

OPINION

A role for natural killer T cells in asthma

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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-cell-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 [AU:proliferation, production?] and differentiation of eosinophils, basophils, mast cells and IgE-producing B cells, as well as their recruitment to the lungs, and they directly induce airway hyper-reactivity (AHR), a cardinal feature of asthma (BOX 1). Therefore, conventional MHC-class-II-restricted [AU: see e-mail (1)] 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 AHR⁵⁻⁷, 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 a semi-invariant [AU:(2)] 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-cell-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 immune cells — 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 relationship 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.

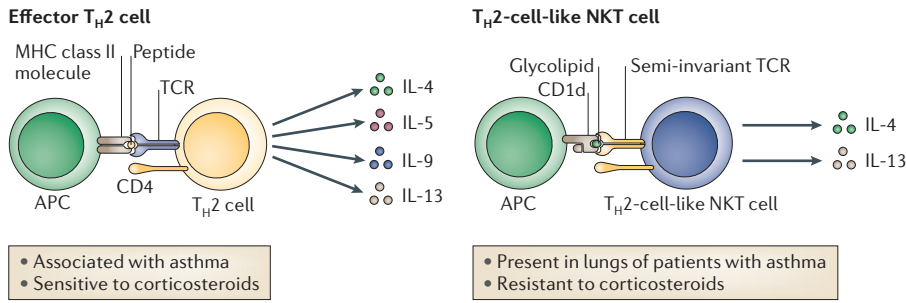


Figure 1 | The relationship between T helper 2 cells and T-helper-2-cell-like natural killer T cells. Effector T helper 2 (T_H2) cells and T_H2 -cell-like natural killer T (NKT) cells have similar features, such as the expression of CD4 and the production of the T_H2 cytokines interleukin-4 (IL-4) and IL-13. However, NKT cells express a semi-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, NKT cells, but not T_H2 cells, might be resistant to corticosteroid therapy. APC, antigen-presenting cell.

as *i*NKT cells or classical NKT cells) express a highly restricted (also called conserved or semi-invariant) repertoire of $\alpha\beta$ -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 *i*NKT cells, type II NKT cells (also known as non-classical or non-invariant NKT cells) are CD1d restricted, but type II NKT cells have a diverse TCR repertoire. These cells have been associated with oxazolone-induced colitis in mice, 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, *i*NKT 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, *i*NKT cells are the best characterized, mainly because of the availability of reagents to isolate and examine *i*NKT cells. These cells have a CD4⁺ or CD4[−]CD8[−] (double negative) phenotype, and in humans, a small subset of *i*NKT cells expresses CD8. In contrast to the TCRs of conventional MHC-class-II-restricted T cells, the semi-invariant TCR of *i*NKT 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 *i*NKT cells is highly conserved across species, indicating that these cells have a pivotal role in immunity.

When *i*NKT cells are activated through their semi-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 *i*NKT cells has been shown to regulate the development of autoimmune^{10,13,21}, antimicrobial²², antitumour²³ and antitransplant immune responses²⁴, with either disease-inducing or disease-protective effects. For example, *i*NKT cells can either promote or prevent tumour growth, colitis and experimental allergic encephalomyelitis in mice, depending on the strain of mouse and the conditions of stimulation. Therefore, activation of *i*NKT cells with α -GalCer suppresses systemic-lupus-erythematosus in BALB/c mice but promotes it in SJL/J mice, presumably owing to differences in IL-4 expression by *i*NKT cells in these mice²⁵.

***i*NKT-cell-dependent pathways in asthma**

In mice, we and others have shown that *i*NKT cells are required for the development

of AHR^{15,16,26}. In these models, CD1d-deficient mice — which lack *i*NKT 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 *i*NKT cells are required for the development of asthma.

We confirmed the requirement for *i*NKT cells in the development of AHR by examining allergen-induced AHR in J α 18-deficient mice, which lack the α -chain of the semi-invariant TCR and therefore lack *i*NKT cells²⁷. Similar to CD1d-deficient mice, J α 18-deficient mice failed to develop allergen-induced AHR. Moreover, adoptive transfer of purified wild-type *i*NKT cells into J α 18-deficient mice before allergen challenge fully restored airway inflammation and AHR¹⁵. However, adoptive transfer of *i*NKT 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 *i*NKT 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 *i*NKT cells that produce IL-4 and IL-13 are required for the development of allergen-induced AHR.

The requirement for *i*NKT cells for the development of AHR is curious, because antigen-induced T_H2 -cell responses and antigen-specific T_H2 cells develop normally in CD1d- and 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 *i*NKT cells^{28,29}. These results indicate that adaptive immune responses that involve T_H2 cells and IgE production do not require the presence of *i*NKT 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

Above it says “strongly indicates” iNKT are required] that 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, iNKT 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 iNKT 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 iNKT 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 [AU:OK?] and therefore contain more iNKT 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_2 m) to form the complete heterodimeric CD1d molecule. Mice deficient in β_2 m lack all MHC class I molecules, including CD1d, and are devoid of CD8⁺ cells and iNKT cells. Treatment of mice deficient for β_2 m 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 iNKT 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 iNKT cells modulate T_H2-cell and IgE responses are poorly understood at present. Nevertheless, these studies show that there might be several roles for iNKT cells in the development of [AU:OK?] 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 iNKT cells not only regulate adaptive immunity in asthma but also are sufficient for the development of AHR. When pulmonary iNKT cells were directly activated by

glycolipid antigens, such as α -GalCer or α -glucuronosylceramide (a glycolipid constituent of the membrane of *Sphingomonas* spp.) [AU:OK?], 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 iNKT cells, showing that iNKT-cell-driven AHR can occur in the absence of conventional CD4⁺ T cells. Together, these results indicate that iNKT cells are potent effector cells in the lungs and are sufficient for inducing AHR.

Possible NKT-cell-independent pathways in asthma [AU:cut to one line please]

Although the requirement for iNKT cells for 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 iNKT cells has not been found to be required. For example, one study concluded that iNKT 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 iNKT cells. On the other

hand, in studies using β_2 m-deficient mice, iNKT cells were shown not to be required for the development of AHR^{36,37}. [AU: Allergen?] Sensitization and challenge of β_2 m-deficient mice resulted in eosinophilic airway inflammation and AHR. However, CD1d-independent (type III) NKT cells are present in β_2 m-deficient mice^{38,39}, and some forms of CD1d are expressed in the absence of β_2 m^{38,40}, indicating that some types of NKT cells (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 iNKT cells and therefore have fewer peripheral iNKT cells⁴¹, are known to spontaneously develop AHR⁴². It is possible that the remaining immature iNKT cells in T-bet-deficient mice preferentially produce IL-4 and induce AHR, because immature iNKT cells express IL-4 but little [AU:only small amounts of?] IFN γ ⁴³. These studies, nevertheless, indicate that, although it is possible that iNKT 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 might develop in the absence of iNKT cells.

Human studies of asthma and iNKT cells

The study of allergen-induced AHR in mice indicated that iNKT 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 iNKT cells in humans. The only available method for determining

Box 2 | Subsets of human invariant natural killer T cells

The many distinct functions of invariant natural killer T (iNKT) cells might be explained by the existence of several subsets of iNKT cells with distinct cytokine-expression profiles. Human CD4⁺CD8⁻ (double negative) [AU:i?]NKT cells produce T helper 1 (T_H1) cytokines such as interferon- γ and could be termed T_H1-cell-like [AU: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⁺ [AU: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-cell-like [AU: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 cell types [AU:TH2 and TH2-cell-like NKT?] might be involved in inducing asthma or protecting against autoimmunity.

Human CD4⁺ [AU:i?]NKT cells in the peripheral blood produce an unrestricted cytokine-expression profile and could be termed T_H0-cell-like [AU: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) [AU:are those the only 2 ligands of CCR4?]. By contrast, CXC-chemokine receptor 6 (CXCR6)-expressing [AU:i?]NKT cells seem to localize to the liver and to allografts. These studies indicate that [AU:i?]NKT cells could also be categorized into subsets on the basis of chemokine-receptor expression or tissue of origin¹².

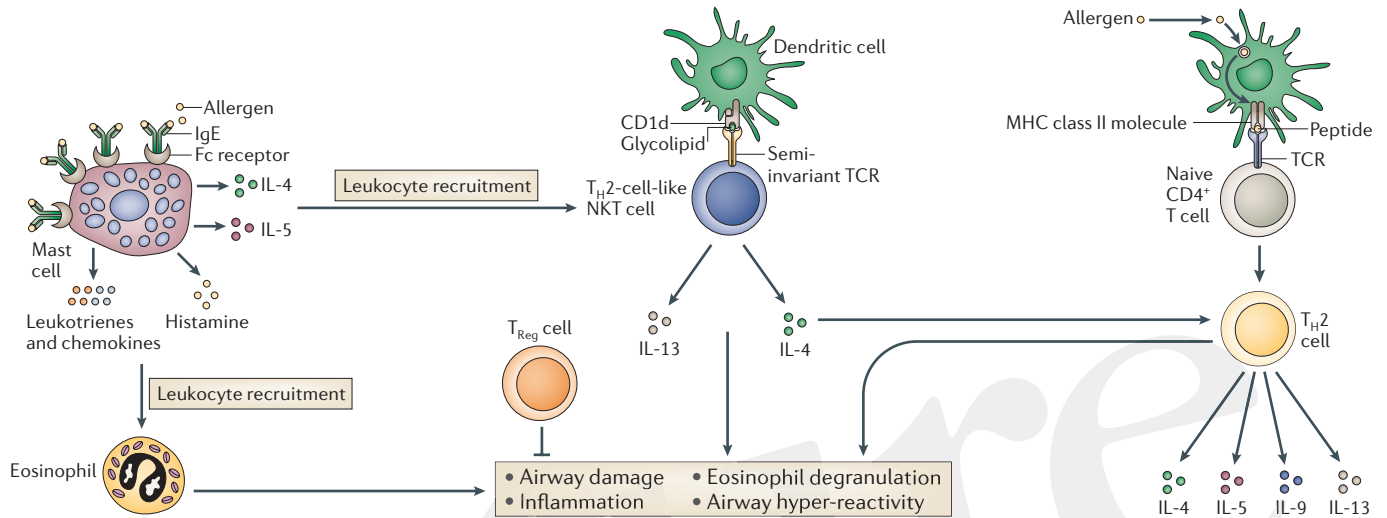


Figure 2 | How natural killer T cells fit in with the current model of asthma. Within minutes of contact with allergen, IgE-sensitized mast cells degranulate, releasing both pre-formed and newly synthesized mediators, including histamine, leukotrienes and cytokines. These factors promote airway hyper-reactivity and damage. Chemokines that are released by mast cells recruit leukocytes, including eosinophils 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⁺ [AU:invariant?] natural killer T (NKT) cells, which have features similar to T_{H2} cells (IL-4 and IL-13 production) but differ by expressing a semi-invariant T-cell receptor (TCR). Both T_{H2} cells and T_{H2}-cell-like [AU:i?]NKT cells might have effector-cell functions in asthma. In addition, other subsets of [AU:i?]NKT cells (for example, T_{H1}-cell-like NKT cells, which produce T_{H1} but not T_{H2} cytokines) might have protect against the development of [AU:OK?] asthma.

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 semi-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 (which expressed the semi-invariant V α 24-J α 18-containing TCR). Furthermore, the pulmonary *i*NKT cells had a cytokine-expression profile similar to that of T_{H2} cells, including expression of IL-4 and IL-13 but not IFN γ . Equally surprising was the finding that more than 95% of the *i*NKT cells in the lungs of patients with asthma express CD4, whereas only ~40% of *i*NKT 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 *i*NKT cells. These studies indicate that *i*NKT 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 *i*NKT 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 *i*NKT cells in the lungs of patients with asthma are CD4⁺ cells (compared with only ~40% in the peripheral blood) indicates that CD4⁺ *i*NKT cells are recruited to the lungs and enriched at least 100-fold [AU:please check fold increase]. Because the number of CD4⁺ *i*NKT cells is not increased [AU:meaning is not higher than in non-asthmatic individuals?] in the peripheral blood of patients with asthma^{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}-cell-like *i*NKT cells that [AU:are there T_{H2}-cell-like iNKT cells that don't produce these cytokines?] produce IL-4 and IL-13 (REFS 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 *i*NKT cells that home to the lungs⁴⁸.

In our studies of patients with asthma, although we showed that *i*NKT cells were present in the lungs, we do not know how

the *i*NKT 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 *i*NKT cells is required for the development of AHR induced by protein antigens, it is probable that *i*NKT 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 are active [AU: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 *i*NKT 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 *i*NKT cells have been shown to respond to [AU:glyco?]lipids from cypress-tree pollen⁵⁰. The range of exogenous (and endogenous) glycolipid antigens that can activate *i*NKT cells and perhaps cause AHR

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

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

α -GalCer, α -galactosylceramide; iNKT, invariant natural killer T; TCR, T-cell receptor.

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 iNKT cells as conventional T_H2 cells. This is not surprising because pulmonary iNKT cells in patients with asthma have many of the features of T_H2 cells (such as CD4 expression and the T_H2 -cytokine production). Nevertheless, T_H2 cells might have an important role in asthma, and the proportion of iNKT 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 iNKT 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 reduce [AU: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, iNKT-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 iNKT 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 iNKT cells might provide effective therapy 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 [AU:OK?] by CD1d and therefore prevents the activation of iNKT 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, iNKT 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 iNKT 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 iNKT cells from the lungs or on selectively reducing iNKT-cell function must be developed for optimal treatment of asthma.

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

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Competing interests statement

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

DATABASES

The following terms in this article are linked online to:

Entrez Gene:

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Author biographies

Dale Umetsu received a B.S. [AU:OK?] in biochemistry from Columbia University (New York, New York, USA) and an M.D./Ph.D. from New York University (New York) in 1979. After completing a residency in paediatrics and a postdoctoral fellowship at the Children's Hospital Boston (Harvard Medical School, Boston, Massachusetts, USA), he moved to Stanford University (Stanford, California, USA) in 1986 and rose to the rank of professor. In 2005, he moved back to the Children's Hospital Boston, to the Division of Immunology, as The Prince Turki al Saud Professor of Pediatrics, at Harvard [AU:University?]. His interests lie in understanding the immunological basis of asthma and allergic disease, focusing on the role of natural killer T cells, regulatory T cells, dendritic cells and TIM genes.

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Links

CD1d

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=912

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ToC Blurb

The importance of T helper 2 cells in asthma has long been known. Now, new evidence indicates that natural killer T cells might have a distinct and crucial role in the development of asthma.

Competing financial interests

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