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Ectodomain shedding and ADAMs in development

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Summary

Proteolytic enzymes belonging to the A Disintegin And Metalloproteinase (ADAM) family are able to cleave transmembrane proteins close to the cell surface, in a process referred to as ectodomain shedding. Substrates for ADAMs include growth factors, cytokines, chemokines and adhesion molecules, and, as such, many ADAM proteins play crucial roles in cell-cell adhesion, extracellular and intracellular signaling, cell differentiation and cell proliferation. In this Review, we summarize the fascinating roles of ADAMs in embryonic and adult tissue development in both vertebrates and invertebrates.

Key words: ADAM, Notch, Ectodomain shedding, Cell fate determination, Differentiation

Introduction

Proteins belonging to the 'A Disintegrin And Metalloproteinase' (ADAM) family are membrane-anchored proteases that are able to cleave the extracellular domains of membrane-bound proteins in a process known as 'ectodomain shedding'. Typical substrates of ADAM proteases are growth factors, cytokines, chemokines and their receptors, as well as cell adhesion molecules and differentiation factors (Reiss and Saftig, 2009). ADAMs were initially discovered as novel type I transmembrane proteins with homology to snake venom integrin ligands and that played a functional role during guinea-pig sperm-egg fusion (Blobel et al., 1992). Subsequently, approximately half of the ADAM family members were predicted and then shown to possess zinc-dependent protease activity related to that exhibited by adamalysins metallopeptidases (Wolfsberg et al., 1993; Huxley-Jones et al., 2007). These active 'sheddases' (ADAM8, 9, 10, 12, 15, 17, 19, 20, 21, 28, 30 and 33) share a typical consensus sequence (HEXGHXXGXXHD) that is present in zinc-binding proteases (Bode et al., 1993). So far, 40 family members have been identified in the mammalian genome (Puente and Lopez-Otin, 2004; Edwards et al., 2008), of which 37 are expressed in mice (most of them in a testis-specific manner) and 22 are thought to be expressed in humans (Table 1). In both mouse and human, intronless coding sequences probably representing pseudogenes (e.g. human ADAM5P and ADAM6) have also been described. The expression of ADAM or ADAM-related proteins has also been described in many different species, including the yeast *Schizosaccharomyces pombe*, the nematode worm *Caenorhabditis elegans*, the frog *Xenopus laevis*, the zebrafish *Danio rerio* and the fruitfly *Drosophila melanogaster* (Alfandari et al., 1997; Nakamura et al., 2004; Huxley-Jones et al., 2007; Iida et al., 2010). It was quickly realized that ADAMs are widely expressed and play fundamental roles during developmental processes, by regulating cell-cell and cell-matrix interactions and by modulating differentiation, migration, receptor-ligand signaling or repulsion (Becherer and Blobel, 2003).

Following studies of the catalytically active ADAMs, ectodomain shedding emerged as a central biological event. This proteolytic process primarily affects type I and type II transmembrane proteins, although glycosylphosphatidylinisotol (GPI)-anchored proteins have also been reported as targets for surface shedding (Vincent et al., 2001). It is still unclear whether multipass transmembrane proteins are also substrates for ADAMs. However, in most cases, ectodomain shedding leads to the modulation of signaling activity on host and neighboring cells either through downregulation of cell surface receptors or increased liberation of soluble ligands such as tumor necrosis factor α (TNFα) or epidermal growth factor receptor (EGFR) ligands (reviewed by Blobel, 2005; Edwards et al., 2008; Reiss and Saftig, 2009). Additionally, ectodomain shedding usually represents a rate-limiting step for further cleavage events within the plasma membrane, a process called regulated intermembrane proteolysis (RIP) that is best understood for the proteolytic processing of Notch receptors (Kopan and Ilagan, 2009; Andersson et al., 2011). RIP can be mediated either by the γ-secretase complex (for type I transmembrane proteins) or the signal peptide peptidase-like (SPPL) proteases (for type II transmembrane proteins) (Fluhrer and Haass, 2007; De Strooper and Annaert, 2010). Ectodomain shedding is a prerequisite for intramembrane proteolysis in the case of type I transmembrane substrates. The same apparently holds true for the SPPL family members 2A and 2B (Martin et al., 2008; Fluhrer et al., 2009; Martin et al., 2009) whereas no information about the mode of RIP is available yet for SPPL2C and SPPL3.

Dysregulation of a properly regulated shedding activity has been shown to be a crucial factor in the development of complex pathologies such as cancer, cardiovascular disease, inflammation and neurodegeneration (Duffy et al., 2009b). Following this, ADAMs have been implicated in a number of human diseases (Box 1). Furthermore, gain- and loss-of-function experiments in various model organisms have revealed that a number of ADAMs are needed to control tissue development and homeostasis. Here, we aim to provide an overview of our current knowledge about the role of ADAM proteases in developmental processes.

Structure and localization of ADAM proteases

ADAMs have a typical modular structure (Fig. 1): they contain a cytoplasmic domain (CD), a transmembrane domain (TMD), an EGF-like domain (EGF) and/or a cysteine-rich domain, a disintegrin domain (DIS), and a protease (PROT) domain, which may or may not contain an active site. They also possess an N-terminal signal sequence that directs the protease into the secretory pathway as a type I transmembrane protein. Adjacent to this signal sequence is a prodomain that controls correct protein folding and is removed by pro-protein convertases or autocatalytic processes during its transit through the Golgi apparatus (Lum et al., 1998; Roghani et al., 1999; Howard et al., 2000; Schlomann et al., 2002).

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Table 1. Human ADAM proteases and their suggested functional roles

Human ADAM gene	Proteolytic activity	Other names	Orthologs in other species	Suggested function
ADAM1	No	fertilin alpha, PH-30a, Ftna, FTNAP	*Bos taurus*, *Cavia porcellus*, *Gorilla gorilla*, *Macaca fascicularis*, *Mus musculus*, *Oryctolagus cuniculus*, *Papio hamadryas anubis*, *Pongo pygmaeus*, *Rattus norvegicus*, *Saguinus oedipus*, *Tupaia glis*	Possibly involved in sperm-egg fusion
ADAM2	No	fertilin beta, PH-30b, FTNB, CRYN1, CRYN2, PH30	*B. taurus*, *C. porcellus*, *M. fascicularis*, *M. musculus*, *O. cuniculus*, *R. norvegicus*, *Sus scrofa*	Possibly involved in sperm-egg fusion
ADAM3A	No	tMDC, CYRN1 (cyritestin), TAZ83	*M. musculus*, *M. fascicularis*, *R. norvegicus*	Possibly involved in sperm-egg fusion
ADAM5P	No	tMDVII	*C. porcellus*, *M. fascicularis*, *M. musculus*	Unknown, possibly a pseudogene
ADAM6	No	tMDCIV, C14orf96	*C. porcellus*, *M. fascicularis*, *M. musculus*, *O. cuniculus*, *R. norvegicus*	Unknown, possibly a pseudogene
ADAM7	No	EAPI, GP83, GP-83	*M. musculus*, *M. fascicularis*, *R. norvegicus*	Possibly involved in sperm-egg fusion
ADAM8	Yes	CD156, MS2, MGC13495	*M. musculus*, *Danio rerio*	Involved in cell adhesion during neurodegeneration; a target for allergic respiratory diseases, including asthma
ADAM9	Yes	MCMP, MDC9, KIAA0021, Mltng, meltrin gamma	*B. taurus*, *M. musculus*, *S. scrofa*, *Xenopus laevis*	Involved in induced ectodomain shedding of membrane-anchored heparin-binding EGF-like growth factor; suggested to cleave APP at the α-secretase site
ADAM10	Yes	CD156c, HsT18717, MADM, kuz	*B. taurus*, *Caenorhabditis elegans*, *D. rerio*, *Drosophila melanogaster*, *Gallus gallus*, *M. musculus*, *R. norvegicus*, *S. scrofa*, *X. laevis*	Involved in shedding of various transmembrane proteins, including cadherins Major Notch-site 2 protease; α-secretase for APP; controls wound healing, neurogenesis, skin homeostasis
ADAM11	No	MDC	*M. musculus*, *X. laevis*	Candidate tumor suppressor gene for human breast cancer, pain transmission, synaptic modulation
ADAM12	Yes	MCMP, MCMPMltna, MLTN, MLTNA	*B. taurus*, *M. musculus*, *Coturnix coturnix*	Involved in myogenesis and skeletal muscle regeneration; upregulated in tumor progression; involved in macrophage-derived giant cell (MGC) and osteoclast formation from mononuclear precursors
ADAM15	Yes	metargidin, MDC15	*M. musculus*, *R. norvegicus*	Involved in cell adhesion through integrin binding; involved in wound healing; mediates heterotypic T-cell interactions; cleaves E-cadherin in response to growth factor deprivation; plays a role in glomerular cell migration and pathological neovascularization; involved in cartilage remodeling and sperm-egg binding
ADAM17	Yes	TACE, CD156B, MGC71942, cSVP	*D. rerio*, *Cricetulus griseus*, *D. melanogaster*, *M. musculus*, *R. norvegicus*, *S. scrofa*	Cleaves TNFα and is responsible for proteolytic release of several other cell-surface proteins, including p75 TNF receptor, interleukin 1 receptor type II, p55 TNF receptor, TGFα, L-selectin, growth hormone receptor, MUC1 and amyloid precursor protein; possibly involved in the activation of Notch pathway
ADAM18	No	ADAM27, MGC41836, MGC88272, tMDCIII	*M. musculus*, *R. norvegicus*, *M. fascicularis*	Possibly involved in sperm-egg fusion
ADAM19	Yes	MADDAM, MLTNB, FKSG34	*M. musculus*, *C. coturnix*	Shedding of beta-type neuregulin isoforms involved in neurogenesis and synaptogenesis; possibly involved in osteoblast differentiation and/or osteoblast activity in bone
ADAM20	Yes			Possibly involved in sperm-egg fusion; testis-specific expression
ADAM21	Yes	ADAM31, MGC125389	*M. musculus*	Possibly involved in sperm-egg fusion and in epithelia functions
ADAM22	No	MDC2, MGC149832	*M. musculus*, *X. laevis*	Ligand for integrin in the brain; involved in regulation of cell adhesion and in inhibition of cell proliferation; neuronal receptor for LGI1
ADAM23	No	MDC3	*M. musculus*	Involved in cell-cell and cell-matrix interactions in brain
ADAM28	Yes	ADAM23, MDC-Lm, MDC-Ls, MDCL, eMDCII	*M. musculus*, *G. gallus*, *M. fascicularis*, *R. norvegicus*	Possible role during lymphocyte emigration; shedding of lymphocyte surface target proteins, such as FASL and CD40L; might be involved in sperm maturation
ADAM29	No	svph1, CT73	*M. musculus*	Involved in spermatogenesis and fertilization
ADAM30	Yes	svph4	*M. musculus*	Involved in spermatogenesis and fertilization
ADAM32	No	FLJ26299, FLJ29004	*M. musculus*, *R. norvegicus*	Involved in spermatogenesis and fertilization
ADAM33	Yes	FLJ36751, MGC1498823, FLJ35308, RP5-964F7.2, dJ964F7.1	*M. musculus*, *Xenopus* (suggested ADAM13)	Possibly involved in asthma and bronchial hyper-responsiveness

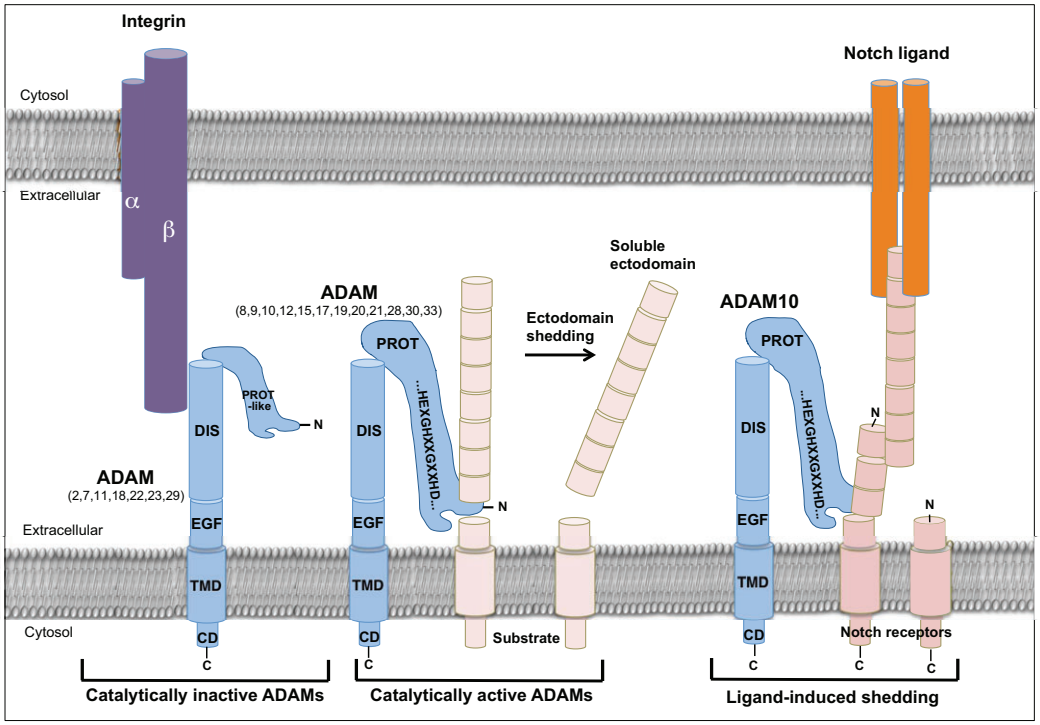

Fig. 1. Proteolytically active and inactive ADAMs. ADAMs (blue) contain a cytoplasmic domain (CD), a transmembrane domain (TMD), an EGF-like domain (EGF), a disintegrin domain (DIS) and the protease (PROT) domain, which may or may not (or PROT-like) contain an active site (HEXGHXXGXXHD). Catalytically inactive ADAMs seem to be important for cell-cell adhesion, and this function is mainly mediated through interactions with integrins (purple) on neighboring cells. The protease-containing ADAMs are involved in ectodomain shedding of type I or type II transmembrane proteins (pink), leading to the release of a soluble extracellular domain and the generation of a membrane stub. In the case of ADAM10 (example shown on right), it is well documented that binding of the Notch receptor (pink) to one of its ligands (orange) located on a neighboring cell induces ectodomain shedding. The remaining membrane-bound stub is subject to intramembrane cleavage by the γ-secretase complex (not shown here).

Interestingly, at steady state, the vast majority of endogenous ADAM10 and ADAM17 is localized in the endoplasmic reticulum (ER) and Golgi apparatus and little protein is observed at the plasma membrane where ectodomain shedding occurs (Schlondorff et al., 2000; Gutwein et al., 2003). For ADAM10, an ER-retention motif within the ADAM10 intracellular C-terminal tail is also observed (Marcello et al., 2010), and the binding of proteins such as tetraspanins in the case of ADAM10 (Prox et al., 2012) and iRHOM2 in the case of ADAM17 (Adrain et al., 2012; McIlwain et al., 2012) can trigger the export of these proteases from the endoplasmic reticulum. The binding of iRHOM2 (also known as RHBDF2) to ADAM17 also contributes to innate immunity and pathogen defense (McIlwain et al., 2012). Interestingly, a very recent study revealed mutations in the gene encoding for iRomb2 in a form of esophageal cancer with disturbed EGFR signaling (Blaydon et al., 2012).

Twelve of the human ADAMs contain a characteristic active site (HEXGHXXGXXHD) in the metalloproteinase domain (Fig. 1). The X-ray structures of the catalytic domains of ADAM17 and ADAM33 revealed a zinc-binding motif with three conserved histidine residues and a methionine-turn in the active site helix (Maskos et al., 1998; Orth et al., 2004). The catalytic part of ADAMs is characterized by a globular structure with two subdomains and an active cleft between these subdomains (Gomis-Ruth, 2003). The groove between these subdomains contains a catalytic zinc atom that directs cleavage specificity, and synthetic metalloproteinase inhibitors are designed to fit in this groove (Gomis-Ruth, 2003; Bode et al., 1993). Regulation of catalytic activity, and possibly also of substrate targeting, is mainly mediated by the cysteine-rich domain (Milla et al., 1999; Smith et al., 2002; Janes et al., 2009). This domain harbors a hypervariable region. The crystal structure of vascular apoptosis-inducing factor-1 (VAP1; also known as AOC3), a conserved snake venom homolog of ADAMs, suggested that the extracellular metalloproteinase/disintegrin/cysteine-rich structure presents as a C-shaped molecule, with part of the cysteine-rich domain being in close contact with the catalytic site in the metalloproteinase domain. This region seems to be important for determining substrate specificity or for regulating protease activity (Takeda et al., 2006). In non-proteolytically active ADAMs, the disintegrin domain was suggested to be critical for binding to surface molecules, including integrins, and thereby regulates cell-cell adhesion (White, 2003) (Fig. 1). However, this concept has been challenged, because the inhibition of ADAM receptors using integrin function-blocking antibodies or integrin-lacking eggs did not affect sperm-egg binding and fusion (He et al., 2003). The EGF-like domain, which is present in most ADAMs, is thought to contribute to the regulation of substrate binding to the cysteine-rich domain and to binding to cell surface proteoglycans (Zolkiewska, 1999; Iba et al., 2000; Janes et al., 2005). The corresponding membrane proximal domains of ADAM17 is involved in protease multimerization and ligand recognition (Lorenzen et al., 2011; Lorenzen et al., 2012). C-terminal to this domain is a short and rather flexible extracellular stalk region followed by the hydrophobic membrane-spanning

Box. 1. ADAMs and their possible involvement in disease

Dysregulation of ADAMs can contribute to the development of human disease. A number of ADAMs are linked to the pathogenesis of cancer, asthma, infection and inflammation, cardiovascular disorders and neurological disorders. Furthermore, the overexpression of ADAMs is associated with human cancer (e.g. ADAM8 in pancreatic cancer, ADAM9, 12, 15, 17 in breast cancer, ADAM10 and 15 in prostate cancer, ADAM12 in bladder cancer, ADAM19 in gliomas). In addition, ectodomain shedding of different substrates by ADAMs has been found to be linked with rheumatoid arthritis (ADAM8, ADAM17), inflammation (ADAM10, ADAM17), ageing (ADAM10), Alzheimer's disease (ADAM10), allergic reactions (ADAM10), multiple sclerosis (ADAM17), diabetes (ADAM17), asthma (ADAM33), cardiovascular disease (ADAM10, ADAM17) and psoriasis (ADAM10, ADAM33). Depending on the disease context, modulation of ADAM function is considered to be an interesting therapeutic option. Upregulation of ADAM10, for example, is thought to decrease the burden of β-amyloid production, thereby possibly preventing the progressive neurodegeneration found in the brains of Alzheimer's disease patients. By contrast, downregulation of ADAM10 and ADAM17 in combination with HER2 (ERBB2) antibody treatment led to clinical improvement in breast cancer patients. Accordingly, downregulation of ADAM17 activity during acute inflammation and sepsis or upregulation after stress-induced tissue damage are reasonable future therapeutic options. However, it should be considered that long-term regulation of at least ADAM10 and ADAM17 will be challenging, given the pronounced phenotypes of ADAM10 and 17 knockout mouse models.

region. Interestingly, the cytosolic tails of ADAMs are very diverse in terms of length, sequence and their capacity to bind cytosolic proteins (Cao et al., 2002; Diaz-Rodriguez et al., 2002; Mori et al., 2003; Seals and Courtneidge, 2003; Sundberg et al., 2004; Wild-Bode et al., 2006; Zhong et al., 2008; Marcello et al., 2010). There is an increasing number of reports highlighting the importance of this cytosolic domain for the regulation of ADAM proteolytic activity, intracellular transport, and localization, as well as for cell signaling (reviewed by Edwards et al., 2008). Unfortunately, the structure of the entire extracellular part of an ADAM has not yet been determined. Knowledge of this structure would certainly be of great value for understanding the 'communication' between individual domains and for visualizing the mode of interaction with membrane substrates.

ADAM proteases: from discovery to evolution

ADAM1 and ADAM2 were the first characterized ADAM proteases (Blobel et al., 1992; Wolfsberg et al., 1993). Soon after, ADAM12 was found to be important for myoblast fusion (Yagami-Hiromasa et al., 1995) and the ADAM10 ortholog *kuzbanian* in *Drosophila* was identified to control cell differentiation during neurogenesis (Rooke et al., 1996; Pan and Rubin, 1997) and axon extension (Fambrough et al., 1996). At the same time, the prominent role of ADAM17 for infection and immunity was realized when it was discovered to mediate the release of TNFα from cells (Black et al., 1997; Moss et al., 1997), and it was hence referred to as TNFα cleavage enzyme, or TACE. Shortly after, the first knockout mouse studies revealed an essential developmental role for ADAM17 (Peschon et al., 1998) as well as a role for the catalytically inactive ADAM2 in fertilization (Cho et al., 1998). In the same year, the three-dimensional structure of the catalytic domain of ADAM17 in complex with a hydroxamic acid inhibitor was resolved (Maskos et al., 1998). In 1999, Lammich and colleagues identified ADAM10 as a major candidate involved in the non-amyloidogenic α-secretase processing of the amyloid precursor protein (APP) (Lammich et al., 1999), which plays a central role in the pathogenesis of Alzheimer's disease. Since then, therapeutic approaches to stimulate ADAM10 activity are being tested to prevent the excessive production of the neurotoxic amyloid beta peptide in Alzheimer's disease (Endres and Fahrenholz, 2010; Saftig and Reiss, 2011). More recent and ongoing studies are exploring ADAMs as potential targets for the treatment of malignancies that are dependent on human epidermal growth factor receptor ligands or TNFα (Duffy et al., 2009a).

From an evolutionary point of view, it appears that the two best-studied ADAM proteases in mammals, ADAM10 and ADAM17, are somewhat separated from the other ADAMs [see overview by Edwards et al. (Edwards et al., 2008)]. This is exemplified by comparisons of the genomes from *Ciona intestinalis*, *Danio rerio*, *Drosophila melanogaster*, *Caenorhabditis elegans*, sea urchin and rodents (Puente and Lopez-Otin, 2004; Angerer et al., 2006; Huxley-Jones et al., 2007). In the sea squirt *Ciona intestinalis*, possibly the closest invertebrate relative to humans, two subgroups of ADAM proteases were identified, with one subgroup (ADAMa, ADAMb) representing orthologs for ADAM17 and ADAM10 and the other subgroup (ADAMc1, ADAMc2) appearing to be related to human ADAMs 2, 7, 8, 9, 11, 12, 15, 17, 19, 22, 23, 28, 32 and 33. The remaining ADAMs might thus have appeared later during vertebrate evolution (Huxley-Jones et al., 2007). In *Drosophila*, the genes encoding kuzbanian and kuzbanian-like (*kuz* and *Kul*) correspond to that encoding ADAM10, and there is one orthologous gene (*Tace*) for ADAM17 and two (*Neu3*, *mmd*) for the other ADAM members (Meyer et al., 2011). Interestingly, despite the apparent central role of ADAM10 in Notch-regulated developmental processes, there is no ortholog in the sea urchin for ADAM10 but two orthologs for ADAM17- and ADAM15-related genes (Angerer et al., 2006).

ADAMs: a protein family with diverse functions and mechanisms of regulation

Proteolytically active ADAMs can control the fate of cell surface molecules in a number of different ways (Fig. 2). For example, ectodomain shedding at the surface of a cell can trigger signaling events within the same cell (Fig. 2A). Alternatively, the released soluble factors can interact in a trans-manner with receptors on cells that may be some distance away from the cell on which shedding has occurred (Fig. 2A). What then happens to the membrane stubs remaining after ectodomain shedding? In most cases, RIP via activity of the γ-secretase complex or SPPLs leads to the release of intracellular fragments that have a direct or indirect influence on transcriptional activity (Fig. 2B). The third consequence of ectodomain shedding at the same cell or a neighboring cell is the regulation of the half-life of surface molecules and the inactivation of receptors or cell adhesion proteins, which is a process that can occur in parallel to the endocytosis of such cell-surface proteins (Fig. 2C). This is exemplified by the interaction of EphB receptors with E-cadherin (cadherin 1) and with the metalloproteinase ADAM10 at sites of adhesion. This activation induces shedding of E-cadherin by ADAM10 and results in asymmetric localization of E-cadherin and, as a consequence, in differences in cell affinity between EphB receptor-positive and ephrin-B-positive cells (Solanas et al., 2011). Another example is the control of neuroepithelial cell adhesion function through the Huntington's disease gene product, huntingtin,

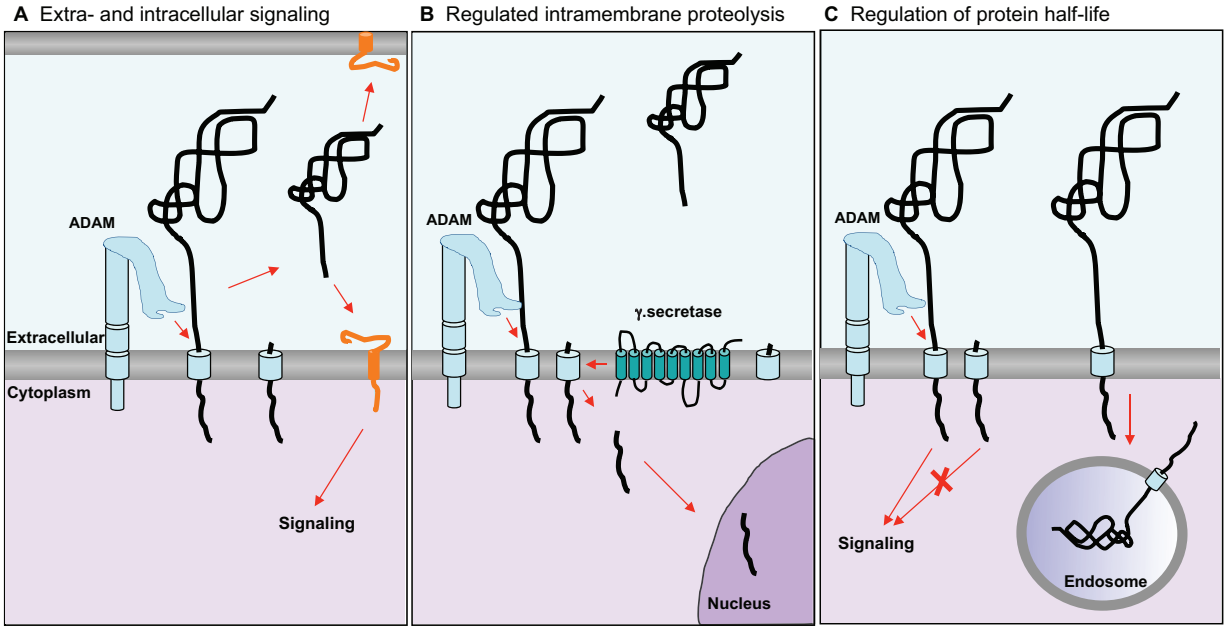

Fig. 2. ADAM activity and intracellular and extracellular signaling. Proteolytically active ADAMs can control the fate of cell surface molecules via three possible mechanisms: (**A**) the activity of ADAMs (blue) can promote extracellular and intracellular signaling by releasing soluble factors (black) that are able to bind to receptors (orange) on other cells or on the same cell; (**B**) ADAM activity can result in the subsequent activation of the regulated intramembrane proteolysis (RIP) pathway. In this pathway, the activity of the γ-secretase complex (green) or signal peptide peptidase-like proteases (SPPLs; not shown) leads to the liberation of intracellular fragments that are able to translocate to the nucleus and activate gene transcription; (**C**) the shedding of receptors or adhesion molecules by ADAMs is a way to regulate the half-life of these transmembrane proteins at the cell surface, a process that occurs in parallel to the endocytosis of surface proteins.

by the regulation of ADAM10 and N-cadherin (cadherin 2) shedding (Lo Sardo et al., 2012).

Taking these mechanisms into account, it is evident that ADAMs exert diverse effects on the behavior of cells. Accordingly, ADAM functions are mainly defined by the selective use of substrates, which are dependent on the cell type-specific expression pattern and the subcellular localization of the substrate and the protease.

The best-studied processing events carried out by ADAM proteases include the shedding of EGFR ligands by ADAM17, the proteolytic processing of the Notch1 receptor by ADAM10 (Fig. 3), and the processing of APP by ADAM10. This is perhaps because a defect in the proteolytic processing of EGFR ligands and also of Notch1 has severe consequences for normal development in animals and has been associated with human diseases, including cancer (Peschon et al., 1998; Hartmann et al., 2002; Kenny and Bissell, 2007; Moss et al., 2008; Sulis et al., 2011). Apart from these established substrates, an increasing number of type I and type II transmembrane proteins (reviewed by Reiss and Saftig, 2009) are subject to ADAM-mediated proteolysis (Table 2), and diverse functions ranging from development to the modification of cell adhesion, migration of cells, cytokine and intracellular signaling are related to these shedding events. Interestingly, and as illustrated in Table 2, some of these substrates can be used by different ADAMs, whereas others appear to be specific for an individual ADAM protease. This also highlights the need for a better understanding of how the substrate specificity and proteolytic activity of ADAMs are determined.

ADAM proteases themselves are also subjected to specific regulation and activation processes. It is known that, in addition to constitutive cleavage, factors such as osmotic and mechanical stress, G protein-coupled receptor activation, activation of protein kinase C, increase in intracellular calcium, serum factors and growth factors can trigger the proteolytic activity of ADAMs (reviewed by Huovila et al., 2005). It has also been reported that transcriptional control, alternative splicing, post-translational modifications (such as pro-domain removal), protein-protein interactions (such as the above-mentioned interaction with iRHOM2 or tetraspanins), the presence of natural inhibitors of ADAMs [such as tissue inhibitors of metalloproteinases (TIMPs)], self-shedding and the intracellular trafficking of ADAMs are major determinants for the activity of ADAMs (Edwards et al., 2008; Reiss and Saftig, 2009) (summarized in Fig. 4).

Revealing the role of ADAM proteases in non-mammalian models

The study of ADAMs in non-mammalian models played a key role in unraveling their functions in neurogenesis, neural crest cell and myoblast migration, heart development, and the development of blood cell circulation (see examples below). Many of the insights into these processes originated from gain- and loss-of-function experiments in bird or frog embryos, and in fish, nematodes and flies (reviewed by Alfandari et al., 2009). This is exemplified by the neurogenic Notch1-specific phenotype of loss-of-function mutants of ADAM10 (Kuzbanian) in *Drosophila*. These mutants, which exhibit abnormally enlarged neural tissues and an impaired axon extension process, revealed a role for the ADAM10 protease in the lateral inhibition event that leads to selective differentiation of neuronal cells (Fambrough et al., 1996; Rooke et al., 1996). The mutants also showed defects in heart morphogenesis (Albrecht et al., 2006). Interestingly, the selective expression of a dominant-negative mutant of Kuzbanian lacking the metalloproteinase

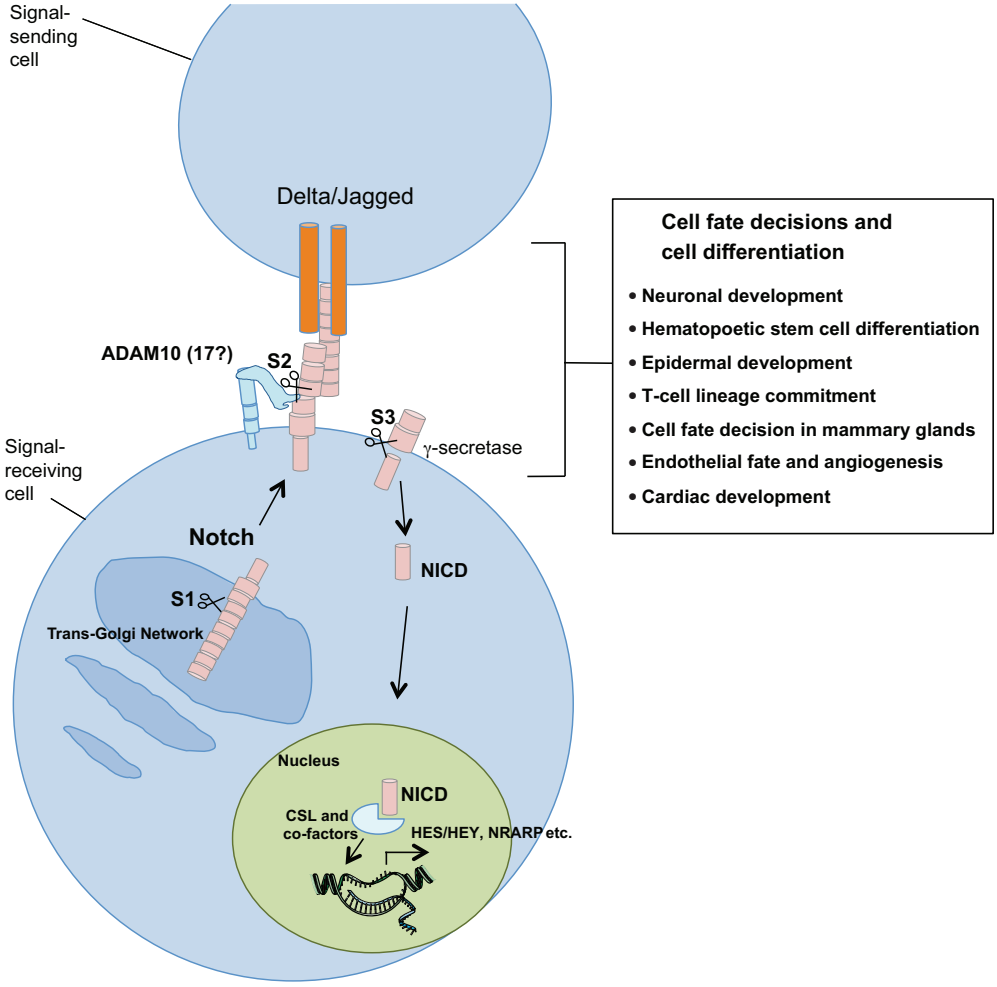

Fig. 3. Notch processing by ADAMs regulates central developmental processes. Notch receptor cleavage by different proteases (during cleavages S1, S2 and S3) is needed to trigger the signaling cascade. The S1 cleavage is involved in regulating the surface expression of Notch receptors. Binding of a Notch ligand (e.g. Delta or Jagged) to the Notch receptor (e.g. Notch1) then triggers the S2 cleavage, which is in most cases mediated by ADAM10 (blue). The remaining membrane stub of the Notch receptor is then subject to intramembrane proteolysis mediated by the γ-secretase complex (composed of presenilin, nicastrin, Aph1 and Pen-2), releasing (in the S3 cleavage) the Notch intracellular domain (NICD). After translocation into the nucleus, the NICD associates with the transcription factor CSL (human CBF1, *Drosophila* Suppressor of Hairless, *C. elegans* LAG-1; also known as RBPJ) and other co-factors and triggers gene expression of Notch-responsive genes (e.g. *Hes*/*Hey*, *Nrarp*). This influence of ADAM-cleavage on the Notch pathway thereby affects cell fate decisions, cell differentiation and important developmental processes, as indicated on the right.

domain (Pan and Rubin, 1997) led to eye and wing phenotypes in *Drosophila* that were almost identical to Notch loss-of-function mutants. In addition, biochemical experiments showed that the processing of Notch at the extracellular juxtamembrane region was impaired in cells that express the dominant-negative ADAM10. This cleavage is absolutely required to initiate the Notch signaling pathway. The central role of ADAM10 for Notch signaling was also confirmed in several studies analyzing the role of the *C. elegans* ADAM10 ortholog (SUP-17); SUP-17-deficient worms exhibit a Notch (LIN-12)-like defect in gonadogenesis. This defect could be partially rescued by the ADAM17 ortholog ADM-4, suggesting that ADAM17 can also contribute, at least when ADAM10 is absent, to the initiation of Notch signaling (Wen et al., 1997; Jarriault and Greenwald, 2005). *C. elegans* mutants that lack only ADM-4 are viable with no overt phenotypical alterations, suggesting that ADAM17-cleavage events are not directly needed for worm development (Jarriault and Greenwald, 2005). Specific phenotypes in flies or worms have not been reported for the other proteolytically active ADAMs (ADAM9, 12, 13, 19 and 33) (Alfandari et al., 2009). This is in line with the lack of severe developmental phenotypes in mice lacking one of these proteases (Table 3), suggesting a redundant function of these proteases. However, in earlier studies, the contribution of *Xenopus laevis* ADAM13 was investigated and, based on expression analyses, ADAM13 was suggested to be involved in neural crest cell adhesion, migration and myoblast differentiation (Alfandari et al., 1997). Furthermore, cranial neural crest development in *Xenopus* seems to depend on cleavage of cadherin-11 by ADAM9 and ADAM13 (McCusker et al., 2009). The extracellular domain of cadherin-11 stimulates neural crest migration. Interestingly, ADAM13 is itself subject to cleavage by γ-secretase thereby releasing a cytoplasmic domain that translocates to the nucleus thereby activating genes essential for neural crest migration (Cousin et al., 2011). Knockdown of ADAM19 in *Xenopus* caused a reduction of neural and neural crest markers, perturbed migration of cranial neural crest cells and a defect in somite organization (Neuner et al., 2009). These studies increase our understanding of cell adhesion and the involvement of proteolytic ADAM-mediated activities in guiding the migration of cranial neural crest cells during frog embryogenesis (Alfandari et al., 2010). More recently, ADAM13 function was found to be required for eye development in *Xenopus tropicalis*, possibly by regulating the Wnt signaling pathway (Wei et al., 2012). Based on the analysis of a morpholino knockdown of ADAM13 in *X. tropicalis*, ADAM13 was found to cleave ephrinB ligand, affecting β-catenin signaling and promoting neural crest cell and eye induction (Wei et al., 2010; Wei et al., 2012).

The function of ADAMs has also been assessed in zebrafish. Monitoring fluorescently labeled blood cells and vessels in zebrafish revealed that ADAM8 triggers the onset of blood circulation (Iida et al., 2010). The detachment of blood cell precursors from vessels is triggered by local proteolysis of

Table 2. Examples of substrates utilized by the catalytically active ADAM proteases

ADAM	Typical substrate	References
ADAM8	CD23, CD-30-ligand, ADAM8 prodomain, APP, L-selectin, MBP	(Schlomann et al., 2002; Fourie et al., 2003; Naus et al., 2006; Gomez-Gaviro et al., 2007)
ADAM9	laminin, insulin-B chain, APP, collagen XVII, delta-like ligand 1, EGF, FGFR2iiib, HB-EGF, IGFBP-5, ADAM10	(Izumi et al., 1998; Koike et al., 1999; Roghani et al., 1999; Franzke et al., 2002; Mohan et al., 2002; Asai et al., 2003; Mazzocca et al., 2005; Peduto et al., 2005; Dyczynska et al., 2007; Tousseyn et al., 2009)
ADAM10	APP, Notch1-4, betacellulin, CD23, CD30, CD44, prion protein, collagen IV and XVII, fractalkine, delta-like ligand 1, desmoglein, E-cadherin, N-cadherin, VE-cadherin, EGF, ephrin A2 and A5, ERBB2, Fas-L, IL6R, Klotho, LAG-3, L1, MICA, Pcdh-γ C3/B4, TRANCE	(Pan and Rubin, 1997; Millichip et al., 1998; Hattori et al., 2000; Vincent et al., 2001; Franzke et al., 2002; Hundhausen et al., 2003; Matthews et al., 2003; Six et al., 2003; Nagano et al., 2004; Postina et al., 2004; Sahin et al., 2004; Janes et al., 2005; Maretzky et al., 2005a; Maretzky et al., 2005b; Reiss et al., 2005; Bech-Serra et al., 2006; Hikita et al., 2006; Liu et al., 2006; Reiss et al., 2006; Weskamp et al., 2006; Eichenauer et al., 2007; Li et al., 2007; Schulte et al., 2007; Schulz et al., 2008; Waldhauer et al., 2008; Bloch et al., 2009; Jorissen et al., 2010; Kuhn et al., 2010; Altmeppen et al., 2011)
ADAM12	collagen IV, delta-like ligand 1, HB-EGF, fibronectin, gelantin, IGFBP-3/-5	(Loechel et al., 2000; Asakura et al., 2002; Roy et al., 2004; Dyczynska et al., 2007)
ADAM15	amphiregulin, CD23, E-cadherin, HB-EGF, collagen IV, ADAM10	(Martin et al., 2002; Fourie et al., 2003; Schafer et al., 2004; Hart et al., 2005; Najy et al., 2008; Tousseyn et al., 2009)
ADAM17	ACE2, amphiregulin, APP, CD30, CD40, CD44, collagen XVII, delta-like ligand 1, desmoglein, epigen, epiregulin, HB-EGF, ICAM-1, IL1R, IL6R, L1, LAG-3, L-selectin, Nectin 4, Neuregulin 1, Notch-1, TGFα, TNFα, TNF receptor I and II, VCAM-1	(Black et al., 1997; Moss et al., 1997; Buxbaum et al., 1998; Peschon et al., 1998; Brou et al., 2000; Hansen et al., 2000; Reddy et al., 2000; Franzke et al., 2002; Contin et al., 2003; Garton et al., 2003; Nagano et al., 2004; Sahin et al., 2004; Fabre-Lafay et al., 2005; Horiuchi et al., 2005; Lambert et al., 2005; Maretzky et al., 2005b; Bech-Serra et al., 2006; Tsakadze et al., 2006; Chalaris et al., 2007; Dyczynska et al., 2007; Li et al., 2007; Sahin and Blobel, 2007)
ADAM19	neuregulin, TRANCE, TNFα, ADAM19	(Shirakabe et al., 2001; Kang et al., 2002; Chesneau et al., 2003; Zheng et al., 2004)
ADAM28	CD23, IGFBP-3, myelin basic protein, connective tissue growth factor	(Howard et al., 2001; Fourie et al., 2003; Mochizuki et al., 2004; Mochizuki et al., 2010)
ADAM33	CD23, Kit ligand-1	(Zou et al., 2005; Meng et al., 2007)

adhesion molecules. Antisense morpholino-mediated knockdown of Adam8 revealed a dramatic failure in blood circulation, which was shown to be a cell autonomous effect in primitive blood cells. The same study also suggested that ADAM8-mediated cleavage of the cell adhesion molecule P-selectin glycoprotein 1 is involved in the early regulation of the onset of blood circulation (Iida et al., 2010).

In one of the few studies in invertebrate models of a non-proteolytic ADAM mutant, it was reported that worms carrying mutations in the disintegrin domain of UNC-71 (ADAM14) display abnormalities in axon guidance, axon fasciculation and sex myoblast migration (Huang et al., 2003). This finding, together with studies in vertebrates, suggests that the non-proteolytic ADAMs act mainly as regulators of cell adhesion in the central nervous system.

Functions of ADAMs in mice: roles in angiogenesis, neurogenesis, skin, lung and heart development

In order to study further the developmental functions of ADAM metalloproteases in vertebrates, ADAM loss- and gain-of-function mouse models were developed and have proven to be versatile tools. Constitutive deletion of the sperm-egg fusion relevant ADAMs 1, 2 and 3 led to male infertility. However, all other ADAMs that are widely expressed in the mouse (e.g. 8, 9, 10, 11, 12, 15, 17, 19, 22, 23, 33) could be comprehensively studied using either knockout or overexpression mouse models. Whereas ADAM11, 22 and 23 might function as adhesion molecules, the remaining ADAMs were shown to be catalatically active, exerting their functions mainly by ectodomain shedding. In line with their widespread expression patterns in murine tissues, the observed phenotypes of ADAM knockout mice are diverse. Table 3 provides an overview of the studies on the respective mouse models and their conclusions regarding the in vivo functions of these proteases. Interestingly, the phenotype of the knockout mice suggested that only ADAM10, 17 and 19 are essential for mouse development. Whereas ADAM19 seems to exert its most important function in cells of the peripheral nervous system and during development of the heart by the processing of type I neuregulins (NRGIs) (Kurohara et al., 2004), the consequences of deleting ADAM10 and ADAM17 are more severe, leading to abnormalities in almost all tissues. Notably, several ADAMs play important roles in pathological situations, such as inflammation, carcinogenesis or stress-mediated angiogenetic response, as revealed by various disease models (Table 3; Box 1).

In the following section, we focus on the well-characterized roles of the two most intensively studied family members, ADAM10 and ADAM17, and their contribution in developmental processes, tissue organization and function, and signal transduction. We also briefly discuss the roles of two other well-studied ADAMs: ADAM19, which is implicated in, amongst other processes, heart development and remyelination processes in the peripheral nervous system; and ADAM33, which is implicated in airway inflammation.

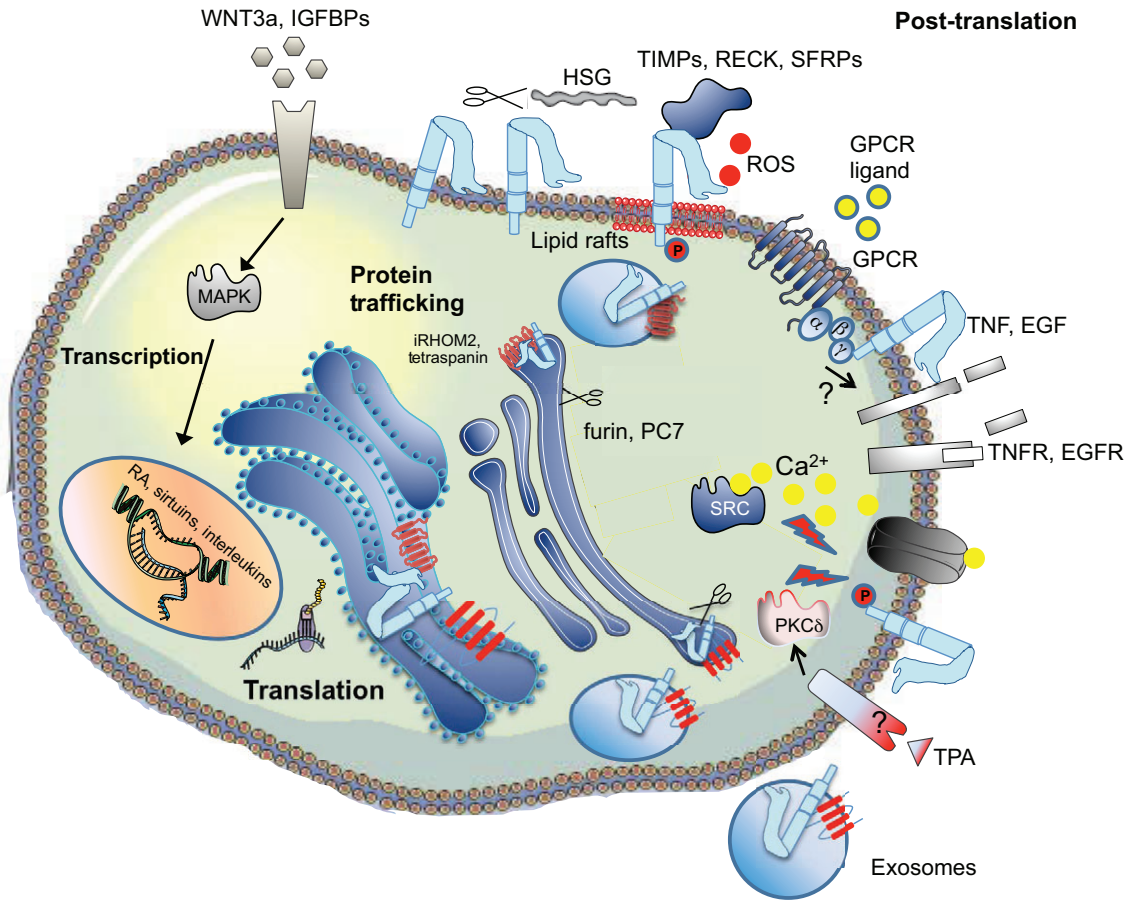

Fig. 4. The regulation of proteolytic active ADAMs. ADAMs (pale blue) can be regulated at the level of transcription, translation and through different post-translational processes. For example, transcription of ADAMs can be modulated by factors such as retinoic acid (RA), sirtuins or interleukins. Protein trafficking of ADAMs can subsequently be regulated by different tetraspanins and, as recently observed, also by iRHOM2. The processing of ADAMs themselves can be controlled by furin and proprotein convertases (PCs), whereas factors such as TIMPs, RECK, HSG, ROS and GPCR ligands regulate the activity of ADAMs via direct and indirect protein-protein interactions. Furthermore, phosphorylation (P) is a common post-translational modification that can be initiated by either calcium influx and subsequent SRC kinase activation or TPA-induced PKCδ mobilization. EGF(R), epidermal growth factor (receptor); GPCR, G protein-coupled receptor; HSG, heparan sulfate glycosaminoglycans; IGFBPs, insulin growth factor-binding proteins; iRHOM2, inactivated rhomboid protein 2; MAPK, mitogen-activated protein kinase; PC7, proprotein convertase 7; PKC, protein kinase C; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; ROS, reactive oxygen species; SFRPs: secreted frizzled-related proteins; TIMPs, tissue inhibitors of metalloproteases; TNF(R), tumor necrosis factor α (receptor); TPA, tetradecanoyl-phorbolacetat.

ADAM10: the Notch sheddase

Deficiency of ADAM10 leads to prenatal lethality around embryonic day (E) 9.5. ADAM10 knockout embryos are characterized by severe growth retardation, impaired somite development, as well as defects in the developing central nervous and cardiovascular systems, all of which point to a central role for ADAM10 during embryonic development (Hartmann et al., 2002). In order to obtain information about ADAM10 function in adult mice and selected tissues, conditional and inducible ADAM10 knockout mice were generated using Cre/loxP recombination technology. Consequently, the first conditional knockout of ADAM10 was reported using the murine lymphocyte-specific protein tyrosine kinase (*Lck*)-Cre deleter strain, which was shown to be most effective within intrathymic T cells (Hennet et al., 1995). Phenotypical analysis of these mice revealed a mild block in the developmental transition from the double negative (DN) 2 to DN3 stage, leading to reduced numbers of double- and single-positive thymocytes (Tian et al., 2008). These results confirmed previous studies using transgenic expression of a dominant-negative form of ADAM10 under the control of the same promoter (Manilay et al., 2005). A role for ADAM10 in B-cell development, involving shedding of the low-affinity IgE receptor (CD23; also known as FCER2A), has been suggested following cell-based studies using ADAM10-deficient fibroblasts (Weskamp et al., 2006), and this role was verified using B cell-specific ADAM10 knockout mice (Gibb et al., 2010). The lack of ADAM10 in B cells prevented development of the entire marginal zone B-cell lineage and led to impaired antibody production as well as a disrupted lymphoid architecture (Gibb et al., 2010; Chaimowitz et al., 2011). Interestingly, transgenic overexpression of ADAM10 in the B-cell lineage did not result in a dramatic phenotypic change in B-cell development, but led to the development of a myeloproliferative disorder, with a substantial increase in myeloid-derived suppressor cells (MDSCs), severe splenomegaly and thymic atrophy (Gibb et al., 2011). Mixed bone marrow chimeras indicated a cell-intrinsic role for ADAM10 during hematopoietic cell-fate decisions. Using an inducible (*Mx1*-Cre driven) model of ADAM10-deficiency,

Table 3. Mouse models used to unravel the function of ADAM proteases

Mutated gene	Tissue(s) with developmental phenotype	Functional role revealed in experimental mouse models
Adam1	Sperm (migration defect) (Nishimura et al., 2004)	Not reported
Adam2	Sperm, testes (Cho et al., 1998)	Not reported
Adam3	Sperm (Shamsadin et al., 1999)	Not reported
Adam8	No major abnormalities (Kelly et al., 2005), thymus (Gossens et al., 2010), bone/osteoclasts (Ishizuka et al., 2011)	Inflammation: allergic/bronchial asthma (Naus et al., 2010; Paulissen et al., 2011), rheumatoid arthritis (Zack et al., 2009), casein-induced peritoneal leukocyte infiltration, oxazolone-induced contact hypersensitivity reactions (Higuchi et al., 2002) Neurodegeneration: motorneuron disease – wobbler mouse (Bartsch et al., 2010) Osteoclastogenesis: TNFα-induced bone remodeling (Ishizuka et al., 2011) Angiogenesis: oxygen-induced retinopathy (Guaiquil et al., 2010) Carcinogenesis: heterotopical injection of tumor cells (Guaiquil et al., 2010)
Adam9	No major abnormalities (Weskamp et al., 2002), retina (age-dependent regeneration) (Parry et al., 2009)	Angiogenesis: oxygen-induced retinopathy, laser-induced choroidal neovascularization (Guaiquil et al., 2009) Skin homeostasis: wound healing (Mauch et al., 2010) Carcinogenesis: transgenic mice expressing SV40 large T antigen, polyoma virus middle T antigen and a mutated adenomatosis polyposis coli gene (Peduto et al., 2005)
Adam10	Cardiovascular system somites, heart, extra-embryonic tissue (Hartmann et al., 2002), central nervous system (Schmitt et al., 2006; Jorissen et al., 2010), immune system (B cells, T cells, myeloid cells and megakaryocytes) (Bender et al., 2010; Gibb et al., 2010; Gibb et al., 2011; Yoda et al., 2011), intestine (Solanas et al., 2011), vascular endothelium (Glomski et al., 2011b), epidermis/hair (Weber et al., 2011), airway epithelium (Inoshima et al., 2011) NB. Classical ADAM10 KO die at ~E9.5	Inflammation/immune response: ovalbumin-induced asthma, antigen-induced B-cell response (Chaimowitz et al., 2011; Mathews et al., 2011; Inoshima et al., 2012) Skin homeostasis: wound healing (our unpublished observations) Angiogenesis: oxygen-induced retinopathy (Glomski et al., 2011) Neurodegeneration/Alzheimer's disease: crossing with a transgenic familial Alzheimer's disease mutation mouse line (Postina et al., 2004)
Adam11	No major abnormalities (Takahashi et al., 2006b)	Nociception: formalin paw test and acetic acid writhing test (Takahashi et al., 2006a) Behavior: hidden water maze, rotating rod task (Takahashi et al., 2006b)
Adam12	No major abnormalities, skeletal muscle (regeneration) (Kurisaki et al., 2003), adipose fat tissue (Kawaguchi et al., 2002), bone (Kveiborg et al., 2006)	Adipogenesis: high-fat diet (Masaki et al., 2005) Myogenesis: crossing with dystrophin- or laminin-deficient mice (Kronqvist et al., 2002; Guo et al., 2005) Carcinogenesis: PyMT Model (Kveiborg et al., 2005) Neuroinflammation: cuprizone demyelination model (Baertling et al., 2010) Skin homeostasis: wound healing (Harsha et al., 2008)
Adam15	No major abnormalities (Horiuchi et al., 2003), bone (age-dependent cartilage remodeling) (Bohm et al., 2005; Marzia et al., 2011)	Angiogenesis: retinopathy of prematurity, oxygen-induced ischemic retinopathy, laser-induced choroidal neovascularization (Horiuchi et al., 2003; Xie et al., 2008) Carcinogenesis: subcutaenous injection of B16F10 melanoma cells (Horiuchi et al., 2003) Apoptosis: DNA damaging by camptothecin (Bohm et al., 2010)
Adam17	Heart, lung, skin/hair, eye, peripheral nervous system, immune system, gastrointestinal tract (energy metabolism) (Peschon et al., 1998; Jackson et al., 2003) NB. Most classical ADAM17 KO mice die perinatally (dependent on genetic background)	Inflammation: DSS-induced colitis (Chalaris et al., 2010), LPS-induced sepsis (Horiuchi et al., 2007), drug/antibody-induced hepatitis (Murthy et al., 2010)
Adam19	Heart (Kurohara et al., 2004; Zhou et al., 2004), (moto)neurons (Yumoto et al., 2008)	Neurogenesis: sciatic nerve crush (Wakatsuki et al., 2009)
Adam22	Peripheral nervous system (Sagane et al., 2005) NB. Classical KO die around weaning	Not reported
Adam23	Not reported NB. Classical KO die at ~P14 (Mitchell et al., 2001)	Not reported
Adam33	Not reported	Inflammation: allergen-induced asthma (Chen et al., 2006)

DSS, dextran sulfate sodium; LPS, lipopolysaccharide; PyMT, mouse mammary tumor virus promoter polyoma middle T-antigen.

Yoda et al. provided evidence to show that ADAM10-dependent myeloproliferative disorders can be initiated by granulocyte colony stimulating factor (G-CSF)-driven and non-cell-autonomous mechanisms (Yoda et al., 2011). In further studies, these mice were used to show that ADAM10 is a key regulator of Notch/RBPJ signaling during inflammatory macrophage polarization via the transcription factor IRF8 (Xu et al., 2012).

Embryonic development and adult homeostasis of the epidermis were also shown to be strictly dependent on ADAM10 expression (Weber et al., 2011). Whereas ADAM10 deficiency during

epidermal development led to accelerated terminal differentiation of keratinocytes, resulting in a severe and perinatal lethal barrier defect, ADAM10 deficiency in adult epidermis provoked disturbed epidermal homeostasis marked by hyperproliferation of basal keratinocytes, alopecia, hyperkeratinization, thymic atrophy and upregulation of the cytokine thymic stromal lymphopoietin (TSLP) (Weber et al., 2011). ADAM10 also plays a role during development and homeostasis of self-renewing epithelium in the intestine; conditional overexpression of a dominant-negative form of ADAM10 in the intestine revealed a role for ADAM10 in the compartmentalization of cells in epithelial tissues as well as in adhesion and polarity of migrating cells within such a complex tissue (Solanas et al., 2011). Furthermore, the development of endothelium depends on ADAM10 expression. As shown by Glomski and co-workers (Glomski et al., 2011), inactivation of this protease in endothelial cells using the endothelial-specific *Tie2*-Cre deleter strain (Kisanuki et al., 2001) leads to increased branching and density of the retinal vasculature, aberrant subcapsular hepatic veins, enlarged glomeruli and intestinal polyps, abnormal endochondral ossification with stunted long bone growth and increased pathological neovascularization following oxygen-induced retinopathy. These findings underline the role of ADAM10 as a central regulator of endothelial cell-fate decisions.

The determination of early cell-fate decisions is also one of the predominant roles of ADAM10 in the central nervous system. ADAM10-specific functions in brain were analyzed using a nestin-Cre driven conditional knockout, which inactivates the metalloprotease in neuronal progenitor cells that can differentiate to neurons and glia (Jorissen et al., 2010). The conditional knockout mice die perinatally with a disrupted neocortex and a severely reduced ganglionic eminence, which possibly arose by precocious neuronal differentiation resulting in early depletion of progenitor cells. Importantly, in the same study, ADAM10 was identified as the in vivo α-secretase responsible for cleaving APP, which plays a decisive role in the development of Alzheimer's disease. Interestingly, the cellular prion protein (PrP^c), which after misfolding can lead to transmissible spongiform encephalopathies, is also a substrate of ADAM10. In the brain of conditional ADAM10 knockout mice PrP^c accumulates in the early secretory pathway. This led to the conclusion that shedding by ADAM10 is a mechanism for regulating the levels of PrP^c at the plasma membrane (Altmeppen et al., 2011).

Taking all the aforementioned developmental phenotypes of the different ADAM10 knockout mouse models into account, the similarity with mice showing a disturbed Notch signaling pathway is obvious (Roca and Adams, 2007; Watt et al., 2008; Pierfelice et al., 2011) (Fig. 3). Ectodomain shedding activity of Notch1 by ADAM10 could be directly demonstrated (Jorissen et al., 2010; Weber et al., 2011), which is also in line with the observed in vivo function of the *Drosophila* ADAM10 ortholog Kuzbanian (Rooke et al., 1996; Pan and Rubin, 1997). However, cell-based experiments have revealed that other substrates of ADAM10 might also contribute to the phenotypes observed in the ADAM10 knockout mice. These substrates include E-cadherin (Inoshima et al. 2011; Maretzky et al., 2005a), CD23 (Weskamp et al., 2006), Fas ligand (Schulte et al., 2007) and ephrin (Janes et al., 2005). Notably, however, the Notch signaling pathway is upstream of all other signaling complexes identified so far and it therefore seems highly likely that disturbed Notch signaling preferentially contributes to the observed developmental defects. Furthermore, the major functional shedding targets of ADAM10 in post-mitotic tissues might be different from Notch and further studies are required to elucidate the functional role of ADAM10 in these tissues.

Independent of all findings discussed in this section, the question of whether ADAM10 may be used as a therapeutic target has not yet been directly addressed. A promising perspective for such a treatment was reported in studies analyzing ADAM10-deficient mouse models during inflammatory processes, such as asthma or *Staphylococcus aureus* infection in normal or wounded skin (Mathews et al., 2011; Inoshima et al., 2012), as well as in stress-induced neovascularization processes in the retina (Glomski et al., 2011). However, prolonged ADAM10 deficiency or activation in developing or self-renewing tissues was shown to have deleterious effects (Weber et al., 2011; Gibb et al., 2011), and it will be essential to monitor carefully the recipients of drugs that modulate ADAM10 activity.

ADAM17: the regulated sheddase

As early as 1998, it was reported that mice with a complete deficiency of ADAM17 display multiple pathological alterations, including disturbed development of eyes, epithelial tissue, lung, heart, immune system, hair and skin (Peschon et al., 1998). Depending on the genetic background, ADAM17-deficient mice die between E17.5 and birth or stay viable until adulthood. The surviving mice exhibit a severe wasting syndrome, leading to an increased rate of mortality (Gelling et al., 2008). Extensive histological analysis revealed that eyelids did not fuse, and eyes lacked a conjunctival sac and had attenuated corneas (Peschon et al., 1998), possibly caused by an impaired epithelial organization. Similarly, epithelial dysgenesis led to decreased lung branching processes and disturbed heart valvulogenesis associated with increased heart size, myocardial trabeculation, mitral valve defects, reduced cell compaction and hypertrophy of cardiomyocytes (Zhao et al., 2001; Shi et al., 2003). ADAM17 expression was also shown to possess regulatory functions during neurogenesis, as the loss of neuronal ADAM17 activity led to hypermyelination possibly caused by defective processing of neuregulin-1 type III (La Marca et al., 2011).

The described ADAM17-deficient mouse phenotypes displayed a striking similarity to EGFR-signaling defective mouse mutants. Most of the developmental defects could be explained by decreased levels of EGFR ligands, such as transforming growth factor α (TGFα), heparin-binding EGF (HBEGF) or amphiregulin, and subsequent inadequate EGFR activation (Zhao et al., 2001; Jackson et al., 2003; Chalaris et al., 2010). This signaling process was therefore termed EGFR transactivation (Prenzel et al., 1999). Despite the wealth of data obtained from the ADAM17 loss-of-function mutants, the generation of conditional ADAM17 mutants was necessary to learn more about the role of ADAM17 during tissue homeostasis and regeneration. As ADAM17 was originally identified as the TNFα cleavage enzyme (TACE), it was of great interest to delete ADAM17 specifically in cells of the immune system. ADAM17-deficient leukocytes were able to drastically reduce the mortality rate following lipopolysaccharide (LPS) and *Escherichia coli*-induced sepsis (Horiuchi et al., 2007; Long et al., 2010), underlining the importance of ADAM17 as the in vivo sheddase for TNFα. In ADAM17 radiation chimeric mice, the migration and rolling of activated leukocytes was impaired by severely reduced shedding of L-selectin (Wang et al., 2010). Although ADAM17 deficiency in immune cells did not impair hematopoiesis, conditional knockout of ADAM17 in stroma cells and also in epidermal cells

led to hematopoietic disorders (Wang et al., 2010; Murthy et al., 2012), which is surprisingly similar to the defects observed in ADAM10-deficient mouse models (Weber et al., 2011; Yoda et al., 2011). Although in most cases ADAM10-deficient mice phenocopy Notch signaling-deficient mice (Weber et al., 2011; Glomski et al., 2011), and ADAM17 knockout mice resemble EGFR or EGFR-ligand knockout mice (Franzke et al., 2012), there might be pathological situations under which both ADAM10 and ADAM17 share substrates in common signaling pathways, as indicated by previous cell-based experiments (Sahin et al., 2004; Bozkulak and Weinmaster, 2009). ADAM17 might also be involved in pathological neovascularization, implicating another functional importance of this protease in epithelial and endothelial maturation (Weskamp et al., 2010).

Recently, a spontaneous recessive mutation in the waved with open eyes (woe) locus was identified, and it was shown that this mutation leads to deletion of murine exon 7 of ADAM17 (Hassemer et al., 2010). In these hypomorphs, the residual ADAM17 activity allows these mice to thrive into adulthood. Similarly, Chalaris and co-workers (Chalaris et al., 2010) were able to generate a hypomorphic mouse model by introduction of an artificial exon with an in-frame translational stop codon between exons 11 and 12. These mice proved to be an excellent tool for examination of inflammation and regeneration. The observation of increased gut inflammation characterized by TGFα-mediated hyperplasia after chronically dextran sulfate sodium (DSS)-induced colitis provided evidence that ADAM17 also exerts a positive effect on regeneration processes after tissue damage, mainly by activation of the EGFR signal transducer and activator of transcription 3 (STAT3) signaling axis.

The studies mentioned above provided multiple lines of evidence for a role of ADAM17 during the in vivo regulation of pro- and anti-inflammatory molecules such as TNFα or TGFα. Following this, the therapeutic modulation of ADAM17 activity is considered to be a favorable target for the treatment of acutely or chronically inflamed tissues. However, therapeutic targeting has to be tightly controlled, as shown by a recent report of a young patient who carried an ADAM17 null mutation suffering from repeated skin and intestinal inflammation in specific tissues or developmental stages (Blaydon et al., 2011).

ADAM19: a regulator of the neuro-cardiovascular signaling axis

Whereas ADAM10 and ADAM17-deficient mice displayed developmental defects in multiple tissues, ADAM19 exerts its most important function predominantly in cells of the cardiovascular and neuronal systems. Different studies showed that the majority of ADAM19-deficient mice die perinatally, probably owing to cardiac defects (Kurohara et al., 2004; Zhou et al., 2004). These include ventricular septum defects and abnormal formation of heart valves leading to valvular stenosis and abnormalities of the cardiovasculature. It was reported that ADAM19 plays an important role during embryonic development of the endocardial cushion, probably by mediating ectodomain shedding of neuregulin β1 (Kurohara et al., 2004). ADAM19 is expressed in epithelial and mesenchymal cells originating from the neural crest, and studies with cell type-specific, ADAM19-overexpressing mice revealed that ADAM19 expression in neural crest cells is solely crucial for proper heart formation (Komatsu et al., 2007). Additionally, ADAM19 is also capable of cleaving HBEGF (Horiuchi et al., 2005), which is likewise important for cardiac developmental processes (Iwamoto and Mekada, 2006).

The functional implication of ADAM19 was demonstrated by phenotypical analysis of neuromuscular junctions (NMJs) in muscles of ADAM19-deficient mice (Yumoto et al., 2008). ADAM19 participated in the formation of NMJs by stabilizing the postsynaptic ephrin-A5–EphA4 complex, which is in turn important for mediating contact-dependent repulsion and thus neurite outgrowth. In a model of sciatic nerve regeneration, ADAM19 was furthermore shown to contribute to remyelination processes in Schwann cells via regulation of the expression of the transcription factor KROX20 (also known as EGR2) (Wakatsuki et al., 2009).

ADAM33: an asthma-causing sheddase?

ADAM33 is a widely expressed member of the ADAMs family (Gunn et al., 2002) that gained increasing recognition following the publication of a genome-wide association study that linked ADAM33 with asthma and bronchial hyper-reactivity (Van Eerdewegh et al., 2002). This study was the first report of a potentially disease-causing mutation within ADAM family members, and many groups tried to reconcile these findings with additional genetic studies in human and mouse. However, genetic studies in human patients led to contradictory results (Raby et al., 2004; Blakey et al., 2009; Jie et al., 2011; Miyake et al., 2012) and ADAM33-deficient mice did not display phenotypical differences when assessed in established models of airway inflammation (Chen et al., 2006). Nevertheless, cell-based studies revealed a putative role for ADAM33 as an ectodomain sheddase for the IgE receptor CD23, which is a key player during allergic reactions (Weskamp et al., 2006; Meng et al., 2007). Transgenic ADAM33 mice might be useful for solving this question in the future.

Conclusions

Despite considerable advances in our understanding of how ADAM proteases might control central developmental processes, we still urgently need to address a number of unresolved questions. It still remains largely unclear how different physiological regulators of ADAM activity modulate their activity and contribute to developmental decisions and tissue homeostasis. What is the spectrum of substrates used by a specific ADAM under a given physiological or developmental condition? We also do not fully understand how this ADAM substrate fingerprint and the coordinated activity of other proteases (protease network) (Overall and Blobel, 2007) are affected when environmental conditions or experimental conditions are changing. Can suitable modulators of ADAM activity be specifically designed to affect ADAM functions in vitro and in vivo? What regulates the time frame during which a specific ADAM can be active on a given substrate? Is there a relationship between the evolutionarily conserved role of ADAMs as cell-cell adhesion proteins and the more recently discovered role of ADAMs as proteases? Finally, what are the implications of genetic polymorphisms or mutations of ADAMs on human disease? Newly developed experimental tools, animal models and new technologies will certainly pave the way towards a better understanding of ADAM biology and will also open new avenues for influencing the proteolytic activities of these fascinating enzymes for therapeutic purposes.

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Competing interests statement
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