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ORIGINAL ARTICLE

Serum tenascin-C level is associated with coronary plaque rupture in patients with acute coronary syndrome

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Abstract Tenascin-C, a large oligometric glycoprotein of the extracellular matrix, increases the expression of matrix metalloproteinases that lead to plaque instability and rupture, resulting in acute coronary syndrome (ACS). We hypothesized that a high serum tenascin-C level is associated with plaque rupture in patients with ACS. Fifty-two consecutive ACS patients who underwent emergency percutaneous coronary intervention (PCI) and, as a control, 66 consecutive patients with stable angina pectoris (SAP) were enrolled in this study. Blood samples were obtained from the ascending aorta just prior to the PCI procedures. After coronary guide-wire crossing, intravascular ultrasonography (IVUS) was performed for assessment of plaque characterization. Based on the IVUS findings, ACS patients were assigned to two groups according to whether there was ruptured plaque (ruptured ACS group) or not (nonruptured ACS group). There were 23 patients in the ruptured group and 29 patients in the nonruptured group. Clinical characteristics and IVUS measurements did not differ between the two groups. Tenascin-C levels were significantly higher in the ruptured ACS group than in the SAP group, whereas there was no significant difference between the nonruptured ACS and SAP groups. Importantly, in the ruptured ACS group, tenascin-C levels were significantly higher than in the nonruptured ACS group (71.9 ± 34.9 vs 50.5 ± 20.5 ng/ml, $P < 0.005$). Our data demonstrate that tenascin-C level is associated with pathologic conditions in ACS, especially the presence of ruptured plaque.

Keywords Tenascin-C · Intravascular ultrasonography · Plaque instability · Coronary plaque rupture · Acute coronary syndrome

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Introduction

Cardiovascular diseases such as myocardial infarction (MI), hypertrophy, or heart failure are accompanied by changes in the composition of the cardiac extracellular matrix (ECM) [1]. The components of the ECM are basic structural proteins including collagen, elastin, and specialized proteins such as fibronectin, proteoglycans, and matricellular proteins. Tenascin-C is a large glycoprotein found in the ECM and specifically expressed upon tissue injury [2]. Upon tissue damage, tenascin-C plays a multitude of different roles that mediate both inflammatory and fibrotic processes to enable effective tissue repair. Tenascin-C also has multiple functions, such as cell proliferation [3], migration [4], differentiation [5], and apoptosis [6], and it is known as a useful biomarker not only for tissue remodeling but also inflammation [7]. In the heart, tenascin-C is expressed in various pathologic conditions, including coronary atherosclerotic plaque [8], MI [9], myocarditis [10], and dilated cardiomyopathy [11]. Furthermore, tenascin-C increases the expression of matrix metalloproteinases (MMPs) [12], which stimulate collagen degradation and lead to atherosclerotic plaque instability [13]. MMPs are increased in patients with acute coronary syndrome (ACS) [14].

Eroded atheroma and atherosclerotic plaque rupture are major causes of ACS [15], and it is thought that

inflammation plays an important role in these coronary events [16]. Tenascin-C is expressed during arterial wall injury, and accumulating evidence demonstrates that it contributes to both plaque inflammation and rupture [17]. Although the precise mechanisms responsible for tenascin-C in atherosclerosis remain unknown, these findings suggest that coronary plaque instability due to the inflammatory effect and the breakdown of the ECM are important in the development of ACS. Tenascin-C may also play a critical role in promoting the development of atherosclerotic pathology.

Therefore, we hypothesized that a high serum tenascin-C level is associated with plaque rupture in ACS patients.

Patients and methods

Study population

In this study, 52 ACS patients were enrolled and 68 consecutive stable angina pectoris (SAP) patients were also enrolled as controls. Of the SAP patients, two patients who had coronary plaque rupture evaluated by pre-PCI intravascular ultrasonography (IVUS) observation were excluded from this study. The study population therefore contained 118 patients, including 42 patients with acute MI (AMI), 10 patients with unstable angina pectoris, and 66 patients with SAP. ACS patients were divided into two groups according to whether or not they had ruptured plaque (ruptured ACS group and nonruptured ACS group), evaluated by pre-PCI IVUS examination.

The ACS patients were either AMI within 24 h of onset or unstable angina of Braunwald class IIIB. The diagnosis of AMI was determined by the presence of >30 min of continuous chest pain, ST-segment elevation >2.0 mm on at least two contiguous electrocardiogram leads, greater than threefold increase in serum creatine kinase (CK) levels, and Thrombolysis in Myocardial Infarction (TIMI) flow grade 0, 1, or 2 at the time of the initial emergency coronary angiography [18].

We assessed coronary risk factors, including histories of smoking, hypertension, dyslipidemia, diabetes mellitus, hyperuricemia, and obesity. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and/or under antihypertensive treatment. Dyslipidemia was defined as total cholesterol ≥220 mg/dl, fasting triglycerides ≥150 mg/dl, or under lipid-lowering treatment. Diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl, postprandial blood glucose ≥200 mg/dl, and/or under glucose-lowering treatment. We defined body mass index (BMI) as weight (kg) divided by the square of the height (m), and obesity as BMI ≥25 kg/m^2.

We also calculated the estimated glomerular filtration rate (eGFR) from age and serum creatinine (SCr) using the Japanese GFR estimation equation proposed by the Japanese Society of Nephrology as follows: eGFR = $194 \times SCr^{-1.094} \times age^{-0.287}$ (if female, × 0.739) [19].

The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all patients before the study.

IVUS imaging

We used a commercially available IVUS system (Boston Scientific/Scimed, Natick, MA, USA) with a 40-MHz transducer. IVUS imaging was performed before intervention and after the intracoronary administration of 200 μg nitroglycerin. After guide-wire crossing, the IVUS catheter was carefully advanced distal to the culprit lesion, and was withdrawn automatically at 1 mm/s to perform the imaging sequence, which started at 10 mm distal to the culprit lesion and ended at the aorto-ostial junction.

IVUS analysis

The culprit lesion site was the image slice with the smallest lumen cross-sectional area (CSA). The proximal reference is the site with the largest lumen proximal to a stenosis but within the same segment, usually within 10 mm of the stenosis with no major branches. This might not be the site with the least plaque. At each culprit and proximal reference site, external elastic membrane (EEM) CSA and lumen CSA were manually traced. Plaque CSA was calculated as EEM CSA minus lumen CSA, and percent plaque area was calculated as (plaque CSA/EEM CSA) × 100 (%). Ruptured plaque was defined as plaque ulceration with a tear detected in a fibrous cap [20]. The 10-mm long culprit lesion segment, 5 mm proximal and 5 mm distal to the culprit lesion site, was used for the assessment of plaque rupture.

Tenascin-C measurement

Blood samples of the 118 patients were obtained from the ascending aorta. In addition, to assess the impact of plaque rupture for the circulating serum tenascin-C level, we took blood samples from the coronary sinus of another five ACS patients with plaque rupture. All blood samples were obtained just prior to the PCI procedure, and we measured circulating serum tenascin-C in these samples. Serum tenascin-C was measured using a Tenascin-C Large Assay Kit (Immuno-Biological Laboratories, Gunma, Japan).

Statistical analysis

Statistical analyses were performed using one-way analysis of variance with Scheffé's post hoc test when appropriate. Comparison of tenascin-C levels between the ascending aorta and the coronary sinus was performed by a paired *t* test. Data are expressed as mean ± standard deviation. A value of $P < 0.05$ was considered significant.

Results

In ACS patients, there were 23 patients in the ruptured group and 29 patients in the nonruptured group. In both groups, there were 15 ST-segment elevation MI patients (65.2 % in the ruptured group vs 51.7 % in the nonruptured group, $P = 0.33$).

The baseline clinical characteristics of patients in this study are shown in Tables 1 and 2. There were no significant differences in age, gender, BMI, and the prevalence of coronary risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking among the ruptured ACS, nonruptured ACS, and SAP groups. Moreover, in the blood data from the peripheral vein on admission, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, hemoglobin A1c, uric acid, and eGFR were similar among the three groups. High-sensitivity C-reactive protein (CRP) levels were higher in both the ruptured and nonruptured ACS groups than in the SAP group, but there was no significant difference between the ruptured and the nonruptured ACS groups (Table 2). There were also no significant differences among the three groups with respect to IVUS measurements of the culprit lesion site and proximal reference site such as EEM CSA, lumen CSA, and percent plaque area (Table 3).

Serum tenascin-C levels were significantly higher in patients with ACS than in those with SAP (60.8 ± 30.1 vs 48.0 ± 22.0 ng/ml, $P < 0.01$). Serum tenascin-C levels compared among the SAP, nonruptured, and ruptured groups are shown in Fig. 1. Among the three groups, serum tenascin-C levels in the nonruptured ACS group were similar to those in the SAP group. Interestingly, serum tenascin-C levels in the ruptured ACS group were significantly higher than in the nonruptured ACS group (71.9 ± 34.9 vs 50.5 ± 20.5 ng/ml, $P < 0.005$). Moreover, serum tenascin-C levels obtained from the coronary sinus were

Table 1 Baseline clinical characteristics

	SAP ($n = 66$)	ACS		*P*
		Nonrupture ($n = 29$)	Rupture ($n = 23$)	
Age (years)	68.6 ± 9.7	70.4 ± 12.2	66.7 ± 11.4	NS
Male (*n*, %)	47 (71.2)	21 (72.4)	19 (82.6)	NS
BMI (kg/m^2)	25.0 ± 3.2	23.3 ± 2.3	23.7 ± 3.4	NS
Hypertension (*n*, %)	58 (87.9)	27 (93.1)	17 (73.9)	NS
Dyslipidemia (*n*, %)	50 (75.8)	19 (65.5)	16 (69.6)	NS
Diabetes mellitus (*n*, %)	35 (53.0)	11 (37.9)	12 (52.2)	NS
Smoking (*n*, %)	34 (51.5)	15 (51.7)	14 (60.9)	NS
Culprit vessel				
LMT/LAD/LCx/RCA (*n*)	1/26/21/18	0/13/7/9	0/13/3/7	
STEMI (*n*, %)	–	15 (51.7)	15 (65.2)	NS

SAP stable angina pectoris, *BMI* body mass index, *LMT* left main coronary trunk artery, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *RCA* right coronary artery, *STEMI* ST-elevation myocardial infarction, *NS* not significant

Table 2 Blood data

	SAP ($n = 66$)	ACS		*P*
		Nonrupture ($n = 29$)	Rupture ($n = 23$)	
Peripheral vein				
TG (mg/dl)	124.3 ± 56.4	115.3 ± 51.0	161.0 ± 77.8	NS
HDL-C (mg/dl)	49.7 ± 15.5	45.1 ± 6.4	38.4 ± 14.0	NS
LDL-C (mg/dl)	98.9 ± 29.6	103.7 ± 27.6	120.7 ± 56.5	NS
HbA1c (%)	6.1 ± 1.9	6.1 ± 0.8	6.6 ± 2.2	NS
UA (mg/dl)	5.7 ± 1.5	5.7 ± 1.0	5.9 ± 1.9	NS
eGFR (l/min/m^2)	68.7 ± 17.3	72.2 ± 26.0	73.2 ± 30.9	NS
Ascending aorta				
hs-CRP (mg/dl)	0.17 ± 0.19	0.64 ± 1.33		<0.05
		0.62 ± 1.27	0.67 ± 1.45	NS

TG triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HbA1c* hemoglobin A1c, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *hs-CRP* high sensitive-C reactive protein, *NS* not significant

Table 3 IVUS measurements

	SAP ($n = 66$)	ACS		P
		Nonrupture ($n = 29$)	Rupture ($n = 23$)	
Culprit lesion site				
Lumen CSA (mm^2)	2.1 ± 0.7	1.9 ± 0.6	2.1 ± 0.6	NS
Plaque CSA (mm^2)	12.3 ± 5.2	13.6 ± 4.5	12.2 ± 4.8	NS
EEM CSA (mm^2)	14.3 ± 5.3	15.5 ± 4.6	14.4 ± 4.7	NS
Plaque area (%)	83.4 ± 8.3	86.5 ± 5.9	83.1 ± 10.5	NS
Proximal reference				
Lumen CSA (mm^2)	7.3 ± 3.3	7.0 ± 2.5	7.9 ± 3.7	NS
Plaque CSA (mm^2)	9.2 ± 4.2	10.2 ± 4.6	10.3 ± 7.3	NS
EEM CSA (mm^2)	16.5 ± 5.9	17.1 ± 4.2	17.1 ± 6.1	NS
Plaque area (%)	55.2 ± 15.1	57.6 ± 16.5	57.3 ± 23.8	NS

IVUS intravascular ultrasonography, *CSA* cross-sectional area, *EEM* external elastic membrane, *NS* not significant

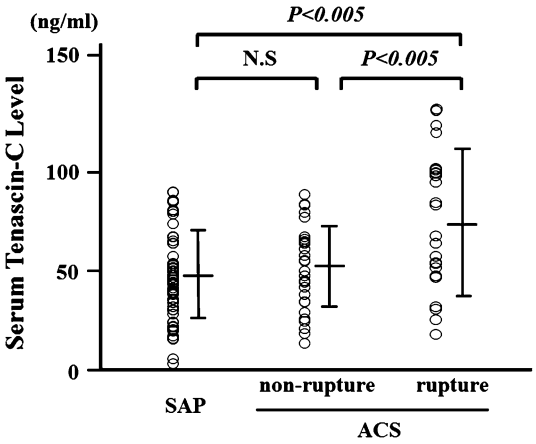

Fig. 1 Serum tenascin-C levels among the stable angina pectoris (*SAP*), nonruptured acute coronary syndrome (*ACS*), and ruptured ACS groups. Although serum tenascin-C levels in the ruptured ACS group were significantly higher than that of the SAP group, there was no significant difference between the nonruptured ACS group and SAP group. The levels in the ruptured ACS group were significantly higher than that of the nonruptured ACS group. *N.S* not significant

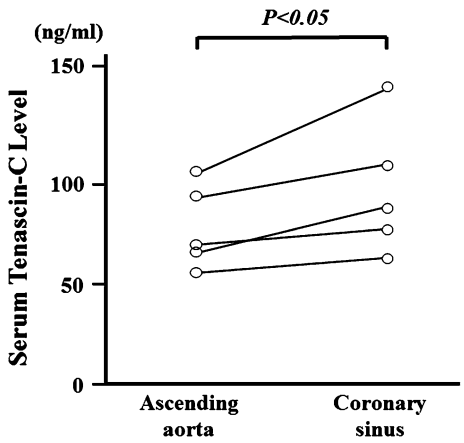

Fig. 2 Serum tenascin-C levels of blood obtained from the ascending aorta and the coronary sinus in ACS patients with plaque rupture. Serum tenascin-C levels of blood obtained from the coronary sinus were significantly higher than those from the ascending aorta

significantly higher than those from the ascending aorta in the ACS patients with plaque rupture (Fig. 2).

Discussion

Major novel findings in the present study were as follows. (1) Serum tenascin-C levels were significantly higher in ACS patients than in SAP patients. However, there were no statistically significant differences between the nonruptured plaque ACS patients and SAP patients. (2) In the ACS patients, serum tenascin-C levels were significantly higher in the group with the ruptured plaque than in those with the nonruptured plaque. To the best of our knowledge, this is the first report to evaluate circulating serum tenascin-C levels comparing SAP and ACS with regard to the existence of plaque rupture estimated by IVUS observation.

It is reported that tenascin-C expression increases at the site of coronary plaque in human atherectomy specimens obtained from patients with ACS [21]. Wallner et al. [8] reported that tenascin-C immunostaining was preferentially concentrated around the lipid core, shoulder lesions, and ruptured area of a human coronary artery obtained from patients who underwent heart transplantation. Thus, although there are large numbers of studies examining the expression of tenascin-C in tissue biopsies, there have been fewer investigations on the association of circulating concentrations of tenascin-C with cardiovascular disease. Sato et al. [22] reported that serum tenascin-C was elevated in patients with AMI in comparison with healthy controls, and our results demonstrated that ACS patients had circulating serum tenascin-C levels higher than those in SAP patients. In animal studies of AMI induced by permanent ligation of the coronary artery, tenascin-C appears transiently during the acute stage and plays several significant roles in myocardial tissue remodeling [23]. The rapid production of

tenascin-C in inflamed tissues is one of mechanisms that control the spread of inflammation [24]. In our study, serum tenascin-C levels elevated in the early stage, within a few hours after ACS onset. Our results may indicate that increased serum levels of tenascin-C possibly reflect the early phase of atheromatous plaque formation.

Plaque rupture is the most common type of plaque complication [15]. It has been reported that ruptured plaque has a large lipid core with increased macrophage density, reduced collagen, and thin smooth muscle cell (SMC) content of the fibrous cap [25]. Reduced collagen content in the fibrous cap is caused by increased breakdown of ECM by MMPs [13]. Cowan et al. [26] demonstrated that MMP-9 gene expression was markedly induced in a mouse macrophage cell line when tenascin-C was used as a substrate, suggesting that tenascin-C modulates the gene expression of MMPs and may affect the stability of atherosclerotic plaque. In addition, inflammatory cells such as macrophages and lymphocytes, which have been associated with the expression of tenascin-C [21], activate the proliferation of SMC in the adventitia, and migrate into the developing intimal plaque site. Together with invading myofibroblasts, SMCs mediate excessive ECM deposition that propagates plaque growth. The expansion of the plaque increasingly occludes vessel blood flow and, as it matures, can rupture, enabling thrombosis to occur [27]. Under these conditions, plaque rupture is caused by plaque instability attributable to the increasing plaque inflammation and breakdown of ECM. Furthermore, Schaff et al. [28] demonstrated that platelets interact with tenascin-C using von Willebrand factor, and the adhesion of platelets to tenascin-C triggered their activation. This result indicates that tenascin-C correlated with not only the formation process of plaque instability but also thrombogenicity after plaque rupture in patients with ACS. In the present study, although serum tenascin-C levels in the ruptured group were significantly higher than in the SAP group, there were no statistically significant differences between the nonruptured plaque and SAP groups. In ACS patients, there was an apparent difference in the mechanism of the plaque-formation process between patients with or without plaque rupture.

In the present study, serum tenascin-C levels obtained from the ascending aorta in the ruptured ACS group were significantly higher than those of the nonruptured ACS group. To clarify whether the tenascin-C is released from the ruptured plaque site, we measured circulating tenascin-C levels in paired blood samples obtained from the ascending aorta and the coronary sinus of ACS patients with ruptured plaque. In the patients with plaque rupture, serum tenascin-C levels obtained from the coronary sinus were significantly higher than those from the ascending aorta. These results indicate that the high circulating tenascin-C levels reflect the existence of coronary artery plaque rupture in ACS patients.

Study limitations

The limitations of this study should be acknowledged. First, the role of tenascin-C in modulating an inflammatory response seems to be complex, and both pro- and anti-inflammatory roles have been reported. Wang et al. [29] have recently demonstrated the increased monocyte-endothelial interaction and trafficking in the absence of the tenascin-C gene using tenascin-C knock-out mice. Second, the present study was performed in a single center and was on a small scale that included 118 patients, which may not be representative of the Japanese population in general.

Conclusions

Our data demonstrate that serum tenascin-C level is associated with pathologic conditions in ACS, especially the ruptured plaque estimated by IVUS observation. The results suggest that serum tenascin-C level is a novel candidate as a sensitive biomarker for coronary plaque rupture in patients with ACS.

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