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Dust mites' dirty dealings in the lung

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The normal pulmonary response to harmless airborne particles such as pollen, animal dander and house dust mites is tolerance, achieved by a complex network of cells and molecules within the lung. In contrast, asthmatic individuals respond with inflammatory reactions, leading to cellular infiltration of the lungs coupled with changes to lung function, airway hyperresponsiveness and bronchospasm, or 'wheezing'.

A combination of genetic and environmental factors is thought to influence whether an inflammatory reaction is initiated, and the pulmonary epithelium is increasingly implicated as a key player in this process¹. However, the molecular mechanisms underlying interactions between the immune system and the epithelium are not well understood. In this issue of *Nature Medicine*, Hammad *et al.*² show that triggering of Toll-like receptor 4 (TLR4), a receptor that recognizes conserved components of microbes, on epithelial cells helps drive the development of allergic reactions to a common household antigen.

The pulmonary epithelium provides a barrier between the outside environment and the internal tissues. This barrier is maintained by tight junctions located at the apical surface of epithelial cells, which enable the cells to adhere together. Apart from providing a physical barrier, the pulmonary epithelium actively contributes to pulmonary immune responses. Lung epithelial cells secrete a range of cytokines and chemokines and are in intimate contact with the immune system. Epithelial cells sense microbes via pattern recognition receptors, which include the TLRs that recognize pathogen-associated molecular patterns from viruses, bacteria, fungi, protozoa and multicellular parasites¹. This innate process is clearly important for host defense, but whether it also has a role in the development of allergic reactions is controversial.

The TLR4 ligand lipopolysaccharide (LPS), a constituent of Gram-negative bacteria, is also commonly found within inhaled allergens such as pollens, house dust and animal dander. To investigate the contribution of TLR4 to allergic responses, Hammad *et al.*² reconstituted irradiated wild-type or TLR4-deficient mice with either wild-type or TLR4-deficient bone marrow to generate groups of mice that had selective ablation of TLR4 expression on either lung structural cells or hematopoietic cells.

They determined that TLR4 was expressed predominantly on pulmonary epithelial cells and alveolar macrophages². Two-photon dynamic imaging showed, compellingly, that TLR4 expression on airway structural cells was vital for effective migration of dendritic cells. Moreover, TLR4 expression on stromal cells, rather than hematopoietic cells, was required for activation of lung dendritic cells and subsequent priming of allergen specific T helper type 2 (T_H2) response (Fig. 1).

The authors next asked whether TLR4 expression on structural cells is crucial for initiation of responses to a complex, clinically relevant allergen². They administered house dust mite extract, which is known to contain large amounts of LPS, to chimeric mice². Wild-type mice reconstituted with bone marrow from either wild-type or TLR4-deficient mice developed a robust eosinophilic and T_H2 inflammatory response (including interleukin-5 (IL-5) and

IL-13 production). Concentrations of key cytokines known to elicit allergen-driven T_H2 responses, such as thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, were all upregulated in mice that had intact TLR4 expression on the airway stromal cells. In contrast, mice that specifically lacked TLR4 on structural cells did not develop any of these characteristic features of inhaled allergen challenge.

The findings give epithelial cells a pivotal position in the generation of immune responses to inhaled antigen. But how might the findings affect clinical disease?

To address this question, the authors delivered a TLR4 antagonist together with inhaled house dust mite antigen². Not only were eosinophil and T_H2 inflammatory responses reduced to baseline, airway hyperresponsiveness—one of the cardinal features of asthma—was restored to normal. It remains to be seen whether this approach will be successful for other aeroallergens such as animal dander or pollen and whether other chronic features of the disease, such as tissue remodeling, are also successfully treated.

This study is of particular interest in light of recent findings that one of the major house dust mite allergens, Derp2, shares structural homology with a component of the TLR signaling complex³. This shared homology may also promote allergic reactions. By mimicking the function of TLRs, Derp2 may function as an adjuvant to drive adaptive immune responses.

It is well known that dendritic cells are crucial for the polarization of allergen-specific T_H2 cells, leading to generation of T_H2 cytokines that promote the key pathophysiological features of allergic reactions⁴. However, recent evidence shows that the cytokines IL-33, TSLP and IL-25 are able to directly elicit eosinophilia, T_H2 cytokines and airway hyperreactivity^{5,6,7}. Interestingly, IL-33 is capable of driving allergic inflammation even in the absence of IL-4 (ref. 8), and IL-25 exacerbates airway hyperreactivity in the absence of T_H2 cytokines⁹. This group of innate proallergic cytokines is able to promote allergen-specific T_H2 responses via dendritic cell recruitment and activation and, in addition, drives pathology directly, even in the absence of T_H2 cytokines. The study by Hammad *et al.*² provides a mechanism for the generation of IL-25, IL-33 and TSLP—via triggering of TLR4 on pulmonary epithelium (Fig. 1).

The new findings should open up avenues of research for studying genetic susceptibility to asthma. Studies of polymorphisms in the *TLR4* locus hint at an association with asthma susceptibility—particularly in children. However, results have been mixed, and it remains to be seen whether such polymorphisms truly affect asthmatic disease susceptibility and outcome¹⁰. Furthermore, many asthma susceptibility genes are located within the pulmonary epithelium.

It has long been held that environmental triggers such as infection or pollution exacerbate allergic reactions, and the study by Hammad *et al.*² defines a potential mechanism. In addition, these results challenge the current concept of asthma as a disease of the adaptive immune system and provide evidence that both innate and adaptive immune pathways are involved—opening the door to new therapeutic approaches.

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Figure 1.

Direct route for dust mite. Endotoxin-containing allergens such as house dust mite extract activate TLR4 on lung structural cells such as epithelial cells—thereby promoting the secretion of cytokines and chemokines (such as C-C motif chemokine ligand-2 (CCL2) and CCL20) that promote dendritic cell (DC) recruitment and maturation². Activated dendritic cells have high surface expression of major histocompatibility complex class II (MHC II), CD86 and CD40 and promote generation of allergen-specific T_H2 cells. These T_H2 cells secrete the classical cytokines associated with allergic reactions—IL-4, IL-5 and IL-13, which are responsible for the symptoms such as eosinophilia and airway hyperreactivity (AHR). Hammad *et al.*² found that HDM triggering of TLR4 on epithelial cells also induced the production of the innate cytokines TSLP, IL-25 and IL-33. Each of these cytokines is also associated with generation of allergic immunopathology and airway hyperresponsiveness.