

PERSPECTIVES

OPINION

A role for natural killer T cells in asthma

Dale T. Umetsu and Rosemarie H. DeKruyff

In several mouse models, natural killer T cells have recently been found to be required for the development of airway hyper-reactivity, a cardinal feature of asthma. Moreover, in patients with chronic asthma, natural killer T cells with a T-helper-2-like phenotype (that is, that express CD4 and produce T helper 2 cytokines) are present in the lungs in large numbers. In this Opinion article, we suggest that natural killer T cells, which express a restricted T-cell receptor and respond to glycolipids rather than protein antigens, have a previously unsuspected but crucial role, distinct from that of T helper 2 cells, in the pathogenesis of asthma.

Bronchial asthma is a major public-health problem in industrialized countries and causes significant morbidity and mortality. Asthma is associated with an inflammatory process that is characterized by the presence of numerous eosinophils and CD4⁺ T cells in the airways. Pulmonary CD4⁺ T cells produce the T helper 2 (T_H2) cytokines interleukin-4 (IL-4), IL-5, IL-9 and IL-13, which have essential roles in the development of asthma. These cytokines increase the growth and differentiation of eosinophils, basophils, mast cells and IgE-producing B cells, as well as the recruitment of these cells to the lungs, and they directly induce airway hyper-reactivity (AHR), a cardinal feature of asthma (BOX 1). Therefore, conventional, MHC-class-II-restricted CD4⁺ T cells have been thought to have a crucial and obligatory role in the pathogenesis of bronchial asthma. Recently, however, we and others have shown that CD4⁺ invariant natural killer T (iNKT) cells are required for the development of allergen-induced AHR in mouse models of asthma. Therefore, we propose that CD4⁺ iNKT cells have as important a role as conventional CD4⁺ T cells in the pathogenesis of asthma.

Since 1986, when the T_H1/T_H2 paradigm was first proposed, T_H2 cells and adaptive immunity have been thought to regulate the development of asthma. There is now

extensive experimental evidence indicating that conventional, MHC-class-II-restricted CD4⁺ T cells have a crucial role in the pathogenesis of asthma. Several studies have shown that the depletion of CD4⁺ T cells improves or prevents the development of asthma^{1,2}. Investigators have also shown the presence of numerous CD4⁺ T cells that produce T_H2 cytokines in the lungs of patients with asthma^{3,4}. Moreover, adoptive transfer of antigen-specific T_H2 cells into naive recipients has been found to result in the development of AHR^{5–7}, and adoptive transfer of CD4⁺

T cells into recombination-activating gene (RAG)-deficient mice, which lack T cells and B cells and fail to develop AHR, restores the development of AHR⁸. These results strongly indicate that conventional, antigen-specific T_H2 cells coordinate the inflammatory response that is associated with asthma. Because T_H2 cytokines (that is, IL-4, IL-5, IL-9 and IL-13) are crucial regulators of asthma, it is easy to understand the assumption that the main source of T_H2 cytokines in asthma is conventional, MHC-class-II-restricted T_H2 cells.

CD4, however, is also expressed by NKT cells, which have many of the same features as conventional CD4⁺ T cells, including the capacity to produce T_H2 cytokines. CD4⁺ NKT cells that express an invariant T-cell receptor (TCR; known as iNKT cells) and that produce T_H2 cytokines might therefore look similar to conventional CD4⁺ T cells and function in a similar manner (FIG. 1). We propose that these T_H2-like iNKT cells have a crucial role in regulating the development of asthma.

Characteristics of NKT cells

The newly described subset of lymphocytes known as iNKT cells expresses characteristics of both natural killer (NK) cells and conventional T cells. These cells belong to a broader heterogeneous group of cells known as NKT cells, which have been categorized into three types on the basis of their TCR repertoire⁹. Type I NKT cells (also known

Box 1 | Airway hyper-reactivity

Asthma is characterized by chronic inflammation of the airways that involves several types of immune cell — including mast cells, eosinophils, T cells and basophils — and results in the symptoms of wheezing, breathlessness, chest tightness and coughing. Asthma symptoms are often associated with air-flow obstruction, which is usually reversible (for example, with medication), and with bronchial or airway hyper-reactivity (AHR) to non-specific stimuli, such as cold air, aerosolized water, smoke or fumes. The degree of AHR roughly correlates with the severity of asthma and can increase in patients with viral infection or after exposure to allergens.

AHR is a cardinal feature of asthma and can be measured in humans and in mice by delivering progressively increasing doses of a provocative stimulus (for example, methacholine or histamine) while assessing pulmonary function. Greater loss of pulmonary function with smaller doses of stimulus indicates greater AHR. In experimental models, pulmonary function can be measured by assessing the relationship between lung volume and airway pressure using instruments that measure variations in the size of the lungs in relation to the amount of air passing into them (known as whole-body plethysmography) or by directly measuring airway resistance and compliance in intubated and mechanically ventilated animals.

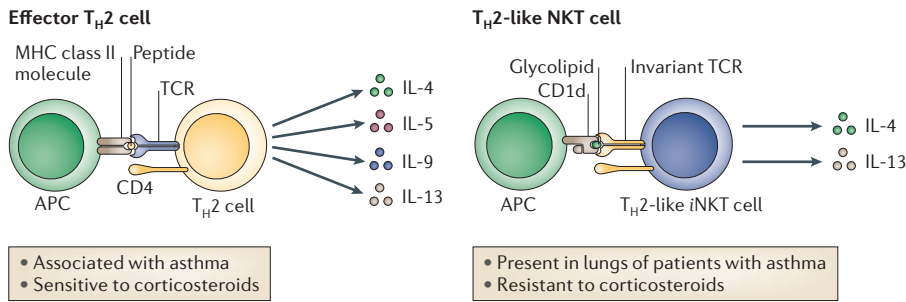


Figure 1 | The relationship between T helper 2 cells and T-helper-2-like invariant natural killer T cells. Effector T helper 2 (T_H2) cells and T_H2-like invariant natural killer T (iNKT) cells have similar features, such as the expression of CD4 and the production of the T_H2 cytokines interleukin-4 (IL-4) and IL-13. However, iNKT cells express an invariant T-cell receptor (TCR) and natural killer (NK)-cell markers, and they respond to CD1d-associated glycolipids rather than to MHC-class-II-associated peptides. Furthermore, iNKT cells, but not T_H2 cells, might be resistant to corticosteroid therapy. APC, antigen-presenting cell.

as iNKT cells or classical NKT cells) express a highly restricted repertoire of invariant (conserved) $\alpha\beta$ -TCRs, with each TCR having an invariant α -chain. In mice, the TCR α -chain contains a region encoded by the V α 14 variable gene segment and the J α 18 joining gene segment (V α 14–J α 18), whereas the TCR α -chain contains V α 24–J α 18 in humans¹⁰. These cells are also restricted by the non-polymorphic MHC-class-I-like protein CD1d, and can be identified and isolated by using CD1d tetramers loaded with the glycolipid α -galactosylceramide (α -GalCer). Similar to iNKT cells, type II NKT cells (also known as non-classical or non-invariant NKT cells) are CD1d restricted, but these NKT cells have a diverse TCR repertoire. These cells have been associated with ulcerative colitis in humans and with suppression of tumour growth^{11–14}. Type III NKT cells (also known as CD1d-independent NKT cells) express a diverse repertoire of TCRs that are restricted by MHC class I and class II molecules. As discussed in this article, iNKT cells regulate the development of asthma^{15,16}, although the possible role of type II and type III NKT cells in the pathogenesis of asthma has not been critically evaluated.

Of the three types of NKT cells, iNKT cells are the best characterized, mainly because of the availability of reagents to isolate and examine iNKT cells. These cells have a CD4⁺ or CD4⁺CD8[−] (double negative) phenotype, and in humans, a small subset of iNKT cells expresses CD8. In contrast to the TCRs of conventional, MHC-class-II-restricted T cells, the invariant TCR of iNKT cells recognizes glycolipid antigens that are presented in the context of CD1d^{17–19}. CD1d is widely expressed, including by intestinal and airway epithelial cells,

hepatocytes, T cells, B cells, macrophages and dendritic cells (DCs)^{17,20}. The recognition of CD1d-associated glycolipids, such as α -GalCer, by iNKT cells is highly conserved across species, indicating that these cells have a pivotal role in immunity.

When iNKT cells are activated through their invariant TCR, they rapidly produce large quantities of cytokines such as IL-4 and interferon- γ (IFN γ) within hours. This cytokine production occurs much more rapidly than cytokine production by conventional T cells, and this innate-like immune response can amplify and regulate adaptive immunity by influencing the function of DCs, NK cells and B cells, as well as conventional CD4⁺ and CD8⁺ T cells⁹. Moreover, the rapid production of cytokines by iNKT cells has been shown to regulate the development of autoimmunity^{10,13,21}, antimicrobial²², antitumour²³ and antitransplant²⁴ immune responses, with either disease-inducing or disease-protective effects. For example, iNKT cells can either promote or prevent tumour growth, colitis and experimental autoimmune encephalomyelitis in mice, depending on the strain of mouse and the conditions of stimulation. Similarly, activation of iNKT cells with α -GalCer suppresses systemic-lupus-erythematosus-like autoimmunity in BALB/c mice but promotes it in SJL/J mice, presumably owing to differences in IL-4 expression by iNKT cells in these mice²⁵.

iNKT-cell-dependent pathways in asthma

In mice, we and others have shown that iNKT cells are required for the development of AHR^{15,16,26}. In these models, CD1d-deficient mice — which lack iNKT cells — failed to develop allergen-induced AHR, as measured by whole-body plethysmography

or by direct measurement of airway resistance and dynamic compliance in intubated and mechanically ventilated mice (BOX 1). These mice did develop some eosinophilic airway inflammation and mucus production, although to a lesser extent than did wild-type mice^{15,26}. Wild-type mice that were treated with CD1d-specific monoclonal antibody before allergen sensitization and challenge also failed to develop AHR¹⁶, strongly indicating that iNKT cells are required for the development of asthma.

We confirmed the requirement for iNKT cells in the development of AHR by examining allergen-induced AHR in J α 18-deficient mice, which lack the α -chain of the invariant TCR and therefore lack iNKT cells²⁷. Similar to CD1d-deficient mice, J α 18-deficient mice failed to develop allergen-induced AHR. Moreover, adoptive transfer of purified wild-type iNKT cells into J α 18-deficient mice before allergen challenge fully restored airway inflammation and AHR¹⁵. However, adoptive transfer of iNKT cells from mice deficient in both IL-4 and IL-13 to J α 18-deficient mice failed to restore AHR, indicating that the production of IL-4 and IL-13 by iNKT cells is required for the development of AHR. Taken together, these studies, which were carried out by several research groups and in several mouse strains, show that iNKT cells that produce IL-4 and IL-13 are required for the development of allergen-induced AHR.

The requirement for iNKT cells in the development of AHR is curious, because antigen-induced T_H2-cell responses and antigen-specific T_H2 cells develop and respond normally in CD1d-deficient mice and in J α 18-deficient mice, but these responses are clearly insufficient for the induction of AHR^{15,28}. Moreover, the induction of antigen-specific IgE production during adaptive immune responses is unaffected by the absence of iNKT cells^{28,29}. These results indicate that adaptive immune responses that involve T_H2 cells and IgE production do not require the presence of iNKT cells, but such responses *per se* seem to be insufficient for the development of AHR. These mouse studies provide a possible explanation for the observation that many patients with allergic rhinitis, who develop allergen sensitization and have allergen-specific T_H2-cell and IgE responses, do not automatically develop asthma, a disease that in humans might also require the involvement of iNKT cells.

Although iNKT cells are not required for the induction of T_H2-cell-associated immune responses, they have been shown to influence T_H2-cell-biased responses¹⁰.

For example, *i*NKT cells are an important source of T_H2 cytokines and can promote the development of T_H2 -cell-biased responses. Therefore, investigators have found that co-administration of exogenous protein antigen with α -GalCer, which specifically activates *i*NKT cells and can induce the production of both IL-4 and IFN γ , results in an increase in T_H2 -cell-associated sensitization of mice to these antigens³⁰. Similarly, activation of *i*NKT cells *in vivo* with α -GalCer or other glycolipid antigens results in a rapid increase in total serum IgE³¹. In addition, V α 14-J α 18-transgenic mice, which express more TCRs that contain this invariant α -chain than do wild-type mice and therefore contain more *i*NKT cells, have higher serum concentrations of the T_H2 -cell-associated immunoglobulins, IgG1 and IgE³².

The α -chain of CD1d associates with β_2 -microglobulin (β_2m) to form the complete heterodimeric CD1d molecule. Mice deficient in β_2m lack all MHC class I molecules, including CD1d, and are devoid of CD8⁺ cells and *i*NKT cells. Treatment of mice deficient in β_2m with polyclonal antibodies specific for IgD, which normally induce IgE production in most mouse strains, failed to induce IgE production in these mice³³. These results indicate that CD1d-dependent activation of *i*NKT cells might be involved in increasing T_H2 -cell and IgE responses, either by providing a rapid source of IL-4 to promote development into T_H2 cells and class switching to IgE or by interacting directly with DCs, T cells and B cells to promote development into T_H2 cells³⁴. However, the precise mechanisms by which *i*NKT cells modulate T_H2 -cell and IgE responses are poorly understood at present. Nevertheless, these studies show that there might be several roles for *i*NKT cells in the development of asthma, including functioning as an adjuvant to increase T_H2 -cell-associated responses to exogenous protein antigens early in the immune response and increasing the development of immunological memory and adaptive immunity.

Recently, we showed that *i*NKT cells not only regulate adaptive immunity in asthma but also are sufficient for the development of AHR. When pulmonary *i*NKT cells were directly activated by glycolipid antigens, such as α -GalCer or α -glucuronosylceramide (a glycolipid constituent of the membrane of *Sphingomonas* spp.), AHR and eosinophilic airway inflammation were rapidly induced³¹. The induction of AHR with glycolipids did

not require the presence of eosinophils (as shown in mice treated with IL-5-specific monoclonal antibody) or the presence of B cells (as shown in B-cell-deficient mice)³¹. Moreover, these glycolipids induced AHR in MHC-class-II-deficient mice, which lack conventional CD4⁺ T cells but have large numbers of *i*NKT cells, showing that *i*NKT-cell-driven AHR can occur in the absence of conventional CD4⁺ T cells. Together, these results indicate that *i*NKT cells are potent effector cells in the lungs and are sufficient for inducing AHR.

Possible NKT-cell-independent pathways

Although the requirement for *i*NKT cells in the development of allergen-induced AHR has been established and confirmed by several research groups, there are some mouse models of asthma in which the presence of *i*NKT cells has not been found to be required. For example, one study concluded that *i*NKT cells were not required for asthma, because allergen-induced airway inflammation, as measured by increased eosinophilic airway inflammation, developed in mice deficient in CD1d³⁵. Importantly, AHR, which does not always correlate with eosinophilic airway inflammation, was not assessed in these studies, but it might be the crucial feature that requires the presence of *i*NKT cells. On the other hand, in studies using β_2m -deficient mice, *i*NKT cells were shown not to be required for the development of AHR^{36,37}. Allergen sensitization and challenge of β_2m -deficient mice resulted in eosinophilic airway inflammation and AHR. However, CD1d-independent (type III) NKT cells are present in β_2m -deficient mice^{38,39}, and some forms of CD1d are expressed in the absence of β_2m ^{38,40}, indicating that some

types of NKT cell (that is, type II or type III NKT cells) might indeed be involved in the development of AHR in these mice. Mice that lack the transcription factor T-bet, which have a defect in the maturation of *i*NKT cells and therefore have fewer peripheral *i*NKT cells⁴¹, are known to spontaneously develop AHR⁴². It is possible that the remaining immature *i*NKT cells in T-bet-deficient mice preferentially produce IL-4 and induce AHR, because immature *i*NKT cells express IL-4 but only small amounts of IFN γ ⁴³. These studies, nevertheless, indicate that, although it is possible that *i*NKT cells are required for the development of allergen-induced AHR in most circumstances, there might be situations in which some forms of airway inflammation or AHR develop in the absence of *i*NKT cells.

Human studies of asthma and *i*NKT cells

The study of allergen-induced AHR in mice indicated that *i*NKT cells might be important in human asthma. However, mouse models of asthma do not replicate all features of human asthma, so it is important to assess the role of *i*NKT cells in humans. The only available method for determining the role of these cells in humans is direct assessment of *i*NKT-cell activity in human patients with asthma. Using CD1d tetramers loaded with α -GalCer and reverse-transcription-PCR analysis of the invariant TCR of *i*NKT cells, we examined the frequency and distribution of *i*NKT cells in the lungs of patients with moderate to severe persistent asthma⁴⁴. Surprisingly, ~60% of the pulmonary CD4⁺CD3⁺ cells in these patients were not MHC-class-II-restricted CD4⁺ T cells as was previously thought but were *i*NKT cells

Box 2 | Subsets of human invariant natural killer T cells

The many distinct functions of invariant natural killer T (*i*NKT) cells might be explained by the existence of several subsets of *i*NKT cells with distinct cytokine-expression profiles. Human CD4⁺CD8[−] (double negative) *i*NKT cells produce T helper 1 (T_H1) cytokines such as interferon- γ and could be termed T_H1 -like *i*NKT cells. These cells are important in induction of autoimmunity and in protection against the development of cancer and allergic diseases. By contrast, CD4⁺ *i*NKT cells that are found in the lungs of patients with asthma produce T_H2 cytokines (interleukin-4 (IL-4) and IL-13 and not interferon- γ) and could be termed T_H2 -like *i*NKT cells. These cells have a phenotype that is similar to conventional T_H2 cells, making it difficult to distinguish the two. But this phenotype indicates that both T_H2 cells and T_H2 -like *i*NKT cells might be involved in inducing asthma or protecting against autoimmunity.

Human CD4⁺ *i*NKT cells in the peripheral blood have an unrestricted cytokine-expression profile and could be termed T_H0 -like *i*NKT cells. These cells preferentially express CC-chemokine receptor 4 (CCR4), which might be important for localization to the lungs and the skin, where epithelial cells produce large amounts of the CCR4 ligands CC-chemokine ligand 17 (CCL17; also known as TARC) and CCL22 (also known as MDC). By contrast, CXCR6-expressing *i*NKT cells seem to localize to the liver and to allografts. These studies indicate that *i*NKT cells could also be categorized into subsets on the basis of chemokine-receptor expression or tissue of origin¹².

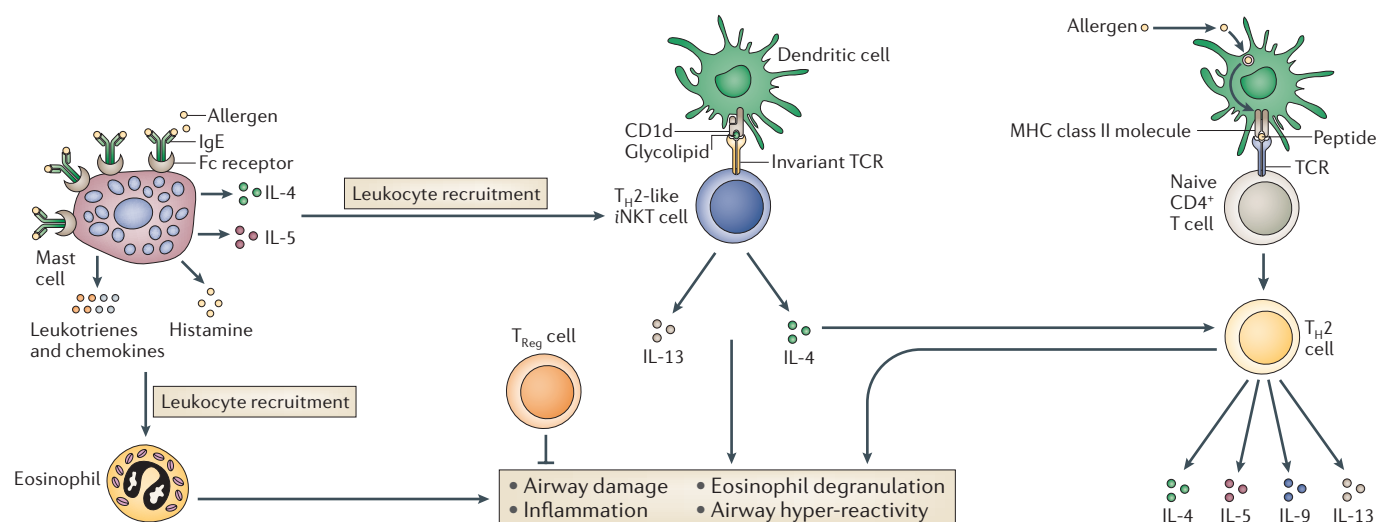


Figure 2 | How natural killer T cells fit in with the current model of asthma. Within minutes of contact with allergen, IgE-sensitized mast cells degranulate, releasing both pre-formed and newly synthesized mediators, including histamine, leukotrienes, chemokines and cytokines. These factors promote airway hyper-reactivity and damage. Chemokines and cytokines that are released by mast cells (as well as by endothelial and T cells) recruit leukocytes, including eosinophils, invariant natural killer T (iNKT) cells and T cells. Several CD4⁺ T-cell populations regulate the development of asthma. These include the

following: effector T helper 2 (T_{H2}) cells, which secrete interleukin-4 (IL-4), IL-5, IL-9 and IL-13 and increase airway inflammation; CD4⁺CD25⁺ regulatory T (T_{Reg}) cells, which inhibit airway inflammation; and CD4⁺ iNKT cells, which have features similar to T_{H2} cells (IL-4 and IL-13 production) but differ by expressing an invariant T-cell receptor (TCR). Both T_{H2} cells and T_{H2}-like iNKT cells might have effector-cell functions in asthma. In addition, other subsets of iNKT cells (for example, T_{H1}-like iNKT cells, which produce T_{H1} but not T_{H2} cytokines) might protect against the development of asthma.

(which expressed the invariant Vα24–Jα18-containing TCR). Furthermore, the pulmonary iNKT cells had a cytokine-expression profile similar to that of T_{H2} cells, including expression of IL-4 and IL-13 but not IFNγ. Equally surprising was the finding that more than 95% of the iNKT cells in the lungs of patients with asthma express CD4, whereas only ~40% of iNKT cells in the peripheral blood of both normal and asthmatic individuals express this marker (BOX 2). By contrast, the CD4⁺ T cells found in the lungs of patients with sarcoidosis (an inflammatory disease in which large numbers of CD4⁺ cells are found in the lungs) were conventional CD4⁺CD3⁺ T cells and not iNKT cells. These studies indicate that iNKT cells are indeed present in the lungs of patients with asthma and have a prominent pathogenic role in human asthma (FIG. 2).

The large number of iNKT cells in the lungs of patients with moderate to severe asthma is striking, especially given that these cells constitute less than 0.1% of the mononuclear cells and less than 1% of the CD4⁺ cells in the peripheral blood in normal individuals. In addition, our finding that more than 95% of the iNKT cells in the lungs of patients with asthma are CD4⁺ cells (compared with only ~40% in the peripheral blood) indicates that CD4⁺ iNKT cells are recruited to the lungs and enriched at least

100-fold. Because the number of CD4⁺ iNKT cells is not higher in the peripheral blood of patients with asthma than in non-asthmatic individuals^{44,45}, our study indicates that studying the immunology of asthma needs to involve evaluation of cells from within the lungs and not examination of the peripheral blood. Precisely which mechanisms selectively recruit or stimulate the preferential proliferation of these T_{H2}-like iNKT cells^{46,47} in the lungs are not yet clear, although the selective recruitment of these cells might be associated with differential expression of chemokine receptors by iNKT cells that home to the lungs⁴⁸.

In our studies of patients with asthma, although we showed that iNKT cells were present in the lungs, we do not know how the iNKT cells might become activated and induce the symptoms of asthma. In mice, sensitization and challenge with protein antigen (for example, ovalbumin or bovine serum albumin, which do not contain glycolipids) clearly induces AHR without any further requirement for administration of glycolipid antigen^{15,16}. Because the activation of iNKT cells is required for the development of AHR induced by protein antigens, it is probable that iNKT cells (which respond to glycolipid antigens and not protein antigens) are activated by endogenous glycolipids that become expressed in the inflammatory environment that is elicited

by the protein antigen and T_{H2} cells. It is unclear precisely which endogenous glycolipids function in this way, but isoglobotrihexosylceramide (iGb3)^{19,49} (and possibly other glycolipids) might be involved.

In other situations, exogenous glycolipids from microorganisms or plant pollens that enter the lungs might activate iNKT cells directly and cause wheezing. This possibility is supported by the findings that AHR can be induced directly with glycolipids from the *Sphingomonas* spp. of bacteria³¹ and that human iNKT cells have been shown to respond to lipids from cypress-tree pollen⁵⁰. The range of exogenous (and endogenous) glycolipid antigens that can activate iNKT cells and perhaps cause AHR is only now being investigated. Given the evidence that iNKT cells are both necessary and sufficient for AHR, future studies that examine the capacity of glycolipids from respiratory pathogens and plant pollens to activate iNKT cells and induce AHR could greatly improve our understanding of respiratory pathobiology.

Implications

The idea that iNKT cells are crucial for the development of asthma is clearly unexpected, but if this hypothesis is true, there are several important implications. First, the hypothesis that iNKT cells are required for the development of AHR implies that

previous studies showing the importance of T_H2 cells in the lungs of patients with asthma might have mistakenly identified *i*NKT cells as conventional T_H2 cells. This is not surprising because pulmonary *i*NKT cells in patients with asthma have many of the features of T_H2 cells (such as CD4 expression and T_H2 -cytokine production). Nevertheless, T_H2 cells might have an important role in asthma, and the proportion of *i*NKT cells to conventional CD4⁺ T cells in the lungs of patients with asthma should be further assessed, because this ratio might vary with disease severity.

A second implication of the idea that *i*NKT cells are important for the development of asthma is that it might provide an explanation for the 10–30% of patients with asthma who respond poorly to treatment with corticosteroids. Corticosteroids are central to the treatment of asthma, because they have potent anti-inflammatory effects and therefore inhibit the function of eosinophils, T_H2 cells, epithelial cells and endothelial cells. Until now, corticosteroid-resistant asthma, which accounts for half or more of the health-care costs that are associated with asthma^{51,52}, has been difficult to explain, given that eosinophils and T_H2 cells respond promptly to corticosteroids. By contrast, *i*NKT-cell function is relatively resistant to corticosteroid therapy^{53,54}, consistent with our findings that treatment with inhaled corticosteroids did not affect the frequency of *i*NKT cells in the lungs of the limited number of asthmatic patients who have been studied so far⁴⁴.

Third, the findings discussed here indicate that treatments that reduce the function or the number of pulmonary *i*NKT cells might be effective treatments for asthma, particularly in those patients who are resistant to treatment with corticosteroids. For example, when given early

during the development of allergen-induced AHR, a monoclonal antibody that blocks antigen presentation by CD1d and therefore prevents the activation of *i*NKT cells has been shown to be effective at preventing the development of AHR¹⁶ (TABLE 1). The effectiveness of this approach is limited, however, because it seems that, after initial activation, *i*NKT cells are less dependent on CD1d-mediated signalling through the TCR and might retain their activity despite blockade of CD1d (E. H. Meyer and D.T.U., unpublished observations). Another possible approach could involve the administration of α -GalCer. Administration of α -GalCer intravenously or intraperitoneally 24 hours before respiratory challenge of sensitized mice with ovalbumin has been shown to reduce airway inflammation and to inhibit allergen-induced AHR^{55–57}. This result might be due to increased production of IFN γ and/or development of regulatory T cells⁵⁵, or it could be a consequence of rendering *i*NKT cells unresponsive or anergic to further stimulation for a period of days to weeks⁵⁸. Such a therapeutic approach with α -GalCer might be problematic in that α -GalCer could function as an adjuvant and increase allergen sensitization³⁰, thereby exacerbating allergy and AHR. Therefore, other therapeutic approaches that are focused on selectively eliminating *i*NKT cells from the lungs or selectively reducing *i*NKT-cell function must be developed for optimal treatment of asthma.

Last, glycolipid antigens might have an important role in asthma in the activation of *i*NKT cells and the triggering of the development of asthma, a role that has not been previously suspected. Therefore, future immunotherapies for allergy and environmental control measures for asthma must take this issue into account.

Dale T. Umetsu and Rosemarie H. DeKruyff are at the Division of Immunology, Children's Hospital Boston, Department of Pediatrics, Harvard Medical School, 1 Blackfan Circle, Boston, Massachusetts 02115, USA.

Correspondence to D.T.U.

e-mail: dale.umetsu@childrens.harvard.edu

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Table 1 | Possible therapies that target invariant natural killer T cells in asthma

Treatment	Proposed mechanism	Limitations
CD1d-specific monoclonal antibody	Prevents activation of <i>i</i> NKT cells	Activity of antibody might be limited in situations in which <i>i</i> NKT cells are already activated, because activated <i>i</i> NKT cells might have a reduced requirement for restimulation of the TCR through CD1d
α -GalCer	Induces anergy in <i>i</i> NKT cells	α -GalCer activates <i>i</i> NKT cells before inducing anergy, so the initial activation might exacerbate asthma or increase allergen sensitization
<i>i</i> NKT-cell-depleting monoclonal antibody	Targets specific <i>i</i> NKT-cell antigen and eliminates <i>i</i> NKT cells from lungs	No known <i>i</i> NKT-cell-specific molecule, except the invariant TCR
Immunomodulation of <i>i</i> NKT cells	Alters cytokine-expression profile of <i>i</i> NKT cells	Mechanisms to alter cytokine production by <i>i</i> NKT cells are not yet known

α -GalCer, α -galactosylceramide; *i*NKT, invariant natural killer T; TCR, T-cell receptor.

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Competing interests statement

The authors declare **competing financial interests**: see web version for details.

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