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Production of Colony-Stimulating Factors (CSFs) during Infection: Separate Determinations of Macrophage-, Granulocyte-, Granulocyte-Macrophage-, and Multi-CSFs

C. CHEERS,[1]* A. M. HAIGH,[1] A. KELSO,[2] D. METCALF,[2] E. R. STANLEY,[3] AND A. M. YOUNG[1]

Department of Microbiology, University of Melbourne,[1] and Walter and Eliza Hall Institute for Medical Research, P.O. Royal Melbourne Hospital,[2] Parkville, Victoria, 3052, Australia, and Department of Microbiology and Immunology and Department of Cell Biology, Albert Einstein College of Medicine, The Bronx, New York 10461[3]

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After infection of mice with *Listeria monocytogenes*, elevated levels of colony-stimulating factors (CSFs) in the serum were quantitated by six different assays: ability to stimulate colony formation, the proliferation of 2 suspension of bone marrow cells (both measuring total colony-stimulating activity), a radioimmunoassay for macrophage-CSF (CSF-1), the WEHI-3B differentiation assay for granulocyte-CSF, and proliferation of 32D-c1-3 and FDC-P1 cell lines (specific for multi-CSF and either multi- or granulocyte-macrophage-CSFs, respectively). The great bulk of serum colony-stimulating activity represented macrophage- and granulocyte-CSFs, with small but measurable amounts of granulocyte-macrophage-CSF. The degree of elevation of serum CSF depended on the infecting dose used and the numbers of bacteria growing in the spleens and livers of the two mouse strains compared, i.e., *L. monocytogenes*-resistant C57BL/10 and susceptible BALB/cJ. The increase in serum CSFs occurred before the peak in bone marrow granulocyte-macrophage progenitors and before the reduction in bacterial numbers which follows the onset of specific cell-mediated immunity.

Colony-stimulating factors (CSFs) are a group of growth factors which regulate the growth and differentiation in vitro of the hemopoietic cell precursors, colony-forming cells (CFCs) (15). When injected in vivo CSFs induce an increase in CFCs and the end cells (macrophages, granulocytes, and eosinophils) which they generate (2, 10, 16, 25). There are four well-defined CSFs for the granulocyte-macrophage lineage in mice: macrophage (M)-CSF (or CSF-1), controlling the production of macrophages; granulocyte (G)-CSF, controlling the production of granulocytes; granulocyte-macrophage (GM)-CSF, stimulating production of both granulocytes and macrophages; and multi-CSF (or interleukin-3 [IL-3]), which stimulates the proliferation of a broad range of hemopoietic cells (15).

Granulocytes and macrophages are vital to defense against bacterial infection. In particular, facultative intracellular bacteria, such as the mycobacteria, the brucellae, some salmonellae, and *Listeria monocytogenes* have the capacity to survive and multiply within macrophages. Of these, *L. monocytogenes* has perhaps been the most closely studied experimentally. The infection in mice is either controlled or eradicated when the bactericidal mechanisms of the macrophages become activated by T lymphocytes producing lymphokines (22). Even before the onset of this specific acquired cell-mediated immunity, the inflammatory response by macrophages, and probably to a lesser extent by polymorphonuclear leukocytes, to the site of infection is critical to the survival of the animal (6, 20, 32). There is, furthermore, evidence that higher numbers of CFCs in the bone marrow and spleen before infection favor survival of the mice after *Listeria* infection (30, 33). After infection, there is an increase in serum colony-stimulating activity and later in the number of CFCs in spleen and bone marrow (31, 33).

The present paper therefore seeks to define which CSFs are released into the serum after infection and what their relationship is to the course of infection and CFC response. *Listeria* infection of mice was chosen as an ideal model in which to study these questions.

MATERIALS AND METHODS

Infection of mice. C57BL/10 and BALB/cJ mice were pedigree bred at the Department of Microbiology, University of Melbourne (Parkville, Victoria, Australia), and held under conventional but disease-free conditions. C57BL/10 mice are genetically resistant to *L. monocytogenes* (50% lethal dose = 2×10^5), whereas BALB/cJ mice are susceptible (50% lethal dose = 2×10^3). The difference is determined by a single autosomal non-*H-2*-linked gene, *Lsr* (4). Male mice were infected intravenously at 6 to 8 weeks of age with a suspension of known opacity of *L. monocytogenes* prepared as previously described (33), and the dose was checked retrospectively by viable counts (19). The mice were bled from the heart under ether anesthesia, and sera from individual mice were collected after clotting for 1 h at room temperature and overnight at 4°C. Bone marrow cells were collected by aspiration from the tibia and suspended in Dulbecco modified Eagle medium with 10% fetal calf serum (33). Bacterial counts were performed on homogenized spleens and livers (5).

CFCs in bone marrow. Bone marrow cells were prepared from mice infected at intervals before the time of assay. They were placed in triplicate 1-ml semisolid agar cultures in 35-mm petri dishes with 0.1 ml of an optimal dilution of pooled serum from lipopolysaccharide-injected C57BL/10 mice as a source of CSF (12). After 7 days, the numbers of colonies containing 50 or more cells were counted under a dark field at a magnification of ×40 with an Olympus dissection microscope (17).

Assays for serum CSF levels. (i) Colony-stimulating activity. Dilutions of serum from infected mice were used to stimulate the formation of granulocyte-macrophage colonies in cul-

* Corresponding author.

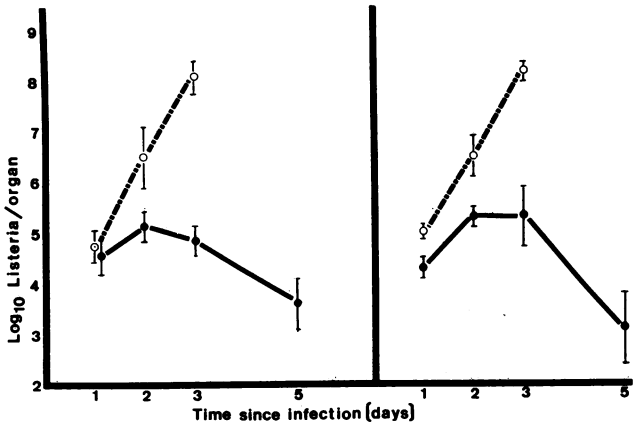

FIG. 1. Growth of *Listeria* cells in the spleen (left) and liver (right) of C57BL/10 (●) and BALB/cJ (○) mice infected with 10^4 *Listeria* cells. Each point represents the mean ± standard deviation of samples from five mice.

tures of 75,000 C57BL/10 bone marrow cells as described previously (13). Results were expressed as units per milliliter, where 50 U is the CSF concentration stimulating the development of half the maximum possible number of colonies.

(ii) Tritiated-thymidine uptake by bone marrow cells. The tritiated-thymidine assay was based on that of Horak et al. (9). Dilutions of serum were prepared in 0.1 ml of Dulbecco modified Eagle medium with 10% fetal calf serum in flat-bottom 96-well microtiter trays (Disposable Products Pty. Ltd., Adelaide, South Australia, Australia), and 4×10^5 bone marrow cells were added. After 4 days of incubation, 2 μCi of tritiated thymidine (Amersham International, Amersham, United Kingdom) was added. The cultures were harvested onto filter paper (Titertek Microtitration Equipment, Flow Laboratories, United Kingdom) 6 h later, and the radioactivity in the dried filters was counted in 2,5-diphenyloxazole-1,4bis(phenyloxazolyl) benzene (PPOPOP-OP) scintillant in a Tricarb liquid scintillation spectrometer, model 3320 (Packard Instrument Co., Inc., Rockville, Md.). Counts per minute were calculated from triplicate cultures, and the maximum counts per minute for each serum was taken as a relative measure of the CSF activity of that serum. Developing macrophages could be seen in these cultures by using an inverted microscope, and control experiments showed that proliferation was not mediated by lipopolysaccharide in the serum.

(iii) RIA for CSF-1. A competitive radioimmunoassay (RIA) was used to measure CSF-1 in the serum, as described by Stanley (26, 28). Results were expressed in units per milliliter, where 1 U is equal to 0.44 fmol of CSF-1 protein, approximately the amount of CSF-1 required to produce 1 colony in an agar culture containing 7.5×10^4 bone marrow cells (27, 29).

(iv) WEHI-3B D^+ differentiation assay for G-CSF. The ability to induce differentiation in WEHI-3B D^+ colonies is unique to G-CSF. Semisolid agar cultures containing 300 WEHI-3B D^+ cells and dilutions of serum were examined after 7 days with a dissection microscope. The percentage of differentiated colonies was scored as those with a characteristic dispersed appearance compared with the compact appearance of undifferentiated colonies (21). The units of differentiation-inducing activity were calculated by assigning 50 U to the midpoint of a standard titration curve and multiplying the dilution factor by 10 to obtain units per milliliter. This standard corresponds closely to the number of CFU per milliliter assayed in bone marrow culture.

(v) FD and 32D cell proliferation. The 32D-cl-3 mast cell line is uniquely dependent on multi-CSF for proliferation, whereas the FDC-P1 cell line responds to either multi-CSF or GM-CSF (7, 8, 14). Triplicate serial dilutions of serum starting at 1/5 were incubated with an equal volume of 200 FD or 32D cells in 10 μl of Dulbecco modified Eagle medium with 5% fetal calf serum in the wells of Terasaki microtest plates (Lux no. 5260; Miles Laboratories, Inc., Naperville, Ill.). After 2 days, cultures were scored microscopically for viable cells. CSF titers were compared by using the serum dilution which stimulated the survival and proliferation of 50 cells and were converted to the equivalent of bone marrow colony assay units by reference to a standard curve of purified recombinant bacterial IL-3 (multi-CSF), provided by J. DeLamarter (Biogen, Geneva, Switzerland).

RESULTS

Mice were infected intravenously with 10^4 *Listeria* cells. Serum was collected from groups of five mice at intervals after infection and subjected to a number of assays for colony-stimulating activity. Comparison of the growth of 10^4 *Listeria* cells in the spleen and liver of the two strains (Fig. 1) showed that there were already higher numbers of bacteria in the BALB/cJ mice by 24 h postinfection, and the difference increased markedly until all BALB/cJ mice were dead by day 4. Figure 2 shows the ability of the mouse sera to stimulate colony formation by bone marrow cells in semisolid agar and to stimulate the uptake of tritiated thymidine by bone marrow cells. These two assays of total colony-stimulating activity produced closely parallel results and emphasized the difference in response of the two mouse strains, the *L. monocytogenes*-resistant C57BL/10 mice and the susceptible BALB/cJ mice (for the latter, 10^4 organisms were a lethal dose). The BALB/cJ mice, in which bacterial

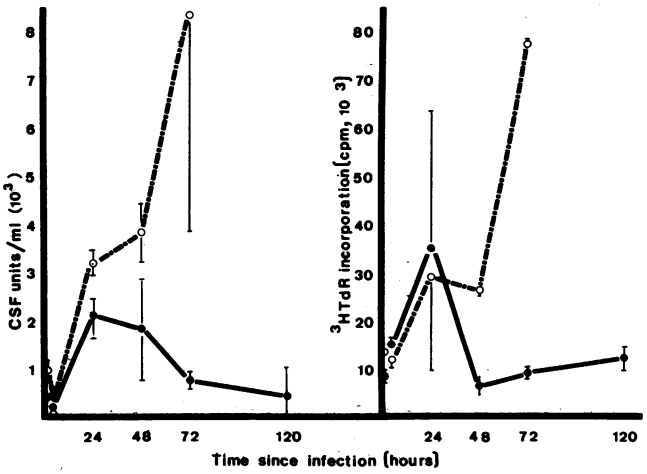

FIG. 2. Total colony-stimulating activity in serum samples of C57BL/10 (●) and BALB/cJ (○) mice (infected with 10^4 *Listeria* cells and bled at various times later) assayed as the ability to support colony growth and expressed as CSF units per milliliter (left); see Materials and Methods. Total colony-stimulating activity was assayed as the ability to support in vitro proliferation of bone marrow cells and expressed as maximum counts per minute of uptake of tritiated thymidine (right); see Materials and Methods. Each point represents the mean ± standard deviation of a group of five mice.

numbers reached such high levels, also showed very high titers of colony-stimulating activity compared with C57BL/10 mice.

Specific assays for particular CSFs were also performed, and the results are shown in Fig. 3 and Table 1. The predominant CSFs detected in the serum were M-CSF (CSF-1) and G-CSF (Fig. 3). In genetically resistant C57BL/10 mice, they reached a peak and then declined with the resolution of the infection. In the susceptible BALB/cJ mice, the levels continued to rise to a maximum at 3 days, just before the remaining mice died.

GM-CSF and multi-CSF were measured by their abilities to support proliferation, respectively, of the FD cell line or both FD and 32D cell lines (Table 1). There was no multi-CSF detectable, since the serum failed to support proliferation of 32D, so the proliferation of FD cells must have been due to GM-CSF. GM-CSF showed a modest rise in the C57BL/10 mice and a greater one in the BALB/cJ mice after mice were infected with 10^4 *Listeria* cells. Higher titers of GM-CSF were found in mice given 10^6 *Listeria* cells, but still no multi-CSF was detected. The mice died 2 to 3 days after this dose was given.

Table 2 summarizes the results of other assays on sera collected after a dose of 10^6 *Listeria* cells was given, which was lethal for both C57BL/10 and BALB/cJ mice. As might be expected after such a strong stimulus, there was a dramatic increase in colony-stimulating activity detected in all the assays.

The numbers of CFCs in the bone marrow of C57BL/10 and BALB/cJ mice after infection with 10^4 *Listeria* cells are shown in Fig. 4. Uninfected *L. monocytogenes*-resistant C57BL/10 mice had more CFCs in their bone marrow than did uninfected susceptible BALB/cJ mice. After infection with 10^4 *Listeria* cells, C57BL/10 mice showed a temporary dip in the number of CFCs in their bone marrow, but by day 3, the number of CFCs was twice the normal level. Thereafter, the number returned to normal. The number of CFCs in BALB/cJ mice dipped slightly after infection with 10^4 *Listeria* cells and only just exceeded normal levels by day 3, after which time the remaining mice died.

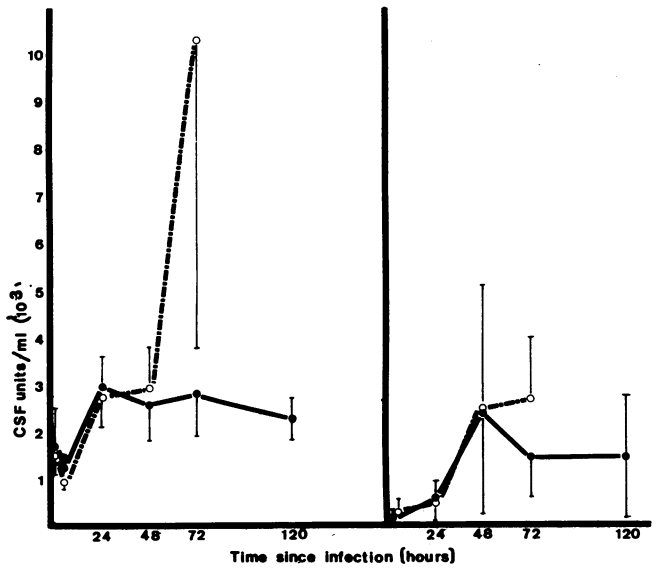

FIG. 3. M-CSF (left) and G-CSF (right) titers in serum of C57BL/10 (●) and BALB/cJ (○) mice infected with 10^4 *Listeria* cells and bled at various times later. M-CSF was assayed by RIA, and G-CSF was assayed by measuring the ability to support differentiation of WEHI-3B cells. Each point represents the mean ± standard deviation of a group of five mice.

TABLE 1. GM-CSF and multi-CSF in serum samples of mice infected intravenously with *Listeria* cells

Mouse strain	*L. monocytogenes* dose	Time postinfection (h)	Units/ml[a]: FD	32D
C57BL/10	Control	0	4.9	<1.3
	10^4	24	9.5	<1.3
		72	4.5	<1.3
	10^6	24	34.2	<1.3
BALB/cJ	Control	0	5.3	<2.5
	10^4	24	19.2	<1.3
		72	18.5	<2.5
	10^6	24	42.9	<2.5

[a] Ability of serum samples pooled from five mice per group to support survival and proliferation of FD or 32D cells was titrated in triplicate. FD cell proliferation was supported by either GM-CSF or multi-CSF, whereas 32D cell proliferation was supported by multi-CSF.

DISCUSSION

These experiments were undertaken to quantify the levels of particular CSFs in a systematic fashion after an experimental infection, one caused by *L. monocytogenes* in mice. The experiments show that levels of the total and individual CSFs in serum increased after infection. M-CSF, which supports the production of macrophages, and G-CSF, which supports granulocyte production, were the major CSFs detected in the serum, with a minor component of GM-CSF. Given the differences in their method of assay, it may or may not be significant that the rise in M-CSF preceded that in G-CSF. Multi-CSF was not detected, although as little as 1 U/ml (2×10^{-12} M) would have caused proliferation of the 32D or FD cells in this assay.

Large standard deviations noted at some time points reflected mouse-to-mouse variation, rather than variability in the assays themselves. In fact, where an individual mouse showed a high or a low titer of CSF by one assay (e.g., bone marrow colony formation) it was likely also to show the same trend in other assays (RIA for M-CSF or WEHI-3B D^+ differentiation for G-CSF). This variability was often seen when some of the mice were moribund or were at the turning point of resolution of their infection.

A high infecting dose of *Listeria* cells was required to induce rises in serum CSF. The concentration reached depended on the dose of *Listeria* cells administered, with 10^6 organisms inducing a greater rise in serum CSF than did 10^4. Fewer than 10^4 organisms were not effective. Nevertheless, a dose of 10^3 *Listeria* cells leads to an increase in the numbers of CFCs in the bone marrow and spleen (33), which might therefore be due to local production of CSFs in the tissues. We have confirmed the presence of M-CSF, which is known to be produced by fibroblasts and probably other cell types, in spleen, liver, lungs, and salivary glands as early as 24 h after *Listeria* infection (Cheers et al., unpublished observations). It seems likely that both multi- and GM-CSF could be produced by T lymphocytes at the site of infection (spleen and liver) once cell-mediated immunity is induced, at day 2 to 3 in resistant C57BL/10 mice and day 3 to 4 in susceptible BALB/cJ mice (5), since both these CSFs are known to be produced by T cells (15). Presumably, soluble products of the bacteria themselves, or products released

TABLE 2. Colony-stimulating activity in serum samples of mice infected intravenously with 10^6 *Listeria* cells

Mouse strain	Time postinfection (h)	Colony-stimulating activity (U/ml)[a]	Bone marrow cell proliferation (cpm/well)[a]	CSF-1 RIA (U/ml)[a]	G-CSF (U/ml)[a]
C57BL/10	0	450 ± 140	8,912 ± 1,321	1,723 ± 186	ND[b]
	4	190 ± 140	15,136 ± 352	1,896 ± 1,118	250 ± 190
	24	2,330 ± 12,930	128,824 ± 49,000	2,092 ± 5,442	7,990 ± 6,900
BALB/cJ	0	1,000 ± 210	13,804 ± 321	1,518 ± 339	ND
	4	420 ± 720	14,154 ± 329	815 ± 124	30 ± 60
	24	50,790 ± 28,210	194,984 ± 56,205	>32,000	17,600 ± 6,900

[a] Figures represent determinations from groups of five serum samples from individual mice ± standard deviation.
[b] ND, Not determined.

from the infected tissues by the action of the bacteria, induce production of CSF in distant tissues. One might speculate that IL-1, released by macrophages which have phagocytosed bacteria, could be such a messenger, since it has been shown to stimulate release of CSFs from various cell types in vitro (1, 11, 23, 24, 34).

When the two strains of mice studied, *L. monocytogenes*-resistant C57BL/10 and susceptible BALB/cJ, were given the same dose of *Listeria* cells, it was the BALB/cJ mice which produced higher levels of CSFs in the serum. We have shown previously, by measuring total serum CSF activity (33), that there is no early peak (before 24 h) in CSF production by the resistant C57BL/10 mice which would account for their greater resistance. If, instead of comparing the responses to the same doses of *Listeria* cells, one compares comparable 50% lethal doses (five times the 50% lethal dose for BALB/cJ is 10^4 *Listeria* cells, and for C57BL/10, it is 10^6 *Listeria* cells), the CSF concentration is similar for the two strains. Thus, comparing Fig. 2 with Table 2, we find that BALB/cJ mice given 10^4 *Listeria* cells have approximately 3,000 CSF U/ml at 24 h, whereas C57BL/10 mice given 10^6 *Listeria* cells have approximately 2,500 U/ml. It seems, therefore, that the level of CSF produced by the two strains reflects the numbers of *Listeria* cells in their spleens or livers at a particular time, and that the high response of BALB/cJ mice compared with C57BL/10 mice given the same dose reflects the high numbers of *Listeria* cells reached in the susceptible mice. There was no significant difference in their ability to respond to high numbers (10^{10}) of killed *Listeria* cells (results not shown), nor was there a difference between the two strains in the total serum colony-stimulating activity induced by *Brucella abortus* infection (C. Cheers and A. M. Young, Microb. Pathogen., in press) or in serum M-CSF levels induced by injection of lipopolysaccharide (Cheers et al., unpublished observations).

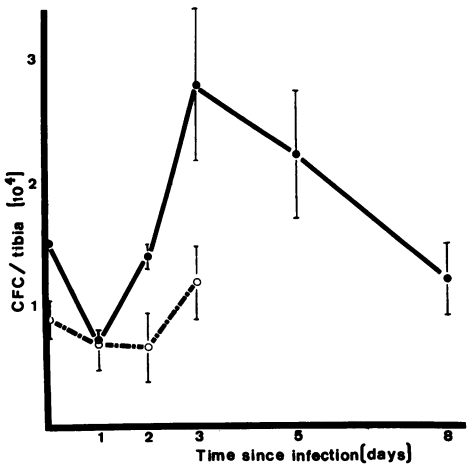

FIG. 4. CFCs in bone marrow of C57BL/10 (●) and BALB/cJ (○) mice infected with 10^4 *Listeria* cells at various times before assay. Marrow samples from two mice were pooled for each point and cultured in triplicate. Results are expressed as mean ± standard deviation of those triplicate samples.

In contrast to the CSF levels, the resistant C57BL/10 mice contained more CFCs in their bone marrow than did the BALB/cJ mice both before and after infection, confirming our previous results (33). Although C57BL/10 cells are more responsive to CSF than are BALB/cJ cells (18), this finding is unlikely to explain fully the difference in numbers of CFCs, since the numbers of cells in the bone marrow of uninfected C57BL/10 mice with receptors for CSF-1 (CSF-1-binding cells) (3) is also twice that in BALB/cJ mice (Cheers, unpublished observations). Therefore, it is likely that there is a true difference in the number of CFCs in the bone marrow, and it is of interest that the large excess in CSF production in BALB/cJ mice does not compensate for this difference during *Listeria* infection.

Although the production of CSFs apparently does not contribute to the greater resistance of the C57BL/10 mice, it could be considered to contribute to the immunopathology of infection in both strains. Splenomegaly is a major feature of *Listeria* infection, and macrophages are the major cell type invading the spleen. Such a contribution has also been shown in a murine brucellosis model where the degree of splenomegaly in different strains of mice correlates with the percentage of CFCs in the spleen (Cheers and Young, in press).

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