endobronchial ultrasound to access an intracardiac sarcoma (Irfan and colleagues, pp. e73–e74).

Look out also for the page highlighting our emerging young investigators who have done so much to make this and all our prior issues so stellar, and who are the future of the specialty. Above all, the patient education and information section reminds us that we all exist to serve patients.

Finally, huge thanks are due to the *AJRCCM* family, Associate Editors and the Editorial Board, the authors and editorialists who have sent us such fantastic manuscripts, and the unseen army of reviewers, without whose hard grunt work we could not function. If you are in Washington, come along to the ceremony honoring our top reviewers and vow to be one of them in 2024. And, of course, a huge shout out to the editorial team, without whose largely unseen work in the engine room the *Journal* would not exist. And to the ATS members and beyond: keep sending us your best work, as we seek to drive the *Journal* to ever greater heights going forward. Vivat, vivat ATS and *AJRCCM*! ■

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Can Allergen Immunotherapy Improve Antiviral Immunity in Patients with Allergic Asthma?

Allergen exposure and respiratory virus infections are the key triggers for acute asthma exacerbations (1). The susceptibility to virus infections and asthma exacerbations is often attributed to deficient IFN synthesis in the airway mucosa because virus-infected bronchial epithelial cells (BECs) from people with asthma seem to produce less innate antiviral IFNs *in vitro* relative to BECs from healthy people (2). Understanding whether altered IFN production is an intrinsic property of BECs in asthma or arises secondary to immune-mediated inflammation has important implications for developing therapies for viral infections and asthma exacerbations. It is known experimentally that allergic inflammation can impair IFN production via alarmins such as IL-33 (3), T2 cytokines such as IL-4 and IL-13 (4), and allergen–IgE interactions (5), prompting researchers to determine if inhibiting allergic pathways in patients with asthma enhances antiviral IFN production and protects against viral infections.

Evidence that allergen immunotherapy (AIT) is beneficial in allergic diseases has accumulated in recent decades (6). AIT induces immunological tolerance, reduces asthma exacerbations, and probably has a disease-modifying effect, with some improvements persisting long after treatment concludes (6). The beneficial effects of AIT involve direct effects on mast cells and basophils and induction of regulatory cells, cytokines, and IgE-blocking antibodies. AIT is associated with fewer lower respiratory tract infections in people with allergic asthma (7), though the mechanisms involved and whether there is protection against viral or bacterial infections are not clear.

In this issue of the *Journal*, Woehlk and colleagues (pp. 1161–1170) report the findings of their randomized, double-blind, placebo-controlled trial of house dust mite sublingual allergen immunotherapy (HDM-SLIT) to determine if this intervention enhances BEC antiviral responses in allergic asthma (8). The study recruited 39 people with HDM sensitization and suboptimal asthma control despite maintenance inhaled corticosteroids, to which HDM-SLIT or placebo was added for 24 weeks. BECs (collected by bronchoscopy at baseline and at Week 24) were activated *in vitro* with the viral nucleic acid mimic polyinosinic:polycytidylic acid (poly I:C). The primary outcome measure was IFN-β and IFN-λ gene expression in BECs and the extent to which this changed between baseline and Week 24. Recruited patients had asthma of varying severity, and the placebo and HDM-SLIT groups were generally well matched.

The key findings were as follows. At baseline, there were no between-group differences in poly I:C–induced IFN-β and IFN-λ expression. At Week 24, poly I:C–induced IFN-β mRNA and protein

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were higher than at baseline in BECs from the HDM-SLIT–treated group but not the placebo-treated group. IFN-λ expression followed a similar pattern, with an increase in the HDM-SLIT–treated group but not the placebo group (8). Reductions were seen in IL-33 mRNA and protein release by BECs in the HDM-SLIT–treated group; diminished IL-33 was significantly associated with enhanced IFN-β mRNA expression. Epithelial cell T2 cytokine expression did not change, though greater IL-6 expression was observed in the HDM-SLIT treatment group. Asthma symptom scores, quality-of-life measures, and airway obstruction improved over 24 weeks in both groups (8), but no differences between treatment groups were observed. These clinical improvements were probably a consequence of study participation *per se* rather than the intervention itself.

The authors interpret these findings as evidence that HDM-SLIT can improve innate airway epithelial responses to viral infection, thereby providing a mechanism by which HDM-SLIT might reduce asthma exacerbations and respiratory viral infections (8). One intriguing aspect of this study is the concept that controlled allergen delivery to the oral mucosa can have a distant, beneficial effect on BEC innate immune function. How might this occur? Microaspiration of allergens into the lower airway is possible but unlikely. The key immunological processes are much more likely to be occurring in the oral mucosa and draining lymph nodes, followed by delivery of a "regulatory signal" to the airway mucosa. The nature of this regulatory signal is unclear but is likely to involve induction of multiple components of adaptive immunity, including regulatory T and B cells, regulatory cytokines, and blocking antibodies. Such "long-distance regulation" has precedence in the ability of systemic anti-IgE therapy to enhance type I IFN synthesis *in vitro* (9) and to reduce virus-associated asthma exacerbations (10).

Before proceeding further, it is important to raise questions about the desirability of enhancing antiviral IFN production capacity in asthma. The recent observation that AIT is associated with reductions in lower respiratory tract infection risk in allergic asthma supports this hypothesis (7) but will ultimately require longer studies of AIT to provide evidence that augmenting IFN synthesis is responsible for fewer viral infections. The notion that antiviral IFN deficiency is characteristic of asthma is controversial. Deficient IFN synthesis *in vitro* may be confined to a minority inflammatory phenotype among those with poorly controlled asthma (11) rather than being a universal trait, whereas some *in vivo* studies of viral infections actually report that IFN release is higher in those with asthma than in those without asthma (12, 13). If IFN release during a viral infection is already high, is further augmenting IFN release a desirable goal? Unfortunately, the benefits of inhaled IFN for viral infections in asthma have been underwhelming in recent clinical trials (14, 15). More evidence is needed to advance the field.

The authors acknowledge the limitations of their present study (8). BEC function was assessed at 24 weeks, well before clinical improvements usually become apparent, whereas standard courses of AIT usually last for 3 years. The study was underpowered for some outcomes, and it will be important to design longer and larger studies of AIT that examine the extent to which changes in BEC function, specifically IFN-β, IFN-λ, and IL-33 release, antedate prevention of respiratory viral infections. The present report provides a solid foundation on which to design such future studies. ■

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Taking Small Airways in Chronic Obstructive Pulmonary Disease to TASC

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and the only chronic disease for which mortality rates continue to increase (1). Despite these alarming statistics, treatments remain inadequate, and early diagnosis of the disease is hampered by inadequately sensitive diagnostic tests. Recent high-resolution computed tomography (i.e., micro-CT) imaging studies have identified that loss of the smallest conducting airways (terminal and preterminal bronchioles) and respiratory bronchioles is an early pathological change in the COPD lung and can be observed before emphysematous tissue destruction (2–4). Indeed, volumetric micro-CT imaging has demonstrated that >41% of terminal and 57% of respiratory bronchioles are lost by the time a patient is diagnosed with mild (Global Initiative for Chronic Obstructive Lung Disease stage 1) COPD (4). The questions now remain: what are the pathological mechanisms underlying small airway loss, and how can these pathways be targeted to develop COPD-modifying therapies?

In this issue of the *Journal*, Rustam and colleagues (pp. 1171–1182) address this question by performing dissections of human lungs to isolate proximal airways and the distal conducting and respiratory bronchioles (5). The investigators then performed single-cell RNA sequencing (scRNAseq) of these dissected airways to better understand the biology of the distal airways in health and COPD. In contrast to traditional bulk RNA sequencing performed collectively on a large number of cells, scRNAseq generates transcriptomic profiles of each cell individually. The resolution provided by scRNAseq allowed the authors to investigate the cellular heterogeneity of immune and structural cells and identify transcriptional patterns along the proximal–distal airway axis. The authors identified a population of cells enriched specifically in the distal airways of healthy donor lungs, which they name terminal airway-enriched secretory cells (TASCs) (5). These TASCs were described to represent 8–23% of epithelial cells in preterminal bronchioles and >40% of cells at the terminal and respiratory bronchioles (5).

TASCs possess features of secretory and alveolar cells, expressing SCGB3A2 (Secretoglobin, Family 3A, Member 2) and SFTPB (Surfactant Protein-B). While SCGB1A1$^+$ SCGB3A2$^-$ secretory cells are found in the proximal and distal airways, SCGB3A$^+$ TASCs are only found in the distal airways, and maintain a spatial expression pattern in which SCGB1A1 expression is gradually lost from the preterminal bronchiole region towards the respiratory bronchioles. Notably, airway cells expressing SCGB3A2$^+$SFTPB$^+$ have recently been identified by other scRNAseq studies performed on microdissected distal airways from nondiseased lungs. Kadur Lakshminarasimha Murthy and colleagues found SCGB3A2$^+$SFTPB$^+$ cells that lose SCGB1A1 expression in the transition from preterminal bronchioles to terminal bronchioles (6). Similarly, Basil and colleagues identified a similar population of SCGB3A2$^+$SCG1A1$^-$SFTPB$^+$ cells in respiratory bronchioles and suggested that they may serve as progenitor cells for alveolar type II cells (7).

A key finding of the study by Rustam and colleagues was the demonstration that TASCs are lost within the distal airways of patients with end-stage COPD (5). The authors hypothesized that the loss of TASCs may result in the loss of surfactant production in the distal airways, leading to loss of surface tension and collapse of these bronchioles during expiration, contributing to airway obstruction (5). However, several questions remain on the relationship between TASC loss and small airway disease. Although it has been shown that a large number of terminal and respiratory bronchioles are lost in COPD, it has also been demonstrated that the remaining airways within COPD lungs are remodeled and often obstructed with mucus (4). It, therefore, begs the question of whether TASC loss results in distal small airway remodeling or is part of a continuum of the cellular and molecular changes that occur within the small airways that are also lost. Thus, although the study by Rustam and colleagues demonstrates that TASCs are decreased in the remaining distal airways in COPD lungs, it is not clear if the loss of TASCs causes small airway loss in COPD.

Additionally, the authors suggest that the loss of TASCs occurs as a consequence of chronic inflammation. The accumulation of lymphoid and myeloid cells, including CD8$^+$ T cells and macrophages in the distal airways, is well described and highlighted in the study (5). Here, Rustam and colleagues identified enrichment for IFN-γ signaling genes in COPD airway epithelial cells, and was

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