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Role of Granulocytes in Increased Host Resistance to *Candida albicans* Induced by Recombinant Interleukin-1

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The effect of human recombinant interleukin-1α (IL-1α) on a systemic candidal infection in mice under various conditions of immunosuppression was investigated. In normal mice and in mice pretreated with cyclophosphamide, hydrocortisone acetate, or sublethal total body irradiation, the outgrowth of *Candida albicans* in the kidney was significantly reduced by the administration of a single intraperitoneal dose of 80 ng of IL-1 ($P < 0.05$). In mice treated with either cyclophosphamide or irradiation, IL-1 also significantly reduced the outgrowth of *C. albicans* in the spleen. The protective effect of IL-1 was present when given 24 h before injection of *C. albicans* but also when IL-1 was given simultaneously with or 6 h after injection of *C. albicans* in cyclophosphamide-treated mice. The effect of IL-1 was independent of the presence or recruitment of granulocytes, since IL-1 inhibited the outgrowth of *C. albicans* in the kidneys and spleens of mice that were rendered severely granulocytopenic (<50 granulocytes per mm^3) throughout the duration of the infection by either repeated injections of cyclophosphamide or sublethal total body irradiation. These results indicate that the enhancement of host resistance by IL-1 is not due solely to increased granulocytopoiesis or chemotaxis of granulocytes but strongly suggest that other mechanisms play a role in the protective effect of IL-1 against systemic infections.

Patients with impaired host resistance are at risk for development of severe bacterial or fungal infections. These infections usually respond poorly to antimicrobial chemotherapy, and a cure is often achieved only after the host resistance has been restored (1, 11). Therefore, strategies have been sought to increase the host resistance to infections in these patients. Substances known to enhance host defense mechanisms, such as bacterial lipopolysaccharides, *Mycobacterium bovis* BCG, and muramyl peptides, appear to be able to stimulate mononuclear phagocytes to synthesize and secrete the cytokine interleukin-1 (IL-1) in vitro (16). It has been suggested that these immunomodulatory effects of such drugs are at least partly mediated by IL-1 (6, 7).

Evidence has been presented that intraperitoneal (i.p.) injection of purified recombinant human IL-1 protects mice from a lethal infection with *Pseudomonas aeruginosa* (17, 21), *Klebsiella pneumoniae* (17, 20), *Listeria monocytogenes* (4), or *Candida albicans* (18, 25) and from the lethal effects of *Escherichia coli* endotoxin (20). The mechanism responsible for the protective effect of IL-1 against death from systemic infections in these animals is not known, but some authors have suggested that the main role of IL-1 is to enhance the production of granulocytes, their release from the bone marrow, and the subsequent migration of the site of infection (3, 5, 13).

The present study was performed to evaluate further the role of granulocytes in human recombinant IL-1α-mediated protection against infections. For that purpose, the effect of IL-1 on a systemic infection with *C. albicans* was studied in mice treated with cyclophosphamide, hydrocortisone acetate, or sublethal total-body irradiation. We also investigated whether the protective effect of IL-1 was dependent on the number of microorganisms injected or the treatment schedule of IL-1.

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MATERIALS AND METHODS

Mice. Specific pathogen-free female Swiss Webster mice weighing 25 to 30 g (Broekman Institute, Someren, The Netherlands) were kept in cages and fed standard lab chow and water ad libitum.

Treatment regimens. (i) Cyclophosphamide. Mice were rendered granulocytopenic by two subcutaneous (s.c.) injections of cyclophosphamide (Astra Pharmaceutica BV, Rijswijk, The Netherlands): 150 mg/kg of body weight in 200 μl of phosphate-buffered saline 4 days before injection of *C. albicans* and 100 mg/kg 1 day before injection of *C. albicans* (24). In several experiments, an additional dose of 100 mg of cyclophosphamide per kg was administered 1 day after the injection of *C. albicans* to ensure persisting granulocytopenia.

(ii) Hydrocortisone. Hydrocortisone acetate (Organon NV, Oss, The Netherlands) was administered s.c. at 100 mg/kg of body weight 2 days before injection of *C. albicans*.

(iii) Irradiation. Mice were placed in plexiglass containers and were given total-body irradiation with 5-MV X rays with a Philips SL-75 linear accelerator at a dose of 8 Gy, as described in detail elsewhere (24).

IL-1. Recombinant human IL-1α, which contained less than 20 pg of endotoxin per mg of protein, was a generous gift from Peter Lomedico (Hoffman-LaRoche Inc., Nutley, N.J.). The IL-1 was given as a single i.p. injection of 80 ng of IL-1 in 2% (vol/vol) newborn calf serum (GIBCO Ltd., Paisley, Scotland) in 200 μl of pyrogen-free saline 24 h before the injection of microorganisms. Control mice received 200 μl of pyrogen-free saline with 2% newborn calf serum i.p.

C. albicans. *C. albicans* UC820, maintained on agar slants at 4°C, was inoculated into 100 ml of Sabouraud broth and cultured for 24 h at 37°C. After three washes with pyrogen-free saline by centrifugation at 1,500 × *g*, the yeast cells were counted in a hemocytometer and the suspension was diluted to the appropriate concentration with pyrogen-free

TABLE 1. Outgrowth of *C. albicans* in the kidney and spleen after i.v. injection of various numbers of *C. albicans* into mice injected with saline i.p. (control mice) and mice injected with 80 ng of IL-1 i.p. on day −1

Treatment of mice	No. of CFU injected	Time (h) after injection	Log CFU/g[a] in:			
			Kidneys of:		Spleens of:	
			Control mice	IL-1-treated mice	Control mice	IL-1-treated mice
None	10^4	24	4.22 ± 0.24	3.45 ± 0.61	2.51 ± 0.15	2.34 ± 0.22
	10^5	24	4.67 ± 0.24	4.16 ± 0.53	4.12 ± 0.60	3.96 ± 0.37
	10^6	24	5.63 ± 0.58	4.62 ± 0.21	4.69 ± 0.47	4.91 ± 0.51
Cyclophosphamide[b]	10^3	24	4.77 ± 0.16	2.48 ± 0.29	2.93 ± 0.78	2.40 ± 0.26
	10^4	24	5.48 ± 0.43	4.73 ± 0.45	3.98 ± 0.63	3.46 ± 0.79
	10^5	1	3.40 ± 0.53	3.46 ± 0.63	3.37 ± 0.33	3.34 ± 0.45
		4	2.96 ± 0.41	3.46 ± 0.25	2.91 ± 0.26	3.39 ± 0.15
		24	6.08 ± 0.19	4.65 ± 0.57	4.47 ± 0.41	3.95 ± 0.49
Hydrocortisone acetate[c]	10^3	24	4.31 ± 0.37	3.75 ± 0.73	2.78 ± 0.24	2.80 ± 0.42
	10^4	24	5.09 ± 0.12	4.02 ± 0.77	3.47 ± 0.08	3.21 ± 0.49
	10^5	24	6.11 ± 0.38	5.39 ± 0.94	4.56 ± 0.12	4.45 ± 0.19
Irradiation[d]	5×10^3	24	5.31 ± 0.41	4.71 ± 0.27	4.57 ± 0.30	4.00 ± 0.48

[a] Numbers represent the means ± standard deviations for 3 to 6 animals.
[b] 150 mg/kg s.c. 4 days before infection and 100 mg/kg 1 day before infection.
[c] 100 mg/kg s.c. 2 days before infection.
[d] Total-body irradiation totalling 8 Gy 5 days before infection.

saline. Viability was confirmed by plating serial dilutions on Sabouraud dextrose agar plates.

Infection model. Mice treated with cyclophosphamide, hydrocortisone, or irradiation and mice given no immunomodulatory treatment (henceforth to be called normal mice) were randomized to receive various numbers of *C. albicans* CFU in 200 μl of phosphate-buffered saline injected intravenously (i.v.) into the lateral tail vein. At different time points after infection, animals were killed by CO_2 asphyxia. Under sterile conditions, organs were removed, trimmed of adventitious tissue, weighed, and homogenized in sterile phosphate-buffered saline in a Potter-Elvejhem glass tissue grinder. Serial 10-fold dilutions of these homogenates were prepared in phosphate-buffered saline, and samples (0.1 ml) of appropriate dilutions were plated in duplicate on Sabouraud dextrose agar plates. After overnight incubation at 37°C, the CFU were counted, and the result was expressed as the log CFU per gram of tissue.

Blood leukocyte counts. Blood samples (20 μl) taken from the retroorbital plexus were collected in plastic cups containing 40 μl of heparin (400 U/ml). The leukocytes were counted in a Coulter counter (model ZF, Coulter Electronics Ltd., Luton, England). The total numbers of granulocytes, lymphocytes, and monocytes per cubic millimeter were calculated from the total number of leukocytes per cubic millimeter and differential counts of 400 leukocytes in two Giemsa-stained blood smears.

Statistical analysis. The results obtained for the various treatment groups were analyzed for statistical significance by analysis of variance. Comparisons between peripheral blood counts were made by two-tailed Student *t* tests. For all comparisons, the level of significance between groups was set at $P < 0.05$.

RESULTS

Effect of IL-1α in a 1-day infection model. In normal mice, the number of *C. albicans* CFU cultured from the kidney (Table 1), spleen (Table 1), and liver (data not shown) after 24 h was dependent on the number of *C. albicans* CFU injected. Irrespective of the number of *C. albicans* CFU injected, the number cultured from the kidneys was significantly lower in IL-1-treated mice than in mice not treated with IL-1 (control mice) ($P < 0.05$). A similar reduction in the number of CFU after treatment with IL-1 was seen in the liver (data not shown). For the spleen, the difference between IL-1 treated mice and controls was not significant (Table 1).

In mice pretreated with either cyclophosphamide or hydrocortisone acetate, the number of *C. albicans* CFU cultured from the kidneys, spleen (Table 1), and liver (data not shown) 24 h after injection was significantly higher than in normal mice given the same number of *Candida* CFU ($P < 0.05$). In mice pretreated with cyclophosphamide, the number of *C. albicans* CFU cultured from the kidneys, spleens, and livers of IL-1-treated mice was significantly lower than that in control mice ($P < 0.01$).

The effect of IL-1 on the number of *C. albicans* CFU cultured from the kidneys of mice treated with hydrocortisone acetate, although statistically significant ($P < 0.025$), was lower than that in cyclophosphamide-treated mice. For the spleens of hydrocortisone-treated mice, the differences between IL-1-treated mice and controls were not significant (Table 1).

In mice that had been rendered profoundly pancytopenic by irradiation, IL-1 also significantly inhibited outgrowth of yeast cells in the kidneys and the spleen 24 h after injection of 5×10^3 CFU of *C. albicans* (Table 1; $P < 0.05$).

To investigate whether the reduced number of *C. albicans* CFU found in the kidneys and spleen after pretreatment with IL-1 was due to a difference in distribution during the early phase of candidemia, we studied the initial course of the infection in a separate experiment. Mice were pretreated with cyclophosphamide and received 10^5 CFU of *C. albicans* i.v. The number of *Candida* CFU in the kidneys and spleen at 1 and 4 h after injection of 10^5 CFU was similar in control

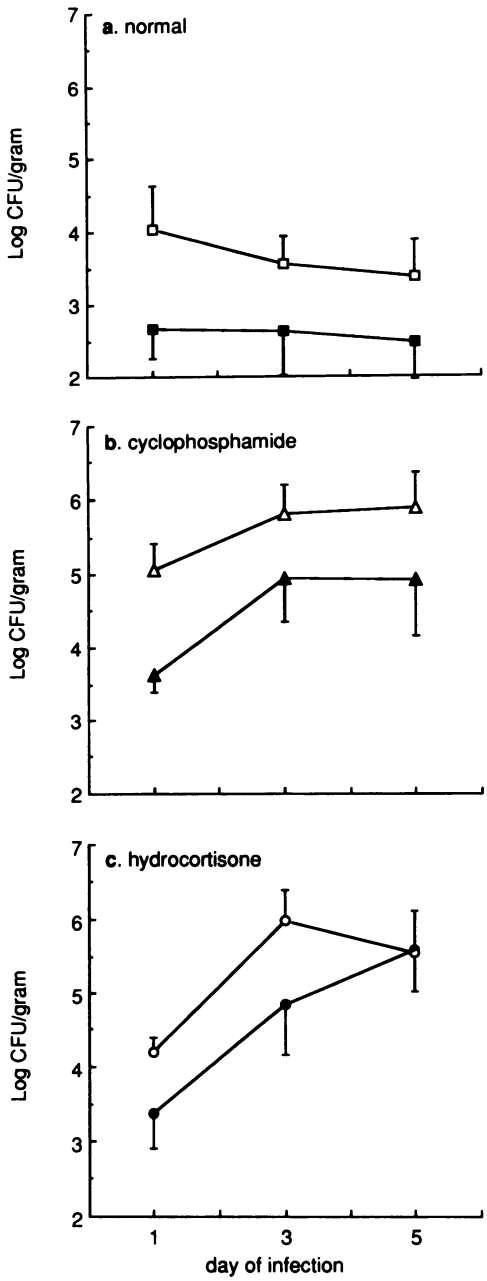

FIG. 1. Outgrowth of *C. albicans* in the kidney after i.v. injection of 5×10^3 CFU of *C. albicans* into normal mice (a) and into mice treated with cyclophosphamide (b) or hydrocortisone acetate (c). Closed symbols represent mice pretreated with 80 ng of IL-1 i.p. on day −1; open symbols refer to control mice injected i.p. with saline on day −1. Each point represents the mean ± standard deviation for five animals.

mice and mice given a single i.p. dose of IL-1α 24 h earlier (Table 1). These results suggest that the differences found between IL-1-treated and control mice were not due to differences in organ distribution early in the course of infection but to a difference in the rate of outgrowth after the infection had been established.

Effect of IL-1α in a 5-day infection model. Mice were killed on various days after i.v. injection of 5×10^3 *C. albicans* CFU. For normal mice, the number of *C. albicans* CFU cultured from the kidneys of IL-1-treated animals was more than 10-fold lower than the number cultured from control mice during the entire experiment ($P < 0.05$; Fig. 1a). In the spleen, the difference between IL-1-treated and control mice was significant only on day 1 (data not shown).

Mice treated with cyclophosphamide received a third dose (100 mg/kg) 24 h after the injection of *C. albicans* to ensure persistence of granulocytopenia throughout the experiment. In these mice, the number of CFU in the kidneys ($P < 0.025$; Fig. 1b) and the spleen ($P < 0.05$; data not shown) was significantly lower in IL-1-treated mice than in control mice during the entire experiment. In mice pretreated with hydrocortisone acetate, the difference in the number of CFU between the IL-1-treated group and the control group was significant on days 1 and 3 ($P < 0.05$) but not on day 5 of the infection (Fig. 1c). For the spleens of hydrocortisone-treated mice, the difference between IL-1-treated mice and controls was significant only on day 1 ($P < 0.05$).

The weights of the kidneys and spleens were not influenced by treatment with IL-1 in any of the experiments. Therefore, the results were not influenced when the data were expressed as the number of microorganisms per organ rather than per gram of tissue.

Effect of IL-1α on the number of peripheral blood cells. Before injection of *C. albicans* into normal mice, the number of granulocytes was 1,718 ± 353/mm^3 in control mice and 2,461 ± 510/mm^3 in mice given IL-1 1 day earlier ($P > 0.05$). The course of the number of peripheral blood granulocytes during 5 days of *C. albicans* infection in IL-1-treated mice did not differ significantly from the course in control mice (Fig. 2a). In cyclophosphamide-treated mice, granulocyte numbers remained below 500/mm^3 until 3 days after injection of *C. albicans* in both controls and IL-1-treated animals (Fig. 2b). On day 5, the number of granulocytes increased to 1,329 ± 1,649/mm^3 in control mice and to 820 ± 367/mm^3 in IL-1-treated mice ($P > 0.05$). The number of granulocytes of cyclophosphamide-treated mice was significantly lower than that observed in normal mice throughout the experiment. After pretreatment with hydrocortisone acetate, the number of peripheral granulocytes before infection was higher than that in normal mice ($P < 0.01$). The different in granulocyte counts between IL-1-treated and control mice was not significant at any of the days of the experiment (Fig. 2c). Irradiation of mice with 8 Gy 5 days before injection of *C. albicans* caused severe granulocytopenia. Peripheral blood granulocytes numbered 48 ± 62/mm^3 on the day of injection of *C. albicans* and 13 ± 23/mm^3 24 h after injection in control mice. In IL-1-treated mice, granulocytes numbered 43 ± 38/mm^3 before infection and 0 ± 0/mm^3 24 h after injection of *C. albicans*. The differences between IL-1-treated and control mice were not significant.

In normal mice, the number of lymphocytes before injection of *C. albicans* was 8,496 ± 806/mm^3 in control mice and 7,527 ± 1,020/mm^3 in mice given IL-1 ($P > 0.05$). Lymphopenia was found at the moment of injection of *C. albicans* in mice pretreated with cyclophosphamide (4,085 ± 623/mm^3), hydrocortisone acetate (2,132 ± 954/mm^3), or whole-body irradiation (237 ± 99/mm^3). Mice pretreated with hydrocortisone acetate showed a significant rise in the number of lymphocytes on day 5 of the infection (3,915 ± 972; $P < 0.05$). In the other treatment groups, the number of lymphocytes did not change significantly during the infection. The differences between IL-1-treated and control mice were not significant.

The number of peripheral blood monocytes was below 250/mm^3 at the moment of injection of *C. albicans* into mice

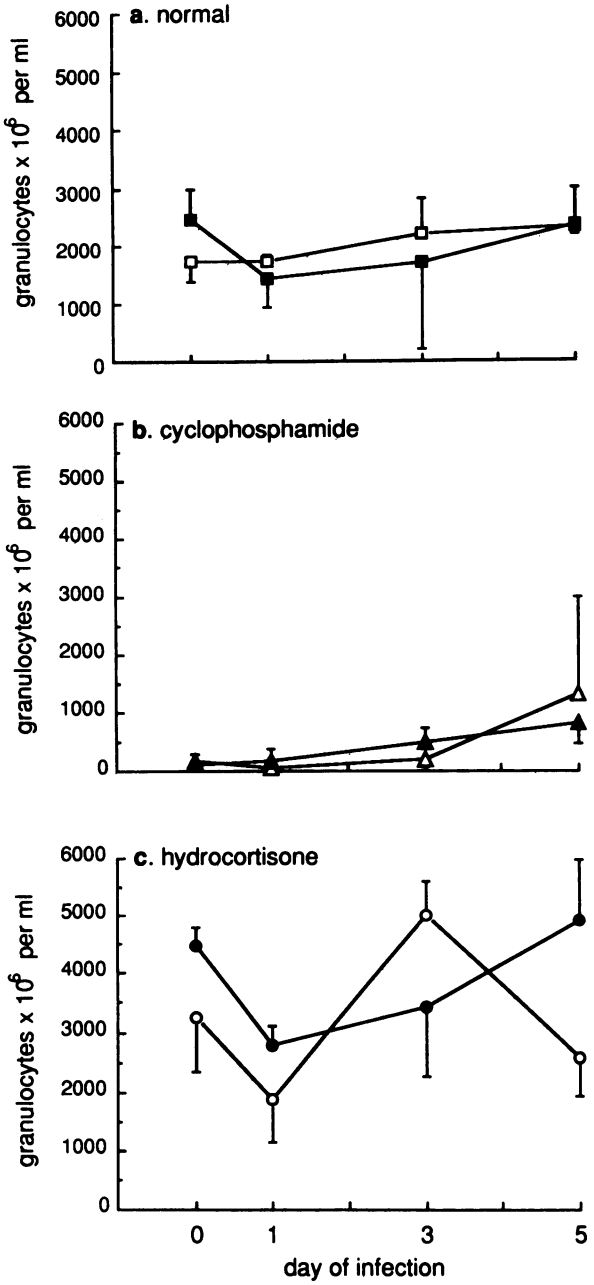

FIG. 2. Number of peripheral blood granulocytes just before and 1, 3, and 5 days after injection of *C. albicans* into normal mice (a) and into mice treated with cyclophosphamide (b) or hydrocortisone acetate (c). Closed symbols represent mice pretreated with 80 ng of IL-1 i.p. on day −1; open symbols refer to control mice injected i.p. with saline on day −1. Each point represents the mean ± standard deviation for three animals.

pretreated with either cyclophosphamide or hydrocortisone acetate. In cyclophosphamide-treated mice, an increase in the number of monocytes was found on day 5 both in controls and in IL-1-treated mice ($P > 0.05$). In irradiated mice, the number of monocytes remained virtually nil. Significant differences in the numbers of peripheral blood monocytes between IL-1-treated mice and controls were not found in any of the treatment groups.

Effect of different dosage regimens of IL-1α. The efficacy of IL-1 given at different time points in relation to the moment of injection of *C. albicans* and the effects of repeated administration of IL-1 were investigated in mice rendered granulocytopenic by three doses of cyclophosphamide. The protective effect of IL-1 on the number of *C. albicans* CFU at 72 h after injection was similar whether IL-1 was given as a single i.p. dose of 80 ng 24 h before, 5 min before, or 6 h after injection of *C. albicans*. The effect of IL-1 given 12 h after injection of *C. albicans* was not significant. Repeated i.p. administration of 80 ng of IL-1 at 24 or 48 h after the initial administration did not enhance the effect of the single-dose regimen (data not shown).

DISCUSSION

The results of this study show that a single injection of recombinant human IL-1α significantly decreases the number of *C. albicans* CFU in the kidneys and spleens of normal mice and of mice treated with cyclophosphamide, hydrocortisone acetate, or irradiation. No correlation was found between the numbers of peripheral blood cells and the effect of IL-1, and even during complete agranulocytosis after total-body irradiation, the outgrowth of *C. albicans* was reduced by IL-1. IL-1 was effective even when given as late as 6 h after the injection of *C. albicans*.

In an earlier study, no difference was found between the numbers of *C. albicans* CFU cultured from the organs of IL-1-treated and control mice, although IL-1 significantly improved survival (25). These data were in agreement with the findings for *P. aeruginosa* (21) and *K. pneumoniae* (20). In the present study, however, IL-1 caused a decrease in the outgrowth of *C. albicans* in the kidneys, liver, and spleen, as reported earlier for *L. monocytogenes* (4, 12) and *Staphylococcus aureus* (9). We have no explanation for the discrepancy between the present results and our earlier finding (25).

The precise mechanism by which IL-1 enhances resistance to infection remains obscure. In an earlier study, a direct anticandidal effect of IL-1 in vitro could not be demonstrated (25). The beneficial effects of IL-1 in *C. albicans* infection suggest that the mode of action cannot be induction of an endotoxin-binding protein, as suggested by studies with gram-negative bacteria (21). In view of the duration of the protective effect after a single dose of IL-1 and the short half-life of IL-1 (22), it is conceivable that the effect of IL-1 is mediated through other cytokines. Although IL-1 is a potent inducer of IL-6 synthesis in vivo, the administration of IL-6 in granulocytopenic mice gave hardly any protective effect (22). Another possibility is that the early administration of IL-1 induces a down regulation of the receptors for IL-1 and tumor necrosis factor (10) that eventually attenuates the unfavorable effects of IL-1 (15) and tumor necrosis factor (19) during a subsequent severe systemic infection. Although this mechanism might explain the prolonged survival of mice with disseminated candidiasis caused by IL-1, this hypothesis does not explain the effect of IL-1 on the outgrowth of *C. albicans* in the kidney and spleen.

The role of monocytes and macrophages in the resistance to *C. albicans* infections is probably limited (2, 23). However, recently it has been shown that IL-1α inhibits the outgrowth of *C. albicans* in blood monocytes and alveolar macrophages in vitro (26). In a limited number of experiments, we were unable to show enhanced intracellular killing of *C. albicans* by peritoneal macrophages of mice treated with IL-1 in vivo (unpublished data). Earlier, it has been shown that IL-1 does not have an effect on superoxide production by peritoneal macrophages (21).

Since IL-1 is an inducer of granulocyte-macrophage colony formation in bone marrow (8), several authors have suggested that the protective effect of IL-1 on the course of disseminated infections in normal mice is due to an increase in the number of granulocytes (4, 5) and to earlier recovery of the number of granulocytes in granulocytopenic mice (13, 14). In some of these studies, however, the rapid recovery of the bone marrow in IL-1-treated mice can be attributed to moderate granulocytopenia in these animals (14). McIntyre et al. showed that repeated injections of IL-1 cause a significant granulocytosis after prior myelosuppression caused by a single moderate dose of cyclophosphamide (13). Mice treated in this way had already recovered from granulocytopenia before the injection of microorganisms and showed better survival after subsequent infection with *S. aureus* or *K. pneumoniae* than did control mice which were still granulocytopenic when the microorganisms were injected (13). Although the results of such experiments suggest a causal relationship among the administration of IL-1, the number of granulocytes, and resistance to infections, they do not preclude an effect of IL-1 in the absence of granulocytes. In our study, we prevented bone marrow recovery both before and after injection of the microorganisms by repeated administration of cyclophosphamide or by total-body irradiation with a sublethal dose, both of which have been shown to prevent bone marrow recovery (24). In the present study, IL-1 enhanced resistance to *C. albicans* even in severely granulocytopenic mice with a peripheral blood granulocyte count of less than 50/mm^3 throughout the course of the infection. Similar findings have been reported for granulocytopenic mice infected with *S. aureus*, which showed no influence of IL-1 on peripheral blood cell counts, whereas IL-1-treated mice showed both reduced mortality and a reduction of the number of microorganisms in the liver (9). Likewise, IL-1 protected nongranulocytopenic mice against a sublethal challenge with *L. monocytogenes* even though no colony-stimulating activity of IL-1 was demonstrable (12).

One point to be considered is whether in our study IL-1 led to a migration of inflammatory cells to the site of infection (i.e., the kidneys, the liver, and the spleen) without causing a detectable increase in the number of peripheral blood cells. However, histologic examination of the kidneys and livers at 1 and 5 days after injection of *C. albicans* did not show any differences in the numbers of granulocytes at the foci of infection between IL-1-treated mice and controls. In another series of experiments with granulocytopenic mice, we showed that the migration of granulocytes and monocytes to the site of an acute inflammation was not stimulated by IL-1 (unpublished data).

In previous studies of bacterial infections in granulocytopenic mice, it proved necessary to administer the IL-1 at least 24 h before injection of the microorganisms (4, 14, 21), which would make therapeutic application of IL-1 unavailing. In disseminated *C. albicans* infections, IL-1 is effective when given as late as 6 h after injection, even in granulocytopenic mice, probably because of the relatively slow course of disseminated candidiasis compared with the rapid progression of gram-negative bacteremia. This finding holds promise in that the application of IL-1 might influence candidal infections in patients with severe granulocytopenia. Because fever can be expected to be a serious side effect of IL-1, the finding that cyclooxygenase inhibitors do not influence the protective properties of IL-1 could be important for future clinical use. In addition to earlier studies which showed that the administration of a single dose of ibuprofen did not abrogate the protective effect of IL-1 (20, 21), we administered the cyclooxygenase inhibitor diclofenac (2.5 mg/kg s.c.) at 12-h intervals, starting 12 h before the administration of IL-1. This treatment did not influence the beneficial effect of IL-1 on the number of CFU in the kidneys and spleen at 24 h after injection with 10^4 CFU of *C. albicans* in cyclophosphamide-treated or hydrocortisone-treated mice (data not shown).

The present study has shown that a single injection of recombinant human IL-1α enhances host resistance to systemic *C. albicans* infection in severely granulocytopenic mice. The results of our experiments do not support the hypothesis that the enhancement of host resistance by IL-1 may be due mainly to increased granulopoiesis or chemotaxis of granulocytes but do strongly suggest that other mechanisms play a role in the protective effect of IL-1 in systemic infections.

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