

Requirement of Interleukin 17 Receptor Signaling for Lung CXC Chemokine and Granulocyte Colony-stimulating Factor Expression, Neutrophil Recruitment, and Host Defense

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Abstract

Bacterial pneumonia is an increasing complication of HIV infection and inversely correlates with the CD4⁺ lymphocyte count. Interleukin (IL)-17 is a cytokine produced principally by CD4⁺ T cells, which induces granulopoiesis via granulocyte colony-stimulating factor (G-CSF) production and induces CXC chemokines. We hypothesized that IL-17 receptor (IL-17R) signaling is critical for G-CSF and CXC chemokine production and lung host defenses. To test this, we used a model of *Klebsiella pneumoniae* lung infection in mice genetically deficient in IL-17R or in mice overexpressing a soluble IL-17R. IL-17R-deficient mice were exquisitely sensitive to intranasal *K. pneumoniae* with 100% mortality after 48 h compared with only 40% mortality in controls. IL-17R knockout (KO) mice displayed a significant delay in neutrophil recruitment into the alveolar space, and had greater dissemination of *K. pneumoniae* compared with control mice. This defect was associated with a significant reduction in steady-state levels of G-CSF and macrophage inflammatory protein (MIP)-2 mRNA and protein in the lung in response to the *K. pneumoniae* challenge in IL-17R KO mice. Thus, IL-17R signaling is critical for optimal production of G-CSF and MIP-2 and local control of pulmonary *K. pneumoniae* infection. These data support impaired IL-17R signaling as a potential mechanism by which deficiency of CD4 lymphocytes predisposes to bacterial pneumonia.

Key words: IL-17 • T lymphocyte • granulocyte-colony stimulating factor • *Klebsiella pneumoniae* • chemokine

Introduction

The development of bacterial pneumonia depends on a complex interplay between virulence factors of the organism and lung host defenses. Host resistance requires both innate and adaptive immune responses, which are largely initiated by growth factors termed cytokines. Bacterial pneumonias are an increasingly recognized complication of HIV infection and the incidence of these infections inversely correlates with the CD4⁺ lymphocyte count (1, 2). Some investigators have hypothesized that the increased susceptibility to bacterial pneumonia is due to lack of T cell help and generation of opsonic antibody by B cells (3). Re-

cently a novel cytokine, IL-17, has been found to be produced largely by activated CD4⁺ lymphocytes (4, 5). IL-17 has been shown to stimulate granulopoiesis both in vitro (6) and in vivo (7). Our laboratory has demonstrated that induction of in vivo granulopoiesis by IL-17 is partly due to stimulation of G-CSF and the transmembrane form of stem cell factor (8). Moreover, IL-17 has been shown to induce the production of TNF- α (9) and CXC chemokines (10) in the lung, and our lab has demonstrated its release into the lung in experimental *Klebsiella pneumoniae* infection (11). In contrast to the relative restriction of IL-17, the IL-17R is ubiquitously expressed in a variety of tissues (12). Based on these data we hypothesized that IL-17R signaling is critical for lung CXC chemokine generation, induction of G-CSF, a cytokine required for ongoing neu-

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trophil production in response to infection, and lung host defense (13). We tested this hypothesis in mice deficient in IL-17R signaling using IL-17R knockout (KO)* mice or mice overexpressing a soluble IL-17R:Fc fusion protein to exclude a development defect associated with the IL-17R KO mice. Using a well-described model of *K. pneumoniae* infection we found that IL-17R signaling is critical for early neutrophil recruitment and local induction of G-CSF and macrophage inflammatory protein (MIP)-2 at both the mRNA and protein level. Moreover, IL-17R-deficient mice had a significantly greater incidence of bacteremia and mortality in response to *K. pneumoniae* infection.

Materials and Methods

Generation of IL-17R-deficient Mice by Homologous Recombination. Genomic clones encoding murine IL-17R were isolated from a 129 derived lambda library using a murine IL-17R cDNA probe (4) and mapped by a combination of PCR, restriction digest, and sequence analyses using deposited genomic sequences corresponding to IL-17R locus on mouse chromosome 6 (GenBank/EMBL/DBJ accession no. AC018559). A gene targeting vector was constructed by replacing 5.7 kb of genomic sequence containing exons 4–11 (corresponding to nucleotides 445–1,172 of the murine IL-17R cDNA) with a PGKneo cassette. A thymidine kinase cassette (MC-TK) was inserted into the 5' end of the vector. 129 derived embryonic stem (ES) cells were electroporated with the targeting vector and selected in the presence of G418 and ganciclovir as described (14). ES clones carrying a targeted mutation in IL-17R were identified by a combination of PCR and genomic Southern blot analyses and were injected into C57BL/6 blastocysts. The resulting male chimeras were crossed to C57BL/6 females to generate mice heterozygous for the IL-17R mutation (IL-17R^{+/-}), which were subsequently intercrossed to generate IL-17R-deficient mice (IL-17R KO). These mice were moved to a C57BL/6 background by five successive backcrosses to C57BL/6 mice.

Animals. Specific pathogen-free C57BL/6 mice (6–8-wk-old, male, average weight 25 g; National Cancer Institute, Frederick, MD) were used in all experiments as the control mice. IL-17R KO mice were obtained from Immunex Corporation and bred in LSUHSC Animal Care Facilities. The IL-17R KO mice were confirmed genetically by PCR. Male 6–8-wk-old IL-17R KO and C57BL/6 mice were used in this study. IL-17R^{+/-} mice were generated by crossing IL-17R KO mice with C57BL/6 mice. All mice were housed in specific pathogen-free room within the Animal Care Facility of Louisiana State University Medical Center Vivarium under an IACUC-approved protocol, provided with water ad libitum and food, and housed under 12-h light/dark cycles until date of experiment.

IL-17 Binding and Flow Cytometry. Surface IL-17R expression was detected by flow cytometry using murine IL-17:Fc on gated populations of either splenocytes, or peritoneal exudate cells obtained 18 h after intraperitoneal injection of 3 ml 3% thioglycollate broth (Sigma-Aldrich). Briefly, after incubation in 50 μ l blocking buffer containing 2% normal mouse serum, 2%

normal goat serum, and 10 μ g Fc Block (BD PharMingen), 10⁶ cells were incubated with either 20 μ g/ml murine IL-17:Fc or the negative control, human IL-4R:Fc, and then stained with biotinylated mouse anti-human IgG1 Fc (Jackson ImmunoResearch Laboratories) and streptavidin-allophycocyanin (APC; BD PharMingen). PE- and FITC-conjugated antibodies against CD4, CD8, Gr-1, and CD19 were purchased from BD PharMingen.

***K. pneumoniae* Infection.** *K. pneumoniae* strain 43816, serotype 2 (American Type Culture Collection) was grown in tryptic soy broth (Difco) for 18 h at 37°C. 1 ml of the culture was added into 200 ml of fresh tryptic soy broth, and grown for another 2 h until the organism reached log phase. Bacteria was pelleted by centrifugation at 5,000 rpm for 15 min, washed twice in PBS, and resuspended at desired concentration. The concentration of *K. pneumoniae* was determined by measuring the absorbency at 600 nm. A standard of absorbencies based on known CFUs was used to calculate inoculum concentration. For inoculation, mice were briefly anesthetized with ether. The bacterial inoculum (50 μ l) was applied to the nose tip of mouse with a pipet tip and involuntarily inhaled. Mice were held vertically for 2 min after the inoculation.

Bronchoalveolar Lavage. At serial time points, mice were anesthetized with Ketamine (Schering-Plough Animal Health Corp). A tracheal cannula was inserted into the upper cervical trachea through a tracheotomy. The lungs were lavaged with 0.5-ml aliquots of warmed PBS + 0.5 mM EDTA up to 11 ml. The first ml of recovered bronchoalveolar lavage (BAL) fluid was centrifuged at 500 g and the supernatant was stored at -80°C for subsequent cytokine ELISAs. The remaining cell pellet was combined with the other lavage fluid and analyzed for total cell count followed by differential cell counts performed in cytopins stained with Wright-Giemsa (Baxter McGaw Park).

Lung Histological Examination. At serial time points, mice were anesthetized followed by euthanasia by transection of the abdominal aorta. The lungs were removed en bloc and inflated with 10% formalin up to 20 cm H₂O. The lungs were placed in 10% formalin and subsequently embedded in paraffin. Sections were stained with hematoxylin and eosin for histological examination.

***K. pneumoniae* CFU in Lung Homogenates.** At serial time points after *K. pneumoniae* challenge, mice were killed and the lungs were then removed aseptically. The lung was placed in sterile PBS (volume ml = 0.9 \times the lung tissue weight g) and homogenized with a tissue homogenizer. The lung homogenates were placed on ice, and serial 1:10 dilutions were made. 10 μ l of each dilution were plated on soy base blood agar plates (Difco) and incubated for 18 h at 37°C, then colonies were counted. Bacterial concentrations were expressed in terms of CFU/lung.

Total RNA Isolation and Ribonuclease Protection Assays. At serial time points after *K. pneumoniae* infection, mice were euthanized and the lungs were perfused blood free by injection of PBS through the right ventricle. Lungs were homogenized in Trizol solution (Life Technologies). 20 μ g of total RNA from each sample was used for ribonuclease protection assay (RPA) with mCK-4 and mCK-5 templates, purchased from BD PharMingen, following the manufacturer's protocol.

ELISA for MIP-2, G-CSF, and IL-17. MIP-2 and IL-17 was measured by ELISA kits (R&D Systems) following the manufacturer's protocol. G-CSF was measured using a sandwich ELISA using matched antibody pairs from R&D Systems.

Statistical Analysis. Comparison between means was performed with analysis of variance (ANOVA) followed by Fisher's follow-up testing. Survival comparisons were performed using Kaplan-Meier analysis (StatView; Abacus Concepts). *P* < 0.05 was considered to represent a significant difference.

*Abbreviations used in this paper: ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; ES, embryonic stem; KO, knockout; MIP, macrophage inflammatory protein; RPA, ribonuclease protection assay; SCF, stem cell factor.

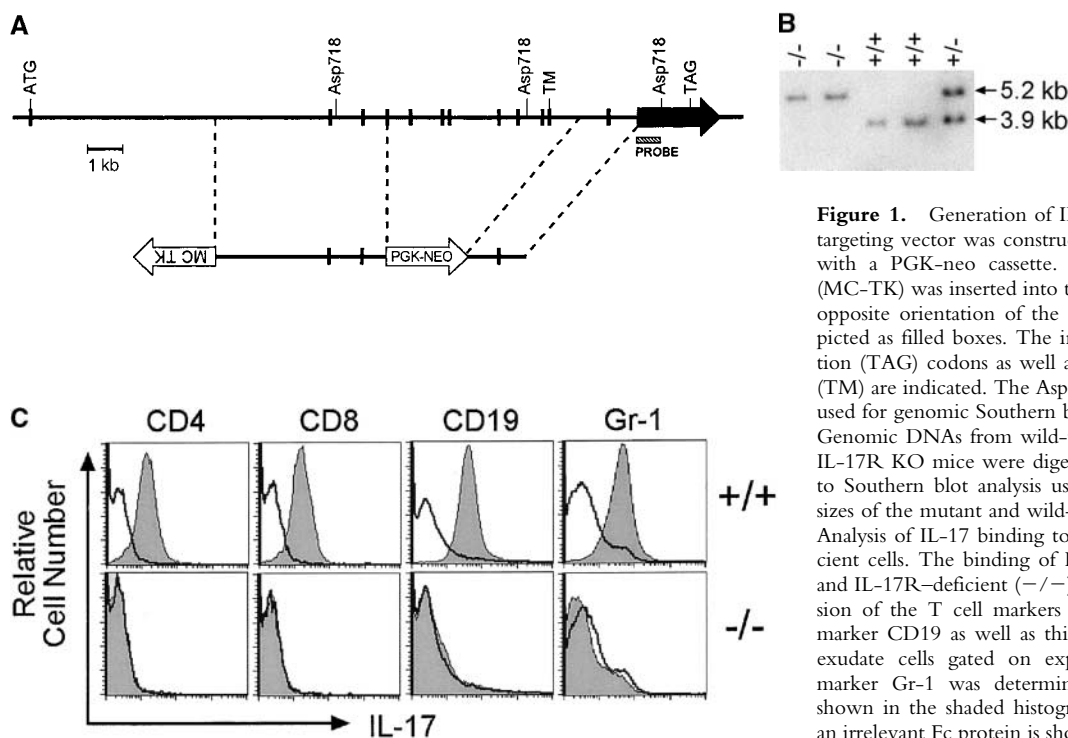
Results

Generation of IL-17R KO Mice. Mice genetically deficient in IL-17R (IL-17R KO) were generated by homologous recombination in ES cells using a targeting vector that replaces exons 4–11, encoding nucleotides 445–1,172 of the IL-17R cDNA (4), with a PGK-neo cassette (Fig. 1 A). Southern blot analyses of genomic DNAs derived from wild-type, IL-17R^{+/-}, and IL-17R KO genomic confirmed that the IL-17R gene was disrupted by specific gene targeting (Fig. 1 B). IL-17R KO mice were born at the expected Mendelian frequency from IL-17R^{+/-} intercrosses (data not shown) and displayed no gross external phenotype. To confirm that the targeted mutation abrogates IL-17 binding, flow cytometric analyses using IL-17:Fc (4) were performed on subpopulations of wild-type and IL-17R KO spleen and peritoneal exudate cells. As shown in Fig. 1 C, IL-17R KO T cells, B cells, and myeloid cells fail to bind IL-17, whereas binding is clearly observed to wild-type cells.

IL-17R Signaling Is Required for Survival Against *K. pneumoniae* Infection. Pilot studies were performed with varying doses (3×10^3 – 10^6 CFU) of *K. pneumoniae* given intranasally to 6–8-wk-old male C57BL/6 mice ($n = 56$). Based on these experiments, the LD₅₀ (at 12 d) of *K. pneumoniae* was determined to be 3×10^4 CFU. We have previously shown that this inoculum can induce IL-17 within 12 h of infection in the lungs of mice (11). Based on these studies we chose 3×10^3 and 10^4 CFU for subsequent intranasal challenges in control and IL-17R-deficient mice. IL-17R KO mice showed a significantly reduced survival rate after *K. pneumoniae* inoculation. At the 10^4 CFU dose, 100% of IL-17R KO mice perished by 48 h, compared with only

20% of the controls (Fig. 2 A). At 3×10^3 CFU dose, 80% of IL-17R KO mice were dead by day 7, compared with only 40% of the controls (Fig. 2 A). Although IL-17R KO mice have normal peripheral blood counts and normal numbers of CD4⁺ and CD8⁺ lymphocytes in the blood and spleen (12), we needed to exclude any potential developmental defects in these mice, which could, in part, explain a reduced survival to *K. pneumoniae* challenge. To accomplish this, we constructed a fusion protein consisting of the IL-17R extracellular domain with the murine IgG₁ CH2 and CH3 domains using recombinant PCR as described previously by our group with the TNF p55 extracellular domain (15). The IL-17R:Fc fusion protein migrated as a 140-kD dimer on nonreduced SDS-PAGE (Fig. 2 B). Moreover, this protein is biologically active, as it significantly inhibited recombinant IL-17-induced production of IL-6 by 3T3 fibroblasts (data not shown). To express this construct in vivo we generated an E1-deleted recombinant adenovirus (AdIL17R/Fc) as described previously (15). C57BL/6 mice were administered 10^9 PFU of AdIL17R/Fc or AdLuc (which encodes firefly luciferase) as a control. 72 h later (the time of maximal expression of the IL-17R:Fc fusion protein), mice were given an intranasal challenge with 3×10^3 CFU *K. pneumoniae*. Parallel studies were performed in IL-17R KO mice or littermate controls. Both AdIL-17R/Fc-treated mice and IL-17R KO mice had a similar phenotype in that their survival was significantly worse than control mice (Fig. 2 C).

Lung Bacterial Burden after *K. pneumoniae* Intranasal Challenge. The bacterial burden of *K. pneumoniae* was determined by quantitative culture of lung homogenates. Intra-



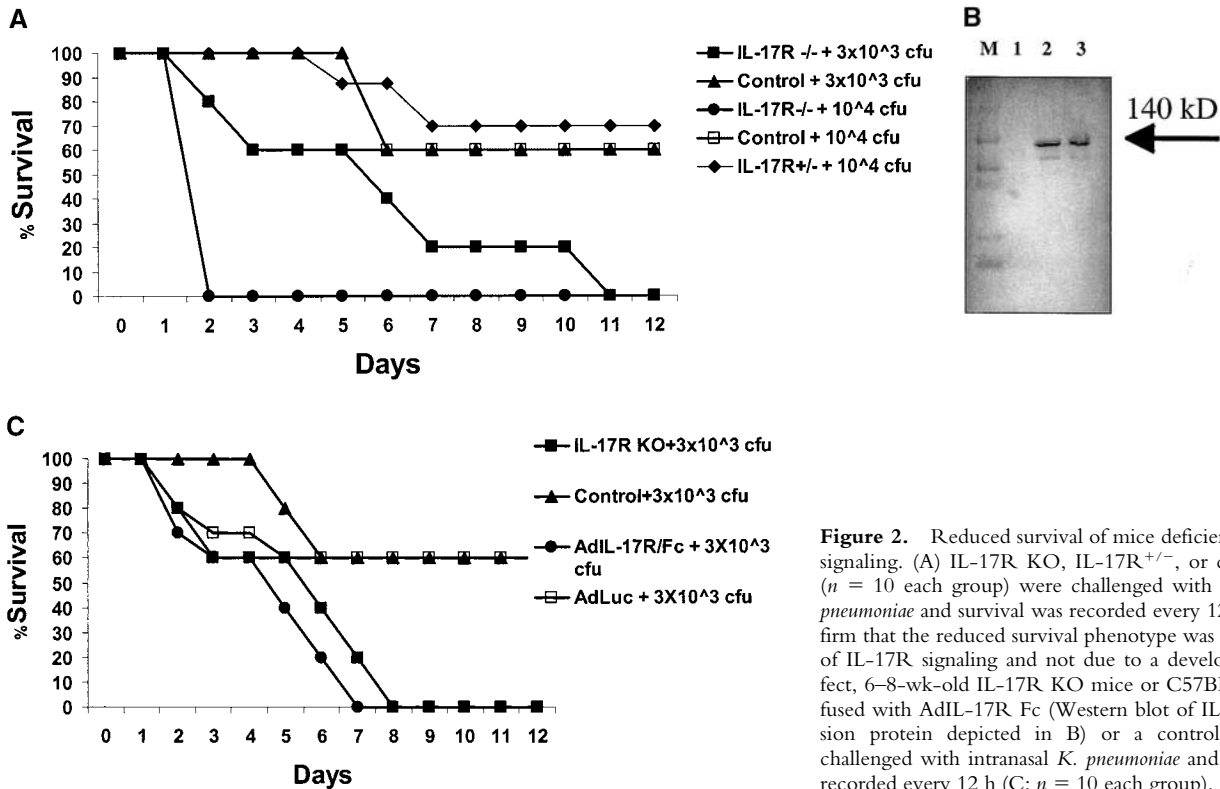


Figure 2. Reduced survival of mice deficient in IL-17R signaling. (A) IL-17R KO, IL-17R^{+/-}, or control mice ($n = 10$ each group) were challenged with intranasal *K. pneumoniae* and survival was recorded every 12 h. To confirm that the reduced survival phenotype was due to a lack of IL-17R signaling and not due to a developmental defect, 6–8-wk-old IL-17R KO mice or C57BL/6 mice infused with AdIL-17R Fc (Western blot of IL-17R/Fc fusion protein depicted in B) or a control virus were challenged with intranasal *K. pneumoniae* and survival was recorded every 12 h (C; $n = 10$ each group).

pulmonary growth of *K. pneumoniae* was similar in control and IL-17R KO mice for the first 18 h of infection (Fig. 3). However, by 24 h there were significantly greater organisms in the lungs of IL-17R KO mice compared with control mice. This accentuated growth was observed up to 48 h. Thereafter, there was significant mortality in the IL-17R KO mice and thus comparisons of bacterial burdens at late time points between the IL-17R KO mice and control mice were not made due to selection bias for surviving mice. However, surviving control mice showed a decline in lung burden by 56 h (data not shown). Moreover, IL-17R KO mice all had positive spleen culture at 18 h after *K. pneumoniae* challenge ($n = 10$) compared with only 2 of 10 control mice.

Failure of IL-17R KO Mice to Mobilize and Recruit Neutrophils to the Lung. Absolute neutrophil counts (ANCs) were

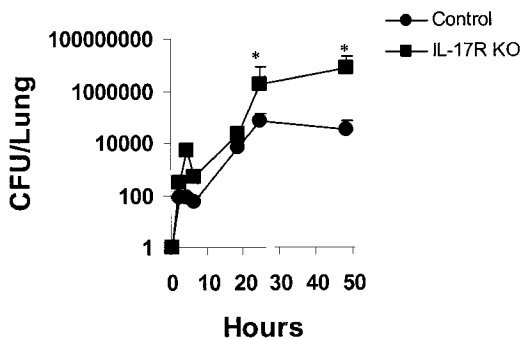


Figure 3. *K. pneumoniae* growth curves in control and IL-17R KO mice ($n = 4-6$, $*P < 0.05$).

measured in blood and BAL fluid over time in control and IL-17R KO mice after *K. pneumoniae* challenge. Baseline blood ANC was similar in both groups of mice (Fig. 4 A). After *K. pneumoniae* challenge, control mice demonstrated a mild increase in blood ANCs up to 6 h, which was not observed in IL-17R KO mice (Fig. 4 A). Both groups of mice showed a transient fall in blood ANCs at 6 h. This was followed by a significant increase in blood ANCs in control mice, which peaked at 18 h, and slowly declined as the infection was controlled (Fig. 4 A). In contrast, IL-17R KO mice showed a significant attenuation in blood ANCs at 18, 24, and 48 h and these mice were significantly neutropenic by 48 h, consistent with overwhelming infection. Control mice demonstrated the ability to recruit significant numbers of neutrophils into the lung, as measured by the ANCs in the BAL fluid (Fig. 4 B). In contrast, IL-17R KO mice displayed decreased neutrophil recruitment, which was statistically lower than control mice up to 18 h into the infection (Fig. 4 B). This decreased neutrophil recruitment was also supported by a reduced level of lung myeloperoxidase activity measured at 12 h into the infection (Fig. 4 C).

Lungs from both control and IL-17R KO mice were morphologically normal before *K. pneumoniae* challenge (Fig. 5). 18 h after 10⁴ CFU, both groups of animals showed focal peribronchiolar inflammation (Fig. 5). However, by 24 h, IL-17R KO mice developed significant areas of perivascular edema and associated with large number of organisms in the perivascular space (Fig. 5). The combination of delayed neutrophil recruitment and the early dissemination of bacteria as measured by splenic culture and

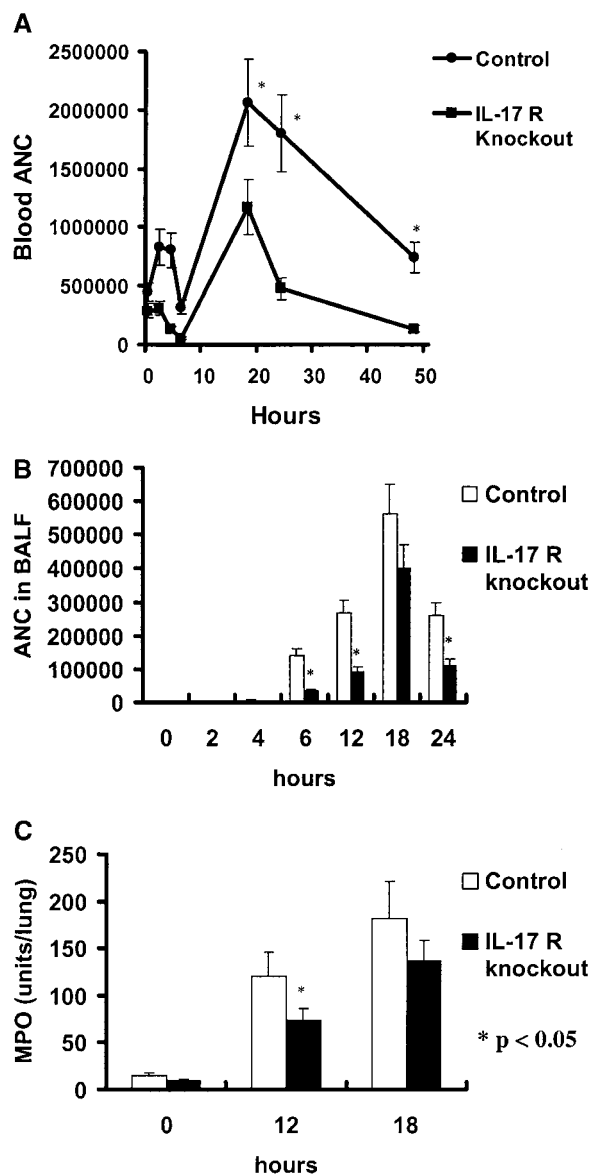


Figure 4. Reduced ANCs in the blood and lungs of IL-17R KO mice in response to *K. pneumoniae* infection. (A) Attenuation of increase in blood ANC in IL-17 R KO mice ($n = 5-8$, * denotes $P < 0.05$). (B) Reduction in lung neutrophil recruitment as measured as ANCs in BAL fluid (BALF) in IL-17R KO mice ($n = 5-8$, * denotes $P < 0.05$). (C) The reduced lung neutrophil recruitment was associated with a significant decrease in lung MPO activity in IL-17 R KO mice ($n = 5-8$, * denotes $P < 0.05$).

histologically by perivascular organisms led us to investigate known factors involved in early host defense against *K. pneumoniae*, specifically the CXC chemokine, MIP-2 (16). Moreover, a failure to increase peripheral blood ANCs suggested that IL-17R signaling was required for infection-induced granulopoiesis, which is partly dependent on G-CSF and stem cell factor (SCF; reference 8). This led us to investigate whether IL-17R signaling was involved in lung MIP-2, G-CSF, and SCF production.

Failure of IL-17R KO Mice to Induce expression of MIP-2, G-CSF, and SCF. For these experiments both IL-17R

KO and control mice were challenged intranasally with 10^4 CFU of *K. pneumoniae*. 12 h later when bacterial burdens were similar, but myeloperoxidase (MPO) and neutrophil recruitment were significantly different between both groups of animals, mice were killed and total RNA was isolated from whole lung. Transcripts for G-CSF, SCF, and MIP-2 were measured by RPA. Transcripts were normalized to the L32 transcript. The results indicated that after the *K. pneumoniae* challenge, IL-17R KO mice failed to significantly induce either G-CSF or SCF (Fig. 6). No G-CSF or SCF transcripts were detected in unchallenged IL-17R KO or control mice (data not shown). Moreover, IL-17R KO mice also demonstrated significantly lower transcripts for MIP-1 α , MIP-1 β , and MIP-2 (Fig. 6). Attenuation of lung MIP-2 in IL-17R KO mice was also confirmed at the protein level at both 12 and 24 h after *K. pneumoniae* infection. No G-CSF protein was detected in the BAL fluid 12 h after *K. pneumoniae* infection. However, G-CSF was readily detectable at 24 h in BAL fluid of control mice but was reduced by over 60% in IL-17R KO mice (Fig. 7). IL-17 was also readily detectable in BAL fluid at 12 and 18 h after *K. pneumoniae* infection in both control and IL-17R KO mice (Fig. 7) and thus, local release of IL-17 is part of the normal host response to this infection.

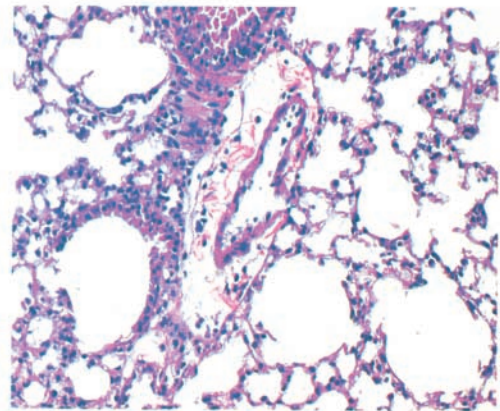
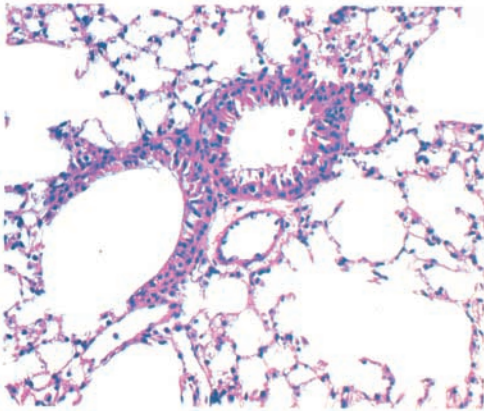
Our laboratory has previously shown that G-CSF is not compartmentalized in the lung such as other growth factors such as TNF (17, 18). Thus, the lung may be a significant source of G-CSF during infection, which results in an appropriate granulopoietic response (17). To investigate whether granulopoiesis was altered in response to infection, splenic CFU-GM and high proliferative potential (HPP) colonies were measured at 0 and 18 h after *K. pneumoniae* infection, as described previously (7). Control mice demonstrated a $98 \pm 16\%$ increase in CFU-GM and a $189 \pm 31\%$ increase in HPP, whereas IL-17R KO mice showed a $7 \pm 5\%$ and a $15 \pm 8\%$ decrease ($P < 0.01$, ANOVA). These data are consistent with the fact that IL-17R KO could not appropriately increase their ANCs in response to *K. pneumoniae* infection (Fig. 4).

Discussion

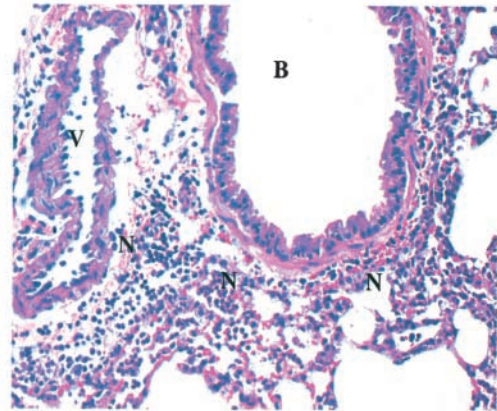
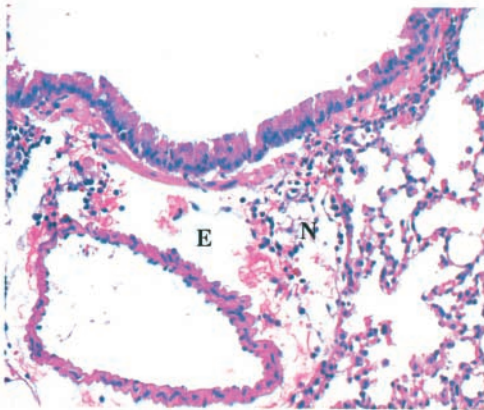
IL-17, a 32-kD dimer, is a cytokine produced principally by activated CD4⁺ T cells. It signals through a unique type I transmembrane receptor, which is ubiquitously distributed. Interestingly, the cytoplasmic domain has no known homology with existing known signaling pathways (12). IL-17 clearly supports hematopoiesis both in vitro and in vivo (6, 7). IL-17-induced hematopoiesis results in maturation of cells along the granulocytic pathway (6, 7). Moreover, IL-17 has been shown to induce translocation of nuclear factor (NF)- κ B and production of IL-1 and TNF by monocyte/macrophages (9). The proinflammatory nature of this cytokine has also been implicated in inflammatory arthritis (9, 19, 20), lung inflammation (10, 21), organ allograft rejection (22), and infection with *K. pneumoniae* (11). To further define the role of this ligand/receptor in

Control

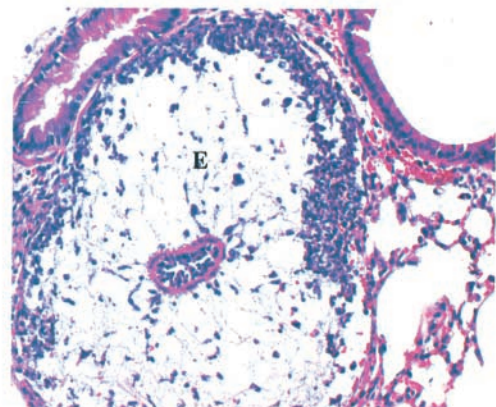
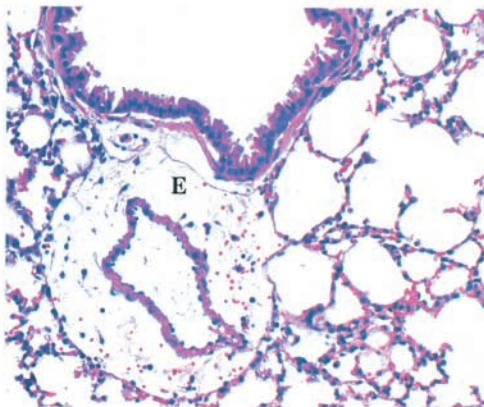
IL-17 R -/-



Time = 0 hours



Time = 18 hours



Time = 24 hours

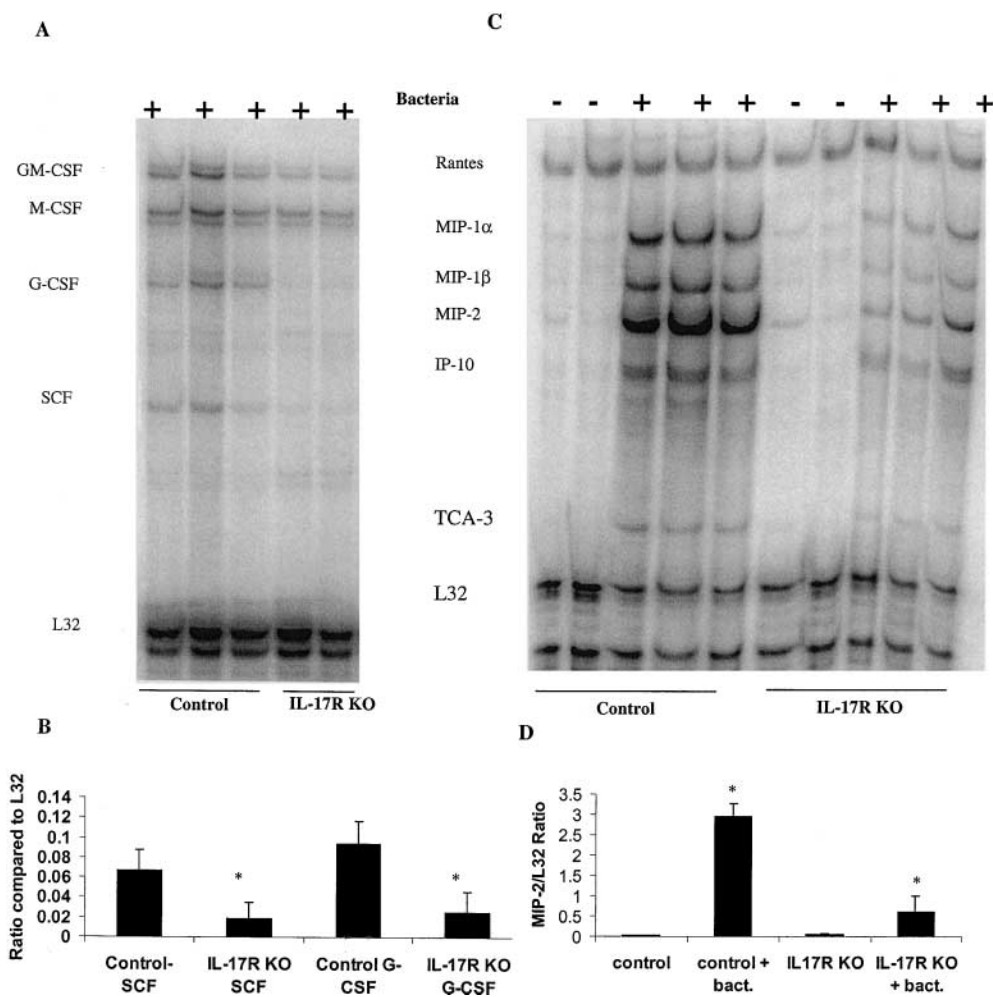


Figure 6. Analysis of lung gene expression by RPA. (A) Representative gel of lung G-CSF and SCF gene expression after *K. pneumoniae* challenge. (B) Densitometric analysis of G-CSF and SCF gene expression ($n = 3-4$, $*P < 0.05$). (C) Representative gel of lung chemokine gene expression after *K. pneumoniae* challenge. (D) Densitometric analysis of MIP-2 gene expression ($n = 3-4$, $*P < 0.05$). bact., bacteria.

regulating inflammatory response, we analyzed the response of mice deficient in IL-17 signaling to *K. pneumoniae* infection. We chose this model because host defense is dependent on CXC chemokine expression (16) and data

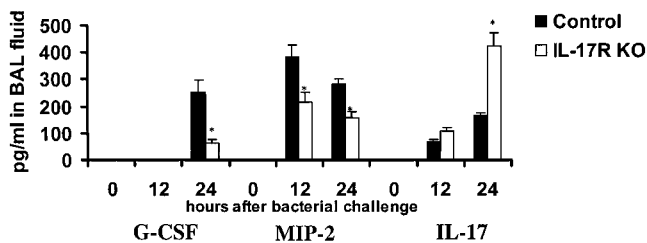


Figure 7. BAL fluid levels of G-CSF, MIP-2, and IL-17 after *K. pneumoniae* challenge.

Figure 5. Representative lung histology of control and IL-17R KO mice after *K. pneumoniae* challenge. At 0 h, the lungs of control wild-type mice and IL-17R KO mice were essentially normal with no inflammatory infiltrate and mild edema. 18 h after infection there is minimal perivascular infiltration of neutrophils and moderate edema in the lungs of wild-type mice at 18 h after infection. In contrast, IL-17R KO mice had perivascular, peribronchiolar, and intraalveolar neutrophils at 18 h after infection associated with moderate diffuse perivascular edema. At 24 h after infection, wild-type mice had minimal perivascular infiltration of neutrophils and moderate edema in the lungs. In contrast, IL17R^{-/-} mice had severe perivascular edema that partially compressed and distorted adjacent alveoli. Within, and marginating the edema were large numbers of degenerate neutrophils and large numbers of bacterial rods compared with few visible bacteria in control mice (all images 40 \times).

from our laboratory and others has demonstrated that IL-17 is a potent inducer of lung chemokine expression (10). Moreover, microbial lipopeptides have been shown to be potent inducers of IL-17 in T cells (23).

Our data demonstrate that IL-17R signaling is critical for lung chemokine gene expression, early lung neutrophil recruitment, and survival against *K. pneumoniae* challenge. Moreover, IL-17 was readily detectable in BAL fluid as early as 12 h after *K. pneumoniae* infection and thus is a normal response to infection with this pathogen. In fact, IL-17R KO mice had higher levels of IL-17, suggesting that this receptor is important in clearance of IL-17 from the lung. Although we did not directly investigate the source of IL-17 in the lung in these studies, studies ongoing in our laboratory support the fact that both CD4⁺ and CD8⁺ T cells are detectable in the lung as early as 6 h after *K. pneu-*

moniae infection, and represent a significant source of IL-17 in this infection model, as described previously (4, 5). These data further suggest that lung lymphocytes can influence antibacterial host defenses within the first 12–24 h of infection, which is largely an innate response. In further support of this concept, our laboratory has previously shown that depletion of CD4⁺ T cells can attenuate lung macrophage production of TNF after intratracheal endotoxin administration (24).

In summary, our study shows that the lack of signaling via IL-17Rs severely impairs host defense against *K. pneumoniae* infection in a mouse model. We found that the ANC both in blood and lungs in IL-17R KO mice was significantly lower compared with control mice after infection. Moreover, this failure to increase the ANCs in blood was associated with failure to increase neutrophil progenitors in splenic CFU assays. IL-17R KO mice failed to normally induce MIP-2, a chemokine gene critical for neutrophils diapedesis and chemotaxis into the lung (16), and G-CSF, a growth factor that is produced in the lung in response to infection, which secondarily increases granulopoiesis (13). The excessive growth of bacteria in the lungs of IL-17R KO mice was associated with significantly more perivascular edema and bacterial dissemination compared with control mice. These data demonstrate that signaling through the IL-17R is critical for lung PMN recruitment and host defenses against *K. pneumoniae*. We speculate that relative IL-17 deficiency may in part explain the pulmonary host defense defect associated with either HIV infection or congenital immunodeficiency of CD4⁺ lymphocytes.

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