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

Kazuko Tajiri, Kyoko Imanaka-Yoshida, Akihiro Matsubara, Yusuke Tsujimura, Michiaki Hiroe, Tetsuji Naka, Nobutake Shimojo, Satoshi Sakai, Kazutaka Aonuma and Yasuhiro Yasutomi

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

Supplementary Material
http://www.jimmunol.org/content/suppl/2012/07/13/jimmunol.110361
0.DC1.html

References
This article cites 56 articles, 26 of which you can access for free at:
http://www.jimmunol.org/content/189/4/2043.full#ref-list-1

Subscriptions
Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscriptions

Permissions
Submit copyright permission requests at:
http://www.aai.org/ji/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/cgi/alerts/etoc
Suppressor of Cytokine Signaling 1 DNA Administration Inhibits Inflammatory and Pathogenic Responses in Autoimmune Myocarditis

Kazuko Tajiri,*§† Kyoko Imanaka-Yoshida,**§§ Akihiro Matsubara,*§†† Yusuke Tsujimura,* Michiaki Hiroe,*‡ Tetsuji Naka,*# Nobutake Shimojo,† Satoshi Sakai,‡ Kazutaka Aonuma,†* and Yasuhiro Yasutomi*††

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-mysin 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.  


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.

*Laboratory of Immunoregulation and Vaccine Research, Tsukuba Primate Research Center, National Institute of Biomedical Innovation, Tsukuba, Ibaraki 305-0843, Japan; **Department of Cardiovascular Medicine, Majors of Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan; †Department of Pathology and Matrix Biology, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan; ‡Department of Pathobiology, Mie University, Tsu, Mie 514-8507, Japan; §Department of Pathology, Mie University, Tsu, Mie 514-8507, Japan; ††Department of Cardiology, National Center for Global Health and Medicine, Shinjuku, Tokyo 162-8655, Japan; and ‡‡Laboratory of Immune Signal, National Institute of Biomedical Innovation, Ibaragi, Osaka 565-0871, Japan

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.

Address correspondence and reprint requests to Dr. Yasuhiro Yasutomi, Laboratory of Immunoregulation and Vaccine Research, Tsukuba Primate Research Center, National Institute of Biomedical Innovation, 1-1 Hachimandai, Tsukuba, Ibaraki 305-0843, Japan. E-mail address: yasutomi@nibio.go.jp

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, knock-out; 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.

Copyright © 2012 by The American Association of Immunologists, Inc. 0022-1767/12S16/00

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