

CD8⁺ T cells in atopic disease

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In recent years there has been a tremendous expansion in our understanding about CD8⁺ T cells. We now know that, as for CD4⁺ T cells, they can be divided into subsets (Tc1 and Tc2) according to the cytokines they secrete. These subsets may differ in their capacity to kill and may even, in some cases, provide help for B cell antibody production or be involved in the induction of inflammatory responses. In addition, there is a host of cross-regulatory networks between different CD4⁺ and CD8⁺ subsets that control the magnitude and duration of immune responses. The observation that some antigens that are normally presented by MHC class II and seen by CD4⁺ T cells can be presented by MHC class I and stimulate CD8⁺ T cells increases the possibility for such interactions. During the next few years we can expect that our understanding of the biology of CD8⁺ T cells and their role in immunity will increase.

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Abbreviations

BHR bronchial hyper-reactivity
CTL cytotoxic T lymphocyte
IFN-γ interferon γ
OVA ovalbumin

Introduction

Shortly after IgE was discovered, in 1967, it became clear that this class of immunoglobulin is more closely regulated than other immunoglobulin classes. Of major importance are genetic factors — children of allergic parents are more likely to become allergic and some strains of mouse (BALBc and B6) and rat (Brown Norway, Hooded Lister and PVG) are good IgE responders while others (mouse SJL and rat Lewis and Wistar) are not. This genetic restriction is independent of other isotypes of antibody. The ability of different animals to make IgE responses is not simply a function of whether or not they process and present antigen via the appropriate HLA molecules. Pioneering studies by Okamura and Tada [1] showed that IgE responses had a very high requirement for T cell help; however not all T cells provided help and Okamura and Tada [2] showed that a subset of T cells that expressed the Lyt2 antigen (i.e. CD8⁺ T cells; [3]) suppressed IgE production; however the picture is more complex for, as well as inhibiting IgE responses, there is now accumulating evidence that CD8⁺ T cells have the potential to both stimulate IgE class-switching and promote allergic inflammation.

CD8⁺ T cell subsets

In 1986 Mosmann *et al.* [4] reported that long-term murine CD4⁺ T cell clones could be segregated according to their patterns of cytokine secretion. The following year Snapper and Paul [5] reported that IL-4 was a switch factor for the expression of the immunoglobulin ε heavy chain gene and that this process could be inhibited by IFN-γ. CD4⁺ T cell subsets comparable to murine Th1 and Th2 have been described in the rat [6] and human [7]. Other CD4⁺ T cell subsets — including Th0 cells (which exhibit an unrestricted cytokine profile) [8] and Th3 cells (which secrete IL-4, IL-10 and high levels of transforming growth factor β) [9,10] — have since been described. Similar studies of CD8⁺ T cells have now revealed the existence of distinct subpopulations (Tc1/Tc2/Tc0 cells) that can be compartmentalised along broadly similar lines to CD4⁺ T cells [6,11–13] — with IFN-γ secretion representing Th1/Tc1 cells, IL-4 secretion representing Th2/Tc2 cells and an unrestricted cytokine profile representing Th0/Tc0 cells. Tc1 and Tc2 memory cells are stable and retain their cytokine pattern [14••].

Functionally, much less is known about CD8⁺ T cell subsets. CD8⁺ T cells protect against infection [15,16] and may restrict tumour growth [17•]. Le Gros and co-workers [18] reported that purified CD8⁺ T cells, vigorously stimulated in the presence of high concentrations of IL-4, became noncytolytic CD8⁺ CD4⁺ cells and made type 2 cytokines (IL-4, IL-5 and IL-10). These cells were later shown to be capable of switching B cells to make IgE [19]. It was also observed that freshly isolated human peripheral blood CD8⁺ T cells have the potential to make IL-4 at similar [20], and sometimes greater [21], levels than those produced by comparable CD4⁺ cells. This is true also in the rat, where freshly purified CD8⁺ T cells stimulated with phorbol myristate acetate and ionomycin expressed more IL-4 mRNA than similarly activated CD4⁺ T cells [6]. CD8⁺ T cells that secrete type 2 cytokines have also been isolated in a variety of diseases. Salgame *et al.* [22] reported that some of the *Mycobacterium-leprae*-specific CD8⁺ clones generated from patients with lepromatous leprosy made IL-4, IL-5 and IFN-γ but not IL-6 or IL-10. These clones were termed type 2 clones or suppressor clones and inhibited *M.-leprae*-specific CD4⁺ cytotoxic T lymphocytes (CTLs). These CD8⁺ cells were atypical, as they were MHC-class-II restricted [23]. Th2-like CD8⁺ T cells secreting IL-4 and/or IL-5 but not IFN-γ have also been found in HIV-infected individuals [24].

CD8⁺ T cell inhibition of IgE production

Rat [25] and mouse [26] IgE-inhibitory CD8⁺ T cells have been generated both following inhalation of antigen and following parenteral immunization [27–30]. More recently,

MHC-class-I-restricted mouse CD8⁺ T cells that are specific for exogenous protein (bovine casein) and that suppress IgE have been described [31] as well as MHC-class-II-restricted [32] and TCR $\gamma\delta$ ⁺ [26] IgE-inhibitory CD8⁺ T cells. The importance of CD8⁺ T cells in regulating IgE responses was confirmed by Holmes *et al.* [33^{••},34[•]] who showed that depletion of CD8⁺ T cells enhanced IgE production. The mechanism is not known but antigen-stimulated CD4⁺ T cells from animals depleted of CD8⁺ T cells produced more IL-4 and less IFN- γ . Interestingly this phenomenon was only seen if CD8⁺ T cell depletion was performed after the primary immune response. Depletion of CD8⁺ T cells prior to immunisation rendered the rats IgE-hyporesponsive [35].

In BALB/c mice, Openshaw and co-workers [36^{••}] have shown that CD8⁺ T cells regulate the CD4⁺ Th1/Th2 balance in the immune response to infection with respiratory syncytial virus. CD8⁺ T cells also accumulate in nonatopic chronic respiratory diseases such extrinsic allergic alveolitis [37[•]] and chronic obstructive bronchitis [38^{••}]. In asthmatic patients there is controversy about the source of lung IL-5, with studies of bronchoalveolar lavage cells showing that CD8⁺ T cells do not contribute to the IL-5 detected [39^{••}], while studies of lung biopsies showed that IL-5-producing CD8⁺ T cells were present in the airway submucosa [40^{••}].

How CD8⁺ T cells regulate the allergic immune response is not known. Secretion of IFN- γ by CD8⁺ T cells is the most obvious explanation for their ability to inhibit IgE production. IFN- γ production during the formative stages of a CD4⁺ T cell response could inhibit the growth of Th2 cells directly, whilst favouring the expansion of Th1 cells [41]. Alternatively CD8⁺ T cells could stimulate macrophages to produce nitric oxide as part of a nonspecific suppressive process. IFN- γ that is derived from CD8⁺ cells could act directly on B cells to inhibit immunoglobulin synthesis [5] and cytolytic CD8⁺ T cells could target antigen-specific B cells or antigen-presenting cells. MacAry *et al.* [42^{••}] produced rat ovalbumin (OVA)-specific CD8⁺ T cell clones. These clones were MHC-class-I restricted and varied in their ability to regulate IgE; however, their ability to inhibit IgE was unrelated to the levels of IFN- γ they produce or to their *in vitro* cytolytic activity for OVA-pulsed targets [42^{••}]. Thus IgE-suppressor cells may be distinct from the Tc1, IFN- γ -producing subset and may produce other cytokines that suppress IgE responses [43^{••}]. For example Noble *et al.* [44^{••}] have shown that CD8⁺ T cells can selectively inhibit Th2 CD4⁺ T cells via a Fas-ligand-mediated apoptotic pathway.

CD8⁺ T cells are normally restricted by MHC class I — as in our experiments [42^{••}] — but exceptionally recognise antigen presented by MHC class II [10,22,23,32] or by other HLA products such as Qa1, which may suppress either Th1 cells [45^{••}] or Th2 responses [46^{••}]. Adjuvants and vaccines that promote class-I-restricted processing of

allergen enhance CD8⁺ T cell responses [47,48^{••}–50^{••}] and appear to be more effective in suppressing Th2 and IgE immune responses. There is evidence for CD8⁺ T cell activation in allergic patients, where oligoclonal activation of CD8⁺ as well as CD4⁺ T cells was described following challenge with antigen [51^{••}]; furthermore, CD8⁺ T cells accumulate in the lungs following bronchial provocation [17[•],37[•]]; allergen-specific CD8⁺ T cell responses have been detected both to a variety of different protein antigens [52[•]–54[•]] and to drugs [55^{••},56[•],57^{••},58^{••}]. CD8⁺ T cells respond to a range of antigen-presenting cells, including mast cells [59[•]], and to a wide range of antigens — including carbohydrate determinants [60^{••}].

Non-CD8⁺ T cell inhibition of IgE production

A recent paper has challenged the importance of CD8⁺ T cells in the regulation of IgE responses. Coffman and co-workers [61^{••}] showed that, following inhalation of OVA, it was possible to inhibit IgE responses independently of CD8⁺ T cells. This contrasts with Holt and co-workers [25,26,41] who have shown that CD8⁺ T cells activated by inhalation suppressed IgE responses; however, recent experiments by Holt and co-workers [62^{••}] on regulation of the gastrointestinal IgE response have shown IgE regulation that is independent of CD8⁺ T cells. Lamb and co-workers [63^{••}] generated MHC-class-I-restricted CD8⁺ T cells in the mouse and these suppressed IgE production; Renz *et al.* [64] showed the same thing in mice following OVA inhalation as did Kapp and co-workers [65^{••},66^{••}] using TCR $\gamma\delta$ ⁺ CD8⁺ T cells. Lam and co-workers [67^{••}] have also identified regulation of mouse Th2-type immune responses that was independent of CD8⁺ T cells. What these CD8⁺-cell-independent IgE-regulatory systems seem to have in common is that they involve T cell anergy. Indeed being fed antigen can inhibit both delayed-type hypersensitivity and Th1 or Th2 immune responses, depending on the dose of antigen [68^{••}]. The explanation for these different mechanisms may lie in the pathogen status of the animals used. We found that rats that were not free of *Syphacia oblongata* (a nematode) made the best IgE responses (M Kemeny, D Diaz-Sanchez, A Noble, BJ Holmes, unpublished data); it is well recognised that infection by nematodes promotes IgE responses to bystander antigens [69]. A second, surprising, variable is the preparation of antigen. The late Ellen Jarrett reported optimal doses of antigen varying from tens of μ g to mg; we have observed that in the same strain of rat from the same supplier this optimum can vary from 0.1 μ g to 100 μ g. OVA is a potent inducer of IgE responses but different batches vary considerably. This has been attributed to the degree of aggregation [70], which may affect antigen processing.

CD8⁺ T cells and asthma

As well as inhibiting IgE responses, there is evidence that — under certain circumstances — CD8⁺ T cells can actually be required for IgE responses. For example, rats depleted of CD8⁺ T cells or nude rats reconstituted with

CD4⁺ but not CD8⁺ T cells prior to immunisation failed to mount an IgE response [35]. *In vitro*, Tc2 CD8⁺ T cells could promote IgE class switching [18,19,71[•]]. Interestingly, it appears to be IL-13 (a Tc2 cytokine) rather than IL-4 that is responsible for this [72^{••}]. In allergic patients there is ample evidence that Th2-like CD8⁺ T cells are present at sites of allergic inflammation [40^{••},73[•]] but it is not clear either whether sufficient antigen is available to activate them or the extent to which they contribute to allergic inflammation. Experimental asthma models in animals have provided compelling evidence that CD8⁺ T cells can moderate antigen-induced airway inflammation and bronchial hyper-reactivity (BHR) [74^{••}]. Adoptively transferred OVA-specific CD4⁺ T cells induce eosinophilic airway inflammation and BHR in naive rats following experimental challenge with OVA. These cells, isolated from spleens of sensitised donor rats, induced BHR and airway eosinophilia in naive recipient animals [75]. Purified CD8⁺ T cells, on the other hand, did not — rather, they inhibited BHR and airway inflammation [76^{••}].

Conclusions

Regulation of the allergic immune response occurs by a number of different processes. It is quite clear that CD8⁺ T cells play a major role in determining whether or not an IgE response will occur. Their role in the established IgE response is less clear although recent experiments in my laboratory indicate that they could be induced to suppress this. CD8⁺ T cells are now being found in a variety of different tissues and are associated with an ever increasing number of diseases. The challenge for the next few years is to determine whether they are simply hanging around or whether they are active participants in allergic disease.

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In this paper, inhalation challenge of patients with ragweed allergen caused V gene families of both CD4⁺ and CD8⁺ bronchoalveolar lavage T cells to either become oligoclonal or to develop a new oligoclonal pattern of junctional region lengths – indicating that ragweed challenge is associated with polyclonal influx and oligoclonal activation of both CD4⁺ and CD8⁺ T cells in the lungs.

52. Sparholt SH, Larsen JN, Ipsen H, Schou C, van Neerven RJ:
• **Crossreactivity and T-cell epitope specificity of Bet v 1-specific T cells suggest the involvement of multiple isoallergens in sensitization to birch pollen.** *Clin Experiment Allergy* 1997, **27**:932-941.

This reports that CD8⁺ as well as CD4⁺ T cell clones (TCCs) could be generated against birch pollen allergen (Bet v 1). Such specific TCCs (19/21 CD4⁺, 2/21 CD8⁺) reacted with affinity-purified Bet v 1 but showed different reactivities with recombinant Bet v 1 and with group 1 allergens from other *Fagales* species.

53. Werfel T, Hentschel M, Kapp A, Renz H: **Dichotomy of blood- and skin-derived IL-4-producing allergen-specific T cells and restricted V beta repertoire in nickel-mediated contact dermatitis.** *J Immunol* 1997, **158**:2500-2505.

This demonstrates that 21% of 253 nickel-specific T cell clones (TCCs) were CD8⁺ positive. In contrast to blood-derived TCCs, the majority of skin-derived CD4⁺ or CD8⁺ T lymphocytes were type 0 or type 2 – indicating that their cytokine profile was modified by their environment.

54. Lack G, Nelson HS, Amran D, Oshiba A, Jung T, Bradley KL,
• Giclas PC, Gelfand EW: **Rush immunotherapy results in allergen-specific alterations in lymphocyte function and interferon-gamma production in CD4⁺ T cells.** *J Allergy Clin Immunol* 1997, **99**:530-538.

The authors show that, following rush immunotherapy against house dust mite antigen, there was a significant reduction in T-cell proliferative responses to mite antigen but that numbers of CD8⁺ T cells were increased.

55. Pichler WJ, Zanni M, von Greysz S, Schnyder B, Mauri-Hellweg D,
•• Wendland T: **High IL-5 production by human drug-specific T cell clones.** *Int Arch Allergy Immunol* 1997, **113**:177-180.

This study analysed drug-induced activation of T cell subsets, TCR V β usage and cytokine secretion of T cells from the peripheral blood of drug-allergic individuals. Haptens like penicillin G stimulate CD4⁺ and CD8⁺ T cells *in vitro*. All CD8⁺ clones had a Th1-like phenotype, with high IFN- γ and TNF- α production.

56. Zanni MP, Mauri-Hellweg D, Brander C, Wendland T, Schnyder B,
• Frei E, von Greysz S, Bircher A, Pichler WJ: **Characterization of lidocaine-specific T cells.** *J Immunol* 1997, **158**:1139-1148.

Here, T cell lines and clones were generated from the peripheral blood of four patients with proven allergy to lidocaine. The majority of reactive T cells belonged to the CD4⁺ cell lineage and were MHC-class-II restricted but cloning also revealed some MHC-class-I-restricted CD8⁺ clones. A total of 2 of 56 lidocaine-specific T cell clones were CD4⁺ CD8⁺ and expressed TCR $\gamma\delta$.

57. Schnyder B, Mauri-Hellweg D, Zanni M, Bettens F, Pichler WJ: **Direct, MHC-dependent presentation of the drug sulfamethoxazole to human $\alpha\beta$ T cell clones.** *J Clin Invest* 1997, **100**:136-141.

This shows that sulfamethoxazole is presented in an immunogenic form to T cell clones and could stimulate both CD4⁺ and CD8⁺ sulfamethoxazole-specific T cell clones with glutaraldehyde-fixed antigen-presenting cells (APCs). There was no cross-reactivity with other sulphonamides. The continuous presence of sulfamethoxazole and MHC-compatible APCs was required. This suggests that binding to MHC did not require antigen processing.

58. Xu H, Banerjee A, Dilulio NA, Fairchild RL: **Development of effector CD8⁺ T cells in contact hypersensitivity occurs independently of CD4⁺ T cells.** *J Immunol* 1997, **158**:4721-4728.

The authors demonstrate that hapten sensitization induces two populations of hapten-reactive T cells: CD8⁺ T cells producing IFN- γ , which mediate the

response; and CD4⁺ T cells producing IL-4 and IL-10, which function to limit the magnitude and the duration of the response.

59. de Pater-Huijsen FL, Pompen M, Jansen HM, Out TA: **Products from mast cells influence T lymphocyte proliferation and cytokine production relevant to allergic asthma?** *Immunol Lett* 1997, **57**:47-51.

This describes how activated mast cells drive a CD8⁺ T cell clone towards a more pronounced Tc1 type of response, simultaneously decreasing T cell numbers. This might represent a negative feed-back mechanism operating in allergic subjects, by which the Th2-driven IgE production and eosinophilia are counteracted.

60. Corinti S, Palma RD, Fontana A, Gagliardi C, Pini C, Sallusto F: **Major histocompatibility complex-independent recognition of a distinctive pollen antigen, most likely a carbohydrate, by human CD8⁺ $\alpha\beta$ T cells.** *J Exp Med* 1997, **186**:899-908.

The authors demonstrate that CD8⁺ TCR $\alpha\beta$ ⁺ T cells recognise a carbohydrate antigen that is present in an allergenic extract from *Parietaria judaica* pollen (PjCHOAg). Presentation of this antigen is independent of the expression of classical MHC molecules or CD1. After activation, the CD8⁺ clones from an atopic patient expressed CD40 ligand and produced high levels of IL-4 and IL-5.

61. Seymour BW, Gershwin LJ, Coffman RL: **Aerosol-induced immunoglobulin IgE unresponsiveness to ovalbumin does not require CD8⁺ or T cell receptor (TCR)- $\gamma\delta$ T cells or interferon (IFN)- γ in a murine model of allergen sensitization.** *J Exp Med* 1998, **187**:721-731.

This shows that IgE responses in ovalbumin-aerosol-treated mice were not affected by CD8⁺ cell depletion and were comparable in mice deficient in β 2-microglobulin and depleted of TCR $\gamma\delta$ ⁺ T cells. These results demonstrate that the loss of the IgE response was not dependent upon CD8⁺ T cells, TCR $\gamma\delta$ ⁺ T cells or IFN- γ .

62. van Halteren AG, van der Cammen MJ, Cooper D, Savelkoul HF, Kraal
•• G, Holt PG: **Regulation of antigen-specific IgE, IgG1, and mast cell responses to ingested allergen by mucosal tolerance induction.** *J Immunol* 1997, **159**:3009-3015.

The authors show that oral tolerance abrogated subsequent Th2-driven antigen-specific IgE and IgG1 responses while intranasal tolerance induction only blocked the production of IgE but not IgG1 – thereby separating oral and respiratory tolerance which here is mediated by CD4⁺, not CD8⁺, T cells.

63. Harris SJ, Roth JF, Savage N, Woodrow SA, Hemingway IK,
•• Hoyne GF, Lamb JR, Layton GT: **Prediction of murine MHC class I epitopes in a major house dust mite allergen and induction of T1-type CD8⁺ T cell responses.** *Int Immunol* 1997, **9**:273-280.

This reports that *Dermatophagoides pteronyssinus* contains potential binding motifs for MHC class I. These Der p 1 residues 111–119 (FGIS-NYQQL, using single-letter code for amino acids) contain motifs for H-2Db and H-2Kb. Immunization of C57BL/6 mice with virus-like particles carrying Der p 1 (111–139) primed Der p 1 (111–119)-specific H-2Db-restricted CTLs.

64. Renz H, Lack G, Saloga J, Schwitzer R, Bradley K, Loader J, Kupfer A, Larsen GL, Gelfand EW: **Inhibition of IgE production and normalization of airways responsiveness by sensitized CD8⁺ T cells in a mouse model of allergen-induced sensitization.** *J Immunol* 1994, **152**:351-360.

65. Ke Y, Pearce K, Lake JP, Ziegler HK, Kapp JA: **$\gamma\delta$ T lymphocytes regulate the induction and maintenance of oral tolerance.** *J Immunol* 1997, **158**:3610-3618.

Mucosal immunisation via the gastrointestinal tract is well known to induce tolerance (a state of immune unresponsiveness). The authors show that this can be mediated by CD8⁺ TCR $\gamma\delta$ ⁺ T cells which are not CTL precursors and which inhibit responses by CD8⁺ CTLs.

66. Ke Y, Ma H, Kapp JA: **Antigen is required for the activation of effector activities, whereas interleukin 2 is required for the maintenance of memory in ovalbumin-specific, CD8⁺ cytotoxic T lymphocytes.** *J Exp Med* 1998, **187**:49-57.

This demonstrates that CTLs cultured with or without antigen can act as memory T cells when parked for 100 days in unirradiated, syngeneic recipients without antigen. The precursor frequency was identical in the spleens of normal and β 2-microglobulin-knockout recipients but significantly less in IL-2-knockout mice.

67. Hoyne GF, Jarnicki AG, Thomas WR, Lamb JR: **Characterization of the specificity and duration of T cell tolerance to intranasally administered peptides in mice: a role for intramolecular epitope suppression.** *Int Immunol* 1997, **9**:1165-1173.

In this report, induction of tolerance by the nasally administered immunodominant allergen lead to a diminution in all T-cell-derived cytokines and modulation of delayed-type hypersensitivity responses but IgE production did not seem to be affected.

68. Leishman AJ, Garside P, Mowat AM: **Immunological consequences of intervention in established immune responses by feeding protein antigens.** *Cell Immunol* 1998, **183**:137-148.

Here, the ability of food protein antigen to suppress naive and established immune responses was compared. Feeding high doses of OVA to mice seven days after immunisation produced a dose-dependent suppression of delayed-type hypersensitivity, T cell proliferation and both Th1 and Th2 cytokines although serum IgG levels were unaffected. Feeding OVA before immunisation suppressed all these responses.

69. Ishizaka K: **IgE-binding factors and regulation of the IgE antibody response.** *Annu Rev Immunol* 1988, **6**:513-534.

70. Hayglass KT, Stefura WP: **Antigen-specific inhibition of ongoing murine IgE responses. II. Inhibition of IgE responses induced by treatment with glutaraldehyde-modified allergens is paralleled by reciprocal increases in IgG2a synthesis.** *J Immunol* 1991, **147**:2455-2460.

71. Meissner N, Kussebi F, Jung T, Ratti H, Baumgarten C, Werfel T, Heusser C, Renz H: **A subset of CD8⁺ T cells from allergic patients produce IL-4 and stimulate IgE production *in vitro*.** *Clin Experiment Allergy* 1997, **27**:1402-1411.

This shows that in allergic patients twice as many CD4⁺ T cells and six times as many CD8⁺ T cells produced IL-4 compared with nonallergic controls. In contrast, the frequency of IFN- γ -producing cells was comparable between the allergic and nonallergic individuals.

72. Punnonen J, Yssel H, de Vries JE: **The relative contribution of IL-4 and IL-13 to human IgE synthesis induced by activated CD4⁺ or CD8⁺ T cells.** *J Allergy Clin Immunol* 1997, **100**:792-801.

These authors show that IL-4 is the dominant IgE-synthesis-inducing cytokine derived from highly polarized Th2 cells while IL-13 appears to be the major IgE-synthesis-inducing cytokine from Th1 and CD8⁺ T cells.

73. Gemou-Engesaeth V, Bush A, Kay AB, Hamid Q, Corrigan CJ: **Inhaled glucocorticoid therapy of childhood asthma is associated with reduced peripheral blood T cell activation and 'Th2-type' cytokine mRNA expression.** *Pediatrics* 1997, **99**:695-703.

This demonstrates that asthmatic children had increased levels of activated (i.e. expressing IL-2R α chain) CD4⁺ and CD8⁺ T cells in the peripheral blood, compared with normal children.

74. Watanabe A, Mishima H, Kotsimbos TC, Hojo M, Renzi PM, Martin JG, Hamid QA: **Adoptively transferred late allergic airway responses are associated with Th2-type cytokines in the rat.** *Am J Respir Cell Molec Biol* 1997, **16**:69-74.

Late allergic-airway responses can be transferred by CD4⁺ T cells in the rat. Here, recipients of CD8⁺ T cells showed an increase in INF- γ mRNA expression after challenge with OVA. The increased expression of INF- γ in allergen-challenged recipients of antigen-primed CD8⁺ T cells suggests that CD8⁺ T cells may be important in modulating allergic responses.

75. Haczku A, Macary P, Haddad EB, Huang TJ, Kemeny DM, Moqbel R, Chung KF: **Expression of Th-2 cytokines interleukin-4 and -5 and of Th-1 cytokine interferon- γ in ovalbumin-exposed sensitized Brown-Norway rats.** *Immunology* 1996, **88**:247-251.

76. Haczku A, Macary P, Huang TJ, Tsukagoshi H, Barnes PJ, Kay AB, Kemeny DM, Chung KF, Moqbel R: **Adoptive transfer of allergen-specific CD4⁺ T cells induces airway inflammation and hyperresponsiveness in brown-Norway rats.** *Immunology* 1997, **91**:176-185.

This shows that airway hyper-responsiveness (AHR) was significantly increased in rats given ovalbumin-sensitized T cells. Purified CD4⁺ T cells from sensitized donors induced AHR in naive recipients (probability level 0.05), while sensitized CD8⁺ and naive CD4⁺ cells failed to do so. These data indicate that CD4⁺ T cells may have a direct effect on AHR in Brown-Norway rats.