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Review

The "A Disintegrin And Metalloprotease" (ADAM) family of sheddases: Physiological and cellular functions

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ABSTRACT

There is an exciting increase of evidence that members of the disintegrin and metalloprotease (ADAM) family critically regulate cell adhesion, migration, development and signalling. ADAMs are involved in "ectodomain shedding" of various cell surface proteins such as growth factors, receptors and their ligands, cytokines, and cell adhesion molecules. The regulation of these proteases is complex and still poorly understood. Studies in ADAM knockout mice revealed their partially redundant roles in angiogenesis, neurogenesis, tissue development and cancer. ADAMs usually trigger the first step in regulated intramembrane proteolysis leading to activation of intracellular signalling pathways and the release of functional soluble ectodomains.

Contents

1. Introduction

Proteolytic ectodomain release, a process known as "shedding", has emerged as a key mechanism for regulating the function of a diversity of cell surface proteins. Shedding of integral membrane proteins is to our knowledge limited to type I and type II transmembrane proteins or GPI-anchored molecules in which the cleavage site is generally located close to the membrane surface. A Disintegrin And Metalloproteases (ADAMs) have emerged as the major proteinase family that mediates ectodomain shedding. ADAM-mediated shedding and non-proteolyic ligand binding are important in a number of biological processes such as the

Abbreviations: ADAM, A Disintegrin And Metalloprotease; APP, amyloid precursor protein; CAM, cell adhesion molecule; CNS, central nervous system; EGF, epidermal growth factor; EGFR, EGF receptor; GPCR, G protein-coupled receptor; HB-EGF, heparin-binding EGF; ICAM, intercellular adhesion molecule; ICD, intracellular domain; MMP, matrix metalloproteinase; PKC, protein kinase C; Pcdhs, protocadherins; RIP, regulated intramembrane proteolysis; SPP, signal peptide peptidase; SPPL, SPP-like protease; TACE, tumor necrosis factor α-converting enzyme; TIMP, tissue inhibitor of metalloproteinases; VCAM, vascular cell adhesion molecule.

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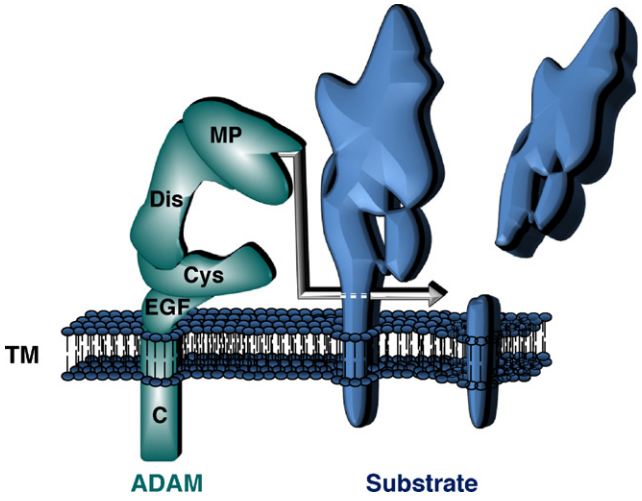

Fig. 1. Postulated domain structure of ADAMs. ADAMs consist of an extracellular domain with an N-terminal prodomain, a metalloprotease domain (MP), a disintegrin domain (Dis), a cysteine-rich domain (Cys) and an EGF domain. Within the cytosolic domain (C) phosphorylation sites or proline-rich regions with SH3 domains are present. The prodomain is removed during maturation. ADAM-mediated shedding of transmembrane proteins leads to the release of soluble extracellular domains and provides a mechanism for the down-regulation of cell surface proteins but also for extracellular signalling.

interaction of sperm and egg, cell fate determination, cell migration, wound healing, neurite and axon guidance, heart development, immunity, cell proliferation and angiogenesis. This proteolytic event through a cut in the juxtamembrane region seems to be the rate-limiting step for further cleavage within the membrane plane, releasing an intracellular domain which in some cases might act as signal-transducing molecule. Dependent on the cell type a considerable percentage of the proteins on the cell surface undergo ectodomain shedding affecting functionally diverse proteins, such as cadherins, L-selectin, Fas ligand, TNFα, EGFR ligands, ErbB2, ErbB4, amyloid precursor protein (APP), Notch receptor and ligand, and many others (Table 1). ADAMs as proteins of about 750 amino acid length are characterised by a conserved domain structure (Fig. 1), consisting of an N-terminal signal sequence followed by a prodomain, a metalloprotease domain, a disintegrin domain with a cysteine-rich region, an EGF domain, a transmembrane domain and a cytoplasmic tail [1]. ADAM-mediated shedding is both constitutive and inducible dependent on G-protein coupled receptors, protein kinase C (PKC), intracellular Ca^{2+} levels, membrane lipid composition and other experimental and natural stimuli. Also modulation of ADAM activity by removal of the inhibitory prodomain, by changing their intracellular distribution and by interaction of proteins, and/or posttranslational modifications of their cytoplasmic tails are reported, which further complicates the understanding of the regulation of proteolysis through ADAMs. The role of ADAMs and their pathophysiological roles are also covered in a number of excellent recent reviews [2–5].

2. The ADAM superfamily

2.1. History and phylogeny

ADAMs belong to the metzincin family of metalloproteases which also includes astacins and matrix metalloproteinases (MMPs). Together with snake venom metalloproteinases (SVMPs) and ADAMTS (ADAMs containing thrombospondin motifs), they form the adamalysin subfamily. The domain structure of ADAMs is responsible for their proteolytic, adhesive, and putative signalling activities [6].

Based upon similar structural features of the first cloned testicular ADAMs with snake venom disintegrin proteinases the term "ADAM" was introduced [7]. To date 40 *ADAM* family members have been identified in the mammalian genome. Registries of all ADAM family members in different species can be found at http://www.people.virginia.edu/%7Ejw7g/Table_of_the_ADAMs.html.

Whereas in the mouse genome 37 *ADAM* genes are found, many of them with testis-specific expression, in the human genome 21 *ADAMs* have been described [8]. The additional non-proteolytic roles of some ADAMs are underlined by the fact that only 12 of these human *ADAM* genes (ADAM8,9,10,12,15,17,19,20,21,28,30,33) encode proteins that express the typical metalloprotease Zn-binding active site [9].

ADAMs have been discovered in a variety of species ranging from filamentous fungi, yeast (*Schizosaccharomyces pombe*), *Caenorhabditis elegans*, *Drosophila melanogaster* to vertebrates [10–12]. Following the identification of the ADAMs, a number of different approaches were taken to unravel their function. These included purification and biochemical characterisation, analysis of the expression pattern, analysis of putative substrate cleavage, evaluation of adhesive and proteolytic functions and analysis of knockout mice.

2.2. ADAM synthesis and structure

After synthesis and translocation in the endoplasmic reticulum ADAMs are delivered and further matured in the Golgi compartment. This involves, next to complex glycosylation, the removal of the prodomain through the proprotein convertase 7 or furin from the ADAM precursor protein [13]. The prodomain of some ADAMs may act as an intramolecular chaperone facilitating the correct protein folding and maintaining the proteinase in a latent state [14]. Isolated prodomains of ADAMs may be selective inhibitors of the mature and active forms of the enzymes [15,16]. At steady state most ADAMs are predominantly found in the Golgi apparatus [17,18], but they are localised to a minor degree at the plasma membrane [19]. Despite the fact that a number of important physiological events mediated by the activity of ADAMs are well understood surprisingly little is known about the intracellular localisation and transport of these proteins.

The catalytic metalloprotease domain is highly conserved among the various ADAM family members. The mechanism of proteolytic activity could be better understood after resolving the structure of the metalloprotease domain of ADAM17 and ADAM33 [20,21]. The hydrolytic processing of protein substrates requires a zinc-binding motif containing three histidine residues (HEXGHXXGXXHD) and a highly conserved methionine-turn in the active-site helix.

While the disintegrin domain of ADAMs may participate in cell–cell adhesion processes [22], it is in concert with the cysteine-rich domain also involved in the regulation of catalytic activity [23], substrate targeting [24,25] and removal of the prodomain from the catalytic domain [26]. The structure of the ADAM10 disintegrin and cysteine-rich domain was resolved and it revealed that it is needed for substrate-recognition. After binding to the substrate the proteinase domain is positioned for an effective cleavage of the substrate [25]. The cysteine-rich domain may be involved in regulation of the biological activity of a number of ADAM proteases [24,27]. It may be necessary for improving the binding capacity of the disintegrin domain [28] and may function in the binding of cell surface proteoglycans [27].

The cytoplasmic tail of ADAMs varies in length and sequence and it may be involved in the regulation of protease function through modulation of maturation, activity and intracellular transport of the protease. It contains binding site motifs for SH3 domain-containing proteins and potential sites for phosphorylation. The tail has been

Table 1
Potential ADAM substrates and phenotypes of ADAM knockout mice.

ADAM	Other name	Substrates	Phenotype of knockout mice
8	CD156, MS2, mCD158	ADAM8 [114] APP [115] CD23 [116] CD30-ligand [116] CHL-1 [91] L-Selectin [117] MBP [115]	Viable, fertile, no obvious pathology [90]
9	Meltrin gamma, MDC9	APP [93,118] Collagen XVII [119] Delta like ligand-1 (DLL1) [77] EGF [120] FGFR2iiib [120] HB-EGF [92] IGFBP-5 [121] Insulin B chain [122] Laminin [123]	Viable, fertile, no obvious pathology [85]
10	MDAM, kuzbanian	APP [89] Axl [124] Betacellulin [61] CD23 [125] CD30 [126] CD44 [127] Cellular prion protein [128] cMet [129] Collagen IV [130] Collagen XVII [119] CX3CL1/Fractalkine [131] CXCL16 [52] Delta like ligand-1 (DLL1) [76] Desmoglein-2 [132] E-cadherin [40] EGF [61] Ephrin A2 [39] Ephrin A5 [25] ERBB2 (HER2/neu) [133] FasL [134] IL-6 Receptor [135] Klotho [136] LAG-3 [137] L1 [19,138] MICA [139] N-cadherin [41] Notch-1 [10] Pcdh-γ C3/B4 [42] Thyrotropin Receptor [140] TRANCE [141] VE-cadherin [43]	Embronical lethal (E9.5), defective heart and CNS development, vasculogenesis and somitogenesis, defective Notch signalling [73]
12	Meltrin alpha	Collagen IV [142] Delta like ligand-1 (DLL1) [77] HB-EGF [143] Fibronectin [142] Gelatin [142] IGFBP-3/-5 [144] S-carboxymethylated transferrin [145]	Viable, fertile, 30% embryonic lethality, Abnormalities of brown adipose tissue [146]
15	Metargidin, MDC15	Amphiregulin [147] CD23 [116] E-cadherin [148] HB-EGF [149]	Viable, fertile, age onset osteoarthritis, defects in pathological neovascularisation [98]
17	TACE	ACE2 [150] ALCAM [132] Amphiregulin [61] APP [151] CD30 [152] CD40 [153] CD44 [127] Cellular prion protein [128] Collagen XVII [119] Colony stimulating factor 1 [154] CX3CL1/Fractalkine [155] CXCL16 [53] Delta like ligand-1 (DLL1) [77] Desmoglein 2 [132] Epigen [62]	Perinatal lethality, defects in development of epithelia, defective heart and lung development, phenotype resembles that of mice deficient for EGFR or EGFR ligands [55,63,174,175]

Table 1 (*Continued*)

ADAM	Other name	Substrates	Phenotype of knockout mice
		Epiregulin [61] ErbB4/HER4 [156] Growth hormone receptor [157] HB-EGF [61] ICAM-1 [51] IL1 Receptor II [24] IL6 Receptor [158] IL15R [124] L1 [138] LAG-3 [137] L-selectin [55] Kit Ligand 1 and 2 [159] Klotho [136] MICA [139] MUC1 [160] NCAM [161] Nectin 4 [162] Neuregulin1/2 [96] Neuronal pentraxin receptor [163] Notch-1 [70] Platelet glycoprotein V [164] Semaphorin 4D [165] TGF-alpha [61] TNF-alpha [166,167] TRANCE [168] TrkA neurotrophin receptor [169] TNF receptor I and II [24,55] P75 neurotrophin receptor [170] Pref-1 [171] PTP-LAR [172] Vps10p-D [173] VCAM-1 [50]	
19	Meltrin beta MADDAM	Neuregulin-1 [176] TRANCE [177] TNF-alpha [178] ADAM19 [179]	80% postnatal lethality 1–3 days after birth, cardiovascular defects [100,101]
28	MDC-L	Myelin basic protein [180] CD23 [116] IGFBP-3 [181]	
33		CD23 [182] Kit Ligand-1 [183]	No distinct phenotype [184]

postulated to be involved in the inside-out signalling, the outside-in regulation of cell signalling, and the control of maturation and subcellular localisation [1]. There are a number of adaptor proteins with binding capacity to the cytoplasmic tails of individual ADAMs [29,30]. The cytoplasmic domain possibly play a role in ADAM function, either by regulating catalytic activity, by coupling ADAM activity to signalling or by trafficking the protein to the correct cellular location. The regulated translocation of ADAM12 to the plasmamembrane requires the cytoplasmic domain and is dependent on PKCε [31]. PACSIN3 is an example for a SH3-domain-containing protein which is able to interact with the cytoplasmic domains of several ADAMs including ADAM9, -10, -12, 15 and -19 [32]. This interaction may regulate endocytosis of ADAM proteases. Another example is the identification of a proline-rich region in the cytoplasmic domain of ADAM10 [33]. This region was shown to be responsible for the correct basolateral sorting of ADAM10 therby influencing E-cadherin shedding and the cellular migration. Synapse Associated Protein-97 (SAP97) is another SH3-domain-containing protein that interacts with the cytosolic tail of ADAM10 [34] and is responsible for correct localisation of ADAM10 in synaptic membranes, thereby promoting its α-secretase activity. SAP97 is also able to bind the cytosolic tail of ADAM17 [35].

2.3. ADAM functions

ADAMs are unique transmembrane proteins as they are capable of mediating cell adhesion via their disintegrin and cysteine-rich domain as well as the proteolytic release of cell surface molecules. Therefore, these proteases have been implicated in diverse (patho)physiologic processes including fertilisation, neurogenesis, inflammatory diseases or cancer (Fig. 2). The inactive

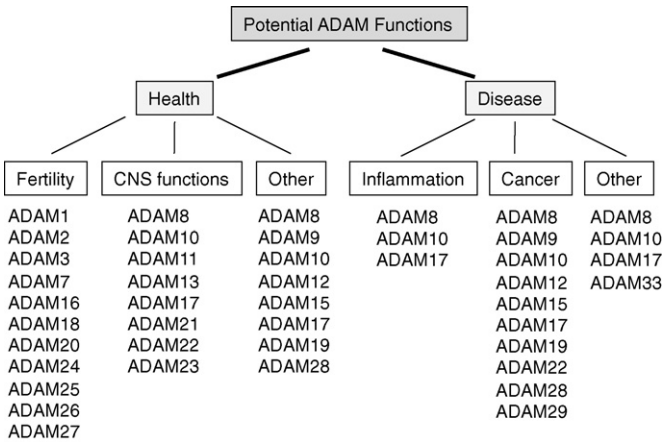

Fig. 2. ADAM functions in Health and Disease. Because of their adhesive and proteolytic activities ADAMs have been implicated in diverse (patho)physiologic processes. They play a critical role during fertilisation but also for CNS development and development of the cardiovascular system. Recent findings also suggest that dysregulation of ADAM functions may be related to inflammatory diseases, cancer progression, or other diseases like rheumatoid arthritis or asthma.

as well as the proteolytically active ADAMs participate in cell adhesion and cell fusion events. All ADAMs, except ADAM10 and ADAM17, contain an aspartatic-acid sequence in their disintegrin loop motif, which can be recognised by the α4/α9 subfamily of integrins (reviewed in [22]). Human ADAM15 as an exception also has a conserved RGD sequence in the disintegrin domain and can interact with integrins in an RGD-dependent manner. Since most ADAM-integrin interaction studies are based on cell culture and *in vitro* protein–protein interaction experiments the physiologic relevance of these interactions is still a matter of debate. Most data exist for the functional role of ADAMs in fertilisation. In particular, ADAM2-deficiency leads to impaired sperm migration and adhesion capacity even though ADAMs are apparently not essential for sperm–egg fusion [36].

Besides their potential adhesive functions, ADAMs have a prominent role in releasing soluble factors like growth factors, hormones, or chemokines. The cleavage "activates" the membrane-bound proforms by release of the extracellular peptide that retains biological activity (e.g., tumor necrosis factor alpha or EGFR ligands). The released peptides can bind to their receptors and mediate signals in an autocrine or paracrine fashion (Fig. 3A). The ADAM mediated proteolysis is not only essential for providing extracellular signals but also represents a prerequisite for intracellular signalling by regulated intramembrane proteolysis (RIP) [37]. The ectodomain shedding of type I proteins promotes further proteolysis of the remaining transmembrane fragment by the γ-secretase complex, while type II proteins are further degraded through the signal peptide peptidase like proteins (SPPLs) [38]. Both degradation pathways lead to the intracellular release of soluble substrate fragments and the dissociation of associated molecules, which may transcriptionally alter gene expression (Fig. 3B).

Besides signalling function, ADAM mediated ectodomain shedding has emerged as an important mechanism to rapidly decrease selective proteins from the cell surface and to inactivate receptors. Solubilised receptors could also potentially function as decoys that sequester soluble ligands (Fig. 3C). The downregulation of cell surface proteins may occur on the same cell but also in trans on the surface of the opposing cell, like the ADAM10-mediated inactivation of the ephrin/Eph complex by ephrin shedding (Fig. 3C) [25]. ADAM-dependent proteolysis of ephrins, which are critically involved in the local navigation of axonal growth cones, might represent an axon repulsion signal [39].

2.4. ADAMs as mediators of cell adhesion and migration

ADAMs exert diverse effects on cell adhesion and cell migration. Besides their own adhesive capacity (e.g. integrin binding) they modify cell signalling pathways essential for migration guidance cues (e.g. ephrin signalling). Additionally, the ADAM-dependent proteolysis of cell adhesion molecules (CAMs) has emerged as an important mechanism for the dynamic coordination of cell adhesion and cell migration processes during development but also during inflammatory diseases or tumor metastasis [5]. In some cases (e.g. CD44, N-cadherin) this CAM proteolysis additionally initiates an intracellular signalling pathway by the subsequent release of intracellular protein fragments, which participate in signal transduction.

Many CAMs such as cadherins, selectins or members of the immunoglobulin superfamily are released as soluble forms *in vitro* and *in vivo*. In particular, members of the cadherin family, which mediate Ca^{2+}-dependent homophilic cell–cell adhesion, are released by ADAM10-mediated cleavage [40–43]. Neuronal (N-)cadherin is critically involved in heart tube formation, neurulation and somitogenesis, and in connective tissue remodelling and wound healing. E-cadherin plays an important role in tissue morphogenesis, wound healing and the maintenance of tissue integrity. The cytoplasmic domain of these classical cadherins is linked to the cytoskeleton via β-catenin. Both cadherins are substrates for ADAM10-mediated processing. The release of the extracellular domain, which contains the homophilic binding sites, is functionally of major importance for the regulation of cell adhesion, cell migration and cell signalling [40,41,44,45]. Dysregulation of ADAM10 in the human epidermis might contribute to impaired cohesion of keratinocytes and blister formation observed in eczematous dermatitis as evidenced by *in situ* examination and immunoblot analyses of diseased skin [46].

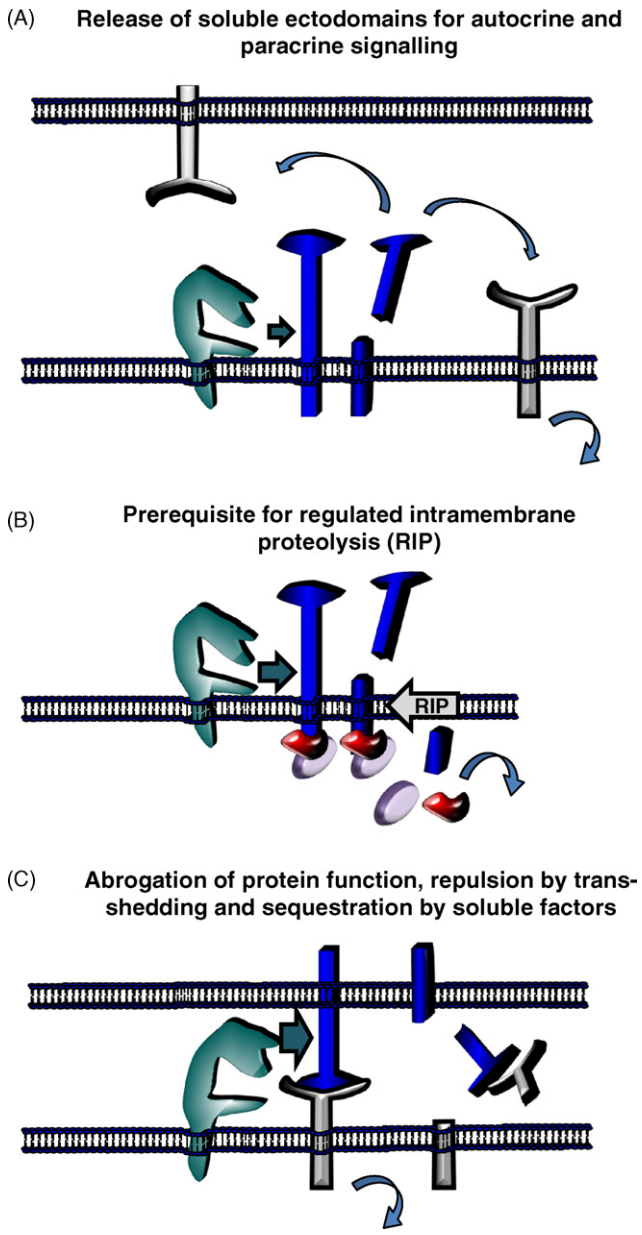

Fig. 3. ADAM mediated proteolysis can have multiple functional roles. (A) Shedding can be necessary for the release of active peptides from pro-proteins such as TNF-alpha and therefore mediate autocrine and paracrine signalling. (B) Ectodomain proteolysis also represents a prerequisite for further degradation through intramembrane proteases like the γ-secretase complex or the SPPLs. This regulated intramembrane proteolysis (RIP) releases intracellular fragments or associated molecules that might directly act as transcription factors or indirectly modulate cell signalling pathways. (C) ADAMs can rapidly downregulate cell surface molecules like cell adhesion proteins, receptors or their ligands. The released ectodomains might also function as soluble antagonists. In principle ADAMs can also cleave substrates on the opposing cell. This trans-shedding might induce cellular repulsion of two interacting cells.

The recently discovered protocadherins (Pcdhs) are the largest and most diverse group of cadherins. The *Pcdh* genes are arranged in three clusters: *Pcdhs-α*, *-β*, and *-γ*. The Pcdhs-γ are predominately expressed in the nervous system and play a role in neuronal survival and synaptogenesis [47]. Analysis of ADAM10-deficient fibroblasts and embryos extracts demonstrated that ADAM10 is not only responsible for the constitutive but also for the regulated shedding of Pcdh-γ C3. The ADAM10-dependent proteolysis led to further processing of the protein and the intracellular release of a C-terminal fragment that can translocate to the nucleus [48]. Pcdh-γ C3 shedding as well as N-cadherin proteolysis was found to be differentially regulated in neuronal cell lines and primary neurons by glutamate receptor activation indicating a potential role in synaptic plasticity.

The proteolytic release of cell surface molecules also provides a mechanism to coordinate the multistep process of leukocyte recruitment in response to inflammatory stimuli [49]. During leukocyte trans-endothelial migration, the density of vascular endothelial (VE)-cadherin in the membrane adjacent to the advancing leukocyte decreases dramatically. VE-cadherin is known to control endothelial permeability, vascular integrity and leukocyte transmigration. Recently, Schulz et al. demonstrated that ADAM10 mediates the shedding of VE-cadherin [43]. This processing could be activated by thrombin treatment and contributed to the thrombin-induced dissolution of adherens junctions. Knockdown of ADAM10 in endothelial cells as well as in T-cells by small interfering RNA impaired T-cell transmigration in a transwell migration assay. Apart from ADAM10, ADAM17 seems to be a key protease for the regulation of CAM functions in the immune system. Several cell adhesion molecules like ICAM-1, VCAM-1 or transmembrane chemokines that play important roles for leukocyte adhesion/de-adhesion, rolling velocity or cell migration can be processed by ADAM17 [50–54]. ADAM17 has also been discussed to be the major L-selectin sheddase [55,56]. But it is likely that also other metalloproteases are involved in this cleavage event [57]. Several additional CAMs have been identified as ADAM substrates in the last years but many of the postulated functional roles also still require *in vivo* validation e.g. with the help of conditionally targeted ADAM knockout mice.

2.5. ADAMs and EGFR signalling

The epidermal growth factor receptor (EGFR/ErbB) family participates in the regulation of several cellular functions such as proliferation, migration, differentiation, and cell survival [58]. Correct EGFR function is essential for normal embryonic development and adult tissue homeostasis, and deregulation of EGFR signalling has been associated with many human diseases, including cancer [59]. The EGFR family includes four related receptors (ErbB1–4) and eleven ligands namely amphiregulin, betacellulin, EGF, epigen, epiregulin, heparin-binding EGF-like growth factor (HB-EGF), neuregulin 1–4, and TGF-alpha. These ligands are initially synthesised as membrane-bound precursors that have to be released by proteolytic cleavage to generate the mature, soluble forms. In the last years ADAMs have emerged as the key metalloproteases involved in the release of the EGFR ligands and in EGFR activation (reviewed in [2,60]). ADAM17 has been identified as a critical sheddase for TGFα, HB-EGF, epiregulin, and amphiregulin, while ADAM10 is particularly involved in the shedding of EGF and betacellulin [61,62]. The *in vivo* relevance of ADAM17 for EGFR activation is underlined by the fact that *Adam17−/−* mice have developmental defects resembling those in animals lacking TGFα, HB-EGF, amphiregulin or the EGFR [55,63,64]. The release of the EGFR ligands can be regulated by different mechanisms. While calcium influx stimulates ADAM10 mediated shedding, phorbol esters predominantly activate ADAM17-dependent release of EGFR-ligands [65]. Another important way of ADAM-dependent EGFR activation is transactivation by G protein-coupled receptors (GPCR) [60]. A wide variety of GPCR agonists including thrombin, ANG II, endothelin-1 (ET-1) have been described to transactivate EGFR signalling. However little is known about the detailed machinery involved in ADAM activation by G-protein derived signalling molecules. Besides PKC, Ca^{2+} or ROS-dependent activation, ADAM phosphorylation, localisation or ADAM-substrate interaction may be modified. Dysregulation of ADAM activity and EGFR activation might also contribute to human diseases. ADAM12 and ADAM33 mediated EGFR-transactivation has been linked to cardiac pathophysiology and asthma-susceptibility, respectively. ADAM10, ADAM15 and ADAM17 were shown to contribute to tumourigenesis, migration and invasion by GPCR–EGFR transactivation in different tumours and cell lines [60].

3. ADAM shedding as a prerequisite for intracellular signalling

RIP has emerged as an unusual but important mechanism of signal transduction [66]. This sequential processing of transmembrane proteins in their extracellular domain and the subsequent further processing in the intramembrane region leads to the release of an intracellular domain (ICD), which might participate in signal transduction. Even though the extracellular processing may be mediated by several distinct ectodomain sheddases, the ADAMs play the most prominent role in this context. While the intramembranous proteolysis of truncated type I proteins is mediated by the γ-secretase complex, type II proteins like TNF-alpha, FasL and Bri2, can be further degraded by the signal peptide peptidase like proteins [38]. The soluble ICDs are in most cases intermediates that are destined for degradation, but for an increasing number of "RIPped" proteins a translocation into the nucleus and transcriptional activation of target genes has been described (reviewed in [67]). However since most of these studies are based on artificial overexpression of ICDs, the physiological relevance of such signalling events is still a matter of debate.

3.1. The Notch Paradigm

Notch signalling is an evolutionarily conserved mechanism to control cell fates and developmental processes. Notch-like proteins have been identified and characterised in several species, ranging from sea urchins to humans [68]. The *Notch* gene family encodes four type I transmembrane receptors in mammals. The large Notch 1 ectodomain is composed of 36 tandem EGF-like repeats and three cystein-rich LIN-12/Notch repeats (LNR). It is cleaved within the trans-Golgi network by a furin like convertase (site 1 or S1 cleavage) [69], generating an extracellular and a transmembrane fragment, which remain associated (Fig. 4A). This heterodimer is thought to be the only form of the Notch receptor found on the cell surface. Notch is activated upon binding to one of its membrane-anchored ligands like Delta (Dl) and Serrate (Ser) in *Drosophila,* Delta-(like) (Dll) and Jagged in vertebrates or LAG-2 and APX-1 in *C. elegans*. Interaction of Notch receptors and ligands results in a conformational change followed by sequential proteolytic processing. First the ectodomain is processed by an ADAM protease at site 2 (S2 cleavage) [70,71] leading to the formation of a carboxyterminal fragment called Notch extracellular truncation (NEXT) (Fig. 4A). Afterwards the remaining fragment is further processed through the γ-secretase complex in the transmembrane domain (S3 cleavage) (Fig. 4A). The latter cleavage releases the Notch intracellular domain (NICD) that translocates to the nucleus and functions as a transcriptional activator that forms a complex with transcriptional factors containing CSL (also known as RBP-Jκ and CBF1). This complex transactivates

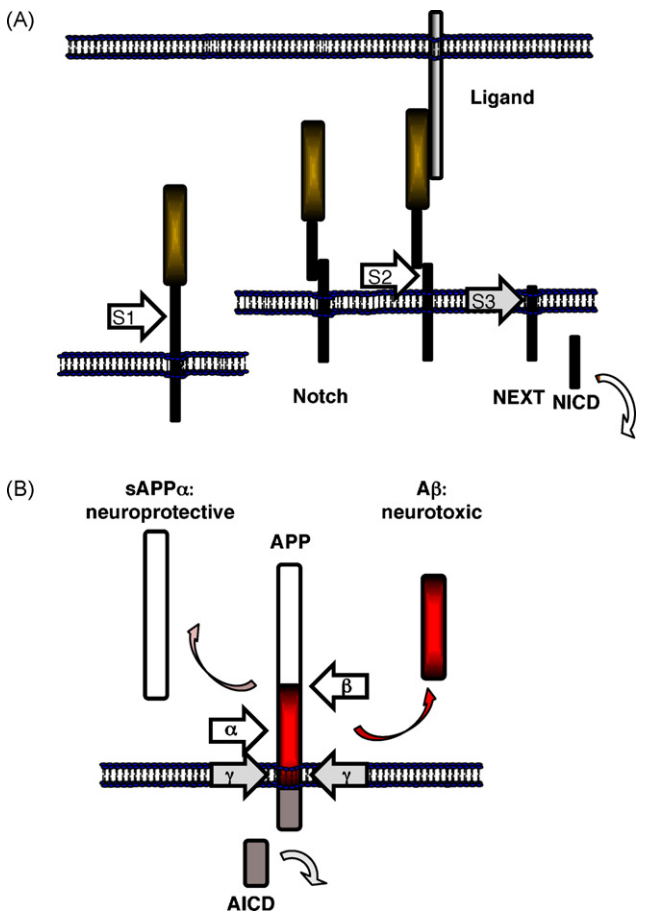

Fig. 4. ADAM shedding and intracellular signalling. (A) Notch receptor proteolysis. The Notch receptor undergoes ectodomain processing in the trans-Golgi network by a furin-like convertase (S1 cleavage) resulting in a heterodimeric protein that is transported to the cell surface. Ligand binding triggers processing by ADAM family members (S2 cleavage). The remaining Notch extracellular truncated fragment (NEXT) is a substrate for further γ-secretase dependent intramembranous cleavage (S3 cleavage) resulting in the release of a Notch intracellular domain (NICD), that translocates to the nucleus and modulates signal transduction. (B) APP ectodomain shedding is either mediated by an α-secretase or the β-secretase. This cleavage leads to further processing of the APP transmembrane fragment by the γ-secretase complex releasing an APP intracellular domain (AICD). While the APP ectodomain released by α-secretase activity has been shown to have neurotrophic and neuroprotective functions, β-secretase/γ-secretase cleavage leads to the release of neurotoxic amyloid β peptides.

the critical downstream effectors of the Notch signalling process, such as hairy and enhancer of split (Hes1) and Hes5.

The exact involvement of ADAM10 and ADAM17 in Notch signalling is still a matter of debate. While the ADAM10 orthologue *Kuzbanian* has been established as Notch sheddase in *Drosophila* by genetic and biochemical studies [72], the situation in mammalians is still controversial. Mumm et al. showed that S2 processing still occurs in *Kuzbanian*-deficient cells transfected with active Notch constructs [71]. Moreover, TACE-deficent fibroblasts expressing a chimeric Notch construct did not exhibit any S2 cleavage activity [70], indicating a critical role of ADAM17 for Notch processing. On the other hand, the phenotype of ADAM17-deficient mice is not related to Notch-deficiency at all, while ADAM10-deficient mice phenocopy many Notch knockout defects, strongly arguing for a major role of ADAM10 for Notch signalling [73]. This is further supported by a recent report describing an essential role of ADAM10 for proteolytic activation of Notch during thymocyte development [74].

Interestingly, the Notch ligands Delta and Jagged are processed in a similar manner to Notch [75]. ADAM10 has been suggested to mediate Delta processing in *Drosophila* and to be partially responsible for Dll1 processing in mammals [76,77]. These studies suggest that the critical role of ADAM10 for Notch signalling is rather due to Notch ligand processing than to Notch shedding. Taken together Notch signalling requires ADAM activity and this activity can positively and negatively regulate Notch functions either by initiating Notch signalling or by downregulating the Notch ligands.

3.2. ADAMs and shedding of APP

The accumulation of β-amyloid peptides in the cerebral cortex is a key step in the pathogenesis of Alzheimer's disease. These small neurotoxic peptides of 37–43 amino acids are generated by processing of the amyloid precursor protein APP by the β-secretase BACE (beta-site APP cleaving enzyme) in the ectodomain and the subsequent γ-secretase cleavage in the intramembranous region (Fig. 4B). In contrast to this amyloidogenic APP processing, the majority of APP is cleaved in the non-amyloidogenic pathway by α-secretase and γ-secretase activity. The α-secretase cleavage site is located in the Aβ sequence and thus prohibits formation of pathogenic Aβ peptides and Alzheimer's disease pathogenesis. Moreover, the soluble APP ectodomain released by α-secretase activity has neurotrophic and neuroprotective functions [78]. Therefore, increasing α-secretase activity is discussed as a strategy for the treatment of Alzheimer's disease.

APP ectodomain shedding by either α-secretase or β-secretase is followed by further cleavage of the transmembrane fragment by the γ-secretase complex releasing an APP intracellular domain (AICD). In contrast to the ligand-induced RIP of the Notch receptor, APP processing most likely represents ligand-independent RIP. The AICD was shown to reach the nucleus [79], and proposed to regulate transcription of target genes through a complex with the adaptor protein Fe65 and the histone acetyltransferase Tip60 [80,81]. However, increasing evidence is accumulating suggesting that APP does not play a direct role in gene transactivation but instead acts as membrane bound anchoring protein by recruiting and activating Fe65 [82,83]. Therefore, the definite role of AICD in cell signalling is still a matter of debate.

Similar to the Notch situation the nature of the metalloprotease responsible for the physiologic processing of APP is not completely clear. Overexpression studies and *in vitro* cleavage assays indicate that ADAM9, ADAM10 and ADAM17 are able to act as α-secretase (reviewed in [4,84]). However, ADAM9 deficient mice do not show an impaired APP shedding in hippocampal neurons, arguing against a critical role as the physiologic relevant α-secretase [85]. ADAM17 is also unlikely to act as an essential α-secretase since it is predominantly expressed in endothelial cells and astrocytes in the human central nervous system (CNS), while high expression of ADAM10 has been described in neurons in the mouse CNS [86–88]. Consistent with these findings, overexpression of ADAM10 in an Alzheimer mouse model resulted in a decrease of β-amyloid deposition and cognitive deficits [89]. Taken together these findings strongly argue for ADAM10 as a major physiological α-secretase.

4. Roles of ADAMs for health and disease revealed by studies from ADAM knockout mice

Knockout mice for a number of widely expressed ADAMs were generated. The phenotype of these mice revealed important information about functions and substrates of these proteases. The availability of these mice but also of cell lines derived from these mice allowed the in depth analysis of potential functions of these proteins under physiological and pathological conditions. Interestingly, whereas knockout strains for ADAM8,9,12,15 did not present overt phenotypes, mice lacking ADAM10,17,19 and 22 suffered of severe developmental defects leading to early death.

ADAM8-deficient mice are viable and fertile with no apparent abnormalities in development, adult survival and fertility [90]. No apparent abnormality of the hematopoetic system, where this protease is primarily expressed, was found. However, shedding of the close homologue of L1 (CHL1) adhesion molecule was reduced in brain extracts of ADAM8-deficient mice [91]. ADAM9 is ubiquitously expressed, but mice lacking this metalloprotease are viable and fertile and develop normally. Although this protease was implicated in the shedding of HB-EGF [92] and in the shedding of the amyloid precursor protein [93] no processing defects were observed in ADAM9-deficient cells, which suggests efficient compensation by other ADAM proteinases [85].

Deletion of ADAM10 leads to early embryonic lethality and multiple defects of the developing CNS, somites, and cardiovascular system, which resemble those seen in the absence of Notch/Delta signalling [73] and which are similar to findings in mutants of *Drosophila* [10,94]. A putative role of ADAM12 has been described for muscle formation [95]. However, mice with a targeted deletion of ADAM12 but also triple deficient ADAM9/12 and 15 mice and ADAM9/12/15/19-quadruple knockout mice are viable and fertile without an increased lethality [61,96]. A defect in adipocyte function has been suggested due to a reduced weight gain and number of adipocytes [97]. The lack of ADAM15 does not lead to an overt phenotype in mice. Due to the high levels of ADAM15 in endothelial cells its role in neovascularisation was analysed. In a mouse model for retinopathy of prematurity a major reduction in neovascularisation was observed. After implantation of melanoma cells a reduced tumor growth was described and suggested that ADAM15 may represent a suitable target for the design of inhibitors of pathological neovascularisation [98]. It was also reported that ADAM15 deficiency leads to an accelerated development of osteoarthritic lesions in aging mice [99]. Mice with a targeted disruption of the zinc-binding domain of ADAM17 have a perinatal lethality with open eye lids, a lack of a conjunctival sac, thinned corneas, and epidermal and hair defects [55]. The phenotype of these mice implicates ADAM17 functions in EGFR signalling.

ADAM19-deficient mice have severe defects in cardiac morphogenesis and abnormalities of the cardiac vasculature, which result in early postnatal lethality and suggest an important role of ADAM19 in remodelling of the endocardial cushion of the developing heart [100,101]. ADAM22-deficient mice die before weaning. After one week of age ataxia, convulsions and peripheral neuropathy were observed [102]. The neuronal phenotype may be linked with a recently recognised role of ADAM22 as a receptor for LGI1, a secreted neuronal protein. Mutations in the gene encoding LGI1 cause autosomal dominant lateral temporal epilepsy [103].

5. Aspects of regulation of ADAM proteases

Apart from the constitutive cleavage by ADAM proteases a number of stimuli for such shedding events are known. Serum factors, growth factors, changes in the intracellular calcium concentration, osmotic and mechanical stress, and PKC activation are known inducers for ADAM-mediated ectodomain shedding. Regulation of ADAM activity may happen at different levels such as transcriptional control, alternative splicing, post-translational modifications, changes in the stability of ADAM proteinases, interaction of other proteins, cellular localisation, and localisation within the plasma membrane and availability of the ADAM substrates [6].

Alternative splicing has been described for several *ADAM* genes. The splicing events often give rise to different cytosolic tails, thereby modulating the binding capacity to cytosolic interacting proteins and possibly also the intracellular localisation [104]. This is exemplified by the observation that aberrant combinations of ADAM15 mRNA isoforms in the cancer cells are able to interact differentially with Src family protein tyrosine kinases [105]. Interestingly, although not much is known about the regulation of transcription of ADAM proteases it is speculated that microRNAs are also involved in the level of ADAM17 expression during malignancy [106].

One of the central questions in the field of ADAM protease research is what determines ADAM substrate selectivity. A consensus sequence for cleavage is missing and in many substrates the cleavage sites are highly variable [22,107]. It appears that the secondary structure of the juxtamembrane stalk seems to be of critical importance for efficient substrate recognition [1].

The activity of ADAM proteases can also be modulated by inhibitory proteins, which bind to the metalloprotease domain. Tissue Inhibitors of Metalloproteinases (TIMPs) are physiological inhibitors of MMPs and ADAMs. TIMP1 is able to inhibit ADAM10 but not ADAM17 while TIMP3 leads to efficient inhibition of ADAM17 and inhibits ADAM10 with lower effectivity [108,109]. It is still not clear what is the exact physiological role of TIMPs. Synthetic inhibitors against ADAM10 and ADAM17 are also developed and currently tested in clinical trails as therapeutic agents for rheumatoid arthritis and cancer [110,111]. Unfortunately, the efforts so far have failed largely due to unfavorable toxicology of these synthetic compounds. A likely problem is the fact that ADAMs like ADAM10 or ADAM17 are involved in the shedding of various physiological important membrane-bound proteins, including several adhesion molecules but also several cytokines and growth factors, increasing the possibility of side effects.

In most reported cases ADAM17 appears to be one of the critical proteinases, which is susceptible to different experimental (e.g., phorbol esters, pervanadate, ionomycin) and natural (e.g., NMDA or ligands of G protein-coupled receptors, GPCR) stimulants [2]. However, other ADAM family members, e.g., ADAM10, can be also be induced by such stimulation [40,41], which mainly involve PKC activation. Analysis of the intracellular signalling pathways that modulate shedding revealed that mitogen-activated protein kinases can trigger the shedding of selective substrates such as proHB-EGF [112], L-selectin, L1 and syndecan-1 and -4 [113].

6. Conclusions

It is well recognised that ADAM-mediated ectodomain shedding is of major importance to regulate cell-cell interaction and cell communication. Dysregulation of ectodomain shedding is associated with autoimmune and cardiovascular diseases, infection, inflammation and cancer and ADAMs are attractive targets for novel therapies. It becomes increasingly clear that further research especially on the regulation and control of ADAM activity, ADAM redundancy in substrate processing, ADAM structure, interaction of ADAMs with regulatory proteins and the physiologically relevance of ectodomain shedding is needed. There is also still a lack of knowledge about how cellular localisation of ADAMs is regulated and how this may be related to proteolytic functions. Regarding the latter aspect the use of conditionally targeted mice in conjugation with disease models will be extremely helpful for elucidation of ADAM functions in selected tissues and developmental stages.

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