

EDITORIALS



Natural Killer T Cells and Asthma

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Invariant natural killer T cells, originally characterized in mice and more recently defined in humans, are a unique, conserved T-cell sublineage possessing a rearrangement of the T-cell antigen receptor ($V\alpha 14J\alpha 18$ in mice and $V\alpha 24J\alpha 18$ in humans). Human natural killer T cells also have an invariant β chain ($V\beta 11$). $V\alpha 24V\beta 11$ binds to glycolipids presented by CD1d, a major-histocompatibility complex class I-like molecule expressed on dendritic cells, monocytes, and subgroups of B cells.¹ The glycolipid antigens are also highly conserved and include the synthetic glycolipid α -galactosylceramide, self glycolipids, and glycolipids from bacteria and plant pollens.

The hallmark response of invariant natural killer T cells is the rapid and copious production of cytokines, in particular interferon- γ and interleukin-4, but also interleukin-13, interleukin-5, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor α . In mouse models, invariant natural killer T cells facilitate a wide range of beneficial host responses, including tumor surveillance, protection from various infectious agents, prevention of autoimmune diseases (such as diabetes and experimental allergic encephalomyelitis), and maintenance of self-tolerance. Conversely, invariant natural killer T cells also participate in pathologic processes such as experimental colitis, maternal intolerance of the fetus, formation of atherosclerotic plaque, and induction of airway hyperreactivity. In experiments involving mice that are deficient in invariant natural killer T cells, Akbari et al. showed evidence of a crucial role of $V\alpha 14$ -invariant natural killer T cells that secrete interleukin-4 and interleukin-13 in the development of allergen-induced airway hyperreactivity, a murine model of some features of asthma.² Moreover, they found that an

absence of the development of airway hyperreactivity was not due to an inability to produce conventional type 2 helper (Th2) T cells that in turn produce interleukin-4 and interleukin-13, confirming that invariant natural killer T cells are involved in the induction of pathways leading to the asthma phenotype.

In this issue of the *Journal*, Akbari et al.³ report that CD4⁺ natural killer T cells may also play a role in the pathogenesis of human asthma. Using flow cytometry and CD1d-tetramers loaded with α -galactosylceramide to study T cells from bronchoalveolar-lavage fluid, the authors showed that the majority (about 60 percent) of CD4⁺ or CD3⁺ T cells from patients with moderate-to-severe persistent asthma, but not those from normal subjects or patients with sarcoidosis, expressed the invariant T-cell receptor $V\alpha 24V\beta 11$ and were functional (they produced interleukin-4 and interleukin-13, but little interferon- γ). Nearly all of the normal subjects and patients with sarcoidosis had conventional CD4⁺CD3⁺ T cells but not natural killer T cells. In addition, the authors examined endobronchial-biopsy specimens from the patients with asthma; nearly all the lymphocytes in the lamina propria expressed both CD4 and $V\alpha 24$.

These findings confirm and extend a recent report by Sen et al.,⁴ who found that $V\alpha 24$ -invariant natural killer T cells in the blood of patients with asthma selectively expressed CCR9 and that large numbers of CCR9⁺ and $V\alpha 24$ -cells were present in bronchial-biopsy samples from patients with asthma but not from control subjects. Sen et al. also showed that conventional CD3⁺ $\alpha\beta$ T cells could be polarized to a Th2 phenotype by cell-to-cell contact with $V\alpha 24$ -invariant natural killer T cells, with enhanced expression

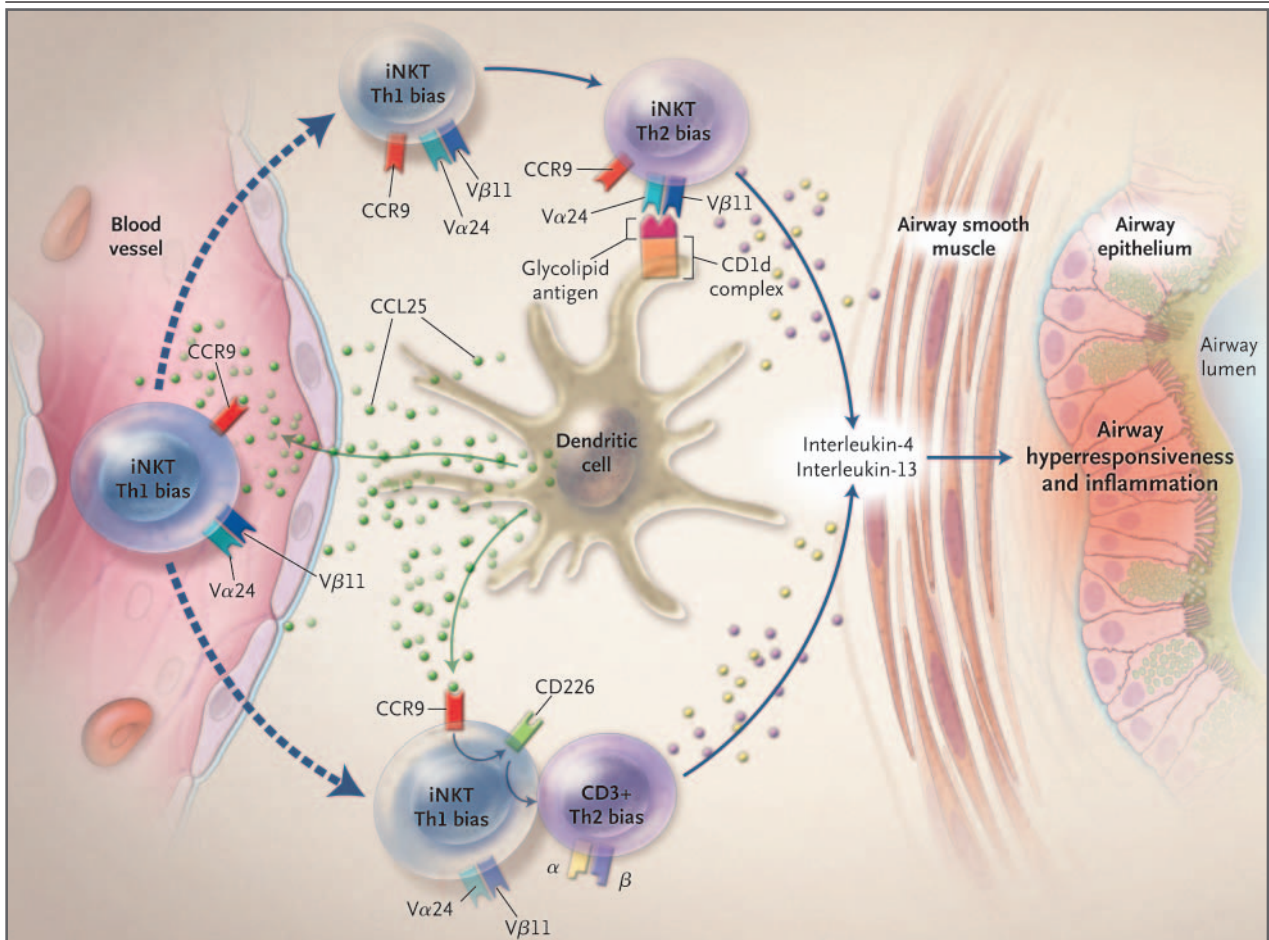


Figure 1. Two Pathways by Which Interleukin-13 and Interleukin-4 May Be Mobilized by Invariant Natural Killer T (iNKT) Cells in the Airways of Patients with Asthma.

These pathways involve recruitment of Vα24+Vβ11+ iNKT cells with enhanced expression of CCR9 by CCL25 derived from dendritic cells (and probably also epithelial cells). One pathway (top) involves the binding of glycolipid antigens (e.g., α-galactosylceramide) to Vα24+Vβ11 in a CD1d-restricted fashion. In the context of the airway microenvironment, this binding changes the bias of iNKT cells from becoming type 1 helper (Th1) T cells (found in blood) to becoming type 2 helper (Th2) T cells (found in the airway). The other pathway (bottom) involves the signaling by Th1-biased Vα24+Vβ11+ iNKT cells to T cells that are CD3+ αβ to adopt a Th2 bias. This step requires cell-to-cell contact and phosphorylation of CD226 as a result of adjacent membrane signaling by CCL25-ligated CCR9. Th2 cells then secrete interleukin-4 and interleukin-13, which results in airway hyperreactivity and inflammation. The two pathways are suggested by the findings of Akbari et al.³ and Sen et al.⁴ Dashed lines represent the migration of iNKT cells from the blood vessel to airway tissue.

of CCR9, from patients with asthma. This induction requires CCL25 and CCR9 to activate adjacent membrane signaling by CD226, a leukocyte-adhesion molecule that is widely expressed on mononuclear cells.⁵ The CD226 appears to be critical in activating Vα24+ invariant natural killer T cells for the induction of this Th2 bias in CD3+ T cells. Dendritic cells and epithelial cells (at least those in the intestinal mucosa) are major sources of CCL25 (also known as thymus-expressed chemokine, or TECK).

The findings of Akbari et al.³ and the report by Sen et al.⁴ support the concept of two broad pathways of interleukin-13 and interleukin-4 production by invariant natural killer T cells in the bronchial submucosa of patients with asthma (Fig. 1). Both potential pathways involve the activation of Vα24+ T cells, one by means of CD1d loaded with glycolipids and the other by means of CCR9, CCL25, and CD226 and cell-to-cell contact with conventional CD3+ αβ cells.

Further experiments are needed to confirm

this exciting finding of a potentially essential role of invariant natural killer T cells in asthma. For example, it must be established that the prominence of CD4⁺ natural killer T cells in the airway mucosa is specific for asthma rather than constituting a nonspecific response to airway inflammation (such as that in chronic obstructive pulmonary disease). Such specificity is especially important to show because natural killer T cells have a varied cytokine profile and are found at many mucosal surfaces, in both mice and humans, in association with multiple disease processes.

The case for implicating invariant natural killer T cells in the pathogenesis of asthma would be particularly strengthened by clear evidence that the numbers of invariant natural killer T cells in bronchial mucosa correlate with both the severity of asthma (including airway hyperreactivity) and the response to treatment with corticosteroids. The results of Sen et al.⁴ are encouraging, in that the numbers of CCR9⁺ V α 24⁺ invariant natural killer T cells from the peripheral blood of symptomatic patients with asthma decreased when the asthma was clinically silent and after steroid treatment. Also of interest would be the determination of whether asthma provoked by the inhalation of whole allergens, or T-cell peptide epitopes,⁶ results in the mobilization of invariant natural killer T cells to the bronchial mucosa, which in turn would result in the enhanced expression of interleukin-4 and interleukin-13. Another intriguing finding of the study by Akbari et al.³ was that 4 of the 14 patients with asthma were nonatopic. This finding suggests a role of invariant natural killer T cells in intrinsic asthma, in which T cells also have a Th2 bias.⁷ Thus, in intrinsic asthma, abnormal regulation of the immune response in the bronchial mucosa caused by viral or bacterial infection, for example, could lead to the recognition of self-lipid antigens that load onto CD1d, thereby activating invariant natural killer T cells by stimulating the invariant T-cell receptor. All of these possibilities are testable.

If the present findings are confirmed, what are the implications for the treatment of asthma? One obvious strategy is to target the invariant natural

killer T cells by inhibiting, or blocking, V α 24, although the consequences of disturbing cells that may benefit the overall immune response (for example, by performing tumor surveillance) must be kept in mind. An alternative, more focused strategy is to target activated invariant natural killer T cells in patients with asthma by inhibiting CCL25 or CCR9. This approach could spare local V α 24⁺ cells not involved in asthma events. Finally, there is the possibility of treatment with α -galactosylceramide to divert nonpulmonary invariant natural killer T cells to a type 1 helper T-cell phenotype that secretes cytokines. In mice, α -galactosylceramide reduced airway inflammation induced by an allergic response, but only when given in a single injection; continuous infusion had the opposite effect.⁸

In summary, these recent findings of an association between invariant natural killer T cells and asthma may have far-reaching consequences for patient care. However, more work is required to establish proof of the concept that the cell plays an active role in the disease process.

No potential conflict of interest relevant to this article was reported.

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1. Kronenberg M. Toward an understanding of NKT cell biology: progress and paradoxes. *Annu Rev Immunol* 2005;23:877-900.
2. Akbari O, Stock P, Meyer E, et al. Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. *Nat Med* 2003;9:582-8.
3. Akbari O, Faul JL, Hoyte EG, et al. CD4⁺ invariant T-cell-receptor⁺ natural killer T cells in bronchial asthma. *N Engl J Med* 2006;354:1117-29.
4. Sen Y, Yongyi B, Yuling H, et al. V α 24-invariant NKT cells from patients with allergic asthma express CCR9 at high frequency and induce Th2 bias of CD3⁺ T cells upon CD226 engagement. *J Immunol* 2005;175:4914-26.
5. Shibuya A, Tahara-Hanaoka S, Shibuya K. DNAM-1 (CD226): a two-sword fencer for innate and adaptive immunity. *Curr Med Chem Antiinflamm Antiallergy Agents* 2005;4:53-8.
6. Ali FR, Oldfield WL, Higashi N, Larché M, Kay AB. Late asthmatic reactions induced by inhalation of allergen-derived T cell peptides. *Am J Respir Crit Care Med* 2004;169:20-6.
7. Humbert M, Menz G, Ying S, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol Today* 1999;20:528-33.
8. Matsuda H, Suda T, Sato J, et al. Alpha-galactosylceramide, a ligand of natural killer T cells, inhibits allergic airway inflammation. *Am J Respir Cell Mol Biol* 2005;33:22-31.

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