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The Biochemistry and Physiology of A Disintegrin and Metalloproteinases (ADAMs and ADAM-TSs) in Human Pathologies

Deepti Sharma and Nikhlesh K. Singh

Contents

Abstract Metalloproteinases are a group of proteinases that plays a substantial role in extracellular matrix remodeling and its molecular signaling. Among these

D. Sharma and N. K. Singh (✉)
Department of Ophthalmology, Visual and Anatomical Sciences, Integrative Biosciences Center (IBio), Wayne State University School of Medicine, Detroit, MI, USA
e-mail: nsingh2@wayne.edu

metalloproteinases, ADAMs (a disintegrin and metalloproteinases) and ADAM-TSs (ADAMs with thrombospondin domains) have emerged as highly efficient contributors mediating proteolytic processing of various signaling molecules. ADAMs are transmembrane metalloenzymes that facilitate the extracellular domain shedding of membrane-anchored proteins, cytokines, growth factors, ligands, and their receptors and therefore modulate their biological functions. ADAM-TSs are secretory, and soluble extracellular proteinases that mediate the cleavage of non-fibrillar extracellular matrix proteins. ADAMs and ADAM-TSs possess pro-domain, metalloproteinase, disintegrin, and cysteine-rich domains in common, but ADAM-TSs have characteristic thrombospondin motifs instead of the transmembrane domain. Most ADAMs and ADAM-TSs are activated by cleavage of pro-domain via pro-protein convertases at their N-terminus, hence directing them to various signaling pathways. In this article, we are discussing not only the structure and regulation of ADAMs and ADAM-TSs, but also the importance of these metalloproteinases in various human pathophysiological conditions like cardiovascular diseases, colorectal cancer, autoinflammatory diseases (sepsis/rheumatoid arthritis), Alzheimer's disease, proliferative retinopathies, and infectious diseases. Therefore, based on the emerging role of ADAMs and ADAM-TSs in various human pathologies, as summarized in this review, these metalloproteases can be considered as critical therapeutic targets and diagnostic biomarkers.

Keywords A disintegrin and metalloproteinases · ADAM-TSs · Cardiovascular diseases · Colorectal cancer · Proliferative retinopathies

Abbreviations

ACE-2	Angiotensin-converting enzyme 2
AD	Alzheimer's disease
APC	Adenomatous polyposis coli
APP	Amyloid-beta precursor protein
COVID-19	Coronavirus disease 2019
CYS1	Cystin1
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor 2
EGR1	Early growth response 1
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
GPCR	G protein-coupled receptor
GRP	Gastrin releasing peptide
HSCs	Hepatic stellate cells
HVR	Hyper variable region
IL-6	Interleukin 6
iRhom	Inactive rhomboid protein

LPS	Lipopolysaccharides
MI	Myocardial ischemia
miR-342	Micro RNA 342
MMPs	Matrix metalloproteinases
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PKC	Protein Kinase C
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SNP	Single-nucleotide polymorphism
SVMPs	Snake venom metalloproteases
TGF-α	Transforming growth factor-α
TIMPs	Tissue inhibitors of metalloproteinases
TNFR2	Tumor necrosis factor receptor 2
TNF-α	Tumor necrosis factor α
TrkA	Tropomyosin receptor kinase A
TSP1	Thrombospondin 1
VEGF	Vascular endothelial growth factor
VEGFR2	Vascular endothelial growth factor receptor 2

1 Introduction

The extracellular matrix (ECM) is an essential scaffold for the cellular components that initiate biomechanical signals necessary for cellular differentiation, tissue homeostasis, and morphogenesis (Frantz et al. 2010). ECM is important for cell-to-cell and cell-to-matrix interactions for the normal growth and functioning of the organism. Changes in physiological or pathological conditions induce ECM remodeling by enzymes called proteases. ECM remodeling is a sequence of alterations that occur in ECM components which is important for regulation of ECM structure and composition, as well as for expression and secretion of bioactive molecules to affect DNA synthesis, cell differentiation, inflammation, angiogenesis, fertilization, blood coagulation, wound repair, neurogenesis, apoptosis, senescence, and necrosis (Cui et al. 2017). Among various proteases, matrix metalloproteinases (MMPs) or matrixins are the most studied proteases and their proteolytic actions on ECM is important for organogenesis and branching angiogenesis (Cui et al. 2017; Wang and Khalil 2018; Egeblad and Werb 2002). MMPs or matrixins are zinc-dependent metallopeptidases that belong to the metzincin superfamily, other family members include adamalysins, astacins, serralysins, and pappalysins (Djuric and Zivkovic 2017).

A disintegrin and metalloproteinase (ADAMs) and a disintegrin and metalloproteinase with thrombospondin-like motif (ADAM-TSs) belong to the adamalysin family, which are often termed as MDC proteins (metalloproteinase-like, disintegrin-like, cysteine-rich proteins) (Edwards et al. 2008). ADAMs and ADAM-TSs are similar to the MMPs in their metalloprotease domains, except they

have a unique disintegrin domain. The molecular structure of ADAMs and ADAM-TSs is similar, both have a pro-domain, a metalloprotease domain, disintegrin domain, and a cysteine-rich domain. ADAMs have both membrane-associated and secreted forms (due to alternative splicing or cleavage), whereas ADAM-TSs have only secreted forms (as they lack the transmembrane domain and cytoplasmic tail) (Takeda et al. 2012). ADAMs display their proteolytic activity via their metalloproteinase domain that regulates the cleavage of membrane-anchored receptors, growth factors, and cytokines. ADAMs disintegrin domain regulates their adhesive activity, particularly of its binding to integrins (Edwards et al. 2008). The metalloprotease domain of ADAM-TSs processes procollagens I, II, and II and is important for depositing collagen on to the ECM in a tissue-specific manner (Bonnans et al. 2014). ADAM-TSs also cleave various proteoglycans such as aggrecan, versican, brevocan, and neurocan. ADAM-TSs, particularly ADAMTS13 cleaves von Willebrand factor (vWF) and regulates coagulation and thrombotic thrombocytopenic purpura (TPP) (Bonnans et al. 2014).

ADAMs group comprises around 38 members, found in various species (Edwards et al. 2008). The evolution and diversification studies have also found the homologs of ADAMs and ADAM-TSs in other organisms, including fruit fly (*Drosophila melanogaster*), nematodes (*Caenorhabditis elegans*) (Edwards et al. 2008; Souza et al. 2020; Nicholson et al. 2005). Until now 21 ADAMs (13 are proteolytically active) and 19 ADAM-TSs have been classified in the human genome (Zhong and Khalil 2019). In addition to humans, 37 and 34 ADAMs are present in rats and mice, respectively (Takeda et al. 2012; Zhong and Khalil 2019). Most of the ADAMs (1–7, 18, 20, 20–22, 24–30, 32, and 33) express in reproductive tissues, except ADAM-8-12, 15, 17, and 19, which are present in other human tissues. ADAM-TSs 1, 2, 4, 5, 9, and 16 have a wider human tissue distribution and extensive connection with various biological processes. ADAM-TSs 3, 8, 10, and 13 are present in heart, placenta, and brain. ADAM-TSs 7, 10, 13, and 14 are expressed in liver, whereas ADAM-TSs 16, 17, and 20 are mostly expressed in ovary (Porter et al. 2005).

To date, many studies have uncovered the crucial role of ADAMs and ADAM-TSs in tumor formation and embryonic development and pathologies of the eye, lung, heart, liver, kidneys, muscles, and joints. Besides it, ADAMs and ADAM-TSs are considered as potential biomarkers for various pathophysiological conditions such as cancer, inflammation, autoimmune diseases, and cardiovascular diseases (Seals and Courtneidge 2003). Presently, considerable interest is growing to understand the pivotal role of ADAMs and ADAM-TSs family members in human pathology and physiology. In the present manuscript, we are summarizing the biochemistry, regulation, and prospective role of ADAM and ADAM-TSs in various human pathological conditions (Fig. 1), such as Alzheimer's disease, proliferative retinopathies, rheumatoid arthritis, cardiovascular and colon cancer. Despite the implications of many ADAMs and ADAM-TSs across cancers, this review focuses only on the role of ADAMs and ADAM-TSs in colon cancer. Lastly, we will discuss how we can employ ADAMs and ADAM-TSs as potential biomarkers for the detection and management of various human pathologies.

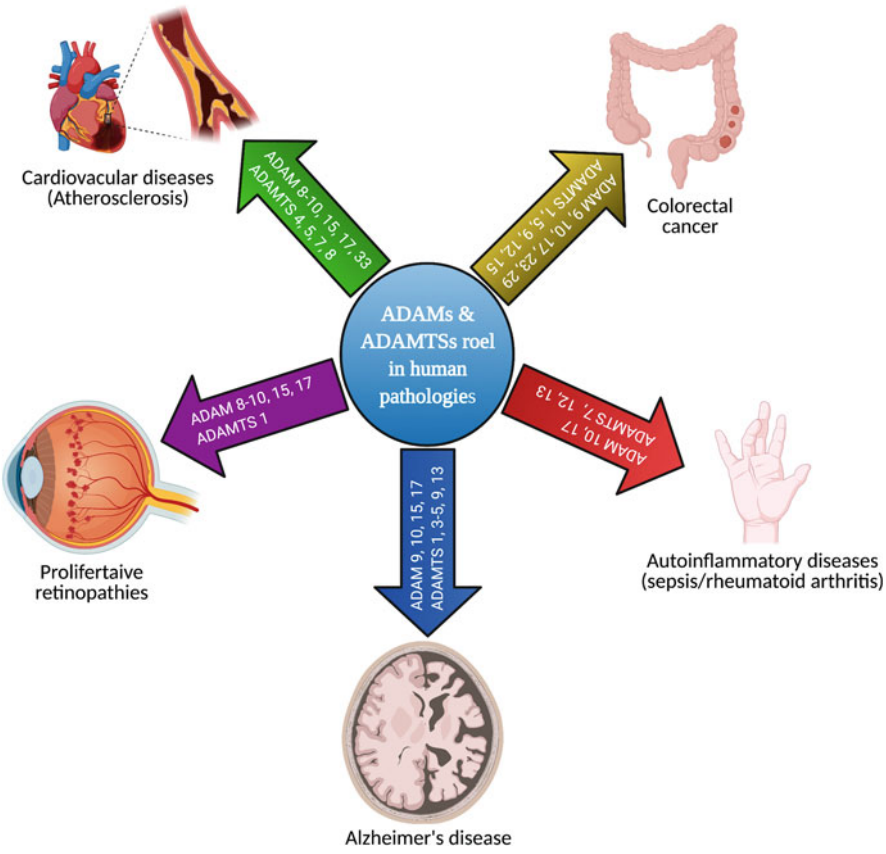

Fig. 1 Role of various ADAMs and ADAM-TSs in various human pathologies

2 Structure of ADAMs and ADAM-TSs Proteins

The adamalysins subfamily members ADAMs and ADAM-TSs have many similarities with snake venom metalloproteases (SVMPs) in protein sequences, spatial structures, and domain organization (Takeda 2016). The basic structure of all adamalysin family members (ADAMs, ADAM-TSs) is similar, as they have pro-domain, metalloproteinase, disintegrin, and cysteine-rich domains (Zhong and Khalil 2019). Despite many structural similarities ADAMs and ADAM-TSs individually possess a lot of structural and domain-specific variability exhibiting their function and tissue-specificity (Fig. 2). Furthermore, the ADAMs and ADAM-TSs are characterized based on their sequence differences within the domains (Table. 1).

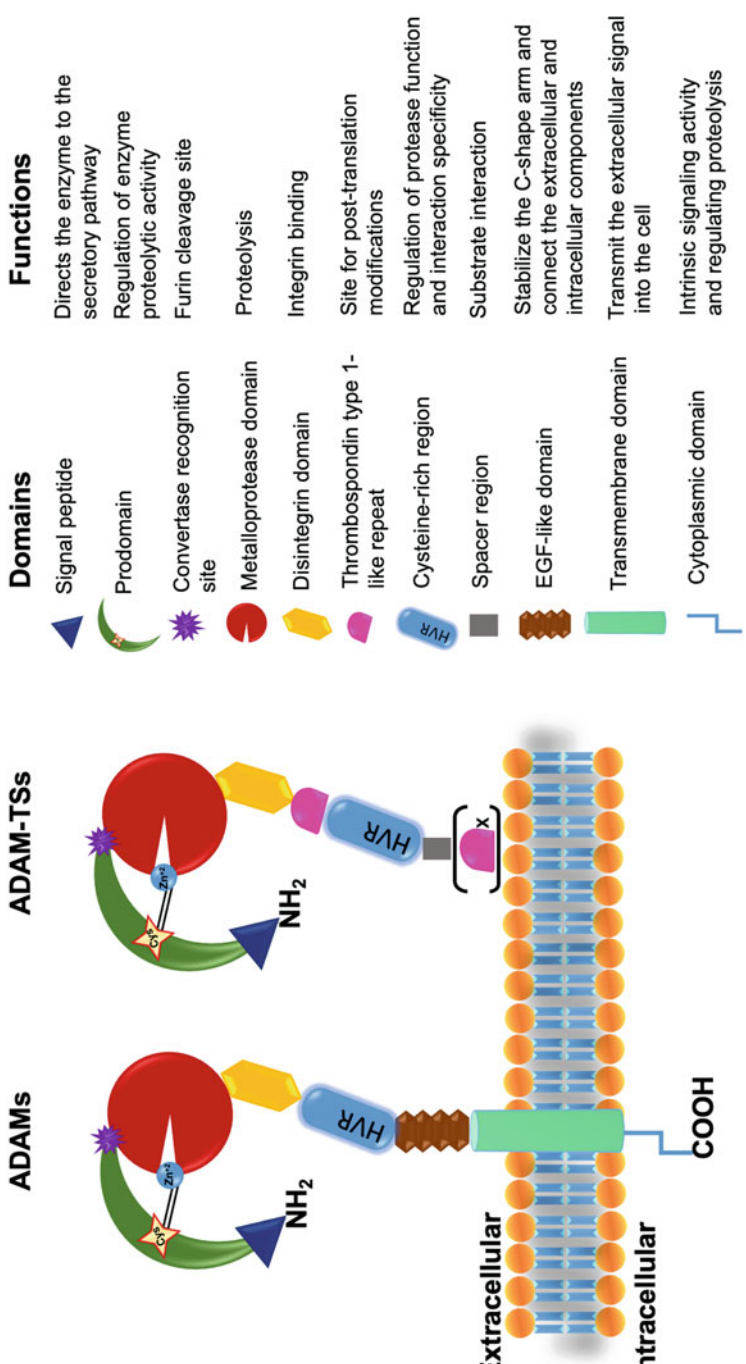

Fig. 2 Basic structure of the prototypical ADAM and ADAM-TS prior to proteolytic removal of the pro-domain at the N-terminus

Table 1 Types of ADAMs and ADAM-TSs based on sequence differences within the domains

Metalloproteases	Members	Type	Structural domains (sequence difference)
ADAMs	1, 8, 9, 12, 13, 16, 19, 20, 21, 24, 26, 28, 30, 33, 40	I	Catalytically active Zn^{2+} binding signature sequence (HExGHxxGxxHD) in M-domain and xCD sequence in D-domain
	2, 7, 11, 18, 22, 23, 27, 29, 32	II	Highly variable catalytical site in M-domain
	15	III	Catalytically active Zn^{2+} binding signature sequence, RGD sequence in D-domain instead of xCD sequence in most ADAMs members
	10, 17	IV	Catalytically active Zn^{2+} binding signature sequence, xCD sequence in D-domain, unlike type I, II, and III EGF-like region is absent
ADAM-TSs	1, 4, 5, 8, 15	I	Comprise of all basic domains
	9, 20	II	TSR modules connected to unique GON-1 domain
	2, 3, 14	III	TSR modules connected to procollagen *N*-Propeptidase
	13	IV	TSR modules connected to complement C1r/C1s, Uegf, Bmp1 (CUB) domain
	7, 12	V	TSR modules connected to mucin/proteoglycan domain and protease and lacunin (PLAC) structure
	6, 10, 16, 17, 18, 19	VI	TSR modules connected to only PLAC domain

2.1 The Pro-Domain

ADAMs and ADAM-TSs metalloproteases consist of an N-terminus peptide sequence which signals the metalloprotease to enter into a secretory pathway to execute its function. The pro-domain follows this signal sequence and is crucial for enzyme maturation. The pro-domain consists of a conserved cysteine residue that interacts with zinc ion (Zn^{2+}) present at the catalytic site, thereby blocking the active site for substrate-binding and cleavage. The pro-domain also remains non-covalently associated with some mature ADAMs and keeps them in an inactive state via the "cysteine-switch" mechanism. In addition to maintaining metalloprotease (ADAMs and ADAM-TSs) enzyme latency, the pro-domain also exhibits multiple subordinate functions such as ensuring stability and proper folding of ADAMs and ADAM-TSs and their entry into the secretory pathway (Edwards et al. 2008; Takeda et al. 2012; Zhang et al. 2016).

2.2 The Metalloprotease Domain

ADAMs and ADAM-TSs enzymes possess their proteolytic activity in the metalloprotease domain adjacent to the pro-domain. The metalloprotease domain retains the highest sequence homology between the metalloproteinases (Djuric and Zivkovic 2017). This domain includes the zinc and water atoms within the catalytic active site required for the hydrolytic processing of protein substrates. This catalytic domain consists of a Zn^{2+} binding motif (HExGHxxGxxHD; where "H" is for histidine, "E" is for glutamic acid, "x" is for variable amino acid, "G" is for glycine, and "D" is for aspartic acid), which comprises three histidine residues and a downstream conserved methionine, which forms a methionine loop or "Met-turn" (Edwards et al. 2008; Blobel 2005). This conservative motif is responsible for the proteolytic cleavage of several receptors, ligands, and ion channels present on the same cell or neighboring cells' membranes. Due to the catalytic activity of the metalloprotease domain, ADAMs and ADAM-TSs can act as sheddases and upstream regulators of various cell signaling pathways. ADAMs and ADAM-TSs not only regulate cell proliferation or apoptosis but also have a role in cell differentiation and tissue remodeling (Arribas et al. 2006).

2.3 The Disintegrin Domain

The disintegrin domain is a ~90 amino-acid long protein fragment of ADAMs and ADAM-TSs. The disintegrin protein is first isolated from snake venom and found to be present in the snake venom metalloproteases (SVMPs). In general, disintegrin protein binds with integrin receptors, thereby preventing its interaction with matrix protein (fibrinogen) and subsequently inhibiting platelet aggregation (Cominetti et al. 2009). The disintegrin domains of SVMPs and ADAMs/ADAM-TSs possess structural similarities (Macêdo et al. 2010). The disintegrin domain not only contributes to the protease activity but also helps in substrate recognition by ADAM and ADAM-TSs. The disintegrin domain in ADAM15 has a characteristic consensus Arg-Gly-Asp (RGD) sequence, which facilitates the binding of ADAMs to integrin receptors (αIIbβ3 and αvβ3) (Lu et al. 2006). Unlike ADAM15, most ADAMs lack the highly conserved RGD recognition sequence and instead have an ECD or xCD sequence (Blobel 1997). Although ADAM-TSs have disintegrin-like domains, there are no reports to show that they interact with integrin receptors (Jones and Riley 2005).

2.4 The Cysteine-Rich and EGF-Like Domain

ADAMs possess the cysteine-rich domain just next to the disintegrin domain, whereas ADAM-TSs comprise a series of thrombospondin type 1 repeat (TSP1) motifs between the disintegrin domain and cysteine-rich domain. In ADAM-TSs, the TSP1 motifs have high sequence homology to that of the region I of thrombospondin 1 and 2 (Lu et al. 2006). This TSP1 motif mediates the binding of ADAM-TSs to the extracellular matrix and contributes to apoptosis and angiogenesis (Kuno and Matsushima 1998; Guo et al. 1997). The function of the cysteine-rich domain present in ADAM and ADAM-TSs structure is not fully known. The ADAM12 cysteine-rich and disintegrin domain promotes the adhesion of myoblasts and fibroblasts (Zolkiewska 1999). Besides it, the cysteine-rich domain of ADAM12 interacts with cell surface syndecan to mediate the cell adhesion process (Iba et al. 2000). Furthermore, the interaction of ADAM13 with extracellular matrix protein fibronectin exhibits the adhesive property of both disintegrin and cysteine-rich domains (Gaultier et al. 2002). The cysteine-rich domain of ADAMs also contains a variable sized loop of 27–55 amino acids with hyper-variable region (HVR). Therefore, the structural information and the involvement of cysteine-rich and disintegrin domains in a cell to matrix or cell to cell interactions suggests them to represent as one functional entity: the "adhesive" domain. In addition, the X-ray crystal structural analysis of ADAM10 has shown that the cysteine-rich domain of ADAM10 blocks the enzyme active site after the pro-domain release, thereby suggesting an additional mode of enzyme regulation (Seegar et al. 2017).

The cysteine-rich domain is succeeded by an epidermal growth factor (EGF)-like region in ADAMs, whereas in ADAM-TSs, it is followed by a spacer region. The EGF-like region connects the extracellular region of ADAMs (that form a characteristic "C-shaped" arm structure) to the transmembrane domain (Takeda et al. 2006). The C-shape arm includes the M (metalloprotease), D (disintegrin), C (cysteine-rich) domain, and a highly variable region of cysteine-rich domain. The spacer region in ADAM-TSs family members is responsible for its interaction with the substrate (de Groot et al. 2009). Therefore, the C-shape architecture of ADAMs and ADAM-TSs structure is essential for their vital functions such as target identification, protein interaction, and proteolytic activity.

2.5 The Transmembrane Domain, Cytoplasmic Tail and Ancillary Domain

Most of the ADAMs are membrane-anchored proteins and thus possess a transmembrane domain located next to the EGF-like region. Due to the absence of the transmembrane domain, ADAM-TSs are mostly secretory proteins. ADAMs C-terminal region consists of an intracellular cytoplasmic tail, whereas ADAM-TSs have an extracellular spacer region followed by 0 to 14 TSP1 motifs. The

cytoplasmic tail is the most variable protein part among the ADAMs family members, both in size and in amino-acid sequence. Proline-rich (PXXP) motifs present within the cytoplasmic tail of ADAMs (ADAMs 7, 8, 9, 10, 12, 15, 17, 19, 22, 29, and 33) facilitate its binding to the proteins containing SH3 (Src homology region-3)-domain (Kang et al. 2000). Besides this, the cytoplasmic tail also contains several (tyrosine, serine, and threonine) residues that are possible sites for phosphorylation (Poghosyan et al. 2002). The transmembrane domain and the cytoplasmic tail of ADAMs interact with proteins that are involved in cell trafficking and intracellular signaling (Stone et al. 1999).

The ADAM-TSs members possess a unique ancillary domain that consists of Thrombospondin type 1 repeats (TSP1) that plays a vital role in enzymes' interaction with ECM components, substrate selection or recognition, and regulation of its enzyme activity. The ADAM-TSs C-terminus ancillary domain is connected to four different domains described (Table 1; Fig. 3) as GON-1 domain, Complement-Uegf-BMP-1 (CUB) domain, protease and lacunin (PLAC) domain, and Mucin-like domain (Porter et al. 2005; Kim and Nishiwaki 2015; Somerville et al. 2003; Bork and Beckmann 1993; Nardi et al. 1999; Somerville et al. 2004).

3 Activation, Inhibition, and Regulation of ADAMs

3.1 Activation

ADAMs family members are generated as inactive pro-enzymes in the endoplasmic reticulum (ER), where the N-terminal pro-domain inhibits the enzymatic cleavage activity via the "cysteine-switch" mechanism (Van Wart and Birkedal-Hansen 1990). Various stimulants such as G-protein coupled receptor (GPCR) ligands, protein kinase C (PKC) activators, Ca^{2+} ionophores, cytokines, and proteinases activate ADAMs. The intracellular enzymatic cleavage of pro-domain via pro-protein convertases (Fig. 4) during their transit through the trans-Golgi network results in the maturation of enzyme (Lum et al. 1998). However, some ADAMs such as ADAM8 and ADAM28 are processed auto-catalytically to their mature form (Schlomann et al. 2002; Howard et al. 2000). The activation process of MMPs is different from ADAMs, as the pro-domain separation and activation occur outside the cell surface (Takawale et al. 2015). The pro-protein convertases, a specialized serine endoproteinase, are primarily responsible for the activation of ADAMs. These pro-protein convertases (furin) predominantly cleave the di-basic consensus RXXR motif at the boundary of the catalytic domain and pro-domain (Wong et al. 2015). Consequently, the Zn^{2+} coordination gets switch toward the metalloprotease domain resulting in the activation of ADAMs which enable it to perform its physiological function and sheddase activity (Anders et al. 2001). Conversely, for some ADAMs like ADAM12, pro-domain remains non-covalently associated with the mature protease following cleavage, thereby influence the functional activity of ADAM12 (Wewer et al. 2006).

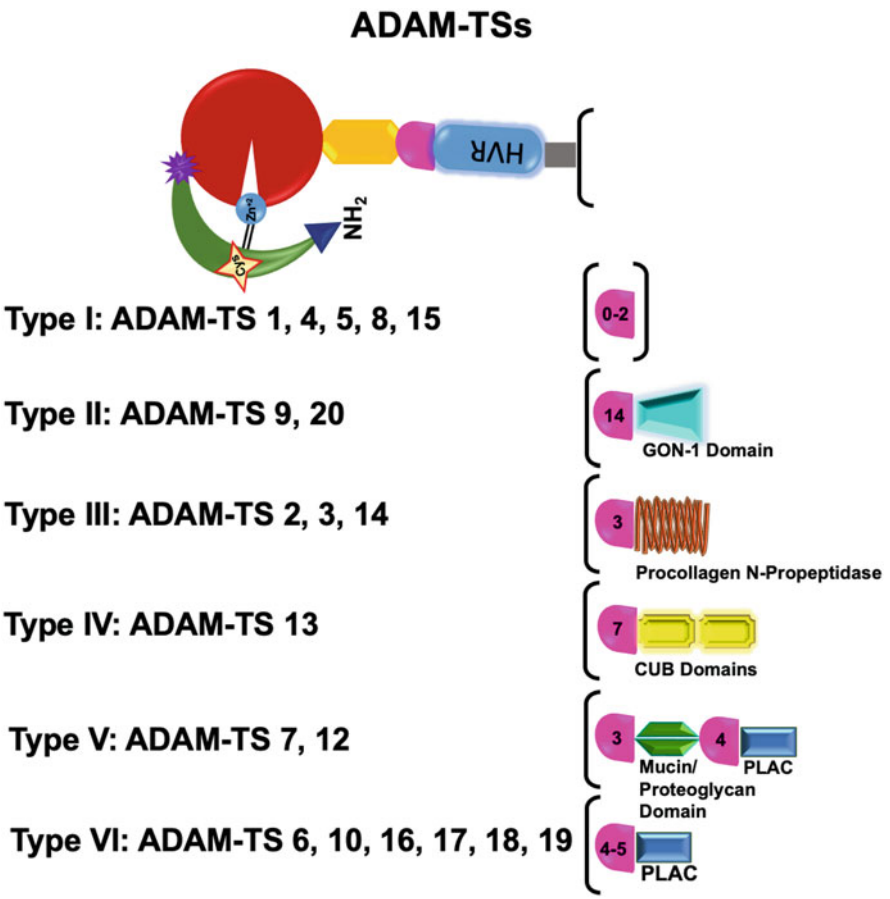

Fig. 3 Basic structure of the prototypical ADAM-TSs prior to proteolytic removal of the pro-domain at the N-terminus

Phosphorylation at the cytoplasmic domain of several membrane-associated proteins is an essential posttranslational modification that is of utmost importance for their activation. Therefore, tyrosine or serine/threonine phosphorylation of various putative residues within the intracellular cytoplasmic tail of ADAMs modulates its activation, adaptor interaction, or trafficking of proteins for substrate identification and interfacing. The cleavage of ADAM12 by furin-peptidase makes it a constitutively active protein that remains intracellular, and the phosphorylation of its cytoplasmic domain helps in its translocation to the cell membrane (Sundberg et al. 2004). Nevertheless, some reports have suggested that ADAM17 and ADAM19 activity depend on their transmembrane domain rather than their cytoplasmic domain (Reddy et al. 2000; Wakatsuki et al. 2004). Some studies have shown that phorbol 12-myristate 13-acetate (PMA) induces ADAM17 phosphorylation at Ser819, but neither its mutation nor deletion of the cytoplasmic domain affected

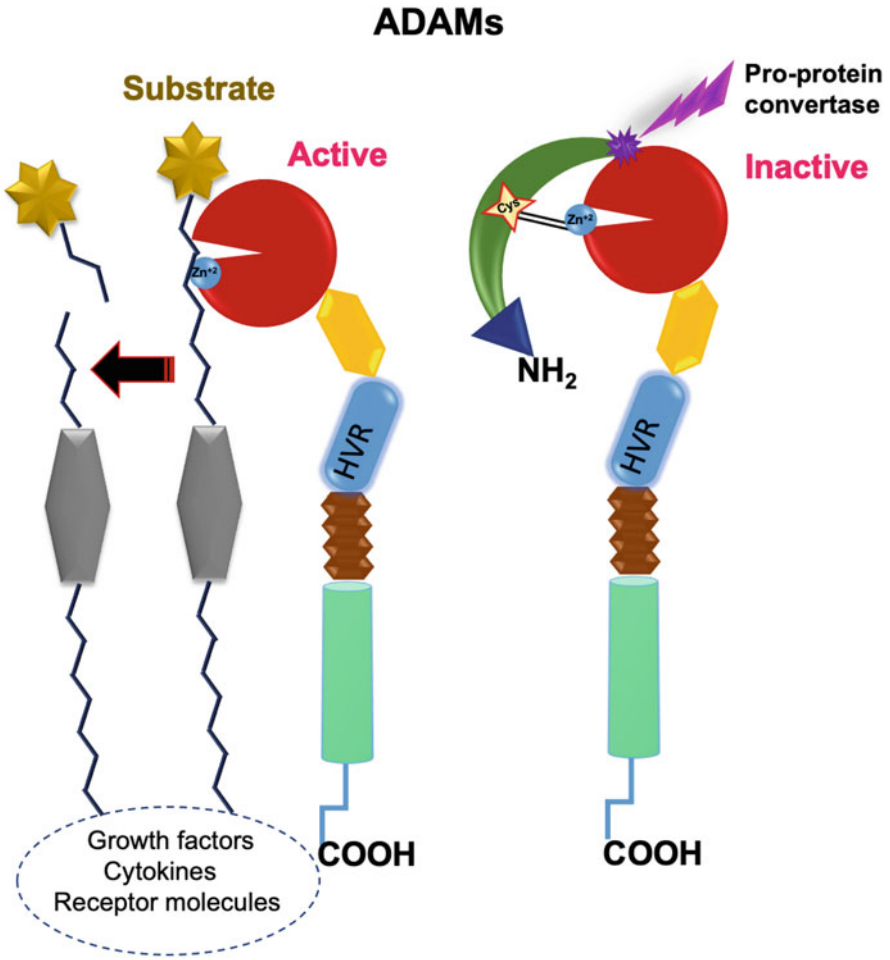

Fig. 4 Activation of ADAMs enzyme through cleavage of the N-terminal pro-domain by pro-protein convertases such as furin. Active ADAMs cleave various membranous substrates

ADAM17 catalytic activity (Fan et al. 2003; Doedens et al. 2003). On the contrary, a critical involvement of the ADAM17 cytoplasmic domain in GPCR-mediated epidermal growth factor receptor activation and signaling is observed in squamous cell carcinoma (Fischer et al. 2003). The gastrin-releasing peptide (GRP)-induced GPCR stimulation results in activation of cSrc-PI3K (phosphatidylinositol 3-kinase)-PDK1 (phosphatidyl inositol-dependent kinase-1) signaling, which leads to phosphorylation and translocation of ADAM17 (Zhang et al. 2006). Furthermore, studies have shown that ADAM17 phosphorylation at threonine 735 (Thr735) residue enhances cleavage of the tropomyosin receptor kinase A (TrkA) neurotrophin receptor in cardiomyocytes and tumor cells (Diaz-Rodriguez et al. 2002; Xu and Derynck 2010; Patel et al. 2014a). Additionally, ADAM17 phosphorylation at Thr735 is

considered necessary for its protein trafficking and maturation (Soond et al. 2005). Recently, a study has reported that src-mediated phosphorylation of ADAM17 at Tyrosine 702 residue is reported as a bona fide phosphorylation site in skeletal myoblasts and mechanically stressed cardiomyocytes, resulting in increased TNF-α-shedding (Niu et al. 2013; Niu et al. 2015).

3.2 Inhibition

ADAMs and ADAM-TSs family members are regulated by physiological and endogenous protein regulators known as TIMPs (tissue inhibitors of metalloproteinases). There are 4 TIMP family members in mammals and one in lower eukaryotes. The inhibitory amino-terminal domain of TIMPs binds non-covalently to the active site of MMPs and forms a tight 1:1 complex (Murphy 2011). TIMPs exhibit a wide range of similarities in their inhibitory function for MMPs, but for ADAMs they are more specific. TIMP1 and TIMP3 inhibit the catalytic activity of ADAM10 in vitro, whereas none of the TIMPs can inhibit ADAM8, 9, and 19 (Amour et al. 2000; Amour et al. 2002; Chesneau et al. 2003). TIMP3 can inhibit the activity of ADAM17, but it requires dimerization of ADAM17 so that it can interact with TIMP3 (Amour et al. 1998). Likewise, TIMP2 and *N*-TIMP3 exhibited potent inhibition for ADAM12-S (secreted splice variant) and transmembrane ADAM12-L (full-length) form (Jacobsen et al. 2008). ADAM33 shows an inhibitory profile distinct from other ADAMs, as its catalytic activity is inhibited weakly by TIMP2 and moderately by TIMP3 and TIMP4 but not by TIMP1 (Zou et al. 2004).

The mechanism of inhibition by TIMPs involves the (1) chelation of Zn^{2+} ion at the enzyme (ADAMs) active site by the α-amino and carbonyl groups present on the amino-terminal Cys1 of the TIMPs; (2) interaction of Ser/Thr (OH group) with the nucleophilic Glu of the metalloproteinase catalytic cleft, causing displacement of a water molecule, necessary for peptide hydrolysis (Murphy 2011). The mode of inhibition of TIMPs described for MMPs was found to vary among ADAMs family of metalloproteases. In contrast to MMPs, where interaction with the N-terminal domain of TIMPs is required for MMPs inhibition, the c-terminal domains of TIMP1 and TIMP3 interact and inhibit ADAM10 (Rapti et al. 2008; Schlondorff and Blobel 1999). The full-length TIMP3 and its N-terminal domain inhibit the isolated catalytic domain of ADAM17 (Lee et al. 2002, 2003; Wei et al. 2005). However, the addition of C-terminal domains and subsequently only cysteine-rich domains of ADAM17 significantly attenuated the inhibitory potency of the TIMP3 (Moss et al. 2007; Gonzales et al. 2004; Muraguchi et al. 2007). The phosphorylation of ADAM17 cytoplasmic domain by p38MAPK or ERK resulted in the reduction of its dimers, and thus inhibition by TIMP3 (Xu et al. 2012). Other than the TIMPs, some ADAMs (ADAM10 and ADAM17) demonstrate specific and selective inhibition via their isolated pro-domain, which is independent of the "cysteine-switch" mechanism (Moss et al. 2007; Gonzales et al. 2004). RECK (a reversion-inducing cysteine-

rich protein with Kazal motifs) is also an inhibitor of the ADAM10 activity during embryonic brain development (Muraguchi et al. 2007). Also, several pharmacological inhibitors have been developed to target the catalytic Zn^{2+} ion, but these are highly non-specific and unselective for both ADAMs and MMPs inhibition. Among them, some Zn^{2+} chelators such as hydroxamate and 1,10-phenanthroline are considered potent inhibitors of ADAMs proteolytic activity (Seals and Courtneidge 2003).

In addition, some small synthetic compounds have been reported that show specific inhibition to ADAMs activity. The hydroxamate-based inhibitors such as INCB3619 and INCB7839 inhibit ADAM10 and ADAM17 activity in cell-based experiments with better selectivity and bioavailability (Duffy et al. 2011; Fridman et al. 2007; Zhou et al. 2006). The knockout cell studies have found that INCB4298, a selective inhibitor of ADAM-17 blocks the shedding of heregulin, transforming growth factor-alpha (TGFα), heparin-binding epidermal growth factor (HB-EGF), and androgen receptor (AR). However, the ADAM10-selective inhibitor INCB8765 blocks EGF ligand processing (Hundhausen et al. 2003; Zocchi et al. 2016). TAPI-1, TAPI-2, and Batimastat (BB-94) and GW280264X have been reported as potential inhibitors of ADAM-17 (TACE) and mediate their inhibitory effect by blocking the shedding of cytokine receptors, but also affect the activity of MMPs and ADAM10 (Wetzel et al. 2017). Another small molecule inhibitor GI254023X is considered a selective inhibitor of ADAM10, but it additionally targets ADAM17, MMP2, and MMP9 (Zhou et al. 2006; Mathews et al. 2011). Zocchi et al. have recently reported that newly synthesized hydroxamate inhibitors, LT4 and MN8, have higher specificity for ADAM10 over ADAM17 and MMPs in a Hodgkin lymphoma (HL) cell line. The in vitro and cell-based assays used to study the inhibitory profile of ADAM8 demonstrated that BB-94, GW280264, FC387, and FC143 exhibit an inhibitory effect on ADAM8 activity, whereas GM6001, TAPI2 and BB2516 (Marimastat) and GI254023 showed significantly low and negligible inhibition (Schlomann et al. 2019). Furthermore, monoclonal antibodies (mAb 8C7) raised against the substrate-binding pocket within the ADAM10 C-domain demonstrated the specific blocking of Ephrin uptake and cleavage in a cell-based model (Atapattu et al. 2012). The monoclonal antibodies (mAb 8C7) based blocking was more efficient than the GM6001 (Atapattu et al. 2012).

In addition to synthetic compounds, some natural compounds such as Rapamycin and Triptolide have also been shown to inhibit ADAM10. Zhang et al. demonstrated that rapamycin treatment significantly decreases the activation of ADAM10, thereby increases the levels of the β-carboxyl-terminal fragment of β-amyloid precursor protein in vitro and in vivo (Zhang et al. 2010a). Furthermore, natural compound Triptolide (diterpenoid epoxide) obtained from Tripterygium wilfordii also significantly decreases the ADAM10 expression upon treatment in U937 and MCF-7 cells (Soundararajan et al. 2009).

3.3 Regulation

The posttranslational modifications such as phosphorylation and glycosylation regulate the function and structure of ADAMs family members. ADAM8 contains three *N*-glycosylation sites, which are necessary for its processing, cell surface localization, stability, and activity (Srinivasan et al. 2014). In breast cancer cells, the splice variants of ADAM9, such as transmembrane (ADAM9-L), and the secreted variant (ADAM9-S) were found to possess glycosylation sites (Fry and Toker 2010). Although one *N*-glycosylation sites in ADAM12 and 5*N*-glycosylation sites in ADAM15 have been reported, neither of the glycosylation sites in ADAM12 and ADAM15 exhibits any functional significance (Kodama et al. 2004; Krätzschmar et al. 1996). Conversely, substrate and inhibitor binding along with the catalytic activity of ADAM17 have been extremely influenced by glycosylation. Human ADAM17 exhibits a high level of glycosylation in the mammalian cell which potentially reduces its sheddase activity towards various TNFα-based substrates along with its significant inhibition by non-zinc binding inhibitor (Chavaroche et al. 2014). In addition, some ADAMs (ADAM8, 9, 10, 12, and 17) substrates also exhibit various degrees of glycosylation which influence their physiological functions (Minond et al. 2012).

Furthermore, the gene expression of ADAMs is regulated epigenetically, primarily in cancer cells. In general, the known developmental effects of epigenetic regulation (DNA methylation) involve long-term silencing of gene expression. Likewise, Z-DNA-mediated epigenetic silencing of ADAM12 has been observed in breast cancer cells (Ray et al. 2013; Nakao et al. 2014). Histone deacetylation has been found essential for the TGFβ1-induced expression of ADAM19 in ovarian cancer (Chan et al. 2008), whereas inhibition of histone deacetylation induces expression of ADAM19 in monocytic THP-1 cells (Ehrnsperger et al. 2005). Also, the methylation status of the promoter region of the ADAM33 gene has been shown to tightly regulate its expression in a cell type-specific manner (Yang et al. 2008).

The interaction of ADAMs with MMPs also regulates their function. Therefore, ADAMs act as substrates for MMPs or sheddases. For instance, it has been reported that ADAM12 influences the redistribution and activity of MT1-MMP (membrane-tethered MMP), thus forming a ternary protein complex with integrin αvβ3 at the cell surface (Albrechtsen et al. 2013). Furthermore, MT1-MMP has been stated as a critical negative modulator of ADAM9 proteolytic activity as it forms a complex with ADAM9 and FGFR2, thus protecting ADAM9-mediated FGFR2 ectodomain shedding. Also, loss of ADAM9 completely restores the defective FGFR2 signaling and largely rescued the impaired calvarial osteogenesis in MT1-MMP-deficient mice embryos (Chan et al. 2012). Likewise, MMP-7 processes proADAM28s (65 kDa) into active ADAM28s of 42- and 40-kDa forms, which selectively digest insulin-like growth factor binding protein-3 (Mochizuki et al. 2004).

It has been revealed that MMP7 controls the transcription of ADAM12 downstream of the angiotensin II-induced signaling pathway, resulting in the development of hypertension and cardiovascular hypertrophy (Wang et al. 2009a). Also,

ADAM17 has a role in cancer (prostate) cell invasion by shedding of TGF-α, which consequently results in activation of the EGFR-MEK-ERK pathway and increased levels of MMP-2 and MMP-9 (Xiao et al. 2012). In addition, the lentiviral RNAi-mediated silencing of the ADAM17 gene inhibits the TNF-α/NF-κB signaling along with the MMP9 expression in LPS treated A549 lung epithelial cells (Li et al. 2013a). During cardiovascular disease development, ADAM17 regulates MMP2, a mediator of angiotensin II-induced hypertension (Odenbach et al. 2011).

The tetraspanins and rhomboids, a superfamily of multi-transmembrane proteins, are associated with ADAM10 and ADAM17, respectively (Matthews et al. 2017). These proteins regulate their maturation, trafficking to the cell membrane, and activity (Matthews et al. 2017). Among all, only six tetraspanins (Tspan5, 10, 14, 15, 17, and 33) have been co-immunoprecipitated with ADAM10 in stringent lysis buffers (Dornier et al. 2012; Haining et al. 2012). The catalytic activity of ADAM10 is regulated by anti-tetraspanin mAbs that further stimulate the shedding of epidermal growth factor (EGF) and tumor necrosis factor-α (TNF-α) (Arduise et al. 2008). In vitro studies involving the knockdown of highly expressed tetraspanins in various primary cells and cell lines showed a reduction in ADAM10 enzyme activity and its trafficking to the plasma membrane (Dornier et al. 2012; Haining et al. 2012; Prox et al. 2012). Furthermore, six different tetraspanins reported till now exhibit different subcellular localizations. In addition, each tetraspanin regulates ADAM10 differently, such as some are involved in stimulation or suppression of ADAM10 sheddase activity and some in trafficking to intracellular compartments, and others to the plasma membrane (Dornier et al. 2012). iRhom1 and iRhom2, two non-protease rhomboids, have been reported as the regulators of ADAM17. iRhom2 is expressed majorly in hematopoietic cells, however, iRhom1 is more widely expressed except hematopoietic cells (Issuree et al. 2013; Christova et al. 2013). Studies using iRhom2 knockout mice have reported a reduced release of the proinflammatory cytokine, TNF-α upon LPS stimulation (Adrain et al. 2012; McIlwain et al. 2012). In addition, these mice failed to control Listeria monocytogenes infection (Adrain et al. 2012; McIlwain et al. 2012). These results indicate that iRhom2 directly regulates the catalytic activity of ADAM17, a major sheddase of TNF-α. Furthermore, iRhom1/2 double knockout mice have shown a considerable reduction in the mature ADAM17 levels and EGFR phosphorylation (Li et al. 2015). Lastly, the regulatory mechanisms of ADAMs, as briefly illustrated in Fig. 5, enhance our understanding of their role and mode of action in health and disease conditions.

4 ADAM-TSs Regulation

The ADAM-TSs are secreted as extracellular metalloproteases that do not contain EGF-like, cytoplasmic, and transmembrane domains. ADAM-TSs has a multi-domain structure that includes N-terminal signal peptide, a pro-domain, metalloprotease domain, disintegrin domain, a thrombospondin type 1 repeat, spacer region, and cysteine-rich domain. Their C-terminal region is composed of ancillary

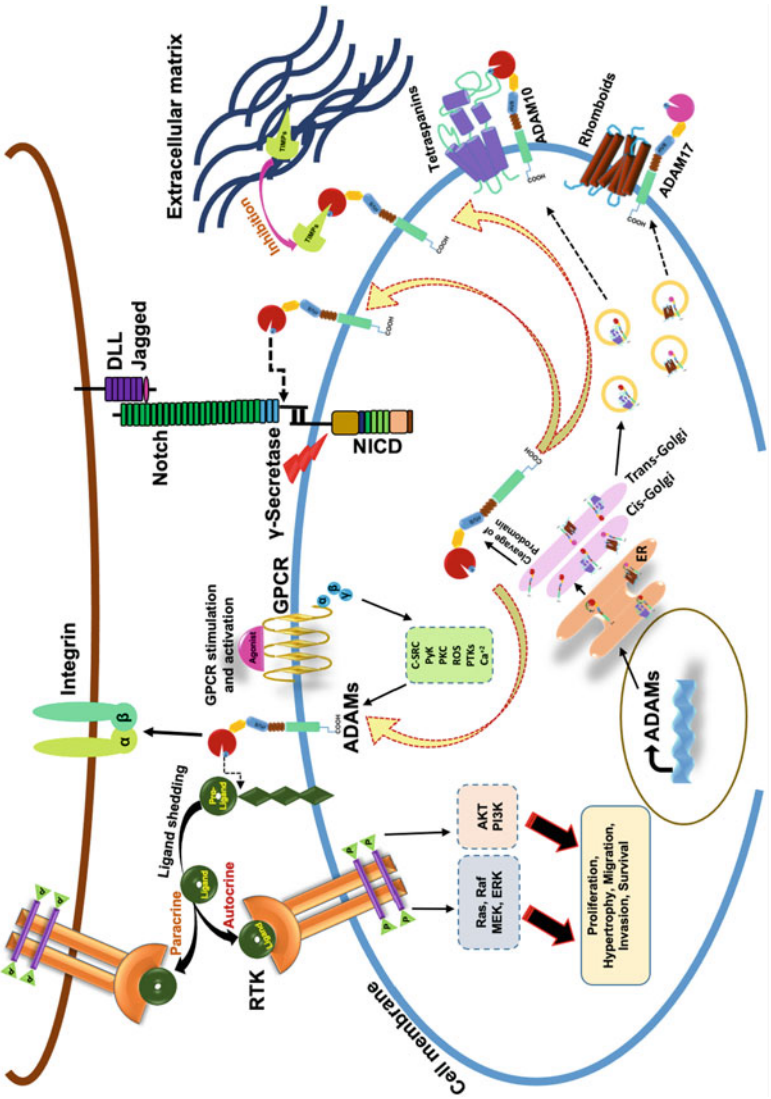

Fig. 5 Basic synthesis, regulation, and function of ADAMs. The pro-domain of ADAMs is cleaved by pro-protein convertase in the Golgi resulting in translocation of active ADAMs to the plasma membrane. The cytoplasmic domain of ADAMs is phosphorylated by different intracellular signaling mediators via stimulation of GPCRs with an agonist. Ligand generated by ADAMs proteolytic cleavage mediates autocrine and paracrine activation of RTK. ADAMs also shows non-proteolytic function via their interfacing with integrin dimers. ADAM10 and ADAM17 have been shown to be regulated by tetraspanins and rhomboids, respectively. ADAMs (e.g., ADAM10) are well-known for their involvement in the canonical Notch signaling via ectodomain shedding of Notch

Fig. 5 (continued) receptor after binding to one of its ligands located on a neighboring cell. The resulting membrane-anchored stub further undergoes cleavage by the γ-secretase complex. ADAMs also get inhibited by endogenous inhibitors (TIMPs)

domain following thrombospondin type 1 repeat domains that determine its substrate specificity, localization, and interaction of the protease. Unlike ADAMs, ADAM-TSs do not demonstrate any binding with integrins, despite having a disintegrin-like domain.

4.1 Activation

Like ADAMs, the ADAM-TSs metalloprotease zymogens get activated after cleavage of N-terminal pro-domain by pro-protein convertase (Fig. 6) at consensus sequence RX(K/R)R in trans-Golgi or at the cell surface (Colige et al. 2005; Somerville et al. 2004; Koo and Apte 2010). Unlike other ADAM-TSs, the ADAM-TS13 pro-domain is unusually short, poorly conserved, and lacks cysteine-switch motif, indicating that the pro-domain is not required for folding or secretion and enzyme latency (Majerus et al. 2003). Furthermore, the processing of proADAM-TS1 and proADAM-TS4 to their mature form occurs intracellularly in the trans-Golgi network, involving two separate proteolytic actions that affect their localization, ECM binding, and activity (Rodriguez-Manzaneque et al. 2000; Wang et al. 2004). The proADAM-TS5 is processed extracellularly, whereas proADAM-TS9 is processed at the cell surface by pro-protein convertase, thus distinct from those of other ADAM-TSs proteases (Longpre et al. 2009; Koo et al. 2007). Studies have shown that pro ADAM-TS2 not only gets activated via conventional N-terminal cleavage by pro-protein convertase but also through the autocatalytic

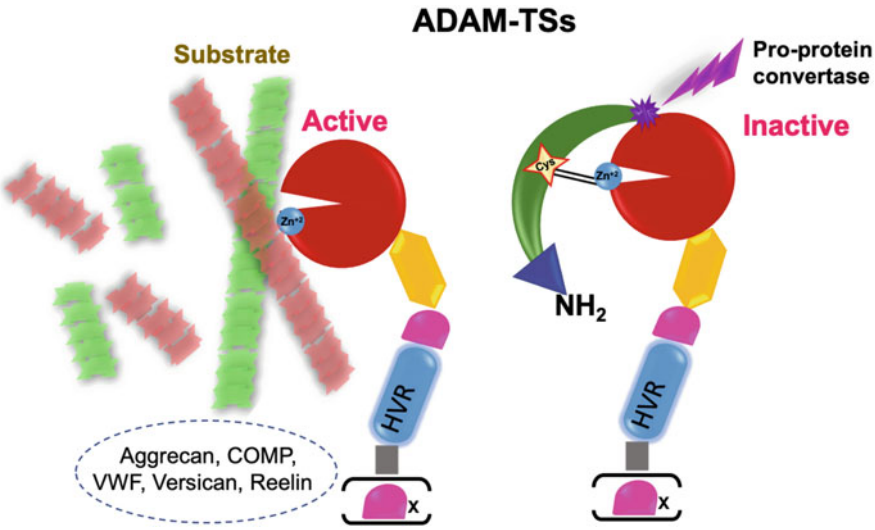

Fig. 6 Activation process ADAM-TSs enzyme through cleavage of the N-terminal pro-domain by pro-protein convertases such as furin. Active ADAM-TSs cleave various extracellular proteins as substrates

cleavage of its C-terminal end (Colige et al. 2005; Bekhouche and Colige 2015). The autocatalytic activation by C-terminal cleavage has also been reported for ADAM-TS1, 4, 8, 9, and 12, however, best characterized in ADAM-TS1 and -4 (Porter et al. 2005).

4.2 Inhibition

ADAM-TSs are inhibited by TIMPs, where ADAM-TS4 and ADAM-TS5 are potently inhibited by TIMP3, similar to ADAM17 (Lim et al. 2010). TIMP3 has also been shown to be an effective inhibitor of ADAM-TS2 and ADAM-TS4 (Wang et al. 2006; Hashimoto et al. 2001). TIMP2 and TIMP3 catalytically inhibit ADAM-TS1, but not TIMP1 or TIMP4 (Rodriguez-Manzaneque et al. 2002). In addition to TIMP3, α2-macroglobulin is also shown to inhibit ADAM-TS4 and ADAM-TS5 (Tortorella et al. 2004).

It was also reported that the use of chondroitin sulfate E and heparan sulfate increases the inhibitory affinity of TIMP-3 towards ADAM-TS5 (Troeberg et al. 2014). Paplilin, an extracellular matrix glycoprotein has also been shown to inhibit ADAM-TS proteinase (Kramerova et al. 2000). Furthermore, the anti-ADAM-TS5 monoclonal antibody, GSK2394002, was used as a therapeutic agent for osteoarthritis (OA) (Larkin et al. 2015; Apte 2016).

In addition, a series of cis-1(S)2(R)-amino-2-indanol-based compounds have been reported as selective inhibitors for the catalytic domain of aggrecanases, ADAM-TS4 and -5 over other metalloproteases (Tortorella et al. 2009). Calcium pentosan polysulfate (CaPPS), from beechwood, reported as a multifaceted exosite inhibitor of aggrecanases, interacts with the noncatalytic spacer domain of ADAM-TS4 and the cysteine-rich domain of ADAM-TS5. CaPPS also increased the cartilage level and affinity of TIMP-3 for ADAM-TS4 and -5 (Troeberg et al. 2008; Takizawa et al. 2008). In addition, a series of cis-1(S)2(R)-amino-2-indanol-based compounds have been reported to selectively bind to the catalytic domain and inhibit aggrecanases, ADAM-TS4 and ADAM-TS5 (Tortorella et al. 2009). Calcium pentosan polysulfate (CaPPS), from beechwood, is a multifaceted exosite inhibitor of aggrecanases that interacts with the noncatalytic spacer domain of ADAM-TS4 and the cysteine-rich domain of ADAM-TS5. CaPPS also increased the cartilage level and affinity of TIMP-3 for ADAM-TS4 and -5 (Troeberg et al. 2008; Takizawa et al. 2008). Also, granulin-epithelin precursor (GEP), a secreted growth factor, binds to ADAM-TS7 and ADAM-TS12 and inhibits the cleavage of cartilage oligomeric matrix protein. In addition, GEP inhibits the expression of these aggrecanases (Guo et al. 2010). Furthermore, hypermethylation of ADAM-TS1, 8, 9, 12, 18, and 19 leads to silencing of its activity in tumor cells (Lind et al. 2006; Moncada-Pazos et al. 2009; Lung et al. 2008; Jin et al. 2007).

4.3 Regulation

The posttranslational modifications of ADAM-TSs, such as glycosylation and proteolytic cleavage of ancillary domains, regulate their localization, secretion, activation, and catalytic functions (Kelwick et al. 2015). All ADAM-TSs except ADAM-TS4 exhibit N-terminal glycosylation, with *N*-glycosylation of ADAM-TS9 pro-domain is essential for its secretion (Apte 2009). Unlike other ADAM-TSs, ADAM-TS13 has thrombospondin type 1 repeats which contain a consensus sequence for O-fucosylation, which is functionally significant for ADAM-TS13 secretion and ensures proper protein folding (Ricketts et al. 2007). Also, proteolytic processing by membrane-type 4-matrix metalloproteinase within the C-terminal domains of ADAM-TS4 is essential for its activation (Gao et al. 2004).

5 ADAMs and ADAM-TSs Role in Cardiovascular Diseases

The ADAMs and ADAM-TSs play a crucial role in cardiovascular diseases (CVD) such as atherosclerosis, hypertension, coronary artery disease, myocardial infarction, and heart failure.

The ADAMs and ADAM-TSs play a crucial role in cardiovascular diseases (CVD) such as atherosclerosis (Table 2). Atherosclerosis is a chronic inflammatory disease in which narrowing of arteries occurs due to the abnormal deposition of lipids and inflammatory cytokines in blood vessels. During atherogenesis, ADAMs not only promote the recruitment and differentiation of inflammatory cells, but also act as sheddases for various crucial mediators such as growth factors, cytokines, chemokines, and adhesion molecules. For instance, junctional adhesion molecule-A (JAM-A) and vascular endothelial (VE)-cadherin, which regulates leukocyte transendothelial migration and vascular permeability, are a substrate for ADAM10 or ADAM17 (Ponnuchamy and Khalil 2008; Koenen et al. 2009; Schulz et al. 2008). Furthermore, CX3CL1 (fractalkine) and CXCL16, described as substrates for ADAM10 and ADAM17, mediate adhesion and migration of leukocytes through the vascular wall (Hundhausen et al. 2007; Ludwig and Weber 2007). ADAM17 is responsible for ectodomain shedding of adhesion molecules like vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 (Tsakadze et al. 2006; Garton et al. 2003). These adhesion molecules play critical roles during different stages of atherosclerosis development. Recently, a distinct association between ADAM17 substrates and recurring atherosclerosis in human subjects has been reported, emphasizing the positive role of ADAM17 activity in predicting cardiovascular events (Rizza et al. 2015). Also, in atherosclerotic cerebral infarction (ACI) patients, the rs653765 polymorphism is positively correlated with ADAM10 promoter activity and expression (Li et al. 2013b). Furthermore, ADAM10 role in vascular diseases has been elucidated, where a significant increase in ADAM10 expression was observed during plaque development from early to advanced, and to

Table 2 Functions of ADAMs and ADAM-TSs involved in cardiovascular disease (CVD)

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/tissues	Reference
ADAM8	L-selectin, PSGL-1, TNF-α, TNFR-1, VCAM-1	↑ Expression in atherosclerotic development and myocardial infarction (MI), neutrophils, and macrophages Diagnostic/prognostic biomarker	(Sun et al. 2012; Holloway et al. 2010; Levula et al. 2009; Raitoharju et al. 2011; Kessler et al. 2015)
ADAM9	TNF-α, EGF, HB-EGF	Interaction with integrin Monocyte homing, migration, or proliferation in aorta, carotid, and femoral arteries	(van der Vorst et al. 2017)
ADAM10	VE-cadherin, JAM-A, Fractalkine, CXCL16	↑ Vascular permeability ↑ Leukocyte adhesion and trans-endothelial migration, plaque fibrosis, contribute to atrial dilation	(Gao et al. 2004; Ponnuchamy and Khalil 2008; Koenen et al. 2009; Schulz et al. 2008; Rizza et al. 2015; Li et al. 2013b; Donners et al. 2010; Eerenberg et al. 2016)
ADAM12	HB-EGF	↑ Levels in arteriovenous fistula (AVF) patients	(Arndt et al. 2002)
ADAM15	EGF, TGF-α, HB-EGF, BTC and EPR	Interaction with integrin Monocyte homing, migration, or proliferation in aorta, carotid, and femoral arteries contribute to atrial dilation	(van der Vorst et al. 2017; Oksala et al. 2009; Bültmann et al. 2011; Sun et al. 2010; Eerenberg et al. 2016)
ADAM17	ICAM-1, VCAM-1, TNF-α, TNF receptors I and II, TGF-α, L-selectin, IL-6 receptor, M-CSF receptor 1,	↑ Inflammation, leukocyte recruitment Monocyte homing, migration, or proliferation in aorta, carotid, and femoral arteries Atheroprotective in myeloid and Atheroprogressive in epithelial cells ↑ Hypertension, role in post-MI repair	(Gao et al. 2004; Schulz et al. 2008; Hundhausen et al. 2007; Ludwig and Weber 2007; Tsakadze et al. 2006; Garton et al. 2003; van der Vorst et al. 2015; Holdt et al. 2008; Nicolaou et al. 2017; Zheng et al. 2016; Fan et al. 2015; Canault et al. 2006; Zhao et al. 2015; Wang et al. 2009b; Zhu et al. 2018; Vuohelainen et al. 2011)
ADAM33	KL-1, tumor necrosis factor-related activation-induced cytokine	↑ Expression by VSMC in the arterial wall (including the intima, media, and adventitia), inflammatory	(Sun et al. 2012; Holloway et al. 2010)

(continued)

Table 2 (continued)

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/tissues	Reference
		cells and in atherosclerotic lesions	
ADAM-TS1	Versican	Promotes aortic VSMC migration, ↑ serum levels in acute myocardial infarction (AMI)	(Theodorou et al. 2017; Jönsson-Rylander et al. 2005; Wågsäter et al. 2008; Norata et al. 2004; Fan et al. 2015)
ADAM-TS2	Fibrillar procollagens	↑ Levels in AMI and failing human hearts and hypertrophic murine hearts	(Hirohata et al. 2017; Mishra et al. 2010)
ADAM-TS4	Versican, aggrecan, α2-macroglobulin	↑ Expression in macrophages Expression upregulated during the development of atherosclerosis in $LDLR^{-/-}ApoB^{100/100}$ mice ↑ Plasma levels in coronary artery disease (CAD).	(Theodorou et al. 2017; Jönsson-Rylander et al. 2005; Rizza et al. 2015)
ADAM-TS5	Biglycan, versican	Proteoglycan turnover and lipoprotein retention	(Didangelos et al. 2012)
ADAM-TS7	COMP	VSMC migration and intimal thickening after vascular injury ↑ Plasma levels in CAD and AMI. Inhibits re-endothelialization	(Bongrazio et al. 2000; Chen et al. 2011; Yu et al. 2016; Mead and Apte 2018; Reilly et al. 2011; Lee et al. 2012)
ADAM-TS8	Aggrecan	Expressed in macrophage enrich areas of human atherosclerotic carotid plaques and coronary unstable plaques	(Theodorou et al. 2017; Jönsson-Rylander et al. 2005)
ADAM-TS13	Von Willebrand factor (VWF)	Low activity in intramyocardial hemorrhage	(Wu et al. 2015)
ADAM-TS18	Aggrecan	ADAM-TS18 deficiency causes increase	(Shen et al. 2017)

ruptured atherosclerotic plaques (Donners et al. 2010). Due to the embryonic lethality of ADAM10 full knockout mice, the effect of ADAM10 deletion on atherosclerosis has been evaluated using myeloid-specific ADAM10-knockout mice. The myeloid-specific deletion of the Adam10 gene increases plaque fibrosis and reduces macrophage accumulation but has a negligible effect on plaque size (van der Vorst et al. 2015). The metalloprotease ADAM17 has been attributed as a unique genetic factor of atherosclerosis vulnerability. Quantitative trait locus mapping in

mice demonstrated that elevated levels of ADAM17 are associated with decreased lesion formation (Holdt et al. 2008). Additionally, an atheroprotective role of ADAM17 has been observed in ADAM17-deficient mice, in which the endogenous TNFR2 signaling in vascular cells has been overactivated due to reduced shedding of membrane-anchored TNFα and TNFR2 (Nicolaou et al. 2017). However, in rats elevated level of ADAM17 along with increased expression of TNF-α has been found associated with cardiac remodeling after acute myocardial infarction (Zheng et al. 2016). Cardiomyocyte-specific ADAM17 knockdown in mice subjects demonstrated that ADAM17 plays an important role in post-myocardial infarction (MI) repair by suppressing activation of VEGFR2 and impairing angiogenesis, thus limiting left ventricular dilation and dysfunction (Fan et al. 2015). In mice, ADAM17 expression is found to be linked with lesions in atherosclerosis-prone sites (aortic sinus and arch), thereby contributing to the increased levels of soluble TNF receptors (TNFR1 and TNFR2) in the plasma, parallel to atherosclerosis progression (Canault et al. 2006). Also, lentiviral-mediated ADAM17 gene silencing in abdominal aortic plaques of rabbits enhances plaque stability via down-regulating ERK-NF-κB signaling and upregulating TGF-β1 signaling (Zhao et al. 2015). Recently, cell-type-specific and curative effects of ADAM17 deficiency on atherosclerosis have been demonstrated in myeloid and epithelial cells. The authors used $ApoE^{-/-}LysMCreADAM17^{fl/fl}$, and $ApoE^{-/-}BmxCreADAM17^{fl/fl}$ mice to demonstrate that ADAM17 expression in myeloid cells is atheroprotective and atheroprogressive in endothelial cells (van der Vorst et al. 2017). The above results suggest the cell-specific role of ADAM17 in cardiovascular diseases.

In addition to ADAM17, high levels of ADAM9 and ADAM15 have been reported in macrophages present in advanced atherosclerotic plaques (Oksala et al. 2009). In addition, overexpression of ADAM15 in western diet-fed rabbits attenuates the progression of atherosclerosis (Bültmann et al. 2011). In contrast, some reports have shown that enhanced expression of ADAM15 in endothelial cells induces endothelial permeability, promoting monocyte and neutrophil transmigration (Sun et al. 2010, 2012). These observations indicate the physiological significance of ADAM15 in atherosclerosis progression, even though the underlying mechanisms are yet unclear. Moreover, ADAM33 expression has been found in the inflammatory cells of human atherosclerotic lesions, and single nucleotide polymorphisms (SNP) of both ADAM8 and ADAM33 genes are shown to be associated with pathogenesis and development of atherosclerosis (Holloway et al. 2010; Levula et al. 2009). Likewise, ADAM8 polymorphism (rs2275725) is associated with elevated ADAM8 serum levels and myocardial infarctions (MI) risk (Raitoharju et al. 2011). Recently, a study reported that although a significant increase in ADAM8 expression was observed in the active human plaques lesion area, no significant change in atherosclerotic lesion area was observed in hematopoietic or whole-body ADAM8 deficient mice (Theodorou et al. 2017).

The presence of ADAM-TSs is reported in intimal thickenings and advanced atherosclerotic lesions. ADAM-TSs contribute to lipid retention and affect the adhesion and recruitment of macrophages. ADAM-TS1 exhibits its potential role in atherogenesis by cleaving extracellular matrix (ECM) proteins and inducing

vascular smooth muscle cells (VSMC) migration and neointima formation (Jönsson-Rylander et al. 2005). The expression of the ADAM-TS proteases, particularly ADAM-TS1 and ADAM-TS4 have shown their importance in atherosclerosis by inducing the cleavage of versican, a vital constituent of the vascular ECM. Furthermore, ADAM-TS4, 5, and 8 expressions were also observed in human carotid artery lesions and advanced coronary plaques. The ADAM-TS4, 5, and 8 are highly expressed in macrophage populated areas of atherosclerotic plaques, while ADAM-TS1 expresses predominantly in endothelial and smooth muscle cells (Wågsäter et al. 2008; Norata et al. 2004). ADAM-TS1 mediates tumor necrosis factor-α (TNF-α) and lipopolysaccharide (LPS) induced inflammation in endothelial cells (Bongrazio et al. 2000). Also, shear stress-dependent induction of ADAM-TS1 expression suggests a potential role for ADAM-TS1 vessel structure maintenance under normal flow conditions (Bongrazio et al. 2000). An atheroprotective role of ADAM-TS5 has been observed in ADAM-TS5-deficient mice, where its deficiency leads to the accumulation of proteoglycans (biglycan and versican) and its binding to lipoproteins in atherosclerosis (Didangelos et al. 2012). ADAM-TS7 is involved in VSMC migration and neointima development in response to vascular injury during atherogenesis (Wang et al. 2009b).

Hypertension is considered a primary risk factor for CVD. ADAMs and ADAM-TSs have shown their association with hypertension. In vitro and in vivo studies showed that ADAM17-knockdown suppressed the angiotensin II-induced hypertension and end-organ damage (Shen et al. 2017). On the contrary, ADAM-TS18 deficient mice showed augmented metabolic disorders and a higher risk of cardiovascular disease and hypertension (Zhu et al. 2018).

ADAMs and ADAM-TSs also play a significant role in coronary artery disease, myocardial infarction, and heart failure. Increased circulating levels of ADAM17 substrates have been detected in patients with established atherosclerosis (Rizza et al. 2015). High plasma levels of ADAM-TS4 were observed in patients with coronary artery disease (Zha et al. 2010), and statin therapy reduces it (Zha et al. 2010; Chen et al. 2011). Elevated plasma ADAM-TS7 levels were observed in patients with coronary artery disease, which subsequently promotes atherosclerosis (Yu et al. 2016; Mead and Apte 2018). Furthermore, $Ser^{214}Pro$ substitution in the ADAMTS-7 pro-peptide reduced ADAM-TS7 proteolytic activity and was associated with coronary artery disease (Reilly et al. 2011). Studies using ADAM-TS7 knockout mice showed the potential role of ADAM-TS7 in post-injury vascular intimal hyperplasia (Kessler et al. 2015).

Rat cardiac transplantation model showed an elevated expression of ADAM8 in myocardial infarction (MI) over controls (Vuohelainen et al. 2011). In cardiomyocyte-specific ADAM17 deficient mice, lower survival, higher cardiac rupture rates, increased left ventricular dilation, and decreased ejection fraction have been observed over control mice, demonstrating the protective role of ADAM17 in post-MI repair (Fan et al. 2015). ADAM-TS1 is expressed optimally in normal tissues, but its serum levels were found elevated in patients with acute myocardial infarction (Hirohata et al. 2017). Tissue samples from patients with acute myocardial infarction (AMI) showed augmented expression of ADAM-TS2, −3,

and -13 in culprit plaques and most likely in endothelial cells and macrophages (Lee et al. 2012). Furthermore, elevated plasma levels of ADAM-TS7 show an association of ADAM-TS7 with ventricular remodeling after AMI (Wu et al. 2015). Studies performed using patients with intramyocardial hemorrhage (IMH) showed significantly lower activity of ADAM-TS13. However, no significant change in infarct size or IMH has been observed after the intracoronary administration of recombinant ADAM-TS13, indicating a negative correlation between ADAM-TS13 and infarct size (Eerenberg et al. 2016).

An increased expression of ADAM10 and ADAM15 at both the transcript and protein levels has been observed in patients with atrial fibrillation (AF), demonstrating their role in structural remodeling of the fibrillating atria (Arndt et al. 2002). ADAM12 levels increased significantly in arteriovenous fistula (AVF) mice model under oxidative stress conditions. Furthermore, ADAM12 levels were significantly decreased after treatment of AVF mice with hydrogen sulfide donor molecule (NaHS) (Mishra et al. 2010). In addition, an increased expression of ADAM-TS2 was observed in failing human hearts and hypertrophic murine hearts. The deletion of ADAMTS2 in mice significantly enhanced pressure overload-induced cardiac hypertrophy, and ADAMTS2 overexpression in cardiac tissues attenuated this phenotype, suggesting a protective function of ADAM-TS2 in the development of cardiac hypertrophy under pathological conditions (Wang et al. 2017).

6 ADAMs and ADAM-TSs Role in Colorectal Cancer

Several reports have suggested a role for ADAMs and ADAM-TS families in the etiopathogenesis of colorectal cancer (Table 3). The hepatic stellate cells (HSCs) secrete a spliced variant of ADAM9 (ADAM9-S), which promotes colon carcinoma cell invasion. Furthermore, the colon carcinoma cell invasion depends on both the protease activity of ADAM9 and its binding to the α6β4 and α2β1 integrins on the plasma membrane of colon carcinoma cells (Mazzocca et al. 2005). The ADAM9 overexpression enhances growth factor-mediated VE-cadherin internalization and cell–cell contact disruption in HT29 human colon cancer cells (Hirao et al. 2006). The tissue microarray analysis of colorectal cancer (CRC) showed a significant correlation of Adam10 gene expression with late stage of cancer (Knosel et al. 2005). Also, proteomic characterization of the tetraspanin web identified ADAM10 as one of the components of the tetraspanin network (Le Naour et al. 2006). Furthermore, expression of ADAM10 along with L1-CAM (neuronal cell adhesion receptor) in human CRC cells confers to the metastatic capacity in CRC cells to the liver, thus significantly contributing to the development of the invasive stage of colon cancer (Gavert et al. 2007). The overexpression of ADAM 10 and C-erbB-2 in gastric cancer lesions plays a key role in gastric cancer invasion and metastasis (Wang et al. 2011a). The increased expression of ADAM17 in liver metastases than primary colorectal tumor cells has revealed the potential role of ADAM17 in the metastatic process (Lin et al. 2007). Also, ADAM17 has shown a

Table 3 Functions of ADAMs and ADAM-TSs involved in colorectal cancer

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/tissues	Reference
ADAM9	Laminin, gelatin, E-cadherin	Promotes carcinoma invasion and colonizes the liver	(Wang et al. 2017; Mazzocca et al. 2005)
ADAM10	L1-CAM	*Adam10* gene correlates with a late stage of cancer Component of tetraspanin web Enhanced metastasis in colon cancer cells Tumor progression and prognostic biomarker	(Hirao et al. 2006; Knosel et al. 2005; Le Naour et al. 2006; Gavert et al. 2007)
ADAM17	TGF-α, amphiregulin, heregulin	Promotes metastatic invasion, colonization, tumor progression and drug resistance in CRC tumors	(Wang et al. 2011a; Lin et al. 2007; Kyula et al. 2010)
ADAM23	No protease activity available	Gene down-regulated in CRC cells	(Schmidt et al. 2018; Choi et al. 2009)
ADAM29	No protease activity available	Gene undergoes mutation	(Wang et al. 2011b)
ADAM-TS1	No protease activity available	Gene epigenetically deregulated, early tumorigenesis biomarker	(Sjoblom et al. 2006; Lind et al. 2006)
ADAM-TS5	No protease activity available	Gene epigenetically deregulated, mRNA expression down-regulated	(Ahlquist et al. 2008)
ADAM-TS9	No protease activity available	Tumor-suppressor protease	(Kim et al. 2011)
ADAM-TS12	No protease activity available	Tumor-suppressor protease, prognostic biomarker	(Zhang et al. 2010b; Moncada-Pazos et al. 2009)
ADAM-TS15	No protease activity available	Tumor-suppressor protease	(Wang et al. 2011c)

significant role in drug resistance mechanisms during colorectal cancer chemotherapy (5-fluorouracil) treatment. The in vitro and in vivo studies have shown an increase in ADAM17 activity after chemotherapy treatments, therefore, blocking ADAM17 activity using siRNA in conjunction with chemotherapy may have therapeutic potential for the treatment of CRC (Kyula et al. 2010). Furthermore, the study using $APC^{Min/+}$ and $ADAM17^{ex/ex}$ mouse models demonstrated that shedding of IL-6 via ADAM17 is a prerequisite for IL-6 trans-signaling that induces β-catenin–dependent tumorigenesis in CRC. Therefore, knockdown of ADAM17 activity resulted in abrogation of tumor formation (Schmidt et al. 2018). In colorectal

cancer cell lines, an aberrant silencing of Adam23 gene has been reported due to epigenetic modification, resulting in abnormal cell–cell interactions, and increased cell migration and metastasis (Choi et al. 2009). However, in another study downregulation of DNA-methyltransferase-1 (DNMT1) by restoring the expression of miR-342 resulted in ADAM23 reactivation (Wang et al. 2011b). The elucidation of the genome sequence of human CRC tissues revealed that Adam29 gene undergoes mutations that probably affect the cellular functions, including transcription, adhesion, and invasion (Sjoblom et al. 2006).

The microarray screening has identified ADAM-TS1 as one of the genes deregulated epigenetically in colorectal tumorigenesis (Lind et al. 2006). Therefore, methylated ADAM-TS1 is considered a suitable marker for the early detection of colorectal cancer (Ahlquist et al. 2008). The methylation profiling-based studies on bead-chip arrays have exhibited hypermethylation of ADAM-TS5 gene promoter in CRC (Kim et al. 2011). A large group study of CRCs conducted using a high-resolution melting method showed a significant correlation between ADAM-TS9 promoter methylation and its decreased expression (Zhang et al. 2010b). ADAM-TS12, a novel anti-tumor protease with an anti-proliferative effect on tumor cells, is epigenetically silenced in colon cancer cell lines and tumor tissues (Moncada-Pazos et al. 2009). Furthermore, ADAM-TS12 plays a vital role in inhibiting tumor progression and has been considered a potential prognostic biomarker for colorectal cancer (Wang et al. 2011c). The presence of genetically inactive ADAM-TS15 in various in vitro and in vivo colon cancer studies revealed that ADAM-TS15 markedly promotes tumor growth and invasion. Further, microarrays analysis showed a negative correlation between ADAM-TS15 expression and histopathologic differentiation grade of colon carcinomas (Viloria et al. 2009).

7 ADAMs and ADAM-TSs Role in Autoinflammatory Diseases (Sepsis/Rheumatoid Arthritis)

The ADAMs and ADAM-TSs also influence various autoinflammatory diseases like sepsis and rheumatoid arthritis (Table 4), caused by an abnormal innate immune system. The role of ADAM17 in sepsis is shown in mice, where conditional deletion of ADAM17 in myeloid cells protects the mice from endotoxin shock and has considerably low serum TNF levels compared to control animals (Horiuchi et al. 2007). However, in the acute pulmonary inflammation model of mice, ADAM10 has been reported essential for chemokine-induced migration of monocytic cells and neutrophils, thereby stimulating accumulation of leukocytes in alveoli and the development of pulmonary edema (Pruessmeyer et al. 2014). The ADAM10 variant with rs653765 polymorphism in the promoter region is associated with the progression of severe sepsis in humans (Cui et al. 2015). This polymorphism functionally activates ADAM10 gene expression and concomitantly elevates relevant substrates (Cui et al. 2015). Also, the above ADAM10 functional variant confers the

Table 4 Functions of ADAMs and ADAM-TSs involved in autoinflammatory diseases (sepsis/rheumatoid arthritis)

ADAMs/ADAM-TSs	Substrates	Pathological effect in cells/tissues	Reference
ADAM10	TNF-α, Fractalkine (CCL2, CXCL1, CX3CL1 and CXCL16), sIL6R, JAM-A, JAM-C	Promotes leukocyte recruitment and edema formation in a mice model of acute pulmonary inflammation ADAM10 genetic polymorphism associated with progression of sepsis ↑ Expression in RA	(Horiuchi et al. 2007; Pruessmeyer et al. 2014; Cui et al. 2015; Moss et al. 2008)
ADAM17	TNF-α, TGF-α	Sheddase activity promotes rheumatoid arthritis and endotoxin shock ↑ Expression in RA	(Viloria et al. 2009; Chen et al. 2019; Dreymueller et al. 2012; Lin et al. 2016; Patel et al. 1998; Charbonneau et al. 2007)
ADAM-TS7	COMP	↑ Expression in cartilage and synovium of patients with RA	(Isozaki et al. 2013)
ADAM-TS12	COMP	↑ Expression in cartilage and synovium of patients with RA Genetic polymorphisms are associated with RA	(Isozaki et al. 2013; Liu 2009)
ADAM-TS13	vWF	Significantly lower levels in patients with sepsis and pediatric sepsis syndrome Prognostic biomarker	(Liu et al. 2020; Levi et al. 2018)

progression of sepsis in a large group of patients, modulates the EGR1/ADAM10 pathway, and influences the severity of sepsis (Chen et al. 2019). These results illustrate the clinical significance of ADAM10 in the pathogenesis and development of sepsis. ADAM17 also plays a critical role in endotoxin-mediated acute pulmonary inflammation. An increased ADAM17 expression in endotoxin-treated lung microvascular endothelial cells enhances the ectodomain shedding of chemokines and the junctional adhesion molecules. Furthermore, endotoxin-triggered vascular permeability, edema formation, pulmonary leukocyte recruitment, and the release of TNF-a & IL-6 have also been abrogated in endothelial-specific adam17-knockout mice (Dreymueller et al. 2012). ADAM12 is expressed in naïve T-cells and acts as a costimulatory molecule to activate and induce the proliferation of T-helper 1 (Th1) cells (Liu et al. 2020).

The decreased level of ADAM-TS13 in sepsis patients leads to thrombotic microangiopathy, clinically manifesting as a syndrome with multiple organ dysfunction, most importantly brain and kidneys, and potentially influencing almost all organs (Levi et al. 2018). Furthermore, a decrease in ADAM-TS13 activity has

been reported in different pediatric sepsis syndromes, including sepsis, severe sepsis, and septic shock. The ADAM-TS13 activity is negatively correlated with the severity of pediatric sepsis, whereas decreased ADAM-TS13 activity on day 1 has been found related to increased risk of mortality (Lin et al. 2016).

Rheumatoid arthritis (RA) is an autoimmune and chronic inflammatory disease that causes joint inflammation and tissue destruction that results in functional damage. The first evidence associating ADAMs in RA has demonstrated the upregulation of ADAM17 mRNA in arthritis-affected cartilage compared to normal cartilage (Patel et al. 1998). Furthermore, hypoxia-inducible factor-1 α (HIF-1 α) and TNF-α mediated enhancement of ADAM17 mRNA levels have been reported in RA-affected joints (Charbonneau et al. 2007). The high efficacy in the treatment of preclinical mouse models of RA with specific ADAM17 inhibitors, such as TMI-2 (Wyeth) and BMS-561392 (Bristol Myers Squibb), further supports the role of ADAM17 in arthritis (Moss et al. 2008). Significantly elevated levels of ADAM10 mRNA and protein in human rheumatoid arthritis synovial tissue suggest the involvement of ADAM10 in the pathogenesis of rheumatoid arthritis (Isozaki et al. 2013). ADAM-TS7 and ADAM-TS12 are found associated with cartilage oligomeric matrix protein (COMP) degradation in vitro and are also overexpressed in the synovium and cartilage of rheumatoid arthritis patients. The α2-macroglobulin and granulin-epithelin precursors (GEP) were reported as endogenous inhibitors of ADAM-TS7 and ADAM-TS12 (Liu 2009). Furthermore, rs10461703 genetic polymorphisms of ADAM-TS12 are associated with the development of RA (Nah et al. 2012).

8 ADAMs and ADAM-TSs Role in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive brain disorder in which toxic amyloid-β (Aβ) peptides get accumulated in the brain. Amyloid-β (Aβ) peptide is produced when β- and γ-secretase cleave amyloid precursor protein (APP). Alternative cleavage of the APP by the α-secretases (i.e., ADAMs) is neuroprotective and hence prevents the development of AD (Table 5). Several ADAMs, including ADAM9, ADAM10, and ADAM17 are suggested to possess the α-secretase activity and may consequently contribute to neuroprotection (Asai et al. 2003; Kuhn et al. 2010). Furthermore, while ADAM10 has both constitutive and regulated α-secretase activity, ADAM9 and ADAM17 have only regulated secretase activity (Lammich et al. 1999; Postina et al. 2004). The in vivo studies have shown that even a moderate neuronal overexpression of ADAM10 strongly enhanced α-secretase cleavage of APP, delays formation of plaque, and reduces cognitive defects observed in a transgenic AD mouse model (Endres et al. 2014). A small clinical study reported an enhanced ADAM10 α-secretase activity and a significant increase in APPs-α levels in patients receiving oral administration of synthetic retinoid acitretin (Endres et al. 2014). A declined ADAM10 levels in patients with AD indicates the importance of ADAM10 in the molecular pathogenesis of AD (Colciaghi et al. 2002).

Table 5 Functions of ADAMs and ADAM-TSs involved in Alzheimer's disease

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/tissues	Reference
ADAM9	Amyloid precursor protein (APP)	Regulated α-secretase activity, neuroprotective	(Nah et al. 2012; Kuhn et al. 2010; Bernstein et al. 2003)
ADAM10	APP, notch	Constitutive α-secretase activity, neuroprotective Delays plaque formation and alleviates cognitive defects	(Asai et al. 2003; Kuhn et al. 2010; Lammich et al. 1999; Postina et al. 2004; Endres et al. 2014; Colciaghi et al., 2002)
ADAM12	APP	Interacts with FISH protein, influenced susceptibility to late-onset AD	(Slack et al. 2001; Malinin et al. 2005)
ADAM15		Expresses in few diffuse plaques Linked via interaction with integrin and/or Src protein tyrosine kinases	(Colciaghi et al. 2002)
ADAM17	APP	Role in regulated and constitutive α-secretase activity in cultured cells	(Asai et al. 2003; Kuhn et al. 2010; Lammich et al. 1999; Hotoda et al. 2002; Buxbaum et al. 1998)
ADAM-TS1	Aggrecan, Versican	Overexpression of ADAM-TS1 as marker protein for neurodegeneration	(Satoh et al. 2000)
ADAM-TS3	Reelin	Protease cleaves and inactivates Reelin in the cerebral cortex and hippocampus	(Krstic et al. 2012)
ADAM-TS4	Reelin, APP	Facilitates large fraction of insoluble Aβ peptides generation Protease cleaves Reelin	(Clark et al. 2001; Miguel et al. 2005; Ogino et al. 2017)
ADAM-TS5	Reelin	Protease cleaves Reelin	(Miguel et al. 2005)
ADAM-TS9		Remodeling the basement membrane and ECM	(Harold et al. 2007)
ADAM-TS13	vWF	Overexpression of ADAM-TS13 attenuates BBB disruption, increased micro-vessels, capillary perfusion, and cerebral blood flow	(Walter et al. 2019)

Immunoreactive staining showed that ADAM10 is associated with diffuse and neuritic plaques, whereas ADAM15 is observed in diffuse plaques. These findings suggest a direct involvement of ADAM10 in the pathology of AD, whereas ADAM 15 might be influencing the disease through its interaction with integrins and/or tyrosine kinases, particularly src tyrosine kinases (Bernstein et al. 2003). The overexpression of soluble and an alternatively spliced form of ADAM9 in COS cells results in enhanced phorbol ester-mediated digestion of APPs-α, suggesting α-secretase-like activity of ADAM9 (Hotoda et al. 2002). Additionally, in vitro

studies reported ADAM17 as an α-secretase, where disruption of the Adam17 gene and inhibition of ADAM17 enzyme activity eliminates regulated and constitutive α-cleavage of APP, respectively, in cultured cells (Buxbaum et al. 1998; Slack et al. 2001). Amyloid-β peptide (Aβ) is a causative agent for Alzheimer's disease (AD), and various in vitro studies have shown that ADAM12 mediate the neurotoxic effect of Aβ and influenced susceptibility to late-onset of AD (Malinin et al. 2005; Harold et al. 2007).

Unlike ADAMs, little is known regarding the role of the ADAM-TS in neurodegenerative disorders such as AD. Cloning and characterization of rat ADAM-TS9 fragment from a beta amyloid-treated astrocyte cDNA library indicate the possible role of ADAM-TS9 in the events leading to Alzheimer's disease (Clark et al. 2001). The Aβ induces the expression of ADAM-TS4 in cultured rat astrocytes indicating induced ECM degradation in the AD brain (Satoh et al. 2000). The frontal cortex of adult brains from AD patients showed more than five-fold overexpression of ADAM-TS1, but ADAM-TS5 levels were comparable to controls (Miguel et al. 2005). ADAM-TS4 and ADAM-TS5 have been recognized as Reelin (extracellular signaling protein) cleaving enzymes in a mouse model of AD (Krstic et al. 2012). Recently, it has been observed that ADAM-TS3 cleaves the N-terminal site of Reelin in the cerebral cortex and hippocampus, thereby negatively regulating Reelin. Therefore, for the prevention or treatment of AD, inhibition of ADAM-TS3 could be considered as a potential therapeutic strategy (Ogino et al. 2017). In autopsy brain samples from AD patients, metalloprotease ADAM-TS4 has been reported for the generation of a large fraction of insoluble Aβ peptides truncated at the N-terminus with Aβ4–x peptides (Walter et al. 2019). Furthermore, virus-mediated expression of ADAM-TS13 in the brain of APPPS1 mice is beneficial, as it reverses the vascular phenotype, AD-type pathologies, and behavioral deficits (Cao et al. 2019). These effects may be due to increased Aβ clearance from the brain to plasma, which may be due to improved blood-brain barrier (BBB) function (Bradley et al. 2007).

9 ADAMs and ADAM-TSs Role in Proliferative Retinopathies

The development of new blood vessels from existing vasculature is a critical process involved during tissue repair and any abnormality in the above process leads to pathological conditions such as retinal neovascularization. Retinal neovascularization is a leading cause of blindness in humans and is a clinical manifestation of several eye diseases including hypoxia-induced neovascularization, proliferative diabetic retinopathy, retinopathy of prematurity, and macular degeneration (Bradley et al. 2007; Chen and Smith 2007).

Several studies have shown the role of ADAMs and ADAM-TSs (Table 6) in pathological retinal neovascularization. The ADAM9 contribution to pathological neovascularization has been evaluated using a murine model of retinopathy of

Table 6 Functions of ADAMs and ADAM-TSs involved in proliferative retinopathies

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/ tissues	Reference
ADAM8	CD31, Tie-2, Flk-1, Flt-1, EphrinB2, EphB4, VE-cadherin, KL-1, E-selectin, neuregulin-1β2	ADAM8 negatively regulates retinal neovascularization	(Horiuchi et al. 2003)
ADAM9	EphB4, Tie-2, Flk-1, CD40, VCAM, VE-cadherin	↑Expression in endothelial cells in pathological vascular tufts in the OIR model Important role in ischemia-induced retinal neovascularization	(Chen and Smith 2007)
ADAM10	Notch	ADAM10-deficient mice died at 9.5 days of embryogenesis Adam10 gene deletion in endothelial cells affects vascular structures in developing and adult mice	(Edwards et al. 2008; Guaiquil et al. 2010; Hartmann et al. 2002)
ADAM15	Notch1 and -4, PECAM-1, VE-cadherin, TIE-2, membrane-type 1 MMP, Kit-ligand	*adam15*$^{-/-}$ mice show a strongly reduced angiogenic response in a model of hypoxia-induced proliferative retinopathy	(Guaiquil et al. 2009)
ADAM17	VE-cadherin, V-CAM, EphB4, EMMPRIN, IGFR1 or PECAM, HB-EGF	ADAM17 inactivation in endothelial cells significantly reduced pathological neovascularization in a mouse model for retinopathy of prematurity	(Glomski et al. 2011)
ADAM-TS1		ADAM-TS1, an endogenous regulator of endothelial cell proliferation Inhibits angiogenesis in vivo and suppresses endothelial cell proliferation in vitro	(Weskamp et al. 2010)

prematurity where the level of ADAM9 expression predominantly increased in endothelial cells of the pathological vascular tufts. Also, the upregulated ADAM9 sheddase activity was largely dependent on reactive oxygen species production (Guaiquil et al. 2009). Likewise, in the oxygen-induced retinopathy (OIR) model, elevated levels of ADAM15 were observed in endothelial cells compared to the wild-type controls, and mice deficient in ADAM15 showed a significant reduction in neovascularization (Horiuchi et al. 2003). On the contrary, ADAM8-deficient mice showed enhanced neovascularization in retinas following the OIR model, which suggests that ADAM8 inhibits neovascularization (Guaiquil et al. 2010). The ADAM10-deficient mice died at 9.5 days of embryogenesis with numerous defects in the cardiovascular system and vasculogenesis, indicating the importance of

ADAM10 on Notch signaling and (neo)vessel formation (Edwards et al. 2008; Hartmann et al. 2002). Furthermore, mice (ADAM10-Tie2-Cre) with endothelial cell-specific inactivation of ADAM10 showed severe vascular abnormalities in the retina and various specialized vascular compartments during development (Glomski et al. 2011). Similarly, endothelial cell-specific inactivation of ADAM17 resulted in a significant reduction in tube formation and retinal neovascularization in a mouse model of retinopathy of prematurity (Weskamp et al. 2010).

In the OIR mice model, VEGF rapidly and strongly stimulates the expression of ADAM-TS1 in an endothelial cell in a PKC-dependent manner, thereby inhibiting endothelial cell proliferation and angiogenesis. Also, the deletion of endogenous ADAM-TS1 in endothelial cells results in increased endothelial cell proliferation indicating its role as a negative regulator of retinal neovascularization (Zhenhua et al. 2006).

10 ADAMs Role in Infectious Diseases

ADAMs have a prominent role in infectious diseases via pathogen/viral recognition and clearance, along with cytokine release and leukocyte recruitment (Table 7). ADAMs are mainly involved in infectious diseases through catalytic ectodomain

Table 7 Functions of ADAMs involved in infectious diseases

ADAMs/ ADAM-TSs	Substrates	Pathological effect in cells/ tissues	Reference
ADAM8		ADAM8 promotes leukocytes recruitment	(Kononchik et al. 2018; Dreymueller et al. 2017)
ADAM9		Upregulated during hepatitis B virus–related hepatocellular carcinoma metastases	(Olvera-Garcia et al. 2016)
ADAM10	Notch1, pattern-recognition receptors (PRRs), viral receptors	Uptake and clearance of pathogens, promotes viral recognition and entry	(Aljohmani and Yildiz 2020; Kneidl et al. 2012; Etzerodt et al. 2010; Gopal et al. 2015; Cappenberg et al. 2019; Kondratowicz et al. 2011; Mikulicic et al. 2019; Oliviero et al. 2017)
ADAM17	Notch1, viral receptors, ACE2, TNF-α, IL-6R	Uptake and clearance of pathogens, promotes viral recognition and entry	(Aljohmani and Yildiz 2020; Kneidl et al. 2012; Etzerodt et al. 2010; Gopal et al. 2015; Cappenberg et al. 2019; Kondratowicz et al. 2011; Mikulicic et al. 2019; Oliviero et al. 2017; Yan et al. 2020; Lambert et al. 2005)

shedding of their numerous substrates such as adhesion molecules, junction molecules, chemokines, and cytokines (Aljohmani and Yildiz 2020). ADAM10 and ADAM17 influence the uptake and clearance of pathogens by shedding of pattern-recognition receptors (PRRs), particularly receptor for advanced glycation end products (RAGE), CD163, and L-selectin (Kneidl et al. 2012; Etzerodt et al. 2010; Gopal et al. 2015; Cappenberg et al. 2019). In addition to bacterial entry, ADAM10 and ADAM17 are involved in viral recognition and entry via shedding of various viral receptors facilitating their cell/nuclear entry and replication (Kondratowicz et al. 2011; Mikulicic et al. 2019; Oliviero et al. 2017; Kononchik et al. 2018). Furthermore, ADAM8 and ADAM9 protein expression was found to be upregulated during viral infection (Dreymueller et al. 2017; Ma et al. 2009; Olvera-Garcia et al. 2016; Xiang et al. 2017). Besides this, ADAMs are shown to protective against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. During SARS-CoV2 infection, angiotensin-converting enzyme II (ACE2) is a cellular receptor for the virus' spike (S) protein (Yan et al. 2020). ACE2 is a critical shedding substrate for ADAM17 and is highly expressed in the lung and myocardium (Lambert et al. 2005). Therefore, overexpression of ADAM17 might protect us against SARS-CoV2 infection via shedding of ACE2. ACE2 inhibition prevents SARS-CoV2 entry and blocks the circulation of virus particles (Patel et al. 2014b).

There are clear shreds of evidence available that SARS-CoV2 virus entry is facilitated by proteolytic cleavage of the S glycoprotein via furin, an endoprotease, just after the binding of virus spike proteins with ACE2 (Walls et al. 2020). Notch1, a key regulator of furin expression at the transcriptional level and is a direct substrate of both ADAM10 and ADAM17 (Weskamp et al. 2010). Therefore, activation of Notch 1 via ADAM10/ADAM17 shedding results in upregulation of Notch targeting genes such as furin (Qiu et al. 2015). Consequently, blocking of Notch1 signaling via inhibition of ADAM10/ADAM17 sheddase activity may downregulate the furin expression and might provide a potential approach to prevent SARS-CoV2 entry and infection (Rizzo et al. 2020). Furthermore, high serum levels of TNF-α and IL-6 are reported as predictive biomarkers for COVID-19 patients (Del Valle et al. 2020). Both TNF-α and IL-6R are the potent substrates of ADAM17. Hence inhibition of ADAM17 sheddase activity might serve as a critical preventive measure against SARS-CoV2 infection. In vitro and in vivo studies have shown that inhibition of ADAM17 markedly decreases the SARS-CoV2 infection and also attenuates its severe clinical outcome (Haga et al. 2010). The role of ADAM proteases during SARS-CoV2 infection is still in its infancy, therefore careful evaluation is required for its potential therapeutics.

11 Conclusion and Future Perspectives

ADAMs and ADAM-TSs are the metalloproteases involved in the extracellular matrix remodeling and degradation, but in recent years they are also shown to regulate the development and pathology of various diseases. They are structurally

related to MMPs in terms of their domains except for ADAM-TSs, which have thrombospondin motifs instead of a transmembrane domain. The ADAMs regulate cell phenotype and behavior by ectodomain shedding and influence cell–cell communication via adhesive interactions. The ADAMs are widely related to various human pathologies, as they regulate multiple cellular functions and physiological conditions. Unlike ADAMs, our fundamental understanding of ADAM-TS proteins' functions in human development and pathologies is still in its infancy. The association of ADAM-TS proteases with various diseases will continue to emerge, and we might understand their significance in days to come.

Although the in vitro regulation and functions of the ADAMs are known, further research is needed to confirm the physiological relevance of ADAMs and ADAM-TSs in vivo. Despite satisfactory evidence presented on the role of ADAMs and ADAM-TSs enzymes, further studies are greatly required to determine their complete mechanism of action, their activators, and inhibitors. Studies are needed to understand the significance of their downstream signaling molecules in disease development and progression. Although a reduction in ADAMs or ADAM-TSs levels causes adverse outcomes, abnormal upregulation or overexpression of these enzymes can lead to detrimental effects. Therefore, enormously competent and promising approaches are required to design novel therapeutics targeting ADAMs and ADAM-TSs. There are redundancy and overlap in the function of ADAMs and ADAM-TSs due to their crosstalk with various other proteins. Therefore, targeting multiple members of these families may exhibit sufficient effects. Consequently, cell- and tissue-specific functions and their physiological levels along with the activation process of these enzymes should also be considered in designing therapies.

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