Letters to the Editor

Up-regulated expression of suppressor of cytokine signalling (SOCS) proteins mRNAs in peripheral blood mononuclear cells from patients with systemic lupus erythematosus

Sirs,

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterised by the activation of helper T cells and B cells, and defects in the clearance of apoptotic cells and immune complexes (1, 2, 3). Increased expressions of interleukin-2 (IL-2), IL-6, IL-10, IL-12, and IFN-α have been observed in peripheral blood mononuclear cells (PBMCs) from SLE patients (1, 2). These cytokines activate Janus kinases (JAKs) (4, 5). Signal transducer and activator of transcription factors (STATs) are tyrosine phosphorylated by JAKs. The family of suppressor of cytokine signalling (SOCS) protein is an important negative regulator for the JAK/STAT signalling pathways (4, 5). Fujimoto *et al*. (6) observed that mice with inadequate expression of SOCS1 spontaneously exhibited hyperactivation of lymphocytes, an increase in the levels of serum immunoglobulins and anti-DNA autoantibodies, and glomerulonephritis with glomerular IgG deposition. These findings are similar to those in human lupus. Recently, Tsao *et al*. (7) showed that the transcript levels of CIS, but not SOCS1, SOCS2 or SOCS3, in SLE patients determined by reverse transcription-polymerase chain reaction (RT-PCR) are higher than those in the controls. However, it is unclear whether these levels are related to disease activity and laboratory data.

In the present study, we performed quantitative real-time RT-PCR analyses of peripheral blood mononuclear cells (PBMCs) from 27 SLE patients and 27 healthy subjects, to estimate CIS, SOCS1, SOCS2, and SOCS3 mRNA expression levels. We also compared expression levels of these SOCSs mRNAs with those of TLR7, TLR9, and IFN-α mRNAs, and with SLE disease activity score and laboratory parameters such as titers of anti-dsDNA antibodies. Expression levels of CIS, SOCS1, and SOCS3 mRNAs in SLE patients were significantly higher than those in healthy controls (control *vs*. SLE: CIS; 0.025±0.017 *vs*. 0.054±0.042, p=0.008, SOCS1; 0.023±0.014 *vs*. 0.041±0.014, p=0.009, SOCS3; 0.032±0.017 *vs*. 0.063±0.054, p=0.008). Expression level of SOCS1 mRNA correlated with those of TLR7, TLR9, and IFN-α mRNAs in SLE patients (p=0.00004, 0.012, and 0.004, respectively). Expression level of SOCS2 mRNA correlated with that of TLR7 in SLE patients (p=0.024). Expression level of SOCS3 mRNA correlated with those of TLR7 and TLR9 mRNAs in SLE patients. (p=0.001 and 0.018). Expression level of SOCS1 mRNA correlated inversely with titers of anti-dsDNA antibodies in SLE patients (p=0.022).

Expressions of IL-2, IL-6 and IL-10 are increased in PBMCs from SLE patients (1). Since IL-2, IL-6, and IL-10 induce CIS, SOCS1, and SOCS3 in PBMCs, but not SOCS2 (4), increased expressions of these cytokines seem to result in up-regulation of mRNA expressions of CIS, SOCS1, and SOCS3 in PBMCs, as observed in our SLE patients. Our recent study demonstrated that expression levels of TLR2, TLR7, TLR9 and IFN-α mRNAs in PBMCs from SLE patients were significantly higher than those in healthy controls (8). Expression levels of TLR7 and TLR 9 mRNAs correlated with that of IFN-α mRNA in SLE patients. These results suggest that up-regulated expression of TLR7 and TLR9 mRNAs together with increased expression of IFN-α mRNA in PBMCs may contribute to the pathogenesis of human lupus. Dalpke *et al*. (9) demonstrated that triggering of TLR9 by CpG-DNA resulted in induction of SOCS1 and SOCS3. They showed that SOCS induction by TLR ligands is a direct consequence of TLR stimulation. Thus, our results suggest that up-regulated expression of SOCSs mRNAs in PBMCs may contribute to avoid overaction of cytokines and overshooting TLR stimulation in SLE patients.

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References

1. MOK CC, LAU CS: Pathogenesis of systemic lupus erythematosus. *J Clin Pathol* 2003; 56: 481-90.
2. RAHMAN A, ISENBERG DA: Systemic lupus erythematosus. *N Engl J Med* 2008; 358: 929-39.
3. COOKE A, FERRACCIOLI GF, HERRMANN M *et al*.: Induction and protection of autoimmune rheumatic diseases. The role of infections. *Clin Exp Rheumatol* 2008; 26 (Suppl. 48): 1-7
4. YOSHIMURA A, NISHINAKAMURA H, MATSUMURA Y, HANADA T: Negative regulation of cytokine signaling and immune responses by SOCS proteins. *Arthritis Res Ther* 2005; 7: 100-10.
5. DALPKE A, HEEG K, BARTZ H, BAETZ A: Regulation of innate immunity by suppressor of cytokine signaling (SOCS) proteins. *Immunobiology* 2008; 213: 225-35.
6. FUJIMOTO M, TSUTSUI H, XINSHOU O *et al*.: Inadequate induction of suppressor of cytokine signaling-1 causes systemic autoimmune diseases. *Int Immunol* 2004; 16: 303-14.
7. TSAO JT, KUO CC, LIN SC: The analysis of CIS, SOCS1, SOSC2 and SOCS3 transcript levels in peripheral blood mononuclear cells of systemic lupus erythematosus and rheumatoid arthritis patients. *Clin Exp Med* 2008; 8: 179-85.
8. KOMATSUDA A, WAKUI H, IWAMOTO K *et al*.: Up-regulated expression of Toll-like receptors mRNAs in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. *Clin Exp Immunol* 2008; 152: 482-7.
9. DALPKE AH, OPPER S, ZIMMERMANN S, HEEG K: Suppressors of cytokine signaling (SOCS)-1 and SOCS-3 are induced by CpG-DNA and modulate cytokine responses in APCs. *J Immunol* 2001; 166: 7082-9.