In vitro and in vivo modulation of human T lymphocytes from allergic asthmatic subjects
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CD8 T cells: potential therapeutic targets?

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Abstract

CD8⁺ T cells differentiate to distinct subpopulations with unique functions. There are clear abnormalities in CD8⁺ T cells both in asthma and in COPD when compared with healthy subjects. It is not clear whether CD8⁺ T cells are protective or contribute to pathology. The role of CD8-specific T cell products, such as perforin, if any, in asthma and COPD is not understood. It is clearly impossible at present to formulate valid conclusions as to the possible role of CD8⁺ T cell modulation for the therapy of asthma and COPD. A tailored therapeutic approach in different circumstances might be required.

Functional spectrum of CD8 T cells

T lymphocytes, which may be of the CD4 or CD8 phenotype in the circulation, regulate antigen-specific immune responses. CD4⁺ T cells recognize antigenic peptides in the context of MHC class II molecules. CD8⁺ T cells do so in the context of MHC class I molecules. As a rule, soluble antigens like proteins associate with MHC II and are handled by CD4 cells; intracellularly synthesized antigens such as those derived from intracellular microorganisms associate with MHC I and are handled by CD8 cells (Figure 1).

Figure 1. CD8⁺ T cells recognize antigen in the context of MHC1, CD4⁺ T cells in the context of MHC II molecules.
CD8+ T cells in asthma and COPD

CD8+ T cells are well known for their cytotoxic functions: they kill malignant-transformed and virus-infected cells. To this end they are equipped with two types of killing machinery. One involves Fas-ligand expressed at the cell surface; the other involves release of perforin and granzymes from intracellular granules. In addition, these cells produce high amounts of IFN-γ. These CD8+ cells are now denoted as type 1, or Tc1. A distinct CD8+ T-cell subset, termed Tc2, may have other regulatory functions, in particular the regulation of function of other immune cells by cytokine secretion. Tc2 CD8+ T cells may produce IL-4 and IL-5. An IL-4 rich environment contributes to the shift of CD8+ T cells from the Tc1 to the Tc2 phenotype [1].

Both Tc1 and Tc2 CD8+ T cells can be functionally divided as naive, memory and, at least in the case of Tc1, 'memory-effector' cells (Figure 3). These functional subsets can be discriminated on the basis of the surface marker phenotypes CD45RA+CD27+CD28+, CD45RO+CD27+CD28+ and CD45RA+CD27+CD28−, respectively [2]. The latter population corresponds to the chemokine receptor CCR7− population that preferentially migrates into inflammatory tissues [3]. The CD45RA+CD27+CD28− cells have the same capacity for IFN-γ production as the CD45RO+ population, but fail to produce IL-4 [2,3], at least in the peripheral blood. Mediators of cellular cytotoxicity are mainly expressed in the memory-effector subset [2,3]. These cells have been demonstrated to contain antigen-specific cells recognizing among others viral antigens [2].

CD8+ T cells in asthma

Activation of CD4+ T cells appears to be a universal feature of asthma. In allergic asthma, these may be allergen-specific T cells. These cells are of a Th2 phenotype, producing relatively high amounts of IL-4 and IL-5, and low amounts of IFN-γ, and are typically seen in the inflamed airways of symptomatic asthma patients [4]. Interestingly, CD8+, as well as CD4+ T cells show expression of IL-4 and IL-5 mRNA and protein in the bronchial mucosa of both atopic and non-atopic asthmatics [4], suggesting that CD8+ T cells may be a potential source of asthma-promoting cytokines. The activating stimulus for CD8+ T cells is not clear.

In contrast to CD4+ T cells, peripheral blood CD8+ cells do not consistently show higher expression of activation markers such as CD25 in asthematics than in controls. The CD8+ T cells may show variable Th2 type cytokine expression [5,6] and higher expression of perforin [7] as compared with controls. The latter matches with a higher percentage of CD8+CD28− [8], which was confirmed by our own findings, as shown in Figure 3. Thus, there appears to be an increase in the CD8+ memory-effector cell population in asthma.
Experimental allergen challenge results in significant increases in both the CD4+ and the CD8+ T-cell populations in the airways [9,10], and the numbers of CD8+ T cells were negatively associated with the likelihood of a late-phase bronchoconstrictor response, suggesting a possible protective effect of CD8+ T cells [9]. On the other hand, viral infection of the respiratory tract may exacerbate asthma, possibly by augmenting eosinophilic infiltration. This may reflect involvement of virus-specific Tc2 CD8+ T cells.

**CD8+ T cells in COPD**

Recent studies have characterized the inflammatory cellular infiltrate in central and the peripheral airways of smokers with stable, chronic COPD, smokers with normal lung function and non-smoking controls [11-14]. COPD patients showed higher CD8+ T cell numbers [11,12]. However, it appeared that these findings may be related to smoking habits of the populations investigated [13,14].

Studies in the peripheral blood of COPD patients have shown increased CD8+ T cell numbers [15], which may be largely memory-effector CD8 cells, as defined by the membrane surface markers CD45RA+CD27−CD28− [16].

If CD8+ T cells do contribute to airway inflammation in COPD, the mechanisms by which they do so, as well as the mechanisms of their initial activation, remain at present speculative.

**Present therapy**

**Drugs.** Both CD4+ and CD8+ T cells are inhibited to a similar degree by phosphodiesterase inhibitors [17]. Dexamethasone and cyclosporin A inhibit re-expression of surface CD4, but not CD8, on activated T cells *in vitro* [18], which may reflect differential sensitivity of CD4+
and CD8+ T cells to these drugs. Further studies of the effects of glucocorticoids and other drugs on CD8+ T cells in a disease setting in vivo are sorely needed.

Desensitization. Early studies have already suggested a possible role for CD8+ T cells in favourable clinical responses to allergen immunotherapy [19].

Animal models
Animal models have suggested prominent roles for CD8+ T cells in the regulation of IgE synthesis. Repeated challenge of rats with ovalbumin resulted in the activation of CD8+ T cells that could inhibit the development of IgE responses after adoptive transfer [20]. In virus infection models, the effects of CD8+ T cells critically depended on the conditions chosen. CD8+ T cells were essential in the induction of airway inflammation and airway hyperresponsiveness in a mouse model of intranasal administration of respiratory syncytial virus (RSV) [21]. In other models where the animals were vaccinated with polypeptides of RSV before the challenge, the CD8+ T cells significantly contributed to suppression of airway inflammation [22]. It is difficult to translate these conditions of acute antigen challenges and acute infections with the chronic allergen exposure that underlies much of the pathophysiology in allergic asthma patients. There is no animal model that mimics the chronic airway inflammation and airway destruction with increased numbers of tissue CD8+ T cells as found in COPD.

Anti-CD8 antibody therapy in humans
Treatment with anti-CD8 antibodies has not as yet acquired a place in experimental or routine clinical practice. Experimental animal models have shown the potential of anti-human CD8 antibodies in depleting CD8+ T cells. The humoral immune response and at least some aspects of cell mediated responses seem not to be affected by such treatment. In a patient with a chronic hepatitis C virus infection, CD8+ T-cell depletion resulted in improvement of the anti-viral immune response and clinical status [23]. On the other hand, in rhesus macaques, anti-CD8 treatment resulted in rapid emergence of a pathogenic strain of HIV-1 from an initially non-pathogenic virus [24].

With current knowledge, it would be difficult to formulate a cogent rationale for CD8+ T-cell depletion in asthma or COPD.
Figure 2. Scheme of the development and the characteristics of CD8 T lymphocytes.

References


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