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INTEGRATIVE PHYSIOLOGY OF PNEUMONIA

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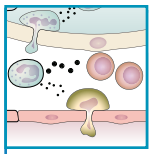

Quinton LJ, Walkey AJ, Mizgerd JP. Integrative Physiology of Pneumonia. *Physiol Rev* 98: 1417–1464, 2018. Published May 16, 2018; doi:10.1152/physrev.00032.2017.—Pneumonia is a type of acute lower respiratory infection that is common and severe. The outcome of lower respiratory infection is determined by the degrees to which immunity is protective and inflammation is damaging. Intercellular and interorgan signaling networks coordinate these actions to fight infection and protect the tissue. Cells residing in the lung initiate and steer these responses, with additional immunity effectors recruited from the bloodstream. Responses of extrapulmonary tissues, including the liver, bone marrow, and others, are essential to resistance and resilience. Responses in the lung and extrapulmonary organs can also be counterproductive and drive acute and chronic comorbidities after respiratory infection. This review discusses cell-specific and organ-specific roles in the integrated physiological response to acute lung infection, and the mechanisms by which intercellular and interorgan signaling contribute to host defense and healthy respiratory physiology or to acute lung injury, chronic pulmonary disease, and adverse extrapulmonary sequelae. Pneumonia should no longer be perceived as simply an acute infection of the lung. Pneumonia susceptibility reflects ongoing and poorly understood chronic conditions, and pneumonia results in diverse and often persistent deleterious consequences for multiple physiological systems.

I. INTRODUCTION

Pneumonia is responsible for an extremely large burden of disease across the earth, more than diseases such as cancer, diabetes, HIV/AIDS, malaria, and many other diseases recognized as leading global health problems (330, 335, 336, 350, 351). Burden of disease is calculated from disability-adjusted life years lost, and the appalling global burden of pneumonia results in part from the fact that pneumonia kills more children worldwide than does any other disease (425, 528). In the United States (US), children more commonly survive pneumonia, but even in such advantaged countries pneumonia is the most common reason for children to be hospitalized (566). A fifth of those children need to be in the intensive care unit (ICU), and a third of those require mechanical ventilation (228). After children are released from the hospital, they have increased risk of chronic respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD) (123, 188), which is a further burden of this disease that does not get factored into such calculations.

As dispiriting as those pediatric statistics are, the population most afflicted by pneumonia is older adults, who have incidence and risk of death from pneumonia that are orders of magnitude greater than for children (174, 407). For seniors, pneumonia hospitalization has a higher risk of death than any of the other common causes of hospitalization (147). Pneumonia causes more deaths in the US (and globally) than does any other infectious disease (185). However, most of even the oldest do survive (131). The economic costs are staggering, with estimates ranging from nearly 20 billion dollars to more than 80 billion dollars per year in the US (136, 189, 565). And after all this immediate suffering and cost, additional indirect and longer term consequences include cognitive decline comparable to traumatic brain injury, greater incidence and severity of depression, worsened cardiovascular and cerebrovascular health, physical limitation, and decreased life-span (39, 88, 196, 376, 431, 445). Pneumonia prevention measures like influenza and pneumococcal vaccines are sufficient to decrease risk, thereby demonstrating causal relationships between pneumonia and longer term extrapulmonary outcomes (415, 503).

Pneumonia demands extraordinary attention from the biomedical community, as a direct cause of morbidity and mortality and as a contributor to unhealthy aging and decline. While pneumonia results from microbial infection, the pathogenesis of this disease is driven by the host response. Within the host, pneumonia is by definition within the lungs, but it is a complex disease that involves diverse physiological systems working together. Although pneumo-

nia is an acute event, it is prompted by preexisting chronic conditions, and it has long-term consequences. Thus pneumonia is an acute lower respiratory tract infection that is more than acute, more than lower respiratory tract, and more than infection.

Our goal with this review is to highlight evolving concepts related to pneumonia biology. First, we emphasize the importance of the host response. Pneumonia is an unusual result of infection with commonly encountered microbes; disease is the exception rather than the norm. Knowing "what goes right" to prevent pneumonia during the vast majority of times that these microbes get into our lungs seems key to conceptualizing methods to better prevent and cure this disease. Second, we advocate reenvisioning pneumonia as not just an acute event, but rather as a chronic condition of heightened susceptibility. The mechanisms responsible for susceptibility must be better elucidated so they can be interrupted. Third, we wish to increase attention on pneumonia consequences outside of the lung. Physiological pathways are only beginning to be defined for the extrapulmonary manifestations of pneumonia. And fourth, we highlight that pneumonia has physiological consequences that persist beyond the time course of the pneumonia itself. Pneumonia events lead to prolonged morbidity and earlier mortality, with greater mechanistic insight needed. Improved knowledge in these areas could lead to adjunct therapies that target the wider and longer impacts of pneumonia on its victims.

II. HOST-PATHOGEN INTERACTION

Pneumonia is an infection of the lung causing exudative fluid to accumulate in the pulmonary parenchyma, compromising respiratory function. Diagnosis depends on evidence of pulmonary consolidation (based on auscultation or radiology) in conjunction with evidence of infection (based on microbiology or on general signs such as fever, malaise, leukocyte shifts, etc.) with an acute onset. It does not have a clinical definition that is established by an adjudicating body and uniformly applied by the medical community. Pneumonia is by far the most common cause of sepsis (320, 516), which has been defined by an international task force as organ dysfunction due to a dysregulated host response to infection that is severe enough to be life-threatening (454). Pneumonia is distinguished from other forms of sepsis by the location; when the infection causing dysregulated host response is in the lungs, then it is pneumonia. Pneumonia causes the majority (33, 62) of cases of the acute respiratory distress syndrome (ARDS), which has been defined (486a) as being acute in onset (<1 wk) with diffuse (bilateral) pulmonary edema (not due to elevated hydrostatic pressure) and arterial hypoxemia (the degree of which stratifies severity). Pneumonia is distinguished from other forms of ARDS by etiology; when the lungs contain fluid because of microbes present there, then pneumonia is the cause of ARDS. The fact that patients with pneumonia often become reclassified as patients with sepsis or ARDS when they advance to those stages confounds the discussion and understanding of pneumonia. Sepsis and ARDS are immediately life-threatening forms of severe pneumonia. Characteristics of sepsis and of ARDS, including their pathophysiological mechanisms and poor patient outcomes (19, 315), should be recognized as consequences of severe pneumonia. The definitions of sepsis and ARDS help advance research related to those diseases. The lack of an unambiguous, uniform, and accepted clinical definition for pneumonia may complicate research on this disease.

A. The Microbes Causing Pneumonia

Microbe-targeted approaches have proven useful for pneumonia. The advent of antibiotics was profoundly important, dramatically reducing pneumonia mortality rates in the US during the mid-20th century (336). Vaccines also decrease rates of pneumonia in populations in which they are adopted, modestly but importantly (154, 174, 175). Thus interfering with the microbial side of this host-pathogen interaction driving pneumonia is productive.

Because microbes initiate this disease, changes among microbes infecting the respiratory tract influence pneumonia biology. The mutations and reassortments leading to antigenic drift and shifts of influenza viruses are prominent examples (574). Infamously, a strain of H1N1 influenza virus that emerged in 1918 led to a pandemic with particularly overwhelming increases in morbidity and mortality, largely due to secondary bacterial pneumonias (341, 342). A more recent antigenic shift for influenza virus in 2009 caused a pandemic that included severe pneumonias (574). Sporadic but very severe cases of zoonotic pneumonias caused by animal-tropic influenza viruses demonstrate that highly pathogenic influenza viruses are always nearby (150, 545). Although the influenza viruses presently circulating in animals are not readily transmissible among humans, a few mutations can change that (291). Other zoonoses cause rare pneumonias but get considerable attention because of their bioterrorism potential, including *Brucella anthracis*, *Yersinia pestis*, and *Francisella tularensis*. Some fungi are important causes of pneumonia within restricted geographic regions, such as *Coccidioides immitis* in the southwestern US or *Histoplasma capsulatum* in the Missouri, Ohio, and Mississippi River valleys. Microbes that have prominently emerged as pneumonia threats in recent decades include *Legionella*, *Pneumocystis*, hantavirus, SARS coronavirus, MERS coronavirus, and more. Some microbes that have recently become recognized as important causes of pneumonia may represent a recent emergence of knowledge more than of microbes, including rhinoviruses C and D, coronaviruses NL63 and HKU1, human metapneumoviruses, and more (230). Among pneumonia-caus-

ing bacteria, the emergence and spread of antibiotic resistance is a continuous threat (280). Plasmids containing carbapenem resistance genes are being passed among *Klebsiella pneumoniae* and other pneumonia agents, including bacteria already resistant to most other antibiotics (133). The recent discovery of plasmid-mediated colistin resistance (294, 402, 527) suggests the frightening prospect of bacterial pneumonias that are resistant to all currently licensed antibiotics. The expanding myriad of microbes combined with future prospects of increasingly ineffective antibiotics mean microbe-targeting such as with antimicrobials and vaccines can achieve successes but not victory. Alternative and supplementary approaches, such as modifications of host responses during pneumonia, are needed.

The etiology of pneumonia is complex and poorly understood, because the microbes causing pneumonia are extraordinarily numerous and extremely varied **(FIGURE 1)**. The agents identified include many different viruses and bacteria, and these microbes do not appear to share any particular characteristics (RNA viruses, DNA viruses, enveloped viruses, nonenveloped viruses, Gram-positive bacteria, Gram-negative bacteria, cell wall-free bacteria, extracellular bacteria, intracellular bacteria, etc.). Pneumonia can also be caused by fungal and other infectious agents. Any given microbe accounts for only a small minority each of all pneumonia cases (227), with the most common three for adults hospitalized with community-acquired pneumonia being rhinoviruses (9%), influenza viruses (6%), and pneumococci (5%). Different populations (children, hospi-

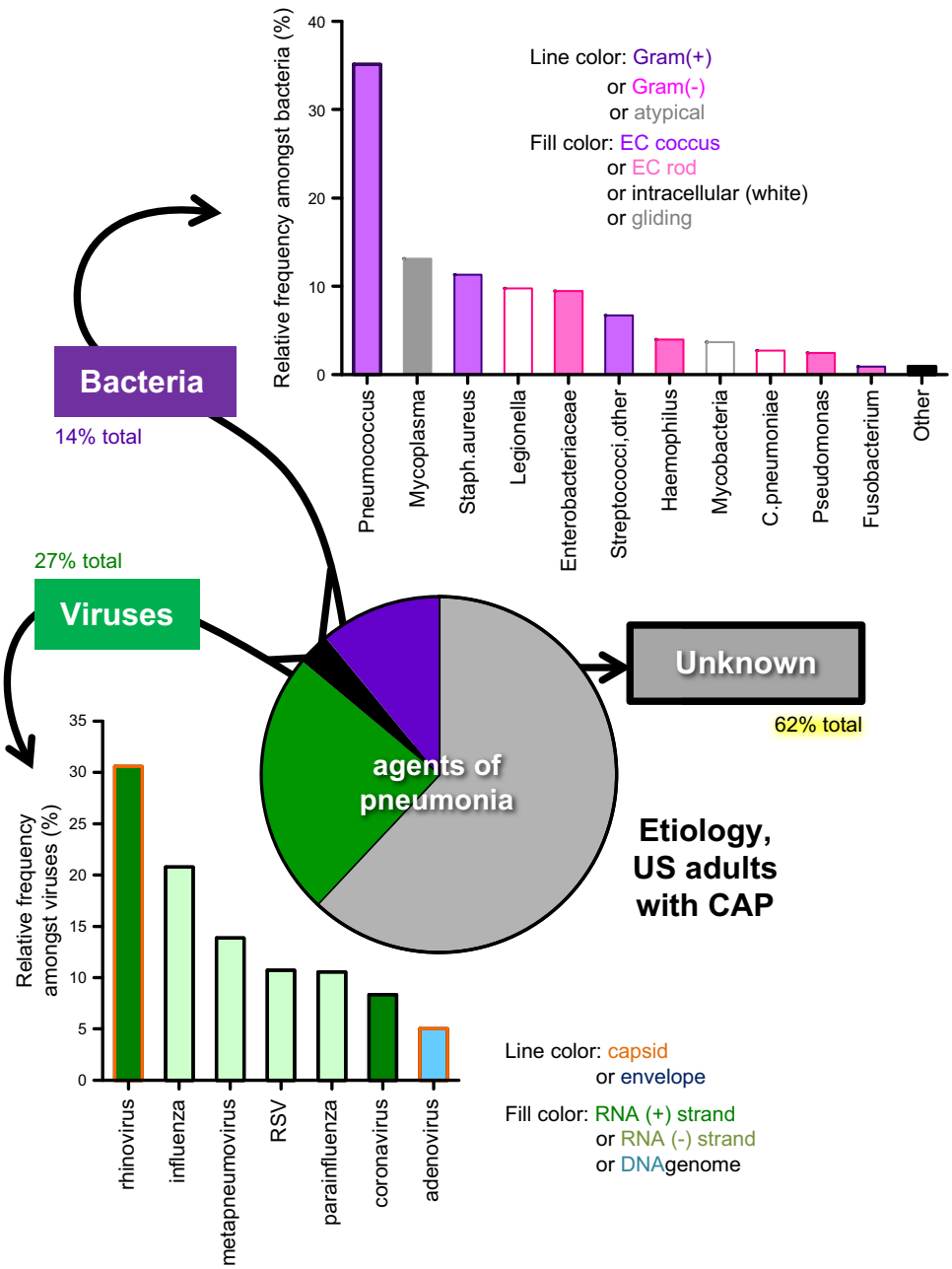

FIGURE 1. The microbial agents that cause pneumonia are numerous, diverse, and poorly understood. Data represent nonimmunocompromised adult patients hospitalized for community-acquired pneumonia (CAP). Despite intensive efforts, no microbial agent can be identified in the majority of pneumonia cases. Among the viral agents detected, no virus or type of virus was especially prominent. Among bacteria, pneumococcus was most common, but a great many species and types of bacteria were detected. [Data from Jain et al. (227).]

talized patients, nursing home residents, etc.) have different microbes implicated (15, 79), but in each population it is a spectrum of responsible agents rather than a specific microbial type. There are few, if any, unifying principles to the types of microbe that cause pneumonia. These diverse etiologic agents encode a wide variety of microbe-specific virulence pathways that influence the likelihood that respiratory infection will cause pneumonia. While contributing to pneumonia pathogenesis, microbial virulence pathways are beyond the scope of this discussion of host physiology, and readers may wish to consult other reviews specific to relevant microbes (135, 321, 339, 374, 380, 436, 508).

In many cases, a microbial suspect is not identified **(FIGURE 1)**. Even in studies designed for the purpose of identifying etiologic agents, a potentially responsible microbe fails to be detected in about one-fifth of childhood pneumonias (228) and more than half of adult pneumonias (227). When one or more microbes are identified, the degree to which it or they are truly causal is uncertain. In virtually all cases, the agents recognized as responsible are ubiquitous opportunistic microbes. Most people who encounter these microbes do not develop pneumonia and do not get seriously ill. Rather, the interaction usually results in asymptomatic carriage or subclinical infection. The presence of the microbe does not mean an individual gets pneumonia. While the microbe is relevant, whether or not these microbes cause pneumonia depends more on the host and the host response than on the microbe or any specific microbial characteristics.

B. Host Responses to Microbes in the Lung

Whether or not microbes in the lung exceed a host's capacity to maintain pulmonary homeostasis depends on a complex integration of physiological processes, together which aim to prevent the onset of pneumonia. For these processes to be effective they must provide adequate levels of both immune resistance and tissue resilience (407). Immune resistance refers to the eradication of living pathogens during an infection, whereas tissue resilience involves the prevention of or resolution of injury resulting from the pathogen and/or from the host response to the pathogen. Inappropriate amounts of either disrupt homeostasis, making both equally essential. Despite important advances in our understanding the pathways comprising resistance and resilience, the degree to which certain biological signals under certain circumstances in certain individuals collaborate to dictate pneumonia outcome remains largely unclear.

III. INNATE IMMUNITY AGAINST MICROBES IN THE LUNGS

Innate immunity represents the initial preexisting determinant of resistance against invading pathogens. While innate immunity involves an elaborate network of cells and signals that actively function to eliminate invading organisms and maintain tissue integrity, defense also includes the anatomical barriers that restrict the deposition of microbes within the respiratory tract. Airway architecture not only offers the means to heat, humidify, and distribute air throughout the respiratory tract, but it also provides an efficient physical barrier against microbes and other potentially toxic substances. Examples of anatomic protective measures include nasal hairs, the mucociliary escalator, and the epithelial barrier itself, which ultimately provides the protective interface separating the external and internal environments (429). Even the branching pattern of the respiratory tract represents a critical innate defense. Materials over 3 μm in diameter have extremely limited access to the lower respiratory tract due to filtration and impaction in more proximal airways (21), which has important implications for the dispersal of infectious substances. Yet, this is insufficient to wholly prevent microorganisms from accessing the deeper lung, including the respiratory zone of the alveolocapillary interface. Defense against microbes within the lower respiratory tract then relies on a carefully coordinated immune response that includes both resident and recruited features. Resident defenses such as soluble antimicrobial factors in airway lining fluid and alveolar macrophages (AMs) provide the initial tier of protection against microbes, followed quickly thereafter by recruited elements such as extravasated leukocytes and other immunomodulatory plasma constituents. The resulting inflammation is a hallmark of innate immunity, involving a panoply of intra- and extrapulmonary cells and signals, some of which are highlighted below, that ideally exert an appropriate balance of resistance and resilience in an effort to re-establish lung homeostasis.

A. Lung Innate Immunity

The recognition of lung pathogens elicits robust remodeling of the pulmonary transcriptome (e.g., as described in Refs. 162, 246, 259, 409, 546), resulting in the production and release of mediators that coordinate early protection. These mediators include a plethora of multifactorial cytokines, chemokines, growth factors, antimicrobial substances, opsonins, enzymes, enzyme inhibitors, adhesion molecules, receptors, apoptotic factors, anti-apoptotic factors, and more. This response involves the recruitment and/or activation of numerous cell types, some of which have only recently become appreciated in the setting of lung immunity. Moreover, some of these cells function within the lungs, whereas others do not. All of this must be considered in the context of an integrated physiological response to lung infection. The initial responses are from cells already present within the uninfected lung.

1. Alveolar macrophages

AMs are professional phagocytes that reside on the surface of the lower respiratory tract. They represent an initial line of leukocytic antimicrobial defense. Studies in mouse models indicate that AMs, like other tissue-resident macrophages (387), are yolk sac-derived and extremely long-lived (177, 229, 349). In fact, experiments with GFP-expressing chimeric mice strongly support that the lifespan of AMs approaches the mouse lifespan (229). Examination of human lung transplants mismatched for HLA or for sex chromosomes reveal that alveolar macrophages of the donor lung persist for all of the several years that have been included in analyses (124, 357). This population of resident phagocytes is often maintained over the course of lung injury and infection, remaining after the recruited inflammatory cells have been removed from the airspaces by apoptosis and efferocytosis (229).

Functionally, AMs are extremely diverse, with essential roles in both immune resistance and tissue resilience (4) **(FIGURE 2)**. Under normal homeostatic conditions, AMs suppress inflammation through a variety of mechanisms to be further discussed below. This is critical for limiting immunopathology, as macrophages clear environmental debris, excess surfactant, apoptotic cells, and other innocuous materials (211, 497). In the setting of infection, however, AMs exert significant plasticity, transitioning from an anti-inflammatory housekeeping cell into a central node of immune activity. Macrophages bear an armament of pattern recognition receptors (484), allowing them to respond to a diverse repertoire of pathogens. Upon pathogen recognition, AMs directly contribute to immune resistance through the ingestion and phagocytosis of microbes (244) **(FIGURE 2)**. Transmembrane transport of ions by CFTR, TRPC6, TRPM2, and other channels and pumps coordinately render the phagosome acidic and inhospitable to microbes (103, 104, 418). In addition, synthesis of reactive oxygen and nitrogen intermediates also contributes to alveolar macrophage killing of phagocytized microbes (176, 199). In concert with phagocytosis, apoptosis can contribute to maximal macrophage-mediated killing (111) **(FIGURE 2)**, for example, when triggered by release of cathepsin D into the cytosol to degrade the anti-apoptotic factor Mcl-1 (312). AM apoptosis can also be triggered by extracellular cues such as recognition of the cytokine TRAIL by the DR5 receptor on macrophages (468). Both TRAIL and apoptosis are required for efficient clearance of bacteria in the lungs (35, 468). AM death by pathways other than apoptosis can be stimulated by agents of pneumonia, such as necroptosis mediated by RIP1 and RIP3 kinases and MLKL (85, 165, 255) **(FIGURE 2)**. This does not kill bacteria but instead exacerbates infection (85, 165). Therefore, AM apoptosis is a specialized pathway of immune resistance, while other macrophage death pathways are instead detrimental to the host. The antimicrobial effector functions of AMs can be sufficient to control low pathogen burdens without recruiting additional cells (2, 111).

The direct microbicidal capacity of AMs is complemented by their exceptional ability to coordinate the immune activity of other cells, both neighboring and remote, which is essential when microbes are too virulent or too numerous to be efficiently handled by resident innate immunity. To do so, AMs use RelA from the NF-κB transcription factor family to dispatch numerous cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1α, IL-1β, chemokines, IL-6, and granulocyte colony stimulating factor (G-CSF),

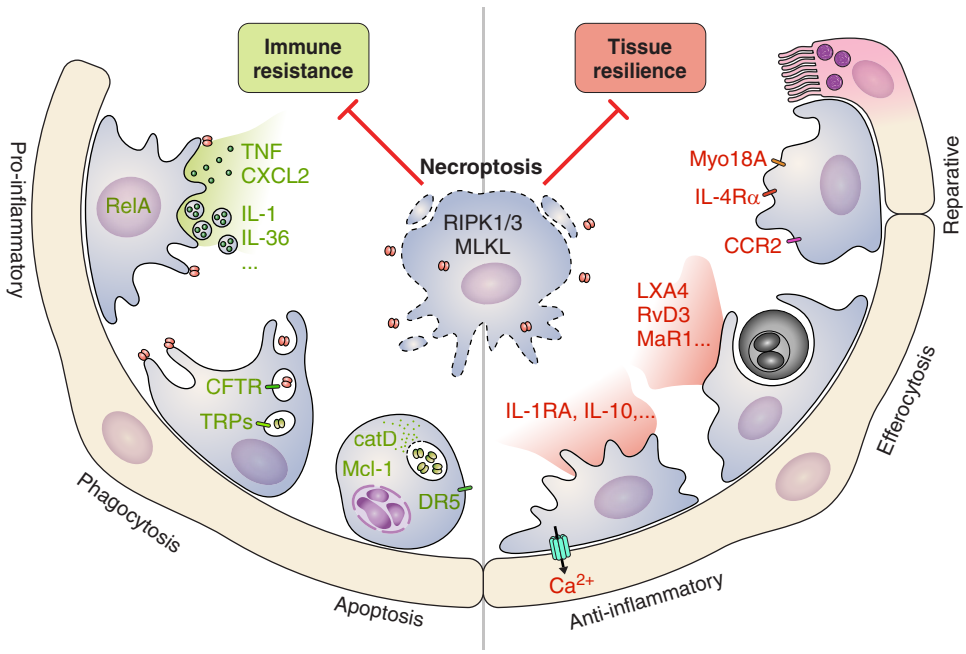

FIGURE 2. During pneumonia, macrophages have multiple critical roles in protecting the host against infection (immune resistance) and against injury (tissue resilience). The molecules identified were for illustrative purpose and do not represent an exhaustive presentation.

all of which are important for eliciting lung innate immunity (61, 171, 173, 194, 239, 240, 392, 408, 413) **(FIGURE 2)**. Isolates of pneumococcus collected from complicated pneumonia patients tend to be lower activators of macrophage NF-κB compared with pneumococci collected from other individuals, and such lower NF-κB activators induce slower cytokine expression and pulmonary defense in mouse models of pneumonia (85), further supporting the concept that the capacity of AMs to elaborate cytokines is key to initiating immune responses in the lung. This capacity may be shaped by prior encounters with invading pathogens. Macrophage NF-κB activation and cytokine elaboration are altered for prolonged periods of time after the resolution of prior respiratory infections (211), suggestive of trained immunity (363). The degree to which such alterations in AM responsiveness may improve or worsen antimicrobial resistance, and mechanisms responsible for altering these macrophage behaviors, demand further attention.

An emerging area of focus related to AMs is the release of cytokines and other immunomodulating agents within membrane-bound vesicles such as exosomes and microparticles **(FIGURE 2)**. IL-36γ, which is essential for efficient resistance against bacterial pneumonia in mouse models, is one such AM product (267). Following bacterial stimulation of human and mouse AMs, this cytokine is released in membrane-bound particles, and it appears within lipid vesicles in the air spaces of human patients with bacterial pneumonia (267). Mechanisms determining which cytoplasmic constituents are encapsulated within the secreted vesicles and how these signal to recipient cells are ongoing areas of research in pulmonary immunity.

Thus macrophages are important as antimicrobial effector cells and as sources of cytokines in the lungs **(FIGURE 2)**, promoting the recruitment and activation of other cells mediating immune resistance, some of which are highlighted below. The profound influence of AMs on pneumonia outcome is further supported by reports of targeted disruption of macrophage function, either pharmacologically or genetically, which impairs innate defense in mouse models of lung infection (55, 111, 187, 198, 389, 392).

2. Epithelial cells

While the accessibility of AMs by bronchoalveolar lavage has provided a wealth of information regarding their functions and regulation in the context of pneumonia and other lung diseases, contributions of other cell types have recently emerged with the advent of more sophisticated isolation and targeting strategies. Among these additional immunomodulatory cell types are those that comprise the lung epithelium, a complex network of epithelial subsets differentially distributed throughout the upper and lower respiratory tract (536). In the alveoli, surfactant proteins (SP) A and D, synthesized by the alveolar epithelial type II cells, have critical roles in immune resistance, by directly inhibiting microbes (184) and also by influencing immune activities (381). In the upper respiratory tract and conducting airways of the lung, a prominent feature is mucociliary clearance. The importance of ciliary action is highlighted by the severe lung disease, particularly recurrent respiratory infections, in patients with primary ciliary dyskinesia (258). Airway ciliated cells are more heterogeneous than previously recognized, and subsets of airway ciliated cells (e.g., those marked by the MIWI2 expression) have immunomodulatory roles that extend beyond the mechanical clearance of mucus (529). Secreted airway mucins, largely synthesized by goblet and club cells, are the primary constituents of the mucus layer, and are independently essential for immune resistance. Genetic targeting of MUC5B but not MUC5AC has been shown to render mice more susceptible to bacterial infection, revealing the former to represent a particularly important mucin in the context of innate immunity (423). CFTR mutations, which compromise the fluidity of mucus in cystic fibrosis patients (191), also underscore the importance of mucus in lung immunity given the prevalence of lung infections in CF patients. In addition to mucus, numerous soluble immunomodulators are constitutively present in epithelial lining fluid throughout the respiratory tract, including but not limited to SP-A, SP-D, lactoferrin, lysozyme, and others (both known and likely unknown), all of which exhibit defense properties (536).

Besides the constitutive defense properties of the epithelial surface, epithelial function is immunologically dynamic following exposure to invading pathogens. Lung epithelial cells can undergo dramatic transcriptional remodeling in response to infection or infectious stimuli (82, 246), and such activity is elicited by both pathogen- and host-derived mediators, as enabled by a wide gamut of receptors for pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), cytokines, and other immunomodulatory agents (181, 455, 536). Epithelial-specific genetic targeting of NF-κB activity, downstream of many of these receptors (408), is necessary and sufficient for the elaboration of innate lung defense (73, 74, 406, 554, 555). With regards to pathogen-elicited responses, several studies in genetic mouse models support Toll-like receptor (TLR) signaling as an important source of immune activation (118, 180, 332, 367, 388, 413). Myeloid differentiation factor 88 (MyD88) is a central adapter protein for much but not all TLR signaling and is essential for pulmonary immune resistance as evidenced by profound susceptibility to lung infections in individuals with genetic MyD88 deficiency, particularly children (518). Mice lacking MyD88 in either hematopoietic and/or nonhematopoietic cells are vulnerable to lung infection (10, 118, 180), and the targeted genetic manipulation of MyD88 in the epithelium specifically yields substantial changes in pulmonary inflammation and defense (118, 332).

Microbial engagement of pathogen recognition receptors (PRRs), while significant, is insufficient for maximal epithelial responses. This is again evidenced by the influence of MyD88 on pulmonary inflammation. MyD88 deficiency appears to have a larger consequence on the development of acute pulmonary inflammation than do combinations of TLR deficiency (456), possibly owing to MyD88's involvement in signaling downstream of the IL-1 receptor IL-1R1 (332). Along these lines, cytokine stimulation of epithelial cells, particularly that due to IL-1 and TNF-α, is a requirement for maximal epithelial responses in some settings. For instance, direct in vitro stimulation of epithelial cells with *Streptococcus pneumoniae* fails to elicit an NF-κB response, whereas stimulation with pneumonic airway lining fluid robustly activates this transcription factor in an IL-1- and TNF-α-dependent manner (406). Expression of these cytokines requires macrophage activity (392), which can occur in direct response to pneumococcus (392, 406), suggesting that AMs are a critical relay for initiating epithelial responses to certain microbes (like pneumococcus). The combined importance of IL-1 and TNF-α is consistent with evidence that mice lacking all signaling receptors for these cytokines are exquisitely susceptible to infection (240), and additional studies consistently support the notion that macrophage-derived products such as IL-1 are requisite for epithelial-derived innate immunity (198, 283, 313).

The ability of epithelial cells to respond to AMs does not preclude epithelial activation by other cytokines and cells. IL-22, which has numerous protective properties during pneumonia (23, 71, 220, 272, 371, 395, 498, 510, 549), is produced by multiple cell types, including Th17 cells and innate lymphocytes (71, 272, 371, 373, 510, 549). IL-22-dependent protection includes its capacity to activate epithelial cells via the transcription factor STAT3 to produce the antimicrobial siderophore binding protein lipocalin 2 (LCN2) (23), which is itself required for maximal lung immunity (24, 66, 141). STAT3 activity in lung epithelium also promotes expression of the antimicrobial factor Reg3γ (76). Likewise, the IL-6 family cytokine oncostatin M (OSM) can activate epithelial STAT3 to promote induction of the chemokine CXCL5 (495), which is important for lung neutrophil recruitment (234, 327, 554). Although CXCL5 is induced by STAT3, it is also dependent on NF-κB in epithelial cells of the infected lung (554, 555), and CXCL5 can be stimulated by IL-17 as well (69). CXCL5 is especially interesting because it is derived exclusively from epithelial cells during diverse settings (234, 246, 554, 555). The epithelium can also signal directly to neutrophils by producing granulocyte-macrophage colony stimulating factor (GM-CSF) and secreted and transmembrane 1 (Sectm1) proteins (246, 465, 554). Additional epithelial-specific products induced by lung infection include CCL20 (466, 555), short palate, lung, and nasal epithelial clone 1 (SPLUNC1) (292), thymic stromal lymphopoietin (TSLP) (470), and many others (246) which can confer local immune resistance.

The capacity of epithelial cells to control the immunological tone of the lungs is further exemplified by studies showing that their activation is highly protective against subsequent infectious challenges (130). The intranasal administration of nontypeable *Hemophilus influenza* lysates confers remarkable protection against subsequent challenges with *S. pneumoniae* (83). The protective signaling components of this stimulation have been narrowed down to a combination of ligands for TLR2/6 and TLR9 (119). Importantly, this broadly effective inducible resistance conferred by TLR ligand administration appears to solely rely on the activity of epithelial cells (82, 119, 284), which has important implications regarding the functional capacity of this cell type to control pulmonary immune resistance. Pharmacological activation of TLRs is safely tolerated in vivo (11) and confers significant protection against not only *S. pneumoniae*, but also other bacterial, viral, and fungal pathogens (115, 129). This epithelial stimulation was demonstrated to be sufficiently robust for pneumonia protection in the severely immunocompromised setting of leukemia and its treatment (284). These studies highlight the potential significance of harnessing immune resistance provided by the lung epithelium to prevent pneumonia.

3. Neutrophils

Following exposure to harmful microbes, a major role of AMs, epithelial cells, and other resident cells of the lung is to recruit additional effector cells in the event that initial local defenses are insufficient. This requires the elaboration of cytokines and other intermediates that facilitate the migration of cells into the airspaces of the lungs. Neutrophils, which are sparse or absent in the airspaces of uninfected lungs, are the earliest and most abundantly recruited leukocyte in response to infectious stimuli, representing a hallmark feature of recruited innate immunity in the lungs. Neutrophils have many and diverse roles during pneumonia, as microbe killers and also as important modifiers of the immune milieu **(FIGURE 3)**.

The known biological mechanisms governing lung neutrophil recruitment are vast, with many more almost certainly remaining to be discovered (90). Indeed, numerous local signals coalesce to drive this response, such as pathogen recognition (by PRRs), transcriptional remodeling of responding resident cells (by transcription factors such as NF-κB and STAT3), production of early-response cytokines and growth factors (which further stimulate neighboring and remote cells), generation of a chemotactic or haptotactic gradient (as accomplished by chemokines, eicosanoids, complement fragments, and other host factors), an appropriate display of adhesion molecules, and the cytoskeletal rearrangements and locomotion of the neutrophils themselves (90, 112). Rapid transmigration is

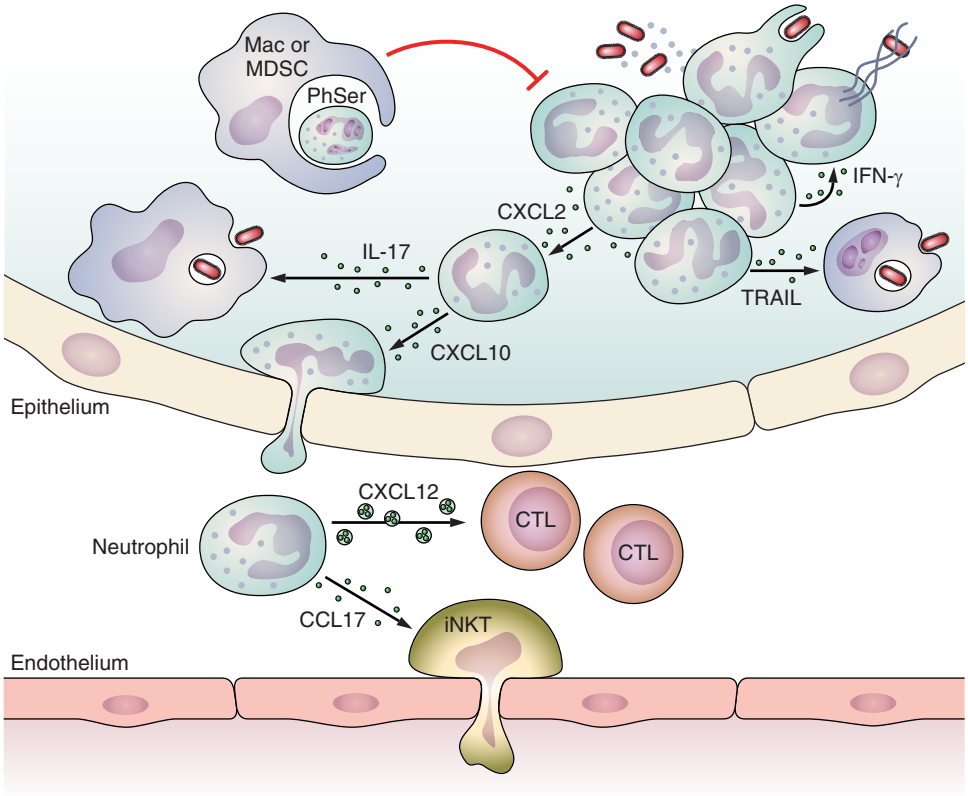

FIGURE 3. During pneumonia, neutrophils have both effector (antimicrobial) and affector (immunomodulatory) roles. Effector roles include microbial elimination via phagocytosis and degranulation as well as NET formation (*top right*). Affector roles include activities that enhance antimicrobial activities by other cells, such as macrophage stimulation by neutrophil-derived IL-17 and TRAIL and neutrophil stimulation by IFN-γ. Other immunomodulating activities involve the recruitment of antimicrobial cells (e.g., by CXCL12, CCL17, CXCL10, CXCL2). Signals provided from apoptotic neutrophils are immunoregulatory, enhancing the resolution of inflammation. The molecules identified are for illustrative purpose and do not represent an exhaustive presentation. PhSer, phosphatidylserine.

aided by the large marginated pool of neutrophils in the pulmonary vasculature, which means that neutrophil numbers that can exceed the total circulating pool are microns away at the start of infection (113). Neutrophils are relatively short-lived cells (391, 491) compared with other leukocytes, surviving on the order of hours to days, but their survival time can be modified by signals within the inflammatory milieu (86).

Neutrophils are antimicrobial cells **(FIGURE 3)**. Upon activation within the airspaces, neutrophils exert an expansive repertoire of intra- and extracellular antimicrobial activities (260), and their importance in the context of lung infections is evidenced by extreme susceptibility to infection in the absence of functional neutrophils both clinically (during neutropenia and with disorders of neutrophil function such as chronic granulomatous disease) and in animal models (following depletion or targeting of neutrophil-specific factors) (61, 151, 179, 386, 421, 539, 547). The primary means of neutrophil-mediated killing are *1*) phagocytosis, during which phagolysosomal fusion exposes ingested organisms to reactive oxygen species (via NADPH-oxidase activity) and acidity; *2*) degranulation, during which granules release toxic factors such as myeloperoxidase (MPO), gelatinase B (MMP9), cathepsins, defensins, and other antimicrobial proteins into the phagosome and/or extracellular space; and *3*) the formation of neutrophil extracellular traps (NETs), which result from the extrusion of DNA associated with histones and granule-derived antimicrobial proteins. All of these killing mechanisms cooperate to eradicate pathogens. For instance, genetic deletion of neutrophil elastase and cathepsin G in mice increases vulnerability to lung infections with *S. pneumoniae* (179), whereas *S. pneumoniae* lacking endonuclease A are less efficient at evading NETs, causing less severe pulmonary infections (32). Thus, while short-lived, the bactericidal capacity of this critical phagocyte population is a consequence of both great numbers and diverse function.

Outside of these effector roles, neutrophils also function in a governing capacity, producing cytokines, chemokines, and other factors that coordinate the ongoing immune functions in the lung (226). Lung neutrophils dispatch a variety of signals that shape acute pulmonary inflammation, providing a second wave of immunomodulatory cargo to expand upon initial responses from resident cells **(FIGURE 3)**. For example, neutrophils recruited in response to lung injury induced by influenza virus or acid aspiration release the chemokine CXCL10, which subsequently enhances both neutrophil activity and recruitment through its receptor CXCR3 (213). Neutrophils produce the neutrophil-attracting and -activating chemokine CXCL2, and neutrophilic production of CXCL2 can drive a self-amplifying feed-forward loop of localized neutrophilia that is important to defense but also a contributor to lethal lung injury (51). Neutrophil production of chemokines like CXCL10 and CXCL2 may contribute to "swarming" behavior of neutrophils (253), in which neutrophil activation amplifies the local recruitment of neutrophils within the air spaces of infected lungs **(FIGURE 3)**. In some cases, neutrophils also

can be a source of IL-17 (60, 533), a cytokine driving protective immunity through the induction of CXCL5, CXCL1, G-CSF, and enhanced phagocytic antimicrobial defense (69, 559). Interferon (IFN)-γ, the prototypical driver of type I immunity, is another typically lymphocyte-derived cytokine that can be produced by neutrophils in some settings of lung infection. In mouse models of pneumonia induced by Gram-positive (but not Gram-negative) bacteria, emigrated but not circulating neutrophils represent a prominent source of IFN-γ, which then enhances NET formation to facilitate bacterial killing (163, 553). This finding expands the catalog of neutrophil defense functions while highlighting the need to elucidate the causes and consequences of neutrophil reprogramming as they shift between the extra- and intrapulmonary environments.

While CXCL10, IL-17, and IFN-γ are examples of neutrophil-derived cytokines empowering neutrophil-driven defense, neutrophil products affect other cells as well **(FIGURE 3)**. For instance, neutrophils can enhance macrophage-mediated immunity by serving as a source of TRAIL, which drives antimicrobial apoptotic responses (468). Neutrophils are a requirement for the extravasation of iNKT cells from the pulmonary vasculature, where they are abundant before infection (486). To do so, migrating neutrophils release the chemokine CCL17, which recruits iNKT cells to the interstitium, and this is essential to optimal defense in mice with pneumococcal pneumonia (486). Similarly, neutrophils can recruit lymphocytes for adaptive immunity purposes; after influenza infections, the recruitment of antiviral CD8+ T cells to the lung and optimal influenza elimination requires CXCL12, which is produced exclusively by the migrating neutrophils within the infected lung and deposited in membrane-bound packets along the neutrophil's path within the interstitium (289). Therefore, neutrophils serve as both a consequence and cause of acute pulmonary inflammation, mediating both effector and affector actions of immune resistance **(FIGURE 3)**.

4. Recruited macrophages

While AMs may be the exclusive resident leukocyte of the airspaces, they do not represent the only macrophage population driving innate immunity. Perhaps this has been somewhat overlooked by the accessibility of AMs through lavage and the overwhelming numbers of recruited neutrophils in the early stages of pneumonia, not to mention the technical challenge of distinguishing resident versus recruited cells of the same type. It is evident that a distinct population of recruited bone marrow-derived macrophages can have an indispensable role in pulmonary innate immunity. In response to inflammatory stimulation, induction of the chemokine CCL2 acts as the primary signal to recruit monocytes into airspaces (72, 317–319), which then become further primed (316), expanding the available macrophage pool. This newly recruited inflammatory monocyte/macrophage population is functionally similar to classically activated (M1) resident macrophages in that they are phagocytes capable of producing inflammatory cytokines such as IL-1, TNF-α, and IL-12, and they can be distinguished from resident cells by a variety of differentially expressed surface markers, the most notably of which is high expression of CD11b (4).

Multiple studies support an essential role for recruited macrophages in maintaining immune resistance in the lungs. CCL2, for example, is both sufficient and necessary for inflammatory monocyte/macrophage recruitment in mice challenged intratracheally with *S. pneumoniae*, and its expression level is inversely proportional to the number of living bacteria recovered from the lungs (540, 541). Recent studies in mice infected with *K. pneumoniae* suggest that not only are CCR2+ recruited monocytes critical for lung bacterial clearance, but also that, for a subset of *K. pneumoniae* isolates, the antibacterial contribution of this cell population exceeds that of neutrophils (547). As discussed with other cell types above, recruited monocytes/macrophages also function to enhance the accumulation of other recruited immune cells. In the setting of sterile inflammation induced by intratracheal lipopolysaccharide (LPS), neutrophil and inflammatory monocyte responses were similarly diminished following interruption of CCR2, suggesting that the neutrophil accumulation requires signaling to monocytes (318). Inflammatory monocytes may also be required for the recruitment of IL-17-producing innate lymphocytes; in mice challenged with *K. pneumoniae*, recruited monocytes were identified as the prominent source of TNF-α, contributing to the lung recruitment of ILC3s and IL-17-mediated defense (548). Thus the integration of recruited monocytes with other innate defenses has surfaced as a key determinant of immune resistance.

5. Innate lymphocytes

The roles of innate lymphocytes in the context of pneumonia biology are receiving considerable interest. Their study is enabled by increasingly sophisticated tools for characterizing and manipulating lymphocyte subsets. While innate lymphocytes bear functional similarities to the B and T lymphocytes well recognized for their roles in adaptive immune responses, they are innate with regards to pathogen recognition. Natural killer (NK) cells, which were discovered over four decades ago, represent one type of innate lymphocyte enriched in lung tissue, important for defense against both viral and bacterial pathogens (197). Patients with genetic mutations causing NK cell deficiency are especially prone to viral infections (369), and the direct requirement of NK cells for maximal antiviral immunity has been observed in animal models as well (1, 467). While the impact of NK cells on bacterial infections is less delineated, pro-defense roles are beginning to emerge. Mice lacking the NK cell activating receptor NCR1 (NKp46) as well as mice depleted of NK cells (via anti-asialo GM1) exhibit increased lung bacterial burdens and mortality upon infection with *S.*

pneumoniae (125). NK cells also are essential for clearance of *K. pneumoniae* (549) and *S. aureus* (457) in murine models of pneumonia, possibly due to their roles in synthesizing IL-22 (549) and IL-15 (457), each of which is independently essential for defense against those respective microbes (23, 457). NK cells may also function at the interface of viral and bacterial pneumonias by limiting the likelihood of superinfection. The number of NK cells and their capacity to produce TNF-α were diminished in mouse lungs with *S. aureus* pneumonia following influenza infection compared with mice with *S. aureus* pneumonia and no prior influenza, and adoptive transfer of NK cells (but not TNF-α-deficient or influenza-exposed NK cells) was sufficient to restore antibacterial defense to influenza-infected mice (458).

NK cells were the first recognized subset of the innate lymphocytes now known as innate lymphoid cells (ILCs). These cells have been categorized in three distinct groups: *1*) group 1 including ILC1s and NK cells, *2*) group 2 including ILC2s, and *3*) group 3 including ILC3s and lymphoid tissue-inducer (LTi) cells (461, 462, 519). The categorization of ILCs across three distinct groups is consistent with their capacity to produce cytokines reflective of Th1, Th2, and Th17 adaptive lymphoid cells, yet ILCs are devoid of the known lineage markers associated with adaptive T cells, and they are not antigen specific (461, 519). Research into ILCs and lung infection is in early stages.

ILCs have been identified in the lungs of humans (96) and mice (338), and despite their relatively low abundance, they can play important roles. To our knowledge, ILC1s do not reside or function within the healthy lung. In contrast, ILC2s are present under unchallenged homeostatic conditions (152), although their functional contributions to immune resistance are uncertain. RSV infection promotes accumulation of IL-13-expressing ILC2s in the lung, which associates with increased type 2 inflammatory responses (470), suggesting at least one connection of ILC2s to lower respiratory infection. ILC2s help repair and regenerate injured lung tissue (44, 279, 333), but ILC2-mediated repair after pneumonia specifically is presently speculative. ILC3s are perhaps the most relevant to pneumonia biology and acute pulmonary inflammation, particularly with regards to their influence on IL-17-mediated defense. ILC3s are a prominent source of this cytokine in response to multiple microbial stimuli in the lungs, including *P. aeruginosa* (31, 347), *K. pneumoniae* (548), and LPS (347). Similarly, IL-22, often associated with Th17 biology and IL-17-dependent lung immunity (23), has been shown to derive from ILC3 cells during pneumococcal pneumonia (510). In all of these cases, the physiological significance of lung ILC3s is inferred from the already recognized influence of the cytokines they express. In some cases, ILC3-dependent immune effects are more directly supported through depletion strategies (347, 548), although a limitation of these studies is their use of Rag−/− mice lacking adaptive immunity lymphocytes. More precise targeting strategies will be required to definitively distinguish the functional contributions of ILCs during pneumonia.

In addition to ILCs, unconventional T cells (160) are another group of innate lymphocytes promoting lung defense. Invariant natural killer T (iNKT) cells possess an invariant TCR alpha chain and recognize lipid antigens presented by the MHC-like molecule CD1d (53). During pneumococcal pneumonia, Jα18$^{-/-}$ mice lacking iNKT cells exhibit increased mortality in association with impaired bacterial clearance from the lungs (54). Moreover, iNKT cells produce IFN-γ and IL-22 in response to influenza infection (373), although this did not alter immune resistance in this particular setting, it may have defense implications in other infections. $\gamma\delta$-T cells have a limited diversity of TCRs with poorly understood antigen specificity, but they demonstrably function in an innate capacity to modulate pulmonary inflammation (42). During pneumonia, $\gamma\delta$-T cells can be a major source of both TNF-α and IL-17, and mice lacking these cells are more susceptible to lung infections with *K. pneumoniae* or *S. pneumoniae* (71, 340, 356). Mucosa-associated invariant T (MAIT) cells recognize riboflavin-related products produced by diverse bacteria when presented by the MHC-related molecule MR1 (145). While MAIT ligands are unexpected in viral infections of any animal, MAIT cell numbers in the peripheral blood during severe avian influenza infections were elevated in human patients who survived, and MAIT activation by the cytokine IL-18 might possibly improve defenses against influenza (297). Although relevant to tuberculosis infection (161), roles of MAIT cells during bacterial pneumonia have yet (to our knowledge) to be demonstrated, but demand further attention.

Beyond ILCs and unconventional T cells, innate-like B cells also can impact early defense in the lungs. B1 cells are a self-renewing B cell population that is a major producer of cross-reactive natural IgM antibodies (30). The innate response activator (IRA) subset of B1a cells has been shown to reside in the pleural space and migrate to the lung parenchyma in response to *E. coli* pneumonia, where these cells then provide a protective GM-CSF-dependent IgM response (530). Additional studies in the setting of pneumococcal pneumonia also support a requirement for B1a cells to achieve maximal innate defense in the first days of infection (556).

6. Platelets

While best recognized for their roles in coagulation, platelets contribute to innate immunity as well, with multiple potential connections to pneumonia (46, 550). Platelets and their associated platelet GTPases and adhesion molecules enhance LPS-induced neutrophil recruitment in the lung and host defense during *Klebsiella* pneumonia (98, 99, 375), demonstrating roles in immune resistance. Their myr-

iad effects on coagulation, inflammation, and other aspects of physiology (46, 550) likely shape immune resistance, but also platelets may contribute in some cases through direct antimicrobial activities (269). During severe influenza infections, excess platelet activation amplifies inflammation, lung injury, and mortality (278), consistent with the notion that the challenge to tissue resilience from exuberant inflammation can at times be downstream of platelet activities. The lung is the site for much platelet production by megakaryocytes during homeostasis (282), and platelet production during acute inflammation is increased by maturation of committed progenitors into new megakaryocytes (178). It will be of interest to determine whether and how megakaryocytes in the lung and the differentiation of stem-like precursors into megakaryocytes are influenced by, and in turn influence, pneumonia.

B. Extrapulmonary Innate Immune Physiology

The immunological capacity of the lungs is shaped by a complex and highly dynamic pool of local constituents, some of which are discussed above. Typically, the lungs are remarkably efficient at compartmentalizing both infections and the response that they elicit, with a breach in containment representing insufficient resistance and resilience, potentially resulting in ARDS and/or sepsis. While it is logical, and certainly necessary, to investigate innate immune responses to lung infections from a local intrapulmonary perspective, lung defense does not and cannot occur in a vacuum. Rather, it involves an integrated physiological response in which the lungs selectively send and receive input from extrapulmonary tissues. Elucidating the identity and functional relevance of these signals has been historically challenging, due in large part to limited tools for interrogating tissue-specific contributions and the ever-present complications in distinguishing cause from effect. Yet, advances in gene targeting and other experimental approaches continue to expand our understanding and appreciation for remote processes controlling local immune resistance during pneumonia.

1. Liver

The liver has long been appreciated for its role in mounting the acute phase response (APR). Liver hepatocytes synthesize and secrete significant quantities of circulating acute phase proteins (APPs), whose expression can be dramatically altered in response to virtually any infection or injury (91, 148). The APR was discovered almost 90 yr ago in pneumonia patients, when researchers identified changes a substance (now known as C-reactive protein, CRP) in blood that bound to a polysaccharide-containing fraction of *S. pneumoniae* (490). There are now dozens of known [and likely many more unknown (403)] APPs, which are functionally diverse, and primarily expressed in the liver (148). The clinical utility of APPs is largely restricted to their application as biomarkers of disease severity, including that of pneumonia (13, 460, 564). The regulation and physiological relevance of APP expression is beginning to be understood.

Lung infections elicit robust hepatic transcriptome remodeling within hours of experimentally induced pneumonia, before the detection of any living organisms into the circulation (403, 404, 531). Regulation of hepatic gene programs guiding APP synthesis is attributed to multiple transcription factors (427), including STAT3, which was originally known as the "acute phase response factor" before it was cloned in the early 1990s (9, 571). In the setting of lung infections, NF-κB and STAT3 are particularly important for hepatic acute phase changes based on studies in mouse models (403). Following a lung infection with *S. pneumoniae* sufficient to induce over 1,000 gene changes in the liver, targeted simultaneous deletion of NF-κB RelA and STAT3 in hepatocytes virtually eliminated the pneumonia-induced APR (403). This response requires a combination of early-response cytokines (TNF-α, IL-1α, and IL-1β) with IL-6, as mice lacking these cytokine signals exhibit marked defects in hepatic activation of RelA and STAT3, respectively, in association with abrogated APP synthesis (404). These findings confirm the presence of a lung-liver axis, whereby cytokine signals from the lung elicit a rapid hepatic response to remodel the blood proteome. Consequently, APR-null mice lacking hepatocyte RelA and STAT3 not only lack changes in circulating APPs during pneumonia (despite unaffected baseline levels), but they also have diminished amounts of some APPs in alveolar exudate during pneumonia (200, 201). Failure to mount a liver APR is associated with increased mortality and impaired immune resistance both systemically and locally in mice lacking hepatocyte RelA and STAT3 (200, 201, 403), directly demonstrating the physiological significance of lung-liver communication.

While the existence of liver-derived protection during pneumonia is supported by the aforementioned studies, unveiling distinct mechanisms of protection presents a major challenge due to the breadth and diversity of hepatic acute phase changes. Enhancing opsonophagocytosis is one important function. It has been known for over a half century that acute phase serum can enhance opsonophagocytosis (233), and serum obtained from pneumonic mice lacking hepatocyte RelA and STAT3 has a diminished capacity to do so (403), proving that hepatic activity is essential to this blood-borne defense during pneumonia. The reduced opsonophagocytosis after hepatic transcription factor targeting invovlves decreased deposition of complement component 3 (C3) on the surface of pneumococci (403). A role for pneumonia-induced C3 expression is also supported by a recent study showing that IL-22, which is essential for innate defense against intrapulmonary *S. pneumoniae*, in-

creases hepatic and serum C3 levels to a degree that is sufficient to increase its bacterial deposition as well as pulmonary defense (498). Targeted deletion of the IL-22 receptor on hepatocytes reduces local lung clearance of pneumococcus, indicating that this STAT3-activating cytokine works alongside IL-6 in the context of the lung-liver axis. Short pentraxins such as CRP and serum amyloid P (SAP) are other APPs that bind to bacterial surfaces, where they both activate complement deposition and promote recognition and phagocytosis through FcγRs (299). CRP and SAP are necessary and sufficient to enhance host defense in mouse models of pneumococcal pneumonia (452, 567). Another potential mechanism for liver-derived lung immunity is enhancement of macrophage responsiveness, including increases in the respiratory burst that depend on yet-to-be-identified liver-derived factors (201). Regulation of metal homeostasis may also be an important form of immune resistance provided by the liver. For instance, iron acquisition is essential for bacteria to thrive (414), and host factors that limit iron availability can be protective (235). Hepcidin, which is largely driven by IL-6-dependent STAT3 activity in the liver (361), limits iron availability by controlling its absorption in the intestines (362), and this factor was recently shown to be both sufficient and necessary for promoting defense against *K. pneumonia* in the lungs (331). Beyond opsonophagocytosis, leukocyte activation, and metal homeostasis, additional relevant APP functions may include protease regulation, hemostasis, toxin inhibition, microbial starvation, and more. In addition to those mentioned above, individual APPs such as lipopolysaccharide binding protein (LBP), serum amyloid A (SAA), and mannose binding lectin (MBL) have been demonstrated significant to pneumonia and acute pulmonary inflammation (52, 149, 164, 416).

Secreted APPs represent only a fraction of the many hepatic gene changes constituting the acute phase response (8, 403), and the importance of liver responses for lung defense demands consideration of non-APP functions. While some "APP-independent" hepatic gene programs, such as those linked to metabolism, protein synthesis, and protein secretion, almost certainly play a support role for APP responses (8), others likely operate to promote defense that is entirely distinct from that afforded by APPs themselves. Cholesterol regulation represents one interesting example of APP-independent liver-derived protection (531). *S. pneumoniae* lung infections in mice were shown to promote liver gene expression of numerous factors connected to cholesterol biosynthesis (531). In this study, hepatic gene changes were associated with increased plasma cholesterol, and this increase was shown to abrogate pneumolysin-dependent alveolar macrophage necrosis, suggesting that acute phase exudate in the alveolar space directly impairs pneumococcal virulence (531). The functional relevance of the lung-liver axis is now firmly established, and mechanisms governing liver-derived lung immunity are beginning to be resolved.

2. Bone marrow

As outlined above, effective local immune resistance requires both resident and recruited leukocytes in the lungs, the latter of which includes the rapid emigration of neutrophils from the blood to the airspaces. As neutrophils are extracted from the circulation, their supply must be maintained to meet the demand of the infected lung, which is primarily established by the egress of newly formed cells out of the bone marrow. This shift from homeostatic granulopoiesis to "emergency" granulopoiesis in the marrow requires the lung to function in an endocrine capacity, much like it does with the liver to elicit the APR. While multiple cytokines and other immunomodulators have been shown to impact the complex process of granulopoiesis, the most prominent is G-CSF (311), the primary intermediate through which pneumonic lungs trigger bone marrow responses. G-CSF is required for steady-state granulopoiesis and is used therapeutically in patients with neutropenia (379). By inhibiting osteoblast expression of the chemokine CXCL12, G-CSF disrupts the retention of bone marrow neutrophils, which is largely maintained by CXCR4-CXCL12 interactions (121, 441, 442, 480). Diminished CXCL12 content in the bone marrow then enables neutrophils to respond more readily to CXCR2 ligands, such as CXCL1, CXCL2, and CXCL8, promoting neutrophil release from the bone marrow (120, 480).

G-CSF is a pleiotropic neutrophil-targeting cytokine, and a major role of G-CSF during pneumonia is to signal to the marrow from the lung. Lung infections stimulate abundant G-CSF in the blood during pneumonia in both patients and in animal models (382, 410). The intratracheal administration of recombinant G-CSF alone is sufficient to elicit increases in circulating G-CSF, blood neutrophils, and bone marrow granulopoiesis (447), consistent with the notion that lung-derived G-CSF is decompartmentalized to access the bone marrow during pneumonia (410). Consequently, intrapulmonary G-CSF delivery can also significantly amplify alveolar neutrophil recruitment, as demonstrated in multiple settings of acute pulmonary inflammation (26, 137, 360, 570). Genetic targeting of the G-CSF receptor impairs clearance of *P. aeruginosa* in mouse lungs, and this is associated with reduced survival and dramatic decreases in both circulating and lung-recruited neutrophils (173). Similar consequences are observed in response to pharmacological G-CSF blockade in mice challenged with pneumococcal pneumonia (257). Conditions that alter G-CSF expression also support an important role for this cytokine in immune resistance. For example, impaired G-CSF expression in the setting of alcohol exposure associates with reduced granulopoiesis and enhanced growth of *S. pneumoniae* in the lungs (451).

3. Spleen

Experimental splenectomy renders pneumonic mice highly vulnerable to systemic infection (449), and this outcome is consistent with increased occurrence and reoccurrence of pneumonia in splenectomized patients (270, 346). Precise contributions of splenic function to local lung defense are presently unknown. Like that of the liver, the anatomy and distribution of phagocytes within the spleen enable reticuloendothelial clearance of circulating pathogens (324), which is essential for controlling systemic defense and inflammation during pneumonia. This is unlikely a direct contributor to immune resistance in the lung, though. As a secondary lymphoid organ, the spleen has essential roles in adaptive immune responses, and these may contribute to local lung defense, particularly the delivery of plasma antibodies in the exudate of an infected lung. The IgM produced by marginal-zone B cells (324) may be particularly important for some respiratory pathogens, like pneumococcus (556). The activation mechanisms and functional roles of splenic B cells involve other leukocytes linked to pneumonia outcome such as neutrophils (78, 400), ILCs (304), and macrophages (263). Beyond the loss of phagocytes, neutropenia may predispose to pneumococcal pneumonia because of defects in T cell-independent antibodies from the spleen; IgM, IgG, and IgA against pneumococcal capsular polysaccharides are produced by splenic B cells requiring neutrophils as helper cells, and all are diminished in the blood of neutropenic patients (400).

4. Gastrointestinal tract

The intestinal mucosa is an immunologically rich environment, containing a microbial landscape shaped by interactions among microbiota, invading pathogens, and host immune functions (438). These interactions also have immunologic consequences in tissue sites outside of the intestines, including the lungs. For instance, meso-diaminopimelic acid-containing peptidoglycan derived from the intestinal microbiota engages the NOD1 receptor of neutrophils in bone marrow, enhancing their in vitro microbicidal capacity against *S. pneumoniae* and *S. aureus* (81). Depletion of gut microbiota with antibiotics impairs *K. pneumoniae* clearance in the lungs in association with reduced pulmonary cytokine responses and impaired ROS synthesis by AMs (80). Oral administration of NOD-like receptor ligands is sufficient to rescue innate immune responses following microbiome depletion, consistent with the hypothesis that gut-derived microbial products promote defense at other tissue sites (80). Similar immunodeficiency is also observed in mice with pneumococcal pneumonia following gut microbiome depletion; broad-spectrum antibiotic treatment ablates intestinal microbiota and significantly increases the number of viable bacteria recovered from the lungs, concurrent with reduced cytokine expression and phagocytosis by AMs (437). Gut-derived pulmonary defense is also evident in the setting of viral pneumonia, in which case microbiome ablation impairs immune responses reliant on inflammasome activity (214). Despite the risk of deleterious effects on immune defenses as well as potentially fostering antibiotic resistance, selective decontamination of the digestive tract has clinical utility; reducing the presence of potentially infectious agents in the gastrointestinal and respiratory systems of vulnerable patients can decrease rates of pneumonia and death in the ICU (43, 97). In addition to microbe-derived substances, host-derived metabolites from the intestines have also been shown to have important immunomodulatory properties. For example, select intestinal short-chain fatty acids have numerous effects on leukocyte recruitment and activation (517). These effects appear to be context specific, and at present their direct influence on immune activity in the respiratory tract is unknown.

5. Fat

Adipose tissue represents another remote contributor to innate pulmonary defense. Leptin is derived primarily from adipocytes, and leptin signaling is essential to optimal immune defense in multiple mouse models of lung infection (308–310, 502). Conversely, excess leptin including hyperleptinemia, a hallmark of obesity, may increase risk of pneumonia (390). Higher leptin levels associate with greater pneumonia risk in nonhospitalized adults, and with greater severity of pneumonia among hospitalized patients, independent of body mass (502). High circulating leptin content in mice, elevated by diverse strategies, can compromise innate immunity in the lungs (502). A specific role for leptin is further supported by the observation of no adverse effects on lung defense in a leptin-independent mouse model of obesity (307). The precise role of leptin is complicated by indirect metabolic consequences of its manipulation and the widespread physiological impacts of obesity (479). Adiponectin is another adipokine with inflammation-regulating properties that may influence pulmonary immune resistance. In the setting of sterile inflammation induced by LPS, adiponectin deficiency exaggerates immune responses (59, 262), but whether or how this factor directly contributes to pneumonia biology is currently unclear. While elements of the obesity phenotype including changes in adipokines may influence pneumonia biology, the evidence does not conclusively demonstrate that obesity per se increases risk of community acquired pneumonia, independent of obesity-associated comorbidities (265, 390).

6. Other extrapulmonary influences on lung innate immunity

The liver, bone marrow, spleen, gut, and adipose tissue are highlighted above for their impact on intrapulmonary immune responses, perhaps all of which involve endocrine activities from these tissues **(FIGURE 4)**. The systemic re-

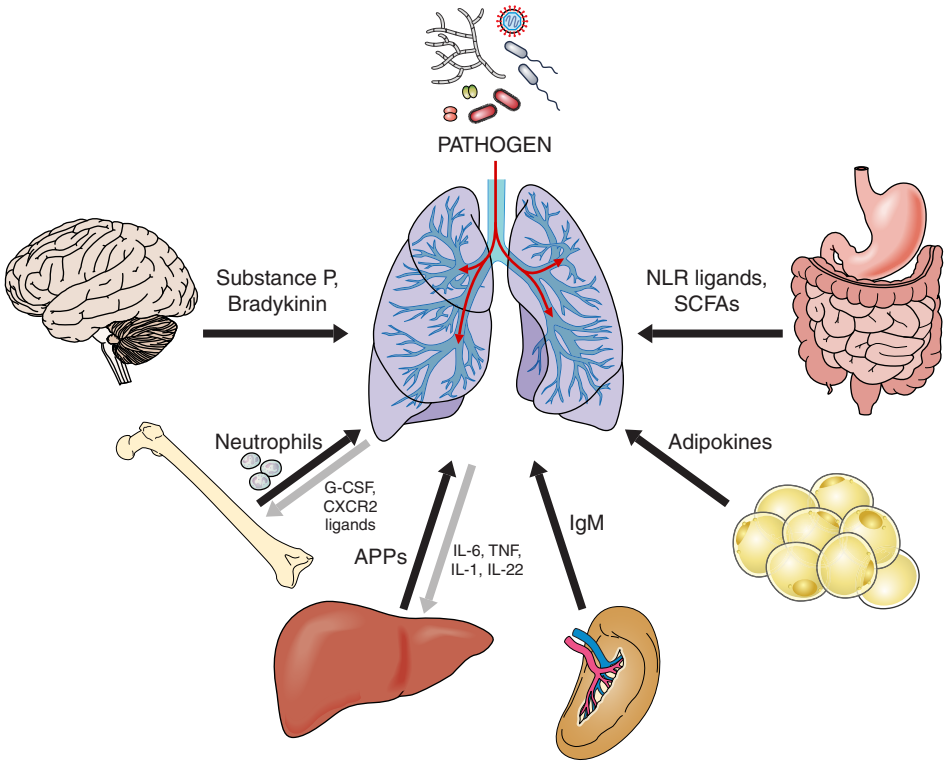

FIGURE 4. Multiple extrapulmonary organs contribute to immune resistance against pulmonary infection. The molecules identified are for illustrative purpose and do not represent an exhaustive presentation. In the few instances where signals have been identified by which pulmonary infection signals to the extrapulmonary organ, this communication is denoted in gray. APPs, acute phase proteins; SCFAs, short-chain fatty acids.

sponse to pathogens in the airspaces has other origins, as well. For example, procalcitonin (PCT), which is the thyroid-derived precursor to calcitonin, increases in the blood of critically ill patients and rises in the blood during pneumonia, and it can be used as a biomarker to help distinguish infections of bacterial versus viral origin (22) and as a predictor of pneumonia severity (483). The functional significance of PCT elevation during bacterial pneumonia is unknown. Likewise, febrile-range hyperthermia has numerous consequences on pulmonary inflammation and immunity (186), including elevated neutrophil accumulation and earlier clearance of *K. pneumoniae* from the lungs (419), suggesting that fever may serve as a systemic mechanism of brain-derived pulmonary defense. Direct biological contributions of fever to pneumonia biology, either good or bad, are largely speculative. Brain function may also influence pneumonia susceptibility, particularly that caused by aspiration, through coordination of airway reflexes such as cough (122). For instance, pneumonia incidence has been shown to correlate with cough reflex sensitivity (355), and among patients with mixed primary neurological disorders the incidence of ARDS is significantly greater in those lacking cough and/or gag reflexes (204). Interestingly, a recent meta-analysis indicated markedly higher pneumonia incidence in subjects with a specific polymorphism in angiotensin converting enzyme that reduces substance P and bradykinin, both of which drive the cough reflex (524), also consistent with the notion that airway reflex sensitivity contributes to pulmonary defense.

IV. ADAPTIVE IMMUNITY AND PNEUMONIA

The adaptive immune system is well recognized in the fight against pneumonia. One of the earliest effective treatments for pneumonia, used until antibiotics became available, was "serum therapy" in which antibodies collected from horses or rabbits that had previously been serially exposed to pneumococci were administered to pneumonia patients (64, 65). If the antibodies were appropriate to the pneumococcal serotype and were administered soon after pneumonia symptoms developed, "serum therapy" decreased mortality by approximately one-third (64, 65). Along similar lines, but using hybridomas rather than animal sera as an immunoglobulin source and for prevention rather than cure, delivery of a monoclonal antibody against RSV is currently in clinical use for high-risk children (16). The vaccines against influenza, pneumococcus, and *Hemophilus influenzae* stimulate the host to generate their own circulating antibodies against these microbes, which reduce risk of pneumonia (154, 174, 175). Thus the humoral arm of adaptive immunity can protect the lungs. The emergence of HIV/AIDS in the last half of the 20th century emphasized the importance of cellular immunity in immune defense of the lungs. Patients with low CD4+ T cell counts are highly susceptible to pneumonias caused by diverse organisms including especially *Pneumocystis* and pneumococcus (169, 440). Although not yet feasible in humans, the adoptive transfer of microbe-specific CD4+ or CD8+ T cells is capable of fighting respiratory infection in inbred animals (182, 232, 558), similar to the

transfer of protection achieved with antibodies. Thus cellular immunity also protects the lungs against pneumonia. The regulation and function of specific components of the adaptive immune system in fighting respiratory infection are discussed in several recent reviews (47, 70, 75, 407, 481).

The earliest infections of the youngest children elicit primary adaptive immune responses, and subsequent encounters with those or related microbes trigger secondary or recall responses from memory cells. The immunological memory established by repeated respiratory infections is almost certainly key to the immune defense that helps prevent pneumonia in older children and adults (407). Such "real world" encounters with microbes profoundly rewire immunity, including both innate and adaptive immunity in the lungs **(FIGURE 5)**. Effects of "real world" exposures on immunity were elegantly demonstrated by studies in which the circulating leukocyte transcriptomes of mice and humans were compared (34). In short, laboratory mice have immune systems that reflect those of human infants, whereas mice that were caught in barns or purchased from pet stores have immune systems that more closely match human adults (34). The co-housing of laboratory mice with those purchased from pet stores leads to *1*) transcriptional remodeling of blood leukocytes to more closely match that of human adults, *2*) circulating antibodies against multiple pathogens of mice, *3*) seeding of the lungs **(FIGURE 5)** and other organs with lymphocytes of the innate and adaptive immune systems, and *4*) dramatically improved defenses against experimental infection (34). Here, we overview two important ways in which adaptive immunity is remodeled by prior microbial infections, the establishment of heterotypic immunity and of resident memory, both of which are rapidly advancing areas of research with profound implications for pneumonia defense.

A. Naturally Acquired Heterotypic Adaptive Immunity

Heterotypic immunity refers to adaptive immunity directed against a microbe that is similar but not identical to the microbe originally establishing immunological memory. Examples include memory to influenza viruses across different seasons (e.g., H1N1 from 2009 and H1N1 from 2010) or across different subtypes (e.g., H3N2 and H1N1), or to multiple of the 94 different serotypes of pneumococcus. Because they are such commonly encountered microbes **(FIGURE 1)**, healthy young adult humans probably have some degree of heterotypic immune memory against all of the most common causes of pneumonia.

Pneumonia defense is strongly influenced by the earliest infections with respiratory pathogens, based on evidence of immunological "imprinting" against influenza viruses (167). Those born before 1968 were likely first infected with influenza viruses containing hemagglutinins (HAs) from phylogenetic group 1 (which includes H1, H2, and H5 HAs), whereas those born after that date were more likely to be first infected by influenza viruses with group 2 HAs (which includes H3 and H7 HAs). For the unfortunate humans who get infected with highly pathogenic zoonotic influenza viruses, the severity of pneumonia correlates strongly with their birth dates; those born before 1968 are more likely to get severe pneumonia from H7N9 rather than H5N1 avian influenza viruses, whereas those born after 1968 are more likely to get severe pneumonia from H5N1 rather than H7N9 (167). These individuals likely did not have neutralizing antibodies against the avian influenza viruses, but their acquired immunity against related viruses (within the same phylogenetic group) provided some level of protection. Such early imprinting of immunity may influence many or all types of respiratory infections.

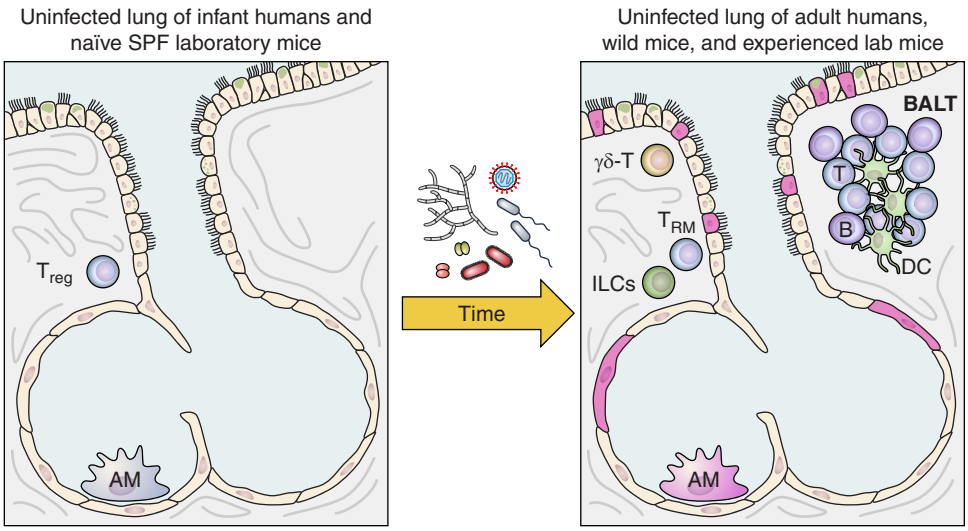

FIGURE 5. Lungs that have experienced prior infections are different from naive lungs that have not. The T-cell population most notable in lungs from neonatal humans is regulatory T (Treg) cells, whereas the healthy lungs of adults or of laboratory animals that have experienced prior respiratory infections contain abundant resident memory T (T_{RM}) cells. In addition, lungs that have experienced prior respiratory infections exhibit varying degrees of immunological changes including bronchus-associated lymphoid tissue (BALT), innate lymphoid cells (ILCs), and γδ-T cells. In addition, the alveolar macrophages (AM) and epithelial cells of experienced lungs behave differently from their counterparts in naive lungs, likely due to a combination of trained immunity and direction from adaptive immunity.

A combination of humoral and cellular protection is implicated in mediating the naturally acquired heterotypic immunity that protects young adult humans against respiratory infection of the airways. When healthy young adults are experimentally infected with influenza virus or RSV, the amount of heterotypic antibodies in their blood before experimental infection inversely correlates with their viral burden and symptoms after infection (25, 231). In seronegative individuals who have not seen a particular influenza virus before, those with greater numbers of influenza-responsive CD4+ T cells in their blood before infection **(FIGURE 6)** have less severe infection as measured by viral burden and symptoms during the experimental infection (537). By design necessity, the experimental human infections described above cause mild disease; correlates of protection observed there are inferred to be relevant to pneumonia. Supporting this inference, antibodies with respiratory pathogen specificity found in the blood of seronegative healthy uninfected adults can be sufficient to protect mice against severe viral or bacterial pneumonia (157, 543). Also supporting the association of preexisting heterotypic immunity with more severe infections is an epidemiologic study of a population first experiencing the reassortant H1N1 influenza virus that emerged in 2009 (463). Although all subjects were naive to this particular virus, patients with greater circulating numbers of CD8+ T cells recognizing epitopes conserved in that coming influenza virus **(FIGURE 6)** demonstrated less symptoms during their naturally acquired infections with that virus (463), suggesting that the preexisting heterotypic immunity provided protection. These results from the epidemiologic study differ in detail from results of experimental infections with influenza or RSV, which showed correlation with elements of preexisting heterotypic immunity but not with blood CD8+ T cells (243, 537). In animal models of influenza infection, both CD4+ T cells and CD8+ T cells are sufficient to transfer heterotypic immunity against pneumonia (182, 232). Together, such studies demonstrate that preexisting heterotypic immunity varies across hosts and pathogens, and variations in the parameters of heterotypic immunity make critical contributions to the outcome of respiratory infection.

Some heterotypic antibodies in human blood can be neutralizing, preventing viral infection of cells (354, 543). Other heterotypic antibodies direct immune effector activities. Heterotypic antibodies against the conserved stalk region of influenza HA trigger a respiratory burst in phagocytes and provide heterotypic defense against respiratory infection that is Fc receptor (FcR) dependent, whereas homotypic protection provided by antibodies against the more variable head regions of HA do not protect via such pathways (109, 348). This applies uniformly across anti-HA antibodies and to anti-neuraminidase antibodies as well (108), suggesting that FcR-mediated activities may be generally required for protection by heterotypic antibodies. Young adult humans have antibodies recognizing hundreds

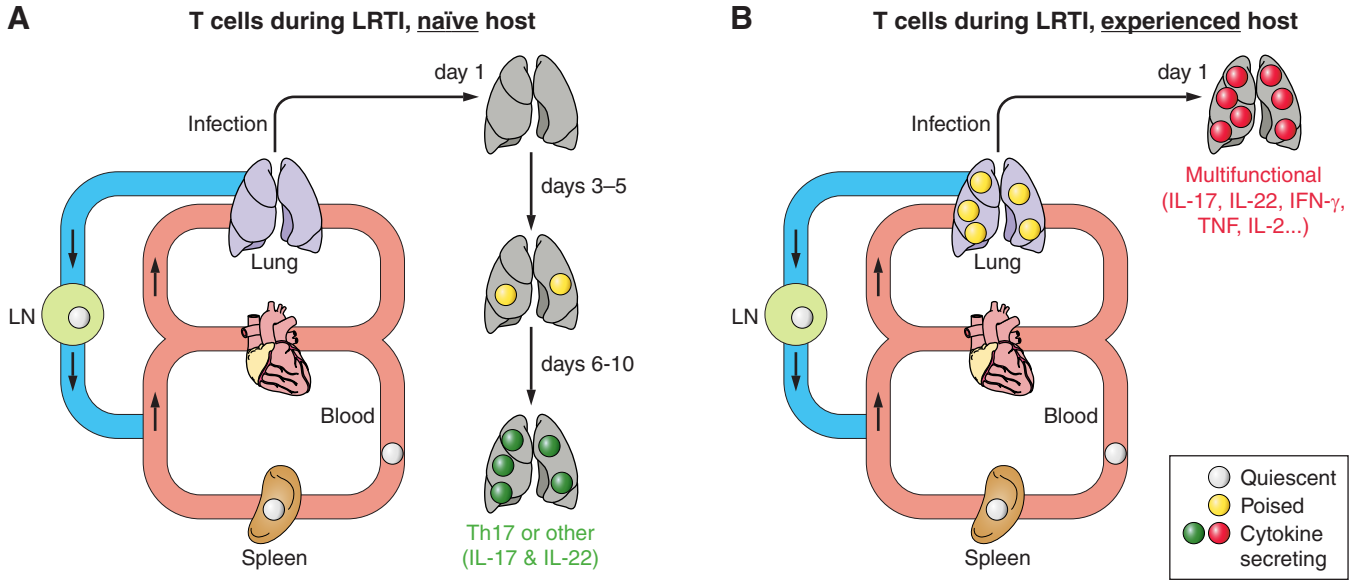

FIGURE 6. T lymphocytes contribute differently to respiratory infection in naive and experienced hosts. *A*: in naive individuals, who have not previously seen relevant respiratory infections, T lymphocytes responsive to the microbe in the lungs are found in the circulating blood (red) and secondary lymphoid organs such as the spleen (purple) and lymph nodes (LN, blue). It takes several days for them to appear in the lungs and a week for their activities to be manifest. *B*: in contrast, in experienced hosts who have previously been infected with relevant respiratory pathogens, there are greater numbers of responsive T lymphocytes in the blood and secondary lymphoid organs, and there is a resident memory population of responsive T cells already present in the lungs before infection. These lung T cells are poised to respond more rapidly and to elaborate a broader repertoire of protective cytokines. Thus responsive T cells in experienced hosts are more numerous, localized to the right place, able to respond more quickly, and prone to becoming multifunctional, altogether leading to T cell-mediated defense in the lung that is quicker and more efficacious.

of protein epitopes from pneumococcus (157), and raising antibodies against some of these pneumococcal antigens by vaccinating mice can improve defense against pneumococcal pneumonia (157, 334), by mechanisms including opsonophagocytosis, decreased adherence, disruption of toxins, and more. Human blood from any of at least three different continents consistently contains IgG antibodies against a common set of diverse pneumococcal proteins, and delivering human IgG (without antigen selection) to mice is sufficient to diminish the severity of infection during pneumococcal pneumonia (538). However, pneumococcus-recognizing antibodies found in the blood after pneumococcal infection are not necessarily capable of mediating heterotypic protection (84, 157). Whether and when the heterotypic antibodies present in human blood can help to prevent pneumonia demands more investigation.

Cellular immunity makes many contributions to heterotypic protection of the lungs **(FIGURE 6)**. Memory CD4+ T cells established by prior respiratory infections are superior to primary effectors in their protection of the respiratory tract, because they are more multifunctional (i.e., producing a greater variety of cytokines) and more prone to yield T follicular helper (T_{FH}) cells in the relevant lung tissue (473). The expansion of such memory CD4+ T cells in the infected lungs requires IL-6 (474). Activities of these virus-specific memory CD4+ T cells include the lysis of infected cells (153, 537) as well as the acceleration and amplification of pathways described above under "innate immunity" but here directed by memory T cell-derived cytokines (472, 475). Similar phenomena apply to bacterial pneumonias. Adult humans have CD4+ T cells that proliferate and produce IL-17 in response to acapsular pneumococcus or pneumococcal proteins, which are heterotypic responses in the sense that they are independent of serotype (301). In humans, experimental pneumococcal infections of the upper airways increase the numbers of cognate multifunctional CD4+ Th17 cells in the blood and lungs (544). IL-17 stimulates host defense against extracellular bacteria and fungi in the lungs (70). Heterotypic protection against pneumococcus in the lungs can be modeled in mice by infecting them with one serotype before challenging them with another, and both IL-17 and CD4+ T cells are necessary for heterotypic protection against pneumonia in this model (526). Furthermore, CD4+ T cells from the spleens of such mice are sufficient to confer defense against respiratory infection, if and only if they have intact genes for IL-17 (526), demonstrating that this systemic cellular immune memory can provide heterotypic protection against bacterial pneumonia.

B. Resident Memory Cells

In addition to the circulating or systemic immune memory described above, which can protect the lungs and all tissues, there are also localized depots of immune memory within the respiratory tract that specifically protect these tissues against respiratory infection. The best recognized such structures are the tertiary lymphoid organs of the upper airways, the tonsils and nasal-associated lymphoid tissue (443), as well as the variable amounts of bronchus-associated lymphoid tissue (BALT) in the lower airways (412). These are sites of local antibody production, as well as sources of memory B cells and plasma cells providing systemic protection. More recently, it has become evident that lung tissue contains numerous memory T cells that reside stably in the interstitium but are not in tertiary lymphoid organs (401, 485, 501). The biology of such resident memory T (T_{RM}) cells has been reviewed (134, 434). Here, we discuss aspects of lung T_{RM} cells that are especially pertinent to pneumonia defense **(FIGURE 6)**.

While identified previously (205), many fundamentals of lung T_{RM} cells in respiratory infection were established with a seminal study from 2011 (485). Mice with a transgenic TCR specific to influenza HA were used to restrict analyses to antigen-specific cells. Memory CD4+ T cells were collected from the lungs or the spleen of mice with a fully resolved influenza virus infection, and then adoptively transferred to normal uninfected mice; the lung-derived memory cells were then found exclusively in the lungs, whereas the spleen-derived cells were found in the spleen and other tissues of the recipient mice. When the bloodstreams of such recipient mice were connected via parabiosis to other uninfected mice who had not received T cell transfers, the lung-derived T cells did not appear in the parabiotic host, whereas the spleen-derived cells did. These data demonstrated that the resolution of lung infection resulted in a population of lung-resident memory cells, retained in the tissue rather than recirculating with a lung-homing propensity. When mice that had received comparable numbers of TCR-transgenic (hence identical antigen specificity to influenza HA) memory T cells from the lungs or from the spleen were challenged with an influenza infection, the lung-derived cells provided better protection as measured by weight loss, survival, and viral burdens, indicating that lung T_{RM} cells have superior abilities to protect against respiratory infection compared with central memory cells. Therefore, the resolution of lower respiratory infection can seed the lungs with T_{RM} cells that remain local and protect that pulmonary tissue against further infections.

Resident memory cells populate the lung tissues after bacterial pneumonia as well (459). When pneumococcus causes a lobar pneumonia, the resulting CD4+ T_{RM} cells concentrate selectively in the previously infected lobe, rather than dispersing throughout the lower respiratory tract (459). Because systemic immunity applies equally to the entirety of the respiratory tract yet T_{RM} cells are restricted to a single lobe, this provides an elegant opportunity to examine the contributions of resident memory above

and beyond the combined abilities of all central memory cells, circulating antibodies, and other components of systemic heterotypic adaptive immunity. The lobe with T_{RM} cells demonstrates far superior lung defense against virulent pneumococci compared with the contralateral lobes without T_{RM} cells **(FIGURE 7)**. Trained innate immunity (363), such as improved AM functions, could additionally contribute to the localization of heterotypic immune defense after lobar pneumonia, but the fact that depletion of CD4+ cells compromises such defense (459) highlights a T_{RM} cell role. Thus lung T_{RM} cells protect against diverse types of respiratory pathogens, and the lung protection characteristic of young adults with naturally acquired heterotypic immunological memory cannot be provided by systemic adaptive immunity alone.

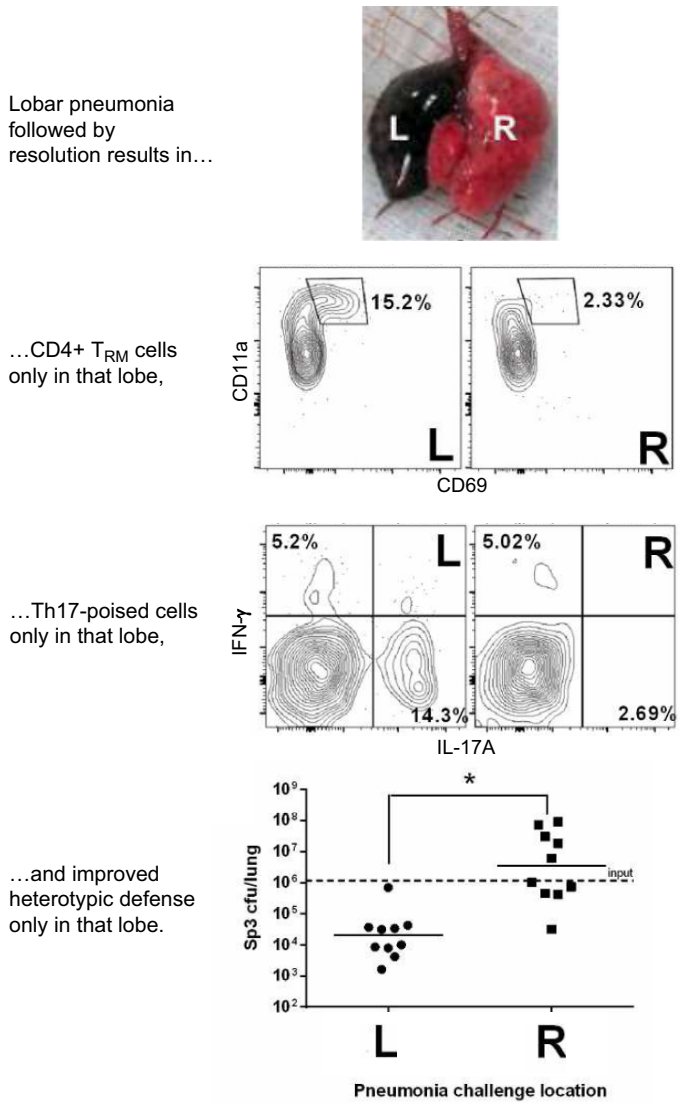

FIGURE 7. The site of respiratory infection determines where protection resides. After pneumococcal lobar pneumonia in mice, CD4+ resident memory T (T_{RM}) cells are found 1–2 mo later in the previously infected lobe rather than contralateral lobes. Polyclonal stimulation of cells collected from the different lobes shows that CD4+ T cells are poised to elaborate Th17 cytokines only in the previously infected lobe. Furthermore, the previously infected lobe is significantly more protected against infection by pneumococci of a different serotype compared with contralateral lobes. [Adapted from Smith et al. (459).]

Human lungs contain T_{RM} cells. A 2011 publication analyzing lobectomy samples from lung cancer patients revealed that the noncancerous regions of lung tissue include an unexpectedly large number of T cells (401), and this has now been reproducibly found in human lung tissues without cancer or any pulmonary disease, from young children through senior citizens (433, 487, 488). These lung lymphocytes include both CD4+ and CD8+ T cells (433, 487, 488). While imperfect, CD69 expression on nonactivated T cells is used as a marker for T_{RM} cells (134, 434), and lung T cells tend to express CD69 (401, 433, 487, 488). Memory T cells begin accumulating in human lungs as early as infancy (487, 488). T cells from human lungs are more likely to proliferate in response to influenza virus antigen presentation than are T cells from the blood or the skin (401), suggesting antigen specificity may be skewed towards respiratory pathogens. While cytokine expression from human lung T_{RM} cells stimulated by presentation of microbial antigens has not (to our knowledge) been reported, pneumococcus presentation to mouse lung T_{RM} cells (459) induces the MHCII-dependent expression of a wide variety of cytokines (including IL-17A, IFN-γ, TNF-α, IL-2, and more), and the antigen-independent polyclonal activation of human lung-derived T cells (401, 433, 487, 488) stimulates the coexpression of many cytokines (e.g., IFN-γ, TNF-α, and IL-2 together), altogether suggesting a predilection for "multifunctional" phenotypes. Thus the human lung contains a preponderance of T_{RM} cells, which likely have specificity for respiratory pathogens and exert multifunctional roles.

The CD8+ T_{RM} cells have been the most extensively studied resident memory cells in the lung, largely by characterizing the cells found in human lungs or by influenza infections of mice. The heterotypic protection against influenza provided by CD8+ T_{RM} cells depends on IFN-γ expression, which is more rapid from T_{RM} cells compared with circulating effector memory T (T_{EM}) cells (323). CD8+ T_{RM} cells from human lungs have distinct transcriptomes compared with CD8+ T_{EM} cells from the blood, including steady-state expression of mRNAs for effector molecules, suggesting that the lung cells are not just better-positioned anatomically but also are better poised molecularly to respond quickly during lower respiratory infection (208) **(FIGURE 6)**. Distinct patterns of expression for chemokine receptors and adhesion molecules (208) may contribute to the prolonged lung localization of CD8+ T_{RM} cells in the lungs. After influenza infection in mice, CD8+ T_{RM} cells reside selectively at sites of prior damage to the tissue (482). The maintenance of CD103+ CD8+ T_{RM} cells in the lung requires signaling from Notch, low levels of T-bet, and the IL-15 receptor (208, 302). Administration of 4–1BB ligand

amplifies CD8+ T_{RM} cell accumulation after mucosal vaccination, while 4–1BB-deficient CD8+ T cells fail to seed the lungs after recovery from influenza infection (572), suggesting a requirement for this costimulation pathway. The development of CD103+ CD8+ T_{RM} cells in the lungs after influenza infection also requires IFN-γ from helper CD4+ T cells (276). Whether the pathways described above are broadly applicable, for example, to multiple types of respiratory infection or to CD4+ lung T_{RM} cells, demands more study. The fundamental biology of lung T_{RM} cells, and how lung T_{RM} cells are normally involved in resistance and susceptibility to diverse respiratory infections as well as the roles of alterations in lung T_{RM} cells in diverse populations of susceptible or resistant hosts, remains poorly defined and presents especially great promise for improving our understanding of pneumonia defense.

C. Other Long-Term Changes to Lung Cells After Acute Pneumonia Infection

In addition to changes in adaptive immunity as outlined above, other persistent changes to lung tissue **(FIGURE 5)** have been noted to result from resolution of respiratory infection, potentially relevant to immune resistance against subsequent pneumonias. Severe respiratory infections can cause BALT formation, and these tertiary lymphoid organs can contribute to local antimicrobial defense (412). Presumably because of the infections experienced, the co-housing of laboratory mice with mice purchased from pet stores is sufficient to thereafter increase the numbers of innate lymphocyte populations in the lungs, including ILC1, ILC2, ILC3, and γδ-T cells (34). Infection with influenza virus is capable of altering the phenotypes of alveolar macrophages and epithelial cells in the mouse lung for months afterwards (107, 247, 394). The degrees to which BALT, innate lymphocyte accumulation, and such remodeling of epithelial cells and macrophages reflects chronic inflammation, trained immunity (363), aberrant repair, or all of the above, and the factors influencing these and other long-term changes in the lung occasionally observed after respiratory infection, are largely unclear.

V. TISSUE RESILIENCE AND PNEUMONIA

Like the local and remote resistance pathways outlined above, biological processes driving tissue resilience also include input from intra- and extrapulmonary sources. The shared goal of these signals is to limit injury resulting from all aspects of infection, which requires countermeasures to damage elicited from the microbes, as well as that from the host response (i.e., immunopathology). Failure to achieve this goal progresses pneumonia to ARDS and sepsis (19, 315). Two major avenues for fortifying tissue resilience in the airspaces are events that *1*) provide negative feedback on inflammation, which left unchecked can cause injury; and *2*) retain the function and number of viable lung parenchymal cells to ensure an environment supportive of gas exchange. Some of these events will be highlighted below, with consideration to both intra- and extrapulmonary contributions.

A. Resilience in the Lungs

An excess of the signals described above as promoting immune resistance against microbes can be dangerous to the lung tissue itself. Perhaps the most direct and immediate element controlling the magnitude of this response is the size and strength of the initial stimulus, which wanes as a consequence of adequate defense. But the self-limiting nature of infection, or lack thereof, cannot apply a sufficient level of control to ensure tissue protection. This is accomplished, in part, through inducible processes that actively limit innate immunity and acute pulmonary inflammation. For example, classic anti-inflammatory cytokines such as IL-10, transforming growth factor (TGF)-β, and IL-1 receptor antagonist (IL-1RA) are sufficient and necessary to reduce innate immune responses and inflammatory lung injury during pneumonia (94, 170, 195, 505, 507). Of course, this comes with the risk of overly blunting immune resistance and exacerbating infection (507), highlighting the complexity of achieving effective but balanced immune responses to invading pathogens.

Just as AMs are central for establishing pulmonary immune resistance, they are also essential for tissue resilience. The activation state of AMs is tightly regulated by their microenvironment (211). In a state of baseline homeostasis, engagement of CD200R, TGF-βR, and IL-10R by their corresponding ligands at the epithelial surface is an important negative regulator of alveolar macrophage activity (211), desensitizing these cells to innocuous environmental particles common to the airspaces. As the alveolar microenvironment is altered (e.g., during infection), AMs become activated and can exhibit M1 (classical) or M2 (alternative) characteristics, with the former more typically bearing the pro-inflammatory features highlighted in the aforementioned section on immune resistance (4). On the other hand, alternatively activated (M2) AMs generate anti-inflammatory factors such as IL-10 and IL-1RA, and the size of this cell population has been shown to expand during the resolution phase of pneumonia, helping to restore tissues to baseline homeostasis (93, 238, 525).

In addition to fine-tuning inflammation through the release of anti-inflammatory cytokines, an essential role of macrophages in the aftermath of an acute inflammatory event is to remove accumulated debris, a large amount of which includes dead or dying leukocytes. This is largely achieved through phagocytosis of apoptotic cells presenting increased levels of phosphatidylserine and other "eat me" signals on their surface, in a complex and tightly regulated

process known as efferocytosis (192, 193). Efferocytosis steers the environment away from an accumulation of necrotic cells, which are inherently pro-inflammatory. Additionally, efferocytosis actively reprograms AMs to release a suite of anti-inflammatory mediators (193), limiting the likelihood of immunopathology. While this includes cytokines like TGF-β (212), it also involves the release of pro-resolving lipid mediators such resolvins, lipoxins, maresins, and protectins (285). These factors elicit resilience responses, including but not limited to inflammatory cytokine regulation, epithelial repair, and efferocytosis itself (28). Pro-resolving lipid mediators limit immunopathology in numerous settings of viral and bacterial pneumonia (28), and recent evidence suggests that inhibition of these pathways may even serve as a virulence determinant for *P. aeruginosa* and perhaps other important causes of pneumonia (140).

Use of in situ imaging has compellingly revealed a population of nonmotile macrophages in the airspaces, which also appear to have a major influence on tissue resilience (534). These "sessile" macrophages remain adherent to the alveolar surface, where upon stimulation they employ gap junctions to propagate immunosuppressive Ca^{2+} waves throughout the epithelium. Disruption of these connexin-43-containing gap junctions is sufficient to amplify cytokine expression and alveolar neutrophilia in response to bacteria or bacterial stimuli (534), suggesting that these interactions apply negative feedback to reduce injury in the setting of acute inflammation. Notably, the identification of sessile macrophages challenges existing paradigms of alveolar macrophage biology, produced by decades of studies focused on macrophages lavaged from the airspaces (38). Only a fraction of alveolar macrophages are recovered by bronchoalveolar lavage, which may be a consequence of differential lavageability among several functionally distinct macrophage subsets. The alveolar macrophages that are connected to epithelial cells via gap junctions and not collected by bronchoalveolar lavage may have specialized roles in lung resilience during pulmonary inflammation.

The alveolar-capillary barrier is maintained and restored by the presence of tight junctions and the expression of epithelial Na^+ channels (e.g., ENaC and Na^+-K^+-ATPase) and other membrane transporters (e.g., CFTR and aquaporin 5) which actively limit the airspace liquid accumulation characteristic of pneumonia (37). These surface proteins are dynamically regulated by host factors such as cAMP agonists, glucocorticoids, thyroid hormone, and TRAIL, and disruption of these pathways can enhance acute lung injury (37, 389).

Structural integrity of the epithelial barrier also relies on cellular viability, which is actively supported during pneumonia by tissue-protective signaling networks. STAT3 activity is a critical determinant of epithelial resilience, enabling this cell population to better withstand the barrage of toxic stimuli accrued at the air-liquid interface in an infected lung. Mouse models employing targeted lung-specific epithelial STAT3 deficiency have consistently demonstrated a requirement for this transcription factor to limit cytotoxicity and acute lung injury in response to a variety of stimuli, including virus (314), bacteria (405), LPS (215), hyperoxia (206), and naphthalene (252). Mechanisms of STAT3-mediated epithelial protection likely involve, at least in part, the induction of gene programs that inhibit apoptosis and drive tissue repair (252, 314). Conversely, gain of STAT3 function in lung epithelium can limit acute lung injury, as shown in the setting of hyperoxia (287), but protective STAT3-dependent signals require precise regulation given the potential for the development of epithelial adenocarcinoma (286). Host-derived signals upstream of epithelial STAT3 activation, therefore, represent an important control point for guiding tissue resilience during pneumonia. Leukemia inhibitory factor (LIF) may represent a particularly prominent player in this regard. LIF is induced in lung epithelial cells in response to infection (144, 405, 496), and it is necessary and sufficient to activate lung epithelial STAT3 (409). Pharmacological blockade of LIF causes significant injury in response to bacterial and viral pneumonias (144, 409). Not only does this phenocopy the consequence of epithelial STAT3 inhibition (405), but it is also notable that LIF neutralization does not impact pathogen burdens (144, 409), suggesting that the benefits of LIF are solely attributable to increased tissue resilience. In addition to STAT3, other contributors to epithelial protection and/or repair in the setting of lung infections include β-catenin (568, 569), FOXM1 (293), and p63 (273). The promising and burgeoning area of stem cell-mediated tissue regeneration, while still nascent, is also likely to reveal important mechanisms of epithelial barrier control as the field develops (247, 266).

In addition to its viability and fluid clearance, the epithelium of the lung has significant resilience roles in producing anti-inflammatory signals. SAM Pointed Domain Containing ETS Transcription Factor (SPDEF) is best recognized for driving mucus metaplasia (68), but a nonpathological role of SPDEF is to limit inflammatory gene expression downstream of MyD88 and TRIF (264). The goblet cell promoting factor transcription factor FOXA3 also diminishes antiviral immune resistance gene programs (67). And some mucus proteins exhibit anti-inflammatory roles in the pneumonic lung (254), as highlighted by protective immunosuppressive effects of MUC1 following *P. aeruginosa* infection in mice (506).

While AMs and lung epithelium represent resident sources of pulmonary resilience, recruited leukocyte populations also have the capability to elicit tissue protective responses. For example, recruited exudate macrophages have been identified as an important source of IL-1RA-dependent pre-

vention of epithelial apoptosis and inflammatory injury in mice with pneumonia caused by LPS or *K. pneumoniae* (195). Macrophages support the growth of alveolar epithelial cells and of lung epithelial "pneumospheres" in vitro (279), and the CCR2-mediated migration of blood monocytes into lung tissue is essential to maximizing lung regeneration after pneumonectomy (279), together suggesting that the repair of lungs injured by infection may be downstream of monocyte recruitment; although not tested in pneumonia yet, an emerging body of evidence consistently suggests that type 2 immune signals drive macrophage-mediated tissue repair after diverse infections and insults, dependent on macrophage receptors including IL-4Rα and myosin 18A (44, 279, 333). Neutrophils, perhaps the most prototypical "proinflammatory" cell type, cause elastase-dependent activation of a cytoprotective β-catenin response as they migrate across the epithelial barrier (568, 569). Myeloid-derived suppressor cells (MDSCs), which bear resemblances to neutrophils, also accumulate in pneumonic lungs, where they limit immunopathology through synthesis of IL-10 and enhanced efferocytosis of apoptotic neutrophils (396). Recruited cells derived from lymphoid progenitors can also limit inflammatory injury in the lungs. Regulatory T cells (Tregs) accumulate in the lungs of patients and mice with lung injury, and these cells are sufficient and necessary to curb inflammatory cytokine induction and to stimulate resolution in mouse models of acute pulmonary inflammation (5, 94). Antiviral effector T cells, including particularly CD8+ but also CD4+ T cells, can be important additional sources of IL-10-mediated tissue protection during respiratory viral infections (477, 478), thereby exhibiting both pro-resistance and pro-resilience characteristics. Recruited ILC2s can limit immunopathology during pneumonia, as evidenced by their accumulation in the airspaces of mice and humans following influenza infection, combined with their release of the tissue protective factor amphiregulin (338). NK cells can also be tissue protective, producing IL-22 to mediate epithelial repair in response to viral or bacterial lung infections (272, 276, 549). Thus resident and recruited cell types enhance intrapulmonary resilience during pneumonia **(FIGURE 8)**.

B. Resilience From Outside the Lungs

Tissue resilience of the lungs, like immune resistance (see above), can originate from extrapulmonary sources. The brain is one example. As discussed above, brain-dependent processes such as fever and reflex control appear to promote immune defense in the lungs (122, 186), but the central nervous system can also function to limit inflammation potentially reducing immunopathology. For instance, neuroendocrine control of immunity, such as that achieved by autonomics and the hypothalamic-pituitary-adrenal (HPA) axis, is well appreciated (372). Crosstalk between the sympathetic and parasympathetic activity has been attributed

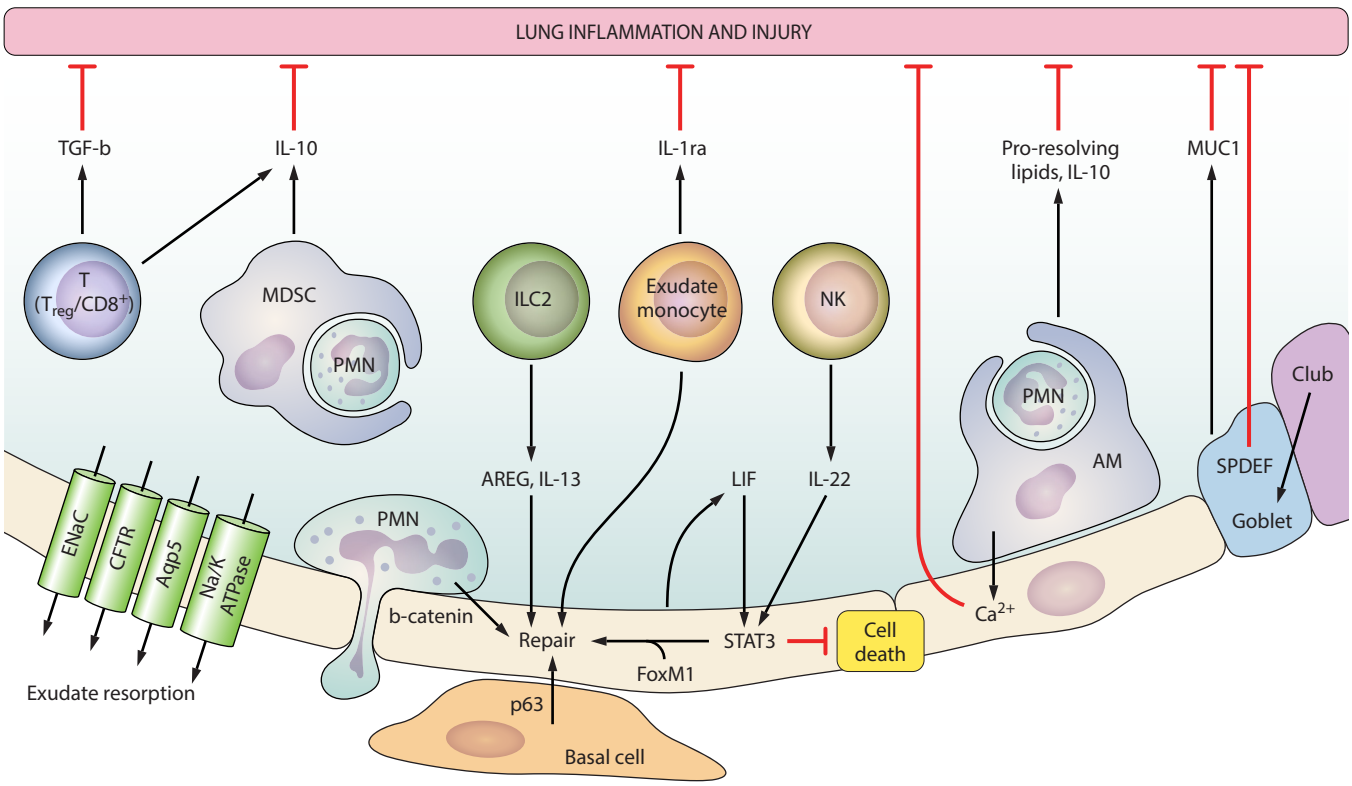

FIGURE 8. Multiple different cell types provide activities to help accomplish tissue resilience and prevent lung injury during pneumonia. Examples shown are not an exhaustive list and pictorialize some of the mechanisms described in text.

to myriad immunological processes, with ACh and catecholamines, particularly norepinephrine, now mechanistically linked to the suppression of cells across the immune system, including but not limited to macrophages, dendritic cells, T cells, and B cells (372). Meanwhile, glucocorticoids derived from the HPA axis are quintessentially anti-inflammatory. The anti-inflammatory effects of glucocorticoids on CXCL5 expression and neutrophilic inflammation in the lungs involve circadian rhythms in airway epithelial cells (156). While the direct impact of endogenously synthesized glucocorticoids such as cortisol on pneumonia is not entirely clear, the HPA axis has long been a target for pharmacological intervention. Many studies have examined the application of corticosteroids for pneumonia patients. While plausible that steroids may pose risk for pneumonia patients (422), results have suggested general trends towards a protective effect, perhaps reducing the risk of ARDS and shortening hospital stays (523). Because it entails risk and only subsets of patients may respond favorably, precision medicine may be needed to apply corticosteroid therapies most effectively for pneumonia. Consistent with this premise, a recent clinical trial showed that severe community-acquired pneumonia patients with the highest levels of inflammation (based on serum CRP) showed significant reductions in treatment failure if they received methylprednisone (494). Investigations in animal models have shed further light on functional connections between neural input and pulmonary immune responses. Vagal denervation reduces acute pulmonary inflammation and mortality in mice with pneumonia induced by *E. coli*, likely owing to decreased engagement of the anti-inflammatory α7 nicotinic acetylcholine receptor (α7 nAChR) on alveolar macrophages and neutrophils (476). This is further supported by enhanced injury in mice lacking α7 nAChR itself under the same conditions (476). In another example of brain-derived lung resilience, adrenalectomy impairs circadian suppression of airway epithelial cells and exaggerates the lung CXCL5 response, seemingly due to disruption of glucocorticoid receptor occupancy (156), which is consistent with the possibility of an endogenous HPA-dependent reduction of inflammatory injury. Similarly, adrenalectomy promotes inflammatory injury following intrapulmonary challenges with LPS or immune complexes, although this could be more attributable to modulation of catecholamine responses rather than glucocorticoids based on blockade studies of the latter (139). A recently identified anti-inflammatory role of pulmonary neuroendocrine cells also suggests neural regulation of lung immunity (49). These innervated lung epithelial cells release excessive neuropeptides and enhance pulmonary inflammation when their organization is disrupted by targeted mutation of the *Robo* receptor (49), suggesting that the organization and function of these innervated cells is essential to curbing inflammatory responses to pulmonary challenges such as infection.

Some of the APPs produced in the liver in response to pulmonary infection serve to counter inflammatory injury. Perhaps the most revealing example of liver-dependent tissue protection in the lungs is the pathological consequence of α1-antitrypsin (AAT) deficiency. Patients with this inherited disorder can present with severe liver and lung injury, the latter of which can result in COPD, bronchiectasis, and increased pneumonia incidence (172). Therapeutic treatment with AAT reduces inflammatory injury in patients and animal models (63, 241), and this protective effect may extend beyond AAT's seminal function of inhibiting neutrophil elastase. Liver-derived APPs contributing to metal homeostasis may also influence pulmonary tissue resilience. For example, in addition to their roles in immune resistance (e.g., bacteriostatic iron sequestration) (235), iron-handling proteins also prevent iron toxicity, oxidative stress, and lung injury (155). Thus it is feasible that APPs including but not limited to antiproteases and those regulating metal homeostasis confer liver-dependent tissue protection in pneumonic lungs. An indirect example of liver-dependent immunoregulation in the lungs relates to MDSC mobilization. Egress of these anti-inflammatory cells from the bone marrow requires gp130-dependent liver activity during sepsis (430), suggesting that the liver may be a requisite intermediate for the lung-protective roles of MDSCs observed in pneumonia (396).

Extrapulmonary organ injury is a common sequela of severe pneumonia, posing concern for sepsis secondary to pulmonary infections (320) and indicating that signals governing extrapulmonary tissue resilience are critical to pneumonia outcome. Liver injury is a prominent feature of sepsis (471). As discussed above, hepatic acute phase changes occur in response to lung infections in mice (403, 404). Pneumonia-induced transcript changes in hepatocytes include hepatoprotective means to limit liver injury, and disturbance of such transcriptome remodeling by interruption of either RelA or STAT3 in hepatocytes can lead to hepatotoxicity (8, 201). The ER stress and antiapoptotic pathways induced by STAT3 and RelA in hepatocytes are examples of inducible tissue resilience outside of the lungs. Increased gut permeability, which is both a cause and consequence of sepsis (256), is also regulated during pneumonia. Results from animal models recapitulate pneumonia-induced intestinal injury and provide evidence for its occurrence being dictated by signals including surfactant proteins A and D (117), PARP (295), EGF (114), Bcl2 (210), and p53 (87). Acute injury to the kidneys and brain is also associated with sepsis, and increased damage to either organ occurs up- and downstream of that of the lung (345, 435, 453). In the heart, pneumococcal pneumonia can lead to bacterial growth and macrophage necroptosis within the mycocardium that leads to acute injury and prolonged scarring (56, 159, 417). The mechanistic basis for most of the crosstalk between these tissues and the lungs is poorly understood, requiring further investigation into biological pathways

that promote or limit damaging interactions. Further insights regarding extrapulmonary tissue resilience will be essential for illuminating physiological determinants preventing disseminated injury and sepsis during pneumonia.

VI. LUNG MICROBIOME AND PNEUMONIA

While the lung was previously considered to be a sterile organ, a microbiome in the lung has become appreciated due to culture-independent techniques for detecting, identifying, and quantifying bacteria (105). The bacteria in the lungs of healthy individuals are likely transients that represent a balanced equilibrium of incoming bacteria (from inhalation, aspiration, etc.) with bacterial elimination (by resident innate immunity including the mucociliary escalator, alveolar macrophages, and biochemical components in lung lining fluids, as described above). While healthy lungs are not likely a niche for stable populations of resident bacteria growing there, they are never sterile and those microbes in the lung have physiological consequences (105).

In healthy individuals, the microbiota in the lung are similar to that of the mouth (29, 513). The bacteria are most abundant in the largest airways and diminish with increasing distance into the respiratory tract, suggesting an oral source for the lung microbiome during health (209). Healthy subjects with greater amounts of this microbiota in their air spaces have evidence of low level subclinical inflammation in their BAL fluid (439), implying that recruited immunity may at times need to supplement resident immunity to control lung microbiota and prevent pneumonia. Consistent with the notion that exposure to respiratory pathogens is not sufficient to cause pneumonia, it is not unusual to find bacterial agents that cause pneumonia in the lung microbiome of healthy individuals (127, 202, 337).

One perspective on pneumonia is to frame it as a shift in the lung microbiome (105). During pneumonia, the lung microbiome becomes dominated by the etiologic agent causing infection (105, 221, 385, 492). Thus the pneumonia microbiome is differentiated by low microbial diversity, high microbial biomass, and local bacterial growth (105). A feature that may differentiate the bacteria that cause pneumonia **(FIGURE 1)** from other bacteria of the normal respiratory tract microbiome is that the causative agents of pneumonia better thrive in a setting of lung inflammation (with differences in nutrients, temperature, biochemical and immune components, etc.). Subsets of organisms within the respiratory microbiome may be better adapted to growth in such environments, and these may be most likely to be causes of pneumonia (209).

In addition to providing agents that cause pneumonia, the microbiome importantly influences pneumonia susceptibility and outcome. Microbes in the respiratory tract microbiome can limit or favor growth of the causative agents of pneumonia (105, 306, 448, 450, 535). Furthermore, the respiratory microbiome shapes the immune system that defends the lungs against pathogens (209, 306). The lung microbiome and lung immunity are both influenced by extrapulmonary microbiomes (58, 81, 106, 190, 209), including that of the gastrointestinal tract as detailed above, highlighting roles of microbiota outside the lungs affecting pneumonia.

Finally, the lung microbiome is altered in chronic pulmonary diseases (105). As discussed below, chronic pulmonary diseases increase the risk of pneumonia, and pneumonia accelerates the course of chronic pulmonary diseases. Changes in the lung microbiome may mediate some of these relationships between chronic pulmonary diseases and pneumonia.

VII. PNEUMONIA SUSCEPTIBILITY

We propose a change in how pneumonia is approached, that the medical community should address pneumonia as a chronic condition of susceptibility rather than merely an acute infection. The argument for such a shift in approach is motivated by the inspiring successes from the cardiovascular community. Deaths from infarction (i.e., heart attacks and strokes) are presently a third of their levels from a half-century ago (353), contrasting sharply with the unchanging mortality rates for pneumonia over this timeframe (20, 147, 290, 336). Both pneumonia and infarction are acute events with disastrous consequences. Infarction is attacked with blood-thinners and anticoagulants that prevent or eliminate clots, analogous to attacking pneumonia using vaccines and antibiotics that prevent or eliminate infections. However, so much more is done to address the underlying chronic disease predisposing to acute infarctions. With so little biological understanding at present, little or nothing can be done to address the underlying chronic disease predisposing to acute pneumonia.

A pivotal event in cardiology was the demonstration that subjects who would later get infarctions already had measurable biological changes: higher blood pressure and serum cholesterol (248). This discovery led to individualized risk factor assessments, behavioral changes (e.g., in diet, exercise, and smoking) designed specifically to alter the relevant risk factors, and the use of drugs such as beta-blockers and statins that target risk factors (rather than acute clots) and thereby lower infarction risk (353). Successful prevention of infarctions results in part from treating the underlying chronic disease process. The approach to pneumonia should move in similar directions. Finding ways to measure and interfere with the chronic processes underlying pneumonia susceptibility should be major goals for the coming years. The ability to approach pneumonia by differentiating those with susceptibility and effectively treating that susceptibility has exceptional promise for diminishing the burden of pneumonia.

So who gets pneumonia? Who are the susceptible? As detailed above, young children and older adults have higher rates of pneumonia then those aged in-between **(FIGURE 9A)**. Multiple clinical and behavioral conditions have been identified as risk factors for pneumonia (discussed further below), and these conditions associate with increased pneumonia risk across the age spectrum **(FIGURE 9A)** (384). However, while those with recognized risk factors have higher rates of pneumonia, this results from an increased degree of susceptibility rather than a switch from resistant to susceptible. People get pneumonia at every age, even without recognized risk factors **(FIGURE 9A)**. About half of children hospitalized with pneumonia have recognizable underlying conditions, especially premature birth or asthma, while the other half do not (228). Similarly, young adults with pneumonia more often do not have recognized risk factors **(FIGURE 9B)**. In contrast, most older adults hospitalized with pneumonia have underlying conditions that are known risk factors for pneumonia **(FIGURE 9B)**, including chronic respiratory, cardiovascular, neurologic, or metabolic diseases (227). A large fraction of aging adults suffer from one or more of these chronic conditions, tilting the demographics of pneumonia towards the aging group, resulting in a disproportionate number of pneumonia cases in the 60-and-over cohort **(FIGURE 9B)**. Despite this, among adults hospitalized for pneumonia in the US, the majority (around two-thirds) are younger than 65 yr of age (227). This is probably because the chronic conditions that increase pneumonia susceptibility begin in middle age, and there are more middle-aged than elderly people (e.g., over twice as many 55 as 75 yr olds in the US, based on 2016 census data). Finally, only a fraction of the population with any of the recognized risk factors will get pneumonia, but there are presently no means of predicting which subjects within these risk groups are most likely to get pneumonia. Underlying conditions or risk factors are pivotal, but not well understood. We summarize here some of the currently recognized connections between underlying factors and pneumonia susceptibility. However, this is an area that needs more research. Deeper epidemiologic and especially physiological insights are needed before we can recognize, prevent, or reverse pneumonia susceptibility.

A. Age

Although pneumonia can occur across a lifespan, the very young and old are at highest risk. Both the old and young have impaired immune responses to pulmonary pathogens, as well as increased risk of pathogens breaching impaired anatomic barriers to the lower respiratory tract, such as aspiration of oral or gastric contents. The combination of

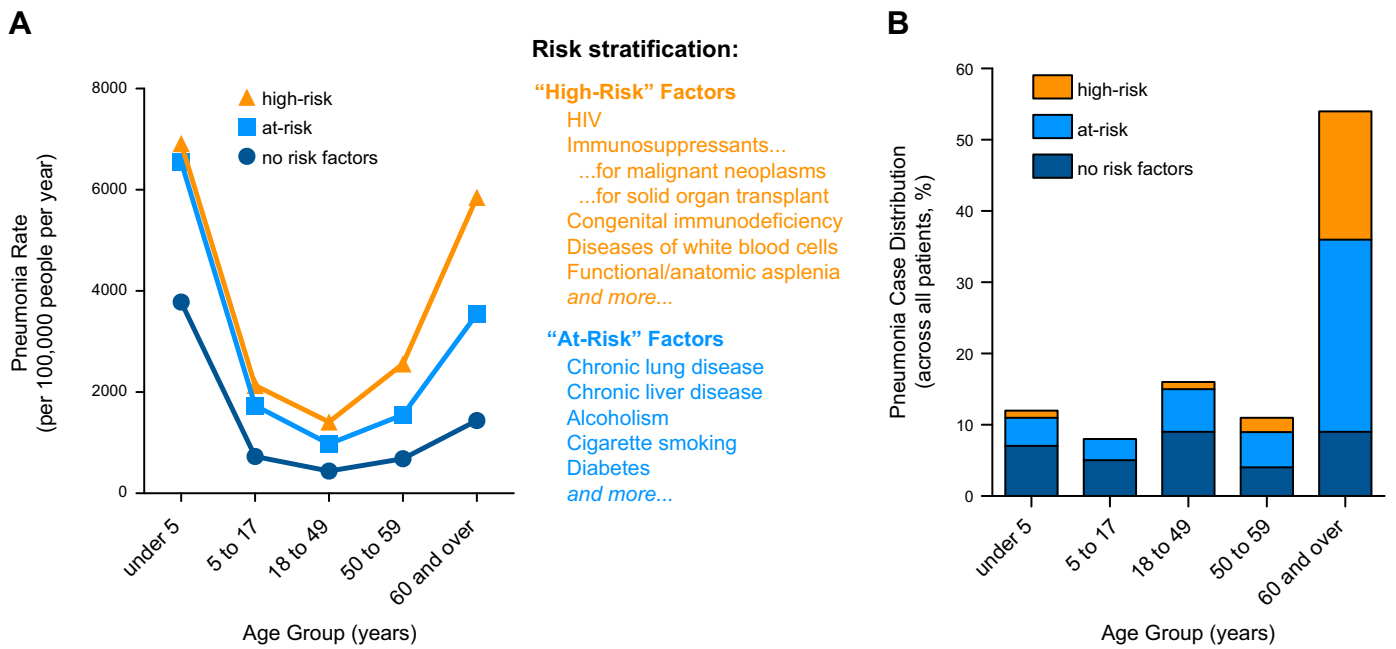

FIGURE 9. Known risk factors for pneumonia are relevant and important, but insufficient to differentiate the susceptible from the resistant. Figure panels were generated from data reported by Pelton et al. (384), representing analyses of 3.4 million individuals in Germany from 2008 to 2012. *A*: pneumonia rates for individuals stratified by age group and risk factors. For all age groups, the recognized risk factors associate with elevated rates of pneumonia. Rather than susceptible versus resistant, these risk factors associate with an increased pneumonia susceptibility up to severalfold. Even those without recognized risk factors get pneumonia. For all risk groups, pneumonia rates are highest at either end of the age spectrum. *B*: the distribution of all pneumonia cases among age groups and risk groups. The majority of pneumonias occur in older individuals, most of whom have recognized risk factors. For younger subjects, including children and adults through age 49, more pneumonias are in subjects without recognized risk factors than in those with recognized risk.

poorer immune clearance and increased alveolar pathogen burden potently increases age-associated risks for developing pneumonia.

Young children have scant prior history with pathogens, leaving them less protected by adaptive immune memory and more dependent on innate immune responses (as detailed above). Their lack of heterotypic immunologic memory against the etiologic agents of pneumonia is likely a predominant predisposing factor for childhood pneumonia. In addition, many specific immune alterations have been noted in the very young, including altered phagocyte function and cytokine production by their AMs (219, 274, 275), a preponderance of T_{reg} cells in their lungs (487), different patterns of cytokine release by their blood leukocytes (261), and altered recruitment and activity of their ILCs during respiratory infection (432). While both are involved, it is unclear whether getting older or gaining experience with microbes (34) is most responsible for "maturing" these and other immune parameters in young children.

Whereas the very young have immature and inexperienced immune systems that predispose to development of pneumonia, excessive activity and chronic inflammation may paradoxically impair immune responses and contribute to pneumonia risks in the aged (45). There is evidence of smoldering inflammation in the aging lung as well. In one study of bronchoalveolar lavage fluid, healthy volunteers older than 65 yr old had increased neutrophil, immunoglobulin, and IL-6 concentrations when compared with younger volunteers (329). The chronic inflammatory milieu of aging induces multiple changes that contribute to increased pneumonia risk. Chronic inflammation increases pathogen adhesion to host cells (92), induces tolerance of TLRs (107), impairs monocyte pathogen clearance (399), and blunts pulmonary innate immune responses to *S. pneumoniae* (203). In short, the cells of the lung and their inter-communication that is necessary for coordinated immune responses become dysregulated with advancing age (50). In addition, multiple changes in the adaptive immune system associate with aging and reflect a growing state of immunosenescence with diminished efficacy of responses to diverse microbial challenges (166, 322, 557), which may further contribute to the increased susceptibility to pneumonia among the elderly. Modification of compromised immunity resulting from the chronic inflammation and/or immunosenescence of aging may represent targets of future pneumonia risk reduction, once better defined.

B. Comorbidities

At any age, a wide spectrum of comorbidities associates with increasing risk of pneumonia **(FIGURE 9)**. While pneumonia rates are two- to threefold higher in those with comorbidities compared with those without, it is also evident that only a small fraction of those that are young or old and have high risk conditions will get pneumonia in a given year, on the order of 3,000 per 100,000 or 3% per year **(FIGURE 9*A*)**.

Multiple environmental and behavioral exposures act together to increase pneumonia susceptibility. Tobacco smoke represents the most important modifiable risk factor for pneumonia (368), with nearly one in three pneumonia cases attributable to tobacco smoking (14). Both active and passive tobacco smoke exposures increase nasopharyngeal pathogen (e.g., *S. pneumoniae*) carriage (281, 366) and alter acute respiratory tract immune responses. Short-term exposure to tobacco smoke disrupts airway mucociliary clearance, alters interferon response to viral pathogens, and attenuates alveolar macrophage, natural killer cell, and dendritic cell responses to pathogens (464). Chronic exposures to cigarette smoke substantially derail antibacterial adaptive immunity, diminishing bacteria-specific antibodies (both IgA and IgG in the BAL fluid and IgG in the blood) and skewing bacterial antigen-induced T-cell responses (whether from lung or spleen) towards IL-17 and away from IFN-γ and IL-4 (300). Such changes worsen host defense while exaggerating inflammation. Mechanisms by which cigarette smoke alters immune cells are multifaceted, involving many diverse particulate materials, toxic chemicals (acrolein, acetone, benzopyrenes, methylcholanthrene, etc.), catalytic agents, noxious gases, and more in cigarette smoke (464). Many of the >4,000 components of cigarette smoke are individually capable of dysregulating immunophysiology, and the habit of cigarette smoking ensures prolonged exposures to large doses of these in combination. High levels of secondhand smoke or of air pollution also associate with increased risk for and severity of pneumonia (7, 364, 538). These exposures contain similar particulate matter and toxic compounds like acrolein, so pneumonia susceptibility due to secondhand smoke and air pollution may be from overlapping mechanisms with tobacco smoking.

Long-term tobacco and poor air quality exposure leads to chronic lung diseases that further exacerbate pneumonia risks. COPD is the most common clinically observed pathological response to long-term exposure to noxious inhaled particles. COPD is characterized by development of fixed airway obstruction, emphysematous remodeling of the alveolar air spaces, and mucus metaplasia with impaired mucociliary clearance in the conducting airways. The AMs of COPD patients adapt to increased oxidative stress by increasing expression of the anti-apoptotic protein Mcl-1, which diminishes antibacterial efficacy of these cells and may be a biological factor contributing to pneumonia susceptibility in these patients (36). Responses of COPD lungs to pathogens are further influenced by alterations in the airway microbiome (305) as well as COPD treatments such

as inhaled and systemic immunosuppressive corticosteroid therapies (138, 251). This leads to a three- to fourfold increased risk for pneumonia in COPD patients (444, 493). Smoking cessation reduces the elevated pneumonia risk for COPD patients, but it is not sufficient to eliminate it, and COPD patients maintain an excessive pneumonia susceptibility despite smoking cessation (12). Importantly, patients with COPD who get pneumonia experience acute decrements of lung function that worsen COPD severity and chronic inflammation, both of which increase risk for future pneumonia and perpetuate a cycle of COPD decline (444).

Asthma, defined by reversible airways obstruction, is associated with a 1.5- to 2-fold increased risk for pneumonia, substantially lower than COPD (216). Reasons for lower rates of pneumonia associated with asthma as compared with COPD likely include the younger age, less tobacco smoke exposure, and different anatomical pathologies observed in patients with asthma as compared with COPD. Factors predisposing asthma patients to pneumonia include airways with excessive mucus and immune profiles skewing towards anti-helminthic defense and allergic responses rather than protection against bacteria and viruses (132, 207).

In addition to the increased risk of pneumonia accompanying chronic lung diseases, comorbid conditions involving other organ systems also increase pneumonia risk. Despite the substantial differences in each condition, diabetes mellitus, chronic liver disease, kidney disease, and heart failure all show strong increases (e.g., 1.5- to 4-fold) in pneumonia risks (216, 493). The hyperglycemia of diabetes impairs neutrophil chemotaxis (100) and superoxide-mediated antimicrobial effects (383), although clinical trials of strict control of hyperglycemia fail to demonstrate reductions in pneumonia (6, 486b), implying additional mechanisms contributing to susceptibility. Impaired neutrophil function during liver disease (40) is in part related to tuftsin deficiency (499). Tuftsin modulates activities of phagocytic cells, but requires activation in the spleen; splenic congestion from cirrhotic liver disease is hypothesized to impair tuftsin activation. Uremia during chronic kidney disease impairs neutrophil intracellular killing through unclear mechanisms; however, dialysis partially restores neutrophil function (17). Mechanisms of increased pneumonia risk associated with heart failure have not been experimentally elucidated, although some hypothesize that chronic pulmonary edema may generally impair neutrophil and monocyte chemotaxis and function. Importantly, chronic diseases cluster together (e.g., diabetes is a risk factor for liver and kidney disease as well as heart failure). With the exception of targeted vaccination against influenza and pneumococcus, methods to reduce pneumonia risks among patients with chronic disease are unclear and warrant further study. Understanding the pathophysiological interactions between multiple chronic diseases that lead to pneumonia may identify novel opportunities to interrupt etiological pathways.

Drug and alcohol abuse, dementia, and stroke are also associated with increased risks of pneumonia (168). Increased pneumonia risks associated with these conditions that result in altered mental status occur through immunosuppression, altered host microbiome, and disruption of physical barriers that allow larger burdens of pathogens entry into the lower respiratory tract. Alterations in upper airway reflexes and depressed mental status increase dysphagia risk and the number of pathogens aspirated into lung in patients with either acute or chronic conditions that impair mental status. The risks for pneumonia in conditions disrupting basic anatomical airway protection are further exacerbated by alterations in nasopharyngeal pathogen carriage and local immune suppression, including impairments in alveolar macrophage function with alcohol and drug abuse (57, 288, 325, 326, 424). For example, chronic alcohol ingestion results in oxidative mitochondrial stress leading to dysfunctional alveolar macrophage phagocytosis and increased risks of ARDS during pneumonia; both opiates and opiate withdrawal syndromes have protean immunosuppressive actions involving innate and adaptive immunity (424). Effects of alcohol consumption on redox imbalance and oxidative stress in alveolar macrophages have been attributed, in part, to diminished glutathione availability (57, 95, 288, 560). The inverse relationship between alcohol consumption and glutathione levels has been observed in patients and animal models, and more recent studies have indicated that glutathione supplementation can be used to circumvent alcohol-related macrophage dysfunction (326, 344, 560). Acute neurological insults such as stroke act through vagal α7 nAChR-mediated anti-inflammatory pathways to increase pneumonia risks. Increased vagal tone after stroke activates α7 nAChRs on macrophages and alveolar epithelium to impair the innate immune response and promote pneumonia (126). Compounding risks for patients with substance abuse or dementia, neurological conditions, and impaired physical barrier defenses are comorbid nutritional deficiencies (including vitamin D, zinc, and protein-calorie malnutrition) that exacerbate innate immune dysfunction (27, 183, 296, 411, 420). The aging populace, heralding more strokes and dementia, plus the growing prevalence of opiate abuse suggest increasing burdens of pneumonia over coming years, putting added pressure on elucidating mechanisms by which these major risk factors predispose to pneumonia.

For young children, additional major factors associated with increased risk of pneumonia are factors common in areas of lower socioeconomic status, including malnutrition, vitamin deficiencies, incomplete vaccination, crowded living conditions, indoor air pollution/parental smoking, prematurity or low birth weight, lack of breastfeeding, and HIV infection (142, 225, 277, 365, 514, 542). Breastfeed-

ing is considered one of the most cost-effective interventions to reduce childhood pneumonia, by supplying humoral and cellular adaptive immune components to the neonate with a naive and immature immune system. In addition to being immunocompromised from HIV, childhood comorbid conditions such as gastroesophageal reflux, asthma, and congenital heart diseases also increase pneumonia risk, although diverse mechanisms including increased penetration of pathogens to the lower respiratory tract, recurrent subclinical lung injury, airways disease, pulmonary edema, and chronic inflammation.

C. Acute Illness and Pneumonia

Healthcare-associated pneumonia represents an important and potentially preventable burden to the healthcare system (573). Pneumonia is the most common healthcare-associated infection in the US (303), and ventilator-associated pneumonias alone contributed approximately $3 billion in US healthcare costs in 2009 (573). Healthcare-associated pneumonias represent a "perfect storm" of pneumonia risk factors. Patients in the healthcare setting often have multiple comorbid conditions that increase pneumonia risks, disruptions to airway barriers from sedative medications and/or endotracheal tubes, sepsis-induced (41) and drug-induced immunosuppression, increased exposures to opportunistic and antibiotic-resistant bacteria, and an altered microbiome from recent antibiotic exposure. It is thus not surprising that hospitalized patients are at high risk for recurrent pneumonias: ~20% of patients hospitalized with pneumonia and 5% of patients hospitalized with sepsis, heart failure, or myocardial infarction are rehospitalized within 30 days with pneumonia (102, 397). Typical of pneumonias occurring during other acute illnesses, ventilator-associated pneumonias represent a pathophysiology driven by simultaneous disruptions to upper airway barrier protection, to lower airway clearance mechanisms, and to immunological responses. Despite efforts such as routine chlorhexidine-based oropharyngeal care and measures to prevent gastroesophageal reflux among patients requiring mechanical ventilation, ~1 in 10 patients requiring mechanical ventilation for more than 2 days develop ventilator-associated pneumonia (328). Endotracheal tubes and sedatives remove epiglottic airway protection and facilitate entry of oropharyngeal flora into the distal lung. Furthermore, preexisting lung injury from prior illness and damage due to mechanical ventilation, combined with the high prevalence of multidrug-resistant pathogens in the nosocomial setting, favors infection with pathogenic bacteria differing from the common causes of community acquired pneumonia, including *Staphylococcus aureus*, Enterobacteriaceae (especially *Klebsiella* and *E. coli*), *Pseudomonas*, and *Acinetobacter* (79). Immune suppression due to critical illness, such as impaired leukocyte glycolysis (511), expansion of myeloid-derived suppressor cells (504), and blunted type I interferon signaling (512) may contribute to the inability to mount an effective response to the increased bacterial load faced by the ventilated lung.

Acute viral upper respiratory infections may lead to superinfection with bacterial pathogens in the absence of mechanical ventilation and impaired upper airway protection. Bacterial infections (most commonly *S. pneumoniae*) complicated nearly all deaths resulting from the 1918 H1N1 influenza pandemic (321, 342) and 25–50% of severe influenza deaths during the 2009 H1N1 pandemic (158). Many mechanisms for bacterial superinfection after viral infection are shared with ventilator- and hospital-acquired pneumonia during critical illness, including epithelial damage increasing susceptibility to bacterial invasion, macrophage depletion and dysfunction, type I interferon dysregulation, and attenuated T_H17 responses necessary for bacterial clearance.

The numerous and complex mechanisms by which acute viral infections transiently suppress innate and adaptive immune responses against bacteria in the lung have been excellently summarized by others (101, 242, 249, 321, 428). Most current knowledge relates to interactions between influenza infections and pneumonias caused by pneumococcus or *S. aureus*, but information may be greatest for these interactions because they have been examined more extensively because of special relationships among these organisms. Many immunological mechanisms for how influenza viruses predispose to secondary infections (101, 242, 249, 321, 428), such as epithelial damage, ineffective macrophages, exuberant interferons, and T_H17 cell dysfunction, should also apply to viral infections other than influenza. Supporting such pan-viral generalization, mimicking viral signaling by administering noninfectious polyI:C (as a surrogate for viral double-stranded RNA) is sufficient to render mice susceptible to pneumonia caused by pneumococcus or *S. aureus*, dependent on signaling from type I IFNs (489) as was previously demonstrated for influenza virus-induced susceptibility (446). Viruses other than influenza, such as RSV and rhinovirus, predispose to secondary bacterial infections in animal studies and associate with secondary bacterial infections in patient studies (101). More than one-tenth of all hospitalized adult pneumonia patients in whom virus could be detected also have evidence of bacterial co-infection, and the fraction of pneumonias in which a copathogen is identified appears roughly similar across all the different viruses (227). Similarly, a plethora of bacterial agents beyond pneumococcus and *S. aureus* are identified in studies of secondary bacterial pneumonias, including *H. influenzae*, *S. pyogenes*, and more (101, 242, 249, 321). Thus, although many virus-specific and bacteria-specific contributions to bacterial superinfections after acute viral infection have been elucidated (249, 321), we suspect that most lower respiratory tract viral infections increase

risk for most bacterial pneumonias, through immune pathways triggered by diverse viruses that compromise immune defenses against diverse bacteria.

In summary, aging, tobacco, alcohol or drug abuse, poor air quality, nutritional deficiencies, pulmonary disease, nonpulmonary comorbid conditions, and acute illnesses or exposures interact to increase pneumonia susceptibility. Conditions predisposing to pneumonia enhance susceptibility by increasing upper respiratory colonization, decreasing locally protective barrier mechanisms, and altering local and systemic innate and adaptive immune responses. Importantly, conditions that predispose to pneumonia tend to cluster within individuals and communities, further magnifying pneumonia risks. Because an incident of pneumonia can exacerbate the underlying comorbidity predisposing to pneumonia, this becomes a vicious cycle **(FIGURE 10)**. Increased efforts to interrupt pneumonia susceptibility in those with comorbidities will help break these feed-forward cycles of comorbidity and pneumonia. However, better biological understanding is needed first. At present, we have no biologic metrics that can distinguish those with elevated pneumonia susceptibility from their more resistant peers. Our understanding of the physiological underpinnings of pneumonia susceptibility are too rudimentary and incomplete to guide useful countermeasures that will preserve or restore defects in resistance and resilience that develop due to comorbidities or exposures. In this instance, the epidemiology is leading the way, and biological understanding needs to catch up.

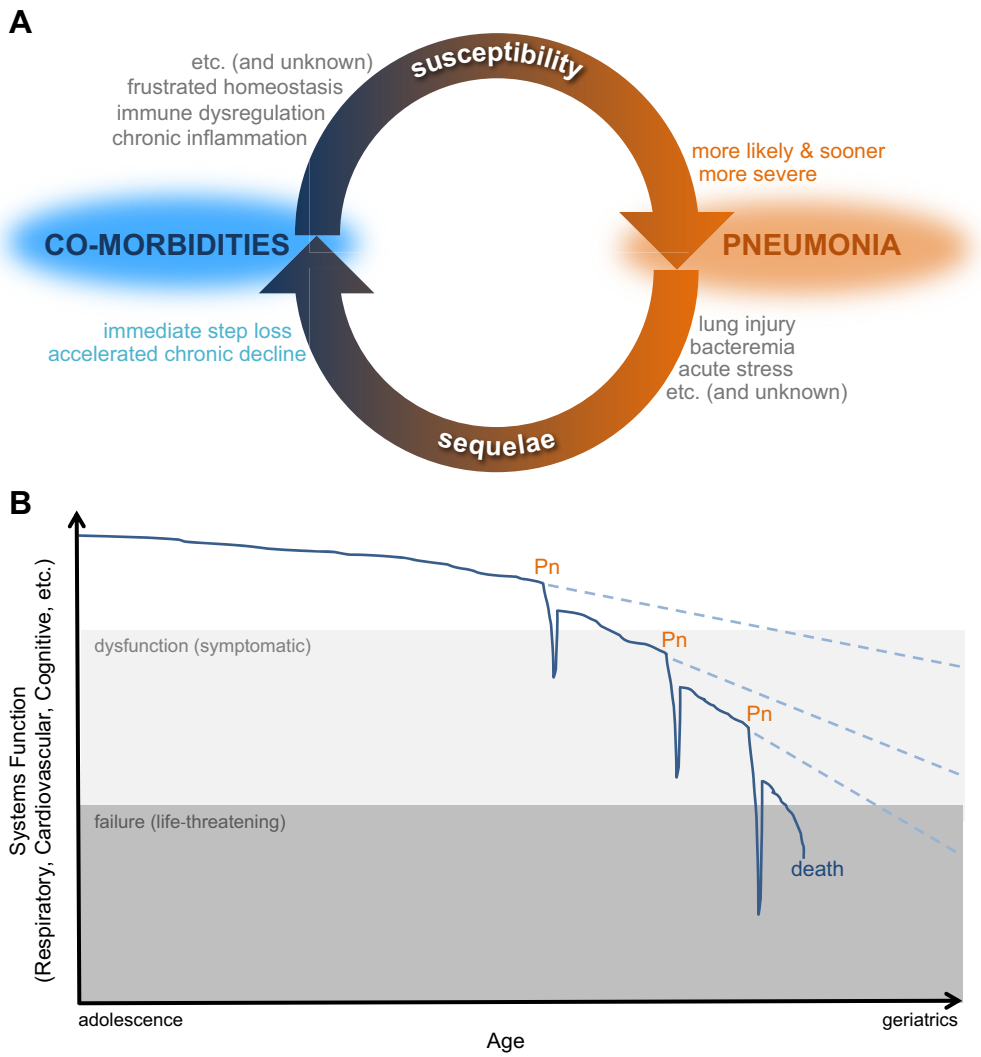

FIGURE 10. The vicious cycle by which pneumonia drives unhealthy aging. Pneumonia susceptibility is raised by a wide variety of chronic diseases that are recognized as general risk factors for pneumonia (comorbidities). Pneumonia elicits a predisposition to and worsening of those same comorbidities. Thus comorbidities make people more likely to get pneumonia, and pneumonia precipitates and exacerbates comorbidities, which makes individuals yet more likely to get pneumonia, which yet further accelerates comorbidities, and so on. *A*: the self-amplifying cycle of interactions between pneumonia and comorbidities. *B*: the decline in physiological function driven by this self-amplifying cycle, schematically rendered to communicate the concept (not actual data).

VIII. PNEUMONIA SEQUELAE

The prior section highlights that pneumonia cannot simply be considered as an acute event, but that conditions preceding infection must be considered as responsible for enabling the pneumonia occurrence. Similarly, the outcomes of pneumonia also should be considered in physiological and temporal context. Death from pneumonia is one potential result, perhaps the most emphasized of the possible outcomes. In addition, pneumonia has other long-term consequences for survivors, which degrade health and hasten mortality after the acute event is over.

An unfortunate aspect of the strong relationship between aging, pneumonia, and death is the prominent notion of pneumonia as the "old man's friend." This metaphor is off-base and counterproductive, encouraging some to conclude that pneumonia is inevitable and merciful for the elderly. To our knowledge, this metaphor first appeared in the fifth edition of William Osler's textbook *The Principles and Practice of Medicine*, used to imply that pneumonia can provide a quick and painless end for some elderly patients suffering from other slow terminal conditions (370). However, pneumonia is not universally quick, or painless, or in terminal patients. Ironically, Dr. Osler enjoyed good health until he developed pneumonia at age 70, leading to months of distress, decline, and recurrent illness before he eventually succumbed to this disease (3).

Pneumonia is not typically lethal, but rather it is usually survived. The likelihood of survival decreases with age, but even those over 90 yr of age have a 75% survival rate (3). Those elderly pneumonia cases (the vast majority) that end in survival cannot possibly be framed as merciful in any way. They are costly, distressing, and major contributors to morbidity for the aged. It is difficult to precisely quantify the toll pneumonia exacts beyond its (important) impact on mortality, but it is undeniably large. Pneumonia requires hospitalization in 10–20% of cases (with more than 5 days of stay typical), necessitates ICU admission in >20% of hospitalizations, incurs 30-day readmission rates of ~20% after hospitalization, and costs tens of billions of dollars per year in the US (136, 189, 227, 228, 352, 565). For Medicare alone (hence only a subset of the population), pneumonia costs 13 billion dollars in healthcare per year (565). In addition to its immediately attributable burden, pneumonia increases the risk for and worsens the progression of many of the other chronic diseases that also commonly afflict older individuals. For example, as expanded upon below, after matching for initial disease severity and controlling for confounders, survivors of pneumonia consistently experience worse degrees of cognitive decline and dementia, functional disability and limitations, heart attacks, strokes, depression, and risk of death over the ensuing years (39, 88, 196, 376, 431, 445). Implicating causal relationships, vaccination against respiratory pathogens decreases cardiovascular and cerebrovascular disease morbidity and mortality (503, 515). Thus, far from a merciful agent of relief as often and erroneously conceptualized, pneumonia is a major problem for the aged and forms a catastrophic positive feedback loop with other chronic diseases **(FIGURE 10)**, preventing healthy aging and worsening overall decline.

A. Short-Term Consequences of Pneumonia

Severe pneumonia results in direct lung injury from the infectious pathogen, impairing alveolar gas exchange and causing respiratory failure **(FIGURE 11)**. Pneumonia is the leading cause of ARDS, when it causes a bilateral injury that includes the diffuse influx of protein-rich edema and inflammatory cells into the alveolar space, destruction of surfactant, formation of fibrin-rich intra-alveolar hyaline membranes, and loss of gas-exchanging type 1 pneumocytes (315). Treatment of ARDS currently consists of supportive therapy and use of measures to decrease further lung injury caused by mechanical ventilation practices. Patients with ARDS have mortality rates of 30–40%.

Severe pneumonia may also result in injury to organs distant from the lung **(FIGURE 11)**. Prior sections communicated that lung resistance and resilience depended on extrapulmonary tissues, and it is also clear that extrapulmonary tissues can be involved in the acute and severe manifestations of pneumonia. The occurrence of life-threatening organ injury from an infection such as pneumonia is defining for sepsis (454). Extrapulmonary organ damage resulting from pneumonia may have diverse manifestations including encephalopathy, coagulopathy, kidney and liver failure, as well as cardiovascular complications (e.g., shock or arrhythmias). With the exception of antibiotics, intravenous fluid therapy, and organ-supportive treatments (e.g., renal dialysis and mechanical ventilation), no sepsis-specific treatments have been shown to improve patient outcomes. Despite the absence of sepsis-specific therapies, improvements in the processes of critical care delivery have resulted in nearly a 50% reduction in short-term case-fatality rates from sepsis over the past two decades (469), revealing that improvements in healthcare delivery can have substantial impact for this disease. However, this outcome of pneumonia is as grim as ARDS, and severe sepsis patients currently have mortality rates of 33% (469).

Considered in isolation as an acute event, pneumonia is a major cause of morbidity and mortality, often due to ARDS and/or sepsis. But pneumonia is much more than this acute event.

B. Long-Term Consequences of Pneumonia in Adulthood

In the century-plus since Osler depicted pneumonia as friendly to the aged and deemed it "Captain of the Men of

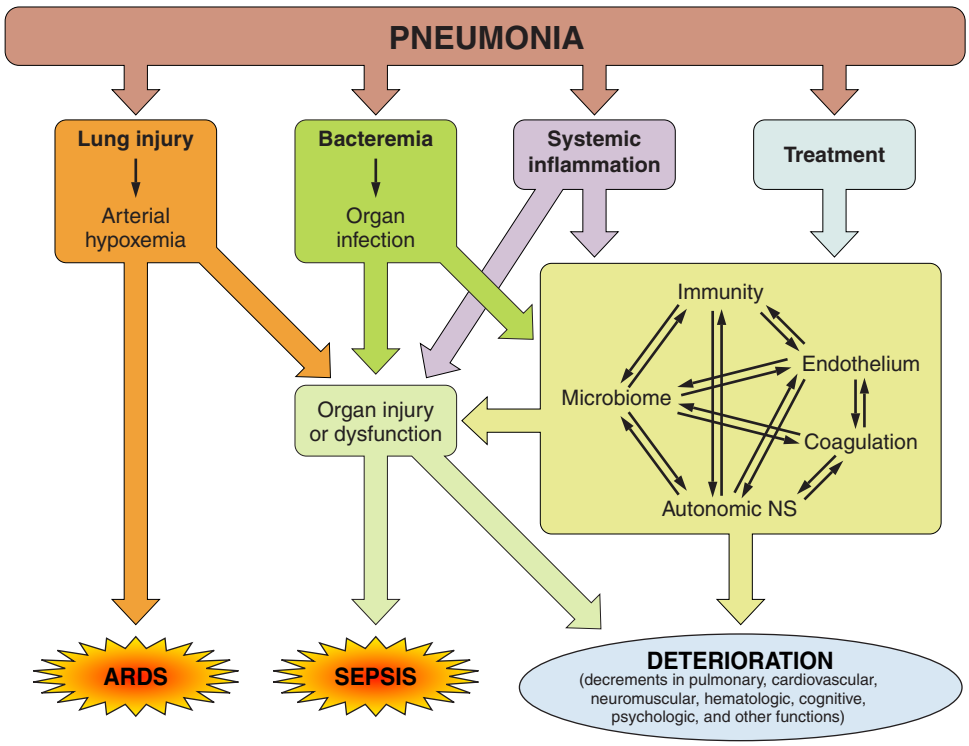

FIGURE 11. Pneumonia sequelae. Pneumonia causes direct injury to the lungs, from a combination of microbial and inflammatory signals. When the degree of injury crosses a physiological threshold defined by blood gases, this is diagnosed as acute respiratory distress syndrome (ARDS). When infection and inflammation disseminate from the lungs and injure other organs, this is diagnosed as sepsis if severe enough to be life-threatening. ARDS and sepsis are well-recognized outcomes of pneumonia. Perhaps less well-recognized are the indirect consequences, including the predisposition to or exacerbation of ongoing chronic diseases such as COPD, atherosclerosis, cognitive decline, and more. The mechanisms driving the sequelae of pneumonia are multifactorial, including systemic inflammation and infection plus localized and diffuse aberrations involving the immune, cardiovascular, microbiome, hematologic, and nervous systems.

Death" (370), pneumonia case-fatality rates in advantaged communities such as the US have dramatically declined (407). ARDS and sepsis have high mortality rates, but they occur in only a fraction of pneumonia cases, and fewer than 10% of all elderly patients hospitalized for pneumonia die from this disease (290). The public health impact of pneumonia in the 21st century is perhaps most driven by its contribution to progressive health decline from long-term complications that often involve extrapulmonary organs (222, 223). Unlike in Dr. Osler's day, most pneumonia patients today suffer, survive, and deteriorate **(FIGURE 11)**.

Among older adults, survivors of an acute pneumonia hospitalization have higher mortality risks that persist for years following discharge compared with matched patients hospitalized for reasons other than pneumonia (48, 128). Increased mortality risks following pneumonia appear to be less dependent on age or acute severity of pneumonia, but strongly influenced by the nature of the preexisting comorbid conditions (48, 88, 128, 343). However, even after adjusting for comorbid conditions as well as age, patients with pneumonia appear to have worse long-term mortality rates when compared with similar patients who have not suffered pneumonia (398, 561, 563).

Long-term effects of pneumonia are manifest in extrapulmonary organs. Pneumonia accelerates or precipitates declines in cognition (445) and functional status (224), as well as raising risks for cardiovascular complications such as stroke, myocardial infarction, and heart failure (88) and for recurrent infections (397, 398). For example, after accounting for multiple comorbid conditions and prior trajectories of cognitive and functional status, pneumonia (and not other reasons for hospitalization) associates with a 57% increase in risk of developing dementia (445). The risk of myocardial infarction, stroke, or heart failure increases fourfold in patients with pneumonia within 30 days, and remains twofold elevated 1 yr later (88). Risks of cardiovascular events associated with pneumonia exceed what can be accounted for by other cardiovascular risk factors such as diabetes or smoking (88, 89). Finally, nearly one in five pneumonia hospitalizations results in rehospitalization within 30 days, and most of these readmissions are for infection (102). Thus hospital discharge after pneumonia should not imply a full recovery.

The mechanisms through which pneumonia affects long-term risk for cognitive, functional, cardiovascular, and infectious disease are poorly understood. Current hypotheses implicate residual inflammation in the many complications that occur following pneumonia. For example, IL-6 levels measured in the blood at the time of pneumonia hospitalization discharge are associated with increased risk of later death from cardiovascular disease and infection (561). Circulating levels of inflammatory cytokines and acute-phase reactants such as IL-6 and CRP also associate with subsequent cognitive decline (551, 552). Poor cognitive and functional outcomes following pneumonia may additionally result from hypoxia and hypoperfusion during acute illness (445) and from ancillary treatments common to severe pneumonia (e.g., benzodiazepine sedatives and bed rest) that appear to increase inflammation, acute delirium, and long-term cognitive risks (376, 378, 393, 532). Increased risks of recurrent and new infections may be due in part to

postinfectious immune paralysis (18, 41). Risks of stroke, myocardial infarction, and heart failure may be increased due to prolonged coagulopathy (562), endothelial injury with accelerated atherosclerosis (250), large volume shifts (116), cardiac injury (218, 245, 426), and arrhythmias (521, 522) that result from pneumonia **(FIGURE 10)**. At least for some types of pneumonia (e.g., pneumococcus), cardiac complications may result from direct infection of cardiac tissue with macrophage necroptosis followed by scarring (56, 159). Use of physical rehabilitation (110, 358, 359, 500), avoidance of benzodiazepines (146, 268), targeted immune modulation (494), and use of cardiovascular risk reduction medications such as statins and aspirin (520) are active areas of investigation seeking to attenuate myriad long-term risks following pneumonia (271). Further studies are required to determine the mechanistic links between pneumonia and these longer term extrapulmonary consequences, as well as the extent to which these complications after pneumonia are modifiable.

C. Long-Term Consequences of Pediatric Pneumonia

Pneumonia affects 50% of children each year in the most economically disadvantaged regions (77) and is the most common reason for childhood hospitalization in regions such as the US that have a more privileged socioeconomic status (566). Studies of childhood pneumonia further refute the notion that pneumonia is an acute illness with limited ramifications for survivors. Rather, children experience high rates of subsequent pulmonary comorbidity following pneumonia, with 10% of children suffering complications following resolution of pneumonia (123). Unlike multisystem disease of adults, the best recognized long-term complications of childhood pneumonias are localized to the affected organ, the lungs. The most common complications following childhood pneumonia are development of restrictive lung disease, asthma, bronchiectasis, and chronic bronchitis (123, 298). Acute effects of pneumonia in children also result in altered lung development that increases the predilection for pneumonia later in life (236, 237). Biological links between early life acute infections and persistent chronic respiratory diseases are not yet well established, to our knowledge.

D. Positive Feedback Loop of Pneumonia and Progressively Declining Health

As shown by the overlap between pneumonia risk factors and pneumonia consequences, iterative positive feedback loops are prominent features of this disease **(FIGURE 10)**. Poor health begets pneumonia, and pneumonia diminishes health. COPD predisposes patients to lung infection, and lung infections accelerate the decline of COPD (444, 493). Cardiovascular diseases raise pneumonia risk, and pneumonia events hasten cardiovascular deterioration (89, 493, 509). Neurological and psychological diseases make pneumonia more likely, and pneumonia compounds the severity of neurological and psychological diseases (39, 376, 445). Such iterative positive feedback loops apply to most of the comorbidities associated with pneumonia. In short, pneumonia is both a symptom of and a cause of unhealthy aging.

IX. CONCLUSIONS AND FUTURE DIRECTIONS

Exposures to the ubiquitous microbes that cause pneumonia are routine and unavoidable. Whether and which subjects get pneumonia upon exposure is dictated by mammalian biology. When the integrated responses of the pulmonary, immune, cardiovascular, neurological, and other systems are appropriate to eliminating microbes while preserving physiological function, respiratory infection is subclinical or mild. Too often, though, this is not the case. We need to develop a better understanding of how the body normally successfully defends itself against respiratory pathogens so that we can recognize and counter decrements in these protective pathways. Comorbidities and exposures render individuals more susceptible to pneumonia, but the biology of this susceptibility is not yet well delineated. The physiology underlying the long-term and extrapulmonary sequelae of pneumonia that accelerate chronic disease and unhealthy aging is only speculative still.

We need new ways to approach pneumonia, to diminish the burden of this disease that has stayed too high for too long. Continued research into fighting microbes will be helpful, hopefully resulting in more and better antibiotics and vaccines, but these directions cannot be enough. The responsible microbes are too numerous, too ubiquitous, and too diverse. We need to reconceptualize pneumonia. Improved understanding of the physiology of the acute infection will lead to new approaches for limiting lung injury and the dissemination of infection, inflammation, and injury beyond the lung. This will reduce ARDS and sepsis. Improved understanding of the biological mechanisms connecting acute pneumonia events to their long-term sequelae will beget new approaches to interrupting the vicious cycle that drives unhealthy aging. This will help people live longer, better. Before people get pneumonia, changes in their physiology are responsible for rendering them susceptible, and these changes are a biological process that is not yet identified but needs to be defined. Pneumonia susceptibility must be considered as a chronic condition so that we can develop medical approaches to combat this chronic condition before pneumonia occurs. Improved understanding of the mechanisms underlying pneumonia susceptibility will direct such development. Just as lowering blood pressure and cholesterol levels help prevent acute infarctions, understanding which biological changes render individuals most susceptible to pneumonia will provide opportunities for in-

terventions that target those biological pathways and reverse or slow the progression of pneumonia susceptibility. Greater physiological insight is needed to more effectively prevent and treat pneumonia.

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