Pulmonary Expression of Leukemia Inhibitory Factor Induces B Cell Hyperplasia and Confers Protection in Hyperoxia*

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Leukemia inhibitory factor (LIF) is produced by a large number of pulmonary cells in response to diverse stimuli. Exaggerated levels of LIF have also been detected in the adult respiratory distress syndrome and other disorders. The biologic effects of LIF in the lung, however, have not been elucidated. To define the respiratory effects of LIF, we generated transgenic mice in which human LIF was selectively targeted to the mature lung. In these mice, transgene activation caused an impressive increase in bronchoalveolar lavage (BAL) cellularity with a significant increase in BAL and tissue B lymphocytes. LIF also conferred protection in 100% O₂ where it decreased alveolar-capillary protein leak and enhanced survival. This protective effect was associated with the induction of interleukin (IL)-6 mRNA and protein. LIF transgenic mice with a null mutation in IL-6 were more sensitive to the toxic effects of 100% O₂ than LIF-transgenic animals with a wild-type IL-6 locus. These studies demonstrate that LIF induces B cell hyperplasia and confers protection in hyperoxic acute lung injury. They also demonstrate that LIF induces IL-6 and that the protective effects of LIF are mediated, in part, via this inductive event. LIF may be an important regulator of B cell-mediated responses and oxidant injury in the lung.

Leukemia inhibitory factor (LIF) is a highly glycosylated 38-kDa member of the IL-6-type cytokine family. It is produced by a large number of normal and neoplastic cells and mediates its effects by interacting with a diffusely distributed multimeric receptor complex made up of gp130 and gp190 molecules (1–3). Under normal conditions, LIF production is tightly regulated in the adult respiratory distress syndrome (ARDS) and the regulation of this cytokine has been extensively studied in vitro. However, the in vivo effector properties of LIF in the lung, we used an externally regulatable overexpression transgenic system to inducibly express LIF in the mature murine lung. These studies demonstrate that LIF is a potent stimulus of B cell accumulation. They also demonstrate that LIF has protective effects in oxidant-induced pulmonary injury and demonstrate that these effects are mediated, at least in part, via the ability of LIF to induce IL-6 elaboration.

EXPERIMENTAL PROCEDURES

Generation of Transgenic Mice—We used an externally regulatable, dual construct overexpression transgenic system to generate CC10-
rtTA-LIF mice. The constructs used in this system have been described previously by our laboratories (20, 21). The CC10-rtTA-hGH construct contains the CC10 promoter, the reverse tetracycline transactivator (rtTA), and human growth hormone (hGH) intronic and polyadenylation sequences (Fig. 1). The rtTA is a fusion protein made up of a mutated tetracycline repressor and the herpes virus VP-16 transactivator. The tet-O-CMV-LIF-hGH construct contains a polymeric tetracycline operator (tet-O), minimal CMV promoter, human LIF cDNA, and hGH intronic and polyadenylation signals (Fig. 1). In this system, the CC10 promoter directs the expression of rtTA to the lung. In the presence of doxycycline (dox), rtTA is able to bind in trans to the tet-O, and the VP-16 transactivator activates LIF gene transcription. In the absence of dox, rtTA binding occurs at very low levels, and only low level gene transcription is noted. The preparation of the CC10-rtTA construct has been described previously (20). The tet-O-CMV-LIF-hGH construct was prepared by replacing the IL-11 cDNA in the construct tet-O-CMV-hIL-11-hGH described previously by our laboratory (20) with the human LIF cDNA. This construct was checked for correct insert orientation by restriction enzyme digestion and sequencing. Both constructs were purified, linearized, separated by electrophoresis through agarose, and purified as described previously (20, 21). Transgenic mice were prepared in (CBA and C57BL/6)F2 eggs by mixing and simultaneously injecting the constructs into pronuclei as described previously (20, 21). Transgenic mice were purified, linearized, separated by electrophoresis through agarose, and confirmed by nucleotide sequencing. Ribonuclease protection assays were performed using the RiboQuant kit purchased from Pharmingen. These assays were performed according to instructions provided by the manufacturer.

Documentation of Transgene Status—The presence or absence of the transgenes was initially evaluated using Southern blot analysis and later by PCR. Southern analysis was performed as described previously using cDNA encoding human LIF or rtTA (20, 21). PCR for rtTA was also performed using protocols described by our laboratory (20, 21). PCR for the LIF-containing construct was undertaken using the following primers: upper primer, 5' GCC ATC CGG CCG TTC CTC CAA GGC CCT CTG 3'; lower primer, 5' AGC ACT GGA TCC GAC CTC CTG CTG 3'. The cycling conditions were 1 cycle at 94 °C for 5 min, 35 cycles of 94 °C for 1 min, followed by 60 °C for 1 min and 72 °C for 1 min, 1 cycle at 72 °C for 5 min, and 1 cycle at 4 °C to end. All CC10-rtTA-LIF lineage animals were evaluated for the presence of both the rtTA- and LIF-containing transgenic constructs. Comparisons were undertaken of mice with both transgenic constructs (transgene (+) mice) and mice with neither construct (transgene (−) mice)

Dox Water Administration—CC10-rtTA-LIF animals were maintained on normal water until 4–6 weeks of age. At that time they were randomized to receive normal water or water containing dox (0.5 mg/ml) as described previously (20, 21).

Bronchoalveolar Lavage and Quantification of LIF Levels—Mice were killed; the trachea was isolated by blunt dissection, and small caliber tubing was inserted and secured in the airway. Two volumes of 1.0 ml of PBS with 0.1% bovine serum albumin were then instilled and gently aspirated and pooled. Each BAL sample was centrifuged, and the supernatants were stored at −70 °C until used. The levels of LIF were determined using a commercial ELISA (R & D Systems Inc., Minneapolis, MN) as per the manufacturer's instructions. In the RT-PCR assays, RNA samples were reverse-transcribed, and gene-specific primers were used to amplify selected regions of the LIF target moiety. To verify that equal amounts of undegraded RNA were added in each RT-PCR, β-actin was used as an internal standard. Amplified PCR products were detected using ethidium bromide gel electrophoresis, quantitated electronically, and confirmed by nucleotide sequencing. Ribonuclease protection assays were performed using the RiboQuant kit purchased from Pharmingen. These assays were performed according to instructions provided by the manufacturer.

ELISA Evaluations—The levels of LIF and IL-6 protein in murine BAL were quantitated by ELISA using commercial assays (R & D Systems Inc., Minneapolis, MN) as per the manufacturer's instructions.

Fluorescence-activated Cell Sorting (FACS) Analysis—Transgenic and non-transgenic mice were treated for 2 weeks with dox or normal water as described above. The animals were then sacrificed. The pulmonary vascular tree was perfused with calcium- and magnesium-free PBS (pH 7.4) via a right heart catheter, and lung lymphocytes were prepared using collagenase III digestion, mechanical tissue disruption, and Ficoll density centrifugation. The resulting cells were prepared for three-color staining by incubating with phycoerythrin-labeled anti-mouse CD3, FITC-labeled anti-mouse CD8, CyChrome-labeled anti-CD4, and FITC-conjugated anti-B220 (Pharmingen) for 1 h on ice. Analysis was performed on a FACS Calibur flow cytometer (BD Biosciences). Data are displayed as dot plots of FITC (x axis) versus phycoerythrin-like or CyChrome (y axis) fluorescence (log scales). Quadrant markers were positioned to include ≥99% of control Ig-stained cells in the left lower quadrant.

Exposure to 100% O2—Mice were exposed to 100% oxygen in a 50 × 30 × 30-cm airtight chamber as described previously (24, 25). The fractional inspired O2 concentration in the chamber was monitored with an in-line oxygen analyzer (Vascular Technology, Inc., Chelmsford, MA) and maintained with a constant flow of gas (−3 liters/min). The mice were fed food and water ad libitum and kept on a 12-h dark-light cycle
To characterize the effects of LIF in the adult lung, we used an externally regulatable, dual construct overexpression transgenic system previously described by our laboratory (20, 21). The constructs required for these transgenics (Fig. 1) were prepared, purified, and simultaneously microinjected. Tail biopsies were obtained from potential founder animals; DNA was isolated, and the presence or absence of LIF and rtTA transgenic sequences was determined via PCR. Three dual positive founder animals were obtained. They were subsequently back-crossed with C57BL/6 mice to generate transgene (−) and transgene (+) progeny. 

Generation and Organ Specificity of LIF Production—Transgene (−) and transgene (+) mice were kept on normal water until they were 4–6 weeks of age. They were then randomized to normal water or dox water. In the absence of dox administration, BAL LIF levels ≤10 pg/ml were appreciated. Dox administration caused a significant increase in BAL LIF. This increase was noted within 48 h of dox administration, persisted for extended intervals, and returned to base line within 4 days of removing dox from the animal’s drinking water. The different transgenic animals had BAL LIF levels between ~200 and 500 pg/ml after 1–4 weeks of dox administration.

To determine whether LIF was appropriately targeted to the lung, RNA was obtained from the lungs and a variety of other tissues from transgene (+) mice that had received dox water for 2 weeks. LIF mRNA was then evaluated via RT-PCR analysis. Impressive levels of LIF mRNA could be appreciated in lungs from transgene (+) mice on dox water. In contrast, transgene-induced LIF mRNA was not noted, and histologic abnormalities were not appreciated in a variety of visceral tissues from transgene (+) animals (Fig. 2 and data not shown). This demonstrates that our CC10-driven system appropriately targeted LIF to the lungs of these transgenic animals.

Effect of LIF on BAL Cellularity—Transgene (+) and transgene (−) mice were kept on normal water until they were 4–6 weeks of age. They were then placed on normal water or dox water and maintained on this regimen for an additional 1–3 months. At intervals, BAL cellularity and lung histology were evaluated. The cell recovery and cellular differentials of the BAL from transgene (−) mice on normal water and dox water and transgene (+) mice on normal water were almost identical at all time points that were evaluated (Fig. 3). In contrast, LIF induction caused an impressive increase in BAL cell recovery (Fig. 3). This increase could be appreciated after 1 month and was even more striking after 3 months of dox administration to transgene (+) mice (Fig. 3). This increase was largely the result of an increase in mononuclear cells with an increase in the percentage of BAL cells that were lymphocytes and an increase in lymphocyte and macrophage recovery (Fig. 3 and data not shown). Abnormalities in neutrophil recovery and eosinophil recovery were not noted.

RESULTS

Generation of Transgenic Mice—To characterize the effects of LIF in the adult lung, we used an externally regulatable, dual construct overexpression transgenic system previously described by our laboratory (20, 21). The constructs required for these transgenics (Fig. 1) were prepared, purified, and simultaneously microinjected. Tail biopsies were obtained from...
Effect of LIF on Lung Histology—Inflammation was not seen in the hematoxylin and eosin stains of the lungs from transgene (-) mice on normal or dox water. Similarly, inflammation was not noted in histologic sections from transgene (+) mice on normal water at all time points that were evaluated. In contrast, inflammation was noted in the lungs from transgene (+) animals. This response was made up almost entirely of lymphocytes. It was mild, occasionally nodular, and noted in peribroncholar locations (Fig. 4). The periodic acid-Schiff with diastase stains and Alcian blue stains did not reveal mucus metaplasia or an alteration in histologically apparent mast cells. In addition, the trichrome stains and hematoxylin and eosin stains did not reveal airway wall or alveolar thickening, fibrosis, or remodeling in any of the transgenic animals (data not shown). When viewed in combination, these studies demonstrate that LIF elaboration in the lung causes a lymphocytic infiltrate without mucus metaplasia, eosinophilia, or airway or alveolar remodeling.

Characterization of the Lymphocytic Infiltrate—Studies were next undertaken to define the lymphocytic infiltrate that was present in lungs from dox-treated transgene (+) mice. This was done by isolating the parenchymal cells from transgene (+) and transgene (-) mice that had been randomized for 3 months to normal water or dox water. FACS was then used to compare the surface markers on these cells. As can be seen in Fig. 5, differences in CD3, CD4, and CD8 cells were not readily appreciated. In contrast, an impressive increase in B220+ cells was appreciated in lungs from transgene (+) mice on dox for 3 months. These studies demonstrate that the majority of the lymphocytes in the lungs from the LIF transgenic mice are B lymphocytes.

Effect of LIF in Hyperoxic Acute Lung Injury (HALI)—To investigate the contribution(s) that LIF makes in ARDS, we compared the survival in 100% O2 of transgene (-) and transgene (+) mice on normal water and dox water. As can be seen in Fig. 6, transgene (-) mice on normal water and dox water died after 3–5 days of 100% O2 exposure. In contrast, transgene (+) mice on dox water manifested a markedly enhanced survival with 100% of the animals living for at least 6 days and >50% living for 8 days or more in these hyperoxic conditions (p < 0.002). Interestingly, transgene (+) mice on normal water lived for a slightly longer interval than transgene (-) mice on normal or dox water. This difference, however, was not statistically significant.

To characterize further the protective effects of LIF, we also compared the levels of protein in the BAL from the transgene (+) and transgene (-) animals on normal or dox water before and after the initiation of the hyperoxic exposure. At base line the levels of BAL protein were similar in the transgene (+) and transgene (-) mice on normal water or dox water (Fig. 6B). In contrast, impressive differences were noted after 100% O2 administration. These differences were readily appreciated after 48 h of 100% O2 exposure and were even more prominent after 72 h of hyperoxia. At the latter time point, transgene (-) mice on normal water or dox water and transgene (+) animals on normal water or dox water had BAL protein concentrations of 5.9 ± 1.2, 6.8 ± 1.7, 3.9 ± 0.5, and 1.6 ± 0.8 mg/ml, respectively (p < 0.01 comparing transgene (+) on dox water versus the other 3 groups; Fig. 6B). When viewed in combination, these studies demonstrate that transgenic LIF ameliorates HALI.

Effect of LIF on IL-6 Production—Studies were next undertaken to determine whether LIF induced the production of IL-6 or IL-11 which are known to ameliorate HALI (24, 25). IL-6 mRNA could not be detected in lungs from transgene (-) mice on normal water or dox water breathing room air or 100% O2 for up to 72 h (Fig. 7). Similarly, IL-6 mRNA was not appreciated in lungs from transgene (+) mice on normal water breathing room air or 100% O2 for up to 72 h (Fig. 7). In contrast, IL-6 mRNA...
mRNA was readily appreciated in lungs from dox-treated transgene (+) mice exposed to hyperoxia. This effect could be appreciated after 48 h of 100% O₂ exposure and was most prominent after 72 h of 100% O₂ exposure (Fig. 7 and data not shown). In all cases, the induction of IL-6 mRNA was associated with comparable alterations in IL-6 protein measurable by ELISA in BAL fluid (Fig. 7B). Comparable alterations in IL-11 were not appreciated. These studies demonstrate that LIF is a potent stimulator of IL-6 mRNA and protein accumulation in lungs from mice exposed to 100% oxygen.

**Role of IL-6 in LIF-induced Protection**—Because LIF induced IL-6 in the presence of hyperoxia, studies were undertaken to determine whether IL-6 played an important role in mediating the effects of LIF in this setting. To accomplish this, CC10-rtTA-LIF transgenic mice were bred with mice that were sufficient in IL-6 and mice with a null mutation in IL-6 (IL-6 (-/-)). The oxygen sensitivity of the resulting LIF (+)/IL-6 (+/+) mice (solid circles) and IL-6 (+)/IL-6 (-/-) animals (open circles) and wild-type mice (solid triangles) were then evaluated as described under “Experimental Procedures.” Each curve represents the survival of a minimum of eight animals (*, p < 0.05 versus LIF (+)/IL-6 (+/+)) animals).

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transgene (+) mice that had a null mutation in IL-6 because 100% of the LIF transgene (+)/IL-6 (-/-) animals died after 7.75 days of 100% O₂ exposure (p < 0.05) (Fig. 8). These studies demonstrate that the protective effects of LIF in 100% oxygen are mediated, in part, by endogenous IL-6.

**DISCUSSION**

In keeping with the large number of lung cells that elaborate LIF and the appreciation that elevated levels of LIF can be found in lungs from patients with ARDS, studies were undertaken to define the in vivo effector functions of this important cytokine. To accomplish this we used an inducible overexpression transgenic modeling system to generate transgenic mice in which LIF could be selectively overexpressed in the adult murine lung. The CC10 promoter was chosen to drive the system because airway epithelial cells are well documented producers of this cytokine (3, 14). These studies define, for the first time, the in vivo effector profile of viscerally targeted transgenic LIF in the lung or any other visceral organ. They demonstrate that
LIF selectively induces B cell hyperplasia, without inducing other inflammatory, mucus, or remodeling abnormalities. They also demonstrate that LIF has impressive protective effects in HALI that manifest as a decrease in alveolar-capillary permeability and enhanced survival. Finally, they demonstrate that, in 100% oxygen, LIF stimulates the production of IL-6 and that the protective effects of LIF in HALI are mediated, in part, via this inductive response. The IL-6-type cytokines, LIF, IL-6, IL-11, oncostatin-M, ciliary neurotropic factor, and cardiotoxin-1 are grouped together based on their shared use of gp130 as the β-subunit of their receptor complexes and the well documented overlap of their effector profiles (1, 24, 25). In accord with these commonalities, we expected to see structural similarities in comparisons of the phenotypes of the LIF transgenic mice and transgenic mice in which the CC10 promoter was used to drive the expression of IL-6 or IL-11 (26, 27). In accord with these expectations, B cell hyperplasia was noted in all three experimental systems. In contrast to the LIF transgenic, elevated levels of CD3+, CD4+, and of CD8+ cells were seen in the IL-11 and IL-6 transgenic animals (26, 27). In addition, airway remodeling with subepithelial fibrosis was a prominent feature in the lungs from the IL-6 and IL-11 transgenic mice (27, 28). Remodeling was conspicuous for its absence in the LIF transgenic animals. This lack of remodeling is in accord with recent studies (29) that demonstrate that LIF down-regulates myocardial cell remodeling responses including collagen production. Overall, these findings highlight similarities and prominent differences in the in vivo effector functions of LIF and other IL-6-type cytokines in the lung.

Supplemental oxygen is commonly given to patients with cardiopulmonary disorders to enhance tissue oxygenation. Unfortunately, the prolonged administration of a fractional inspired concentration of oxygen of more than 50–60% leads to acute lung injury and, when severe, ARDS. The pathophysiology of this pulmonary toxicity has been characterized in animal models. These studies demonstrated that toxic concentrations of oxygen generate oxygen-derived free radicals that damage lung epithelial cells and endothelial cells allowing a protein-rich fluid to flood the alveolar space (30–33). Jorens et al. (17) recently demonstrated that elevated levels of LIF can be found in BAL fluid from patients with ARDS. Interestingly, LIF was not detected in BAL from healthy controls and was detected in only 1 of 25 patients at risk for ARDS. These authors pointed out that the biologic role of LIF in the BAL fluids was not readily explained by the currently known actions of this cytokine and that it was not known if LIF contributed to or was a response to local tissue damage (17). To begin to address this issue, we determined if transgenic LIF altered the acute lung injury caused by 100% O2. Importantly, these were physiologically appropriate investigations because the levels of BAL LIF in our transgenic animals were comparable with those (10–985 pg/ml) in the human BAL fluids (17). These studies demonstrate that LIF has impressive protective effects in HALI. These effects manifest as a marked decrease in alveolar-capillary protein leak and a striking enhancement in survival. This is the first demonstration of a protective effect of LIF in the lung. The findings are in accord with previous studies demonstrating protective effects of LIF on cardiac myocytes in vitro (29) and in Escherichia coli sepsis in vivo (34).

IL-6 is a pleiotropic cytokine that is produced at sites of tissue inflammation. It induces fever, activates B and T lymphocytes, and stimulates hepatocytes to produce acute phase proteins (35). IL-6 has also been shown to have potent anti-inflammatory and protective properties. These include the ability to inhibit the production of tumor necrosis factor, IL-1, and MIP-2, decrease sequestration of neutrophils, increase the levels of IL-1 receptor antagonist and TNF soluble receptor, stimulate the production of matrix metalloproteinase inhibitors, reduce intracellular superoxide production, reduce matrix degradation, and inhibit cellular apoptosis (24, 36–38). Particularly relevant to these studies is our prior demonstration that IL-6 confers protection in the setting of HALI (24). The present studies demonstrate that LIF has a similar ability to ameliorate the ravages of hyperoxia. Interestingly, they also demonstrate that LIF and hyperoxia interact to induce the production of IL-6 and that this induction of IL-6 plays a critical role in LIF-induced tissue protection. IL-6 is known to induce LIF directly and augment the LIF production induced by other stimuli (3, 39, 40). When these observations are coupled with our observation that LIF induces IL-6, one can envision a positive feedback loop in which LIF and IL-6 induce the elaboration of one another. This amplification loop would serve to intensify the effects of LIF and IL-6 at sites of inflammation and injury.

In summary, the present studies demonstrate that transgenic LIF induces B cell hyperplasia and confers protection in the setting of hyperoxic lung injury. They also demonstrate that LIF is a potent inducer of IL-6 in hyperoxia in vivo and that the protective effects of LIF in HALI are mediated, in part, via this inductive response. When viewed in combination, these studies suggest that LIF, alone or in combination with IL-6, may contribute to B cell-mediated responses and disorders in the lung. They also suggest that LIF may play an important role in limiting oxidant injury states in the respiratory system. LIF is produced in many different circumstances in the lung, and toxic concentrations of oxygen are prescribed on a daily basis to a large number of patients throughout the world. Thus, additional investigations are warranted to define the mechanism(s) that mediate the protective effects of LIF and evaluate the utility of LIF (alone or in combination with IL-6) as a therapy for HALI and other oxidant-induced pulmonary disorders.

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