

Infiltration pattern of gammadelta T cells and its association with local inflammatory response in the nasal mucosa of patients with allergic rhinitis

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Background: gammadelta ($\gamma\delta$) T cells play important roles in allergic lower airway inflammation. However, little is known about their infiltration pattern in the nasal mucosa during upper airway inflammation. This study investigated $\gamma\delta$ T cell distribution in nasal tissues of allergic rhinitis (AR) patients and the relationship between $\gamma\delta$ T cells and other inflammatory cell types.

Methods: A total of 30 patients with septal deviation were examined, including 22 with and 8 without AR. The localization of $\gamma\delta$ T cells and other cells (eosinophils, neutrophils, mast cells, macrophages, B cells, cluster of differentiation [CD]4+ T cells, CD8+ T cells, regulatory T cells [Tregs], interferon [IFN]- γ + cells, interleukin [IL]17+ cells, and IL10+ cells) was evaluated by histological analysis and immunohistochemistry. T helper cell (Th)1/Th2/Th17 and Treg gene expression was analyzed by quantitative polymerase chain reaction (PCR).

Results: $\gamma\delta$ T cells were localized in the epithelium or subepithelial region of nasal mucosa, and their infiltration was higher in AR patients relative to control subjects. The

number of $\gamma\delta$ T cells was associated with the presence of eosinophils, macrophages, mast cells, B cells, CD8+ T cells, Forkhead box (Fox)p3+ Tregs, IL17+ cells, and IL10+ cells but not of neutrophils or IFN- γ + cells. The messenger RNA (mRNA) level of a $\gamma\delta$ T cell subunit was positively correlated with those of Th1 genes (T-bet and IFN- γ), Th2 cytokine (C-C motif chemokine ligand 18), and Treg genes (Foxp3 and IL10).

Conclusion: $\gamma\delta$ T cells play multiple roles in mucosal inflammation in AR including immune surveillance and adaptive and innate immune responses. © 2019 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; mucosa inflammation; gammadelta T cells; infiltration pattern; local inflammatory response

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Allergic rhinitis (AR) is a complex chronic upper airway inflammatory disease characterized by the infiltration of multiple inflammatory cells such as T cells, eosinophils, neutrophils, and mast cells. T cells perform essential functions in allergic airway diseases by regulating different T cell subtypes that produce a variety of cytokines. Depending on the antigen recognition receptor that is expressed, T cells can be categorized as alphabeta ($\alpha\beta$) T or gammadelta ($\gamma\delta$) T cells. The former can be divided into cluster of differentiation (CD)4+ and CD8+ T cells. Most studies have focused on CD4+ T cell subsets such as T helper (Th)1, Th2, and Th17 cells and regulatory T cells (Tregs), which play important roles in AR.

Compared with conventional $\alpha\beta$ T cells, $\gamma\delta$ T cells are abundant in various tissues and are essential for

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TABLE 1. Patient characteristics and histopathological evaluation

Characteristic	Healthy controls	AR patients	P
Sample size (n)	8	22	NA
Age (years), median (1st–3rd quartile)	35 (22–47)	32 (28–39)	NS
Sex (M/F), n	5/3	10/12	NA
Number of immune cells (median, 1st–3rd quartile) ^a			
$\gamma\delta$ T cell	3.8 (3.0–6.8)	22.0 (12.5–34.0)	<0.001
Eosinophil	1.0 (0.8–1.0)	14.0 (6.0–31.0)	<0.001
Neutrophil	1.8 (1.3–14.3)	5.8 (3.5–14.5)	NS
Macrophage	5.3 (3.5–8.0)	24.5 (13.5–78.5)	0.002
Mast cell	6.3 (3.8–9.0)	20.0 (15.0–23.5)	<0.001
B cell	18.5 (6.3–26.0)	72.3 (47.0–115.5)	<0.001
CD4+ T cell	19.0 (7.5–32.3)	33.8 (19.0–61.5)	NS
CD8+ T cell	16.0 (6.5–41.8)	47.5 (34.0–76.0)	0.01
Regulatory T cell	6.8 (3.0–14.5)	10.8 (5.5–26.0)	NS
Number of cells with positive cytokine staining, median (1st–3rd quartile) ^a			
IFN- γ + cell	2.8 (1.5–4.8)	6.5 (4.0–9.5)	0.007
IL17+ cell	1.8 (1.3–2.5)	4.0 (2.5–7.5)	0.004
IL10+ cell	18.0 (14.5–23.8)	40.5 (34.0–47.5)	0.001

^aThe number of positively stained cells were counted at high magnification ($\times 400$), and 3 randomly selected fields were analyzed.

CD = cluster of differentiation; IFN = interferon; IL = interleukin; M/F = male/female; NA = not applicable/not available; NS = not significant.

maintaining mucosal homeostasis in the gastrointestinal and respiratory tracts.¹ The localization of $\gamma\delta$ T cells suggests an important role in innate immunity. Several studies have revealed that $\gamma\delta$ T cells are activated following the recognition of certain pathogens and are responsible for producing cytokines with cytotoxic activity.¹ On the other hand, $\gamma\delta$ T cells also accumulate in tissues during allergic inflammation. Th2-related chemokines (eg, C-C motif chemokine ligand [CCL]2) or mediators (eg, leukotriene B4) can facilitate the migration of $\gamma\delta$ T cells² as they rapidly respond to antigens during the early phase of inflammation, and experimental allergic animal models indicate that the number of $\gamma\delta$ T cells remains high during the late phase of inflammation and that these cells coordinate eosinophil influx.³ In addition to their pathological functions in allergic diseases, $\gamma\delta$ T cells also negatively regulate airway hyperresponsiveness in asthmatic mice, suggesting a role in the regulation of pulmonary homeostasis.⁴ Additionally, $\gamma\delta$ T cell counts are elevated in the bronchoalveolar lavage fluid of asthmatic subjects.^{5,6} Thus, $\gamma\delta$ T cells are involved in multiple aspects of allergic asthma.

Compared with lower airway inflammation, the functions of $\gamma\delta$ T cells in chronic nasal inflammation (eg, chronic rhinosinusitis and AR) are poorly understood. A recent study demonstrated that the messenger RNA (mRNA) levels of $\gamma\delta$ T cell V γ 1 genes were upregulated in nasal polyps, which was associated with eosinophilic infiltration

and edematous changes.⁷ Our previous examination of peripheral blood mononuclear cells revealed a dynamic equilibrium in the number of $\gamma\delta$ T cell subfamily members in AR patients before and after allergen-specific immunotherapy.⁸ However, little is known about $\gamma\delta$ T cells in the nasal mucosa. To address this issue, the current study characterized $\gamma\delta$ T cell distribution and abundance and its relationship with other inflammatory cell types in the nasal tissue of AR patients.

Patients and methods

Patients and tissue samples

A total of 30 patients with septal deviation were enrolled in the study, including 22 with AR and 8 without AR (AR and control groups, respectively). AR patients were diagnosed by an ear, nose, and throat/allergy specialist according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.⁹ The inclusion criteria were as follows: (1) significant nasal symptoms (nasal itching, sneezing, nasal obstruction, and rhinorrhea); (2) allergic sensitization to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and common pollens confirmed by a skin-prick test; and (3) age older than 18 years old. Patients with allergic asthma or chronic rhinosinusitis were excluded. The demographics of the study population are summarized in Table 1. Biopsies of inferior turbinate mucosa were

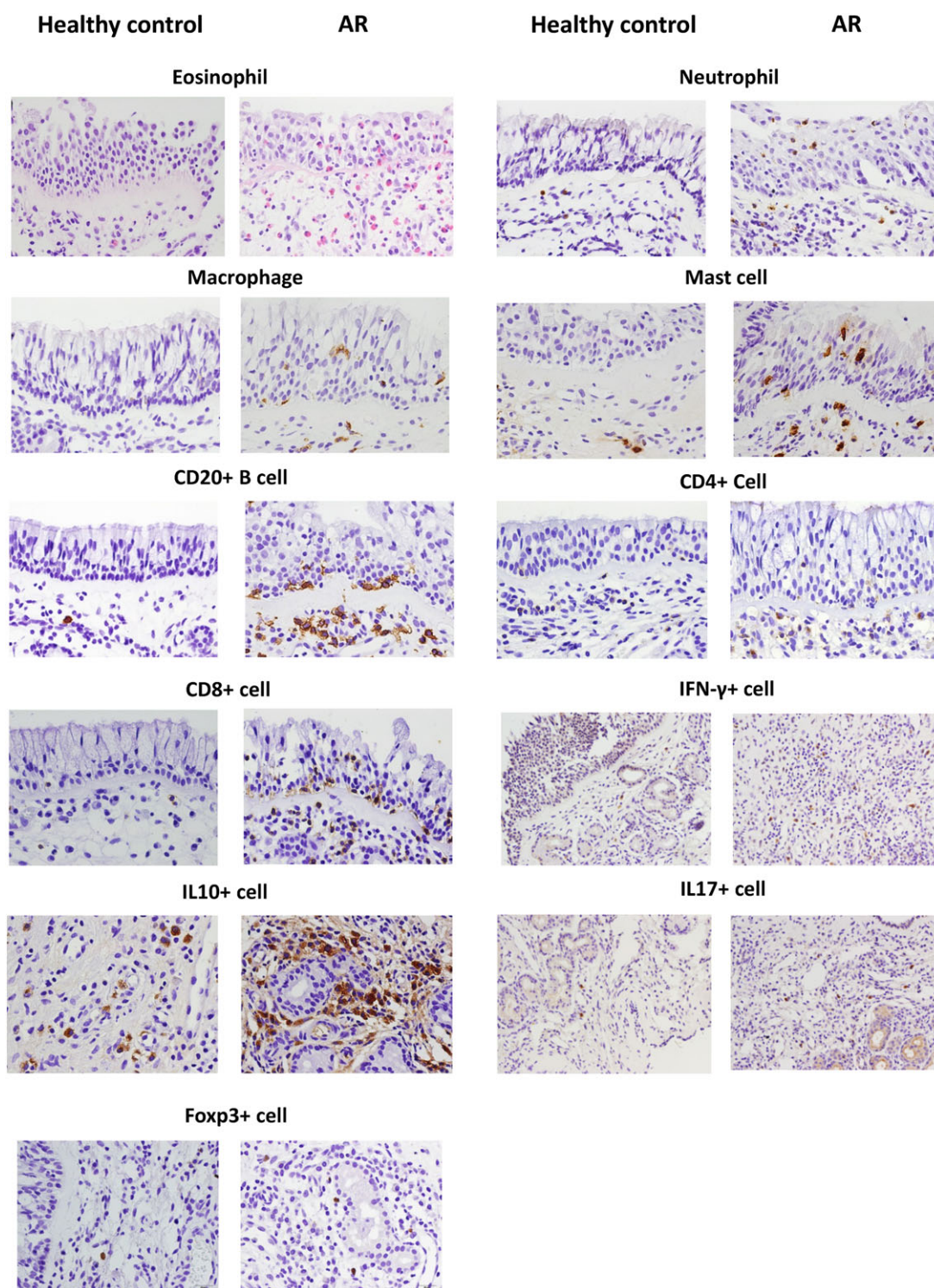


FIGURE 1. Representative images of histochemical and immunohistochemical staining showing the infiltration of eosinophils, neutrophils, macrophages (CD68+), mast cells, B cells (CD20+), CD4+ cells, CD8+ cells, IFN- γ + cells, IL10+ cells, and IL17+ cells. The nasal mucosa of AR patients showed significantly higher infiltration of multiple inflammatory cell types. Original magnification: $\times 400$. AR = allergic rhinitis; CD = cluster of differentiation; IFN = interferon; IL = interleukin.

obtained during septal plastic surgery. None of the subjects had been treated with any oral or nasal glucocorticoid steroids or antihistamines or had received allergen-specific immunotherapy, and none had any sinus symptoms,

concurrent upper respiratory infections, or other systemic diseases. All subjects were recruited from the Department of Otolaryngology of the Third Affiliated Hospital, Sun Yat-Sen University. Written consent was obtained from

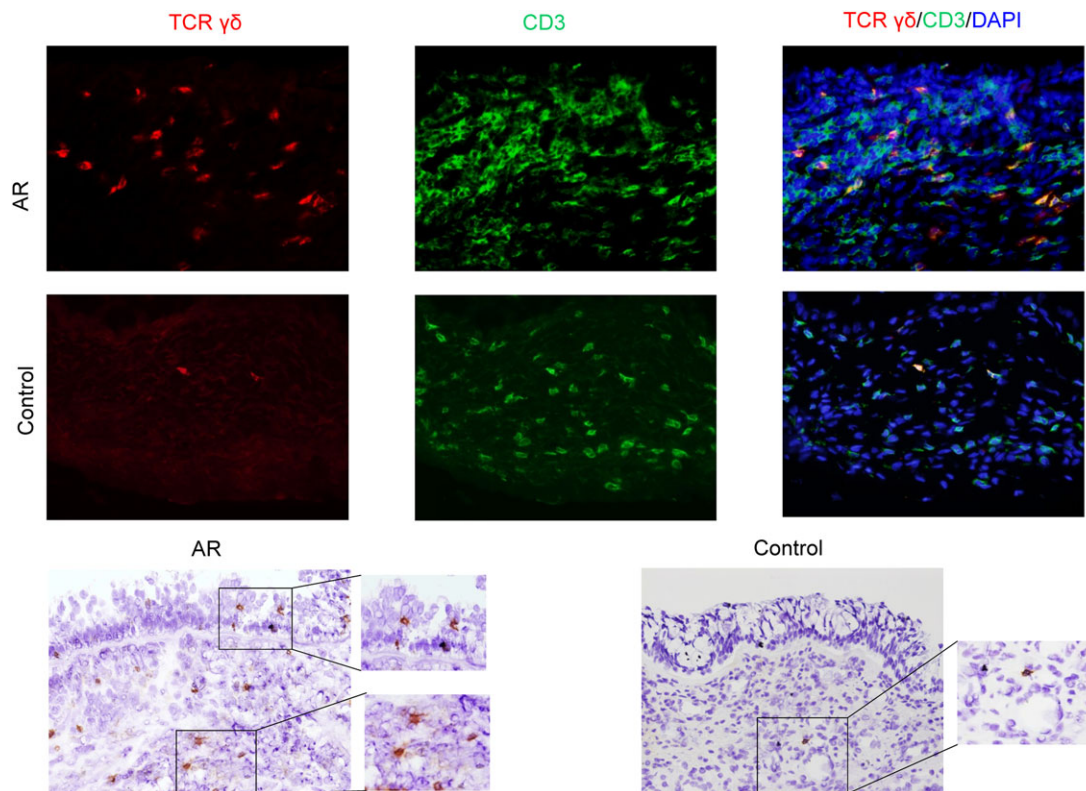


FIGURE 2. Representative images of immunofluorescence and immunohistochemical staining showing the infiltration and distribution of $\gamma\delta$ T cells, all of which were CD3+ and distributed inside or close to the epithelium of the nasal mucosa. Original magnification: $\times 400$. CD = cluster of differentiation.

all participants, and the study protocol was approved by the Institutional Review Boards of Sun Yat-Sen University [(2012)2-15].

Histological, immunohistochemical, and immunofluorescence analyses

Nasal tissue samples were fixed with formalin and embedded in paraffin and sectioned with a microtome (Leica, Wetzlar, Germany). A portion of each sample was frozen in liquid nitrogen and embedded in optimal cutting temperature medium. The sections were stained with hematoxylin and eosin (H&E) for general histological evaluation and eosinophil infiltration analysis. $\gamma\delta$ T cells, neutrophils, macrophages, mast cells, B cells, CD3+ cells, CD4+ T cells, CD8+ T cells, Tregs, interferon (IFN)- γ + cells, interleukin (IL)10+ cells, and IL17+ cells were detected by immunohistochemistry using the following antibodies: mouse monoclonal anti-human neutrophil elastase (Clone NP57) (Dako A/S, Glostrup, Denmark); mouse monoclonal anti-human CD68 (Clone KP1), mouse monoclonal anti-human mast cell tryptase (Clone AA1), mouse monoclonal anti-human CD4 (Clone BC/1F6), mouse monoclonal anti-human Forkhead box (Fox)p3 (Clone 236A/E7), rabbit polyclonal anti-human IFN- γ , rabbit polyclonal anti-human IL10, and rabbit polyclonal anti-human IL17A (all from Abcam, Cambridge, UK); mouse monoclonal anti-human CD20 (Clone L26) (eBioscience, San Diego, CA); and rabbit

monoclonal anti-human CD3 (Clone SP7), mouse monoclonal anti-human T cell receptor (TCR) $\gamma\delta$ (Clone 5A6.E91), and mouse monoclonal anti-human CD8 (Clone C8/144B) (all from Thermo Fisher Scientific, Waltham, MA). Co-localization of 2 different cell types was evaluated by double immunofluorescence labeling. $\gamma\delta$ T cell staining was performed on frozen sections.

For both immunohistochemical and immunofluorescence analyses, sections were processed with Target Retrieval Buffer (Dako A/S) and then blocked with 10% serum and incubated overnight at 4°C with primary antibodies. To visualize the immunoreaction, the sections were incubated with DAKO EnVision+ System-HRP (Dako A/S) for 30 minutes at room temperature and developed using diaminobenzidine as a substrate. For double immunofluorescence labeling, a rabbit monoclonal antibody against CD3 was combined with a mouse monoclonal antibody against TCR $\gamma\delta$. The sections were incubated with the primary antibodies followed by Alexa Fluor 488-conjugated secondary antibody or Alexa Fluor 594-conjugated secondary antibody (goat-anti mouse or rabbit immunoglobulin G [IgG] (H+L); Molecular Probes, Carlsbad, CA) in the dark at room temperature for 1 hour. The sections were mounted with Antifade reagent with 4',6-diamidino-2-phenylindole (DAPI) (Molecular Probes). Species-matched and subtype-matched antibodies were used as negative controls for both immunohistochemical and immunofluorescence labeling.

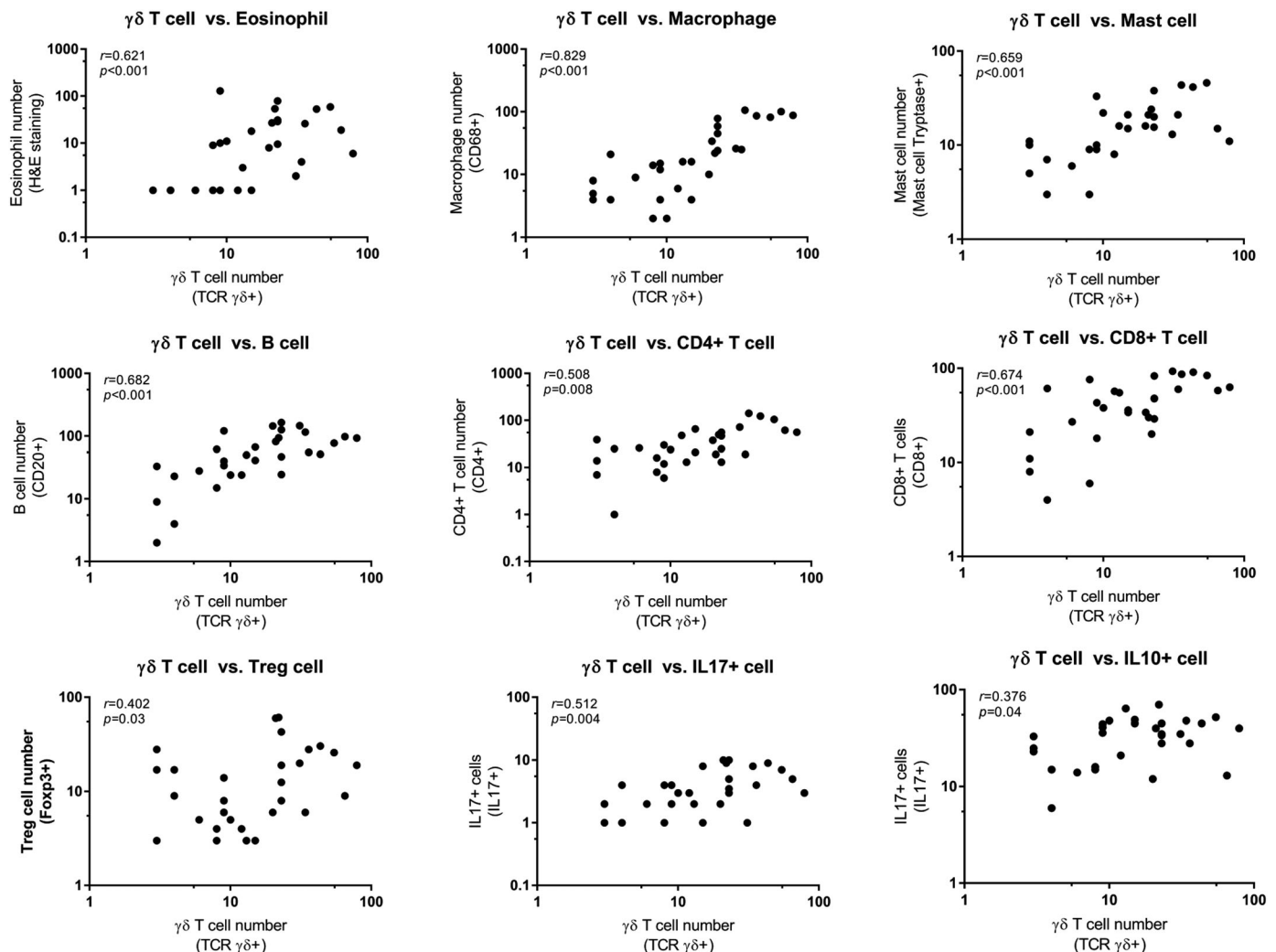


FIGURE 3. Correlation between $\gamma\delta$ T cells and eosinophils, macrophages, mast cells, B cells, CD4+ T cells, CD8+ T cells, Tregs, IL17+ cells, and IL10+ cells evaluated with Spearman's rank correlation coefficient (r). $\gamma\delta$ T cells were closely associated with all cell types except for neutrophils and IFN- γ + cells. CD = cluster of differentiation; IFN = interferon; IL = interleukin; Treg = regulatory T cell.

Evaluation of inflammatory cell infiltration

Eosinophils, neutrophils, $\gamma\delta$ T cells, macrophages, mast cells, CD20+ B cells, CD4+ T cells, CD8+ T cells, Tregs, IFN- γ + cells, IL17+ cells, and IL10+ cells were analyzed in H&E-stained sections or by immunohistochemical detection. Each of the cell types was counted in 3 random high-powered fields (magnification $\times 400$) in each nasal tissue section. Two independent observers who were blinded to the subject's clinical information performed the counts.

mRNA expression of target genes in nasal tissues

A portion of nasal mucosa tissue sample from AR patients and control subjects was stored in RNAlater solution (Applied Biosystems, Foster City, CA). Because of the small size of the tissue biopsy, RNA extraction was not performed on tissues from 6 of the AR patients. Total cellular RNA was isolated from the tissue samples with a RiboPure Kit

(Applied Biosystems) and reverse transcribed into complementary DNA (cDNA). The expression of cell type-specific genes and related cytokines was analyzed by quantitative real-time polymerase chain reaction (PCR). Gene expression levels were determined with the TaqMan gene expression assay (Applied Biosystems), including the delta subunit of the CD3 complex (CD3D, Hs00174158_m1), gamma subunit of the CD3 complex (CD3G, Hs00962186_m1), T-bet (Hs00203436_m1), GATA3 (Hs00231122_m1), RAR-related orphan receptor C (RORC, Hs01076112_m1), Foxp3 (Hs01085834_m1), IFNG (Hs00989291_m1), CCL13 (Hs00234646_m1), CCL18 (Hs00268113_m1), IL17A (Hs00174383_m1), transforming growth factor β (TGFB1, Hs00998133_m1), IL10 (Hs00961622_m1), matrix metalloproteinase (MMP)7 (Hs00159163_m1), and MMP9 (Hs00234579_m1). Relative gene expression levels were calculated with the comparative $2^{-\Delta\Delta C_t}$ method¹⁰ using glyceraldehyde 3-phosphate dehydrogenase as the internal control gene.

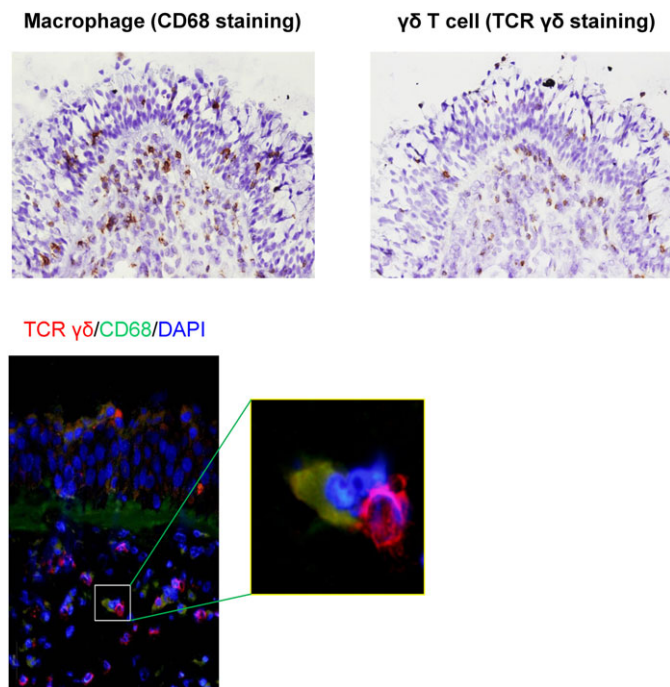


FIGURE 4. Representative images and immunofluorescence and immunohistochemical staining. $\gamma\delta$ T cells (TCR $\gamma\delta$) and macrophages (CD68) were colocalized in consecutive sections. Original magnification: $\times 400$. CD = cluster of differentiation; TCR = T cell receptor.

Statistical analysis

Data were analyzed using SPSS v.23.0 software (IBM Corp., Armonk, NY). The Mann-Whitney 2-tailed test was used to compare the AR and control groups in terms of cell infiltration and mRNA levels of target genes. Correlation analyses between $\gamma\delta$ T cells and other inflammatory cell types or between mRNA levels of CD3D/CD3G and other selected genes were performed with Spearman's rank correlation coefficient (r). Values of $p < 0.05$ were considered statistically significant.

Results

Inflammatory cell infiltration in AR patients

The characteristics of inflammatory cell infiltration in AR patients and control subjects are summarized in Table 1. In healthy controls there were few $\gamma\delta$ T cells, which were ranked 7th out of the 9 leukocyte types in terms of abundance; in contrast, in AR patients $\gamma\delta$ T cells ranked 5th and were more abundant than eosinophils (Table 1). With the exception of neutrophils and CD4+ T cells, the nasal mucosa of AR patients had higher infiltration of multiple inflammatory cell types including eosinophils, $\gamma\delta$ T cells, macrophages, mast cells, B cells, CD8+ T cells, Tregs, IFN- γ + cells, IL17+ cells, and IL10+ cells (Fig. 1). $\gamma\delta$ T cells were distributed in the epithelium or nearby areas in the nasal mucosa, and the median $\gamma\delta$ T cell number was 5.8-fold higher in the AR group than in the control group (Fig. 2).

Relationship between $\gamma\delta$ T and other inflammatory cell types

The number of $\gamma\delta$ T cells was significantly associated with the number of eosinophils ($r = 0.621$, $p < 0.001$), macrophages ($r = 0.829$, $p < 0.001$), mast cells ($r = 0.659$, $p < 0.001$), CD20+ B cells ($r = 0.682$, $p < 0.001$), CD8+ T cells ($r = 0.674$, $p < 0.001$), Foxp3+ Tregs ($r = 0.402$, $p = 0.03$), IL17+ cells ($r = 0.512$, $p = 0.004$), and IL10+ cells ($r = 0.376$, $p = 0.04$) but not the number of neutrophils or IFN- γ + cells (Fig. 3). $\gamma\delta$ T cell and macrophage counts were highly correlated, and immunofluorescence labeling of consecutive sections revealed close localization of (or contact between) these 2 cell types in the nasal mucosa (Fig. 4).

Expression of cell type-specific genes and relationship to $\gamma\delta$ T cells

The mRNA expression levels of cell type-specific genes and cytokines were evaluated in the nasal mucosa of AR patients ($n = 16$) and control subjects ($n = 8$). The expression levels of $\gamma\delta$ T cell subunits (CD3D and CD3G) and a Treg transcription factor (Foxp3) were upregulated in the AR group compared to controls, whereas the expression of Th1/Th2/Th17-specific transcription factors did not differ between the 2 groups (Fig. 5). Th2 cytokines (CCL13 and CCL18) and tissue remodeling factors (TGFB1, MMP7, and MMP9) were upregulated in AR relative to control tissues. However, the expression of cytokines specific for Th1 (IFN- γ), Th17 (IL17A), and Tregs (IL10) was similar between the 2 groups (Fig. 5).

CD3D and CD3G levels were closely related ($r = 0.927$, $p < 0.001$), and a correlation analysis revealed that expression of CD3D was positively correlated with that of Th1 genes (T-bet, $r = 0.763$, $p < 0.001$; IFN- γ , $r = 0.437$, $p = 0.03$), Th2 cytokines (CCL18, $r = 0.539$, $p = 0.006$), Treg genes (Foxp3, $r = 0.857$, $p < 0.001$; IL10, $r = 0.648$, $p < 0.001$), and tissue remodeling genes (MMP9, $r = 0.638$, $p < 0.001$) (Fig. 6).

Discussion

The results of this study demonstrate that $\gamma\delta$ T cells are more abundant in the nasal mucosa of AR patients compared with control subjects, and that $\gamma\delta$ T cell number and distribution in patients are positively correlated with those of a variety of other leukocytes that frequently infiltrate into the nasal mucosa. Furthermore, a positive correlation was observed between the transcript level of a $\gamma\delta$ T subunit and Th1/Th2/Treg cytokines or tissue remodeling factors. Although details of the relationship between $\gamma\delta$ T cells and other leukocyte types remain unclear, our data suggests that $\gamma\delta$ T cells play an essential role in mucosal inflammation in AR patients and may regulate innate and adaptive immune responses and their interactions.

Our results confirm that $\gamma\delta$ T cells are resident leukocytes of the nasal mucosa and that their numbers were

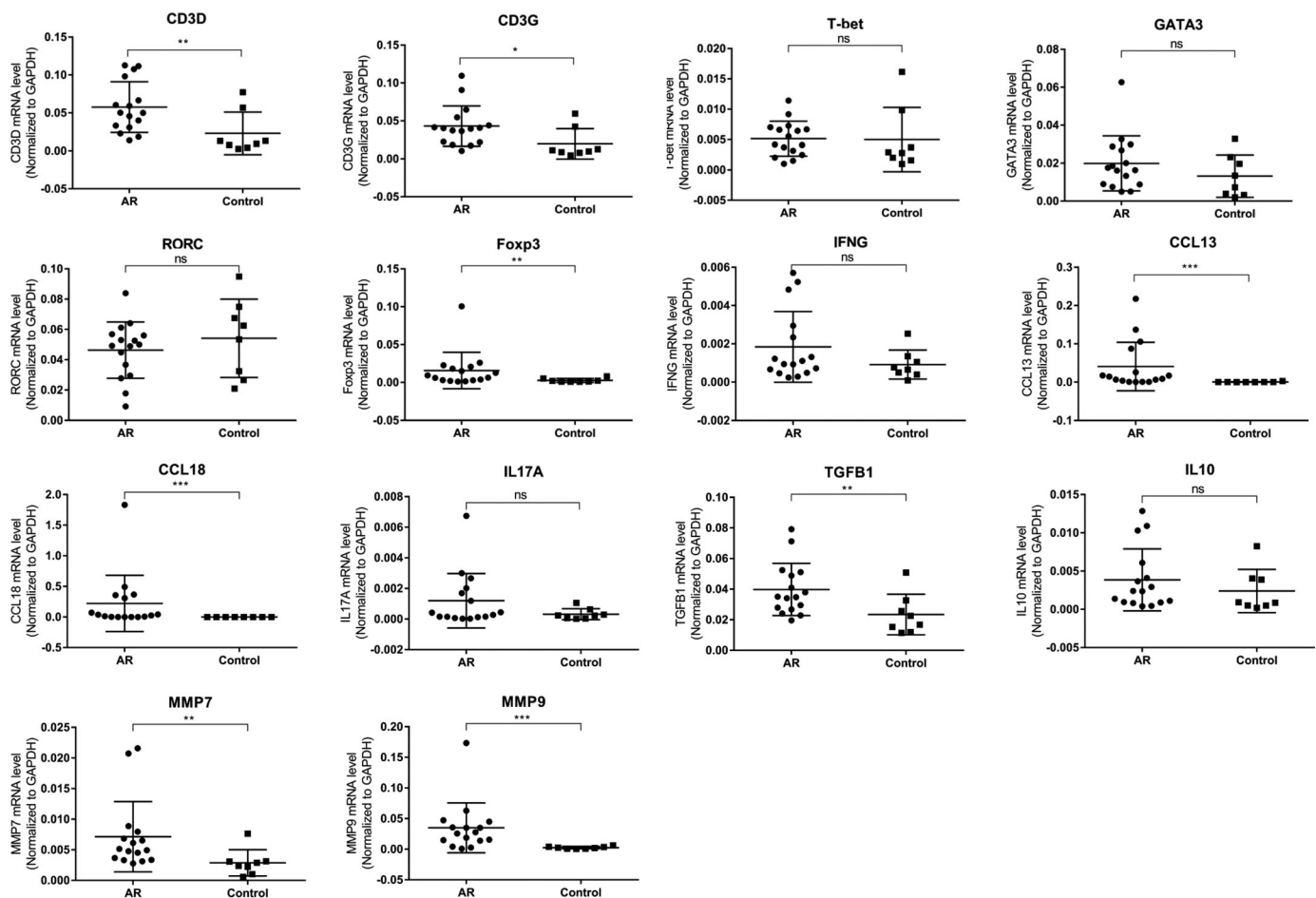


FIGURE 5. Quantitative analysis of mRNA levels by real-time reverse transcription-PCR for $\gamma\delta$ T cell subunits (CD3D and CD3G), T-bet, GATA3, RORC, Foxp3, IFNG, CCL13, CCL18, IL17A, TGFB1, IL10, MMP7, and MMP9 in tissues from control subjects and AR patients. Statistically significant differences were observed in the expression of $\gamma\delta$ T cell subunits (CD3D and CD3G), Foxp3, CCL13, CCL18, TGFB1, MMP7, and MMP9 between the 2 groups with the Mann-Whitney 2-tailed test. CCL = C-C motif; CD = cluster of differentiation; chemokine ligand; Fox = forkhead box; GATA = globulin transcription factor; IFN = interferon; IL = interleukin; mRNA = messenger RNA; PCR = polymerase chain reaction; ROR = retinoic acid–related orphan receptor; TGF = transforming growth factor.

increased under inflammatory conditions. The cells were particularly enriched inside or beneath the epithelium, implying that they are a first line of defense against noxious external stimuli (eg, pathogens) that cause cellular stress. $\gamma\delta$ T cell infiltration was highly correlated with the presence of macrophages, and immunofluorescence analysis revealed their close localization and possible contact between the 2 cell types. $\gamma\delta$ T cells can induce or activate macrophage-mediated innate immunity during pathogen infection or in response to environmental factors.^{11,12} Macrophages also express multiple ligands for TCR $\gamma\delta$ and may have reciprocal effects on $\gamma\delta$ T cells.^{13,14} $\gamma\delta$ T cells may also cooperate with CD8+ cells in cytotoxic processes, given their colocalization in the nasal mucosa. Thus, $\gamma\delta$ T cells have a close relationship with the major sentinel cells (macrophages and CD8+ cells) of the airway mucosa and are likely involved in innate immunity or immune surveillance in this tissue.^{15,16}

Tissue eosinophilia is a hallmark of allergic diseases including AR and asthma. $\gamma\delta$ T cells activated by

invading pathogens or danger signals produce a wide range of chemokines/cytokines such as IL-5 and CCL11 or inflammatory peptides that are important for eosinophil migration.¹⁷ Our results showed a parallel accumulation of $\gamma\delta$ T cells and eosinophils in nasal tissues and a positive correlation between the mRNA levels of a $\gamma\delta$ T cell subunit and Th2 cytokine (CCL18). Similar results have been reported in nasal polyps, showing that the level of V γ 1+ $\gamma\delta$ T cells was higher in eosinophilic polyp than those without eosinophilia.¹⁸ These results provide evidence that $\gamma\delta$ T cells coordinate eosinophil influx and are involved in the Th2 response during the late phase of allergic inflammation.¹⁷ $\gamma\delta$ T cells were also found to be associated with the infiltration of B cells and mast cells in the mucosa from AR patients. Although $\gamma\delta$ knockout mice exhibit defects in IgE response and B cell migration with reduced eosinophilia in allergic airway inflammation, a direct functional interaction between $\gamma\delta$ T cells and B cells has not been demonstrated.¹⁹ Moreover, there is currently no evidence for a functional relationship between $\gamma\delta$ T cells

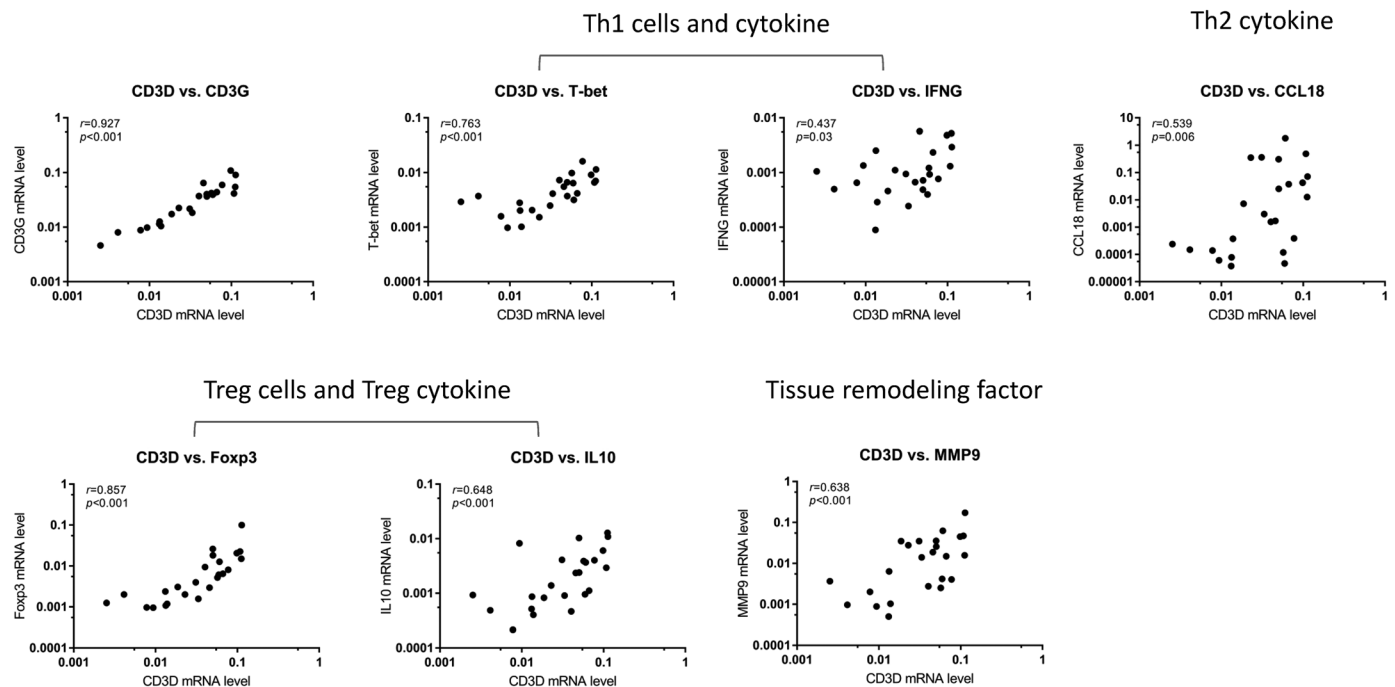


FIGURE 6. Correlations between mRNA levels of CD3D and CD3G, T-bet, IFN- γ , CCL18, Foxp3, IL10, and MMP9 were evaluated with Spearman's rank correlation coefficient (r). The expression of CD3D was positively correlated with that of Th1 genes and tissue remodeling genes. CCL = C-C motif chemokine ligand; CD = cluster of differentiation; Fox = forkhead box; IFN = interferon; IL = interleukin; MMP = matrix metalloproteinase; mRNA = messenger RNA; Th1 = T helper 1.

and mast cells, suggesting that they may indirectly interact following eosinophilic inflammation in AR. Our results indicate that $\gamma\delta$ T cells are required for Th2-skewed adaptive immunity during allergic inflammation.

We also observed a positive correlation between mRNA levels of a $\gamma\delta$ T cell subunit and Foxp3 and IL10, implying that $\gamma\delta$ T cells regulate Foxp3⁺ Tregs and IL10⁺ cells in the nasal mucosa. Although the role of $\gamma\delta$ T cells in homeostatic regulation of the immune response has been described in other inflammatory diseases,²⁰ there are no reports of a interaction between $\gamma\delta$ T cells and Tregs in airway allergic inflammation.

IL-17 is the representative cytokine of Th17 cells although it is also produced by other cells types such as $\gamma\delta$ T cells, epithelial cells, and natural killer cells in the mucosa of the airway or gastrointestinal tract.²¹ IL-17-producing cells both positively and negatively regulate Th2 response in allergic inflammation²²; these opposite functions may be shaped by the various IL-17 cell sources.²³ In addition, previous study reported that $\gamma\delta$ T cells were positively correlated with Th17 cells in peripheral blood from patients with AR.²⁴ In this study we further observed a positive correlation between IL-17⁺ cells and $\gamma\delta$ T cells in the local tissues from AR patients. Although we could not distinguish IL-17⁺ $\gamma\delta$ T cells from other IL-17-expressing cell types, these results support the possibility that $\gamma\delta$ T cells

are involved in IL-17-mediated pro-inflammatory responses or have a protective function during allergic inflammation, although the underlying mechanisms remain to be further determined.

This study had 2 major limitations. First, given the limited number of tissue biopsies that were obtained from AR patients and control subjects, we were unable to perform flow cytometry experiments to separate different subsets of $\gamma\delta$ T cells or analyze the production of cytokines such as IL-17 and IFN- γ by $\gamma\delta$ T cells. Second, we did not establish any functional correlations between $\gamma\delta$ T cells and other immune cell types and cytokines. Nevertheless, our results reveal the $\gamma\delta$ T cell infiltration profile and show for the first time the relationship between $\gamma\delta$ T cells and a variety of other immune cell types in the nasal mucosa. These findings indicate that $\gamma\delta$ T cells participate in both innate and adaptive immune responses and may have a protective function in allergic inflammation. Thus, therapeutic strategies targeting $\gamma\delta$ T cells may be effective for the treatment of AR.

Conclusion

$\gamma\delta$ T cells play multiple roles in mucosal inflammation in AR including immune surveillance and adaptive and innate immune responses. ④

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