The function and roles of ADAMTS-7 in inflammatory diseases

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Abstract: The ADAMTS proteinases are a group of multi-domain and secreted metalloproteinase containing the thrombospondin motifs. ADAMTS-7 is a member of ADAMTS family and plays a crucial role in the pathogenesis of arthritis. Overexpression of ADAMTS-7 gene promotes the breakdown of cartilage oligomeric matrix protein (COMP) matrix and accelerates the progression of both surgically-induced osteoarthritis and collagen-induced arthritis. Moreover, ADAMTS-7 and tumor necrosis factor-α (TNF-α) form a positive feedback loop in osteoarthritis. More significantly, granulin-epithelin precursor, a growth factor has important roles in bone development and bone-associated diseases, disturbs the interaction between ADAMTS-7 and COMP and prevents COMP degradation. This review bases on our results and provides an overview of current knowledge of ADAMTS-7, including its structure, function, gene regulation and inflammatory diseases involvement.

1. An introduction to ADAMTS family of proteinases

The family of ADAMTS (a disintegrin and metalloproteinase with thrombospondin-like motifs) proteinases consists of 19 secreted, multidomain proteolytic enzymes and plays a crucial role in several pathophysiological processes including extracellular matrix (ECM) assembly and degradation, hemostasis, organogenesis, angiogenesis, genetic diseases, cancer and arthritis (1). The ADAMTS gene was first cloned as inflammation-associated gene in mice containing the TSP type I motif (2). In general, the structure of ADAMTS proteins comprises a pro-domain, a metalloproteinase domain, a disintegrin-like and spacer domain, and a thrombospondin (TS) repeats (3). The human ADAMTS proteins can be divided into four subgroups according to the sequence alignments and functional difference (4). The first subgroup contains ADAMTS-1, -4, -5, -8, -9, -15 and -20 and degrades aggrecan. ADAMTS-2, -3, and -14 consist of the second subgroup and degrade peptides of procollagen (5-8). ADAMTS-13 alone represents the third subgroup and is essential for von Willebrand factor cleavage (vWF) (9). ADAMTS-7 and -12 that specifically associate with and degrade cartilage oligomeric matrix protein (COMP) belong to the fourth subgroup (10-13). The detailed biological characteristics of ADAMTS proteins are summarized in Table 1.

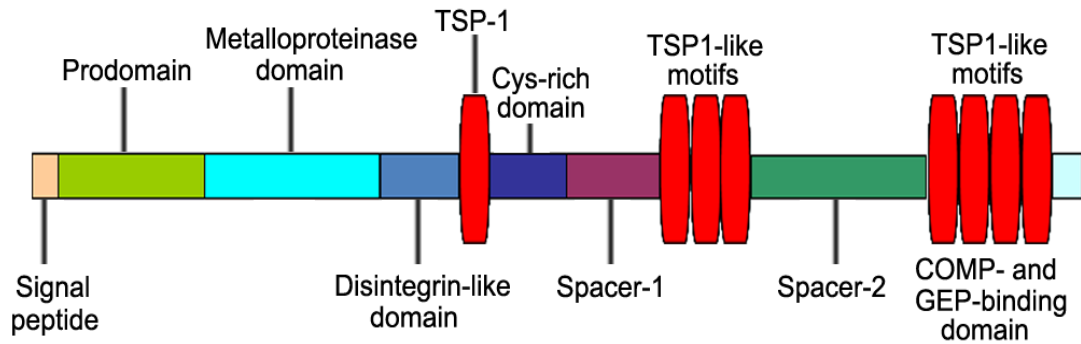**2. ADAMTS-7**

2.1 Structure

Figure 1 Domain structure and organization of ADAMTS-7

As shown in Fig.1, ADAMTS-7 is a proteolytic member of the ADAMTS family comprising a signal peptide, a pro-domain, a metalloproteinase domain, a disintegrin-like domain, and several thrombospondin type I repeats (TSP1), interspaced by spacer domains (14, 15). The pro-domain is generally considered to be essential for maintaining enzyme latency. Cleavage of the ADAMTS propeptide by convertases (furin or furin-like enzymes) is typically required for enzyme activity. For example, furin is the main convertase required for the maturation of ADAMTS-7 as compared with PACE4, PC6B and PC7 convertases (13). A metalloproteinase catalytic domain has a high degree sequence similarity of reprolysin-type zinc-binding motif, HEXXHXXG/N/SXXHD, and a methionine residue-containing Met-turn which plays an important role in the structure of the active site (16). α2-Macroglobulin (α2M) associates with ADAMTS-7 and is a novel substrate of ADAMTS-7 (10), and the metalloproteinase domain of ADAMTS-7 alone is essential for cleavage of α2M (15). The catalytic domain is also responsible for digestion of COMP at more than one site (14). The disintegrin-like domain has a sequence similarity to the soluble snake venom disintegrins and may serve a function in

regulating activity through providing an essential binding surface for substrates (17). The C-terminal TS repeats between the disintegrin-like domain and cysteine-rich domain (CRD) of ADAMTS proteins are variable and interspaced by spacer domains, for instance, ADAMTS-4 lacks of TS repeats (18), whereas ADAMTS-7 and ADAMTS-20 have four and fourteen TS repeats respectively (14, 19). The four C-terminal TS repeats of ADAMTS-7 are required and sufficient for interaction with EGF domains of COMP substrate and each granulin (GRN) unit of progranulin (PGRN) (10, 12, 20). The spacer domain is the least homologous domain and in combination with a mucin domain between the third and fourth C-terminal TS repeats (13). Unlike other ADAMTS proteins, the function of spacer domain appears not to be essential for interaction with ADAMTS-7 substrates, but involvement in location of the enzyme (15).

2.2 Regulation of ADAMTS-7

ADAMTS-7 was expressed in bone, cartilage, synovium, tendon, and ligament, all of which contain COMP (12, 14). ADAMTS-7 was also detectable in meniscus, skeletal muscle, and fat tissue (12, 14). *ADAMTS-7* mRNA transcripts of 8.0 kb and 4.5 kb were detected in skeletal muscle (15). The identification of splice variants of ADAMTS-7 suggested that a potential post-transcriptional regulation might be a mechanism for gene regulation of ADAMTS-7. For example, miR-29a/b served a function in ADAMTS-7 mediated COMP degradation and subsequent vascular smooth muscle cells (VSMCs) calcification through directly targeting the 3'

untranslated region of ADAMTS-7 and markedly inhibited high-phosphate-induced ADAMTS-7 expression (21). Furthermore, the ADAMTS-7 protein was also regulated at post-translational levels since the recombinant protein from HEK293 stable lines showed a larger molecular weight (15). Anyway, the physiological functions of ADAMTS-7 gene, which is expressed in many tissues at a basal level, need to be further elucidated.

TNF-α and interleukin (IL)-1β strongly upregulated the mRNA expression of ADAMTS-7 in human cartilage explants cultures (10). Furthermore, the upregulation of ADAMTS-7 was also associated with the increased level of TNF-α in rheumatoid arthritis (RA) patients (12) and patients with femoral neck fracture (FNF) and osteonecrosis of femoral head (ONFH) at different stages (22). Interestingly, TNF-α also induced the expression of ADAMTS-7, and the binding sites of inflammatory transcription factors NF-κB and AP-1 were identified in the promoter of ADAMTS-7 gene by chromatin immunoprecipitation (ChIP) (23). Our in vivo results also supported the relationship of ADAMTS-7 and TNF-α. Briefly, the surgically-induced osteoarthritis (OA) model was established using *ADAMTS-7* transgenic mice and ADAMTS-7 small interfering (si)RNA knockdown mice, the results demonstrated that TNF-α activates the expression of ADAMTS-7 through NF-κB mediator and ADAMTS-7 upregulates TNF-α and form a positive loop between ADAMTS-7 and TNF-α in the pathogenesis of OA (24, 25).

2.3 The role of ADAMTS-7 in inflammatory diseases

2.3.1 Arthritis

Cells in all tissues are surrounded by extracellular matrix (ECM). ECM has an important role in providing structural support as a scaffold and regulating the cell activity and behavior, including cell shape, survival, differentiation, proliferation and cell death (17). The progression of arthritic diseases are characterized by the breakdown the ECM components and subsequent loss of articular cartilage and bone. COMP is a 524 kDa disulfide-bonded, multidomain glycoprotein composed of five 110 kDa subunits. COMP constitutes approximately 1% of the wet weight of the cartilage tissue and is a prominent noncollagenous component of cartilage ECM (26). Mutations in the human COMP gene in a region that encoding the calmodulin-like repeat elements had been linked to the development of pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED) , which were dominantly inherited chondrodysplasias characterized by short stature and early-onset osteoarthrosis (27-30). The pathophysiological function of COMP may be related to stabilize the ECM of arthicular cartilage through interaction with matrix components such as collagen type II and IX, aggrecan, and fibronectin (31-34). Dedgradative fragments of COMP had been observed in diseased cartilage, synovial fluid, and serum of patients with post-traumatic knee injuries, primary osteoarthritis (OA) and rheumatoid arthritis (RA) (35, 36). Thus, the isolation of COMP-degradative enzymes is of great significance from both a pathophysiological mechanism and a therapeutic standpoint (14).

Several matrix metalloproteinases (MMP) can digest purified COMP *in vitro*,

including MMP-1, MMP-3, MMP-9, MMP-13, MMP-19, and MMP-20 (37, 38). In addition, ADAMTS-4 proteinase also can cleave COMP protein *in vitro* (39). In these assays, the concentration of degradative enzymes and substrates is higher than physiological and pathological conditions. Furthermore, the exact role of ADAMTS proteinases in COMP degradation still needs to be further elucidated by *in vivo* animal studies. ADAMTS-7 and ADAMTS-12 were identified as the physiological enzymes responsible for COMP degradation by a functional genomic study (11, 12). The interaction between ADAMTS-7 and COMP *in vitro* was verified using a glutathione S-transferase (GST) pulldown assay, and the specifically binding between ADAMTS-7 and COMP *in vivo* was further confirmed by coimmunoprecipitation assay. ADAMTS-7 co-localized with COMP both in the cytoplasm and on the surface of human chondrocytes and selectively interacted with the EGF repeat domain of COMP, whereas the four C-terminal TSP motifs of ADAMTS-7 were essential for association with COMP (12), supporting the notion that C-terminal domain of metalloproteinases are important for determining substrate specificity (40).

The recombinant enzyme of ADAMTS-7 purified from condition medium is able to digest COMP *in vitro*. The catalytic domain of ADAMTS-7 produced in transgenic bacteria as a GST fusion protein also can digest COMP in a time-dependent manner (12). Intriguingly, the catalytic domain alone can degrade COMP and produce three fragments, suggesting that ADAMTS-7 might digest COMP at more than one site (12). Furthermore, ADAMTS-7 was also involved in inflammatory cytokines TNF-α and IL-1β-meidated digestion of COMP protein, whereas anti-ADAMTS-7 antibody

efficiently blocked the production of 110 kDa COMP fragments (10). These finding had been further verified using small interfering RNA silencing of ADAMTS-7 in human chondrocytes. Animal results from surgically-induced OA and collagen-induced arthritis models using ADAMTS-7 transgenic mice also supported the digestion of COMP by ADAMTS-7 *in vivo*. Overexpression of ADAMTS-7 in chondrocytes led to increasing COMP degradation in cartilage tissues using immunohistochemistry and significantly elevating serum levels of COMP proteolytic fragments by a novel sandwich enzyme linked immunosorbent assay (ELISA) (25) which is able to recognize epitopes of the COMP protein prone to degradation during the cartilage destruction (41). The COMP fragments in joint sections and serum were significantly higher in collagen-induced arthritic ADAMTS-7 transgenic mice than that of the arthritic wild type controls (42).

No evident differences in ADAMTS-7 gene expression was observed between normal and OA patients tissue (14). However, ADAMTS-7 mRNA was found to be significantly increased in cartilage and synovium tissues from RA patients. The increasing COMP fragments were observed in cartilage, synovial fluid, and serum of OA and RA patients. And the COMP fragments degraded by recombinant ADAMTS-7 enzyme have a similar size to those seen in OA patients (10). These findings suggested that the COMP degradation observed in OA and RA patients might associate with upregulation of ADAMTS-7.

Real-time PCR results of micromass cultures of a mouse embryonic mesenchymal stem cell line suggested that ADAMTS-7was strongly induced during

the terminal differentiation of chondrogenesis (43). ADAMTS-7 was also highly expressed in both the early and later stage of cartilage development, as well as in chondrocytes throughout the mature growth plate (43). These findings suggested that ADAMTS-7 may play a crucial role in chondrogenesis, and may regulate various stages of cartilage development. Overexpression of ADAMTS-7 in murine mesenchymal stem cells resulted in efficient inhibition of chondrocyte differentiation, specifically during the stage of chondrocyte hypertrophy (43). And the inhibitory effect of ADAMTS-7 on chondrocyte differentiation and endochondral bone growth was associated with inactivating granulin-epithelin precursor (GEP) and regulated by parathyroid hormonerelated peptide (PTHrP) signaling (43). Granulin epithelin precursor (GEP), also known as progranulin (PGRN), PC-cell-derived growth factor (PCDGF), proepithelin, and acrogranin, is a 593-amino-acid secreted growth factor (44, 45). GEP contains seven-and-a-half repeats of a cysteine-rich motif in the order P-G-F-B-A-C-D-E (46). GEP was highly expressed in chondrocytes of the musculoskeletal system (47) and played a key role in musculoskeletal development and diseases (48). Recent reports suggested that GEP played a protective role in surgically-induced OA (49, 50) and inflammatory arthritis (46). Recombinant GEP decreased destruction of cartilage matrix and protected against OA progression in surgically-induced OA models (49). Moreover, PGRN was also involved in BMP-2 induction of osteoblastogenesis and ectopic bone formation (50). PGRN-deficient mice were more susceptible to collagen-induced arthritis, and administration of PGRN reversed inflammatory arthritis through the inhibition of TNF-α signaling (46).

Data from yeast-2-hybrid and coimmunoprecipitation assays demonstrated that ADAMTS-7 binds to GEP (43). GEP co-localized with ADAMTS-7 on the surface of chondrocytes and inhibited COMP degradation by ADAMTS-7 in a dose-dependent manner (20). Intact GEP had anti-inflammatory effect through, while the proteolytic peptides of GEP exerted proinflammatory effect through stimulating the production of proinflammatory cytokines such as interleukin 8 (51). However, ADAMTS-7 also exerted its function as a GEP convertase and was involved in the proteolytic processing of GEP with the production of small fragments (43). Overall, ADAMTS-7 metalloproteinases, COMP matrix protein, GEP growth factor, and TNF-α inflammatory cytokine all act in concert to form a key interaction and interplay networks in the pathogenesis of arthritis.

In order to further elucidate the role of ADAMTS-7 in cartilage development and endochondral bone growth *in vivo*, the transgenic mice were generated thorugh targeting overexpression of ADAMTS-7 in chondrocytes regulated by Col II promoter, and knockdown mice were generated using Cre/loxp system (25). Targeted overexpression of ADAMTS-7 in chondrocytes resulted in chondrodysplasia characterized by short-limbed dwarfism and a delay in endochondral ossification in 'young mice' and a spontaneous OA-like phenotype in 'aged' mice (25). In surgically-induced OA model, evidently cartilage loss was found in transgenic mice at 4 weeks after surgery, whereas moderate cartilage loss was observed in wild type mice at 8 weeks after surgery. However, no evident cartilage loss occured in ADAMTS-7 small interfering (si)RNA knockdown mice even at 12 weeks after

surgery (25). Anyway, these findings suggested that overexpression of ADAMTS-7 exaggerated destruction of cartilage and accelerated development of OA, while knockdown of ADAMTS-7 attenuated breakdown of cartilage matrix and protects against OA progression. The potential mechanism of ADAMTS-7 in the regulation of OA progression is summarized in Figure 2. In collagen-induced arthritis (CIA) mode, ADAMTS-7 transgenic mice were more susceptible to induction of CIA, and arthritic transgenic mice displayed significantly higher clinical and histological arthritis scores as compared with wild type mice (42). The role of ADAMTS-7 in the pathogenesis of collagen-induced inflammatory arthritis was also summarized in Figure 3. Thus, ADAMTS-7 expression was elevated during disease progression in surgically-induced OA and collagen-induced arthritis model, and the increasing ADAMTS-7 upregulated the level of inflammatory cytokines including TNF-α (24, 25). The elevated expression of ADAMTS-7 led to accelerated degradation of COMP. In addition, the upregulation of inflammatory cytokine TNF-α induced the expression of MMP and other ADAMTS members. Eventually, these factors resulted in accelerated progression of arthritis (24, 25). Collectively, the role of ADAMTS-7 in the pathogenesis of arthritis is associated with degradation of COMP, upregulation of inflammatory cytokines and other metalloproteinases.
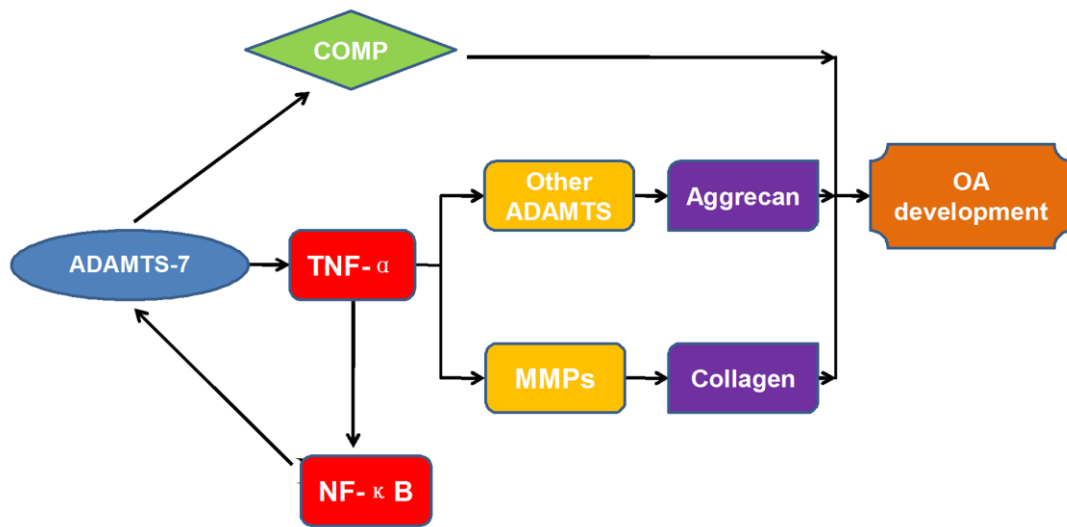
Figure 2 A proposed model for the potential role and mechanism of ADAMTS-7 in the regulation of OA development (Edited according to the reference [25]).
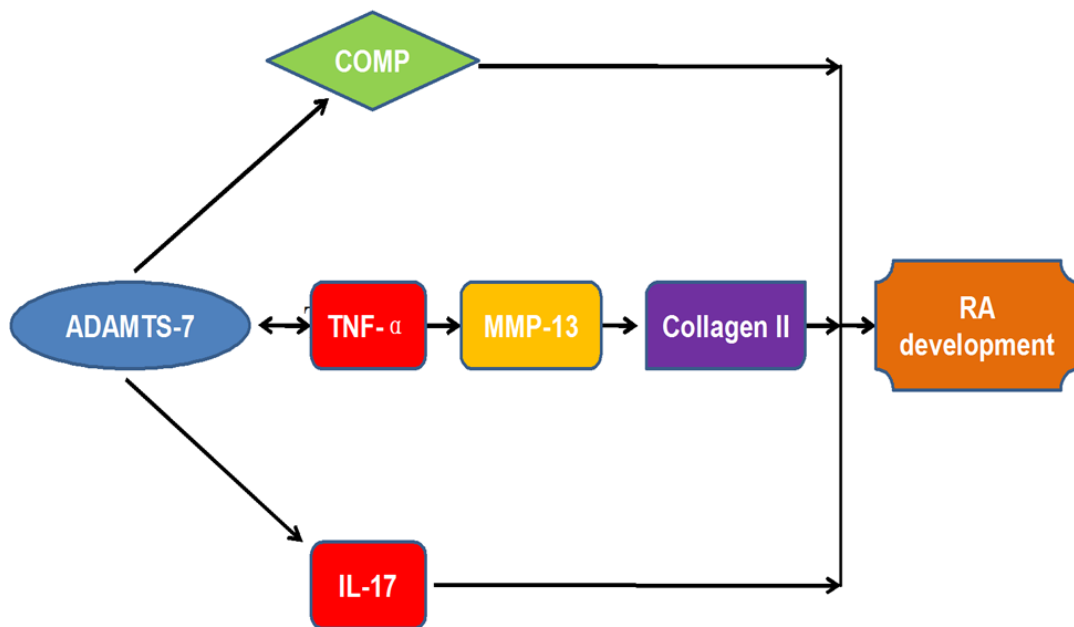

Figure 3 A proposed model for the potential role and regulation of ADAMTS-7 in the pathogenesis of inflammatory arthritis (Edited according to the reference [42]).

In addition, ADAMTS-12 also played a critical role in the pathogenesis of arthritis since ADAMTS-7 and ADAMTS-12 share the common substrate (COMP) (11). The expression of ADAMTS-12 was significantly increased in the cartilage and synovium of OA or RA patients (52, 53). ADAMTS-12 expression is required for normal cartilage development and its dysregulation results in defects in the musculoskeletal system including brachydactyly type E (BDE) (54). The potential role of ADAMTS-7 in OA is related to association and degradation of COMP matrix (14, 54). ADAMTS-12 as an inflammatory protein and also played a role in RA (55). The genotyping results of three single nucleotide polymorphisms (SNPs) of ADAMTS-12 in 303 RA patients and 495 control subjects suggested that the genotype frequency of rs10461703 was associated with the RA development (55). Overall, ADMTS-12 has an essential role in the progression of arthritis and may serve as a therapeutic target for arthritis treatments. And results from ADAMTS-12 mice are helpful for investigating its exact role in arthritic conditions.

2.3.2 Atherosclerosis

Atherosclerosis is a progressive inflammatory disease triggered by damage to the vascular endothelium by many risk factors such as genetic predisposition, hypertension, and type 2 diabetes mellitus (56). The inflammatory process ultimately leads to the development of complex plaques composed of cholesterol, lipids, inflammatory cells and debris resulting from cell apoptosis (56, 57). ADAMTS proteinases and their ability to interaction with ECM have been implicated in the pathogenesis of vascular disease processes including atherosclerosis. These disease

processes characterize by media-to-intima migration of vascular smooth muscle cells (VSMCs), which resulting in thickening of the intimal layer of vessel (58-60). The matrix metalloproteinase-mediated degradation and remodeling of ECM plays an essential role in these disease processes and form a barrier to VSMC migration (61). In atherosclerosis progression, macrophages and monocytes secrete the ADAMTS proteinases to influence the stability of the complex plaque (62). Several ADAMTS members were highly expressed in human carotid lesions and advanced coronary atherosclerotic plaques, including ADAMTS-1, -4, -5 and -8 (63). In the mouse carotid artery flow cessation model, ADAMTS-1 transgenic/apoE-deficient mice show a significant increase in intimal hyperplasia as compared with apoE-deficient mice (64). These findings suggested that the potential role of ADAMTS proteinases in atherosclerosis might associate with accelerated degradation of ECM of vessel.

Results from genome-wide association studies (GWAS) demonstrated that ADAMTS-7 was tightly associated with the development of coronary atherosclerosis in existing coronary atherosclerosis (65-68). A common SNP near ADAMTS-7 was a common genetic risk factor for coronary atherosclerosis, with a 19% increased risk for carriers (69). The casual link between ADAMTS-7 and atherosclerosis progression has yet to be established. Neointima formation is considered as a response to vessel injury. The ADAMTS-7 protein was expressed preferentially in neointima of the carotid artery wall in response to balloon injury and **co-**localized with VSMCs in the newly formed neointima (70-72).The augmented expression of ADAMTS7 increased the proliferation and migration of VSMCs, while suppression of ADAMTS-7 level

using small interfering RNA (siRNA) had the opposite effect in the rat model. The notion was supported by the results from knockout mice mode which demonstrate that ADAMTS-7 deficiency led to reduce neointima formation following carotid artery injury induced by ligation (73). These findings suggested that ADAMTS-7 had a critical role in intimal hyperplasia after vascular injury.

COMP, a component of vascular ECM which has been observed in atherosclerotic lesions, is thought to be involved in migration of VSMCs (74). Overexpression of COMP markedly inhibited VSMC dedifferentiation and the expression of phenotype-dependent markers (23), while knockdown of ADAMTS-7 evidently attenuated COMP degradation and retarded VSMCs calcification (21), suggesting that the ADAMTS-7-mediated migration of VSMCs might associate with degradation of COMP matrix. However, ADAMTS-7 also can bind directly to thrombospondin-1 (TSP-1) and be involved in endothelium repair through COMP-independent pathways since COMP deficiency did not affect re-endothelialization in injured arteries (75). These findings suggested that ADAMTS-7 is a potential therapeutic target for atherosclerosis and vascular disorders (23, 66, 75, 76). In conclusion, ADAMTS-7 is involved in the pathogenesis of vascular disorders through degradation of COMP matrix and TSP-1, accelerated migration and proliferation of VSMCs, and regulation of inflammatory cytokines.

2.3.3 Other pathological conditions

ADAMTS-7 as a connective tissue growth factor (CTGF) binding and processing protein and has been reported to be an important regulator in oval cell (OC)

activation and biliary fibrosis, and its deficiency decreased CTGF turnover ability and enhanced hepatic progenitor/oval cell (HPC/OC) activation and biliary fibrosis during 3,5-diethoxycarbonyl-1,4-dihydrocollidin (DDC)-induced liver injury (77).

ADAMTS-7 expression had been found in urine from patients with prostate, bladder and breast cancer, suggesting a diagnostic and prognostic role of ADAMTS-7 in the detection and therapeutic value in tumor growth, invasion and metastasis (78). In addition, ADAMTS-7 was also found to be involved in host-pathogen interaction (79, 80). ADAMTS-7 played a critical role in influenza virus replication and was involved in host cell pathways such as NF-κB activation, and its gene expression resulted in reduced influenza virus replication through inhibition of miR-106B (79). ADAMTS-7 had been addressed to be involved into *V. splendidus* challenged sea cucumber and had significantly global proteome changes in expression at all examined time points using isobaric tags for relative and absolute quantification (iTRAQ) as compared with control group (80).

3. Conclusion

ADAMTS-7 is a member of the ADAMTS family, which are a group of secreted enzyme containing 19 members. The ADAMTS proteinase members play a key role in a variety of pathophysiological processes including development, human genetic diseases, and chronic inflammatory conditions. In the present review, we focused on the role of ADAMTS-7 in the progression of inflammatory diseases including arthritis and atherosclerosis. Overexpression of ADAMTS-7 accelerated the degradation of

COMP and the onset and progression of arthritis through formation a positive feedback loop with TNF-α. ADAMTS-7 has potential to serve as a therapeutic drug target in arthritis conditions. To do so, the precise understanding of the exact role played by ADAMTS-7 and its binding partners in inflammatory diseases appears of particular importance.

Abbreviations

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs

TNF-α: Tumor necrosis factor-α

COMP: Cartilage oligomeric matrix protein

ECM: Extracellular matrix

TSP: Thrombospondin

vWF: von Willebrand factor

α2-M: α2-Macroglobulin

CRD: Cysteine-rich domain

VSMCs: Vascular smooth muscle cells

RA: Rheumatoid arthritis

FNF: Femoral neck fracture

ONFH: Osteonecrosis of femoral head

GEP: Granulin-epithelin precursor

MED: Multiple epiphyseal dysplasia

ELISA: Enzyme linked immunosorbent assay

MMP: Matrix metalloproteinases

PCDGF: PC-cell-derived growth factor

PTHrP: Parathyroid hormonerelated peptide

GWAS: Genome-wide association studies

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Table 1 Biological characteristics of ADAMTS family members

Gene	Proteolytic	Expression in	Substrates	Role	References
ADAMTS-1	+	liver, endotheliocyte, skeletal	Aggrecan,	Cancer, atherosclerosis, fibrosis,	(81-89)
ADAMTS-2	+	connective tissue, placenta	Procollagen	Ehlhers-Danlos syndromes,	(90-93)
ADAMTS-3	+	skin, lung, brain	Procollagen	Dermatosparaxis, osteoar- thritis,	(7, 94, 95)
ADAMTS-4	+	heart, lung, skeletal muscle,	Aggrecan,	Glioma, atherosclerosis, arthritis,	(63, 96-99)
ADAMTS-5	+	macrophage, bladder,	Aggrecan,	Arthritis, cancer	(96, 100, 101)
ADAMTS-6				Tissue repair	(102)
ADAMTS-7	+	heart, liver, kidney, skeletal	COMP, α2M	Arthritis, atherosclerosis, kidney	(14, 42, 70, 103)
ADAMTS-8	+	heart, lung, kidney	Aggrecan	Cancer, atherosclerosis, arthritis,	(63, 104-106)
ADAMTS-9	+	heart, lung, skeletal muscle	Aggrecan, versican	Cancer, atherosclerosis, arthritis,	(107-109)
ADAMTS-10		lens, cartilage, skin		Weill-Marchesani syndromes	(110)
ADAMTS-12	+	chondrocyte, lung, kidney, liver	COMP, α2M,	arthritis, cancer, normal inflammatory	(14, 54, 111-113)
ADAMTS-13	+	liver, placenta, heart, skeletal	von Willebrand	Thrombotic thrombocytopenic purpura	(9)
ADAMTS-14	+	collagen-rich tissue, lung,	Procollagen	Fibrosis, osteoarthritis,	(114-118)
ADAMTS-15	+	kidney, lung, heart, ovary, stem	Aggrecan	Cancer, follicle rupture, myogenesis,	(1, 119-122)
ADAMTS-16	+	lung, kidney, ovary, cartilage,	α2M	Cancer, cryptorchidism,	(22, 123-125)
ADAMTS-17		epidermis, brain, heart, liver, lung,		Weill-Marchesani syndromes, short stature, pediatric stroke	(126-128)
ADAMTS-18		Lung, kidney, liver,		Ocular disease, cancer, stroke, bone	(129-133)
ADAMTS-19		lung, endothelium, ovary,	Aggrecan	Premature ovarian failure,	(134-137)
ADAMTS-20		ovary, heart, lung, placenta,	Aggrecan	Melanocyte differentiation,	(19, 138)