Regulatory effects of interleukin-11 during acute lung inflammatory injury

Alex B. Lentsch,* Larry D. Crouch,[§] Jacqueline A. Jordan,[†] Boris J. Czermak,[‖] Edward C. Yun,[†] Renfeng Guo,[†] Vidya Sarma,[†] Kathleen M. Diehl,[‡] and Peter A. Ward[†]

*Department of Surgery, University of Louisville School of Medicine, Kentucky; Departments of [†]Pathology & [‡]Surgery, University of Michigan Medical School, Ann Arbor; [§]Department of Oral Biology, University of Nebraska Medical Center, Lincoln; and [‖]Department of Trauma Surgery, University of Freiburg, Germany

Abstract: The role of interleukin-11 (IL-11) was evaluated in the IgG immune complex model of acute lung injury in rats. IL-11 mRNA and protein were both up-regulated during the course of this inflammatory response. Exogenously administered IL-11 substantially reduced, in a dose-dependent manner, the intrapulmonary accumulation of neutrophils and the lung vascular leak of albumin. These *in vivo* anti-inflammatory effects of IL-11 were associated with reduced NF-κB activation in lung, reduced levels of tumor necrosis factor α (TNF-α) in bronchoalveolar lavage (BAL) fluids, and diminished up-regulation of lung vascular ICAM-1. It is interesting that IL-11 did not affect BAL fluid content of the CXC chemokines, macrophage inflammatory protein-2 (MIP-2) and cytokine-inducible neutrophil chemoattractant (CINC); the presence of IL-11 did not affect these chemokines. However, BAL content of C5a was reduced by IL-11. These data indicate that IL-11 is a regulatory cytokine in the lung and that, like other members of this family, its anti-inflammatory properties appear to be linked to its suppression of NF-κB activation, diminished production of TNF-α, and reduced up-regulation of lung vascular ICAM-1. *J. Leukoc. Biol.* 66: 151–157; 1999.

Key Words: *neutrophils · tumor necrosis factor α · ICAM-1 · NF-κB · chemokines · C5a*

INTRODUCTION

Interleukin-11 (IL-11) was originally identified as a stromal cell product that stimulated proliferation of IL-6-dependent plasmacytoma cells [1]. Subsequent studies have demonstrated that IL-11 has effects similar to IL-6, including megakaryocyte proliferation [2] and induction of acute phase response proteins [3]. Functional similarities between IL-6 and IL-11 can be explained by the fact that signal transduction for both of these cytokines is mediated through the transmembrane glycoprotein 130 (gp130) receptor component, which is common to both IL-6 and IL-11 receptor complexes [4, 5].

We have previously shown that IL-6 functions as an intrinsic regulator of lung inflammation induced by intrapulmonary deposition of IgG immune complexes in rats [6]. The development of lung injury in this model is characterized by neutrophil recruitment and increased vascular permeability in the lung, these events being linked to production of TNF-α and IL-1β by activated lung macrophages [7, 8]. Furthermore, activation of the transcription factor, NF-κB, occurs in a time course similar to that for the appearance of TNF-α and IL-1β [9]. In this model of lung injury, exogenous administration of IL-6 caused substantial reductions in bronchoalveolar lavage (BAL) levels of tumor necrosis factor α (TNF-α), neutrophil accumulation, and lung vascular permeability [6]. Conversely, blockade of endogenous IL-6 augments these parameters of lung injury.

Recent studies *in vitro* have suggested that IL-11 suppresses proinflammatory cytokine production in activated macrophages by attenuating NF-κB activation [10]. Other studies have demonstrated anti-inflammatory effects of IL-11 in models of chronic inflammation, including trinitrobenzene sulfonic acid (TNBS)-induced colitis [11], endotoxemia [12], and radiation-induced thoracic injury [13]. Mice transgenically overexpressing IL-11 in lung develop pulmonary lymphocytic infiltrates, airway remodeling, and subepithelial fibrosis [14]. In the current studies we sought to determine the physiological role of IL-11 during acute lung inflammation induced by IgG immune complexes. Our data indicate that in this model IL-11 is up-regulated in lung at both the mRNA and protein levels. Exogenous administration of IL-11 suppresses IgG immune complex-induced neutrophil accumulation and lung vascular permeability. IL-11 also suppresses lung NF-κB activation in association with reduced BAL levels of TNF-α and decreased pulmonary vascular expression of ICAM-1. At the same time, C5a levels in the lung are reduced but BAL levels of the CXC chemokines, MIP-2 and CINC, are unaffected. These data indicate that IL-11 has the ability to regulate the acute lung inflammatory response.

Abbreviations: IL-11, interleukin-11; TNF-α, tumor necrosis factor α; BAL, bronchalveolar lavage; MIP-2, macrophage inflammatory protein-2; CINC, cytokine-inducible neutrophil chemoattractant; TNBS, trinitrobenzene sulfonic acid; BSA, bovine serum albumin; RT-PCR, reverse transcriptase-polymerase chain reaction; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; EMSA, electrophoretic mobility shift assay; MPO, myeloperoxidase; ELISA, enzyme-linked immunosorbent assay.

Correspondence: Alex B. Lentsch, Ph.D., Department of Surgery, University of Louisville School of Medicine, J.G. Brown Cancer Center, Rm. 426, 529 South Jackson Street, Louisville, KY 40202. E-mail: ablent01@ulkyvm.louisville.edu

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METHODS

Reagents

Human recombinant IL-11 and mouse monoclonal IgG1 anti-human IL-11 (clone 11h3/19.6.1) were gifts from Genetics Institute, Inc. (Cambridge, MA). Mouse monoclonal IgG1 anti-rat ICAM-1 (clone 1A29) was purchased from PharMingen, Inc. (San Diego, CA). Irrelevant mouse IgG1 (clone MOPC-21) was purchased from ICN Biomedicals, Inc. (Costa Mesa, CA). All other reagents, unless otherwise indicated, were purchased from Sigma (St. Louis, MO).

IgG immune complex-induced alveolitis

Pathogen-free male Long-Evans rats (275–300 g; Harlan Sprague-Dawley, Indianapolis, IN) were anesthetized with ketamine HCl (150 mg/kg, intraperitoneally). Rats received intratracheal administration of 1.5 mg antibody to bovine serum albumin (anti-BSA; ICN Biomedicals, Inc.) in a volume of 0.3 mL phosphate-buffered saline (PBS). Negative control rats received intratracheal administration of PBS, pH 7.4. Immediately thereafter, 10 mg BSA (<1 ng endotoxin/mg) in 0.5 mL PBS was injected intravenously. For analysis of pulmonary vascular permeability, trace amounts of ^{125}I-labeled BSA were injected intravenously. Four hours after IgG immune complex deposition, rats were exsanguinated, the pulmonary circulation was flushed with 10 mL PBS by pulmonary artery injection, and the lungs surgically removed. The extent of lung injury was quantified by calculating the lung permeability index [dividing the amount of radioactivity (^{125}I-labeled BSA) in the perfused lungs by the amount of radioactivity in 1.0 mL of blood obtained from the inferior vena cava at the time of death]. For measurement of lung NF-κB activation, lungs were surgically dissected and immediately frozen in liquid nitrogen.

Reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA from whole lung tissue was extracted using a guanidinium-isothiocyanate method as described previously [15]. Total RNA (20 μg) was reverse transcribed to cDNA. The cDNA products were amplified by PCR (35 cycles; 1 min each at 95, 55, and 72°C). The 5′ primer (5′-ATGAACTGTGTTT-GTCGCCTG-3′) and 3′ primer (5′-GTTGTTAAAGACTCGACTGTG-3′) were complementary to 5′ and 3′ regions of the open reading frame of the human IL-11 sequence. PCR products were sequenced for verification. RT-PCR of the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) cDNA was performed (5′ primer, 5′-TCACCATCTTCCAG GAGC-3′; 3′ primer, 5′-CTGCTTCAC-CACCTTCTTGA-3′) under the same conditions described above to confirm equal loading of RNA. PCR products were electrophoresed in a 1% agarose gel and stained with ethidium bromide. Photographs of PCR products were digitized and analyzed using image analysis software (Adobe Systems, San Jose, CA).

Western blot analysis

BAL fluids were concentrated approximately 100-fold and 40 μL were separated in a denaturing 15% polyacrylamide gel and transferred to a 0.1-μm-pore nitrocellulose membrane. Nonspecific binding sites were blocked with TBS (40 mM Tris, pH 7.6, 300 mM NaCl) containing 5% nonfat dry milk for 12 h at 4°C. Membranes were then incubated in monoclonal mouse IgG anti-IL-11 (2 μg/mL) in TBS with 0.1% Tween 20 (TBST). After three washes in TBST, membranes were incubated in a 1:10,000 dilution of horseradish peroxidase-conjugated sheep anti-mouse IgG (Amersham, Arlington Heights, IL). Immunoreactive proteins were detected by enhanced chemiluminescence.

NF-κB activation by electrophoretic mobility shift assay (EMSA)

Nuclear extracts of whole lung tissues were prepared by the method of Deryckere and Gannon [16]. Protein concentrations were determined by bicinchoninic acid assay with trichloroacetic acid precipitation using BSA as a reference standard (Pierce, Rockford, IL). Double-stranded NF-κB consensus oligonucleotide (5′-AGTGAGGGGACTTTCCCAGGC-3′; Promega, Madison, WI) was end-labeled with [γ-^{32}P]ATP (3,000 Ci/mmol at 10 mCi/mL, Amersham). Binding reactions containing equal amounts of protein (10 μg) and 35 fmol (~50,000 cpm, Cherenkov counting) of oligonucleotide were performed for 30 min in binding buffer (4% glycerol, 1 mM $MgCl_2$, 0.5 mM EDTA, pH 8.0, 0.5 mM dithiothreitol, 50 mM NaCl, 10 mM Tris, pH 7.6, 50 μg/mL poly (dI-dC); Pharmacia, Piscataway, NJ). Reaction volumes were held constant at 15 μL. Reaction products were separated in a 4% polyacrylamide gel and analyzed by autoradiography. NF-κB activation was quantitated from digitized autoradiography films using image analysis software (Adobe Systems).

Lung vascular expression of ICAM-1

Rats were injected intravenously with 1.5 μCi of ^{125}I-labeled anti-ICAM-1 3.75 h after induction of lung injury. The specific activity of the anti-ICAM-1 was 11.3 μCi/μg. Fifteen minutes later (4 h after induction of lung injury), rats were killed and the lung vasculature was flushed with 10 mL PBS. Lung vascular ICAM-1 expression (binding index) was calculated by dividing the amount of radioactivity (^{125}I-labeled antibody) in perfused lungs by the amount of radioactivity in 1.0 mL of blood. To control for nonspecific binding and potential accumulation of anti-ICAM-1 antibody in lung parenchyma due to injury, 1.5 μCi of ^{125}I-labeled nonspecific mouse IgG1 were administered in a separate set of rats undergoing IgG immune complex lung injury. The specific activity of the irrelevant IgG antibody was 13.0 μCi/μg. This technique has been described in detail elsewhere [17].

Lung myeloperoxidase (MPO) content

Whole-lung MPO activity was quantitated as described previously [18]. Briefly, whole lungs homogenates were diluted in 50 mM potassium phosphate buffer containing 0.5% hexadecyltrimethylammonium bromide, pH 6.0. After sonication and two freeze-thaw cycles, samples were centrifuged at 4000 *g* for 30 min. The supernatants were reacted with H_2O_2 (0.3 mM) in the presence of tetramethylbenzidine (1.6 mM). MPO activity was assessed by measuring the change in absorbance at 655 nm.

BAL fluid neutrophil and cytokine content

BAL fluids were collected by instilling and withdrawing 5 mL of sterile PBS three times from the lungs via an intratracheal cannula. Cellular contents were recovered by centrifugation and neutrophils were counted by microcytometry. BAL content of TNF-α was measured using a standard WEHI cell cytotoxicity assay as previously reported [19]. Measurement of CINC, macrophage inflammatory protein-2 (MIP-2), and C5a in BAL fluids was by enzyme-linked immunosorbent assay (ELISA) as described elsewhere [20, 21].

Statistical analyses

All values are expressed as means ± SEM. Data were analyzed with a one-way analysis of variance and individual group means were then compared with a Student-Newman-Keuls test. Differences were considered significant when $P < 0.05$. For calculations of percent change, negative control values were subtracted from positive control and treatment group values.

RESULTS

Pulmonary expression of IL-11 during IgG immune complex alveolitis

Expression of IL-11 mRNA in lung extracts from rats undergoing IgG immune complex-induced lung injury was determined by RT-PCR. IL-11 mRNA was constitutively expressed at very low levels in lung, the RT-PCR product being present at the initiation of lung injury (time 0; **Fig. 1**). IL-11 mRNA expression increased 30 min after intrapulmonary deposition of IgG immune complexes, reaching a maximal level after 1 h, declining at 2 h, and returning to baseline 4 h after initiation of injury. In accordance with IL-11 mRNA, IL-11 protein was constitutively expressed at low levels in lung before initiation of

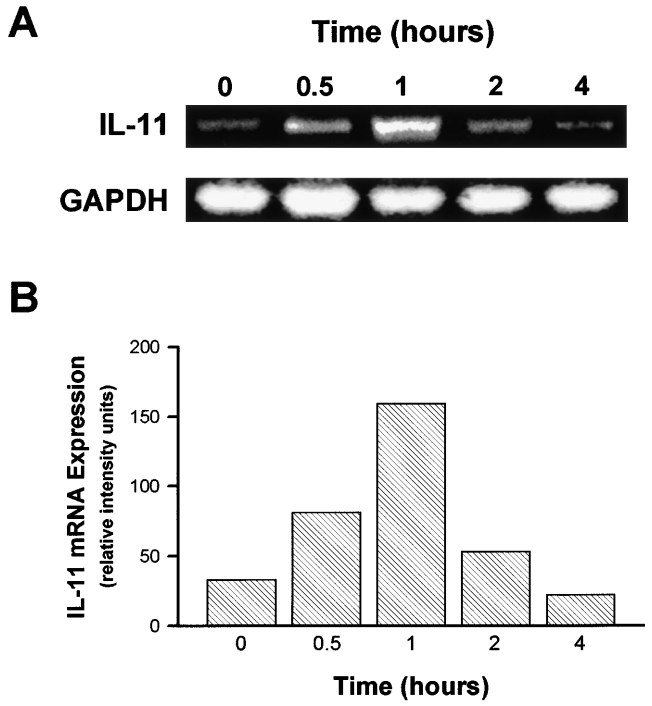

Fig. 1. Expression of rat IL-11 mRNA during IgG immune complex alveolitis. Lung RNA extracts were analyzed by RT-PCR (A) and ethidium bromide-stained PCR products were digitized using image analysis (B). Equal loading of RNA was confirmed by RT-PCR of the housekeeping gene, GAPDH. Results are representative of three independent experiments.

the lung inflammatory reaction. Western blot analysis of concentrated BAL fluids demonstrated barely detectable levels of IL-11 protein at the initiation of lung injury (time 0; **Fig. 2**). Expression of IL-11 protein was markedly increased 1 h after IgG immune complex deposition and further increases were detected at 2 and 4 h.

Effects of exogenous IL-11 on IgG immune complex-induced neutrophil accumulation and lung injury

Experiments were designed to assess the effects of exogenously administered recombinant human IL-11 on lung vascular permeability and lung neutrophil recruitment in the IgG immune complex model of lung injury. The extent of lung injury was determined by extravascular leakage of albumin. Intrapulmonary deposition of IgG immune complexes caused a three-fold increase in the lung permeability index (**Fig. 3A**).

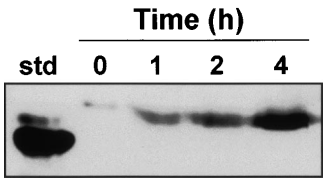

Fig. 2. BAL fluid content of IL-11 protein during IgG immune complex alveolitis. BAL fluids were concentrated (100-fold) and 40 μL were analyzed by Western blot. Recombinant human IL-11 was used as a reference standard (std) in the extreme left lane. Results are representative of two independent experiments.

Intratracheal administration of IL-11 (administered with the anti-BSA) caused a dose-dependent reduction in the lung permeability index. In the presence of 10, 30, or 60 μg IL-11, the permeability index was reduced 29% (*P*, NS), 43% (*P*, NS) and 66% ($P < 0.05$), respectively. To assess whether the protective effects of IL-11 were related to reduced pulmonary recruitment of neutrophils, lung MPO content and the number of neutrophils in BAL fluids were determined. Treatment with IL-11 caused dose-dependent decreases in lung MPO content (Fig. 3B). Intratracheal administration of 10, 30, or 60 μg IL-11 reduced lung MPO content by 12% (*P*, NS), 58% ($P < 0.05$), and 67% ($P < 0.05$), respectively. Similarly, 60 μg IL-11 decreased the number of neutrophils present in BAL fluids from $65.9 \pm 3.5 \times 10^3$ cells/mL in positive controls to $22.0 \pm 3.6 \times 10^3$ cells/mL, a reduction of 67% ($P < 0.05$).

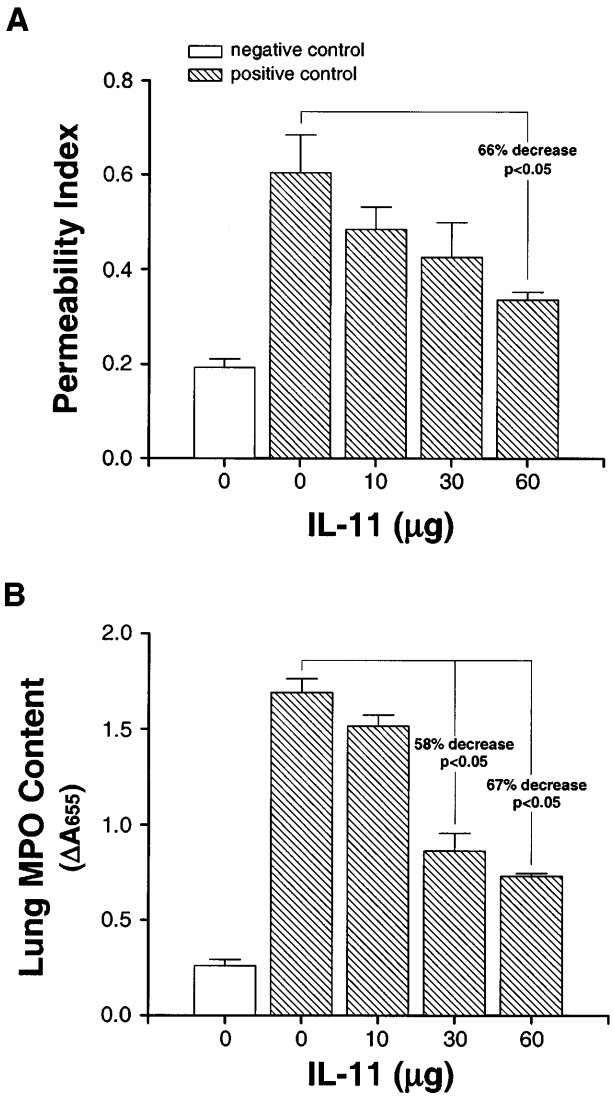

Fig. 3. Effects of IL-11 on IgG immune complex-induced lung vascular permeability (A) and lung neutrophil accumulation (B). Permeability index ($n = 5$–9) and lung MPO content ($n = 3$–7) were assessed 4 h after intratracheal administration of 1.5 mg anti-BSA followed by intravenous infusion of 10 mg BSA. IL-11 was administered intratracheally with the IgG anti-BSA. Values represent mean ± SEM.

Effects of IL-11 on lung NF-κB activation

In the IgG immune complex model, development of lung inflammatory injury is associated with a progressive increase in lung NF-κB activation as defined by nuclear translocation of NF-κB [9]. *In vitro* studies have shown that IL-11 suppresses NF-κB activation in macrophages [10]. Therefore, to investigate whether the protective effects of IL-11 might be related to inhibition of pulmonary NF-κB activation, nuclear extracts from whole lungs harvested 4 h after IgG immune complex deposition were analyzed by EMSA. Little NF-κB was present in lung nuclei from rats treated intratracheally with PBS (negative control, **Fig. 4A**). As expected, intrapulmonary deposition of IgG immune complexes caused a significant increase in nuclear translocation of NF-κB. Image analysis of digitized EMSA blots demonstrated that, in the presence of 10, 30, or 60 μg IL-11, NF-κB activation was reduced by 12 (*P*, NS), 28 (*P*, NS), and 34% ($P < 0.05$), respectively (Fig. 4B).

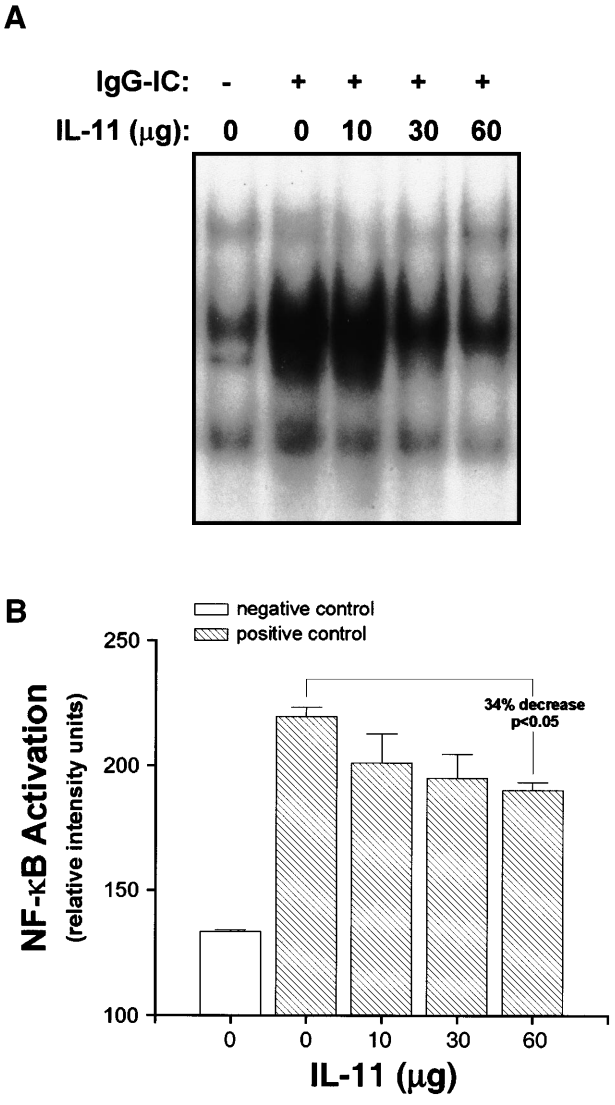

Fig. 4. Effects of exogenously administered recombinant human IL-11 on IgG immune complex-induced lung NF-κB activation. (A) NF-κB activation in whole lung tissues harvested 4 h after intratracheal administration of PBS or 1.5 mg anti-BSA (IgG-IC) followed by intravenous infusion of 10 mg BSA. IL-11 was administered intratracheally with the IgG anti-BSA. (B) Quantitation of EMSA blots by image analysis. Values represent mean ± SEM, with $n = 4$–5 for each group.

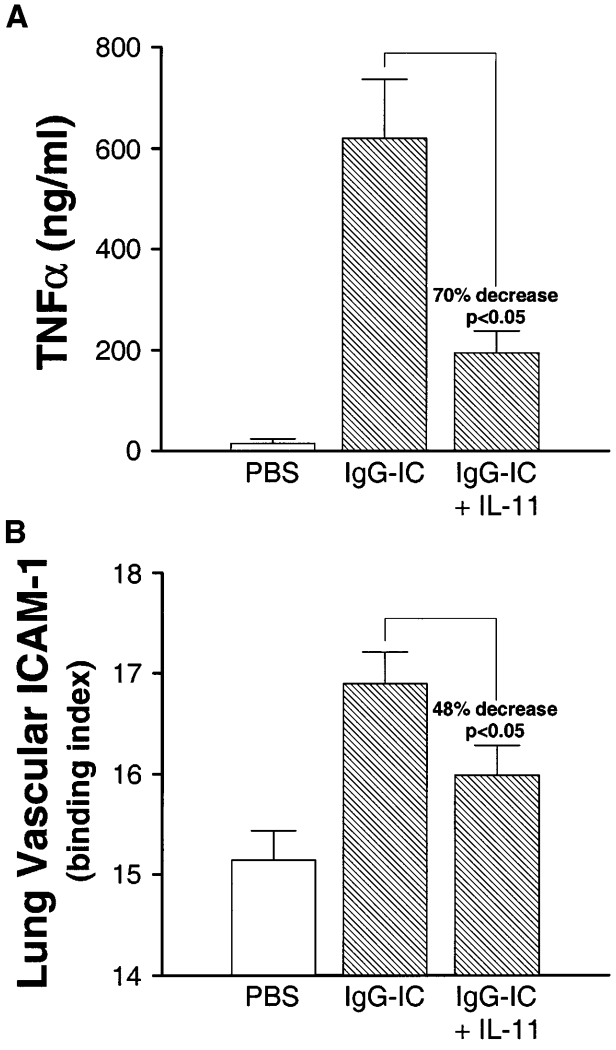

Fig. 5. Effects of IL-11 on IgG immune complex-induced BAL TNF-α and lung vascular ICAM-1 expression. (A) BAL fluids harvested 4 h after intratracheal administration of PBS or 1.5 mg anti-BSA (IgG-IC) followed by intravenous infusion of 10 mg BSA were analyzed by the WEHI assay for TNF-α bioactivity. (B) lung vascular ICAM-1 expression was determined 4 h after IgG-IC deposition using vascular fixation of ^{125}I-anti-rat ICAM-1. Values represent mean ± SEM, with $n = 5$–6 for each group.

Effects of IL-11 on BAL Levels of TNF-α and lung vascular expression of ICAM-1

NF-κB is known to control, at least in part, the gene expression of both TNF-α and ICAM-1 [22, 23]. Furthermore, TNF-α regulates lung vascular expression of ICAM-1 [17], which is required for pulmonary neutrophil recruitment [24]. Therefore, we performed experiments to determine whether exogenously administered IL-11 affected BAL levels of TNF-α and lung vascular expression of ICAM-1. BAL TNF-α content was determined by the WEHI bioassay. The lung inflammatory response led to significantly increased BAL levels of TNF-α (from <20 ng/mL to >600 ng/mL, **Fig. 5A**). In the presence of 60 μg IL-11 BAL levels of TNF-α were reduced by 70% ($P < 0.05$). Pulmonary expression of ICAM-1 was determined by the lung binding index of ^{125}I-anti-ICAM-1. As expected, intrapul-

monary deposition of IgG immune complexes caused a significant increase in the ICAM-1 binding index (Fig. 5B). In the presence of 60 μg IL-11, the binding index for ICAM-1 was reduced by 48% ($P < 0.05$). The increase in binding index for the anti-ICAM-1 could not be attributed to nonspecific binding or sequestration due to lung injury because the binding index for the irrelevant IgG control antibody was less than 0.10 in both inflamed and non-inflamed lungs (data not shown).

Effects of IL-11 on neutrophil chemoattractants in BAL fluids

To determine the effects of IL-11 on chemotactic mediators known to be involved in pulmonary neutrophil recruitment in this inflammatory model, we assessed the effects of 60 μg IL-11 on IgG immune complex-induced BAL content of the CXC chemokines, MIP-2 and CINC, and the complement activation product, C5a. BAL fluids were obtained 4 h after the initiation of the lung inflammatory reaction. MIP-2, CINC, and C5a were evaluated by ELISA. Intrapulmonary deposition of IgG immune complexes caused significant increases in BAL levels of MIP-2, CINC, and C5a, with a 38-fold increase of MIP-2, a nearly 300-fold increase of CINC, and a 7-fold increase of C5a (**Table 1**). In the presence of 60 μg IL-11, the BAL levels of MIP-2 and CINC were not significantly altered but there was a 29% decrease ($P < 0.05$) in BAL levels of C5a (Table 1).

DISCUSSION

There is mounting evidence that IL-11 plays an important regulatory role in the inflammatory response. Previous studies have suggested that exogenously administered IL-11 reduced tissue injury in a number of experimental models of chronic inflammatory disease, including TNBS-induced colitis, endotoxemia, and radiation-induced thoracic injury [11–13]. In the last example, the protective effects of IL-11 correlated with reduced intrapulmonary production of TNF-α [13]. In the current study, we investigated whether IL-11 could suppress the acute inflammatory response in lung and if so, by what mechanism. Intrapulmonary deposition of IgG immune complexes causes distal airway activation of the complement system and generation of the complement activation product, C5a. Blockade of intrapulmonary C5a with antibody reduced lung production of TNF-α, diminished up-regulation of vascular ICAM-1, and reduced neutrophil accumulation and the intensity of lung injury [25]. In this lung inflammatory model, enhanced production of TNF-α and IL-1β by activated macrophages is required for up-regulation of the adhesion molecules, ICAM-1 and E-selectin, on pulmonary vascular endothelial cells [17, 26]. Interactions of these vascular adhesion molecules with their respective ligands on blood neutrophils causes leukocyte adhesion to the endothelium and CXC chemokine-dependent recruitment of neutrophils into the alveolar compartment. The ensuing lung injury is mediated by oxidants and proteases released by neutrophils and from activated lung macrophages. Injury is characterized by increased vascular permeability and alveolar hemorrhage [27]. In this study we found that IL-11 was up-regulated at the mRNA and protein levels during the lung inflammatory response. Exogenously administered IL-11 attenuated intrapulmonary activation of NF-κB, reduced lung production of TNF-α, and diminished pulmonary vascular expression of ICAM-1. In the presence of IL-11, intrapulmonary generation of C5a was reduced by an unknown mechanism. These effects were accompanied by reduced neutrophil accumulation and lung injury. The data suggest that IL-11 may function as an intrinsic regulator of the acute inflammatory response in lung. The lack of availability of a blocking antibody to rat IL-11 precludes the definitive *in vivo* experiments to settle this question.

TABLE 1. Effects of IL-11 on BAL Levels of MIP-2, CINC, and C5a

Group	MIP-2 (ng/mL)	CINC (ng/mL)	C5a (ng/mL)
PBS	15.1 ± 8.6	5.6 ± 6.3	0.35 ± 0.05
IgG-IC	572.6 ± 63.9*	1589.8 ± 137.9*	2.42 ± 0.13*
IgG-IC + IL-11	503.6 ± 31.7*	1478.6 ± 78.7*	1.82 ± 0.14†

Values represent mean ± SEM, with $n = 5$ for each group. Human recombinant IL-11 was used at a dose of 60 μg, administered intratracheally. IC, immune complexes. * $P < 0.05$ compared to PBS group; † $P < 0.05$ compared to IgG-IC group.

Exogenous administration of IL-11 attenuated activation of NF-κB in lung. These findings are consistent with *in vitro* studies which showed that IL-11 inhibited LPS-induced NF-κB activation in macrophages [10]. It is interesting that IL-11 reduced IgG immune complex-induced lung NF-κB activation by 34%, whereas TNF-α production was reduced by 70%. Previous studies in this model have demonstrated that exogenous administration of the anti-inflammatory cytokines, IL-10 and IL-13, almost completely inhibits lung NF-κB activation and suppresses TNF-α production by more than 95% [9, 28]. Despite the fact that IL-10 and IL-13 signal through receptor pathways different from the pathway for IL-11, it would seem that the reduction in lung NF-κB activation caused by IL-11 may only partially explain inhibition of TNF-α in BAL fluids. If it is predominantly macrophages that are the target for the suppressive effects of IL-11, nuclear extracts from whole lungs may underestimate the suppression of NF-κB in lung macrophages.

In the lung inflammatory response, intrapulmonary generation of C5a is known to be required for the full production of TNF-α [25]. The present report provides evidence that IL-11 reduces the generation of C5a during IgG immune complex alveolitis. How IL-11 might affect the intrapulmonary generation of C5a is unclear. IL-11 is known to stimulate the production of the tissue inhibitor of metalloproteinase-1 [29]. If a non-complement-related C5-cleaving enzyme in lung, such as a matrix metalloproteinase, is responsible for production of at least some C5a, it is possible that IL-11 induces up-regulation of natural inhibitors for such an enzyme (e.g., by up-regulating tissue inhibitor of metalloproteinase-2), thereby reducing the amount of C5a generated. Until the nature of the C5-cleaving enzyme in lung is known, the possible mechanism of the suppressive effects of IL-11 on C5a generation remains speculative. Accordingly, the effects of IL-11 *in vivo* suggest that IL-11 may reduce lung production of TNF-α by two separate mechanisms involving NF-κB and C5a. These mechanisms may

also be relevant to the regulation of pulmonary vascular expression of ICAM-1. Both NF-κB and C5a are known to regulate, by direct or indirect mechanisms, vascular endothelial cell expression of ICAM-1. NF-κB directly controls gene expression of ICAM-1 as well as the ICAM-1 inducer, TNF-α [22, 23], whereas C5a regulates ICAM-1 expression through effects on TNF-α production [25]. It seems likely that IL-11-induced inhibition of pulmonary neutrophil recruitment and ensuing lung injury can be attributed to reductions in intrapulmonary C5a, TNF-α, and pulmonary vascular expression of ICAM-1 because IL-11 had no effect on the CXC chemokines, MIP-2 and CINC. As indicated above, both of these CXC chemokines are known to be required for full recruitment of neutrophils in this model of lung injury. It remains to be determined how the presence of IL-11 affects intrapulmonary generation of C5a. Thus, the regulatory effects of IL-11 on the lung inflammatory response are restricted in scope.

Why transgenic expression of IL-11 in murine lung leads to accumulation of lymphocytes and increased airway resistance is not clear [14]. However, the predominantly B cell phenotype of the lung lymphocytic infiltrates in IL-11 transgenic mice suggests that the B cell stimulatory activity of IL-11 may contribute to this outcome [30]. The mechanisms for the fibrotic airway obstruction in IL-11 transgenic mice remains to be determined. Whether intermittent expression of IL-11 in lung would yield an outcome different from persistent expression of IL-11 in transgenic mice is unclear.

This report further extends our current knowledge concerning the biology of IL-11. We demonstrate the anti-inflammatory effects of IL-11 and have identified the protective mechanisms of IL-11 in lung after intrapulmonary deposition of IgG immune complexes. The data demonstrate that IL-11 functions as a down-regulator of the acute inflammatory response. Furthermore, IL-11 is up-regulated at the mRNA and protein levels during the course of inflammation. These findings are similar to those described previously for IL-6, suggesting that IL-11 may have overlapping functions with IL-6 in the regulation of acute lung inflammation. The dose responses of IL-6 and IL-11 are similar and are a log dose greater than for the effects of IL-10 and IL-13 [28]. All of these interleukins appear to achieve these effects via a common mechanism: suppression of NF-κB activation and related TNF-α production in lung, leading to reduced expression of lung vascular ICAM-1. In turn, neutrophil recruitment is reduced, as is the development of lung injury. At present, IL-11 can be added to the list of regulatory cytokines, which also include IL-4, IL-6, IL-10, IL-12, and IL-13.

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