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# $\beta_2$-Agonist therapy may contribute to the air pollution and IL-6–associated risk of developing severe asthma with dual-positive $T_H2/T_H17$ cells

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## To the Editor

We read the recently published manuscript by Irvin et al[1] with great interest. The authors identified 3 distinct subgroups of asthma based on CD4 T-cell analysis in bronchoalveolar lavage fluid: $T_H2^{predominant}$, $T_H2/T_H17^{predominant}$, and $T_H2/T_H17^{low}$. The $T_H2/T_H17^{predominant}$ subgroup was defined as patients with $T_H2$-predominant asthma whose $T_H2$ cells coexpress IL-17. Patients in this subgroup with increased numbers of dual-positive $T_H2/T_H17$ cells had significantly more airflow limitation and increased airway reactivity in response to methacholine challenge and higher numbers of eosinophils in their blood when compared with patients in the other subgroups. Furthermore, $T_H2/T_H17$ cells were also resistant to steroid-induced cell death.

In their discussion they proposed $T_H2$ cells as the most likely precursors for $T_H2/T_H17$ cells.[2] They speculated that environmental factors known to aggravate asthma, such as air pollution, might be responsible for the differentiation of $T_H2$ cells into $T_H2/T_H17$ cells through their ability to induce IL-6, which induces differentiation of $T_H2/T_H17$ cells from $T_H2$ cells.[1–4] They suggested that patients with $T_H2$-predominant asthma can switch their endotype to $T_H2/T_H17$-predominant asthma over time in the presence of increased IL-6 production because of recurrent respiratory tract infections or exposure to environmental toxicants, such as air pollution.[1,3–5]

We agree with the authors' conclusion. In human subjects exposure to particulate matter (PM) air pollution is associated with impaired lung development, worsening lung function, and increased asthma exacerbations.[6–9] Supporting the role of air pollution as a risk factor for the development of $T_H2/T_H17$-predominant asthma, we previously reported that mice exposed to PM air pollution have a dose-dependent lung inflammation characterized by the release of IL-6, which was the predominant proinflammatory cytokine in the lungs.[10,11] We

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have recently published that the administration of $\beta_2$-adrenergic agonists, such as formoterol, causes a further increase in IL-6 release after exposure to PM. Furthermore, administration of short-acting $\beta_2$-adrenergic agonists, such as albuterol, augmented the PM-induced IL-6 release from primary human alveolar macrophages.[12] In view of these results by Irvin et al[1] and our recent findings about the effect of $\beta_2$-adrenergic receptor stimulation on IL-6 release during exposure to air pollution, we speculate that increased $\beta_2$-agonist therapy use in patients who reside in areas of higher levels of PM air pollution might contribute to the induction of $T_H2/T_H17$ cells.

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