REVIEW

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All roads lead to Rome: pathways of NKT cells promoting asthma

Tan Jinquan, Wang Li, He Yuling and Chen Lang

Department of Immunology, and Laboratory of Allergy and Clinical Immunology, Institute of Allergy and Immune-related Diseases and Center for Medical Research, Wuhan University School of Medicine, 430071 Wuhan, China

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Abstract

NKT cells are the prominent manipulator in asthma development. Asthmatic NKT cells migrate from thymus, spleen, liver and bone marrow into blood vessels, and then concentrate in airway bronchi mucosa. This recruitment is dependent on high expression of CCR9 and engagement of CCL25/CCR9. NKT cells promote asthma in two different pathways. One is an indirect pathway. NKT cells contact with $CD3^+$ T cells and induce them secreting large quantity of Th2 cytokines (IL-4, IL-13), which requires the participation of dentritic cells and the synergic signaling of CCL25/CCR9 and CD226. The other is a direct pathway. Circulating asthmatic NKT cells selectively highly express Th1 cytokines (IFN-γ). Once reached airway epithelium, most NKT cells shift to Th2-bias, highly expressing IL-4, IL-13, but not IFN-γ. Both pathways lead to airway hyperresponsiveness and inflammation, asthma development. Comparing to the well documented suppressive regulatory T cells, $CD4^+CD25^+$ T cells, NKT cells perform as a novel active regulator in asthma. These recent understanding of NKT cells performance in the development of asthma might unveil new therapy targets and management strategies for asthma.

Key words: NKT cells, asthma, chemokines, cellular signal transduction.

Abbreviations: AHR – airway hyperreactivity, NKT – natural killer T cells, α-GalCer – α-galactosylceramide, DC – dendritic cell, Tr – regulatory T cell, CCL25 – CC chemokine ligand 25, CCR9 – CC chemokine receptor 9.

Corresponding author: Tan Jinquan, Department of Immunology, Wuhan University School of Medicine, Wuhan University, Dong Hu Road 115, Wuchang 430071, Wuhan, P. R. China, tel.: +86 27-68759039, fax: +86 27-68759039, e-mail: jinquan_tan@hotmail.com

INTRODUCTION

Natural killer T (NKT) cells were originally characterized in mice as cells that express both a T cell receptor (TCR) and NK1.1 (CD161) [3, 22]. Increasing research provided a more detailed definition: cells that have an invariant TCR α chain consisting of the Vα14--Jα18 arrangement in mouse or the Vα24-Jα18 Vα14*i* arrangement in humans, presented by the CD1d molecule [9]. Therefore they are also termed invariant (*i*) NKT cells, i.e. Vα14*i* NKT cells (mouse) or Vα24*i* NKT cells (human).

NKT cells bear markers of both innate immunity and adaptive immunity, TCR and NK1.1, but are regarded as belonging to the innate arm of the immune system. Their invariant TCRs recognize glycolipid antigens rather than peptide antigens. Glycolipid antigens are presented by the major histocompatibility complex (MHC)-I-like molecule CD1d, which is expressed on antigen-presenting cells [22]. They are activated very early in an immune response and are capable of activating a variety of cell types, but lack immunological memory [35].

NKT cells play a critical role in modulating upcoming immune responses involving protection against bacterial or parasitic infections and prevention of autoimmune diseases [16, 30, 32]. The capacity of NKT cells to express cytokines rapidly is closely related to the outcomes of autoimmunity and cancer [21]. Once activated, NKT cells rapidly produce both Th1 (interferon (IFN)--γ) and Th2 cytokines (interleukin (IL)-4), which enhance the function of dendritic cells (DCs), NK cells, B cells, as well as the conventional $CD4^+$ and $CD8^+$ T cells [21]. This rapid production of cytokines by NKT cells links the innate and adaptive immune responses and critically regulates adaptive immunity and many inflammatory diseases [2, 7, 14, 24, 28, 33, 36]. NKT cells now excite many immunologists' interest as "active" regulatory lymphocytes, in contrast to $CD4^+CD25^+$ T cells, the typical suppressive regulator [5]. In this review we

will focus on the NKT cell, a key member of activating manipulator in asthma development.

The exact location and precise timing of the emergence of NKT cells, as well as of other lymphocytes, depend on a series of adhesion and migration steps which are mediated by adhesion molecules and chemokine receptors [20]. Several chemokine receptors, such as CC chemokine receptor 1 (CCR1), CCR4, CCR6, and CXCR6, are differentially expressed by $CD4^+$, $CD8^+$, and double-negative NKT cell subsets (Table 1) [12, 19, 23]. The expression of chemokine receptors is often tightly controlled by cytokines and other signals that restrict their tissue distribution and cellular location. For example, CCR9 expresses mainly on T cells in the human small intestine [27] and expresses at a very low level on normal human NKT cell subsets [19, 34], but surprisingly expresses a high level in circulating and airway NKT cells from patients with allergic asthma [31].

NECESSITY OF NKT CELLS IN ASTHMA

Asthma is characterized by airway inflammation dominated by the presence of eosinophils and $CD4^+$ T lymphocytes [4, 8]. The pulmonary $CD4^+$ cells produce large quantities of Th2 cytokines (IL-4, IL-5, and IL-13) which promote asthma by enhancing the growth, differentiation, and recruitment of eosinophils, basophils, mast cells, and IgE-producing B cells and directly inducing airway hyperreactivity (AHR) [11, 15, 37]. Thus, conventional $CD4^+$ Th2 cells in airways are thought to play an essential role in the pathogenesis of bronchial asthma [6, 29]. The CD4 molecule is expressed not only on conventional MHC-II restricted $CD4^+$ T cells, but also on NKT cells. In humans, NKT cells express CD4 and CD8 (a small subgroup) molecules, or neither ($CD4^-CD8^-$) [22].

In a mouse model of asthma, NKT cells are required to participate in allergen-induced Th2 airway inflammation through a CD1d-dependent mechanism. Local NKT cells in the lung regulate the development of airway eosinophilia, hyperresponsiveness, Th2 cytokine production, and elevated levels of IgE antibodies [2, 24]. In humans, NKT cells are important regulators in immune responses through their efficient secretion of Th1 and Th2 cytokines [20]. However, it is not understood how NKT cells selectively regulate Th1 vs. Th2 responses *in vivo*, while they can produce both Th1 cytokine (IL-4) and Th2 cytokine (IFN-γ). Some of these differences are thought to depend on the stimulatory conditions, including cell-cell interactions, cytokine balance in the microenvironment, and the nature of the antigen [13, 17, 26].

PATHWAYS OF NKT CELLS PROMOTING ASTHMA

Recently, two independent teams shed new light on NKT cells performance in asthma development (Fig. 1) [31, 1].

Recruitmen

In asthma, NKT cells selectively express CCR9 at high frequency [31]. When ligated with CCL25, activated CCR9-positive NKT cells are induced to migrate from their prevalent locations, i.e. the thymus, spleen, liver, and bone marrow [22], to penetrate into the blood vessels and then concentrate at the pathological focus in

Table 1. Chemokine receptor expression on NKT cells and conventional $CD4^+$ T cells

Chemokine receptor	Percent positive (%)[a]						
	normal NKT[b]		asthmatic[c]	conventional $CD4^+$ T[d]			
	$CD4^+$	$CD4^-$[e]	NKT	$CD56^+CD3^+$[f]	Th1	Th2	naïve T
CCR1	15	60	15	40	–[g]	–	–
CCR2	75	90	75	60	45	20	–
CCR4	30	–	30	–	–	>90	–
CCR5	75	90	75	90	50	10	–
CCR6	61[h]	80	66	–	–	–	–
CCR7	–	20	–	70	70	60	100
CCR9	6*[h]	–	87*	–	–	–	–
CXCR3	64[h] >90	>90	69	90	90	20	–
CXCR4	100	100	100	100			100
CXCR5	–	85	–	–	10	–	–
CXCR6	–	–	–	60	15	–	–

[a] Data in this table (except for those marked) represent the percentage of human peripheral blood cells positive for the specific receptor [20]. [b] CD1-restricted invariant NKT cells isolated from healthy volunteers [20, 31]. [c] CD1-restricted invariant NKT cells isolated from patients with allergic asthma [31]. [d] MHC I/II-restricted $CD4^+$ T cells isolated from healthy volunteers [18, 24]. [e] $CD4^-$ NKT cells include $CD8^+$ and $CD4^-CD8^-$ NKT. [f] Unrestricted NKT cells. [g] No detectable level. [h] Data shown in [31]. * Statistically significant differences were found between the asthmatic NKT cells and normal NKT cells ($p<0.001$) [31].

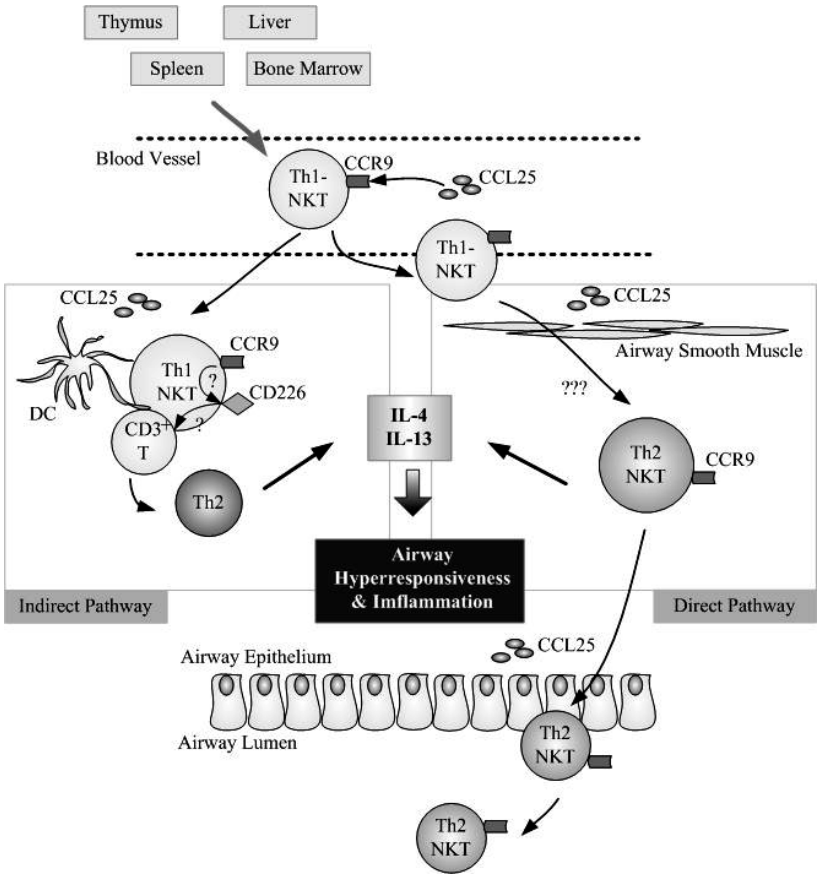

Fig. 1. Pathways of NKT cells that promote asthma. Recruitment of asthmatic NKT cells in the airways – asthmatic NKT cells migrate from the thymus, spleen, liver, and bone marrow, penetrate into the blood vessels, and then concentrate in the airway bronchial mucosa. The recruitment of NKT cells is dependent on the highly expressed CCR9 and the ligation of CCR9/CCL25 (CCL25 is derived from dentritic cells, DCs, and airway tissue cells). During their journey, asthmatic NKT cells promote asthma in two different ways [31]. Indirect pathway (left panel) – NKT cells directly contact with $CD3^+$ T cells and polarize them to a Th2 bias, secreting large quantities of IL-4 and IL-13, which requires DC participation and the synergic signaling transduction between CCL25/CCR9 and CD226 [31]. Direct pathway (right panel) – while circulating in the blood, asthmatic NKT cells selectively highly express Th1 cytokines (IFN-γ). Once reaching the airway epithelium, the asthmatic NKT cells shift to a Th2 bias, highly expressing IL-4 and IL-13, but not IFN-γ. Th2-biased NKT cells constitute most of the T cells in the airway bronchial mucosa and airway lumen. Both pathways lead to airway hyperresponsiveness and inflammation, i.e. asthma development [1].

the airways [31]. Interestingly, CCR9/CCL25 ligation selectively induces the chemotaxis of NKT cells in patients with allergic asthma, but not normal NKT cells in healthy volunteers. CCR6 and CXCR3 are expressed on normal and asthmatic NKT cells with identical frequency. CCL20 (a ligand for CCR6) and CXCL9 (a ligand for CXCR3) do not induce different levels of chemotaxis activity between normal and asthmatic NKT cells.

Indirect pathway

Our group demonstrated an indirect pathway for NKT cells regulating the development of asthma. During their journey from the blood vessels to the airway bronchial mucosa, NKT cells might contact directly with $CD3^+$ T cells and polarize them to a Th2 bias [31]. This regulatory function is dependent on DC participation and CCR9/CD226 synergic activation. CD226 is an adhesion molecule overexpressed on asthmatic NKT cells. CCL25/CCR9 ligations directly phosphorylate CD226, the lack of which will block the NKT cell--induced Th2-bias effect. This finding indicates that CCL25/CCR9 signals can cross-talk with CD226 signals to activate asthmatic NKT cells (Fig. 1, left panel).

Direct pathway

At the same time, research from Umetsu's group confirmed the dominant roles of NKT cells located in the bronchial mucosa of asthma patients [1]. However, Umetsu showed a much different scenario, i.e. a direct pathway, in the final part of this process. Bronchial mucosa NKT cells express a large quantity of Th2 cytokines (IL-4, IL-13). In the mouse model, even without the help of conventional $CD4^+$ T cells and adaptive immunity, NKT cells can increase AHR, a distinctive feature of asthma (Fig. 1, right panel) [25]. It is clear

that both the direct or the indirect pathways lead to the same effect, i.e. asthma aggravation.

Influencing factors

Which way to take, the direct or the indirect pathway? There are several things which should be considered. Firstly, the effect of cell-cell contact determines the performance of NKT cells [31]. Th1-biased asthmatic NKT cells express high levels of CCR9 and CXCL9. CCR9 induces NKT cells to recruit in the lung and airway epithelium, as has been mentioned before in this review, while CXCL9, the ligand for CXCR3, is highly expressed on activated $CD3^+$ T cells. Upon arrival at the site of allergic inflammation, NKT cells induce $CD3^+$ T cells to a Th1 or a Th2 bias. The highly expressed CCR9 is capable of activating CD226, a newly found adhesion molecule presenting on NKT cells. With the help of CD226, NKT cells contact to $CD3^+$ T cells and induce them towards a Th2 bias, secreting high levels of IL-4 and IL-13.

Secondly, the airway microenvironment influences NKT cell performance in asthma. Normal NKT cells express low levels of Th1 (IFN-γ and IL-2), Th2 (IL-4 and IL-13), and regulatory T cell (Tr)-derived (IL-10 and TGF-β) cytokines. While circulating in the blood, asthmatic NKT cells selectively highly express Th1 cytokines as well as Tr-derived cytokines, whether activated by α-galactosylceramide (α-GalCer) or unstimulated [31]. However, once they enter the airway epithelium, stimulated asthmatic NKT cells shift to a Th2 bias, highly expressing IL-4 and IL-13, but not IFN-γ. Moreover, not all NKT cells in the lung shift to a Th2 bias [1]. This indicates the existence of some asthma-specific label for NKT cells, including certain antigens or cytokines.

Another possibility may excite great interests in the clinic. Do asthmatic NKT cells differentiate into a specific subgroup of cells and go on clonally expanding in the airways? There are quantitative and qualitative differences between local airway NKT cells and circulating NKT cells in peripheral blood. Most NKT cells found in the airway epithelium and bronchoalveolar lavage fluid of asthma patients are Th2 biased [1], but circulating NKT cells are Th1 biased [31], and these Th2-biased NKT cells are only found in patients with asthma, not in other lung diseases [1]. In asthma patients, NKT cells dominantly concentrate in the lung, accounting for 80 percent of the local T cells, but only constitute less than 0.1 percent of the mononuclear cells and less than 1 percent of the $CD4^+$ T cells in the peripheral blood [1]. In addition, more than 90 percent of NKT T cells in the lungs of patients with asthma are $CD4^+$ cells, whereas only 50 percent of NKT cells in the peripheral blood are $CD4^+$ cells, suggesting that a subgroup of NKT cells has been recruited and enriched or expanded in the lung, resulting in the NKT cells percentage in the lung being 100 times the level in the peripheral blood [1, 18, 25].

If this asthma-specific NKT cell subgroup does exist, the most exciting thing is how to identify and target this group in clinical strategy, such as targeting the NKT cells by inhibiting or blocking Vα24. An alternative, more focused strategy is to target activated NKT cells in patients with asthma by inhibiting CCL25 or CCR9. There is some possibility to treat circulating NKT cells with α-GalCer to divert to a Th1 bias.

CONCLUSION

NKT cells are the prominent manipulator in asthma development. A large quantity of NKT cells migrate and concentrate in the airways and exert a Th2-bias effect, promoting asthma along a direct or an indirect pathway. Different from circulating NKT cells, an asthmatic-specific $CD4^+$ subgroup of NKT cells might exist in the lung, which consists of a striking percentage of local lymphocytes and expresses high levels of Th2 cytokines (IL-4, IL-13). Compared with suppressive regulatory $CD4^+CD25^+$ T cells, NKT cells perform as an active regulator in asthma. No matter what part NKT cells play in the process of asthma, as regulators or executors, the end effect is the same, i.e. promoting asthma. The advances in the understanding of NKT cells' role in asthma excite great interest regarding clinical application. Some new possible targets and strategies for therapy emerge, such as inhibiting the migration and concentration of NKT cells to the airways or identifying and blocking the asthma-specific airway NKT cells.

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