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A Disintegrin and Metalloproteinase (ADAM) and ADAM with Thrombospondin Motifs (ADAMTS) Family in Vascular Biology and Disease

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Abstract

A Disintegrin and Metalloproteinase (ADAM) is a family of proteolytic enzymes that possess sheddase function and regulate shedding of membrane-bound proteins, growth factors, cytokines, ligands and receptors. Typically, ADAMs have a pro-domain, and a metalloproteinase, disintegrin, cysteine-rich and a characteristic transmembrane domain. Most ADAMs are activated by proprotein convertases, but can also be regulated by G-protein coupled receptor agonists, Ca^{2+} ionophores and protein kinase C activators. A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) is a family of secreted enzymes closely related to ADAMs. Like ADAMs, ADAMTS members have a pro-domain, and a metalloproteinase, disintegrin, and cysteine-rich domain, but they lack a transmembrane domain and instead have characteristic thrombospondin motifs. Activated ADAMs perform several functions and participate in multiple cardiovascular processes including vascular smooth muscle cell proliferation and migration, angiogenesis, vascular cell apoptosis, cell survival, tissue repair, and wound healing. ADAMs may also be involved in pathological conditions and cardiovascular diseases such as atherosclerosis, hypertension, aneurysm, coronary artery disease, myocardial infarction and heart failure. Like ADAMs, ADAMTS have a wide-spectrum role in vascular biology and cardiovascular pathophysiology. ADAMs and ADAMTS activity is naturally controlled by endogenous inhibitors such as tissue inhibitors of metalloproteinases (TIMPs), and their activity can also be suppressed by synthetic small molecule inhibitors. ADAMs and ADAMTS can serve as important diagnostic biomarkers and potential therapeutic targets for cardiovascular disorders. Natural and synthetic inhibitors of ADAMs and ADAMTS could be potential therapeutic tools for the management of cardiovascular diseases.

Graphical Abstract

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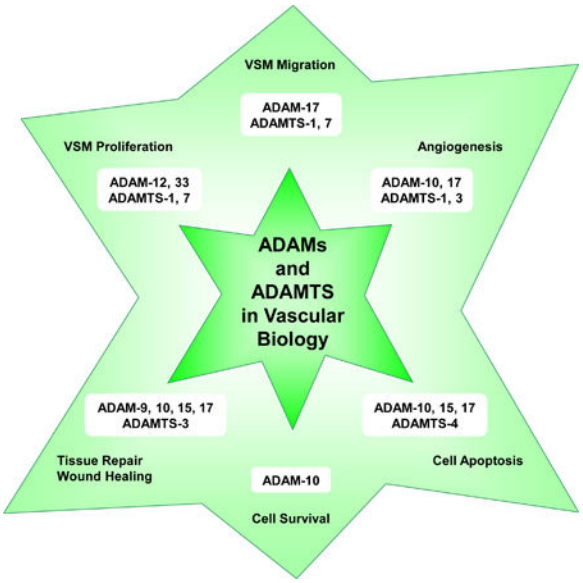
Conflict of Interest

None



Keywords

cytokines; metalloproteases; sheddase; vascular smooth muscle; zinc

1. Introduction

Cardiovascular remodeling and degradation of extracellular matrix (ECM) proteins play an important role in the regulation of cardiovascular function, and can also be involved in pathological processes such as inflammation, oxidative stress, tumor metastasis and cardiovascular disease [1, 2]. Matrix metalloproteinases (MMPs) are major regulators of ECM protein degradation and tissue remodeling [3, 4]. In addition to MMPs, two families of enzymes termed a disintegrin and metalloproteinase (ADAM) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) have been implicated in the regulation of cardiovascular function through modulation of ECM, growth factors and cytokines. ADAMs, ADAMTS and snake venom metalloproteinase (SVM) belong to the adamalysin protein family that has a close relationship with other metalloenzymes such as MMPs and membrane-type MMPs (MT-MMPs). ADAMs and ADAMTS are very similar in their structural domains and protein sequence sharing highly conservative structure and protein homology. Both ADAM and ADAMTS members have a pro-domain, and a metalloproteinase, disintegrin and cysteine-rich domain. The metalloproteinase domain of ADAMs regulates shedding of membrane-bound growth factors, cytokines and receptors with the help of the disintegrin domain which specifically binds to integrins. The main differences are that ADAMs are largely membrane-bound proteins that are fixed on the cell membrane by a transmembrane domain, although secreted forms of ADAMs generated by alternative splicing or cleavage have also been identified in the circulation and peripheral tissues. In comparison, ADAMTS members are secreted enzymes that lack the transmembrane domain and cytoplasmic tail, but have extra ancillary thrombospondin motifs.

Most ADAMs such as ADAM 1, 2, 3, 6, 7, 18, 20, 21, 22, 28, 29, 30, 32 and 33 play a role in the reproductive system and embryo development. However, ADAM-8, 9, 10, 11, 12, 15, 17 and 19, along with ADAMTS-1, 4, 5, 16 have a broader distribution in human tissues and a wide connection with various biological processes and cardiovascular functions. Additionally, some ADAMs and ADAMTS have been suggested as potential factors in pathological conditions such as oncogenesis, autoimmune diseases, inflammation and cardiovascular diseases [5].

In this review, we will use research data published in PubMed, Web of Science and other scientific databases, as well as some information from our previous reports to provide an overview of the biochemical and biological properties of ADAM and ADAMTS family and their role in cardiovascular pathophysiology. We will discuss the ADAM and ADAMTS family structure, tissue distribution, activation process, substrates, and biological functions. The relationship between ADAMs and ADAMTS and other related families of proteases such as MMPs and SVM will also be briefly described [6]. We will describe the potential role of ADAMs and ADAMTS family members in pathological processes and cardiovascular disease. We will also describe some of the endogenous and synthetic inhibitors of ADAMs and ADAMTS and their potential usefulness in biological assays of these enzymes. We will conclude the review with insights on how ADAMs and ADAMTS can be used as potential biomarkers and therapeutic targets for the detection and management of cardiovascular disease.

2. Historical Overview of ADAM and ADAMTS Family

The discovery and classification of the ADAM family involved a large amount of important research work. ADAM-1 was first identified in 1987 as a new fertilization protein PH-30 [7]. In 1992, ADAMs were demonstrated as a new family with a close relationship to the snake venom disintegrins family, also known as snake venom metalloproteinases (SVM). In 1995, ADAM-1 was suggested to belong to the metalloproteinase/disintegrin/cysteine-rich (MDC) family and was confirmed to have a role in the fertilization process. ADAM-17 was recognized in 1997 as a TNFα converting enzyme (TACE), and subsequently ADAMs became known as sheddases [8]. Because of the large interest in ADAM-17, and its wide functions and pathological roles described in numerous publications, its crystal structure was determined in 1998. To further elucidate the role of ADAMs in biological processes and physiological functions, ADAM-17 and ADAM-10 knock-out mice were developed in in 1998 and 2002, respectively. In 2006, the crystal structure of Vascular Adhesion Protein-1 (VAP1) was revealed and helped to decipher the ADAMs' MDC domain architecture and their unique activity sites [8]. The discovery of the C-shape scaffold, was a landmark study in deciphering the crystal structure of ADAMs and how they function [9]. In 2010 and the following years, more ADAMs knock-out mice were developed to verify their biological roles, and further research suggested potential role of ADAMs in multiple pathological conditions such as inflammation, oncogenesis and cardiovascular disease. ADAMTS family was first identified as an inflammation factor in 1997 [10]. The role of ADAMTS-2, 3, and 14 as procollagen N-endopeptidases was demonstrated in 2001 [11, 12]. In the following years, the role of different ADAMTS in various diseases such as cancer, osteoarthritis and cardiovascular disease has been illuminated.

3. ADAM Family Structure

ADAMs, formerly known as metalloproteinase/disintegrin/cysteine-rich (MDC) proteins, are a subfamily of the Metzincins superfamily of metalloproteases. ADAMs, ADAMTS, and snake venom metalloproteases (SVMs) are Zn^{2+}-dependent catalytic enzymes (Fig. 1). They comprise the adamalysin subfamily of the metallopeptidases family of proteins.

ADAMs have various forms in different species including ciona intestinalis, mice, rats and humans [1] (Fig. 2). Currently, 37 ADAMs have been identified in rats, 34 ADAMs have been discovered in mice, and 22 ADAMs have been found in the human genome, among which 13 proteins are proteolytically active [13]. There are wide similarities in domain organization, spatial structures and protein sequences between ADAMs, ADAMTS and SVMs [14]. The common feature of the adamalysin subfamily is a pro-domain, a metalloproteinase, disintegrin, and cysteine-rich domain with some differences in protein sequence and biological function [15]:

3.1 Signal peptide and pro-domain

ADAMs family of proteins usually have an N-terminus signal peptide which directs the enzyme to carry out its function. In most ADAMs, the signal peptide is the initial part of the molecule followed by the pro-domain. The pro-domain serves to correct protein folding, stabilize the protein, and maintain the enzyme function and catalytic latency via a “cysteine switch” mechanism, which involves blocking the catalytic zinc (Zn^{2+}) activation site by the conserved cysteine residue in the pro-domain [16]. The cysteine switch in the pro-domain should not be confounded with the distinct cysteine-rich domain in the ADAM molecule [17].

3.2 C-shape arm

The C-shape arm is a characteristic structure in the ADAMs family, and is connected to the transmembrane domain via the EGF-like region [9]. The C-shape arm comprises the Metalloproteinase domain (M-domain), Disintegrin domain (D-domain), Cysteine-rich domain (C-domain) and the Highly Variable Region (HVR) of the C-domain. The C-shape arm is crucial for ADAM structure and function as it is responsible for target recognition, protein interaction, and proteolytic activity.

3.3 Metalloproteinase domain

Similar to other metalloenzymes such as MMPs and MT-MMPs, ADAMs have a metalloprotease domain in its active region. The metalloproteinase domain is the main functional region that proteolytically interacts with various ligands, receptors and ion channels on their own cell surface or on their neighboring cells’ membrane. Generally, the metalloproteases domain is characterized by its catalytic Zn^{2+} binding signature (HExGHxxGxxHD), where H denotes histidine, E glutamic acid, G glycine, D aspartic acid, and x means variable amino acid (aa). The catalytic domain assists ADAMs to serve as sheddases and mediators of cell signaling and thereby determine cell fate (proliferation or apoptosis), and contribute to cell differentiation, tissue organization and physiological function [18, 19].

3.4 Disintegrin domain

Disintegrins are small proteins that were first isolated from snake venom. Disintegrins are recognized by their common Arg-Gly-Asp (RGD) sequence, which could inhibit platelet aggregation via integrin binding. The disintegrin domain is another important functional region in the C-shape arm of ADAMs, and typically consists of 14 amino acid. The term “disintegrin” was initially assigned to this domain because it is highly similar to RGD-containing proteins in snake venom, which are highly conservative among different members of the Metzincins superfamily, and are able to adhere to integrins, thus suppressing platelet aggregation and inducing severe hemorrhage in snake bite victims [20]. However, in most ADAMs the disintegrin domain is not exactly the same as in SVMs. Instead of the highly conserved RGD recognition sequence in SVMs, the binding sequence is replaced by an ECD or xCD sequence in most ADAMs, Only ADAM-15 still conserve the RGD sequence, and is therefore considered unusual among ADAMs family members. Thus, to be more accurate, ECD or xCD sequence in ADAMs should be referred to as “disintegrin-like” domains rather than “disintegrin” domain [21]. ADAMs family present their disintegrin domain on the cell surface, which explains why integrins are common receptors for ADAMs [22].

3.5 Cysteine-rich domain

The Cysteine-rich domain (C-domain) is strongly-related to the cell adhesive and fusogenic potential. Along with cell surface syndecan, the C-domain in ADAM-12 regulates cellular adhesive interactions and in turn modulates the spreading of cells (especially inflammation cells) and their tissue distribution by mediating integrin-dependent cell spreading [23]. Compared to other ADAMs, ADAM-10 and ADAM-17 have a unique sequence and structure in the C-domain, which may partly account for their wide role in various diseases [9]. The C-domain of ADAM-13 is closely related to cell fixation, and can bind to the basement membrane proteins laminin and fibronectin [24]. Also, the highly variable region (HVR) of the C-domain is a potential protein-protein adhesive interface [9]. We should emphasize that the cysteine-rich (C-domain) is one component of the C-shape arm, and is completely different from the cysteine switch which comprises cysteine residues that are unique and exquisite structure in the ADAM pro-domain which maintains the enzyme latency by regulating the Zn^{2+} binding site [13, 16].

3.6 EGF-like Region, Transmembrane Domain and Cytoplasmic Tail

The epidermal growth factor (EGF)-like region, transmembrane domain and cytoplasmic tail are also important components of the ADAM molecule. These regions connect the extracellular and intracellular components of ADAMs together, and also help to fix the C-shape arm to the cell membrane and transmit the extracellular signal into the cell, and thereby regulate mRNA expression and protein phosphorylation. The cytoplasmic tail of ADAMs also has some intrinsic signaling activity and is a crucial part in regulating proteolysis [25].

3.7 Structural Differences among ADAMs Family Members

Although ADAMs share common components in the signal peptide, pro-domain, C-shape arm (which comprises the metalloproteinase M-domain, disintegrin D-domain, and cysteine-rich C-domain with the highly variable region HVR), and the EGF-like region, transmembrane domain and cytoplasmic tail, there are some differences between various ADAMs members (Fig. 2).

ADAMs members can be divided into four types. Type I is the most common and classic type among all ADAMs, its members have the common domain structure, and it includes ADAM-1, 8, 9, 12, 13, 15, 19, 20, 21, 24, 26, 28, 30, 33, 40. In type I ADAMs, the M-domain have the characterized catalytic Zn^{2+} binding signature (HExGHxxGxxHD), the D-domain is based on xCD sequence, and they also include the EGF-like region in their structure.

Type II is another common pattern among ADAMs members, and includes ADAM-2, 7, 11, 18, 22, 23, 27, 29, 32. In type II ADAMs, the metalloproteinase domain does not have the characteristic catalytic-Zn^{2+} binding signature (HExGHxxGxxHD), and is more variable than type I.

Type III is unique for ADAM-15, where the M-domain still contains the characteristic catalytic-Zn^{2+} binding signature (HExGHxxGxxHD). However, similar to SVM, its disintegrin domain is based on RGD sequence rather than the xCD sequence in most ADAMs members.

Type IV is unique for ADAM-10 and 17, where the disintegrin domain is based on xCD sequence. However, they lack the EGF-like region found in type I, II, and III. The high similarity in the structure of ADAM-10 and 17 may explain the similarities in some of their functions.

3.8 Unique ADAMTS Family Structure

There are 19 ADAMTS genes in mammalian genomes denoted from 1 to 20, except ADAMTS-11 which was assigned to a gene previously identified as ADAMTS-5. Therefore, there are totally 19 ADAMTS proteins in humans, the structure of which is in large part similar to that of ADAMs. Like ADAMs, ADAMTS have the common components including the signal peptide and pro-domain, metalloproteinase M-domain, disintegrin D-domain and cysteine-rich C-domain. The most obvious difference is that ADAMTS lack the EGF-like region, transmembrane domain and cytoplasmic tail, and instead, these domains are replaced by thrombospondin repeats and spacer (Fig. 3). This makes ADAMTS soluble in the circulation, where they can conduct their function in remote tissues.

The ADAMTS unique ancillary thrombospondin-like repeats (TSR) are critical part for the enzymes' interaction with ECM components, regulation of enzyme activity, and substrate selection and recognition. ADAMTS members have a 50 aa thrombospondin-like repeat (TSR), which is highly similar to thrombospondins 1, 2, hence the name ADAMTS [26]. After thrombospondin-like repeat (TSR), is the cysteine-rich domain, which usually consists of more than 100 aa residues. This is followed by the cysteine-free spacer region, which

consists of 103 to 160 aa. The spacer region is then followed by 0 to 14 TSR modules, which in some ADAMTS are connected to GON-1 domain (present in the ADAMTS GON-1 identified in C. elegans), CUB (complement C1r/C1s, Uegf, Bmp1) domain, or PLAC (protease and lacunin) domain (Fig. 3).

ADAMTS members are generally divided into six types. Type I has the basic structure of ADAMTS, and includes several members of ADAMTS. ADAMTS type I structure comprises the pro-domain, metalloproteinase, disintegrin, cysteine-rich domain, followed by thrombospondin repeats and spacer. Type II ADAMTS has a unique GON-1, type III has a procollagen N-propeptidase, Type IV has a complement C1r/C1s, Uegf, Bmp1 (CUB) domain, type V has a protease and lacunin (PLAC) structure and mucin/proteoglycan domain, and type VI has only PLAC domain.

4. Sources and Tissue Distribution of ADAM and ADAMTS Family

ADAM and ADAMTS members are produced by different cells and have wide tissue distribution (Table 1, 2). Of note, most ADAMs, including ADAM-1, 2, 3, 4, 5, 6, 7, 20, 21, 24, 25, 26, 27, 28, 29, 30, 32 and 34 are involved in the reproduction process and therefore are often localized in the reproductive system and organs of generation such as the testis and epididymis [27]. On the other hand, ADAM-8, 9, 10, 12, 15, 17 and 19 are involved in cardiovascular development, and the abnormal expression or aberrant function of these ADAMs may lead to cardiovascular disease.

5. ADAMs and ADAMTS Activation

ADAM family can be activated by cytokines, proteinases, protein kinase C activators, G-protein coupled receptor (GPCR) agonists and Ca^{2+} ionophores. Compared to MMPs, whose activation occurs in ECM after the pro-domain is removed [2], ADAMs activation occurs in intracellular region where their pro-domain is removed by pro-protein convertases in the Golgi system during transit process. Pro-protein convertase is the most important proteinase during ADAMs activation, as it is responsible for cleaving the Rx(R/K)R motif of the pro-domain. The pro-protein convertase then adds Zn^{2+} coordination to the metalloprotease domain so that ADAM can be catalytically activated and perform its physiological function and sheddase activity [28].

There are some exceptions in ADAMs activation, and the activation process and the cellular location of active proteinase are markedly different among various ADAMs. For example, ADAM-8 and ADAM-28 are activated in ECM. Also, whether cleavage of the pro-domain is required for the biological activity of ADAM members with an inactive metalloproteinase domain remains an important question. Some ADAMs such as ADAM-12 are stored as already active proteins in the cell, and are transferred to the cell membrane to perform their function when the cell is simulated by cytokines [29]. Therefore, the pro-domain removing procedure is not necessary for ADAM-12 activation, and ADAM-12 can still conserve its function without proteolytic processing which is crucial for other ADAMs [30]. Although, the pro-domain and metalloprotease domain are crucial components for most ADAMs, and the pro-domain acts as an activation switch through its cysteine residue (cysteine switch),

some ADAMs auto-catalytically remove the pro-domain in order to complete their transformation from inactive pro-protein to active protein, and proceed to the following activation process [31].

The intracellular cytoplasmic tail and protein phosphorylation may also contribute to ADAMs activation, signal transmit and interaction with other proteins and receptors. However, the role of cytoplasmic tail has been debated, and some reports suggest that ADAM-17 and ADAM-19 can still act as sheddases without a cytoplasmic tail, and rely mainly on their transmembrane domain [32]. For example, although phosphorylated Ser819 was suggested as an important reaction site during activation of ADAM-17, mutation of this site did not suppress ADAM-17 activity and cleavage of its substrates transforming growth factor-α (TGFα), TNFα or TNFα receptors. These observations suggested that the cytoplasmic tail is not responsible for ADAM-17 sheddase activity [32], and instead may have other unique functions. For instance, the cytoplasmic tail of ADAM-17 is strongly correlated with G-protein coupled receptor (GPCR) mediated activation of epidermal growth factor receptor (EGFR) signaling [19]. During these activation processes, Src causes stimulation of phosphatidylinositol 3-kinase (PI_3K) and subsequent activation of phosphoinositide-dependent kinase-1 (PDK1), which directly phosphorylates ADAM-17 [33]. Also, agonist-induced phosphorylation of Thr735 of ADAM-17 enhances cleavage of the TrkA neurotrophin receptor in tumor cells and cardiomyocytes. Thr735 phosphorylation also accounts for the transfer of ADAM-17 from the endoplasmic reticulum to the cell surface [34].

The activation process of ADAMTS is basically similar to that of ADAMs. In this respect, ADAMTS activation involves cleavage of the N-terminal pro-domain by proprotein convertases such as furin and furin-like enzymes [35]. These serine proteases efficiently cleave after a consensus sequence Arg-Xaa-(Arg/Lys)-Arg, and the cleavage likely occurs in the trans-Golgi or at the cell surface [36, 37]. Similar to other metalloproteases, the activity of ADAMTS requires a neutral to slightly basic pH and the presence of Zn^{2+} and Ca^{2+} ions [38]. However, there are some exception as to the importance and the site of cleavage for ADAMTS activation. ADAMTS-13 has an unusually short propeptide, and ADAMTS-9 and ADAMTS-13 zymogens appear to be active despite retention of the propeptide [39, 40]. Also, for some ADAMTS, cleavage could occur in their C-terminal domain. Studies on ADAMTS-2 have shown that an autocatalytic cleavage occurring within the C-terminal end, possibly in the procollagen N-propetidase domain, increases its activity [35, 41]. A similar autocatalytic activation process has been reported for ADAMTS-1, 4, 8, 9 and 12 [42], suggesting that this autocatalytic activation and regulation could be a common feature of most ADAMTS proteases [41]. C-terminal cleavage of ADAMTS could also have crucial impacts on their bio-disponibility, substrate recognition and activity.

6. ADAMs and ADAMTS Substrates

ADAMs and ADAMTS have multiple substrates in different tissues and organs (Table 1, 2). Similar to MMPs and SVMs, which have a metalloprotease in their crystal structure, ADAMs were initially presumed to cleave ECM components and substrates. ADAM family of enzymes was then recognized to be active proteases. The C-shape arm in ADAMs,

comprising the metalloproteinase M-domain, disintegrin D-domain, and the cysteine-rich C-domain with the highly variable region (HVR), is crucial for ADAM function and substrate recognition, proteolytic processing and degradation. HVR regulates cell-cell and cell-matrix interactions in proteolytically inactive ADAMs, and guide ADAMs to recognize specific substrates and mediators. After recognition by HVR, the metalloproteinase M-domain can conduct its cleavage function as a sheddase or proteolytic enzyme (Fig. 4).

'Sheddases' refers to the enzymes which regulate 'Ectodomain shedding'. Shedding is a proteolytic cleavage process of the extracellular domain of membrane-bound molecules. The shedding could have one of two aspects: 1) converting the extracellular domain into a soluble protein or cytokine that enters into the circulation to perform its whole-body effect; 2) inhibiting or suppressing the activation of a specific receptor and thus down-regulating its signal pathway and function. In addition to their extracellular sheddases activity, ADAMs also possess the ability to regulate intracellular functions and various signaling pathways (Table 1).

There are three models of ADAM-mediated ectodomain shedding. Model I and II involve an extracellular recognition process, whereas Model III is an inter-cellular process (Fig. 4). In Model I, the highly variable region (HVR) of ADAM directly recognizes specific region of membrane-anchored substrate and the M-domain accounts for proteolytic activity. In Model II, the substrate recognition requires a specific factor to combine with the substrate so that HVR can recognize and interact with the substrate. Model III is an inter-cellular interaction model, where with the help of a specific factor, ADAM on one cell surface can shed the cytokine from receptor on another cell surface.

In comparison with ADAMS, ADAMTS are secreted proteases that are primarily associated with proteolytic events in ECM. Most ADAMTS substrates are ECM components (Table 2) [43, 44].

7. ADAMs and ADAMTS Inhibitors

Basically, there are two ways to inhibit ADAMs activity, one way is turn off the cysteine switch, and the other way is to generate more pro-domains to inactivate the active ADAMs. Similar to MMPs, ADAMs activity is suppressed by tissue inhibitor of metalloproteinases (TIMPs) in normal physiological conditions. TIMPs are endogenous four-member family that block the functions of MMPs [2]. While TIMPs have a wide-range inhibitory effect on most of the MMP family, its inhibitory effect on ADAMs is more specific. For instance, TIMP-1 and TIMP-3 can suppress the catalytic activity of ADAM-10 in *in vitro* conditions, while ADAM-8, 9 and 19 are not inhibited by any TIMP [45, 46]. TIMP-3 inhibits ADAM-17 activity by forming chemical bonds with ADAM-17 dimer on the cell membrane [46]. ADAM-33, which is closely related to the reproduction system, can be inhibited by TIMP-3 and TIMP-4, but is not affected by TIMP-1 [47].

Although TIMPs could inhibit both MMPs and ADAMs, the underlying mechanisms are different for the two families of metalloproteinases. The N-terminal domain of TIMPs is the main domain that account for inhibiting MMPs activity, while the N-terminus of TIMP-1 or

TIMP-3 almost has no effect on ADAM-10. Also, the N-terminus of TIMP-2 possesses a potent effect on MMPs, but does not exhibit measurable effects on ADAM-17 activity. Additionally, while TIMP-3 has a solid inhibitory effect on the isolated catalytic domain of ADAM-17, when the other domains are added or some parts of the domains such as cysteine-rich domain are modified, the TIMP-3 inhibitory effect is markedly decreased [18]. Of note, the 'cysteine-switch' is another potent ADAMs inhibitory mechanism, whereby the cysteine residues in the pro-domain of some ADAMs have a selective inhibitory effect on themselves, as has been shown for ADAM-10 and ADAM-17 [48, 49].

In addition to endogenous inhibitors, several synthetic small molecule ADAM inhibitors have been developed (Table 3). Most synthetic inhibitors target the catalytic Zn^{2+}, and therefore are not very specific and often have a broad inhibitory spectrum towards both ADAMs and MMPs. Small molecule drugs such as Zn^{2+} chelators 1,10-phenanthroline and hydroxamate exhibit a potent inhibitory effect on ADAMs activity [50]. Other small molecule synthetic inhibitors have shown relative specificity to ADAMs. For instance, small molecule inhibitor INCB3619 have a potent inhibitory effect on ADAM-10 and ADAM-17, with less potent effect on ADAM-8, 9, and 33 [51]. TAPI-1, TAPI-2, GI254023 and Batimastat (BB-94) are also potent inhibitors of ADAM-17 (TACE), and therefore block the shedding of cytokine receptors effectively, but could also affect MMPs. ,Other inhibitors such as CGS27023, GW280264, and GI254023 exhibit specific inhibitory effect on ADAM-9, 10 and 17 [52]. Recent evidence also suggests that glycosylation of a substrate such as TNFα, upregulated ADAM-8 and 17 activities, but inhibited ADAM-10 activity [53]. Based on this mechanism, more novel drugs which target ADAM-17 can be developed, and could be useful in cardiovascular diseases and cancer treatment.

Similar to ADAMs, ADAMTS also show restricted susceptibility to endogenous and synthetic inhibitors [54]. As for other proteinases, α2-macroglobulin can physically entraps ADAMTS-2 after cleavage within its bait region [41]. TIMP-3 is an effective inhibitor of ADAMTS-2 and ADAMTS-4 [55, 56]. The function of ADAMTS-1 can be suppressed by TIMP-2 and 3, but is not affected by TIMP-1 and 4 [57]. While TIMP-3 can effectively inhibit ADAMTS-4 and 5, aggrecan may promote this inhibitory effect by reacting with TSR and spacer regions of ADAMTS-4 [58]. Also, heparan sulfate glycosaminoglycans (GAGs) enhance TIMP-3 activity and therefore modulate its inhibitory effect on ADAMTS [59]. Papilin inhibits ADAMTS-2 by binding both the enzyme and its substrate [60]. Other selective small molecule inhibitors such as cis-1(S)2(R)-amino-2-indanol-based compounds are effective inhibitors of ADAMTS-4 and 5. Calcium pentosan polysulfate or granulin-epithelin precursor can block substrate interactions by binding to the ancillary domains of ADAMTS-7 and 12 [61].

8. ADAMs Functions

ADAMs have multiple functions and roles under physiological condition. There are 22 ADAMs in human [62], 14 of these ADAMs including ADAM-1, 2, 3, 6, 7, 18, 20, 21, 22, 28, 29, 30, 32 and 33 are restricted to embryo development, and are mainly expressed and conduct their function in the reproductive system such as testis, epididymis and uterus. Other ADAMs including ADAM-8, 9, 10, 11, 12, 15, 17 and 19 have a broader expression

and distribution in human tissues, and wide connection to different pathological conditions. These ADAMs also interact with substrates in the cardiovascular system and regulate cardiovascular physiological condition and may be involved in the pathogenesis of cardiovascular disease, and therefore will be discussed in more details.

ADAM-8 is related to multiple pathological conditions and plays a wide role in rheumatoid arthritis, asthma and inflammation. ADAM-8 also regulates the ovulation process, osteoclast differentiation, neutrophil rolling, and trans-endothelial extravasation. ADAM-8 is expressed in human breast cancer, hematopoietic cells, and human neutrophils, where it is usually stored in granules and transported to the cell surface when it is stimulated. ADAM-8 can also mediate L-selectin, which acts as a “homing receptor” for lymphocytes, and its shedding by ADAM-8 plays an important role in regulation of neutrophil rolling and trans-endothelial extravasation. To further investigate the role of ADAM-8, an inactive mutant of ADAM-8 mouse was developed and showed suppressed reaction to autoimmune arthritis. Although ADAM-$8^{-/-}$ mice develop and grow normally without a disease phenotype [63], ADAM-8 could contribute to cardiac inflammation as its levels are increased in the peri-infarct myocardium following myocardial infarction, which is often associated with infiltration of inflammatory cells [64].

ADAM-9 has a broad expression and is catalytically active. It is involved in heparin-binding EGF-like growth factor (HB-EGF) ectodomain shedding, and may protect against the development of Alzheimer’s disease by reducing the processing of Amyloid Precursor Protein (APP). ADAM-9 was initially found to regulate the fusion of muscle cells development and to have a regulatory role in myogenesis and formation of myotubes and myocardium development. However, when ADAM-$9^{-/-}$ mice were later developed, no major defects in muscle formation, HBA-EGF shedding function or APP α-secretase products formation were observed (73), suggesting that the function of ADAM-9 can be compensated by other ADAMs under physiological conditions.

ADAM-10 is mainly involved in embryonic development, ECM degradation, ectodomain shedding of cell surface proteins, and signal regulation in distant cells. ADAM-10 is one of the hub regulatory factors during the Notch and Eph/ephrin pathways processing. By inducing Notch cleavage and controlling subsequent “regulated intramembrane proteolysis” (RIP), ADAMs regulate the generation of cleaved intracellular domains which conduct its function by transferring to the nucleus and regulating gene transcription and mRNA expression. ADAM-10 regulation of Notch signaling is an important step in the cardiovascular system embryonic development [65, 66]. Both ADAM-10 and Notch signaling are of great importance for cardiovascular development [67, 68]. Because of the crucial role of ADAM-10 in various physiological process including RIP, Notch/Delta signaling and APP processing, ADAM-10 knock-out mice do not survive during early embryonic development. ADAM-$10^{-/-}$ mice usually show multiple defects in the central nervous system, cardiovascular system and somites, which closely resemble those seen in mice deficient in Notch/Delta signaling [65]. ADAM-10 mice die of severe cardiovascular defects after embryonic day 10, which is very similar to Notch1 deficient mice [66].

ADAM-11 is mainly distributed in the nervous system especially in the hippocampus and cerebellum, with little expression in other tissues such as the heart, kidney, eyes and brown fat. ADAM-11 may serve as an adhesion component for synapses formation in the heart, kidney and eyes. ADAM-$11^{-/-}$ mice have a normal development phenotype, but suffer from learning deficiency [69].

ADAM-12 was initially thought to mainly take part in myogenesis during embryonic development [70]. ADAM-12 has two splice-variants, ADAM-12L and ADAM-12S, both have proteolytic activity and affect distant cell physiological targets by controlling the shedding of various membrane-bound ectodomain substrates from the cell surface. ADAM-12L can mediate cardiomyocyte hypertrophy by controlling the shedding of HB-EGF [71, 72], and Notch signal pathway [73], and thereby regulates the disease progression [73, 74]. ADAM-$12^{-/-}$ mice usually develop as adults without specific signs or functional deficiencies, although some reports found 30% mortality in ADAM-$12^{-/-}$ pups within the first week [75], and therefore there is no agreement regarding the physiological necessity of ADAM-12.

ADAM-15 cleaves E-cadherin, thus compromising epithelial and endothelial connections and reducing cell connections and tissue stability, and in turn inducing migration and infiltration of inflammatory cells in the cardiovascular system [76, 77]. By activation of Src kinase, phosphorylation of ERK1/2 and cleaving E-cadherin, ADAM-15 decreases the stability of endothelial cells thus promoting endothelial cell permeability, neutrophil trans-endothelial migration and inflammatory cell infiltration [78]. By inducing inflammation, ADAM-15 could contribute to cardiovascular diseases such as atherosclerotic lesions, myocarditis and myocardial infarction. ADAM-15 is also related to vessel formation, and has been shown to induce the expression of vascular endothelial growth factor (VEGF), VEGFR1 and VEGFR2, which are closely related to angiogenesis [79]. ADAM-15 could also participate in cancer metastasis by increasing the migration and invasiveness of tumor cells [80]. ADAM-$15^{-/-}$ mice have been developed, and while no overt phenotype is found, tumor cell migration and invasion are reduced in these mice [81].

ADAM-17 was first and simultaneously described by two research groups in 1994 as the enzyme that releases membrane-bound TNFα precursor to a soluble form. Because of this sheddase function of membrane-bound TNFα, ADAM-17 was first termed TNFα converting enzyme (TACE) [82–84], but was later classified as a member of ADAM family. ADAM-17 has very similar sequence and crystal structure to ADAM-10, suggesting similarity in function. ADAM-17 has wide functions during embryonic development including fertilization, neurogenesis, and angiogenesis. Because of its wide involvement in development, ADAM-$17^{-/-}$ embryos die perinatally [85], supporting its essential role in embryonic development [86]. ADAM-17 plays a regulatory role on TNFα processing and function. TNFα is over-expressed and its plasma levels are elevated in cardiovascular disease. Experimental studies in animal models have suggested that inhibiting the TNFα pathway could have therapeutic benefits in cardiovascular disease [87, 88]; however, anti-TNFα treatment did not show much improvement in patients with late-stage heart failure [89, 90]. In contrast with the perinatal death in ADAM-17 deficient mice, TNFα-deficient mice develop normally and are viable and fertile, indicating that ADAM-17 has other

important functions and is not limited to TNFα processing [86]. Of note, TNFα processing is not completely inhibited by the lack of ADAM-17 in ADAM-17 knockout cells, and other proteins including ADAM-9 and 10 [91, 92], and MT4-MMP (MMP17) [93] may also be involved in the shedding of TNFα. Interestingly, ADAM-17 could have a dual role in modulating TNFα. On one hand, ADAM-17 helps release soluble TNFα into the circulation to activate its receptor. On the other hand, ADAM-17 can also cleave TNFα receptors, especially TNFα-RI (p55) and TNFα-RII (p57), and the shedding of the TNFα receptors could reduce the sensitivity to TNFα and ultimately lead to a negative effect even if large amount of the TNFα ligand is released into the circulation [32, 94]. Some studies suggest that ADAM-17 mediated cleavage of TNFα receptor accounts for the primary effect [95, 96]. ADAM-17 also regulates the shedding of other ectodomain membrane-anchored proteins including the adhesion molecules selectins, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), the cytokines interleukin-1 receptor-2 (IL1-R2) and IL6-R, and the growth factors TGFα, HB-EGF, VEGF, neuregulins and VEGFR2 [18, 97]. Activation of EGFR, through the shedding of membrane-anchored pro-TGFα [85] and pro-HB-EGF [98], is among the critical functions of ADAM-17 [99–101], when compared to other candidate HB-EGF sheddases such as ADAM-9, 12 and 15 [18, 102]. ADAM-17 knock-out mice embryos' heart valves are aberrant, thickened and mis-shaped, similar to the mice lacking HB-EGF, demonstrating wide pathogenic role of ADAM-17 [99–101, 103]. Thus, ADAM-17 could regulate various physiological functions including inflammation, growth, angiogenesis and neural function through regulation of multiple substrates, and could play a role in cardiovascular physiological and pathological changes.

ADAM-19 is mainly distributed in the peripheral nervous system, skeletal muscle and the heart [70, 104]. ADAM-19 is responsible for endocardial cushion development and controls the epithelial-to-mesenchymal transformation of embryonic endocardial epithelial cells which generates most of the cushion mesenchymes that constitute the main components of the cardiac septa and valves. To verify its physiological role, ADAM-19$^{-/-}$ mice have been developed and show severe deficiency in ventricular septum development and other system development failure, and ultimately die soon after birth [105].

9. ADAMTS Functions

ADAMTS are widely distributed in different tissues and organs, and could play crucial embryologic or physiological roles in humans. The important role of ADAMTS in mammalian physiology has been supported by strong phenotypes compromising morphogenesis, mobility or reproduction in several ADAMTS gene knockout mice. Mutations in ADAMTS-2, 3, 10, 13, 17 and 20 have been associated with Mendelian disorders or birth defects [43]. The procollagen N-proteinases ADAMTS-2, 3 and 14 play an important role in procollagen processing and collagen fibrils formation, maturation and assembly [41]. ADAMTS-2 deficient mice have been developed and phenotypically characterized. Although ADAMTS-2 heterozygous male and female mice display a normal phenotype at birth, they show progressively fragile skin by two weeks of age, and adult males display abnormal seminiferous tubules and lack of spermatozoids production and become sterile [106]. ADAMTS-3 is important for lymphangiogenesis, and ADAMTS-3

deficient mouse embryos do not survive past 15 days of gestation due to severe lymphedema resulting from lack of lymphangiogenesis [107]. ADAMTS-5 has been implicated in the pathogenesis of osteoarthritis via degradation of its substrate aggrecan, a major structural proteoglycan in cartilage [43]. Mutations in ADAMTS-10 and 17 have been associated with Weill–Marchesani syndrome, characterized by short stature, acromelic dysplasia and disproportionate distal limb shortening [43, 108, 109]. ADAMTS-13 cleaves ultra-large vWF multimers, which are prothrombogenic and favor platelet adhesion, into an optimal size required for normal hemostasis [110]. Therefore, ADAMTS-13 may function as a hemostatic agent [111]. Genetic association studies have linked ADAMTS-14 to the predisposition to multiple sclerosis and knee osteoarthritis in women by unclear mechanisms [41, 112–114]. ADAMTS-20 variant has been associated with cleft lip and palate [115].

10. Role of ADAMs and ADAMTS in Vascular Biology

ADAM and ADAMTS family members play an important role in numerous vascular biological functions including VSM cell proliferation and migration, angiogenesis, vascular cell apoptosis and survival, and tissue repair and wound healing (Fig. 5).

ADAM-12 and 33 are crucial factors in airway smooth muscle and VSM proliferation, and are therefore closely related to bronchial asthma [116] and carotid artery lesions [117]. ADAM-17 is strongly associated with hypertrophy and hyperplasia of VSM cells [118]. ADAMTS-7 promotes VSM proliferation both *in vivo* and *in vitro* [119].

ADAMTS-1 appears to promote VSM proliferation and migration, as MiR-365b-3p and miR-362–3p inhibit VSM proliferation and migration and attenuates atherosclerosis by targeting ADAMTS-1 [120, 121]. ADAMTS-7 mediates VSM cell migration and neointima formation in balloon-injured rat arteries [122]. Also, ADAMTS-7 knock-out mice show reduced risk of atherosclerosis likely due to loss of the effect of ADAMTS-7 on VSM migration [123]. ADAMTS-7 accumulates in VSMCs in coronary and carotid atherosclerotic plaques, and genome-wide association studies have suggested an association between variation at ADAMTS-7 locus and susceptibility to coronary artery disease. In a population-based study cohort, an inverse association was observed between atherosclerosis prevalence and rs3825807, a nonsynonymous single nucleotide polymorphism SNP (A to G) leading to a Ser-to-Pro substitution in ADAMTS-7 pro-domain. Additional mechanistic studies of this rs3825807 variant associated with protection from atherosclerosis and coronary artery disease showed reduced ADAMTS-7 maturation and pro-domain cleavage and function, a decrease in the substrate thrombospondin-5 cleavage, and reduced VSMC migration [124].

During angiogenesis, ADAMs are activated by VEGF, and in turn induce Notch ectodomain shedding. Although ADAM-10 and ADAM-17 have been implicated in Notch-signaling, they appear to have different roles in angiogenesis. In mouse retinas, ADAM-10 inhibition induced vascular sprouting, whereas inhibition of both ADAM-10 and ADAM-17 produced the opposite phenotype. Besides Notch, ADAM-17 appeared to regulate other cytokines and signaling pathways during angiogenesis, and these pathways were not affected by ADAM-10. ADAM-17 inhibition induced the expression of a naturally occurring inhibitor of

angiogenesis thrombospondin 1 (TSP1), whereas ADAM-10 inhibition did not [125]. These observations have suggested that ADAM-10 and ADAM-17 have opposite effects on sprouting angiogenesis that may be unrelated to Notch signaling and may involve differentially expressed anti-angiogenic proteins such as TSP1 [125]. ADAMTS-1 has been associated with angiogenesis in gastric cancer [126] and metastasis [127], and lung cancer [128]. ADAMTS-3 could cleave and activate the substrate pro-VEGF-C into active VEGF-C and in turn play a role in embryonic lymphangiogenesis and the regulation of placental angiogenesis [107]. ADAMTS-3 also participates in triggering VEGFR-3 signaling, a cornerstone for the differentiation and function of lymphatic endothelial cells [129], and loss of ADAMTS-3 activity has been associated with Hennekam lymphangiectasia-lymphedema syndrome [130]. On the other hand, recombinant ADAMTS-2 reduces proliferation of endothelial cells, decreases branching of capillary-like structures formed by endothelial cells, and inhibits vessels formation in embryoid bodies [131]. These ADAMTS-2 antiangiogenic properties may not require catalytically active enzyme, and may involve interaction of one of its C-terminal domains with nucleolin, a nuclear protein and potential receptor [41, 131]. Similarly, ADAMTS-12 shows antiangiogenic effects independent of its enzymatic activity as a mutated inactive form of the enzyme is similarly efficient in inhibiting endothelial cell sprouting in the aortic ring assay when compared to the control wild-type form, and these ADAMTS-12 antiangiogenic properties could protect the host from tumor progression [132]. ADAMTS-15 also inhibits angiogenesis and liver cancer metastasis by modulating cell-ECM interactions [133].

ADAM-10, 15 and 17 are involved in vascular cell apoptosis. ADAM-10 regulates the cleavage of N-cadherin to increase apoptosis in human atherosclerotic lesions and promote the risk of vulnerable plaque [134]. Recombinant human ADAM-15 induces vascular apoptosis and inhibits tumor formation and angiogenesis [135]. ADAM-17 can induce vascular apoptosis and mediate the invasion and migration of liver cancer stem cells, and suppression of ADAM17 could be a promising target to enhance cancer therapy [136, 137]. Also, deletion of Cdc42 increases the activity of ADAM-17 and enhances VEGFR-2 shedding and reduces vascular endothelial cell survival and angiogenesis, and inhibition of ADAM-17 can partially reverse Cdc42 deletion-induced EC apoptosis [137]. Also, ADAMTS-4 induces VSMC apoptosis, degrades versican, and promotes inflammatory cell infiltration of blood vessels [138]. Conversely, some studies suggest that ADAM-10 may be associated with vascular cell survival as ionizing radiation reduces ADAM-10 expression and induces neurovascular cell senescence and death [139].

ADAM and ADAMTS show different expression in wound healing tissues and normal tissues, suggesting that they play a role in tissue repair and wound healing processes. ADAM-9, 10, 15 and 17 are highly expressed in wound healing tissues [140]. ADAMTS-3, also shows differential expression in wound healing tissues [140].

11. Role of ADAMs and ADAMTS in Cardiovascular Pathology

ADAMs and ADAMTS have been associated with pathological changes associated with cardiovascular diseases such as atherosclerosis, hypertension, aneurysm, coronary artery disease, myocardial infarction and heart failure (Fig. 6).

Atherosclerosis is a chronic inflammatory disease characterized by aberrant accumulation of lipids and inflammatory cytokines in blood vessels, and ADAM-10, 15, 17 could promote the atherosclerotic process through inflammatory cell recruitment and differentiation. ADAM-10, 15, 17 control macrophage phenotype and function by cleaving TNFα and TNFα-Rs. ADAM-17 also decomposes the scavenger receptor CD163 and in turn modulates macrophage polarization and M2 macrophage activity. ADAM-10 and 17 are also involved in the shedding of VEGF-R2 and Tie-2. Also, angiogenesis plays a role in atherosclerotic lesion growth and plaque stability, and ADAM-10, 17 could regulate the atherosclerotic process through modulating neovessel formation [141].

ADAMs and ADAMTS are also associated with hypertension. Loss and mutation of ADAM-17 suppress angiotensin II-induced hypertension and end-organ damage [118]. On the other hand, ADAMTS-18 knock-out mice show visceral adiposity and metabolic syndrome with increased risk of diabetes, cardiovascular disease and hypertension [142].

ADAM-10, ADAM-17, and ADAMTS-1, 4, 5, 7 and 16 have been associated with aortic aneurysm formation. Clinical studies have suggested that ADAM-10 and ADAM-17 positive microvesicles are linked to increased risk of abdominal aortic aneurysm in smokers [143]. ADAM-17 has also been linked to the formation of abdominal aortic aneurysm induced by angiotensin II [144]. ADAMTS-1, 5, and 16 are increased in patients with acute aortic dissection and thoracic aortic aneurysm [145, 146]. ADAMTS-4 has been linked to sporadic aortic aneurysm and dissection in mice. ADAMTS-4 has been shown to decompose and degrade poly ADP-ribose polymerase-1, which is a key factor in DNA repair and cell survival, leading to smooth muscle cell apoptosis, vascular damage and aortic aneurysm and dissection. In support, ADAMTS-4 knock out mice show reduced challenge-induced aortic diameter enlargement, aneurysm and dissection formation, and risk of artery rupture [147]. Upregulation of ADAMTS-7 and downregulation of cartilage oligomeric matrix protein (COMP) could also be important factors underlying the pathogenesis and formation of aortic aneurysm [148].

Genetic ADAMTS-2 variant rs11750568 has been associated with cerebral aneurysm and pediatric stroke [149, 150]. Also, genetic ADAMTS-13 variants rs2301612 and rs2285489: have been associated with the risk of cerebral aneurysm, While ADAMTS-12 variant rs1364044: and ADAMTS-13 variants rs739469 and rs4962153 have been associated with a protective effect in cerebral aneurysm pathogenesis [149].

ADAMs and ADAMTS may play a role in coronary artery diseases, ADAM-17 related substrates have been linked to the recursion of cardiovascular events in patients suffering from atherosclerosis [151]. ADAM-17 may also regulate angiogenesis and myocardial cell repair post-myocardial infarction in patients with coronary artery disease [141, 152]. ADAMTS-4 is increased in the serum of patients who suffer from coronary artery disease and acute coronary syndromes [153], and statin therapy reduces the serum levels of ADAMTS-4 and ameliorates the symptom of coronary artery disease [154]. ADAMTS-7 promotes atherosclerosis and has been associated with coronary artery disease [43]. Plasma ADAMTS-7 is elevated in patients with coronary artery disease [155]. Genome-wide association studies (GWAS) and single nucleotide polymorphism (SNP) maps have led to a

Ser^{214}Pro substitution in the ADAMTS-7 propeptide that could be associated with coronary artery disease [156]. The Pro variant likely impairs ADAMTS-7 propeptide excision by furin, which is required for its proteolytic activity. Therefore, the Pro variant may have lower activity and individuals with the Pro/Pro ADAMTS-7 protein could have reduced protease activity compared to those with Ser/Ser variants [124]. ADAMTS-7 may also inhibit re-endothelialization and promote neointima formation in wire-injured carotid arteries of mice, as ADAMTS-7 deficiency in ADAMTS-7$^{-/-}$ mice promoted vascular re-endothelialization and ameliorated neointima formation post-injury. ADAMTS-7 may be a potential treatment target for post-injury vascular intimal hyperplasia [157].

ADAMs and ADAMTS could play a role in myocardial infarction. In a rat model of myocardial infarction induced by ligation of the left anterior coronary artery, the expression of ADAM-8 was increased in myocardial infarction rats compared with controls. Immunohistochemistry in the myocardial infarction grafts revealed that ADAM-8 was localized to the vicinity of the area of the developing infarction as well as in intramyocardial arteries remote to the infarction area, suggesting global myocardial impact of myocardial infarction [64]. On the other hand, ADAM-17, through regulating angiogenesis may play a role in post-myocardial infarction repair. Cardiomyocyte-specific ADAM-17 knockdown mice are more vulnerable to myocardial infarction following ligation of the left anterior descending coronary artery [152]. ADAM-17 knockdown mice have unfavorable survival, higher rates of cardiac rupture, more severe ventricular dilation and decreased ejection fraction compared with control wild-type group. ADAM-17 knockdown mice also have suppressed VEGFR2 expression likely through modulation of nuclear factor-κB activation and DNA binding [152]. ADAMTS-1 usually have a medium expression in normal tissues, but is markedly increased in pathological conditions associated with inflammation and hypoxia [158]. ADAMTS-2 and 3 are more abundant in the culprit plaques from patients presenting with acute myocardial infarction versus stable angina, and they colocalize with CD31 and CD68 suggesting their expression by endothelial cells and macrophages [159]. Plasma ADAMTS-7 levels have also been associated with ventricular remodeling in patients with acute myocardial infarction [160]. Other studies have shown that ADAMTS-13 markedly decreases in patients with ST-elevation myocardial infarction (STEMI) and intramyocardial hemorrhage, and that intracoronary administration of recombinant ADAMTS-13 does not decrease infarct size or intramyocardial hemorrhage in a porcine model of myocardial ischemia-reperfusion [161]. Myocardial infarction may also affect some ADAM members, it can induce increased remote ADAM-8 expression of rat hearts after cardiac arrest in a very early period [64].

ADAMs and ADAMTS could be involved in heart failure. Excessive expression of ADAM-10, 12, 15 and 17 cause cardiac hypertrophy and dilated cardiomyopathy, whereas the aberrant expression of ADAM-10 and 15 induce atrial fibrillation [14, 162]. ADAM-12 is differentially expressed in the heart during cardiac hypertrophy. In a mouse model of heart failure induced by aorta-to-vena cava arteriovenous shunt, the cardiac levels of ADAM-12 and tissue fibrosis were increased [163]. Other data suggest that hydrogen sulfide (H_2S) donors could ameliorate heart failure by decreasing ADAM-12 [163–165]. ADAMTS-2 has been implicated in the pathogenesis of cardiac hypertrophy and cardiomyopathy [166]. ADAMTS-2 participates in the cleavage of the N-propeptide from types I, II, III, and V

procollagens, thus allowing the formation and assembly of collagen fibrils. ADAMTS-2 knockout mice exhibit severe cardiac hypertrophy and heart failure likely because in the absence of ADAMTS-2 collagen fibrils are abnormal and do not provide the required mechanical strength to counterbalance the pressure overload, and overexpression of ADAMTS-2 in mice reverses this damaging phenotype [167].

12. Perspective

ADAMs are metalloproteases related to MMPs with characteristic disintegrin and transmembrane domains. ADAMTS members lack the transmembrane domain and instead have thrombospondin motifs. ADAMs play a role in the shedding of various membrane-bound proteins, and can regulate multiple cellular functions and physiological conditions by regulating various cytokines and their receptions. ADAMs are widely related to different disease processes, especially cardiovascular diseases. ADAM-10, and 17 are promising biomarkers and therapeutic targets in cardiovascular diseases. Like ADAMs, ADAMTS have important functions and roles in cardiovascular biology and disease. TIMPs are endogenous inhibitors of ADAMs and ADAMTS. Synthetic ADAM and ADAMTS inhibitors have been developed with varying specificity and selectivity. Further research into the potential substrates and function of ADAMs and ADAMTS should help develop specific modulators with potential usefulness in the management of cardiovascular disease.

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List of Abbreviations:

aa	amino acid
ADAM	A Disintegrin and Metalloproteinase
ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motifs
APP	amyloid precursor protein
C-domain	cysteine-rich domain
COMP	cartilage oligomeric matrix protein
CUB	C1r/C1s Uegf Bmp1
D-domain	disintegrin domain
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR	EGF Receptor
GPCR	G-protein coupled receptor

HB-EGF	heparin-binding EGF-like growth factor
HVR	highly variable region
M-domain	metalloproteinase domain
MDC	metalloproteinase/disintegrin/cysteine-rich
MMP	matrix metalloproteinase
MT-MMP	membrane-type MMP
PLAC	protease and lacunin
RGD	Arg-Gly-Asp
RIP	regulated intramembrane proteolysis
SVM	snake venom metalloproteinase
TNFα	tumor necrosis factor-α
TACE	TNFα-converting enzyme
TIMP	tissue inhibitor of metalloproteinases
TSR	thrombospondin repeat
VAP1	vascular adhesion protein-1
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor
VSM	vascular smooth muscle
VSMC	VSM cell
VWF	von Willebrand factor

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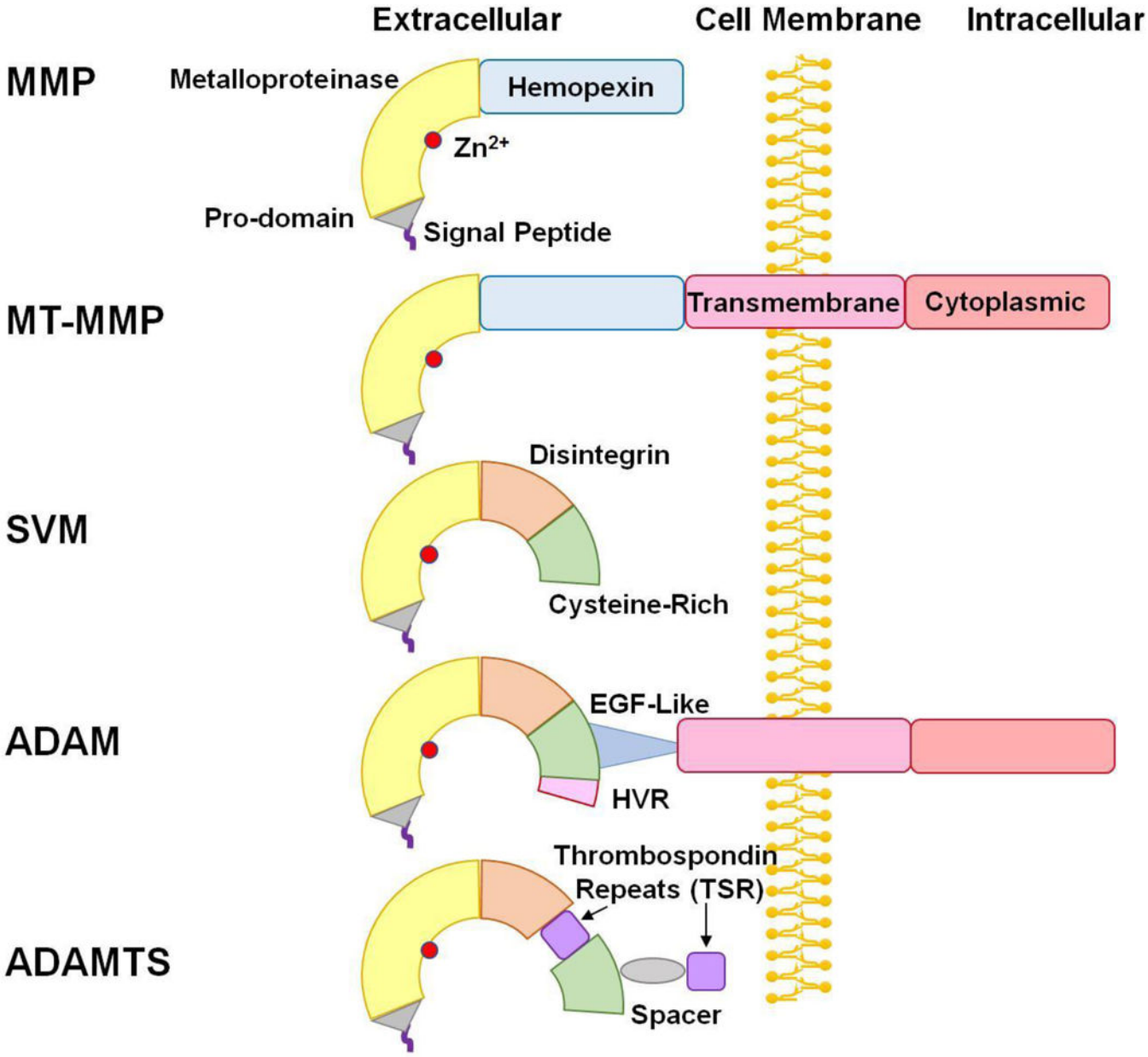

Fig. 1.

Structure of ADAM and ADAMTS. In addition to the signal peptide, pro-domain, and metalloproteinase domain in matrix metalloproteinases (MMP) and membrane-type MMPs (MT-MMP), snake venom metalloproteinases (SVM) have a disintegrin and cysteine-rich domain. Compared with SVM, ADAMs have a highly variable region (HVR) in the cysteine-rich domain, and an additional epidermal growth factor (EGF)-like region, transmembrane domain and cytoplasmic tail. ADAMTS members are similar to ADAMs, but lack the EGF-like region, transmembrane domain and cytoplasmic tail, and instead have thrombospondin repeats (TSR) and spacer.

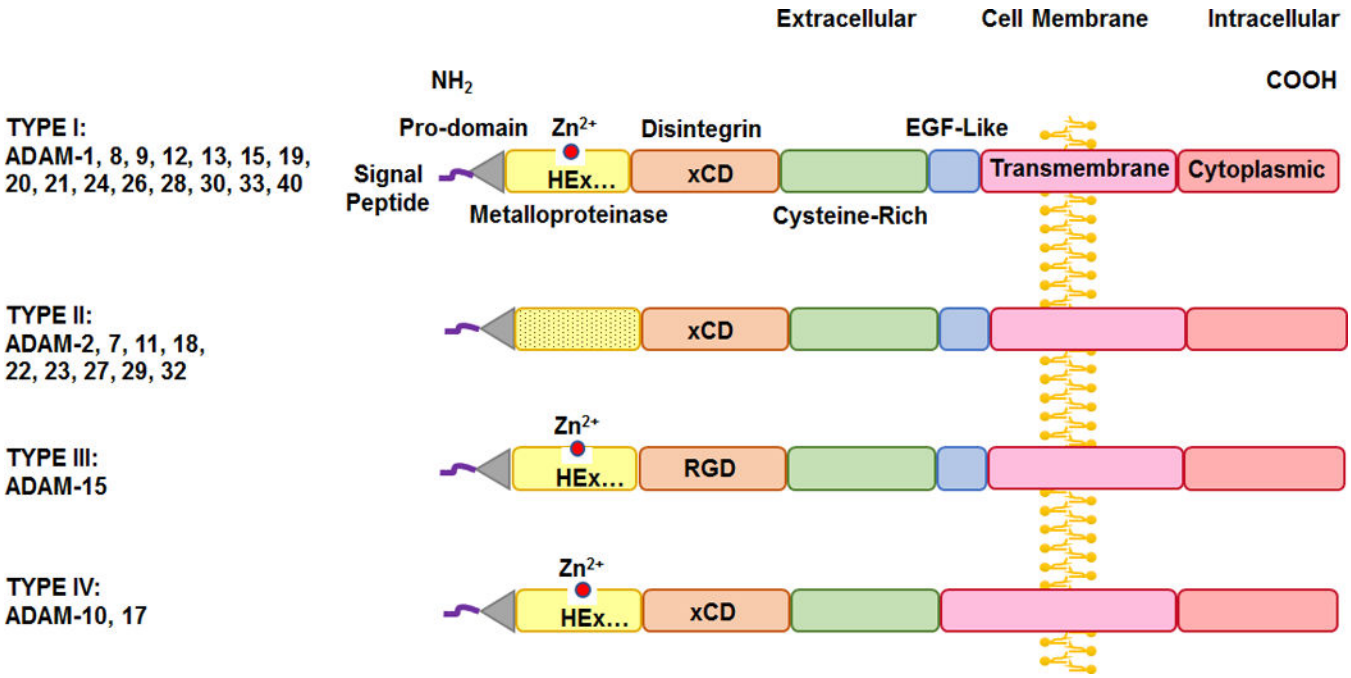

Fig. 2.

Sequence difference among different types of the ADAM family. ADAM members have four types. In Type I ADAMs the metalloprotease M-domain has the characteristic catalytic Zn^{2+} binding signature (HExGHxxGxxHD), and the disintegrin D-domain is based on xCD sequence. In Type II ADAMs the M-domain does not have the characteristic catalytic-Zn^{2+} binding signature and is more variable compared to Type I. In Type III ADAMs the M-domain contains the characteristic catalytic-Zn^{2+} binding signature, but similar to SVM, the D-domain is based on RGD sequence rather than the xCD sequence in most ADAMs. In Type IV ADAMs the D-domain is based on xCD sequence, but they lack the EGF-like region found in Type I, II, and III.

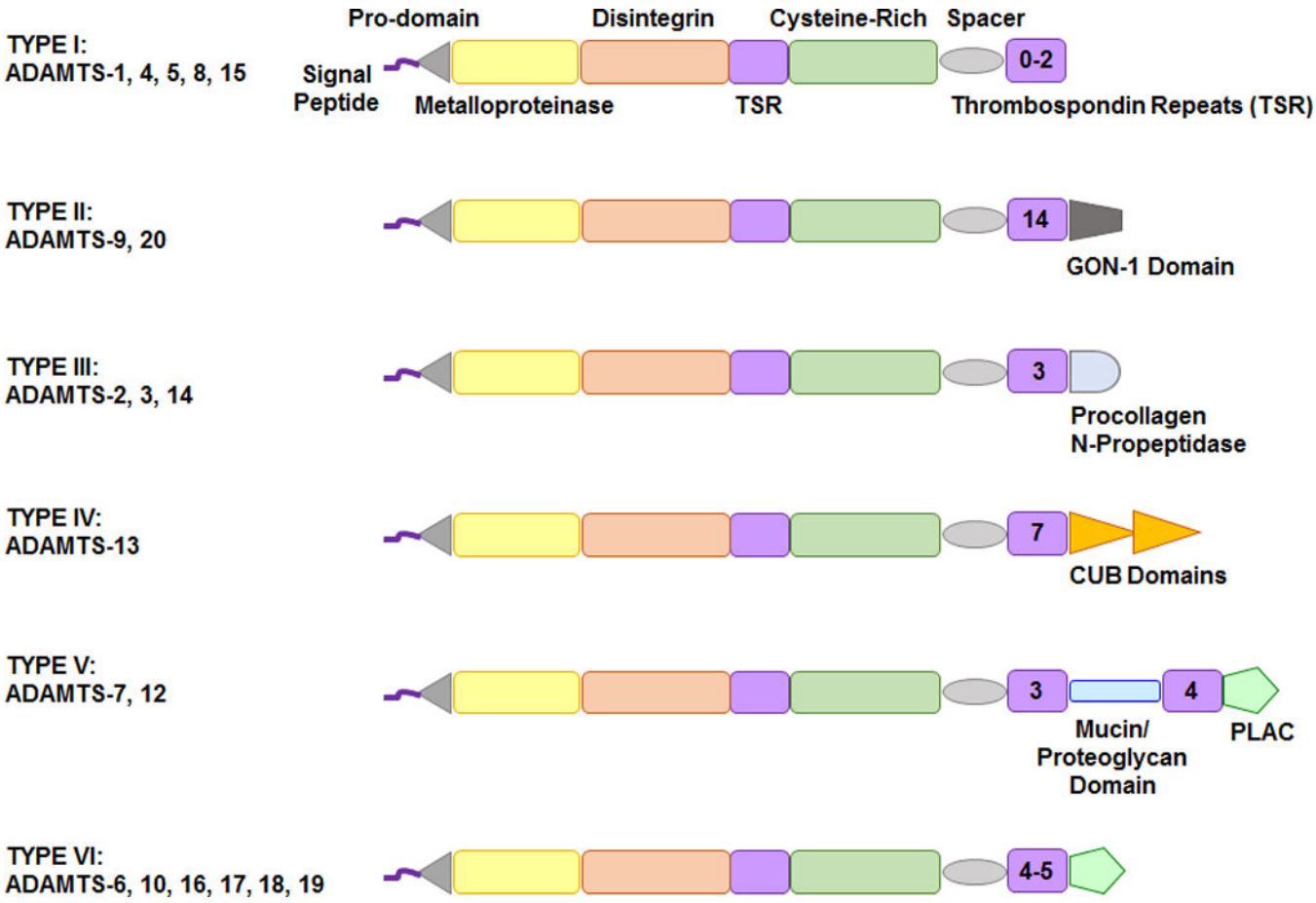

Fig. 3.

Sequence difference among different types of ADAMTS. ADAMTS members are generally classified into six types. Type I includes several members of ADAMTS and its structure comprises the basic pro-domain, metalloproteinase, disintegrin, cysteine-rich domain, thrombospondin repeats (TSR) and spacer. Type II ADAMTS has a unique GON-1 domain, type III has a procollagen N propeptidase, Type IV has a complement C1r/C1s, Uegf, Bmp1 (CUB) domain, Type V has a protease and lacunin (PLAC) structure and mucin/ proteoglycan domain, and Type VI has only PLAC domain. The number inside the final TSR indicates the number of TSR repeats.

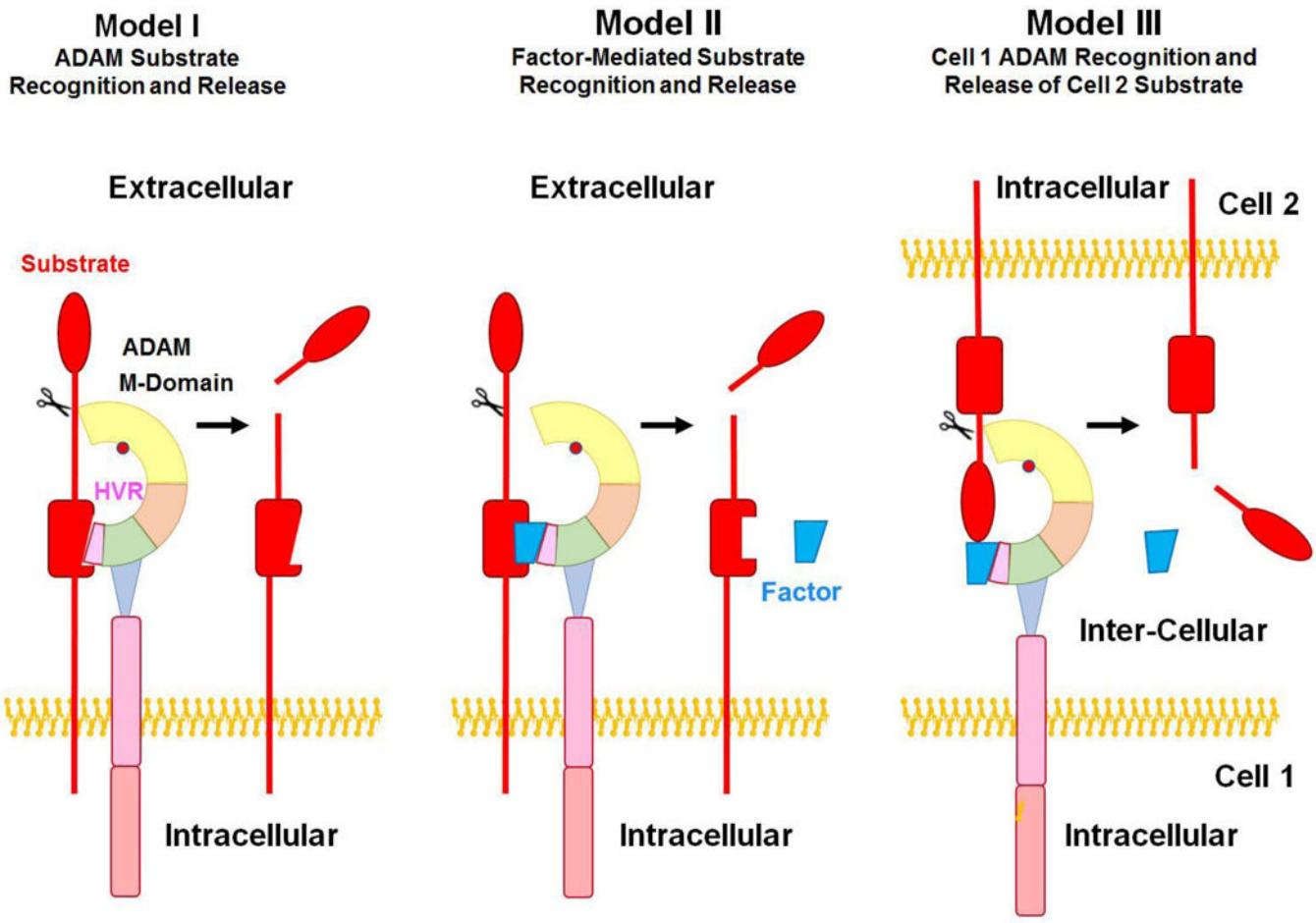

Fig. 4.

ADAM-substrate interaction. There are three models of ADAM-substrate interaction and ectodomain shedding. In Model I, the highly variable region (HVR) of the cysteine-rich domain directly recognizes specific region of membrane-anchored substrate and the metalloproteinase M-domain accounts for proteolytic activity and substrate shedding and release. In Model II, the substrate recognition requires a specific factor to combine with the substrate so that HVR can recognize and interact with the substrate. Model III is an inter-cellular interaction model, where ADAM on cell 1 surface, with the help of a factor, can shed the substrate from cell 2 surface.

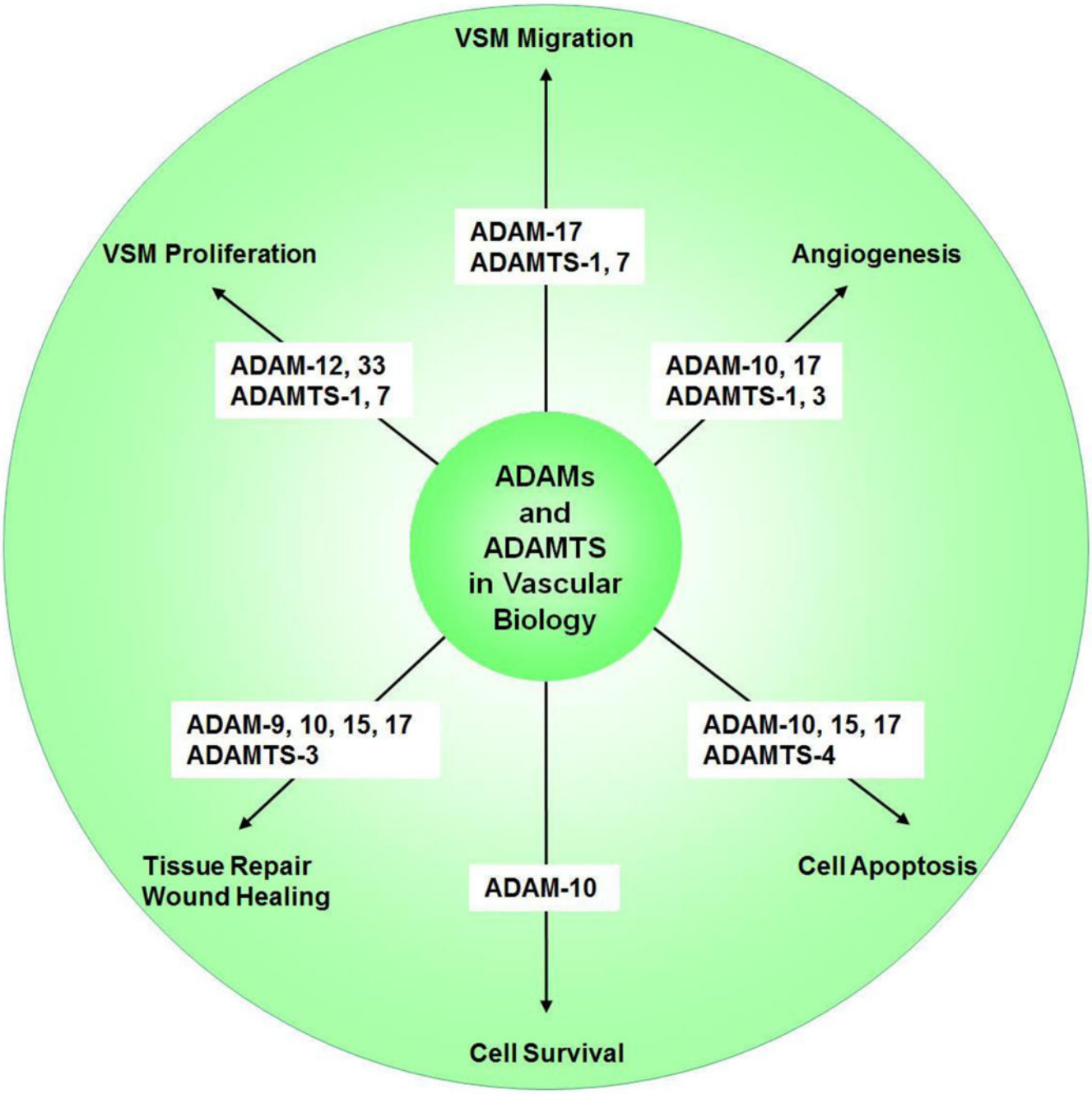

Fig. 5.
Role of ADAMs and ADAMTS in vascular biology.

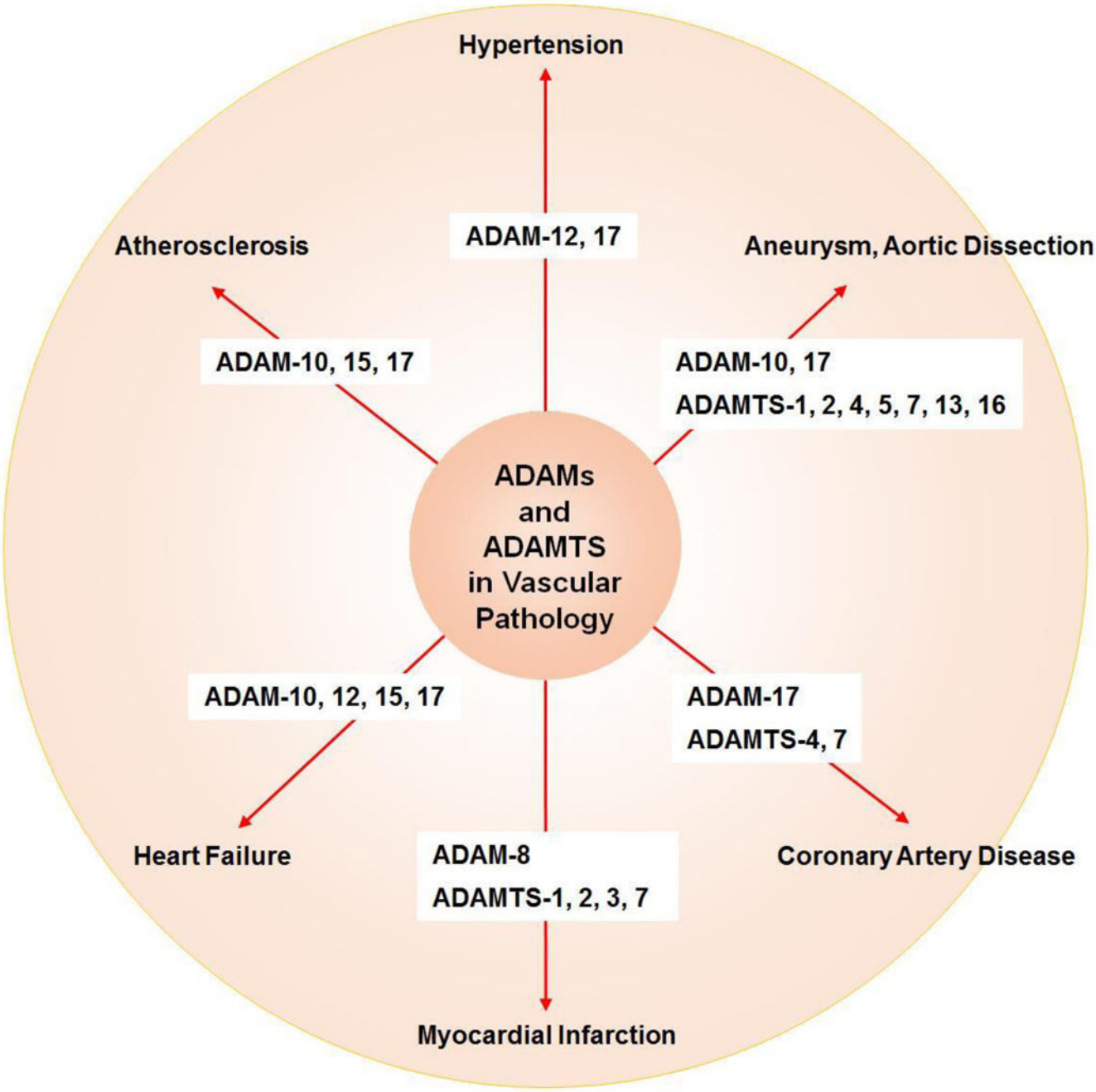

Fig. 6.
Role of ADAMs and ADAMTS in cardiovascular pathology.

Table 1.

Human ADAM Family Members, Gene Locus, Molecular Weight, Tissue Distribution, and Substrates.

ADAM	Other name	Gene Locus	MW (kDa)	Tissue Distribution	Substrate/Target	Biological or Pathological Role	Ref
1	Fertilin α, PH-30 α.	12q24.12	84	Nonfunctional pseudogene, testis	TBD	Sperm form complex, sperm-egg interaction.	[27]
2	Fertilin β, PH-30 β, Cancer/testis antigen 15	8p11.22	100	Testis, epididymis	TBD	Sperm form complex, sperm-egg interaction.	[27]
3	Cyritestin, tMDC I	8p11.22	80	Testis, epididymis	TBD	Sperm form complex	[27]
6	tMDC IV	14q32.33	60	Testis	TBD	Sperm form complex	[27]
7	EAP-1, Sperm maturation-related glycoprotein GP-83	8p21.2	84	Reproductive system, epididymis, testis	TBD	Transmembrane protein.	[27]
8	Cell surface antigen MS2, CD156a	10q26.3	90	Human neutrophils	CHL-1, PSGL-1, CD23, CD-30-ligand, ADAM8 pro-domain, APP, L-selectin, MBP	Osteoclast differentiation, rheumatoid arthritis, neutrophil rolling, trans-endothelial extravasation, neurodegeneration	[62–64]
9	MDC9, Meltrin γ Myeloma cell metalloprotease	8p11.22	91	Muscle cell, brain	Pro-HB-EGF, APP, fibronectin, gelatin, Angiotensin-I converting enzyme (ACE), laminin, insulin-B chain, collagen XVII, delta-like ligand 1, EGF, FGFR2IIIb, insulin-like growth factor binding protein-5	Myogenesis, formation of myotubes; participate in endocardial cushion development (overlap with ADAM-19)	[168]
10	Kuzbanian protein homologue, CD156c	15q21.3	84	Embryonic fibroblast, endothelial cells, cardiomyocytes	Pro-HB-EGF, pro-TNFα, Notch, ephrin-α2, APP, cellular prion precursor, gelatin, DDR-1, β-cellulin, CD23, CD30, CD44, prion protein, collagen IV and XVII, fractalkine, delta-like ligand 1, desmoglein, E-cadherin, N-cadherin, VE-cadherin, EGF, ephrin A2 and A5, ERBB2, Fas-L, IL-6R, Klotho, LAG-3, L1, MICA, Pcdh-γ	Increased in dilated cardiomyopathy, atrial fibrillation. Deficiency causes embryonic lethality	[67, 68]
11	MDC	17q21.31	83	Nervous system, brain	TBD	TBD	[69]
12	Meltrin α	10q26.2	100	Placenta	IGFBP-3 & 5, pro-HB-EGF, EGF, betacellulin, Delta-like1, p-LAP, fibronectin, gelatin, collagen IV	VSMC proliferation, hypertrophic cardiomyopathy. Inhibition prevents cardiac hypertrophy, Down syndrome	[73, 74, 169]
15	Metargidin, MDC-15	1q21.3	93	Cardiomyocyte, endothelial cell.	collage IV, gelatin, amphiregulin, CD23, E-	Inflammation. Contributes to pathological retina neovascularization.	[81, 170]

ADAM	Other name	Gene Locus	MW (kDa)	Tissue Distribution	Substrate/Target	Biological or Pathological Role	Ref
					cadherin, HB-EGF, ADAM10	Increased in dilated cardiomyopathy, and in atrial fibrillation.	
17	TACE, CD156b, Snake venom-like protease	2p25.1	110	Embryonic fibroblast, cardiomyocyte, smooth muscle	ECM, collagen, pro-TNF-α, pro-TGF-α, proHB-EGF, pro-amphiregulin, TRANCE, pro-neuregulin-a-2C, Notch, Fas ligand, fractalkine, L-selectin, collagen XVII, TNF receptor I and II, interleukin-1 receptor II, interleukin-6 receptor, Erb-B4/HER4, macrophage colony-stimulating factor receptor I, nerve growth factor receptor (TrkA), growth hormone receptor MUC1, APP, cellular prion precursor.	Cardiomyocyte-specific knockout exacerbates post-MI left ventricle dilation and dysfunction due to reduced angiogenesis. ADAM-17 deficient mice die perinatally due to multiple defects including thickened and mis-shaped semilunar and atrioventricular valves, and ventricular septal defect.	[101, 102]
18	tMDC III, ADAM-27	8p11.22	79	Testis, sperm surface protein	TBD	Highly expressed in conotruncus and endocardial cushion.	[27]
19	Meltrin β, MADDAM, Metalloprotease and disintegrin dendritic antigen marker	5q33.3	105	Peripheral nervous system, skeletal muscle, bone, heart	Pro-HB-EGF, ErbB ligands, NGR-β1 and β4, neuregulin, TNF-α, ADAM-19	ADAM19−/− mice show defects in ventricular septum formation, immature valves, neuronal defects, and die soon after birth.	[105, 171]
20	NG	14q24.2	83	Testis specific	TBD	Embryo development	(21)
21	ADAM-31	14q24.2	85	Testis specific	TBD	Present in mature sperm	(21, 22)
22	MDC2	7q21.12	100	Reproductive system, brain	TBD	Expressed in both testicular somatic and germ cell	(21, 23)
28	MDC-L, ADAM-23	8p21.2	87	Reproductive system, brain	TBD	Present in mature sperm	(21)
29	Cancer/testis antigen 73	4q34.1	127	Testis	TBD	Present in mature sperm	(21, 25)
30	NG	1p12	55	Testis	TBD	Embryo development	[27]
32	NG	8p11.22	88	Testis	TBD	Embryo development	[27]
33	NG	20p13	87	Reproductive system	TBD	Embryo development asthma	[27]

IGFBP-3, insulin growth factor binding protein-3; MW, molecular weight; TBD, to be determined

Table 2.

Human ADAMTS Family Members, Gene Locus, Molecular Weight, Tissue Distribution, and Substrates.

ADAMTS	Gene Locus	MW (kDa)	Tissue Distribution	Substrate/Target	Biological or Pathological Role	Ref
1	21q21	105	Heart, bronchial epithelial cells, fetal lung, liver, aorta, smooth muscle, colon, uterus, kidney, adrenal gland, adipocytes, placenta, uterus, ovary, prostate, bladder, spinal cord, ciliary ganglion, olfactory bulb, breast stromal fibroblasts and myoepithelial cells	Aggrecan, versican, syndecan 4, TFPI-2, semaphorin 3C, nidogen-1, −2, desmocollin-3, dystroglycan, mac-2, gelatin (denatured collagen type I), amphiregulin, TGF-α, heparin-binding EGF, VEGF	Cancer (both pro- and antitumorigenic/metastatic), antiangiogenic	[172–174]
2	5q35	135	Breast stromal fibroblasts adipocytes, heart, lung, liver, kidney, bladder, aorta, smooth muscle, skeletal muscle, tendon, bone, skin, retina, superior cervical ganglion, uterus, placenta	Fibrillar procollagens types I, II, III and V N-propeptide	Ehlers-Danlos syndrome type VIIc, dermatosparaxis (in sheep and cattle)	[41, 172, 175]
3	4q21	140–150	CD105+ endothelial cells, CD34+ cells, heart, lung, pineal gland, cartilage, bone, skeletal muscle, tendon, breast myoepithelial cells, placenta, brain	Fibrillar procollagen type II N-propeptide, biglycan, pro-VEGF-C, reelin	Lymphangiogenesis, placental angiogenesis, brain functions	[11, 41, 107, 129, 172, 176, 177]
4	1q23	90	Ovary, adrenal cortex, ciliary ganglion, trigeminal ganglion, brain, spinal cord, retina, pancreas (islets), heart, fetal lung, bladder, uterus, skeletal muscle, breast myoepithelial cells, synovial fluid	Aggrecan, versican, neurocan, reelin, biglycan, brevican, matrilin-3, α2-macroglobulin, oligomeric matrix protein (COMP)	Arthritis	[44, 172, 178]
5 (11)	21q21	73	Adipocytes, bladder, uterus, placenta, breast myoepithelial cells	Aggrecan, versican, reelin, biglycan, matrilin-4, brevican, α2-macroglobulin	Osteoarthritis, cancer (anti-tumorigenic, anti-angiogenic)	[44, 172, 179, 180]
6	5q12	116	Superior cervical ganglion, trigeminal ganglion, appendix, heart, breast myoepithelial cells	TBD	TBD	[172, 180]
7	15q24	182	Trigeminal ganglion, adrenal cortex, kidney, liver, pancreas, heart, smooth muscle, skeletal muscle, intervertebral disc,	Cartilage oligomeric matrix protein (COMP)	Coronary artery disease (smooth muscle cell migration)	[172, 180, 181]

ADAMTS	Gene Locus	MW (kDa)	Tissue Distribution	Substrate/Target	Biological or Pathological Role	Ref
			breast stromal fibroblasts			
8	11q25	80	Skeletal muscle, heart, lung, liver, superior cervical ganglion, adrenal cortex, breast stromal fibroblasts and luminal epithelial cells, placenta, brain	Aggrecan	Anti-angiogenic	[172, 174]
9	3p14	217	Heart, lung, kidney, pancreas, colon, ovary, skeletal muscle, dorsal root ganglion, capillary endothelial cells, breast myoepithelial cells	Aggrecan, versican	Cancer	[172, 182–184]
10	19p13	121	Heart, lung, liver, pancreas, kidney, brain, placenta, CD8+ T-cells, brain, uterus, breast stromal fibroblasts	Fibrillin-1	Weill-Marchesani syndrome	[172, 185, 186]
12	5q35	178	Liver, bone marrow, intervertebral disc, atrioventricular node, smooth muscle, breast stromal fibroblasts and myoepithelial cells	oligomeric matrix protein (COMP)	Cell adhesion, cancer	[172, 187]
13	9q34	190	Heart, lung, liver, pancreas. kidney, brain, placenta, CD71+ early erythroid cells, endothelial cells, thyroid, breast myoepithelial cells	von Willebrand factor	Deficiency leads to thrombotic thrombocytopenic purpura	[43, 110, 172, 188–191]
14	10q21	134	Fibroblasts, lung, liver, prostate, retina, placenta, thalamus, bone marrow, fetal thyroid, adipocytes, cerebellum, bone, skin, breast myoepithelial and luminal epithelial cells	Fibrillar procollagen type I N-propeptide (pNα1 and pNα2 chains)	Linked to multiple sclerosis, osteoarthritis in women	[41, 112–114, 172, 190]
15	11q25	103	Colon, brain, heart, uterus, musculoskeletal system, breast myoepithelial cells	Aggrecan, versican	Cancer (anti-tumorigenic/metastatic, anti-angiogenic)	[172, 192]
16	5p15	136	Brain, ovary, breast myoepithelial cells, aorta	TBD	Hypertension	[172, 190]
17	15q24	121	Ovary, breast myoepithelial cells	TBD	Weill-Marchesani-like syndrome	[172, 190]
18	16q23	135	Endothelium, prostate, brain,	TBD	Microcornea, myopic chorioretinal atrophy and telecanthus	[43, 44, 142, 172, 190]

ADAMTS	Gene Locus	MW (kDa)	Tissue Distribution	Substrate/Target	Biological or Pathological Role	Ref
			ciliary ganglion, heart, skin, breast myoepithelial cells			
19	5q31	134	Dorsal root ganglion, breast myoepithelial cells	TBD	TBD	[172]
20	12q12	215	Heart, lung, pancreas, prostate, testis, ovary, placenta, brain, appendix, liver, skeletal muscle, pituitary, trigeminal ganglion, breast myoepithelial cells	Versican	Colorectal cancer	[172, 183, 193]

MW, molecular weight of full-length protein; TBD, to be determined

Table 3.

Endogenous and synthetic inhibitors of ADAMs and ADAMTS.

Inhibitor	Target	Reference
Endogenous: TIMP-1	ADAM-10, 17	[194]
TIMP-2	ADAM-17, 33	[195]
	ADAMTS-1	
TIMP-3	ADAM-10, 12, 17, 28, 33	[41, 55, 194,
	ADAMTS-1, 2, 4, 5	196]
TIMP-4	ADAM-17, 28, 33	[197]
α−2 macroglobulin	ADAMTS-2, 4, 5	[41, 55, 198]
Papilin	ADAMTS-2	[60]
Synthetic: Batimastat (BB-94)	ADAM-17, MMPs	[197]
Calcium pentosan polysulfate	ADAMTS-7, 12	[199]
CGS27023	ADAM-9	[200]
Cis-1(S)2(R)-amino-2-indanol-based compounds	ADAMTS-4, 5	[201]
GI254023	ADAM-10	[16]
GI254023X	ADAM-10, MMP9	[16]
Granulin-epithelin precursor	ADAMTS-7, 12	[172]
GW280264	ADAM-10, 17	[16]
INCB3619	ADAM-8, 9, 10, 17, 33	[16]
KP457	ADAM-10, ADAM 17	[16]
TAPI-1	ADAM-17/TACE	[202]
TAPI-2	TACE, ADAMs, MMPs	[202]