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J Immunol 2012; 189:2043-2053; Prepublished online 13 July 2012;
doi: 10.4049/jimmunol.1103610
http://www.jimmunol.org/content/189/4/2043

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
9650 Rockville Pike, Bethesda, MD 20814-3994.

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

Suppressor of Cytokine Signaling 1 DNA Administration Inhibits Inflammatory and Pathogenic Responses in Autoimmune Myocarditis

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Myocarditis and subsequent dilated cardiomyopathy are major causes of heart failure in young adults. Myocarditis in humans is highly heterogeneous in etiology. Recent studies have indicated that a subgroup of myocarditis patients may benefit from immune-targeted therapies, because autoimmunity plays an important role in myocarditis as well as contributing to the progression to cardiomyopathy and heart failure. Suppressor of cytokine signaling (SOCS) 1 plays a key role in the negative regulation of both TLR- and cytokine receptor-mediated signaling, which is involved in innate immunity and subsequent adaptive immunity. In this study, we investigated the therapeutic effect of SOCS1 DNA administration on experimental autoimmune myocarditis (EAM) in mice. EAM was induced by s.c. immunization with cardiac-specific peptides derived from α myosin H chain in BALB/c mice. In contrast to control myocarditis mice, SOCS1 DNA-injected mice were protected from development of EAM and heart failure. SOCS1 DNA administration was effective for reducing the activation of autoreactive CD4$^+$ T cells by inhibition of the function of Ag-presenting dendritic cells. Our findings suggest that SOCS1 DNA administration has considerable therapeutic potential in individuals with autoimmune myocarditis and dilated cardiomyopathy. ***The Journal of Immunology*****, 2012, 189: 2043–2053.**

Dilated cardiomyopathy (DCM) is a potentially lethal disorder of various etiologies for which no treatment is currently satisfactory (1); it often results from enteroviral myocarditis (2, 3). Many patients show heart-specific autoantibodies (3, 4), and immunosuppressive therapy can improve cardiac function in DCM patients who show no evidence of viral or bacterial genomes in heart biopsy samples (5). These observations suggest that autoimmunity plays an important role in myocarditis as well as contributing to the progression to cardiomyopathy and heart failure (6).

Experimental autoimmune myocarditis (EAM) is a model of postinfectious myocarditis and cardiomyopathy (7). A number of proinflammatory cytokines, including IL-1β, IL-6, IL-12, TNF-α, and GM-CSF, have been shown to contribute to the development of autoimmune myocarditis in animal models and human cases (8–13). EAM is a CD4$^+$ T cell-mediated disease (7, 14), and activation of self-Ag–loaded dendritic cells (DCs) is critical for expansion of autoreactive CD4$^+$ T cells. Activation of TLRs and IL-1 type 1 receptor and their common downstream signaling adaptor molecule, MyD88, in self-Ag–presenting DCs is also critical for the development of EAM (11, 15, 16). Compared with inhibition of a single cytokine, a more effective treatment might be inhibition of various signaling pathways to induce production of cytokines through both innate and adaptive immunity. One strategy that could accomplish this would be to target shared cytokine and TLR signal transduction pathways using suppressor of cytokine signaling (SOCS) molecules.

Recent lines of evidence indicate that SOCS proteins, originally identified as negative-feedback regulators in cytokine signaling, are involved in the regulation of TLR-mediated immune responses (17, 18). The SOCS family is composed of eight members: cytokine-inducible Src homology 2 domain-containing protein and SOCS1 to SOCS7 (19, 20). SOCS1 plays a key role in the negative regulation of both TLR-mediated signaling and cytokine receptor-mediated signaling, which are involved in innate immunity and subsequent adaptive immunity (21). The expression of SOCS1 is induced by various cytokines, including IFN-γ, IL-4, and IL-6, and also by TLR ligands, such as LPS and CpG-DNA (22). Several studies have demonstrated that SOCS1 is a negative regulator of LPS-induced macrophage activation and plays an essential role in suppression of systemic autoimmunity mediated by DCs (23–25). Thus, SOCS1 regulates not only adaptive immunity

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Received for publication December 13, 2011. Accepted for publication June 5, 2012.

This work was supported by Health Science Research grants from the Ministry of Health, Labor and Welfare of Japan and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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The online version of this article contains supplemental material.

Abbreviations used in this article: BMDC, bone marrow-derived dendritic cell; DC, dendritic cell; dnSOCS1, dominant-negative suppressor of cytokine signaling 1; EAM, experimental autoimmune myocarditis; FS, fractional shortening; KO, knockout; LV, left ventricular; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; MyHC-α, cardiac myosin-specific peptide; pdnSOCS1, plasmid vector encoding dominant-negative suppressor of cytokine signaling 1; pSOCS1, plasmid vector encoding suppressor of cytokine signaling 1; QRT-PCR, quantitative real-time RT-PCR; SOCS, suppressor of cytokine signaling.

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1103610