

CD8⁺ T lymphocytes and leukotriene B₄: Novel interactions in the persistence and progression of asthma

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The contribution of CD8⁺ T cells to the development of airway hyperresponsiveness and airway inflammation has received increased attention recently. CD8⁺ T cells, which are capable of secreting T_H2 cytokines, including IL-4, IL-5, and IL-13, have been described in asthmatic subjects and in animals sensitized and challenged with allergen. A subset of these IL-13–producing CD8⁺ T cells, effector memory CD8⁺ T cells in the mouse, express a high-affinity receptor for leukotriene B₄ (BLT1), and expression of this receptor is essential for their accumulation in the lung and development of airway hyperresponsiveness and airway inflammation. A similar subset of CD8⁺/BLT1⁺/IL-13⁺ T cells has also been identified in the bronchoalveolar lavage fluid of asthmatic subjects, suggesting a pathogenic role for this unique subset of CD8⁺ T cells in asthma. (*J Allergy Clin Immunol* 2006;117:577-82.)

Key words: CD8, T cells, leukotriene B₄, IL-13, asthma

CURRENT PERSPECTIVES ON ASTHMA PATHOGENESIS

Asthma is a common but complex disease that is generally characterized by airway hyperresponsiveness (AHR), reversible airway obstruction (at least initially), and inflammation, marked mainly by eosinophilic infiltration but also by increases in lung neutrophils, T lymphocytes, and infiltrating mast cells.¹ In an individual patient or at different stages of the disease, the features of asthma and the nature of the lung inflammatory response might differ, unmasking the important heterogeneity of chronic asthma. It is this heterogeneity that likely underlies the paucity of new and sustained therapies in the

Abbreviations used

AHR: Airway hyperresponsiveness
BAL: Bronchoalveolar lavage
BLT1: Receptor for leukotriene B₄
5-LO: 5-Lipoxygenase
LTB₄: Leukotriene B₄
T_{CM}: Central memory CD8⁺ T cells
T_{EFF}: Effector memory CD8⁺ T cells

clinic and the identification of numerous candidate genes. Furthermore, asthma in children appears to differ considerably from adult asthma.² Children tend to manifest more atopic features, increased allergen sensitivities, and higher IgE levels, and for the most part, asthma in children is more of a peripheral airway disease. The latter is most obvious when examining FEV₁ in children, in whom it is an unreliable indicator of asthma severity.³

The bulk of the evidence from patients with asthma and from mouse models of allergen-induced airway disease identifies α/β ⁺, CD4⁺ T_H2 cells as having a pivotal role in mediating the inflammation that is central to asthma.^{1,4,5} From animal models, the initiation of pulmonary inflammatory responses is absolutely dependent on CD4⁺ T lymphocytes and to this can be added an essential role for IL-4; genetic elimination or manipulation of α/β ⁺ T cells or IL-4 during the initiation or sensitization phase is associated with a lack of AHR, allergen-specific IgE, and airway eosinophilia development.^{6,7} Increasingly, it is being recognized that the cell and cytokine requirements during the initiation-sensitization phase differ considerably from those that might be necessary during the challenge–maintenance–progression phase.⁸ In mice this is most evident when contrasting the roles of IL-4 and IL-13. Whereas IL-4 appears essential in the initiation phase, targeting IL-4 in the challenge phase is without effect. By contrast, reducing IL-13 levels during the initiation phase has little effect but, when targeted during the challenge phase, attenuates development of AHR, airway inflammation, goblet cell metaplasia, and mucus hyperproduction.⁸⁻¹⁰

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This distinction between the initiation and maintenance or progression stages of asthma is not only well founded in human asthma but also has important clinical ramifications. If, as reported, upward of 70% of adult allergic asthmatic subjects can trace the origin of their disease to the first 3 years of life,¹¹ then for most asthmatic subjects, treatment is being focused on the maintenance-persistence or progression phase, often many years after completion of the initiation or sensitization phase. This distinction is supported by the differences reported between subjects with childhood and adult asthma and the findings that infants are more predisposed to demonstrating T_H2 -biased responses.^{2,12,13} This would point to the need to consider different treatment strategies depending on the age of the patient and stage of the disease and also accounts for the limited success of many interventions, including targeting of IL-4¹⁴ or IL-5¹⁵ during the maintenance phase.

Over the last several decades, there has been an almost dogmatic reverence to the notion that $CD4^+$ T lymphocytes are the responsible cells accounting for the pathologies associated with allergic airway disease. However, distinguishing between the stages of the disease also challenges the omnipotence of $CD4^+$ T cells throughout the natural history of allergic asthma. In animal studies depletion of $CD4^+$ T cells after sensitization has much less, if any, effect on the response to later allergen challenge.¹⁶ This suggests that other cell types primed or activated by $CD4^+$ T cells or their products during the initiation phase can sustain AHR and airway inflammation. For example, after sensitization, allergen-specific IgE is generated, which, when bound to high-affinity receptors on mast cells and basophils and cross-linked by allergen, can liberate a panoply of mediators fully duplicating and even extending those produced by activated $CD4^+$ T lymphocytes.¹⁷

IDENTIFICATION OF THE ROLE OF $CD8^+$ T CELLS AND LEUKOTRIENE B_4 IN ASTHMA

Despite a number of articles describing $CD8^+$ T cells as suppressors of AHR and airway inflammation,¹⁸⁻²⁰ it is now becoming apparent that $CD8^+$ T cells are important contributors to the development of allergic responses in the lung. Using an animal model, we first suggested that $CD8^+$ T cells do contribute and might be necessary for AHR and eosinophilic airway inflammation.²¹ These findings have now been confirmed with small-animal models.^{22,23} Importantly, IL-4 produced by $CD4^+$ T cells might be necessary for the priming and transition of $CD8^+$ T cells to a T_C2 phenotype, secreting IL-4, IL-5, and IL-13.²³

Increasingly, descriptions of allergen-specific $CD8^+$ T cells are appearing in studies of asthmatic patients as well. $CD8^+$ T cells from atopic asthmatic subjects express IL-5,²⁴ contain more IL-4 than nonatopic donors,²⁵ and are increased in cases of fatal asthma.²⁶ In the latter study a cross-sectional relationship between $CD8^+$ T cells and

asthma outcome was observed. Similarly, increased cytokine production (IL-4 and IL-5) from sputum $CD8^+$ cells has been shown in patients with asthma, and this was related to disease severity.²⁷ Furthermore, a recent study showed that the outcome of asthma, as determined by the annual decrease in FEV₁, can be predicted by the bronchial $CD8^+$ T-cell infiltrate but not by airway eosinophilia or reticular layer thickness.²⁸

In concert with these findings, we have explored this association of $CD8^+$ T cells in asthma, translating recent findings in mouse models to human asthma. Confirming our earlier studies, we showed that $CD8^+$ T cell-deficient mice ($CD8^{-/-}$) are less capable of AHR development and airway eosinophilia.²⁹ Serum levels of allergen-specific IgE and bronchoalveolar lavage (BAL) fluid levels of IL-4, IL-5, IFN- γ , IL-10, and IL-12 were no different in $CD8^{-/-}$ mice than in $CD8^{+/+}$ mice; only levels of IL-13 and mucus production were decreased in the $CD8^{-/-}$ animals. Reconstitution of the $CD8^{-/-}$ mice with $CD8^+$ T cells from sensitized but not from naive wild-type mice fully restored all of the deficient responses. Moreover, in the lung the transferred $CD8^+$ T cells were shown to be an important, if not essential, source of IL-13.

In parallel to the heterogeneity observed among $CD4^+$ T cells, 2 distinct antigen-experienced populations of $CD8^+$ T cells have been identified on the basis of cell-surface marker expression and their functional and migratory properties.^{30,31} Central memory $CD8^+$ T cells (T_{CM}) home preferentially to lymph nodes, whereas effector memory $CD8^+$ T cells (T_{EFF}) traffic to sites of inflammation. In culture, IL-2 promotes differentiation of T_{EFF} , whereas IL-15 leads to differentiation of T_{CM} . When adoptively transferred into sensitized and challenged $CD8$ -deficient mice, only T_{EFF} (but not T_{CM}) migrated to the lung and reconstituted AHR, airway eosinophilia, IL-13 levels, and mucus hyperproduction.³² When recovered from the lung tissue and reactivated *in vitro*, these $CD8^+$ T_{EFF} produced IL-13, further demonstrating that they were primed to do so *in vivo*.

What is unique about these $CD8^+$ /IL-13⁺ effector memory T cells? Among the differences between T_{CM} and T_{EFF} identified initially by means of gene-array analysis was the marked induction of mRNA for receptor for leukotriene B_4 (BLT1), the high-affinity receptor for leukotriene B_4 (LTB₄), on T_{EFF} but not T_{CM} .^{33,34} LTB₄ has primarily been classified as a chemoattractant for myeloid leukocytes.^{35,36} Of interest, several years ago, it was shown that LTB₄ could bind specifically to a small proportion of human peripheral blood T cells,³⁷ but these findings were never exploited. Although BLT1 mRNA is also detected in $CD4^+$ T cells (in fact, several subsets of $CD4^+$ T cells express LTB₄ receptor mRNA [T_H0 , T_H1 , and T_H2]),³⁴ subsets of antigen-experienced $CD8^+$ T cells do show a differential induction of BLT1 expression. Until recently, antibodies to human BLT1 have been available, although not to the corresponding receptor in mice. Antibodies to mouse BLT1 have now been developed, demonstrating at the protein level the exclusive expression of BLT1 on T_{EFF} but not T_{CM} (unpublished data).

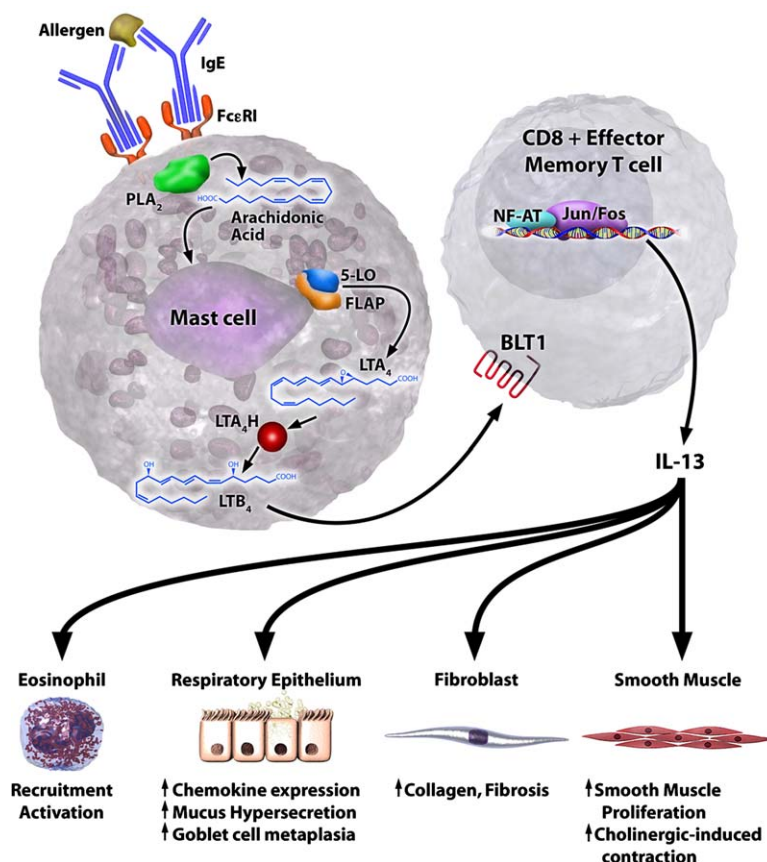


FIG 1. Model of the CD8⁺/BLT1⁺/IL-13⁺ axis in asthma pathogenesis. Mast cells, activated through the high-affinity receptor (*FcεRI*) after cross-linking with allergen, initiate a cascade resulting in the rapid synthesis and release of LTB₄. Binding of LTB₄ to its high-affinity receptor, BLT1, on a subset of CD8⁺ T cells results in their accumulation in the lung. This CD8⁺ subset is an important source of IL-13, which affects many of the cell types involved in asthma pathogenesis. PLA₂, Phospholipase A₂; FLAP, 5-LO activating protein; LTA₄, leukotriene A₄; LTA₄H, LTA₄ hydrolase.

Given the differential expression of BLT1 on T_{EFF} and T_{CM}, we examined whether BLT1 expression was essential for CD8⁺ T-cell recruitment to the lung. Genetic deletion of BLT1 on T_{EFF} or CD8⁺ T cells impaired their recruitment to the lung, and after transfer to CD8^{-/-} mice, they failed to reconstitute AHR, airway eosinophilia, BAL IL-13 levels, or mucus hyperproduction.^{38,39} In more recent experiments examining IgE and the mast cell-dependent development of AHR and lung eosinophilia, treatment of the mice with a specific blocker of the LTB₄ receptor prevented the development of AHR and inflammation,⁴⁰ further supporting the essential role of this LTB₄ receptor in triggering allergic responses in the lung.

All of these data identify a novel pathogenic cell in the development of AHR, eosinophilic airway inflammation, and mucus hyperproduction. This CD8⁺/BLT1⁺/IL-13⁺ subset of T cells appears to play a unique and important role in the development of allergen-induced disease in the lung (Fig 1).

To determine whether an equivalent of these cells exists in human asthma, we performed immunofluorescence

staining of human airway tissue and BAL fluid cells from asthmatic subjects. In these initial studies we identified CD8⁺/BLT1⁺/IL-13⁺ T cells in BAL fluid specimens from asthmatic subjects and CD8⁺/BLT1⁺ T cells in asthmatic lung tissue (Fig 2) but not in lung tissue or BAL fluid cells from control subjects.⁴¹ In the BAL fluid, lymphocytes represented 6% to 10% of total recovered cells, and 60% were CD3⁺; of these, 20% to 30% were CD8⁺. Approximately 70% to 75% of the CD8⁺ T cells coexpressed BLT1 and, after stimulation with phorbol myristate acetate and ionomycin, were IL-13⁺. CD8⁺ T cells were also prominent in the submucosa of asthmatic airway tissue (approximately 214 CD8⁺ T cells/mm²), with approximately half of these tissue-infiltrating T cells expressing BLT1.

On the basis of these findings, we propose that the identification of the critical role of these CD8⁺/BLT1⁺/IL-13⁺ cells in mice might be central to the human disease as well, especially in the maintenance-progression phase of asthma. It is of interest to note that BAL LTB₄ levels correlate with asthma disease severity,⁴² and as noted, bronchial CD8⁺ T cell numbers correlate with disease

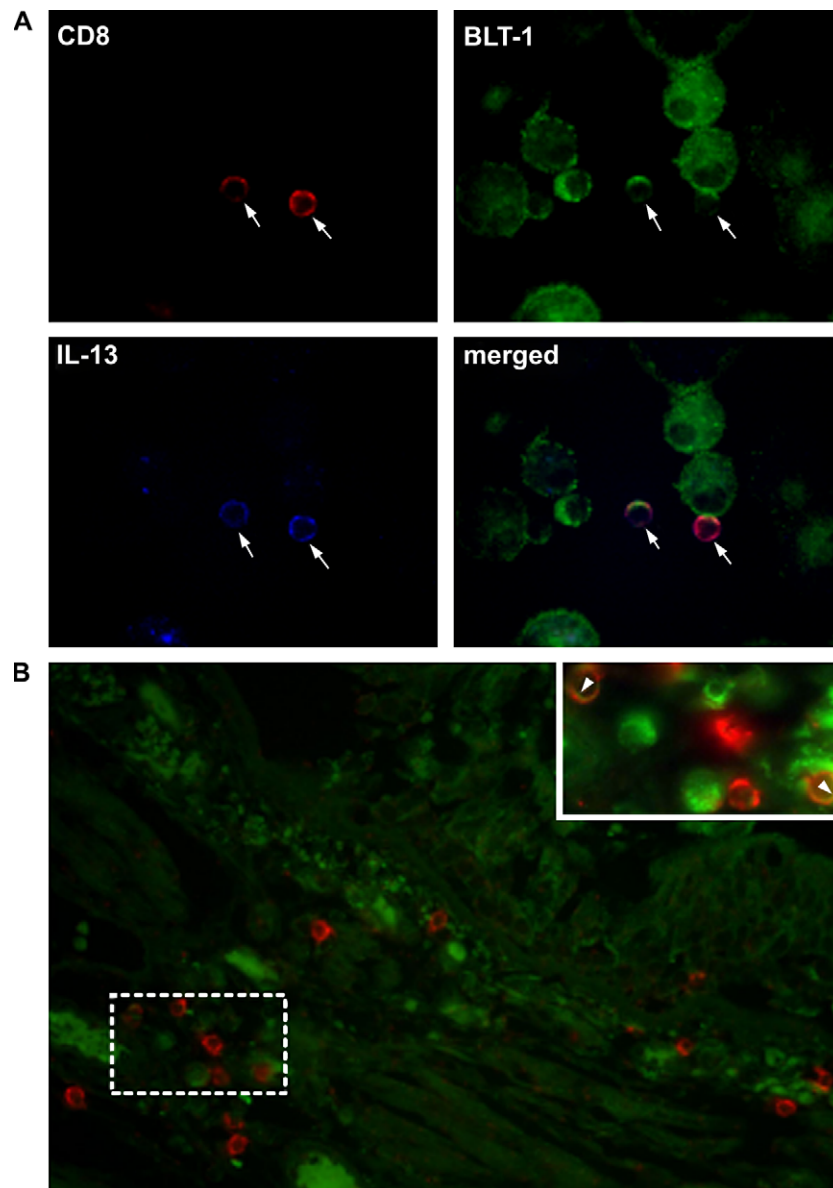


FIG 2. Immunofluorescent detection of CD8⁺, BLT1⁺, and IL-13⁺ cells in BAL fluid (**A**) and tissue (**B**) of asthmatic subjects. Fresh BAL fluid cells were stimulated for 4 hours in culture with phorbol 12-myristate 13-acetate (5 ng/mL) and ionomycin (500 ng/mL) in the presence of brefeldin A (10 μ g/mL). Cells were stained in suspension with mouse monoclonal anti-human CD8 antibody (DakoCytomation, Carpinteria, Calif) and then fixed with paraformaldehyde (4% in PBS, 10 minutes) and permeabilized with saponin (0.1% in staining buffer). Cells were then incubated with allophycocyanin (APC)-conjugated rat anti-human IL-13 (Biolegend, San Diego, Calif) and rabbit anti-human BLT1 (Cayman Chemicals, Ann Arbor, Mich), followed by fluorescein isothiocyanate (FITC)-conjugated goat anti-rabbit Ig (Jackson ImmunoResearch Laboratories, Inc, West Grove, Pa). This anti-BLT1 antibody recognizes the C-terminus of the BLT1 receptor, which is located on the intracellular side of the plasma membrane. After washing, cells were incubated with alkaline phosphatase-conjugated goat anti-mouse Ig (DakoCytomation), followed by incubation with fluorescent Permanent Red alkaline phosphatase substrate (DakoCytomation), and mounted with Vectashield mounting medium (Vector Laboratories, Burlingame, Calif). For tissue staining, 5- μ m sections of formalin-fixed and paraffin-embedded lung tissue specimens were permeabilized with 0.1% Triton X-100, incubated with rabbit anti-BLT1 and mouse anti-CD8 antibodies, washed with Tris-buffered saline, and incubated with FITC-conjugated goat anti-rabbit Ig and alkaline phosphatase-conjugated goat anti-mouse Ig, followed by incubation with fluorescent Permanent Red alkaline phosphatase substrate and mounting as above. Staining was examined under a Leica DMRXA fluorescent microscope (Leica, Wetzlar, Germany) by using the following filters: Texas Red for CD8 (Orange), FITC for BLT1 (green), and APC for IL-13 (blue). *Arrows* indicate the same cells stained for CD8, BLT1, and IL-13 (Fig 1, A). *Arrowheads* indicate BLT1 staining localized on the intracellular side of the membrane of CD8⁺ cells (Fig 1, B, inset representing the boxed area after Z-scan).

severity,²⁸ supporting the link between these previously assumed independent findings.

Lipid mediators, such as LTB₄, are synthesized by cells that express 5-lipoxygenase (5-LO) and leukotriene A₄ hydrolase (eg, mast cells and macrophages). 5-LO expression is generally restricted to myeloid cells,^{43,44} whereas leukotriene A₄ hydrolase is expressed in many tissues. As shown in Fig 1, IgE-stimulated mast cells might be an important source of LTB₄, necessary for the recruitment of CD8⁺/BLT1⁺/IL-13⁺ cells to the lungs of allergic hosts, as demonstrated in the animal models.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In summary, a number of studies have revealed a novel pathway for the recruitment of pathogenic IL-13-secreting CD8⁺ T cells to the lungs, which is dependent on the release of LTB₄ and the expression of a specific receptor (BLT1) for this lipid mediator on these T cells. Their characterization in allergic mice has now been paralleled by the findings of similar cells in human asthmatic subjects. Whether they play as critical a role in human disease remains to be determined. We have recently identified increased numbers of this subset of CD8⁺ T cells in subjects with steroid-resistant compared with those with steroid-sensitive asthma.⁴¹ An inhibitor of 5-LO, which inhibits production of LTB₄ (as well as the cysteinyl leukotrienes), did provide benefit to asthmatic subjects,⁴⁵ adding support to the potential role of this pathway in human asthma.

Cumulatively, these recent findings suggest that current treatment strategies for chronic asthma might not be effective in preventing or reversing the progressive decrease in lung function in patients with asthma. It is known that glucocorticoid modulation of CD8⁺ T-cell cytokine production is much lower compared with cytokine production from CD4⁺ T cells.⁴⁶ As a result, development of newer therapeutic approaches that target these pathogenic CD8⁺ T cells might be needed if we are to alter the course of severe asthma and limit the progressive loss of lung function.

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