

Correspondence

Reply

To the Editor:

We thank Tsoumakidou¹ for her thoughtful comments, which highlight several important areas. The primary aim of our study was to assess whether nontypeable *Haemophilus influenzae* (NTHi) activates lung T cells in patients with chronic obstructive pulmonary disease (COPD), and we found a strongly positive response.² There have been very few published studies that have measured T-cell immunity in surgical lung tissue; as such, there are no generally accepted methods on how this should be done. We used a whole-lung cell extract because this was the most representative of the *in vivo* situation. We did measure the ratio of classical antigen-presenting cells (CD45⁺, CD3⁻) to T cells and found that there were no clear differences between control and COPD groups (see Fig E8 in the article's Online Repository at www.jacionline.org).² In contrast, the percentage of responding T cells producing TNF- α , IL-13, and IL-17 was 1-2 logs higher in the COPD group. It should be emphasized that our work concentrated on the adaptive rather than the innate immune response. It is highly likely that the innate response has a critical effect on driving the T-cell function.

Which cytokines are the most prevalent in COPD remains a source of ongoing controversy in the published literature. TNF- α is the cytokine that has been clearly demonstrated to be relevant in COPD,³ while IL-13, IL-17, and IFN- γ have also been shown to be important. The cytokine expression is probably also largely driven by the stimulus used. If we had used another stimulus (eg, a mitogen such as phorbol myristate/ionomycin),⁴ we may have found higher levels of IFN- γ in the COPD group.

IFN- γ upregulates host defense to clear bacteria, and a relative deficiency could potentially be important in the failure to clear NTHi in the context of COPD. We have previously published a study of patients with bronchiectasis and persistent NTHi infection that demonstrated that these subjects had a deficient T_H1 response.⁵ However, if an infectious pathogen cannot be cleared by a T_H1 response, a T_H2 response may be less harmful to the host as has been proposed in liver and lung fibrosis.⁶

Cigarette smoking has a variety of deleterious long-term effects on lung immunity that increase the risk of secondary infection and hence lung inflammation.

Significant recent progress has been made in the understanding of mucosal immunity in the gastrointestinal tract. However, the lung immune response to infection is still not well understood. This is highlighted by the example of *Mycobacterium tuberculosis*. Both the innate and adaptive responses are important, but despite intensive investigation over many years, there is not yet a comprehensive picture of the mechanisms or correlates of immunity to this bacterium.⁷

We believe that more work needs to be done to definitively establish that NTHi is an important source of inflammation in COPD and it is not just (as has been previously termed) "an innocent bystander." This would lead onto further studies assessing underlying mechanisms. We also feel that the use of surgical lung tissue is potentially useful in this context.

Paul T. King, MD, PhD

Steven Lim, BSc

Stephen R. Holdsworth, MD, PhD

From Monash University Department of Medicine/Respiratory and Sleep Medicine, Monash Medical Centre, Melbourne, Australia. E-mail: paul.king@monash.edu.

This study was supported by a Monash University Strategic Grant.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Tsoumakidou M. The crucial task of defining a healthy immune response toward respiratory infections. *J Allergy Clin Immunol* 2013;131:XXX-XXX.
2. King PT, Lim S, Pick A, Nqui J, Prodanovic Z, Downey W, et al. Lung T-cell responses to nontypeable *Haemophilus influenzae* in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2012 [Epub ahead of print].
3. Gosselink JV, Hayashi S, Elliott WM, Xing L, Chan B, Yang L, et al. Differential expression of tissue repair genes in the pathogenesis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;181:1329-35.
4. Hodge G, Nairn J, Holmes M, Reynolds PN, Hodge S. Increased intracellular T helper 1 proinflammatory cytokine production in peripheral blood, bronchoalveolar lavage and intraepithelial T cells of COPD subjects. *Clin Exp Immunol* 2007;150:22-9.
5. King PT, Hutchinson PE, Johnson PD, Holmes PW, Freezer NJ, Holdsworth SR. Adaptive immunity to nontypeable *Haemophilus influenzae*. *Am J Respir Crit Care Med* 2003;167:587-92.
6. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat Rev Immunol* 2004;4:583-94.
7. Ernst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol* 2012;12:581-91.

<http://dx.doi.org/10.1016/j.jaci.2013.01.041>