cancer risk existed across GRS categories, and there was additive interaction between these two parameters. Hence, compared with those with low GRS and low air pollution, the high GRS and high pollution group had the highest risk of lung cancer. This occurred using multiple measures of pollution. Of note, exposures below the current regulated threshold levels were significantly linearly associated with lung cancer risk.

The study is not without limitations. The exposure measures were based on a single sampling at baseline. Therefore, there is a potential for exposure misclassification during follow up. Moreover, this cohort design may be prone to left truncation, whereby subjects at risk before baseline do not remain observable until the start of follow up, leading to potential bias in the presence, direction, or magnitude of an association. Some other sources of lung carcinogen exposure were not characterized, such as occupational exposures. Finally, the smoking variables were simple, with 15% missing and imputed, although sensitivity analysis found robust results. The generalizability to other world populations, with different population admixture, requires further study.

Nevertheless, the results are impressive and highlight the importance of improving air quality, even below current thresholds values. Although additional gene–environment interaction studies such as this one are needed to identify specific interactions, the highest priority should remain enforceable societal-level actions to reduce exposure to air pollution globally. Susceptibility to diseases such as lung cancer is conferred not only by heritable factors but also acquired ones, such as comorbidities, age, and socioeconomic disparities. The most effective public health policy is to protect those among us who are more vulnerable, thus affording a wider umbrella of protection for the entire population. ■

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Lung-Resident Memory CD8$^+$ T Cells in Human Influenza: How Innate Are They?

Although the lower respiratory tract is the major site of influenza virus infection and the ensuing immunopathology, respiratory immune responses are understudied; such studies are needed to fully understand the mechanisms underlying recovery from respiratory diseases. In this issue of the *Journal*, Paterson and colleagues (pp. 826–841) used the human experimental influenza virus infection model to define cellular and molecular features of memory CD8$^+$ T cells in BAL in comparison to CD8$^+$ T cells found in the blood (1). Using peptide-MHC class I tetramers, influenza-specific CD8$^+$ T-cell responses were identified and longitudinally tracked in both the blood and BAL before infection and on Days 7 and 28 after infection. Subsequent in-depth analysis of the total CD8$^+$ T-cell population by RNA sequencing revealed interesting innate-like transcriptional signatures in BAL after influenza virus infection, providing novel insights into our current understanding of human CD8$^+$ tissue-resident memory T cells. These intriguing findings were subsequently supported by confocal imaging of endobronchial tissue biopsies, showing infiltrating CD8$^+$ T cells coexpressing innate-like markers during influenza virus infection. With their study, Paterson and colleagues changed the way we think about lung-resident memory CD8$^+$ T cells in influenza and possibly also other respiratory diseases.

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Experimental infection of healthy volunteers with influenza viruses was first pioneered by McMichael and colleagues in 1983 (2). Paterson and colleagues showed that preexisting circulating influenza-specific $CD8^+$ T cells strongly correlated with reduced viral load, which is reminiscent of McMichael's seminal findings. Since then, both circulating influenza-specific $CD4^+$ and $CD8^+$ T cells depict strong correlates of protection in influenza disease (3–5). However, the current study delves deeper into the human respiratory tract using bronchoscopy to unravel direct effector mechanisms of protection at the site of infection, which the authors first pioneered using the respiratory syncytial virus (RSV) human infection model (6). This body of work is truly novel and uses extremely rare longitudinal BAL samples, not to mention the massive costs and ethics approvals of conducting experimental virus infection studies in humans.

Very few studies have identified lung-resident influenza-specific $CD8^+$ tissue-resident memory T cells postmortem using *ex vivo* peptide-MHC class I tetramer staining (7–9). These studies included the immunodominant HLA-A2–restricted $M1_{58–66}$ ($A2/M1_{58}$) epitope, which is also used in the current manuscript together with the well-characterized $A1/NP_{44–52}$ epitope (10). Prominent BAL and blood $tetramer^+$ $CD8^+$ T-cell populations displayed similar kinetics, with $A2/M1_{58}$ and $A1/NP_{44–52}$ $tetramer^+$ $CD8^+$ T cells being minimally detected preinfection and peaking on Day 7 during infection before contracting on Day 28 at convalescence. However, the BAL $tetramer^+$ $CD8^+$ T cells were of much higher frequencies (up to 4–5% of $CD8^+$ T cells) compared with $<1\%$ in the blood during infection, similar to the authors' previous RSV infection study (6) and the postmortem influenza studies (7–9). Nguyen and colleagues also observed low influenza $tetramer^+$ $CD4^+$ and $CD8^+$ T-cell frequencies of $<1\%$ in the peripheral blood, characterized by highly activated HLA-DR, CD38, PD-1, or CD71 phenotypes, in patients hospitalized with influenza disease (11). The authors hypothesized that larger numbers could be migrating to the respiratory tract during acute infection. As such, Paterson and colleagues elegantly provide evidence of enrichment and trafficking of activated influenza-specific $tetramer^+$ $CD8^+$ T cells to the BAL during acute influenza virus infection.

Although the authors performed tetramer staining in a small number of the available $HLA\text{-}A1^+$ and $HLA\text{-}A2^+$ BAL samples, which they diligently acknowledge in the article, the quality of tetramer staining is very convincing. In future studies, it would be enticing to include additional tetramers encompassing a range of influenza class I epitopes spanning several different common HLAs (11) to understand their immunodominance hierarchy and perhaps class II epitopes to examine the role of $CD4^+$ T cells at the site of infection. However, the technical requirements for generating peptide-MHC tetramers or the high costs of purchasing these reagents and HLA typing of the participants remain considerable factors here.

The study paved new avenues for exploring antigen-specific T cells in the respiratory specimens. The authors used a bulk RNA sequencing methodology and cell-sorting strategy to analyze bulk $CD8^+$ T-cell populations from 12 blood and BAL samples at three different time points. Unexpectedly, innate-like genes normally related to monocytes and DCs represented unique features of the lung-resident $CD8^+$ T cells. Taking into account all the caveats of obtaining and assaying the precious BAL samples, it would be a tremendous leap forward if single-cell RNA sequencing could be performed in future studies, as the authors allude to in their discussion, but coupled with antibody-barcoded technology (i.e., barcoded anti-CD69 and anti-CD103 or barcoded streptavidin-labeled tetramers) to further define these $CD8^+$ T-cell subsets and surrounding BAL cell populations at a greater resolution. Perhaps then we could carefully delineate the types of T cells comprising the spectrum of innate-like and more adaptive-like $CD8^+$ T-cell subsets, which can include innate T lymphocytes such as mucosal-associated invariant T (MAIT) cells and natural killer T cells. The role of innate T lymphocytes during influenza disease was previously suggested, with higher numbers of functional MAIT and T cells in the blood being associated with reduced disease severity in hospitalized patients with influenza (11). Another idealistic approach could be the use of highly sophisticated spatial transcriptomics (12) with endobronchial tissue samples. Given how unique these respiratory samples are and the quality of the experimental design, it is easy to get carried away with an endless wish list of elaborate technologies to use in future experiments.

Overall, Paterson and colleagues not only paved the way for conducting valuable human experimental virus infection studies to closely monitor clinical disease and viral load but also defined the immune mechanisms of protection by directly interrogating immune cells at the site of infection. Until now, we have only been able to scratch the surface and describe influenza-specific $CD8^+$ T-cell responses in the blood as correlates of protection, but this article gives absolute insights into the parallel kinetics, phenotype, activation, and trafficking status of influenza-specific $CD8^+$ T cells in the blood versus the respiratory tract during influenza virus infection. Without a doubt, this experimental virus infection model will be paramount to assessing future universal influenza vaccine and therapeutic candidates. ■

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Hit Early and Hit Hard in Pulmonary Arterial Hypertension? Not So Fast!

Despite significant recent progress in medical therapy, pulmonary arterial hypertension (PAH) remains a severe disease with no cure. Effective medical treatment started with calcium channel blockers for the very few patients with idiopathic disease who displayed acute vasodilator response (1). This step forward was followed rapidly by therapy targeting one of the three classical pathways implicated in the pathogenesis of PAH (the endothelin, nitric oxide, and prostacyclin pathways) (2). The success of oral monotherapy targeting one pathway was followed by dual therapy targeting two separate pathways in either sequential or upfront combination modality (3, 4), a logical step akin to strategies employed in other cardiovascular or neoplastic diseases. With this paradigm shift, it was a given that the next intervention for this lethal disease would be therapy targeting all three known pathogenic pathways (5), an approach often adopted clinically without the availability of strong scientific data. Although survival has improved for patients with PAH, many questions remain unanswered: should treatment with three agents immediately after diagnosis be recommended as suggested by some studies (6)? Should "the hit early and hit hard" approach using this three-pronged approach be the new norm? Alternatively, is one of these pathways predominantly pathogenic in a given individual and, as such, the most important early target?

In this issue of the *Journal*, Boucly and colleagues (pp. 842–854) examined, in this context, the impact of initial treatment strategy on long-term survival in PAH (7). The study consisted of a retrospective analysis of 1,611 patients with incident idiopathic, heritable, or anorexigen-induced PAH. Survival was assessed according to initial monotherapy, dual therapy, or triple therapy. The authors concluded that overall survival was better with triple combination compared with monotherapy or dual combination therapy, particularly in high-risk patients. In multivariate Cox regression, initial triple combination therapy including parenteral prostacyclin was independently associated with better survival.

Despite the retrospective nature of this study, the findings have potentially important implications. The treatment cohorts are well defined, and the focus on a limited large subgroup of patients with Group 1 PAH is an obvious strength. There are, however, several concerns about the findings and their clinical implications. The multivariable Cox analysis suggests an "independent effect" of younger age, female sex, and triple combination therapy. It is noteworthy that the patients treated with triple combination were nearly two decades younger than those treated with monotherapy or dual combination therapy. They also tended to more likely be female patients (both younger age and female sex carry better prognosis in PAH). They had more severe hemodynamics compared with the other two groups but were also more likely to have a good response to initial therapy. In addition, their comorbid conditions were less than half those of the other two groups. It is, therefore, risky and incongruous for the authors to conclude, based on a retrospective study, that triple combination therapy may equally apply to all patients with PAH, particularly older males with multiple comorbidities. To their credit, however, the authors did perform a propensity score analysis to match triple therapy patients for confounding factors (e.g., age and sex, which might influence treatment selection) and showed similar results compared with those observed in the entire population. Although this is reassuring, the combination of three vasodilators could still be poorly tolerated in older patients with cardiac or other comorbid conditions. This significant limitation of the study was acknowledged by the authors.

As the French registry enrolled patients from multiple centers, it is surprising that differences in center practices and regimens (e.g.,

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