

REVIEW

$\gamma\delta$ T cells in allergic airway diseases

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Summary

Allergic diseases like atopic rhinitis, bronchial asthma and urticaria are prevalent and on the rise. T cells are known to play a fundamental role in allergic diseases through the recognition of antigen, and secretion of TH2-type cytokines like interleukins (IL) -4, -5 and -13, that not only induce the synthesis of IgE but also recruit effector cells like eosinophils and basophils into the site of allergic inflammation. Yet, not much has been learnt about the character of these allergen-specific T cells, in the target organ. Again, recent studies have suggested that in addition to the $\alpha\beta$ T-cell receptor (TCR) -bearing cells, the less common $\gamma\delta$ TCR bearing cells may play important roles in the development and perpetuation of allergic inflammation as effector and immunoregulatory cells. The present review focuses on the characteristics and roles of $\gamma\delta$ T cells in atopic rhinitis and asthma.

In the last few decades, it has becoming increasingly evident that the prevalence of allergic diseases like allergic rhinoconjunctivitis, atopic asthma and atopic dermatitis has increased, ranging between 10 and 20% of the general population [1–3]. The chain of events that lead to the allergic immune response includes the recognition of allergen by the antigen-presenting cell (APC), antigen presentation to T cells, the production of cytokines like interleukin (IL) -4 and IL-13 by T cells, the synthesis of immunoglobulin (Ig) E by B cells, binding of the IgE to the high affinity IgE receptor (Fc ϵ RI) on the surface of mast cells, and on subsequent exposure to the allergen, the cross-linking of the bound IgE–Fc ϵ RI complex with multivalent allergen resulting in the release of chemical mediators like histamine, leukotrienes and prostaglandins [4–7]. This immediate phase allergic reaction occurs within several seconds to few minutes upon encounter with antigen and the central cell in this response is the mast cell (Fig. 1). This is followed by the late phase allergic reaction which occurs after 4–6 h with a recurrence of symptoms that persists for about 24 h. The late phase allergic reaction is largely inflammatory and is orchestrated by cytokines released from T lymphocytes. The T-cell-derived cytokines upregulate the expression of adhesion molecules like VCAM-1 and

ICAM-1 on endothelial cells, resulting in the infiltration of eosinophils, and basophils which subsequently release a number of soluble products like prostaglandins, leukotrienes, PAF, ECP and MBP [8,9] (Fig. 1).

The reason why only a proportion of individuals develop allergic disease is not yet well understood. An increase in the level of specific IgE is a hallmark of atopic diseases, but the genetic basis for this is as yet unknown. Studies on the major histocompatibility complex (MHC) specificity of allergen-specific T cells are limited and population studies of inheritance of atopic disorders do not suggest a dominant role for HLA genes. There is increasing evidence of a link between environmental factors like air pollution (nitrogen oxides, ozone, volatile organic compounds, etc.) and the increase in prevalence of allergic diseases [10–12]. Yet, the precise mechanisms by which the pollutants exert their effects is not completely known. Again, there is little information about the specific characteristics of T cells in the target/shock organs and their relation to the clinical expression of allergic disease.

T lymphocytes are the principal factors that regulate and co-ordinate immune responses. In allergic diseases, T lymphocytes play a fundamental role first through the recognition of antigen and subsequent secretion of cytokines like IL-4, IL-5 and IL-13, that not only promote the synthesis of IgE but also contribute to the recruitment of effector cells like eosinophils and basophils into the site of allergic inflammation. Lymphocytes with such functional activities are termed T-helper 2 (TH2), whereas the nonoverlapping cell counterpart that secretes interferon-gamma (IFN γ) or interleukin-2 or both is termed T-helper 1 (TH1) and is involved in the delayed hypersensitivity immune reactions [13]. Although several studies have demonstrated the predominance of TH2-like activated T lymphocytes in the nasal mucosa of patients with atopic rhinitis and bronchial mucosa or BAL of patients with atopic asthma [14–17], there are but few reports on whether these cells bear the $\alpha\beta$ T-cell receptor, or the less common $\gamma\delta$ T-cell receptor, and what is their relative contribution in allergic inflammation.

In humans and most animals the vast majority of T cells express a TCR composed of an α -chain and a β -chain, whereas a minor T-cell population bears the $\gamma\delta$ TCR [18]. In contrast with the conventional $\alpha\beta$ T cells that recognize antigenic peptides presented by the MHC class II molecule,

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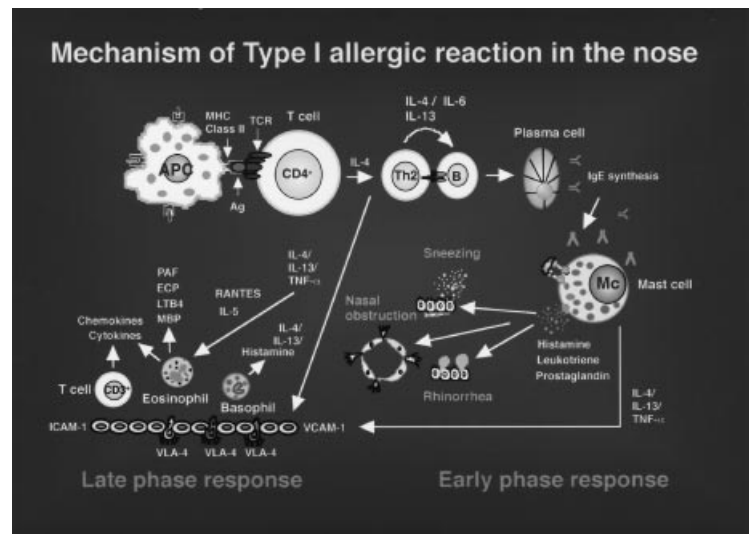


Fig. 1. Mechanism of the Type I allergic reaction in the nose

$\gamma\delta$ T cells can directly recognize proteins. It is proposed that $\gamma\delta$ T cells may act as an extended arm of $\alpha\beta$ T cells, by providing a rapid but weaker response before the $\alpha\beta$ T-cell response has fully developed [19]. This suggestion is based on both the cytokine profile of $\gamma\delta$ T cells and their ability to be restricted by non-classical MHC-like molecules such as CD1 [20]. Again, $\gamma\delta$ T cells are reported to play an important role in humoral responses as essential regulatory T cells in the induction and maintenance of antigen-specific IgA immune response in the mucosal sites [21]. Recent studies have also indicated that $\gamma\delta$ T cells may regulate allergic immune responses through their capacity to induce IgE synthesis in B cells, in the presence of IL-4 [22]. In this context, it is of interest that a locus in the T-cell receptor α/δ region controls the specific IgE reaction to purified allergens, and also has recessive genetic inheritance, similar to the previously identified chromosome 11q atopy locus [23]. The purpose of this review is not to discuss all of the roles of $\gamma\delta$ T cells, but to focus on those that are relevant to allergic inflammation thereby bringing a link between the biology of these cells and the clinical expression of allergic disease.

Cellular changes in the nasal mucosa of allergic rhinitis

Allergic rhinitis is a prototype of a Type I allergic disease mediated by specific IgE antibody to an offending allergen, leading to mucosal inflammation and the clinical expression of disease, characterized by sneezing, itching, rhinorrhoea and nasal blockage. Significant progress has been made toward understanding the cellular and molecular mechanisms in allergic rhinitis. Mucosal inflammation in allergic rhinitis is characterized by the tissue infiltration of

eosinophils and associated activation of mast cells and T lymphocytes. Immunohistological studies of nasal biopsies in patients with seasonal allergic rhinitis as well as perennial allergic rhinitis have revealed an increase in the numbers of intraepithelial mast cells, CD4⁺ T cells, and CD25⁺ (activated) T cells and EG2⁺ cells [24,25]. This is associated with an increase in the numbers of IL-4⁺, IL-5⁺, and IL-13⁺-expressing T cells and/or mast cells [26–30]. The release of cytokines (like interleukin-5) by activated T lymphocytes leads to the local accumulation of eosinophils, their activation, and the secretion of eosinophil-derived proteins with subsequent epithelial damage. Among the many kinds of cytokines, IL-4 and IL-13 are the inducers of IgE synthesis, but additional signals, which are provided by T cells/mast cells (CD40L–CD40 interaction), are required for induction of IgE switching in naive B cells [31,32]. In addition to these histopathological features, what is of considerable interest is the selective increase in the percentage and absolute numbers of intraepithelial $\gamma\delta$ T cells in perennial allergic rhinitis patients [25,30,33]. Moreover, these $\gamma\delta$ T cells secrete IL-4 and IL-13 and, like conventional alpha beta T lymphocytes, induce IgE synthesis in B cells [34].

Phenotypic and functional characteristics of nasal $\gamma\delta$ T cells in allergic rhinitis

$\gamma\delta$ T cells comprise about 25–30% of the total CD3⁺ T-cell population in the allergic nasal mucosa [33], but are less than 5–10% in the normal or nonallergic nasal mucosa. In light of these observations, we asked ourselves whether these nasal $\gamma\delta$ T cells are organ-specific and whether these cells have proliferated locally in response to specific

antigenic stimulation. Interestingly, the phenotypes, proportion and stages of activation of the nasal $\gamma\delta$ T cells differed from those of the peripheral blood [33]. In fact, the expanded population of nasal $\gamma\delta$ T cells in perennial allergic rhinitis patients comprised mainly of $CD4^+$ and $CD4^-8^-$ $\gamma\delta$ T cells with no parallel alteration of the respective $\gamma\delta$ T-cell subsets in the peripheral blood of the same patients [33]. Moreover, these nasal $\gamma\delta$ T cells were $V\gamma1/V\delta1-J\delta1$ TCR^+ and expressed the CD45RO surface antigen (for memory T cells), whereas their counterparts in the peripheral blood were $V\gamma2/V\delta2$ TCR^+ (Fig. 2). More importantly, nasal (but not peripheral blood) $\gamma\delta$ T cells from mite-allergic patients proliferated well *in vitro*, in response to the mite-specific antigen (Der f 2), but not to an unrelated antigen Cry j 1 (major allergen of Japanese cedar pollen) [34]. These findings strongly suggest that the mucosal $\gamma\delta$ T cells (nasal) in allergic rhinitis are organ specific, differ from those in the peripheral blood, and are oligoclonally expanded under specific antigenic stimulation.

Yet, the question remains as to what exactly these cells do in the development or perpetuation of allergic inflammation. Several studies have shown that $\gamma\delta$ T cells can produce high levels of $IFN\gamma$. Some researchers reported that inhalation of aerosolized antigen activates $IFN\gamma$ -secreting $CD8^+$ $TCR \gamma\delta$ T cells resulting in an inhibition of IgE synthesis [35]. In fact, adoptive transfer of small numbers of $\gamma\delta$ T cells from ovalbumin (OVA)-tolerant mice selectively suppressed TH2-dependent IgE antibody production without affecting parallel IgG responses. Unfractionated splenocytes from tolerant animals secreted high levels of $IFN\gamma$ in response to specific antigen, and this secretory response was markedly reduced by depletion of $CD8^+$, but not $CD4^+$ cells. These researchers suggested an important role for antigen-specific $\gamma\delta$ T cells in the maintenance of immunological homeostasis in the lung and airways by providing protection against primary allergic sensitization to environmental antigens associated with immunoinflammatory diseases such as allergic rhinitis and asthma. Again, others reported that some $\gamma\delta$ T cells could suppress IgE synthesis by killing the IgE-producing B cells via an interaction involving the IgE expression on the surface of B cells and the $Fc\epsilon$ receptors that form a part of the CD3-TCR complex in some $\gamma\delta$ T cells [36]. On the other hand, it has also been shown that $\gamma\delta$ T cells are essential for inducing IL-4-dependent IgE synthesis [37]. We hypothesized that like conventional $\alpha\beta$ T cells, $\gamma\delta$ T cells may exhibit phenotype-specific functional heterogeneity. In fact even though nasal $\gamma\delta$ T cells from perennial allergic rhinitis patients (mainly $CD4^+$ and $CD4^-8^-$) dominantly produced IL-4, IL-5 and IL-13, peripheral blood $\gamma\delta$ T cells from the same patients (mainly $CD8^+$) produced high levels of $IFN\gamma$ [33]. Indeed, we recently demonstrated functional heterogeneity in $\gamma\delta$ T cells in that $CD4^+$, but not $CD8^+$ nasal $\gamma\delta$ T-cell clones

derived from patients with allergic rhinitis, expressed the CD40L, secreted IL-4 and IL-13, and provided help to B cells to synthesize IgE (unpublished observations). Moreover, some allergen-specific nasal $\gamma\delta$ T-cell clones could induce the proliferation and activation of $\alpha\beta$ T cells (unpublished observations).

As observed by us in the nose (upper airway), Spinazzi *et al.* also demonstrated an increase in the proportion of

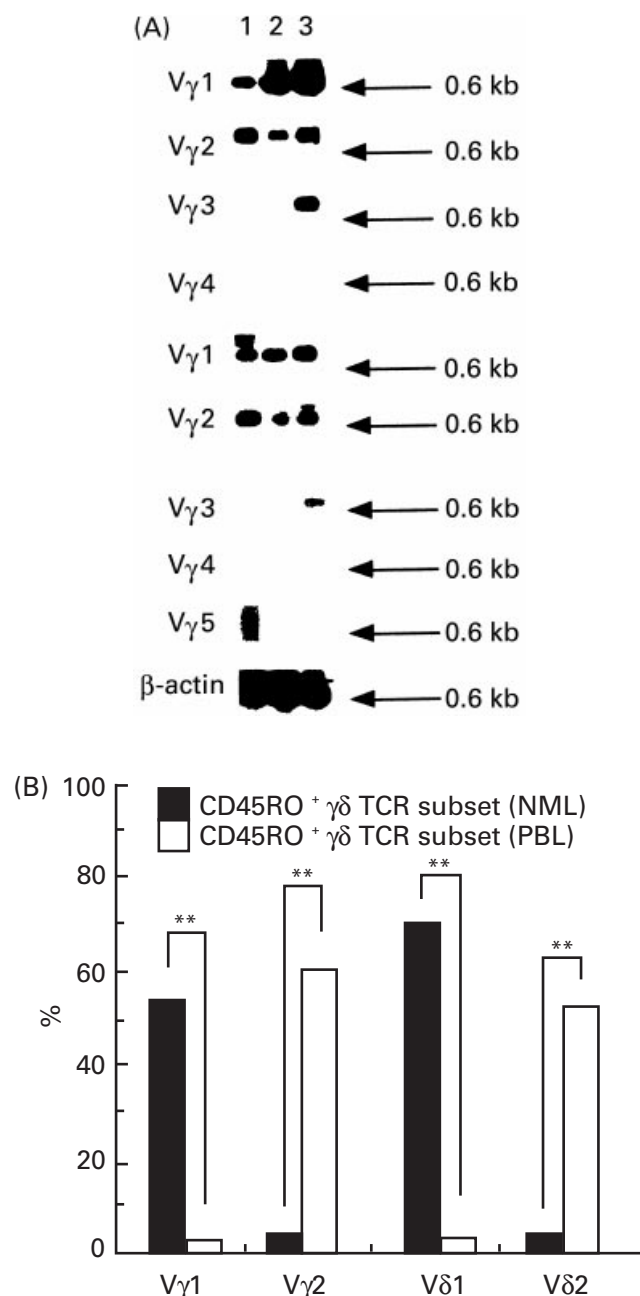


Fig. 2. (a) V gene usage of nasal and peripheral blood $\gamma\delta$ T cells in atopic and nonatopic rhinitis. (b) CD45RO expression in nasal and peripheral blood $\gamma\delta$ T cells of atopic and nonatopic rhinitis

TH2-type secreting $CD4^+$ $\gamma\delta$ T cells in the bronchoalveolar lavage (BAL) of patients with allergic asthma [38,39]. These researchers reported that the percentage and absolute numbers of $\gamma\delta$ T cells, which do not usually exceed 2% of the total T lymphocytes in the normal human lung, are increased in the BAL fluid samples from untreated patients with asthma but not in samples from healthy controls or from persons with other pulmonary diseases. In their *in vitro* proliferation studies, these researchers demonstrated allergen specificity of pulmonary $\gamma\delta$ T cells from asthmatic patients, a result that is consistent with our observations on the antigen specificity of nasal $\gamma\delta$ T-cell clones established from the nasal mucosa of patients with perennial allergic rhinitis to house dust mite [34]. Although some researchers reported that $\gamma\delta$ T cells are decreased in the peripheral blood lymphocytes (PBL) of patients with allergic asthma [40], we did not observe any remarkable changes in the proportions, phenotypes and stages of activation of $\gamma\delta$ T cells in the peripheral blood of allergic rhinitis [34]. These data suggest that mucosal $\gamma\delta$ T cells differ from those in the peripheral blood. Another point in favour of this hypothesis is that the V gamma J gamma gene usage of BAL $\gamma\delta$ T cells of patients with atopic asthma are distinct from those in PBL [41] as is the case in the nose too [33], indicating a mucosal expansion of $\gamma\delta$ T cells in patients with atopic rhinitis and asthma.

$\gamma\delta$ T cells as effector and immunoregulatory cells in allergic diseases

The precise role of $\gamma\delta$ T cells in allergic inflammation remains to be defined. Yet, the local expansion of TH2-type cytokine-secreting, antigen-specific $\gamma\delta$ T cells in

patients with allergic rhinitis and asthma suggests that these cells can be a constant source of TH2-type cytokines providing the necessary environment for the perpetuation of an allergic inflammation through the immunoregulation of mast cells (IL-4, IL-13), recruitment of cells like basophils (IL-4) and eosinophils (IL-5) into the shock organ, and maintaining the numbers of TH2 type cells (IL-4) (Fig. 3). Although, there is much controversy on whether $\gamma\delta$ T cells induce or inhibit IgE production, this is most likely a reflection of a functional heterogeneity between phenotypes of $\gamma\delta$ T cells [35,36,42]. In fact, $CD4^+$ nasal $\gamma\delta$ T cells (but not $CD8^+$), were found to be potent producers of IL-4 and IL-13, and induce IgE synthesis in B cells in an MHC-restricted manner (manuscript in preparation). Thus $\gamma\delta$ T cells may play versatile roles in the development and perpetuation of allergic inflammation.

In this context, it is of interest that 'primed' mast cells in atopics also express the CD40L, and induce IgE synthesis in B cells [28,43]. Despite this redundancy in function between several of these effector cells, it would be relevant to note that the mast cell-induced IgE synthesis occurs in an MHC-unrestricted manner, whereas $\alpha\beta$ - and $\gamma\delta$ -induced IgE synthesis is MHC-restricted. Again, it is known now that IgE can be synthesized locally in the shock organ [44, Pawankar *et al.*, in press], indicating that cells like mast cells and $\gamma\delta$ T cells that normally reside in the tissues may play important roles in the local synthesis of IgE, whereas it may be speculated that $\alpha\beta$ T cells contribute to the systemic IgE synthesis.

Still further, the described increase in either $CD4^+$ or $CD4^-8^-$ $\gamma\delta$ T cells, together with the finding that the common γ chain of the high-affinity IgE receptor (Fc ϵ RI) is a major functional subunit of murine $CD3^+$ cells bearing

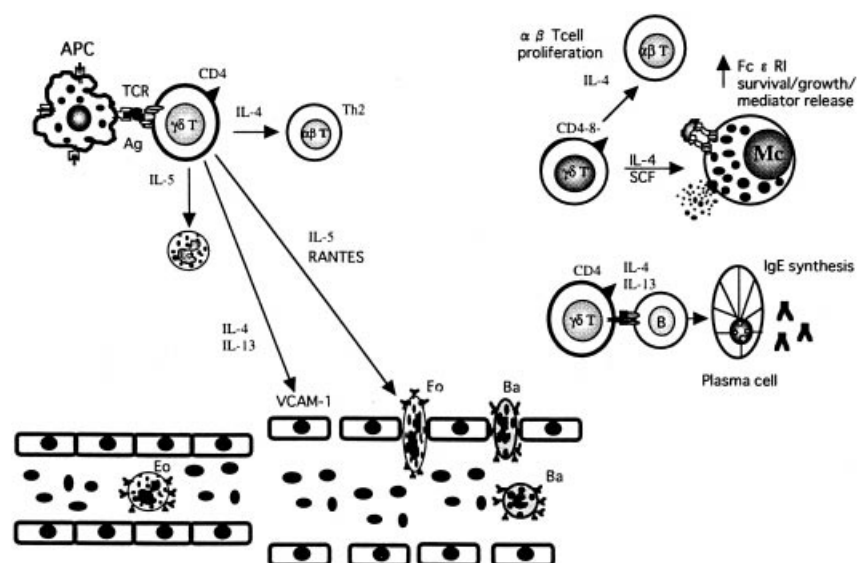


Fig. 3. Integrated roles of $\gamma\delta$ T cells in allergic inflammation

the $\gamma\delta$ T-cell antigen receptor complex [45] suggest that these cells may also contribute to the recognition of IgE-complexed allergens. Indeed, since $\gamma\delta$ T cells are located in the epithelial compartment and are in constant exposure to environmental allergens, such a mechanism may serve to perpetuate the chronic inflammation seen in perennial allergic rhinitis or asthma. Furthermore, since intraepithelial nasal $\gamma\delta$ T cells are potent producers of TH2-type cytokines these cells may regulate the differentiation of $\alpha\beta$ T cells into TH1- or TH2-type cells, early in the primary immune response (Fig. 3). These observations suggest important aspects of the allergic inflammation in that even though several cells may share similar functions each may have comparable importance depending on the stage of disease, the phase of the reaction, or their specific mode of action. Again nasal $\gamma\delta$ T cells can produce RANTES and SCF, suggesting their important roles in the chemotaxis of eosinophils and mast cells into the epithelium (RANTES), and the growth and survival of mast cells (stem cell factor) (unpublished observations). Finally, interaction between $\gamma\delta$ T cells and epithelial cells may also be important since nasal $\gamma\delta$ T cells express high levels of the $\beta 1$ integrin expression (VLA-4 and VLA-5) (unpublished observations) that may be relevant for their retention within the epithelial compartment (since the allergic nasal epithelium expresses increased levels of VCAM-1).

Conclusion

It is suggested that allergic airway inflammation results from a failure in the normal capacity to control otherwise harmful IgE-mediated immune responses. Yet, alternative pathogenetic mechanisms like a genetic predisposition towards an exaggerated defensive IgE response to inhaled allergens and an overexpansion at the mucosal level of allergen-specific $\gamma\delta$ T cells, or an upregulated Fc ϵ RI expression in mast cells may also operate in atopic patients with asthma or rhinitis. This phenomenon — perhaps associated with other underlying genetic defects as well as environmental factors that may alter the nature of the native allergen, or enhance its mucosal penetration — can result in an increase in the prevalence of allergic diseases.

Indeed while this brief review has emphasized on the roles of $\gamma\delta$ T cells in allergic inflammation, the redundancy in the effector mechanisms that potentially participate in allergic inflammation is considerable. Many cells express several cytokines, several mediators, the Fc ϵ RI and/or CD23, and thus have overlapping functions. At the same time the possibility that some of the cells and mediators that participate in the allergic responses may also help to down-regulate the allergic response cannot be ruled out. Thus the delicate balance in directing an effector cell to act in a particular direction (inflammatory or anti-inflammatory) is

vital to the clinical expression of disease. In conclusion, we have highlighted recent evidences that $\gamma\delta$ T lymphocytes may also play crucial roles as both effector and immunoregulatory cells in perpetuating allergic inflammation and that the future management of allergic airway diseases would need to target the $\gamma\delta$ T cell–cytokine cascade at the mucosal level. Alternatively, a therapeutic approach that can suppress the TH2-type cytokine secreting CD4⁺ $\gamma\delta$ T cells, and instead activate IFN γ -secreting CD8⁺ T cells, may prove beneficial.

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