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Pathogenesis of Severe Pneumonia - Advances and Knowledge Gaps

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Abstract

Purpose of review—Pneumonia is a common disease that becomes severe in a subset of patients, dependent on host biology including mechanisms of immune resistance and tissue resilience. This review emphasizes discoveries in pneumonia biology from 2016, highlighting questions and directions that are especially pressing or newly emerging.

Recent findings—Novel cell-cell interactions mediating innate immune responses against microbes in the lung have been elucidated, between distinct leukocyte sub-types as well as between leukocytes and the structural cells of the lung. Adaptive immunity has received growing attention for determining the outcome of pneumonia, particularly the lung resident memory cells that arise from repeated prior respiratory infections and direct heterotypic recall responses. New tissue resilience components have been identified that contribute to anti-inflammatory, pro-resolution, tissue-protective, and reparative regeneration pathways in the infected lung.

Summary—Recent findings will direct research into fundamental mechanisms of lung protection. Over the longer term, manipulating these pathways has implications for clinical practice, as strategies to bolster resistance and resilience have potential to ameliorate severe pneumonia.

Keywords

Pneumonia; Immunity; Resilience; Cytokines; Lungs

Introduction

Pneumonia is a persistent and pervasive burden of disease (1). A 2016 analysis of mortality trends reveals that pneumonia continues to cause more deaths in the US than any other infectious disease, with no improvement at all during the preceding 34 year period analyzed (2). Even if not fatal, pneumonia can be severe; a fifth of the patients hospitalized for pneumonia need to be admitted to intensive care units, and a third of those require mechanical ventilation (3, 4).

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The severity of pneumonia is determined by 2 processes, immune resistance and tissue resilience (5). The term “immune resistance” designates host pathways that diminish the number of living microbes responsible for infection, by killing or removing them. The term “tissue resilience” refers to pathways by which the host withstands, endures, or tolerates the stress of a given microbial challenge. Rather than altering microbial burdens, resilience pathways diminish pathophysiology by limiting damage elicited by pathogens or by immune resistance pathways. Other reviews more comprehensively discuss the contributions of immune resistance and tissue resilience in the lung (1, 5-9). The goal in this review is to highlight recent advances, those that were published during 2016.

Advances in Immune Resistance

The interface between the external environment (including microbes therein) and the internal environment (including leukocytes and other immune cells) is the respiratory epithelium, and immunity roles of this interface was the subject of extensive study. We learned that an essential action of the cytokine IL-17, already well recognized for driving sterilizing immunity against extracellular bacteria and fungi (9), is to activate the lung's epithelial lining (10). IL-17 signals to cells via the IL-17RA receptor, and it has become apparent that humans with mutations in IL-17RA show greater susceptibilities to bacterial pneumonia (11). Although IL-17 receptors are expressed by many different cell types, the mutation of IL-17RA in lung epithelial cells selectively (in mice with CC10-Cre transgenes and floxed *Il17ra*) was demonstrated to be sufficient to increase bacterial burdens during *Klebsiella pneumoniae* pneumonia in mice (10). A protective action observed was the induction of CXCL5 by epithelial cells (10), advancing prior studies that suggested this was an epithelial-specific product during pneumonia that elicits neutrophil recruitment (12, 13).

Transcriptional profiling experiments in mice with pneumococcal pneumonia have now revealed that CXCL5 is only one of many hundreds of genes that are induced preferentially in epithelial cells during infection, dozens of which are secreted products like CXCL5 that can mediate immune cell cross-talk (14). Another epithelial-specific product was identified as a neutrophil activator, secreted and transmembrane 1 (Sectm1), which stimulates recruited neutrophils to make more of the neutrophil-attracting chemokine, CXCL2, thereby amplifying the positive feedback of inflammation within the infected lung (14). Harnessing the power of epithelial innate immunity, pharmacologically triggering these cells is being pursued as a means to provide protection against diverse respiratory infections (15), and it now appears that this can be effective even in mice modeling leukemia patients, despite profound immune dysregulation due to both leukemia and leukemia treatment (16).

Innate lymphocytes in the lungs have become better appreciated as both sources and targets of cytokines upstream and downstream of epithelial cells during pneumonia. IL-17, discussed above as critical for activating epithelial cells, was shown to be derived from newly recruited type 3 innate lymphoid cells (ILC3s) after intrapulmonary delivery of *Escherichia coli* lipopolysaccharide (17), *Pseudomonas aeruginosa* (17), or *K. pneumoniae* (18) to mice. The characteristics of ILC3s in the lungs are only beginning to be defined (17). During *Klebsiella* pneumonia, the recruitment of ILC3s required monocyte-derived TNF- α , which may stimulate lung epithelial cells to synthesize the ILC3-recruiting chemokine CCL20 (18). The cross-talk between epithelial cells and ILCs can vary dramatically from

one infectious setting to another. For example, during respiratory syncytial virus (RSV) infection, epithelial cells used a different cytokine (thymic stromal lymphopoietin, TSLP) to stimulate different ILCs (ILC2s) to make a different cytokine (IL-13) that again acted upon epithelial cells in the infected lung, in this case to stimulate mucus production (19). Epithelial cells are not the only cells that stimulate innate lymphocyte recruitment and activation in the lungs. Intravital imaging of invariant natural killer T (iNKT) cells in the mouse lung revealed exciting new traffic patterns for innate lymphocytes. We learned that the majority of iNKT cells in the uninfected lung are intravascular, but that infection or inflammation triggers rapid diapedesis of these cells (20). Antigen presentation by dendritic cells to the small subset of iNKT cells initially in the interstitium resulted in local extravasation of neutrophils, and these migrating neutrophils synthesized CCL17 and the migration of intravascular iNKT cells into the tissues (20). Blockade of CCL17 was sufficient to impair iNKT cell recruitment and bacterial clearance (20), suggesting that these newly described leukocyte dynamics are functionally significant.

Exciting advances in lymphocyte biology related to pneumonia include the effects of infections on establishing a new immunological “normal” that is pivotal to immune resistance against microbes. This general concept has been receiving growing attention for years, and clearly applies to immune resistance for pneumonia, mediated by immunological memory that can be heterotypic and/or concentrated within the lungs (1, 5, 8). In mice, the resolution of pneumococcal respiratory infections was demonstrated to result in memory Th17 cells that were sufficient to provide heterotypic protection against mismatched serotypes of pneumococcus in the lungs (21). Such Th17 memory responses may help protect the lungs against serotypes of pneumococcus that are not in vaccines or the previous experience of that individual. In humans, immunological “imprinting” from first influenza infections in childhood was observed to help prevent severe pneumonia from multiple subtypes within that phylogenetic group but not from other phylogenetic groups (e.g., H1 infections are good for later infections with H2 or H5 but not H3 or H7, whereas H3 is good against subsequent H7 but not H1, H2, or H5 infections) (22). Such heterotypic protection that results from first infections may explain some of the variations across differently aged cohorts to severe infections from different strains of influenza. Another change that occurs over time in humans is the patrolling and seeding of the lungs by memory T cells. Comparisons of T cell phenotypes across tissues and across ages suggested that the lungs are one of the first sites in which effector memory T cells are found, apparent in the first years of life (23). Resident memory T cells such as CD69+CD103+CD8+ T cells appear later, and are more prominent in the lungs of young adults compared to infants (23). Regulatory T cells, defined by CD25 and Foxp3 expression, were far more common during infancy, in the lungs and all tissues examined, and declined with age (23). The antigen specificity and antigen-induced responses of the memory cells that patrol or reside in the lungs, and the effects of age or other factors on these parameters, remain to be defined.

The extent to which infection history dramatically remodels local and systemic immunity was compellingly demonstrated by studies comparing the immune systems of mice and humans. Based on transcriptional profiles, surface marker phenotyping, tissue residence, and functional assessments, laboratory mice had immune systems that resembled human infants more closely than human adults (24). In contrast, mice that were caught in barns or

purchased from pet stores had immune systems that more closely resembled human adults rather than infants (24). Most intriguingly, co-housing laboratory mouse with pet store mice was sufficient to cause infections but also to transition the immune systems of laboratory mice to better mimic that of pet store mice and human adults, encompassing all immunity measures collected, including lung seeding with both innate lymphocytes and memory cells (24). This dramatically improved immune resistance, even to a microbe (*Listeria*) which was completely unrelated to prior exposures, revealing that this immune maturation mattered immensely and broadly (24). Thus, when it comes to immune resistance, microbial exposures alter everything. We need to gain a better understanding of how microbial exposures that are essentially universal to the human experience (like influenza, pneumococcus, rhinovirus, and nearly all other common causes of pneumonia) alter our immune responses to respiratory infection.

Advances in Tissue Resilience

Tissue resilience is critical to withstanding the stresses caused by inflammation as well as toxicity from microbial virulence properties. Multiple processes contribute to tissue resilience during lung infection, including anti-inflammatory pathways, pro-resolution pathways, tissue preservation pathways, and reparative regeneration pathways. Headway is being made in each of these areas.

Inflammation has been recognized as a double-edged sword for decades, and the community has long sought to limit inflammation in order to diminish the physiological stresses of excess inflammation (6). Narrowing the approach by differentiating pneumonia patients who are most likely to be suffering from extremes of inflammation may have utility, as was recently suggested for the use of corticosteroids in pneumonia patients with especially elevated C-reactive protein (25). When and how to curb inflammation in pneumonia patients demands more research. Nucleosome remodeling and the unwinding of DNA by topoisomerase 1 (Top1) was discovered to facilitate the expression of infection-induced genes, while being dispensable for the expression of housekeeping genes (26). Top1 inhibitors were capable of rescuing mice from multiple severe infections, including *Staphylococcus aureus* pneumonia secondary to influenza infections (26). Further tests will determine whether this represents a new class of drugs that could prove useful for curbing the expression of dangerous inflammatory mediators in subsets of patients in whom excess inflammation is driving pneumonia pathophysiology.

Beyond diminishing inflammation, pro-resolution pathways aim to counter these damaging processes by actively removing inflammatory components. One example is the clearance of edema fluid from the air spaces of the pneumonic lung, essential to restoring pulmonary function to the tissue. Edema clearance is mediated by the activities of ion transport proteins on the surface of the alveolar epithelium (27). A recent study elucidates how inflammatory signals compromise edema clearance during lower respiratory infection, in particular with macrophage-derived TNF-related apoptosis-inducing ligand (TRAIL) stimulating the loss of Na,K-ATPase proteins from the epithelial surface (28). In addition to edema fluid, inflammatory cells that had been recruited to fight infection must be eliminated. Dying neutrophils must be efficiently and effectively disposed of by efferocytosis, and this process

is induced by families of pro-resolving eicosanoids (29). Lipidomics from mouse lungs with Gram-negative bacterial pneumonia demonstrated that aspirin-triggered resolving D1 (AT-RvD1) was dynamically regulated and especially high at times of resolution (30). Supplementation with additional exogenous AT-RvD1 to pneumonic mice was capable of increasing efferocytosis by macrophages and accelerating the removal of lung neutrophils from the lungs (30).

Cell death and tissue degradation are inherent to infection and inflammation. Multiple pathways of cell death mediate epithelial cell loss during influenza infection, and a recent study suggests that apoptosis, pyroptosis, and necroptosis all may be triggered by DNA-dependent activator of IFN regulatory factors (DAI), a cytoplasmic innate immunity receptor recognizing multiple influenza core proteins in infected respiratory epithelial cells (31). Countering this, a component of epithelial protection against cytotoxicity during influenza pneumonia was recently communicated, in which the epithelial cell surface proteoglycan syndecan-1 helps prevent death of those cells and the ensuing acute lung injury, morbidity, and mortality in mice with influenza infection, by facilitating anti-apoptosis pathways mediated by c-Met and AKT (32).

Severe pneumonia injures the lung, and injured lungs need to be repaired. The progenitor cells that respond to injury and repopulate damaged lung structures with new cells are being defined (33). A recent study of influenza infections in mice suggests that the type of progenitor cell elicited and the type of lung repair accomplished may vary across infectious settings, dictated by multiple and largely still poorly understood factors including the severity of lung injury (34). Which cells are stimulated by which signals to differentiate in which ways, to either restore healthy lung architecture or to cause aberrant lung scarring, remains a very important area of ongoing research.

Knowledge Gaps

The fundamental biology underlying the susceptibility to severe pneumonia is understood too poorly. Advances in this biology will provide new avenues for decreasing the burden of disease caused by lower respiratory infection. Some of the biggest knowledge gaps demanding attention are outlined below, at broad conceptual levels. These reflect my own biases and perspectives, and may differ from the perspectives of others.

A better understanding of the biological mechanisms mediating immune resistance and tissue resilience is essential. A critical goal is to delineate the naturally acquired immunological remodeling (which likely involves both adaptive immune memory as well as changes in innate immunity) that protects against pneumonia, including where it is (anatomically), what it recognizes (antigenically), and how it responds (functionally) during lower respiratory tract infection. For tissue resilience, there are many outstanding questions, but perhaps especially pressing because of how little is known is the identity of the progenitor cells that divide and differentiate to reconstitute lung anatomy, and which signals drive this cellular differentiation towards which cell fates and tissue structures.

Pneumonia occurs in individuals who are susceptible, most often due to chronic conditions (e.g., age, smoking, COPD, diabetes, and many more) or to acute events (like intoxication, air pollution spikes, trauma, etc.). We have only inklings of exactly which components of immune resistance and tissue resilience are specifically impacted, and how they are changed, by age, smoking, intoxication, and all of the many different things that render individuals susceptible to pneumonia.

Precision medicine approaches are beginning to be applied to pneumonia, but more is necessary. We need better ways to discriminate different etiologies (e.g., those with influenza infection alone *vs.* those with influenza and a bacterial superinfection) and different pathophysiologies (e.g., those with excessive inflammation *vs.* those with inadequate inflammatory responses), because different types of pneumonia respond differently to different therapeutic approaches. Similarly, individuals become susceptible to pneumonia from a variety of very divergent causes, and different individuals with similar risk factor histories may have differing degrees of pneumonia susceptibility. There is a need to develop metrics that will identify those who are most susceptible, and for what reasons. A major shortcoming in current approaches to pneumonia is the paucity of biological measures that reveal an individual's pneumonia susceptibility, etiology, pathophysiology, or disease course.

Medical approaches applied to pneumonia patients have changed little over the last half a century or more. New approaches and new strategies are required. When more is known about biological mechanisms protecting the lungs, and the dysregulations of these pathways that put the lungs at risk, there will be new opportunities to intervene. The expansion of pneumonia-relevant biomarkers will help better identify appropriate subjects for current and upcoming interventions, and will direct their most effective use.

Conclusions

This is an enormously exciting time in pneumonia research. Mechanisms are being discovered that mediate the immune resistance and tissue resilience which protect the lungs from severe pneumonia. These fundamental insights will help elucidate dysregulations that render subjects susceptible to pneumonia, and are providing potential new avenues for intervening in order to prevent or cure pneumonia.

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Key Points

The severity of pneumonia is determined by interacting processes of immune resistance and tissue resilience.

Contributions of innate immunity to fighting pneumonia include unique and essential roles of lung epithelial cells and innate lymphocytes.

Contributions of adaptive immunity to fighting pneumonia include heterotypic recall responses and lung resident memory cells.

Multiple resilience mechanisms safeguard the lungs during pneumonia, including anti-inflammatory, pro-resolution, tissue protection, and regeneration pathways.

Pulmonary and systemic responses during pneumonia vary dramatically according to a patient's history, including their prior infections of the respiratory tract.