

Effect of Anaphylactic Shock on Suppressors of Cytokine Signaling

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The pathophysiologic mechanisms of anaphylactic shock still remain unclear. In this study, we investigated the changes of expression and translation of SOCS1/SOCS3 in the heart, lungs, kidney, liver and spleen from patients who died of anaphylactic shock. Samples from the same viscera of 8 patients who died of anaphylactic shock and 8 healthy controls who died from accidents were collected in the present study. The level of IgE was measured in heart, and SOCS1/ SOCS3 mRNA and protein expression were determined by RT-PCR and immunohistochemistry, respectively. As a result, the higher IgE level was detected in the blood samples from the patients' heart than the control. SOCS1 and SOCS3 protein were significantly increased in the kidney and liver than the control. After anaphylactic shock, the expression of SOCS1 and SOCS3 mRNA were also increased. The expression level of SOCS3 mRNA was higher than that of SOCS1 in all viscera, and both were the highest in liver and kidney. There was a positive correlation between SOCS1 mRNA and SOCS3 mRNA in liver and kidney after anaphylactic shock. Our results indicate that SOCS1 and SOCS3 may play a regulatory role in anaphylactic shock viscera injury processes during anaphylactic shock.

Keywords Anaphylactic shock, SOCS1, SOCS3, IgE.

INTRODUCTION

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. Acute allergic reaction is an uncommon cause of sudden death. There have been rare studies of further postmortem findings in anaphylactic death

because of difficulty collecting samples. The pathophysiologic mechanisms of anaphylactic shock still remain elusive.

Studies with mouse models demonstrate 2 pathways of systemic anaphylaxis: a classic pathway mediated by IgE, Fc epsilon RI, mast cells, histamine, and platelet-activating factor (PAF) and an alternative pathway mediated by IgG, Fc gamma RIII, macrophages, and PAF (Strait, 2002). However, it has been difficult to define the biological mediators in human beings. Recent studies confirmed that the concentrations of a number of cytokines in serum were elevated in blood during anaphylaxis in human beings. IL-2, IL-6, IL-10, TNF receptor I, MCT, and histamine were significantly elevated in patients with severe reactions. IL-4, IL-5, IL-13, IFN-gamma, and TNF-alpha were marginally elevated in severe reactions (Stone, 2009).

Regarding immunosuppression, SOCS1 and SOCS3 play a role in the immune system as the only members of this family, and could be induced by numerous cytokines (Cassatella, 1999; Dalpke, 2001) and inflammatory factors (Takagi, 2004). SOCS1 and SOCS3 play an important regulatory role in macrophages and dendritic cells (DCs) by modulating TLR signaling (Dennis, 2006). SOCS1 can negatively regulate not only the JAK/STAT pathway, but also the TLR-NF-kappaB pathway. SOCS3 protein was strongly induced by both IL-6 and IL-10 in the presence of LPS, but selectively inhibited IL-6 signaling (Takagi, 2004).

Indeed, it has been found that SOCS-3 could be up-regulated in the liver of septic rats subjected to burn trauma (Johnson, 2001; Kong, 2002). Similarly, the report has shown that SOCS-1 could be up-regulated in the spleen in response to burn trauma (Ogle, 2000). Although it has not been fully elucidated about the exact roles of the SOCS proteins in these models their expression has been linked to organ dysfunction (Kong, 2002).

From these data, we proposed the hypothesis that the up-regulation of SOCS proteins, such as SOCS1 and SOCS3, is triggered by biological mediators whose concentrations increase during anaphylaxis in human beings. In this study, we aimed to investigate the expression levels of SOCS3 and SOCS1 in the viscera of patients and to explore the possible mechanisms of SOCS regulation in anaphylactic shock.

METHODS

Patients

According to the Declaration of Helsinki, human tissues were handled from 8 cases dying of anaphylactic shock and 8 controls dying of trauma caused by accident, with approval from the Institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University. 8 cases including 5 males and 3 females were collected from Feb 2006 to Oct 2006 and were confirmed by autopsy and histological testing in Verification Centre of Forensic Medicine

of Sun Yat-Sen University. 8 controls composed of 6 males and 2 females, were collected without other diseases in the same period (Tables 1 and 2).

Sample Preparation and IgE Testing in the Blood

The IgE level of the blood sampled from the patients' heart was tested by the Clinical Laboratory of the First Affiliated Hospital, Sun Yat-sen University. Within the limitations of test facility, the mast cell tryptase levels were not measured. Tissues of the heart, lung, kidney, liver and spleen were taken and stored in liquid nitrogen to test the mRNA and protein expression of SCOS1 and SCOS3. Tissues of the viscera from both groups were all divided into two portions. One portion was stored in liquid nitrogen (-80°C) immediately after sampling. Another portion was fixed in 4% formalin solution, and then paraffin-embedded for immunohistochemical and HE staining.

Determination of the mRNA Expression Level of SOCS1 and SOCS3 in the Liver Cells and Spleen Cells

Total RNA was extracted from specimens using Trizol reagent (Invitrogen, Carlsbad, CA) and $1\mu\text{g}$ RNA was reverse transcribed using First Strand cDNA Synthesis Kit (MBI) following the manufacturer's instructions. The RNA stored at -80°C until further use. The expressions of SOCS1 and SOCS3 mRNA were detected by reverse transcriptase PCR (RT-PCR) as previously described (Mun et al., 2000). After cDNA synthesis SCOS1 and SCOS3 expression was analyzed with PCR. The primers were as following: β -actin (155bp), forward 5'-CAA GAT CAT TGC TCC TCC TGA-3', reverse 5'-AGT CCG CCT AGA AGC ATT TG-3'; SOCS1 (180bp), forward 5'-TTG GAG GGA GCG GAT GGG TGT AG-3', reverse 5'-AGA GGT AGG AGG TGC GAG TTC AGG TC-3'; SOCS3(202bp), forward 5'-CAT GGC ACA AGC ACA AGA AGC-3', reverse 5'-TTG TGG TTG CTA TCG TCC CAC-3'.

PCR was performed according to RT-PCR kit (MBI) using thermal cycling conditions with 95°C for 10 min and followed by 35 cycles consisting of 94°C for 33 seconds, $T_m^{\circ}\text{C}$ 30 seconds, 72°C for 45 seconds, 72°C for 7 min, $T_m(\beta\text{-actin}) = 60^{\circ}\text{C}$, $T_m(\text{SOCS1}) = 55^{\circ}\text{C}$, $T_m(\text{SOCS3}) = 55^{\circ}\text{C}$. The end-product of PCR was subject to the DNA electrophoresis. β -actin is a housekeeping gene. The targeted bands were compared to the corresponding β -actin bands as the internal control, and the ratio was the expression level. All assays were run in duplicate for the samples.

Immunohistochemical Examination

Each sample was fixated in cold methanol for 10 min at -20°C , the staining procedure was perform as previously described (Chen, 2007). For SOCS1, SOCS3 immunostaining, a DAB kit (Dako, Carpinteria, CA) with an immunoperoxidase kit (ABC kit Vectastain Elite, Vector Labs) was used.

Table 1: Characteristics of patients of anaphylactic shock.

Patient no.	Age	sex	Personal history	Causes of anaphylaxis	IgE level(U/ml)	Characteristics of the histological examination
4214	65	F	Coronary atherosclerosis, Hypertension	Drug (Chinese medicine)	698.80	Edema of the throat and lung; eosinophile granulocytes in throat mucous membrane; multiple organ congestion.
4241	25	F	None	Drug (antibiotic)	1323.40	Multiple organ congestion; edema of the lung.
4268	32	M	None	Unknown	353.60	Edema of the throat and lung; histoleucocytes in heart; multiple organ congestion.
4286	26	F	None	Drug (antibiotic)	277.80	Granulocytes in throat mucous membrane and lung edema.
4371	9	M	None	Unknown	1162.60	Edema of the throat; pneumonorrhagia.
4043	27	M	Renal calculus	Unknown	288.40	Edema of the throat and brain; multiple organ congestion.
4356	46	M	Unknown	Drug (antibiotic)	279.40	Edema of the throat; multiple organ congestion; pneumonorrhagia.
4282	3	M	None	Drug (antibiotic)	211.80	Multiple organ edema and congestion.

Table 2: Characteristics of patients of control.

Patient no.	Age	sex	Personal history	Causes of death	Time interval	IgE level(IU/ml)	Characteristics of the histological examination
3706	42	M	Tonsillitis	Thoracic trauma	102 hours	85.1	Splenic rupture, Hemopneumothorax
3742	37	M	None	Accident	41hours	76.5	Craniocerebral injury
3930	26	F	None	Crash	78 hours	79.3	Draniocerebral injury, Hemopneumothorax
3958	47	M	Diabetes	Accident	49 hours	81.2	Craniocerebral injury
4039	44	M	None	Accident	36 hours	73.4	Craniocerebral injury
4042	32	M	Adiposis hepatica	Fall down	43 hours	82.6	Craniocerebral injury
4067	36	M	Coronary atherosclerosis, coronary heart disease	Accident	25 hours	71.6	Aeropleura, cerebral edema
4190	33	F	Pregnant women	Accouchement	52 hours	78.1	Metrorrhexis

SOCS1 goat anti-human polyclonal antibody and SOCS3 goat anti-human polyclonal antibody were used from Santa Cruz, USA. PBS was used instead of the primary antibody in the negative control group. Images were photographed with a Nikon Te-2000u Eclipse epi-fluorescent microscope (Nikon, Tokyo, Japan). The number of cells with positive immunostaining in 10 random fields was counted in each sample under $200\times$ magnification.

Statistics

All the experiments were repeated at least three times. Percentages of positive cells, expression levels of SOCS1 and SOCS3 were reported as means $\pm$ SD. The data were compared using the unpaired Student's *t*-test in SPSS 11.0 software. Test results were reported as two-sided *P*-values, where $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Characteristic and IgE Level in the Heart-Blood

The mean age of these anaphylaxis patients was 29.13 ± 19.64 years. Anaphylaxis usually happens quickly. The interval between the onset of symptoms and death ranged from less than 10 min to 130 min after initially contacting the allergen. The mean time of death was 34.63 ± 39.78 minutes. Serum tryptase concentrations were not measured. The mean time between patients' death and collection of organ tissues was 55.13 ± 21.09 and 53.25 ± 24.96 hours for anaphylaxis and control group, respectively. Investigation revealed that 1 of 8 cases had a history of asthma and 1 had previous allergic reactions to certain foods. Four deaths resulted from anaphylactic reaction to antibiotics, 1 of which occurred in clinics illegally operated by Chinese medicine.

We first examined the levels of IgE in the heart-blood. The reference value for normal Chinese population was 0–120 IU/ml. We found the mean level of IgE in control group was 78.48 ± 4.56 IU/ml; however, it was elevated to 574.47 ± 440.69 IU/ml in the anaphylactic shock group. The increase was consistent with the diagnosis for anaphylactic shock. And the characteristics of autopsy and histological examination supported the diagnosis of anaphylactic shock (Tables 1 and 2 and Figure 1).

Expression of SOCS1/SOCS3 mRNA and Protein

The expression levels of SOCS1 and SOCS3 protein were all elevated in viscera of the patients from the anaphylactic group. The percentages of positive cells in anaphylactic shock group were significantly higher than that of the control group, indicating that the SOCS signaling was activated in viscera after anaphylactic shock (Figure 2 and Figure 3).

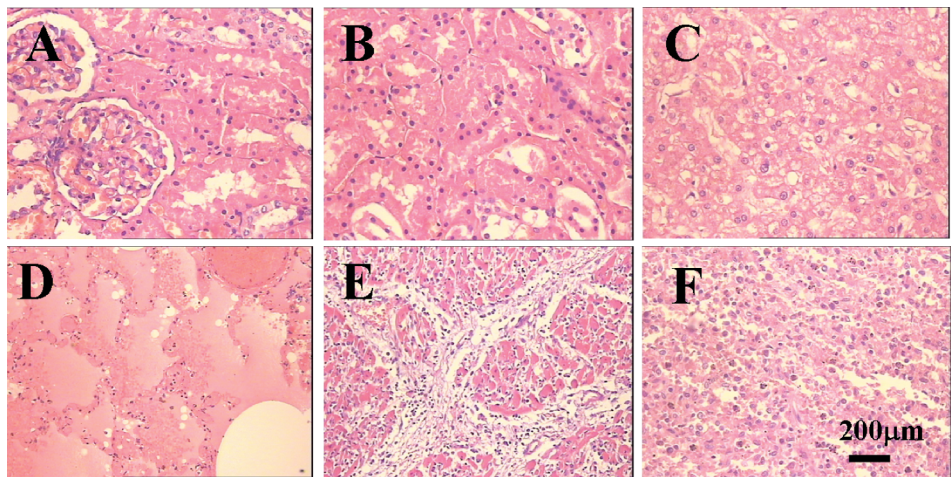


Figure 1: The characteristics of autopsy and histological examination of anaphylactic organs. (A): The anapetia of the acinus renis blood vessels. (B): The cellular edema of proximal convoluted tubule. (C): The hepatic sinusoid congestion. (D): Edema of lung, the alveolar space filled with effusion and erythrocytes. (E): The histoleucocytes in heart interstitial tissue. (F): Normal tissue of spleen.

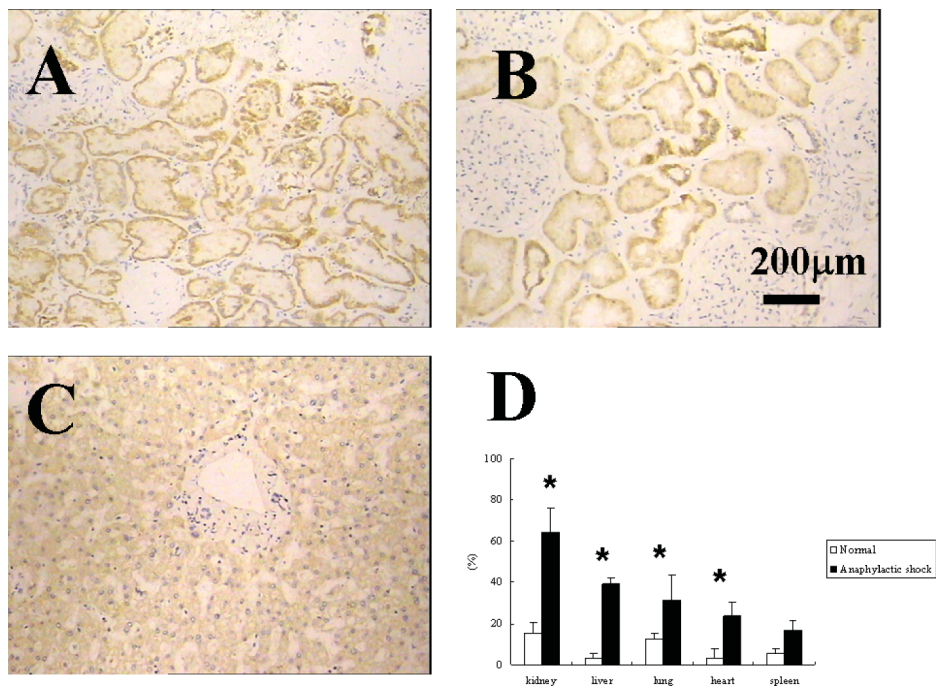


Figure 2: Expression of SOCS1 in various viscera of the anaphylactic group and the normal control group. (A,B): Kidney of the anaphylactic shock group. (C): Liver of the anaphylactic shock group. (D): The percentage of SOCS1-positive cells in various viscera of the anaphylactic group and the normal control group (* $P < 0.05$, $n = 3$; ** $P < 0.01$, $n = 5$). Bar represents 200 µm.

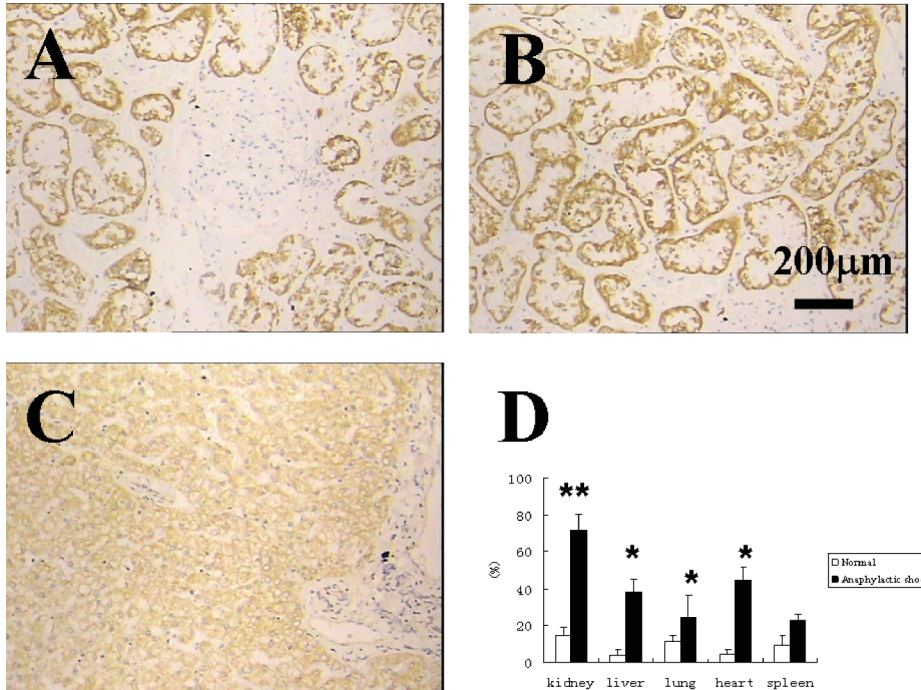


Figure 3: Expression of SOCS3 in various viscera of the anaphylactic group and the normal control group. (A,B): Kidney of the anaphylactic shock group. (C): Liver of the anaphylactic shock group. (D): The percentages of SOCS3-positive cells in various viscera of the anaphylactic group and the normal control group (* $P < 0.05$, $n = 3$; ** $P < 0.01$, $n = 5$). Bar represents 200 μm .

However, there was no significant difference of SOCS1 and SOCS3 in the spleen between the two groups. In anaphylactic shock group, SOCS1 and SOCS3 proteins were strongly expressed in the cytoplasm of endothelial cells of kidney tubules and the hepatic parenchymal cells (Figure 2 and Figure 3).

Compared with the other viscera, the expression levels of SOCS1 and SOCS3 proteins were the highest in the kidney. Meanwhile, SOCS3 level was higher than SOCS1 in all viscera.

We also detected the differences of mRNA expression levels of SOCS3 and SOCS1 in viscera between the anaphylactic shock group and the normal control group by RT-PCR. Compared with the normal control group, the mRNA expression levels of SOCS1 and SOCS3 were all elevated in the anaphylactic shock group, especially in the kidney, the mRNA expression levels of SOCS1 and SOCS3 reached the highest level with statistically significant difference. However, no difference of the mRNA level of SOCS1 was observed in the spleen between the two groups ($P > 0.05$) (Figure 4 and Figure 5).

There was significant positive correlation between the mRNA expression levels of SOCS3 and SOCS1 in the kidney, the liver ($r = 0.965$, $P < 0.00$, $r = 0.947$,

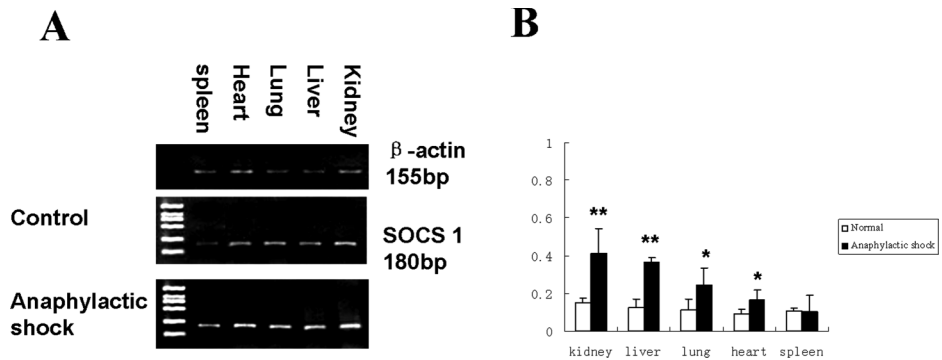


Figure 4: RT-PCR analysis of SOCS1 and β -actin mRNA expressions in various viscera of the anaphylactic group and the normal control group. The data represent 3 independent experiments. (A): DNA electrophoretic analysis of end-product of RT-PCR showed expected sizes (SOCS1: 180bp and β -actin: 155bp). (B): Comparison of mRNA levels of SOCS1 in various viscera of the anaphylactic group and the normal control group.

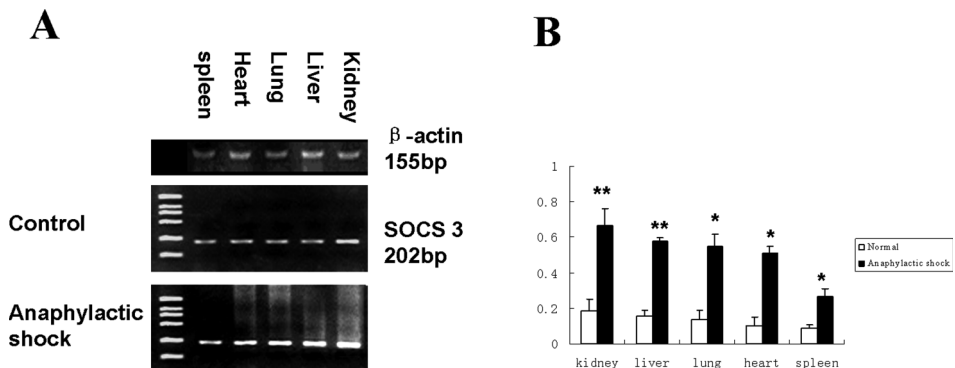


Figure 5: RT-PCR analysis of SOCS3 and β -actin expressions in various viscera of the anaphylactic group and the normal control group. The data represent three independent experiments. (A): DNA electrophoretic analysis of end-product of RT-PCR showed expected sizes (SOCS3: 202bp and β -actin: 155bp). (B): Comparison of mRNA levels of SOCS3 in various viscera of the anaphylactic group and the normal control group.

$P < 0.00$, respectively), then it indicated that the expression trends of SOCS1 and SOCS3 were basically the same in anaphylactic shock (Figure 6).

DISCUSSION

Anaphylaxis, a systemic syndrome of immediate hypersensitivity, presents clinically with bronchospasm, angioedema, hives, and if severe, cardiovascular collapse. (Dickensheets, 2007; Gopalakrishnan, 2009). We found that no specific findings are present at necropsy in many cases of fatal anaphylaxis. It is particularly likely to cause rapid onset of shock after reactions. In this

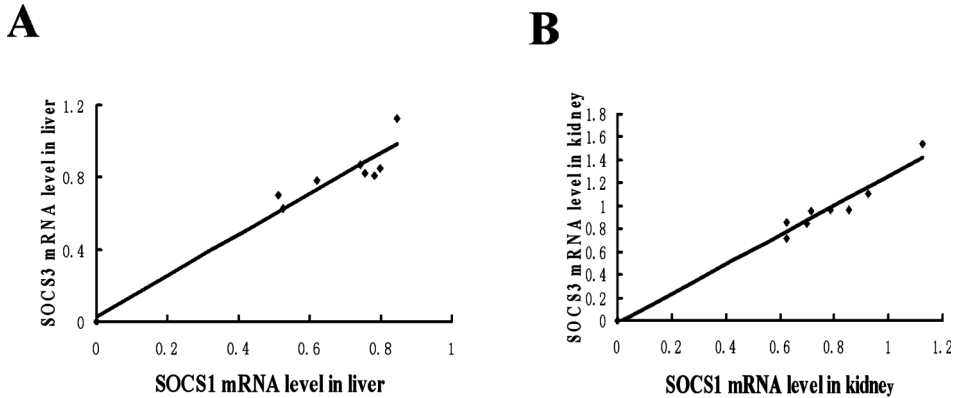


Figure 6: Positive correlation between the mRNA level of SOCS1 and SOCS3 (A): Positive correlation between the mRNA level of SOCS1 and SOCS3 in liver of the anaphylactic group ($r = 0.729$, $P = 0.000$, $n = 8$). (B): Positive correlation between the mRNA level of SOCS1 and SOCS3 in kidney of the anaphylactic group. ($r = 0.821$, $P = 0.000$, $n = 8$).

study, 1 of 8 cases had history of asthma, and then it is possible that many other acute asthma deaths in those with a history of food allergy might have been reactions to food. Further research should been performed for more rigorous investigation as the patients died of other causes for additional control group.

Tests to specific IgE and mast cell tryptase might help to determine whether anaphylaxis is the cause of death. In the present study, the IgE level in the heart-blood in the anaphylactic shock group was significantly higher than that of the control group. Therefore, IgE is an important mediator in anaphylactic shock as previous report (Nakagawa, 2002). However, the serum IgE was not specifically increased in anaphylactic shock, which was elevated in many diseases such as systemic lupus erythematosus patients (Komatsuda A, 2009) and the average concentration of serum IgE was 177.34 ± 89.15 IU/ml in 30 psoriasis patients in the same period (Data was not shown).

It appears that SOCS proteins were only related with allergic diseases. SOCS family is one type of protein that exerts negative regulatory effects on the signaling pathways of cytokines. SOCS1 and SOCS3 are important feedback regulatory proteins of JAK-STAT pathway after induced by cytokines and participate in the development of most inflammatory diseases (Krebs, 2000). Biopsies from patients with psoriasis or dermatitis showed high levels of SOCS1 and SOCS3 (Federici, 2002). In addition, several studies of T-cells from patients with atopic dermatitis and asthma have shown up-regulated SOCS1 or SOCS3. However, there are rare reports on whether SOCS showed effects in anaphylactic shock and their detailed mechanisms. The further mechanism involved in the SOCS expression should be investigated in patients with high serum IgE.

Our results revealed that in the anaphylactic group, the mRNA and protein expression levels of SOCS1 and SOCS3 were elevated in all viscera

compared with the normal group. Anaphylactic shock is characterized by elevated immunoglobulin-E (IgE) antibodies that signal via the high affinity Fc epsilon receptor to release inflammatory mediators such as IL-2, IL-6, IL-10, TNF receptor I, MCT, and histamine (Stone, 2009). IL-10 is a multifunctional anti-inflammatory cytokine whose general effects are essentially targeted to limit the inflammatory response and prevent tissue damage (Donnelly, 1999). Both SOCS1 and SOCS3 are known mediators of the IL-10 anti-inflammatory activity in cells (Berlato, 2002; Ding, 2003; Qasimi, 2006). SOCS3, in particular, was shown to be essential for IL-10 inhibition of LPS-stimulated production of TNF- α , IL-6, GM-CSF, and nitric oxide (NO) in mouse macrophages (Berlato, 2002).

Recent studies also showed that SOCS3 mediated the IL-10 inhibition of LPS-induced inducible NO synthase protein and NO production in mouse macrophages (Qasimi, 2006). Otherwise, members of the SOCS family are potentially key physiological negative regulators of interleukin-6 signaling. Several studies have revealed that SOCS expression as induced by both IL-6 and IL-10 in the presence of LPS, but selectively inhibited IL-6 signaling (Takagi, 2004). It has reported that SOCS3 deficiency results in prolonged activation of signal transducer and activator of transcription 1 (STAT1) and STAT3 after IL-6 stimulation (Rastmanesh, 2009).

Here we demonstrate that SOCS1 and SOCS3 correlate with liver and kidney injuries in anaphylactic shock. SOCS expression was related to increased systemic inflammation, illustrated by a significant correlation between monocytes SOCS1 and plasma IL-6. Researches suggest that increased expression of SOCS3 in monocytes and SOCS1 in lymphocytes correlates with progressive loss of renal function in chronic kidney disease (Rastmanesh, 2009). IL-6 is the major cytokine responsible for STAT3 activation in liver regeneration (Cressman, 1996) and CCl₄-induced liver injury (Kovalovich, 2000).

Several lines of evidence indicate that induction of SOCS1 in the liver is mainly controlled by STAT1 activation in hepatitis. Induction of SOCS3 controlled predominantly by STAT3 in the liver is also suggested in liver regeneration (Campbell, 2001). Probably via regulating the IL-6 signaling and STAT1 activation, SOCS3 and SOCS1 plays an important role in liver and kidney injuries with anaphylactic shock.

We also observed that SOCS expressed by endothelial cells in kidney tubules and hepatic parenchymal cells. These suggested that maybe endothelial cells in kidney tubules and hepatic parenchymal cells were the source of SOCS protein. Previous studies in mice have documented that SOCS proteins significantly increased in glomeruli and tubulointerstitium parallel with proteinuria and renal lesions during immune renal injury (Gomez-Guerrero, 2004). SOCS-2 expression was found to be heterogeneously expressed in murine liver parenchyma (Zellmer, 2009).

Cells in kidney and liver may be playing a potential role in acute fatal anaphylaxis. In our study, SOCS protein was not significantly increased in heart and lung in anaphylaxis. Accumulating evidences indicated that SOCS protein promote the failure and hypertrophy in heart while the expression level was very low (Terrell, 2006). The SCOS1 level increased after 3 days in lung hyperoxic injury (Kolliputi, 2009). These indicated SOCS activation require internal time for production.

However, the acute allergic reaction time was not adequate for SOCS production in heart and lung with anaphylactic shock. However, no significant difference was observed in spleen between the 2 groups in this study. The cytokine produced from maternal spleen cells, mostly present in the serum, contribute to immunopathogenesis of several inflammatory and infectious diseases. Therefore, we speculate that SOCS signaling was not activated in spleen cells, while the effect was significant in target organ cells.

Our work describes the importance of SOCS proteins, especially SOCS-3, in anaphylactic shock viscera injury processes and raises the possibility that therapeutic strategies based on the promotion of SOCS proteins might be of clinical benefit. However, additional studies are required to define the role of SOCS in liver and renal pathologic processes or even in regulating mechanism of cytokines after anaphylactic shock.

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