Pneumonia: an investigation of host defence mechanisms
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Cytokines and innate immunity against bacterial respiratory pathogens
In pneumonia the initiation, maintenance and resolution of inflammation is dependent upon the complex network of pro-inflammatory and anti-inflammatory cytokines. Much of our knowledge of the role of cytokines in the pathogenesis of pneumonia is derived from animal studies on experimental pneumonia. In contrast to systemic infection, where excessive production of pro-inflammatory cytokines is detrimental, causing organ failure and death, local production of pro-inflammatory cytokines is necessary for host defense against the invasive pathogen. Conversely, the anti-inflammatory cytokine IL-10 impairs host defense in local infections like pneumonia, while it protects against excessive immune activation, like sepsis. This article summarizes current information on the roles of specific cytokines in host defense against pneumonia, with emphasis on ongoing investigations into the role of innate immunity against different respiratory bacterial pathogens.

Introduction
With an estimated area of 140 m² and exposure to 7-10 liter of ambient air per minute, the lungs are repeatedly exposed to pathogens, either by inhalation or (micro-) aspiration of micro-organisms that colonize the oropharynx. From this point of view it is not surprising that pneumonia is one of the most common infectious diseases. Both the widespread use of antibiotics, that has led to a rise of antibiotic resistance among micro-organisms, and the growing number of immunocompromised patients susceptible to pneumonia, have made the treatment of pneumonia more difficult. Hence, there is a need for novel therapeutic approaches for pneumonia. One such approach is immunotherapy, aimed at modulating the immune responses that may serve as an important adjuvant therapy in the treatment of infectious diseases. However, knowledge of the immune host defenses needs to increase before such immunotherapies can become a serious tool in the treatment of severe pneumonia.

The normal host defense of the lung includes both innate and acquired immune responses. Innate defenses consist of structural defenses, antimicrobial molecules generated in airways, and phagocytosis by resident alveolar macrophages and recruited polymorphonuclear leukocytes. Acquired immune defense is antigen-specific, and includes cell-mediated and antibody-mediated immune responses. While innate immune responses are primarily responsible for the elimination of bacterial pathogens from the alveolar spaces, specific immune responses are involved in eradication of encapsulated pathogens, and pathogens that survive after phagocytosis.

Both alveolar macrophages and polymorphonuclear cells play a prominent role in innate immunity. Alveolar macrophages are avidly phagocytic and readily kill ingested micro-organisms. In addition, they play an important role in orchestrating inflammatory responses. Alveolar macrophages and polymorphonuclear cells need to communicate in mounting an effective host defense against invading pathogens. After their initiation, innate immune responses need to be localized, reinforced and finally resolved. Cytokines play a critical role in these processes by mediating leukocyte recruitment and by serving as important signals in
the activation of leukocytes. Numerous cytokines have been implicated in pulmonary host defense (e.g. tumor necrosis factor-α (TNF), interleukin-6 (IL), IL-10, interferon-γ (IFN) and chemokines).

In this review the role of cytokines in innate immunity is discussed. Furthermore, we focus on how different cytokines are involved in the defense against different respiratory bacterial pathogens.

**Pulmonary innate host defense: structural defenses and phagocytosing cells**

The mucociliary blanket lining the surface of the airways arrest inhaled particles. Entrapped particles are then cleared by the movement of cilia, propelling the mucus up to the oropharynx for swallowing or expectoration. Small particles, like bacteria, bypass this first line of defense and enter the terminal airways. Sterility of the lung is maintained by additional local production of antimicrobial molecules (e.g., lysozyme, complement, immunoglobulin A, lactoferrin, lipopolysaccharide (LPS-) binding protein and defensins).1

Infectious agents that have passed this first line of defense and have entered the terminal airways are first encountered by the resident macrophages. These cells play a central role in pulmonary host defense, due to their phagocytic, microbicidal and secretory functions. *Streptococcus (S.) pneumoniae, Haemophilus (H.) influenzae*, and *Staphylococcus (S.) aureus* are readily ingested and killed by macrophages, while *Mycobacterium* spp., *Nocardia* spp., and *Legionella (L.)* spp. are resistant to the microbicidal activity of these cells. Eradication of these pathogens requires development of specific immunity.

The recruitment of large numbers of polymorphonuclear cells in the alveolar space from the marginated pool of leukocytes in the pulmonary circulation is initiated when the microbial challenge is too large or too virulent to be contained by the alveolar macrophages alone. These recruited neutrophils provide auxiliary phagocytic capacities, critical for the effective eradication of pathogens.

**Cytokines in pulmonary host defense**

Alveolar macrophages and recruited neutrophils orchestrate the immune response by initiating a complex network of pro-inflammatory and anti-inflammatory cytokines. Cytokines can be considered to be involved in the early response after the recognition of a pathogen (e.g. TNF and IL-1β), to be involved in the recruitment of immune cells to the site of infection (chemokines, such as IL-8 and other members of the CXC family), or to be involved in the activation of alveolar macrophages and recruited cells (e.g. IFN, IL-12, IL-6, IL-10 and granulocyte colony stimulating factor [G-CSF]).

**TNF.** The early response cytokine TNF is the most frequently studied cytokine in pulmonary host defense. Increased expression of TNF has been observed in patients with bacterial pneumonia.2 In animal models, TNF is expressed locally during pneumonia with *S. pneumoniae,3,4 K. pneumoniae,5 Pseudomonas (P.) aeruginosa,6* and *L. pneumophila.7*
Several lines of evidence suggest that TNF is an important component of host defense in bacterial pneumonia. Specifically, systemic neutralization of TNF attenuates host defense in pulmonary infection with *S. pneumoniae*, *K. pneumoniae*, and *L. pneumophila*, resulting in decreased survival. Treatment of granulocytopenic mice with low doses of TNF significantly diminished mortality and enhanced clearance of *P. aeruginosa* from the pulmonary compartment during severe pneumonia. Furthermore, augmented expression of TNF in the lungs of mice through gene therapy, resulting in high levels of TNF in the pulmonary compartment without 'spill-over' systemically, was associated with increased survival, improved bacterial clearance of pathogens from lungs and decreased dissemination of bacteria to the blood, after a challenge with *K. pneumoniae*. 

How TNF mediates beneficial effects in pulmonary host defense is not well defined. TNF activates both macrophages and neutrophils, leading to augmented phagocytosis, oxidative burst, protein release and bacterial killing. TNF contributes to the recruitment of neutrophils by stimulating the expression of adhesion molecules and inducing the production of chemokines. Indeed, decreased neutrophil influx into the lungs has been observed in mice challenged with *K. pneumoniae* and *P. aeruginosa* after TNF neutralization. Administration of a TNF agonist peptide led to an augmented recruitment of neutrophils in *K. pneumoniae* pneumonia. TNF neutralization had no effect on recruitment of neutrophils to lungs in animals infected with *S. pneumoniae*.

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**Figure 1.** IL-1 receptor type I (IL-1R+) deficient mice (solid bars) had more *S. pneumoniae* CFU in lungs compared with wild type mice (open bars) after a challenge with $10^5$ CFU of *S. pneumoniae*. In contrast, IL-1R+ mice demonstrated an enhanced clearance of bacteria after intranasal administration of $10^5$ CFU of *P. aeruginosa*. Data are means ± SEM. *P<0.05 compared with wild type mice. Adapted and modified from 18 and 19.

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**IL-1β.** Elevated IL-1β levels have been found in pleural fluids of patients with empyema, and in bronchoalveolar lavage fluids of patients with pneumonia. In addition, in unilateral pneumonia, alveolar macrophages recovered from the infected lung spontaneously released more IL-1β into cell culture supernatants than macrophages evacuated from the noninvolved site. Animal studies on the role of IL-1β during bacterial pneumonia are currently performed in our laboratory. Considering that IL-1β is generally believed to play a protective role in antimicrobial host defense, we expected IL-1 receptor type I (IL-1R+) deficient mice to be more susceptible to bacterial pneumonia. Indeed, although mortality was not different between IL-1R-/+ mice compared with wild type mice after challenge with *S. pneumoniae*, IL-
1R⁻ mice had two-fold more *S. pneumoniae* CFU in lungs compared with wild type mice, and IL-1R⁻ mice displayed a reduced capacity to form inflammatory infiltrates at 24h after the induction of pneumonia. By contrast, IL-1R⁻ mice demonstrated an enhanced clearance and improved mortality in a *P. aeruginosa* pneumonia model (Figure 1).

![Figure 2.](image)

**Figure 2.** (A) Clearance of bacteria is enhanced in IFN R deficient (IFNR⁻) mice. Mean (± SEM) *P. aeruginosa* CFU in lungs after intranasal inoculation with 10⁵ CFU in wild type mice (open bars) and IFNR⁻ mice (closed bars). *P<0.05 compared with wild type mice. (B) Survival of IFNR⁻ (O-O) and wild type mice (●-●) infected with 10⁵ CFU of *P. aeruginosa*. Differences were not statistically significant. Adapted and modified from 27.

**IFN and IL-12.** The production of the pro-inflammatory cytokine IFN has been found to be enhanced during murine pneumococcal pneumonia, *K. pneumoniae* pneumonia, and *P. aeruginosa* pneumonia. Similarly, the expression of another pro-inflammatory cytokine, IL-12, is enhanced in pneumonia caused by *S. pneumoniae*, *K. pneumoniae*, and *P. aeruginosa* (unpublished data).

IFN is a cytokine mainly produced by antigen activated T and natural killer (NK) cells. The secretion of IFN is induced by TNF and IL-12. IFN exerts several immune regulatory activities, including activation of phagocytes, stimulation of antigen presentation by increasing the expression of major histocompatibility complex MHC molecules class I and II on antigen presenting cells, orchestration of leukocyte-endothelium interactions and stimulation of the respiratory burst. Macrophages are stimulated by IFN to secrete TNF and IL-12, setting up a paracrine positive-feedback cycle.

Neutralization of IL-12 led to reduced bacterial clearance and increased mortality of mice infected with *K. pneumoniae*, while adenoviral mediated transgenic overexpression of IL-12 reduced mortality in *K. pneumoniae* pneumonia. However, IL-12 does not act alone in the defense against invading microorganisms, since passive immunization against TNF or IFN led to a failure of IL-12 overexpression to protect mice.

The essential role of endogenous IFN in host defense against infection has in particular been demonstrated for intracellular growing microorganisms. In models of acute systemic infection with extracellular growing bacteria, IFN has been found to play a detrimental role.
Indeed, treatment with anti-IFN antibodies reduced mortality after intravenous or intraperitoneal injection of high doses of *E. coli*,\(^{40,41}\) and profoundly reduced mortality in mice exposed to high doses of endotoxin.\(^{42,43}\) In a subacute model of *S. aureus* sepsis, resulting in 100% lethality in normal wild type mice over a 10-day period, IFNR\(^{-/-}\) mice were relatively protected against lethality, which was associated with a reduced number of *S. aureus* CFUs in blood when compared to wild type mice.\(^{44}\)

The role of IFN in the setting of bacterial pneumonia is less clear. IFN knockout mice exposed to *S. pneumoniae* demonstrated higher mortality compared to wild type mice.\(^{45}\) Overexpression of IFN by adenovirally mediated gene therapy in rats, resulted in increased clearance of *P. aeruginosa* and *K. pneumoniae* from the lung.\(^{46-48}\) By contrast, anti-IFN treatment had no detectable effect on the clearance of *P. carinii* from lungs.\(^{49}\) Furthermore, we recently demonstrated that IFNR\(^{-/-}\) mice were less susceptible to an intranasal challenge with *P. aeruginosa* compared to wild type mice (Figure 2).\(^{33}\) The detrimental role of IFN in this model of bacterial pneumonia is in line with our findings that clearance of bacteria was attenuated in IFNR\(^{-/-}\) mice, as well as IFN knockout mice in case of *S. pneumoniae* pneumonia, compared to their controls.\(^{50}\) These data indicate that IFN may impair an effective pulmonary defense in pneumonia.

**IL-18.** IL-18, originally named IFN-inducing factor, is a pro-inflammatory cytokine which was identified in mice during endotoxin shock as a co-stimulatory factor for the production of IFN. IL-18 is mainly produced by activated macrophages. Although IL-18 alone is not a potent stimulator of IFN production, it synergistically enhances IL-12 induced IFN production. IL-18 has many other pro-inflammatory effects on T and NK cells, enhancing proliferation and cytotoxicity, and stimulating the production of TNF, IL-2 and GM-CSF.

Neutralization of IL-18 protects against LPS-induced liver injury. In contrast IL-18 was protective during infections with *Y. enterocolitica*,\(^{51}\) and intra-cellular pathogens like *L. major*,\(^{52}\) and *S. typhimurium*.\(^{53}\)

During *S. pneumoniae* pneumonia local IL-18 production is enhanced.\(^{54}\) We recently demonstrated that endogenous IL-18 plays a protective role during pneumonia.\(^{54}\) IL-18 knockout mice had significantly more bacteria in their lungs and were more susceptible for progression to systemic infection after intranasal administration of *S. pneumoniae*. IL-18 knockout mice had lower IFN concentrations in their lungs than wild type mice. Anti-IL-12 antibodies did not influence bacterial clearance in IL-18 knockout mice or wild type mice, indicating that IL-18 mediated effects during pneumonia are independent of endogenous IL-12.

**IL-10.** IL-10 is a cytokine that attenuates the production of TNF, IL-1\(\beta\), CXC chemokines, IFN, and IL-12, and has potent inhibitory effects on neutrophils resulting in reduced phagocytosis and bactericidal killing.\(^{14,16,55}\) IL-10 is produced under different conditions of immune activation by different cell types, including T-cells, B-cells and monocytes.\(^{56}\) IL-10
production is enhanced during sepsis, after LPS administration and in various models of infection. IL-10 plays a protective role in models of overzealous inflammation: IL-10 can inhibit the LPS-stimulated production of pro-inflammatory cytokines in vitro and in vivo. Administration of IL-10 reduces LPS-induced mortality in animals, and neutralization of IL-10 results in increased lethality in LPS-challenged mice. In contrast, to clear the invading pathogen in case of pulmonary infection, the anti-inflammatory properties may hinder innate immunity. IL-10 is produced in the pulmonary compartment in mice with pneumonia caused by either *S. pneumoniae*, or *K. pneumoniae*. Considerable evidence exist that the anti-inflammatory cytokine IL-10 plays a detrimental role in the clearance of bacteria during pulmonary infections with *S. pneumoniae* and *K. pneumoniae*. Administration of exogenous IL-10 reduced survival and increased outgrowth of bacteria from lungs of mice challenged with *S. pneumoniae*. Conversely, neutralization of IL-10 leads to enhanced clearance of bacteria and improved survival in mice with *K. pneumoniae* pneumonia.

**IL-6.** IL-6 is both a pro-inflammatory and an anti-inflammatory cytokine. The production of IL-6 is under the influence of TNF and IL-1β. IL-6 is produced by many cell types, including macrophages, T and B-cells and parenchymal cells. IL-6 is produced in the lung during pneumonia. Evidence for the importance of IL-6 in host defense during pneumonia was obtained from a study on *S. pneumoniae* pneumonia in IL-6 knockout mice. IL-6 knockout mice had more bacteria in their lungs after an intranasal challenge with this pathogen, and died significantly earlier than normal mice, despite higher levels of TNF, IL-1β, IFN and IL-10 in lungs. Hence, IL-6 downregulates the activation of the cytokine network within the lung during pneumonia and contributes to host defense. The mechanism by which IL-6 protects the host during pneumonia has not been determined yet.

**G-CSF.** G-CSF is a cytokine produced by activated T-cells and macrophages, and stromal cells. G-CSF prolongs neutrophil survival and stimulates neutrophil phagocytosis and oxidative burst. Alveolar macrophages from patients with bacterial pneumonia produce G-CSF spontaneously. Evidence for a beneficial role of G-CSF in innate immunity against respiratory pathogens came from studies on *S. pneumoniae* pneumonia and *K. pneumoniae* pneumonia in rats, and *E. coli* pneumonia in mice. These models demonstrated an improved survival in G-CSF treated animals.

Until now, recombinant human G-CSF is the only cytokine that has been used for the treatment of severe pneumonia in a randomized, placebo-controlled trial as an adjunct to antimicrobial therapy. G-CSF reduced the incidence of serious complications, but did not influence mortality or time to resolution of pneumonia.

**Chemokines.** Chemokines, low molecule weight cytokines, are involved in the recruitment of immune cells to the site of infection. CXC chemokines represent a family in which one amino acid separates the first two cysteine residues adjacent to each other (cysteine-X amino acid-
cysteine, or CXC). CXC chemokines can be further subdivided into ELR-positive chemokines, which possess a three amino acid motif termed ELR (glutamic acid-leucine-arginine) near the N-terminal end, and ELR-negative CXC chemokines. ELR-positive CXC chemokines (e.g., IL-8, epithelial neutrophil activating protein (ENA-) 78 in humans; macrophage inflammatory protein-2 (MIP-2), and KC in mice) exhibit chemotactic and activating effects on neutrophils. Elevated levels of IL-8 have been found in bronchoalveolar lavage fluid of patients with pneumonia,\textsuperscript{20,21} and high levels of IL-8 were found in pleural empyema fluids, compared with other types of effusions.\textsuperscript{22} IL-8 levels correlated with neutrophil counts in, and neutrophil chemotactic activity of pleural fluid.\textsuperscript{22} Similarly, elevated levels of KC and MIP-2 have been detected in lungs of mice challenged with \textit{S. pneumoniae};\textsuperscript{23,24} \textit{K. pneumoniae},\textsuperscript{25,26} and \textit{P. aeruginosa}.\textsuperscript{27}

Figure 3. (A) Survival rates of mice infected with 5 $\times$ 10$^5$ CFU \textit{P. aeruginosa}. (■-■, no treatment; □-□, IL-10, 1h before; O-O, IL-10 8h after; Δ-Δ, IL-10 1h before and 8h after inoculation with bacteria). *P<0.05 compared with no treatment. (B) Survival rates of mice infected with 5 $\times$ 10$^5$ CFU \textit{P. aeruginosa}. (■-■, control Ab; □-□, 0.5 mg anti-IL-10 mAb). *P<0.05 compared with control mAb. Adapted and modified from reference 66.

ELR-positive CXC chemokines appear to play an important role in neutrophil-dependent host defense in bacterial pneumonia. A causal role for these chemokines in the recruitment of immune cells to the site of infection is suggested by experiments in which an anti-IL-8 antibody decreased the neutrophil chemotactic activity of pleural fluid in case of empyema.\textsuperscript{22} Administration of neutralizing antibodies against MIP-2 resulted in a 60% reduction in neutrophil influx, which was associated with an attenuation of bacterial clearance from the lung, and increased incidence of bacteremia in a mouse pneumonia model with \textit{K. pneumoniae}.$^{25}$ In transgenic mice in which local KC expression was driven by a Clara cell-specific promoter, resulting in expression of KC within the lung, a four-fold increase in neutrophil influx was found after intra-tracheal administration of \textit{K. pneumoniae} compared to wild type mice.$^{26}$ This was associated with a striking improvement in survival, increased bacterial clearance from the lungs, and reduced incidence of bacteremia. Further, treatment with a blocking antibody directed against the main receptor for ELR-positive CXC
chemokines in mice (CXCR2) was associated with a reduced influx of neutrophils and an enhanced bacterial outgrowth during experimental pneumonia caused by either *N. asteroides* or *P. aeruginosa*. These results point to an important role of ELR-positive CXC chemokines in neutrophil influx and bacterial clearance during pneumonia.

**Different roles for cytokines in innate host defense against various respiratory bacterial pathogens**

The majority of the above mentioned models involved infection with *S. pneumoniae, K. pneumoniae* or *P. aeruginosa*. Cytokines influence host defense during these respiratory tract infections, although their role may vary depending on the pathogen used (Table 1). Indeed, while endogenous IL-10 hampered bacterial clearance in mouse models of *S. pneumoniae* and *K. pneumoniae*, IL-10 improved host defense in a model of pneumonia caused by *P. aeruginosa* (Figure 3). Similarly, while endogenous TNF was important for clearance of *S. pneumoniae* and *K. pneumoniae* from mouse lungs, TNF impaired host defense mechanisms during pneumonia with *P. aeruginosa* (Figure 4). Finally, mice made deplete for alveolar macrophages and challenged with *P. aeruginosa* demonstrated a delayed early neutrophil recruitment, but prolonged subsequent inflammatory cell recruitment. Alveolar macrophage-depleted mice had lesser lung injury in the early phase. However, bacterial clearance was delayed, and mortality was enhanced in these mice.

**Table 1. Cytokines influence host defense during respiratory tract infections, although their role may vary depending on the pathogen used.**

<table>
<thead>
<tr>
<th>Cytokines</th>
<th><em>S. pneumoniae</em></th>
<th><em>K. pneumoniae</em></th>
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<tbody>
<tr>
<td>TNF</td>
<td>+</td>
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<td>IL-1β</td>
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<td>+</td>
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<tr>
<td>G-CSF</td>
<td>+</td>
<td>+</td>
</tr>
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+, indicates a beneficial effect in case of respiratory infection with the specified pathogen; -, indicates a detrimental effect in case of respiratory infection with the specified pathogen; ?, indicates that there are no data on the effect of this cytokine. See text for details.

The protective role of IL-10 in the models with *P. aeruginosa* parallels findings in sepsis models, where damage to the host results from the overzealous immune activation. At present it is not clear whether the protective role of IL-10 in *P. aeruginosa* pneumonia represents IL-10-mediated protection from systemic endotoxin exposure. Alternatively, these
data suggest that in more gradually developing pneumonia, such as caused by *S. pneumoniae* and *K. pneumoniae*, a certain pro-inflammatory cytokine response within the pulmonary compartment is required to combat the invading microorganism, while in a more acute form of pneumonia, such as caused by *P. aeruginosa*, an excessive inflammatory response contributes to an adverse outcome.

These results indicate that the overall effect of a specific cytokine in host defense can be organism-dependent (i.e. neutralization of a specific cytokine can be beneficial or detrimental, depending on the causative pathogen). This may make immunological manipulation of cytokine expression even more difficult in case of polymicrobial pulmonary infections. Future studies are needed to resolve this issue.

**Figure 4.** (A) Clearance of *P. aeruginosa* from lungs of TNFR1 deficient mice (●-●) and control mice (O-O) after inoculation with aerosolized bacteria. (B) Clearance of *P. aeruginosa* from lungs of mice deficient in both type 1 and type 2 TNFR (●-●) and control mice (O-O). Data are means; *P* <0.05 compared with control mice. Adapted and modified from 67.

**Different roles for cytokines in innate host defense in diverse clinical situations**

IL-10 appears to be important in sepsis-induced immunosuppression. Mice with sepsis induced by cecal ligation and puncture demonstrated to be more susceptible for *P. aeruginosa* after intratracheal challenge, with a higher lethality compared to normal mice or mice undergoing sham abdominal surgery. The development of pneumonia in animals undergoing cecal ligation and puncture was associated with a marked increase of IL-10 expression in lungs, and administration of neutralizing IL-10 antibodies resulted in enhanced bacterial clearance from lungs and reduced mortality. Until now there are no studies on local cytokine expression in lungs directly after a septic episode, a severe trauma or previous respiratory infection which may have induced immunosuppression.

**Conclusions**

We have reviewed the literature on the role of cytokines in innate immunity against respiratory pathogens. Although manipulation of innate immunity through modulation of the
cytokine cascade occurred before, at, or directly after the time of challenge with a respiratory, pathogen in the reviewed animal studies, which is not the clinical setting, this novel approach may serve as an important adjuvant therapy in the treatment of patients with severe pneumonia. Several limitations exist. Targeting only one cytokine may be just a too simple thought, as the cytokine cascade is complex, and as cytokines have pleiotropic effects, this can lead to unexpected effects when used in an intervention in vivo. Furthermore, host responses against different respiratory pathogens differ quite substantially, which may make it necessary to develop different strategies for different pathogens. Additional studies are necessary to overcome these issues.

References


