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Expression of ADAMTS-2, -3, -13, and -14 in culprit coronary lesions in patients with acute myocardial infarction or stable angina

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Abstract ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs) proteases are emerging as key participants in the pathogenesis of vascular diseases. We studied the expression of ADAMTS-2, -3, -4 and -14 in the culprit plaques from patients presenting with acute myocardial infarction (AMI) versus stable angina. Tissue samples were gathered from 52 patients with AMI ($n = 35$) or stable angina ($n = 17$) who underwent directional coronary atherectomy. The specimens were stained with hematoxylin-eosin and analyzed immunohistochemically using antibodies specific to ADAMTS-2, -3, -13 and -14, and markers for endothelial cells, macrophages, and smooth muscle cells. Baseline characteristics of the groups were mostly similar. The proportion of smooth muscle α-actin-immunopositive area was smaller in the AMI group than in the stable angina group, but the areas immunopositive for CD31 or CD68 were higher in the AMI group. The relative areas immunopositive for ADAMTS-2, -3, and -13 in AMI were significantly larger than those in stable angina. However, the proportion of areas immunopositive for ADAMTS-14 did not differ between the two groups. Areas that stained for ADAMTS-2, -3, -13, and -14 largely overlapped with those positive for CD31 or CD68. The areas immunopositive for ADAMTS proteases were significantly correlated with CD31- or CD68-immunostained areas. In conclusions, ADAMTS-2, -3, and -13 expression, but not that of ADAMTS-14, are increased in plaques causing AMI compared those associated with stable angina. These results support a role for these enzymes in the pathogenesis of AMI.

Keywords ADAMTS protease · Coronary disease · Plaque stability

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Introduction

Plaque rupture with subsequent thrombus formation is the main event leading to acute myocardial infarction (AMI) [1]. Timely reperfusion of the occluded artery and complete healing of the culprit plaque is critical for limiting cardiac mortality and morbidity. Episodes of plaque rupture, followed by healing, are thought to be responsible for lesion progression [2]. A clearer understanding of the mechanism by which plaques heal is of clinical importance, but the healing process after plaque rupture has not been fully elucidated.

ADAMTS (a disintegrin and metalloproteinase with thrombospondin type 1 motifs) proteases are non-membrane-bound enzymes that are involved in processing procollagens and von Willebrand factor (vWF) as well as cleavage of proteoglycans [3, 4]. ADAMTS-2, -3, and -14

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are termed procollagen-N-proteinases owing to their involvement in the removal of N-terminal peptides from procollagen to form mature collagen. These proteins are considered to play an important role in the regulation of inflammation and wound repair [5–7]. ADAMTS-13 was identified as the protease that cleaves the multimeric glycoprotein, vWF [8]. A lack of ADAMTS-13 leads to thrombotic thrombocytopenic purpura, in which large multimers of vWF accumulate and induce platelet aggregation and vascular occlusions [9]. Furthermore, cleavage of vWF by ADAMTS-13 can attenuate thrombus formation in atherosclerotic plaques [10]. Taken together, these observations indicate that ADAMTS proteases might contribute to plaque healing and thrombus resolution after plaque rupture, but little is known about the expression of ADAMTS proteases in culprit plaques of AMI.

The current study investigated the expression of ADAMTS-2, -3, -13, and -14 in coronary atherectomy tissues obtained from patients with AMI or stable angina, and examined the relationship between their expression levels and clinical manifestations.

Methods

Study patients

Specimens of coronary atherosclerotic plaques from 52 consecutive patients with either AMI ($n = 35$) or stable angina ($n = 17$), defined as typical exertional angina without a change in symptoms within 1 month prior to the procedure, were obtained from a biobank at our institution that collects atherectomy-derived tissues. Patient demographic and clinical characteristics, and procedures applied to each patient were prospectively recorded. Patients were considered suitable for directional coronary atherectomy if they had a significant stenotic lesion with a large plaque burden but lacked heavy thrombi in a non-tortuous epicardial coronary artery >3 mm in diameter [11, 12]. Each sample 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, CA, USA) under intravascular ultrasound guidance. The study protocol was approved by our Institutional Review Committee, and 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 microscope slides, and used for subsequent staining procedures.

Histological analysis

Standard hematoxylin and eosin staining was performed to determine cellularity and general morphologic 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 (i.e., 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 (≥100 spindle cells). All slides were graded by two pathologists (C-S Park and I Hwang) 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-2 (Sigma, St. Louis, MO, USA), ADAMTS-3 (Abcam, Cambridge, UK), ADAMTS-13 (Abcam) and ADAMTS-14 (Sigma), and monoclonal antibodies against smooth muscle α-actin (1:200, mouse anti-human macrophage antibody clone 1A4; DAKO, Carpinteria, CA, USA), CD31 (1:200, mouse anti-human endothelial cell antibody clone WM59; BD Biosciences, Franklin Lakes, NJ, USA) and CD68 (1:200, mouse anti-human macrophage antibody clone KP-1; DAKO), VWF (1:150 mouse anti-human vWF antibody VW40-1, Abnova, Taipei city, Taiwan), procollagen type I (1:100 mouse anti-human procollagen type I antibody PC5-5, Abnova) 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)-labeled 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). As positive controls for anti-ADAMTS antibodies, we used samples obtained from human cerebellum (ADAMTS-2), skin (ADAMTS-3), and kidney (ADAMTS-13, ADAMTS-14). Cell types positive for ADAMTS were identified by immunostaining serial sections with anti-ADAMTS-2, -3, -13, and -14 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 (DakoCytomation, Carpinteria, CA, USA) for 5 min at room temperature, and washed three times in PBS/Tween-20 (PBST). Sections were next incubated for 60 min at room temperature with mouse anti-human CD31 monoclonal antibody (BD Biosciences), mouse anti-human CD68 monoclonal antibody (DakoCytomation), mouse anti-human smooth muscle α-actin monoclonal antibody (DakoCytomation), or rabbit anti-ADAMTS-2, -3, -13, and -14 antibodies. 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 minimize crosstalk between channels. Images were collected on a Leica TCS-NT/SP confocal microscope (Leica Microsystems, Mannheim, Germany) equipped with a 40× objective (Model NA 0.75) and a zoom 1–4×, and processed using Leica TCS-NT/SP software (version LCS) and Adobe Photoshop 7.0.

Statistical analysis

Continuous variables are expressed as means (±standard deviations) or medians (with interquartile ranges [IQR]), whereas categorical variables are expressed as frequencies. Continuous variables were compared using Student's *t* tests or Mann–Whitney *U* tests, and categorical variables were analyzed using the χ^2 test. Linear regression analysis was used to correlate areas positive for ADAMTS proteases 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

The two groups did not differ in baseline clinical characteristics, except lipid profiles and medications (Table 1). The median age of patients was 61 years (range 31–75 years); 76.9% of patients were men; 23.1% had diabetes mellitus. The median time from the onset of chest pain to angioplasty

Table 1 Clinical characteristics

Characteristics	AMI ($n = 35$)	Stable angina ($n = 17$)	*P* value
Age (years)	56.7 ± 11.4	60.5 ± 6.5	0.130
Sex (male/female)	29/6	11/6	0.173
Current smoker	16 (45.7%)	5 (29.4%)	0.369
Diabetes mellitus	7 (20.0%)	5 (29.4%)	0.496
Hypertension	18 (51.4%)	9 (52.9%)	1.000
Total cholesterol (mg/dl)	188.1 ± 46.8	154.0 ± 31.7	0.009
Triglyceride (mg/dl)	173.6 ± 88.1	112.9 ± 47.5	0.003
HDL cholesterol (mg/dl)	35.5 ± 8.3	42.0 ± 14.7	0.105
Hs-CRP (mg/dl)	2.8 ± 3.0	1.6 ± 1.8	0.197
Multivessel disease	16 (45.7%)	6 (35.3%)	0.558
Target artery			0.664
Left anterior descending coronary	18 (51.4%)	11 (64.7%)	
Left circumflex coronary	3 (8.6%)	1 (5.9%)	
Right coronary	14 (40.0%)	5 (29.4%)	
Medications at the time of DCA			
Aspirin	35 (100%)	17 (100%)	1.000
Clopidogrel	35 (100%)	17 (100%)	1.000
ACEI/ARB	2 (5.7%)	2 (11.8%)	0.589
β-Blockers	8 (22.9%)	8 (47.1%)	0.111
Calcium antagonists	4 (11.4%)	10 (58.8%)	0.001
Statins	11 (31.4%)	12 (70.6%)	0.016

hs-CRP high-sensitivity C-reactive protein, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DCA* directional coronary atherectomy

was 5.5 h (IQR 2.5–7.5 h) for ST-elevation myocardial infarction ($n = 27$) and 36 h (IQR 25–96 h) for non-ST-elevation myocardial infarction ($n = 8$). At the time of directional coronary atherectomy, calcium channel blockers and statins were more commonly used in patients with stable angina than in those with AMI.

Histological analysis

The proportion of atheroma areas was significantly higher in the AMI group than in the stable angina group (Table 2). Plaque types tended to be more cellular in the AMI group than in the stable angina group. Thrombi were observed in 71.4% of specimens from patients with AMI and in 11.8% of specimens from those with stable angina ($P < 0.001$).

Immunohistochemistry

A summary of detailed morphometric data is shown in Table 2. The proportion of areas immunopositive for CD31 and CD68 in the AMI group was larger than that in the stable angina group (CD31: 0.7% [0.4–1.5%] vs. 0.1% [0–0.2%], $P < 0.001$; CD68: 12.2% [5.9–21.7%] vs. 1.7% [0.3–7.2%], $P = 0.005$). In contrast, the proportion of smooth muscle α-actin-immunopositive areas in the AMI group (1.9% [0.9–3.8%]) was smaller than that in the stable angina group (6.0% [3.4–20.9%], $P < 0.001$). The relative areas immunopositive for ADAMTS-2 and -3 were significantly greater in patients with AMI than in those with stable angina (ADAMTS-2: 5.1% [1.5–9.1%] vs. 2.5% [1.0–4.2%], $P = 0.028$; ADAMTS-3: 5.7% [2.4–14.5%] vs. 1.1% [0.8–2.9%], $P = 0.001$). Likewise, the relative area for ADAMTS-13 was higher in the AMI group (6.9% [1.8–12.2%]) than in the stable angina group (2.5% [1.5–3.7%], $P = 0.015$). ADAMTS-14 staining, however, did not differ between the two groups (0.7% [0.3–1.4%] vs. 0.1% [0–1.4%], $P = 0.169$). Areas positive for ADAMTS-2, -3, -13, and -14 were significantly correlated with areas immunopositive for CD31 or CD68.

Figure 1 shows representative immunohistochemical staining for ADAMTS-2, -3, -13, and -14 in coronary plaques derived from a patient with AMI and from a patient with stable angina. Plaques from the AMI patient showed stronger immunoreactivity to the anti-ADAMTS-2, -3, and -13 antibodies than those from the patient with stable angina. However, ADAMTS-14 staining was weak and statistically indistinguishable in the two patients. In addition, confocal immunofluorescence analysis of coronary plaques from a patient with AMI revealed that ADAMTS-2, -3, and -13 immunoreactivity colocalized with areas immunopositive for CD31 or CD68 (Fig. 2). Cells immunopositive for ADAMTS-2 also colocalized with cells positive for procollagen type I, and ADAMTS-13 with those for vWF (Fig. 3).

Discussion

In the present study, ADAMTS-2, -3, -13, and -14 were found in human coronary atherosclerotic plaques. ADAMTS-2, -3, and -13 were more strongly expressed in culprit plaques of AMI than in those of stable angina, and immunopositive cells were mostly endothelial cells and macrophages. These findings suggest that ADAMTS-2, -3,

Table 2 Histological characteristics

Variables	AMI ($n = 35$)	Stable angina ($n = 17$)	P value
Histology			
Atheroma	54.7 (33.8–68.3)	24.0 (11.0–37.5)	0.003
Fibrocellular area			
Paucicellular	33.5 (20.6–44.8)	55.3 (24.9–74.9)	0.031
Moderately cellular	5.0 (0–9.2)	3.4 (0–31.4)	0.596
Hypercellular	0 (0–1.0)	0 (0–0)	0.214
Thrombus	1.4 (0–4.3)	0 (0–0)	<0.001
Calcium	0 (0–0.1)	0 (0–0.1)	0.872
Total plaque area (mm^2)	662.2 (416.1–886.2)	478.3 (244.2–646.2)	0.050
Immunohistochemistry			
CD31	0.7 (0.4–1.5)	0.1 (0–0.2)	<0.001
CD68	12.2 (5.9–21.7)	1.7 (0.3–7.2)	0.005
Smooth muscle α-actin	1.9 (0.9–3.8)	6.0 (3.4–20.9)	<0.001
ADAMTS-2	5.1 (1.5–9.1)	2.5 (1.0–4.2)	0.028
ADAMTS-3	5.7 (2.4–14.5)	1.1 (0.8–2.9)	0.001
ADAMTS-13	6.9 (1.8–12.2)	2.5 (1.5–3.7)	0.015
ADAMTS-14	0.7 (0.3–1.4)	0.1 (0–1.4)	0.169

Data are expressed as percent-positive areas (immunostained area/total plaque area × 100), and as median values with interquartile ranges

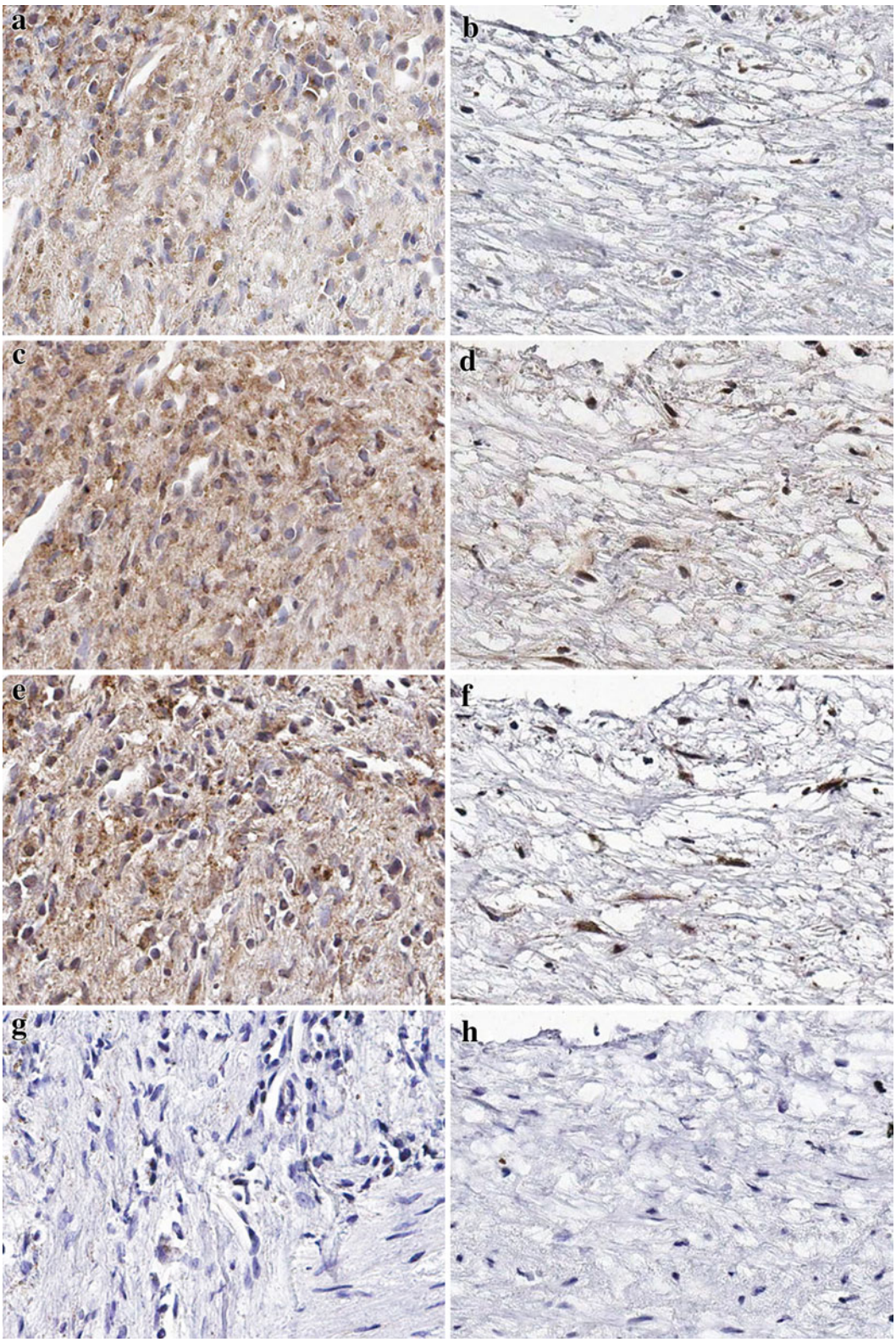

Fig. 1 Representative images of ADAMTS-2, -3, -13, and -14 immunohistochemical staining in coronary plaques from patients with AMI (**a**, **c**, **e**, **g**) or stable angina (**b**, **d**, **f**, **h**). Immunohistochemical staining with anti-ADAMTS-2, -3, and -13 antibodies (*dark brown*) reveals strong positive areas in a patient with AMI (**a**, **c**, **e**), but weak staining in a patient with stable angina (**b**, **d**, **f**). ADAMTS14 staining is similarly weak in both AMI (**g**) and stable angina (**h**). Magnification ×400

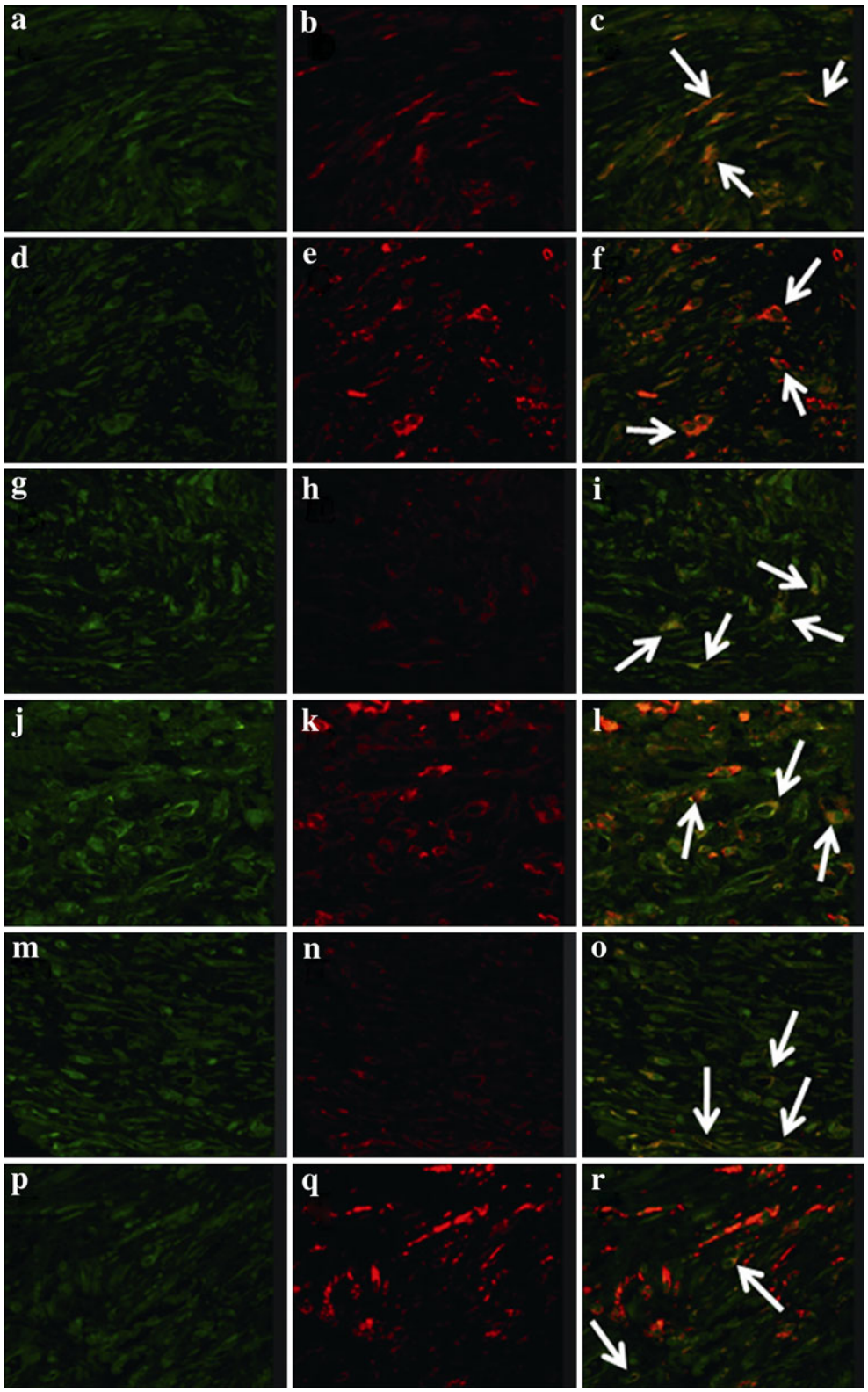

Fig. 2 Confocal immunofluorescence staining of coronary plaques from a patient with AMI using antibodies to ADAMTS proteins, CD31, and CD68: ADAMTS-2 (*green*; **a**, **d**), ADAMTS-3 (*green*; **g**, **j**), ADAMTS-13 (*green*; **m**, **p**), CD31 (*red*; **b**, **h**, **n**), CD68 (*red*; **e**, **k**, **q**). Cells immunopositive for ADAMTS-2, -3, or -13 colocalized with cells positive for CD31 (**c**, **i**, **o**) or CD68 (**f**, **l**, **r**). *Arrows* denote colocalized cells. Magnification, ×800

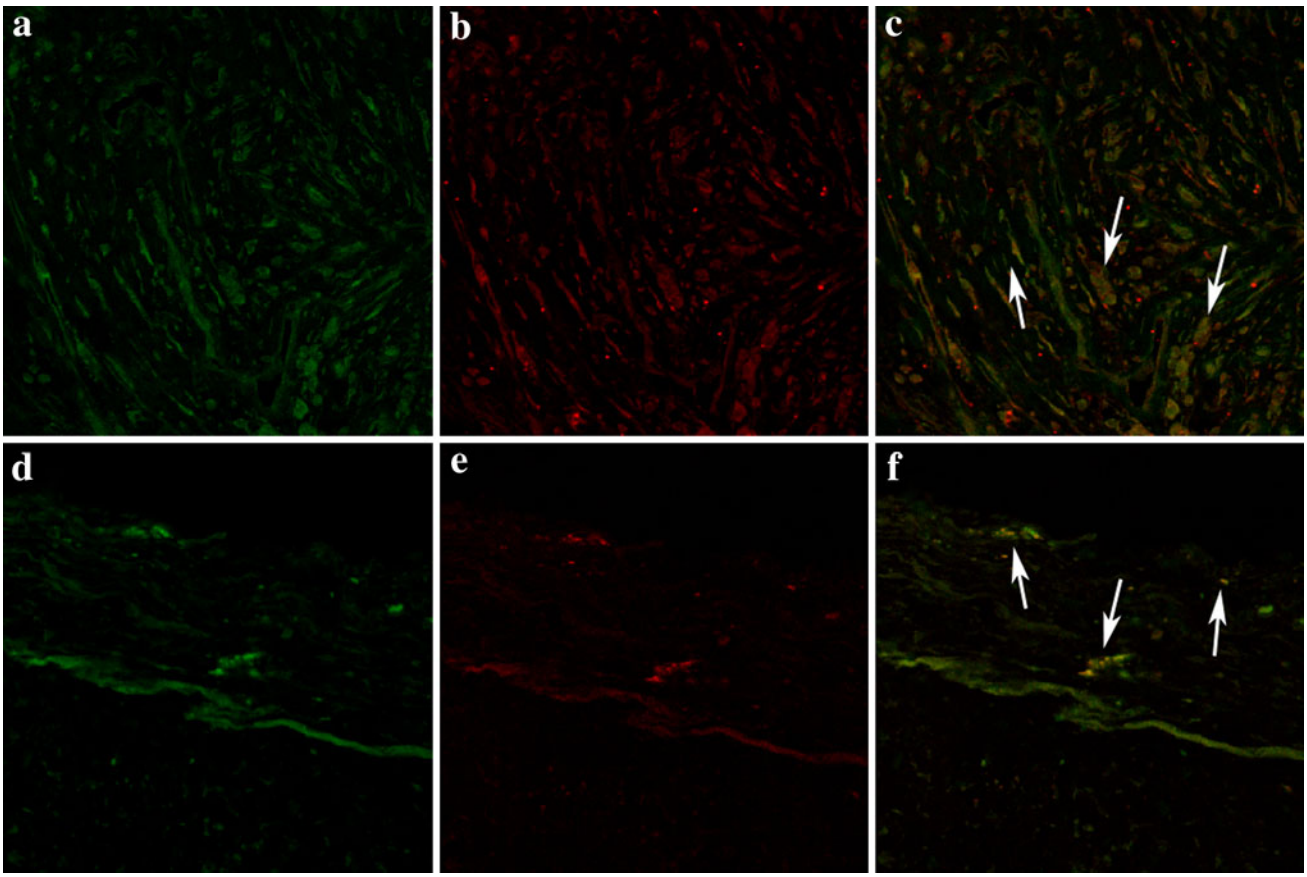

Fig. 3 Confocal immunofluorescence staining of coronary plaques from a patient with AMI using antibodies to ADAMTS-2, ADAMTS-13, procollagen type 1 and vWF: ADAMTS-2 (*green*; **a**), ADAMTS-13 (*green*; **d**), procollagen (*red*; **b**), vWF (*red*; **e**). Cells immunopositive for ADAMTS-2 and -13 colocalized with cells positive for procollagen type I (**c**) or vWF (**f**). *Arrows* denote colocalized cells. Magnification ×800

and -13 are involved in the process of repairing disrupted coronary plaques, providing unique insights into healing responses after plaque rupture.

A ruptured coronary artery plaque is a common finding, and most plaque ruptures do not seem to result in any symptoms. Furthermore, multiple plaque ruptures that increase the risk of recurrent coronary events are frequently observed on a site other than the culprit lesion [13]. In postmortem specimens, acute ruptures overlying healed ruptures are more narrowed than de novo ruptures, suggesting that subclinical episodes of plaque rupture followed by healing are a stimulus for plaque progression [2]. In addition, some ruptured plaques are healed, whereas others are not [14]. Therefore, plaque rupture and healing seem to be dynamic processes, and complete healing of the vulnerable lesions after rupture should help to prevent recurrent events. Most studies, however, have focused on plaque rupture; thus, the healing responses after rupture remain poorly understood.

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 the pathogenesis of vascular diseases, including atherosclerosis, restenosis, and aneurysmal change [3, 4]. ADAMTS-2, -3, and -14, which are procollagen-N-proteinases involved in the processing of procollagens to mature collagens by excising the aminopropeptide [15–18], play a crucial role during the wound-healing process. ADAMTS-2 is responsible for processing procollagen I, II and III, whereas ADAMTS-3 and ADAMTS-14 are involved in procollagen II and procollagen I processing, respectively. Several mutations in the ADAMTS-2 gene have been identified in patients with a type of Ehlers-Danlos syndrome characterized by excessive skin fragility and joint laxity. In addition, ADAMTS-2-null mice develop severe skin fragility after birth. These findings suggest that ADAMTS-2 is essential for maturation of type I collagen fibrils in skin, and that neither ADAMTS-3 nor ADAMTS-14 compensate adequately for ADAMTS-2 deficiency in this tissue. Collagens types I and III largely determine the stability and strength of fibrous caps because they tolerate much greater tensile stress than elastin [19]. In

the present study, we found that ADAMTS-2 was highly expressed in culprit plaques of AMI, and coexpressed with procollagen type I, and immunopositive cells were endothelial cells and macrophages. Vascular smooth muscle cells synthesize new collagens, restoring the injured fibrous cap after rupture [19]. Our findings may reflect the increased collagen synthesis that occurs after an acute plaque ruptures, presumably in an attempt to repair the extracellular matrix. These results may contribute to the understanding of the plaque healing processes, and provide for a framework for developing new strategies to combat plaque instability. However, because very little is known about the specific roles of these enzymes in plaque healing, further studies are required.

A thrombus forms over a disrupted coronary plaque, and its fate is determined by the delicate balance between ongoing thrombosis and clot lysis. Spontaneous recanalization is a common time-dependent occurrence; in $\sim$30% of ST segment-elevation myocardial infarction cases, infarct-related arteries reperfuse within the first 12 h of presentation [20]. Endogenous fibrinolysis is considered an effective mechanism for causing coronary recanalization. vWF, a carrier protein for clotting factor VIII, supports platelet aggregation and mediates platelet adhesion to areas of vascular damage [21, 22]. Ultralarge vWF multimers can bind more effectively to the extracellular matrix than regular multimers, and form stronger bonds with platelet GPIb-IX-V. ADAMTS-13 is synthesized in endothelial cells, and released constitutively [23], and degrading large vWF multimers into smaller forms, decreasing their activity. The absence or a severe reduction in ADAMTS-13 activity leads to accumulation of ultralarge vWF multimers in plasma and results in a familial form of the thrombotic disease, thrombotic thrombocytopenic purpura. In contrast, increased exposure of vWF to ADAMTS-13 would predispose to bleeding by accelerating degradation of vWF [24]. The present study showed that ADAMTS-13 was highly expressed at culprit plaques of AMI and coexpressed with vWF, suggesting that endogenous clot lysis after plaque rupture occurs simultaneously to reduce occlusive thrombus formation. ADAMTS-13 was shown to colocalize with vWF in thrombi of human coronary arteries [10]. Sudden coronary occlusion is often preceded by a variable period of plaque instability and thrombus evolution before the onset of symptoms [25, 26], and few acute plaque rupture events actually progress to AMI. If the balance is tilted away from thrombosis, progression to death or AMI after plaque rupture can be prevented. ADMATS-13 may enhance clearing of the culprit coronary thrombus; thus, elucidating its role is likely to provide new possibilities for the prevention of AMI. Further studies may be needed to determine the temporal relationship between ADMTS-13 expression and endogenous clot lysis.

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, the expression of ADAMTS proteases could not be confirmed by Western blot analysis. Finally, the number of study patients was relatively small.

In conclusions, our results firstly show that ADAMTS-2, -3, and -13 are differentially expressed in culprit coronary plaques between AMI and stable angina, suggesting a potential role for these enzymes in the pathogenesis of AMI.

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Conflict of interest None.

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