

How are airborne allergens remembered by the immune system?

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The reason patients with asthma and allergic diseases have recurrent and persistent respiratory symptoms in response to environmental exposure to allergens or certain infectious agents is not fully understood. Immune responses are divided into 2 arms: innate and adaptive immunity. In general, innate immunity reacts rapidly but less specifically to pathogens, whereas adaptive immunity is slower to develop but more specific and builds up immunologic memory. Immunologic memory that is mediated by gene recombination and clonal expansion is a unique feature of adaptive immunity. However, innate immunity might also demonstrate memory responses even though it may use different and less specific mechanisms. For example, invertebrates (eg, mosquitoes and bumble bees) and plants, which do not have adaptive immune systems, generate memory responses to reinfection with the same pathogens.¹ In animal models, an infection or vaccination with certain microbial products (eg, BCG, *Candida albicans*, LPS, and β -glucan) can protect against infections independent of adaptive immunity.¹ In humans, BCG vaccination in newborn children provides protection not only against tuberculosis but also against respiratory viruses and sepsis induced by other pathogens.² These previous findings suggest the presence of immunologic memory in innate immunity. The concept of “trained immunity” has recently been proposed to define a long-term adaptation of innate immunity to previous exposure to microbes or their products or a *de facto* innate immune memory.^{1,3} From the disease perspective, trained immunity is beneficial, as it improves the host’s defense against subsequent infection from pathogens. However, it could also be detrimental and result in overly active immune responses or chronic inflammation.

In asthma and allergic diseases, adaptive immune cells mediate immunologic memory to allergens by producing antigen-specific T_H2 cell-type CD4⁺ T cells and IgE antibodies. In the current issue of the *Journal of Allergy and Clinical Immunology*, Lechner et al demonstrate that innate immune cells, specifically macrophages, remember previous exposure to house dust mite (HDM) allergens.⁴

Expression of mRNA encoding chemokines and cytokines increased when human monocyte-derived macrophages were exposed to HDM extract *in vitro*. Although most mRNAs returned to baseline levels after a 5-day resting period, the levels of *CCL17* and *IL6* mRNAs remained elevated. When macrophages were re-exposed to HDM extract, the levels of CCL17, IL-6, and cysteinyl leukotrienes increased dramatically beyond the levels achieved during the initial exposure to HDM, suggesting that macrophages are “trained” to produce a large quantity of proinflammatory mediators by previous exposure to HDM. Although these HDM-exposed (or HDM-trained) and rechallenged macrophages produced a large amount of prostaglandin E₂ (PGE₂), macrophages from mice deficient in PGE₂ receptor produced less CCL17, suggesting that autocrine PGE₂ may explain the increased production of CCL17. Furthermore, blocking TNF- α during the training period or deficiency of TNF- α in myeloid cells inhibited production of CCL17 and PGE₂ following re-exposure to HDM, suggesting that autocrine TNF- α also plays a central role in the amplification event cascade. These results were recapitulated in macrophages generated from monocytes from patients with HDM sensitivity and asthma or myeloid progenitors in the bone marrow of mice previously exposed to HDM.⁴ Taken together, these results suggest that the training state is maintained during monocyte and macrophage differentiation. Thus, component(s) in HDM extract activate and likely train macrophages to produce high amounts of CCL17, IL-6, and cysteinyl leukotrienes following re-exposure to HDM through the TNF- α and PGE₂ pathways (Fig 1). Such immunologic memory or trained immunity of macrophages may facilitate recruitment of T_H2 cells and promote airway inflammation during repeated airborne exposure to allergens.

Lechner et al further investigated the molecular mechanisms.⁴ The memory in adaptive immunity is mediated by gene recombination and clonal expansion of T cells and B cells. Although the molecular mechanisms of trained immunity are not fully understood, multiple regulatory events are likely involved, including changes in chromatin organization, DNA methylation, transcription of long noncoding RNAs, and metabolic reprogramming.³ Most of the proinflammatory gene loci are repressed in a cell at a steady state,⁵ whereas epigenetic changes, including histone 3 lysine 27 acetylation (H3K27ac) and histone 3 lysine 4 methylation (H3K4me1 and H3K4me3), mark an open configuration of chromatin in trained myeloid cells.^{3,6} Metabolites regulate the activities of the enzymes that produce these epigenetic changes; for example, the tricarboxylic acid cycle metabolite fumarate and α -ketoglutarate regulate the activities of KDM5 histone demethylases and H3K27 demethylase JMJD3, respectively.⁷ Lechner et al found less abundant H3K4 or H3K9 methylation in HDM-trained macrophages.⁴ Furthermore, bone marrow-derived macrophages from HDM-exposed mice secreted more amino acids to the extracellular milieu than resting macrophages did, and they produced high amounts of the histone demethylase modulator 2-hydroxyglutamate. Supplementation with

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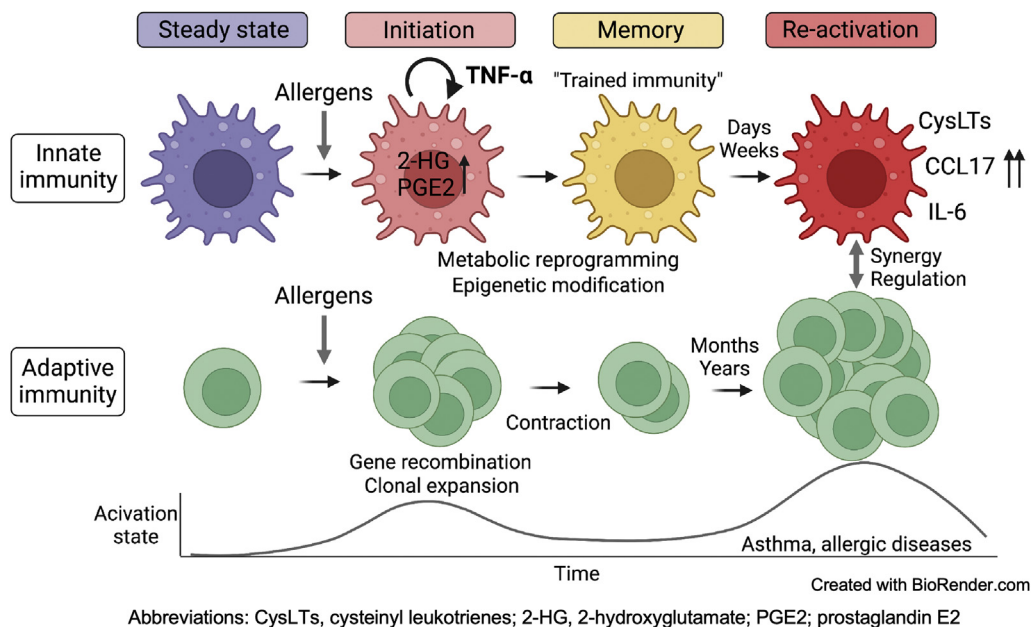
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Model for allergen memory by the immune system

FIG 1. A model for allergen memory by the immune system. The immunologic memory to allergens can be mediated by both innate and adaptive immunity. In innate immunity, component(s) of allergens activate macrophages and induce metabolic reprogramming and epigenetic modifications involving the $\text{TNF-}\alpha$ pathway. These reprogrammed macrophages (ie, trained immunity) produce a large quantity of CCL17, IL-6, and cysteinyl leukotrienes (CysLTs) following re-exposure to the allergens. In adaptive immunity, gene recombination and clonal expansion of T cells and B cells produce antigen-specific memory CD4^+ T cells and IgE and/or IgG antibodies. The interactions between memory innate immune cells and lymphocytes may produce immunopathology of asthma and allergic diseases.

exogenous 2-hydroxyglutamate promoted macrophage production of CCL17 and PGE₂, suggesting that metabolic reprogramming and epigenetic modification are likely involved in the immunologic phenotypes of HDM-trained macrophages (Fig 1).

The study by Lechner et al⁴ elegantly integrated *in vitro* tissue culture, *in vivo* mouse models, and human specimens to provide evidence for trained immunity in promoting proinflammatory functions of macrophages previously exposed to allergens. However, several questions remain. First, how long will the immunologic memory of macrophages last? In the study by Lechner et al, macrophages were rested for 5 or 7 days after the initial exposure to HDM, but immunologic memory of T cells and B cells typically lasts for months or years. Importantly, $\text{TNF-}\alpha$ signaling of macrophage progenitors in the bone marrow was altered by airborne exposure to HDM,⁴ so these progenitors may provide weeks or months of memory as they proliferate and supply peripheral tissues. The second question is related to the pathologic significance of macrophage memory, considering the redundancy of the immune system. For example, CCL17 is produced by macrophages, monocytes, and dendritic cells. Therefore, macrophages may be just a fraction of the entire pool of proinflammatory mediators. Moreover, airway pathology may not be altered significantly in the absence of macrophage memory. However, macrophages may play a pivotal role considering their unique anatomic localizations in mucosal tissues as well as rapid and robust production of cytokines and/or chemokines. Finally, the specificity of HDM-induced macrophage memory is unknown. Future studies are needed to determine whether macrophages

trained by HDM show enhanced inflammatory responses to heterogeneous allergens, such as those from fungi and pollens. If this is true, innate immune memory may provide a model to explain the clinical manifestation of patients who are reactive to many allergens. More studies are necessary to understand the biologic and pathologic roles for memory macrophages.

In summary, the article by Lechner et al⁴ provides a major advance by bringing the novel concept of trained immunity or innate immune memory to the fields of asthma and allergic diseases. As was previously shown, group 2 innate lymphoid cells from mice exposed to a protease papain, *Aspergillus* allergens, or IL-33 responded more vigorously to secondary challenge with IL-33 or papain even after a resting period of several months.⁸ In addition, airway epithelial stem cells from patients with chronic rhinosinusitis retain intrinsic memory of previous exposure to IL-4 and IL-13, which may contribute to basal cell hyperplasia and mucosal barrier dysfunction.⁹ Skin epithelial stem cells maintain accessibility to stress response genes including inflammasome components for 6 months after primary exposure to chemical proinflammatory agents.¹⁰ Therefore, various innate immune cells and stromal cells likely have the capacity to remember previous incidents of inflammation or exposure to microbial products. In the future, it will be important to examine the interactions between cells in innate immune memory and those in conventional memory responses. One might expect a synergistic interaction to promote inflammation and immunopathology, or alternatively, a regulatory interaction to harness inflammation and regain immune and tissue homeostasis. Further studies on

trained immunity will provide opportunities to better understand the immunologic mechanisms of asthma and allergic diseases and to develop new strategies to treat them.

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