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*J Immunol* 2001; 167:4661-4667; doi: 10.4049/jimmunol.167.8.4661
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Production of Colony-Stimulating Factors and IL-5 by Organs from Three Types of Mice with Inflammatory Disease Due to Loss of theSuppressor of Cytokine Signaling-1

Donald Metcalf, Warren S. Alexander, Philip J. Ryan, Sandra Mifsud, and Ladina Di Rago

Organs from neonatal mice dying from IFN-γ-dependent inflammatory disease initiated by loss of the gene encoding the suppressor of cytokine signaling-1 (SOCS-1) had a normal capacity to produce G-CSF in vitro but a reduced capacity to produce GM-CSF, most evident with the lung, and some reduction in the production of M-CSF by muscle tissue. In contrast, organs from mice lacking the genes for both SOCS-1 and IFN-γ had a normal capacity to produce CSFs. Organs from young adult mice dying with polymyositis and myocarditis that lacked SOCS-1 but were heterozygous for IFN-γ had a normal capacity to produce GM-CSF and M-CSF, but muscle tissue produced significantly increased amounts of G-CSF and IL-5 with IL-5 production also being elevated for the salivary gland, thymus, and heart. Loss of the IFN-γ gene alone had no impact on organ production of these cytokines in vitro. In none of the inflammatory disease models was IL-3 production detected. The SOCS-1 protein appears to have no direct influence on the cellular production of these cytokines and the abnormalities observed either depend on the coaction of cytokines in vitro.

The suppressor of cytokine signaling-1 (SOCS-1) is a cellular protein able to block or modulate intracellular signaling initiated by a variety of regulator-activated membrane receptors on normal and leukemic cells (1–4). When overexpressed in M1 leukemic cells, SOCS-1 induces a refractory state to the differentiation-inducing action of LIF, IL-6, OSM, IL-11, or IFN-γ but leaves responsiveness to dexamethasone intact (5). Transient transcription of SOCS-1 can be induced in normal bone marrow cells by stimulation with a number of hemopoietic regulators and SOCS-1 then potentially limits sustained signaling from the receptors involved by blocking phosphorylation of the receptor and/or various signaling intermediates (1–5).

Mice with homozygous inactivation of the SOCS-1 gene develop a neonatally fatal syndrome of fatty degeneration and necrosis of the liver, with infiltration by T lymphocytes, macrophages, and granulocytes also causing damage to the pancreas, heart, lung, and skin (6, 7). This syndrome can be prevented by administration of Abs to IFN-γ from birth or by crossing-breeding to develop mice lacking the genes encoding both SOCS-1 and IFN-γ (8, 9). T lymphocytes are activated in SOCS-1–/– mice (9) and may initiate the disease syndrome by overproducing IFN-γ, which then activates macrophages to cause tissue damage. In support of this possibility, transplantation of SOCS-1–/– marrow cells to irradiated syngeneic recipients induces a fatal disease resembling graft-versus-host disease (Ref. 9 and D. Metcalf and W. S. Alexander, unpublished data).

Although it remains to be established that all tissue damage in SOCS-1–/– mice is initiated by aggressive hemopoietic cells, these mice do exhibit elevated numbers of macrophage precursors and tissue macrophages, and both populations in SOCS-1–/– mice are hyperresponsive to IFN-γ (6, 10).

The major regulatory factors controlling the proliferation and functional activity of macrophages and granulocytes are the four CSFs, GM-CSF, G-CSF, M-CSF, and multi-CSF (IL-3), and stem cell factor (kit ligand) (11). The granulocyte-macrophage progenitor cells in SOCS-1–/– mice were found to exhibit moderately increased responsiveness to GM-CSF but not to M-CSF or IL-3, and SOCS-1 can inhibit responses to stem cell factor (10, 12).

If aberrant or overproduction of CSFs was another cellular consequence of loss of SOCS-1, this might provide an additional mechanism contributing to the increased production and functional activity of granulocytes and macrophages in such mice. In the present study, organs from SOCS-1–/– mice were examined for their capacity to produce CSFs. The results showed however that certain tissues from SOCS-1–/– mice had an impairment in their capacity to produce GM-CSF and M-CSF. Because of the T lymphocyte activation in these mice, this finding of impaired cytokine production was surprising and led to investigation of cytokine production in two other models of inflammatory disease involving loss of the SOCS-1 gene.

Materials and Methods

Mice

The production and breeding of SOCS-1–/– mice have been described previously (6). The SOCS-1–/– mice were generated by cross-breeding phenotypically normal SOCS-1+/+ mice, a procedure also providing control SOCS-1+/+ and SOCS-1–/– mice. IFN-γ–/– mice were obtained from The Jackson Laboratory (Bar Harbor, ME) and were bred in the same animal quarters. SOCS-1–/– IFN-γ–/– mice were generated initially by

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Received for publication April 30, 2001. Accepted for publication August 15, 2001.

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mating of SOCS-1 −/− mice with IFN-γ −/− mice with subsequent in-
terbreeding of SOCS-1 −/− IFN-γ −/− mice and then maintained by SOCS-1 −/− IFN-γ −/− intercrosses (8). The genotype of all mice was determined by Southern blot analysis of tail tip genomic DNA as described previously (6, 8).

All mice were housed in protected animal quarters and regular monitor-
ing was undertaken to verify the absence of bacterial or viral pathogens.

Preparation of organ-conditioned media

Organs were collected sterilely from SOCS-1 −/− and +/+ or +/− mice ages 12–18 days and from mice ages 2–3 mo of other genotypes. Individual organs were minced into coarse fragments using scissors and then incu-
bated in capped tubes in 1 ml (or 2 ml for adult organs) of serum-free DMEM at 37°C in a fully humidified atmosphere of 10% CO2, in air. After 4 days of incubation, tissue fragments were removed by centrifugation and the supernatant-conditioned medium was sterilized by Millipore filtration and stored at 4°C before assay.

Assay cell lines

The Ba/F3 cell line was used for the specific bioassay of IL-3 and responds by proliferation in microwell cultures to concentrations of IL-3 as low as 1.5 pg/ml (13, 14). For the specific assay of G-CSF, M-CSF, and IL-5, stable Ba/F3 sublines expressing inserted murine G-CSF, M-CSF, or IL-5a chain receptors (Ba/F3GR, Ba/F3MR, Ba/F3IL-5R, respectively, cell lines) were used as previously described (13–15). Because no organ-conditioned medium in fact contained detectable IL-3, these cell lines were able to provide specific assays for their respective ligands and were able to detect concentrations as low as 100 pg/ml for G-CSF and M-CSF and 2.5 pg/ml for IL-5.

The FDC-P1 cell line proliferates in response to both GM-CSF and IL-3 (13). Because of the absence of IL-3 from the materials being assayed, the FDC-P1 cell line was able to be used as a specific bioassay for GM-CSF (lower detection limit, 100 pg/ml) (14).

To further verify that what was being detected in the FDC-P1 assays of organ-conditioned medium was in fact GM-CSF, active medium conditioned by organs from all types of experimental animals used in the study were mixed with serial 2-fold dilutions of a neutralizing rat anti-mouse GM-CSF mAb (Genzyme, Cambridge, MA) and reassayed on FDC-P1 cells. Concentrations of organ-conditioned medium were chosen that pro-
duced just maximal stimulation of assay FDC-P1 cells (the concentration used in the calculation of GM-CSF levels) and the serial dilutions of Ab commenced using a concentration of 3 μg/ml. In every case, the Ab was diluted of at least 1/16 specifically neutralized all the proliferative activity of the conditioned media, including those prepared for the experiments described in Table 1 where recombinant murine IFN-γ (PeproTech, Rocky Hill, NJ) was added during preparation of the conditioned media. The latter were of particular relevance because IFN-γ itself was found to have a weak temporary survival action on FDC-P1 cells.

Microwell assays

Cell lines for use in microwell assays were washed three times (or six times for Ba/F3, IL-5 Rz cells) by centrifugation in 10 ml of medium to remove the CSF or IL-5 used in the maintenance cultures.

Microwell assays were performed using 60-well microtiter trays (Sarstedt Australia, Technology Park, South Australia), each well containing 200 of the assay cells in 1 ml of DMEM with a final concentration of 10% newborn calf serum. Material for assay was added to duplicate wells in 5-μl vol of serial 2-fold dilutions before the addition of the target cell suspension. Trays were incubated for 48–72 h at 37°C in a fully humidified atmosphere of 10% CO2, then viable cell counts were performed using an inverted microscope. Where cell counts exceeded 200 per well, the well was scored as containing >200 cells.

All assays included a titration of 1 ng/ml IL-3 to certify the viability and responsiveness of the Ba/F3, Ba/F3GR, Ba/F3MR, and Ba/F3IL-5R cell lines and also a titration of the appropriate purified recombinant regulator starting with an initial concentration of 10 ng/ml for G-CSF and M-CSF and 5 ng/ml for IL-5. For FDC-P1 cells, the standard titrated was 1 ng/ml GM-CSF. The stimuli used were recombinant human G-CSF (kindly supplied by Amgen, Thousand Oaks, CA) and purified recombinant murine GM-CSF, M-CSF, IL-3, and IL-5 purchased from PeproTech.

The observed concentrations of CSF or IL-5 in the conditioned media were calculated as nanograms per milliliter or picograms per milliliter using data from the purified recombinant standards assayed in the same ex-
periments. The figures were then transformed to nanograms or picograms produced per organ during the 4-day incubation period. For many organs, the entire organ had been used (salivary gland, thymus, lung, heart, kidney, liver, spleen, bladder, uterus, and testes); therefore, no correction factor was applied. For the bone marrow and bone shaft, only two femur shafts or femoral marrows were used to generate conditioned media and the data were multiplied by 6 to estimate total marrow or shaft production. For muscle tissue, the tissue normally used was one-thirtieth of the total muscle mass, and the assay results were multiplied by 30 to calculate total muscle production of CSF.

Results

The present studies were initiated to answer the simple question of whether loss of the SOCS-1 gene had any impact on the ability of various organs to produce cytokines of likely relevance for the pathology developed by these mice. However, because of the find-
ings obtained, the studies were extended to a comparative analysis of organ production of these cytokines in three distinct inflam-
atory disease states involving loss of the SOCS-1 gene, each of which has been described in detail elsewhere. In brief, mice lack-
ning SOCS-1 die in neonatal life with fatty degeneration of the liver and inflammatory lesions involving T lymphocytes, macrophages, and granulocytes in the lung, heart, pancreas, and skin, an example of the lung disease being shown in Fig. 1A (6). Mice lacking genes for both SOCS-1 and IFN-γ develop as apparently healthy adult mice but do exhibit focal T and B lymphoid lesions in the lung (Fig. 1B) (16). Mice lacking SOCS-1 and heterozygous for IFN-γ die in young adult life with massive infiltration of T lymphocytes, macrophages, and eosinophils in skeletal muscle (Fig. 1C) and the heart with concomitant infiltration and ulcer formation (16).

Defective cytokine production by organs from neonatal mice lacking SOCS-1

Because SOCS-1 −/− mice die within 21 days of birth, initial studies on organ production of CSFs were performed using SOCS-1 −/− and SOCS-1 +/+ or +/+ − control mice ages 12–18

<table>
<thead>
<tr>
<th>Organ</th>
<th>GM-CSF (ng)</th>
<th>M-CSF (ng)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymus</td>
<td>8, 4, 16</td>
<td>6, 6, 3</td>
</tr>
<tr>
<td>Heart</td>
<td>8, 8, 8</td>
<td>3, 3, 3</td>
</tr>
<tr>
<td>Lungs</td>
<td>32, 256, 512</td>
<td>12, 12, 12</td>
</tr>
<tr>
<td>Muscle</td>
<td>60, 60, 120, 120, 480, 120, 240, 60</td>
<td>90, 180, 180, 180, 180, 180, 90, 90, 24, 24, 24, 24, 24, 90</td>
</tr>
<tr>
<td>Bone shaft</td>
<td>6, 12, 48</td>
<td>18, 18, 18</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2.4, 1.2, 6</td>
<td>18, 18, 36</td>
</tr>
</tbody>
</table>

a Values shown are nanograms of GM-CSF or M-CSF produced per organ. Each value represents data from a separate mouse. Organ cultures were initiated with or without the addition of 200 ng of recombinant murine IFN-γ per milliliter of medium and harvested after 4 days of maturation.

Table 1. Influence of added IFN-γ on the ability of organs from SOCS-1 −/− IFN-γ −/− mice to produce GM-CSF and M-CSF in vitro

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Lung tissue was the striking exception to this generalization because the SOCS-1 −/− lung produced less than one-fiftieth of the amount of GM-CSF produced by +/+ or +/− lung tissue, a deficiency that was highly significant statistically and much larger than ascribable to differences between the weights of the two organs.

In contrast to the results with GM-CSF production, G-CSF production by most SOCS-1 −/− organs was similar to that produced by control +/+ or +/− organs with the possible exception of a barely 2-fold lower production by the lung and bone shaft (Fig. 2). This similarity casts some doubt on ascribing differences in GM-CSF production to lower organ weights. Data for M-CSF showed even lower overall levels of production (Fig. 2). Most SOCS-1 −/− and control organs produced similar amounts of M-CSF, but SOCS-1 −/− muscle and bone shaft produced significantly lower amounts of M-CSF than control organs.

Cytokine production by organs from healthy mice lacking SOCS-1

SOCS-1 −/− mice in which the IFN-γ gene has also been deleted develop as apparently healthy young adults but do have lymphoid foci in their lungs (Fig. 1B) (16). Organs from 2-mo-old SOCS-1 −/− IFN-γ −/− mice were analyzed to determine whether deletion of the SOCS-1 gene in this context had a similar impact on the ability of various organs to produce CSF. The control mice used lacked only the IFN-γ gene or were SOCS +/+ IFN-γ +/+ mice of these genotypes being healthy as young adults.

As shown in Fig. 3, production of GM-CSF by all organs and, in particular, the lung from SOCS-1 −/− IFN-γ −/− mice was not significantly different from that produced by organs from control SOCS-1 +/+ IFN-γ −/− or SOCS-1 +/+ IFN-γ +/+ mice. A comparable analysis of G-CSF and M-CSF production also revealed no differences between SOCS-1 −/− IFN-γ −/− and control mice (data not shown).

The normal pattern of CSF production by SOCS-1 −/− IFN-γ −/− lung tissue was noteworthy because these apparently healthy mice do consistently exhibit foci of B and T lymphocytes in their lungs (Fig. 1B). These foci can be extensive but are not associated with any obvious damage to surrounding lung tissue.

The observation that loss of the IFN-γ gene alone had no impact on the ability of organs to produce CSF was of interest because IFN-γ might have been regarded as a possible inducing agent for organ production of CSFs in vitro.

A possible criticism of this negative study was that the mice used were adults and might not have been entirely comparable to the neonatal mice used in the initial study. To eliminate this possibility, further sets of conditioned medium were prepared from neonatal mice of the above genotypes. Again, no differences in organ production of CSFs were noted between SOCS-1 −/− IFN-γ −/− mice and control mice (data not shown).

The abnormally low production of GM-CSF and M-CSF by organs lacking SOCS-1 and IFN-γ −/− mice therefore appeared either to be secondary to disease development in these mice or depended on an action of IFN-γ to occur.

With regard to the second possibility, it was potentially of relevance that SOCS-1 −/− cells are hyperresponsive to IFN-γ (8, 10) and that IFN-γ levels are elevated in SOCS-1 −/− mice (9). It was therefore investigated whether addition of IFN-γ to organ cultures might decrease the production of GM-CSF or M-CSF by organs from mice lacking the SOCS-1 gene. Organ-conditioned medium was prepared from 3-mo-old SOCS-1 −/− IFN-γ −/− mice as described above with or without the addition of 200 ng of IFN-γ/ml medium at initiation of the cultures. The media were

harvested after 4 days of incubation and assayed for levels of GM-CSF and M-CSF.

Table I shows the data obtained for those organs producing detectable GM-CSF or M-CSF. It can be seen that addition of IFN-γ did somewhat reduce the levels of GM-CSF produced by thymus, heart, lungs, and muscle from SOCS-1 −/− IFN-γ −/− mice. In contrast, addition of IFN-γ consistently increased organ capacity to produce M-CSF. The data support the possibility that an action by IFN-γ might contribute to the reduced ability of SOCS-1 −/− organs to produce GM-CSF. However, IFN-γ did not reduce organ production of M-CSF as seen with SOCS-1 −/− organs and the abnormally low capacity of SOCS-1 −/− organs to produce both CSFs is likely to have a more complex basis.

**CSF and IL-5 production by organs from SOCS-1 −/− mice heterozygous for IFN-γ**

The third animal model analyzed was SOCS-1 −/− IFN-γ +/+ mice that die as young adults with extensive polymyositis (Fig. 1C), myocarditis, and corneal infiltration with ulcer formation (16). The infiltrates in muscle and heart tissue are a mixture of T lymphocytes, macrophages, neutrophils, and a prominent population of eosinophils. In this study, analysis of organ production of CSFs was accompanied by estimation of IL-5 production because IL-5 is the major regulator of eosinophil production (17, 18). Young adult SOCS-1 −/− IFN-γ +/+ mice with clinical illness were compared with healthy and histologically normal SOCS-1 +/+ IFN-γ +/+ mice of the same age.

Although all organ-conditioned media were analyzed, Fig. 4 shows data for GM-CSF, G-CSF, and M-CSF production only by the lung for comparison with the data from the previous two models and for muscle and heart—the two organs extensively involved by inflammatory infiltrates (16).

GM-CSF and M-CSF production by these three organs from SOCS-1 −/− IFN-γ +/+ mice was not significantly different from that by organs from control mice. Similarly, no differences were observed in G-CSF production by lung or heart but muscle tissue from SOCS-1 −/− IFN-γ +/+ mice was significantly more active in producing G-CSF than control muscle.

The only other difference observed in CSF production by other organs from these two types of mouse was an increased production of GM-CSF by SOCS-1 −/− IFN-γ +/+ salivary gland (data not shown).

The data on IL-5 production by all organs analyzed from SOCS-1 −/− IFN-γ +/+ and SOCS-1 +/+ IFN-γ +/+ mice are

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**FIGURE 2.** Production in vitro of GM-CSF, G-CSF, and M-CSF by organs from neonatal SOCS-1 −/− mice (●) and from neonatal SOCS-1 +/+ or +/+ mice (○). Each point represents data from an individual mouse. Bars, median values.
shown in Fig. 5. Levels of IL-5 production by the most active organ, the lung, were similar in the two groups but IL-5 production was generally higher by other organs from SOCS-1 − − IFN-γ − − mice than from control mice, the differences being significant for muscle, salivary gland, heart, and bone shaft.

Discussion

All methods for estimating cytokine production in tissues have their limitations and can be subjected to criticism (14, 15). The present estimates of the capacity of various organs to produce cytokines in vitro share some of these limitations, although the validity and specificity of the bioassays used have been established. The data from the present study therefore have their limits but provide some information of interest on the potential of various organs to produce cytokines and on changes in this capacity in the presence of inflammatory disease.

The question posed initially was whether deletion of the SOCS-1 gene might have a consistent impact on cytokine production in tissues. SOCS-1 can modulate or suppress receptor-initiated signaling for hemopoietic cell proliferation and maturation by tissues. SOCS-1 can modulate or suppress receptor-initiated signaling for hemopoietic cell proliferation and maturation by tissues. The early-responding cytokines IFN-α (1–4) and potentially might interfere with other receptor-initiated cellular processes such as cytokine production. Production of CSFs by cells is highly inducible by a variety of agents (11), and IFN-α has been reported to have some activity (19). Because the early death of SOCS-1 − − mice has been shown to depend on IFN-γ action (8) and SOCS-1 − − cells are hyperresponsive to IFN-γ (8, 10), this agent might potentially stimulate SOCS-1 − − tissues to overproduce cytokines, including the CSFs.

However, the data obtained from the present analysis of CSF production by SOCS-1 − − organs indicated no overproduction of CSFs but instead a subnormal capacity to produce GM-CSF, particularly by lung tissue, and M-CSF, particularly by muscle tissue, with no change in the production of G-CSF and no detectable production of IL-3. The lung in SOCS-1 − − mice is abnormal and infiltrated by extensive populations of T lymphocytes, macrophages, neutrophils, and eosinophils (6). The subnormal capacity of this organ to produce GM-CSF was not simply ascribable to loss of SOCS-1 because the lung in mice lacking both SOCS-1 and IFN-γ had a normal capacity to produce GM-CSF. This suggests that SOCS-1 deficiency only leads to failure to produce normal amounts of GM-CSF in the presence of IFN-γ or, more likely, that a deficiency arises in SOCS-1 − − organs because of inflammatory disease in these organs.

The former possibility received some support from the demonstration that the addition of IFN-γ to cultures of organs from SOCS-1 − − IFN-γ − − mice did result in some reduction in their capacity to produce GM-CSF. However, addition of IFN-γ increased organ production of M-CSF, the opposite of what was observed with media conditioned by SOCS-1 − − organs.

The possibility that abnormal organ production of CSFs was a consequence of disease development prompted an analysis of two additional models in which inflammatory disease develops in SOCS-1 − − mice. Mice lacking both the SOCS-1 and IFN-γ genes remain in good health but do develop foci of T and B lymphocytes in the lung and salivary gland without any histological evidence of damage to adjacent tissues (16). All organs from such mice, including lung, had a normal capacity to produce CSF in vitro. Mice that lack SOCS-1 but are heterozygous for IFN-γ die

FIGURE 3. Production in vitro of GM-CSF by organs from SOCS-1 − − IFN-γ − − mice (○), SOCS-1 +/+ IFN-γ − − mice (●), or SOCS-1 +/+ IFN-γ +/+ mice (▲). Each symbol point represents data from an individual mouse.
as young adults with extensive infiltration and destruction of skeletal muscle and heart tissue, the infiltrating cells being a similar mixture of T lymphocytes, neutrophils, and eosinophils to those infiltrating cells being a similar as young adults with extensive infiltration and destruction of skeletal muscle and heart tissue, the infiltrating cells being a similar mixture of T lymphocytes, neutrophils, and eosinophils to those infiltrating SOCS-1−/− lung tissue (16). Surprisingly, production of GM-CSF and M-CSF was normal by organs from SOCS-1−/− IFN-γ+/− mice. This could imply that IFN-γ, in diploid gene dosage, was necessary in SOCS-1−/− mice for the development of deficient GM-CSF and M-CSF production but, more likely, suggests that the anomalies are based on the presence of disease in these organs.

The obvious anomaly in CSF production by SOCS-1−/− IFN-γ+/− tissues was an elevated capacity to produce G-CSF. In none of the above three inflammatory disease models is it possible to examine the situation before disease development and any observed abnormalities with organs involved in inflammation may be secondary to tissue damage or to CSF production by some of the infiltrating cells. In the context of SOCS-1−/− IFN-γ+/− mice, the inflammatory infiltrate in muscle tissue is rich in macrophages and G-CSF is a known product of macrophages (20).

A somewhat similar situation was observed with IL-5 production by organs from SOCS-1−/− IFN-γ+/− mice. IL-5 is the major regulator of eosinophil production (17, 18) and the inflammatory infiltrates in muscle in these mice are rich in eosinophils. Although no mitotic activity was observable in infiltrating cells (16), local IL-5 might be capable of activating eosinophils present in such tissues and it was not surprising therefore to observe elevated production of IL-5 by skeletal muscle and heart in such mice.

In all of these models, activation of T lymphocytes has been documented (9, 16) and activation of T lymphocytes in vitro leads to a marked rise in the production of GM-CSF, IL-3, and IL-5 (11). It was therefore surprising in all three models with substantial T cell activation to find no evidence of IL-3 production and a defect in GM-CSF production by certain organs.

The present studies have excluded loss of SOCS-1 as having any simple effect on organ production of CSFs or IL-5 but have documented certain abnormalities in the production of these regulators by tissues developing inflammatory disease as a consequence of loss of SOCS-1. In the three inflammatory models, no local mitotic activity is present in the infiltrating populations but the ability of these infiltrating organs to produce CSFs or IL-5 can be presumed to have a potential impact on the functional activity of the infiltrating cells and thus potentially to contribute to the maintenance and progression of the inflammatory states. The importance of such a role could possibly be explored further by examining disease development and progression in mice lacking both SOCS-1 and the β common chain of the receptor for GM-CSF and IL-5, although such a study might require deletion of at least one allele of the IFN-γ gene to allow adequate survival of the animals.

References


