Breaching the Defenses? Mucosal-associated Invariant T Cells, Smoking, and Chronic Obstructive Pulmonary Disease

There can be little doubt that cigarette smoking is one of the primary causes of chronic obstructive pulmonary disease (COPD); however, the precise mechanisms by which cigarette smoke (CS) exposure leads to COPD are yet to be elucidated. Ample evidence suggests CS causes substantial changes to the epithelial barrier (1) as well as to immune cells (2) that persist in COPD. Furthermore, these changes are also associated with microbial dysbiosis in the airways of patients with COPD (3), an important driver of COPD exacerbations and mortality (4, 5). In this issue of the *Journal*, Huber and colleagues (pp. 90–102) describe their investigations into the impact of both smoking and COPD on the interaction between epithelial cells and mucosal-associated invariant T (MAIT) cells (6). MAIT cells are innate-like T cells that play a role in controlling bacterial infection by recognizing nonpeptide antigens derived from the bacterial vitamin B2 pathway presented by the MR1 (major histocompatibility complex–related protein 1) (7).

Huber and colleagues first demonstrate that unstimulated bronchial epithelial cells (BECs) from patients with COPD drive more IFNγ expression from a MAIT cell clone (D426 G11) than do BECs from both healthy and currently smoking control subjects (6). These investigators go on to show that this increase was mediated directly via interaction between the MAIT cell and epithelial-expressed MR1, using blocking antibodies, rather than by increases in soluble cytokines released by the COPD epithelium. Intriguingly, this increase in MAIT cell IFNγ expression in COPD samples was not associated with a significant increase in epithelial MR1 expression of either the mRNA or protein at the cell surface. Indeed, cell surface MR1 expression was lower on COPD BECs at baseline compared with healthy controls. These observations could perhaps be explained by changes in the epithelial expression of coinhibitory molecules, such as programmed death 1, which is known to regulate MAIT cell function and also to be dysregulated in COPD (8, 9). However, further work is required to investigate this hypothesis.

Huber and colleagues (6) then proceeded to investigate the effects of 30% (vol/vol) SC extract (CSE) on the ability of the epithelial cells to activate the MAIT cell clone by incubating the BECs with CSE for 3 hours before removing the CSE media and incubating the BECs with the MAIT cell clone. Exposure of healthy control and COPD BECs to CSE had no effect on MAIT cell activation, whereas CSE caused a reduction in MAIT cell activation by BECs from smokers. Again, these effects appeared to be unrelated to MR1 expression.

To assess the relevance of these findings for bacterial infection of the airway, BECs were then exposed to the respiratory pathogen *Streptococcus pneumoniae* (Spn) for 3 hours. Greater numbers of Spn were associated with COPD BECs at baseline and in response to CSE compared with both healthy and smoker controls. Furthermore, exposure of BECs from all donors to Spn led to significant increases in MAIT cell IFNγ expression that again was demonstrated to be MR1 dependent using blocking antibodies. However, whether the significant reduction in MAIT cell responses to infected COPD BECs, as indicated by the fold-change responses, is a result of a defect in the ability of the COPD BECs to activate MAIT cells or a consequence of the high baseline activation being closer to a maximal stimulation is unclear.

The addition of CSE had a negative effect on the ability of Spn-exposed BECs from all donors to activate MAIT cells, which was counterintuitive given the observation of the CSE-induced increase in BEC-associated Spn. To again assess whether these effects were mediated by differential MR1 expression, BECs were exposed to the known MAIT ligand 6FP (6-formylpterin) or Spn in the presence or absence of CSE. Exposure to 6FP led to increased MR1 expression by healthy control BECs, whereas expression was significantly lower on COPD BECs exposed to both 6FP and CSE. Unfortunately, there are no data shown about the effect of Spn alone on MR1 expression, and only relative MR1 expression level is shown for the effects of CSE on Spn. Although CSE significantly decreases MR1 expression by Spn-exposed healthy control BECs, there is no consistent effect of CSE on MR1 expression by Spn-exposed BECs from patients with COPD and smoking control subjects.

The data presented by Huber and colleagues clearly indicate that CSE reduces the ability of bacteria-exposed BECs to activate MAIT cells, and this may be one mechanism by which CS promotes bacterial colonization of the human airway. However, these data are not without their limitations, not least of which is that exposure of BECs to CSE for 3 hours is unlikely to be representative of the effects that may be caused by a 20 pack-year smoking history. Furthermore, it is recognized that COPD BECs have different responses than healthy controls, which are not always evident when comparing to BECs from currently healthy smokers, even though some of the patients with COPD had been ex-smokers for a number of years. A question that remains, therefore, is what drives these epithelial changes in COPD even after smoking cessation?

A further limitation is that the data presented by Huber and colleagues were generated in monolayer cultures rather than in air–liquid interface (ALI) cultures, where cells differentiate to more closely resemble the human airway. Although ALI cultures may not be compatible with the enzyme-linked immunospot assay, assessment of intracellular cytokine expression using flow cytometry could be feasible. Flow cytometry would also allow assessment of MAIT-derived cytokines beyond IFN-γ, such as IL-17, that are believed to be important in neutrophilic inflammation in COPD (10). In addition to Spn-exposed BECs, it would be interesting to compare the effects of other bacterial species on the interaction between BECs and MAIT, such as *Haemophilus* spp, a key driver of COPD exacerbations (4).

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What is not in doubt is that a CS-free future is needed to both prevent COPD and improve disease outcomes. In that respect, although e-cigarettes may be useful as an aid to smoking cessation (11), the potential deleterious effects of vaping on the lung immune response warrant careful consideration (12), and the impact of long-term vaping on COPD remains to be seen. ■

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