# Can Eosinophils Prevent Lung Injury? Ask PHIL

Pneumonia, triggered by bacteria, viruses, or other pathogens, continues to be a worldwide public health concern with significant morbidity and mortality. It is a leading risk factor for the development of acute respiratory distress syndrome (ARDS), characterized by diffuse alveolar damage, extensive immune cell infiltration, dangerous hypoxemia, and the potential for multisystem organ failure. Many pathogen-derived toxins cause direct tissue damage, but activated immune cells further harm host tissue in the necessary process of pathogen killing.

It is likely that minimizing lung damage while achieving pathogen eradication reflects a balance between proinflammatory and antiinflammatory immune effector responses. Intriguingly, eosinopenia is a risk factor for ARDS mortality, whereas patients with asthma or allergies are more likely to survive. This raises a question of whether type 2 immunity, particularly eosinophilic inflammation, is protective against acute lung injury.

In this issue of the *Journal*, Krishack and colleagues (pp. 569–578) addressed this question by treating mice with the type 2 cytokine IL-33 before infection with *Staphylococcus aureus* (1). Three-day pretreatment with IL-33 decreased pulmonary edema, capillary leak, lung neutrophilia, and hypoxemia in response to *S. aureus*, with marked protection from otherwise rapid mortality. Strikingly, protection occurred without observable effects on infection because the *S. aureus* burden was not significantly reduced by IL-33 pretreatment.

Although it is important to consider that these findings may be pathogen specific, reproducibility is supported by other studies showing that preactivation of type 2 immunity can protect against *Klebsiella pneumoniae* (2), *Streptococcus pneumoniae* (3), and parainfluenza (4). Notably, whereas previous studies induced type 2 immunity through the ovalbumin model and are not without counter evidence (5), Krishack and colleagues isolated the ability of a single cytokine, IL-33, to induce protection.

IL-33 is often considered a type 2 cytokine because of its major role in asthma susceptibility. Both IL-33 and the IL-33 receptor, ST2, have been identified as susceptibility loci in genome-wide studies of asthma (6). However, IL-33 is also implicated in nonallergic diseases (6). IL-33 has a more pleiotropic role than ovalbumin in activating broad innate and adaptive responses. It would be intriguing to compare the protection seen with IL-33 pretreatment with classic type 2 cytokines such as IL-4 and IL-13.

IL-33 treatment alone can induce mild eosinophilia (7), and in the present study, IL-33 has an eosinophil-promoting effect. Intriguingly, IL-33 pretreatment alone caused mice to have an eosinophilic response to a nonspecific stimulus (intratracheal saline) used as a vehicle control for comparisons with mice infected with *S. aureus*. Thus, effects of IL-33 appear to be related to skewing of a generalized inflammatory response characterized by cellular profiles that are not pure innate, type 1, or type 2. Future work in this area could reveal the nature of genetic and environmental factors that orchestrate the inflammatory response observed here.

The authors do not exclude the possibility that IL-33 acts on multiple immune populations. They provide compelling evidence that IL-33–mediated tissue protection relies on eosinophils; IL-33–mediated protection was lost in IL-5–knockout and eosinophil-depleted mice. Described and named in the 1870s, a decade earlier than macrophages, eosinophils remain one of the more mysterious immune cells. They are generally considered damaging to the lung, but recent studies have found beneficial roles for eosinophils in tissue repair, tumor killing, and protection from parasite infection (8). The present findings continue to challenge our conception of eosinophils as mainly injurious, instead connecting them to potent protection from lethal bacterial lung injury.

How eosinophils are involved in protection remains unclear. It would be interesting to know whether IL-5 alone was sufficient to protect against lung injury or required additional IL-33. The former would support a dominant role for eosinophils in protection, whereas the latter would imply that other immune cells, perhaps type 2 innate lymphoid cells or macrophages, were equally critical. Type 2 innate lymphoid cells and macrophages both express ST2, and IL-33 has been shown to promote their prorepair (or profibrotic) functions (9).

The authors posit that eosinophils may decrease lung damage through interactions with neutrophils, sequestration of pathogens, or maintenance of the alveolar barrier. This uncertainty highlights how important questions about eosinophil development and function remain unanswered. In mice, eosinophils and neutrophils arise from shared granulocyte–macrophage precursors in the bone marrow, but little is known about their cross-talk. Neutrophil deficiency has not been reported to affect eosinophil numbers (10), but eosinophil deficiency (through knockout or through the conditional eosinophil mouse strain iPHIL system used by Krishack and colleagues) consistently results in elevated neutrophils (11–14), suggesting that there is a relationship, perhaps through competition for development or perhaps through regulatory factors secreted by mature eosinophils.

It is relevant to highlight the differences between human and mouse eosinophils, including the fact that human eosinophils are believed to split from neutrophils earlier in their development, separate from a neutrophil–macrophage precursor. Thus, competition between eosinophil and neutrophil development may occur in mice but not humans. Furthermore, mouse eosinophils are less prone to degranulation (15) and may be less damaging to



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lung tissue than their human counterparts. These are important questions that have not been addressed by the field.

Together with previously published data, the paper by Krishack and colleagues will advance our understanding of ARDS by increasing our knowledge about the role of type 2 immunity and eosinophils in lung damage. In the context of lethal *S. aureus* infection, the authors demonstrate that ablating eosinophils worsens lung damage and that pretreatment with IL-33 provides robust protection. This motivates further studies to isolate which actions of IL-33 and eosinophils mediate protection and to understand the kinetics of that protection. For future translation, it will be important to assess whether IL-33 is protective after lung injury has been initiated. Eosinophils and type 2 inflammation are often overlooked in the context of ARDS, but these findings show that type 2 inflammation has a critical role to play in modulating tissue damage. Future research on the connection between type 2 inflammation and ARDS may reveal a novel therapeutic angle to treat this often-fatal syndrome. ■

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