



Guest editorial

 T_H1/T_H17 cells in organic dust-induced airway disease

Most asthma, including occupational and environmental asthma, is thought to be a T_H2 cell-driven disease. Recent evidence has indicated other T cells also contribute to the development of asthma.¹ In this issue of the *Annals*, Poole and colleagues² reported the polarization of $\alpha\beta$ T-cell (most T cells are $\alpha\beta$ T cells, which express $\alpha\beta$ heterodimeric T-cell receptors) subsets T_H1/T_H17 in organic dust-induced airway disease. A better understanding of the function of T-cell subsets in organic dust exposure-associated lung disorder may help design targeted therapy. T_H17 cells and interleukin 17 (IL-17) have been proposed to play a role in several mouse models of asthma. However, some of the data from these animal models are conflicting. These controversial results have suggested some doubt about a true environmental effect on airway disease. Moreover, little is known about potential specific determinants of airway disease in the farm environment.

In this issue of the *Annals*, Poole and colleagues² used a mouse airway disease model that involved exposing the animals to organic dust extract from a swine confinement facility. The authors make a valuable contribution with their study because it highlights the local proinflammatory cellular and molecular players in the development of farm occupational asthma. The authors demonstrate the T_H1/T_H17 polarized microenvironment in the lung and establish that production of lung parenchymal mononuclear aggregates and peribronchiolar inflammation after dust extract exposure is $\alpha\beta$ T-cell dependent. More interestingly, similar to the effect of dust extract on T-cell distribution, exposure to peptidoglycan, a major component of large animal farming organic dusts, results in a robust increase in T_H17 and interferon γ -secreting T_H1 cells. These data are in line with a recent report that IL-17 produced by T_H17 cells contributes to allergen-induced airway hyperresponsiveness through direct effects on airway smooth muscle.³ Moreover, a recent study by Quan et al⁴ assessed the role of IL-17 in an allergic rhinitis mouse model. Compared with wild-type mice, IL-17-deficient mice showed significantly weakened allergic symptoms, lower serum IgE levels, and decreased eosinophil infiltration locally into the nasal mucosa.

This study raises several interesting issues, including the significant role of T_H1/T_H17 subsets in organic dust exposure-associated airway disease and the potential of using T_H1/T_H17 -targeted therapies to treat organic dust-associated airway disease.

The strength of this study also lies in the fact that the authors are creative enough to challenge the well-established role of T_H2 polarization and endotoxin in occupational airway disease. Therefore, probably more interestingly, the authors found that peptidoglycan alone can induce the polarization of T_H1/T_H17 cells in the lung.² As mentioned, endotoxin has been widely recognized to play an important role in mediating airway disease-associated inflammation.⁵ It enhances airway phagocyte and antigen presentation surface markers, including Fc receptor, CD86, and HLA-DR. Surprising

to many, despite numerous reports on the association between endotoxin and inflammatory airway disease including asthma, it was documented in a clinical study that childhood environmental exposure to endotoxin may have a crucial role in the development of tolerance to ubiquitous allergens found in natural environments.⁶ It would be extremely interesting to understand the interplay between peptidoglycan, which is a major component of gram-positive bacterial cell wall, and endotoxin in immune response. It is reasonable to suspect that early exposure of endotoxin may induce cross-tolerance to peptidoglycan. On the other hand, peptidoglycan resembles the proinflammatory activity of endotoxin through a distinctive Toll-like receptor 2 (TLR2) pathway. It would also be interesting to investigate the potential synergistic effect of endotoxin and peptidoglycan in the animal model presented by Poole and colleagues.² Peptidoglycan is a TLR2 pathway agonist. Previously, a report⁷ used peptidoglycan on wild-type and TLR-deficient mice and demonstrated that in wild-type mice peptidoglycan resembled dust extract-induced responses, in agreement with the report by Poole et al in this issue of the *Annals*.² In contrast, TLR2-deficient mice have reduced lung pathogenesis after peptidoglycan exposure, which indicates the role of TLR2 in regulating organic dust-induced airway inflammation and farming occupational-associated airway inflammatory diseases.

The merit of this study also includes the characterization of $\alpha\beta$ T cells in both dust extract- and peptidoglycan-induced polarization of T_H1/T_H17 microenvironment characterized by the cytokine milieu and lung pathogenesis.² Thus, identifying the cell-cell interaction, transcriptional machinery, and the various signaling cascades that modulate the dynamic and precise T-cell response, particularly regulatory T cells⁸ and T_H17 to organic dust and peptidoglycan, would greatly advance our understanding of how this mixed T_H1/T_H17 polarization contributes to promoting lung inflammation in occupational and environmental airway disease. This work has demonstrated therapeutic possibilities for gram-positive bacterial cell wall-associated clinical disorders.

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