

A subset of CD8⁺ T cells from allergic patients produce IL-4 and stimulate IgE production *in vitro*

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Summary

Background and Objective A subset of IL-4 producing CD8⁺ T cells was recently identified in HIV patients. Based on these findings we examined whether IL-4 producing CD8⁺ T cells would also be present in allergic patients and what would be the functional relevance of this T-cell population.

Methods We investigated the role of CD8⁺ T cells in IgE production of allergic diseases by analysing the cytokine profile of individual CD4⁺ and CD8⁺ T cells.

Results In allergic patients about twice as many CD4⁺ T cells and six times as many CD8⁺ T cells produced IL-4 as in non-allergic controls. In contrast the frequency of IFN γ ⁺ T-cell subsets did not significantly differ between the allergic and non-allergic individuals. The frequency of IL4⁺CD8⁺ T cells correlated with the level of serum IgE. Coculture experiments with T cells or purified CD8⁺ T cells together with autologous B cells indicated that CD8⁺ T cells enhanced IgE *in vitro*, but not IgM production, even when they were physically separated from B cells. This effect could be partially blocked by addition of an IL-4 binding protein, a soluble IL-4 receptor indicating that IL-4 is involved in CD8⁺ T-cell mediated IgE production.

Conclusions These data indicate a positive role of IL-4 secreting CD8⁺ T cells in IgE regulation in allergic patients.

Keywords: allergy, IgE production, CD8⁺ T cells, IL-4

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Introduction

Mouse CD4⁺ T cell subpopulations with various effector functions can be divided on the basis of their cytokine secretion pattern. TH₁ cells produce IL-2 and IFN γ and mediate delayed type hypersensitivity responses, whereas TH₂ cells produce IL-4, IL-5, IL-10 and IL-13, and provide co-stimulatory signals for B cell-immunoglobulin isotype switching [1,2]. Such a distinction may also exist at the single cell level of human T cells which may be associated with different clinical conditions [3–6]. Recent studies provide evidence that a similar differentiation on the basis

of lymphokine production may also occur within the CD8⁺ T cell population under certain conditions [7,8]. For example, in patients with lepromatous leprosy and AIDS, CD8⁺ T cells secrete a cytokine profile characteristic for CD4⁺ TH₂ cells. High IL-4 and low IFN γ production of CD8⁺ T cells was shown to correlate with loss of cytotoxic activities [9–13].

Cognate T–B cell interaction induces immunoglobulin isotype switching from IgM to IgE in the presence of IL-4 and other co-stimulatory signals in cell culture [14,15]. It has been shown that elevated serum IgE levels in patients suffering from allergic diseases are due, at least in part, to increased IL-4 and decreased IFN γ production, which has been found in peripheral blood and at the site of allergic inflammation [16–19].

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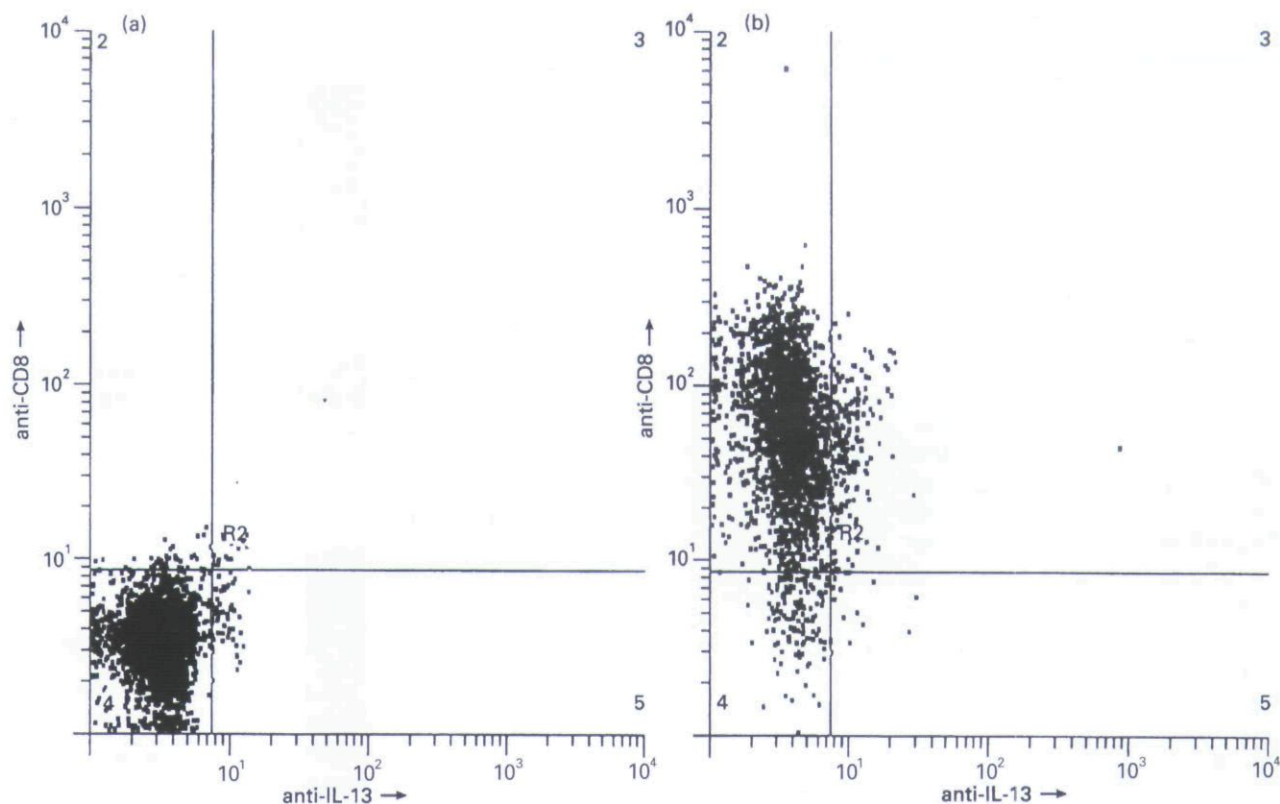


Fig. 7. Intracellular staining of purified CD8 T cells from a representative atopic patient for IL-13 production. Experiment was performed as previously described [24]. (a) isotype control staining; (b) double staining for IL-13 (x-axis) and CD8 (y-axis); 6% of the cells are double positive.

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References

- 1 Mosmann TR, Coffmann RL. Different pattern of lymphokine secretion lead to different functional properties. *Ann Rev Immunol* 1989; 7:145-173.
- 2 McKenzie ANJ, Culpepper JA, De Waal Malefyt R et al. Interleukin 13, a T-cell-derived cytokine that regulates human monocyte and B-cell function. *Proc Natl Acad Sci USA* 1993; 90:3735-9.
- 3 Palliard X, De Waal Malefyt R, Yssel H et al. Simultaneous production of IL-2, IL-4 and IFN- γ by activated human CD4 and CD8 T cell clones. *J Immunol* 1988; 141:849-55.
- 4 Parronchi P, Macchia D, Piccinni MP et al. Allergen- and bacterial antigen-specific T-cell clones established from atopic donors show different profile of cytokin production. *Proc Natl Acad Sci USA* 1991; 88:4538-42.
- 5 Manetti R, Parronchi P, Giudizi MG et al. Natural killer cell stimulatory factor (IL-12) induces T helper type 1 specific immune responses and inhibits the development of IL-4-producing Th cells. *J Exp Med* 1993; 177:1199-204.
- 6 Clerici M, Lucey DR, Berzfsky JA et al. Restoration of HIV-specific cell-mediated immune responses by interleukin-12 in vitro. *Science* 1993; 262:1721-24.
- 7 Croft M, Carter L, Swain SL, Dutton RW. Generation of polarized antigen-specific CD8 effector populations: reciprocal action of IL-4 and IL-12 in promoting type 2 versus type 1 cytokine profile. *J Exp Med* 1994; 180:1715-28.
- 8 Seder RA, Le Gros G. The functional role of CD8⁺ T helper type 2 cells. *J Exp Med* 1995; 181:5-7.
- 9 Maggi E, Giudizi MG, Biagotti R et al. Th2 like CD8⁺ T cells showing B cell helper function and reduced cytolytic activity in Human Immunodeficiency Virus Type 1 infection. *J Exp Med* 1994; 180:486-95.
- 10 Salgame P, Abrams C, Clayberger C et al. Differing lymphokine profiles of functional subsets of CD4 and CD8 T cell clones. *Science* 1991; 254:279-82.
- 11 Erad F, Wild MT, Gracia-Sanz JR, Le Gros G. Switch of CD8⁺ T cells to non cytolytic CD8⁺CD4⁻ cells that make Th2 cytokines and help B cells. *Science* 1993; 260:1802-1805.
- 12 Paganelli R, Scala E, Ansotegui IJ et al. CD8⁺ T lymphocytes

- provide helper activities for IgE Synthesis in Human Immunodeficiency Virus-infected patients with Hyper-IgE. *J Exp Med* 1995; 181:423–8.
- 13 Coy AJ, Erad F, Bertrand C, Walti S, Pircher HP, Le Gros G. Virus specific CD8⁺ cells can switch to Interleukine 5 production and induce airway eosinophilia. *J Exp Med* 1995; 181:1229–33.
 - 14 Pene J, Rouse TF, Briere F et al. IgE production by normal human lymphocytes is induced by interleukine 4 and suppressed by interferons gamma and alpha and prostaglandin E2. *Proc Natl Acad Sci* 1988; 85:6880–4.
 - 15 Finkelman FD, Katona IM, Urban JF et al. Suppression of in vivo polyclonal IgE responses by monoclonal antibody to the lymphokine B-cell stimulatory factor 1. *Proc Natl Acad Sci USA* 1986; 83:9675–8.
 - 16 Rousset F, Robert J, Andary M et al. Shifts in interleukin-4 and interferon gamma production by T cells of patients with elevated serum IgE levels and the modulatory effects of these lymphokines on spontaneous IgE production. *Allergy Clin Immunol* 1991; 87:58–69.
 - 17 van der Heijden FL, Wierenga E, Bos JD, Kapsenberg ML. High frequency of IL-4 producing CD4⁺ allergen specific T lymphocytes in atopic patients. *J Invest Dermatol* 1991; 97:398–94.
 - 18 van Reijssen FC, Bruijnzeel-Koomen CA, Kalthoff FS et al. Skin derived aeroallergen specific T cell clones of Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992; 90:184–92.
 - 19 Durham SR, Ying S, Varney VA et al. Cytokine mRNA expression for IL-3, IL-4, IL-5 and GM-CSF in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol* 1992; 148:2390–4.
 - 20 Jung T, Schauer U, Heusser Ch, Neumann Ch, Rieger Ch. Detection of intracellular cytokines by flow cytometry. *J Immunol Meth* 1993; 159:197–207.
 - 21 Ruegg CL, Rajasekar S, Stein BS, Engleman EG. Degradation of CD4 following Phorbol-induced Internalisation in human T-lymphocytes. *JBC* 1992; 267:18837.
 - 22 Alkan S, Akdis C, Towbin H. Chemiluminescent and enzyme linked immunoassays for sensitive detection of human IFN- γ . *Immunoassay* 1994; 15:217–38.
 - 23 Andersson U, Andersson J, Linfors A, Wagner K, Moeller G, Heuser CH. Simultaneous production of IL-2, IL-4 and IFN- γ by activated human blood lymphocytes. *Eur J Immunol* 1990; 20:1591–6.
 - 24 Jung T, Wijdenes J, Neumann C, de Vries JE, Yssel H. Interleukin-13 is produced by activated human CD45RA⁺ and CD45RO⁺ T cell: modulation by interleukin-4 and interleukin-12. *Eur J Immunol* 1996; 26:571–7.
 - 25 Johnstone A, Thorpe R. *Immunochemistry in Practice*, 2nd. ed. Blackwell Scientific, Oxford, UK. 1987:102.
 - 26 Granger GA, Williams TW. Lymphocyte cytotoxicity in vitro: Activation and release of a cytotoxic factor. *Nature* 1968; 218:1253.
 - 27 Kaufmann SE. Immunity to intracellular microbial pathogens. *Immunol Today* 1995; 16:338–42.
 - 28 Morris AG, Lin YL, Askonas BA. Immune interferon release when a cloned cytotoxic T cell line meets its correct influenza infected target cell. *Nature* 1982; 295:150.
 - 29 Renz H, Lack G, Saloga J, Schwinzer R, Bradley K, Loader J, Larsen G, Gelfand E. Inhibition of IgE production and normalization of airway responsiveness by sensitized CD8 T cells in a mouse model of allergen induced sensitization. *Immunol* 1994; 152:351–60.
 - 30 Kemeny DM, Noble A, Holmes BJ, Diaz Sanchez D. Immune regulation: a new role for the CD8⁺ T cell. *Immunology Today* 1994; 15:107–10.
 - 31 Actor JK, Mutsunori S, Kullberg M, Buller RM, Sher A, Berzof-sky J. Helminth infection results in decreased virus specific CD8⁺ cytotoxic T cell and Th1 cytokine responses as well as delayed virus clearance. *Proc Natl Acad Sci* 1993; 90:948–52.
 - 32 Noble A, Macary PA, Kemeny DM. IFN- γ and IL-4 regulate growth and differentiation of CD8⁺ T cells into subpopulations with distinct cytokine profiles. *J Immunol* 1995; 155:2928–37.
 - 33 Lucey DR, Zajac RA, Melcher GP, Butzin CA, Boswell RN. Serum IgE levels in 622 persons with HIV infection: IgE elevation with marked depletion of CD4⁺ T cells. *AIDS Res Hum Retroviruses* 1990; 6:427–9.
 - 34 Carr A, Cooper DA, Penny R. Allergic manifestation of HIV infection. *J Clin Immunol* 1991; 11:55–64.
 - 35 Byun DG, Demeure CE, Yang LP, Shu U, Ishihara H, Vezzio N, Gately MK, Delespesse G. In vitro maturation of neonatal human CD8 T lymphocytes into IL-4 and IL-5 producing cells. *J Immunol* 1994; 153:4862.
 - 36 Brinkmann V, Kristofic C. TCR stimulated naive Human CD4⁺RO⁺ T cells develop into effector cells that secrete IL-13, IL-5, and IFN γ , but no IL-4 and help efficient IgE production by B cells. *Immunol* 1995; 154:3078–87.
 - 37 Noble A, Staynov DZ, Dia-Sanchez D, Lee TH, Kemeny M. Elimination of IgE regulator rat CD8⁺ T cells in vitro increases the co-ordinate expression of Th2 cytokines IL-4, IL-5, and IL-10. *Immunol* 1993; 80:326–9.
 - 38 Renz H, Brodie C, Bradley K, Leund D, Gelfand EW. Enhancement of IgE production by anti-CD440 antibody in atopic dermatitis. *J Allergy Clin Immunol* 1994; 93:658–68.