IL-13 Protects against SARS-CoV-2?

One of the first mysteries of coronavirus disease (COVID-19) when it became a pandemic in the spring of 2020 was why there was not a surge in asthma exacerbations seen in hospital emergency departments and outpatient clinics. Respiratory tract viral infections are the most common cause of exacerbations in both adults and children who have asthma, and the seasonal peak in asthma exacerbations that occurs each year in the Northern hemisphere is quite predictable, with marked increases in asthma hospitalizations in the fall months that is largely attributed to an increase in rhinovirus infections that occurs during this season (1). However, the anticipated surge in asthma hospital admissions and clinic visits that was anticipated with COVID-19 has not materialized, and perhaps there has actually been a decrease in emergency department visits for asthma exacerbations that has occurred in the time of COVID-19 (2, 3). The question is why. What makes COVID-19 different from rhinovirus, respiratory syncytial virus, and other endemic respiratory viruses for which infections are linked to increased asthma exacerbations? One possibility is that the first-line medications that are prescribed in asthma, such as inhaled corticosteroids, could protect specifically against COVID-19–induced bronchospasm (4). A second possibility is that type 2 inflammation that is pathogenic in the majority of persons with asthma may be uniquely protective against COVID-19–induced asthma exacerbations. Although the first possibility would seem to be more likely, the second possibility would certainly be more serendipitous and intriguing.

Allergic inflammation underlies asthma pathogenesis in 90% of children and more than half of adults with this disease and is largely driven by the type 2 cytokines IL-4, IL-5, IL-9, and IL-13 (5, 6). These cytokines can be released by a variety of cells in varying circumstances. In persons with a genetic predisposition for allergic responses, $CD4^+$ T-helper cell type 2 cells produce these type 2 cytokines when they are activated by dendritic cells that present environmental allergens as part of adaptive immunity. The innate immune response can generate these same cytokines when ILC2s (group 2 innate lymphoid cells) are activated by epithelial derived cytokines such as IL-33, thymic stromal lymphopoietin, and IL-25. Mast cells produce IL-4, IL-5, IL-9, and IL-13 as a result of activation through allergen crosslinking of allergen-specific IgE on the mast cell surface. Similarly, other cells of the innate immune system, such as eosinophils and basophils, also produce these cytokines during allergic inflammation. The importance of IL-5 in asthma pathogenesis has been confirmed by the success of IL-5 antagonists in preventing asthma exacerbations in persons with severe disease that is refractory to inhaled medications. Similarly, blocking the activity of IL-4 and IL-13 with an antagonist to the receptor subunit shared by both of these cytokines has been a highly successful strategy in persons with severe asthma, confirming the importance of these cytokines in asthma pathogenesis. IL-13 is of particular interest, as it has been considered a central mediator of airway responsiveness for more than 20 years, as it is key to airway mucus expression and smooth muscle constriction that are features of airway remodeling (6).

There is increasing evidence that IL-13 may have activity to protect against COVID-19–induced asthma exacerbations. IL-13 decreases the airway epithelial cell expression of angiotensin-converting enzyme-2, the host cell entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19 (7, 8). In this issue of the *Journal*, Bonser and colleagues (pp. 391–401) report on their studies of the effects of IL-13 on SARS-CoV-2 infection of differentiated human bronchial epithelial cells (HBECs) cultured at an air–liquid interface (9). This is a clinically relevant study, as IL-13, as mentioned earlier, is produced by ILC2, CD4 T-helper cell type 2 cells, mast cells, basophils, and eosinophils in the setting of allergen-driven innate and adaptive immune responses and therefore can regulate airway epithelial function. The authors report that IL-13 decreased viral RNA recovered from SARS-CoV-2–infected HBECs and reduced double-stranded RNA, a marker of viral replication. This IL-13–mediated inhibition of SARS-CoV-2 infection of HBECs was independent of either IL-13–induced mucus gel or SAM pointed domain-containing Ets transcription factor expression (SPDEF), suggesting that IL-13 had antiviral effects unrelated to its ability to induce a mucus barrier. They also found that mucus inhibited SARS-CoV-2 infection of HBECs in cells not cultured with IL-13 compared with HBECs in which mucus had been removed by washing. The authors further performed bulk RNA sequencing from HBECs from six subjects who were cultured with IL-13 or IFN-α and were subsequently infected with SARS-CoV-2 and, not surprisingly, found that there were nonredundant differential effects of these cytokines on viral-induced gene expression. Interestingly, these results suggest that these two cytokines induce different antiviral effects. In addition, they performed single-cell RNA sequencing on IL-13–treated HBECs and found that SARS-CoV-2 infection induced cell type–specific responses in basal, ciliated, and secretory cells, suggesting that there are differences in how these cell types respond to SARS-CoV-2 infection. Unfortunately, the authors did not go further with these studies, and the data will be left for other investigators to take this work further. It will also be critical to validate the data presented with other publicly available datasets as these results come online in the future. However, this article is another important piece of the puzzle in our understanding the relationship between allergic inflammation and COVID-19. ■

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