

# CD8<sup>+</sup> T cells in allergy

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## Introduction

Apart from their role in IgE regulation, little attention had been paid to the part played by T cells in allergic disease. CD4<sup>+</sup> T cell involvement in asthma is now clearly established (1) and CD4<sup>+</sup> T cell infiltration of the skin has been demonstrated in the allergen-induced late phase cutaneous skin reaction (2). However, little is known about the importance of CD8<sup>+</sup> T cells in allergic disease which is the subject of this review.

### *The CD8<sup>+</sup> T cell*

Soon after the distinction between T and B cells was made in the 1960's a number of different T cell functions were defined. Some were found to be capable of killing specific target cells, some provided help for antibody production and others appeared capable of mediating a range of suppressive effects. T cells were subdivided according to the presence of the cell surface markers CD4 and CD8 which bind to nonpolymorphic regions of MHC class II and I, respectively (3). In the past CD4<sup>+</sup> T cells were believed to act as helper/inducers and CD8<sup>+</sup> T cells as cytotoxic/suppressors but the subsequent characterisation of functionally distinct CD4<sup>+</sup> T cell subsets which can either help or suppress particular immune responses (4, 5) or can kill specific target cells (6, 7) has rendered this division obsolete, and it is now becoming increasingly clear that a range of different immunological functions can be assigned to the CD8<sup>+</sup> phenotype.

### *Development of CD8<sup>+</sup> T cells*

All T cells originate as pluripotent stem cells in the bone marrow and the majority develop into mature T cells in the thymus. The process of T cell development in the thymus is complex. CD4 and CD8 molecules are believed to play an important part in intrathymic T cell development (8, 9). T cell precursors entering the thymus do not express CD4, CD8 or CD3. In the thymus they differentiate through a series of intermediates (10, 11) into CD4<sup>+</sup> CD8<sup>+</sup> double positive cells (12, 13, 14). Subsequently, these cells acquire the T cell receptor (TcR) and lose either the CD4 or the CD8 marker. Expression of CD8 appears to be required for the successful development of MHC Class I restricted cytotoxic T cells (15). The function of CD4 and CD8 on T cells extends beyond intrathymic selection and they clearly play a part in T cell activation as well (16), although they may work through different intracellular pathways – CD4 and the TcR via protein kinase C (PKC) activation, CD8 by another pathway (17).

### *Phenotypic variants of CD8<sup>+</sup> T cells*

The presence of different isoforms of the leukocyte common antigen CD45 (RO and RA) can be used to distinguish naive (CD45RA<sup>+</sup>, recognised by the monoclonal antibodies 2H4 and HB-11) from memory T cells (CD45RO<sup>+</sup> recognised by the monoclonal antibody UCHL1 (18)). Less than 5% of newborn lymphocytes are UCHL1<sup>+</sup> as compared with approximately 50% of adult lymphocytes, support-

ing the view that they represent cells which have previously encountered antigen (19). CD45RA<sup>+</sup> and CD45RO<sup>+</sup> human CD8<sup>+</sup> T cells differ in their ability to produce IL2 and TNF- $\alpha$  on stimulation with anti-CD3 and may represent unprimed (CD45RA<sup>+</sup>) and primed (CD45RO<sup>+</sup>) cells (20).

CD8<sup>+</sup> T cells have been subdivided according to the level of surface CD8 expression into CD4<sup>-</sup>CD8<sup>+</sup> (70%) and CD4<sup>-</sup>CD8<sup>dim+</sup> (30%) (21). Of those with the CD4<sup>-</sup>CD8<sup>dim+</sup> phenotype, over 90% lack the  $\alpha/\beta$  T cell receptor. A subpopulation of rat CD8<sup>+</sup> T cells (2–4%) which express the  $\gamma\delta$  TcR have also been described (22) and in the mouse, gut intraepithelial lymphocytes (IEL) are mostly CD8<sup>+</sup>  $\gamma\delta$  TcR<sup>+</sup> (23). A further subdivision of CD8<sup>+</sup> T cells has been made on the basis of affinity for *Vicia villosa* (VV) lectin (24). These cells were reported to counter the effects of CD8<sup>+</sup> suppressor T cells and were termed contra suppressor cells.

#### *Specificity of CD4<sup>+</sup> and CD8<sup>+</sup> T cells*

The specificity of CD4<sup>+</sup> and CD8<sup>+</sup> T cells for antigen appears to be very similar, they show markedly different patterns of MHC restriction. However, when CD8<sup>+</sup> T cells respond to superantigens such as MIs they appear to do so via MHC class II (25). Cytotoxic CD8<sup>+</sup> T cells can be induced with antigens, such as ovalbumin, which normally require class II if given in the form of immunostimulating complexes (ISCOM) (26).

Different types of antigen-presenting cells may selectively present antigen to CD4 and CD8 cells (27), and cloned murine splenic macrophages preferentially present alloantigen to CD8<sup>+</sup> T cells (28). Dendritic cells are known to be very potent inducers of primary mixed lymphocyte reactions (29) and alloreactive CD8<sup>+</sup> T cells can be preferentially activated by class I-bearing dendritic cells (30). Primary HIV-specific CTL produced *in vitro* to HIV-pulsed dendritic cells are CD8<sup>+</sup> although they also appear to need help provided by CD4<sup>+</sup> cells (31). Finally, astroglial cells have been reported to prime CD8<sup>+</sup> T cells (32) in allergic encephalomyelitis.

### **Function of CD8<sup>+</sup> T cells**

#### *CD8<sup>+</sup> T cells in infectious disease*

It is becoming increasingly clear that CD8<sup>+</sup> T cells play an important role in immunity to infectious agents (33). As with many aspects of the immune response, there is a tremendous amount of duplication such that a deficiency in CD4<sup>+</sup> T cells can partly be overcome by CD8<sup>+</sup> T cells. CD8<sup>+</sup> T cells seem to be particularly important in defence against bacteria, protozoa and viruses, although TH1 cells are also prominent while CD8<sup>+</sup> cells are less com-

monly associated with metazoan parasitic infection (34).

CD8<sup>+</sup> T cells have been implicated in immune defence against a number of parasites (35, 36, 37). CD8<sup>+</sup> T cell-depleted rats produced less IFN $\gamma$  and failed to kill *Trypanosoma brucei brucei* (38). CD8<sup>+</sup> T cells from convalescent *Toxoplasma gondii*-infected mice are principal mediators of resistance to reinfection by *T. gondii*, and depletion of CD8<sup>+</sup> T cells reduces host survival (39). Protective immunity to *Leishmania* depends on a radio-resistant CD8<sup>+</sup> T cell population which can develop in the absence of CD4<sup>+</sup> T cells. These CD8<sup>+</sup> protective T cells can be down regulated by CD4<sup>+</sup> T suppressor cells (40). However, there is also evidence that CD4 and CD8 T cells may act synergistically (41) through IFN $\gamma$  which augments CD8<sup>+</sup> effector cell function.

The role of CD8<sup>+</sup> T cells in immunity to influenza A virus has been investigated in CD8-depleted mice which were still found able to eliminate virus. Nevertheless, CD8<sup>+</sup> CTL appear to be the principal mediators of virus clearance (6). CD4<sup>+</sup> T cell-depleted mice were still able to generate vaccinia virus-specific CD8<sup>+</sup> CTL cells, although more potent CD8<sup>+</sup> CTL cells were produced when CD4<sup>+</sup> T cells were also present (42). Thus there appears to be synergy between CD4 and CD8 T cells.

#### *CD8<sup>+</sup> T cells in allergy and inflammation*

A number of models and disease states have been used to study the involvement of CD8<sup>+</sup> T cells in inflammation. For example, following infection with lymphocytic choriomeningitis virus there is massive extravasation of lymphocytes and monocytes into the cerebrospinal fluid and widespread inflammation involving the meninges, choroid plexus and ependyma (43). Development of the process of cellular infiltration only occurs after the immune T cell response, and its severity is a direct consequence of the number of effector T cells involved. The infiltrating cells are predominantly CD8 and IL2R positive. Furthermore, the inflammation caused by CD8<sup>+</sup> T cells can occur in the absence of CD4<sup>+</sup> T cells. A predominance of CD8<sup>+</sup> T cells was found in the bronchoalveolar lavage of some asthmatic patients (44); however, biopsies of asthmatic airways did not show such a predominance of CD8<sup>+</sup> T cells (45, 46). CD8<sup>+</sup> T cells are also found in pulmonary sarcoidosis (47).

Indirect evidence for CD8<sup>+</sup> T cell involvement in allergy has been derived from studies of the number and function of T cell subsets in the peripheral blood of atopic and non-atopic individuals. Some workers have failed to find any functional or numerical differences in T lymphocyte subpopulations in patients with allergic asthma (48) while others reported re-

duced numbers of CD8<sup>+</sup> T cells (49, 50, 51). Other groups have found imbalances in the T cell subpopulations in patients with atopic disease (52), and high CD4<sup>+</sup>/CD8<sup>+</sup> ratios have also been observed in patients with atopic dermatitis (53, 54) who have elevated IgE levels and in patients with parasitic infestations such as Loiasis (55).

## Immunoregulation by CD8<sup>+</sup> T cells

### Cytotoxicity

A number of different mechanisms for CD8<sup>+</sup> T cell-mediated target cell cytotoxicity have been proposed. Secretion of porphyrin, which forms a hole in the target cell, has been demonstrated (56), while induction of DNA degradation in the target cells can be induced by either TH1 CD4 or CTL CD8 positive cells (7).

### Suppression

True T suppressor cells have been defined as those cells which suppress immune responses through means other than direct cytotoxicity or secretion of known helper type interleukins (57). CD8<sup>+</sup> T cells are widely reported to mediate a variety of different immunosuppressive effects (58, 59). CD8<sup>+</sup> cells have been shown to act as suppressors in autoimmunity following recruitment by CD4<sup>+</sup> cells (60). CD8<sup>+</sup> suppressor T cell lines have been produced from animals with experimental allergic encephalomyelitis (61), and CD8<sup>+</sup> T cells can suppress autoreactive T cells and inhibit anti-class II CD4<sup>+</sup> T cells in normal rats (62). CD8<sup>+</sup> T cell clones that suppress allogeneic CD4<sup>+</sup> MLR have also been reported (63). Both cytotoxic and suppressor CD8<sup>+</sup> T cells can inhibit the MLR but they appear to do so through different mechanisms, suggesting that T suppressor cells are a sublineage of CD8<sup>+</sup> T cells rather than a variant of CD8<sup>+</sup> T cytotoxic cells.

Antibody responses can be suppressed by antigen-specific, class II-restricted CD8<sup>+</sup> T cells (64) and antigen-induced T cell proliferation can be mediated by antigen specific suppressor CD8<sup>+</sup> clones which do not cause lysis of the target cell (65). Not all suppressor cells are CD8 positive. CD4<sup>+</sup> as well as CD8<sup>+</sup> T cells are reported to be capable of suppressing CMI *in vitro* (66). Depletion of CD4<sup>+</sup> or CD8<sup>+</sup> cells alone did not abrogate suppression of experimental autoimmune thyroiditis while depletion of both cell types did (67); CD4<sup>+</sup> T cells can also inhibit graft rejection (68).

### Help

Less evidence exists to support helper function for CD8<sup>+</sup> T cells. In systemic lupus erythematosus

(SLE) patients HLA-DR<sup>+</sup> CD8<sup>+</sup> T cells support IgG synthesis *in vitro* and their removal inhibits spontaneous IgG production (69, 70). Ricin-enhanced IgE responses are ablated in CD8-depleted rats (see below). Cyclosporin A and radiosensitive CD8<sup>+</sup> T cells are reported to provide help for GvH *in vivo* (71) and Ig synthesis *in vitro* (72). Finally, class I-restricted CD8<sup>+</sup> T cells provide help for MHC class II-restricted CD4<sup>+</sup> CTL (73) which is mediated through antigen-presenting cells (74).

## Role of CD8<sup>+</sup> T cells in IgE regulation

The requirement for T cells for the production of IgE was first demonstrated 20 years ago by Tada and colleagues (75) who showed that neonatally thymectomised rats were unable to produce IgE antibodies unless reconstituted with thymocytes from syngeneic animals. Their observations were confirmed by others who showed that animals depleted of T cells were unable to produce primary IgE responses (76, 77). Ongoing IgE responses were also shown to require continued T cell help, as injection of mice infested with the nematode *Nippostrongylus braziliensis* with anti-CD4 antibodies suppressed ongoing IgE production (78).

As well as providing help for IgE synthesis, T cells have also been shown to be capable of suppressing IgE responses (79, 80) although as yet there is no convincing evidence to show that they can suppress the persistent IgE response once established. The IgE suppressor T cells originally described were antigen non-specific (79), although antigen-specific T cells that suppress IgE have also been described (81, 82). IgE suppressor CD8<sup>+</sup> T cells can be generated following inhalation of antigen (83, 82). These were recently shown to be  $\alpha/\beta$  TcR negative (84).

The effects of T cells on IgE production can be mediated, at least in part, by cytokines. High levels of interleukin 4 (IL4) were shown to induce IgE synthesis from LPS-stimulated murine B cells *in vitro* (4, 5) and this could be antagonised with interferon  $\gamma$  (IFN $\gamma$ ) (4). *In vivo* both anti-IL4 antibody (85, 86) and IFN $\gamma$  (87, 88) have been shown to suppress soluble antigen and *N. braziliensis* and *Heligmosomoides polygyrus* induced IgE (88).

## Castor bean allergy and a rat model of IgE regulation

Most people (atopic and non-atopic) exposed to the dust of the castor bean, *Ricinus communis*, produce IgE antibodies (89, 90). Six years ago we set out to determine why exposure to castor bean dust should override the normal IgE regulatory process, to identify the mechanism for castor bean enhanced IgE

responsiveness and see what it revealed about IgE regulation. In preliminary experiments, using a crude aqueous extract of castor bean, we showed that IgE responses could be produced in rats both to the major castor bean allergen, the 2s albumin (91), and to concomitantly administered ovalbumin (92) without any other adjuvant. This effect was lost if the castor bean extract was heated and we directed our attention to the toxic castor bean lectin ricin which is heat labile and found that the IgE potentiating effects of castor bean extract could be reproduced when animals were injected with pure ricin and ovalbumin. Co-administration of ricin and a bystander antigen enhanced the IgE response in high (Brown Norway), moderate (PVG, Hooded Lister) and low (Wistar, WAG, Lou/M) IgE responder strains of rat (93).

Total serum IgE and antigen-specific IgE levels in rats repeatedly immunised with bystander antigen

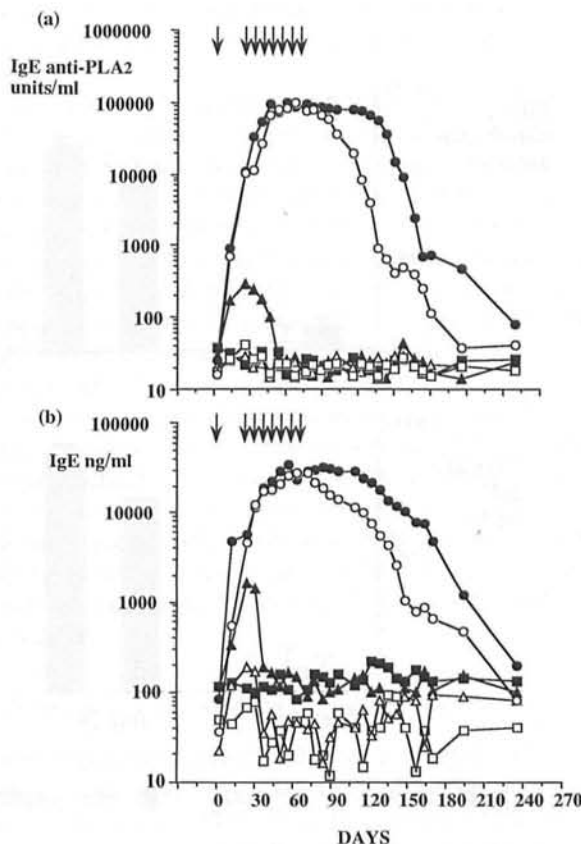


Fig. 1. Generation of a long-lived IgE response by repeated injection of ricin + antigen. The levels of IgE anti-PLA<sub>2</sub> (a) and total serum IgE (b) in both Wistar (open symbols) and Brown Norway rats (closed symbols). The primary and booster injections of PLA<sub>2</sub> and ricin are shown by the arrows. The standard deviation has been omitted in the interests of clarity but did not exceed 18% of the mean for the total IgE or 17% of the mean for PLA<sub>2</sub>-specific IgE. The results for animals given ricin alone were identical to those given saline and so are not shown. Reproduced from (93).

Table 1. The effect of ricin on CD8<sup>+</sup> AND CD4<sup>+</sup> cell proliferation. The percentage of CD4 and CD8 positive cells present following culture with 2.5 µg/ml PHA.

| Ricin concn:     | % CD8 <sup>+</sup> | % CD4 <sup>+</sup> | CD4/CD8    |
|------------------|--------------------|--------------------|------------|
| None             | 17.0(16.8)         | 35.6(35.8)         | 2.09(2.13) |
| 10 <sup>-9</sup> | 16.8(17.1)         | 36.3(35.3)         | 2.10(2.06) |
| 10 <sup>-8</sup> | 10.1(16.5)         | 40.1(35.0)         | 3.97(2.12) |
| 10 <sup>-7</sup> | 5.1(16.3)          | 45.2(35.4)         | 8.86(2.17) |

The figures in brackets are the percentage of cells present when 0.1M lactose was present. Reproduced from (98)

and ricin persisted for many months (Fig. 1). Identical IgE levels were produced in both high and low IgE responder strains, although IgE declined earlier in the low as compared with the high responder strain, suggesting that the IgE suppressor mechanism is more readily reimposed in these animals.

Other agents which increase IgE production have also been shown to be preferentially toxic for CD8<sup>+</sup> (suppressor/cytotoxic) cells. Cyclosporin A has been reported to suppress ongoing IgE responses (94); however, if administered during the nascent IgE response it will enhance murine IgE production (95). Murine CD8<sup>+</sup> T cells have been shown to be particularly sensitive to suppression by cyclosporin A *in vivo* (71). Cyclophosphamide, low-dose X-irradiation and HgCl<sub>2</sub> are believed to be preferentially toxic for suppressor cells and enhance IgE responses (96, 97).

Cellular immune function in the ricin-enhanced IgE producing rats was studied. Spleen cells from

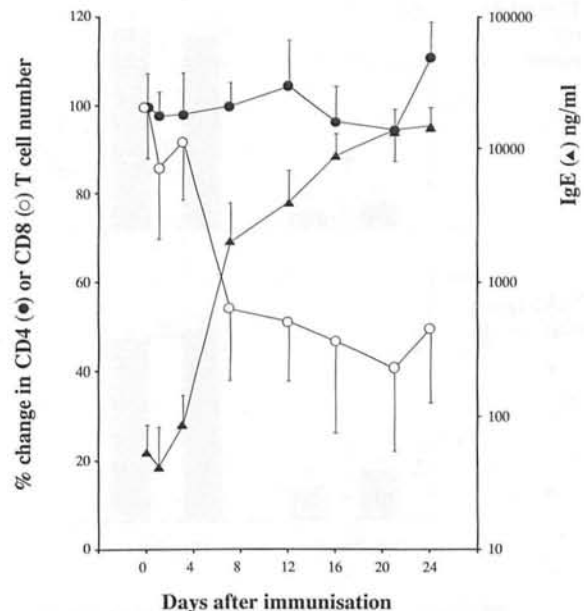


Fig. 2. The mean level of IgE and the % change in CD4 and CD8 positive T cell numbers in the spleens of rats immunized with 10 µg PLA<sub>2</sub> + 50 ng ricin. Error bars indicate the standard deviation.

Table 2. Ricin binding sites per cell. The number of ricin binding sites on purified splenic CD4 and CD8 positive T cells prepared by panning to 98% purity were compared using  $^{125}\text{I}$  radiolabelled ricin. A binding site is defined as the capacity to bind one molecule of ricin.

|                          | Unimmunized                             | Immunized                               |
|--------------------------|-----------------------------------------|-----------------------------------------|
| CD8 <sup>+</sup> T cells | $3.16 \times 10^6 \pm 1.76 \times 10^6$ | $3.92 \times 10^7 \pm 2.21 \times 10^6$ |
| CD4 <sup>+</sup> T cells | $2.94 \times 10^6 \pm 1.43 \times 10^6$ | $3.19 \times 10^6 \pm 1.08 \times 10^6$ |

these animals showed a 5-fold increase in phytohaemagglutinin (PHA)- and Con A- induced proliferation compared with rats given saline or antigen alone (98). Thus the conditions that produced the optimum IgE response also resulted in enhanced T cell function. Antigen had to be given at the same time or 24 h before the ricin for the IgE response to be enhanced, suggesting that it was acting on cells activated by the immunising antigen.

### The effect of ricin on CD4<sup>+</sup> and CD8<sup>+</sup> T cells

The putative target cell for ricin was initially investigated *in vitro*. Ricin inhibits Con A and PHA-induced T cell proliferation *in vitro* in a dose dependent manner (99). PHA and Con A-stimulated CD4<sup>-</sup> (>98% CD8<sup>+</sup>) spleen cells were found to be nearly 100 times more susceptible to the inhibitory effects of ricin than unfractionated or CD8<sup>-</sup> (>98% CD4<sup>+</sup>) spleen cells (98). In the presence of lactose (which prevents ricin binding) there was no change in the ratio (Table 1).

Complementary results were observed *in vivo*. 24 days after immunisation the CD4/CD8 ratio was increased in rats which had received both ricin and antigen but not in those animals immunised with ricin or antigen alone (98). Following immunisation with antigen + ricin the number of CD8<sup>+</sup> cells in the spleen declined by up to 60% (Fig. 2). The decline in CD8<sup>+</sup> T cells paralleled the increase in serum

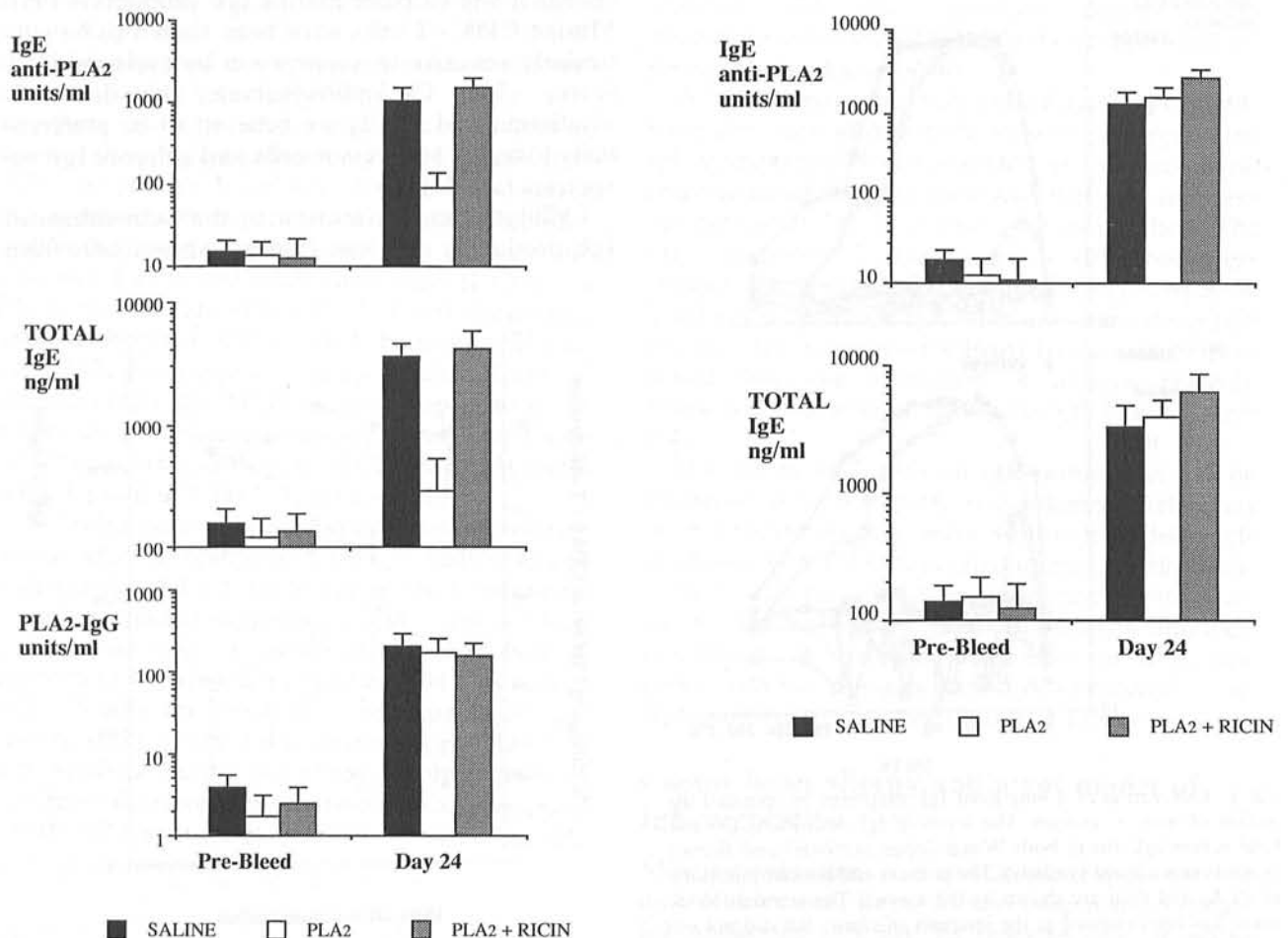


Fig. 3. (a) The IgE and IgG antibody response to bee venom phospholipase A<sub>2</sub> (PLA<sub>2</sub>) and total IgE levels in the sera of rats immunized with 10 µg PLA<sub>2</sub> and 100 µg A1OH<sub>3</sub> after receiving 1 × 10<sup>8</sup> CD8<sup>+</sup> T cells from donor rats immunized with saline, PLA<sub>2</sub>, or PLA<sub>2</sub> + ricin. (b) The IgE antibody response to PLA<sub>2</sub> and total IgE levels in the sera of rats immunized with 10 µg PLA<sub>2</sub> and 100 µg A1OH<sub>3</sub> after receiving 1 × 10<sup>8</sup> CD4<sup>+</sup> T cells from donor rats immunized as above.

IgE. The number of CD4<sup>+</sup> cells remained unchanged (100). Ricin, therefore, seems to be primarily toxic for some CD8<sup>+</sup> T cells *in vivo* as well as *in vitro*.

#### Binding of ricin to T lymphocyte subpopulations

The explanation for the greater sensitivity of CD8<sup>+</sup> T cells to ricin was investigated by studying the binding of radiolabelled ricin to purified CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Although CD8<sup>+</sup> T cells are more sensitive to ricin than CD4<sup>+</sup> cells neither the  $K_a$  nor the number of ricin binding sites on T cells from untreated rats were significantly different between the two subsets. However, within 24 h of immunisation with 10 µg of antigen, there was a substantial increase in the number of ricin binding sites on CD8<sup>+</sup> but not CD4<sup>+</sup> T cells (Table 2). Preferential binding of ricin to the surface of activated CD8<sup>+</sup> T cells leads to greater internalisation of the toxin, thereby resulting in cell death. This mechanism may explain why the number of CD8<sup>+</sup> T cells in the spleens of rats immunised with ricin and antigen decreased but did not do so in those given ricin alone.

It is unlikely that the explanation for the difference in ricin sensitivity between T cell subsets lies in the rate and amount of toxin internalisation since this was the same for both subpopulations. Using the LIGAND computer programme (101) only a one site model could be generated, suggesting that only one class of ricin binding site was present on the T cells. The  $K_a$  for this binding site agreed with that previously reported using erythrocytes, HeLa cells (102), fibroblasts and monocytes (103).

The reason for the increase in ricin binding sites on activated CD8<sup>+</sup> T cells is not known. It is possible that activation of these cells by antigen causes an increase in activation markers which contain additional galactose to which ricin may bind; alternatively, activation may result in the formation of blast cells whose larger surface area may offer more ricin binding sites.

#### Adoptive transfer of CD4 and CD8 positive T cells

The experiment described above suggests that ricin potentiates IgE responses by preferentially deleting or inactivating CD8<sup>+</sup> T cells activated early in the immune response which normally suppress IgE. To test this hypothesis, CD8<sup>+</sup> and CD4<sup>+</sup> T cells were prepared 3 days after immunisation of Brown Norway rats with antigen or antigen and ricin.  $1 \times 10^8$  purified CD4 or CD8 positive T cells from these animals were adoptively transferred to naive, syngeneic, recipients which were then immunised with antigen and aluminium hydroxide. CD8<sup>+</sup> T cells derived from donor rats given both antigen and ricin

were unable to suppress IgE, while those from donor rats immunised with antigen alone suppressed the IgE but not the IgE response in the recipient animals (Fig. 3a). This effect was not antigen-specific. Further, adoptively transferred CD4<sup>+</sup> T cells from the same donor animals had no effect on IgE production (Fig. 3b). The finding that IgE suppressing CD8<sup>+</sup> T cells were generated within 3 days of immunisation differs from that of other investigators (83), who showed that IgE formation could be suppressed in Brown Norway rats if CD8<sup>+</sup> T cells from the spleen or lymph nodes were transferred from donor rats receiving 6 weekly exposures to aerosolised antigen (82). These CD8<sup>+</sup> IgE suppressor T cells produced later in the immune response were antigen-specific (84, 82).

#### IgE responses in CD8 deficient rats

We hypothesised that elimination of all CD8<sup>+</sup> T cells would result in an increase in IgE production. Euthymic Hooded Lister rats were, therefore, depleted of CD8<sup>+</sup> cells by repeated injection with the

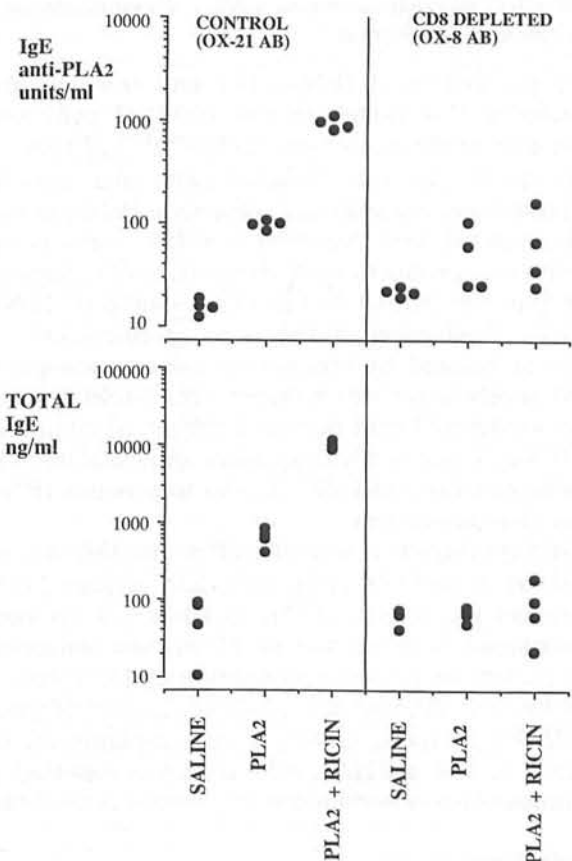


Fig. 4. Total and antigen-specific IgE levels in CD8-depleted rats IgE immunised with saline, antigen or antigen + ricin. IgE responses were not enhanced in CD8-depleted animals. Ricin potentiation of the IgE response was not seen in CD8-depleted animals.

monoclonal antibody OX8 (104) and were immunised with ricin, antigen or ricin and antigen together. CD8-depleted rats did not mount a greater IgE response when immunised with antigen alone, and to our surprise the IgE response normally seen with ricin and antigen was absent in CD8-depleted rats (Fig. 4), suggesting that some CD8<sup>+</sup> T cells may actually be required to mount an IgE response. Similar results were obtained with nude rats reconstituted with CD8-depleted thoracic duct lymphocytes, indicating that there may be two populations of CD8 positive cells one of which is sensitive to ricin and suppresses IgE and another which is ricin-insensitive and is needed for IgE production.

This putative CD8<sup>+</sup> IgE helper cell may work either by interacting with T cells or by direct action on B cells or antigen-presenting cells. There is evidence that CD8<sup>+</sup> T cells can modulate the lymphokine release from class II MHC-restricted (CD4) T cells by altering the number of target cells required to interact with a single T cell to trigger this release (74); this T-T collaboration seems to be mediated by antigen-presenting cells and not by soluble factors.

#### *The effect of early activated CD8<sup>+</sup> T cell depletion on cytokine production*

The production of IFN- $\gamma$ , IL2 and IL4 was also studied in this model. *In vitro*, CD8<sup>+</sup> T cells were found to be the major source (50–70%) of IFN- $\gamma$  in rat spleen. In rats infected with the parasite *Trypanosoma brucei brucei* splenocyte IFN- $\gamma$  is rapidly induced, and depletion of CD8<sup>+</sup> cells *in vivo* suppresses production of this cytokine (38), suggesting that this subset is the main source of IFN- $\gamma$  *in vivo*. Production of IFN- $\gamma$  by splenic CD8<sup>+</sup> T cells stimulated by mitogen or calcium ionophore and phorbol ester was reduced over 5-fold in those rats immunised with ricin and antigen as compared to those immunised with saline or antigen alone. The ability of CD4<sup>+</sup> OX-22<sup>+</sup> T cells to produce IFN- $\gamma$  was also diminished.

IL4 message was also measured and this was increased in animals given ricin and antigen (105), although the source of this IL4 has not yet been determined. The manner in which ricin influences the pattern of cytokine production by rat T cells is not known, although it is possible that the decrease in IFN- $\gamma$  secreting CD8<sup>+</sup> T cells explains the increase in IL4 mRNA (105) as IL4 is reported to suppress IFN- $\gamma$  production by lymphocytes (106).

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