

A Disintegrin and Metalloproteases (ADAMs) in Cardiovascular, Metabolic and Inflammatory Diseases: Aspects for Theranostic Approaches

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Abstract

A disintegrin and metalloproteases (ADAMs) are membrane-bound enzymes responsible for the shedding or cleavage of various cell surface molecules, such as adhesion molecules, cytokines/chemokines and growth factors. This shedding can result in the release of soluble proteins that can exert agonistic or antagonistic functions. Additionally, ADAM-mediated cleavage can render these membrane proteins inactive. This review will describe the role and association of ADAMs in various pathologies with a main focus on ADAM10 and ADAM17 in atherosclerosis, including a brief overview of atherosclerosis-related ADAM substrates. Furthermore, ADAMs involvement in other metabolic and inflammatory diseases like diabetes, sepsis, Alzheimer's disease and rheumatoid arthritis will be highlighted. Subsequently, we will briefly discuss an interesting emerging field of research, i.e. the potential implications of ADAM expression in extracellular vesicles. Finally, several ADAM-based therapeutic and diagnostic (theranostic) opportunities will be discussed, while focusing on key questions about the required specificity and selectivity.

Keywords

- ▶ a disintegrin and metalloprotease
- ▶ pathologies
- ▶ cardiovascular disease
- ▶ atherosclerosis
- ▶ therapy

The ADAMs Family: Function and Regulation

The mammalian genome consists of 40 a disintegrin and metalloprotease (ADAM) family members, although only 12 ADAM genes encode for proteolytically active proteases able to cleave/shed surface molecules, i.e. ADAM8, 9, 10, 12, 15, 17, 19, 20, 21, 28, 30 and 33.¹ ADAM cleavage or shedding can result in the release of soluble factors, such as tumour necrosis factor (TNF), or of intracellular domains like Notch after regulated intra-membrane proteolysis.² Besides the

metalloproteinase domain, ADAMs also contain a disintegrin domain, capable of binding to various integrins, although this function is still poorly understood.³ Especially ADAM10 and ADAM17 are the best studied family members and have been shown to be involved in the shedding of inflammatory mediators like cytokines/chemokines and adhesion molecules. The list of substrates that can be shed by these proteases is substantial and still increasing (reviewed in Dreytmueller et al,⁴ van der Vorst et al,⁵ Zhang et al,⁶ and Zunke and Rose-John⁷). For ADAM17, one of the best known substrates is TNF, hence the alternative nomenclature for this protease is TNF converting enzyme.⁸

While ADAM expression and activity is regulated at various levels, e.g. at the transcriptional and post-transcriptional level

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(reviewed in Drey Mueller and Ludwig⁹ and Grötzinger et al¹⁰), evidence is emerging that substrate-specificity is regulated by membrane localization.¹¹ ADAM proteases are produced as latent enzymes, which are activated by removal of the pro-domain by furin-like convertases.¹ Post-transcriptionally, tissue inhibitors of metalloproteases (TIMPs) regulate ADAM activities as TIMP1 blocks ADAM10, whereas TIMP3 inhibits both ADAM10 and ADAM17 activity.¹² No consensus sequence exists that determines whether these ADAMs cleave a specific substrate. Recently, it has been shown that the surface exposure of phosphatidylserine (PS) is necessary for ADAM17 to exert its sheddase activity.¹³ ADAM17 has been shown to bind to PS and this interaction speculatively directs the protease to its substrate.^{10,13} Increasing evidence suggests that (co-)localization of the enzyme and substrate regulate cleavage activities. Lipid rafts, for example, are cholesterol-rich areas in the membrane where many receptors and signalling molecules cluster together.¹⁴ Previously, it has been shown that ADAM17 is preferentially located in these rafts. Lipid raft disruption resulted in increased shedding of TNF as disruption brought the ADAM17 protease in close vicinity of its substrate TNF, further confirming a crucial regulatory role of this membrane localization in ADAM activity.¹⁵ Besides ADAM17, ADAM10 has also been shown to be regulated by lipid raft modulation as cholesterol depletion affected both ADAM10- and ADAM17-mediated shedding of Fas ligand.¹⁶ Besides lipid rafts, also other membrane domains gained interest for ADAMs regulation, i.e. the tetraspanin-enriched micro-domains. For example, ADAM10-mediated amyloid precursor protein (APP) cleavage was shown to be regulated by tetraspanin 12,¹⁷ whereas ADAM10-dependent cleavage of epidermal growth factor is regulated by tetraspanins CD9, CD81 and CD82.¹⁸ The Tspan C8 family was shown to regulate ADAM10 maturation and trafficking to the cell surface in endothelial cells.¹⁹ Interestingly, data from Noy et al suggested that different members of this Tspan family regulate substrate selectivity of ADAM10, as further discussed below.²⁰ While tetraspanins seem to mainly regulate ADAM10, maturation and trafficking of ADAM17 is specifically regulated by the catalytically inactive family of rhomboid proteases.^{21–23} Research focusing on the regulation of ADAM activity is still a very dynamic and evolving field.

ADAMs in Cardiovascular Disease

Focusing on cardiovascular disease (CVD) and its underlying pathogenesis of atherosclerosis development, various crucial mediators have already been identified as substrates for ADAM10 and/or ADAM17 (extensively reviewed by van der Vorst et al and Drey Mueller et al^{4,5}). For example, we and others identified the junctional molecules vascular endothelial (VE)-cadherin and junctional adhesion molecule A, which play a crucial role in vascular permeability and leukocyte transmigration as ADAM10/17 substrates.^{24–26} Additionally, ADAM10/17 have been shown to shed the platelet receptors glycoprotein I (GPI) and GPVI which are important in thrombus formation,²⁷ although the precise impact of ADAM10/17 shedding on thrombosis itself remains controversial. Furthermore, both proteases have been shown to be involved in the cleavage of

CX₃CL1 and CXCL16, which are chemotactic proteins that are synthesized as transmembrane molecules with adhesive properties and upon cleavage produce a soluble chemoattractant. Cleavage of these proteins by ADAM10/17 can thus result in a reduction of leukocyte adhesion and even detachment of bound cells, although the attraction of new cells increases by the release of the soluble chemoattractant.^{28,29} Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) are two other essential leukocyte adhesion molecules that are critically involved in atherosclerotic lesion initiation/development and that can be shed by ADAM17.^{30,31} Furthermore, ADAM17-mediated shedding of syndecans has been reported which may affect leukocyte recruitment by altering chemokine/cytokine signalling.^{32,33} Importantly, many soluble forms of ADAM substrates, like sICAM, sVCAM, sRAGE (receptor for advanced glycation end-products), sCD40L, sIL6R and TNF, have been shown to correlate with (clinical events of) CVD and were identified as potential biomarkers.^{34–36} Recently, Rizza et al showed a clear correlation between ADAM17 substrates and recurring cardiovascular events in human subjects with atherosclerosis.³⁷ Considering their role in inflammation and leukocyte recruitment, ADAMs most likely also play a crucial role in atherosclerosis.

Indeed, several ADAMs have already been associated with atherosclerosis development (→ **Table 1**). For example, the rs653765 polymorphism in the ADAM10 promoter, leading to a significantly enhanced ADAM10 expression, was found to be associated with atherosclerotic cerebral infarction in a Chinese population.³⁸ Moreover, we showed ADAM10 expression to be relatively low in a healthy human vessel wall and early human atherosclerotic lesion, but this significantly increased during plaque progression.²⁴ As ADAM10 full-body knockout mice are embryonically lethal, the effect of total ADAM10 deficiency on atherosclerosis cannot be evaluated. However, using myeloid-specific ADAM10-deficient mice we could observe that a myeloid-specific deficiency of ADAM10 did not alter lesion size, but shifted the balance from inflammation towards fibrosis in these atherosclerotic lesions.³⁹ Additionally, also ADAM17 has been associated with atherosclerosis development. In mouse quantitative trait locus mapping, increased ADAM17 expression has been shown to be associated with atherosclerosis resistance,⁴⁰ while in rats enhanced ADAM17 expression has been associated with cardiac remodelling after acute myocardial infarction.⁴¹ Cardiac myocyte ADAM17 has also been shown to be of crucial importance in post-infarction recovery by regulating VE growth factor receptor 2 transcription and angiogenesis, thereby limiting left ventricular dilation and dysfunction.⁴² A recent review by Chute et al provides a more detailed overview of the role of ADAMs in heart physiology and pathology.⁴³ Furthermore, Canault et al showed that ADAM17 expression is associated with lesions in atherosclerosis-prone sites in mice and may contribute to elevated levels of soluble TNF receptor in the plasma.⁴⁴ Collectively, these results suggest an important role for ADAM17 in atherosclerosis and CVD, although observed associations are still contradicting. Using lentiviral knockdown of ADAM17 in abdominal aortic plaques of rabbits, Zhao et al showed lower plaque burden with

Table 1 ADAMs in atherosclerosis/CVD in humans

ADAM proteases	Main conclusion	Reference
ADAM8	Single nucleotide polymorphism 2662 T/G associated with atherosclerosis development and fatal myocardial infarction	55
	Polymorphism (rs2275725) is associated with atherosclerosis development and the occurrence of myocardial infarctions	56
ADAM9	Up-regulated in macrophages in advanced human atherosclerotic plaques in samples from carotid, aortic and femoral territories compared with samples from internal thoracic artery free of atherosclerotic plaques	50
ADAM10	Increased expression during atherosclerotic plaque progression; highly expressed in plaque micro-vessels and macrophages/foam cells	24
ADAM15	Up-regulated in macrophages in advanced human atherosclerotic plaques in samples from carotid, aortic and femoral territories compared with samples from internal thoracic artery free of atherosclerotic plaques	50
ADAM17	Correlation between ADAM17 substrates (e.g. sICAM-1 and sTNFR1) and recurring cardiovascular events in human patients with atherosclerosis	37
	Up-regulated in macrophages in advanced human atherosclerotic plaques in samples from carotid, aortic and femoral territories compared with samples from internal thoracic artery free of atherosclerotic plaques	50
	Detected and active in micro-particles released from atherosclerotic lesions	84
ADAM33	Expressed in human atherosclerotic lesions in smooth muscle cells and leukocytes	54
	Polymorphism (rs574174) is associated with atherosclerosis development	54
	Individuals homozygous for the rs2280090 polymorphism have an increased risk of all-cause and cardiovascular mortality compared with wild types	97

Abbreviations: ADAM, a disintegrin and metalloprotease; CVD, cardiovascular disease; sICAM-1, soluble intercellular adhesion molecule-1; sTNFR1, soluble tumor necrosis factor receptor 1.

reduced expression of inflammatory genes and increased expression of transforming growth factor- β (TGF β), indicative of enhanced plaque stability.⁴⁵ Recent studies by Nicolaou et al using ADAM17 hypomorphic mice, expressing very low levels of ADAM17,⁴⁶ could clearly show a atheroprotective role of ADAM17 in atherosclerosis development, which they attributed to the cleaving of membrane-bound TNF and TNF-receptor2 preventing endogenous TNF signalling in vascular cells.⁴⁷ Interestingly, they recently also revealed a function of ADAM17 in arterial elastin network maintenance, although the exact underlying mechanism remains to be elucidated.⁴⁸ We could confirm such atheroprotective effects of ADAM17 in a myeloid-specific ADAM17-deficiency (ADAM17-LysM cre) mouse model.⁴⁹ Remarkably, however, endothelial ADAM17 has contrasting atheroprotective effects as was shown in ADAM17-Bmx Cre mice. This is more in line with the findings by Zhao et al, as their lentiviral approach most likely targeted especially the endothelium. The exact mechanisms behind the opposing effects on atherosclerosis development remain to be investigated.

Besides ADAM17, ADAM9 and ADAM15 are also up-regulated in macrophages in advanced human atherosclerotic plaques.⁵⁰ For ADAM15 even a causal relation has been described, showing reduced atherosclerosis development in rabbits over-expressing ADAM15.⁵¹ In sharp contrast, more recently Sun et al showed that ADAM15 deficiency in mice resulted in decreased endothelial permeability, monocyte and neutrophil transmigration and consequently decreased atherosclerotic lesion development.^{52,53} This

clearly indicates that ADAM15 plays a crucial role in atherosclerosis development, although the precise mechanisms are still not completely understood. Furthermore, ADAM33 has been shown to be expressed in human atherosclerotic lesions, and polymorphisms of both ADAM33 and ADAM8 genes are associated with atherosclerosis development.^{54,55} In addition, an ADAM8 polymorphism (rs2275725) has been associated with atherosclerosis development and occurrence of myocardial infarctions.⁵⁶ Recently, we could show that ADAM8 expression was up-regulated in vulnerable human plaques, compared with stable lesions and that this expression was predominantly in the active shoulder region of the lesion.⁵⁷ Remarkably, however, neither a hematopoietic nor whole-body ADAM8 deficiency in mice affected atherosclerotic lesion size.⁵⁷

ADAMs in Other Metabolic and Inflammatory Diseases

Besides a role in CVD and atherosclerosis, ADAMs are also associated with various other metabolic and inflammatory pathologies, like diabetes, sepsis, rheumatoid arthritis and Alzheimer's disease. Especially the role of ADAM17 in diabetes is already thoroughly investigated and nicely reviewed by Menghini et al.⁵⁸ In short, ADAM17 on human white adipocytes has been shown to result in the expression of inflammatory molecules like monocyte chemoattractant protein 1 and interleukin 6 (IL-6) and the secretion of soluble IL-6 receptor,⁵⁹ which mediates IL-6 signalling via activation of

gp130 receptors on cells not expressing the IL-6R themselves (a process called trans-signalling). Interestingly, inhibition of IL-6 trans-signalling reduced atherosclerosis development in mice.⁶⁰ Additionally, ADAM17 on skeletal muscles induces the release of TNF and therefore causes insulin resistance via inhibition of the glucose transport. Finally, ADAM17 present on hepatocytes increases oxidative stress and promotes hepatic steatosis upon hyperinsulinemia. Besides ADAM17, also serum ADAM10 levels, representing extracellular vesicle-associated ADAM10, and its substrate RAGE have been associated with type 1 diabetes in humans.⁶¹

Regarding the role of ADAMs in sepsis, Horiuchi et al showed that ADAM17 inactivation in myeloid cells results in protection against endotoxin shock,⁶² although these effects were not observed in another infection model, i.e. acute lung inflammation.⁶³ Recently, it has also been shown that the rs653765 polymorphism in the ADAM10 promoter is associated with the development of severe sepsis in humans, indicating that ADAM10 might also be clinically important in sepsis.⁶⁴

Especially ADAM17 is also implicated in rheumatoid arthritis, as both the expression of ADAM17 and TNF were up-regulated in arthritis-affected cartilage.⁶⁵ Further supporting a role for ADAM17 in arthritis is the fact that selective inhibitors against ADAM17, including TMI-2 (Wyeth) and BMS-561392 (Bristol Myers Squibb), were effective in the treatment of mouse models of arthritis.⁶⁶ Recently, Isozaki et al showed that ADAM10 is also over-expressed in the human rheumatoid arthritis synovial tissue, suggesting that besides ADAM17, ADAM10 might also be involved in the pathogenesis of rheumatoid arthritis.⁶⁷

Alzheimer's disease is a neurodegenerative disease, which shares a common pathophysiological basis, i.e. hyperlipidaemia-induced endothelial injury and inflammation, with CVDs like atherosclerosis⁶⁸ and is predominantly caused by β - and γ -secretase-mediated production of toxic amyloid- β peptides. The cleavage of the APP by α -secretases (i.e. ADAMs) on the other hand has been shown to have neuro-protective functions in the development of Alzheimer's disease. Interestingly, β -amyloid was also found in atherosclerotic plaques^{69,70} and circulating levels of APP have been shown to correlate with CVD risk.^{71,72} Several ADAMs have been shown to possess α -secretase activity and could therefore potentially contribute to neuro-protection⁷³ and their role in brain inflammation has been nicely reviewed by Pruessmeyer and Ludwig.⁷⁴ ADAM10 is the only ADAM family member that mediates a constitutive α -secretase activity,^{75–77} whereas other ADAM proteases (e.g. ADAM8, 9 and 17) mediate a regulated secretase activity. Until now, it has been shown that ADAM10 can indeed be beneficial as this protease protected against amyloid- β plaque formation by the cleavage of APP in a mouse model.⁷⁸ This notion is further supported by a small clinical trial using the synthetic retinoid acitretin, which results in α -secretase ADAM10 induction, showing enhanced APP processing in patients receiving acitretin.⁷⁹ Furthermore, patients suffering from Alzheimer's disease express less ADAM10, again indicating that this protease could have protective functions.⁸⁰ Interestingly, two polymorphisms in the ADAM12 gene have been

significantly associated with late-onset Alzheimer's disease, although this protease does not possess α -secretase activity suggesting a different mechanism of action.⁸¹

Extracellular Vesicles and ADAMs

In recent years, a highly interesting field of research emerged, investigating extracellular vesicles (e.g. micro-vesicles/micro-particles and exosomes) that are released from various cells under physiological and patho-physiological conditions.⁸² Micro-vesicles are derived from the cell membrane and are enriched with lipid rafts, while exosomes are smaller and of intracellular origin, enriched with tetraspanins.⁸³ As mentioned before, lipid rafts and tetraspanins have also been shown to be key regulators of ADAMs activity. Canault et al indeed confirmed that ADAM17 is present in micro-vesicles released by human atherosclerotic plaques and actively contributes to the shedding of its substrates TNF and TNF receptor.⁸⁴ Additionally, ADAM17 has been shown to be released in exosomes upon cell stimulation in monocytes and primary endothelial cells.⁸⁵ Furthermore, it has been shown that ADAM10 is present in exosomes and can cleave adhesion molecules like L1 and CD44,⁸⁶ while ADAM15 exists in exosomes released from human macrophages.⁸⁷ As extracellular vesicles are considered to be a novel means of intercellular communication, modulating various target cell functions, it will be interesting to further evaluate the systemic effects that ADAMs released in extracellular vesicles can have in different pathologies. Moreover, as extracellular vesicle composition often reflects the phenotype of its parental cell, these vesicles could also serve as (circulating, i.e. non-invasive) biomarkers for CVD.

ADAMs in Therapeutic and Diagnostic Approaches (Theranostics)

As described, ADAMs (and their substrates) are associated with and causally related to CVDs, but also implicated in other pathologies like Alzheimer's disease and rheumatoid arthritis, rendering them interesting candidates for novel diagnostic or therapeutic tools (►Fig. 1). The effects of ADAM activity, either being beneficial or detrimental, vary between different pathologies. Due to this discrepancy, in combination with the variety of ADAM proteases involved, the large list of associated substrates and the cell-specific effects, caution is warranted when developing ADAM-based therapies as unwanted side effects of ADAM inhibition seem almost inevitable. Therefore, inhibition should be very precise with respect to target-protease, -location and -timing. In recent years, research has focused on more specific approaches and developing appropriate inhibitors. As ADAM10 and ADAM17 look like the most suited candidates for targeting, we will focus on these two proteases.

The different levels of ADAM regulation provide several options for therapeutic targeting. The first option is to inhibit the expression of ADAMs, which, for example, has been showed to reduce inflammation by reducing ADAM10 and ADAM17 expression via peroxisome proliferator-activated

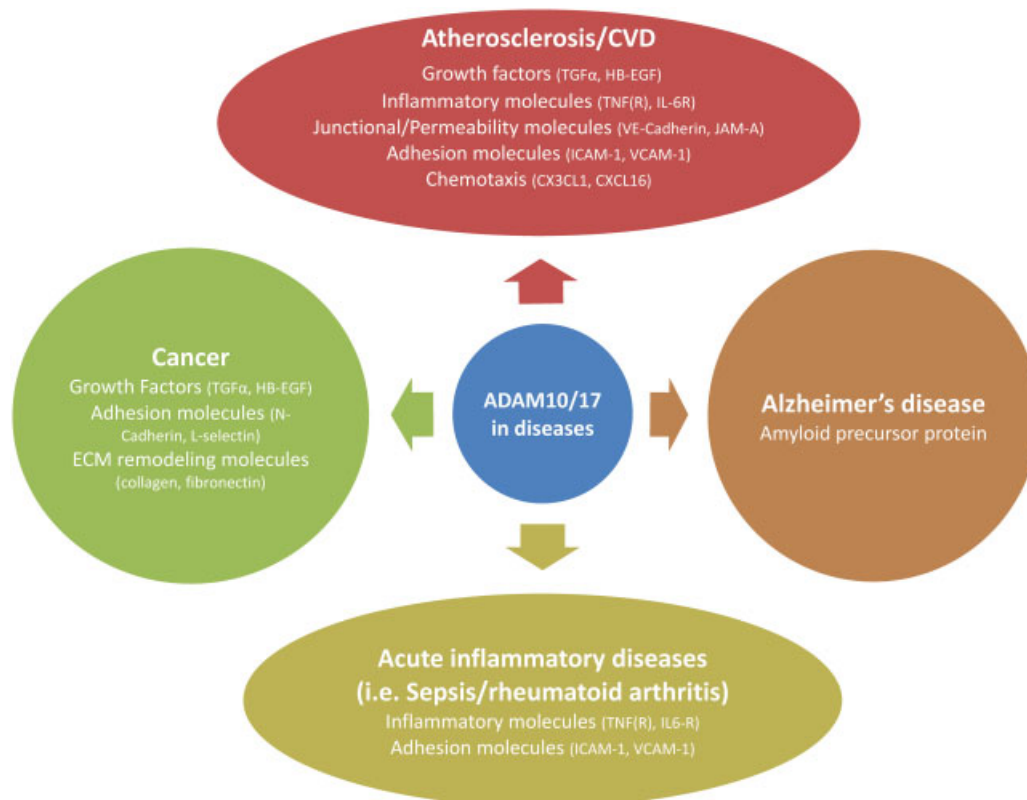


Fig. 1 Generalized overview of a disintegrin and metalloprotease (ADAM)10/17 influences in various pathologies. Depicted are selected main groups of molecules that are influenced by ADAM10/17 in different pathologies. Between brackets is for exemplary purposes, only a small selection of group members shown.

receptor activation.⁸⁸ However, such targeting of course lacks any selectivity for substrates. Several hydroxamate-based inhibitors have already been developed to inhibit the active site of proteases, by inhibiting the zinc-ion binding. For example, the GI254023X compound inhibits ADAM10 100-fold more potently than ADAM17,⁸⁹ although still lacking specificity as it also weakly inhibits ADAM9 and several matrix metalloproteinases.⁹⁰ Various other inhibitors have been developed, although until now no real ADAM-specific inhibition has been observed.⁹¹ Recently, Tape et al developed a specific ADAM17 inhibitor using a two-step phage display approach.⁹² The resulting cross-domain human antibody is a previously undescribed selective ADAM17 antagonist, providing a unique alternative to small-molecule metalloprotease inhibition.⁹² Besides the active zinc-binding domain, also a hyper-variable region called the exosite can come into contact with the substrate. Such exosites recognize specific glycosylation patterns on ADAM substrates and are therefore potential targets for substrate-specific targeting. Recently, inhibitors of these exosites of ADAM17 have been developed, showing substrate selectivity as TNF shedding can be blocked without affecting TGF or CX₃CL1 shedding.⁹³ Recently, it has been shown that inactive rhomboid like protease (iRhom2) is critically involved in the maturation of specifically ADAM17.^{22,23} Interestingly, this iRhom2 involvement is, in the vascular system, mainly observed in leukocytes and can therefore be potentially used to more selectively target ADAM17 in inflammatory diseases.^{23,94} In

contrast, ADAM10 maturation is not mediated by iRhom2, although recently also here some selective targeting opportunities emerged. TspanC8 tetraspanins have been shown to differentially regulate the cleavage of ADAM10 substrates, as Tspan15 was the only TspanC8 member to be able to promote ADAM10-mediated N-cadherin cleavage, whereas Tspan14 distinctively reduced cleavage of the GPVI receptor.^{20,95} As many ADAMs are implicated in the physiological shedding of important proteins like growth factors, such substrate and cellular selectivity will be of great importance to develop suitable ADAM-based therapies. This is also highlighted by the discontinuation of several clinical trials targeting ADAM17 due to unspecific and unwanted side effects.⁶⁶

Besides therapeutic targets, ADAMs could also serve as diagnostic as well as prognostic biomarkers (► **Table 2**). Several reports do already suggest that several ADAMs may be used as biomarkers for cancer.⁹⁶ High urinary ADAM12 levels, for example, were significantly correlated with the presence of breast cancer and bladder cancer. As a more prognostic marker, high levels of ADAM10/17 were even found to predict adverse outcome in patients with breast cancer. Until now, however, research into ADAMs as biomarkers has been limited, especially in the field of atherosclerosis and CVD. Several substrates of ADAM10/17 have already been proposed as biomarkers, although individually it does not appear to be strong enough to obtain a clear association/prediction. It is tempting to speculate that perhaps a panel of several ADAM substrates could increase the predictive and diagnostic potential.

Table 2 ADAMs in diagnosis and therapy

ADAM proteases	Main conclusion	Reference
ADAM9	Increased expression in prostate cancer is associated with shortened relapse-free survival	98
ADAM12	High urinary levels correlate with the presence of breast cancer and bladder cancer	99,100
ADAM17	High expression levels are predictive of a more adverse outcome in patients with breast cancer	101
ADAM28	High diagnostic accuracy of serum levels for non-small cell lung cancer	102

Abbreviation: ADAM, a disintegrin and metalloprotease.

Conclusion

It is clear that several ADAMs can play a crucial role in a large scale of pathologies, such as atherosclerosis. However, the regulation at post-translational level by differential trafficking and activation and the interaction of various ADAMs and their substrates is very complex and not yet fully elucidated. Especially, the precise in vivo and particularly cell-specific effects of ADAMs in the various pathologies still largely needs to be determined as only a few studies so far investigated this. Circulating levels of sADAM8 or a panel of ADAM substrates may become useful biomarkers for CVD, although specificity is an issue as their circulating levels will be affected in many inflammatory diseases and/or cancer. With the prospect of using ADAMs as therapeutic or diagnostic targets, the identification of more specific and perhaps even cell type-specific regulation modalities, such as the iRhom2, is critical. The presence of ADAMs in extracellular vesicles might also be useful in this regard, as this at least allows to detect circulating ADAMs derived from specific cell types. Therefore, future research should focus on elucidating such specificity to create new opportunities to develop suitable ADAM-based theranostics.

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Conflict of Interest
None.

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