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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.

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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 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 repolysins 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,
| 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 | NM_001464        | 8p11.2   | No                    | Yes (NM_009618)           | No study            | Testis                                                                             |
| ADAM3  | CRYN1, tMDCI                       | NR_001569        | 8p21-p12 | Pseudogene            | Yes (NM_009619)           | –                   | –                                                                                 |
| ADAM5  | TMDCII                            | NR_001448        | 8p11.2   | Pseudogene            | Yes (NM_007401)           | –                   | –                                                                                 |
| ADAM6  | tMDCIV; 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, MCM9, 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, HsTi8717, 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 Placenta, mesenchymal stem cells, adult stem cells |
| ADAM12 | RP11-29S3.5, MCM9, MCMPM, Mtna, MLT, MLTNA, Meltrin alpha | v1 NM_003474 v2 NM_021641 | 10q26.3 | Yes                   | Yes (NM_007400)           | TIMP-2 TIMP-3       | –                                                                                 |
| 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) Testis, erythrocytes, bone marrow, pancreas |
| ADAM18 | ADAM27, MGC41836, MGC88272, tMDCIII | NM_014237 | 8p11.22 | No | Yes (NM_010084) | – | |
| ADAM19 | FKSG34, MADAM, MLTNB | v1 NM_023038 v2 v3 NM_033274 | 5q32-q33 | Yes | Yes (NM_009616) | None | Widespread (highest in placenta, mesenchymal stem cells, lymphatic system, heart) Testis, erythrocytes, bone marrow |
| ADAM20 | ADAM31, MGC125389 | NM_003813 | 14q24.1 | Yes | No | No study | Testis, erythrocytes, central and peripheral nervous systems |
| ADAM21 | MDC2, MGC149832 | v1 NM_021723 v2 NM_021722 v3 NM_016351 v4 NM_004194 v5 NM_021721 | 7q21 | No | Yes (NM_00107220, NM_001007221, NM_001098225) | – | Peripheral and central nervous systems |
| ADAM22 | MDC3, MDC-Lm, MDC-Ls, MDC, eMDC | NM_003812 v1 NM_014265 v3 NM_021777 | 2q33 | No | Yes (NM_011780) | TIMP-3 | Peripheral and central nervous systems, heart Testis, erythrocytes, bone marrow, myeloid cells, lymphatic system, respiratory system, bladder |
| ADAM23 | MDC3, MDC-Lm, MDC-Ls, MDC, eMDC | NM_003812 v1 NM_014265 v3 NM_021777 | 2q33 | No | Yes (NM_010082, NM_183366) | TIMP-4 | |
| 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) | TIMP-3 | Blood lymphoid cells |
| ADAM33 | RPS-964F7.2, DJ964F7.1, DKFZp434K0521, FLJ35308, FLJ36751, MGC149823, MGC71889 | v1 NM_025220 v2 NM_153202 | 20p13 | Yes | Yes (NM_033615) | 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 | Lympatic 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).
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 $\alpha_{IIb}\beta_{IIIa}$ 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-Gavirio 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 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-betaCELLuliotherin                         | 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 PrPα                      | 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                                      | Naji 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-eiregulin                                   | 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 iiil                              | Reddy et al. (2000)                            |
|        | Amyloid precursor protein (APP)                 | Buxbaum et al. (1998) and Slack et al. (2001)  |

(continued on next page)
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 (HELGHVLGMPD), 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).
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 (Schloendorf 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

| 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) |
| Adam3         | Male infertility, defects in sperm migration and adhesion | Murose et al. (2008) |
| 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) |
| Adam13        | 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, TGFz, 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) |
Notch, APP is a transmembrane protein subject to RIIping via metallocproteinase 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 (APPsβ) that is non-amyloidogenic (Schlondorf 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 knockout 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−/− 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 Adam17-/- 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 glutamatergic 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 actions, 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-sheet 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 zβ helix of the Adamalydin II 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 (S1S2S3S4S5S6) determining specificity for particular amino acid sequences (P0P1P2P3P4P5) in the substrate, where cleavage occurs between the P1 and P2 residues (Fig. 5B). The topology of this groove, and in particular the depth and hydrophobicity of the S1 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 Ca2+ 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).
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” (Ds) and “arm” (Da) domains. The N-terminus region of the Cys-rich (C) domain that follows is termed a “wrist” (Cw) domain, and together the Ds, Da and Cw 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 Ca2+-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 Cw-domain and is thus inaccessible for binding (Takeda et al., 2006). The “wrist” Cw domain is followed by a “hand” Cb 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
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 known 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 αβ 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-
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 CRXXXXCDXXE (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, αβ1, αβ3, αβ5 (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 αβ3 versus the RGD-independent association with αβ1. This mapped the αβ1-interaction site to a motif RXXXXXDLPEF (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 αβ1, 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 αβ1 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 (αβ4β1, α5β1 or both), ADAM12 inhibited migration of αβ1-expressing cells but not those expressing αβ1, 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 disintegrin-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 from 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 PKCδ (Sundberg et al., 2004). The SH3-domain-containing protein PACSIN3, which is involved in endocytosis and interacts with other 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 inositol 3-kinase (PI3K) via SH3 domain/pro-motif interactions (Kang et al., 2001). 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...
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 PKD1, 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.

Table 5
ADAM cytoplasmic domain interaction partners

| ADAM   | Interaction partners | References                   |
|--------|---------------------|------------------------------|
| ADAM-9 | PKCδ, Endophilin-1, SH3PX1, Src, MAD2β, Eve-1, PACSIN3 | Izumi et al. (1998)          |
| ADAM-10| Lck, MAD2, SAP97, Eve-1, PACSIN3 | Poghosyan et al. (2002)      |
| ADAM-12| Abl, Grb2, Pl-3K p85α, Src, Yes, α-Actinin-1, α-Actinin-2, MAD2β, PKCδ, Src, Pl-3K p85α, PACSIN3, Eve-1, PKCδ, Tks5/Fish | Suzuki et al. (2000)          |
| ADAM-13 (Xenopus) | Grb2, Abl, Fyn, Src, Hck, Lck, Bcr-Abl, MAD2, Grb2, Src, Tks5/Fish, Brk, Erk, Endophilin-1, SH3PX1, MAD2β, Hck, Lck, SNX30, Tks5/Fish, Erk, MAD2, SAP97, Eve-1, FHL2, PTPH1, PKD1, Endophilin-1, ArgBP1, β-cop, ubiquitin, Tks5/Fish, PACSIN3 | Hao et al. (2008), Howard et al. (1999), Nelson et al. (1999), Asakura et al. (2002), Kang et al. (2000), Kang et al. (2001), Mori et al. (2003), Tanaka et al. (2004), Sundberg et al. (2004), Abram et al. (2003), Cousin et al. (2000), Poghosyan et al. (2002) |
| ADAM-15| 14-3-3 family, 14-3-3 zeta PSD-95 | Godde et al. (2006)          |

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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 characterise the nature of the metalloproteinase 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 for MMP inhibition, and a smaller C-terminal domain that provides specificity for additional protein–protein interactions.

The 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 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 observation 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 (Masks et al., 1998) has been exploited to develop a range of compounds showing good selectivity and potency, with Kᵢ’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 Kᵢ 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 (Cortitestrin)-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 protease 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...
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/C0/C0 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),

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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) |
| Angiotensin II           | ADAM12| HB-EGF          | Asakura et al. (2002)                           |
| Lysophosphatidic acid (LPA) | ADAM15| ?               | Schafer et al. (2004b)                          |
| Lysophosphatidic acid (LPA) | ADAM17| HB-EGF          | Hart et al. (2005)                              |
| Thrombin                 | ADAM17| 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 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-TGF\(\alpha\) 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 TGF\(\alpha\)/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 ectodomain shedding 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).](image-url)
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 (Misrha-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 (James et al., 2005). The ICDs generated by RIPping may have multiple roles in cell signaling 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 TGFβx have been clearly documented in human breast cancer (Borrrell-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 Selectin and their ligands; (2) activation and firm adhesion, which depends on chemokine activation of leukocyte integrins and their associations with vascular adhesion molecules such as ICAM-1 and VCAM-1; (3) locomotion to endothelial cell junctions, again dependent on leukocyte integrins and adhesion partners; and (4) diapedesis 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
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 inflammation.

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**Table 7**

Associations of ADAMs with human diseases

| ADAM     | Pathology association | Observation                                                                                                                                       | References                                |
|----------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| ADAM8    | Cancer                | Overexpression in pancreatic cancer associated with reduced patient survival Upregulated in gliomas and associated with local invasion           | Valkovskaya et al. (2007)                |
|          | Rheumatoid arthritis  | Levels of shed ADAM-8 in synovial fluid correlate with joint inflammation Upregulated in breast cancer                                             | Wildeboer et al. (2006)                  |
|          | Cancer                | Promotes invasion of colon cancer cells by binding to α6β4 and α2β1 integrins Upregulation in prostate, breast and intestinal cancers. Mouse knockout suppressed malignancy in a model of prostate cancer | Gomez-Gavio et al. (2007)                |
|          |                       | High ADAM9 levels predict higher efficacy of tamoxifen therapy in ER+ breast cancers                                                               | O'Shea et al. (2003)                     |
|          |                       | Overexpression in non-small cell lung cancer linked to brain metastasis Cytoplasmic ADAM9 overexpression associated with poorer survival in pancreatic ductal adenocarcinoma | Mazzocca et al. (2005)                   |
| ADAM9    | Inflammation          | Cleavage of VE-cadherin and increased endothelial permeability Upregulated in prostate cancer                                                      | D'Abaco et al. (2006)                    |
|          | Cancer                | Nuclear localization associated with Gleason score in prostate cancer Shedding of CD30 from lymphoma cells linked to failure of antibody-based immunotherapy | Kuefer et al. (2006)                     |
|          | Ageing                | Shedding of anti-ageing Klotho protein                                                                                                           | Chen et al. (2007)                       |
|          | Allergic responses    | Shedding of soluble CD23 promotes IgE production                                                                                                 | Weskamp et al. (2006)                    |
|          | 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 Upregulated in breast cancer and associated with decreased tumour cell apoptosis             | Roy et al. (2004)                        |
|          | Pre-eclampsia         | Increased mutation frequency detected in breast cancer genome sequencing                                                                       | Sjoblom et al. (2006)                    |
|          | Down syndrome         | Increased in bladder cancer                                                                                                                     | Fröhlich et al. (2006)                   |
| ADAM15   | Cancer                | Increased expression in aggressive breast and prostate cancer Differential association of splice variants with prognosis in breast cancer Increased expression in lung cancer cells at invasion front Increased copy number in breast cancer cell lines | Kuefer et al. (2006)                     |
|          |                      | Reduced maternal serum ADAM-12 levels                                                                                                              | Liagard et al. (2005)                    |
| ADAM17   | Cancer                | Over-expressed in breast cancer at protein level and required for activation of pro-TGFα Increased protein expression in breast cancer         | Sjoblom et al. (2006)                    |
|          |                      | Over-expressed in breast cancer and associated with tumour progression and metastasis Correlation with TGFα expression in breast cancer and predictive of outcome Predicts adverse outcome in breast cancer | Kenny and Bissell (2007)                 |
|          | Rheumatoid arthritis  | Upregulation in synovial cells in RA but not OA, and associated with HIF-1 expression                                                             | Charnonneau 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                                                                                     | Papaspyridou et al. (2006)               |
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 \( \alpha \)-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 \( \alpha \)-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 RILPping, 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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