

## REVIEW ARTICLE

## MECHANISMS OF DISEASE

## Acute Lower Respiratory Tract Infection

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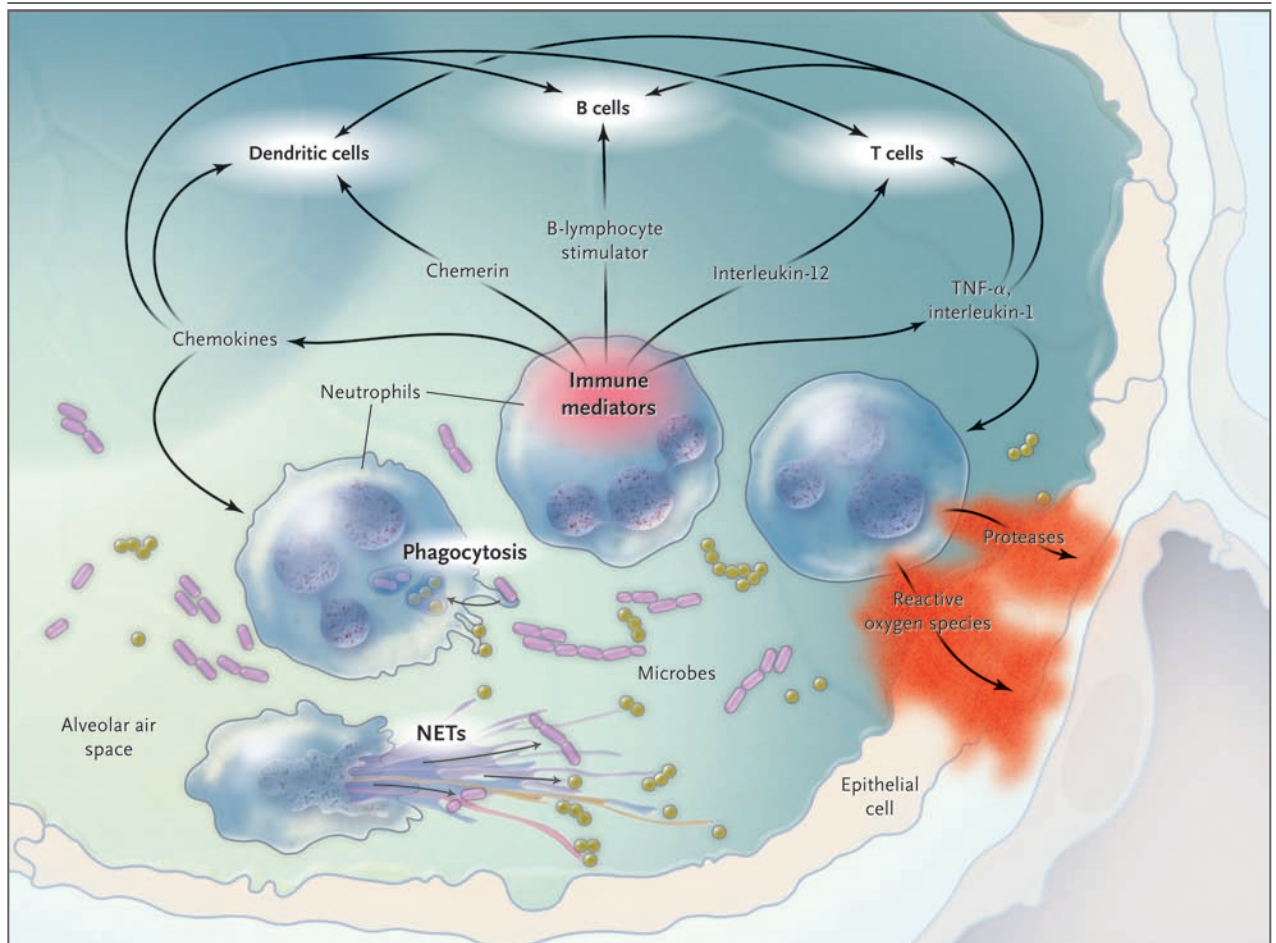
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ACUTE LOWER RESPIRATORY TRACT INFECTIONS ARE A PERSISTENT AND pervasive public health problem. They cause a greater burden of disease worldwide than human immunodeficiency virus infection, malaria, cancer, or heart attacks.<sup>1</sup> In the United States, they cause more disease and death than any other infection, and there has been little change in mortality due to respiratory tract infection for more than five decades.<sup>1,2</sup> The outcome of an acute lower respiratory tract infection depends on the virulence of the organism and the inflammatory response in the lung. When small numbers of low-virulence microbes are deposited in the lungs, an effective defense can be mounted by resident innate immune defenses, such as the mucociliary escalator, antimicrobial proteins in airway surface liquid, and alveolar macrophages. In contrast, numerous or more virulent microbes elicit an inflammatory response. Although this response serves to reinforce innate immunity and is essential to rid the lungs of microbes, it contributes directly to lung injury and abnormal pulmonary function. This article reviews our current understanding of inflammatory responses in infected lungs, emphasizing recent advances and gaps in knowledge. Much of the information originates from animal experiments; studies with human volunteers and patient-derived data are included when appropriate and available.

## INFLAMMATION AND INNATE IMMUNITY

Acute inflammation features the accumulation of neutrophils and a plasma exudate outside of blood vessels. In the pulmonary capillaries of uninfected lungs, these blood contents are normally separated from the alveolar air by less than 1  $\mu\text{m}$ , the thinnest interface between the blood and the environment. The trapping of neutrophils in these capillaries, which is the result of geometric and biophysical constraints,<sup>3</sup> increases their quantity per volume of blood by approximately 50 times as compared with other blood vessels, forming a margined pool of neutrophils that is ready to respond when needed.

During pulmonary infection, neutrophils migrate out of the pulmonary capillaries and into the air spaces.<sup>4</sup> Elie Metchnikoff, the discoverer of phagocytosis, considered neutrophils (or microphages, as he called them) to be “the defensive cells *par excellence* against microorganisms.”<sup>5</sup> After phagocytosis, neutrophils kill ingested microbes with reactive oxygen species (e.g., hypochlorite), antimicrobial proteins (e.g., bactericidal permeability-inducing protein and lactoferrin), and degradative enzymes (e.g., elastase) (Fig. 1).<sup>6</sup> An additional microbicidal pathway has also been identified — the neutrophil extracellular trap (NET). Neutrophils extrude NETs composed of a chromatin meshwork containing antimicrobial proteins, and these NETs ensnare and kill extracellular bacteria.<sup>7</sup> It remains to be determined whether NETs are useful host defense mechanisms against motile microbes in the dynamic and unstructured liquid-filled air spaces of the infected lung.



**Figure 1. Neutrophils and Lung Infection.**

Neutrophils are effector cells of innate immunity, killing microbes using phagocytosis and neutrophil extracellular traps (NETs). Neutrophils also generate a variety of immune mediators to direct immune responses, influencing other cells of innate and adaptive immunity. Finally, neutrophils damage tissues, with products such as proteases and reactive oxygen species injuring cells and digesting matrix. TNF denotes tumor necrosis factor.

The content of plasma proteins in the interstitium and air spaces of infected lungs is determined by the combined actions of pericellular bulk flow and transcellular transport by endothelial and epithelial cells. Many plasma proteins, including natural antibodies, complement proteins, C-reactive protein (originally identified in serum from patients with pneumonia<sup>8</sup>), and pentraxin 3, are important for the defense against microbes in the lungs.<sup>9-13</sup> They serve opsonic, bacteriostatic, and microbicidal functions during infection.

Deficits in neutrophil quantity (neutropenia) and defects in quality (e.g., chronic granulomatous disease) predispose patients to opportunistic lung

infections, as do deficiencies of complement and immunoglobulins. Since neutrophils and plasma proteins mediate innate immune functions and are needed to prevent lung infection, acute inflammation can be considered an essential innate immune response in the lungs.

#### GENERATION OF ACUTE INFLAMMATION IN INFECTED LUNGS

##### MOLECULES THAT DETECT MICROBES

Microbes must be detected by host cells to initiate inflammation in infected lungs. The identification of microbial invaders relies on a set of diverse receptors called pattern-recognition receptors, which

bind molecular moieties that are common to microbes.<sup>14</sup> Discoveries of new families of pattern-recognition receptors, including toll-like receptors, nucleotide-binding and oligomerization-domain proteins, and caspase-recruitment domain helicases, have fueled research in the biology of innate immunity. Table 1 lists some of the pattern-recognition receptors with direct relevance to innate immunity in the lungs or to respiratory infection.

For any one microbe, there are a variety of molecules that can activate many different pattern-recognition receptors. Perhaps for this reason, deficiencies of individual pattern-recognition receptors result in more modest phenotypes during experimentally induced acute lower respiratory infections than deficiencies of downstream adapter proteins, which signal from multiple pattern-recognition receptors.<sup>41,42</sup> The intracellular signaling pathways triggered by diverse pattern-recognition receptors converge on signaling hubs, such as transcription factors of the nuclear factor  $\kappa$ B (NF- $\kappa$ B) and interferon regulatory factor families. These factors integrate signals from diverse stimuli (interacting with pattern-recognition receptors) and initiate responses. NF- $\kappa$ B mediates the transcription of adhesion molecules, chemokines, colony-stimulating factors, and other cytokines that are necessary for inflammatory responses.<sup>43</sup> In mice with bacterial stimuli in the lungs, NF- $\kappa$ B RelA (also known as p65) is required for inducing the production of adhesion molecules and chemokines as well as for initiating neutrophil recruitment and host defense.<sup>44,45</sup> Interferon regulatory factors mediate the expression of type I interferons and interferon-induced antiviral genes.<sup>46</sup> Interferon regulatory factor 3 influences parainfluenza virus infection in mouse lungs,<sup>47</sup> but the genes and immune functions that require it or other interferon regulatory factors during lung infection remain unknown.

#### SENTINEL CELLS IN THE LUNGS

Populations of myeloid cells with specialized functions as sentinels, the alveolar macrophages and dendritic cells, reside in the lungs. These cells are particularly well equipped with pattern-recognition receptors and are anatomically situated to encounter microbes in the air spaces.

Alveolar macrophages are mobile cells that patrol the luminal surfaces of the alveoli. They have been referred to as dust cells because of their abilities to remove and digest relatively inert in-

haled materials. They are also sources of alarm signals when lungs are infected, but inhibition of these signals until the appropriate time is imperative. One possible inhibitory mechanism entails the globular heads of surfactant proteins A and D, which bind alveolar-macrophage receptors and suppress inflammatory activity in uninfected lungs. During infection, these globular heads bind pathogens, and the presentation of oligomerized collagenous tails (a result of the clustering of the surfactant proteins on pathogen surfaces) activates rather than quiets alveolar macrophages.<sup>48</sup> It is plausible that the inflammatory activity of alveolar macrophages is constitutively suppressed by transforming growth factor  $\beta$ , which is presented to them by epithelial-cell integrins; microbial products initiate signaling that interferes with this suppression, thereby activating the inflammatory functions of alveolar macrophages.<sup>49</sup>

Dendritic cells are distributed throughout the respiratory tract. In the conducting airways, intraepithelial dendritic cells extend into the fluid within the airway lumen, where they ingest samples from the materials being swept by mucociliary transport from the alveoli toward the glottis.<sup>50</sup> In response to the presence of microbes in the lungs, more dendritic cells migrate into the lungs, through the tissues, and also into the draining lymph nodes.<sup>50</sup> Dendritic cells are antigen-presenting cells and are therefore central to adaptive immune responses. They also have important functions in innate immunity. Their pattern-recognition receptors render them especially suited to detecting viruses, and when stimulated they produce very high levels of type I interferons.<sup>51</sup> The depletion of dendritic cells or the interruption of type I interferon signaling increases susceptibility to viruses in the lungs.<sup>52,53</sup>

Alveolar macrophages and dendritic cells have a limited ability to kill microbes, but they are particularly important for sensing microbes and passing this information along to other cells, such as epithelial cells and lymphocytes. These cells then recruit the effectors of innate immunity, neutrophils.

#### EFFECTORS OF INNATE IMMUNITY

Neutrophil recruitment is directed by lung cells. Adhesion molecules induced on lung cells provide traction and signaling information to neutrophils.<sup>54</sup> Chemokines from lung cells stimulate chemotaxis and influence the directional motility of neutro-

**Table 1. Pattern-Recognition Receptors Implicated in Acute Lower Respiratory Tract Infections.**

Receptor	Microbial Ligands	References
<b>Transmembrane</b>		
TLRs (toll-like receptors)		
TLR2	Peptidoglycans from bacteria	Knapp et al. <sup>15</sup>
TLR3	Respiratory syncytial virus	Rudd et al. <sup>16</sup>
TLR4	Lipopolysaccharides from gram-negative bacteria, fusion proteins from respiratory syncytial virus, pneumolysin from <i>Streptococcus pneumoniae</i>	Branger et al., <sup>17</sup> Kurt-Jones et al., <sup>18</sup> Malley et al. <sup>19</sup>
TLR5	Flagellin from bacteria	Feuillet et al. <sup>20</sup>
TLR9	CpG DNA from bacteria	Albiger et al. <sup>21</sup>
MARCO (macrophage receptor with collagenous structure)	<i>S. pneumoniae</i>	Arredouani et al. <sup>22</sup>
SRA-I and SRA-II (scavenger receptors AI and AII)	<i>S. pneumoniae</i>	Arredouani et al. <sup>23</sup>
Dectin-1	$\beta$ -glucan of fungi, <i>Pneumocystis carinii</i>	Steele et al. <sup>24,25</sup>
DC-SIGN*	<i>S. pneumoniae</i>	Koppel et al. <sup>26</sup>
FPR (formyl peptide receptor)	N-formylated peptides of bacteria	Fillion et al. <sup>27</sup>
MR (mannose receptor)	<i>P. carinii</i>	Tachado et al. <sup>28</sup>
NKp46 (natural killer cell p46)	Hemagglutinin from influenza viruses, hemagglutinin neuraminidase from parainfluenza viruses	Mandelboim et al., <sup>29</sup> Gazit et al. <sup>30</sup>
<b>Cytosolic</b>		
Naip5 (neuronal apoptosis-inhibiting protein 5)	<i>Legionella pneumophila</i>	Wright et al. <sup>31</sup>
Ipaf†	<i>L. pneumophila</i>	Amer et al. <sup>32</sup>
Nod1 and Nod2 (nucleotide oligomerization domains 1 and 2)	Peptidoglycan components from bacteria	Opitz et al. <sup>33</sup>
RIG-I (retinoic acid-inducible gene I)	Influenza virus RNA	Le Goffic et al. <sup>34</sup>
<b>Extracellular</b>		
SP-A and SP-D (surfactant proteins A and D)	Influenza virus, respiratory syncytial virus, gram-negative bacteria, gram-positive bacteria	Wright <sup>35</sup>
LBP (lipopolysaccharide-binding protein)	Lipopolysaccharides from gram-negative bacteria	Branger et al. <sup>36</sup>
CD14	Lipopolysaccharides from gram-negative bacteria	Frevert et al. <sup>37</sup>
MD-2	Lipopolysaccharides from gram-negative bacteria	Jia et al. <sup>38</sup>
PTX3 (pentraxin 3)	<i>Aspergillus fumigatus</i>	Garlanda et al. <sup>10</sup>
MBL (mannose-binding lectin)	Mannosylated moieties on microbes	Reading et al. <sup>39</sup>
CRP (C-reactive protein)	Phosphocholine on <i>S. pneumoniae</i>	Thomas-Rudolph et al. <sup>40</sup>
Complement	Microbial surfaces	Mold et al. <sup>11</sup>

\* DC-SIGN denotes dendritic-cell-specific ICAM-3-grabbing nonintegrin (ICAM denotes intercellular adhesion molecule).

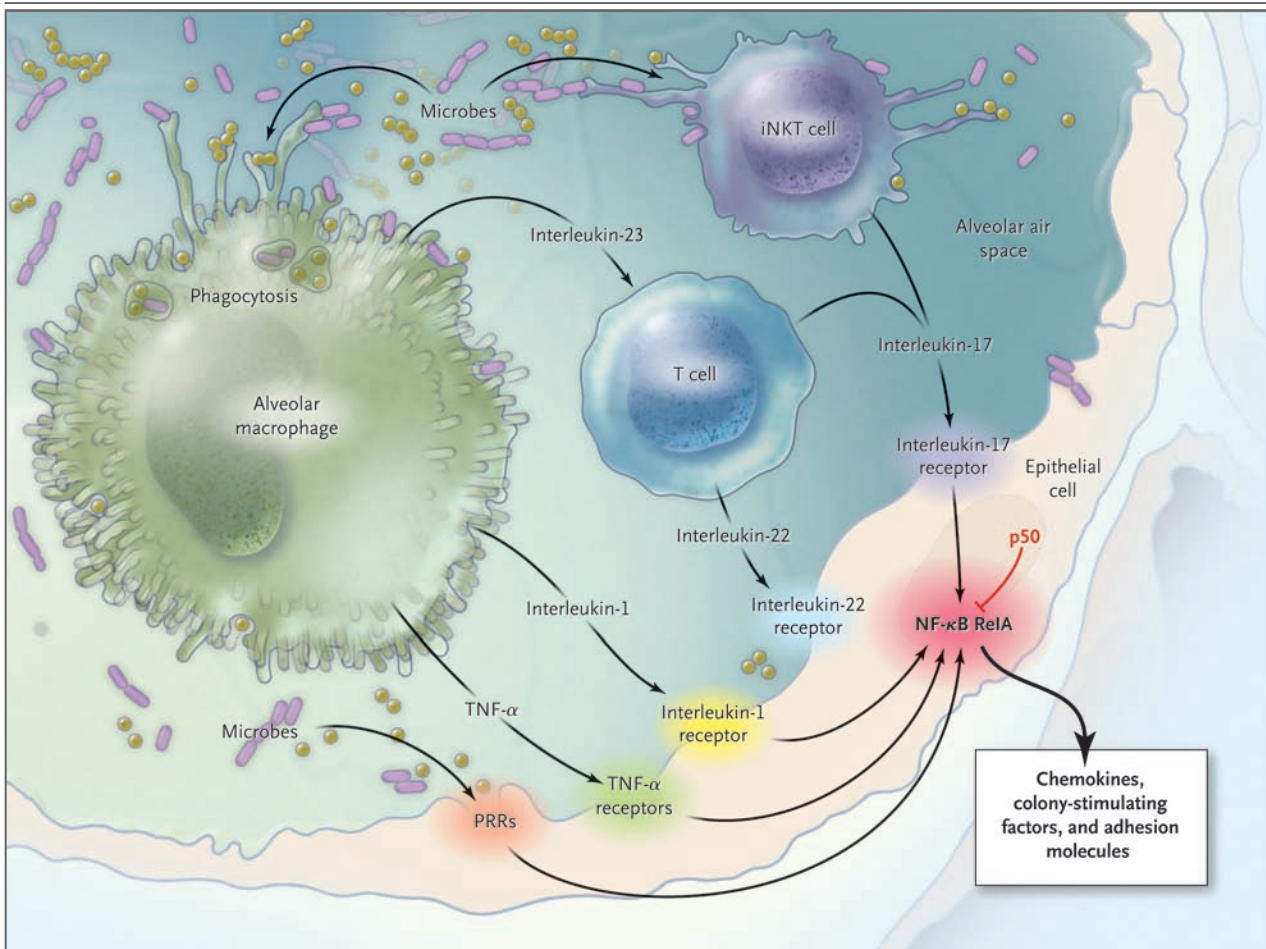
† Ipaf denotes ICE protease-activating factor (ICE denotes interleukin-1 beta-converting enzyme).

phils.<sup>54</sup> Colony-stimulating factors signal neutrophil production and release from hematopoietic tissues.<sup>55</sup>

The epithelial barrier between the air-space content of the lungs (including microbes) and the

rest of the body constitutes a critical interface for information transfer leading to neutrophil recruitment (Fig. 2). In transgenic mice in which an inhibitor of NF- $\kappa$ B activation is expressed exclusively in lung epithelial cells, the interruption of NF- $\kappa$ B





**Figure 2. The Epithelial Interface and Lung Infection.**

Activation of the epithelial cells forming an interface between the air spaces and the body induces the expression of molecules recruiting neutrophils as innate immunity reinforcements. Epithelial cells recognize some microbes directly through pattern-recognition receptors (PRRs). Alveolar macrophages recognizing microbes activate epithelial cells directly and through T-cell intermediates. Invariant natural killer T (iNKT) cells recognizing microbes can also activate epithelial cells. These diverse activation pathways converge on nuclear factor  $\kappa$ B (NF- $\kappa$ B) transcription factors in the epithelial cell, with RelA responsible for inducing and p50 responsible for regulating the expression of proinflammatory mediators, including neutrophil chemokines, colony-stimulating factors, and adhesion molecules. TNF denotes tumor necrosis factor.

activation decreases the expression of cytokines, including neutrophil chemokines.<sup>56,57</sup> This defect in epithelial-cell gene expression compromises neutrophil recruitment and bacterial killing in the lungs.<sup>45,56,57</sup>

With the increasing recognition of the roles of epithelial cells in lung inflammatory responses,<sup>58</sup> efforts are under way to illuminate the pathways of epithelial-cell activation in infected lungs. Lung epithelial cells can be activated directly by some microbes, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.<sup>59,60</sup> However, other microbes, such as pneumococci (the most common cause

of community-acquired pneumonia), are less likely to be or cannot be recognized by epithelial cells.<sup>45</sup> During pneumococcal pneumonia, alarm signals generated by sentinel myeloid cells, particularly tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin-1 ( $1\alpha$  and  $1\beta$ ), are essential for activation of the epithelium and downstream inflammatory responses.<sup>45,61</sup> Blocking the signaling of either TNF- $\alpha$  or interleukin-1 produces modest effects as compared with blocking both pathways simultaneously,<sup>61-63</sup> suggesting that these cytokines have overlapping functions during acute respiratory tract infection. Neutrophil-mediated host

defense against pneumococci in the lungs requires such signaling.

Epithelial cells can also be activated by lymphocyte cytokines (Fig. 2). Interleukin-17 activates lung epithelial cells to express chemokines and colony-stimulating factors, and it is essential for neutrophil-mediated host defense during klebsiella pneumonia.<sup>64</sup> During such infection, interleukin-17 is produced by T cells, and its production is stimulated by another signal from macrophages — interleukin-23.<sup>65</sup> A subpopulation of invariant natural killer T cells in the lungs can also generate interleukin-17 to stimulate epithelial cells and elicit neutrophil recruitment, and the interleukin-17 expressed by these cells may not depend on interleukin-23.<sup>66</sup> Interleukin-17-secreting T cells also release interleukin-22, which functions like interleukin-17 in activating epithelial cells.<sup>67</sup> If, when, and how interleukin-22 influences innate immune responses during lung infection are questions yet to be answered.

Neutrophils are not dead ends in these communication pathways but convey important information that directs immune responses (Fig. 1).<sup>6</sup> They generate proinflammatory signals, including TNF- $\alpha$ , interleukin-1, and chemokines; chemerin, which recruits and activates dendritic cells; and B-lymphocyte stimulator, which promotes the selection, survival, and growth of B cells. Neutrophils are sources of the T-cell-activating cytokine interleukin-12 in the lungs,<sup>68</sup> and interleukin-12 amplifies interferon- $\gamma$  to enhance neutrophil-mediated host defense during pneumonia.<sup>69</sup> Neutrophils constitutively express the extracellular pattern-recognition receptor pentraxin 3, and the compromised host defense of mice with pentraxin 3 deficiency can be improved by the administration of soluble pentraxin 3 or by transfer of neutrophils from wild-type but not pentraxin 3-deficient mice.<sup>10,70</sup> Thus, acquired and innate immune responses against microbes in the lungs are shaped by signals derived from neutrophils.

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#### INFLAMMATION AND ACUTE LUNG INJURY

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Inflammation is critical for innate immunity and host defense, but it can injure the lungs. The accumulation of extravascular plasma fluids, as in noncardiogenic pulmonary edema, is a defining feature of acute lung injury. The neutrophil products generated to kill microbes, such as reactive

oxygen species and proteases, also kill host cells and damage host tissues (Fig. 1). The risks of inflammation are starkly demonstrated in a transgenic mouse model in which the activation of NF- $\kappa$ B in lung epithelial cells is sufficient to cause neutrophil recruitment, pulmonary edema, arterial hypoxemia, and death in the absence of any infection or exogenous stimuli.<sup>71</sup> Thus, the innate immune responses necessary for ridding the lungs of microbes can also cause injury and contribute to the pathophysiology of infection. Perhaps because of this, lung infection is a common underlying cause of the acute respiratory distress syndrome.<sup>72</sup>

Inhibiting inflammatory signals can be protective during lung infections. For example, interrupting both TNF- $\alpha$  and interleukin-1 signaling (but neither alone) decreases the pulmonary edema and the loss of lung compliance that are often found in mice with *Escherichia coli* pneumonia.<sup>62,63</sup> Triggering receptor expressed on myeloid cells 1 (TREM-1), which functions in a positive feedback loop to amplify TNF- $\alpha$ , interleukin-1, and inflammation,<sup>73</sup> is so strongly associated with pneumonia in patients that measurement of soluble TREM-1 in bronchoalveolar-lavage fluid has been proposed as a diagnostic test.<sup>74</sup> Inhibition of TREM-1 diminishes TNF, interleukin-1, and pathophysiological features in rats with *P. aeruginosa* pneumonia.<sup>75</sup> Corticosteroids can be effective albeit nonspecific inhibitors of inflammation. In a clinical trial of corticosteroid infusion in patients with severe community-acquired pneumonia, the 23 patients in the corticosteroid group had less lung injury and a higher rate of survival than the 23 patients in the placebo group.<sup>76</sup> Results from this small study are provocative but must be viewed with caution until further studies are completed.<sup>77</sup> Knowledge gaps remain substantial. It is not yet evident which patients with which infections may benefit from which antiinflammatory therapies at which times. Altogether, however, these studies suggest that inflammation-targeting therapies may be useful in treating certain severe lung infections, encouraging further research along these lines.

Highly pathogenic influenza viruses, such as avian influenza A (H5N1) virus and the virus causing the 1918 pandemic, induce strong inflammatory responses in humans and laboratory animals.<sup>78,79</sup> The seemingly excessive responses bolster the idea that a so-called cytokine storm

mediates pathophysiology during these infections, but direct evidence in support of this concept is scant. Neutrophil depletion increases viral growth and hastens death in mice infected with the H5N1 influenza A virus,<sup>80</sup> suggesting that at least in this experimental infection, neutrophils do more good than harm. Interruptions of cytokine signaling in mice with H5N1 influenza A virus infections have modest or no effects,<sup>81</sup> suggesting that the cytokines so far examined are not individually essential to the pathophysiology of H5N1 influenza virus infection. Further studies will be critical in determining whether and, if so, which inflammatory mediators influence the pathophysiology of highly pathogenic influenza virus infections, and whether the interruption of select cytokines or signaling pathways upstream or downstream from cytokines can protect the host from inflammatory injury during such infections.

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REGULATION OF ACUTE  
INFLAMMATION IN INFECTED  
LUNGS

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The body needs mechanisms to keep acute inflammation in check. Much less is known about these regulatory mechanisms than about the mechanisms initiating and amplifying inflammation. A few examples of how regulatory mechanisms influence the outcome of lung infections are presented here.

One such braking strategy is to limit NF- $\kappa$ B activity. The NF- $\kappa$ B protein p50 has multiple functions, which include curbing the transcription of genes with NF- $\kappa$ B-binding sites in their promoters.<sup>43</sup> During bacterial pneumonia in mice, a deficiency of p50 increases cytokine expression and exacerbates lung injury.<sup>82</sup> Thus, p50 normally functions to prevent excess cytokines and inflammatory injury during pneumonia.

Another mechanism is interference with signaling from pattern-recognition receptors. The interleukin-1 receptor-associated kinase (IRAK)-like molecule (IRAK-M) inhibits IRAK-mediated signaling from the pattern-recognition and cytokine receptors that activate NF- $\kappa$ B. Sepsis induces IRAK-M in mouse alveolar macrophages, and this protein decreases cytokine expression and compromises pulmonary host defense.<sup>83</sup> IRAK-M may therefore contribute to the susceptibility of patients with sepsis to nosocomial pneumonia.

Other regulatory molecules inhibit pattern-recognition-receptor signaling indirectly. For example, carbon monoxide generated by heme oxygenase-1 inhibits signaling from transmembrane pattern-recognition receptors.<sup>84</sup> A deficiency of heme oxygenase-1 increases, whereas its overexpression decreases, inflammation and injury induced by bacteria and influenza virus in mouse lungs.<sup>85-87</sup> Prevention of injury is probably due to both the antiinflammatory and the tissue-protective activities of heme oxygenase-1.

The signal transducer and activator of transcription 3 (STAT3) also has antiinflammatory and tissue-protective effects. Mutations in STAT3 result in the hyper-IgE syndrome, which is characterized by recurrent and severe lung infections.<sup>88</sup> This transcription factor is activated in macrophages and epithelial cells during acute pulmonary inflammation.<sup>89</sup> Macrophage STAT3 mediates antiinflammatory responses induced by the cytokine interleukin-10,<sup>90</sup> which compromises host defense but limits lung injury during pneumonia.<sup>91-94</sup> Epithelial-cell STAT3 is essential in preventing lung injury during infection.<sup>95</sup> The signals that activate epithelial-cell STAT3 are uncertain, but are not likely to include interleukin-10. STAT3 activation in the lungs during *E. coli* infection depends partially on interleukin-6, which is essential for overcoming bacterial pneumonia.<sup>96</sup>

Prostaglandin I<sub>2</sub> (prostacyclin) is generated during respiratory syncytial virus infection and has protective activities that may be mediated by antiinflammatory effects on dendritic cells.<sup>97,98</sup> In addition to having antiinflammatory activities, other lipids, including lipoxins, resolvins, and protectins, help return inflamed tissues to health.<sup>99</sup> During and after pneumonia, the return of the architecture of a lung lobe from complete consolidation to a seemingly normal state is remarkable. Unfortunately, few if any studies have reported the mechanisms underlying this process of resolution during lung infection, so the presumed role of lipids must at present be based on extrapolation.

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RESPONSES OF MICROBES  
TO INFLAMMATION

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Acute lower respiratory tract infections can be monomicrobial or polymicrobial, with organisms ranging in virulence from commensal to highly

pathogenic.<sup>100-102</sup> These microbes have mechanisms for counteracting many of the effector and signaling events described above. Microbial subversion of individual pathways may be a selective pressure driving mammalian hosts to have multiple, parallel, sometimes redundant-seeming pathways for innate immunity, as with epithelial activation (Fig. 2). A few microbial strategies specifically related to lung infections and the pathways of innate immunity described above are highlighted here as examples.

Counteracting effector mechanisms of innate immunity is of obvious advantage to a microbe. Although NETs were discovered only recently,<sup>7</sup> microbial countermeasures are already recognized. For example, NETs extruded by neutrophils fail to contain and kill pneumococci.<sup>103</sup> A pneumococcal DNase cleaves NETs and frees bacteria. During infection, this DNase is a virulence factor that gives the bacteria a competitive advantage against DNase-mutated strains in the lungs of mice, resulting in increased mortality from pneumonia in such mice.

Preventing the host from detecting pathogens is another strategy often used by microbes. For example, the retinoic acid–inducible gene I intracellular pattern-recognition receptor for viral RNA is bound by an influenza virus protein that prevents downstream signaling, activation of interferon regulatory factor, and expression of type I interferon.<sup>104</sup> Deleting this protein attenuates influenza virus infection, increasing type I interferon in the lungs and decreasing mortality.<sup>105</sup> Many pathogens interrupt proinflammatory signaling pathways or mimic antiinflammatory signaling pathways.

Not only do lung pathogens interfere with host signaling, they also listen in on these immune conversations and use this information to guide their responses appropriately. For example, *P. aeruginosa* expresses a receptor that recognizes interferon- $\gamma$ , and in the presence of interferon- $\gamma$ , this receptor stimulates gene expression dictating biofilm formation.<sup>106</sup> Since biofilms render bacteria more resistant to both innate immunity and antibiotics, this is probably an adaptive response during infection. In addition, *P. aeruginosa* and other bacteria respond to TNF- $\alpha$  and other cytokines with increased growth rates.<sup>107</sup> In neutropenic mice, the ability of TNF- $\alpha$  to increase bacterial growth worsens lung infection.<sup>108</sup> Thus, pathogens sense innate immune signaling and respond

in ways that subvert host defense and facilitate infection.

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#### GENETIC VARIATION IN INFLAMMATORY PATHWAYS

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The mechanisms for generating and regulating acute inflammation, described above, determine the outcomes of experimentally induced lung infections in animals. Deficiencies and polymorphisms in human genes for the factors involved in these mechanisms have been associated with lung infection and its consequences, such as disseminated or invasive infection or acute lung injury (Table 2). Although the limitations of such genotype–phenotype associations warrant consideration,<sup>129</sup> these data indicate that knowledge of innate immunity and lung infection derived from experiments in animals can apply to humans. Genetic variations in innate-immunity mediators influence the outcome of inevitable exposures of the human lower respiratory tract to microbes.

Another reason why human genotype–phenotype studies are important is that they occur in natural instead of laboratory environments. Infections involve intersections of host and microbe within complex and dynamic ecosystems not mimicked in laboratory studies. For example, patients with a deficiency of IRAK-4 (which signals from multiple pattern-recognition receptors) are susceptible to a narrower spectrum of microbes, over a narrower age range, and with more variation across the population than in vitro experiments with human cells or in vivo experiments with mice would suggest.<sup>113</sup> Patients with an immunodeficiency tend to present with select subgroups of infections (e.g., patients with chronic granulomatous disease are especially susceptible to five microbes<sup>130</sup>). Environmental and genomic variations result in a range of susceptibility among patients with similar immunodeficiencies. In the future, polygenic analyses may demonstrate that combined polymorphisms in multiple genes influence lung infections more dramatically than monogenic variation, since parallel paths and redundancies are common in innate immunity. An emerging theme is that genetic susceptibility to infection is more common than is now appreciated; susceptibility is probably polygenic, with incomplete penetrance restricted to narrowly defined clinical phenotypes.<sup>131</sup>



**Table 2. Genetic Polymorphisms Associated with Lung Infection Outcomes.\***

Gene Product	Association	References
<b>Initiating and amplifying mechanisms</b>		
TLRs (toll-like receptors)		
TLR4	Legionella pneumonia, severe respiratory syncytial virus infection	Tal et al., <sup>109</sup> Hawn et al. <sup>110</sup>
TLR5	Legionella pneumonia	Hawn et al. <sup>111</sup>
CD14	Respiratory syncytial virus bronchiolitis	Inoue et al. <sup>112</sup>
IRAK-4 (interleukin-1 receptor–associated kinase 4)	Bacterial infections, particularly pneumococcal infection	Ku et al. <sup>113</sup>
NEMO — NF- $\kappa$ B activation	Recurrent invasive pneumococcal disease	Ku et al. <sup>114</sup>
Mal (MyD88 adaptor-like protein) — toll-like receptor signaling	Invasive pneumococcal disease	Khor et al. <sup>115</sup>
MBL (mannose-binding lectin)	Invasive pneumococcal disease, recurrent respiratory infections, acute lung injury	Roy et al., <sup>116</sup> Gomi et al., <sup>117</sup> Gong et al. <sup>118</sup>
Complement C2	Invasive pneumococcal disease and recurrent pneumonias	Jönsson et al. <sup>119</sup>
SP-A, SP-D (surfactant proteins A and D)	Severe respiratory syncytial virus infection	Lahti et al., <sup>120</sup> Löfgren et al. <sup>121</sup>
<b>Regulating mechanisms</b>		
NF- $\kappa$ B p50	Acute lung injury	Adamzik et al. <sup>122</sup>
I $\kappa$ B- $\alpha$	Invasive pneumococcal disease, acute lung injury	Chapman et al., <sup>123</sup> Zhai et al. <sup>124</sup>
Interleukins		
Interleukin-6	Invasive pneumococcal disease	Schaaf et al. <sup>125</sup>
Interleukin-10	Pneumonia outcomes and acute lung injury	Wattanathum et al., <sup>126</sup> Gong et al. <sup>127</sup>
HO-1 (heme oxygenase-1)	Pneumonia susceptibility	Yasuda et al. <sup>128</sup>
STAT3 (signal transducer and activator of transcription 3)	Hyper-IgE syndrome — recurrent severe lung infections	Holland et al. <sup>88</sup>

\* NEMO denotes NF- $\kappa$ B essential modulator, and NF- $\kappa$ B nuclear factor  $\kappa$ B.

## CONCLUSIONS

Innate immune responses to microbes in the lungs determine the outcome of infection; an insufficient response can result in life-threatening infection, but an excessive response can lead to life-threatening inflammatory injury. Further studies will help identify populations that are particularly susceptible to severe lung infection

and will guide the development of prophylactic and therapeutic interventions.

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