

Innate IL-13 in virus-induced asthma?

Stephania A Cormier & Jay K Kolls

Although the role of adaptive immunity in asthma is well characterized, there is relatively little understanding of the contribution of innate immunity to asthma. Studies now suggest that interleukin 13 produced by innate natural helper cells in the lungs has a substantial and underappreciated role in asthma exacerbation.

An emerging story in T cell immunology is that many of the effector molecules expressed by classic helper T cell lineages such as interferon- γ (IFN- γ ; T helper type 1 (T_H1) lineage), interleukin 4 (IL-4) (T_H2 lineage), and IL-17 (T_H17 lineage) are also produced by cells of the innate immune system and are present in mice lacking recombination-activating genes. For example, innate lymphoid cells that lack lineage markers but are positive for the lineage marker Sca-1 can be a critical source of IL-17 and IFN- γ in the gut under conditions of IL-23-driven intestinal inflammation¹. Four independent laboratories have described cells (variously called natural helper cells (NHCs), multipotent progenitor type 2 cells, nuocytes or innate type 2 helper cells) that respond to IL-25 and IL-33, produce T_H2 effector cytokines and influence T_H2 differentiation^{2–5}. In this issue of *Nature Immunology*, Chang *et al.* demonstrate for the first time the presence of NHCs in the lungs and report on their role in the development of virus-induced asthma in a mouse model of influenza infection⁶.

Virus-induced asthma and asthma exacerbations are extremely common and result in substantial morbidity and mortality, as was observed in the 2009 H1N1 influenza pandemic⁷. To understand how influenza infection induces acute airway dysfunction, Chang *et al.* infect mice with influenza A virus subtype H3N1 and observe acute airway hyper-responsiveness (AHR) accompanied by

pulmonary inflammation consisting of neutrophils and macrophages but not eosinophils⁶. This AHR is transient, with a peak within 5 days of infection and resolution by 15 days after infection. The speed with which influenza induces AHR suggests an innate immune mechanism.

Chang *et al.* observe that NHCs are present in the lungs before influenza infection and that their numbers increase substantially during infection. The peak in NHCs corresponds to the peak in IL-5, IL-13 and AHR⁶. They also observe these responses in mice deficient in recombination-activating gene 2, which demonstrates that neither T cells nor B cells are necessary for AHR induction. It seems plausible that influenza could be similar to the model of infection with Sendai virus in which there is triggering of natural killer T cells and that this could be responsible for the acute and chronic production of IL-13 by macrophages⁸. However, this is not the case, as the AHR that develops in response to influenza infection occurs in mice deficient for the antigen-presenting molecule CD1d, which are deficient in natural killer T cells. The authors find that ST2, the receptor for IL-33, is necessary for the development of AHR and airway inflammation after influenza infection but not for the development of AHR in an ovalbumin-induced AHR model. This indicates that NHCs are preferentially involved in influenza-induced AHR. In fact, NHCs are dispensable for the generation of T_H2 responses and allergen-induced AHR, which raises the question of whether these cells have helper function. Depletion-reconstitution experiments with mice deficient in recombination-activating gene 2 further solidify the proposal that NHCs are required in mediating influenza-induced AHR.

Studies of mice deficient in Toll-like receptor 7 and those deficient in the critical Toll-like receptor signaling adaptor molecule MyD88 show that neither molecule is required for the

AHR and airway inflammatory response or the IL-33 production by influenza-infected alveolar macrophages *in vitro*. *In vivo*, IL-33 is produced by alveolar macrophages, dendritic cells and airway epithelial cells, and as an alarmin, it is released during apoptosis or pyroptosis⁹. The ultimate source of IL-33 in the model by Chang *et al.* awaits future research.

Several lines of evidence indicate that the NHCs identified by Chang *et al.* are similar to the nuocytes, NHCs or natural T_H2 cells identified in fat-associated clusters and mesenteric lymph nodes of helminth-infected mice^{2,3,10}. First, their phenotypic markers are similar. Second, IL-33 is sufficient to activate all of these cells^{2,3}. Third, their activation is characterized by population expansion and secretion of IL-5 and IL-13 and is antigen independent^{2,3}, and IL-13 is necessary for influenza-induced AHR and airway inflammation. A considerable difference between the nuocytes and NHCs involved in the response to helminths and the NHCs identified by Chang *et al.* seems to be their ability to enhance T cell and B-1 B cell function^{2,3}. Although Chang *et al.* do not directly investigate the ability of their NHCs to provide helper function, their data demonstrating the development of severe ovalbumin-triggered AHR in mice deficient in ST2 suggests that NHCs may not be 'helper' cells⁶. As some researchers have begun to group nuocytes, NHCs and multipotent progenitors together, it is important to point out that the NHCs in the study presented here⁶ are probably not the multipotent progenitors identified in gut-associated lymphoid tissue⁵, which are phenotypically distinct (ST2⁻) from the NHCs identified in the lungs (ST2⁺), are activated solely by IL-25 to secrete IL-4 and are able to induce T_H2 differentiation.

In summary, Chang *et al.* propose a new IL-33–IL-13 axis involving NHCs that is

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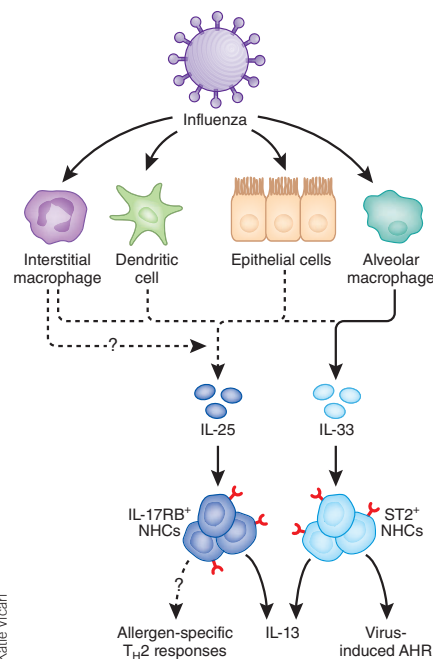


Figure 1 Innate lymphoid cells produce IL-13 and mediate virus-induced AHR. An ST2⁺ population of NHCs has now been shown to exist in the lungs and expand after infection of the host with influenza⁶. Influenza triggers the release of IL-33 from many lung-resident cells, possibly including interstitial macrophages, dendritic cells, epithelial cells and alveolar macrophages. NHCs respond to this IL-33 by producing IL-13 and are required for virus-induced AHR. These newly identified ST2⁺ NHCs⁶ do not affect allergen-induced (T cell-dependent) AHR, which suggests that they do not influence allergen-specific T_H2 differentiation. It remains to be determined if there are other distinct subsets of NHCs in the lungs (such as NHCs positive for IL-17 receptor B (IL-17RB⁺)) that respond to IL-25 and/or IL-33 and function as helpers of T_H2 cells, linking viral infection to allergen-specific immune responses. Dashed lines indicate other potential pathways for the production of IL-25 or IL-33 not actually demonstrated by Chang and colleagues⁶.

responsible for acute AHR after infection with influenza⁵ (Fig. 1). They further propose a mechanism whereby influenza infects alveolar macrophages (or some other cell type in the lungs), which results in the rapid release of IL-33. IL-33 then activates NHCs already present in the lungs through the receptor ST2, which results in the secretion of IL-13. IL-13 is then responsible for the influenza-induced AHR, airway inflammation and mucus hyperproduction. How do these data contribute to the understanding of asthma? The exacerbation of pulmonary dysfunction after acute influenza infection in patients with chronic lung diseases, including asthma, is well documented. Chang *et al.* demonstrate that the consequences of acute influenza infection induce an innate pathway that leads to the production of IL-13 (ref. 6), which has been shown to be responsible for many of the characteristics of asthma (such as mucus hyperproduction, AHR, lung remodeling and so on)¹¹. This work by Chang *et al.*⁶ also adds to published literature supporting the idea of a role for the innate immune system and non-T_H2 cells in asthma^{8,12} and makes it clear that the traditional T_H2 paradigm for asthma needs to be revisited and expanded for full understanding of this complex disease state. The idea that the innate immune system and adaptive immune system act synergistically to prolong immune system dysfunction in the lungs indicates a potential mechanism by which viral infection may affect the development of lung inflammation and airway obstruction seen in asthma.

Indeed, an early increase in IL-13 in the lungs has been observed in other respiratory viral infections in both humans and mouse models^{13,14}. Because the results of Chang *et al.* firmly establish a role for NHC production of IL-13 in influenza-induced AHR⁶, we speculate that NHCs and IL-13 are involved in

the response to infection with other respiratory viruses such as rhinovirus (the most common cause of asthma exacerbations in adult humans) and respiratory syncytial virus (the most common cause of asthma exacerbations in children). Finally, although the presence and role of NHCs in human asthma remain unknown, evidence for the involvement of IL-33 and IL-13 in human asthma suggests that the mechanism identified in mice also exists in humans. This aspect is most exciting, given published data showing that antibodies to IL-13 are protective in the early phases of an allergen-challenge model of human asthma¹⁵. Interestingly, this protection occurs without an effect on the AHR response to methacholine at 14 or 35 days after allergen challenge; thus, the NHC component of the AHR response may be modulated by treatment with antibody to IL-13, but the T cell component may not be modulated that way¹⁵. The data from Chang *et al.* suggest that targeting IL-13 and/or NHCs may also prevent virus-induced asthma exacerbations.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Where, in antiviral defense, does IFIT1 fit?

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New data show that the interferon-induced gene product IFIT1 is a sensor for 5'-triphosphorylated RNA of viral origin and that it functions within a larger IFIT complex to inhibit viral replication.

After being infected with virus, cells initiate the production of type I interferons, which are cytokines that elicit an antiviral state.

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This powerful alarm system ensures that viral replication is suppressed and thereby inhibits further viral spread. Shortly after the discovery of type I interferons, it was noted that viral nucleic acids are potent triggers of type I interferons, and indeed the past decade of research has identified a set of germline-encoded pattern-recognition receptors that function to sense viral infection via the presence of 'foreign'

nucleic acids, which leads to the production of type I interferons¹. Although the initial recognition of viruses is achieved by only a limited number of pattern-recognition receptors, the antiviral effector programs triggered by these receptor systems are based on the concerted action of the products of hundreds of interferon-stimulated genes (ISGs). Although there is an increasingly clear picture of how sensing