The role of interferon-gamma in murine pneumococcal pneumonia


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The Role of Interferon-γ in Murine Pneumococcal Pneumonia

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To determine the role of interferon (IFN)–γ in pneumonia, IFN-γ receptor–deficient (IFN-γ R<sup>−/−</sup>) and 129/Sv (wild-type [wt]) mice were inoculated intranasally with Streptococcus pneumoniae. Although mortality did not differ between the groups 48 h after inoculation, IFN-γ R<sup>−/−</sup> mice had significantly fewer pneumococci in their lungs than the wt mice. Similarly, IFN-γR<sup>−/−</sup> mice had fewer colony-forming units in lungs than wt mice. The relatively increased resistance of IFN-γ R<sup>−/−</sup> mice was not related to favorable effects on defense mechanisms known to contribute to antibacterial immunity—that is, the neutrophilic influx was reduced and the cytokine and nitric oxide levels were similar or lower in IFN-γ R<sup>−/−</sup> mice. In contrast, mice treated with anti–IFN-γ did not demonstrate a consistently altered bacterial outgrowth, compared with mice treated with a control antibody. These data suggest that endogenous IFN-γ, despite its protective role in defense against intracellular pathogens, does not serve a protective role during pneumococcal pneumonia.

Streptococcus pneumoniae is a gram-positive bacterium responsible for >50% of the cases of community-acquired pneumonia. Pneumococcal pneumonia is the fifth leading cause of death worldwide, and, among patients with community-acquired pneumonia who require hospitalization, the mortality rate is as high as 25% [1, 2]. Against this background, and because of the growing resistance of the pneumococcus to antibiotics, the role of IFN-γ in the pathogenesis of pneumococcal pneumonia [3]. Innate defense mechanisms play an important role in the elimination of bacteria from the alveolus. Phagocytic cells, as well as resident NK cells and T cells, participate in this response via the elaboration of chemotactic and regulatory cytokines [4]. Interferon (IFN)–γ is a potent proinflammatory cytokine, produced mainly by antigen-activated T and NK cells. IFN-γ exerts several immune regulatory activities, including activation of phagocytes, stimulation of antigen presentation by increasing the expression of class I and II major histocompatibility complex molecules on antigen-presenting cells, orchestration of leukocyte-endothelium interactions, and stimulation of the respiratory burst [5, 6].

IFN-γ is considered to play a pivotal role in host defense against several infectious diseases. Peritoneal and alveolar macrophages can be activated by IFN-γ in vitro to express enhanced antimicrobial activity [7–10]. Mice deficient in IFN-γ (IFN-γ R<sup>−/−</sup>) or in the IFN-γ receptor (IFN-γ R<sup>−/−</sup>) have demonstrated impaired pulmonary clearance of Toxoplasma gondii, Listeria monocytogenes, Mycobacterium tuberculosis, and Legionella pneumophila [11–15]. Furthermore, treatment with IFN-γ improved the outcome in these models [16–19].

The role of IFN-γ in the pathogenesis of bacterial pneumonia is not well defined. In a rat model of chronic Pseudomonas aeruginosa pneumonia, intraperitoneal administration of IFN-γ resulted in improved clearance of bacteria from the lung [20]. In addition, in one study, IFN-γ R<sup>−/−</sup> mice showed increased mortality during bacteremic pneumococcal pneumonia [21]. In the latter investigation, however, neither bacterial outgrowth in lungs nor associated pulmonary inflammatory responses were reported. Therefore, in the present study, we sought to determine the role of IFN-γ in host defense mechanisms during pneumococcal pneumonia, using IFN-γ R<sup>−/−</sup> and IFN-γR<sup>−/−</sup> mice.

Materials and Methods

Animals. Male IFN-γ R<sup>−/−</sup> and wild-type (wt) mice, 10–12 weeks old, both of the 129/SvEv genetic background, were kindly donated by M. Kopf (Basel Institute for Immunology) [22]. IFN-γ R<sup>−/−</sup> BALB/c mice were purchased from The Jackson Laboratories; wt BALB/c mice were purchased from Harland Sprague Dawley. In all experiments, sex- and age-matched mice were used.

Reagents. The R46A2 rat anti–mouse IFN-γ IgG1 monoclonal antibody (MAb) and LO-DNP-2, a control rat IgG1 MAb [23], were
produced in ascites and were kindly provided by M. Goldman (Université Libre de Bruxelles). The endotoxin levels were <15 pg/mL as determined by a limulus amoebocyte lysate essay (LAL-QCL-1000; Whittaker Bioproducts). A 1-mg dose of anti–IFN-γ MAb or the same amount of control MAb was given to BALB/c mice intraperitoneally 2 h before inoculation with S. pneumoniae. Anti–IFN-γ MAb R46A2, given at a dose of 0.5 mg, has been demonstrated elsewhere to reduce mortality in mice after administration of staphylococcal enterotoxin B [24] or endotoxin [25].

Induction of pneumonia. Pneumonia was induced as described elsewhere [26–28]. In brief, S. pneumoniae serotype 3 was obtained from the American Type Culture Collection (ATCC 6303). Pneumococci were grown for 6 h at 37°C to midlogarithmic phase on Todd-Hewitt broth (Difco), in 5% CO₂, were harvested by centrifugation at 1500 g for 15 min, and were washed twice in sterile isotonic saline. Bacteria were then resuspended in sterile isotonic saline at different concentrations (2 × 10⁶–10⁹ cfu/mL), as determined by plating serial 10-fold dilutions onto sheep-blood agar plates. Mice were lightly anesthetized by inhalation of isoflurane (Abbott), and 100 μL was inoculated intratracheally. Some mice were inoculated intranasally with 50 μL of sterile isotonic saline only (control mice).

Preparation of lung homogenates. At 24 and 48 h after inoculation, mice were anesthetized by intraperitoneal injection of fentanyl and fluanisone (Hypnorm; Janssen Pharmaceutica) and midazolam (Roche), and blood was collected from the vena cava inferior. After mice were killed, whole lungs were harvested and were homogenized at 4°C in 5 vol of sterile isotonic saline with a tissue homogenizer (Biospect Products), which was carefully cleaned and disinfected with 70% alcohol after each homogenization. Serial 10-fold dilutions in sterile isotonic saline were made of these homogenates (and blood), and 50-μL volumes were plated onto sheep-blood agar plates and incubated at 37°C with 5% CO₂. Colony-forming units were counted after 16 h. For cytokine measurements, lung homogenates were lyzed in lysis buffer (300 mM NaCl, 15 mM Tris, 2 mM MgCl₂, 2 mM Triton [X-100], and pepstatin A, leupeptin, and aprotinin [20 ng/mL of each], pH 7.4) and were spun at 1500 g for 15 min. The supernatant was frozen at −20°C until cytokine measurement.

Bronchoalveolar lavage (BAL). The trachea was exposed through a midline incision and was cannulated with a sterile 22-gauge Abbocath-T catheter (Abbott). BAL was performed by instillation of 2 × 0.5-mL aliquots of sterile isotonic saline. A total of 0.9–1 mL of lavage fluid was retrieved per mouse, and total cell numbers were counted from each sample in a hemocytometer (Emrgergo). BAL fluid (BALF) differential cell counts were done on cytospin preparations stained with modified Giemsa stain (Diff-Quick; Baxter). BALF then was spun at 750 g for 5 min at 4°C, and supernatants were frozen at −20°C until measurements were performed.

Histologic examination. For histopathologic examination, only lungs were used. After fixation of lungs in 4% paraformaldehyde in PBS for 24 h and embedding in paraffin, 4-μm-thick sections were stained with hematoxylin-eosin. All slides were coded and semiquantitatively scored by a pathologist without knowledge of the type of mice or treatment.

Cell preparation and FACScan analysis. Flow cytometric analysis was performed on cells in BALF and cells isolated from lungs with a FACScan flow cytometer in conjunction with FACScan software (both from Becton Dickinson). Lung cells were isolated from freshly derived specimens by use of an automated desintegration device (Medimachine System) and were resuspended in RPMI (Biowhittaker-Boehringer) with 1% bovine serum albumin (BSA; Sigma Chemical). The cell suspension was crushed through a 35-μm filter (cell strainer 35μm, Becton & Dickinson Labware). Cells were centrifuged at 600 g for 5 min at 4°C, were washed with cold FACS buffer (PBS supplemented with 0.01% Na₃cit, 0.5% BSA, and 0.3 mM EDTA), and were resuspended in FACS buffer. BALF and lung cells from 3 mice were pooled. For staining, 1 × 10⁶ cells/well in a 96-well microplate (Greiner B.V. Labor Techniek) were incubated for 30 min at 4°C with rat anti–mouse unconjugated CD11b (clone M1/70) [29]. The hybridoma producing anti–mouse CD11b was kindly provided by R. Mebius (Free University, Amsterdam). After being washed in FACS buffer, R-phycoerythrin–conjugated F(ab); fragments of goat anti–rat immunoglobulins (Zymed) were added as a secondary antibody, followed by fluorescein isothiocyanate–labeled rat anti–mouse Gr-1 MAb (clone RB6-8C5; PharMingen), which was used for staining granulocytes. The appropriate isotype controls were included in all experiments. All FACS reagents were used in concentrations recommended by manufacturers; 5000 Gr-1–positive cells were counted. Results are expressed as the mean cell fluorescence intensity after subtraction of control IgG fluorescence.

Determination of cytokines, chemokines, and nitric oxide (NO) concentrations. Cytokine and chemokine levels were measured by commercially available ELISAs according to the manufacturers’ recommendations. The tumor necrosis factor (TNF)–α ELISA was obtained from Genzyme; interleukin (IL)–6, -10, -12p40, and -12p70 ELISAs from Pharmingen; and IFN-γ, macrophage inflammatory protein (MIP)–2, and KC ELISAs from R&D Systems. NO production was assessed by measurement of nitrite and nitrate by a colorimetric assay, according to the instructions of the manufacturer.
(Cayman Chemical). Total NO production was expressed as the sum of both nitrite and nitrate production.

Statistical analysis. SPSS statistical software was used to analyze data. Data are expressed as mean ± SE unless indicated otherwise. The Mann-Whitney U test was used for comparisons between groups. Survival curves were compared by log-rank test. \( P \leq 0.05 \) was considered to represent a significant difference.

Results

Induction of IFN-\( \gamma \). Wt mice did not have detectable levels of IFN-\( \gamma \) in their lung homogenates at baseline or after intranasal inoculation with isotonic saline (figure 1). Induction of pneumonia was associated with enhanced production of IFN-\( \gamma \) within the pulmonary compartment, as reflected by elevated IFN-\( \gamma \) concentrations in lung homogenates (24 h, 13.1 ± 1.0 ng/g; 48 h, 16.8 ± 1.9 ng/g; \( P < 0.05 \) vs. control). IFN-\( \gamma \) R\(^{-/-} \) mice had higher lung IFN-\( \gamma \)-levels than wt mice, although the differences were not statistically significant.

Survival. Considering that IFN-\( \gamma \) is generally believed to play an important role in antimicrobial host defense [13, 22, 30, 31], we expected IFN-\( \gamma \) R\(^{-/-} \) mice to be more susceptible to pneumococcal pneumonia (figure 2). However, when 3 different bacterial inocula (10\(^4\), 2 × 10\(^5\), and 5 × 10\(^5\) cfu) were used to induce pneumonia of increasing severity, no differences in mortality between IFN-\( \gamma \) R\(^{-/-} \) and wt mice were observed until 10 days after inoculation. Mice that survived for 10 days appeared to be permanent survivors.

Bacterial outgrowth. To obtain further insight into the role of IFN-\( \gamma \) in host defense against pneumococcal pneumonia, we evaluated the outgrowth of pneumococci in the lungs of IFN-\( \gamma \) R\(^{-/-} \) and wt mice (figure 3). At 24 h after intranasal inoculation of 5 × 10\(^5\) cfu of \( S. \) pneumoniae, bacterial counts in the lungs were similar in IFN-\( \gamma \) R\(^{-/-} \) and wt mice (data not shown). At 48 h, lungs of IFN-\( \gamma \) R\(^{-/-} \) mice contained 1.5 log\(_{10}\) fewer \( S. \) pneumoniae cfu than wt mice (\( P = 0.01 \)), which suggests that endogenous IFN-\( \gamma \) activity hampers antibacterial host defense. To confirm this finding and to demonstrate that it is not unique for the 129 Sv/Ev background, we repeated this experiment in IFN-\( \gamma \) 2\(^{-/-} \) BALB/c and wt mice. IFN-\( \gamma \) 2\(^{-/-} \) mice had 1.4 log\(_{10}\) fewer \( S. \) pneumoniae cfu in their lungs than wt mice 48 h after inoculation with 5 × 10\(^5\) cfu of bacteria (\( P = 0.01 \)).

Histological changes. At 24 h after inoculation, IFN-\( \gamma \) R\(^{-/-} \) mice showed more pronounced inflammatory infiltrates in the lung, compared with wt mice, with no differences in the composition of the inflammation (figure 4). At 48 h after inoculation with \( S. \) pneumoniae, lungs of IFN-\( \gamma \) R\(^{-/-} \) mice showed clearly more apoptotic bodies and macrophages corresponding to the clearance phase, compared with those of wt mice. At this time point, wt mice still displayed a pronounced and more active inflammation in the lungs.

Figure 2. Survival after intranasal inoculation with (A) 10\(^4\), (B) 2 × 10\(^5\), or (C) 5 × 10\(^5\) cfu of \( S. \) pneumoniae in wild-type (Wt; ○) and interferon-\( \gamma \) receptor-deficient (IFN-\( \gamma \) R\(^{-/-} \); ●) mice (\( n = 15 \) mice per group). Mortality was assessed twice daily for 10 days.

Figure 3. Bacterial outgrowth in lungs. A, Log\(_{10}\) cfu of \( S. \) pneumoniae in lungs of wild-type (Wt) and interferon-\( \gamma \) receptor-deficient (IFN-\( \gamma \) R\(^{-/-} \)) mice 48 h after inoculation with 5 × 10\(^5\) cfu of \( S. \) pneumoniae. B, Log\(_{10}\) cfu in lungs of IFN-\( \gamma \) R\(^{-/-} \) and Wt mice 48 h after inoculation of 5 × 10\(^5\) cfu of \( S. \) pneumoniae. Horizontal lines represent the medians within the groups.
Neutrophilic cell influx and activation markers. In a first attempt to determine the mechanism by which endogenous IFN-γ could facilitate the outgrowth of bacteria during pneumococcal pneumonia, we determined the influx of neutrophils and the activation state of the granulocytes in BALF at 48 h after intranasal inoculation with \textit{S. pneumoniae} (figures 5 and 6). Neutrophil counts in BALF of IFN-γ R²/² mice were lower than those in BALF of wt mice \((P < .05)\). Neutrophils isolated from lung tissue and BALF displayed signs of activation, as reflected by enhanced expression of CD11b, compared with neutrophils obtained from control mice. However, this neutrophil activation marker did not differ between IFN-γ R²/² and wt mice.

Lung concentrations of cytokines, chemokines, and NO. A second mechanism by which IFN-γ could facilitate the outgrowth of bacteria during pneumococcal pneumonia is by modulation of chemokine or cytokine production (table 1). In particular, the cytokines TNF, IL-6, and IL-12 and the chemokines KC and MIP-2 have been found to contribute to the host defense in murine models of pneumonia [27, 28, 32–35]. Of these mediators, lung concentrations of TNF and MIP-2 were found to be similar in IFN-γ R²/² and wt mice. In contrast, IL-6, IL-12(p70), and KC levels were lower in IFN-γ R²/² mice. Hence, alterations in local production of “protective” cytokines and chemokines cannot explain the relatively decreased susceptibility of IFN-γ R²/² mice during pneumonia. IFN-γ is able to enhance NO production [5, 36, 37]. To assess whether this mechanism was affected in the IFN-γ R²/² mice, we measured nitrate levels in BALF of both groups at 48 h after induction of pneumonia. IFN-γ R²/² mice had lower nitrate levels than wt mice (9.5 ± 1.1 and 13.6 ± 1.6 \(\mu\)M, respectively), although this difference was not significant.

Anti–IFN-γ treatment during pneumococcal pneumonia in wt mice. To exclude the possibility that the decreased suscep-

Figure 4. Histological sections of lungs of wild-type (A and C) and interferon-γ receptor–deficient mice (B and D), 24 (A and B) and 48 (C and D) h, respectively, after inoculation with \(5 \times 10^5\) cfu of \textit{Streptococcus pneumoniae}. Hematoxylin-eosin staining, original magnification x50. Sections are representative of the groups at each time point \((n = 5\) mice per group).

Figure 5. Granulocytic influx in bronchoalveolar lavage fluid (BALF). Mean ± SE of granulocytic influx in BALF obtained from wild-type (Wt) mice and interferon-γ receptor–deficient (IFN-γ R²/²) mice at 48 h after intranasal inoculation of \(5 \times 10^5\) cfu of \textit{Streptococcus pneumoniae} \((n = 6\) mice per group).
tibility in these gene-deficient mice was due to compensatory changes, we performed additional experiments in which we pre-treated normal BALB/c mice intraperitoneally with anti-mouse IFN-γ MAb or control MAb 2 h before inoculation with 1 or $5 \times 10^5$ cfu of S. pneumoniae and determined bacterial outgrowth 48 h postinfection. These studies yielded inconsistent results—that is, in the first experiment, anti–IFN-γ-treated mice tended to have an enhanced outgrowth ($2.5 \pm 1.1 \times 10^6$ cfu/mL vs. $2.4 \pm 2.2 \times 10^6$ cfu/mL of lung homogenate in control mice), whereas, in the second experiment, bacterial outgrowth was similar in both groups ($19.3 \pm 4.2 \times 10^6$ vs. $6.5 \pm 4.5 \times 10^6$ cfu/mL of lung homogenate in anti–IFN-γ and control mice, respectively).

Discussion

IFN-γ is a proinflammatory cytokine that has protective effects in a variety of infectious diseases. The essential role of endogenous IFN-γ in host defense against infection has, in particular, been demonstrated for intracellularly growing microorganisms [11–14]. The role of IFN-γ in bacterial pneumonia is not well defined. Recently, Rubins and Pomeroy reported that IFN-γ−/− mice demonstrated an increased mortality, compared with wt mice, in a model of severe pneumococcal pneumonia associated with bacteremia [21]. In that study, however, no data were presented on bacterial outgrowth or on induction of innate host defense mechanisms. We here report that IFN-γ R−/− mice do not have an increased mortality rate after induction of pneumococcal pneumonia by 3 different doses of bacteria. After the first 48 h of the disease, both IFN-γ R−/− and IFN-γ−/− mice had a reduced outgrowth of pneumococci in lungs, compared with their respective wt strains, whereas studies in which a neutralizing anti–IFN-γ MAb was used in wt mice yielded inconsistent results. Our results suggest that endogenous IFN-γ does not improve antibacterial defense in the lung compartment.

Accordingly, in a subacute model of Staphylococcus aureus sepsis that resulted in 100% lethality in normal wt mice over a 10-day period, IFN-γ R−/− mice were relatively protected against lethality, which was associated with a reduced number of S. aureus colony-forming units in blood, compared with wt mice [38]. This study, taken together with our results in knockout mice, suggests that IFN-γ may facilitate bacterial outgrowth in conditions in which the experimental animal is not overwhelmed by a high dose of bacteria. On the opposite side, in models of acute systemic infection with extracellular bacteria, IFN-γ has been found to play a detrimental role. Indeed, treatment with anti–IFN-γ antibodies reduced mortality after intravenous or intraperitoneal injection of high doses of Escherichia coli [39, 40]. The detrimental role of IFN-γ in these acute infection models is in line with findings that treatment with anti–IFN-γ antibodies profoundly reduced mortality in mice exposed to high doses of endotoxin [25, 41].

Our study does not provide a clear explanation for the reduced outgrowth of pneumococci in lungs of mice that lack functional IFN-γ. A protective mechanism could not be demonstrated for the diminished outgrowth of staphylococci during subacute S. aureus sepsis [38]. We evaluated several innate responses known to contribute to antibacterial defense in the lung compartment. None of these responses was altered in IFN-γ R−/− mice in a way that would enhance bacterial clearance. Indeed, the

### Table 1. Cytokine and chemokine levels in lung homogenates 24 and 48 h after intranasal inoculation with $10^7$ cfu of Streptococcus pneumoniae at $t = 0$

<table>
<thead>
<tr>
<th>Level, ng/g lung</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor necrosis factor-α</td>
<td>1215 ± 207</td>
<td>1238 ± 106</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>342 ± 103</td>
<td>202 ± 51</td>
</tr>
<tr>
<td>Interleukin-12p40</td>
<td>30 ± 75</td>
<td>58 ± 19</td>
</tr>
<tr>
<td>Interleukin-12p70</td>
<td>9 ± 0.4</td>
<td>10 ± 0.6</td>
</tr>
<tr>
<td>KC</td>
<td>656 ± 151</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>Macrophage inflammatory protein-2</td>
<td>223 ± 44</td>
<td>458 ± 210</td>
</tr>
</tbody>
</table>

| NOTE. IFN-γ R−/−, interferon–γ receptor deficient. Data are mean ± SE of 8 mice per group per time point. |
| aP < .05 vs. wild type. |
induction of some “protective” responses was even attenuated in IFN-γ R−/− mice, including the recruitment of neutrophils to the lung. Furthermore, although we found an up-regulation of CD11b on granulocytes in BALF of mice with pneumonia, indicative of an enhanced activation state [29, 42], CD11b expression did not differ between IFN-γ R−/− and wt mice. Earlier research has suggested that IFN-γ has the ability to inhibit, rather than to augment, neutrophil recruitment in vivo—that is, neutrophil influx in skin was diminished in mice with thermal wounds after treatment with IFN-γ [43], and intraperitoneally administered IFN-γ decreased the inflammatory response in rats with chronic P. aeruginosa pneumonia by reducing neutrophil influx [20]. Conceivably, the reduced KC concentrations played a role in the attenuated neutrophil reducing neutrophilic influx [20].

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A "protective" cytokine in IFN-γ R−/− mice, considering that inhibition of this CXC chemokine diminished neutrophil accumulation in lungs after intratracheal administration of endotoxin [44] and that transgenic overexpression of KC in mouse lungs resulted in enhanced neutrophil migration within the lung compartment [45]. In addition, the lower bacteria load in lungs of IFN-γ R−/− mice, providing fewer proinflammatory stimuli, could have been responsible for the attenuated neutrophil recruitment. This may also explain the lower concentrations of IL-6 and IL-12, 2 other "protective" cytokines during pneumonia, in IFN-γ R−/− mice [27, 34].

Our results were obtained by use of mice that were genetically deficient for IFN-γ or IFN-γ R and should, therefore, be interpreted with caution. In fact, we could not confirm the diminished pneumococcal outgrowth measured in IFN-γ R−/− and IFN-γ−/− mice in experiments in which we treated wt mice with a neutralizing anti–IFN-γ MAb. Several factors could possibly explain this discrepancy. First, the dose of anti–IFN-γ MAb could have been insufficient to neutralize all IFN-γ. Although this possibility seems less likely, considering that we gave twice the amount of this particular MAb (1 mg) needed to reduce staphylococcal enterotoxin B or endotoxin-induced lethality (0.5 mg) [24, 25], it is not excluded that the MAb did not penetrate well enough in the pulmonary compartment. This could not be checked directly because of the lack of a reliable and specific IFN-γ bioassay. Second, knockout mice may differ from wt mice not only with respect to the product of the deleted gene; hereditary deficiency of a protein may result in compensatory changes. However, it should be noted in this context that the role of endogenous IFN-γ in inflammation and infection has been studied in many investigations that have used knockout mice only, and these results have provided valuable information on the role of IFN-γ in these models [46–51].

IFN-γ has been implicated as a pivotal mediator in host defense against a variety of respiratory pathogens. IFN-γ was found to be important for cell-mediated immunity against fungi and intracellular microorganisms that can cause chronic pneumonias, including Mycobacteria, Mycoplasma, Chlamydia, and Histoplasma (reviewed in [4]). We herein show that endogenous IFN-γ is not required for an effective pulmonary defense in pneumonia due to S. pneumoniae, the most frequently isolated organism in patients with community-acquired pneumonia. These data exemplify the complex role of IFN-γ in innate immunity during pulmonary infection.

References


