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). Fuji moto 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 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 TollR7, TollR9, 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 TollR7, TollR9, 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 TollR7 in SLE patients (p=0.024). Expression level of SOCS3 mRNA correlated with those of TollR7 and TollR9 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 TollR2, TollR7, TollR9 and IFN-α mRNAs in PBMCs from SLE patients were significantly higher than those in healthy controls (8). Expression levels of TollR7 and TollR9 mRNAs correlated with that of IFN-α mRNA in SLE patients. These results suggest that up-regulated expression of TollR7 and TollR9 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 TollR9 by CpG-DNA resulted in induction of SOCS1 and SOCS3. They showed that SOCS induction by TLR ligands is a direct consequence of TollR induction. Thus, our results suggest that up-regulated expression of SOCSs mRNAs in PBMCs may contribute to avoid overreaction of cytokines and overshooting TollR stimulation in SLE patients.

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This study was supported in part by the Global COE Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Competing interests: none declared.

References