

## Plasma Levels of Soluble Glycoprotein 130 in Acute Myocardial Infarction

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### Abstract

**Objectives.** Soluble glycoprotein 130 (sgp130), a circulating form of receptor subunit for the interleukin (IL)-6 cytokine family, modulates the biological actions of its ligands as an inhibitory regulator. The role of sgp130 in cardiovascular diseases such as acute coronary syndrome remains unknown.

**Methods.** Plasma levels of sgp130 were examined by enzyme-linked immunosorbent assay in 33 patients with acute myocardial infarction (AMI; mean age  $67 \pm 2$  years, 21 males and 12 females), who were admitted to our hospital within 24 hr of onset of AMI and survived for 4 weeks.

**Results.** Plasma sgp130 levels were significantly higher at admission ( $260.5 \pm 7.3$  ng/ml), and were significantly lower from day 2 to day 5 ( $202.4 \pm 5.1$  ng/ml at day 3) as compared with normal control subjects ( $n = 38$ ,  $227.1 \pm 5.6$  ng/ml). The lowest sgp130 levels inversely correlated with white blood cell count at admission ( $r = -0.42$ ,  $p < 0.05$ ) and with peak C-reactive protein levels ( $r = -0.43$ ,  $p < 0.05$ ). Additional *in vitro* study revealed that incubation of AMI plasma with exogenous IL-6 plus soluble IL-6 receptor resulted in a decrease in plasma sgp130 levels, suggesting the possible reason for reduced plasma sgp130 levels in AMI.

**Conclusions.** The present study indicates that plasma sgp130 levels were modulated during the time course of AMI and inversely associated with inflammation in AMI.

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### Key Words

■ Blood cells    ■ Cytokines    ■ Myocardial infarction, pathophysiology

### INTRODUCTION

The interleukin (IL)-6 cytokine family, which includes IL-6, IL-11, leukemia inhibitory factor,

oncostatin M, ciliary neurotrophic factor, and cardiotrophin-1, is important in the regulation of complex cellular processes such as gene activation, cell proliferation, and cell differentiation. These

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cytokines share a common receptor subunit glycoprotein (gp)130 for signal transduction, and as a consequence elicit similar and overlapping physiological responses.<sup>1)</sup> Gp130 is widely expressed in a variety of organs including the heart, and mediates multiple biological actions of the IL-6 cytokine family.<sup>2-4)</sup> Gene targeting of gp130 is lethal, and causes the failure of myocardium to mature.<sup>5)</sup> Ventricular-restricted gp130 knockout mice showed no changes in the cardiac structure or function, but displayed rapid onset of dilated cardiomyopathy when exposed to pressure overload.<sup>6)</sup> Transgenic mice with continuously activated gp130 showed hypertrophy of ventricular myocardium.<sup>7)</sup> These findings suggest that the gp130 signaling pathway is not only important in the development of cardiac hypertrophy, but is also pivotal in the transition between cardiac hypertrophy and congestive heart failure.

IL-6 binds to a soluble form of IL-6 receptor (sIL-6R) lacking the transmembrane and cytoplasmic domain, which is present in human blood,<sup>8)</sup> and causes dimerization of membrane-anchored gp130.<sup>9)</sup> Dimerization of gp130 activates Janus kinase-signal transducers and activators of transcription and mitogen-activated protein kinase. Soluble gp130 (sgp130), a circulating form of gp130 lacking transmembrane and cytoplasmic domain, is also present in human blood,<sup>9,10)</sup> and binds to IL-6/sIL-6R complexes.<sup>11,12)</sup> Therefore, sgp130 is considered to act as an inhibitory regulator of IL-6 to prevent dimerization of membrane-anchored gp130.<sup>12-15)</sup>

The plasma level of sgp130 is increased in patients with congestive heart failure.<sup>16,17)</sup> On the other hand, the plasma level of IL-6 is increased, and the plasma level of sgp130 is decreased in patients undergoing cardiac surgery.<sup>18)</sup> The plasma level of IL-6 is increased, and the plasma level of sIL-6R is decreased in patients with acute myocardial infarction (AMI).<sup>19-22)</sup> Specifically, there is a positive correlation between the increment of plasma IL-6 levels and the peak levels of C-reactive protein,<sup>20)</sup> supporting the role of IL-6 as a proinflammatory protein. However, no studies have investigated the time course of plasma sgp130 levels in patients with AMI. In addition, although gp130 was overexpressed in the right and left ventricles in the rat model of AMI,<sup>23)</sup> the regulation of sgp130 in acute coronary syndrome remains unknown.

The present study examined the plasma levels of sgp130 in association with echocardiographic, hemodynamic, and clinical parameters in patients with AMI. In addition, to elucidate the possible mechanisms modulating the plasma sgp130 levels, an *in vitro* study examined the influence of exogenous IL-6 and sIL-6R on plasma sgp130 levels.

## SUBJECTS AND METHODS

### Patient characteristics

The present study included 33 patients (21 males and 12 females, mean age  $67.0 \pm 2.1$  years) with AMI, who were admitted to our hospital within 24 hr after the onset of symptoms and survived for at least 4 weeks (**Table 1**). The diagnosis of AMI was based on the findings of severe prolonged chest pain for at least 30 min, ST-segment elevation of at least two continuous leads by electrocardiography, and elevation of serum creatine kinase (CK)-MB isozyme to more than twice the upper limit of the normal range. Immediately after admission, all patients underwent cardiac catheterization and coronary angiography, followed by mechanical treatment with recanalization of the infarct-related artery by balloon angioplasty and stent implantation. All patients were monitored in our intensive care unit, given standard medication consisting of heparin, acetylsalicylic acid,  $\beta$ -blocker, angiotensin converting enzyme inhibitor, statin, nitrate, and calcium antagonist, and entered into the cardiac rehabilitation programs in our hospital. Thirty eight subjects without cardiovascular diseases (28 males and 10 females, mean age  $44.5 \pm 1.6$  years) were included as normal control subjects. The study protocol (**Fig. 1**) was approved by the Institutional Review Board in our hospital, and written informed consent was obtained from each subject or his/her family.

### Blood sampling

Plasma samples for sgp130 and brain natriuretic peptide (BNP), blood cell counts, and serum samples for CK and C-reactive protein were obtained immediately after admission, daily for 1 week, on day 14, and on day 28 (**Fig. 1**). Blood samples from admission to day 2 were taken from the femoral vein, femoral artery or radial artery, and those after day 3 were taken from the antecubital vein. Plasma samples for sgp130 and BNP were placed in EDTA-coated tubes containing 500 IU/ml aprotinin, centrifuged at  $4^\circ\text{C}$ , and stored at  $-80^\circ\text{C}$

**Table 1 Patient characteristics**

Number of patients	33
Age (yr, mean $\pm$ SEM)	67.0 $\pm$ 2.1
Sex	
Male	21 (63.6)
Female	12 (36.4)
Coronary culprit	
Left anterior descending artery	13 (39.4)
Left circumflex artery	7 (21.2)
Right coronary artery	13 (39.4)
Peak creatine kinase (IU/l, mean $\pm$ SD)	3,213 $\pm$ 339
Killip's classification class	
1	24 (72.7)
2	4 (12.1)
3	2 (6.1)
4	3 (9.1)
Risk factor	
Hypertension	22 (66.7)
Diabetes mellitus	14 (42.4)
Hyperlipidemia	15 (45.5)
Smoking	10 (30.3)
Pre-existing heart disease	
Angina pectoris	21 (63.6)
Previous myocardial infarction	3 (9.1)
Left ventricular hypertrophy	9 (27.3)
Coronary intervention	
Primary angioplasty	32 (97.0)
Prehospital thrombolysis	7 (21.2)
Stent implantation	23 (70.0)
Spontaneous reperfusion	1 (3.0)
Complication	
Congestive heart failure	9 (27.3)
Arrhythmia	8 (24.2)
Pericardial effusion	1 (3.0)
Left ventricular aneurysm	4 (12.1)
Right ventricular infarction	3 (9.1)
Mechanical support	
Intraaortic balloon pumping	10 (30.3)
Medication	
Statins	12 (36.4)
Angiotensin converting enzyme inhibitors	30 (90.9)
Coronary angiography (at 4th week)	
Patent	32 (97.0)
Occluded	1 (3.0)

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until analysis. Blood cell counts, and serum samples for CK and C-reactive protein were analyzed immediately after drawing.

## Echocardiography

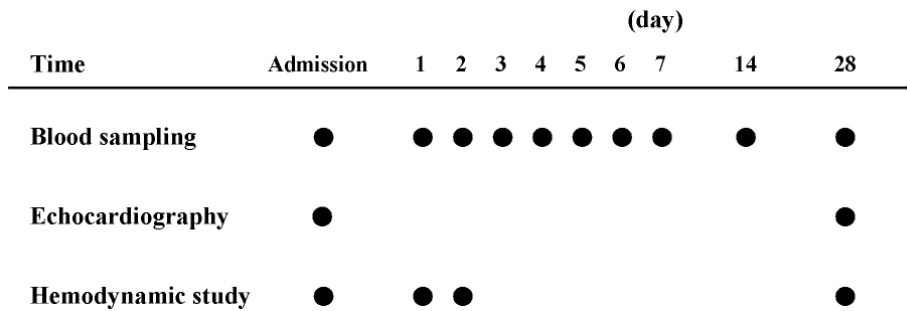
Standard two-dimensional and Doppler echocardiographic examinations were performed at admission and on day 28 with a 2–3 MHz transducer and commercially available phased array sector scanners (GE Logiq 500 and Vivid 7). Left ventricular end-diastolic diameter (LVDd) and end-systolic diameter (LVDs) were measured by two-dimensional and M-mode echocardiography. Ejection fraction (EF, Simpson method) was calculated according to the standard formula. Tei index was calculated by Doppler time intervals.<sup>24)</sup>

## Hemodynamic study

A Swan-Ganz catheter was inserted into the femoral vein immediately after admission and before coronary angiography, and was kept inserted during the first 2 days in all patients with AMI. Hemodynamic parameters, such as heart rate, arterial blood pressure, right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), and cardiac index (CI) were measured during the first 2 days. Cardiac catheterization, which included hemodynamic study, coronary angiography, and left ventriculography, was performed in all patients on day 28 (**Fig. 1**).

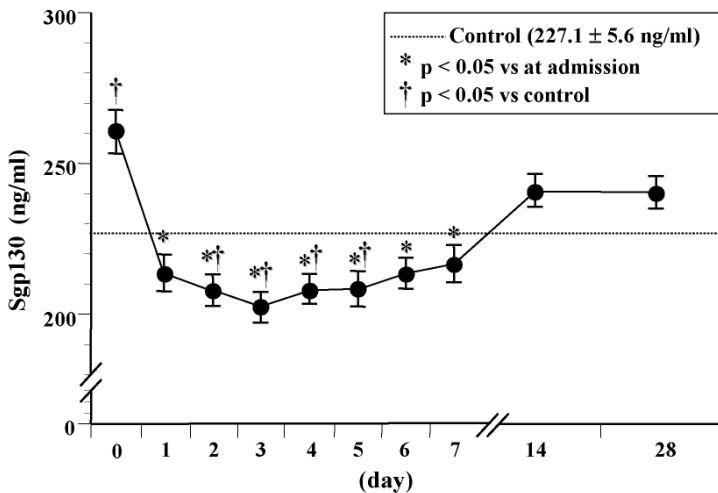
## Measurement of plasma sgp130 and BNP levels

Plasma sgp130 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instruction (Quantikine, R&D Systems). In brief, samples and standards were added to each well of a microtiter plate, which had been precoated with anti-human sgp130 monoclonal antibody, and incubated for 3 hr. Each well was washed with washing buffer and incubated with enzyme-linked polyclonal antibody specific for human sgp130 for 1 hr. Following washes to remove unbound antibody-enzyme reagent, a substrate solution was added to each well. After incubation for 30 min at room temperature, enzyme reaction was stopped. Sgp130 concentration was determined by comparing the optical density results to standard curves. Intra-assay and inter-assay variations were 1.9% and 7.6%, respectively. Of note, heparin did not interfere with the results of sgp130 ELISA (data not shown). Plasma BNP levels were measured by a specific immunoradiometric assay for BNP (Shionoria BNP, Shionori Inc.).<sup>25)</sup>



**Fig. 1 Study protocol**

Blood samples included plasma samples for sgp130 and brain natriuretic peptide, blood cell counts, and serum samples for creatine kinase and C-reactive protein. Echocardiographic measurements included left ventricular end-diastolic diameter, left ventricular end-systolic diameter, ejection fraction, and Tei index. Hemodynamic study included measurements of heart rate, arterial blood pressure, right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, and cardiac index.



**Fig. 2 Time course of plasma sgp130 level in patients with acute myocardial infarction**

Values are mean ± SEM. The broken line represents the mean sgp130 level in the normal control subjects. \*  $p < 0.05$  compared with values at admission. †  $p < 0.05$  compared with values in the normal control subjects.

Sgp130 = soluble glycoprotein 130.

**In vitro study**

To examine the influence of exogenous IL-6 and sIL-6R on plasma sgp130 levels, plasma samples of 8 patients with AMI at admission were incubated with  $10^{-12}$  mol/l of human IL-6 (Pepro Tech Inc.) and sIL-6R (Pepro Tech Inc.) at 37°C for 12, 24, and 48 hr. After incubation, plasma sgp130 levels were immediately measured by ELISA as described above.

**Statistical analysis**

All values were expressed as mean ± SEM unless otherwise indicated. The plasma levels of sgp130 were analyzed over the time course of AMI using analysis of variance (ANOVA). Comparison of parameters between two groups was performed with the unpaired Student's *t*-test. Regression analysis was used to determine the relationship between results. Statistical significance was defined as  $p < 0.05$ .

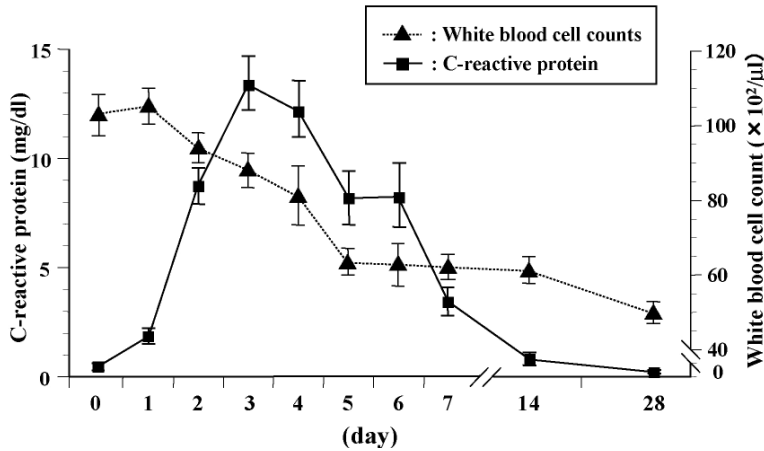
**RESULTS**

**Time course of plasma sgp130 levels in patients with AMI**

**Fig. 2** illustrates the time course of plasma sgp130 levels for 4 weeks in patients with AMI. Plasma sgp130 levels at admission ( $260.5 \pm 7.3$  ng/ml) were significantly higher as compared with those in normal control subjects ( $n = 38, 227.1 \pm 5.6$  ng/ml). Plasma sgp130 levels significantly decreased within 1 day and remained reduced until day 7 ( $p < 0.05$  vs values at admission), and returned to normal levels thereafter. In addition, plasma sgp130 levels from day 2 to day 5 were significantly lower in patients with AMI as compared with those in normal control subjects.

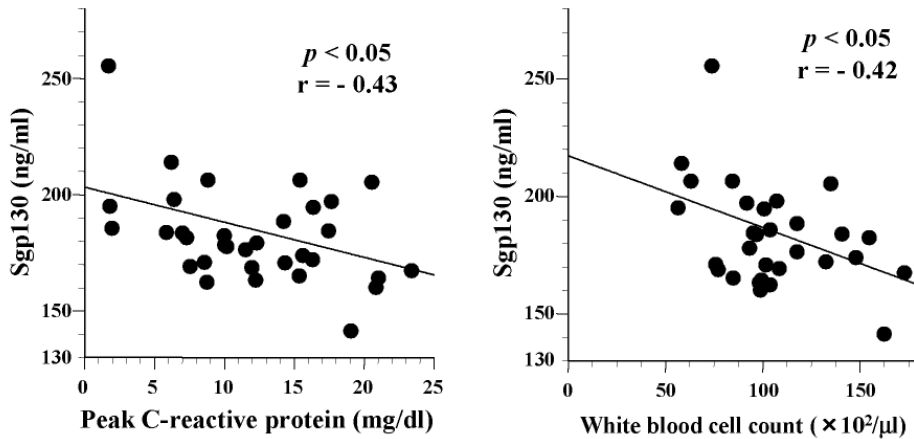
**Time course of white blood cell counts and C-reactive protein levels in patients with AMI**

**Fig. 3** illustrates the time course of white blood



**Fig. 3** Time course of C-reactive protein level and white blood cell counts in patients with acute myocardial infarction

Values are mean  $\pm$  SEM.



**Fig. 4** Relationship between the lowest sgp130 level and peak C-reactive protein levels (*left*), and between the lowest sgp130 level and white blood cell counts (*right*) in patients with acute myocardial infarction

Abbreviation as in Fig. 2.

cell counts and C-reactive protein levels for 4 weeks in patients with AMI. White blood cell counts were high at admission and on day 1, then decreased and normalized on day 5. Within 5 days after admission, white blood cell counts were higher in patients with AMI as compared with the normal values at our hospital. C-reactive protein levels increased and reached its peak on day 3, decreased thereafter, and normalized on day 14.

#### Relationship between plasma sgp130 levels and biochemical parameters

Correlations between plasma sgp130 levels and biochemical parameters in patients with AMI were examined. The lowest sgp130 levels ( $185.4 \pm 3.6$  ng/ml,  $p < 0.0001$  vs normal control subjects) inversely correlated with peak C-reactive protein levels ( $r = -0.43$ ,  $p < 0.05$ ; **Fig. 4 – left**) and with

white blood cell counts at admission ( $r = -0.42$ ,  $p < 0.05$ ; **Fig. 4 – right**).

**Table 2** shows the correlations between plasma sgp130 level on each day during the time course of AMI and peak C-reactive protein level in patients with AMI. Plasma sgp130 levels from day 2 to day 6 were inversely correlated with peak C-reactive protein level. The best correlation between plasma sgp130 level and peak C-reactive protein level was seen on day 4 in these patients with AMI ( $r = -0.575$ ,  $p = 0.0004$ ; **Fig. 5**).

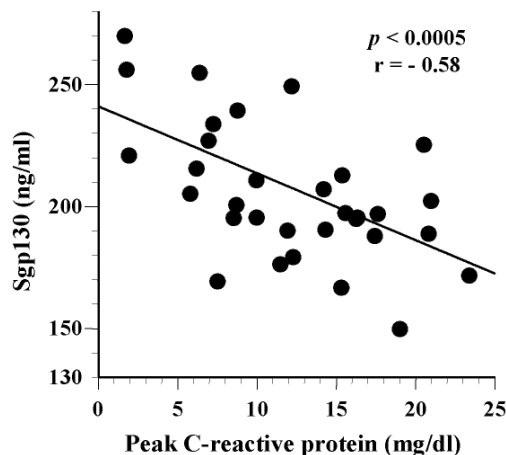
Plasma BNP levels were high at admission ( $103.8 \pm 33.7$  pg/ml) as compared with the upper limit of the normal range ( $\leq 18.4$  pg/ml), peaked at day 6 ( $225.6 \pm 33.7$  pg/ml), and decreased thereafter. There were no significant correlations between plasma sgp130 levels and plasma BNP levels in patients with AMI.

**Table 2 Relationships between plasma sgp130 level on each day and peak C-reactive protein level in patients with acute myocardial infarction**

Hospital day	Sgp130 (ng/ml)	p value	r
0	260.6±7.3	0.0582	-0.338
1	213.8±5.3	0.0924	-0.319
2	208.1±5.3	0.02	-0.401
3	202.4±5.1	0.0017	-0.518
4	208.4±5.0	0.0004	-0.575
5	208.4±5.9	0.0005	-0.560
6	213.6±5.2	0.028	-0.381
7	216.8±6.2	0.0597	-0.336
14	241.0±5.5	0.4454	-0.143
28	240.4±5.4	0.0045	-0.491

Continuous values are mean ± SEM.

Abbreviation as in Fig. 2.

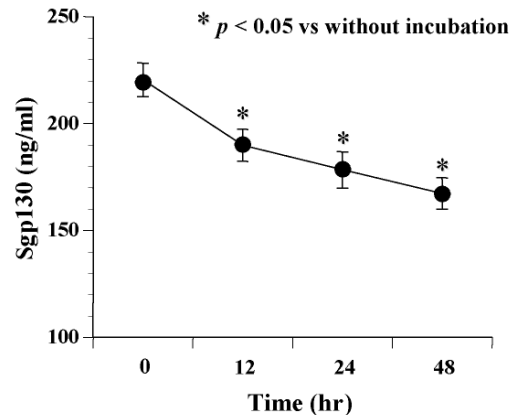
**Fig. 5 Relationship between plasma sgp130 level on day 4 and peak C-reactive protein level in patients with acute myocardial infarction**

Abbreviation as in Fig. 2.

Plasma sgp130 showed no correlations with echocardiographic and hemodynamic parameters such as LVDd, LVDs, EF, PCWP, and CI. In addition, although statins were known to have anti-inflammatory properties, treatment with or without statins did not influence the plasma gp130 levels in the present study.

#### **In vitro study**

**Fig. 6** illustrates the time course of plasma sgp130 levels incubated with  $10^{-12}$  mol/l of IL-6 and sIL-6R in 8 patients with AMI. Plasma sgp130 levels were significantly decreased by the incubation of AMI plasma with IL-6 and sIL-6R for 12 hr,

**Fig. 6 In vitro study**

Plasma samples of 8 patients with acute myocardial infarction at admission were incubated with  $10^{-12}$  mol/l of exogenous human interleukin-6 and soluble interleukin-6 receptor at 37°C for 12, 24, and 48 hr. After incubation, plasma sgp130 levels were immediately measured by enzyme-linked immunosorbent assay. Values are mean ± SEM. \* $p < 0.05$  compared with values without incubation.

Abbreviation as in Fig. 2.

and remained low for 48 hr ( $p < 0.05$  vs without incubation).

## **DISCUSSION**

The present study demonstrated that plasma sgp130 levels in patients with AMI were high at admission and decreased from day 2 to day 5 as compared with normal control subjects, and returned to normal levels thereafter. This study also demonstrated that the plasma sgp130 levels were inversely correlated with white blood cell counts at admission and peak C-reactive protein levels in patients with AMI. *In vitro* study revealed that plasma sgp130 levels were significantly decreased by the incubation of the plasma with exogenous IL-6 and sIL-6R for at least 12 hr.

Gp130 is a common signal transducer for the IL-6 cytokine family.<sup>1)</sup> Sgp130, a soluble form of gp130, is present in the blood and circulates in the body. In general, the soluble form of cytokine receptor is generated by either shedding of the extracellular domain of the membrane-anchored receptor or by alternative splicing of the respective gene. Sgp130 is almost all released due to shedding of membrane-anchored gp130.<sup>26)</sup> Proinflammatory cytokine stimulation causes the membrane-anchored gp130 to be proteolytically cleaved by highly specific "shedding enzymes" and released as soluble protein.<sup>27,28)</sup> In addition, gp130 mRNA and

protein are increased in the infarcted myocardium in the rat model of AMI.<sup>23)</sup> Therefore, we first speculated that plasma sgp130 level was increased not only due to the augmented production of gp130 in the infarcted heart but also due to activated shedding of membrane-anchored gp130 in patients with AMI. We found that plasma sgp130 levels in patients with AMI were significantly higher at admission as compared with those in the normal control subjects. Therefore, production of gp130 and shedding of membrane-anchored gp130 may be increased in the infarcted as well as non-infarcted myocardium, resulting in increases in plasma sgp130 levels in the super-acute phase of AMI. Alternatively, infiltrated neutrophils and monocytes/macrophages in the infarcted myocardium could release sgp130 in AMI.

Unexpectedly, the plasma sgp130 level was reduced from day 2 through day 5 in our patients with AMI as compared with normal control subjects. Several studies showed that plasma sgp130 level was decreased in patients with acute or focal diseases such as acute stroke,<sup>29)</sup> Paget's disease (bone),<sup>30)</sup> head injury,<sup>31)</sup> and Crohn's disease.<sup>32)</sup> In contrast, plasma sgp130 level was increased in patients with chronic or general diseases such as cancer,<sup>33)</sup> regular hemodialysis,<sup>26)</sup> human immunodeficiency virus infection,<sup>34)</sup> and congestive heart failure.<sup>16,17)</sup> IL-6 is also increased in patients with AMI.<sup>19-22)</sup> In the presence of sIL-6R, IL-6 forms a binary complex of IL-6/sIL-6R, which then binds to sgp130 in the plasma.<sup>9,11,12)</sup> Indeed, the *in vitro* study demonstrated that the addition of physiological doses of exogenous IL-6 and sIL-6R to the AMI plasma caused reduced sgp130 levels, suggesting a possible reason for decreased plasma sgp130 levels due to increased circulating IL-6/sIL-6R complexes in these patients with AMI. Although the precise reason why plasma sgp130 level decreased during day 2 and day 5 in these patients with AMI still remains unknown, the sgp130 level might be reduced by the generation of IL-6/sIL-6R/sgp130 complexes in the subacute phase of AMI. This idea is supported by previous studies demonstrating that the actions of the IL-6 cytokine family such as oncostatin M, ciliary neurotrophic factor, and leukemia inhibitory factor are inhibited by the addition of sgp130.<sup>13,15)</sup>

In the present study, 9 of 33 (27.3%) patients were classified as Killip's classification class 2, 3, or 4, and 10 patients (30.3%) underwent intraaortic

balloon pumping, indicating that about 30 percent of AMI patients had mild to severe heart failure. Although previous studies reported that plasma sgp130 levels were increased in patients with chronic congestive heart failure,<sup>16,17)</sup> plasma sgp130 levels in patients with AMI were decreased during day 2 and day 5 in the current study. Plasma sgp130 levels had no correlations with the parameters of cardiac function or remodeling such as Killip's classification, EF, PCWP, CI, LVDd, and LVDs. In addition, there was no correlation between plasma sgp130 levels and plasma BNP levels, that are markers for congestive heart failure. Therefore, we speculate that the mechanisms regulating plasma sgp130 levels in the acute to subacute phase of AMI are different from those in so-called chronic congestive heart failure.

The present study demonstrated that the plasma level of sgp130 was inversely correlated with the peak level of C-reactive protein and white blood cell count at admission. These findings suggest that circulating sgp130 level is inversely associated with inflammation. The white blood cell count is increased in patients with AMI, and this increase results from an increase in neutrophils and monocytes/macrophages.<sup>20)</sup> Activated inflammatory cells such as macrophages might release IL-6 into circulation in AMI.<sup>20)</sup> Thus, increased white blood cell count may contribute to the augmented IL-6 production and secretion in AMI. Previous investigators reported that human C-reactive protein is regulated by the combination of IL-1 and IL-6 in the presence of adequate levels of glucocorticoid.<sup>35,36)</sup> In patients with AMI, plasma level of IL-6 is increased,<sup>20-23)</sup> and IL-6 may contribute to the production of C-reactive protein.<sup>21)</sup> Recent studies have demonstrated that sgp130 acts as an inhibitory regulation of biological effects of IL-6 by preventing dimerization of membrane-anchored gp130.<sup>12-15)</sup> Although the reason why sgp130 level was inversely correlated to white blood cell and C-reactive protein remains unknown, sgp130 could act as an anti-inflammatory regulator to balance "the excess inflammatory storm" caused by the IL-6 cytokine family in the acute phase of AMI.

## CONCLUSIONS

The present study indicates that plasma sgp130 levels were modulated during the time course of AMI in reverse association with inflammation. Although the precise mechanisms by which sgp130

level is influenced in these patients with AMI remain to be elucidated, the plasma sgp130 level seems to be inversely associated with inflammation in AMI.

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### 要 約

#### 急性心筋梗塞症における血漿 Soluble Glycoprotein 130 濃度の検討

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**目的:** Soluble glycoprotein 130 (sgp130) は、インターロイキン-6 (IL-6) サイトカインファミリーの可溶性レセプターで、血中の IL-6 および可溶性 IL-6 レセプターと結合することにより、IL-6 の作用を抑制していると考えられている。急性冠症候群のような循環器疾患における sgp130 の役割についてはいまだ解明されていない。

**方 法:** 当院に入院し 4 週間生存した、発症 24 時間以内の急性心筋梗塞患者 33 例 (平均年齢  $67 \pm 2$  歳, 男性 21 例, 女性 12 例) の血漿 sgp130 濃度を enzyme-linked immunosorbent assay 法を用いて測定した。

**結 果:** 血漿 sgp130 濃度は健常者 (38 例,  $227.1 \pm 5.6$  ng/ml) と比べ、入院時に有意に高く ( $260.5 \pm 7.3$  ng/ml), 2 日目から 5 日目に有意に低下した ( $202.4 \pm 5.1$  ng/ml, 3 日目)。最低 sgp130 濃度は入院時の白血球数 ( $r = -0.42, p < 0.05$ ) および C 反応性蛋白ピーク値 ( $r = -0.43, p < 0.05$ ) と負の相関を示した。また, *in vitro* の実験において、急性心筋梗塞患者の血漿に IL-6 および可溶性 IL-6 レセプターを加えると、血漿 sgp130 濃度は有意に減少することがわかった。これら 3 者の相互作用が急性心筋梗塞患者における血漿 sgp130 濃度減少の機序に關与する可能性が示唆された。

**結 論:** 血漿 sgp130 濃度は急性心筋梗塞患者において経時的に変化し、炎症と負の相関を示した。

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