

Is IL-1 β a Target for Reducing Hospitalization of Infants Infected with Respiratory Syncytial Virus?

Each year, respiratory syncytial virus (RSV) causes acute respiratory tract infections in an estimated 64 million infants and is responsible for 160,000 deaths globally (1). Children younger than 1 year are at the greatest risk for complications and hospitalizations (2). However, RSV also causes severe illness in immunocompromised elderly patients or those who have preexisting conditions (3).

IL-33, a member of the IL-1 cytokine family, is a key mediator of chronic airway disease driven by type 2 immune pathways (4) with relevance for chronic lung disease, such as asthma (5), chronic obstructive pulmonary disease (COPD) (6), and respiratory viral infections (4). Human data have suggested that elevated respiratory IL-33 levels are responsible for RSV-induced immunopathogenesis and that the effects of IL-33 during neonatal RSV infection are mediated by the innate lymphoid cells (ILC2) and adaptive T-helper 2 (Th2) cells (7). Although some studies suggest that IL-1 β negatively regulates the expression of IL-33 (8), others indicate that IL-1 β enhances the expression of pulmonary IL-33 to exacerbate asthma and COPD (9). Therefore, the effects of IL-1 β on IL-33 remain unclear.

Recent studies using a mouse model have improved our understanding of RSV-induced immunological and pathophysiological phenotypes typically seen in human infants with severe RSV infection (10). In this issue of the *Journal*, Vu and colleagues (pp. 312–322) used this mouse model of RSV infection to provide new insight into the effects of IL-1 β on IL-33-expressing cells during early life (11). They found that IL-1 β boosted IL-33 mRNA and protein levels and increased IL-33-producing cells in the lungs and confirmed their previous reported finding that IL-33 responses to RSV were more robust in neonates than adults (12). Their previous study also showed a significant positive correlation between IL-33 and IL-1 β levels in nasal aspirates of RSV-infected infants (13).

The authors now report that elevated levels of IL-1 β enhanced the IL-33-induced effect on pulmonary ILC2 when neonates were treated with IL-1 β at 1 day after RSV infection. However, contrary to the Tc2 response they observed in IL-1 β -treated mice, the frequencies of Th1 (IL-4 $_{\text{neg}}$ IFN- γ $_{\text{pos}}$ IL17A $_{\text{neg}}$ CD4 $^{+}$) and Tc1 (IL-4 $_{\text{neg}}$ IFN- γ $_{\text{pos}}$ IL17A $_{\text{neg}}$ CD8 $^{+}$) in lungs of IL-1 β -treated mice were significantly reduced at 6 days after RSV infection, resulting in a skewed ratio of Th2/Th1 and Tc2/Tc1, indicating type 2-biased responses. Blocking IL-1 β signal before RSV infection did not affect IL-33 levels, implying that IL-1 β positively correlates with IL-33 expression only in RSV-infected neonates. Similarly, IL-1 β in the absence of RSV infection did not cause mucus production, suggesting

that RSV infection must make cells susceptible to IL-1 β -induced mucus production.

The main contribution of the study by Vu and colleagues is their investigation of the mechanism by which IL-1 β enhances IL-33 levels. They show that although exogenous IL-1 β promotes the activation of caspase-1 in neonates at 1 day after infection (14), IL-1 β did not mediate RSV-induced IL-33 expression in a caspase-dependent manner. Importantly, IL-33 and active caspase-1 in the neonatal mice had distinct cellular origins; IL-33 was primarily expressed by leukocyte common antigen-negative epithelial cellular adhesion molecule-positive (CD45-EpCAM $^{+}$) airway epithelial cells (AECs), whereas active caspase-1-positive cells were CD64 $^{-}$ granulocytes and myeloid subsets, including alveolar and interstitial macrophages, and CD64 $^{+}$ monocyte-derived dendritic cells. They found that exogenous IL-1 β induces a significant expansion of IL-33-expressing cells, including EpiSPC and AEC-II, rather than promoting IL-33 expression per cell. Interestingly, most IL-33-expressing cells were in the G1 phase of the cell cycle, with IL-1 β -treated pups showing higher frequencies of IL-33 $^{+}$ EpCAM $^{+}$ cells in the G1 phase than vehicle-treated pups. These data suggest that IL-1 β promotes the proliferation of IL-33-producing epithelial cells.

However, in adult mice, RSV infection showed no IL-1 β -dependent increase of pulmonary IL-33, and exogenous IL-1 β did not alter the abundance of IL-33 $^{+}$ EpCAM $^{+}$, IL-33 $^{+}$ CD45 $^{+}$, and IL-33 $^{+}$ CD31 $^{+}$ cells. Previous studies had shown constriction in IL-33 $^{+}$ lung epithelial cells in adulthood during alveolarization in mice and that IL-33 peaked during postnatal alveolarization and gradually declined in adulthood (15). Their data indicated distinct CD24 $_{\text{low}}$ EpiSPC capable of producing IL-33 in neonatal but not in adult mice.

The study by Vu and colleagues has several limitations. First, what are the conditions in infants that cause elevated IL-1 β levels, and can one identify a translational relevance for the animal model that is studied? Second, although this study identified IL-1 β as a regulator of IL-33 in RSV-infected neonatal mice, it is premature to conclude that IL-1 β is the only cytokine enhancing the effect of IL-33. Could other inflammatory cytokines trigger RSV-induced elevation in IL-33 by the same mechanism described? Third, the role of IL-1 β -activated cells in regulating IL-33 in RSV-infected neonates remains to be determined using lineage tracing studies in IL-33 and Pro-SpC reporter mice to clarify whether IL-1 β in RSV-infected neonates plays a role in the differentiation of IL-33 $^{+}$ CD24 $_{\text{low}}$ EpiSPC into IL-33 $^{+}$ CD24 $_{\text{hi}}$ AEC-II. Such studies may better define the difference between neonates and adults. Finally, whether the role of IL-1 β in regulating IL-33 is specific to RSV-infected neonates or

Ⓞ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

Supported by National Heart, Lung, and Blood Institute Grant R01 HL068111-15 (Y.T.) and National Institute of Allergy and Infectious Diseases grant RO1 AI148180 (Y.A.M.).

Originally Published in Press as DOI: 10.1165/rcmb.2021-0457ED on December 14, 2021

whether it also applies to elderly people with preexisting conditions or to immunocompromised people infected with other respiratory viral diseases, such as influenza, is not clear.

Of major interest would be an investigation of whether the IL-1 β -mediated expansion of IL-33⁺ EpiSPC during RSV infection in early life leaves a permanent mark to predispose these individuals to the development of lung diseases such as COPD and asthma later in life. Other studies have shown that IL-33 exerts nuclear control of cell-cycle activation and cell survival and may affect epigenetic changes that can outlast the virus (16). Similar studies could help determine the importance of IL-1 β or other cytokines as a potential target for treatment of RSV-infected infants and immunocompromised individuals. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Yohannes A. Mebratu, Ph.D.
Yohannes Tesfaigzi, Ph.D.
Pulmonary and Critical Care Medicine
Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

ORCID IDs: 0000-0002-5360-2158 (Y.A.M.); 0000-0002-3997-5839 (Y.T.).

References

1. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, *et al*. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;375:1545–1555.
2. Piedimonte G, Perez MK. Alternative mechanisms for respiratory syncytial virus (RSV) infection and persistence: could RSV be transmitted through the placenta and persist into developing fetal lungs? *Curr Opin Pharmacol* 2014;16:82–88.
3. Dare RK, Talbot TR. Health care-acquired viral respiratory diseases. *Infect Dis Clin North Am* 2016;30:1053–1070.

4. Jackson DJ, Makrinioti H, Rana BM, Shamji BW, Trujillo-Torralbo MB, Footitt J, *et al*. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am J Respir Crit Care Med* 2014;190:1373–1382.
5. Savenije OE, Mahachie John JM, Granell R, Kerkhof M, Dijk FN, de Jongste JC, *et al*. Association of IL33-IL-1 receptor-like 1 (IL1RL1) pathway polymorphisms with wheezing phenotypes and asthma in childhood. *J Allergy Clin Immunol* 2014;134:170–177.
6. Byers DE, Alexander-Brett J, Patel AC, Agapov E, Dang-Vu G, Jin X, *et al*. Long-term IL-33-producing epithelial progenitor cells in chronic obstructive lung disease. *J Clin Invest* 2013;123:3967–3982.
7. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity* 2015;43:29–40.
8. K uchler AM, Pollheimer J, Balogh J, Sponheim J, Manley L, Sorensen DR, *et al*. Nuclear interleukin-33 is generally expressed in resting endothelium but rapidly lost upon angiogenic or proinflammatory activation. *Am J Pathol* 2008;173:1229–1242.
9. Mahmutovic Persson I, Menzel M, Ramu S, Cerps S, Akbarshahi H, Uller L. IL-1 β mediates lung neutrophilia and IL-33 expression in a mouse model of viral-induced asthma exacerbation. *Respir Res* 2018;19:16.
10. You D, Becnel D, Wang K, Ripple M, Daly M, Cormier SA. Exposure of neonates to respiratory syncytial virus is critical in determining subsequent airway response in adults. *Respir Res* 2006;7:107.
11. Vu LD, Phan ATQ, Hijano DR, Siefker DT, Tillman H, Cormier SA. IL-1 β promotes expansion of IL-33⁺ lung epithelial stem cells after respiratory syncytial virus infection during infancy. *Am J Respir Cell Mol Biol* 2022;66:312–322.
12. Saravia J, You D, Shrestha B, Jalgama S, Siefker D, Lee GI, *et al*. Respiratory syncytial virus disease is mediated by age-variable IL-33. *PLoS Pathog* 2015;11:e1005217.
13. Vu LD, Siefker D, Jones TL, You D, Taylor R, DeVincenzo J, *et al*. Elevated levels of type 2 respiratory innate lymphoid cells in human infants with severe respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 2019;200:1414–1423.
14. Madouri F, Guillou N, Fauconnier L, Marchiol T, Rouxel N, Chenuet P, *et al*. Caspase-1 activation by NLRP3 inflammasome dampens IL-33-dependent house dust mite-induced allergic lung inflammation. *J Mol Cell Biol* 2015;7:351–365.
15. Saluzzo S, Gorki AD, Rana BMJ, Martins R, Scanlon S, Starkl P, *et al*. First-breath-induced type 2 pathways shape the lung immune environment. *Cell Rep* 2017;18:1893–1905.
16. Wu K, Kamimoto K, Zhang Y, Yang K, Keeler SP, Gerovac BJ, *et al*. Basal epithelial stem cells cross an alarmin checkpoint for postviral lung disease. *J Clin Invest* 2021;131:e149336.