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Inflammation and Pneumonia: Why Are Some More Susceptible than Others?

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Introduction

Pneumonia is a very unusual outcome of very common host-microbe interactions. Pneumonias are caused by a large variety of ubiquitous and unavoidable microbes such as rhinovirus, influenza virus, pneumococcus, *Staphylococcus aureus*, and many more^{1–3}. These microbes are encountered frequently by most people, yet pneumonia occurs only rarely. What differences in host-microbe interactions determine whether pneumonia ensues?

Some people tend to be more prone to pneumonia, including the very young, the elderly, and those with diverse conditions or diseases such as stress, poverty, poor air quality, obesity, diabetes, atherosclerosis, and more⁴. Mechanisms responsible for rendering these individuals more susceptible to pneumonia are largely speculative⁴. Multiple factors are involved, including variations in the inflammatory response during respiratory infection.

The microbes

No single species of microbe is responsible for more than a small fraction of pneumonia cases^{1–3}. While the microbe may be less pivotal than the host response to the microbe⁴, the biology of the microbe does matter. Properties of microbes can influence pneumonia likelihood and severity^{5–9}. Some of the microbial variations related to pneumonia pathogenesis center on how microbes interact with host inflammatory pathways. As one example of this, pneumococci that are less stimulatory of inflammatory responses in macrophages are more virulent and likely to cause pneumonia¹⁰. Pneumococcus is the most common bacterial cause of community-acquired pneumonia (CAP) in both children and

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adults in the US ^{1,2}. Analyses of pneumococcal isolates found in children, collected from blood or empyema fluid of patients or from nasal passages of carriers without pneumococcal disease, revealed a marked variation in macrophage NF- κ B activation ¹⁰. NF- κ B is a transcription factor essential to induction of diverse pro-inflammatory cytokines ¹¹. Pneumococcal isolates collected from children with complicated pneumonia are more likely to be low NF- κ B activators, compared to isolates from other children ¹⁰. These pneumococci induce lower and slower pro-inflammatory cytokine expression from macrophages *in vitro* and *in vivo*, and they are cleared less effectively from the lungs of mice during experimental infection ¹⁰. These findings suggest that avoiding inflammatory triggering is a virulence property for pneumococcus ¹², supporting the concept that the degree to which inflammation is rapidly and effectively triggered in the lungs is one important determinant of whether pneumonia results from a lower respiratory infection.

Constitutive immune defense of the lung

The respiratory tract is protected by many continuously functioning defenses that work together ⁴. The branching system of conducting airways favors impaction of inhaled organisms before they reach the deep lung. The mucociliary escalator throughout the conducting airways traps impacted microbes and impels them towards the glottis, where they are swallowed for digestion and/or elimination. The surface lining fluids of the respiratory tract are inhospitable to microbes, from nose to alveoli, by limiting essential nutrients and including factors noxious to microbes. Alveolar macrophages patrol the lung surface and phagocytose microbes that manage to evade these above-described defenses. When microbes reaching the lungs are sparse and not highly virulent, these constitutive defenses are often sufficient to prevent clinically relevant microbial accumulations. While the lungs are not sterile and contain a dynamic microbiome ¹³, they typically remain free of infection despite extensive microbial exposure.

Defects in these constitutive defenses can render individuals susceptible to pneumonia. Although beyond the scope of this manuscript focusing on inflammation specifically, it is relevant to recognize that there are many instances where airway structural changes (e.g., in chronic respiratory diseases), mucociliary escalator dysfunction (e.g., primary ciliary dyskinesia), altered surface lining characteristics (e.g., changes in salts, carbohydrates, or other metabolites), or other defects in constitutive lung defenses contribute to pneumonia risk ⁴.

Inflammation for recruited defense of the lung

When constitutive defenses are overwhelmed by numerous or virulent microbes, recruitment of additional defense (i.e., inflammation) becomes necessary. Rapid neutrophil accumulation is especially key to effective microbe elimination. These inflammatory cells kill microbes by phagocytosis, degranulation, and the release of neutrophil extracellular traps ¹⁴. In addition to neutrophils, other leukocytes recruited to aid in antimicrobial lung defense include monocytes, dendritic cells, natural killer (NK) cells, invariant natural killer T (iNKT) cells, gd-T cells, mucosa-associated invariant T (MAIT) cells, and innate lymphoid cells (ILCs) of various types ⁴. Beyond these cell accumulations, there is an accumulation of extravascular

plasma, which results in the radiological infiltrate that is used in pneumonia diagnosis. While pulmonary edema contributes directly to lung injury, this fluid exudate is also important to immune defense because it includes antimicrobial factors such as complement and antibodies. The coordination of these inflammatory processes helps eliminate virulent and/or numerous microbes in the lungs.

While rapidly ramping up inflammation helps fight infection, brakes on the inflammatory response also are critical ⁴. Multiple activities function to slow or reverse inflammation in the infected or previously infected lung. Alveolar macrophages calm the inflammatory responses of epithelial cells using gap junction connections ¹⁵. Removal of inflammatory exudate fluid is accomplished by ion transport proteins in epithelial cells ¹⁶, pumping fluid from the air spaces into the interstitial spaces from where it can be cleared by lymphatics. Dead and dying inflammatory cells such as apoptotic neutrophils are removed via efferocytosis, stimulated by specialized pro-resolving mediators such as Lipoxin A4 and Resolvin D1 ¹⁷. Cells specialized for limiting inflammation and injury, such as regulatory T cells ^{18–19} and myeloid-derived suppressor cells ²⁰, are recruited to the infected lung to govern the resolution of inflammation. The coordinated actions of these anti-inflammatory and inflammation-resolving processes help prevent and limit the clinical severity of pneumonia.

Inborn variations in inflammatory pathways and pneumonia susceptibility

Carefully controlled studies using genetic engineering in mouse models are empowered to demonstrate connections between a gene of interest and pneumonia susceptibility. By comparing groups that differ only in defined genetic elements during a directly comparable exposure to the exact same microbe, unique roles for select gene products in distinct cells can be precisely delineated. Many genes related to inflammation have been demonstrated to be essential to pneumonia defense with such studies ⁴. As one example, the NF- κ B transcription factor that induces expression of myriad inflammatory mediators ¹¹ is essential to preventing pneumonia ²¹, with different but essential roles in many different cell-types ⁴. Interrupting one NF- κ B gene in macrophages or in epithelial cells is sufficient to reduce expression of inflammatory mediators from these cells and slow the recruitment of neutrophils into newly infected air spaces ^{22,23}, enabling microbes to establish more severe lung infection. In parallel, inflammatory pathways involving interferons and interferon stimulated genes (ISGs) are elicited, especially important against respiratory viruses and intracellular bacteria or fungi ^{24–26}. The ISGs and interferon regulatory factor (IRF) transcription factors are necessary for preventing some pneumonias, such as those caused by influenza or *Legionella* ^{27,28}. These animal studies demonstrate that the triggering of inflammatory gene expression via NF- κ B, IRFs, and other transcription factors initiates and guides the effective elimination of virulent microbes that get into the lung.

Similar concepts are supported by human studies. Rare but serious human mutations in genes involved in inflammation support the roles of these inflammatory processes in protecting against pneumonia. At least 24 different genes have been found to result in neutropenia when mutated, and these patients have increased risk of infections including pneumonia ²⁹. Related to NF- κ B activity, patients with mutations in signaling intermediates

upstream of this transcription factor, such as in the *MYD88* or *IRAK4* genes, are profoundly susceptible to infections by respiratory pathogens such as pneumococcus³⁰. Interestingly, invasive pneumococcal disease but not pneumonia is commonly diagnosed in such patients, likely because the inflammatory exudate essential to a pneumonia diagnosis is blunted in the absence of MyD88 or IRAK4 function. In contrast, mutations in which an exudate is not diminished but inflammatory functions are compromised predispose to infections that are readily diagnosed as pneumonia. For example, defective NADPH oxidase components in chronic granulomatous disease leads to fungal and bacterial pneumonias³¹, and defective IFN- α expression due to IRF7 deficiency leads to influenza pneumonias³². While such genetic diseases are rare, they reveal essential roles of inflammatory components in human lung defense against respiratory pathogens.

More common genetic polymorphisms in components of inflammation have been observed, but their connections to pneumonia are less firmly established³³. The significance of such polymorphisms on regulation and function of a gene is often unclear or modest. Furthermore, human studies are generally less well suited than mouse studies to connecting genetic variation to pneumonia defense. Virtually all such human studies involve genomes and also environments and co-morbidities that are very far from uniform across subjects, confounding analyses. Most but not all such human studies are observational and associative by design, involving non-controlled and highly varying exposures to very disparate types of respiratory pathogens. The vagaries of pneumonia diagnosis, including the subjective assessment of the diagnosis itself as well as typically uncertain etiology and inconsistently quantified severity, coupled with the rare and seemingly stochastic nature of this disease in even susceptible populations, further complicate such research. Although the net contributions remain largely unclear, it is plausible that genetic variations in inflammatory and other pathways contribute to many cases of pneumonia.

Acquired variations in inflammatory pathways: improvements due to infection history

The “U-shaped curve” of pneumonia incidence over the age spectrum is well established⁴. The youngest children and older adults have much higher annual incidences of pneumonia than do older children and young adults. The mechanisms protecting older children and young adults against pneumonia are becoming elucidated, and variations in these pathways may influence who does or does not get pneumonia⁴.

The successful resolution of prior respiratory infections results in a substantial improvement in pulmonary defense, conferred by local changes in lung cells (Figure 1). Respiratory infections are inevitable throughout the life-course, and recovery from these infections is a guiding force in reshaping pulmonary inflammation to more effectively prevent pneumonia. Such experienced lungs respond more quickly and more effectively upon subsequent infections, whether microbes are similar to or different from those that infected the lungs previously. One aspect of this inflammatory remodeling is immunological memory, including both memory T cells and B cells, some of which (such as resident memory T cells, T_{RM} cells) persist exclusively in the lung tissue to mediate localized protection (Figure 1)

while other components (such as central memory T cells, or T_{CM} cells) circulate to offer more systemic protection⁴. This memory provides new effector mechanisms that are unavailable in naïve individuals, including neutralizing antibodies and cytotoxic T cells (CTLs). Beyond these antigen-specific immune effector mechanisms, memory lymphocytes confer protection by altering inflammatory processes in the lung⁴. Adaptive immune memory cells help lung immunity by changing the kinetics and amplitudes of inflammatory cytokines and chemokines in the tissue^{34,35}, accelerating and bolstering the antimicrobial defenses that would traditionally be characterized as components of innate immunity (Figure 1). The immunity protecting the lungs against pneumonia must extend across multiple serotypes/sub-types of a given bacteria (such as pneumococcus) or virus (such as influenza). Such heterotypic immunity is mediated by the rewiring of inflammatory responses by adaptive immunological memory, more than by antigen-targeted immune effector actions such as neutralizing antibodies and CTLs⁴.

In addition to adaptive immune memory, innate immunity itself has some capacity for memory. At least 2 components of innate immune memory are relevant to pneumonia and inflammatory responses elicited by microbes in the lung, and both result from the resolution of prior respiratory infections: new types of inflammatory cell-types populating the lung, and altered inflammatory responses from the cells already present in the lung.

The resolution of pulmonary infection in mice leaves behind many types of innate lymphocytes in lung tissue (Figure 1), reflecting the diverse types of innate lymphocytes in adult human lungs⁴ including gd-T cells, MAIT cells, iNKT cells, NK cells, and various ILCs. Some of these cells have specialized receptors allowing them to recognize select types of signals from microbial pathogens. All of them elaborate immunomodulating cytokines that reshape inflammatory responses during lung infection, similar to the adaptive immune memory cells described above. Innate lymphocytes in the lung contribute to pneumonia prevention by steering the local inflammatory responses to respiratory pathogens.

Beyond being under new direction from newly present adaptive and innate lymphocytes in the lung, the constituent cells of the lungs behave intrinsically differently after resolution of prior respiratory infections, making different types and amounts of inflammatory mediators (Figure 1). Often referred to as “trained immunity,” this intracellular remodeling involves a combination of epigenetic and metabolic changes³⁶, causing lung cells to respond differently to microbes in the respiratory tract based on prior experiences of that tissue⁴. This applies to alveolar macrophages and likely many other cells in the lung as well, which generate different types and amounts of inflammatory mediators, depending on prior experience. Typically, these trained immune responses are far more effective at controlling and eliminating microbes.

Acquired variations in inflammatory pathways: impairments due to exposures and conditions

Many exposures (Figure 2) can interfere with the inflammatory responses described above as essential to preventing pneumonia. A profound defect related to inflammation is neutropenia, which is more commonly iatrogenic (such as from bone marrow suppressive

treatments for cancer or organ transplant) than genetic. Pneumonia is a major concern in such neutropenic patients, and efforts to reverse neutropenia with granulocyte-colony stimulating factor (G-CSF) can diminish pneumonia incidence during myeloblastic treatments³⁷. Other drugs that suppress components of inflammation less profoundly than neutropenia, such as corticosteroids or biologics that inhibit TNF or IL-1 signaling, also increase the risk of infections including pneumonia.

Inflammatory dysregulations may play causative roles for many of the risk factors recognized to associate with pneumonia. Multiple risk factors for pneumonia have effects on the inflammatory pathways that defend the lungs against infection⁴. Exposures (Figure 2) that associate with pneumonia, such as cigarette smoking, air pollution, and alcohol abuse, have deleterious effects on neutrophils, macrophages, cytokine signaling, and other components of inflammation⁴. Similarly, many of the co-morbidities (Figure 2) that associate with pneumonia, such as advanced age, chronic diseases (of respiratory, cardiovascular, renal, hepatic, or other systems), diabetes, obesity, etc., include impairments in inflammatory cells and mediators⁴. It is likely that some of these inflammatory dysfunctions are responsible for elevating pneumonia susceptibility, implying that reversing such inflammatory alterations could help sever the link between pneumonia and its risk factors. However, most of these associations remain correlative at present.

Local alterations in pulmonary inflammation can have adverse consequences on lung defense. A prominent example of this is secondary bacterial pneumonia (e.g., caused by pneumococcus) subsequent to a preceding respiratory virus infection (such as influenza). Many mechanisms contribute to this acute pneumonia susceptibility, most of which include dysregulations of inflammation⁴. For example, viral infections cause a local surge in interferon activity, and abundant type I or type II interferons can inhibit subsequent elicitation of neutrophil recruitment and macrophage antimicrobial activities^{38,39}. Stimulating inflammation using polyI:C molecules to mimic viral double stranded RNA without causing any infection is sufficient to render lungs susceptible to bacterial pneumonia, dependent on the same interferon pathways that were responsible in influenza infections⁴⁰. Thus, inflammatory responses to a respiratory viral infection are a clear example of an exposure that renders lungs more susceptible to bacterial pneumonia (Figure 2).

Inflammatory responses outside the lung are also important. Excessive and/or prolonged systemic inflammation compromises lung defense. This applies to acute hyper-stimulation of systemic inflammation such as with extra-pulmonary sepsis, which increases pneumonia risk in human patients and decreases lung defense in animal experiments⁴¹. Triggering systemic inflammation in the absence of infection, such as via intravenous injection of endotoxin or cytokines, is sufficient to compromise local defenses in the lung. Thus, extra-pulmonary inflammation is an exposure that can be detrimental and predispose to pneumonia (Figure 2). This general principle may apply more broadly to chronic smoldering levels of systemic inflammation. Many of the diseases and conditions that are risk factors for pneumonia associate with chronic systemic inflammation, including aging, obesity, diabetes, cardiovascular disease, and more. Those with the recognized pneumonia risk factors tend to have higher circulating levels of inflammatory markers than those without, and those with

more advanced stages of the disease or condition tend to have yet higher levels⁴². After accounting for confounding factors like age and co-morbidities, those subjects with higher concentrations of inflammatory markers such as TNF, IL-6, and C-reactive protein (CRP) in their blood are more likely to suffer from pneumonia in ensuing years⁴³. Since systemic inflammation is sufficient to compromise lung defense, associates with diverse acute and chronic conditions that predispose to pneumonia, and associates independently with the risk of pneumonia, it may contribute to the increased pneumonia risk due to co-morbidities. Systemic chronic inflammation may be a common mechanism linking diverse risk factors to pneumonia (Figure 2).

In addition to chronic inflammation, the elderly and others with elevated pneumonia susceptibility have changes in their microbiota (dysbiosis) and immune activities (immunosenescence) which may contribute to inflammatory dysfunction and impaired pulmonary defense^{4,44,45}. Because chronic inflammation, immunosenescence, and dysbiosis all can influence each other⁴⁵, these factors can form a vicious cycle leading to a downward spiral of ever-worsening lung defense (Figure 2).

If systemic inflammation predisposes to pneumonia, then diminishing systemic inflammation might decrease pneumonia risk. Blunting chronic inflammation is a goal for arthritis, inflammatory bowel disease, cardiovascular disease, and other chronic inflammatory diseases. Diminishing inflammation can slow the progression of these diseases. However, because strategies for limiting chronic inflammation (e.g., TNF or IL-1 inhibitors) often compromise pathways essential to inflammatory antimicrobial defense, such agents instead pose an increased risk for serious infections including pneumonia. Preventing pneumonia susceptibility by targeting inflammation in those at risk may require selectively targeting mechanisms underlying the chronic systemic inflammatory processes but not themselves essential to acute pulmonary inflammation and lung antimicrobial defense.

Summary/Discussion

The biological mechanisms responsible for making some individuals more susceptible to pneumonia need to be better defined. This specific recommendation was forwarded by a group of investigators convened by the United States National Heart, Lung, and Blood Institute to discuss priority areas for pneumonia research⁴⁶. Variations in the inflammatory response are a major component of inter-individual variability in pneumonia risk. However, which specific changes in inflammatory processes in any given individual substantially impact their pneumonia susceptibility demands greater attention from the biomedical research community. The kinetics, quantity, and quality of inflammation help determine whether and when a given microbe in the lung results in pneumonia.

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Synopsis

Pneumonia is an important cause of morbidity and mortality. However, pneumonia is an unusual outcome of respiratory infection. Most of the time, microbes in the lung can be controlled by a combination of constitutive and recruited defense mechanisms.

Inflammation is a key component of recruited defenses. Variations in inflammation that influence pneumonia susceptibility and severity are here considered.

Key Points

The respiratory pathogens that cause pneumonia are ubiquitous and unavoidable, yet pneumonia is an unusual outcome of infection.

When microbes are particularly numerous or virulent, then inflammation is essential to lung defense.

The quantity and quality of inflammation are key determinants of pneumonia susceptibility.

Acute pulmonary inflammation is influenced by prior infections, which remodel the lung immune system in ways that help prevent pneumonia.

Acute pulmonary inflammation is influenced by chronic diseases and conditions, compromising lung defense and increasing pneumonia susceptibility.

Figure 1. Changes in lung cells and inflammatory responses due to resolution of prior respiratory infections.

The cells in the resting uninfected lung differ in early life and after the experience of multiple prior respiratory infections (upper 2 panels). Alveolar macrophages (AM) and epithelial cells (EPI) are present in both cases, but can be pre-programmed to respond differently due to trained immunity in experienced lungs (noted by color changes in upper panels). Furthermore, numerous additional cells are present in the experienced lung (upper right). These include innate immunity cells such as innate lymphocytes (IL) - natural killer cells, invariant natural killer T cells, $\gamma\delta$ -T cells, mucosa-associated invariant T cells, and innate lymphoid cells - as well as adaptive immunity cells, in particular resident memory T cells (TRM). The lung responds differently to infection based on such changes (bottom panels). Due to the epigenetic and metabolic changes of trained immunity plus the newly derived signals coming from IL and TRM cells, the AM and EPI cells elaborate different patterns of mediators with altered kinetics, altogether accelerating the recruitment of immune defense cells such as neutrophils (N) and effector memory T cells (TEM) to improve antimicrobial lung defense.

Figure 2. Changes in lung inflammation and defense lead to pneumonia susceptibility.

Advancing age, exposures (such as cigarette smoke, air pollution, alcohol, resolving viral infection, sepsis, and more), and co-morbidities (diseases or conditions like neutropenia, obesity, diabetes, chronic respiratory disease, etc.) all increase pneumonia risk. Many of these factors involve chronic or acute inflammatory dysregulation, which drives susceptibility. Furthermore, chronic low-level systemic inflammation exists in a feed-forward loop with immunosenescence and dysbiosis to perpetuate a vicious cycle of decline in pulmonary defense. The specific cellular, molecular, or other changes that are caused by these risk factors and physiological changes and then increase pneumonia susceptibility are mostly speculative at present, but may involve loss of training and reprogramming of alveolar macrophages (AM) or epithelial cells (EPI), as well as loss or dysfunction among lung immune cells like innate lymphocytes (IL) and resident memory T cells (T_{RM}).