

The emerging roles of ADAMTS-7 and ADAMTS-12 matrix metalloproteinases

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Abstract: The a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) comprise a family of secreted zinc metalloproteinases with a precisely ordered modular organization. These enzymes play an important role in the turnover of extracellular matrix proteins in various tissues and their dysregulation has been implicated in disease-related processes such as arthritis, atherosclerosis, cancer, and inflammation. ADAMTS-7 and ADAMTS-12 share a similar domain organization to each other and form a subgroup within the ADAMTS family. Emerging evidence suggests that ADAMTS-7 and ADAMTS-12 may play an important role in the development and pathogenesis of various kinds of diseases. In this review, we summarize what is currently known about the roles of these two metalloproteinases, with a special focus on their involvement in chondrogenesis, endochondral ossification, and the pathogenesis of arthritis, atherosclerosis, and cancer. The future study of ADAMTS-7 and ADAMTS-12, as well as the molecules with which they interact, will help us to better understand a variety of human diseases from both a biological and therapeutic standpoint.

Keywords: ADAMTS-7, ADAMTS-12, COMP, GEP, arthritis, chondrogenesis, atherosclerosis

Introduction

The a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) are zinc matrix metalloproteinases (MMPs) with a precisely ordered modular organization. ADAMTS comprises a family of secreted proteinases, many of which bind to and modulate extracellular matrix proteins. The ADAMTSs are translated initially as inactive pre-proenzymes, whose structure includes a signal peptide, pro-domain, catalytic domain, disintegrin-like domain, a central thrombospondin type I-like (TSP) repeat, a cysteine-rich domain, a spacer region, and a variable number of C-terminal TSP repeats. ADAMTSs can occur in multiple isoforms due to alternative splicing.^{1,2}

First identified in 1997, members of the ADAMTS family are involved in diseases ranging from coagulation disorders to malignancy (Table 1).³⁻⁶ ADAMTS-13 plays a role in the development of the coagulation disorder, thrombotic thrombocytopenic purpura.^{5,7-9} Patients with Ehler–Danlos syndrome type 7C, a genetic disorder of collagen synthesis, have mutations in the ADAMTS-2 gene.^{10,11} These mutations have also been associated with bovine dermatopexis, an inherited disorder characterized by severe skin fragility.¹⁰ ADAMTS-1 exhibits angioinhibitory properties and is crucial for the development and function of the urogenital system.¹²⁻¹⁴ ADAMTS-1 may also contribute to atherosclerosis by cleaving versican, a component of extracellular matrix (ECM).¹⁵ Indeed, mutations in ADAMTS-1 have been associated with an increased risk of coronary artery disease.¹⁶ Other ADAMTS, including ADAMTS-4 and 8, have also

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Table I Biological roles of ADAMTS metalloproteinases

ADAMTS	Alternative name(s)	Known substrate(s)	Biological role
1	METH-1	Aggrecan, versican	Antiangiogenesis ¹⁰⁶ Renal interstitial fibrosis ^{14,107} Bone remodeling ^{108,109} Ovarian folliculogenesis ^{110,111} Atherosclerosis ¹⁵ Urogenital development ¹¹² Tumor growth/remodeling ¹¹³
2	PCINP	Collagen I, II and III N-propeptides	Ehler–Danlos syndrome type 7C ^{10,11} Bovine dermatopra ¹⁰
3	KIAA0366	Procollagen II N-propeptide	
4	Aggrecanase-1	Aggrecan, brevican, COMP, decorin, fibromodulin, versican	Arthritis ^{114–117} Atherosclerosis ^{17,18} Tendinopathy ^{118,119}
5	Aggrecanase-2ADAMTS-11	Aggrecan, brevican	Arthritis ^{19–22} Glioblastoma ⁹⁷
6	NA	NA	
7	ADAMTS-7B	COMP, α 2M	Arthritis
8	METH-2	Aggrecan	Antiangiogenesis ¹²⁰ Brain malignancy ¹²⁰ Arthritis ²³ Atherosclerosis ^{17,18}
9	KIAA1312	Aggrecan, versican	Arthritis ¹²¹
10	NA	NA	
12	NA	Aggrecan, COMP, α 2M	Arthritis
13	vWFPC	von Willebrand factor	Thrombotic thrombocytopenic purpura ^{5,7–9}
14	NA	Procollagen I, II N-propeptide	
15	NA	Aggrecan	
16	NA	α 2M	
17	NA	NA	
18	NA	NA	Antithrombosis/stroke ¹²²
19	NA	Aggrecan	
20	NA	Aggrecan	

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; METH, metalloprotease and thrombospondin-1; PCINP, pro-collagen I N-proteinase; COMP, cartilage oligomeric matrix protein; α 2M, alpha 2-macroglobulin; vWFPC, von Willebrand factor-cleaving protease.

been implicated in the formation of atherosclerotic plaque and atherothrombotic disease.^{17,18} ADAMTS-5 has also been associated with osteoarthritis and other inflammatory joint diseases due to its ability to degrade aggrecan.^{19–22} In addition, other ADAMTS, including ADAMTS-1, 4, 8, 9, 12, 16, and 18 have also been shown to cleave aggrecan *in vitro*.^{20,23–27}

Two recently discovered members of the ADAMTS family, ADAMTS-7 and ADAMTS-12, form a subgroup within the ADAMTS family based on their shared domain organization (Figure 1). Emerging evidence suggests that ADAMTS-7 and ADAMTS-12 may play a key role in the pathogenesis of important diseases, such as arthritis, atherosclerosis, and cancer.^{3,28,29} In this review, we summarize

what is currently known about the roles of ADAMTS-7 and ADAMTS-12 in the pathogenesis of these diseases as well as in other important biological processes.

Role in arthritis

The notion that MMPs and ADAMTSs play an important role in osteoarthritis and rheumatoid arthritis has been well established.^{29–36} In one study, ADAMTS-7 was found to be significantly upregulated in arthritic cartilage and synovium compared with normal controls.³⁷ Quantitative real-time polymerase chain reaction (PCR) has revealed that while ADAMTS-7 and -12 are both significantly upregulated in RA cartilage, only ADAMTS-12 is significantly upregulated in OA cartilage (unpublished data).^{37,38}

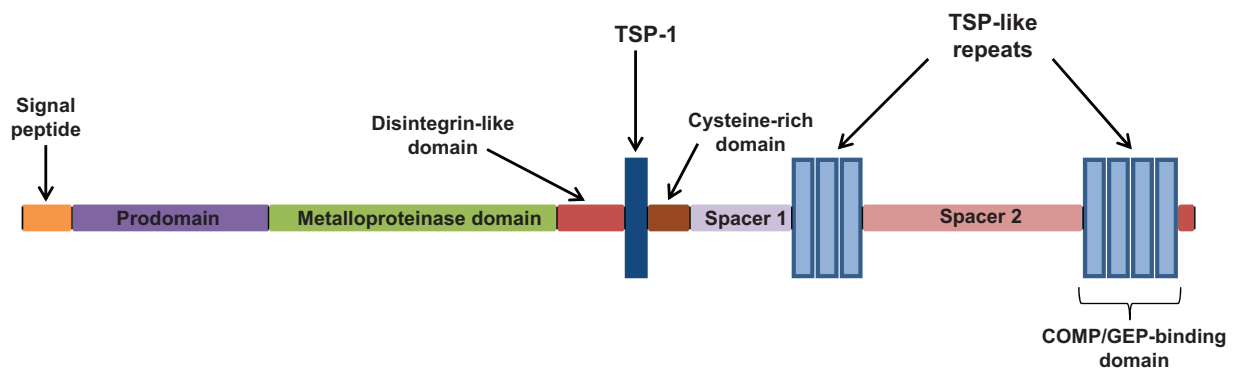


Figure 1 Schematic representation of the domain organization of ADAMTS-7/-12. The C-terminal COMP/GEP-binding TSP1 motifs are indicated.

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; COMP, cartilage oligomeric matrix protein; GEP, granulin-epithelin precursor.

The inflammatory cytokines, tumor necrosis factor (TNF) and interleukin (IL)-1 β have been previously shown to induce the expression of a number of MMPs involved in the development and progression of arthritis.^{39–43} Real-time PCR analysis of cultured human cartilage explants show that both TNF and IL-1 β strongly induce ADAMTS-7 and ADAMTS-12 expression.⁴⁴ Interestingly, this induction does not occur for ADAMTS-12 in human fetal fibroblasts, suggesting that there may be some tissue specificity for this effect.⁴⁵

Interaction with COMP

Arthritis is a disease process characterized by the proteolytic degradation of ECM components with subsequent loss of articular cartilage and bone. Cartilage oligomeric matrix protein (COMP), a 524 kDa disulfide-bonded multidomain glycoprotein composed of five 110 kDa subunits, is a prominent noncollagenous component of cartilage ECM.⁴⁶ Mutations in the human COMP gene have been linked to the development of pseudoachondroplasia and multiple epiphyseal dysplasia, which are autosomal-dominant forms of short-limb dwarfism.^{47–50} Although the function of COMP is not completely understood, it appears to mediate chondrocyte attachment via an integrin receptor.^{51,52} Accumulating evidence suggests that COMP may function to stabilize the ECM of articular cartilage by specific interactions with matrix components including collagen type II and IX, aggrecan, and fibronectin.^{53–56} Fragments of COMP have been detected in the diseased cartilage, synovial fluid, and serum of patients with post-traumatic knee injuries, primary osteoarthritis (OA) and rheumatoid arthritis (RA).^{57,58} This suggests that COMP degradation may play a key role in these disease processes. Furthermore, several recent studies have suggested that monitoring COMP levels in joint fluid

and/or serum may be useful in assessing the progression of arthritis in a clinical setting.^{59–64} Thus, the study of COMP-degradative enzymes is of potential significance; both to elucidate the mechanism of disease as well as for the development of novel approaches to the diagnosis and therapy of arthritis.

Purified COMP is digested by several MMPs *in vitro*, including MMP-1, MMP-3, MMP-9, MMP-13, MMP-19, and MMP-20.^{65,66} A member of the ADAMTS family, ADAMTS-4, has also been reported to cleave COMP *in vitro*.⁶⁷ Despite these findings, the exact role of MMPs in COMP degradation has yet to be confirmed by *in vivo* animal studies.

The relationship between ADAMTS-7, ADAMTS-12, and COMP was first established in our lab via a functional genetic study involving the yeast-hybrid system, which identified both ADAMTS-7 and -12 as binding partners of COMP.^{37,68} This result has also been confirmed by coimmunoprecipitation studies suggesting that ADAMTS-7 and -12 bind specifically to COMP *in vivo*. Furthermore, an analysis of ADAMTS-7 and -12 deletion mutants has revealed that four C-terminal thrombospondin type-1 repeats are conserved in both enzymes and are required for binding to the EGF-like domain of COMP and subsequent COMP cleavage.^{37,68} These findings are in accordance with the notion that C-terminal domains of metalloproteinases are important for determining substrate specificity.⁶⁹

ADAMTS-7 is expressed in bone, cartilage, synovium, tendon, and ligament, all of which contain COMP.^{46,51} Although northern blot analysis has found ADAMTS-12 expression only in the fetal lung, real-time PCR analysis has detected ADAMTS-12 in cartilage, synovium, tendon, skeletal muscle, and fat.^{45,68} ADAMTS-7 is also detectable in meniscus, skeletal muscle, and fat.³⁷ Through immunostaining analysis, we know that ADAMTS-7 and -12 co-localize

with COMP both in the cytoplasm and on the surface of human chondrocytes.^{37,68} These studies also suggest that the interaction between ADAMTS-7 and -12 with the chondrocyte membrane may be mediated by COMP. Immunohistochemistry assays performed on embryonic murine limbs show significant overlap between COMP, ADAMTS-7, and ADAMTS-12 expression patterns *in vivo*.^{37,68}

Subsequent studies involving recombinant enzyme, conditioned medium, and purified protein have demonstrated that ADAMTS-7 and -12 can both digest COMP *in vitro*. An analysis of COMP fragments taken from *in vitro* assays suggests that ADAMTS-7 may cleave COMP at multiple sites.⁵⁷ Interestingly, COMP fragments taken from the cartilage explants of osteoarthritis patients are of similar size to those found with *in vitro* studies (110 kDa).⁴⁴ This highlights the possible role that the digestion of COMP by ADAMTS-7 and -12 may play in degenerative joint disease.

Since inflammatory cytokines TNF- α and IL-1 β have been shown to induce the expression of ADAMTS-7 and -12, these cytokines would also be expected to induce COMP degradation by upregulating these enzymes. Indeed, cells treated with both cytokines give rise to abundant levels of 110 kDa COMP fragments.⁴⁴ Furthermore, these fragments are completely eliminated in the presence of anti-ADAMTS-7 and ADAMTS-12 antibodies, providing strong evidence to suggest that ADAMTS-7 and -12 serve as key links between inflammatory cytokines and disease progression.³⁷ These results have been further confirmed via small interfering RNA silencing of ADAMTS-7 and -12 in human chondrocytes.⁴⁴ The next logical step would be to validate these findings *in vivo* by generating ADAMTS-7 or -12-null mice in an arthritis model. Previous findings involving ADAMTS-5 and aggrecan degradation in osteoarthritis and inflammatory arthritis mouse models have demonstrated the efficacy of this approach.^{24,26}

Interaction with GEP

A recent study has found that COMP associates with a growth factor named granulatin-epithelin precursor (GEP), which is strongly upregulated in the synovium of both OA and RA patients.⁷⁰ GEP is also highly expressed in chondrocytes.⁷⁰ First purified in the early 1990s, GEP is an 80 kDa secreted glycoprotein, which contains seven and a half repeats of a cysteine-rich motif.^{71–74} Acting as an autocrine growth factor, GEP undergoes proteolytic processing with the liberation of ~6 kDa repeating units known as granulin, which retain at least some of the biologic activity of GEP.⁷⁵

These peptides are active in cell growth assays and may be mediators of inflammation.^{76,77} GEP is also known by the names PC-cell derived growth factor, progranulin, proepithelin, and acrogranin.

The finding that COMP associates with both ADAMTS-7³⁷ and GEP⁷⁰ prompted us to determine whether GEP binds to ADAMTS-7 and whether ADAMTS-7, COMP, and GEP form a protein-protein interaction network. Data from our yeast-2-hybrid and coimmunoprecipitation assays show that ADAMTS-7 does indeed bind to GEP.⁷⁸ Further experiments have found that the four C-terminal TSP repeats of ADAMTS-7 are required for this interaction.

GEP has been shown to exhibit a potent antiprotease activity; it is an inhibitor of TNF-induced protease and GEP-derived granulin inhibits the protease thrombin.^{79,80} Unpublished data from our lab demonstrate that GEP specifically inhibits the ability of ADAMTS-7 and -12 to degrade COMP. Co-expression of GEP and ADAMTS-7 in a COMP-stable cell line results in a dose-dependent blockade of ADAMTS-7-mediated COMP degradation (Guo et al, unpublished data). Additionally, data from an *in vitro* digestion assay show that GEP prevents ADAMTS-12 from degrading COMP (Guo et al, unpublished data). Further data show that ADAMTS-7 can also be categorized as a GEP convertase, since it is involved in the proteolytic processing of GEP with the liberation of small fragments.⁷⁸

The available data suggest that GEP inhibits the action of ADAMTS-7 via two distinct mechanisms. First, GEP inhibits the induction of ADAMTS-7 by inflammatory cytokines such as TNF- α . Second, it disrupts the association between ADAMTS-7 and COMP via a direct protein-to-protein interaction.²⁹ Thus, ADAMTS-7 and -12 metalloproteinases, COMP extracellular matrix protein, GEP growth factor, and TNF inflammatory cytokine all act in concert to form an key interaction and interplay network in the pathogenesis of arthritis (Figure 2).

Role in chondrogenesis

Chondrogenesis is a well orchestrated process mediated by interactions between cellular receptors, growth factors, and surrounding matrix proteins. These extracellular enzymes, which include the MMPs, lead to the activation of cell signaling pathways and gene expression in a temporal-spatial-specific manner. Both ADAMTS-7 and -12 are expressed in musculoskeletal tissues, including cartilage, and are thus poised to play key roles in chondrogenesis.^{46,68,81} ADAMTS-7 and ADAMTS-12 are also highly expressed in the proliferative and pre-hypertrophic zones of growth.^{78,82}

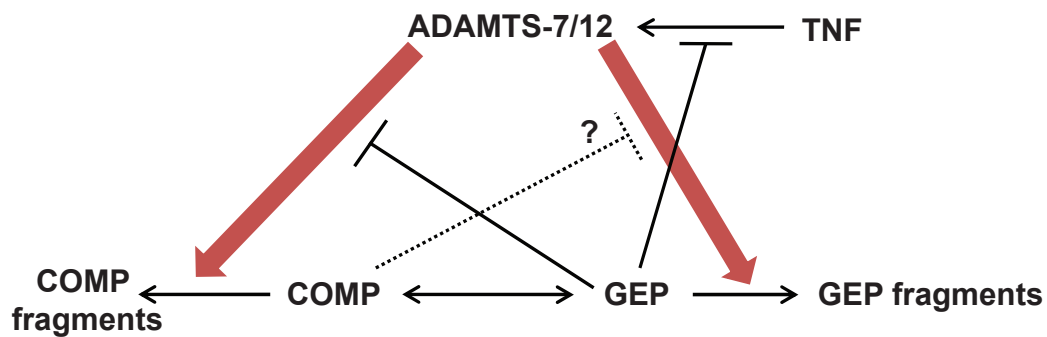


Figure 2 An interaction network among ADAMTS-7/-12, COMP, and GEP. Arrows indicate a stimulatory effect. Crossed lines indicate an inhibitory effect. A dotted line indicates that the relationship is based on unpublished data.

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; COMP, cartilage oligomeric matrix protein; GEP, granulins-epithelin precursor; TNF, tumor necrosis factor.

Initial real-time PCR data involving micromass cultures of a mouse embryonic mesenchymal stem cell line show that ADAMTS-7 is highly induced during the terminal stage of chondrogenic differentiation, which is accompanied by the increase of collagen-X expression.⁷⁸ However, immunohistochemistry performed on mouse embryos show that ADAMTS-7 is abundantly expressed in both the early and late stages of cartilage development, as well as in chondrocytes throughout the mature growth plate.⁷⁸ This suggests that ADAMTS-7 may play a significant role in chondrogenesis, and may influence various stages of cartilage development. ADAMTS-12 is prominently expressed in proliferating and prehypertrophic chondrocytes in the embryonic growth plate.⁸²

Given the expression pattern of ADAMTS-7 and -12 during various stages of chondrogenesis, their role in the process of chondrogenic differentiation has also been elucidated. Overexpression of either ADAMTS-7 or 12 in murine mesenchymal stem cells results in the potent inhibition of chondrocyte differentiation, specifically during the stage of chondrocyte hypertrophy.^{78,82} This effect can also be observed in fetal mouse metatarsal explants, where chondrocyte hypertrophy, mineralization, and bone length are significantly inhibited by ADAMTS-7-rich conditioned medium. Experiments with ADAMTS-12 in human mesenchymal stem cells have also led to similar results.⁸² Further experimentation has established that the chondrogenic inhibitory effect of ADAMTS-7 and -12 depends specifically on four C-terminal thrombospondin motifs.^{78,82}

Once the inhibitory effect of ADAMTS-7 and -12 on chondrogenesis had been established, the focus was then shifted to finding the relevant upstream regulatory molecules of the signaling pathway. Both PTHrP and IHH are known regulators of chondrocyte differentiation.

They function through a negative feedback loop: PTHrP prevents chondrocyte hypertrophy, thus reducing levels of IHH which in turn, stimulates PTHrP expression.^{83–85} IHH is expressed at the prehypertrophic-hypertrophic boundary. Since PTHrP, ADAMTS-7, and ADAMTS-12 all function as negative regulators of chondrogenesis, these molecules have the potential to function within the same regulatory pathway. Data from real-time PCR, immunofluorescent cell staining, and immunoblotting assays all show that this is indeed the case: ADAMTS-7 and -12 are highly induced downstream targets of PTHrP.⁷⁸ These results have also been reproduced *in vivo* in PTHrP knockout mice, which exhibit reduced ADAMTS-7 and -12 expression.⁷⁸ Further experimental data involving fetal mouse metatarsals has not only confirmed the role of ADAMTS-7 as a downstream mediator of PTHrP signaling, but has also confirmed that ADAMTS-7 is crucial for PTHrP-mediated inhibition of chondrocyte hypertrophy.⁷⁸ The inhibition of chondrocyte hypertrophy, mineralization, and bone length by PTHrP is largely abolished by the addition of ADAMTS-7 antibody. Similar results have also been obtained in a micromass cell model with ADAMTS-12.⁷⁸ In addition, ADAMTS-12 can also enhance the expression of PTHrP, suggesting that ADAMTS-12 and PTHrP form a positive feedback regulatory loop in the course of chondrogenesis.⁸²

As discussed above, GEP has been implicated in development, tissue regeneration, tumorigenesis, and inflammation. Our recent data demonstrates that GEP stimulates chondrocyte differentiation in mesenchymal stem cells *in vitro* and endochondral ossification *ex vivo*. GEP knockdown mice display dwarfism and striking skeletal defects. In addition, GEP activates chondrogenesis through Erk1/2 signaling, with JunB transcription factor being one of the key downstream molecules (Feng et al, unpublished data).

Given that GEP enhances chondrocyte differentiation and bone growth, and that ADAMTS-7 associates with and converts GEP,⁷⁸ it may be suggested that ADAMTS-7 inhibits chondrogenesis by inhibiting the chondroinductive function of GEP. Indeed, both *in vitro* chondrogenic differentiation assays and *ex vivo* metatarsal culture experiments indicate this is the case (Figure 3).^{78,82}

Interestingly, although ADAMTS-7 and ADAMTS-12 may negatively regulate chondrocyte differentiation, they can also exert a stimulatory effect on chondrocyte proliferation, a feature that they share with PTHrP.^{78,82} Given these two effects, it remains to be determined how ADAMTS-7 and ADAMTS-12 affect cartilage development and endochondral bone formation *in vivo*.

Role in atherosclerosis

Interestingly, ADAMTS-7 and its ability to interact with COMP, have also been implicated in the pathogenesis of vascular disease processes including atherosclerosis, restenosis after coronary angioplasty, and late failure of vein grafting. These processes all feature media-to-intima migration of vascular smooth muscle cells (VSMCs), which results in thickening of the vessel's intimal layer.⁸⁶⁻⁸⁸ This migratory process requires the protease-mediated

degradation and remodeling of ECM, which forms a barrier to VSMC migration.⁸⁹ MMPs such as MMP-2, MMP-9, and MT1-MMP have been implicated in this process.^{90,91} COMP, which is a component of vascular ECM and has been found in atherosclerotic lesions, is thought to be involved in the migration of VSMCs as well.⁹²

The interplay between ADAMTS-7 and COMP has been examined in a recent study involving a model of balloon-injured rat carotid arteries. ADAMTS-7, which is localized in VSMCs, shows significantly increased levels in response to neointimal vessel injury.²⁸ In addition, ADAMTS-7 in VSMCs is also induced by proinflammatory cytokines, such as TNF- α and IL-1 β .²⁸ This result, similar to the one seen in chondrocytes, suggests that the role of ADAMTS-7 as a mediator of inflammation may be maintained across different tissue types. Of note, the anti-inflammatory signaling molecule TGF- β has been found to downregulate ADAMTS-7.²⁸ Additionally, ADAMTS-7 is induced by TNF-pathway transcription factors NF- κ B and AP-1, further solidifying its role in this regulatory cascade.²⁸

The supportive role of ADAMTS-7 in VSMC migration is established by data showing that VSMCs infected with ADAMTS-7 adenovirus exhibit significantly greater migration activity.²⁸ This result is also seen *in vivo*, where

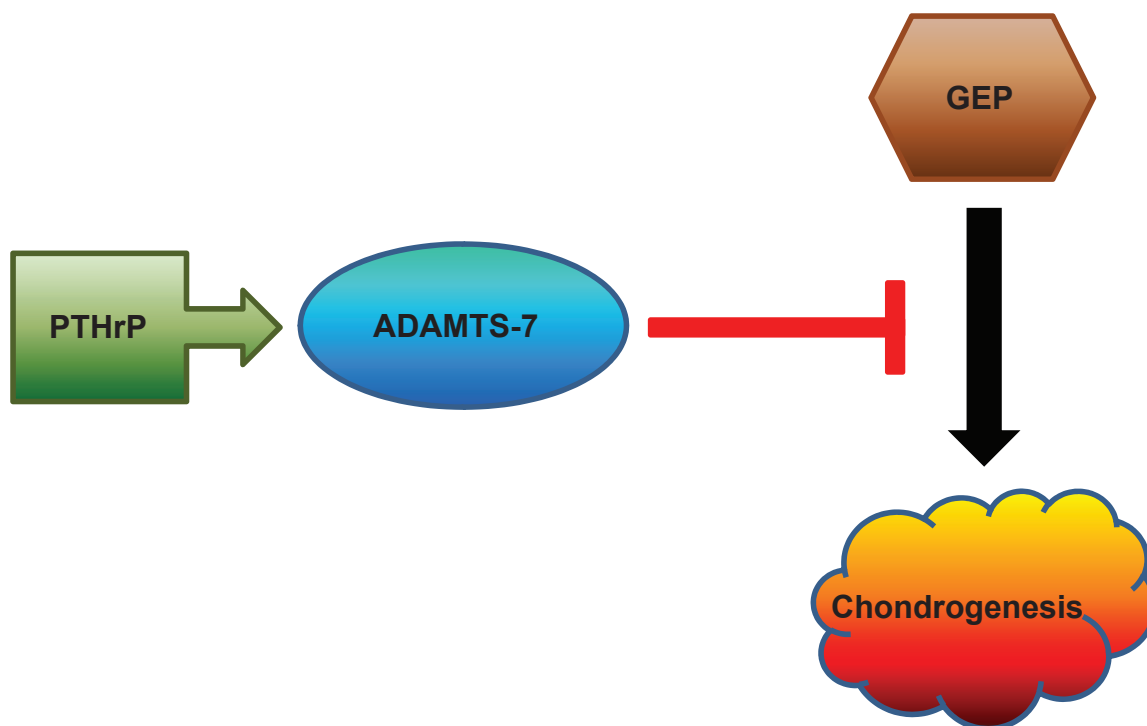


Figure 3 A proposed model for explaining ADAMTS-7-mediated inhibition of chondrogenesis. ADAMTS-7, a direct target of PTHrP, inhibits chondrogenesis by associating with GEP growth factor and inactivating its chondroinductive activity.

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; GEP, granulin-epithelin precursor; PTHrP.

injured rat vessel walls exposed to ADAMTS-7 adenovirus show significantly greater neointima formation. Knockdown of ADAMTS-7 via perivascularly applied ADAMTS-7 siRNA results in significantly reduced neointima area, thus creating the potential that future therapeutic approaches could be developed using this strategy.²⁸

Following vessel injury, levels of full-length COMP are decreased, while levels of COMP fragment are increased.²⁸ Previous *in vitro* and *in vivo* assays have already established that ADAMTS-7 binds and cleaves COMP in chondrocytes and similar data has shown that this is also true in damaged vessels. VSMCs infected with ADAMTS-7 adenovirus display increased levels of COMP fragment. Furthermore, infection with COMP adenovirus resulted in decreased ADAMTS-7-mediated VSMC migration and neointima formation, both *in vitro* and *in vivo*.²⁸ These data strongly suggest that the cleavage of COMP by ADAMTS-7 is a key event which is required for the migration of VSMCs and the pathogenesis of atherosclerotic disease.

Role in cancer

Many members of the ADAMTS family are dysregulated in a variety of tumors. For example, ADAMTS-6 and -18 have been linked to breast cancer and expression of ADAMTS-8 and -15 are predictors of survival;^{4,93} ADAMTS-19 may play a role in osteosarcoma;⁹⁴ ADAMTS-20 is dysregulated in breast and colon cancer;⁹⁵ and ADAMTS-4 and -5 are associated with glioblastoma.^{96,97} This is unsurprising since ADAMTSs belong to the family of MMPs, which are thought to play a key role in tumor growth, invasion, and metastasis.^{98–103} Data concerning the potential role of ADAMTS-7 and -12 in malignancy is just beginning to emerge. One study detected ADAMTS-7 in the urine of patients with prostate, brain, bladder, breast, and liver carcinomas.³ Further analysis has found that ADAMTS-7 is present in the urine of breast, bladder, and prostate carcinoma patients, but not in control urine, suggesting that ADAMTS-7 may play a role in growth and invasion of these tumors.³

Another study involving Madin–Darby canine kidney (MDCK) cells has found that overexpression of ADAMTS-12 confers protection from a tumorigenic phenotype that is generated in the presence of hematocyte growth factor.⁶ Further analysis has found that this effect is mediated by inhibition of the Ras-MAPK signaling pathway, and that such inhibition involves the thrombospondin domains of ADAMTS-12.⁶ The antitumor property of ADAMTS-12 can also be observed *in vivo*, as tumors induced by injecting immunodeficient SCID (severe combined immunodeficient) mice with A549

cells are markedly growth deficient when the injected cells are overexpressing ADAMTS-12, in comparison to control cells.⁶ Overall, the data suggest that ADAMTS-12 exerts a significant antitumor effect; a finding that may pave the way for the development of future therapy.

Other roles

Genetic analysis has also provided evidence that ADAMTS-7 and ADAMTS-12 may be involved in other diseases. Gene mapping data has found several single-nucleotide polymorphisms (SNPs) in the ADAMTS-7 gene which are linked to the gene for keratoconus with cataract, suggesting an association with this disease.¹⁰⁴ However, none of these mutations are considered pathogenic, as they were also found in control samples.

Several variants of ADAMTS-12 are linked to bronchial hyper-responsiveness and asthma. In one study, the SNPs of ADAMTS-12 were found to be significantly different between cases and controls.¹⁰⁵

Summary and perspectives

Although ADAMTS-7 and -12 are both known to play a role in the pathogenesis of arthritis, recent evidence has emerged to implicate these two molecules in a host of other biological and disease processes. Indeed, the potential roles of ADAMTS-7 and -12 in the pathogenesis of today's most common and costly diseases, including arthritis, atherosclerosis, and cancer, highlight the importance of future study (Table 2). Of particular note, elucidating the functional pathways involving these molecules in one disease may lead to open avenues of discovery in the understanding of other disorders. For example, the binding and cleavage of COMP, a feature that is crucial to the role of ADAMTS-7 and -12 in the progression of arthritis, may also help to explain the pathogenesis of atherosclerotic disease. Learning the full relationship between ADAMTS-7 and -12 and their binding partners, such as COMP and GEP, holds the promise of helping us to better understand the pathogenesis of, as well as

Table 2 Role of ADAMTS-7 and -12 in biological and disease processes

Process	Molecules/pathways involved	References
Arthritis	COMP, GEP	27,41,54,65,66,68–70
Chondrogenesis	PTHrP, GEP	68,69
Atherosclerosis	COMP, TGF- β	26
Cancer	Erk1/2	1,4

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; COMP, cartilage oligomeric matrix protein; GEP, granulatin-epithelin precursor; PTHrP, ;TGF- β , transforming growth factor- β .

develop effective therapies for some of today's most common and costly diseases.

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