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REVIEW

Contribution of ADAM17 and related ADAMs in cardiovascular diseases

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Abstract

A disintegrin and metalloproteases (ADAMs) are key mediators of cell signaling by ectodomain shedding of various growth factors, cytokines, receptors and adhesion molecules at the cellular membrane. ADAMs regulate cell proliferation, cell growth, inflammation, and other regular cellular processes. ADAM17, the most extensively studied ADAM family member, is also known as tumor necrosis factor (TNF)-α converting enzyme (TACE). ADAMs-mediated shedding of cytokines such as TNF-α orchestrates immune system or inflammatory cascades and ADAMs-mediated shedding of growth factors causes cell growth or proliferation by transactivation of the growth factor receptors including epidermal growth factor receptor. Therefore, increased ADAMs-mediated shedding can induce inflammation, tissue remodeling and dysfunction associated with various cardiovascular diseases such as hypertension and atherosclerosis, and ADAMs can be a potential therapeutic target in these diseases. In this review, we focus on the role of ADAMs in cardiovascular pathophysiology and cardiovascular diseases. The main aim of this review is to stimulate new interest in this area by highlighting remarkable evidence.

Keywords Signal transduction · Hypertension · Atherosclerosis · Heart disease · Vascular biology · Endothelium · Inflammation · Angiotensin

Introduction

A disintegrin and metalloprotease (ADAM) family proteins belong to a Zn^{2+}-dependent protease superfamily that are expressed as type 1 transmembrane proteins. In human, 22 ADAM proteins have been identified: ADAM1, 2, 3B, 7, 8, 9, 10, 11, 12, 15, 17, 18, 19, 20, 21, 22, 23, 28, 29, 30, 32, and 33 in MEROPS database within the M12B Adamalysin subfamily of metallopeptidases; https://merops.sanger.ac.uk/. Almost half of ADAMs are exclusively or predominantly expressed in testis and epididymis, whereas 11 ADAMs (ADAM8, 9.10, 11, 12, 15, 17, 19, 22. 23 and 33) are ubiquitously expressed [1]. Interestingly, only 12 human ADAMs are proteolytically active (ADAM8, 9, 10, 12, 15, 17, 19, 20, 21, 28, 30 and 33). These ADAMs work as key mediators of cell signaling by ectodomain shedding of various growth factors, cytokines, receptors and adhesion molecules at the cellular membrane. The proteolytically inactive ADAMs are considered to participate in cellular communication through their adhesive properties. Accordingly, ADAMs regulate cell proliferation, cell growth, inflammation, and other cellular processes [2].

Among ADAM family members, ADAM17, also known as tumor necrosis factor (TNF)-α converting enzyme (TACE), is the most well-studied protein. ADAM17 was first purified and cloned in 1997 as a metalloproteinase that specifically cleaves precursor TNF-α [3, 4]. These findings completely changed the significance of ADAMs from mere adhesion molecules to important regulators of cell signaling.

ADAM17 consists of an N-terminal signal sequence, a prodomain, a catalytic domain with a typical HEXXHXXGXXH sequence, a disintegrin domain, a membrane proximal domain, a transmembrane domain and a cytoplasmic tail (Fig. 1) [5, 6]. ADAM17 exists as a multimer at the cell membrane, and this multimerization is mediated by an EGF-like domain [7]. The maturation of ADAM17 proenzyme requires furin-dependent processing at either a canonical proprotein convertase (PC) cleavage site at the boundary between the prodomain and catalytic domain [8] or an upstream PC cleavage site [9]. These cleavages are thought to be essential for adequate activation of ADAM17.

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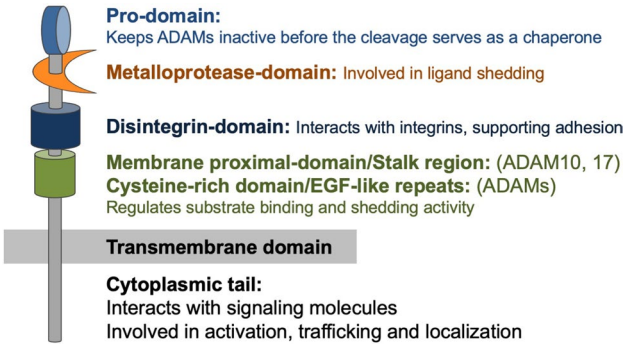

Fig. 1 The general structure of ADAMs. A disintegrin and metalloproteases (ADAMs) consist of several domains. The prodomain keeps ADAMs inactive, and protein convertases such as furin cleave this prodomain in Golgi apparatus to activate ADAM17. The metalloprotease domain is a key domain that is involved in catalytic activity and ligand shedding. The disintegrin domain interacts with integrins and supports adhesion. This domain also serves to maintain the structure of extracellular region. The membrane proximal domain regulates substrate binding and shedding activity. ADAM10 and ADAM17 have membrane proximal domain and other ADAMs have EGF-like repeats, which regulate substrate binding and shedding activity. Cytoplasmic tail of ADAMs interacts with signaling molecules. Phosphorylation of cytoplasmic tail regulates the activation, trafficking and subcellular localization of ADAMs

ADAM17 is expressed very broadly in somatic tissues and a variety of growth factors, cytokines, receptors, adhesion molecules and other molecules have been revealed as substrates of ADAM17 by in vivo or in vitro studies (Table 1). After shedding, cleaved substrates can bind to the receptors on the same cell (autocrine), local cells (paracrine), or non-local cells by transport through blood (endocrine) [10, 11]. In this manner, ADAM17-mediated shedding of cytokines such as TNF-α precursor to produce soluble TNF-α orchestrates immune system or inflammatory cascades.

The shedding of epidermal growth factor receptor (EGFR) ligands is an important process since EGFR is an essential tyrosine kinase receptor in the development of various diseases. The role of EGFR in cancer is widely studied; however, recent evidence has demonstrated the importance of EGFR on cardiovascular physiology and pathophysiology. More specifically, G protein-coupled receptors (GPCRs)-mediated EGFR transactivation has been recognized as a key point of control governing cardiovascular outcomes [12]. GPCR activation causes initial heterotrimeric G protein dissociation. Subsequently, ligand-specific intermediates including intracellular Ca^{2+} and reactive oxygen species (ROS) are elevated and non-receptor tyrosine kinases are activated, followed by metalloprotease activation and shedding of EGFR ligands [13–15]. Among

Table 1 Substrates of ADAM17

Cytokines	Receptors	Adhesion molecules
CD44 [117]	ACE2 [263-265]	ALCAM [291]
CX3CL1 [252, 253]	APOER [266]	CD44 [198, 117]
FLT-3L [254]	CD30 [267]	CD62L [292]
Jagged 1 [38]	CD40 [268]	collagen XVII [293]
Kit-ligand 1 and 2 [255]	CD89 [269]	desmoglein-2 [291]
LAG-3 [256]	EMMPRIN [135]	EpCAM [294]
MICA [257]	EPCR [83]	ICAM-1 [111]
MICB [258]	Ephrin B4 [135]	JAM-A [123]
RANKL [259]	ErbB4 [270, 271]	L-selectin [113]
TNF-α [20, 260, 190, 261, 4, 11]	GHR [272, 273]	L1-CAM [295]
TNF beta [262]	GPIba [274]	PTP-LAR [296]
	GPV [275]	NCAM [297]
	GPVI [276]	nectin-4 [298]
	IL-1R II [21]	PECAM-1 [135]
	IL6R [277, 278]	VCAM-1 [109, 299]
Growth factors	Integrin beta-1 [150]	Others
Amphiregulin [300, 190, 301]	Leptin receptor [279]	APP [308, 309]
CSF-1 [138]	LOX-1 [280]	CD163 [310]
Epigen [302]	M6P/IGF2R [281]	KIM-1 [311]
Epiregulin [190]	Notch1 [282, 283]	Klotho [312]
HB-EGF [135, 300, 190, 303]	NPR [284]	MerTK [313]
IGFR1 [135]	p55 TNF alpha RI [20, 21]	PMEL17 [314]
Neuregulin-1 [199]	P75 TNF receptor [113]	PrPc [315]
Pref-1 [282, 304]	p75NTR [285, 21]	Tim-3 [316]
SEMA4D [305, 306]	Ptprz [286]	VASN [317]
TGF alpha [113, 300]	syndecan 1 and 4 [287]	
Tomoegulin-2 [307]	Toll-like receptor 4 [288]	
	TrkA [289]	
	VEGFR [31]	
	VPS10p [290]	

these metalloproteases, ADAM17 has been recognized as an essential mediator of EGFR ligand shedding and subsequent EGFR transactivation [13, 15, 16]. Upon activation, ADAM17 cleaves EGFR ligands such as heparin binding EGF-like growth factor precursor (HB-EGF) to produce mature soluble HB-EGF which then binds and activates EGFR. In addition, upon shedding, the cytoplasmic tail of EGFR ligands is recognized as a site of protein interactions which mediates several intra- and intercellular phenomena including ligand trafficking or migration to the cell surface, signal transduction, and gene expression via interaction with a transcriptional repressor [17–19]. Therefore, ectodomain shedding of EGFR ligands by ADAM17 can initiate a bidirectional signaling event with released growth factor and free shed remnant. Both TNF receptor 1 (TNFR1) and TNFR2 are also ADAM17 substrates [20, 21]; thus, creation of soluble TNFRs modulates soluble TNF-α availability as well as TNFR activities. In addition to TNF-α precursor and TNFR, interleukin-6 receptor (IL6R) is a critical substrate to mediate ADAM17 function. IL6 primarily binds to IL6R, which is specifically expressed in certain cell types such as leukocyte and hepatocyte. The IL6 IL6R complex then binds to ubiquitously expressed signaling receptor gp130 leading to activation of STAT1, STAT3 and the ERK cascade to mediate inflammatory responses. Cells only expressing gp130 cannot respond to IL6. However during trans-signaling, gp130 can be activated with IL6 complexed with soluble IL6R generated by ADAM17 shedding of the receptor [22]. Taken together, ADAM17-mediated shedding of growth factors and cytokines causes cell growth and inflammation, respectively (Fig. 2).

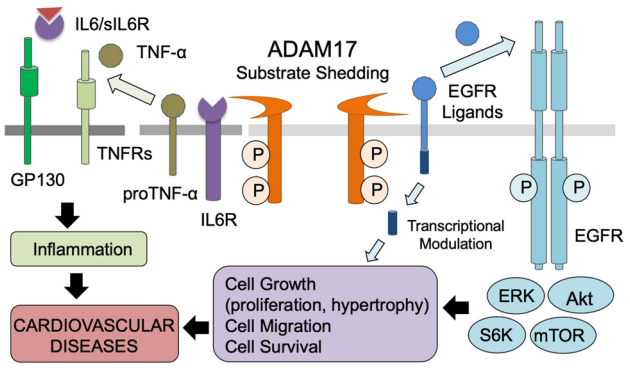

Fig. 2 ADAM17 mediates cardiovascular diseases via ectodomain shedding. A variety of substrates including growth factors, cytokines, receptors, adhesion molecules are cleaved by ADAM17 and initiate or modulate intracellular signaling. The ectodomain sedding events can be occurred in cis (on the same cell) or trans (between two cells), and act in autocrine (on the same cell types), paracrine (on distinct resident cells) and/or endocrine (on distinct organs through circulation) manner. Therefore, these events involve single cell membrane (cis cleavage and autocrine signaling), two (cis and paracrine/endocrine or trans and paracrine) or three distinct cell-type membranes (trans and endocrine) expressing ADAM17, substrates and the receptors. Prototypical examples of ADAM17 substrate relationship are illustrated. Right: upon ADAM17 activation, cleaved EGFR ligands transactivate EGFR and initiate EGFR-mediated intracellular signaling including activation of ERK, Akt, mTOR and p70 S6K, resulting in cell proliferation or hypertrophy in an autocrine manner. In addition, the cytoplasmic tail of EGFR ligands is recognized as a site of protein interaction or translocate to nucleus which acts as a transcriptional modulator. Left: activated ADAM17 also regulate inflammation via the cleavages of inflammatory cytokines and their receptors. The examples shown are pro-NF-α shedding and TNFR activation as well as soluble IL6R (sIL6) generation to lead to the IL6-sIL6 complex, which can activate their receptor, GP130 in the absence of IL6R in a paracrine or endocrine manner

There are numerous regulators of ADAM17-dependent ectodomain EGFR ligand shedding including various extracellular stimuli, cellular protein modulators, phosphorylation in the cytosolic domain and its own disulfide switch [23, 24]. Certain regulators modulate ADAM17 activity via stabilization. Band 4.1 protein, ezrin, radixin, moesin (FERM) domain-containing protein 8 (FRMD8) stabilizes ADAM17 at the cell surface and supports ADAM17-mediated ligand shedding [25]. The sorting protein phosphofurin acidic cluster sorting protein 2 (PACS-2) co-localizes with ADAM17 on early endosomes, and loss of PACS-2 results in decreased ADAM17 recycling, stability upon internalization, cell surface expression, and EGFR ligand shedding [26].

Notably, TNF-α induces ADAM17 and Src-dependent EGFR activation, and initiates the extracellular signal-regulated kinase (ERK)-dependent guanine nucleotide exchange factors (GEF)-H1 and RhoA signaling pathway, suggesting a mechanistic link between inflammatory and proliferative pathophysiology [27]. Platelet-derived growth factor (PDGF) receptor β stimulation activates ADAM17 shedding of TNF-α or transforming growth factor (TGF)-α and subsequently initiates EGFR signaling pathways [28]. p38 mitogen-activated protein (MAP) kinase and Src are reported to activate ADAM17 via interaction with the cytoplasmic domain of ADAM17, increase ADAM17-mediated shedding of TGF-α family ligands and activate EGFR signaling [29–31].

A protein kinase C (PKC) activator, phorbol 12-myristate 13-acetate (PMA), induces ADAM17-mediated HB-EGF shedding and EGFR transactivation. PKC and ADAM17-dependent HB-EGF shedding is triggered by apically localized A1 adenosine receptor stimulation [32]. Notably, in EGFR ligands shedding, regulatory proteins such as PKCα, PKC-regulated protein phosphatase 1 inhibitor 14D (PPP1R14D), and PKCδ affect the shedding of some ADAM17 substrates without significant effect on protease activity [33]. In addition, PKCα and PPP1R14D act on ADAM17-mediated shedding of TGF-β, HB-EGF and amphiregulin, whereas PKCδ is required for ADAM17-mediated shedding of neuregulin [33], suggesting a complex regulation of EGFR ligand shedding.

Several phosphorylation sites such as Thr735 phosphorylation by ERK or p38 MAP kinase appear to be involved in ADAM17 activation [23, 34]. Polo-like kinase 2 (PLK2) interacts with and phosphorylates ADAM17 at Ser794 resulting in shedding of pro-TNF-α and TNF receptors, and PLK2 expression is up-regulated in inflammatory conditions [35]. ADAM17 Tyr702 is another important phosphorylation site for EGFR transactivation induced by G protein-coupled receptor (GPCR) agonist such as angiotensin II [13]. However, phosphorylation of the intracellular domain of ADAM17 may not always be essential for activation. Studies with ADAM17 chimeric construct showed that PMA-induced ADAM17 activation did not require the intracellular domain, but it required the transmembrane domain [36, 37]. While detailed mechanistic dissection of the mode of modulations is beyond the scope of this review article, these conflicting findings indicate that ADAM17 regulation by the modulations and the modulators are likely cell/tissue type and context-specific.

It is well established that mature ADAM17 is associated with lipid rafts, although some substrates such as Jagged-1 are cleaved by ADAM17 in lipid raft-independent pathways [38]. Many signaling proteins which involve ADAM17-mediated EGFR transactivation including EGFR, GPCRs such as AT1R, G proteins, Src family kinases and ADAM17 are localized to caveolae, a subset of lipid rafts [39–41]. Angiotensin II-induced transactivation of EGFR relies on ADAM17 compartmentalization in caveolae [41]. Caveolin-1, a major structural protein of caveolae, is required for TGF-β-mediated ADAM17 activation via phosphorylation of Src and NADPH Oxidase 1 (NOX1)-mediated ROS production [42]. Silencing of caveolin-1 in cultured VSMCs can prevent angiotensin II (AngII)-induced ADAM17 induction and activation [43]. However, inhibition of EGFR transactivation by over-expressing caveolin-1 was also observed in VSMCs stimulated by AngII [41]. Therefore, further investigation is needed to explore the contradictory data observed regarding the signaling relationship of ADAM17 and caveolin-1.

The conformational change in ADAM17 also affects ADAM17 activity. Changes in the redox environment like PMA-dependent induction of mitochondrial ROS enhance ADAM17 activity, and the inactivation of thiol isomerases, specifically protein disulfide isomerase (PDI), is reported as a key player. PDI regulates ADAM17 activity by conformational change in ADAM17 from an active "open form" to an inactive "closed form" [44]. In addition, thioredoxin-1 is reported to interact with the cytoplasmic domain of ADAM17 and negatively regulate ADAM17 activity [45, 46]. The noncatalytic domains of ADAM17 are also reported to regulate the ADAM17 activity via steric hindrance [47]. Conserved ADAM-seventeeN Dynamic Interaction Sequence (CANDIS) encoded by ADAM17 is a short juxtamembrane segment of 17 amino acid residues. CANDIS appears critical in substrate recognition, and also regulates the shedding activity of ADAM17 by interacting with lipid bilayers [48]. It has also been reported that the membrane proximal domain of ADAM17 provides a phosphatidylserine binding motif. ADAM17 is activated upon phosphatidylserine binding in several cell types including endothelial cells. Cells undergoing apoptosis will enhance phosphatidylserine in outer membrane. Thus, CANDIS and the membrane proximal domain likely provide a means to stimulate ADAM17 activity upon extracellular stress, such as those causing apoptosis [49]. In addition, site-specific O-glycosylation in juxtamembrane segment of several ADAM17 substrates mediated by distinct polypeptide N-acetylgalactosamine (GalNAc)-transferase (GalNAc-T) isoforms is also reported to widely modulate ADAM17-mediated shedding in a substrate-specific manner [50].

Catalytically inactive rhomboid protein (iRhom) 2 was identified as a key protein which controls the maturation and function of ADAM17 [51–53], regulating cytokine and growth factor signaling [54]. Due to its preferential expression in leukocytes, iRhom2 –/– mice are defective in myeloid-specific TNF-α shedding [53]. However, iRhom2 –/– mice showed decreased myeloid cell repopulation under stress due to defect in myeloid colony-stimulating factor receptor-1 (CSFR1) shedding. Moreover, in iRhom2 and related iRhom1 double knockout mouse tissues, there is a lack of ADAM17 maturation and reduced EGFR activation [55]. FERM domain-containing 8 (FRMD8) [25]/iTAP (iRhom Tail-Associated Protein[56] has been discovered which enhances stability of ADAM17 and iRhoms. It has also been shown that ERK-dependent phosphorylation of iRhom2 recruits 14-3-3 proteins which leads to iRhom2 dissociation from ADAM17 leading to ADAM17 activation [57]. It is interesting to note that iRom1 is preferentially and constitutively expressed in endothelial cells with transcriptional regulation by shear stress, whereas inflammatory cytokines can induce iRhom2 but not iRom1 [58]. Therefore, iRhoms appear to be the main focus of research into ADAM17 regulation.

Increased ADAM17-mediated shedding contributes to the progression of various cardiovascular diseases such as atherosclerosis or ischemia via both EGFR transactivation and inflammation. Thus, ADAM17 is a potential therapeutic target in these diseases. The role of ADAM17 in cancer and autoimmune diseases has been well documented [59–61]; here, we focus on the role of ADAM17 in cardiovascular pathophysiology and cardiovascular diseases. This review also includes a discussion of other ADAM family proteins which share cell-specific distribution, the HExGHxxGxxHD motif that is required for proteolytic activity, and, therefore, function with ADAM17. Notably, most substrates can be cleaved by a variety of ADAM family members, and this

seemingly nonspecific relationship between substrates and ADAMs makes the physiology of ADAMs more complicated and interesting. The main aim of this review is to rejuvenate interest in ADAM research by highlighting remarkable evidence.

Adam17 and cardiovascular pathophysiology

ADAM17 is expressed in various cells including endothelial cells, vascular smooth muscle cells (VSMCs), fibroblasts, and monocytes. In cultured VSMCs, angiotensin II stimulation increases ADAM17 phosphorylation [13], protein expression, mRNA expression, and promoter activity [62]. Activation of ADAM17 via tyrosine phosphorylation contributes to HB-EGF shedding, EGFR transactivation [63], and subsequent growth promoting signals induced by angiotensin II [13].

Previous investigations of ADAM17 in cardiovascular pathophysiology have revealed ADAM17 to be a highly regulated controller of disease progression. The expression and activity of ADAM17 are regulated in a multi-layered and highly complicated manner as reviewed previously [64], and the regulation of ADAM17 in cardiovascular pathophysiology has also been investigated. Notably, the meaning of increased ADAM17 expression should be carefully interpreted. Systemically, ADAM17 overexpression mice show no enhancement in TNF-α shedding activity, suggesting that ADAM17 activity can be independent of transcriptional regulation and that excess ADAM17 does not necessarily result in enhanced shedding activity in vivo [65]. In this section, we highlight in vivo and in vitro findings regarding the role of ADAM17 and the regulation of ADAM17 in cardiovascular pathophysiology. Moreover, we review the clinical studies investigating the role of ADAM17 in human cardiovascular diseases.

ADAM17 and hypertension

In a mouse model of angiotensin II-induced hypertension with smooth muscle ADAM17 deletion or systemic pharmacological inhibition of ADAM17, vascular medial hypertrophy and perivascular fibrosis were attenuated [66]. This is because ADAM17 mediates angiotensin II-induced EGFR transactivation in vascular smooth muscle cells (VSMCs) causing growth promoting signal transduction [12]. Thus, inhibition of EGFR also mitigated hypertensive vascular remodeling in mice infused with angiotensin II [67]. Interestingly, blood pressure remains high in these models with ADAM17/EGFR inhibition at 2-week time point; whereas, less hypertension was reported at 1-week point [68], suggesting unique roles of ADAM17 in hypertensive vascular pathology. How does the acute signaling events via the ADAM17/EGFR system mediate chronic vascular pathology? This seems to involve feed-forward induction of ADAM17 transcript via ER stress and subsequent unfolded protein response (UPR). Upon AngII stimulation, chronic UPR markers were induced in vitro in VSMCs and in vivo in the vasculature. Suppression of ER stress and UPR via chemical chaperoning, thus, attenuated vascular ADAM17 induction and associated vascular pathology [67]. At the cellular level, AngII-induced UPR seems insufficient to attenuate protein misfolding leading to protein aggregate formation in VSMCs. The sustained proteotoxicity prolongs UPR, enhances inflammatory response and senescence [69, 70]. Accordingly, chronic activation of the vascular ADAM17/EGFR system seems to contribute to premature inflammaging via protein aggregation [71, 72]. Interestingly, vascular ADAM17 promoter can also be activated via hypoxia inducible factor 1α upon AngII stimulation in VSMCs. Thus, vascular ADAM17 activation may be exaggerated under ischemic conditions [62]. This novel concept of ADAM17 in mediating hypertension and chronic vascular pathology is illustrated in Fig. 3.

ADAM17 also influences blood pressure via a brain-dependent mechanism. Deoxycorticosterone acetate (DOCA)-salt treatment enhanced ADAM17 expression and activity in the hypothalamus, significantly reduced an ADAM17 substrate, angiotensin-converting enzyme 2 (ACE2) expression and activity in brain, resulting in increased blood pressure, inflammation, hypothalamic angiotensin II levels, and causing autonomic dysfunction.

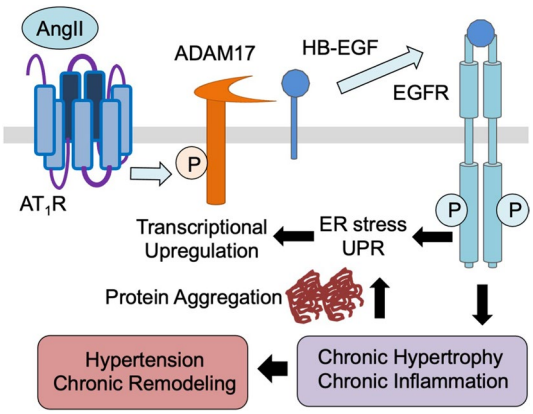

Fig. 3 The potential molecular mechanism by which Angiotensin II signaling via ADAM17 mediates chronic vascular pathology in hypertension. Angiotensin II rapidly activates ADAM17 via its Tyr702 phosphorylation through the GPCR, AT1 receptor (AT_1R) in VSMCs. This leads to proHB-EGF shedding and subsequent EGFR transactivation. Enhanced protein synthesis results in protein misfolding causing protein aggregate formation. Protein aggregates enhance ER stress and UPR which transcriptionally upregulate ADAM17 thus create the feed-forward loop of sustained signaling leading to hypertensive vascular remodeling

Accordingly, knockdown of ADAM17 in the brain can blunt the development of hypertension and restore ACE2 activity and baroreflex function, indicating that ADAM17-mediated shedding of ACE2 contributes to the development of neurogenic hypertension [73]. With neuron selective ADAM17 knockout mice, the mechanism appears to involve ADAM17-dependent ACE2 inactivation in pre-sympathetic neurons within the paraventricular nucleus [74]. Moreover, in the brain of hypertensive patients ADAM17-mediated ACE2 shedding seems to be promoted by angiotensin II suggesting the involvement of ADAM17 in neurogenic hypertension in human [75].

ADAM17, atherosclerosis and neointima formation

ADAM17 is highly expressed in aortic lesions in atherosclerosis-prone sites in high-fat diet-fed apolipoprotein E knockout mice, and ADAM17 may contribute to the elevated levels of circulating soluble TNF-α receptors [76]. In addition, ADAM17 is recognized as a candidate gene of atherosclerosis susceptibility since ADAM17 mRNA expression and activity is increased in association with atherosclerosis resistance in low density lipoprotein (LDL) receptor deficient mice [77]. ADAM17 gene silencing by injecting shRNA into the abdominal aortic plaque enhances plaque stability and improves vascular positive remodeling via attenuation of local inflammation, neovascularization and matrix metalloproteinase (MMP) activation, and enhancement of collagen production [78]. In addition, genetical or pharmacological inhibition of ADAM17 prevents neointimal hyperplasia after vascular injury [79]. Since ADAM17–/– mice are not viable, ADAM17 hypomorphic mice have been generated, which have barely detectable levels of ADAM17 in all tissues [80]. Contrary to results with ADAM17 inhibition, a study using ADAM17 hypomorphic mice revealed that ADAM17 deficiency enhances atherosclerosis via TNF receptor 2 (TNFR2) signaling [81], suggesting that moderate activation of ADAM17 had atheroprotective effects by preventing the endogenous TNFR2 overactivation. The cell-type-specific difference in the role of ADAM17 could be one reason for these controversial findings. Indeed, it has been reported that myeloid ADAM17 deletion is detrimental; whereas, endothelial ADAM17 deletion appears protective against atherosclerosis development [82].

ADAM17 expression is reported in human atherosclerotic plaques [76]. Microparticles isolated from human atherosclerotic plaques are shown to carry active ADAM17 on their surface. These microparticles enhance the shedding of TNF-α, TNF receptor 1 (TNFR1), and endothelial protein C receptor (EPCR) at endothelial cells, indicating ADAM17-positive microparticles could regulate the inflammatory balance in culprit lesions [83]. Moreover, the ADAM17 at advanced human atherosclerotic lesions is in its catalytically active form and ADAM17-expressing cells are co-localized with CD68-positive cells of monocytic origin [84]. These results suggest the contribution of ADAM17 in monocyte homing, migration, and proliferation in human atherosclerotic lesions.

ADAM17 and aortic aneurysms

ADAM17 is identified as a central gene associated with angiotensin II-induced abdominal aortic aneurysm (AAA) in genome-wide transcriptional profiling [85]. ADAM17 expression is enhanced in experimental models of AAA, and temporal and systemic deletion of ADAM17 prevents AAA development in association with attenuating inflammation elicited by TNF-α [86]. AAA as well as enhanced ADAM17 expression and EGFR phosphorylation in experimental AAA are markedly attenuated in caveolin-1 knockout mice, supporting ADAM17 compartmentalization in caveolae in VSMCs [43]. Consistent with these findings, VSMC ADAM17 silencing or systemic pharmacological ADAM17 inhibition attenuated AAA in mice with angiotensin II infusion [87]. Cleavage of an EGFR ligand appears critical since inhibition of EGFR is sufficient to prevent angiotensin II-dependent AAA in mice [88]. How does ADAM17-dependent EGFR transactivation lead to chronic vascular cell dysfunction to contribute to AAA? As recognized in hypertension, ER stress and UPR seem key drivers for the VSMC phenotype involved in AAA [89].

It is also interesting to note the role mitochondrial morphology plays in AAA. Mitochondrial fission fusion events are critical for mitochondrial homeostasis. However, under several stressed conditions such as those with cardiovascular diseases, the balance shifts toward more fission leading to mitochondrial dysfunction and mitochondrial oxidative stress. Thus, mitochondrial fission sustains inflammatory responses [71]. A GTPase Drp1 is a master regulator of mitochondrial fission. In human AAA as well as AngII-dependent model of AAA, Drp1 expression appears enhanced. Moreover, in abdominal aortic VSMC, the critical ADAM17/EGFR downstream effector ERK phosphorylates and activates Drp1 leading to mitochondrial fission. AngII stimulated mitochondrial oxygen consumption which was attenuated with a Drp1 inhibitor. In addition, inhibition of mitochondrial fission attenuated AngII-dependent AAA, which was associated with prevention of aortic ER stress/UPR and senescence. Inflammatory leukocyte infiltration was also attenuated [90]. There is additional evidence linking ADAM17 and mitochondrial fission in the cardiovascular system. In cultured aortic endothelial cells, TNF-α stimulated Drp1-dependent mitochondrial fission and nuclear factor-κB-dependent inflammatory responses. Genetic inhibition of Drp1 attenuated nuclear factor-κB activation and subsequent inflammatory responses in endothelial cells with

TNF-α exposure. Thus, in endothelial Drp1-deleted mice, leukocyte adhesion to endothelium in response to TNF-α injection was attenuated [91]. In addition, Drp1 appears to be indispensable for AngII-induced senescence in endothelial cells [92]. Potential overall contributions of ADAM17 in AAA and associated inflammation via Drp1-dependent mitochondrial fission are illustrated in Fig. 4.

Similar to AAA, experimental thoracic aortic aneurysm (TAA) model showed significant elevation of expression of ADAM17 in the vasculature [93]. Interestingly, VSMC-specific ADAM17 deletion attenuates TAA formation via fibrosis, inflammation, and adverse aortic remodeling, whereas EC-specific ADAM17 deletion also attenuates TAA progression by protecting the integrity of adherens junction and tight junctions in an adventitial elastase exposure model [94].

In human AAA sample obtained during surgical operation, ADAM17 is overexpressed in the aortic wall [86] compared to normal aortae. Enzymatically active ADAM10 and ADAM17 are carried on membrane microvesicles in the intraluminal thrombus of human AAA [95]. ADAM17 expression is higher in the transition zone than in the mid-portion of aneurysm, and ADAM17 is expressed in CD68-positive macrophages in the media and adventitia obtained from the transition zone in AAA [96]. In addition, ADAM17 promoter polymorphism rs12692386 is reported to associate with AAA, enhanced ADAM17 expression and circulated TNF-α [97]. Taken together, these data indicate ADAM17 is important in the pathogenesis of AAA in humans.

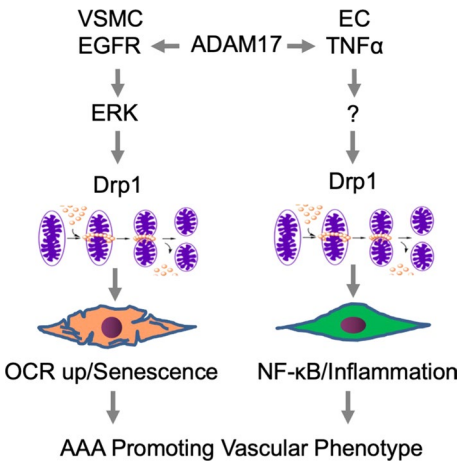

Fig. 4 Vascular ADAM17 activation mediates smooth muscle cell senescence and endothelial inflammation thus changes vascular cell phenotypes leading to AAA. In VSMCs, ADAM17-dependent EGFR activation causes mitochondrial fission via Drp1 which leads to enhanced oxygen consumption and senescence. In EC, ADAM17-dependent TNF-α production stimulates Drp1-dependent mitochondrial fission and subsequent mitochondrial ROS production and NF-κB activation thus sustains EC inflammation. The vascular phenotype changes caused by ADAM17 activation, thus, contribute to AAA development

ADAM17 in mediating vascular inflammation

Atherosclerosis is accelerated by chronic inflammation. Macrophages and monocytes are recognized as contributors to the inflammatory component of atherogenesis [98]. TIMP-3 overexpression in macrophage attenuates atherosclerosis in LDL receptor knockout mice [99]. ADAM17-mediated shedding of colony-stimulating factor 1 (CSF-1) on the cell surface of neutrophils and macrophages enhances macrophage proliferation in state of acute and chronic inflammation [100]. Accordingly, monocyte ADAM17, not endothelial ADAM17, facilitates the completion of transendothelial migration by accelerating the rate of diapedesis [101]. ADAM17 induced shedding of CSF [102] and functional suppression of macrophage via CSFR1 has been reported [103]. However, participation of CSFR1 in atherosclerosis has also been reported [104]. Thus, further clarification seems needed regarding the overall contribution of the ligand as well as the receptor shedding by ADAM17 in atherosclerosis and associated inflammation.

Adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and L-selectin expressed in endothelium are other key players in atherosclerosis development by regulating leukocyte recruitment [105–108]. ADAM17 cleaves these molecules and regulates inflammation. ADAM17-mediated shedding of VCAM-1 produces soluble form of VCAM-1 [109]. This process is supported by the findings suggesting that circulating VCAM-1 can be a marker of atherosclerotic lesions in diabetes patients with atherosclerosis [110]. Ectodomain shedding of ICAM-1 is also ADAM17 dependent, and pharmacological or genetic inhibition of ADAM17 can block the ICAM-1 shedding, resulting in up-regulation of cell adhesive function [111]. Similar to soluble VCAM-1, circulating ICAM-1 is also reported to serve as a molecular marker for atherosclerosis [112]. L-selectin constitutively expressed by most circulating leucocytes including neutrophils is critical in directing these cells to the sites of inflammation. ADAM17-deficient cells are impaired in L-selectin shedding, showing that L-selectin is cleaved by ADAM17 [113], even though there is ADAM17-independent shedding of L-selectin [114]. Rapid ADAM17-mediated L-selectin shedding increases rolling velocity and enhances leukocyte accumulation on the vascular wall [115]. Constitutive shedding by ADAM17 also regulates soluble L-selectin that affects interactions between leukocyte and endothelium [116]. CD44, a glycoprotein which promotes cell adhesion and migration, recruits inflammatory cells to vessel wall and activates vascular cells in atherogenic conditions, and CD44 undergoes ADAM17-dependent cleavage [117].

Stimulation of the thromboxane A2 receptor induces rapid ADAM17-mediated shedding of cell surface CX3CL1, a key factor in recruiting monocytes. Shedding of CX3CL1

results in recruitment of leukocytes to vascular inflammatory sites and enhanced adhesion once recruited [118]. ADAM17 also affects vascular permeability by shedding of adhesion molecules in cell junction. JAM-A is another molecule known to facilitate vascular inflammation by promoting the migration of endothelial cells [119, 120] and monocytes [121, 122], as well as angiogenesis. ADAM17-mediated shedding of JAM-A is caused at vascular inflammation sites, and this shedding of JAM-A down-regulates transmigration of monocytes and increases endothelial permeability within the endothelial junctions [123]. There seem to be certain players that affect vascular inflammation via ADAM17 activity modulation. Neutrophil activation upon E-selectin binding or endothelial adhesion promotes redistribution and co-clustering of ADAM17 and L-selectin, modulating the process of rolling, activation, arrest, and transmigration of neutrophils [124]. Oxidative conditions such as H_2O_2 treatment induce L-selectin shedding and thiol-disulfide conversion occurring in extracellular region of ADAM17 are involved in this reaction [125]. Taken together, ADAM17 regulates vascular inflammation in various manner including inflammatory activation, regulation of vascular permeability, rolling, adhesion, and transmigration of leukocytes.

ADAM17 mechanism of angiogenesis and neovascularization

Accumulating evidence suggests that ADAM17 promotes angiogenesis through stimulation of endothelial cell proliferation, invasion, network formation, and MMP-2 activation [126, 127]. Vascular endothelial growth factor (VEGF)-A and the receptor vascular endothelial growth factor receptor 2 (VEGFR2) are essential for angiogenesis, and VEGFR2 is known to coordinate endothelial cell migration, capillary formation, and vascular permeability [128]. VEGF-A activates ADAM17 via ERK pathway, resulting in shedding of VEGFR2 and other substrates, and ADAM17 selective inhibition attenuates VEGFR2-induced ERK phosphorylation [31]. VEGF-A/VEGFR2 causes migration of human umbilical vein endothelial cells (HUVECs), and fibroblast growth factor 7 (FGF7)/FGF receptor 2-IIIb (FGFR2b) causes cell migration in epithelial cells. These migrations depend on EGFR/ERK signaling and ADAM17-mediated HB-EGF shedding [37]. In addition, a study using HUVECs showed that IL6 and interferon-γ caused ADAM17-dependent shedding of neuregulin. Based on several cytokine measurements, this neuregulin shedding is speculated to contribute to inflammation-associated angiogenesis [129]. ADAM17-mediated HB-EGF shedding and subsequent EGFR transactivation in retinal endothelial cells are also reported as key components in ocular neovascularization [130]. Genetic variation at *Tgfbm3* or pharmacological inhibition of ADAM17 modulates postnatal circulating endothelial progenitor cell (CEPC) numbers through TGF-β receptor 1 activity, suggesting that variant ADAM17 is an innate modifier of adult angiogenesis since CEPC numbers correlate with angiogenic potential [131]. Finally, ADAM17 inhibition enhances the expression of thrombospondin -1 (TSP1), an anti-angiogenic factor, and overexpression of ADAM17 down-regulates TSP1 in endothelial cells, suggesting that ADAM17 positively regulates angiogenesis by its negative feedback of TSP1 [132].

Cdc42, a Ras-related GTPase, has an important role in cell migration, proliferation, and survival. Contrary to the positive regulatory roles of ADAM17 as described, the deletion of Cdc42 increases ADAM17-dependent VEGFR2 shedding, thus impairing angiogenesis in mice [133]. Flt, one of the VEGF receptors at the cell surface, consists of a homodimer or heterodimer with VEGFR2. ADAM17-mediated ectodomain shedding of Flt antagonizes VEGF when Flt is co-expressed with VEGFR [134]. The regulatory roles of ADAM17 in angiogenesis could be varied by the given pathology and require further investigation.

Mice with conditionally inactivated ADAM17 in smooth muscle cells (Adam17/flox/flox/sm22α-Cre mice) show no clear effects on angiogenesis [135]. On the other hand, mice with conditionally inactivated ADAM17 in endothelial cells (Adam17/flox/flox/Tie2-Cre mice) show significantly reduced pathological neovascularization, although they have no obvious defects in developmental angiogenesis [135]. Similarly, endothelial ADAM17 knockdown with both constitutive and inducible VE-cadherin Cre mice is reported to reduce collateral circulation formation [136]. These results indicate the essential role of endothelial ADAM17 in neovascularization. Study showing that retinal neovascularization is attenuated by ADAM17 inhibition with in vivo angiogenesis model supports this finding [137]. The distinct finding regarding the developmental angiogenesis likely involves different endothelial Cre driver-expression in distinct stage of the development. It is also important to determine the detailed substrate(s) and the activation mechanisms by which ADAM17 mediates angiogenesis under physiological (developmental), pathophysiological (retinal angiogenesis) or anti-pathological (collateral angiogenesis upon hypoxia) conditions.

ADAM17, cardiac development and diseases

ADAM17−/− mice die shortly after birth, with defects in the aortic, pulmonic, and tricuspid valves of their heart [138]. Similarly, mice lacking the Zn^{2+} binding domain of ADAM17 (ADAM17 Δzn/Δzn), which inactivates metalloproteinase activity, die shortly after birth [113]. ADAM17 Δzn/Δzn embryos present defective cardiac valvulogenesis [139], abnormal vascular beds and internal hemorrhages [140]. The waved with open eyes (woe) mouse is a model

of syntenic human ocular disorders. Woe is a hypomorphic mutation in ADAM17 where a small amount of functional ADAM17 is produced in woe animals, and they show enlarged heart and defects in the semilunar cardiac valves [141]. In addition, endothelial cell-specific ADAM17-deleted mice show cardiac valve enlargement during embryogenesis and progressive cardiomegaly and pronounced systolic dysfunction as adults, showing that endothelial ADAM17 may be necessary in normal cardiac development and homeostasis [142]. These results demonstrate the role of ADAM17 in the development of cardiac system and valves.

Expression of ADAM17 in the left ventricle is up-regulated in an abdominal artery coarctation-induced model of myocardial hypertrophy with increased expression of a NADPH oxidase, Nox4, showing that ADAM17 activation is required in pathological cardiac hypertrophy [143]. And cardiac protective effects of some drugs such as peroxisome proliferator-activated receptors (PPAR)-α agonists or Nox1/4 inhibitor are involved in a reduction of ADAM17 expression [144, 145]. Furthermore, treatment with ADAM17 small-interfering RNA can prevent angiotensin II-induced cardiac hypertrophy and fibrosis, with inhibition of angiotensin II-induced overexpression of markers of myocardial hypertrophy and fibrosis such as brain natriuretic peptide (BNP), α-skeletal actin, β myosin heavy chain (β-MHC), type I collagen, type II collagen, and fibronectin [146] or MMP-2 [147]. Interestingly, angiotensin II-induced cardiac hypertrophy is attenuated by VSMC-specific ADAM17 silencing [66, 68], showing that angiotensin II-induced vascular EGFR activation may be a specific requirement for the cardiac phenotype.

In addition to these findings, cardiomyocyte-specific ADAM17 knockdown mice showed lower mortality rate and less cardiac dysfunction caused by myocardial infarction with reduced activation and expression of VEGFR2 in infarcted myocardium, highlighting the detrimental role of cardiomyocyte ADAM17 in recovery after myocardial infarction via suppression of angiogenesis [148]. The myocardial infarction experimental model also showed that enhanced ADAM17 expression, along with decreased TIMP-3 and increased TNF-α expression within one week after acute myocardial infarction, is associated with cardiac remodeling [149]. These data indicate the potential benefit of ADAM17 inhibition in cardiac diseases.

On the contrary, myocardial hypertrophy and dysfunction induced by transverse aortic constriction are enhanced in cardiomyocyte-specific ADAM17 knockdown mice, and upregulation of integrin β1 induced by this pressure overload is also enhanced in ADAM17 knockdown animal. However, hypertrophy induced by a sub-pressor dose of angiotensin II is not affected by cardiac ADAM17 knockdown, suggesting that ADAM17 has a protective function in pressure-overload cardiomyopathy [150]. In addition, iRhom2–/– mice showed defective inflammatory responses at both acute M1 and chronic M2 phases resulting in impaired cardiac repair upon myocardial infarction. This phenotype is explained by defective control of myeloid TNF-α/TNFR signaling.

Regarding the role of ADAM17 in human heart, the coronary arteries obtained from aged or obese patients showed increased vascular endothelial ADAM17 activity suggesting the development of remote coronary microvascular dysfunction [151]. Systemic levels of ADAM17 and TNF-α are higher in acute myocardial infarction (AMI) patients compared to patients with stable angina. ADAM17 is highly expressed at the site of ruptured plaques in AMI patients, and this local ADAM17 expression level is independently and significantly correlated with adverse cardiac events during follow-up period [152]. Both spontaneous and ADAM17 activator-stimulated levels of ADAM17 and TNF-α are higher in peripheral blood mononuclear cells obtained from AMI patients compared to normal subjects, and these levels are correlated with in-hospital complications [153]. Moreover, a score evaluated from ADAM17 circulating substrates (soluble ICAM-1, soluble VCAM-1, soluble IL6 receptor, and soluble TNFR1) is reported to be able to predict recurring cardiovascular events [154]. Collectively, clinical studies further support the detrimental roles of ADAM17 in human myocardial diseases.

ADAM17 and kidney diseases

Mice infused with angiotensin II for 2 months suffer from ADAM17-mediated shedding of TGF-α and subsequent EGFR transactivation-dependent renal lesions such as glomerulosclerosis, tubular atrophy, and interstitial fibrosis [155]. In addition, ADAM17 is induced and redistributed in angiotensin II-damaged kidneys and inhibition of ADAM17 can blunt angiotensin II-induced renal lesions [155]. Similarly, fibrosis after ischemia–reperfusion injury or unilateral ureteral obstruction is attenuated in ADAM17 hypomorphic mice or mice with inducible silencing of ADAM17 in proximal tubule [156]. The non-receptor tyrosine kinase, focal adhesion kinase (FAK), is suggested as a key regulator of Src-mediated ADAM17 Tyr702 phosphorylation and subsequent profibrotic responses in mesangial cells under high glucose condition [157]. In streptozotocin-induced diabetic mice, Src inhibitors also attenuate ADAM17 activation in the kidney cortex, albuminuria, glomerular collagen accumulation, that are associated with attenuation of ERK and EGFR phosphorylation [158]. These data suggest the critical role of ADAM17 in renal fibrosis.

In lupus nephritis, iRom2/ADAM17-mediated TNF-α and EGFR signaling pathways also cause renal damage [159]. Polycystic kidney disease (PKD) is a genetic disorder leading to the formation of multiple cysts in kidneys. The study of animal models of autosomal recessive PKD has revealed

that ADAM17 expression is increased in the collecting duct epithelial cells in the cystic kidneys. Activation of ADAM17 induces constitutive shedding of HB-EGF, amphiregulin and TGF-α, resulting in EGFR/ERK pathway activation and maintains higher cell proliferation in PKD cells [160].

Clinical studies further suggest that ADAM17 plays important roles in human renal diseases. Patients with acute kidney injury or chronic kidney disease (CKD) have high soluble amphiregulin in their urine and both ADAM17 and amphiregulin expression are strongly correlated with markers of fibrosis in kidney biopsies [156]. In various human renal diseases, ADAM17 is strongly induced in podocytes, proximal tubules, and peritubular capillaries, and renal ADAM17 expression is significantly associated with glomerular and interstitial injury or renal function [161]. Urinary ADAM17 is increased in type 2 diabetes patients and could be used as an early biomarker to detect CKD [162]. Moreover, large clinical studies showed that high ADAMs activity level is independently correlated with CKD progression and onset of cardiovascular events in CKD patients [163, 164].

ADAM17 and metabolic disorders

ADAM17 activation is considered as one of the major drivers causing insulin resistance associated with metabolic disorders. In insulin receptor haplo-insufficient (Insr ±) diabetic mice, pharmacological inhibition of ADAM17 by TAPI-1 can reduce blood glucose level and vascular inflammation [165]. In addition, knock down of tissue inhibitor of metalloproteinases-3 (TIMP-3), an inhibitor for ADAM17 and MMPs, in Insr ± mice aggravates blood glucose level and vascular inflammation [165]. On the contrary, TIMP-3 overexpression in macrophage can protect mice from increasing insulin resistance, adipose tissue inflammation, and nonalcoholic fatty liver [166].

There is additional evidence to support these findings. High-fat diet causes increased body weight, liver weight, epididymal adipose tissue weight, systolic blood pressure, fasting blood glucose and lipid levels, and decreased adiponectin level, and these changes are attenuated in temporal systemic ADAM17 deletion (TaceMx1) mice. In addition, increased macrophage infiltration and the expression of TNF-α and monocyte chemoattractant protein-1 (MCP-1) in epididymal adipose tissue induced by high-fat diet are also attenuated in TaceMx1, suggesting that ADAM17 is an important mediator in the development of obesity-induced metabolic disorders [167]. ADAM17 ± mice are partially protected from obesity and insulin resistance compared with wild type mice [168], and ADAM17 inhibitor can improve insulin sensitivity in fructose-fed rats [169] or high-fat diet-fed mice [170]. Deletion of iRom2 also protects against diet-induced obesity [171]. In addition, macrophage metabolic reprogramming has been suggested to enhance aortic dissection via hypoxia-inducible factor 1α (HIF-1α)-dependent ADAM17 induction [172]. In line with the requirement of iRhom2 in myeloid TNF-α production, iRhom2–/– mice are protected against high-fat diet-induced adipose tissue inflammation, weight gain and insulin resistance [173]. Taken together, ADAM17 and iRhom2 should be recognized to play an important role in metabolic disorders and diabetes.

ADAM17 SNPs and loss-of-function mutations

ADAM17 SNPs (rs10495565, rs12474540, and rs17524594) associate with the presence of pulmonary arteriovenous malformations in hereditary hemorrhagic telangiectasia 1 (HHT1), indicating genetic variation in ADAM17 can promote a TGF-β-regulated vascular diseases [131]. In addition, ADAM17 SNPs (rs6705408, rs10495563, and rs6432017) are associated with incidence of Kawasaki disease and interaction with TGF-β signaling is suggested [174]. Two ADAM17 SNPs (m1254A > G and i33708A > G) also contribute to obesity risk [175]. However. the relation of these SNPs and ADAM17 expression or activity remains unstudied. ADAM17 SNP Ser746Leu and -154A allele have been reported to increase soluble TNF-α plasma levels and the risk of cardiovascular death [176]. In addition, further studies may enable us to use a tailor-made approach for cardiovascular diseases based on information from ADAM17 SNPs.

Regarding the loss-of-function mutation, a late-onset familial Alzheimer disease was identified to co-segregate with rare heterozygous ADAM17 single nucleotide variant rs142946965 [177]. This causes ADAM17 mutation R215I directly adjacent to pro-protein convertase cleavage motif 210–214 and severely impairs ADAM17 maturation leading to amyloid β formation. In addition, heterozygous mutation of ADAM17 Y42D and L659P are associated with incidence of Fallot tetralogy and loss of HB-EGF shedding [178]. Finally, two distinct homozygous loss-of-function mutations of human ADAM17 have been reported (c.603-606delCAGA and c.308dupA). The siblings with 603-606delCAGA demonstrated skin lesions and diarrhea. While one of the siblings (a girl) died at age of 12, the affected boy has survived with loss of ADAM17 expression, diminished TNF-α production and left ventricular dilatation [179]. The c.308dupA patient demonstrated skin lesions, diarrhea and severely diminished levels of plasma TNF-α and IL2. Interestingly, this patient developed unexpected hypertension. Recurrent sepsis was the cause of death at 10 months [180].

Other ADAMs in cardiovascular pathophysiology

In addition to ADAM17, ADAM8, 9, 10, 12, 15, 19, 28 and 33 are expressed on various cells including endothelial cells, smooth muscle cells, and leukocytes, and they also have proteolytic activity. Accumulating data suggest that other ADAMs play notable roles in cardiovascular pathophysiology by mediating inflammation, angiogenesis, cell proliferation, and cell migration (Fig. 5 and Table 2). Among these ADAM families, ADAM10 is most broadly expressed and is closely related to ADAM17 in its structure and function. Therefore, ADAM10 is recognized as another important shedding proteinase which mediates various signal transduction. Important for cardiovascular pathophysiology, ADAM10 can affect inflammation by cleaving CD44 [117], CX3CL1 [181], C-X-C motif chemokine ligand 16 (CXCL16) [182], IL6 receptor [183], receptor for advanced glycation end products (RAGE) [184], and TNF-α [185]. It also affects angiogenesis by cleaving JAM-A [123], Notch [186], neuropilin 1 (NRP-1) [31, 187], VEGFR2 [188] and vascular endothelial (VE)-cadherin [189]. It affects cell proliferation or migration by cleaving betacellulin [190, 191] and HB-EGF [192], affects collagen turnover by cleaving discordin domain receptor family, member 1 (DDR1) [193], affects apoptosis by cleaving receptor activator of nuclear factor κ-B ligand (RANKL) [194], and affects blood pressure by cleaving corin [195]. Furthermore, ADAM10 can affect acute kidney injury by cleaving meprin A, a membrane-associated metalloproteinase in proximal tubules, since meprin A is one of the key players in acute kidney injury [196]. However, as mentioned previously, most substrates can be cleaved by multiple ADAMs. The interaction between each ADAM and its substrates depends on pathophysiologic condition. Furthermore, some substrates are cleaved by their respective ADAMs in different manner and in different cell component. ADAM10-mediated Notch shedding is ligand dependent; whereas, ADAM17-mediated Notch shedding is ligand-independent [197]. Neural cell adhesion molecule L1/CD171 and CD44 are cleaved by ADAM17 at cell surface and soluble forms are released into the extracellular space; whereas, they are cleaved by ADAM10 in endosomes and soluble forms are released from cell as exosomes [198]. Neuregulin, cleaved by ADAM17 at cell surface, is cleaved in the Golgi apparatus by ADAM19 [199]. There are highly complicated relations between ADAMs and substrates that should be elucidated further. Because of this complexity, the approach to consider ADAMs as therapeutic targets is challenging.

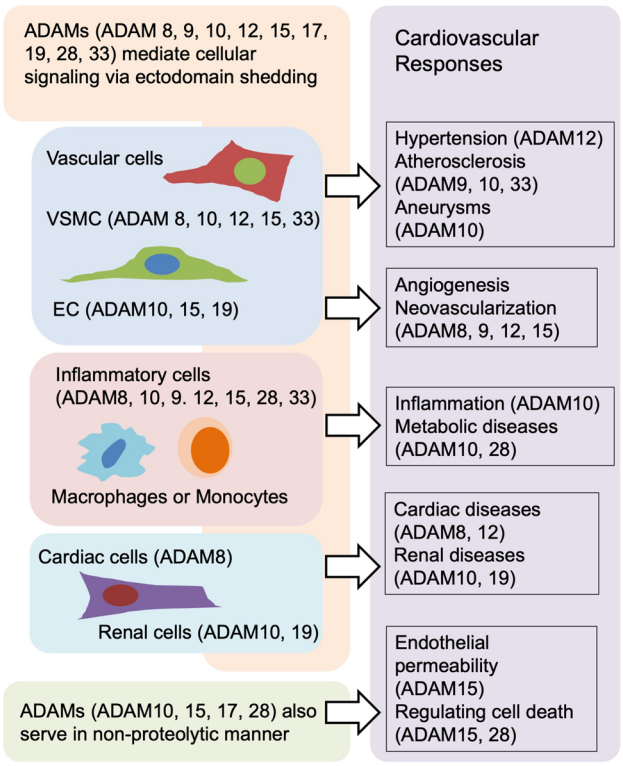

Fig. 5 Cell-type-specific role of non-ADAM17 ADAMs in cardiovascular diseases. Non-ADAM17 ADAMs are expressed in various cell types and regulate cellular signaling within and between these cells. Non-ADAM17 ADAMs thereby mediate cardiovascular pathophysiology including hypertension, atherosclerosis and cardiovascular inflammation. The figures are created based on the references used in the other ADAMs section

ADAMs can also serve in non-proteolytic manner. ADAM15 regulates endothelial permeability and neutrophil migration by promoting Src/ERK signaling in a protease activity-independent manner [200], and subsequently contributes to atherosclerosis [201]. ADAM28 is reported to bind to C1q and attenuates C1q-induced cell death [202]. It binds to P-selectin glycoprotein ligand-1 (PSGL-1) to promote leukocyte rolling, adhesion to endothelial cells and subsequent inflammation [203]. It also binds to integrin α4 β1 and enhances cell adhesion to VCAM-1 and regulates spatial and temporal trans-endothelial migration of lymphocytes [204]. In the following section, we highlight the role of these ADAMs in cardiovascular pathophysiology.

Lessons from genetically modified animal models

ADAM8 –/– mice [205], ADAM9 –/– mice [206], ADAM15 –/– mice [207], and ADAM33 –/– mice [208] are viable and do not show an obvious phenotype under normal conditions. However, there are reduced retinal neovascularization in an experimental retinopathy model in ADAM8 –/– mice [209], ADAM9 –/– mice [210] and ADAM15 –/– mice [207]. ADAM10 –/– mice die before birth with defects in cardiovascular system [211]. ADAM19 –/– mice also die

Table 2 Cardiovascular-related substrates of ADAMs

	Inflammation	Angiogenesis	Proliferation/migration	Others
ADAM8	CD16 [318] CD23 [319] CX3CL1 [318] L-selectin [320] TNF alpha [318] TNFR1 [321] VCAM-1 [322]		TGF alpha [318]	
ADAM9	CD40 [210] VCAM-1 [210]	Notch [282] Tie-2 [210] VE-cadherin [210] VEGFRII [210]	HB-EGF [323]	ADAM10 [324, 325] EphB4 [210]
ADAM10	CD44 [117] CX3CL1 [181] CXCL16 [182] IL6R [183] RAGE [184] TNF alpha [185]	E-cadherin [326] JAM-A [123] N-cadoherin [221] Notch1 [186, 282] Notch2 [327] NRP-1 [31] VEGFRII [188] VE-cadherin [189]	Betacellulin [190, 191] HB-EGF [63]	CD84 [328] Corin [195] DDR1 [193] Klotho [109] Meprin A [196] Neuregulin [329] RANKL [194]
ADAM12		E-cadherin [330] IFGBP3 [331] IFGBP5 [331] Notch1 [282]	Betacellulin [332] HB-EGF [333]	
ADAM15		E-caderin [334] VEGFR [335]	FGFR2iiib [331]	ADAM10 [325]
ADAM17	CD40 [268] CD44 [117] CD163 [310] CX3CL1 [252, 253] ICAM-1 [111] IL-1R II [21] IL6R [277, 278] L-selectin [113] L1-CAM [295] p55 TNF alpha RI [20, 21] P75 TNF receptor [21, 113] PECAM-1 [135] TNF alpha [4, 11, 20, 190, 260, 261] VCAM-1 [109, 299]	JAM-A [123] Notch1 [282, 283] VEGFR [31]	HB-EGF [135, 190, 300, 303] IGFR1 [135] Pref-1 [282, 304] SEMA4D [305] syndecan 1 and 4 [287] TGF alpha [113, 300]	ACE2 [263–265] EPCR [83] Ephrin B4 [135] Jagged 1 [38] Klotho [312] RANKL [259]
ADAM19	Alpha 2 macroglobulin [336] TNF alpha [20, 337]	Neuregulin [231, 338]		(pro)renin receptor [339] RANKL [337]
ADAM28	TNF alpha [234]	IGFBP3 [340]	CTGF [341]	vWF [342]
ADAM33				RANKL [343]

perinatally, likely as a result of cardiac valve and vasculature defects [212, 213]. In addition, knockdown of MMP-7 attenuates angiotensin II-induced myocardial ADAM12 overexpression, hypertension and cardiac hypertrophy, showing the importance of MMP-7/ADAM12 signaling axis in hypertensive cardiac disorders [214].

Mice lacking the ADAM10 gene primarily in endothelial cells show multiple cardiac and vascular defects similar to Notch1 mutants [186, 215], suggesting that Notch signaling pathway is a key player in ADAM10-mediated cardiovascular development. ADAM10-mediated Notch signaling also promotes the development and maturation of the glomerular vasculature [216]. Using a similar model, Notch1 and Notch4 were shown to control the development of several organ-specific vascular beds in an ADAM10-dependent manner [217]. Moreover, collecting duct-specific ADAM10 knockout mice show defects in urine concentration, polyuria, and hydronephrosis, along with reduction of Notch activity in the collecting duct epithelium [218]. Transplantation of bone marrow from myeloid-specific ADAM10 knockout mice to atherogenic model mice does not affect the plaque size, but increases plaque collagen content, indicating that myeloid ADAM10 modulates atherosclerotic plaque stability. ADAM10-deficient macrophages further showed

anti-inflammatory phenotype with increased IL-10 and decreased pro-inflammatory factors such as IL-12 [219]. In addition, AngII-induced AAA in mice is exaggerated in ADAM15–/– mice. This is due to defect in thrombospondin-1 processing by ADAM15 causing thrombospondin-1-dependent apoptosis of VSMCs [220].

Other ADAMs in cardiovascular disease, human findings

In human atherosclerotic lesions, ADAM10 is expressed and its expression is associated with plaque progression and neovascularization [188]. Increased ADAM10 expression in human atherosclerotic lesions is associated with decreased N-cadherin when apoptosis increases [221]. This association between ADAM10 and vascular remodeling is further supported by some animal models. A study with $CaCl_2$-induced TAA model showed that ADAM10 expression was significantly increased in intima and media of TAA [93]. A study using diabetic minipigs showed that ADAM10 expression was increased in vascular segments obtained from coronary artery restenosis, implicating the role of ADAM10 in neointimal formation [222]. ADAM9 and ADAM15 also express in human atherosclerotic lesions [223], co-localized with CD68-positive cells of monocytic origin in the plaques [84]. ADAM8 and ADAM15 are highly expressed in the media layer in patients with ascending aortic dissection compared to that in patients with dilatation of the ascending aorta [224]. Although ADAM8 is up-regulated in atherosclerotic lesions and expressed in circulating neutrophils and macrophages in humans, whole body and hematopoietic ADAM8 deletion did not alter atherosclerotic plaque development [225]. In high-graded carotid artery lesions, macrophages and smooth muscle cells are positive for ADAM8, ADAM10, ADAM12, ADAM15, and ADAM17. The luminal surface of endothelial cells is positive for ADAM15, and neo-vessels are positive for ADAM12 [226]. ADAM33 is expressed in smooth muscle cells and inflammatory cells within human atherosclerotic lesions [227]. Moreover, ADAM33 SNPs are reported to correlate with the extent of atherosclerosis in coronary artery disease patients [227] and cardiovascular mortality [228]. The risk alleles of ADAM8 SNPs are associated with elevated serum soluble ADAM8 and the risk of myocardial infarction in two independent cohorts [229]. This result is supported by animal study showing that myocardial infarction increased remote ADAM8 expression in rat heart [230]. In line with ADAM15–/– mice enhancing AAA, ADAM15 expression appears decreased in human AAA samples as well as AngII model of mouse AAA [220]. Collectively, several ADAMs seem to contribute to arterial physiology, progression of atherosclerosis and ischemic heart diseases in humans.

In human kidneys, mesangial ADAM19 expression is associated with glomerular damage, and ADAM19 in proximal tubules and in peritubular capillaries is associated with interstitial fibrosis, and tubular ADAM19 is associated with declining renal function [231]. These data indicate the role of ADAM19 in renal profibrotic and proinflammatory processes [231]. In addition, study with renal transplant patients showed that ADAM19 mRNA was significantly higher in chronic allograft nephropathy, and ADAM19 expression in renal endothelium was significantly higher in acute rejection [232].

RAGE is widely recognized to have an important role in the pathogenesis of diabetic complications, and Type 1 diabetes patients have significantly higher serum soluble RAGE, along with an increase in serum ADAM10 [233]. Finally, ADAM28 expression in blood mononuclear cells significantly correlates with parameters of metabolic syndrome including body mass index and relative fat, suggesting the role of ADAM28 in human metabolic conditions [234].

Therapeutic potential

As reviewed elsewhere, various ADAM17 inhibitors have been synthesized which selectively inhibit ADAM17 and do not inhibit other metalloproteinases [235, 236]. Using animal models, the efficacy of ADAM17 inhibition is reported in not only inflammatory diseases such as rheumatoid arthritis [237] but also cardiovascular disorders such as renal fibrosis [155, 238], intestinal reperfusion injury [239], or polycystic kidney disease [240, 241]. Similarly, mice with genetically modulated ADAM17 indicate the positive potential of ADAM17 inhibition in inflammation such as septic shock [80, 138, 242]. A9B8 is a human/mouse cross-reactive inhibitory antibody against ADAM17. A9B8 treatment attenuated EGFR transactivation in cultured VSMCs. Moreover, it attenuated cardiovascular pathology in mice infused with angiotensin II [66]. A9B8 also effectively prevented AAA development and rupture in a mouse model [87]. In addition, the auto-inhibitory ADAM17 prodomain which inhibits ADAM17, but not ADAM10, can attenuate TNF-α secretion. This peptide inhibitor appears effective in ADAM17-dependent models of inflammatory diseases including rheumatoid arthritis [243]. In spite of these promising in vivo results, pre-clinical trials and clinical trials using ADAM17 inhibitors had to be discontinued due to hepatotoxicity [237] or lack of efficacy [244]. One of the reasons can be that ADAM17 inhibition affects normal physiological conditions. ADAM17 –/– mice die shortly after birth because of a variety of defects [138] but mice with reduced ADAM17 level in all tissues (ADAM17 ex/ex) show substantially increased susceptibility to inflammation [80],

indicating that adequate therapy window should be set for ADAM17 inhibitors. Since ADAM17 inhibitors have demonstrated adverse side effects clinically, certain regulators of ADAM17 can also be considered as therapeutic targets. One such regulator, iRhom2, is an essential determinant of ADAM17-dependent shedding in leukocytes by mediating ADAM17 maturation, and iRhom2 is potential target for selective inactivation of the pro-inflammatory roles of ADAM17 activation [245].

Another approach is to analyze and utilize ADAMs-modulating aspects of existing drugs. Aspirin is widely used for the prevention of thrombosis of coronary artery and cerebral artery. Aspirin at high concentrations is reported to induce ADAM17-mediated shedding of glycoprotein (GP) Ib α and GPV [246]. Non-steroidal anti-inflammatory drugs (NSAIDs) with diphenylamine structure causes a reduction in the neutrophil intracellular ATP concentration, and this reduction is related with ADAM17-dependent L-selectin shedding at leukocyte surface [247]. 1,25-dihydroxyvitamin D, the hormonal form of vitamin D, has a potential anti-inflammatory and anti-atherosclerotic effect, and is widely used for chronic kidney disease patients, because 1,25-dihydroxyvitamin D is proven to significantly improve not only secondary hyperparathyroidism but patients' survival via renal and cardiovascular protective effects [248]. 1,25-dihydroxyvitamin D inhibits ADAM17 expression through the induction of C/EBP beta [249], and prevents ADAM17/TNF-α-mediated secondary hyperparathyroidism, fibrotic and inflammatory lesions to the renal parenchyma, and systemic inflammation [250]. 1,25-dihydroxyvitamin D also causes ADAM10-dependent TNFR1 shedding, thus blocking TNF-α function in VSMC [251]. These agents regulating ADAMs activity could be considered as a novel therapeutic approach if the mechanisms are clarified further.

Concluding remarks

Since ADAMs are ubiquitously expressed in somatic cells and they cleave various substrates, ADAMs, especially ADAM17, have important and highly intricate roles in cell signaling. The accumulation of research in this area steadily shed light on the role of ADAM17 and other ADAMs in cardiovascular diseases. Although ADAM17 and some of the other ADAMs are essential for normal development or cardiovascular homeostasis, excess of these ADAMs activation aggravates inflammatory response and cardiovascular pathophysiology, and ADAM17 inhibition is thought to be promising therapeutic target for cardiovascular and renal diseases. We hope further research based on existing evidence highlighted in this review will elucidate ADAMs-mediated signal transduction and pathophysiology of cardiovascular diseases, and embody the therapeutic potential with pharmacological targeting.

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Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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