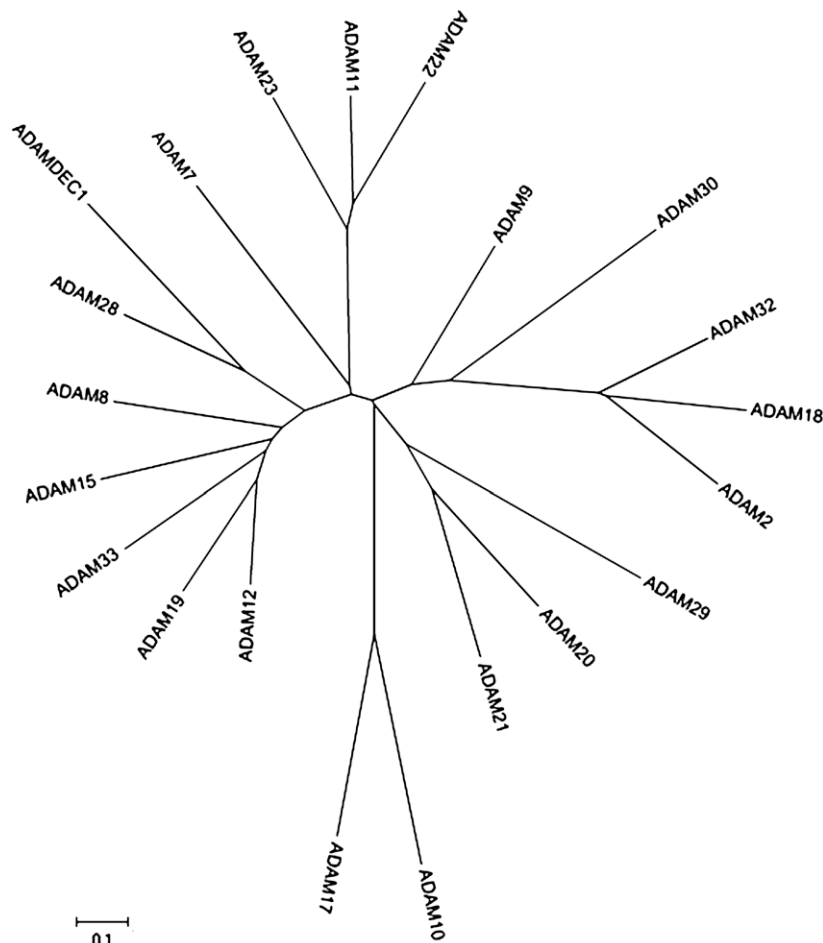

Fig. 3. Phylogenetic tree of human *ADAMs* based on the sequences of their metalloproteinase domains. Phylogenetic and molecular evolutionary analyses were conducted using MEGA version 4 (Tamura et al., 2007). The scale bar represents amino acid substitutions per site, such that 0.1 represents 10% of sites having a substitution.

likely play a role in sperm adhesion to the uterus and oocyte (Glassey and Civetta, 2004). This was not true for the more broadly expressed *ADAMs*, which are subject to purifying selection.

1.3. Insights from gene knockout mice

Table 3 shows a summary of the phenotypes of the *Adam*-null mice that have been generated to date. More details will be provided on particular genetic knockouts (e.g. *Adam1a, Adam1b, Adam2, Adam10, Adam17*) in subsequent sections. We note below a few central observations for particular genes:

Adam8. ADAM8 is primarily expressed in hematopoetic cell types (Table 1) and roles for ADAM-8 in leukocyte infiltration in neurodegenerative diseases have been suggested (Horiuchi et al., 2005). Shedding of the adhesion molecule CHL-1 by ADAM-8 has been linked to neurite extension and promotion of neuronal survival, and though *Adam8*−/− mice have no overt phenotype (Kelly et al., 2005), they show much reduced CHL-1 shedding in the brain (Naus et al., 2004). Elevated expression of *Adam8* has been seen in Wobbler mice, along with increased CHL-1 shedding, suggesting possible involvement of ADAM-8 in the pathology of neurodegeneration (Naus et al., 2004). ADAM-8 has also been linked to asthma since allergens strongly induced *Adam8* expression in peribronchial and perivascular inflammatory cells in an experimental asthma model (King et al., 2004).

Adam10. ADAM-10 is the principal ADAM sheddase involved in Regulated Intramembrane Proteolysis (RIP), with critical actions on Notch/Delta signalling and APP processing (Saftig and Hartmann, 2005; Fig. 4). Notch is a transmembrane protein that undergoes three proteolytic cleavages during its functional lifecycle. The first is cleavage by a pro-protein convertase in the secretary apparatus, so that the protein appears on the surface as a heterodimeric protein (Artavanis-Tsakonas et al., 1999). The second (S2) cleavage occurs upon activation by binding of one of several ligands (e.g. Delta and Jagged), followed by a third cleavage in the plane of the membrane by γ-secretase, which is composed of the aspartate proteases, presenilins 1 and 2 (Selkoe, 2001). This final cleavage releases the cytoplasmic domain of Notch, which then binds to a member of the CSL (CBF1, Su[H], Lag-1) family of transcription factors, which activate downstream genes (Schlondorff and Blobel, 1999). Evidence is now very strong that ADAM-10 is the main protease responsible for the S2 cleavage. Loss of ADAM-10 leads to early embryonic lethality around 9.5 days post coitum, with multiple defects in the developing central nervous and cardiovascular systems and somites, which closely resemble those seen in mice deficient in Notch/Delta signalling (Hartmann et al., 2002). This observation concurs with the findings from *Drosophila*, which indicated that the Kuzbanian (Kuz) gene was essential for controlling neural cell fate decisions in the developing nervous system via proteolytic cleavage of the transmembrane receptor Notch (Pan and Rubin, 1997; Rooke et al., 1996). Likewise the *C. elegans* orthologue (sup-17) was identified as a suppressor of the phenotype caused by constitutively active Notch/LIN-12 (Saftig and Hartmann, 2005). This therefore represents a fundamental biological signalling mechanism that is conserved from worms to mammals (Horiuchi et al., 2005).

Controversially, ADAM-17 was also reported to participate in Notch cleavage in vitro and in cultured mammalian cells (Brou et al., 2000). However, *Adam17*−/− mice do not show any defects related to Notch signalling (see below). Similar to

Table 3
Phenotypes of *Adam* knockout mice

| ADAM knockout	Phenotype	References
Adam1a	Male infertility, defects in sperm migration	Nishimura et al. (2004)
Adam2	Male infertility, defects in sperm migration and adhesion	Cho et al. (1998) and Nishimura et al. (2001, 2007)
	Defects in migration of neuroblasts to olfactory bulb	Murase et al. (2008)
Adam3	Male infertility, defects in sperm migration and adhesion	Cho et al. (1998), Kim et al. (2006), Nishimura et al. (2001), and Stein et al. (2005)
Adam8	Viable, fertile, no pathology (reduced CHL-1 shedding in brain)	Kelly et al. (2005)
Adam9	Viable, fertile, no pathology	Sahin et al. (2004)
Adam10	Early lethality E9.5dpc, defective CNS and heart development, somite formation and vasculogenesis. Phenocopies Notch deficiency (more severe than presenilin 1 and 2 double knockouts.	Hartmann et al. (2002)
Adam11	Viable, fertile, impaired hippocampal-dependent spatial learning and altered nociception responses	Takahashi et al. (2006b) and Takahashi et al. (2006a)
Adam12	Viable, fertile, 30% embryonic lethality, brown adipose abnormalities, no muscle defect	Kurisaki et al. (2003), Masaki et al. (2005) and Sahin et al. (2004)
Adam15	Viable, fertile, tumour neovascularization reduced, age onset osteoarthritis	Bohm et al. (2005), Horiuchi et al. (2003), Sahin et al. (2004)
Adam17	Perinatal lethality, probably due to heart defects; pulmonary hypoplasia; problems with epithelial tissue maturation, phenocopies defects seen in EGFR, TGFα, HB-EGF and amphiregulin knockout mice	Jackson et al. (2003), Peschon et al. (1998), Shi et al. (2003) and Zhao et al. (2001)
Adam19	80% postnatal lethality, multiple cardiovascular defects	Horiuchi et al. (2005), Kurohara et al. (2004), and Sahin et al. (2004)
Adam22	Postnatal lethality, ataxia and peripheral nerve hypomyelination	Sagane et al. (2005)
Adam33	Viable, fertile, no pathology	Chen et al. (2006)
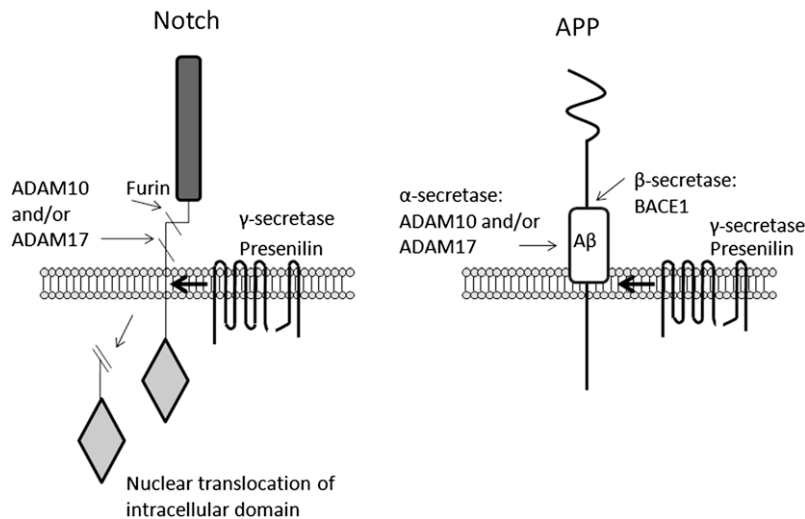
Fig. 4. Regulated intramembrane proteolysis of Notch and Amyloid Precursor Protein (APP).

Notch, APP is a transmembrane protein subject to RIPping via metalloproteinase and γ-secretase action (Saftig and Hartmann, 2005). Ectodomain shedding can involve either α- or β-secretases, which cleave differentially, the latter giving rise to Aβ peptides that result in the deposition of amyloid plaque, whereas the former produces a soluble extracellular fragment (APPsα) that is non-amyloidogenic (Schlondorff and Blobel, 1999). It is clear that both ADAM-10 and -17 can act as α-secretases (Allinson et al., 2003), and fibroblasts from *Adam10*−/− mice showed no deficiency in α-secretase activity, probably due to compensation by ADAM-17 (Hartmann et al., 2002). However, overexpression of functional ADAM-10 in neurons in transgenic mice that also overexpress human APP led to increased production of APPsα and reduced amyloid plaque formation and overall cognitive deficits (Postina et al., 2004). In contrast an inactive ADAM-10 promoted Alzheimer-like pathology. These findings strongly implicate ADAM-10 as a physiologically relevant α-secretase. But in addition to Notch/Delta, ADAM-10 has many other biologically relevant targets, including ephrin-A5 and E-cadherin ((Janes et al., 2005; Maretzky et al., 2005a); Table 1). It is likely that the early lethality of *Adam10*−/− mice due to the Notch signalling defect masks detection of other critical developmental processes in which ADAM-10 participates.

Adam11. Though *Adam11*−/− mice are apparently normal, these mice show defects in learning in the water maze task and motor coordination in the rotating rod task (Takahashi et al., 2006a). This is consistent with the expression of *ADAM11* in the hippocampus and cerebellum. These mice also show reduced pain perception responses (Takahashi et al., 2006b).

Adam12. Several *Adam* knockouts result in viable mice with no obvious pathologies, including *Adam9*−/−, *Adam12*−/− and *Adam15*−/− mice, though 30% mortality of *Adam12*−/− pups in the first week after birth has been seen in one study (Kurisaki et al., 2003). However, in another study triple knockout *Adam9/12/15*−/− are also viable and fertile and are generated in the correct Mendelian ratios (Sahin et al., 2004), suggesting that these differences may in part be attributable to the genetic background (Horiuchi et al., 2005). As meltrin-α, ADAM-12 had originally been implicated in muscle formation, where its expression in myoblasts along with ADAM-19 (Meltrin-β) and ADAM-9 (Meltrin-γ) was linked to myoblast fusion to generate multinucleated myotubes (Yagami-Hiromasa et al., 1995). [Parenthetically, the notion that ADAMs had roles in cell fusion arose from their first identification as Fertilins, with a suggested role in sperm–egg fusion via a fusion peptide sequence in the Cys-rich sequence of fertilin-α (Blobel et al., 1992) but to date experimental proof of a role for any ADAM in cell fusion is lacking (Tousseyn et al., 2006)]. No defect in muscle formation has been observed in *Adam12*−/−, or in *Adam9*−/− animals. Overexpression of ADAM-12 on a muscle-specific promoter was shown to alleviate the muscular dystrophy pathology in *mdx* mice in the short term (Moghadaszadeh et al., 2003), but in aged *mdx* mice this situation was reversed, with accentuation of the dystrophic phenotype and suppression of muscle regeneration following freeze-thaw injury (Jorgensen et al., 2007). Expression of ADAM-12 has been linked to the formation of quiescent reserve cells, otherwise known as satellite cells, that have the properties of self-renewing stem cells and are stimulated to proliferate and contribute to muscle formation following injury or repair (Cao et al., 2003). Conceivably forced overexpression of ADAM-12 may interfere with subsequent recruitment of these cells. Thus the role of ADAM-12 in muscle formation is unclear, particularly as *Adam9/12/15/19*-quadruple-null mice show no apparent muscle defect, arguing against possible compensation by other Meltrins (Horiuchi et al., 2005). However, *Adam12*-null animals show minor defects in brown adipose tissue formation (Kurisaki et al., 2003), and transgenic over-expression enhanced adipogenesis (Kawaguchi et al., 2002). Furthermore, *Adam12*−/− mice showed reduced weight gain and numbers of adipocytes when fed a high fat diet, suggesting a role in adipocyte proliferation and differentiation (Masaki et al., 2005).

Adam15. Mice deficient in ADAM-15 show no overt phenotype, though tumour neovascularisation and growth was reduced (Horiuchi et al., 2003). Aged male *Adam15*−/− mice displayed accelerated development of osteoarthritis, which

may be associated with the ability of ADAM-15 to promote adhesion of chondrocytes to cartilage collagens types II and VI (Bohm et al., 2005).

Adam17. The characterization of ADAM-17 as the TNF-α converting enzyme (TACE) has unlocked an unexpected wealth of information about protein ectodomain shedding that has had repercussions throughout cell and developmental biology. In particular, since mice lacking TNF-α are overtly normal, a key finding from knockout mice in which *Adam17* was disrupted (by deletion of the Zn-binding site in the MP domain) was that ADAM-17 has roles in addition to pro-TNF-α activation, and is in fact required for EGF receptor (EGFR) signalling during normal development (Peschon et al., 1998). The *Adam17*−/− mice died close to birth (at around 17.5 days post coitum), with open eye lids, hair and skin abnormalities and defects in epithelial maturation of multiple organs, all of which resemble defects seen in mice lacking EGFR or its ligands heparin-binding-EGF (HB-EGF), amphiregulin and transforming growth factor-α (TGF-α) (Blobel, 2005; Horiuchi et al., 2005). In particular, *HB-EGF*−/− mice die before weaning with defects in valvulogenesis in the heart and hypoplastic, poorly differentiated lungs that parallel those seen in *Adam17*−/− mice (Jackson et al., 2003; Shi et al., 2003; Zhao et al., 2001). It appears that both ADAM-9 and -19 also contribute to heart development, since double knockouts with *Adam17* led to exacerbated heart phenotypes, suggesting redundant or compensatory roles for these ADAMs, which are only unmasked in the absence of the major HB-EGF sheddase, ADAM-17 (Horiuchi et al., 2005).

Adam22. Adam22−/− mice are born in the appropriate Mendelian ratio but die before weaning, which has been linked to hypomyelination of peripheral nerves, leading to ataxia (Sagane et al., 2005). ADAM-22 has been shown to be the receptor for a secreted neuronal protein LGI1, mutations in which cause a genetically determined form of epilepsy [autosomal dominant lateral temporal epilepsy, ADLTE; (Fukata et al., 2006)]. The LGI1 is expressed from the presynaptic neuron and binds to ADAM-22 on the surface of post-synaptic neurons. A model has been presented in which the cytoplasmic domain of ADAM-22 interacts with a scaffold protein PSD-95, which in turn can interact with the AMPA receptor responsible for glutaminergic signalling (Snyder, 2006). Defects in this pathway may lead to the aberrant excitation associated with epilepsy. However no mutations were found in ADLTE patients previously identified as negative for LGI1 mutations (Chabrol et al., 2007), so the role of ADAM-22 in neuronal function requires further exploration.

2. ADAM structure and regulation

2.1. Overall topology

There is detailed knowledge on the structure of the metalloproteinase domain of ADAM proteins drawn from X-ray crystal data, though for the most part this has been derived from studies of the SVMPs (reviewed in Gomis-Ruth (2003)). However, most of this information has come from study of the isolated catalytic domain, and only recently has the overall molecular architecture of the complete metalloproteinase/disintegrin/cysteine-rich (MDC) structure begun to emerge (Igarashi et al., 2007; Takeda et al., 2006). These new structures have again come from the SVMPs, namely, vascular apoptosis-inducing factor-1 (VAP-1) and VAP-2B, but as the residues identified in these studies as important for stabilizing the multidomain architecture appear to be strictly conserved throughout all the ADAMs, they no doubt shed light on general mechanisms of substrate recognition and cleavage by mammalian ADAMs. The key message from the recent findings is that the overall MDC domain structure results in a C-shaped molecule, whereby part of the Cys-rich domain faces towards the catalytic site in the M domain (Takeda et al., 2006). This part of the C-domain is comprises a hyper-variable region (HVR) that differs markedly between ADAM family members and it is proposed that this plays an important role in substrate binding. This "C-shape" structure also has implications for the potential of the disintegrin domain to participate in adhesive interactions, which will be discussed further.

The metalloproteinase catalytic domain in the ADAMs is typical of the metzincin clan, which is a globular structure divided into two subdomains, with the active site cleft running between the two (Gomis-Ruth, 2003). The upper, N-terminal subdomain consists of a highly twisted, 5-stranded β-pleated sheet, the strands of which lie parallel to each other and to the substrate, which binds in an extended fashion, essentially running horizontally, left to right along the groove in the schematic of the SVMP Adamalysin II shown in Fig. 5A. Multiple α-helices also create structural features in the upper subdomain, with the lower αB helix of the Adamalysin II structure containing the HEXXH of the catalytic Zn-binding site. The clan-defining feature of the Metzincins is an absolutely conserved methionine residue creating a 1,4-β-turn (Met-turn) (Bode et al., 1993) that then correctly positions the lower subdomain to create the catalytic cleft. This lower subdomain has relatively few features apart from an α-helix towards the C-terminus. The catalytic Zn atom sits at the bottom of the groove between the subdomains, with subsites in the groove ($S_3S_2S_1S_1'S_2'S_3'$) determining specificity for particular amino acid sequences ($P_3P_2P_1P_1'P_2'P_3'$) in the substrate, where cleavage occurs between the P_1 and P_1' residues (Fig. 5B). The topology of this groove, and in particular the depth and hydrophobicity of the S_1' specificity pocket, is critical for building selectivity into the design of synthetic metalloproteinase inhibitors. Three disulfide bonds are also involved in stabilizing the ADAM metalloproteinase domain structure, along with a structural Ca^{2+} in many, including ADAM-33 (Orth et al., 2004), but not in ADAM-17 (Maskos et al., 1998). Within this overall consensus structure, the presence of different numbers of α-helices and insertion loops between them create unique surface features that would be expected to affect substrate recognition. Thus although ADAM-17 and ADAM-33 (which to date are the only members of the mammalian ADAM family proper for which the structures have been solved) possess the same layout of secondary structure elements, their catalytic domains share only 26% identity (Orth et al., 2004).
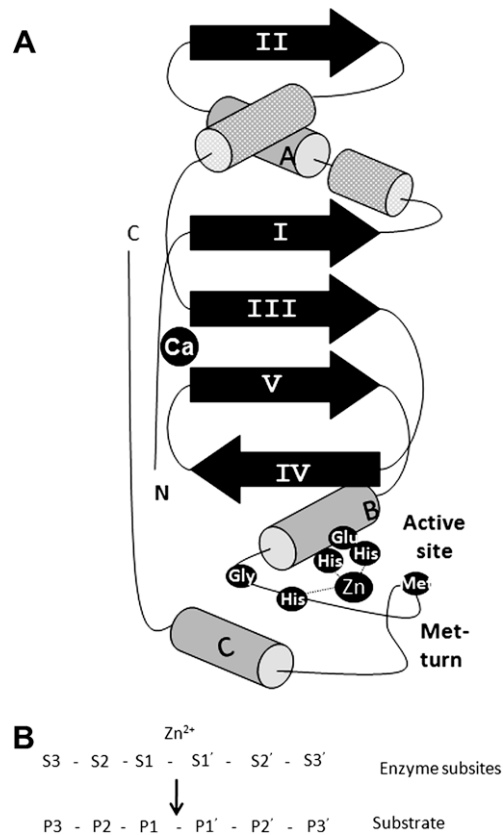
Fig. 5. Structure of the ADAM metalloproteinase domain. (A) The schematic depicts structural features determined by X-ray crystallographic analysis of the SVMP Adamalysin II (Gomis-Ruth, 2003). (B) Nomenclature for the amino acid sequence in the cleavage site of substrates and the corresponding sub-sites in the active site of the protease.

The disintegrin (D) domain that follows the metalloproteinase domain has been seen in the VAP1 and VAP2B structures to be subdivided again into 2 sub-domains, described as the "shoulder" (D_s) and "arm" (D_a) domains. The N-terminus region of the Cys-rich (C) domain that follows is termed a "wrist" (C_w) domain, and together the D_s, D_a and C_w domains shape the whole molecule into the form of a C (Takeda et al., 2006). There are few secondary structure elements in the resulting C-shaped arm, with disulfide bonds and two Ca^{2+}-binding sites holding the structure together. Most importantly in this structure, the disintegrin loop that is widely considered to be responsible for the interactions between ADAMs and integrins (which will be discussed in detail in Section 2.3) is packed against the C_w-domain and is thus inaccessible for binding (Takeda et al., 2006). The "wrist" C_w domain is followed by a "hand" C_h segment, which contains at its distal portion the hypervariable region (HVR), which is proposed by Takeda and co-workers to be a key exosite involved in target recognition (Igarashi et al., 2007). The crystal structure of ADAMTS-1 has also recently been solved, and here again the Cys-rich domain appears to stack against the active site (Gerhardt et al., 2007).

These main structural features are summarised in the schematic shown in Fig. 6.

The overall C-shaped MDC structure has flexibility via a hinge between the metalloproteinase and disintegrin domains. In many SVMPs and also in sperm ADAMs such as ADAM-2 (fertilin-β) there is cleavage of the molecules in this region. In contrast ADAM1 (fertilin-α) is cleaved at Ca-binding site-III. So in addition to regulating the proteolytic aspect of ADAM function, such modifications would profoundly affect protein–protein interaction capabilities. Whether this might unmask the disintegrin loop for association with integrins remains to be established.

2.2. Activation of ADAM zymogens, maturation and trafficking

For the majority of the ADAMs, pro-domain removal likely involves the action of pro-protein convertases (PCs) such as furin and takes place intracellularly in the secretory pathway (Endres et al., 2003; Seals and Courtneidge, 2003). These enzymes cleave at a consensus RX(R/K)R motif. The pro-domain functions via a Cysteine switch mechanism, as in the MMPs (Loechel et al., 1999; Roghani et al., 1999). Further support for this view comes from mutational studies of the putative
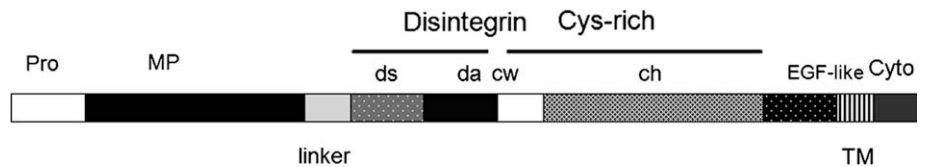
Fig. 6. The disposition of the modular domains of ADAMs. The schematic shows a representation of the likely arrangement of ADAM domains based on the crystallographic data of Takeda et al. (2006) and Igarashi et al. (2007).

PC site, which is shown to block the activation of ADAM-10 (Anders et al., 2001). However, since the autocatalytic processing of PCs is itself regulated, in some cases involving retention of the cleaved pro-domain in complex with the PC, there is potential for regulated activation of their ADAM zymogens at the cell surface (Mayer et al., 2008). Moreover for at least two ADAMs (ADAM-8 and -28) there is evidence from analysis of inactive E-A mutations in the Zn-binding site for autocatalytic removal of the pro-domain (Howard et al., 2000; Schlomann et al., 2002).

As discussed above, following activation by pro-domain removal, further proteolytic processing of downstream ADAM domains may significantly affect protein conformation and function. In addition to the processing of sperm ADAMs, this has been documented for ADAM-8, which has been observed as a cleaved, cell-associated form lacking the metalloproteinase domain (Schlomann et al., 2002). ADAM-19 also undergoes autolytic processing in its Cys-rich domain, but the N-terminal metalloproteinase-disintegrin modules remain associated with the C-terminal fragment via disulfide bonding (Kang et al., 2004).

The isolated pro-domains of ADAMs can act as potent, selective inhibitors of the active mature forms of the enzymes, as has been documented for ADAM-10 and ADAM-17 (Gonzales et al., 2004; Moss et al., 2007b). Interestingly, at least for ADAM-17 the inhibition of active forms via isolated pro-domains does not seem to involve the Cys-switch mechanism involved in maintaining latency (Gonzales et al., 2004), and indeed it has been suggested that the main functions of the pro-domain are to act as a chaperone and to protect the enzymes from degradation in the secretory system (Anders et al., 2001; Milla et al., 2006). This is suggested by the ability of the pro-domain of ADAM-10 to rescue in *trans* an otherwise inactive ADAM-10 mutant lacking the pro-domain (Anders et al., 2001). For ADAM-12 the excised pro-domain has been observed to remain non-covalently associated with the mature form of the molecule extracellularly, with the whole molecule adopting a "four-leaf clover" structure where one of the four globular domains is the pro-domain (Wewer et al., 2006). Thus the pro-domains of ADAMs have multiple functions in maintaining latency and stability, ensuring proper folding and entry into the secretory pathway, and perhaps also functional interactions outside the cell.

Other potential control points for ADAM activity include the trafficking of enzymes to particular sites within the cell, the activation of enzyme activity following cell stimulation, and the subsequent removal of active enzyme by internalization or other mechanisms. There are striking examples for all of these types of controls acting for particular ADAMs. Recent data indicate that ADAM-19 and mature, active ADAM-17 are sequestered within cholesterol-rich membrane microdomains, otherwise know as lipid rafts or detergent-resistant microdomains (DRMs) (Tellier et al., 2006; Wakatsuki et al., 2004). Numerous substrates of ADAM-17 and -19 are also localized in these rafts, along with furin. Depletion of cholesterol from the lipid rafts by cyclodextrin or high-density lipoprotein treatment increased the shedding of ADAM-17 substrates without increasing ADAM-17 activity (Tellier et al., 2008, 2006).

2.3. The disintegrin–integrin connection

Integrins are α and β chain heterodimeric adhesion receptors that are encoded by 18 α and 8 β chain genes in mammals, to give 28 different $\alpha\beta$ combinations, each of which has distinctive ligand binding characteristics (reviewed in Hynes (2002)). "True" snake venom disintegrins are small 50–90 amino acid proteins that competitively inhibit integrin-mediated adhesion of platelets to RGD sequences in fibrinogen, by virtue of an RGD or related sequence that is presented at the end of an extended loop, termed the disintegrin loop. In the SVMPs, ADAMs and ADAMTSs, the disintegrin domain should more accurately be called "disintegrin-like", because with the exception of human ADAM-15 they lack the RGD sequence in their disintegrin loops and they also have additional Cys residues missing from "true" venom disintegrins (Evans, 2001). The initial identification of disintegrin-like domains when the first mammalian ADAMs were identified led to the hypothesis that these regions would interact with integrins, like the related sequences in snake venoms (Wolfsberg et al., 1995). There is now con-

Table 4
ADAM-Integrin associations

	α2β1	α4β1	A4 β7	α5β1	α6β1	α6β4	α9β1	αVβ3	αVβ5
ADAM1							•		
ADAM2		•			•		•		
ADAM3		•			•		•		
ADAM7		•	•				•		
ADAM9	•				•	•	•		•
ADAM12		•					•		
ADAM15				•			•	•	
ADAM17				•					
ADAM19		•		•					
ADAM23								•	
ADAM28		•	•				•		
ADAM33		•		•			•		

• Indicates an association has been reported.
 ADAM–Integrin interactions, adapted from Arribas et al. (2006).

siderable evidence that extracellular domains of ADAMs do indeed interact with integrins, and studies of recombinant disintegrin domains have identified a consensus motif present in their disintegrin loops, namely CRXXXXXCDXXEXC (White et al., 2005). In many cases these interactions have been shown to influence cell adhesion and cell–cell interactions. Table 4 summarizes the known interactions of ADAMs with specific integrins, including α2β1, α4β1, α4β7, α5β1, α6β1, α6β4, α9β1, α2β1, αVβ3, αVβ5 (Arribas et al., 2006; Eto et al., 2002; Tomczuk et al., 2003; White et al., 2005).

Human ADAM-15 provided interesting insights due to the unique RGD motif in its disintegrin loop, which allowed Eto et al. (2002) to dissect the requirements for RGD-dependent binding to integrin αVβ3 versus the RGD-independent association with α9β1. This mapped the α9β1-interaction site to a motif RXXXXXXDLPEF (residues 481–492 in human ADAM-15, in which the RGD motif occurs at residues 484–486) that is conserved in all ADAMs except ADAM-10 and -17. Indeed, they then demonstrated that the disintegrin domains of several ADAMs associated with α9β1, but not those of ADAM-10 and -17 (Eto et al., 2002).

A potential issue concerning many of these studies is that they have been conducted with recombinant disintegrin domains, removed from the context of the native proteins, and as we have seen earlier, the current structural view of the ADAMs is that the disintegrin-loop region is buried internally in the full-length molecule, unavailable for interaction. However a few studies have looked at the effects of ADAMs on adhesion and migration of cells by studying the intact molecule. If we consider ADAM-12, whose disintegrin domain has previously been shown to interact with integrin α4β1, expression of full-length ADAM-12 in 3T3-L1 preadipocytes revealed an ADAM-12/β1 association, which impaired integrin-mediated adhesion and spreading (Kawaguchi et al., 2003). When expressed in CHO cells that carried defined integrins (α4β1, α5β1 or both), ADAM12 inhibited migration of α4β1-expressing cells but not those expressing α5β1, i.e. the pattern mirrored that of the recombinant disintegrin domain (Huang et al., 2005). Likewise ADAM-19 and ADAM-33 inhibited migration consistent with the binding preferences of their isolated disintegrin domains. Bax et al. (2004) have also presented evidence for interactions between the full extracellular portion of ADAM-17 and α5β1 both in cis and in trans, and then narrowed the association down to the distintegrin-cysteine-rich region.

It is clear that full length ADAMs can influence adhesion in either a positive or negative manner, independently of their metalloproteinase functions, and likely through their associations with integrins (for further review see Arribas et al. (2006)). These observations raise interesting mechanistic questions, which might be resolved by detailed crystal structure information of intact cellular ADAMs. Also, a key aspect may relate to the involvement of intracellular interaction partners of the ADAMs via their cytoplasmic domains. We have recently observed that two splice variants of ADAM-15 that differ only in their cytoplasmic domains by the inclusion of an additional proline-rich sequence in the longer of the two, have opposing effects on adhesion and migration (Zhong et al., 2008). These different cytoplasmic domain have common (Grb2, FISH) and distinct (Src, Brk) interaction partners, which may lead to isoform-specific effects on intracellular signalling or protein localization or trafficking.

2.4. The Cys-rich domain

There is strong support for a role for the Cys-rich domain in regulating ADAM function. For ADAM-12, the Cys-rich domain mediates adhesive interactions with syndecans, leading subsequently to engagement with β1-containing integrins (Iba et al., 2000; Thodeti et al., 2003). In *Xenopus laevis* the metalloproteinase activity of ADAM-13 is required for cranial neural crest cell migration (Alfandari et al., 2001), and when ADAM-13 is over-expressed in embryos it leads to hyperplasia of the cement gland (Smith et al., 2002). Though the catalytic domain of ADAM-10 can be substituted for that of ADAM-13, the cement gland hyperplasia phenotype critically requires the Cys-rich domain, which is consistent with involvement of the Cys-rich domain in substrate interactions. This is further supported by demonstration of the association of the ADAM-13 disintegrin/Cys-rich domains with fibronectin (Gaultier et al., 2002). Also, domain deletion analysis showed that the Cys-rich

domain of TACE is required for the shedding of the IL-1 Receptor-II, but not for its ability to shed TNF-α or the p75TNF receptor (Reddy et al., 2000).

An exciting recent insight into role of the Cys-rich domain has come fro m the study of the role of ADAM-10 in ephrin-Eph signalling (Janes et al., 2005; Mancia and Shapiro, 2005). Ephrins are cell-associated ligands (either GPI-anchored in the case of the ephrin-A ligands or transmembrane for the ephrin-B class) for Eph tyrosine kinase receptors which generate bidirectional signalling in adjacent cells upon ephrin-Eph engagement (Pasquale, 2008). Fundamentally, ephrin-Eph signalling involves cell repulsion following engagement, which is important for neuronal guidance and also for establishment of the arterial and venous vascular networks. This repulsion involves cleavage of the ephrin ligand following binding to its cognate Eph (Hattori et al., 2000). Janes et al. (2005) have shown that ADAM-10 constitutively associates with the ephrin binding domain of EphA3, and that formation of the EphA3/ephrin-A5 complex creates a high affinity binding site for the Cys-rich domain of ADAM-10, which binds to neither component alone. This in turn results in a conformational switch such that the ADAM-10 metalloproteinase domain is positioned to be able to cleave the ephrin-A5 in *trans*. The key feature is an acidic pocket in the C-terminus of the Cys-rich domain, likely the hypervariable region observed by Takeda et al. (2006). This model may be a paradigm for a much wider range of ADAM actions.

2.5. The cytoplasmic domain

The transmembrane ADAMs have cytoplasmic domains that vary widely in length and sequence, ranging from the 11 residues of ADAM-11 to 231 residues for ADAM-19 (Seals and Courtneidge, 2003). Several contain one or more PXXP motifs that can act as binding sites for SH3-domain containing proteins, and Ser, Thr and tyrosine residues that are potential sites for phosphorylation by diverse kinases. This led to speculation that the cytoplasmic domains may play important roles in regulating protease function in response to intracellular signalling events (i.e. inside–out signalling), or also that they could be involved in outside–in signalling following engagement of their ectodomains with substrates or adhesion partners, leading to recruitment of signalling molecules and adapters. A large number of interaction partners have now been identified using yeast 2-hybrid, pull-down assay and co-immunoprecipitation, and Table 5 summarises current knowledge of these interactions. The ADAMs that contain potential SH3 binding sites are: ADAM-7, -8, -9, 10, -12, -15, -17, -19, -22, -29 and -33. ADAM-12 and -15 contain the most extensive repertoires of Pro-rich motifs (9 and 13, respectively, depending on the splice variant for *ADAM15*), and have been most extensively studied with regard to their interaction partners.

The significance of the cytoplasmic domains for ADAM functions rests on several observations. First, although the overall sequence identity between *ADAM* orthologues is less in the cytoplasmic tail regions than in sequences encoding the ectodomains, the Pro-rich motifs are generally well conserved. For example, comparison of mammalian and zebrafish *ADAM12* shows that 5 of the PxxP are conserved with good identity in surrounding sequence blocks and several others may be substituted functionally since the *Danio rerio* gene has 12 copies of the motif overall in its cytoplasmic domain. Second, there are now clear examples where the cytoplasmic domain plays a key role in ADAM function, either by regulating catalytic activity or by trafficking the protein to the correct cellular location (Cao et al., 2002). ADAM-12 is stored intracellularly as a mature, active protein but appears on the surface in response to PMA stimulation (Hougaard et al., 2000), and this regulated translocation requires the cytoplasmic domain and is dependent on PKCε (Sundberg et al., 2004). The SH3-domain-containing protein PACSIN3, which is involved in endocytosis and interacts with proteins such as dynamin and N-WASP, interacts with the cytoplasmic domains of several ADAMs including ADAM-9, -10, -12, 15 and -19, but not that of ADAM-17 (Mori et al., 2003). The ADAM-12/PACSIN3 association was shown to be functionally important for ADAM-12 mediated shedding of HB-EGF in response to PMA or the GPCR agonist angiotensin II. Likewise another ADAM-12 interactor, Eve-1, which is an SH3-containing adapter protein that also binds with several ADAM cytoplasmic domains including ADAM-17 has been shown by siRNA knockdown studies to be important for stimulus-activated shedding by ADAM-12 (Tanaka et al., 2004). Yet another ADAM-12 interacting protein is the scaffolding protein Tks5/Fish, which is a Src substrate that contains 5 SH3 domains and a Phox homology domain that binds phosphatidyl inositols (Abram et al., 2003). Tks5/Fish co-localizes with ADAM-12 in actin-rich podosomes, sometimes known as invadopodia, suggesting that it may be important for spatially organizing ADAM-12 activity. This suggests an interesting interplay of factors regulating signalling at the cell surface, since ADAM-12 itself binds Src and has been reported to activate Src activity in C2C12 cells (Kang et al., 2000), whilst also recruiting and activating phosphatidylinositol 3-kinase (PI3K) via SH3 domain/pro-motif interactions (Kang et al., 2001).

A proline-rich stretch in the cytoplasmic domain of ADAM-10 has recently been shown to be important for the correct basolateral location of ADAM-10 in polarized epithelial cells, endowing the enzyme with the ability to cleave E-cadherin and promote cell migration when it is correctly localized (Wild-Bode et al., 2006). It is unclear at present what intracellular protein mediates this trafficking, though Synapse Associated Protein-97 (SAP97) is an SH3-domain containing protein that interacts with this region of ADAM-10 (Marcello et al., 2007) and is responsible for correct localization of ADAM-10 in synaptic membranes, thereby promoting its α-secretase activity. Interestingly SAP97 also interacts with the extreme C-terminal region of ADAM-17, but in this case it involves the third PDZ domain of SAP97 (Peiretti et al., 2003). This suggests a common control point for integration of the α-secretase activities of ADAM-10 and -17.

Despite the intense activity on the study of ADAM-17 and its involvement in stimulus-induced ectodomain shedding, there are still conflicting views as to the role of its cytoplasmic domain. Its association with the PDZ-domain containing protein tyrosine phosphatise-1H (PTP1H) inhibits PMA-stimulated pro-TNF-α activation (Zheng et al., 2002). ADAM-17 is able to associate with Erk MAP kinase and is phosphorylated by it on Thr 735 leading to enhanced cleavage of the TrkA neurotrophin

Table 5
ADAM cytoplasmic domain interaction partners

ADAM	Interaction partners	References
ADAM-9	PKCδ	Izumi et al. (1998)
	Endophilin-1, SH3PX1	Howard et al. (1999)
	Src	Weskamp et al. (1996)
	MAD2β	Nelson et al. (1999)
	Eve-1	Tanaka et al. (2004)
	PACSIN3	Mori et al. (2003)
ADAM-10	Lck, MAD2	Poghosyan et al. (2002)
	SAP97	Marcello et al. (2007)
	Eve-1	Tanaka et al. (2004)
	PACSIN3	Mori et al. (2003)
ADAM-12	Abl, Grb2, PI-3K p85α, Src, Yes	Suzuki et al. (2000)
	α-Actinin-1	Cao et al. (2001)
	α-Actinin-2	Galliano et al. (2000)
	MAD2β	Nelson et al. (1999)
	PKCδ	Asakura et al. (2002)
	Src	Kang et al. (2000)
	PI-3K p85α	Kang et al. (2001)
	PACSIN3	Mori et al. (2003)
	Eve-1	Tanaka et al. (2004)
	PKCε	Sundberg et al. (2004)
	Tks5/Fish	Abram et al. (2003)
ADAM-13 (Xenopus)	PACSIN2, Src	Cousin et al. (2000)
ADAM-15	Grb2, Abl, Fyn, Src, Hck, Lck, Bcr-Abl, MAD2	Poghosyan et al. (2002)
	Grb2, Src, Tks5/Fish, Brk, Erk	Zhong et al. (2008)
	Endophilin-1, SH3PX1	Howard et al. (1999)
	MAD2β	Nelson et al. (1999)
	Hck	Hiipakka and Saksela (2007)
	Lck	Tran et al. (2005)
	SNX30	Karkkainen et al. (2006)
	Tks5/Fish	Abram et al. (2003)
ADAM-17	Erk	Diaz-Rodriguez et al. (2002)
	MAD2	Poghosyan et al. (2002)
	SAP97	Zheng et al. (2002) and Nelson et al. (1999)
	Eve-1	Peiretti et al. (2003)
	FHL2	Tanaka et al. (2004)
	PTPH1	Canault et al. (2006)
	PDK1	Zhang et al. (2006)
	Endophilin-1	Howard et al. (1999)
	ArgBP1, β-cop, ubiquitin	Huang et al. (2002)
	Tks5/Fish	Abram et al. (2003)
	PACSIN3	Mori et al. (2003)
ADAM-22	14-3-3 family	Godde et al. (2006)
	14-3-3 zeta PSD-95	Zhu et al. (2003)

receptor in CHO cells (Diaz-Rodriguez et al., 2002). Moreover, Soond et al. (2005) have reported that trafficking of ADAM-17 from the endoplasmic reticulum to the cell surface was dependent on Erk phosphorylation at Thr 735. Meanwhile Fan et al. (2003) observed PMA-induction of phosphorylation at Ser819, but neither mutation of this site or deletion of the entire cytoplasmic domain affected serum-induced pro-TGF-α cleavage, which is consistent with the studies from Black and co-workers (Doedens et al., 2003; Reddy et al., 2000), where full PMA-inducible ADAM-17 activity occurred with inclusion of just the membrane spanning region for correct insertion in the membrane (Reddy et al., 2000; Doedens et al., 2003). Thus the mechanism responsible for PMA activation of ADAM-17 is still unclear. This could involve PMA-induced release of an inhibitor, such as the pro-domain of ADAM-17 itself, or TIMP-3, though the experiments of Doedens et al. (2003) argue against these proposals. An alternative may be that PMA activation may modify another protein leading to an interaction with ADAM-17, potentially altering its engagement with substrates within the lipid-rich domains where it is primarily localized (see Section 2.2).

On balance, however, it seems likely that the cytoplasmic domain does indeed play a key role in coupling ADAM-17 and other ADAMs to specific signalling events such as GPCR activated ADAM-mediated EGFR ligand release, termed "triple membrane-passing signal" (TMPS), which will be discussed further in Section 3.3. Recent data have helped unravel the GPCR-EGFR crosstalk elicited by gastrin-releasing peptide, which involves phosphorylation of ADAM-17 by PDK1, as a result of Src and PI3K activation by the GRP receptor (Zhang et al., 2006). This leads to amphiregulin release and EGFR signalling. Thus the cytoplasmic domains of ADAMs likely couple ADAM activity to signalling pathways in a cell- and stimulus-specific fashion.

Finally, further support for the notion of functional relevance for the cytoplasmic domain comes from analysis of ADAM-15 cytoplasmic domain variants, whose expression in human breast cancer shows isoform-specific associations with clinical outcome and also with effects on cell adhesion and migration (Zhong et al., 2008). Recent studies indicate differential abilities of two of the main cytoplasmic variants of ADAM-15 to cleave fibroblast growth factor receptor-2 IIIb (FGFR2-IIIb), with the Src-associating ADAM15B isoform displaying enhanced activity compared to the ADAM15A variant that lacks the ability to associate with Src (Maretzky et al., submitted for publication).

2.6. ADAM inhibitors

The ability of natural TIMPs to inhibit ADAMs is summarised in Table 1. In general, TIMPs display much greater selectivity towards the ADAMs than MMPs, and several ADAMs are inhibited exclusively by TIMP-3 (Baker et al., 2002). Indeed this latter characteristic has often been used to characterize the nature of the metalloprotease involvement in a shedding event, though as we learn more about the interplay between TIMPs and ADAMs more detailed evidence should be presented if ADAM involvement is suggested. TIMPs are two-domain molecules, with a larger N-terminal domain that is responsible for MMP inhibition, and a smaller C-terminal domain that provides specificity for additional protein–protein interactions including the pro-forms of particular MMPs. The mechanism of TIMP-MMP inhibition was solved by the crystal structure of the MMP-3/TIMP-1 complex (Gomis-Ruth et al., 1997), which revealed an elongated wedge-shaped ridge of TIMP-1 that docks with the active site cleft. This mechanism critically depends upon the sequence of the N-terminus of the mature TIMP molecule, since the first four residues lie in the active site in a fashion equivalent to the P1–P1′–P2′–P3′ residues of a peptide substrate. The N-terminal Cys1 residue is responsible for Zn-chelation via its α-amino and carbonyl groups. Extension of TIMPs by a single residue at the N-terminus renders them non-functional against MMPs, however a N-terminal domain TIMP-3 mutant extended by an Ala residue at its N-terminus retained activity against ADAM-17, indicating that the inhibitory mechanism is dissimilar (Wei et al., 2005). Moreover, a Thr2Gly replacement at position 2, which reduces the affinity of TIMP-1 for MMPs by three orders of magnitude, retained potency against ADAM-17. Further protein engineering studies of TIMPs have dissected the basis of TIMP-MMP and TIMP–ADAM interactions, and it is clear that sites distal to those involved in interactions in the active site cleft have profound influences. Indeed, although the N-terminal domain and full-length form of TIMP-3 are equally potent against the isolated catalytic domain of ADAM-17 (Lee et al., 2001), the extra-catalytic domains of ADAM-17, and in particular the Cys-rich region, substantially weakened the inhibitory effects of N-TIMP3 (Lee et al., 2003). The TIMP-3 forms studied by Wei et al. (2005) show positive co-operativity in binding to the whole ectodomain of ADAM-17, implying multiple interactions. Recent studies using stopped-flow X-ray spectroscopy show dynamic charge transitions at the active site Zn of ADAM-17 prior to substrate engagement with the ion, which implies communication between distal sites of the molecule and the catalytic core (Solomon et al., 2007). Further support for the importance of distal protein interactions between TIMPs and exosites away from the catalytic cleft come from the observations that the N-terminal domains of TIMP-1 and TIMP-3 are ineffective as inhibitors of ADAM-10 compared to the full-length TIMPs (Rapti et al., 2008).

There has been considerable interest in the development of synthetic inhibitors of ADAMs as therapeutic agents (Moss and Bartsch, 2004). Given the central importance of ADAM-17 in inflammatory processes, and the success of anti-TNF-α therapies in the treatment of rheumatoid arthritis, there is a strong case for the design of selective TACE inhibitors (Moss et al., 2008a). Likewise, ADAM-10 involvement in the shedding of HER2 from the cell surface (Liu et al., 2006) makes it a promising target for anti-cancer therapy (Moss et al., 2008b). As we have seen, the metalloproteinase catalytic domain has overall structural similarity with other metzincins (Section 2.1), but there are distinctive features that have allowed the development of a number of selective compounds. In particular the deep, curved hydrophobic S1′ pocket of ADAM-17, which merges below the surface with the deep S3′ pocket (Maskos et al., 1998) has been exploited to develop a range of compounds showing good selectivity and potency, with K_i's in the lower nM range (Condon et al., 2007; Huang et al., 2007; Niu et al., 2006; Wasserman et al., 2003). Four selective ADAM-17 inhibitors are in clinical trials for treatment of rheumatoid arthritis: BMS-561392 and TMI-005 (apratastat) progressed to phase II trials, and GI5402 and R618 are in phase I (Moss et al., 2008a). However further development of some of these compounds has already halted, including those in phase II trials, due to mechanism-based liver toxicity. It is possible that despite their toxicity profiles some of these potent, selective compounds might find clinical utility in other diseases such as cancer. In this regard, INCB3619 is a potent inhibitor of both ADAM-10 and -17 which reduced the processing of multiple EGFR ligands in vitro and in vivo in tumour-bearing mice, and reduced tumour growth appreciably (Fridman et al., 2007).

Among inhibitors that have proved to be selective for other ADAMs, G1254023X has 100× higher inhibitory activity against ADAM-10 compared to ADAM17 (Ludwig et al., 2005). This compound was used to provide evidence that ADAM-10 is involved in constitutive shedding of IL6R from cells, whereas PMA-stimulated shedding was inhibited by GW280264X, a mixed ADAM10/ADAM-17 inhibitor (Hundhausen et al., 2003; Ludwig et al., 2005). CGS27023 is a very efficient inhibitor of ADAM-9, with a K_i of 1 nM (Mochizuki and Okada, 2007). KB-R7785 is a potent ADAM-12 inhibitor that was identified by virtue of its ability to block HB-EGF shedding in cardiomyocytes (Asakura et al., 2002). This inhibitor blocked HB-EGF shedding and attenuated hypertrophy in mice treated with GPCR agonists.

Further insights into ADAM regulation will no doubt come from the demonstration that RECK (reversion-inducing cysteine-rich protein with Kazal motifs) inhibits ADAM-10-mediated Notch signalling in neural precursor cells (Muraguchi et al., 2007).

3. The biological functions of the ADAMs

In the sections that follow we review information on the actions of particular ADAMs in fertility, ectodomain shedding and cell signalling.

3.1. Fertility

The first mammalian ADAMs identified were the two subunits of the heterodimeric sperm protein fertilin, ADAM1 (fertilin-α) and ADAM2 (fertilin-β; Blobel et al., 1992), whose functions have been studied extensively in rodents (Primakoff and Myles, 2000; Primakoff and Myles, 2002). These proteins were originally proposed to be important for sperm–egg binding and fusion, since an anti-fertilin-β monoclonal antibody blocked guinea pig sperm–egg fusion. Fertilin-α and -β are proteolytically processed at different stages of sperm maturation by cleavage after the MP domain, leaving the disintegrin as the N-terminus of the sperm-associated proteins and thus potentially free to engage with egg integrins (Primakoff and Myles, 2000). In support of this, fertilin-β was shown to bind to α6β1 integrin (Almeida et al., 1995), and a peptide based on the disintegrin domain of fertilin-β blocked sperm–egg binding (Primakoff and Myles, 2000). Fertilin-β-null mice are infertile, but fertilin-β−/− sperm fuse with eggs in vitro at approximately 50% of the level of wild-type sperm, so fertilin-β is not essential for fusion (Primakoff and Myles, 2002). Sperm from these animals in fact show multiple defects in sperm–egg adhesion and fusion, in migration from the uterus, and in binding to the zona pellucida surrounding the egg (Cho et al., 1998). It transpires that there are complex relationships between ADAMs that are expressed in spermatogenic cells and sperm, such that deficiencies in one ADAM lead to reductions in the levels of several others that appear on the sperm surface (Kim et al., 2006). *Adam3* (Cyritestin)-null male mice are also infertile (Primakoff and Myles, 2002) and ADAM-7 and ADAM-5 are reduced on the surface of sperm from fertilin-β- and *Adam3*-null mice (Kim et al., 2006) Moreover, eggs from integrin α6-null mice bind and fuse normally with sperm (Primakoff and Myles, 2002). Thus the precise contributions of ADAMs in sperm function are still not clear. Some may function at early stages in spermatogenesis and in sperm migration in the uterus/oviduct and in zona pellucida binding, while some may function as chaperones to allow the correct assembly of ADAMs or other proteins on the sperm surface. How the situation in rodents relates to spermatogenesis and fertility in humans is also unclear, since many of the testis-specific *Adam* genes of rodents are represented only as pseudogenes in humans, including *ADAM1* and *ADAM3* (Puente and Lopez-Otin, 2004).

These testis-specific ADAMs are in an interesting state of evolutionary flux: *ADAMs 1, 4, 6, 20, 21, 24, 25, 26, 29, 30* and *34* – where present in a particular mammalian species – lack introns in their coding sequences, suggestive of pseudogenization (e.g. *ADAM20* is human-specific; *ADAM25* is a pseudogene in humans; *Adam26* is missing from humans, and a pseudogene in rat). *Adam24* encodes Testase-1, an apparently functional metalloprotease that is activated on the sperm plasma membrane (rather than in the Golgi apparatus) as sperm mature during transit in the epididymis (Zhu et al., 2001), implicating it in sperm function; again, however, the gene is missing in humans. Perhaps these testis- and sperm-specific ADAMs are indeed drivers of speciation events, whose substrates or adhesion partners on the egg or other female reproductive structures may mirror their rates of evolutionary change?

3.2. Ectodomain shedding The ADAM-17/TACE paradigm

The identification of the metalloproteinase responsible for the activation of the membrane-associated precursor form of tumour necrosis factor-α (TNF-α) was a landmark event in the protease field (Black et al., 1997; Moss et al., 1997). The involvement of the cytokine TNF-α in a variety of diseases associated with inflammation, including rheumatoid arthritis, cancer and Crohn's disease, made the mechanism of its activation of great clinical and pharmaceutical relevance. However, as discussed in Section 1.3, ADAM-17 has emerged as a sheddase with an extremely broad substrate range, with fundamental links to EGFR signalling. Since EGF and related ligands (HB-EGF, TGF-α, epiregulin, amphiregulin and betacellulin) are all produced initially as membrane-associated molecules that require proteolytic processing, this identifies ADAM-17 (and related sheddases) as upstream regulators of one of the most important signalling pathways in vertebrates.

Shedding of a membrane-anchored cytokine or growth factor by an ADAM proteinase could be relevant to various modes of signal transduction, including paracrine, autocrine and juxtacrine (Fig. 7). On the one hand, shedding may be required for the ligand to diffuse to engage with a receptor on the same cell (autocrine), or on neighbouring cells to act in a paracrine fashion; in addition proteolytic processing may activate a ligand that remains membrane associated, which can activate cells in a juxtacrine or autocrine fashion. Shedding may remove signalling ligands to down-modulate or terminate signalling. Likewise, cleavage and release of signalling receptors may down-modulate signalling capability on the cell surface, or generate soluble receptors that act as decoys by sequestering ligands.

In the years since its discovery, the repertoire of membrane-associated proteins that are susceptible to shedding/processing by ADAM-17 has grown immensely, as shown by the detailed listing in Table 2. However, other proteolytically active ADAMs can also act as sheddases, and two of the key concepts that have emerged are (1) that constitutive shedding may involve different enzymes from those that participate in signal-activated ectodomain cleavage and (2) different members of a family of substrates may be acted upon by different ADAM proteases in the same cell. The availability of cells from gene knockout mice has revolutionized the analysis of ADAM involvement in ectodomain shedding. For instance, study of cells
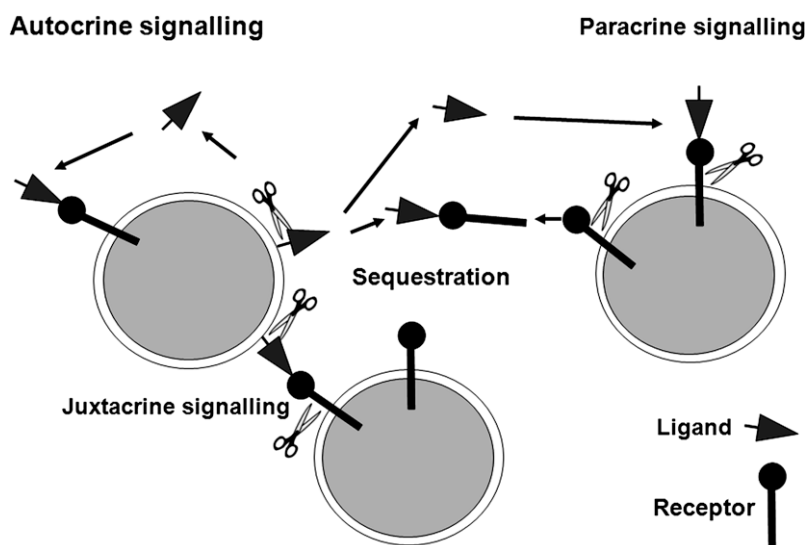
Fig. 7. ADAM metalloproteinases can influence autocrine, paracrine and juxtacrine signalling. The schematic depicts the potential actions of ADAMs (scissors) on receptor–ligand pairs, acting to release ligand that acts upon receptors on the cell of origin (autocrine), or on distant cells (paracrine). Juxtacrine signalling involving adjacent cells may involve ADAMs for correct presentation of the ligand, or for cleavage of the ligand following receptor engagement, or for receptor activation. Shed receptors may act as decoys, or cleavage of the receptor may itself activate or modulate signalling.

from cells derived from mice deficient in either ADAM-9, -10, 12, -15, 17 or -19 has shown that within the EGFR ligand family, ADAM-10 is the main sheddase for EGF and betacellulin, whilst ADAM-17 is largely responsible for cleavage of TGF-α, epiregulin, amphiregulin and HB-EGF (Sahin et al., 2004).

In many studies ADAM-17 has been shown to be responsible for induced shedding following activation of protein kinase-C (PKC) by phorbol esters such as PMA, whereas constitutive, PKC-independent shedding involves a distinct activity (Horiuchi et al., 2007b). For instance, using *Adam*-null cell lines and transfecting in functional ADAM proteins, Zheng et al. (2004) demonstrated involvement of ADAM-17 in phorbol-stimulated TNF-α shedding, but ADAM-19 was able to cause constitutive release following transfection of *Adam17*−/− cells, whereas ADAM-9, 10, and -19 could not. A typical pattern is shown by the L1 adhesion molecule, for which ADAM-10 mediates constitutive shedding while ADAM-17 carries out cleavage after phorbol stimulation or cholesterol depletion (Maretzky et al., 2005b). The calcium ionophore ionomycin activates ADAM-10 mediated shedding of CD30 (Eichenauer et al., 2007) and the chemokines CX3CL1 and CXCL16 (Hundhausen et al., 2007). It is important to understand the full physiological repertoire of the shedding events controlled by ADAMs such as ADAM-17 and the redundancy and compensation by multiple ADAM family members if these enzymes are to be targeted by pharmacological inhibitors.

3.3. GPCR-EGFR crosstalk: "Triple Membrane-Passing Signalling"

There is now a wealth of evidence that the activation of G-protein coupled receptors (GPCRs) leads to downstream activation of EGFR signalling via activation of ADAM-mediated EGFR ligand release (Blobel, 2005; Fischer et al., 2003). Table 6 lists several of these studies and further information can be found in the review by Ohtsu et al. (2006). The first clear demonstration that this GPCR-EGFR crosstalk involved cleavage of an EGFR ligand came from the work of Prenzel et al. (1999),

Table 6
ADAM involvement in GPCR-EGFR Crosstalk

Agonist	ADAM	EGFR ligand	References
Angiotensin II	ADAM17	HB-EGF TGFα	Lautrette et al. (2005), Mifune et al. (2005) and Schafer et al. (2004a)
	ADAM12	HB-EGF	Asakura et al. (2002)
Lysophosphatidic acid (LPA)	ADAM15	?	Schafer et al. (2004b)
	ADAM17	HB-EGF	Hart et al. (2005)
Thrombin	ADAM17	HB-EGF	Hart et al. (2005)
	ADAM15	HB-EGF	Hart et al. (2005)
Phenylephrine	ADAM12	HB-EGF	Asakura et al. (2002)
Bombesin	ADAM10	HB-EGF	Yan et al. (2002)
Carbachol	ADAM17	Amphiregulin	Gschwind et al. (2003)
Serotonin	ADAM-17	HB-EGF	Gooz et al. (2006)

who highlighted an absolute requirement for metalloproteinase activity by using batimastat, a broad spectrum synthetic inhibitor of MMPs and ADAMs, and further showed that that HB-EGF was involved from use of a mutant diphtheria toxin (Crm 7) that blocks HB-EGF function. This study explained the inability to identify free ligand in conditioned medium, since shed HB-EGF was retained in the pericellular ECM, and activation of EGFR signalling was critically dependent on high cell density. The transmembrane form of pro-TGFα is inactive in stimulating the EGFR on adjacent cells, such that ADAM-17 is essential for juxtacrine signalling (Borrell-Pages et al., 2003). In part this may involve ligand solubilisation to allow diffusion and action in a paracrine fashion, but by analogy with the ephrin-A5/EphA3 signalling scenario discussed earlier (Janes et al., 2005) it is possible that ADAM-17-mediated cleavage of the TGFα/EGFR complex may be necessary to elicit EGFR activation.

Depending on the cell and the stimulus involved the mechanisms involved in this cross-talk may differ, though the basic strategy of the "Triple Membrane-Passing Signal" (TMPS; Fischer et al., 2003) remains the same. This concept is encapsulated in Fig. 8. The intracellular linkages between GPCR and ADAM activation are still opaque, but participation of the cytoplasmic domain of the ADAM seems both logical and efficient. This aspect has been addressed by Grandis and colleagues, who have studied activation of EGFR signalling following stimulation of cells with gastrin-releasing peptide. They have demonstrated that Src is essential downstream of GPCR signalling to facilitate metalloproteinase-mediated amphiregulin release and EGFR activation (Zhang et al., 2004). Src was required for the GPCR-mediated activation of phosphatidyl inositol-3 kinase (PI-3K), which in turn led to activation of phosphatidyl inositol-dependent kinase-1 (PDK1), which directly phosphorylated ADAM-17 (Zhang et al., 2006). It is possible that in some circumstances TMPS may not involve the ADAM cytoplasmic domain since as we saw previously, phorbol ester activation of ADAM-17 can occur – at least in transfected cells – in the absence of the cytoplasmic domain (Reddy et al., 2000). However this type of mechanism is appealing since it provides a way to build specificity into the GPCR-ADAM crosstalk. This also could provide insights into the functional significance of the cytoplasmic domain splice variants seen, for example, for *ADAM15* (Zhong et al., 2008) and *ADAM22* (Godde et al., 2006; Sagane et al., 2005).

3.4. Regulated intramembrane proteolysis (RIP)

Regulated intramembrane proteolysis (RIP) can be defined as a sequential proteolytic cascade that involves an initial ecto-domain sheddase action on a transmembrane protein, followed by a subsequent cleavage within the membrane itself, which in many cases generates a signal-transducing intracellular domain fragment. The classical examples of regulated intramembrane proteolysis are Notch signalling and APP processing, which we have discussed in Section 1.3 in relation to the results from knockout mouse studies. These two processes are illustrated in Fig. 4, and further details can be found in Saftig and Hartmann, 2005; Tousseyn et al., 2006 and Murphy et al., 2008. The number of proteins that are now known to be subject to RIPping is growing. Many of these are adhesion molecules and substrates of ADAM-10, though RIPping is likely to be a widespread phenomenon involving many ADAM sheddases. RIPping substrates include CD44 (Nagano et al., 2004), N-cadherin (Reiss et al., 2005), E-cadherin (Maretzky et al., 2005a) and L1 (Maretzky et al., 2005b). In each of these cases, as with the Notch paradigm, cleavage by the extracellular ADAM creates a truncated transmembrane stub that becomes accessible for cleavage by an intramembrane-cleaving protease (I-CLiP), of which four types are known: the presenilins (which are the
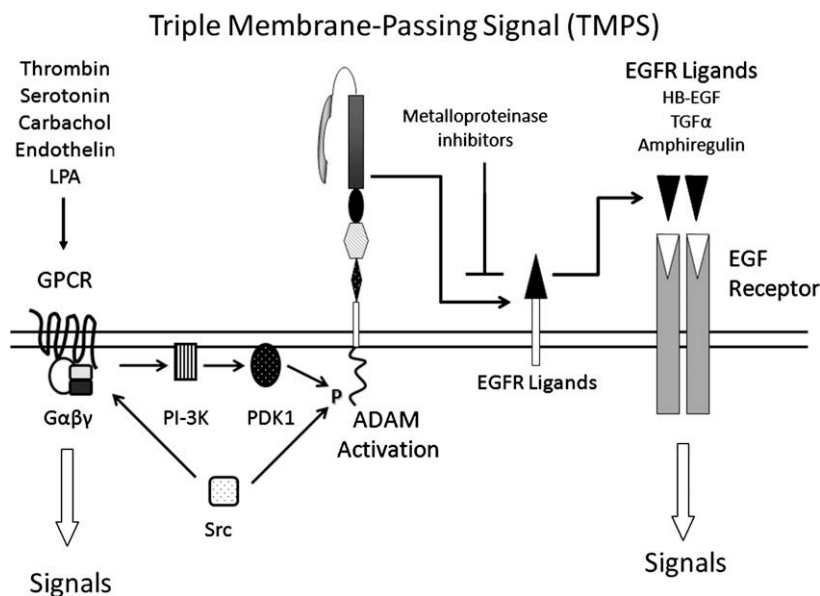

Fig. 8. Triple membrane passing signal: involvement of ADAMs in the crosstalk between GPCR and EGFR signalling. The model proposed is based on studies reported in Zhang et al. (2006).

proteolytic component of γ-secretase), the signal peptide peptidases, S2P, and the rhomboids (Spasic and Annaert, 2008). In many instances these cleavages generate an intracellular domain (ICD) that moves off to the nucleus and influences gene transcription, as is the case for Notch (Fig. 4). For both N- and E-cadherin, cleavage leads to disruption of cell adhesion mediated by the extracellular domains, and a redistribution of β-catenin from the cell surface to the nucleus to activate target genes, leading to epithelial–mesenchymal transition in the case of E-cadherin (Maretzky et al., 2005a; Reiss et al., 2005). In addition the N-cadherin ICD is reported to act as a signal transducer by binding to the transcriptional coactivator CBP and inducing its proteasomal degradation (Marambaud et al., 2003).

In addition to Notch, the Notch ligand Delta 1 is also subject to RIPping (Six et al., 2003). Cleavage of Delta by ADAM-10 had originally been considered to allow the ligand to diffuse to distant Notch receptors (Qi et al., 1999) but subsequently it was recognized that the released ligand was inactive, leading to the suggestion that this was a mechanism to allow spatial control of Notch signalling (Mishra-Gorur et al., 2002). However it was subsequently realized that the ADAM-10-mediated cleavage of Delta1 led to γ-secretase-mediated processing of the transmembrane stub generating an ICD that translocated to the nucleus (Six et al., 2003). Thus this could represent the same bidirectional signalling that has been seen for the proteolysis of the ephrin-A5/EphA3 complex by ADAM-10 (Janes et al., 2005). The ICDs generated by RIPping may have multiple roles in cell signalling in addition to effects on transcription in the nucleus: for instance, the ICD generated by γ-secretase action on ephrinB2 causes activation of Src by binding and inhibiting Csk, a kinase that phosphorylates and inhibits Src. Src in turn phosphorylates ephrinB2, preventing its cleavage by γ-secretase and establishing a feedback loop (Georgakopoulos et al., 2006).

Although much of the current data focus on ADAM-10 as the major "RIPping sheddase", we should not exclude other ADAMs from consideration in this role. There are reports that ADAM-17 cleaves the p75 neurotrophin receptor (p75NTR), followed by nuclear translocation of the ICD and induction of apoptosis (Srinivasan et al., 2007). RIPping is an important and much-employed biological mechanism in which many ADAMs likely participate.

4. ADAM involvement in human disease

The fundamental nature of the biological processes controlled by ADAM proteinases mandates that dysregulation of these enzymes will contribute to pathogenetic mechanisms of human disease. ADAMs have been implicated in cancer, neurological and cardiovascular diseases, asthma, infection and inflammation. Table 7 provides information on some of the known disease associations and further information can be found in two excellent recent reviews (Mochizuki and Okada, 2007; Tousseyn et al., 2006). Here we will highlight some of the key mechanistic principles.

As active metalloproteinases, ADAMs may have a role in promotion of tumour invasion and metastasis via cleavage of extracellular matrix proteins. Certainly ECM targets are included among lists of known substrates (Table 2), but in general this does not seem to be the major connection of these enzymes to cancer progression. That said, there are exceptions, as is the case for ADAM-9 which can cleave laminin and promote invasion (Mazzocca et al., 2005). ADAMs may directly modulate tumour cell adhesion in by interactions with integrins and proteoglycans as discussed in Sections 2.3 and 2.4 (and see also (Arribas et al., 2006)). Isolated domains of ADAMs can have potent effects on these aspects of tumourigenesis, as evidenced by the antiangiogenic and anti-metastatic actions of the disintegrin domain of ADAM-15 (Trochon-Joseph et al., 2004); whether these effects are relevant to naturally occurring forms of these molecules is still unclear. Several studies have however linked ADAM-10 to cleavage of the adhesion molecules N-, E- and VE-cadherin (Maretzky et al., 2005a; Reiss et al., 2005; Schulz et al., 2008). These will have profound effects on tumour cell phenotype, resulting in altered patterns of adhesion and migration, and influence on downstream gene expression via activation of β-catenin signalling or direct effects of the RIPped intracellular domain. Likewise, the shedding of adhesion molecules such as Selectins, ICAM-1, VCAM-1, PECAM-1 by ADAMs will affect tumour cell adhesion to the vasculature. By ectodomain shedding ADAMs may mobilize growth factors, chemokines and other soluble mediators or influence signalling via cognate receptors as we have discussed in Section 3.2. This is particularly pertinent for ADAM-17 and EGFR signalling, where direct relationships between ADAM-17 and TGFα have been clearly documented in human breast cancer (Borrell-Pages et al., 2003; Kenny and Bissell, 2007).

An important area of ADAM participation in normal and pathogenetic processes is their influence on inflammatory responses (reviewed by Garton et al., 2006; Ponnuchamy and Khalil, 2008; Murphy et al., 2008). Leukocyte recruitment in response to inflammatory stimuli is a multistep process that involves (1) rolling and tethering on the vascular endothelium, which is mediated by Selectins and their ligands; (2) activation and firm adhesion, which depends on chemokine activation of leukocyte integrins and their associations with vascular adhesion moledules such as ICAM-1 and VCAM-1; (3) locomotion to endothelial cell junctions, again dependent on leukocyte integrins and adhesion partners; and (4) diapediesis across the endothelial layer and basement membrane, which involves PECAM-1 and CD99 (Garton et al., 2006; Ponnuchamy and Khalil, 2008). L-selectin shedding by ADAMs affects the rolling of leukocytes across the endothelium such that blockade of shedding promotes leukocyte adhesion and activation (Hafezi-Moghadam and Ley, 1999). ADAM-mediated L-selectin shedding is necessary also to allow transendothelial migration (Faveeuw et al., 2001). Evidence points to involvement of ADAM-17 in shedding of L-selectin, ICAM-1 and V-CAM-1 (Garton et al., 2006) and ADAM-10 in cleavage of VE-cadherin, thereby enhancing vascular permeability and transmigration of leukocytes (Schulz et al., 2008). Moreover, both ADAM-10 and -17 process chemokines (see Table 2) which drive the activation process and facilitate chemoattraction. ADAM-17 controls TNF-α-mediated inflammation by regulating pro-TNF-α activation and the shedding of TNFRs. The importance of TNFR shedding is

Table 7
Associations of ADAMs with human diseases

ADAM	Pathology association	Observation	References
ADAM8	Cancer	Overexpression in pancreatic cancer associated with reduced patient survival	Valkovskaya et al. (2007)
		Upregulated in gliomas and associated with local invasion	Wildeboer et al. (2006)
	Rheumatoid arthritis	Levels of shed ADAM-8 in synovial fluid correlate with joint inflammation	Gomez-Gaviro et al. (2007)
ADAM9	Cancer	Upregulated in breast cancer	O'Shea et al. (2003)
		Promotes invasion of colon cancer cells by binding to α6β4 and α2β1 integrins	Mazzocca et al. (2005)
		Upregulation in prostate, breast and intestinal cancers. Mouse knockout suppressed malignancy in a model of prostate cancer	Peduto et al. (2005)
		High ADAM9 levels predict higher efficacy of tamoxifen therapy in ER+ breast cancers	Sieuwerts et al., 2005
		Overexpression in non-small cell lung cancer linked to brain metastasis	Shintani et al. (2004)
		Cytoplasmic ADAM9 overexpression associated with poorer survival in pancreatic ductal adenocarcinoma	Grutzmann et al. (2004)
ADAM10	Inflammation	Cleavage of VE-cadherin and increased endothelial permeability	(Schulz et al., 2008
	Cancer	Upregulated in prostate cancer	McCulloch et al. (2000)
		Nuclear localization associated with Gleason score in prostate cancer	Arima et al. (2007)
		Shedding of CD30 from lymphoma cells linked to failure of antibody-based immunotherapy	Eichenauer et al., 2007
	Ageing	Shedding of anti-ageing Klotho protein	Chen et al. (2007)
	Allergic responses	Shedding of soluble CD23 promotes IgE production	Weskamp et al. (2006) and Lemieux et al. (2007)
	Alzheimer's disease	Reduced immunostaining in neurons in AD brains versus controls	Bernstein et al. (2003)
ADAM12	Cancer	Increased levels in urine of breast cancer patients	Roy et al. (2004)
		Upregulated in breast cancer and associated with decreased tumour cell apoptosis	Kveiborg et al. (2005)
		Increased mutation frequency detected in breast cancer genome sequencing	Sjoblom et al. (2006)
		Increased in bladder cancer	Fröhlich et al. (2006)
	Pre-eclampsia	Reduced maternal serum ADAM-12 levels	Laigaard et al. (2005)
	Down syndrome	Reduced maternal serum ADAM-12 levels	Laigaard et al. (2003)
ADAM15	Cancer	Increased expression in aggressive breast and prostate cancer	Kuefer et al. (2006)
		Differential association of splice variants with prognosis in breast cancer	Zhong et al. (2008)
		Increased expression in lung cancer cells at invasion front	Schutz et al. (2005)
		Increased copy number in breast cancer cell lines	Ortiz et al. (2004)
ADAM17	Cancer	Over-expressed in breast cancer at protein level and required for activation of pro-TGFα	Borrell-Pages et al. (2003)
		Increased protein expression in breast cancer	Santiago-Josefat et al. (2007)
		Over-expressed in breast cancer and associated with tumour progression and metastasis	McGowan et al. (2007)
		Correlation with TGFα expression in breast cancer and predictive of outcome	Kenny and Bissell (2007)
		Predicts adverse outcome in breast cancer	McGowan et al. (2008)
	Rheumatoid arthritis	Upregulation in synovial cells in RA but not OA, and associated with HIF-1 expression	Charbonneau et al. (2007)
	Multiple sclerosis	Increased expression in blood vessels, macrophages and astrocytes in active lesions	Plumb et al. (2006)
	Diabetes	Increased expression in monocytes in response to LDL from diabetic patients versus controls	Worley et al. (2007)
ADAM19	Cancer	Upregulated in gliomas and associated with local invasion	Wildeboer et al. (2006)
ADAM22	Cancer	Decreased expression in gliomas	D'Abaco et al. (2006)
ADAM29	Cancer	Increased mutation frequency detected in colorectal cancer genome sequencing	Sjoblom et al. (2006)
ADAM33	Asthma	SNPs associated with asthma susceptibility	Van Eerdewegh et al. (2002)
	Psoriasis	SNPs associated with psoriasis	Lesueur et al. (2007)
ADAMDEC1	Atherosclerosis	Upregulated in unstable versus stable atherosclerotic plaque	Papaspyridonos et al. (2006)

highlighted by the discovery that the dominantly inherited chronic inflammatory disorder TNFR-associated periodic syndrome (TRAP) is caused by mutations that impair shedding of TNF-R1 (McDermott et al., 1999). Inflammation is essential for the body to cope with infectious agents, but excessive inflammation contributes to disease pathogenesis in arthritis, cancer, cardiovascular disease, and a host of autoimmune conditions. Thus many of the disease connections of ADAMs may actually be underpinned by fundamental roles in inflammation.

Extending the immunological connection of ADAMs in human pathologies, we come to the association of *ADAM33* with asthma. Linkage studies identified *ADAM33* as a candidate asthma-susceptibility locus, and numerous polymorphisms were identified in both coding and non-coding regions, the latter suggestive of effects on splicing or transcriptional control (Van Eerdewegh et al., 2002). The function of ADAM-33 in asthma is currently unknown. It is expressed by smooth muscle cells and fibroblasts of the airway rather than inflammatory cells, and many splice variants have been reported, some of which omit the metalloproteinase domain (Powell et al., 2004). Thus its role may be in adhesion or via critical protein–protein interactions. Notably *ADAM8*, which is predominantly expressed by hematopoietic cells, is upregulated in inflammatory cells in an experimental allergen-induced model (King et al., 2004). Expression of both *ADAM33* and *ADAM8* increases in line

with disease severity in bronchial samples from patients with asthma, consistent with roles in promoting disease progression (Foley et al., 2007).

Finally with regard to Alzheimer's disease, it is now clear that ADAM-9, -10, and -17 can act as α-secretases, possibly acting as a team (Allinson et al., 2003), and thus potentially alter the balance of metabolism of APP towards the non-amyloidogenic pathway. The reduced expression of ADAM-10 in neurons in AD brains compared to controls is consistent with a primary role for this enzyme (Bernstein et al., 2003). Conceivably, therapies could be envisaged that increase α-secretase levels and there is evidence to support positive effects of steroid hormones, non-steroidal anti-inflammatory drugs, metal ions and cholesterol lowering drugs (Allinson et al., 2003). However, the caveat is that we need to understand much more about the multifaceted roles of ADAMs in tissue homeostasis and their positive links with disease pathogenesis that are summarised in Table 7.

5. Concluding remarks

Our knowledge of the remarkable mammalian ADAM family has come a long way since the discovery of the first members as sperm-associated proteins in the early 1990s (Blobel, 1997). It is now clear that these proteases regulate cell phenotype and behaviour by ectodomain shedding and RIPping, and that separately from their proteolytic functions, many influence cell-cell communication via adhesive interactions. There are growing links with human diseases, many reflecting involvement in inflammatory processes, and ADAMs are thus attractive targets for novel therapies. There are several priority areas for future investigations. Firstly, we need more information on ADAM structure, and in particular the structure of full-length molecules. The recent crystallographic analysis of SVMPs have provided radical new insights into the topology of the molecules and how domains may act together to execute substrate docking and catalysis. In these new structures the disintegrin loop is buried and inaccessible, which raises questions about its role in protein–protein interactions. Thus more knowledge of the post-translational processing of the ADAMs and the structures of these proteolytically cleaved or otherwise modified forms will unlock a wealth of mechanistic information. This information will also be valuable for the design of more selective inhibitors that might interfere with function via interactions with exosites involved in substrate recognition or protein–protein interactions, rather than catalysis *per se*. A second and related issue is the need to understand the significance of variant form of the ADAMs that are produced by alternative splicing. As we have seen, many of these affect the cytoplasmic domain, and we need to look more closely at the how these domains may be involved in particular aspects of ADAM function such as regulated trafficking, interaction partner selection and coupling to signal transduction pathways. Thirdly, given the critical roles of many ADAMs in key developmental processes, use of conditional and inducible mouse knockouts in conjunction with disease models is essential. Finally, this review has not dealt extensively with the control of ADAM expression since very little is known at present. Though it is clear that several *ADAMs* are subject to transcriptional regulation (Worley et al., 2003), it is likely that control at this level may not be as significant as that of their relatives the MMPs (Clark et al., 2008) since there are already strong clues that post-transcriptional regulation is key, at least for *ADAM17* (Santiago-Josefat et al., 2007). Thus the study of the roles of microRNAs in *ADAM* control may prove very revealing (Dalmay and Edwards, 2006).

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