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$\gamma\delta$ T cells, allergen recognition and airway inflammation

Fabrizio Spinozzi, Elisabetta Agea, Onelia Bistoni, Nicolino Forenza and Alberto Bertotto

Allergic immune responses in atopic subjects are characterized by the induction of allergen-specific IgE synthesis and activation of polymorphonuclear granulocytes, such as mast cells, eosinophils and basophils. When sensitized airways of atopic individuals are triggered by exposure to the specific allergen, a biphasic response occurs. Crosslinking of specific IgE bound to Fc ϵ receptors on the primary effector cells results in an immediate reaction, due to the release of preformed mediators, such as histamine. The subsequent or late-phase response is largely inflammatory: airways are infiltrated by eosinophils, neutrophils, macrophages, lymphocytes and basophils, which together release a number of soluble products including prostaglandins, leukotriene B₄ (LTB₄), LTC₄ and platelet-activating factor (PAF)^{1,2}.

Why only some individuals mount an IgE response is not understood. Although elevated levels of specific IgE are a common feature in atopic patients, the genetic basis for this is unknown³. Analysis of the major histocompatibility complex (MHC) specificity of allergen-specific T cells is limited, and expansion of this database is required to establish certain HLA associations. However, population studies of inheritance of allergic disorders argue against sole regulation by the HLA gene products. Potential interactions between the non-MHC-linked genes are intriguing and suggest that such genes (specifically those recently described on chromosome 5q31–33)⁴ determine overall predisposition to allergic disease, while the MHC haplotype influences the specificity of the allergic response². More importantly, the type of allergen-specific T cell that is

The ability of T-cell receptor (TCR) $\gamma\delta$ cells to recognize foreign non-peptide antigens suggests a role in mucosal surveillance. However, their expansion, together with the presence of antigen-presenting cells (APCs) expressing CD1 antigens (a ligand for $\gamma\delta$ TCRs), in the respiratory tract of allergic subjects also suggests a pathogenic role for these cells in allergic diseases. Here, the hypothesis is presented that $\gamma\delta$ T cells and CD1⁺ APCs may operationally distinguish healthy from atopic status.

resident in target tissues, such as airways, gut epithelium and skin, has not been widely investigated.

It has been proposed that $\gamma\delta$ T cells complement $\alpha\beta$ T cells by providing a rapidly induced, but weaker, response before the $\alpha\beta$ T-cell response has fully developed⁵. This suggestion is based on both the cytokine secretion profile of $\gamma\delta$ T cells and their ability to be restricted by nonclassical MHC-like molecules, such as CD1 (Ref. 6). However, human CD4⁺ $\gamma\delta$ ⁺ T cells activated *in vitro* have been shown to provide a contact signal that can induce B cells to switch to IgE production in the presence of interleukin 4 (IL-4)⁷. Furthermore, a locus in the T-cell receptor (TCR) α/δ region has been found that controls the specific IgE reaction to purified allergens, and also has recessive genetic inheritance, similar to the previously identified chromosome 11q atopy locus⁸. Together, these data suggest that $\gamma\delta$ T cells might be implicated in allergic inflammation.

This article will argue that allergen-specific $\gamma\delta$ T cells are involved in the induction of airway inflammation in patients suffering from allergic asthma. This necessitates their secretion of a T helper 2 (Th2)-type cytokine profile and their interaction with pulmonary macrophages or dendritic cells (DCs).

Cellular components in the airways of allergic subjects

Biopsy studies have revealed that, even in mild, stable or newly diagnosed asthma, eosinophilic and lymphocytic infiltration consistently occurs in the epithelium and lamina propria^{9–11}. Eosinophils

are essentially absent in biopsies from control subjects, and lymphocytes comprise the great majority of mononuclear cells that infiltrate the asthmatic airway. However, an increase in macrophages expressing activation (CD68 or MHC class II) antigens was also observed¹². Most of the lymphocytes in the bronchial mucosa were identified as T cells with Th2-type functional activity (IL-4 and/or IL-5 production), a profile that is never seen in normal controls¹³.

Since a major source of IL-4 in atopic subjects is the pulmonary resident basophil/mast-cell compartment and eosinophils¹⁴, it has been proposed that the Th2-like T-cell-mediated response in allergic individuals is determined by the earliest contact between allergen and components of the nonspecific, innate immune defence system¹⁵. However, this hypothesis does not take into account that innate immune defences also occur in normal individuals exposed to the same environmental particulate allergens. A second possibility is that the endogenous source of IL-4 required for *in situ* Th2 development is the L-selectin (CD62L)^{duil} subset of CD4⁺ T cells, which contains the majority of the memory/activated CD4⁺ cells that secrete significant amounts of IL-4 upon primary stimulation *in vitro*¹⁶, as well as the CD4⁺NK1.1⁺ T-cell subset¹⁷. The latter cells appear to represent a specialized population of CD4⁺ T cells (of both $\alpha\beta$ and $\gamma\delta$ TCR) that are particularly effective in producing cytokines and are positively selected by the recognition of CD1 (Ref. 18).

Thus, apart from a defect in the reciprocal innate natural killer (NK)-cell- and/or macrophage-dependent Th1 responses¹⁴, one of the key mechanisms that could operationally drive the switch from a Th1 to a Th0/Th2 immune response is the type of allergen-responsive T cell. Although a transient decrease in circulating CD4⁺ cells after allergen challenge has been revealed in asthmatic patients¹⁹, it is unknown whether their pulmonary T cells are of mucosal or systemic origin, nor is it known what role these cells play in the induction of airway dysfunction. Presumably, a difference between mucosal and systemic T cells exists, as recently revealed by studies performed on subjects suffering from allergic perennial rhinitis. The alterations in the proportions and stages of differentiation and the activation of T-cell subsets in the nasal mucosa were not shown to reflect the changes in these subsets in the peripheral blood, which strongly suggests that, in allergic individuals, the T-cell subsets of the nasal mucosa (enriched in $\gamma\delta$ ⁺ T cells) are distinct from those of the peripheral blood²⁰.

Phenotypical characterization of pulmonary T cells in asthma patients
In vivo allergen-provocation studies that employ the bronchoalveolar lavage (BAL) procedure or bronchial biopsies for enumerating

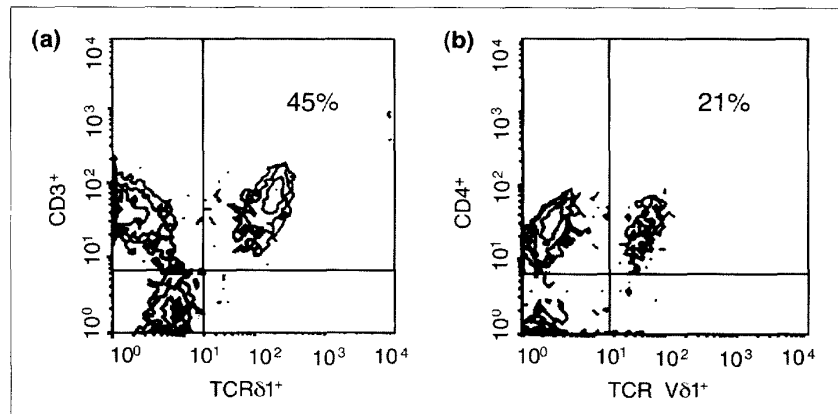


Fig. 1. T-cell receptor (TCR) $\gamma\delta$ expression on T cells obtained from bronchoalveolar lavage (BAL) fluids of untreated asthmatic subjects. (a) The expression of TCR $\gamma\delta$ on CD3⁺ cells. Double-stained cells were identified by two-colour cytofluorimetric analysis using fluorescein isothiocyanate (FITC)-conjugated anti-TCR $\delta 1$ monoclonal antibody (mAb) (T Cell Science, Cambridge, MA) and phycoerythrin (PE)-conjugated anti-CD3 mAb (Ortho, Raritan, NJ). (b) The expression of the TCR V $\delta 1$ chain on CD4⁺ cells. Double-stained cells were identified by FITC-conjugated anti-V $\delta 1a$ mAb (T Cell Science) and PE-conjugated anti-CD4 mAb (Ortho). A representative experiment is depicted and the percentages of co-stained cells are indicated. In both experiments, $\gamma\delta$ T cells were virtually absent, or were present at very low concentrations, in BAL samples both from normal controls and from patients with sarcoid or extrinsic allergic alveolitis (data not shown).

pulmonary inflammatory cells prior to and after allergen stimulation have yielded conflicting results. It has been clearly demonstrated that eosinophils, and often neutrophils, rise in absolute numbers 6–24 h after allergen challenge^{21,22}. Data on T-cell subsets are less well defined since, depending on the procedure adopted for cell recovery (BAL versus lung biopsies), both a drop in total T cells²³ and a rise in CD4⁺CD8⁺ (Ref. 21) or CD4⁺CD8⁺ (Ref. 22) T cells have been described. On the basis of published data on allergic rhinitis^{20,24}, and considering that $\gamma\delta$ T cells are believed to provide a first line of defence on epithelial surfaces⁶, we asked whether the detection of Th2-like cells in the BAL fluid during allergic asthma¹³ could be accounted for by a local expansion of double-negative (CD4⁺CD8⁺)CD3⁺ T cells coexpressing the $\gamma\delta$ TCR. Indeed, the percentage and absolute numbers of $\gamma\delta$ T cells were significantly higher in asthmatics than in controls, mainly due to an increase in cells bearing the TCR V $\delta 1$ chain. Surprisingly, a consistent proportion of these cells displayed the CD4⁺ phenotype (Fig. 1), whereas the remainder were of the conventional CD4⁺CD8⁺ subtype²⁵.

Since the CD30 molecule has recently been proposed as a marker for defining differentiated and/or activated T cells that produce Th2-type cytokines²⁶, its expression on pulmonary T cells was assessed. In contrast to controls and Th1 cells obtained from BAL fluid of patients with sarcoid alveolitis, which were always CD30⁺, more than half of the BAL $\gamma\delta$ T cells from the asthmatic group expressed CD30 on their surface²⁷. However, recent *in vitro* experiments on human T-cell clones argue against a definite role for this molecule in distinguishing Th1- and Th2-type cells²⁸. In addition, precursor helper T cells (i.e. naive cord-blood-derived T cells) acquired surface CD30 expression upon *in vitro* stimulation with allergen or IL-4, but lacked the capacity to secrete cytokines other than IL-2 (Ref. 29). Although the subject is still a matter of debate, it

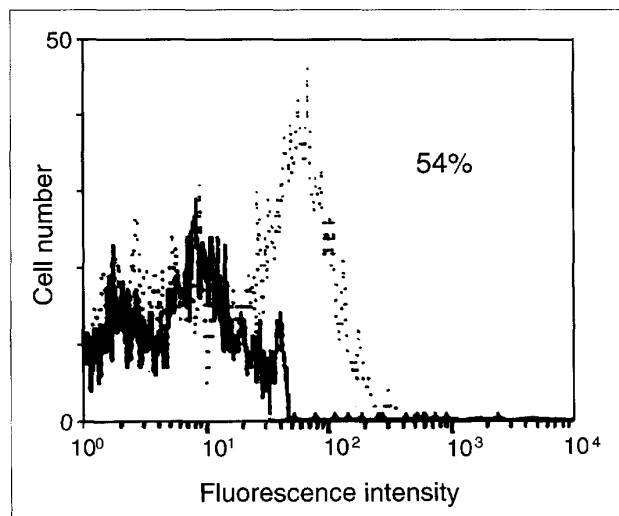


Fig. 2. B70 surface antigen expression on plastic-adherent alveolar macrophages (AMs) obtained from bronchoalveolar lavage fluids of untreated patients with asthma ($n = 5$). AMs of patients with pulmonary sarcoidosis (PS) ($n = 5$) or extrinsic allergic alveolitis (EAA) ($n = 5$) were similarly analyzed and used for comparison. Histograms represent the result of a paradigmatic experiment performed by an indirect immunofluorescence staining technique followed by cytofluorimetric analysis. The solid line is the superimposed cytofluorographic profile of the negative control, whereas the dotted line represents the profile of an asthmatic patient. The monoclonal antibody IT2.1 (M. Azuma, Dept of Immunology, Juntendo University, Tokyo, Japan) was used to identify B70⁺ AMs. B70 antigen expression was greatly enhanced on AMs of asthmatic patients, with a mean percentage of positive cells ($49 \pm 5\%$; $\pm$ SD) significantly different from those calculated in the other lung diseases (PS = $1.7 \pm 0.5\%$; EAA = $2.1 \pm 1\%$) (both $p < 0.0001$ by one-way Kruskal-Wallis analysis of the variance).

has recently been suggested that this marker may be useful to identify activated Th2-type cells³⁰.

Thus, it seems that the airways of atopic patients may be equipped with a particular subset of T cells that differ phenotypically from their counterparts circulating in the bloodstream³¹. Blood $\gamma\delta$ T cells are CD30⁻ [in fact, data obtained from normal volunteers have shown that the percentage of CD30⁺ circulating T cells represents less than 1% of total circulating T cells (F. Spinozzi and A. Bertotto, unpublished; Ref. 26)] and normally express the V γ 9/V δ 2 TCR gene segments³².

Functional properties of pulmonary $\gamma\delta$ T cells

Highly purified lung $\gamma\delta$ T cells from allergic patients co-cultured with autologous macrophages proliferate after *in vitro* exposure to the specific allergen, whereas proliferation is negligible when the cells are cultured in the presence of an unrelated allergen. Moreover, BAL T cells from healthy subjects and from patients with sarcoidosis were unable to respond to the proliferative stimulus elicited by the specific allergen extract³³.

The $\gamma\delta$ T cells from BAL fluid of asthmatic patients, but not from sarcoid alveolitis controls, contain intracellular stores of IL-4, suggesting a Th2-like bias²⁷. By contrast, Walker *et al.*³⁴ found similar

percentages of $\gamma\delta$ T cells in BAL fluid of asthmatic patients and controls. However, this study population was treated with inhaled and/or systemic corticosteroids until two weeks before the investigation, and data in human subjects have demonstrated that the apoptosis-mediated suppressive effect of steroids on T cells continues for more than four weeks after treatment is withdrawn³³.

APC function of pulmonary macrophages in asthmatic patients

The lung is a gas-exchange organ exposed to a large amount of aerodispersed particulate contaminants and antigens. Consequently, biopsy and cytological studies have concentrated on the presence of macrophages in the asthmatic airways. These cells have been shown to express CD68 but not CD14 or MHC class II molecules³⁵. More importantly, after allergen challenge, they become activated³⁶. However, despite normal MHC class II expression and normal bactericidal activity, alveolar macrophages (AMs) do not activate resting peripheral blood T cells in the primary mixed lymphocyte reaction (MLR)³⁷. Immune responses in mucosal tissues that are continuously exposed to abundant quantities of antigen are limited by poor expression of CD80 (B7-1) and CD86 (B7-2; B70) costimulatory molecules on AMs (Ref. 38). By contrast, phenotypical analysis of AMs from asthmatic patients revealed that these cells overexpress the B70 antigen, whereas those from normal controls and patients with sarcoidosis or extrinsic allergic alveolitis did not (Fig. 2). This may explain why AMs can function as APCs when $\gamma\delta$ T cells are exposed *in vitro* to specific allergen stimulation (see below).

Allergen recognition in the atopic respiratory tract: a hypothesis

On the basis of the findings summarized above, it is postulated that atopic subjects differ from nonatopic individuals by the presence at the mucosal surfaces of a particular $\gamma\delta$ T-cell subset and an unusual mechanism of allergen recognition. The recent demonstration that small molecules can themselves selectively stimulate $\gamma\delta$ T cells³⁹ supports this hypothesis. Thus, allergen recognition by $\gamma\delta$ T cells may not require MHC-restricted antigen processing and presentation; rather, it depends on the formation of a complex comprising native allergen or allergen-derived macromolecular epitopes and the $\gamma\delta$ TCR (Ref. 6). The complex genetic background that predisposes to atopy (recently reviewed by Sandford *et al.*⁴⁰) may, therefore, require that a particular subset of T cells that recognizes allergens via a particular TCR be expanded at the surface of the target organ. Such allergen recognition would seem to mimic that occurring in the B-cell compartment, where antigen is recognized through interactions with surface antibody molecules.

Alternatively, a growing body of data suggests that the CD1 system is capable of presenting non-protein (glycolipid) antigens to T cells⁴¹. In contrast to MHC class I and II molecules, certain CD1 molecules appear to restrict presentation of non-peptide antigens¹⁸, expanding the potential scope of T-cell recognition. Figure 3 shows a model in which $\gamma\delta$ T cells recognize allergen in the context of the non-MHC-encoded CD1 antigens expressed on the surface of

activated (CD86⁺) AMs in atopic subjects. Both cell types are presumably involved in the induction of airway inflammation⁴², since CD80⁺ or CD86⁺ macrophages³⁸ and $\alpha\beta$ T cells are the only other immunocompetent cells present in normal lung tissue⁴³. Furthermore, blockade of costimulation with CTLA-4-Ig, an immunoglobulin fusion protein known to prevent costimulation by inhibiting CD28-B7 interactions, also inhibits airway hyperresponsiveness, inflammatory infiltration, expansion of thoracic lymphocytes, and allergen-specific responsiveness of pulmonary T cells in a murine model of allergic asthma⁴⁴. Studies on CD1 expression on AMs obtained from BAL fluids should reveal whether it is overexpressed by AMs of asthma patients, compared with normal controls. Preliminary data suggest this may be the case (F. Spinozzi *et al.*, unpublished).

Conclusions and future directions

It has been suggested that allergic airway inflammation results from a failure in the normal capacity to control otherwise harmful IgE-mediated immune responses⁴⁵. Here, it is suggested that an alternative pathogenetic mechanism is operating in atopic patients with asthma. In parallel with a genetic predisposition towards an exaggerated defensive IgE response to inhaled pollutants^{1,2,40}, there may be an overexpansion of the mucosal level of activated macrophages and allergen-specific $\gamma\delta$ T cells. This phenomenon, perhaps associated with other underlying genetic defects^{8,40} and environmentally conditioned by the nature of the native allergen (a glycolipidic and glycoprotein compound)¹⁸, might result from a block of some homeostatic mechanisms operating on $\gamma\delta$ T cells. These could include a failure in Fas-mediated programmed cell death (PCD)⁴⁶, and/or the presence of autocrine growth factors such as IL-4 (Ref. 47), both of which have been shown to exert anti-apoptotic activities in mouse thymocytes and double-negative human $\alpha\beta$ and $\gamma\delta$ T cells exposed *in vitro* to mitogenic agents⁴⁸.

Future management of allergic respiratory diseases should take into account some of the recent experimental data on the pathogenesis of airway inflammation, especially since the exact mechanism of action of drugs used for long duration, such as theophylline⁴⁹ or corticosteroids⁵⁰, is now known. Eosinophils and $\gamma\delta$ T cells may both be induced to undergo PCD in response to such agents^{49,51}, resulting in an *in situ* modification of the pulmonary cellular infiltrate without a release of proinflammatory products by dead cells. These new insights will doubtlessly improve the way in which the wide clinical spectrum of respiratory allergic diseases is treated.

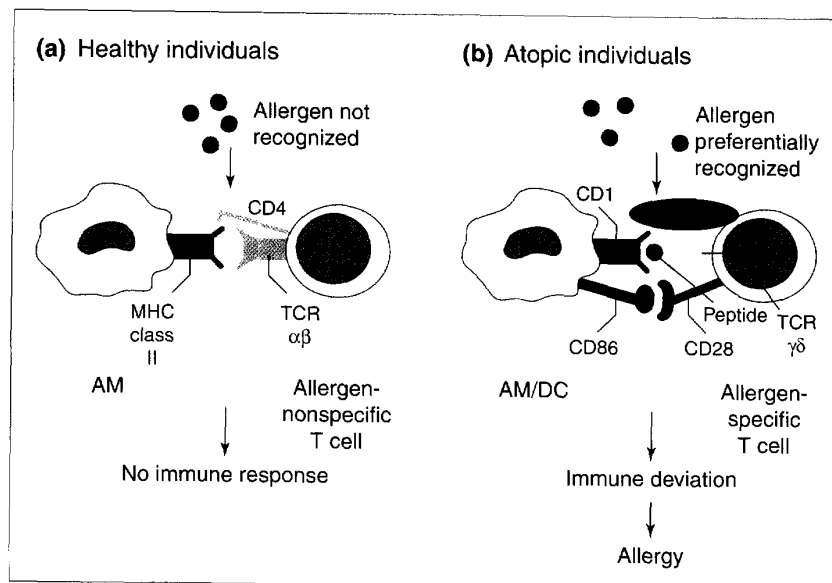


Fig. 3. Hypothetical mechanisms involved in $\gamma\delta$ T-cell recognition of aeroallergens. (a) The lack of receptors specific for aerodispersed allergen recognition on the surface of alveolar macrophages (AMs) and $\alpha\beta$ T cells resident in normal lung favours the clearance of foreign particles, thus preventing otherwise harmful cellular and/or IgE-mediated immune reactions. (b) As a consequence of an overexpansion in the asthmatic airways of AMs/dendritic cells (DCs) and T cells equipped with particular surface structures [CD1, T-cell receptor (TCR) $\gamma\delta$ and perhaps NK1.1 antigens] and costimulatory molecules (B70 and CD28), the mucosal immune system of genetically susceptible (atopic) individuals recognizes native inhaled allergens. A local, specific cellular and, perhaps, humoral (T-cell help for IgE production) immune response is mounted against these allergens.

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