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Interleukin-1 Is Involved in Mouse Resistance to *Mycobacterium avium*

MICHEL DENIS[1]* AND ESFANDIAR GHADIRIAN[2]

Pulmonary Research Unit, Faculty of Medicine, University of Sherbrooke, Sherbrooke, Quebec J1H 5N4,[1] and Montreal General Hospital Research Institute, Montreal, Quebec H3G 1A4,[2] Canada

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In this study, we examined the contribution of the monokine interleukin-1 (IL-1) in mouse resistance to the intracellular pathogen *Mycobacterium avium*. The effect of neutralizing endogenous IL-1 in mouse macrophage resistance to *M. avium* infection was investigated. Infection of mouse peritoneal macrophages with *M. avium* B101 was shown to result in significant IL-1β release by cells at 4 and 7 days postinfection. Addition of IL-1 receptor antagonist (IL-1ra) at doses of 5 μg daily, which neutralized endogenous IL-1, failed to significantly modify the intracellular growth of *M. avium*. Mice were injected with *M. avium* B101 by the intravenous route, and the growth of the mycobacteria was monitored in the organs of intact mice and in those of mice that received repeated high doses of IL-1ra. The infection with *M. avium* elicited the production of large amounts of IL-1 in the lungs, livers, and spleens. Repeated injections of IL-1ra into *M. avium*-infected mice resulted in moderately enhanced growth of the bacilli in the livers and spleens but in much enhanced growth in the lungs. The enhanced growth of *M. avium* in the lungs correlated with a diminished inflammatory influx of cells (particularly neutrophils) in the bronchoalveolar space. These data argue for a role for IL-1 in host resistance to *M. avium* infections.

Mycobacterium avium is an important intracellular pathogen which infects immunosuppressed subjects, such as AIDS patients (27); it is a ubiquitous, opportunistic pathogen which rarely infects normal subjects, and normal host resistance mechanisms appear sufficient to prevent infection with this pathogen (27). *M. avium* in vivo mainly infects cells of the phagocyte series, such as macrophages (5, 7). There is a large variation in the virulence of the different strains, with transparent colonies being more virulent and opaque colonies being less so (7). Infections with *M. avium* in immunosuppressed individuals progress despite evidence of macrophage activation, and the actual mechanisms of host resistance remain unclear (5, 23).

Interleukin-1 (IL-1) is an important host defense cytokine secreted mostly by macrophages and monocytes (3, 12, 13). IL-1 has a number of proinflammatory effects, which include activation of T lymphocytes and neutrophils and induction of monokine production (including IL-6 and/or IL-8) by macrophages (12, 13 [and references therein]). Phagocytosis of *M. avium* or exposure to mycobacterial components leads to the copious release of IL-1 by macrophages (26). Recent data show a role for IL-1 in host resistance to a number of pathogens, including *Listeria monocytogenes*, *Salmonella typhimurium*, and *Pneumocystis carinii*, although the exact mechanism involved was not clarified (4, 19, 21).

Our objective in this report was to investigate the contribution of IL-1 in mouse resistance to infections with *M. avium*. To this end, we made use of a recently described IL-1 receptor antagonist (IL-1ra), which neutralizes the action of IL-1 in vivo and in vitro (1, 2, 9).

* Corresponding author. Mailing address: Pulmonary Research Unit, Faculty of Medicine, University of Sherbrooke, 3001 12th Ave. North, Sherbrooke, Quebec, Canada J1H 5N4. Phone: (819) 564-5223. Fax: (819) 564-5377.

MATERIALS AND METHODS

Mice. Female BALB/c mice, weighing 18 to 20 g, were obtained from Charles River Inc. (St. Constant, Quebec, Canada). Mice were given Purina Chow and acidified tap water ad libitum.

Bacteria. A clinical strain of *M. avium* B101 (serovar 4) was isolated from the blood of an AIDS patient. This strain formed smooth transparent colonies on 7H11 agar (Difco, Detroit, Mich.) (10). The strain was routinely grown in Dubos liquid medium (Difco).

Infections. Mice were infected with 10^6 CFU of *M. avium* B101 by the intravenous route. Groups of mice received intraperitoneal infusions of phosphate-buffered saline (PBS) with 1% bovine serum albumin or 25 mg of IL-1ra in PBS-bovine serum albumin per kg twice a day beginning at day 0 for the duration of the experiments. The IL-1ra was a kind gift of Synergen Inc. (Boulder, Colo.). The material contained less than 25 pg of endotoxin per mg. The amounts of antagonist used were based on the literature (particularly, references 1 and 18, which presented data in mice) as well as on the amounts of IL-1 in the organs of *M. avium*-infected mice (see Fig. 1). At indicated intervals, mice were killed, and serial decimal dilutions of organ homogenates (obtained after 45 s of griding with mortar and pestle) were plated on 7H11 agar; colonies were counted after 21 days of incubation.

Organ homogenates. Organs were homogenized in 5 ml of PBS containing 0.01% 3-[(3-cholamidopropyl)-dimethyl-ammonio]-1-propanesulfonate (CHAPS; Sigma, St. Louis, Mo.) and 10 U of aprotinin per ml. Homogenates were centrifuged, and the supernatants were frozen at −70°C prior to cytokine analysis.

Macrophage-*M. avium* interaction. The interaction between mouse peritoneal macrophages and *M. avium* was assessed as described in detail elsewhere (11). Briefly, resident peritoneal macrophages, obtained by peritoneal lavage, were plated at 10^6 cells per well in 24-well plates in Neuman-Tytell medium supplemented with 2 mM glutamine and 20 mM HEPES (*N*-2-hydroxyethylpiperazine-*N′*-2-ethanesulfonic

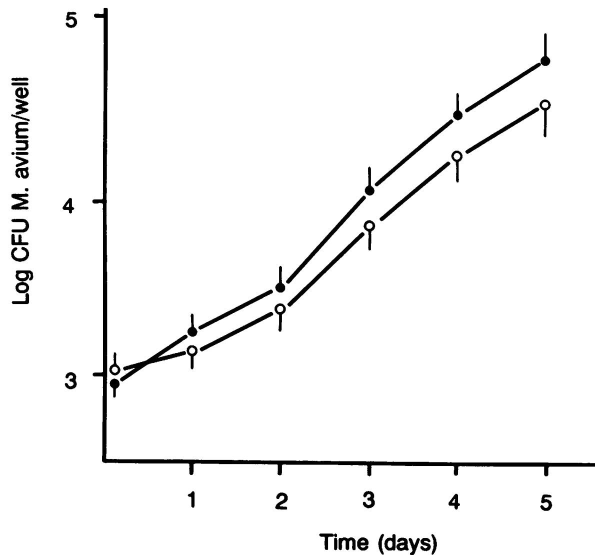

FIG. 1. Growth of *M. avium* in resident peritoneal macrophages from BALB/c mice. Macrophages infected with *M. avium* B101 were left untreated (○) or were treated daily with 5 μg of IL-1ra per ml (●). Each point is the mean ± SEM of six wells.

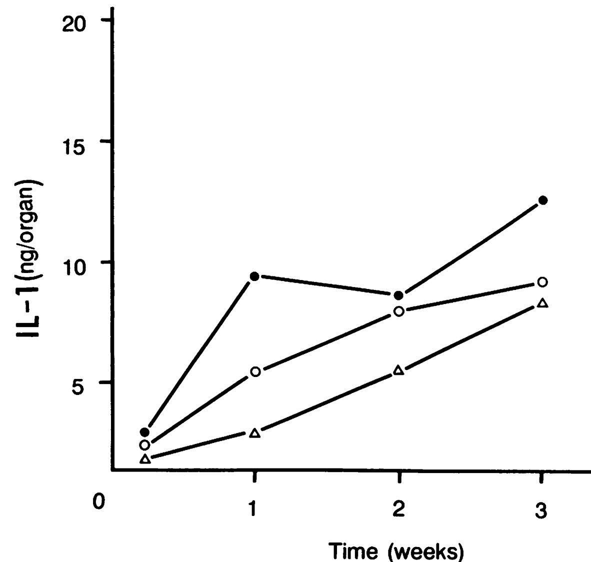

FIG. 2. IL-1 in organs of mice infected with *M. avium* B101. Mice were infected with 10^5 CFU of *M. avium*, and levels of antigenic IL-1 in the spleens (△), liver (○), and lungs (●) were assessed. Each point represents the mean of five mice. SEMs are omitted for clarity; they did not exceed 10% of the means.

acid; GIBCO, Grand Island, N.Y.). After phagocytosis, cells were washed extensively to remove extracellular bacilli. Growth of the bacilli was assessed by plating serial dilutions of cell lysates on agar at indicated intervals, as described in detail elsewhere (11). In this system, extracellular growth was always less than 10% of the amounts in infected cells (11).

IL-1 measurement. IL-1β and IL-1α levels were measured by enzyme-linked immunosorbent assay (ELISA), using a Genzyme immunoassay kit (Genzyme, Boston, Mass.). The sensitivity of the assay was approximately 25 pg/ml. In selected experiments, IL-1 levels were measured in a mouse thymocyte comitogenesis assay (4). Briefly, 5×10^5 thymocytes from young C3H/HeJ mice were aliquoted into each well of a 96-well microtiter plate in RPMI 1640 medium with 10% fetal calf serum (GIBCO) supplemented with 5 μg of phytohemagglutinin (Sigma) per ml or not supplemented, and dilutions of samples were added. After a 72-h incubation, cell growth was determined by measurement of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; thyazol blue] reduction and levels of bioactive IL-1 derived from a recombinant IL-1β (Genzyme) standard curve. More than 95% of the bioactivity was neutralized with a rabbit polyclonal anti-mouse IL-1β. The sensitivity of this bioassay was 150 pg/ml.

Bronchoalveolar lavage. Cannulas were inserted into the tracheae of mice, and airways were lavaged with three 1-ml portions of PBS. Cells were pelleted, counted with trypan blue, and stained with Diff-Quik (Baxter, McGaw Park, Ill.) for cell differentiation.

RESULTS

Neutralization of IL-1 activity by IL-1ra. In a first set of experiments, we tested the IL-1 neutralizing activity of IL-1ra in a mouse thymocyte comitogenesis assay. Addition of 100 μg of IL-1ra per ml was effective in neutralizing 10^6 U (5 to 10 μg) of mouse recombinant IL-1β (data not shown).

Neutralizing IL-1 in macrophage-*M. avium* interaction. Next, we examined the effect of neutralizing IL-1 in macrophage-*M. avium* interaction. As shown in Fig. 1, blocking endogenous IL-1 did not significantly modify the growth kinetics of *M. avium* B101 in mouse peritoneal macrophages. Infection of mouse macrophage monolayers with *M. avium* B101 led to an increase of 2.0 $\log_{10}$ CFU over a 7-day incubation period (Fig. 1). Supernatants were sampled at days 0, 4, and 7 after infection (media were not changed during this period), and levels of IL-1 were assessed by ELISA for IL-1β. At day 0, macrophage supernatants contained 85 ± 32 pg of IL-1β per ml (mean ± standard error of the mean [SEM] of five samples); at day 4, they contained 475 ± 116 pg/ml, and at day 7, they contained 872 ± 213 pg/ml. Very low levels of IL-1α were present in these supernatants. To assess the role of endogenous IL-1 in this *M. avium*-macrophage interaction, 5 μg of IL-1ra per ml was added daily and *M. avium* growth was monitored. To ensure that this quantity of IL-1ra was neutralizing the IL-1 released, daily aliquots of supernatants were obtained and processed in an IL-1 bioassay (see Materials and Methods); no bioactive IL-1 was detected in the supernatants at days 0, 4, and 7 in infected macrophages treated with IL-1ra, whereas untreated macrophages that phagocytosed *M. avium* contained high levels of bioactive IL-1 (data not shown).

IL-1 synthesis in organs of *M. avium*-infected mice. Next, we examined the synthesis of IL-1 in various organs of mice infected with *M. avium* B101 (Fig. 2). Total IL-1 was quantified by using an ELISA procedure with antibodies against both IL-1α and IL-1β. Uninfected mice had very low levels of IL-1 in spleen, liver, and lungs (less than 0.1 ng per organ). Infection with *M. avium* resulted in the presence of elevated levels of IL-1 in the spleen, lungs, and liver, with approximately 10 ng per organ at 3 weeks postinfection (Fig. 2). In pilot experiments, 10 ng of recombinant IL-1β was mixed with 5 ml of lung homogenates from uninfected mice, and IL-1 levels were assessed; levels of 1.7 to 2.1 ng/ml were measured (in four separate experiments), indicating a successful recovery.

Neutralization of IL-1 in vivo in murine *M. avium* infections. The effect of neutralizing IL-1 in mouse *M. avium* infections was investigated (Fig. 3). Infusion of IL-1ra in *M. avium*

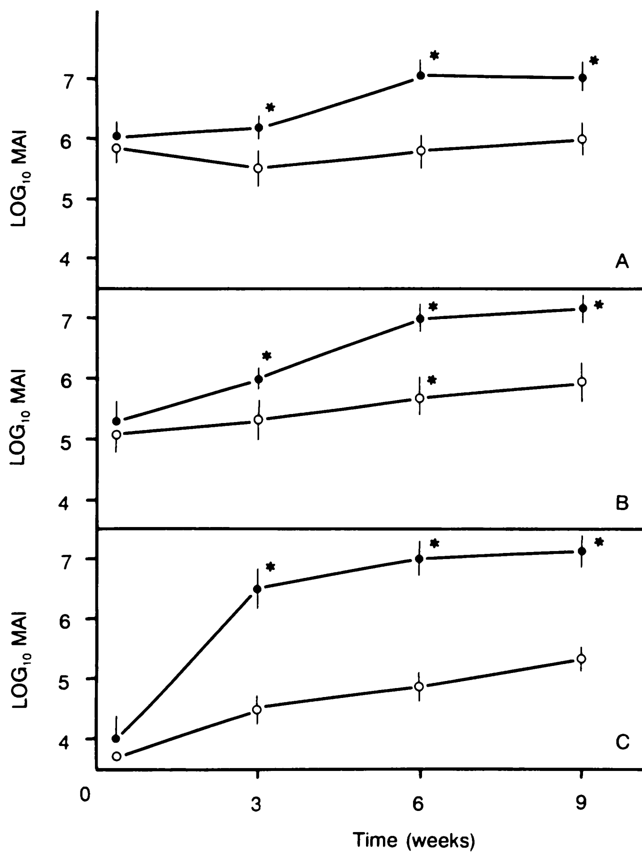

FIG. 3. Effect of IL-1 neutralization on *M. avium* growth in organs of mice. BALB/c mice received 10^6 CFU of *M. avium* B101 and repeated infusions of IL-1ra (●) or diluent (○). Growth in the liver (A), spleens (B) and lungs (C) is shown. Results are means ± SEMs of six mice. Asterisk (*) designates $P < 0.05$ (Student's *t* test). The test was repeated once with similar results. MAI, *M. avium*.

B101-infected mice resulted in enhanced *M. avium* growth in every organ sampled. Enhancement of growth in the liver was approximately 1 $\log_{10}$ CFU at 3, 6, and 9 weeks postinfection. In the spleen, at 9 weeks postinfection, a 1.2-$\log_{10}$ CFU difference was observed. Differences were more impressive in the lungs, where at 9 weeks postinfection a 2-$\log_{10}$ difference in CFU was observed. Organs were obtained 9 weeks postinfection from mice that had received diluent or IL-1ra; the organs were homogenized, and the clarified supernatants were processed for IL-1 bioactivity by the thymocyte assay. Data showed the presence of more than 5 ng of bioactive IL-1 in spleens, livers, and lungs of infected mice, whereas we could not detect any IL-1 bioactivity in the organs of infected mice that had received IL-1ra (data not shown), suggesting an efficient neutralization. As a control for endotoxin contamination, infected mice were infused with boiled IL-1ra. Such infusions had no effect on the growth of *M. avium* in the organs. At 9 weeks, mice given boiled IL-1ra had means ± SEMs of 6.1 ± 0.4 CFU per liver, 5.28 ± 0.21 CFU per spleen, and 5.31 ± 0.17 CFU per lung, with eight mice per group; these values were not significantly different from those of control mice (Fig. 3). Moreover, boiled IL-1ra failed to neutralize IL-1 bioactivity.

Bronchoalveolar lavage fluid cells. We were intrigued by the ability of IL-1ra to very significantly inhibit the resistance in the lungs and decided to investigate the cellular composition of the bronchoalveolar lavage fluid cell population. Table 1 shows the results obtained; neutralization of IL-1 resulted in a drastic reduction of the neutrophilic response in the early stages of infection. Cells other than polymorphonuclear leukocytes (PMN) were macrophages, with a very low proportion of lymphocytes. Representative micrographs are shown in Fig. 4.

TABLE 1. Brochoalveolar lavage fluid cellular composition

Day	Infection[a]	Treatment[b]	% PMN	No. of PMN (10^5)
0	None	IL-1ra	0.5 ± 0.3	0.2
		Diluent	0.6 ± 0.4	0.3
10	*M. avium*	IL-1ra	7 ± 3[c]	0.3[c]
		Diluent	60 ± 11	5.6
20	*M. avium*	IL-1ra	8 ± 4[c]	0.6[c]
		Diluent	71 ± 17	7.3
30	*M. avium*	IL-1ra	3 ± 1[c]	0.7[c]
		Diluent	56 ± 19	4.1
40	*M. avium*	IL-1ra	4 ± 2[c]	0.6[c]
		Diluent	72 ± 16	3.2
50	*M. avium*	IL-1ra	7 ± 3[c]	0.5[c]
		Diluent	36 ± 14	1.9
	None	IL-1ra	0	
		Diluent	0	

[a] Groups of mice received 10^6 CFU of *M. avium* intravenously, where indicated.
[b] Treatment schedule was as described in Materials and Methods.
[c] $P < 0.05$ versus diluent-treated mice (Student's *t* test).

DISCUSSION

IL-1 is a pivotal proinflammatory cytokine which is involved in mediating inflammation and host physiological responses to infections and various inflammatory stimuli (3, 12, 13). IL-1 mediates a wide variety of responses, including the induction of neutrophil chemotactic cytokines (IL-8), B- and T-cell activation, and the secretion of acute-phase proteins (13). Direct infusion of IL-1 has been shown to enhance mouse resistance to infections with *L. monocytogenes*, *S. typhimurium*, and *Brucella abortus* (8, 19, 28). Moreover, small doses of IL-1 have been shown to protect granulocytopenic mice from lethal infections with a variety of pathogens, including *Candida albicans*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (16, 24). The increased survival in these models did not correlate with an enhanced bacterial clearance from the tissues and did not appear to involve a corticosteroid response (25). Neutralization experiments, using antibodies or antagonists against IL-1, have indicated a role for this cytokine in resistance against *Pneumocystis carinii* and *L. monocytogenes* (4, 14, 21). In both cases, neutralization of IL-1 diminished the inflammatory response to the infection and enhanced bacterial growth in the tissues (4, 18).

The exuberant synthesis and release of IL-1 in the setting of an acute infection may either play a protective role or contribute to the host's death, presumably via tissue-damaging reactions, hypotension, etc. Indeed, Mancilla et al. (17) observed that infusion of IL-1ra in rats infected with *K. pneumoniae* could enhance or reduce the mortality, depending on the dose infused and the exact kinetics of infusion. Zhan et al. (28) observed an enhancement of mouse resistance to infection with *B. abortus* following infusion of low doses of IL-1 given before or after microbial infections. The protocol used here for IL-1 neutralization was based on the studies of Alexander et al. (1) and McCarthy et al. (18) which used IL-1ra as an antago-

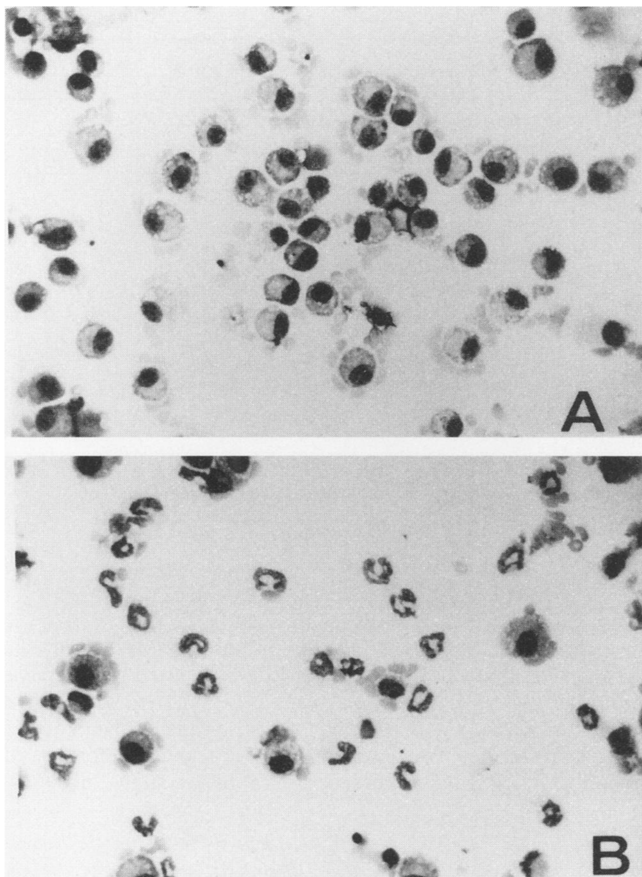

FIG. 4. Representative photographs of bronchoalveolar lavage fluid samples from *M. avium*-infected mice at day 10, treated with IL-1ra (A) or diluent (B).

nist in mice. Our finding that IL-1 bioactivity was effectively neutralized in the organs of infected mice suggested an effective neutralization.

Mycobacteria and their components stimulate the copious release of IL-1 from monocytes or macrophages in vitro (26). We provide evidence that IL-1 has a host-protective role in resistance against *M. avium* infections. IL-1 appeared to play a particularly important role in the resistance of lungs to *M. avium* growth, and depletion of IL-1 appeared to interfere with the focusing of an inflammatory influx of neutrophils in the lungs, judging from the lung-free cell phenotype (Table 1 and Fig. 4). A direct role for PMN in killing of virulent mycobacteria has not been clearly demonstrated to our knowledge, although PMN defensins kill AIDS-associated strains of *M. avium* in vitro (20). A study by Smith et al. has shown that freshly derived mouse neutrophils do not affect the viability of virulent mycobacteria, even at very high effector/target ratios (22). The PMN influx may also serve to focus a stronger inflammatory response in the tissues and to lyse infected cells, exposing intracellular bacilli to rounds of phagocytosis by fresh, activated inflammatory phagocytes with an elevated microbicidal activity (6). Our present understanding of the cytokine network, with regard to PMN recruitment, suggests that IL-1 induces a PMN influx mainly via the synthesis and release of IL-8 (12). An additional, but not exclusive, role for IL-1 in this system may relate to an enhanced T-cell responsiveness or activation and subsequent release of macrophage-activating cytokines by T cells (3). This could be verified by assessing the effect of IL-1 antagonism in mice devoid of active T cells, such as severe combined immunodeficient mice (4). Disseminated mycobacterial infections are associated with a variety of immunosuppressive activities, either T cell or macrophage mediated (5, 19). The beneficial effects of IL-1 may be immunostimulatory in nature, linked to a multiplication of protective T cells. Although the important role of IL-1 in vivo was shown in this study, neutralization of endogenous IL-1 in macrophages infected with *M. avium* had no effect on *M. avium* growth, suggesting a lack of direct effect of IL-1 on macrophage mycobactericidal or mycobacteriostatic activity. This finding argues for an enhancement of resistance by a mechanism distinct from a direct stimulation of macrophage bacteriostatic activity. A recent study by Kenefick et al. has shown that treatment of mice infected with *M. paratuberculosis* with an anti-IL-1 receptor antibody significantly enhanced the growth of bacilli in the liver (15).

Overall, our data suggest an important role for IL-1 in mouse resistance to an AIDS-associated strain of *M. avium*, particularly in the lungs.

ACKNOWLEDGMENTS

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