

Regulation of allergic airway inflammation by class I-restricted allergen presentation and CD8 T-cell infiltration

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Background: CD8 T cells are known to respond to exogenous antigens through cross-presentation. The importance of the CD8 cell response in the lung after inhalation of allergen and its effects on asthmatic inflammation are less clear.

Objective: We sought to determine the dynamics, nature, and immunoregulatory activities of the class I CD8 T-cell response to inhaled allergen.

Methods: We studied a murine model of respiratory allergen sensitization, adoptive transfer of transgenic T cells, and flow cytometric analysis of lung infiltrates.

Results: Class I-restricted CD8 T cells responded rapidly to inhaled allergen and dominated the acute infiltration of T cells into the lung after secondary exposure. CD8 cells in the lung expressed a type 1 phenotype and suppressed the systemic IgE response to subsequent immunization. Dendritic cells purified from conducting airways or lung tissue were highly efficient at cross-presentation of antigen into the class I pathway after intranasal challenge. Adoptive transfer of transgenic antigen-specific CD8, but not CD4, cells resulted in increased IL-12 levels and reduced IL-13 and IL-5 levels in bronchoalveolar lavage fluid, coupled with substantially reduced airway eosinophilia after repeated allergen inhalation, a process mimicked by intranasal administration of IL-12 and inhibited by anti-IL-12 antibody.

Conclusion: The data suggest that CD8 cells specific for inhaled allergens are generated in draining lymph nodes but suppress allergic airway inflammation through induction of IL-12 in the lung during interaction with respiratory dendritic cells.

Clinical implications: Novel peptide immunotherapeutics targeting the class I-restricted CD8 T-cell response to allergen represent a promising strategy for extrinsic asthma. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: CD8⁺ T lymphocytes, dendritic cells, inflammation, lung, IL-12

Abbreviations used

BAL: Bronchoalveolar lavage
CFSE: Carboxyfluorescein diacetate succinimidyl ester
DC: Dendritic cell
FITC: Fluorescein isothiocyanate
OVA: Ovalbumin
PE: Phycoerythrin
VSV: Vesicular stomatitis virus

Allergic asthma is known to be driven primarily by CD4 T_H2-type T cells responding to MHC class II-restricted allergen-derived epitopes in the lungs and airways.^{1,2} The role of CD8 MHC class I-restricted T cells in allergic airways inflammation has been less clear. Although it is well known that exogenous antigens, including allergens, can be processed and presented in the context of MHC class I,^{3,4} the ability of respiratory tract antigen-presenting cells to process inhaled antigen through MHC class I and induce CD8 cell inflammation has not been well defined.

Allergen-specific CD8 cells generally suppress allergic sensitization and IgE responses^{5,6} and were initially shown to inhibit airway hyperreactivity and T_H2 responses in the murine model of allergic asthma.^{7,8} More recently, however, several studies have demonstrated the ability of CD8 cells to develop into T_C2 cells that promote allergic airways inflammation after prolonged pulmonary inflammation in mice⁹⁻¹¹ or in human asthma.^{12,13}

Here we studied the activation CD8 T cells immediately after allergen administration to the lung. Respiratory dendritic cells (DCs) readily presented allergen through the MHC class I pathway, and CD8 cells dominated the acute inflammatory influx into the lung. Our results suggest that early T_C1-type responses are critical for ensuring a balanced response to inhaled allergen by enhancing IL-12 production in the lung and suppressing development of T_H2-driven inflammation.

METHODS

Mice

C57BL/6 mice (6-8 weeks) from Harlan (Oxford, United Kingdom) were used. OT-I¹⁴ and OT-II¹⁵ T cell receptor-transgenic mice

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were bred in our facility. CD8⁺ OT-I T cells recognize ovalbumin (OVA₂₅₇₋₂₆₄ peptide; SIINFEKL) associated with H-2K^b; CD4⁺ OT-II cells recognize OVA₃₂₃₋₃₃₉ (ISQAVHAAHAEINEAGR) and I-A^b. Protocols complied with UK Home Office regulations and were approved by our Animal Welfare Committee.

Antibodies and reagents

For detailed information on reagents, please see the [Methods](#) section in the Online Repository at www.jacionline.org. Alum-precipitated OVA was as previously described.¹⁶ OVA-specific IgE levels were assessed as previously described.¹⁷

Analysis of T-cell responses and lung inflammation

CD8⁺ or CD4⁺ T cells were purified from spleens/lymph nodes of OT-I and OT-II mice by using autoMACS (Miltenyi Biotec, Bisley, United Kingdom; 95% purity), labeled with 2.5 μ mol/L carboxy-fluorescein diacetate succinimidyl ester (CFSE; Invitrogen, Paisley, United Kingdom; for 10 minutes at 37°C), washed, and transferred into tail veins of mice (5×10^6 each in 100 μ L of PBS). Twenty-four hours later, mice received 50 μ g of OVA (in 50 μ L of PBS) intranasally. Three days later, mediastinal lymph nodes were analyzed by means of flow cytometry (BD FACSCalibur; BD Bioscience, Oxford, United Kingdom). Analysis of lung T-cell responses is described in the [Methods](#) section of the Online Repository at www.jacionline.org. Inflammatory cells in bronchoalveolar lavage (BAL) fluid were measured as previously described.¹⁸ BAL IL-12 p40 was measured by means of ELISA (PeproTech, London, United Kingdom). IL-13 and IL-5 ELISAs were performed as previously described.¹⁶

Allergic airway disease model

Mice were sensitized to OVA with 400 μ g of OVA/alum administered intraperitoneally on days 0 and 13 and then challenged daily between days 22 and 27 with 50 μ g of OVA with or without 15 ng of recombinant murine IL-12 intranasally and killed on day 28. OT-I CD8⁺ or OT-II CD4⁺ cells (5×10^6) were transferred intravenously on day 21, followed by intranasal OVA on days 22 to 27. Some mice also received 25 μ g of anti-IL-12 on days 22 to 27.

Data analysis

Unpaired Student *t* tests were used to compare groups. Data from groups of mice (*n* = 4–7) were expressed as means $\pm$ SEM (*P* < .005 and *P* < .05 are indicated). Flow cytometric profiles are representative of groups of 3 to 4 mice in 2 to 3 experiments with similar results.

RESULTS

Class I-restricted presentation of exogenous OVA occurs at a similar antigen dose to class II processing

Allergen responses are generally considered to be dominated by CD4, class II-restricted T-cell responses because of inefficient cross-presentation of exogenous protein antigens onto class I molecules. We compared the efficiency of cross-presentation with that of the conventional class II pathway in CD11c⁺ myeloid DCs purified from untreated lung or spleen tissue. OT-I CD8 cells, which all express the class I-restricted T-cell receptor (not

shown), proliferated to exogenous OVA at similar doses to OT-II CD4 cells ([Fig 1, A](#)). Cells did not respond to BSA. The response with lung DCs was greater in CD8 cells than in CD4 cells. Lung DCs, which are more immature, were able to stimulate only poor CD4 cell responses in comparison with splenic DCs. However, CD8 cells responded similarly with both DC populations. Efficient cross-presentation did not require the addition of CD4 cells or adjuvants.

Acute inflammation in the lung after intranasal administration of OVA is dominated by CD8 T cells

OT-I CD8 cells and OT-II CD4 cells labeled with CFSE (5×10^6 each) were transferred into C57BL/6 mice challenged the following day with 50 μ g of OVA intranasally. Seventy-two hours later, mediastinal (lung draining) lymph nodes were analyzed for cells that had undergone cell division, resulting in dilution of CFSE fluorescence ([Fig 1, B](#)). OT-I CD8 cells expanded rapidly, going through as many as 9 divisions. By contrast, OT-II CD4 cells underwent fewer divisions and expanded in number to a far lesser extent. A single dose of OVA recruited very few CFSE⁺ cells to the lung (not shown).

We gave adoptively transferred mice 4 doses of OVA over the course of 9 days to induce recruitment of transferred cells to the lung. Because CFSE was rapidly diluted, OVA-specific cells were identified in BAL fluid by their expression of the V α 2/V β 5 transgenes. Forty percent of CD8 cells in BAL fluid were V α 2⁺V β 5⁺ on day 9 compared with 15% of CD4 cells ([Fig 1, C](#); *P* < .05). Levels of V α 2⁺V β 5⁺ CD4 and CD8 T cells present in the mediastinal lymph nodes were similar by day 9, suggesting that dividing CD8 cells had left the lymphoid tissue and been recruited to the lung.

CD8 T cells recruited to the lungs display a T_C1 phenotype after intranasal administration of OVA

Mice were transferred with OT-I CD8 cells on day 0 and challenged intranasally on days 1 and 4 with PBS or OVA. The presence of OVA-specific CD8 cells in lung tissue on day 6 was determined with H-2K^b/SIINFEKL pentamers ([Fig 2, A](#), and [Table E1](#), which is located in the Online Repository at www.jacionline.org). OVA-treated mice showed a significant increase in OVA-specific CD8 cells, confirming recruitment to the lung. Production of IFN- γ in response to SIINFEKL peptide indicated a T_C1 effector phenotype ([Fig 2, B](#), and [Table E1](#)). This was confirmed by means of analysis of BAL T cells activated with anti-CD3/CD28, which were predominantly CD8⁺ and contained a large proportion of IFN- γ ⁺ IL-4[−] IL-10[−] cells ([Fig 2, C](#), and [Table E1](#)).

Lung-primed CD8 T cells regulate systemic IgE responses

We administered 2 doses of PBS or OVA intranasally to C57BL/6 mice after OT-I cell transfer, followed by immunization with 400 μ g of OVA/alum. PBS control

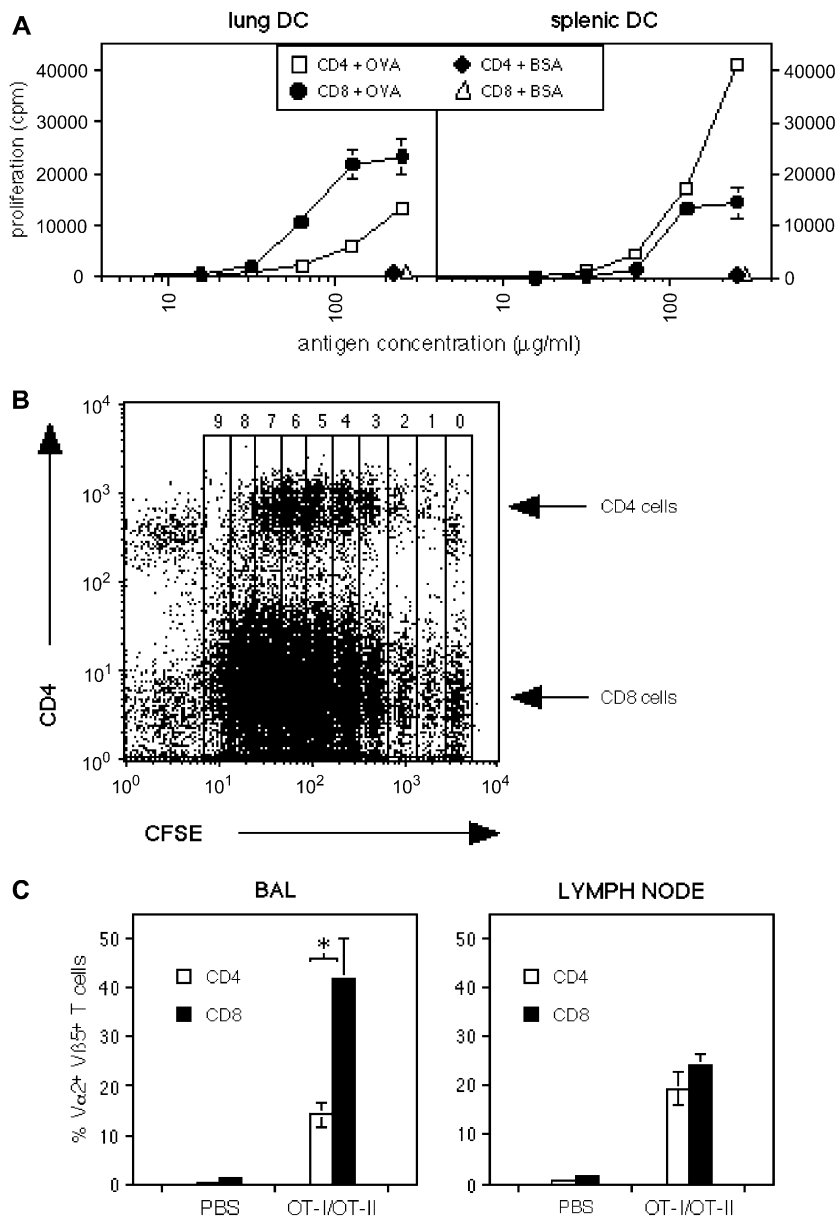


FIG 1. A, Class I/II presentation by lung/splenic DCs to OT-I CD8 or CD4 OT-II cells. B, CFSE dilution in gated $V\alpha 2^+ V\beta 5^+$ CD4 or CD8 T cells from mediastinal lymph nodes after primary intranasal challenge. C, Percentage of $V\alpha 2^+ V\beta 5^+$ CD4/CD8 OVA-specific cells in BAL fluid and lymph nodes after secondary challenge. * $P < .05$.

mice made an OVA-specific IgE response that peaked at day 8 (Fig 3) and decreased to basal levels by day 15. In mice challenged intranasally with OVA, there was complete inhibition of IgE at day 8 ($P < .0001$) and at day 11 ($P < .05$). The data indicate that the primary OVA-specific CD8 cells generated through the lung with this protocol were indeed T_C1 -type cells that suppressed IgE.

Respiratory DCs cross-present inhaled allergen and induce T_C1 differentiation

CD11c⁺ myeloid DCs within distinct respiratory tract compartments display major functional differences.^{19,20}

We determined whether there are differences in the ability of DCs from the airway mucosa or lung parenchyma to cross-present OVA. Twenty-four hours after intranasal OVA administration to unprimed mice, CD11c⁺ cells were positively selected from the main conducting airways (trachea and main bronchi, referred to as mucosal DCs), peripheral lung tissue (referred to as lung DCs), and mediastinal and cervical lymph nodes and cultured with CD11c⁺ CD8⁺ OT-I T cells (Fig 4, A). CD11c⁺ DCs from inguinal lymph nodes were a negative control. DCs present in the main conducting airways, peripheral lung tissue, and mediastinal lymph nodes were all able to cross-present OVA to a

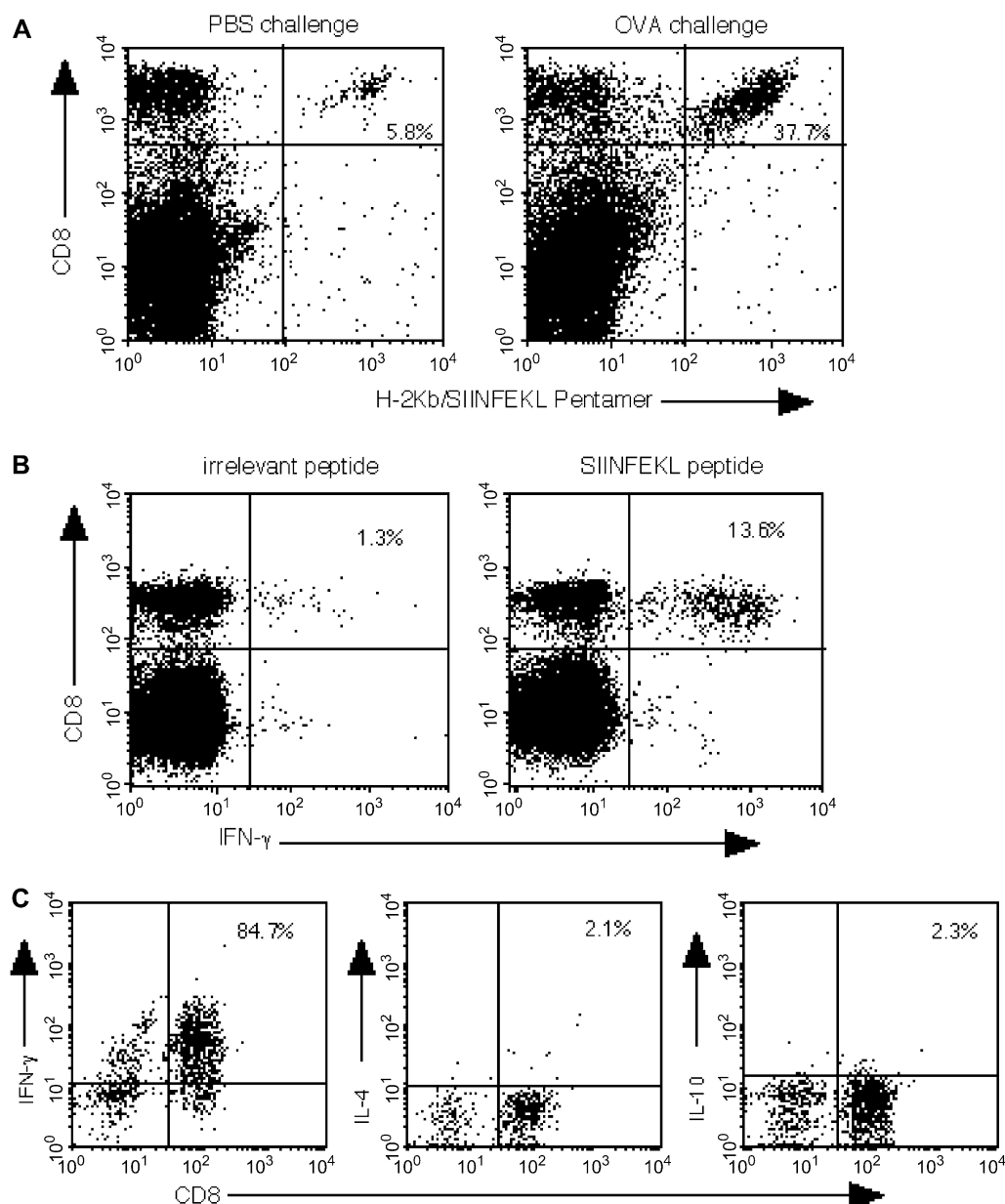


FIG 2. OVA-specific T_C1 cells are recruited to the lungs. OT-I CD8 cells were transferred to C57BL/6 mice, followed by intranasal OVA (days 1 and 4). **A**, OVA-specific CD8 cells in lung cell extracts determined by using H-2K^b/SIINFEKL pentamers. **B**, IFN- γ production in response to peptide determined by means of intracellular staining. **C**, BAL T-cell intracellular cytokine staining. Figures indicate percentages of the CD8⁺ cell population.

similar degree. Significantly less OVA presentation was observed in cervical lymph nodes. Thus lung-resident DCs cross-present allergen through MHC class I to CD8 cells in the lung tissue before or during migration from the airway mucosa to draining lymphoid tissue.

Lung DCs have been reported to induce weak, or T_H2-skewed, T-cell responses.^{21,22} We used DCs from lung tissue or spleen to generate T-effector cells in culture from OT-I CD8 or OT-II CD4 cells in response to OVA. The cytokine profiles of these effector cells are shown in Fig 4, B. Both lung and splenic DCs induced strong T_C1

(>30% IFN- γ ⁺) responses in CD8 populations. However, lung DCs induced significantly fewer T_H1 CD4 cells in comparison with splenic DCs. Few T_H2 or T_C2 IL-4⁺ cells were induced by lung or splenic DCs.

Allergen-specific CD8 T cells suppress T_H2 responses in an allergic airway disease model

CD8 cells initiate immune deviation from T_H2 to T_H1 by stimulating DC IL-12 release after OVA/alum immunization.¹⁶ We postulated that lung-resident DCs presenting OVA peptides to CD8 T cells release IL-12 into

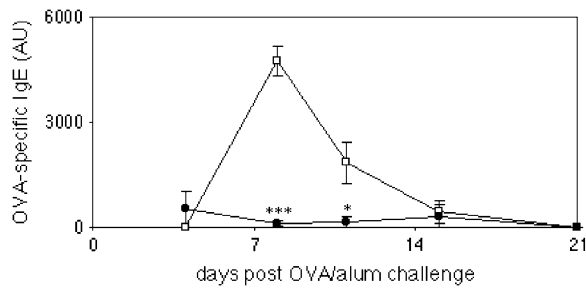


FIG 3. IgE inhibition by intranasally primed OT-I CD8 cells. OT-I CD8 cells were transferred intravenously to C57BL/6 mice, followed by 2 intranasal administrations of PBS (squares) or OVA (circles) on days 1 and 4. Mice were immunized with OVA/alum on day 6 and subsequently bled every 4 to 7 days from the tail. Serum OVA-specific IgE levels were measured in arbitrary units by means of ELISA. * $P < .05$; *** $P < .001$.

the lung tissue and thus suppress T_H2 -mediated airway inflammation. To investigate this, we introduced unprimed OT-I CD8 cells into a murine model of asthma that results in sustained OVA-induced bronchial hyperresponsiveness and eosinophilia.²³ Mice were immunized twice with OVA/alum on days 0 and 13, followed by daily OVA challenge (days 22–27). OT-I CD8 cells from unprimed mice (or CD4 cells from unprimed OT-II mice as a control) were transferred intravenously on day 21 (Fig 5, A). OVA-specific CD8 cells were found in the lung tissue after repeated challenge (Fig 5, B) and retained their T_C1 cytokine profile, as determined by means of production of IFN- γ in response to SIINFEKL peptide.

The effect of airway-sensitized CD8 cells on inflammatory cell infiltration was determined by using flow cytometric counting of eosinophils ($CCR3^+$, $Class\ II^lo$, $CD11c^-/CD3^-/B220^-$), neutrophils (marker negative granulocytes), macrophages/DCs ($CD11c^+$), and T cells ($CD3^+$) in BAL fluid cells from euthanized mice on day 28. Transfer of OT-I CD8 cells resulted in marked suppression of airway eosinophilia ($P < .01$; Fig 5, C). Addition of IL-12 to the daily administrations of OVA in nontransferred mice also suppressed eosinophilia ($P < .05$). There was no significant eosinophil suppression ($P > .05$) in mice that had received OT-I cells plus IL-12–neutralizing antibody in addition to daily OVA, despite the observation that the anti-IL-12 did not reduce IL-12 levels in BAL fluid to the same extent as in the control group (Fig 5, D). The results suggest that OT-I CD8 cells inhibit eosinophilia at least partly through stimulation of IL-12 in the lung. Similar suppression of eosinophilia was observed in lung cell extracts (data not shown). Interestingly, the level of neutrophil infiltration between adoptively transferred and control mice was unchanged, suggesting that CD8 cells antagonize the T_H2 response without superimposing T_H1/T_C1 -associated inflammatory pathology. CD4 cells from OT-II mice had little effect on lung eosinophil infiltration.

Mice receiving OT-I CD8 cells had significantly increased IL-12 levels in BAL fluid ($P < .005$; Fig 5, D),

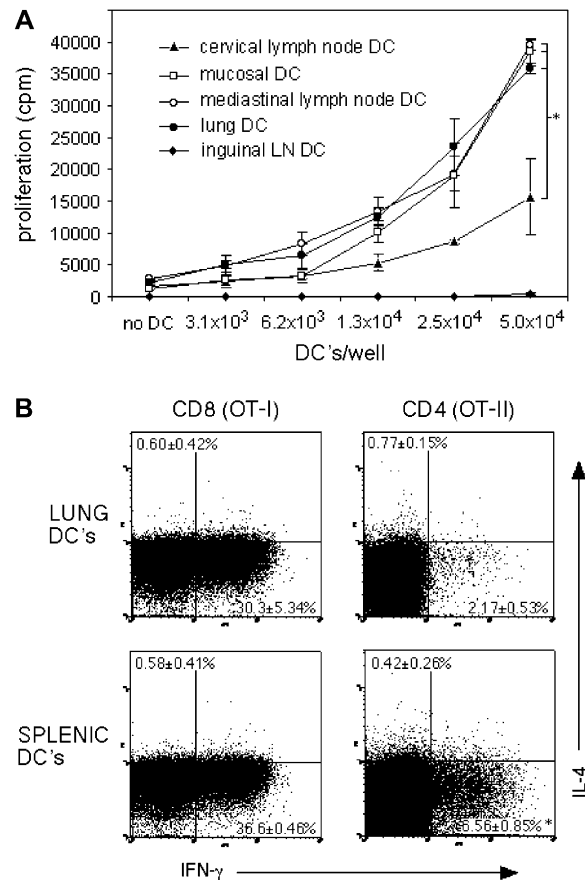


FIG 4. Respiratory DCs cross-present inhaled allergen and prime T_C1 but not T_H1 differentiation. **A**, Mice were challenged with OVA intranasally. Twenty-four hours later, DCs were purified from indicated tissues and cultured with OT-I CD8 cells, and proliferation was assessed. **B**, Lung/splenic DCs from naive mice were cultured with OT-I CD8/OT-II CD4 cells plus OVA for 6 days and restimulated for cytokines. * $P < .05$.

which is consistent with the hypothesis that CD8 T cells act through induction of IL-12 in lung tissue. OT-I transfer also significantly suppressed IL-13 ($P < .01$) and IL-5 ($P < .05$) levels in BAL fluid. Thus lung CD8 cells alter the balance of T_H1/T_H2 effectors in favor of a T_H1 profile. These data underline the distinct nature, kinetics, and effector functions of airway-sensitized CD4 and CD8 T-cell responses.

DISCUSSION

CD8 T cells play a major role in both the regulation and progression of allergic diseases, including asthma. It is clear from the literature that such cells do not exhibit a fixed phenotype but can differentiate into functionally distinct subsets that might suppress, enhance, or deviate immunopathologic processes in response to their environment. Early cloning studies of CD8 cells suggested that they develop exclusively into T_C1 -type cytotoxic cells. T_C2 -type cells were then described by using T_H2 -polarizing conditions *in vitro*,²⁴ and such cells were found in

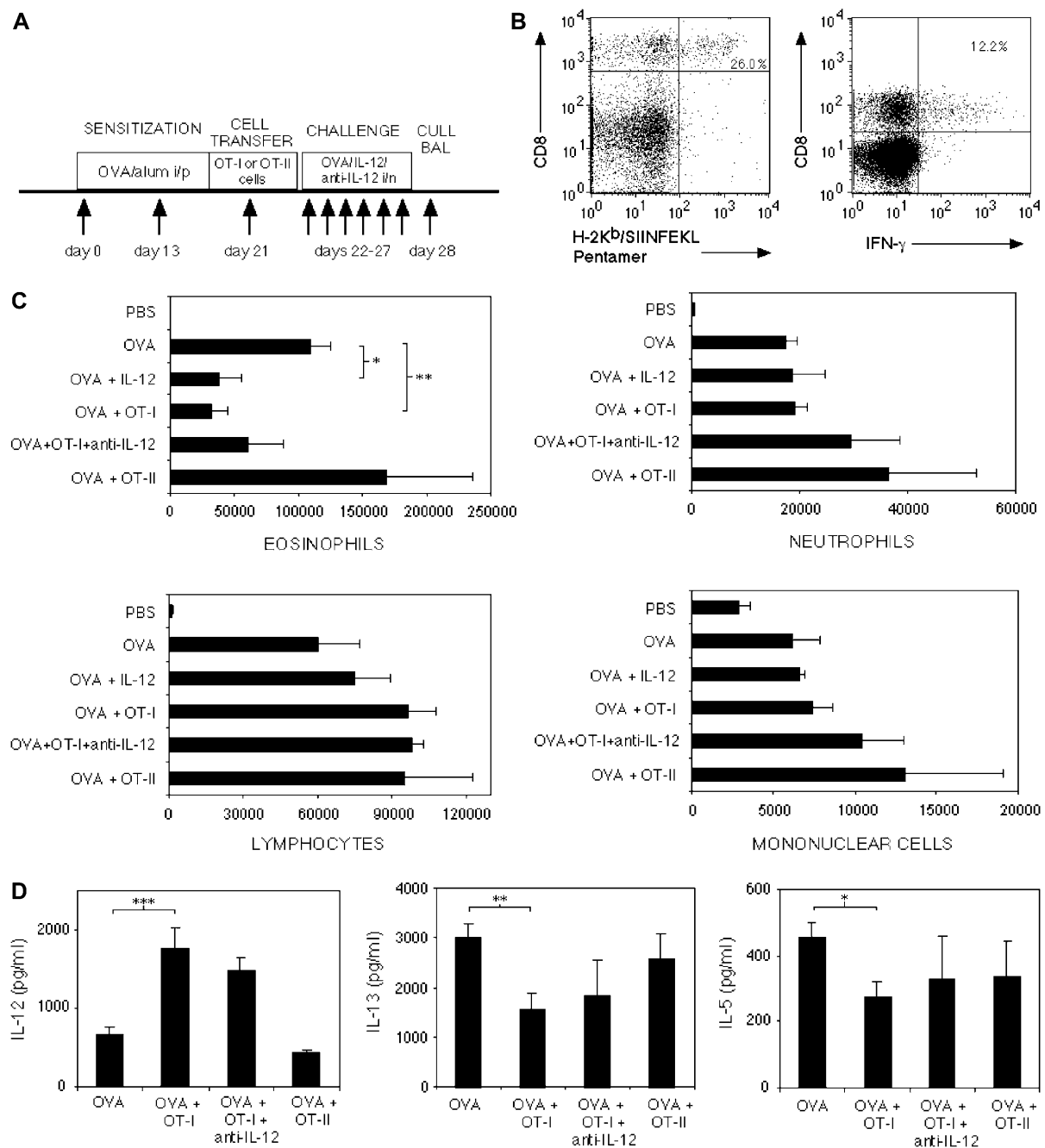


FIG 5. OVA-specific T_C1 cells suppress allergic airway inflammation. OVA-sensitized mice were injected with unprimed OT-I CD8 cells or OT-II CD4 cells and challenged as shown in panel **A**. **B**, Percentage of OVA-specific CD8 cells and peptide-induced IFN- γ . **C**, IL-12/anti-IL-12 was administered alongside 6-day OVA challenge, and inflammatory cells in BAL fluid were measured. **D**, Effect of transferred OT-I/OT-II cells on BAL cytokines. * $P < .05$; ** $P < .005$.

the asthmatic lung.¹² It now appears that the lung microenvironment might preferentially induce both T_H2 - and T_C2 -type cells because of the weaker T_H1 -polarizing capacity of respiratory DCs.^{11,22} However, a large amount of data from our laboratory and others indicates that CD8 cells play a potent suppressive role in allergic disease by skewing immunity toward a T_H1 phenotype.^{5,6,16} This function

is achieved by the ability of CD8 cells to produce large quantities of IFN- γ , other factors, or both early in the immune response⁵ and to induce IL-12 from DCs.²⁵ Development of T_H1 effectors from naive T cells requires IL-12, but T_C1 development does not, resulting in a strong bias of CD8 cells toward the T_C1 pathway.^{26,27} Important differences also exist between CD4 and CD8 cells in the

kinetics, intensity, and memory T-cell development of their *in vivo* response.

Our study addressed the role of CD8 cells that respond to allergens in the lung presented by respiratory DCs to clarify the function of CD8 responses in asthma. By using combinations of transgenic class I- and class II-restricted T cells, we were able, for the first time, to examine the earliest responses to inhaled allergen, which cannot be detected in normal mice. We showed that respiratory DCs, like conventional splenic DCs, readily process exogenous OVA protein into the MHC class I and class II pathways. Although this cross-presentation pathway is well known, our data are the first, to our knowledge, that indicate the high efficiency of functional cross-presentation by lung DCs when compared with the conventional class II pathway. It has been generally assumed that strong CD8 responses to exogenous proteins require transfection of the material into the cytoplasmic compartment. Our data indicate that uptake by DCs is sufficient for the initial proliferative response of CD8 cells to protein allergens, although sustained expansion and functional maturation of the CD8 response most likely requires signals from CD4 T cells or Toll-like receptor ligation.^{28,29} The functional immaturity of lung compared with splenic DCs was apparent in the class II/CD4 cell pathway but not in the class I/CD8 cell pathway. This might be due to distinct costimulatory requirements of CD8 T cells.

Respiratory DCs present OVA through class I in the airways, lung tissue, and draining lymph nodes very shortly after intranasal challenge, suggesting that processing occurs immediately, before DCs have migrated to the draining lymph nodes. It is known that effective cross-presentation can result from transfer of antigenic material from dying cells into lymph node-resident DCs.³⁰ However, cross-presentation can occur in the absence of lymph nodes if CD4 help is present.³¹ Our data suggest that respiratory DCs directly process exogenous protein onto class I without a requirement for cell-to-cell transfer. However, because live DCs can pass antigen to each other,³² such transfer might occur in the lung. The pathway for cross-processing of material from endosomes into the class I pathway can involve translocation to the cytosol and endoplasmic reticulum or association with class I in the endosomal compartment.³³ Provision of DC activation signals is probably required for cross-presentation,³⁴ as well as mobilization, of lung DCs. In our model it is possible that such signals are provided by endotoxin present in the OVA solution or from rapid expression of CD40 ligand on responding CD8 cells. Lastly, our data indicate cross-presenting function is similar in mucosal, lung, and lymph node DCs, suggesting the pathway is common to all myeloid DCs independent of environmental cues.

CD8 responses dominated primary airway inflammation. More rapid division and greater clonal expansion of CD8 cells has been previously demonstrated in murine models³⁵ and also occurs in human subjects.³⁶ Our data show that similar distinctions in the dynamics of T-cell immunity also apply to exogenous antigens and inhaled allergens. Not surprisingly, data using OVA expressed

intracellularly show an even more dramatic difference between expansion of CD4 and CD8 cells.³⁵ Extensive proliferation of CD8 cells might result from an uncoupling of ongoing division from continued antigen presentation.³⁷ The data have important implications for asthma because the initial inflammatory cascade will determine the cytokine environment that directs the subsequent nature of immune responses to allergen. Key factors are the availability of IL-12 and IFN- γ early in the response, which direct T_H1 development.³⁸ A lack of rapid IFN- γ secretion, coupled with poor DC activation for IL-12 synthesis, might contribute to T_H2 polarization after inhaled allergen challenge.³⁹

Allergen-specific CD8 cells generated through respiratory sensitization were able to suppress IgE responses induced by parenteral immunization, suggesting migration of proliferating cells from respiratory lymph nodes to distant lymphoid tissues, as well as to the lung. Despite the T_H2-polarizing influence of OVA/alum immunization, transfer of unprimed OT-I cells was able to strongly suppress eosinophilic airway inflammation and T_H2 lung cytokine responses, reflecting their bias toward the T_C1 pathway. Immunotherapies targeting the CD8 population are therefore promising as novel treatments for allergy and asthma because they could antagonize both T_H2- and IgE-dependent components of the disease. Nonetheless, the rapid expansion and contraction of the initial T_C1-type CD8 response might be replaced by distinct CD8 phenotypes after prolonged allergen provocation, as indicated by studies reporting T_C2-type, IL-13-secreting lung CD8 cells in similar murine models.^{11,40-42} Differences in the protocols used in our study might explain the absence of a T_C2 response. In the study of Stock et al,⁴⁰ BALB/c mice, rather than the more T_H1-prone B6 strain used here, were immunized repeatedly with OVA/alum, and T_C2 cells were confined to the lung; central memory CD8 cells appear to retain a T_C1 phenotype.^{11,43} Although CD8^{-/-} mice show reduced allergic airway inflammation,⁹ CD8 is expressed on a number of innate cells, including natural killer T cells⁴⁴ and $\gamma\delta$ T cells,⁴⁵ which might be important in initiating early T_H2 responses.^{46,47} Adoptive transfer of CD8 cells leading to enhanced allergic lung responses has been shown by using CD8 cells from repeatedly OVA/alum-primed mice⁹ or OT-I cells cultured extensively in IL-2.¹¹ This priming of CD8 cells is likely to favor T_C2 development because in our hands T_C1 cells die after 1 week of culture in IL-2, whereas T_C2 cells are relatively resistant to apoptosis.⁴⁸ It should also be noted that lung eosinophilia might not correlate with airway hyperreactivity because CD8 cells secreting IL-5 were found in sensitized CD4^{-/-} mice, resulting in hyperreactivity in the absence of eosinophilia.⁴¹

The precise mechanism that allows CD8 cells to induce IL-12 in DCs is unclear. Early release of IFN- γ in draining lymph nodes is known to be critical for T_H1 priming through IL-12, and CD8, as well as natural killer cells and natural killer T cells, are capable of providing this signal.^{38,39} We have shown that DCs in peripheral tissue, such as the lung, can also receive IL-12-inducing signals from

infiltrating CD8 cells. However, IFN- γ is not essential for the T_H1-skewing properties of CD8 cells.¹⁶ CD8-assisted DC activation is likely to be important in responses to inhaled allergen, which would not trigger as many Toll-like receptors on DCs as many infectious agents. Rapid influx of newly generated effectors would sustain the activation of respiratory DCs, inducing IL-12 production and migration to draining lymphoid tissue. That such inflammation appears to prevent rather than exacerbate allergic airway disease can be explained by observations that type 1 and type 2 T-cell development is antagonistic.^{49,50} Also, CD8 responses, although intense and inflammatory, rapidly contract because of extensive apoptosis. This resolution phase is promoted by IFN- γ secretion.⁵¹ By contrast, CD4 cells are relatively resistant to apoptosis in the face of repeated stimulation, especially T_H2 cells.⁵² Appropriate responses to inhaled antigen might require an array of cytokines and effector subsets to ensure the correct balance between immunity and tolerance, thus avoiding damaging immunopathologic consequences, including asthma. Development of peptide vaccines containing class I-restricted allergen epitopes is a promising new approach that might help correct the imbalanced and polarized T_H2 responses that lead to allergic disease.

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