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ADAMTS proteins in human disorders

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Abstract

ADAMTS proteins are a superfamily of 26 secreted molecules comprising two related, but distinct families. ADAMTS proteases are zinc metalloendopeptidases, most of whose substrates are extracellular matrix (ECM) components, whereas ADAMTS-like proteins lack a metalloprotease domain, reside in the ECM and have regulatory roles vis-à-vis ECM assembly and/or ADAMTS activity. Evolutionary conservation and expansion of ADAMTS proteins in mammals is suggestive of crucial embryologic or physiological roles in humans. Indeed, Mendelian disorders or birth defects resulting from naturally occurring *ADAMTS2, ADAMTS3, ADAMTS10, ADAMTS13, ADAMTS17, ADAMTS20, ADAMTSL2* and *ADAMTSL4* mutations as well as numerous phenotypes identified in genetically engineered mice have revealed ADAMTS participation in major biological pathways. Important roles have been identified in a few acquired conditions. ADAMTS5 is unequivocally implicated in pathogenesis of osteoarthritis via degradation of aggrecan, a major structural proteoglycan in cartilage. ADAMTS7 is strongly associated with coronary artery disease and promotes atherosclerosis. Autoantibodies to ADAMTS13 lead to a platelet coagulopathy, thrombotic thrombocytopenic purpura, which is similar to that resulting from *ADAMTS13* mutations. ADAMTS proteins have numerous potential connections to other human disorders that were identified by genome-wide association studies. Here, we review inherited and acquired human disorders in which ADAMTS proteins participate, and discuss progress and prospects in therapeutics.

Keywords

Osteoarthritis; atherosclerosis; genome-wide association studies (GWAS); metalloprotease; protease; extracellular matrix

1. INTRODUCTION

Most reviews on secreted proteases view them as destructive entities and drug targets, but in fact, their evolutionary expansion uncovered by genome sequencing suggests otherwise. Indeed, they have evolved to serve essential roles in morphogenesis, tissue remodeling and immunity [1]. This may be particularly true for the ADAMTS proteases, which do not appear to be capable of indiscriminate destruction by virtue of having an apparently high

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catalytic specificity, and whose mutations both in humans and mice suggest participation in distinct pathways [2]. The few instances where ADAMTS proteases are excessively active in disease are overwhelmingly outnumbered by disorders arising from loss of function, typically by gene mutations. Genetic disorders of ADAMTS proteases were reviewed in detail recently [2]. We provide an update on those here and focus the review on ADAMTS proteins in acquired human conditions. Many acquired disorders have a small, but significant genetic component that can be revealed, with inherent limitations, using genome-wide association studies (GWAS). Indeed, GWAS made an initial association of ADAMTS7 with atherosclerosis, which now appears to be widely accepted. On the other hand, several published ADAMTS associations with disease were made solely using ELISA assays or transcriptome analysis to link higher or lower levels of ADAMTS proteins and genes with disease states, but without further analysis. These associations are not discussed here. Several ADAMTS proteases are implicated as anti-cancer or pro-tumorigenic molecules and undoubtedly have a role in the biology of many cancers. However, there are no instances where ADAMTS proteins are unequivocally identified as causal (i.e., primary oncogenes), or substantially protective (i.e., primary tumor suppressors) in specific cancer types. The reader is referred to a recent review of ADAMTS proteases in cancer for coverage of this complex topic [3]. Here, we offer a curated discussion of the most robust established disease roles and emerging disease associations.

1.1. ADAMTS proteases and ADAMTS-like proteins

Of the 26 ADAMTS superfamily genes known in humans and mice, 19 encode zinc metalloproteinases, constituting the ADAMTS protease family (Figure 1). Although their numbering extends from *ADAMTS1* to *ADAMTS20*, the symbols *ADAMTS5* and *ADAMTS11* described the same protease, and *ADAMTS11* is no longer used. The discovery of genes encoding 7 ADAMTS-like proteins (*ADAMTSL1* through *ADAMTSL6* and *PAPLN*) (Figure 2) completed genetic cataloguing of the superfamily. ADAMTSLs are the products of distinct genes and none arise from alternative splicing of ADAMTS protease genes. They lack the zinc metalloproteinase domain as well as the propeptide and disintegrin-like domain present in all ADAMTS proteases. The latter two domains may therefore be required for regulation of ADAMTS catalytic activity, and there is evidence that they do so. Specifically, the ADAMTS propeptide may function as an intramolecular chaperone for correct folding of the catalytic domain, e.g. as shown for ADAMTS9 [4], and akin to matrix metalloproteinase propeptides, it may also have a role in inhibiting catalytic activity [5, 6]. High-resolution structural analysis has suggested that the ADAMTS4 and ADAMTS5 disintegrin-like module may extend the substrate-binding region and thus contribute to catalytic specificity [7, 8]. ADAMTSLs retain all other ADAMTS modules, i.e., those comprising the C-terminal ancillary domain of ADAMTS proteases, namely the thrombospondin type 1 repeats (TSRs), cysteine-rich and spacer modules and protease and lacunin (PLAC) domain in specific configurations (Figure 2). However, as is evident from Figure 1 and Figure 2, none of the ADAMTSLs have the precise composition of any of the ADAMTS ancillary domains. Since ADAMTS protease ancillary domains have a substantial role in substrate recognition, and therefore in ADAMTS specificity, it is likely that ADAMTSLs also have specific extracellular ligands. Current evidence suggests that several are ECM-binding proteins that function at the cell-matrix interface [9–11]. Fibrillin

microfibrils are known to bind ADAMTSL2, ADAMTSL4, ADAMTSL5 and ADAMTSL6 [12–15] and members of the lysyl oxidase family were also recently identified to bind ADAMTSL2 and ADAMTS10 [16]. Additionally, ADAMTSL2 binds latent TGFβ-binding protein 1 and is thought to regulate TGFβ activity via its interaction with this molecule and fibrillin-1 [12, 17]. Thus, ADAMTSLs could be viewed as matricellular proteins, which are dynamically expressed non-structural proteins that reside in ECM and have regulatory roles.

Although the structural similarities of ADAMTS proteases and ADAMTSLs intuitively suggest a functional relationship of ADAMTSLs vis-à-vis ADAMTS proteases, direct evidence of biochemical or physiological interactions is limited. For example, Drosophila papilin was shown to regulate activity of bovine ADAMTS2 in procollagen processing and to bind fibrillin-1, which interacts with several ADAMTS proteases as well as ADAMTSL2 [18, 19]. The physiological relevance of these interactions is unknown. However, a putative relationship is supported by phenotypically similar disorders arising from mutations of ADAMTS proteases (i.e., ADAMTS10, ADAMTS17) and ADAMTSLs (ADAMTSL2, ADAMTSL4) [20, 21]. Systematic testing of interactions between individual ADAMTS proteases and ADAMTS-like proteins remains to be undertaken and will be relevant to human disorders.

Altogether, evolutionary conservation and expansion of ADAMTS proteins suggests that they are crucial for mammalian physiology, which is supported by strong phenotypes compromising morphogenesis, mobility or reproduction observed in many ADAMTS gene knockouts in mice (see Table 2 in [2]). Because of inherent challenges in expressing and purifying ADAMTS proteases, their enzymology and substrate repertoire are relatively poorly characterized. In contrast, modern genetic tools are not similarly constrained and have provided a wealth of insights on ADAMTS mendelian disorders in humans and other animals and complex multifactorial acquired conditions in humans.

1.2. Relevance of ADAMTS homologous pairing

Several ADAMTS proteases (e.g., ADAMTS9 and ADAMTS20, ADAMTS7 and ADAMTS12) as well as ADAMTSLs (e.g. ADAMTSL1 and ADAMTSL3, ADAMTSL4 and ADAMTSL6) form highly homologous pairs reflecting their evolutionary origin by duplication of ancestral genes and suggesting overlapping function (sub-functionalization) (Figure 1 and 2). Spatial and temporal co-expression of homologous ADAMTS proteins, as well as overlapping activity [22–24] is common, which may ensure over-engineering of key biological pathways and morphogenetic processes. This should be anticipated as a primary consideration in analysis of human disorders and their treatment. Many of the ADAMTS mouse knockouts have more severe phenotypes when combined with knockout of their homologs [22–24]. Thus, the effects of single ADAMTS gene mutations may be masked or modified in human Mendelian conditions by concurrent or compensating expression and functional overlap of a homolog, which then constitutes a key modifier gene. Homologous pairing is also relevant to development of drugs intended to block specific ADAMTS proteases, since cross-inhibition of closely related homologs could cause more severe side effects than may be expected from blockade of a single protease. Active consideration of

homologs is therefore vital in thinking about the function and targeting of ADAMTS proteins in disease.

2. ADAMTS gene mutations and genetic associations

2.1. Update on Mendelian disorders resulting from ADAMTS mutations

Table 1 provides an update on human Mendelian disorders discussed in detail in a previous review in this journal, which also described outcomes of inactivation of ADAMTS protease genes in mice [2]. Befitting enzymes and/or non-structural molecules, most ADAMTS mutations act recessively, i.e., requiring two mutant alleles to be manifest. *ADAMTS*2 mutations lead to Ehlers-Danlos syndrome (dermatosparactic type or VIIc), whose major manifestation is severe skin fragility, although other anomalies, including abnormal dentition have been described [25, 26]. *ADAMTS10, ADAMTS17* and *ADAMTSL2* mutations result in acromelic dysplasias, syndromes characterized by short stature and disproportionate distal limb shortening, each accompanied by other characteristic anomalies. These conditions have been extensively reviewed [20, 21, 27, 28]. *ADAMTSL4* mutations lead to ectopia lentis and ectopia lentis et pupillae, which arise from defects in the ocular zonule, an acellular structure comprising fibrillin microfibrils that centers the lens in the optic path and in the iris, respectively [21, 29].

2.1.1. ADAMTS3 and primary lymphedema—The most recent incrimination of an ADAMTS protease in a Mendelian disorder occurred via identification of recessive *ADAMTS3* mutations in Hennekam lymphangiectasia-lymphedema syndrome 3 [30]. Primary lymphedema, which typically affects lower extremities, results from abnormal lymphatic morphogenesis or function. Mutations in several different genes result in this condition, many affecting VEGF-C to VEGFR3 signaling, a central pathway in lymphangiogenesis [31]. VEGF-C is synthesized as a precursor with restricted ability to activate VEGFR3, and its N- and C-terminal propeptides require proteolytic excision for maximal receptor activation by the central VEGF homology domain. ADAMTS3 was implicated as the protease responsible for proteolytic activation of VEGF-C via its interaction with the N-terminal domain of collagen and calcium-binding EGF domain 1 (CCBE1), a secreted, ECM- and VEGF-C-binding molecule. CCBE1 is also essential for lymphangiogenesis, and is mutated in a different form of Hennekam syndrome [32]. VEGF-C is located both at the cell surface and sequestered in the ECM; these localizations contribute in specific ways to proliferation of lymphatic endothelium and formation of organized lymphatic networks, respectively [33]. The C-terminal domains of VEGF-C, ADAMTS3 and CCBE1 each bind to cell-surface heparan-sulfate proteoglycans (HSPGs), forming an obligate activation complex localized to the cell-surface, where VEGF-C activation occurs [33]. *Adamts3*-deficient mouse embryos do not survive past 15 days of gestation owing to severe lymphedema resulting from lack of lymphangiogenesis [34]. Interestingly, ADAMTS3 is closely related to the procollagen I amininopropeptidase ADAMTS2, which is mutated in Ehlers-Danlos syndrome dermatosparaxis type (also designated as VIIc) [26]. Indeed, ADAMTS3 was previously shown to cleave the N-propeptide of procollagen II, a major component of cartilage ECM where it is strongly expressed during development [35, 36]. However, the observed human and mouse lymphatic

phenotypes argue that VEGF-C activation is a definitive ADAMTS3 function whereas its predicted role in procollagen maturation and cartilage health is yet to be similarly validated.

2.1.2. ADAMTS disease associations arising from genome-wide analysis—The challenge of unequivocally establishing causality in acquired disorders is a daunting one requiring a heavy burden of proof, i.e., consistent disease association in independent studies, convincing statistical significance, support from animal models, and precise mechanisms of causality. A number of ADAMTS proteins were connected to disease via GWAS, which are large population-based analyses with significant statistical power to elicit multi-gene contributions to complex common disorders (Table 2). In contrast to fully penetrant Mendelian conditions, the caveats of GWAS caution against immediate presumption of causality. First, GWAS generally links the vicinity of gene loci to traits and only a few variants map to protein coding sequences. Second, variants occurring in inter-gene regions are frequently identified by the nearest known locus, but a presumption that the most proximate locus is associated with the disease may be in error. Third, directionality of an observed variant (whether it is protective or deleterious) is unclear unless specific mechanistic testing is undertaken. Fourth, multiple ethnic groups need to be analyzed to determine effect size in distinct populations, i.e., variants causally involved in one ethnic group may not be relevant to another. Finally, many acquired disorders are truly multifactorial and individual genes that emerge from GWAS analysis probably have very small effects that may not justify therapeutic targeting. The most compelling disease associations are those supported by multiple studies over an extended period of time that utilize well-characterized study populations and demonstrate high experimental rigor. This benchmark has been achieved in only a few specific ADAMTS-disease connections, which are discussed in detail (sections on ADAMTS7 and ADAMTS13 below).

Table 2 lists diverse phenotypic traits and complex disorders with which ADAMTS gene loci have been associated, with the caveats listed above applying to nearly all of them. Nevertheless, this metadata provides specific insights that may be instructive. It is notable that the initial GWAS linkage of *ADAMTS7* to atherosclerosis and coronary artery disease was validated in a mouse model [37] and supported independently by other studies, suggesting that subsequently observed associations with peripheral vascular disease [38] and vascular calcific disease [39] are worthy of detailed investigation. *ADAMTS9* is associated with diverse traits and phenotypes, perhaps because it is widely expressed, for example, by capillary endothelial cells of nearly all organs [40], or cleaves a widely distributed ECM component, versican [41] or because the associated genome variants may be highly polymorphic. Nevertheless, its associations with metabolism, i.e., obesity, diabetes and associated traits appear to be consistent in several ethnic groups (Table 2). Because efficient ADAMTS9 secretion depends on the activity of one of its modifying enzymes B3GLCT (also known as B3GALTL) [42], it is intriguing that *B3GLCT* and *ADAMTS9* are strongly expressed in the eye [42] and vascular endothelial cells [40] and each is associated with age-related macular degeneration [43]. Since ADAMTS5 is indisputably causal in cartilage aggrecan destruction in osteoarthritis (OA) [44, 45], association of the conjoint locus for ADAMTS5 and another aggrecanase, ADAMTS1 in degenerative disk disease [46, 47] is intriguing, since the intervertebral disk is similar in its composition to cartilage.

ADAMTS12 is highly homologous to ADAMTS7 [24], and it may have a similar role in smooth muscle cells in association with vascular/hemostatic disorders [48, 49]. *ADAMTS17* mutations result in a Mendelian condition characterized by skeletal and eye anomalies, in support of its independent association by GWAS in canine open angle glaucoma and variation in human height [50, 51]. Reinforcing possible *ADAMTS20* variant association with cleft lip and palate in humans, a canine *ADAMTS20* mutation was identified to cause cleft lip and palate and syndactyly in Nova Scotia Duck Tolling Retrievers [52]. Indeed, cleft palate was previously characterized in detail in combined mouse mutants of *Adamts20* and *Adamts9* and syndactyly was identified in combined mutants of *Adamts20* with *Adamts9* or *Adamts5* [22, 23]. An association of *ADAMTSL4* and *ADAMTS2* loci with syndromic myopia has credence arising from their association with connective tissue assembly, providing a potential role in axial growth of the eye globe, whose outermost layer, the sclera, is a dense connective tissue [53]. Association of the *ADAMTS18* locus with myopia and bone density [53, 54] suggests a role in collagen metabolism, since collagen I mutations leading to osteogenesis imperfecta esult in “blue” sclera and collagen I is the major component of the sclera.

3. ADAMTS proteins in acquired disorders

3.1. ADAMTS proteases as primary aggrecanases in osteoarthritis

Osteoarthritis (OA) arises from degenerative loss of articular cartilage in synovial joints with presumed secondary changes in bone and synovium, and is a common condition in the population. It has a multi-factorial etiology, with a strong genetic contribution in some instances that leads to structurally defective cartilage, but more frequently results from enzymatic breakdown of cartilage ECM initiated by unknown factors. Of these, prior injuries, altered joint biomechanics or increased loading are probably the most significant. One of the major structural components of articular cartilage is the chondroitin sulfate (CS) proteoglycan aggrecan, which forms giant aggregates with the glycosaminoglycan hyaluronan (HA). The CS chains of aggrecan, which carry a net negative charge, absorb large quantities of water, leading to swelling of the HA-aggrecan aggregates. The swollen aggregates are constrained by entrapment within networks of collagen II, another major cartilage component, and this composite structure gives cartilage ECM its compressive strength and endows articular cartilage with shock-absorbing properties. Several ADAMTS proteases, but not matrix metalloproteases (MMPs), cleave the aggrecan core protein at the Glu^{373}-Ala^{374} peptide bond between the G1 and G2 domains (known as the interglobular region) [55, 56], releasing the entire CS-bearing region [57]. This compromises the mechanical properties of cartilage and exposes other structural molecules such as collagen II to proteolysis [58]. A key study generated transgenic mice with a mutation of this ADAMTS cleavage site and found reduced aggrecan loss and cartilage erosion in a surgical model of OA [59]. This model not only demonstrated the significance of ADAMTS-mediated aggrecan proteolysis, but also appeared to show an anabolic effect in the wake of acute inflammation [59]. Notably, the pro-inflammatory activity of cleaved ECM fragments such as from fibronectin and aggrecan is known to amplify disease pathology [60, 61]. Both ADAMTS4 and ADAMTS5 are thought to contribute to aggrecan cleavage, but ADAMTS5 was implicated as the major culprit by demonstration of favorable enzymatic properties

against specific aggrecanase cleavage sites in aggrecan, its association with OA, lack of susceptibility to surgically-induced OA in *Adamts5*- but not *Adamts4*-deficient mice and protection against aggrecan breakdown by ADAMTS5-specific antibody blockade [62, 63]. The availability of highly specific ADAMTS5 blocking antibodies [63–65] is a major breakthrough, since small molecule active-site inhibitors, despite the advantage of oral bioavailability, generally lack exquisite specificity and have broad side-effects, as noted with MMP inhibitors developed for cancer therapy [66]. Nevertheless, concerns about side effects of ADAMTS5 inhibitors are valid, mostly arising from observed roles of ADAMTS5 in embryogenesis, as well as potentially in ECM turnover in the adult cardiovascular system [67–69]. A possible solution to bypassing a systemic toxicity is intra-articular administration of the blocking antibodies, but it has not been explored. Another challenge presented by OA is its long sub-clinical period, such that ADAMTS5 inhibition may be most effective early in the disease process. Early treatment necessitates not only improvement of biomarkers for early OA diagnosis, but due consideration to long-term side-effects, or complications that may only become apparent decades after treatment initiation.

3.2. ADAMTS7 and cardiovascular disease

3.2.1. Novel locus for coronary atherosclerosis and mechanisms of action in vascular disease—GWAS of coronary artery disease (CAD) identified highly associated *ADAMTS7* single nucleotide polymorphisms (SNPs). Although the lead SNPs in two of the GWAS, i.e., rs1994016 [70] and rs4380028 [71] are located in intron 8 and 7.6 kb upstream of *ADAMTS7*, respectively, rs3825807 represents an A to G coding SNP, resulting in replacement of Ser214 by Pro [72]. Each SNP is in linkage disequilibrium with ADAMTS7, with rs3825807 possibly affecting protein function. Moreover, rs3825807 is significantly associated with coronary artery calcification [39, 73] and independently predicts the severity and survival of angiographically documented CAD [74, 75]. Individuals with the GG variant (Pro substitution) showed approximately three times fewer cardiovascular events in relation to the AA (Ser) genotype [74]. The G allele is also associated with lower obstructive CAD and angiographic severity [76]. Expression of ADAMTS7 constructs carrying the Pro (G) substitution [77] demonstrated reduced furin-mediated ADAMTS7 propeptide excision, which occurs at the cell-surface [78] and is presumably an activating step. Consistent with this, cells expressing the GG variant of ADAMTS7 had lower migratory activity than cells of the AA genotype [77], possibly owing to reduced proteolysis of a reported ADAMTS7 substrate COMP, which is strongly associated with vascular smooth muscle cell migration and neointima formation.

Several subsequent studies undertook functional analysis to test the genetic association and together they strongly suggest that ADAMTS7 contributes to atherogenesis. Analysis of an intragenic lacZ reporter mouse allele identified *Adamts7*-expressing vascular smooth muscle cells in early atheroma lesions (4 weeks) formed in $Adamts7^{-/-}ApoE^{-/-}$ mice fed a western diet [37]. Despite lack of expression in older atheromatous lesions (10 weeks), $Adamts7^{-/-}ApoE^{-/-}$ mice formed smaller atheromatous plaques than $ApoE^{-/-}$ littermates. These mouse studies suggested that ADAMTS7 acted early in atheroma development in this mouse model of atherosclerosis, possibly in response to TNFα in the inflammatory milieu [37]. A corresponding analysis of human atheroma lesions demonstrated ADAMTS7

localization to smooth muscle cells, but not macrophages in the lesion, and pinpointed its localization to their cell surface and filopodia [37], consistent with the demonstrated effect of ADAMTS7 in facilitating SMC migration in vitro [79]. Another analysis suggested that ADAMTS7 content in atherosclerotic plaques from symptomatic patients was increased over that of asymptomatic patients and was associated with a vulnerable plaque phenotype [80]. ADAMTS7 was co-localized with macrophages and smooth muscle cells in coronary and carotid atherosclerotic plaque with staining present throughout the plaque, including the shoulder, cap and core [77, 80].

Plasma *ADAMTS7* was elevated in patients with severe obstructive CAD [81]. Indeed, the level of ADAMTS7 increased the risk for future cardiovascular events in the symptomatic patients, but not the asymptomatic patients [80]. rs7177699, which is in strong linkage disequilibrium with coronary artery-associated SNP rs3825807, is associated with postoperative cardiovascular death [80]. In a further study, SNP rs3825807, which impairs ADAMTS7 function, is associated with reduced CAD burden [76]. Specifically, the SNP is associated with a smaller fibrous cap and percentage area of smooth muscle cells in the intima [76]. The *ADAMTS7* SNPs, rs1994016 and rs3825807 were further shown to be over-represented at the mRNA and protein level in peripheral artery disease, which like CAD, is most commonly caused by atherosclerosis [38]. CAD has a complex etiology and several lifestyle factors are contributory. For example, in a further GWAS analysis, the allelic variant rs7178051 was associated with reduced *ADAMTS7* expression, which conferred stronger CAD protection in never-smokers than in ever-smokers [82]. Therefore, *ADAMTS7* expression has a specific correlation to and may contribute to loss of CAD protection in smokers.

3.2.2. Ventricular remodeling—Acute myocardial infarction (AMI) is associated with high morbidity and mortality. Following AMI, myocardial ECM is degraded, which causes dilation and thinning of the infarcted zone with catastrophic consequences. Plasma levels of ADAMTS7 were elevated in patients with diminished left ventricular ejection fraction, an indicator of poor ventricular contraction [83, 84]. Therefore, elevated ADAMTS7 levels may contribute to deleterious ventricular remodeling after AMI.

3.2.3. Response to arterial injury—Wire injury of the carotid artery in *Adamts7*$^{-/-}$ mice promoted greater re-endothelialization than in wild-type mice [85]. ADAMTS7 inhibits both endothelial cell proliferation and migration; these effects appear to be independent of COMP, one of the reported ADAMTS7 substrates [85]. Instead, thrombospondin appears to be the relevant substrate for this effect, since the impact of *Adamts7* deficiency on re-endothelialization was not seen in *Tsp1*$^{-/-}$ mice [85].

3.2.4. ADAMTS7 as a therapeutic target in vascular disease—ADAMTS7 is an attractive drug target for vascular disease, based on the cumulative evidence from population genetics, animal models and in vitro analysis. Its pro-atherogenic and anti-endothelial roles could conceivably be countered using systemic or local administration (such as via drug eluting stents) of ADAMTS7 blocking agents, respectively. The limited analysis of *Adamts7*$^{-/-}$ mice to date has suggested that they lack major phenotypes, promising a low-risk of side effects from the use of anti-ADAMTS7 inhibitors or antibodies [24, 37].

Whereas the development of such targeting agents is necessary, there is also an urgent need for a better understanding of the substrates targeted by this protease, its cooperative roles and regulatory relationships with its homolog ADAMTS12 [24], and potential side-effects related to its physiological functions, which remain to be fully elucidated. For example, musculoskeletal tissues from *Adamts7*$^{-/-}$ mice were shown recently to have upregulation of *Adamts12* [24], whose roles in cardiovascular disease remain unexplored, and *Adamts7* is constitutively expressed in smooth muscle cells of the pulmonary arterial tree, where its functions are unknown [37]. Notably, consistent with the introductory emphasis on ADAMTS homologous pairs and functional overlap, ADAMTS7 and ADAMTS12 constitute a distinct homologous pair of metalloprotease-proteoglycans that shows high evolutionary conservation [24], suggesting vital (for supporting mammalian evolution) and protected functions. Moreover, a recent study identified tendon, meniscal and ligamentous heterotopic ossification in *Adamts7*$^{-/-}$*Adamts12*$^{-/-}$ mice, and significantly lower *ADAMTS7* mRNA levels were seen in human tendons having degenerative morphology, including heterotopic ossification [24]. Thus, one requirement for specific inhibitors is that they should not cross-inhibit ADAMTS12. It remains to be determined whether pharmacologic inhibition of ADAMTS7 activity might result in ADAMTS12 upregulation, and what impact that could have on cells. Nothing is known about ADAMTS12 in cardiovascular disease, and none of the work on ADAMTS7 in cardiovascular disease has considered a potential role for ADAMTS12. A salutary historical lesson was provided by clinical trials of MMP inhibitors in cancer, which were found to have potential toxicity related to connective tissue turnover as well as to be unsuccessful in cancer therapy [86, 87]. Recently, remarkably specific ADAMTS5 inhibitory antibodies with a high level of target engagement have been generated, but their clinical application is proceeding cautiously owing to implication of ADAMTS5 in a number of morphogenetic events in the embryo, as well as potential contribution of reduced ADAMTS5 to atherosclerosis and ascending aortic aneurysms [67, 68]. Ideally, development of ADAMTS7 inhibitors should proceed alongside an equal emphasis on elucidating ADAMTS7 and ADAMTS12 regulation, molecular structure, life cycle, interacting partners, expression profile and in vivo functions at the sites of expression, which remain woefully understudied.

3.3. ADAMTS13 in platelet coagulopathy

3.3.1. Clinical characteristics and mechanisms—ADAMTS13 is primarily synthesized by stellate cells of the liver and vascular endothelial cells and proteolyzes ultra-large von Willebrand factor (vWF) multimers (ULvWF) at the Tyr1605-Met1606 bond in the A2 domain [88]. This site is cryptic until exposed to the action of ADAMTS13 by shear-mediated extension vWF. When ADAMTS13 levels are reduced, pro-hemostatic ULvWF accumulates in plasma, promoting platelet aggregation and resulting in microthrombi that imperil the circulation of vital organs. ADAMTS13 cleavage of ULvWF into smaller fragments mitigates the procoagulative function (reviewed in [89]). ADAMTS13 deficiency can have two origins. Acquired thrombotic thrombocytopenic purpura (aTTP), the more common form, is an autoimmune disorder caused by antibodies to ADAMTS13 [90], whereas, congenital TTP (cTTP) is much rarer and caused by *ADAMTS13* mutations [91]. TTP is a blood coagulation disease characterized by the presence of VWF and platelet-rich microthrombi in the microvasculature of many organs [92]. cTTP has been associated with

over eighty mutations in *ADAMTS13* that cause severe *ADAMTS13* deficiency. An imbalance of ADAMTS13 and VWF has also been noted in other acquired cardiovascular disorders as well as preeclampsia, sepsis, inflammatory bowel disease and liver cirrhosis [93–98].

3.3.2. ADAMTS13 replacement for treatment of thrombotic thrombocytopenic purpura—TTP treatment requires replacement of ADAMTS13, and this has been done to date by fresh frozen plasma infusion for cTTP and plasma exchange for aTTP [92]. aTTP additionally requires some measure of immunosuppression to combat its autoimmune basis. These treatments have largely been successful, reducing the mortality of an acute TTP episode from 100% to ~20% [92]. Plasma infusion is relatively straightforward and inexpensive, and plasma exchange not only replaces ADAMTS13, but also removes anti-ADAMTS13 antibodies and supplies other coagulation factors that may have been consumed in the acute episode. However, it is a prolonged infusion with attendant risks of volume overload, hyperviscosity, allergic reactions ranging from mild to severe and pathogen transmission. Furthermore, catheter-related complications can occur in patients undergoing long-term infusion. Given these risks, the possibility of preventing cTTP or treating aTTP with recombinant ADAMTS13 has been an attractive one, since the effective levels of activity needed to prevent platelet coagulation have a broad range, the infused volume can be small, and there is reduced risk of allergic reactions or pathogen transmission [99, 100]. High vWF levels seen in stroke and cardiovascular disease could also potentially be mitigated by recombinant ADAMTS13 more safely than by plasma transfusion.

Baxalta, a biopharmaceutical company, generated a recombinant ADAMTS13, BAX390, in genetically engineered Chinese hamster ovary cells cultured in a chemically defined medium. The pharmacokinetics of rADAMTS13 was characterized in knockout mice, rats and monkeys, whose vWF was effectively cleaved, and efficacy was demonstrated in *Adamts13* knockout mice [101]. BAX390 was recently used in a prospective Phase I study of 15 cTTP patients ranging from 12–65 years of age using dosages of 5–40 units/kg [100]. It was well tolerated in all patients without allergic reactions and without development of an immune response to the recombinant ADAMTS13, and the appropriate response of ULvWF and cleaved vWF fragments was observed.

4. Future needs and anticipated challenges

At the present rate of progress, associations of ADAMTS proteases with disease will continue to emerge. They will need to be validated systematically in a sufficiently large population using diverse approaches that include rigorously validated antibodies, specific functional assays and animal models, otherwise the findings will remain preliminary and unconvincing. ADAMTS knockout mice have yielded a plethora of knowledge and a blueprint for anticipated human disease connections. At the same time, our fundamental understanding of ADAMTS proteins is in its infancy. ADAMTS5 and ADAMTS13 offer superb case studies on inhibitor targeting and enzyme replacement, respectively, for the field. Each case study has a fascinating history and translational development was based on a comprehensive fundamental understanding. Whereas these two enzymes have been intensively studied, there are a number of family members about which virtually nothing is

known. It is vital to “fill in the blanks” because they will help to elucidate general principles of ADAMTS proteins and determine similarities and contrasts between the family members. A detailed dissection of ADAMTS domain structure, key residues, molecular dynamics, post-translational modification, and life cycle should therefore be made a priority, since it will be necessary for understanding their involvement in disease and seeking therapeutic strategies. One of the major steps yet to be taken by the field is the widespread use of proteomics for identification of ADAMTS substrates [102], so that assays can be developed for inhibitor evaluation, the protease’s specificity bandwidth is known, and the pathways in which the proteases act can be defined. With this information in hand, drug development will be better informed about potential side-effects and benefit-to-risk ratio. Continued fundamental research on the ADAMTS molecules should therefore continue hand in hand with drug development.

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Highlights

- The ADAMTS superfamily comprises an important group of extracellular matrix modifying proteases and non-structural proteins.
- ADAMTS gene mutations lead to diverse genetic disorders and ADAMTS variants are associated with several complex acquired diseases.
- Inhibition of ADAMTS protease activity has emerged as a translational possibility in treatment of osteoarthritis and atherosclerosis.
- Enzymatic replacement with recombinant ADAMTS13 is under development for thrombotic thrombocytopenic purpura.

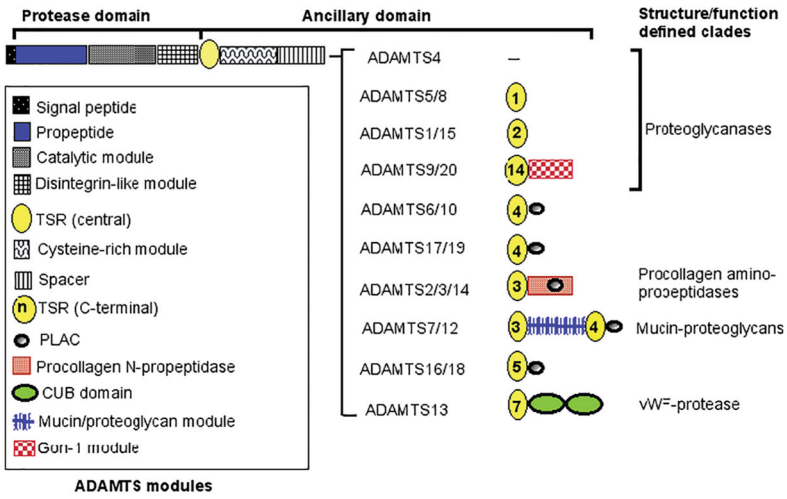

Figure 1. Mammalian ADAMTS proteases

The domain backbone shared by each ADAMTS protease is shown at the top and modules present in each ADAMTS are shown in the box at left. The modular organization of specific ADAMTS homologous pairs or groups is indicated on the right and the key to these modules is located at the bottom of the figure. The homologous pairs are named according to structural or functional characteristics that best defines them. Domain structures are based on reference sequences obtained from GenBank.

The figure was originally published in the Journal of Biological Chemistry: Apte, S.S. The ADAMTS Superfamily- Functions, Structure and Mechanisms. J. Biol. Chem. 2009; 284(46): 31493–31497.

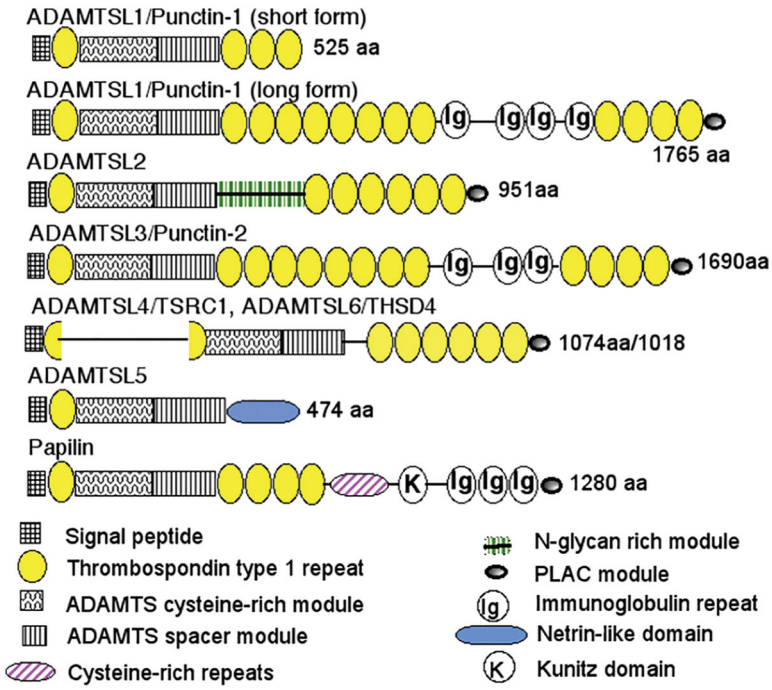

Figure 2. Mammalian ADAMTSLs

The domain structure of each ADAMTSL is shown according to the key at the bottom. The short and long forms of ADAMTSL1 are splice variants and the long form comprises a homologous pair with ADAMTSL3. ADAMTSL4 and ADAMTSL6 comprise a homologous pair in which TSR1 is split by an insertion. Domain structures are based on reference sequences obtained from GenBank.

The figure was originally published in the Journal of Biological Chemistry: Apte, S.S. The ADAMTS Superfamily- Functions, Structure and Mechanisms. J. Biol. Chem. 2009; 284(46): 31493–31497.

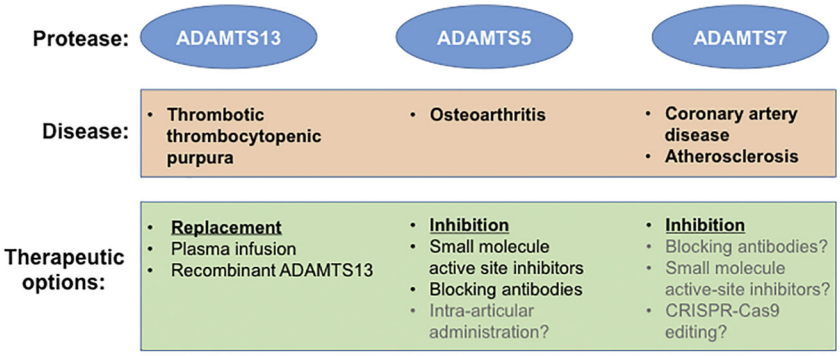

Figure 3.

Current translational targets in the ADAMTS family. The figure shows three targets with strong associations with disease, ADAMTS13, ADAMTS5 and ADAMTS7 which are at various stages of development of clinical therapeutics, the specific approach (replacement versus inhibition) and additional specifics. The text in gray indicates untested/undeveloped possibilities.

Table 1

Mendelian disorders resulting from mutations in human ADAMTS genes

Mendelian condition	MIM number	Gene name, chromosomal locus	Inheritance
Ehlers-Danlos syndrome (EDS), dermatosparaxis type or type VIIC	225410	ADAMTS2, 5q35.3 [26]	Autosomal recessive
Hennekam lymphangiectasia-Lymphedema syndrome 3	None available	ADAMTS3, 4q13.3 [30]	Autosomal recessive
Weill-Marchesani Syndrome 1/Weill-Marchesani syndrome, Autosomal recessive/Mesodermal Dysmorphodystrophy, Congenital	277600	ADAMTS10/19p13.2 [103]	Autosomal recessive
Thrombotic thrombocytopenic purpura, congenital/Upshaw-Schulman Syndrome	274150	ADAMTS13, 9q34.2 [91]	Autosomal recessive
Weill-Marchesani-like Syndrome	613195	ADAMTS17, 15q26.3 [104]	Autosomal recessive
Microcornea, Myopic Chorioretinal atrophy and Telecanthus (MMCAT)	615458	ADAMTS18, 16q23.1 [105]	Autosomal recessive
Geleophysic dysplasia 1	231050	ADAMTSL2, 9q34.2 [17]	Autosomal recessive
Ectopia lentis et pupillae	225200	ADAMTSL4, 1q21.2 [29]	Autosomal recessive
Ectopia lentis, isolated, autosomal recessive	225100	ADAMTSL4, 1q21.2 [106]	Autosomal recessive

Table 2

GWAS-identified ADAMTS locus associations with human and animal phenotypic traits and complex disorders

ADAMTS1	Degenerative intervertebral disc disease [47]
ADAMTS2	Syndromic, common myopia [53]; cerebral aneurysm [49]; pediatric stroke [48]
ADAMTS3	Bronchodilator response [107]; lipoprotein subclasses and triglyceride measurement [108]; height [109]
ADAMTS5	Degenerative intervertebral disc disease [46, 47]
ADAMTS6	Inguinal hernia [110]
ADAMTS7	Coronary atherosclerosis; peripheral arterial disease [38, 39, 70, 71, 75, 76, 82, 111]
ADAMTS8	Pulse pressure and mean arterial pressure [112]
ADAMTS9	Diabetes mellitus type 2/insulin resistance [113–115]; obesity/waist-hip ratio and other anthropomorphic traits [116, 117]; asthma [118]; psoriatic arthritis [119]; smoking and coronary artery calcification [120]; age at menopause [121]; age-related macular degeneration [43, 122–124]; cognitive aging [125]; altitude adaptation (pig) [126];
ADAMTS12	Cerebral vascular aneurysm [49]; pediatric stroke [49]
ADAMTS13	Ischemic stroke [127]; pediatric stroke [49]; prolonged gestation [128]
ADAMTS14	Suicidal behavior [129]
ADAMTS16	Urgency urinary incontinence in women [130]; functional impairment in schizophrenia [131]; hypertension (rat) [132]
ADAMTS17	Primary open angle glaucoma (dog) [50]; height [51]; pediatric stroke [49]
ADAMTS18	Syndromic, common myopia [53]; Bone mass/bone mineral density [54, 133]
ADAMTS19	Premature ovarian failure [134, 135]
ADAMTS20	Cryptorchidism (dog) [136]; cleft palate (dog and human) [52]
ADAMTSL1	Systemic lupus erythematosus [137]
ADAMTSL3	Lean body mass [138]; height (human) [139, 140]; birth, weanling and yearling weight (cow) [141]; schizophrenia [139]
ADAMTSL4	Syndromic common myopia [53]; coronary artery disease protection [142]
PAPLN	Suicidal ideation [143]