Comparison of ADAMTS-1, -4 and -5 expression in culprit plaques between acute myocardial infarction and stable angina

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ABSTRACT

Background ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs) proteases might contribute to plaque destabilisation by weakening the fibrous cap. However, little is known about the expression of ADAMTS proteases in coronary atherosclerotic plaques.

Objective To examine the expression of ADAMTS proteases in coronary atherectomy samples obtained from patients with acute myocardial infarction (AMI) or stable angina.

Methods Atherectomy specimens were obtained from 34 patients with AMI (n=23) or stable angina (n=11) who underwent directional coronary atherectomy. The specimens were stained with H&E and analysed immunohistochemically using antibodies specific to ADAMTS-1, -4 and -5; versican cleavage products; and markers for endothelial cells, macrophages and smooth muscle cells.

Results Baseline characteristics were similar between the two groups. The proportion of CD31 and CD68 immunopositive areas did not differ between the two groups, but the area immunopositive for smooth muscle α -actin was smaller in the AMI group. The relative area immunopositive for ADAMTS-1 in AMI (1.04% (IQR 0.59–2.09%)) was significantly greater than that in stable angina (0.24% (0.15–0.39%); p<0.001). In contrast, the proportion of areas immunopositive for ADAMTS-4 or -5 was similar in the two groups. Areas that stained for ADAMTS-1 largely overlapped with those positive for CD68 and versican cleavage products. The areas immunopositive for ADAMTS-1 were significantly correlated with CD68 immunostained areas (r=0.50, p=0.003).

Conclusions ADAMTS-1, -4 and -5 were present in human coronary atherosclerotic plaques, and ADATS-1 was more strongly expressed in AMI plaques than in stable plaques. ADAMTS-1 may play a role in plaque instability.

Plaque rupture is a primary underlying cause of acute myocardial infarction (AMI), and loss of extracellular matrix (ECM) in the fibrous cap is generally considered a prelude to rupture.¹ ² ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs) proteases, members of a large family of metalloproteases with common structural motifs,^{3–6} have been shown to act on the ECM proteoglycan substrates, aggrecan and versican.^{7–10} ADAMTS-1, -4 and -5 are the major aggrecanases, and collectively are largely responsible for the degradation of cartilage aggrecan in arthritis

diseases.^{6–8} Aggrecan is homologous to versican, a key proteoglycan that contributes to the structural integrity of the fibrous cap.¹¹ ¹² ADAMTS-1 was reported to be present in human atherosclerotic plaques, where it is suggested to promote atherogenesis by cleaving ECM.^{13–15} ECM plays a crucial role in both plaque stability and thrombogenicity.¹ Given their important role in ECM metabolism, ADAMTS proteases might contribute to plaque destabilisation by weakening the fibrous cap. However, little is known about the expression of ADAMTS proteases in human coronary atherosclerotic plaques or its relation to plaque instability.

Here, we investigated the expression of ADAMTS-1, -4 and -5 in coronary atherectomy samples obtained from patients with AMI or stable angina, and examined the relationship between expression patterns and clinical manifestations.

METHODS Study patients

Tissue samples were obtained from a biobank at our institution that collected atherectomy-derived specimens from 34 consecutive patients with either AMI (n=23) or stable angina (n=11), defined as typical exertional angina without a change in symptoms within 1 month before the procedure. Patient demographic and clinical characteristics, and procedures applied to each patient were prospectively recorded. Patients were suitable for directional coronary atherectomy if they had a significant stenotic lesion with a large plaque burden but lacked heavy thrombi in a nontortus epicardial coronary artery >3 mm in diameter.¹⁶ ¹⁷ Each specimen corresponded to the de novo lesion from a single patient that was responsible for the clinical presentation. Directional coronary atherectomy was performed using a Flexi-Cut catheter (Abbott Laboratories/Guidant Vascular Interventions, Santa Clara, California, USA) under intravascular ultrasound guidance. All patients provided written informed consent.

Tissue preparation

Tissue specimens were formalin-fixed and embedded in donor paraffin blocks. Tissue microarrays were produced by re-embedding tissues from the preexisting donor paraffin blocks into an array on a recipient paraffin block. Sections from the master block were cut using a microtome, mounted on a microscope slide, and used for subsequent staining.

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Histological analysis

Standard H&E staining was performed to determine cellularity and general morphological features. The area of each plaque was measured using a microscopic image analysis system (Motic Images Advanced 3.2, Motic, Xiamen, China). Plaques were classified as atheromatous (ie, with necrotic cores and cholesterol clefts but without connective tissue matrix) or fibrocellular, and graded as paucicellular (<30 spindle cells per high-power field), moderately cellular (30–100 spindle cells) or hypercellular (\geq 100 spindle cells). All slides were graded by two pathologists (C-SP and IH) without knowledge of patient clinical status. Any discrepancies between the findings of the two pathologists were resolved by discussion.

Immunohistochemistry and immunofluorescence staining

Sections of each tissue specimen were stained with polyclonal antibodies against ADAMTS-1 (Abcam, Cambridge, UK), ADAMTS-4 (Aviva Systems Biology, San Diego, California, USA), ADAMTS-5 (Novus, Littleton, Colorado, USA) and versican V0/V1 neoepitope (anti-DPEAAE; Thermo, Rockford, Illinois, USA), and monoclonal antibodies against smooth muscle α -actin (1:200, mouse anti-human macrophage antibody clone 1A4; DAKO, Carpinteria, California, USA) and CD68 (1:200, mouse anti-human macrophage antibody clone KP-1, DAKO) using an Envision-plus immunostaining kit and 3,3-diaminobenzidine or 3-amino-9-ethylcarbazole as the chromogen, as described by the manufacturer (DAKO). Briefly, samples were incubated with primary antibodies (diluted in antibody diluent; DAKO) for 1 h, washed twice (5 min each) with Tris-buffered saline/Tween-20, incubated with secondary antibodies conjugated with horseradish peroxidase (HRP)labelled polymer (DAKO) for 1 h, and again washed. As negative controls, adjacent sections were stained with species and isotype matched irrelevant antibodies, including normal rabbit IgG (Abcam). A sample of human placenta was used as a positive control for anti-ADAMTS-1, -4 and -5 antibodies. Cell types positive for ADAMTS were identified by immunostaining of serial sections with anti-ADAMTS-1, -4 and -5 antibodies. The immunopositive area was calculated as the ratio of positively stained regions to the total plaque area.

For immunofluorescent staining, fixed sections were hydrated in phosphate-buffered saline (PBS) for 10 min at room temperature, incubated with DakoCytomation Protein Block (Dako-Cytomation, Carpinteria, California, USA) for 5 min at room temperature, and washed three times in PBS/Tween-20 (PBST). Sections were next incubated with mouse anti-human CD68 monoclonal antibody (DakoCytomation), mouse anti-human smooth muscle α -actin monoclonal antibody (DakoCytomation), or rabbit anti-ADAMTS-1, -4 and -5 antibodies for 60 min at room temperature. After three additional washes in PBST, sections were incubated with fluorescein isothiocyanate (FITC) conjugated anti-rabbit IgG or allophycocyanin (APC) conjugated anti-mouse IgG for 60 min at room temperature, and washed three times with PBST. Coverslips were mounted onto glass slides using DAKO fluorescent mounting medium (DakoCytomation). FITC was excited using an argon laser at 488 nm and APC was excited by a helium-neon laser at 633 nm. Detector slits were configured to minimise any crosstalk between channels. Images were collected on a Leica TCS-NT/SP confocal microscope (Leica Microsystems, Mannheim, Germany) equipped with a $40 \times$ objective (model NA 0.75) and a zoom $1-4\times$, and processed using Leica TCS-NT/SP software (version LCS) and Adobe Photoshop 7.0.

Continuous variables are expressed as means (±SD) or medians (with IQR), whereas categorical variables are expressed as frequencies. Continuous variables were compared using Student t tests or Mann–Whitney U tests, and categorical variables were analysed using the χ^2 test. Linear regression analysis was used to correlate areas positive for ADAMTS-1 with those positive for endothelial cell, macrophage or smooth muscle cell markers. Statistical significance was defined as a two-sided p value <0.05.

RESULTS

Clinical characteristics

Baseline patient characteristics were similar between the two groups (table 1). The median age of patients was 62 years (range 38-77 years); 85.3% of patients were men, and 29.4% had diabetes mellitus. The median time from symptom onset to reperfusion was 7.3 h (range 2.5-72.0 h) for ST-elevation myocardial infarction (n=18) and 48 h (range 23.0-144.0 h) for non-ST-elevation myocardial infarction (n=5). With the exception of calcium channel blockers, concomitant medications at the time of directional coronary atherectomy were similar between the two groups.

Histological analysis

Neither total plaque areas nor the proportion of atheroma areas were different between the groups (table 2). Plaque types were more likely to be cellular in the AMI group than in the stable angina group. The presence of thrombi was more common in AMI than in stable angina (69.6% vs 27.3%; p=0.030). Calcium was detected in 34.8% of specimens from patients with AMI and in 27.3% of specimens from those with stable angina (p=1.000).

Immunohistochemistry

Detailed morphometric data are summarised in table 2. The proportion of smooth muscle α -actin immunopositive areas in

Table 1 Clinical characteristics

Characteristics	AMI (n = 23)	Stable angina (n=11)	p Value
Age, years	60.5 ± 10.4	61.7±6.9	0.722
Sex, male/female	20/3	9/2	1.000
Current smoker	11 (47.8%)	3 (27.3%)	0.295
Diabetes mellitus	7 (30.4%)	3 (27.3%)	1.000
Hypertension	9 (39.1%)	5 (45.5%)	1.000
Total cholesterol (mg/dl)	196.3 ± 45.3	173.6 ± 25.4	0.132
Triglyceride (mg/dl)	128.4 ± 67.9	153.8 ± 34.2	0.251
HDL cholesterol (mg/dl)	42.2 ± 11.4	38.5 ± 6.5	0.322
Hs-CRP (mg/dl)	4.1 ± 5.6	1.5 ± 0.7	0.181
Multivessel disease	12 (52.2%)	5 (45.5%)	1.000
Target artery			0.365
Left anterior descending coronary	15 (65.2%)	5 (45.5%)	
Left circumflex coronary	3 (13.0%)	1 (9.0%)	
Right coronary	5 (21.7%)	5 (45.5%)	
Medications at the time of DCA			
Aspirin	23 (100%)	11 (100%)	1.000
Clopidogrel	23 (100%)	10 (90.9%)	0.324
ACEI/ARB	1 (4.3%)	2 (18.2%)	0.239
β-blockers	4 (17.4%)	3 (27.2%)	0.356
Calcium antagonists	2 (8.7%)	8 (72.7%)	0.001
Statins	2 (8.7%)	4 (36.4%)	0.070

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; DCA, directional coronary atherectomy; HDL, high-density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein.

Variables	AMI (n=23)	Stable angina $(n=11)$	p Value
Histology			
Atheroma	13.17 (6.17-22.75)	7.25 (1.45-19.14)	0.363
Fibrocellular area			
Paucicellular	71.24 (38.41-76.99)	92.74 (67.00-98.51)	0.071
Moderately cellular	4.70 (1.68-11.98)	0 (0—0)	0.004
Hypercellular	0 (0—3.75)	0 (0—0)	0.201
Thrombus	1.42 (0-6.39)	0 (0-0.04)	0.071
Calcium	0 (0-0.13)	0 (0-0.02)	0.885
Total plaque area (mm²)	270.8 (195.0-517.2)	156.7 (84.1-340.0)	0.060
Immunohistochemistry			
Smooth muscle α -actin	1.59 (1.10-4.73)	4.85 (1.80-9.75)	0.028
CD31	0.16 (0.07-0.42)	0.12 (0.06-0.33)	0.690
CD68	3.38 (0.96-8.64)	1.90 (0.29-2.87)	0.164
ADAMTS-1	1.04 (0.59-2.09)	0.24 (0.15-0.39)	< 0.001
ADAMTS-4	9.56 (3.95-14.18)	2.79 (2.51-10.15)	0.123
ADAMTS-5	2.18 (1.36-4.50)	1.73 (0.90-2.81)	0.411

 Table 2
 Histological characteristics

ADAMTS, a disintegrin and metalloproteinase with thrombospondin type 1 motifs; AMI, acute myocardial infarction.

Data are expressed as percent positive areas (immunostaining area/total plaque area imes 100), and as median values with IQR.

the AMI group (1.59% (1.10-4.73%)) was smaller than that in the stable angina group (4.85% (1.80-9.75%); p=0.028). However, the proportion of areas immunopositive for CD31 and CD68 was similar between the two groups (CD31: 0.16% (0.07-0.42%) vs 0.12% (0.06-0.33%) for AMI and stable angina, respectively, p=0.690; CD68: 3.38% (0.96-8.64%) vs 1.90% (0.29-2.87%) for AMI and stable angina, respectively, p=0.164). The relative area immunopositive for ADAMTS-1 was significantly greater in patients with AMI (1.04% (0.59-2.09%)) than in those with stable angina (0.24%)(0.15-0.39%); p<0.001). In contrast, despite the more pronounced staining, there were no between-group differences in relative areas positive for ADAMTS-4 or ADAMTS-5 (ADAMTS-4: 9.56% (3.95-14.18%) vs 2.79% (2.51-10.15%) for AMI and stable angina, respectively, p=0.123; ADAMTS-5: 2.18% (1.36-4.50%) vs 1.73% (0.90-2.81%) for AMI and stable angina, respectively, p=0.411). There was a significant correlation between areas positive for ADAMTS-1 and CD68 (r=0.50, p=0.003). The others did not correlate with areas positive for ADAMTS-1.

Representative immunohistochemical staining for ADAMTS-1, -4, and -5 in coronary plaques obtained from a patient with AMI and from a patient with stable angina is shown in figure 1. Plaques from the AMI patient showed stronger immunoreactivity to the anti-ADAMTS-1 antibody than those from the patient with stable angina. However, the regions with ADAMTS-4 and -5 positive immunostaining were not different between the two patients.

To determine the cellular localisation of ADAMTS-1, we performed double-immunofluorescence staining on coronary plaques from a patient with AMI (figure 2). Confocal immunofluorescence staining showed that ADAMTS-1 immunoreactivity was present in CD68-immunopositive areas. In addition, immunostaining for truncated versican product (DPEAAE) prepared from a patients with AMI showed that DPEAAE is present in the plaques. Staining of serial sections of these plaques showed a similar distribution of both ADAMTS-1 and DPEAAE immunopositive areas (figure 3).

DISCUSSION

The major findings of this study are: ADAMTS-1, -4 and -5 were present in human coronary atherosclerotic plaques; ADAMDTS-1

was differentially expressed between AMI and stable angina; and ADAMTS-1 immunopositive cells were mainly macrophages. This is the first study to relate the ADAMTS proteases to an acute coronary syndrome. Our findings suggest that ADAMTS-1 may be involved in the pathogenesis of acute coronary syndrome, providing new insight into the biological process of plaque destabilisation.

Coronary artery disease is largely asymptomatic for decades, until plaque rupture suddenly triggers the development of an acute coronary syndrome. A number of explanations have been proposed to account for plaque rupture, but the mechanisms remain poorly defined. Autopsy studies have revealed that the vulnerability of a plaque to rupture is related to specific morphological characteristics, including a large lipid core, a thin fibrous cap, and marked inflammation.¹⁸ ECM is the main component of the fibrous cap, and proteases play a key role in ECM degradation. Matrix metalloproteinases have been extensively studied as critical factors in provoking plaque rupture,² but little attention has been paid to the ADAMTS proteases.¹⁴ Given the importance of ECM integrity in the atheroma, an exploration of the expression profiles of individual proteases at the site of plaque rupture is warranted.

ADAMTS are a subfamily of ADAM proteases that possess an additional distinct feature not present in other ADAM proteases. These proteases are emerging as key participants in ECM degradation in vascular pathologies, including atherosclerotic plaques, restenosis and aneurysmal change.^{12–15} ADAMTS-1 (aggrecanase-3) is known to cleave the proteoglycan versican, which provides the structural integrity of the fibrous cap.⁹ ¹⁴ In our study, we found that the areas stained for ADAMTS-1 and versican cleavage products were similarly distributed on the plaques, suggesting that ADAMTS-1 is functionally active in the culprit plaques of AMI. In an autopsy study, a loss of proteoglycans and hyaluronan within the ECM was observed at the sites of plaque rupture, suggesting that these molecules are involved in the process of plaque rupture.¹¹ In a mouse model of arterial remodelling, overexpression of ADAMTS-1 was shown to increase neointimal hyperplasia with positive vessel remodelling.¹⁴ This may be beneficial for preservation of the lumen, but detrimental for plaque stability. On the other hand, ADAMTS-1 cleaves and alters the extracellular location of tissue-factor pathway inhibitor-2, which directly inhibits matrix

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Figure 1 Representative images of ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs)-1, -4 and -5 immunohistochemical staining in coronary plaques from patients with acute myocardial infarction (AMI) (A, C, E) or stable angina (B, D, F). Immunohistochemical staining with anti-ADAMTS-1 antibody (dark brown) shows strong positive areas in patients with AMI (A) (\times 200), but no staining in patients with stable angina (B). Areas of ADATS-4 and -5 immunostaining are similar in both AMI (C, E) (\times 200) and stable angina (D, F) (\times 200). Positive control: staining of ADAMTS-1 in human placenta (G) (\times 200). Negative control: staining of specimen A with rabbit isotype primary antibody (H) (\times 200).



metalloproteinase 1, -2, -9 and -13 activities.¹⁹ Thus, ADAMTS-1 may promote ECM remodelling by inhibiting the function of tissue-factor pathway inhibitor-2, an inhibitor of plaque-destabilising matrix metalloproteinases.²⁰ In our study, ADAMTS-1 was more strongly expressed in the culprit plaques of AMI compared to those in stable angina, supporting an active role of ADAMTS-1 in plaque destabilisation. In addition, ADAMTS-1 staining areas coincided with those of macrophages, suggesting that these cells may primarily produce ADAMTS-1 in response to inflammatory stimuli, such as IL-1 or tumour necrosis factor- α .^{3 14 21} ADAMTS-1 may also be involved in the inflammatory process through processing of the ECM.²² Taken together, these

diverse properties of ADAMTS-1 are thought to promote local destruction of the ECM in coronary atherosclerotic plaques, rendering it susceptible to rupture.

Since the initial discovery of ADAMTS-1 in 1997,³ a total of 19 similar genes, numbered ADAMTS-1 to -20 (ADAMTS-5 was originally termed ADAMTS-11), have been found in the human genome.²³ Compared with matrix metalloproteinases, ADAMTS proteases recognise a more diverse range of substrates, including procollagens and proteoglycans.⁶ ²⁴ ²⁵ ADAMTS-1, -4 and -5 show a high degree of sequence homology and have overlapping activities, exhibiting proteolytic modification of cellsurface proteins and ECM.⁶ ADAMTS-4 (aggrecanase-1) and -5 **Figure 2** Immunofluorescence staining of coronary plaques of a patient with acute myocardial infarction using antibodies to ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs)-1 (A, green, $\times 800$) and CD68 (B, red, $\times 800$). ADAMTS-1 immunopositive cells are colocalized with cells positive for CD68 (D, green and red), as indicated by arrows ($\times 800$). DAPI nuclear staining (C) ($\times 800$).



(aggrecanse-2) are major aggrecanases in osteoarthritic cartilage, playing a major role in early stages of cartilage destruction in osteoarthritis and rheumatoid arthritis.^{6–8} Inhibition of ADAMTS-4 and -5 has been shown to prevent aggrecan degradation in diseased cartilage, highlighting the potential of these proteases as therapeutic targets in arthritic diseases. There are, however, some discrepancies between results obtained from murine models and observations in human osteoarthritis tissues. In human chondrocytes, inflammatory cytokines upregulate the expression of ADAMTS-4, but not ADAMTS-5⁸ In knockout mouse models of arthritis, deletion of ADAMTS-5 protects joints from cartilage destruction following surgical induction of osteoarthritis, whereas ablation of ADAMTS-4 does not.^{26 27} In

addition, ADAMTS-4 and -5 were reported to be expressed in macrophage-rich areas of human atherosclerotic plaques.²⁵ In our studies, ADAMTS-4 and -5 were also present in coronary atherectomy tissues obtained from patients with both AMI and stable angina, but their expression levels were not different between the two groups. It seems likely that ADAMTS-4 and -5 are present constitutively in coronary atherosclerotic plaques, but ADAMTS-1 is induced through unknown mechanisms during plaque destabilisation. In a recent report, the risk of coronary heart disease and non-fatal myocardial infarction was higher in patients homozygous for ADAMTS-1 227 Pro/Pro than in 227 Ala carriers.¹⁵ These findings suggest that ADAMTS-1 is more likely than ADAMTS-4 and -5 to be involved in plaque

Figure 3 ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs)-1 and versican neoepitope immunostaining of coronary plaques from a patient with acute myocardial infarction. Serial sections of ADAMTS-1 (A, dark brown, ×200) and versican neoepitope (B, dark brown, \times 200) immunostaining show strong positive areas with a similar spatial distribution. Positive control: staining of versican neoepitope in aortic wall with atherosclerosis (C) (\times 200). Negative control: staining of aortic wall with rabbit isotype primary antibody (D) (×200).



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Take-home messages

- ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs) proteases might contribute to plaque destabilisation by weakening the fibrous cap.
- ADAMTS-1, -4 and -5 were present in human coronary atherosclerotic plaques, and ADAMTS-1 was differentially expressed between acute myocardial infarction and stable angina.
- If these findings are confirmed, ADAMTS proteases may play a key role in the pathogenesis of AMI, providing new insight into the biological process of plaque destabilisation.

destabilisation. The differential effects of ADAMTS proteases may have implications for the potential development of plaque stabilising therapies. However, it remains unclear how the roles of ADAMTS proteases in plaque destabilisation are regulated. To date, most data implicating ADAMTS proteases in ECM remodelling has been obtained from patients with arthritis diseases. Information on the clinical relevance of ADAMTS proteases in the context of plaque instability is sparse. Our findings provide the first evidence for protein-level expression of ADAMTS proteases in human coronary atherosclerotic plaques and relate the expression profiles of these proteases to an acute coronary syndrome, thus improving our understanding of plaque rupture.

Study limitations

Several potential limitations should be noted. First, tissues specimens were obtained from selected lesions in large vessels because calcified, tortuous, small vessels or those with heavy thrombotic lesions are not suitable for directional coronary atherectomy. Thus, it may not be possible to extrapolate our findings to all culprit lesions of AMI. Second, because of the small sizes of specimens, ADAMTS proteases expression could not be confirmed by western blot analysis. Finally, the number of study patients was relatively small.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Institutional Review Committee of the University of Ulsan.

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REFERENCES

1. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-50.

- Newby AC. Do metalloproteinases destabilize vulnerable atherosclerotic plaques? Curr Opin Lipidol 2006;17:556–61.
- Kuno K, Kanada N, Nakashima E, et al. Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene. J Biol Chem 1997;272:556–62.
- Tortorella MD, Burn TC, Pratta MA, et al. Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. *Science* 1999;284:1664–6.
- Tang BL. ADAMTS: a novel family of extracellular matrix proteases. Int J Biochem Cell Biol 2001;33:33–44.
- Porter S, Clark IM, Kevorkian L, et al. The ADAMTS metalloproteinases. Biochem J 2005;386:15–27.
- Malfait AM, Liu RQ, Ijiri K, et al. Inhibition of ADAM-TS4 and ADAM-TS5 prevents aggrecan degradation in osteoarthritic cartilage. J Biol Chem 2002;277:22201–8.
- Song RH, Tortorella MD, Malfait AM, et al. Aggrecan degradation in human articular cartilage explants is mediated by both ADAMTS-4 and ADAMTS-5. Arthritis Rheum 2007;56:575–85.
- Sandy JD, Westling J, Kenagy RD, et al. Versican V1 proteolysis in human aorta in vivo occurs at the Glu441-Ala 442 bond, a site that is cleaved by recombinant ADAMTS-1 and ADAMTS-4. J Biol Chem 2001;276:13372-8.
- Russell DL, Doyle KM, Ochsner SA, et al. Processing and localization of ADAMTS-1 and proteolytic cleavage of versican during cumulus matrix expansion and ovulation. J Biol Chem 2003;278:42330–9.
- Kolodgie FD, Burke AP, Farb A, et al. Differential accumulation of proteoglycans and hyaluronan in culprit lesions: insights into plaque erosion. Arterioscler Thromb Vasc Biol 2002;22:1642-8.
- Wight TN, Merrilees MJ. Proteoglycans in atherosclerosis and restenosis: key roles for versican. *Circ Res* 2004;94:1158–67.
- Theocharis AD, Tsolakis I, Hjerpe A, et al. Human abdominal aortic aneurysm is characterized by decreased versican concentration and specific downregulation of versican isoform V(0). Atherosclerosis 2001;154:367–76.
- Jönsson-Rylander AC, Nilsson T, Fritsche-Danielson R, et al. Role of ADAMTS-1 in atherosclerosis: remodeling of carotid artery, immunohistochemistry, and proteolysis of versican. Arterioscler Thromb Vasc Biol 2005;25:180-5.
- Sabatine MS, Ploughman L, Simonsen KL, et al. Association between ADAMTS1 matrix metalloproteinase gene variation, coronary heart disease, and benefit of statin therapy. Arterioscler Thromb Vasc Biol 2008;28:562–7.
- Kurisu S, Sato H, Tateishi H, et al. Directional coronary atherectomy for the treatment of acute myocardial infarction. Am Heart J 1997;134:345–50.
- 17. **McKnight J**, Studeny M, Roberts G, *et al*. Directional coronary atherectomy in acute myocardial infarction. *W V Med J* 2001;**97**:109–10.
- Finn AV, Nakano M, Narula J, et al. Concept of vulnerable/unstable plaque. Arterioscler Thromb Vasc Biol 2010;30:1282–92.
- Herman MP, Sukhova GK, Kisiel W, et al. Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis. J Clin Investig 2001;107:1117–26.
- Torres-Collado AX, Kisiel W, Iruela-Arispe ML, et al. ADAMTS1 interacts with, cleaves, and modifies the extracellular location of the matrix inhibitor tissue factor pathway inhibitor-2. J Biol Chem 2006;281:17827–37.
- Wight TN. The ADAMTS proteases, extracellular matrix, and vascular disease waking the sleeping giant(s)! Arterioscler Thromb Vasc Biol 2005;25:12–14.
- Moss ML, Jin SL, Milla ME, et al. Cloning of a disintegrin metalloproteinase that processes precursor tumour-necrosis factor-alpha. *Nature* 1997;385:733-6.
- Apte SS. A disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motifs: the ADAMTS family. Int J Biochem Cell Biol 2004;36:981-5.
- Fernandes RJ, Hirohata S, Engle JM, et al. Procollagen II amino propeptide processing by ADAMTS-3. Insights on dermatosparaxis. J Biol Chem 2001;276:31502-9.
- Wågsäter D, Björk H, Zhu C, et al. ADAMTS-4 and -8 are inflammatory regulated enzymes expressed in macrophage-rich areas of human atherosclerotic plaques. Atherosclerosis 2008;196:514–22.
- Glasson SS, Askew R, Sheppard B, et al. Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis. *Nature* 2005;434:644–8.
- Glasson SS, Askew R, Sheppard B, et al. Characterization of and osteoarthritis susceptibility in ADAMTS-4-knockout mice. Arthritis Rheum 2004;50:2547–58.



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