

Correspondence

Reply

To the Editor:

We thank Chiarella et al.¹ for their interest in our article. The authors made some interesting observations related to the role of environmental pollution and β -agonists. They showed that exposure of animals to inhaled particulate matter induced airway inflammation and an increase in IL-6 levels, which was further augmented by formoterol.^{2,3} Albuterol caused heightened IL-6 production by particulate matter-stimulated macrophages.⁴

There are other studies that demonstrated IL-6 production by air pollution and β -agonists.⁵⁻⁷ IL-6 signals through the signal transducer and activator of transcription 3 (STAT3) pathway. We observed increased STAT3 phosphorylation in airway T_H2/T_H17 cells from our patients. Heightened STAT3 phosphorylation adds credence to this hypothesis.

On the basis of these findings, the authors speculate that air pollution and β -agonist treatment might have contributed to T_H2/T_H17 differentiation in our patients. Although this hypothesis is plausible, we believe that it would be very difficult to prove. Most patients from our study cohort lived in large cities. The exposure to air pollution was likely very similar in all 3 study groups: T_H2 predominant, T_H2/T_H17 predominant, and T_H2/T_H17 low. Likewise, all of our patients were taking as-needed short-acting β -agonists, and the vast majority of them were taking long-acting β -agonists (LABAs). The use of LABAs did not distinguish the T_H2/T_H17 -predominant group from the T_H2 -predominant group. Thus air pollution and β -agonist use by themselves could not explain the T_H2/T_H17 -predominant phenotype.

We showed that T_H2/T_H17 cells were high IL-4 producers. We believe that the patients with IL-4^{high} T_H2 cells are at a risk for the T_H2/T_H17 endotype. It is possible that when these high IL-4-producing patients are exposed to air pollution and, at the same time, take LABAs, their airway IL-6 production increases, which facilitates transdifferentiation of T_H2 cells into T_H2/T_H17

cells. The differentiation of T_H2/T_H17 requires additional cytokines, such as IL-1 β , IL-21, and IL-23. The production of IL-1 β is likely to be induced by air pollution.⁸ Thus it is likely that multiple factors converge to induce this complex phenotype.

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Disclosure of potential conflict of interest: R. Alam has received research support from the National Institutes of Health.

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<http://dx.doi.org/10.1016/j.jaci.2014.09.038>