Modulation of Pulmonary Innate Immunity during Bacterial Infection: Animal Studies

MARCUS J. SCHULTZ¹, ²* and TOM VAN DER POLL¹, ³

¹ Laboratory of Experimental Internal Medicine, ² Department of Intensive Care Medicine, ³ Department of Infectious Diseases, Tropical Medicine and AIDS, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands

Abstract. Both the increasing number of immunocompromised patients susceptible to pneumonia and the development of bacterial resistance are significant problems related to the treatment of pneumonia. The primary outcome of treatment for pneumonia is to tip the balance towards a successful host response. An ideal approach would be a combination of immunomodulation and conventional antimicrobial therapy. It is of increasing importance to understand the components of innate immunity, before immunomodulatory therapy can be applied to patients. Much of our knowledge of the role of alveolar macrophages, cytokines and chemokines in the pathogenesis of pneumonia is derived from animal studies on experimental pneumonia. This article summarizes current information on the role of an alveolar macrophage (AM) and AM-derived mediators in host defense against pneumonia.

Key words: innate immunity; pneumonia; alveolar macrophages; cytokines; immunotherapy.

Introduction

Bacteria may invade the lower respiratory tract by aspiration of oropharyngeal organisms, inhalation of aerosols containing bacteria, or, less frequently, by hematogenous spread from a distant body site. In addition, bacterial translocation from the gastrointestinal tract, most frequently through gastric aspiration, has been hypothesized as a mechanism for infection. Bacteria can also gain entry into the lower respiratory tract of hospitalized patients through inhalation of aerosols generated primarily by contaminated respiratory-therapy or anesthesia breathing equipment. Both the growing number of immunocompromised patients susceptible to pneumonia and the development of bacterial resistance are significant problems related to the treatment of pneumonia. The primary outcome of treatment for pneumonia is to tip the balance towards a successful host response. Immunotherapy may serve as an important adjuvant to antibiotic therapy in the treatment of infectious diseases. More specifically, immunotherapy aimed at modulating the pulmonary host response may be a novel therapeutic approach for pneumonia. However, before such immunotherapies can become a serious tool in the treatment of severe pneumonia, knowledge of the immune host defense needs to increase.

The normal pulmonary host defense includes both innate and acquired immune responses. While the innate immune system, consisting of structural defenses, antimicrobial molecules generated in the airways, and phagocytosis by resident alveolar macrophages (AM) and recruited polymorphonuclear cells (PMN), is pri-
primarily responsible for the elimination of bacterial pathogens from the alveolar spaces, the specific immune system, consisting of antigen-specific cell-mediated and antibody-mediated immune responses, is involved in the eradication of encapsulated pathogens as well as those that survive after phagocytosis. The first line of defense during respiratory tract infection is the AM. At low levels of bacterial challenge, or challenge with low-virulent bacteria, AM are capable of eradicating the invading pathogens. At higher inoculums, or challenges with more virulent pathogens, these cells become overwhelmed and are unable to overcome the invasion. Then, a complex network of cytokines is activated, necessary for the recruitment and activation of PMN and monocytes. After initiation, the innate immune response needs to be restricted to the site of infection, and during the resolution of infection the immune response needs to be reinforced and, finally, resolved. Numerous cytokines have been implicated in the initiation and reinforcement of pulmonary host defense (e.g. tumor necrosis factor α (TNF), interleukin 1β (IL-1β), IL-6, IL-10, interferon γ (IFN-γ) and cytokines with chemo- tactic activities).

Considerable evidence suggests that the success of a particular immunomodulating therapy during pneumonia can be dependent on the causative pathogen. This may be of influence on the future use of immunomodulating strategies. In this review, the role of AM and cytokines in innate immunity against different respiratory pathogens will be discussed.

The Principle Accessories of Innate Immunity

Alveolar macrophages

In the respiratory tract, AM respond to pathogens by two means. First, AM directly bind, phagocytose, and kill pathogens. Second, AM secrete a large range of mediators, some acting directly on the pathogens, while others, such as chemokines, exert their effects indirectly by recruiting other components of the host defense system. Therefore, AM (or AM-derived substances) play a crucial role in the pathogenesis of acute lung injury during pneumonia. The crucial role of AM in the recruitment of PMN in response to invading pathogens or their products has become clear from several studies. The role of AM as regulators of inflammation has been illustrated by studies demonstrating that AM engulf apoptotic PMN and release anti-inflammatory mediators. These data indicate that the role of AM in host defense is not limited to the generation of the initial inflammatory response, but extends to regulation of inflammation, including elimination of phagocytosed pathogens.

Cytokines

AM and recruited PMN 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. the pro-inflammatory cytokines TNF and IL-1β), in the recruitment of immune cells to the site of infection (chemokines, such as IL-8), or in the activation of AM and recruited PMN (e.g. pro-inflammatory cytokines, such as IFN-γ, IL-12, IL-17, IL-18, cytokine with both anti- and pro-inflammatory activities, such as IL-6, and anti-inflammatory cytokines, such as IL-10).

TNF and IL-1β. The pro-inflammatory cytokine TNF activates both AM and PMN, leading to augmented phagocytosis, oxidative burst, protein release and bacterial killing. TNF contributes to the recruitment of PMN by stimulating the expression of adhesion molecules and inducing the production of chemokines. IL-1β is another potent pro-inflammatory cytokine that has been implicated in numerous physiological processes as well as in inflammatory diseases. IL-1β is an important mediator of pulmonary inflammation induced by bacteria and bacterial products. IL-1β is produced in the lungs after intratracheal administration of lipopolysaccharide (LPS), and inhibition of IL-1β activity attenuates lung inflammation caused by LPS. In addition, recombinant IL-1β causes neutrophil infiltration in the lung comparable to LPS.

TNF and IL-1β have both been studied in pulmonary host defense. Increased expression of TNF and IL-1β has been observed in bacterial pneumonia, both in humans and in animals. Several lines of evidence suggest that TNF is an important component of host defense in bacterial pneumonia. Chemokines. Chemokines are low-molecular-weight cytokines involved in the recruitment of immune cells to the site of infection. CXC chemokines (e.g. IL-8, epithelial neutrophil-activating protein (ENA)-78 in humans; macrophage inflammatory protein (MIP)-2 and KC in mice) exhibit chemotactic and activating effects on PMN.

Elevated levels of IL-8 have been found in the bronchoalveolar lavage fluid of patients with pneumonia, and IL-8 levels correlated with PMN counts in, and
PMN chemotactic activity of, pleural fluid. Similarly, elevated chemokine levels have been detected in the lungs of mice with pneumonia. Several studies suggest a regulatory role for chemokines in pneumonia. Administration of chemokine-neutralizing antibodies resulted in a reduction in PMN influx, which was associated with an impaired bacterial clearance from the lungs, and an increased incidence of bacteremia in several murine pneumonia models. Local chemokine over-expression in the lungs of transgenic mice led to an increase in PMN influx after intratracheal administration of bacteria, which was associated with a striking improvement in survival, increased bacterial clearance from the lungs, and reduced incidence of bacteremia.

**IFN-γ and IL-12.** IFN-γ is a cytokine mainly produced by antigen-activated T and natural killer (NK) cells. The secretion of IFN-γ is induced by TNF and IL-12. IFN-γ 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-γ to secrete TNF and IL-12, setting up a paracrine positive-feedback cycle.

The production of the pro-inflammatory cytokine IFN-γ has been found to be enhanced during murine pneumonia. Similarly, the expression of another pro-inflammatory cytokine, IL-12, is enhanced in bacterial pneumonia. The roles of IL-12 and IFN-γ in host defense during pneumonia have been demonstrated in different animal studies.

**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. Many cell types, including macrophages, T and B cells, and parenchymal cells, produce IL-6. IL-6 is produced in the lung during pneumonia. Evidence for the importance of IL-6 in host defense during pneumonia was obtained from one animal study.

**IL-10.** IL-10 is a cytokine that attenuates the production of TNF, IL-1β, chemokines, IFN-γ, and IL-12, and has potent inhibitory effects on PMN, resulting in reduced phagocytosis and bactericidal killing. IL-10 is produced in the pulmonary compartment in mice with pneumonia. Considerable evidence exists that the anti-inflammatory cytokine IL-10 plays a detrimental role in the clearance of bacteria during pulmonary infections.

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**Results of Immunomodulating Strategies: Animal Studies**

Until now, several immunomodulating therapies have been applied to animals with experimental respiratory tract infections. Results of immunotherapies depend on the causative pathogen (Table 1).

**Table 1. The role of alveolar macrophages and cytokines in host defense during respiratory tract infections with three different pathogens**

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<th><em>S. pneumoniae</em></th>
<th><em>K. pneumoniae</em></th>
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+ beneficial role in case of respiratory infection with the specified pathogen; − detrimental role in case of respiratory infection with the specified pathogen; +/- conflicting data; ? no data available; 0 no effect. See text for details.

**Streptococcus pneumoniae pneumonia**

Considerable evidence exists for the importance of AM in the host defense against this pathogen. We recently demonstrated that depletion of AM resulted in impaired survival of mice in a *S. pneumoniae* pneumonia model. The detrimental outcome was accompanied by pronounced elevations of pro-inflammatory cytokines (TNF, IL-1β) and the chemokine KC, enhanced recruitment of PMN, and excessive inflammation in the lungs as indicated by histopathology. In this model, we observed no difference in bacterial spread.

We, and others, have demonstrated that systemic neutralization of TNF attenuated host defense in pulmonary bacterial infections with *S. pneumoniae*, resulting in increased mortality. Similar data exist for IL-1. After a bacterial challenge, IL-1 receptor type I deficient mice demonstrated an impaired clearance of *S. pneumoniae* and a reduced capacity to form inflammatory infiltrates. Of considerable interest, treatment with a neutralizing anti-TNF antibody made IL-1 receptor (R) deficient mice extremely susceptible to pneumococcal pneumonia, more so than *IL-1 R−/−* mice treated with a control antibody and wild-type mice treated with anti-TNF (Fig. 1). These data indicate that the concurrent action of TNF and IL-1 is required.
for an adequate host defense against pneumococcal pneumonia.

Investigations examining the role of IL-12 and IFN-γ in host defense during pneumococcal pneumonia revealed different data. IL-12−/− mice had a normal host defense against S. pneumoniae, i.e., bacterial spread in lung tissue and survival were similar to wild-type mice in a pneumonia model with this pathogen36. The role of IFN-γ in the setting of pneumococcal pneumonia is less clear. Whereas in one study IFN-γ−/− mice demonstrated higher mortality compared with wild-type mice46, other data suggest that endogenous IFN-γ may impair an effective pulmonary defense in pneumococcal pneumonia, since pulmonary clearance of S. pneumoniae was attenuated in IFN-γR−/− mice as well as in IFN-γ−/− mice compared with wild-type mice46.

IL-18 deficient mice demonstrated a reduced clearance of S. pneumoniae and were more susceptible to progression to systemic infection at 24 and 48 h after intranasal challenge with this pathogen38. Although survival was not different between knock-out mice and wild-type mice, these data suggest that IL-18 plays a protective role in the early host response during pneumococcal pneumonia.

Evidence of the importance of IL-6 in host defense during pneumonia was obtained from a study on pneumococcal pneumonia in IL-6−/− mice65. IL-6−/− mice had more bacteria in their lungs after intranasal challenge with this pathogen, and died significantly earlier than normal mice (Fig. 2).

The anti-inflammatory cytokine IL-10 plays a detrimental role in the clearance of bacteria during pulmonary infections. Administration of exogenous IL-10 reduced survival and increased the spread of bacteria in the lungs of mice with S. pneumoniae pneumonia66.

Conversely, neutralization of endogenous IL-10 led to an enhanced clearance of bacteria and improved survival in mice with pulmonary infection with S. pneumoniae66.

**Klebsiella pneumoniae pneumonia**

As in pneumococcal pneumonia, systemic neutralization of TNF attenuated host defense in pulmonary bacterial infections with K. pneumoniae, resulting in decreased survival53, while augmentation of the local expression of TNF in the lungs through gene therapy significantly diminished mortality and enhanced bacterial clearance from the pulmonary compartment during severe pneumonia with this pathogen59.

Several studies have suggested a regulatory role for chemokines in Klebsiella pneumonia. Administration of chemokine-neutralizing antibodies resulted in a reduction in PMN influx, which was associated with an attenuation of bacterial clearance from the lung and an increased incidence of bacteremia in Klebsiella pneumonia models52, 38, 55, whereas local chemokine over-expression in the lungs of transgenic mice led to an increase in PMN influx after intratracheal administration of bacteria, which was associated with a striking improvement in survival, increased bacterial clearance from the lungs, and reduced incidence of bacteremia59.

The role of IL-12 in host defense against K. pneumoniae has been investigated in a murine pneumonia model with this pathogen. Neutralization of IL-12 led to reduced bacterial clearance and increased mortality.
of mice with *K. pneumoniae* pneumonia, while overexpression of IL-12 reduced mortality\(^\text{20}\).

The release of IL-17 in the lungs in *K. pneumoniae* pneumonia has been demonstrated recently\(^{67}\). IL-17 \(R^+\) mice were extremely sensitive to intranasal *K. pneumoniae*, with 100% lethality after 48 h compared with 40% mortality in control mice. The IL-17 \(R^+\) mice displayed a significant delay in PMN recruitment into the lungs, associated with significant reductions in local granulocyte colony-stimulating factor and MIP-2 levels\(^{67}\). From these data it can be concluded that IL-17 signaling is critical for the host defense against *K. pneumoniae*.

Comparable to the role of IL-10 in pneumococcal pneumonia, evidence exist that the anti-inflammatory cytokine IL-10 plays a detrimental role in the clearance of bacteria during infections with *K. pneumoniae*: Neutralization of endogenous IL-10 led to the enhanced clearance of bacteria and improved survival in mice with pulmonary infection with this pathogen\(^{21}\).

**Mycoplasma pneumonia**

In a murine *Mycoplasma* pneumonia model, AM depletion in mice resulted in an enhanced spread of *Mycoplasma* from the lungs\(^{36}\). In this study, AM depletion exacerbated the *Mycoplasma* infection in *Mycoplasma*-resistant mice by reducing the killing of the pathogen to a level comparable to that in *Mycoplasma*-susceptible mice without AM depletion, suggesting that defective AM function is the likely explanation for the difference between susceptible and resistant mice. Interestingly, higher levels of PMN in lavage fluids were recovered from the AM depleted mice, indicating that the differences in the killing of the invading pathogen could not be explained by an effect on neutrophil recruitment. Furthermore, depletion of AM in a *K. pneumoniae* pneumonia model in mice influenced mortality dramatically, with 100% lethality after 3 days in AM depleted mice compared with 100% long-term survival in non-depleted mice\(^{5}\). This was accompanied by an increased spread of *K. pneumoniae* from lungs and blood in AM depleted mice and, similar to the former study, an increase in PMN influx into the pulmonary compartment together with elevated levels of TNF and MIP-2. Decreased bacterial clearance in this murine *Klebsiella* pneumonia model was confirmed by others\(^{36}\).

**Legionella pneumonia**

Cellular immunity in concert with cytokine and chemokine responses is believed to be essential for the resolution of infection with this pathogen, since intracellular growth is a critical characteristic of *L. pneumophila*. TNF plays an important role in the resolution of *Legionella* pneumonia, as inhibition of endogenous TNF activity, via *in vivo* administration of TNF-neutralizing antibody, resulted in enhanced growth of *L. pneumophila*\(^6\). Furthermore, important roles for IFN-\(\gamma\)\(^4\), and IL-12\(^7\) have been found. The role of chemokines was recently investigated in a murine *Legionella* pneumonia model\(^7\). Administration of anti-KC or anti-MIP-2 antibody resulted in an approximately 20% decrease in neutrophil recruitment on day 2. This did not influence mortality. In contrast, blockade of CXC chemokine receptor 2 (CXCR2), a receptor for CXC chemokines, such as KC and MIP-2, strikingly enhanced mortality. Interestingly, anti-CXCR2 antibody did not affect bacterial growth on day 2, even in the presence of a lethal challenge of *L. pneumophila*. Unexpectedly, a significant decrease in IL-12 levels, in contrast to the increases in KC, MIP-2, and LIX levels, was demonstrated for CXCR2-blocked mice\(^{57}\). These data indicate that CXCR2-mediated neutrophil accumulation plays a crucial role in the host defense against *Legionella* pneumonia. The decrease in the levels of IL-12 may explain the high mortality in the setting of reduced neutrophil recruitment.

**Pseudomonas aeruginosa pneumonia**

Compared with studies on the above-mentioned respiratory pathogens, studies on the effect of immunomodulating therapies in *Pseudomonas* pneumonia demonstrate opposite results.

In a murine pneumonia model with *P. aeruginosa*, AM depletion resulted in higher local chemokine levels, a prolonged inflammatory PMN recruitment, and a delayed bacterial clearance compared with control mice\(^{33}\). Furthermore, destruction of alveolar structures and thickening of the interstitial spaces were evident in the AM depleted mice. In contrast to the respiratory infections with *S. pneumoniae* or *Mycoplasma* spp., however, it was also demonstrated that, early after the initiation of pneumonia, AM depleted mice had lower concentrations of chemokines and less PMN in BALF, and a significant improvement in lung edema compared with control mice. Importantly, although AM-depletion improved early-phase inflammation, late survival was not altered.

While endogenous TNF was important for the clearance of *S. pneumoniae* and *K. pneumoniae*\(^{35, 64}\) from mouse lungs, it has been demonstrated that TNF im-
pairs host defense mechanisms during pneumonia with *P. aeruginosa*\(^{32}\). Similarly, while IL-1 receptor I deficient mice demonstrated an impaired bacterial clearance and a reduced capacity to form inflammatory infiltrates during infection with *S. pneumoniae*\(^{43}\), during infection with *P. aeruginosa* IL-1 receptor I deficient mice demonstrated an enhanced bacterial clearance (Fig. 3)\(^{45}\). In line with these results, we recently found that IFN-γ \(R^+\) mice had an accelerated clearance of *Pseudomonas* from their lungs compared with normal wild-type mice (Fig. 4)\(^{50}\). Furthermore, while endogenous IL-10 hampered bacterial clearance in mouse models of *S. pneumoniae* and *K. pneumoniae*\(^{21, 66}\), IL-10 improved host defense in a model of pneumonia caused by *P. aeruginosa*\(^{48}\). It is not clear whether the protective role of IL-10 in *P. aeruginosa* pneumonia represented IL-10-mediated protection from systemic endotoxin exposure.

IL-10 appears to be important in sepsis-induced immunosuppression. Mice with abdominal sepsis induced by cecal ligation and puncture were more susceptible for intratracheally administered *P. aeruginosa*, with a higher lethality than normal mice or mice undergoing sham abdominal surgery\(^{34}\). The development of pneumonia in animals undergoing cecal ligation and puncture was associated with a marked increase of IL-10 expression in the lungs, and administration of IL-10-neutralizing antibodies resulted in enhanced bacterial clearance from the lungs and reduced mortality.

**Considerations**

The data on AM depletion before induction of pneumonia with different respiratory pathogens illustrate both the beneficial and deleterious effects of AM during the orchestration of inflammation during pneumonia. Depletion of AM in the early phase of *Pseudomonas* pneumonia may initially improve lung injury, but may worsen the eventual outcome, as seen in the models of pneumonia with this pathogen and, such as pathogens like *K. pneumoniae*, *S. pneumoniae*, and *M. pneumoniae*. It remains unclear why the overzealous PMN infiltration, as seen in the absence of AM, does not lead to a complete clearance of bacteria from the lungs in these models, but this again indicates a prominent role of AM in host defense.

AM are regarded as major modulators of pulmonary host defense. Whereas early on AM readily phagocytose and (thereby) eliminate certain inhaled pathogens, they later represent important effector cells in the resolution process\(^{12, 25}\). The above-mentioned observation of overzealous and persistent PMN infiltration in the absence of AM may be related to the equally important function of AM during the resolution of inflammation. To reestablish tissue homeostasis, all the processes involved in the initiation of inflammation must be reversed, and one important prerequisite for resolution to occur is the removal of extravasated PMN. Several lines of evidence support the hypothesis that PMN undergo programmed cell death (apoptosis) followed by rapid clearance by AM\(^{12, 28}\). Apoptosis thereby provides an injury-limiting mechanism, since the membrane of PMN remains intact, preventing potentially injurious granule contents from being released. Thus, to prevent the potentially harmful event of secondary necrosis, where membrane integrity gets lost and histotoxic granule contents are exposed to the surrounding tissue, the immediate recognition of apoptotic PMN by AM is required. A variety of recognition mechanisms, including phosphatidylserine, exposed on apoptotic cell surfaces, have been described so far\(^{38, 47}\). Moreover, it has been nicely demonstrated that the uptake of apop-

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**Fig. 3.** Clearance of *P. aeruginosa* is enhanced in mice lacking the IL-1 signal. Mean (±SE) *P. aeruginosa* CFU in lungs 6 and 24 h after intranasal inoculation with \(10^4\), \(10^5\) and \(2 \times 10^6\) CFU in wild-type (open bars), and IL-1 \(R^+\) mice (solid bars). N = 6–8 mice per group at each time point.

**Fig. 4.** Mean (± SE) *P. aeruginosa* CFU in lungs 6 and 24 h after intranasal inoculation with \(10^3\) CFU in wild-type mice (open bars) and IFN-γ \(R^+\) mice (solid bars). N = 6 per strain at each time point. *p<0.05 vs. wild-type mice
totic PMN by macrophages not only cleared PMN, but also actively induced anti-inflammatory properties in human macrophages, illustrated by the suppressed release of pro-inflammatory cytokines (IL-1β, IL-8, TNF) and an increased release of agents with anti-inflammatory properties (such as transforming growth factor-α and prostaglandin-E2)\(^{16-18, 47}\).

It is important to emphasize that the role of cytokines in the innate immune response to respiratory tract infections differs in models in which different pathogens are used. The overall conclusion that can be drawn from the investigations on the role of cytokines during pneumonia is that pro-inflammatory cytokines induced by *P. aeruginosa* in models of subacute pneumonia, such as TNF, IL-1, and IPN-γ, are likely to impair bacterial clearance from the pulmonary compartment, and that the anti-inflammatory cytokine IL-10 induced by *P. aeruginosa* diminishes bacterial spread in this model. In contrast, in experimental pneumonia caused by the Gram-negative bacterium *K. pneumoniae*, pro-inflammatory cytokines are important for the clearance of bacteria from the lungs, whereas the anti-inflammatory cytokine IL-10 impairs host defense in this model. Similar results have been found for pneumonia with *S. pneumoniae*. At present it is unclear what the cause of these overt differences between these models is. A possible explanation includes differences in the extent and rapidity by which these strains induce inflammation in the lung. One could speculate that in more gradually developing pneumonias, such as those 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 that caused by *P. aeruginosa*, an excessive inflammatory response contributes to an adverse outcome.

Conclusion

We have reviewed the literature on innate immunity against respiratory pathogens.

In the last decade, we have come to a better understanding of the host response during pulmonary infection through detailed analysis of the cytokine networks during experimental pneumonia. Manipulation of innate immunity through deletion of AM or modulation of the cytokine cascade may serve in the future as an adjuvant therapy in the treatment of patients with severe pneumonia. However, several limitations exist. Targeting only AM or only one cytokine may be too simplistic, as the innate responses are complex, and as cytokines have pleotropic effects, which can lead to unexpected effects when used in an intervention *in vivo*. Furthermore, host responses against different respiratory pathogens differ quite substantially. Additional studies are necessary to overcome these issues.

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