MINI-REVIEW
Neutrophil Infiltration and Function in the Pathogenesis of Inflammatory Airspace Disease
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Introduction: Lungs and the Immune Response
The lungs are the largest epithelial surface of the body in constant contact with nonsterile air. With this constant exposure to outside allergens, pollutants, pathogens, and irritants, the immune response in the lungs must be carefully regulated. The lung is an innate immune organ, with marginated pools of innate immune cells present even at physiological homeostasis. Some researchers have suggested that, because of this unique conditions, the lungs serve as a functional immune niche. As a result, there are major differences in the regulation, function, and mechanisms of the immune response in the lung microvasculature compared to those in the systemic vasculature. Identifying unique functions and recruitment of neutrophils in the lungs is important for the development of therapies, as well as for deepening the understanding of inflammation in the lungs.

Relevance of Neutrophils in Airspace Diseases
In the lungs, there are two main types of inflammatory disease: interstitial disease and airspace disease. In interstitial disease, inflammation takes place in, and expands, the interstitium of the lungs. Leukocytes cross the endothelial barrier of the blood vessel and crowd into the interstitium (eg, acute respiratory distress syndrome and idiopathic pulmonary fibrosis). In airspace disease, leukocytes such as neutrophils move in large numbers into the alveolar space, requiring cells to cross the endothelium, the basement membrane, and the alveolar epithelium (eg, bronchopneumonia and gastric aspiration pneumonia). This review focuses on airspace diseases in which the role of neutrophils is prominent and well understood. Neutrophils are strongly implicated in the pathophysiology of inflammatory lung diseases: Neutrophilia in the blood is a commonly used clinical indication of disease in hospitalized patients, with the number of neutrophils used as an indicator of prognosis and severity. The current understanding of the contributions of neutrophils to inflammatory disease of the lungs is complex and incomplete. Neutrophils were previously thought to be a relatively simple subset of granulocytic cells, extremely short-lived and universally destructive. However, there is a growing understanding that neutrophils are longer-lived and their recruitment and function more nuanced than previously thought, underlined in the lungs.

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Inflammatory Cascade in the Lungs

Inflammation and the immune response are necessary for response to injury. While inflammation is essential for clearing pathogens and promoting healing, it also contributes to injury. The lungs must exact tight immune regulation to maintain physiological homeostasis despite exposure to many outside antigens, including allergens and pathogens. Neutrophils traffic from sites of synthesis to sites of inflammation through the vasculature via a process known as the inflammatory cascade. The inflammatory cascade in systemic circulation is well characterized and reviewed elsewhere. Briefly, leukocytes tether and roll via selectin interactions,8–10 are activated by chemokines,11 adhere by leukocyte integrin adhesion to intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 in endothelial cells,9,11 and diapedese using homophilic platelet endothelial cell adhesion molecule 1 and CD99 interactions.12–14 Classically, this process occurs in postcapillary venules.15,16 The inflammatory cascade has been shown to differ between the lungs and the systemic circulation, in both the molecules that control these interactions and the places where they occur.16,17 While leukocytes typically migrate through the endothelial cells of the post-capillary venules, in the lungs, they migrate through the true capillaries, some of which are as narrow as, or narrower than, the migrating neutrophils themselves.15,18,19 This naturally tight apposition may be the reason that leukocyte recruitment in the pulmonary circulation is selectin independent.20 In a model of lipopolysaccharide (LPS)-mediated inflammation, leukocyte recruitment was β2 integrin dependent, while in a model of Streptococcus pneumoniae, recruitment was integrin independent.21–23 Although the mechanism(s) behind this stimulus-induced β2 integrin specificity is not known, its relevance to disease is underlined by the pathology of leukocyte adhesion deficiency type I, in which neutrophils are recruited to the lungs but not to other tissues.24

Neutrophils in the Lungs during Homeostasis

In the lungs, there exists an unusual pool of nonactivated neutrophils known as margained cells. This pool is maintained as circulating blood neutrophils stagnant in the capillaries of the lungs, where they then form this reservoir of lung-margained neutrophils.25,26 Marginated neutrophils were previously thought to accumulate passively due to the width of the capillaries being narrower than the width of the neutrophil, the length of time required for neutrophils to take a more oval shape in response, and the dynamics of blood flow.27 However, the findings from recently published work suggest that interactions between the marginated neutrophils of the lungs and the endothelium are actively regulated. It has been reported that neutrophil margination was reduced with the dampening of selectins.28–30; L-selectin-deficient mice had no defect in margination under inflammatory conditions, but maintaining neutrophil sequestration in the pulmonary vasculature under homeostatic conditions was shown to require both L-selectins and CD18. The CXCL12/CXC receptor (CXCR)-4 axis has been shown to be required for margination in the lungs.31 With treatment with a CXCR4 antagonist, neutrophils were released from their margination in the lungs, which is the only known reservoir of neutrophils other than their point of synthesis, the bone marrow. Marginated neutrophils in the lungs are understudied; it is not fully clear how their function differs from that of recruited neutrophils once activated.28 Lung-margained neutrophils are first responders to Escherichia coli infection, and the constant contact that the lungs maintain with the outside world suggests a benefit with regard to a quick response to invading pathogens. Yipp et al31 found that marginated neutrophils can crawl along the endothelium using CD11b during homeostasis, then crawl farther immediately after exposure to bacteria or LPS, suggesting that marginated cells could be better or quicker in responding to insults. Additionally, marginated neutrophils of the lungs interact with B cells, undergoing B-cell–induced neutrophil apoptosis via CD18 expression on neutrophils, leading Granton et al32 to suggest that the lung is its own immunologic niche. With the depletion of B cells, the presence of aged, profibrotic neutrophils was increased. The findings from these studies point to the unusual nature of neutrophils in the pulmonary vasculature as a point of interest with regard to neutrophil subpopulations and disease mechanics. The potential for interactions suggests that the inflammatory environment in the lungs is more complexly regulated than in other organs. The mechanisms and role of neutrophil margination in the lungs are unknown. There is a potential role for neutrophils in maintaining the homeostatic niche in the lungs, but more research is needed to characterize this function.

Disease-Fighting Functions

Many diseases of the lungs are diagnosed on the basis of the presence of neutrophils, and the level of neutrophilia can be commensurate with the severity of disease. However, the simplest endorsement of the importance of the cell population in responding to lung infection is that neutrophil depletion worsens infection and subsequent disease outcomes in numerous bacteria-induced pneumonias, suggesting that neutrophils are protective in patients with infectious diseases. The mediators produced by neutrophils often serve a disease-fighting purpose in at least one type of acute lung injury (Table 1).33–46 Neutrophil elastase (NE), a potent mediator of lysis in E. coli, is particularly important in the response to other Gram-negative bacteria in many organ systems and disease manifestations, including in the lungs.32 However, this serine protease also plays a vital role in the clearance of...
Table 1 Known Neutrophil-Produced Regulators and their Effects in Experimental Disease Models

<table>
<thead>
<tr>
<th>Regulator</th>
<th>Positive/negative regulation of disease</th>
<th>Disease model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil elastase</td>
<td>Positive</td>
<td>Gram-negative bacterial induced injury</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td><em>Streptococcus pneumoniae</em>-induced pneumonia</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Respiratory syncytial virus</td>
<td>34</td>
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<tr>
<td></td>
<td>Negative</td>
<td>Ventilation-induced lung injury</td>
<td>35</td>
</tr>
<tr>
<td>Cathepsin G</td>
<td>Positive</td>
<td><em>S. pneumoniae</em>-induced pneumonia</td>
<td>39</td>
</tr>
<tr>
<td>Proteinase 3</td>
<td>Positive</td>
<td><em>S. pneumoniae</em>-induced pneumonia</td>
<td>39</td>
</tr>
<tr>
<td>Matrix metalloproteinase 8</td>
<td>Positive</td>
<td>Acute lung injury</td>
<td>36</td>
</tr>
<tr>
<td>NETs</td>
<td>Positive</td>
<td><em>Klebsiella pneumoniae</em>-induced pneumonia</td>
<td>37</td>
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<tr>
<td></td>
<td>Positive</td>
<td>Community-acquired pneumonia</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td><em>Pseudomonas aeruginosa</em>-induced pneumonia</td>
<td>39</td>
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<tr>
<td></td>
<td>Negative</td>
<td>House dust mite-related inflammation</td>
<td>40</td>
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<tr>
<td>ROS</td>
<td>Negative</td>
<td>Polymicrobial-induced pneumonia</td>
<td>41</td>
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<tr>
<td></td>
<td>Positive</td>
<td>LPS-induced lung injury</td>
<td>42</td>
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<tr>
<td>LXA4</td>
<td>Positive</td>
<td>Acute airway inflammation</td>
<td>43</td>
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<tr>
<td></td>
<td>Positive</td>
<td><em>Escherichia coli</em>-induced pneumonia</td>
<td>44</td>
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<tr>
<td>RvD1</td>
<td>Positive</td>
<td>Acute airway inflammation</td>
<td>43</td>
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<tr>
<td></td>
<td>Positive</td>
<td>Ventilator-induced lung injury</td>
<td>45</td>
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<tr>
<td></td>
<td>Positive</td>
<td><em>P. aeruginosa</em>-induced pneumonia</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td><em>E. coli</em>-induced pneumonia</td>
<td>44</td>
</tr>
</tbody>
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LPS, lipopolysaccharide; LXA4, lipoxin A4; NET, neutrophil extracellular traps; ROS, reactive oxygen species; RvD1, resolvin D1.

Gram-positive bacteria, such as *S. pneumoniae*, from the lungs. Using an opsonophagocytic assay, Standish and Weiser found that granular products, and elastase in particular, were powerful killers of pneumococci. Neutrophil-produced cathepsin G and proteinase 3 are not necessary, but are sufficient, for killing *S. pneumoniae*. Another neutrophil granule component, matrix metalloproteinase-8 (MMP-8), is known to reduce inflammation by proteolysis of the proinflammatory chemokine C-C motif chemokine ligand (CCL)-3 (alias MIP-1α). In a murine model of acute lung injury, Quintero et al. found that MMP-8-deficient mice had greater lung injury and mortality than did wild-type mice because in the MMP-8-deficient mice, CCL3 could not be cleaved. Neutrophil granules function as potent responders to infection, and fight external inflammatory stimuli in the pulmonary disease milieu, and can be introduced only when airspace neutrophils are recruited to be present.

Some neutrophils undergo a process known as NETosis, in which they release chromatin mixed with granules and proteins, including serine proteases such as NE. Neutrophil extracellular traps (NETs) can be used as physical traps for bacteria as a potent antimicrobial force in disease. In a model of polymicrobial sepsis (induced not in the lungs, but in the cecum), mice with depleted NETs had greater colony-forming units of bacteria in the lungs along with greater infiltration of neutrophils responding to the insult. Neutrophil products can also work in synergy during disease. In a murine model of *Klebsiella pneumoniae* infection of the lungs, by Papayannopoulos et al., mice with NE knockdown were unable to produce NETs, leading them to become highly susceptible to infection. Neutrophils are also important responders to fungal respiratory infection, to which patients with compromised innate immune systems are highly susceptible. In a murine model of *Aspergillus fumigatus* infection, mortality was much greater in mice with neutrophil depletion than in those without it. To this end, lung infection induced by aerosol *Aspergillus* is studied specifically in neutropenic mice, because mice with intact neutrophil production are typically resistant to infection.

Neutrophils are important in responding to, and clearing, opsonized pathogens via phagocytosis. In a rat model of LPS-induced acute lung injury, neutrophils taken from the lungs displayed decreased uptake of opsonized yeast, suggesting that the decreased clearance of bacteria during lung inflammation could be due to impaired neutrophil response to opsonized microbes. Another method of killing foreign invaders by neutrophils is complement-mediated killing, in which pathogens are labeled with complement fragments to which immune cells can respond and then phagocytose. Neutrophils capably phagocytose *E. coli* coated with C3b complement proteins. Mice with two-hit transfusion-related acute lung injury (LPS and major histocompatibility complex I antibodies) treated with inhibitors of the complement protein C1 showed improved lung injury scores but persistent and increased inflammation and cytokine expression.

Neutrophils are known to be important in responding to viral infection as well, as general neutrophil depletion in mice infected with influenza led to severe disease and high mortality because the virus was able to replicate uninhibited in the lungs. The reduction in neutrophil response induced by viruses can also leave the lungs more susceptible to infection. In a murine model of influenza A with
postinfective aspergillosis, neutrophil recruitment to the lung was decreased, with no changes in blood neutrophil levels, as a result of viral targeting of innate immune cells in the lung tissue. With this lack of neutrophil response, disease burden and susceptibility to postinfluenza fungal infection were increased, a growing concern in patients with pulmonary diseases. Neutrophils also assist in the adaptive immune response to influenza infection. It has been reported that neutrophil-produced CXCL12 is vital in recruiting CD8\(^+\) T cells that then localize and fight viral infection. The body of work on necessary or helpful neutrophil components in the lungs during disease is vast and clear: Neutrophil components perform essential disease-fighting functions. The products produced by neutrophils are important in combatting disease. Yet, the function of neutrophils in diseased lung is far more complex.

**Disease-Exacerbating Functions**

The number of neutrophils in the lung has been reported to be correlated with the severity of acute airspace disease, and in severe cases, neutrophils and the general host immune response can become the primary cause of morbidity and/or mortality through nonresolving inflammation. Neutrophilia, an elevated concentration of neutrophils in the blood, has been reported to be highly correlated with poorer outcomes in several airspace diseases. The mere presence of these cells in the alveolar space contributes to pathology. In patients with neutrophil crowding and inflammatory edema, the oxygenation of blood moving through the pulmonary vasculature is decreased. In some patients, this passive negative regulation of respiration makes neutrophils a key contributor to symptoms of later-stage severe pneumonia. When present in tissue, neutrophils also have various active functions that combat disease but that can result in tissue damage. Some examples of mediators of neutrophil-caused tissue damage include the contents of neutrophil granules, NETosis, and the release of reactive oxygen species (Table 1).

NE is essential in recruiting neutrophils to sites of inflammation by activating proinflammatory signaling (eg, epithelial cell CXCL8-induced signaling of myeloid differentiation primary response 88 protein, IL-1 receptor–associated kinase, and tumor necrosis factor receptor–associated factor 6) but can induce further damage. The presence of NE can damage the formation of the essential mucus of the airway epithelial cells, and triggers further white blood cell recruitment and degranulation. In a model of airway epithelium, studied by Deng et al, the addition of neutrophils to cultures infected with respiratory syncytial virus was associated with high epithelial damage. In epithelial cells plated with neutrophils, ciliary activity and the expression of tight junction proteins such as zona occludens 1 were decreased; this phenomenon was associated with the presence of NE. In cystic fibrosis, the chronic recruitment of neutrophils and subsequent uninhibited production of NE have been associated with structural lung damage. NE has also been reported to contribute to ventilation-induced lung injury. Bai et al found that production of IL17A prompted neutrophil release of S100A8/A9 and resulted in increased apoptosis of alveolar basal epithelial cells during Mycoplasma pneumoniae–induced pneumonia.

The release of NETs can attenuate disease but also contributes to lung injury during pathogenesis. In a study in patients with severe community-acquired pneumonia, NETosis pathways were highly up-regulated and correlated with poorer outcomes. In a murine model of *Pseudomonas aeruginosa*–induced pneumonia, NETs were associated with acute lung injury and inflammation. This effect might have been attenuated by blocking C-type lectin domain family 5 member A induction of caspase-1–dependent NET formation and led to a better survival rate and reduced collagen deposition. Zhao et al explained mechanistically that NETs activate the proinflammatory cGAS-STING (cyclic GMP-AMP synthase–stimulator of interferon genes) pathway, and that lung injury can be reversed by inhibiting this pathway and subsequently reducing NET production. Neutrophils are also known to produce highly reactive oxygen species. In a mouse model of polytrauma instigated pneumonia, Leonard et al showed that neutrophils were primed to produce reactive oxygen species which increased the severity of lung injury. The use of various reactive oxygen species scavengers has been reported to be effective in reducing lung injury.

Neutrophils can exacerbate damage during viral infections, including influenza. In a murine model of influenza infection, pulmonary ATP levels were increased, and neutrophils entered the lungs and activated the production of reactive oxygen species, inducing pulmonary tissue damage. This damage may also be found in age-related illness. Although it has long been assumed that age-related immunodeficiency was due to inefficient or insufficient immune cell response, Kulkarni et al reported that aged mice with influenza infection had greater recruitment of neutrophils to the lungs, and that survival was improved with the depletion of these neutrophils after infection. Contrary to the findings from historical publications outlining the necessity of neutrophils in the response to pathogenic infection, in a recent study in influenza-infected mice, mortality and lung inflammation were reduced with the complete depletion of neutrophils. Taken together, the findings from these studies support the concept that neutrophils contribute to inflammatory disease in the lungs; however, questions remain as to whether the scales are balanced by resolving functions (Figure 1).

**Inflammation-Resolving Functions**

The findings from numerous studies in pneumonia have suggest that a reduced number of responding neutrophils in...
the lungs improves disease outcomes. However, NE is required for the clearance of certain types of bacteria in the lungs, and neutropenia caused by advanced age reduces the capacity to respond to and clear lung infections.\textsuperscript{71,72} Whether it is the mere presence of neutrophils or the dysregulation of neutrophil components that leads to negative regulation of lung diseases is unknown. In the past few decades, researchers have discovered that neutrophils are also involved in the production and function of mediators that assist in resolving damaging inflammation. This lends support to the hypothesis that it is dysregulation of neutrophil function, rather than the cell type itself, that contributes to inflammatory disease.

Neutrophils can produce a number of specialized pro-resolving mediators (SPMs), including lipoxin (LX)-A4 and resolvin (Rv)-D1. In a murine model of acute airway inflammation, neutrophil apoptosis and phagocytosis were regulated, and the resolution of inflammation was accelerated, with LX4A and RvD1.\textsuperscript{73} In a murine model of ventilator-induced lung injury, oxygenation and histologic scoring for injury were improved with i.p. administration of RvD1.\textsuperscript{74} In a model of \textit{P. aeruginosa}-induced pneumonia, bacterial growth, neutrophil response, and lung tissue damage were attenuated by RvD1 through enhanced phagocytosis by neutrophils, while in a model of lung inflammation induced by \textit{E. coli}, bacterial clearance by neutrophils was restored by SPMs, LXA4, and RvD1.\textsuperscript{75,76} Flitter et al.\textsuperscript{77} found that \textit{P. aeruginosa} secreted an epoxide hydrolase that impairs the production of LXA4, leading to increased neutrophil activation and inflammation. El Kebir et al.\textsuperscript{78} showed that neutrophils treated with RvE1 phagocytosed \textit{E. coli} and yeast at an accelerated rate. When mice with a pulmonary \textit{E. coli} infection were treated with RvE1, they showed improved resolution of pulmonary injury and better outcomes. Neutrophils also produce antimicrobial peptides, including defensins and cathelicidins. Defensins are unique in that they are involved in both the infection-fighting and inflammation-resolving functions of the innate immune response to infection. They have been shown to promote the clearance of influenza A virus from the airway, as alpha-defensins derived from human neutrophils neutralized and aggregated the virus during infection of A549 respiratory epithelial cells.\textsuperscript{79} In this same model of infection, the uptake of influenza A virus by neutrophils was increased with human defensin production by neutrophils, without increased respiratory burst response, suggesting that their functions are both disease-fighting and inflammation-resolving, with the capacity to temper neutrophil damage.\textsuperscript{80} Human cathelicidin LL-37 has been shown to bind LPS and inhibit innate immune-induced inflammation with great importance due to the role of LPS in promoting sepsis.\textsuperscript{81} Human neutrophil production of cathelicidin LL-37 has been reported to reduce proinflammatory cytokine release by macrophages when stimulated with LPS.\textsuperscript{82} The production of antimicrobial peptides is an area of increasing interest, as it seems to promote the vital balance of disease-fighting and inflammation-resolving functions in early pathogenesis.

Neutrophils are indirectly involved in the function of SPMs produced by other cells in the lung environment. Maresins (MaRs), another family of SPMs, are typically
produced by macrophages during phagocytosis of apoptotic neutrophils.\textsuperscript{79–81} In a murine model of airway inflammation induced by organic dust hypersensitivity (ie, farmer’s lung), the infiltration of neutrophils and subsequent inflammation were reduced with MaR1.\textsuperscript{82} Another SPM, protectin D1 (PD1), is produced by Th2 cells, and when injected i.p. reduced production of NETs and reduced inflammatory damage in lung tissue during LPS-induced lung injury.\textsuperscript{83} This regulation is complex and understudied, but it appears that neutrophils could be negatively regulated by their own production of SPMs and the production by other cells during the resolution of lung inflammation.

The beneficial or harmful effect of neutrophils in many of the murine models described here might have resulted from differences in the mouse strains, the dose of pathogen used, and/or the timing of the intervention and analysis.

**Therapeutic Interventions**

Because of their relationship with disease outcomes, neutrophils have been proposed as a target for therapeutic intervention in patients with inflammatory lung diseases.\textsuperscript{84} Therapeutic manipulation could involve altering their recruitment, the production of inflammatory mediators and/or resolving mediators, or functions. One neutrophil-targeting drug proposed for the treatment of patients with airway inflammation utilized a nanoparticle-delivered neutrophil degranulation inhibitor, Nexinhib20, that reduced neutrophil presence and cytokine production, attenuating inflammation in the airway.\textsuperscript{85} There is recent interest in the repurposing of statins as a neutrophil-targeting therapy for lung diseases. In a series of studies of the immunosencence of neutrophil function in a murine model of infectious lung disease, neutrophil migration that had been impaired by aging during early and mild infectious disease, but not in severe sepsis, was improved with the use of simvastatin. This finding suggests that the function of the neutrophils themselves could be changed. In a clinical trial in healthy elderly patients, it improved the accuracy of migration of neutrophils, suggesting that neutrophils could be used as a form of early intervention for age-induced susceptibility to lung diseases.\textsuperscript{86} In elderly patients with mild to moderate community-acquired pneumonia, NET production and NETosis were reduced, and chemotaxis and hospitalization-free survival were increased, with simvastatin treatment.\textsuperscript{87} Neutrophils pose a difficult target for drug therapies because, as noted in this review, they have both beneficial and harmful effects in airspace diseases. Because they are crucial cells of the innate immune system, they are also necessary for combating any other immunologic threats that may arise outside the lung. The heterogeneity of the inflammatory cascade in the pulmonary vasculature, however, provides the potential for precision targeting of lung neutrophils to attenuate these concerns. The process of inflammation and its contribution to sickness can be heterogeneous between individuals and disease states. The increasing understanding that neutrophils have subpopulations could be beneficial in guiding treatments. Because the causes and pathogenesis of lung diseases, including pneumonia, are extremely varied, more work is needed with careful regulation of dosing, targeting, and measurement of outcomes to understand potential therapeutic interventions in neutrophil function in inflammatory lung diseases.

**Conclusion**

The past two decades of research have revealed that neutrophils are more complex than previously thought. This complexity is underlined in the lungs, where neutrophils are unique in their presence, recruitment, migration, and function. There are major knowledge gaps in the differences between recruited and margined neutrophils in the lungs, functional dysregulation of neutrophils in inflammatory insult, and the role of neutrophils in the resolution of inflammation. The pathogenesis of inflammatory airspace diseases in the lungs poses a unique opportunity for further study of these unknowns.

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**Disclosure Statement**

None declared.

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