Review Article
The Role of the γδ T Cell in Allergic Diseases

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The predominant distribution of γδ T cells in the mucosal and epithelial tissues makes these unconventional lymphocytes the “guards” to contact external environment (like allergens) and to contribute to immune surveillance, as well as “vanguards” to participate in initiating mucosal inflammation. Therefore, γδ T cells have been considered to bridge the innate and adaptive immunity. The role these cells play in allergy seems to be complicated and meaningful, so it makes sense to review the characteristics and role of γδ T cells in allergic diseases.

1. Introduction
γδ T cells are a minor population of lymphocytes expressing γ and δ T cell receptor (TCR) chains, which are often considered to bridge innate and adaptive immune responses. Recent studies have shown that γδ T cells can comprise up to 50% of the T cells within epithelium or mucosa-rich tissues and less than 10% in peripheral blood [1]. The specific localization and abundance of these cells suggest that they might be markedly implicated in epithelial/mucosal immunity [2, 3]. In contrast to recognition of antigens by αβ T cells, γδ T cells recognize antigens directly without any requirement for antigen processing and presentation or major histocompatibility complex (MHC) molecules [4]. It has been indicated that γδ T cells may play crucial roles in the development and perpetuation of allergic inflammation as effector and immunoregulatory cells, via production of T helper (Th)1-, Th2-, and Th17-associated cytokines [5], which not only induce the synthesis of IgE but also recruit effector cells like eosinophils and basophils into the site of allergic inflammation [6]. Besides, different subsets of γδ T cells can show different functions, depending on what tissue they are found in and which specific TCRs they bear [7]. Even though there is a growing consensus about the importance of these cells in allergic immune responses, the specific mechanisms remain elusive. The present review focuses on the latest knowledge on characteristics and role of γδ T cells in allergic diseases.

2. γδ T Cells Have Diverse Subsets with Specific Locations and Functions
As research continues, it has been realized that γδ T cells are not a homogeneous population of cells with a single physiological role, and their subset complexity is being characterized, both in mice and humans [7]. TCR Vγ- and Vδ-encoded chain pairs may interact with distinct ligands in different tissues and be expanded on that basis. Defined by the usage of either Vδ1 or Vδ2 TCR (Vδ3 and Vδ5 making up minor populations), human γδ T cells fall into two major subsets: Vδ2 T cells account for the majority (50–95%) of circulating γδ T cells, whereas Vδ1 T cells are rare in the blood but appear at increased frequencies in mucosal tissues and in the skin [7–10].

The Vγ9Vδ2 (also termed Vγ2Vδ2, collectively designated Vδ2) T cells in the peripheral blood can sometimes identify over 50% of leukocytes after certain bacterial or parasitic infections and rapidly get activated; therefore, such TCR-dependent activation of Vγ9Vδ2 T cells enables them to respond to a diverse range of pathogens [11]. According to the surface expression of CD45RA and
CD27, markers more commonly used to identify the naive, effector, or memory status of conventional γδ T cells, are often subdivided into four subsets: “naive” (Tnaive) CD45RA⁺CD27⁺ cells; “central memory” (TCM) CD45RA⁺CD27⁺ cells; “effector memory” (TEM) CD45RA⁺CD27⁻ cells; “CD45RA⁻ effector memory” (TEMRA) CD45RA⁺CD27⁻ cells [7, 12]. Tnaive and TCM cells express lymph node homing receptors, abound in lymph nodes, and lack immediate effector functions. Conversely, TEM and TEMRA cells, which express receptors for homing to inflamed tissues, are poorly represented in the lymph nodes while abounding in sites of inflammation and display immediate effector functions. It indicates a lineage differentiation pattern for human Vδ2 T cells that generates naive cells circulating in lymph nodes, effector/memory cells patrolling the blood, and terminally differentiated effector cells residing in inflamed tissues [12].

In contrast to Vδ2, the TCR-γ chain usage by the tissue-associated Vδ1 T cells varies at distinct anatomic locations. Vδ1 T cells in the periphery express a naive phenotype and may migrate preferentially to localized sites when they are activated [13]. For instance, Vγ2, Vγ3, Vγ5, Vγ6, and Vγ7 are used predominantly by γδ T cells in peripheral lymphoid organs, skin, small intestine, tongue, and reproductive system, respectively [14, 15]. In contrast, Vγ1 and Vγ4 are preferentially expressed in the respiratory system like nasal mucosa and lung [16–18]. Recent studies have indicated that these tissue-associated Vδ1 T cells may play an important function not only in maintaining immune homeostasis in the local microenvironment [19] but also in wound healing, removing distressed or transformed epithelial cells and subduing excessive inflammation, in both mice and humans [20–22].

Besides, the role of these mucosa predominantly expressed γδ T cells in allergic diseases has also been noticed. Our preliminary studies found that the infiltration of γδ T cells significantly increases in the nasal mucosa of patients with perennial allergic rhinitis (AR) (data not shown). Moreover, Pawankar et al. [23] proved that the increased population of γδ T cells in the perennial AR patients’ nasal mucosa mainly comprises of Vγ1Vδ1 subsets. In mice sensitized and challenged with OVA, Cook et al. [24] observed that Vγ1⁺T cells spontaneously enhance airway hyperresponsiveness (AHR), whereas Vγ4⁺ T cells, after being induced by allergen sensitization and challenge, suppress AHR. These data suggest that γδ T cells of distinct phenotypes may play different, sometimes opposed, functions in airway allergic inflammation. However, it is still premature to speculate whether the Vγ4⁺ subsets of γδ T cells may exert an important role in maintaining immune homeostasis in local microenvironment of healthy humans; on the other hand, the Vγ1⁺ subsets may take an essential part in the development and perpetuation of allergic inflammation as effectors in atopy patients. Besides, our another recent study showed that different subsets of γδ T cells in peripheral blood of perennial AR patients before and after specific immunotherapy (SIT) appear with distinct expression patterns [25]. But whether γδ T cells in peripheral blood and in mucosa function separately or synergistically remains an unsolved problem.

3. γδ T Cells in Different Age and Gender Groups

With age, there comes the change from having fairly diverse pairs of γδ T cells (of which Vδ1⁺ subsets serve as the majority in cord blood at birth) to increasingly restricted pairings (with Vγ9Vδ2 T cells becoming the major subsets with very limited receptor diversity by adulthood). From birth to about 10 years of age, the absolute number of γδ T cells in the periphery increases, with the Vγ9Vδ2 T cell subsets expanding from a minor population at birth to usually more than 75% of circulating γδ T cells [15, 26]. Vγ9Vδ2 T cells are known to respond to many different phosphoantigens, so it is likely that the exposure to a variety of pathogens results in the selection of these cells in early life [27]. This clonal expansion has been seen as evidence of the vital role these T cells play in responding to environmental challenges in early life. However, it has not been demonstrated whether this phenomenon is in fact primary in response to environmental challenges but not, at least in part, endogenous stimuli, as an extension of the adaptive changes taking place within the newborn [10].

Previous longitudinal cohort studies have shown that most childhood asthma begins in infancy, and between 40% and 75% of children with asthma will have complete resolution of symptoms by adolescence or adulthood [28]. Respiratory syncytial virus (RSV) infection in lower respiratory tract in early childhood is a risk factor for the subsequent development of allergic sensitization such as wheezing up to age of 11 years [29]. Aoyagi et al. [30] reported that compared to age-matched controls, infants affected by RSV-bronchiolitis have lower frequencies of IFN-γ-producing γδ T cells in peripheral blood. Moreover, they noticed normalization of this frequency during the convalescent phase, suggesting that the defective IFN-γ production by these cells may play an important role in the development of asthma. However, it is too early to conclude whether the expansion of Vδ2Vγ9 T cells with age is associated with childhood asthma spontaneous remission by adolescence.

In adulthood, studies have also found the possible great impact of age and gender on the γδ T cell repertoires: in contrast to childhood, the absolute number of γδ T cells decreases, as the result of reduction of Vδ2, but not Vδ1 T cells. Besides, the number of total γδ T cells and Vδ2 T cells are both significantly higher in males than in females [31, 32]. It indicates that age- and gender-matched controls are essential for clinical studies of γδ T cell repertoires in patients.

The term “allergic march” refers to the natural history of atopic manifestations, which is characterized by a typical sequence of IgE antibody responses and clinical symptoms that appear early in life, persist over years or decades, and often remit spontaneously with age. Several studies have shown that the “new” allergy can occur throughout life; generally, allergy prevalence and severity tend to decrease after young adult life [33], and Th2-type responses may weaken with age [34]. Hansen et al. [35] found that immunization dose, sex, and age are highly influential on allergy
4. The Antigen Recognition of γδ T Cells in Allergy

Selective allergen recognition by TCR that binds specific regions of the antigen molecules is the priming and initiation of antigen-specific T cell immune responses. So far, more than 4000 substances in the environment, the vast majority of which are proteins, mostly enzymes, have been identified as allergens that elicit an IgE-mediated immune response in allergic diseases [42, 43]. In contrast, Th1-type cytokines (IL-4, -5, and -13) and thus enhance airway pathology by Th2-type cytokines IL-4, -5, and -13, which not only induce the synthesis of IgE but also recruit effector cells like eosinophils and basophils into the site of allergic inflammation [42]. However, inflammatory responses in allergic diseases are more complex than simple overexpression of Th2 cytokines. A recent hypothesis has been put forward to rely on...
that are dependent on classical help provided by $\alpha\beta$ T cells. An increase in $\gamma\delta$ T cells expressing Th2-type cytokines has been reported in bronchoalveolar lavage (BAL) fluids of allergen challenged asthmatic patients [57]. In addition to proinflammatory function, the $\gamma\delta$ T cells also engage as regulators of Th2 immunity [41], in particular regulating the IgE antibodies [3, 38, 40]. Svensson et al. [58] showed that $\gamma\delta$ T cell-deficient mice exhibited a diminished allergen specific IgE response compared with wild-type (WT) mice, indicating that $\gamma\delta$ T cells contribute to B cell secretion of allergen-specific IgE, either by promoting Ig class switch to IgE or by providing activation signals to differentiated IgE-producing cells. Likewise, Zuny-Amorim et al. [59] reported a low antigen specific IgE and IL-5 release and a decrease in T cell infiltration in the same mouse models. They further found that the response could be restored when IL-4 was administered, suggesting that $\gamma\delta$ T cells contribute to type 2-mediated airway inflammation by inducing IL-4 dependent IgE and IgG1 responses. In contrast, Lahn et al. [60] showed that $\gamma\delta$ T cells exert a suppressive role in the Th2 response to allergen challenge. Therefore, it is clear that $\gamma\delta$ T cells might have various, possibly opposing roles for CD4$^+$ T cells.

Studies have demonstrated that, in the airway, distinct subsets of $\gamma\delta$ T cells, defined by their expression of TCR-$\gamma$, seem to exhibit differential and sometimes opposed Th-like reactivities in allergen-induced allergic inflammation [7, 47]. In mouse models of allergic diseases, it has been shown that the V$\gamma$1$^+$ subsets can enhance AHR as well as levels of Th2 cytokines in the airways and eosinophilic infiltrates in the lungs [61, 62], and, in contrast, the V$\gamma$4$^+$ subset can be induced to inhibit AHR [63, 64]. Lahn et al. [64] selectively depleted either subset in the lungs (using aerosolized, inhaled anti-TCR Abs) following airway challenge and observed that AHR is altered in the predicted fashion; that is, depletion of V$\gamma$1$^+$ cells decreases and depletion of V$\gamma$4$^+$ cells increases AHR. After transferring few purified V$\gamma$1$^+$ cells into OVA/alum immunized TCR-$\delta^{-/-}$ mice, Huang et al. [65] observed the increase of the OVA-specific IgE responses, suggesting that individual enhancer cells are quite potent. However, the relative importance of $\gamma\delta$ T cells in human asthma remains to be determined.

It has been shown for some time that murine $\gamma\delta$ T cells become functionally competent in the thymus, particularly regarding the production of proinflammatory cytokines IFN-$\gamma$ and IL-17 [60]. McMenamin et al. [66] found that $\gamma\delta$ T cells regulate IgE responsiveness to inhaled antigens by high production of IFN-$\gamma$. By using mice immunized with recombinant vaccine virus expressing RSV F protein and challenged with live RSV, Dodd et al. [63] reported that V$\gamma$4$^+$ subsets are recruited into the lungs and produce IFN-$\gamma$ in a time-dependent manner. These studies suggest that antigen-specific $\gamma\delta$ T cells are able to suppress the pathogenic Th2 response in allergic asthma, whereas a recent study by Chen et al. [67] found that the serum levels of IL-4 and IL-13 in peripheral blood of children with AR and asthma markedly decrease while IFN-$\gamma$ increases after receiving SIT, suggesting that IFN-$\gamma$+$\gamma\delta$ T cells might exert their Th2 immunosuppression under certain conditions like

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**Figure 1:** A simplified paradigm illustrating where in the continuum of immune protection and homeostasis $\gamma\delta$ T cells fall in relation to innate NK cells and the adaptive $\alpha\beta$ T cells. Innate NK and adaptive $\alpha\beta$ T cells respond to the “missing self” and the “dangerous nonself,” respectively, while, between these two extremes, $\gamma\delta$ T cells respond to the “safe nonself” and deal with the inevitable “distressed self.” These different “selves” and the immuneresponse(s) that they trigger exist in a continuum and are modulated by the context in which they are presented. Besides, NK cells could contribute to responding to the “distressed self,” whereas $\alpha\beta$ T cells have some regulatory training to temper the response to the “safe nonself” (cited from [10]).

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the genetically determined barrier deficiency and disruption by environmental and endogenous proteases in the epithelial barrier (distressed self), which might result in the allergen uptake as a primary defect in the pathogenesis of allergic reactions [51]. It seems that allergy is both an epithelial disease and a disease of the immune system. Using an adoptive cell transfer approach, Jin et al. [52] found that NK and $\gamma\delta$ T cells (only V$\gamma$1V$\delta$5 subsets) are necessary for the acute stages of AHR in mice but not for the later airway eosinophilic inflammation. Another study on AHR demonstrated that NK cells secreted IL-4 and -13 to produce their effector function, but $\gamma\delta$ T cells did not have this effect [53]. In addition, $\gamma\delta$ T cells, similar to NK cells, express the NKG2D receptor that may contribute to effective stress-responses as well as immune surveillance, which may be relevant in the induction of food allergy [54]. These data suggest that the interaction of innate and adaptive immune cells and the impact of the inflammatory responses on this collaboration seem to be important and worthy of further research.

Abundant populations of $\gamma\delta$ T cells have been found in the epidermis of rodents [55]. The respiratory mucosa such as nasal mucosa, bronchial mucosa, and lung contain $\gamma\delta$ T cells as well [56]. This may be of importance in the remarkable resistance of the airway against environmental stimuli. Substantial evidence has been accumulated to indicate that $\gamma\delta$ T cells take part in Th2 immune responses. $\gamma\delta$ T cells themselves can not only take the function of follicular Th cells in certain responses but also can support responses
SIT. Our recent study showed that the serum levels of IL-17 and IL-23 in the AR patients were significantly higher than those in the healthy subjects, and positive correlations exist between the IL-17 and the IL-23 levels, as well as the IL-17 level and γδ γδ T frequencies [68]. Accordingly, we conjecture that the IL-23R+ IL-17γδ γδ T cells may promote αβ T cell-mediated traditional Th2 inflammation via producing abundant IL-17. In addition, IL-17-producing γδ γδ T cells could directly promote the development of other IL-17-producing T cells [69], and these innate IL-17-producing T cells are involved in sensing stress, injury, or pathogens and serve an immunoregulatory role at epithelial sites [63].

Gonçalves-Sousa et al. [70] reported that murine CD4+ CD25+ FOXP3+ regulatory T cells (Treg) abolish key effector functions and proliferation of γδ γδ T cells both in vitro and in vivo. They further showed that the suppression is dependent on cellular contact between Treg and γδ γδ T cells and is partially mediated by glucocorticoid-induced TNF receptor-related proteins. It reveals a novel mechanism, by which γδ γδ T-cell function is regulated, and suggests that endogenous Treg may prevent the desired effects of γδ γδ T cell-based immunotherapies. It has also been shown by Hahn et al. [71] that γδ γδ T cells affect the level of IL-10 in the airways and block their function resulting in an increase of Treg in the lung, which suggests that γδ γδ T cells might inhibit Treg function. While these data highlight the importance of understanding how the proinflammatory and immunoregulatory functions of γδ γδ T cells are regulated, the detailed processes remain poorly understood.

7. γδ γδ T Cells with the Prevention and Treatment of Allergic Diseases

γδ γδ T cells stimulated with biphosphonate compounds, which are clinically well tolerated and used for γδ γδ T cell expanders in vitro and in vivo, have been considered to be good candidates for cancer immunotherapy, because of their IFN-γ production and cytotoxic effect [72]. Therefore, the adoptive transfer of autologous γδ γδ T cells expanded in vitro might also be an effective strategy for IL-4-mediated allergy.

It has been shown that oral tolerance, which refers to the active state of nonresponsiveness to food and food protein intake, is a unique feature of the (gut-associated) mucosal immune system. And the defects in this process result in allergic sensitization to food proteins [73]. Most intestinal epithelial lymphocytes (IELs) in the mouse consist of γδ γδ T cells, which are localized in the paracellular space between intestinal epithelial cells at the luminal site of the basement membrane [74]. Mengel et al. [75] showed that treating mice with a TCR-δ-specific antibody results in impaired oral tolerance induction and that oral tolerance could be transferred by means of γδ γδ T cells. It suggests that targeting intestinal γδ γδ T cells may provide preventing and therapeutic strategies for food allergy. However, currently IELs are among the least studied cells in the process of allergic sensitization.

Studies have shown that many phosphoantigens and fungal immunomodulators play an important role in γδ γδ T cell-mediated immunotherapy. For example, (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate is characterized as a very potent agonist of Vγ9Vδ2 responses and could strengthen the principle of γδ γδ T cell based immunotherapy [76]. In contrast, Gonçalves-Sousa et al. [70] described that Treg could negatively modulate the γδ γδ T cell activities and stressed the importance of combining Treg inhibition with γδ γδ T cell activation for future immunotherapeutic strategies.

In animal models, chronic allergen challenge induces suppression of the Th2 response and reduces AHR and airway inflammation [77, 78]. Reductions of late-phase asthmatic responses to allergen after long-term allergen challenge have also been reported in clinical studies [79, 80]. Lahn et al. [64] indicated that the Vγ4+ subsets appear to mediate such suppressive effect of long-term allergen challenge on AHR. In addition, γδ γδ T cells could also suppress Th2-dependent IgE responses without affecting parallel IgG responses to inhaled antigens [66].

Taken together, γδ γδ T cells may have the potential to help alter the Th2-skewed immunity in patients with allergic diseases. Further accumulated studies to clarify the ability of γδ γδ T cells as an allergic immunotherapy candidate are thus called for.

8. Concluding Remarks

There is ample evidence that γδ γδ T cells are involved in allergy. Recent studies in humans and mice suggest that they can both drive and regulate allergic immune responses through different mechanisms. However, many aspects of the characteristics and role of γδ γδ T cells in allergy remain to be fully elucidated in near future, for instance, the exact effects of various γδ γδ T cell subsets on allergic inflammation; the underlying relations between blood- and mucosa-associated γδ γδ T cells; how age and gender influence the population, distribution, and function of γδ γδ T cells in allergic diseases; the specific regulatory mechanisms of γδ γδ T cells in allergy; how γδ γδ T cells could be applied to prevent and treat allergic diseases, and so on.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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