

IgE-dependent enhancement of Th2 cell-mediated allergic inflammation in the airways

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SUMMARY

T helper 2 (Th2) cell-derived cytokines, including interleukin (IL)-4, IL-5 and IL-13, play important roles in causing allergic airway inflammation. In contrast to Th2 cells, however, the role of IgE and mast cells in inducing allergic airway inflammation is not understood fully. In the present study, we addressed this point using transgenic mice expressing trinitrophenyl (TNP)-specific IgE (TNP-IgE mice), which enable us to investigate the role of IgE without the influence of antigen-specific T cell activation and other immunoglobulins. When the corresponding antigen, TNP-BSA, was administered intranasally to TNP-IgE mice, a large number of CD4⁺ T cells were recruited into the airways. In contrast, TNP-BSA administration did not induce eosinophil recruitment into the airways or airway hyperreactivity. Furthermore, when ovalbumin (OVA)-specific Th2 cells were transferred to TNP-IgE mice and the mice were challenged with inhaled OVA, TNP-BSA administration increased OVA-specific T cell recruitment and then enhanced Th2 cell-mediated eosinophil recruitment into the airways. These results indicate that IgE-induced mast cell activation principally induces CD4⁺ T cell recruitment into the airways and thus plays an important role in enhancing Th2 cell-mediated eosinophilic airway inflammation by recruiting Th2 cells into the site of allergic inflammation.

Keywords eosinophils IgE mast cells transgenic mice

INTRODUCTION

Allergic airway inflammation is a cardinal feature of asthma and is associated with intense eosinophil and CD4⁺ T cell infiltration in the airways, and the chronic inflammatory process causes epithelial damage and airway hyperreactivity (AHR) [1–3]. It has been shown that T helper 2 (Th2) cells and their cytokines such as interleukin (IL)-4, IL-5 and IL-13 play important roles in inducing allergic airway inflammation [2,4,5]: IL-5 mediates antigen-induced eosinophil recruitment into the airways [6,7] and IL-13 induces goblet cell hyperplasia and AHR [8,9].

In addition to Th2 cell-mediated allergic inflammation, IgE-dependent activation of mast cells is suggested to be involved in the pathogenesis of asthma [10–13]. IgE cross-linking by specific antigens triggers the activation of mast cells, resulting in the synthesis and release of a variety of mediators and cytokines that

induce the early phase asthmatic response [12,13]. However, the role of IgE and mast cells in allergic airway inflammation and AHR is not well defined. While it has been demonstrated that features of asthma, including eosinophilic airway inflammation and AHR, can be elicited in the absence of IgE antibodies [14–16] or mast cells [17], it has been shown recently that mast cells play an important role in antigen-induced eosinophil recruitment into the airways and AHR in the situation in which mice are sensitized and challenged with antigens under weak protocols but not under strong protocols [18,19]. The fact that antigen sensitization and challenges induce IgE production, Th2 cell activation and cytokine production and eosinophilic inflammation altogether makes it difficult to evaluate the role of IgE and mast cells in allergic airway inflammation and AHR in asthma [1,20,21]. Thus, the role of IgE-dependent mast cell activation in inducing allergic airway inflammation and AHR still remains to be determined.

To determine whether IgE-dependent mast cell activation induces allergic airway inflammation and AHR, we examined the effect of IgE cross-linking by antigens on airway inflammation using trinitrophenyl (TNP)-specific IgE transgenic mice (TNP-IgE mice) [22], which enables us to investigate the role of IgE

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without the influence of antigen-specific T cell activation and other immunoglobulins. Our results indicate that IgE-dependent mast cell activation induces CD4⁺ T cell but not eosinophil recruitment into the airways and thus enhances Th2 cell-mediated eosinophilic airway inflammation by recruiting Th2 cells into the site of allergic inflammation.

MATERIALS AND METHODS

Mice

TNP-specific IgE transgenic mice (TNP-IgE mice) [22] with a BALB/c background and littermate wild-type (WT) mice were used in this study. Ovalbumin (OVA)-specific TCR transgenic mice (DO11·10 mice) with a BALB/c background were described previously [23]. All experiments were performed according to the NIH guidelines.

Antigen-induced airway inflammation in TNP-IgE mice

To determine whether IgE cross-linking by a relevant antigen induces airway inflammation, polyvalent TNP-BSA solution in saline (the molar ratio of TNP:BSA = 22:1, 6·7 mg/ml, 80 µl/mouse) [22] was administered intranasally to TNP-IgE mice or WT mice. As a control, BSA solution (6·7 mg/ml) was used. At indicated times after TNP-BSA or BSA administration, the number of lymphocytes, eosinophils, neutrophils and macrophages in bronchoalveolar lavage fluid (BALF) was evaluated as described previously [24]. A fraction of cells were subjected to a flow cytometric analysis for surface phenotyping of CD4, CD8 and B220 [24]. The expression of CD25 and CD69 on CD4⁺ T cells was also evaluated using the corresponding antibodies (BD PharMingen, San Diego, CA, USA).

To determine whether prostaglandins are involved in IgE-dependent airway inflammation, we examined the effect of acetylsalicylic acid, a well-defined cyclooxygenase inhibitor, on antigen-induced airway inflammation in TNP-IgE mice. TNP-IgE mice were injected intraperitoneally with acetylsalicylic acid (3 or 6 mg/mouse in 0·5 ml of saline) at 30 min before the intranasal TNP-BSA administration and the number of lymphocytes, eosinophils, neutrophils and macrophages in BALF was evaluated at 48 h after TNP-BSA administration. We also examined the effect of a cysteinyl leukotriene 1 receptor antagonist pranlukast and anti-tumour necrosis factor (TNF)- α antibody on antigen-induced airway inflammation in TNP-IgE mice. TNP-IgE mice were injected intraperitoneally with pranlukast (75 µg/mouse in 0·2 ml of saline) (Ono Pharmaceutical, Osaka, Japan) or goat antimouse TNF- α antibody [75 µg/mouse in 0·2 ml of phosphate buffered saline (PBS) (Genzyme, Cambridge, MA, USA)] at 30 min and at 12 h, respectively, before the intranasal TNP-BSA administration and the number of inflammatory cells in BALF was evaluated 48 h after TNP-BSA administration.

Cytokine levels in BALF

The amounts of IL-4, IL-5 and IFN- γ in the BALF were determined by the enzyme immunoassay as described previously [24]. The detection limits of these assays were 15 pg/ml of IL-4 and IL-5 and 50 pg/ml of IFN- γ .

Measurement of airway reactivity

Forty-eight hours after intranasal TNP-BSA or BSA administration, airway reactivity to aerosolized methacholine (3·1–50 mg/ml) was measured using whole body plethysmograph (Buxco

Electronics, Sharon, CT, USA) as described previously [25]. Briefly, unrestrained conscious mice were placed in whole body plethysmographic chambers and, after 5 min of stabilization, dose-response curves to aerosolized methacholine were generated. Increasing concentrations of methacholine were aerosolized for 3 min each, and mean airway bronchoconstriction readings, as assessed by enhanced respiratory pause (Penh), were obtained over 10-min periods. As controls, BALB/c mice (age 7–8 weeks, Charles River Laboratories, Atsugi, Japan) were immunized intraperitoneally twice with 4 µg of OVA (Sigma Chemical Co., St Louis, MO, USA) in 4 mg of aluminium hydroxide at a 2-week interval. Fourteen days after the second immunization, sensitized mice were challenged with the inhaled OVA (50 mg/ml in saline) or saline for 20 min three times every 24 h. Twenty-four hours after the final OVA challenge, airway reactivity to aerosolized methacholine was measured as described above.

Adoptive transfer experiments for antigen-induced eosinophil recruitment into the airways

To determine whether IgE cross-linking enhances Th2 cell-mediated allergic inflammation in the airways, we performed adoptive cell transfer experiments in which OVA-specific Th2 cells from DO11·10 mice were transferred to TNP-IgE mice and the eosinophilic airway inflammation was induced by inhaled OVA challenge in the mice. Briefly, splenocytes from DO11·10 mice were stimulated with OVA323–339 peptide (50 ng/ml) in the presence of recombinant IL-4 (5 ng/ml) at 37°C for 48 h. Cells were then cultured with IL-4 and IL-2 (5 ng/ml) for another 72 h. After dead cells were removed by centrifugation on Ficoll-Paque (Amersham Pharmacia Biotech, Piscataway, NJ, USA), the recovered cells were injected intravenously to TNP-IgE mice or WT mice ($2\cdot0 \times 10^6$ cells/mouse). The frequency of cell populations of transferred cells was 80–90% of OVA-specific CD4⁺ T cells as KJ1-26⁺ CD4⁺ T cells [23], 2–5% of CD8⁺ T cells, and 5–10% of B220⁺ cells. Two days after the cell transfer, these mice were challenged with inhaled OVA (50 mg/ml) or saline (as a control) for 20 min and TNP-BSA or BSA was then administered intranasally to the mice 30 min after the OVA challenge. The number of eosinophils and antigen-specific CD4⁺ T cells derived from DO11·10 mice (KJ1-26⁺ T cells) in BALF was evaluated at 48 h after the intranasal TNP-BSA or BSA administration.

Data analysis

Data are summarized as mean $\pm$ s.d. The statistical analysis of the results was performed by unpaired *t*-test. *P*-values < 0·05 were considered significant.

RESULTS

IgE cross-linking induces CD4⁺ T cell recruitment into the airways

We first examined whether IgE cross-linking by a relevant antigen induced airway inflammation using TNP-IgE mice. As shown in Fig. 1a, the intranasal administration of the corresponding antigen, TNP-BSA, significantly increased the number of inflammatory cells in BALF at 8–48 h in TNP-IgE mice but not in WT mice (*n* = 8 mice at each time-point). As expected, however, intranasal administration of BSA did not induce inflammatory cell recruitment into the airways in TNP-IgE mice or WT mice (Fig. 1a). The analysis of BALF cells showed that the number of lymphocytes was significantly increased after TNP-BSA

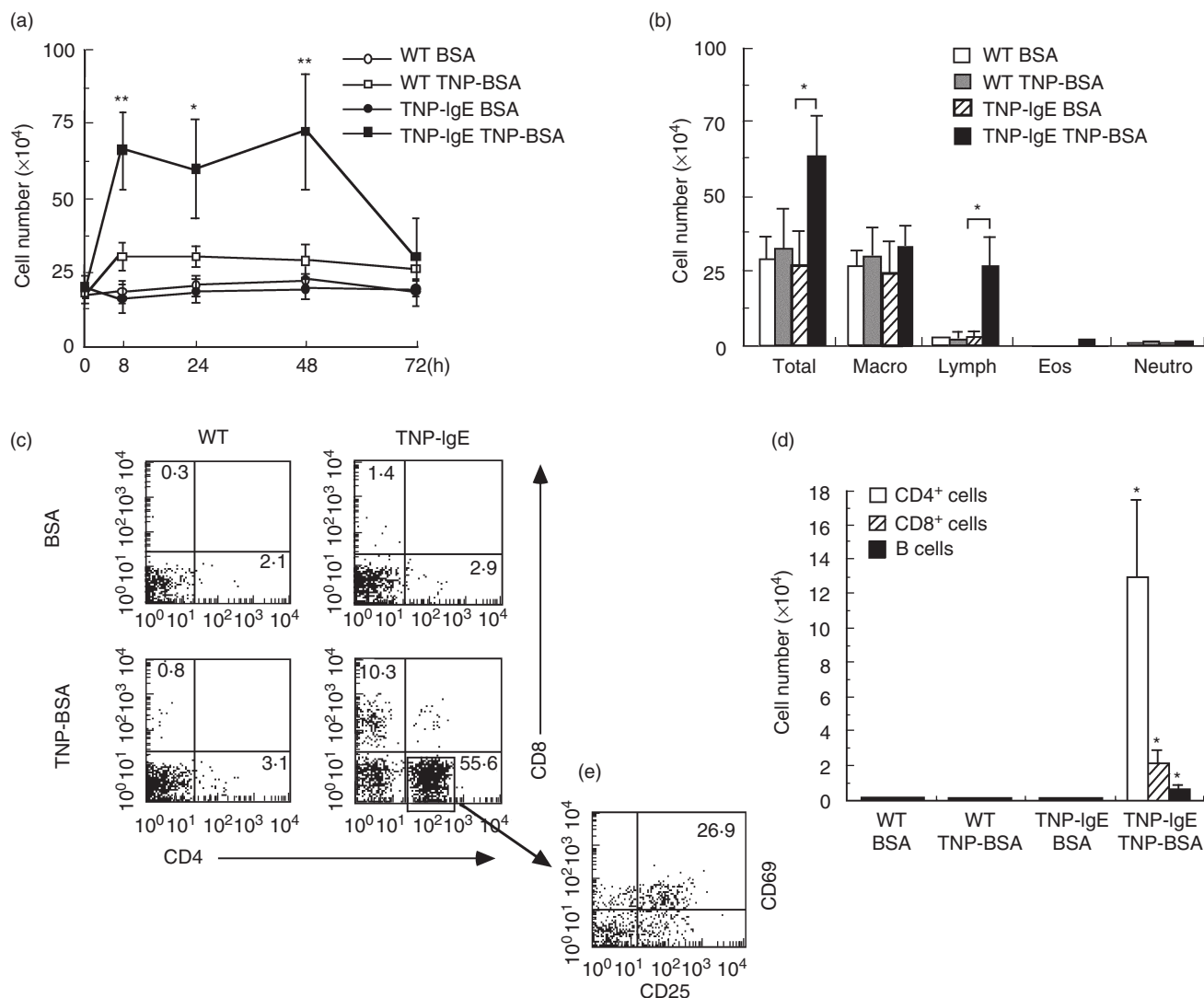


Fig. 1. IgE cross-linking induces CD4⁺ T cell recruitment into the airways. (a) Kinetics of antigen-induced airway inflammation in TNP-IgE mice. TNP-BSA or BSA (as a control) was administered intranasally to TNP-IgE mice and the littermate WT mice. At indicated times after the administration, bronchoalveolar lavage (BAL) was performed and the number of cells in BAL fluid (BALF) was counted. Data are means $\pm$ s.d. for eight mice in each group. * $P < 0.05$, ** $P < 0.01$, significantly different from the mean value of the corresponding control response. (b) Cellular components in BALF. The number of lymphocytes, eosinophils, neutrophils and macrophages in BALF was evaluated 48 h after TNP-BSA or BSA administration by counting 500 cells stained with Wright-Giemsa solution. $n = 8$ mice in each group, * $P < 0.01$. (c) CD4 versus CD8 staining of BALF cells. BALF cells were subjected to FACS analysis 48 h after TNP-BSA or BSA administration. Shown is a representative staining of CD4 versus CD8 (gating on lymphocyte population) from five independent experiments. (d) The number of CD4⁺ cells, CD8⁺ cells and B cells in BALF 48 h after the challenge. $n = 8$ mice in each group, * $P < 0.01$, significantly different from the mean value of the corresponding control response. (e) CD25 versus CD69 staining of CD4⁺ T cells. BALF cells were subjected to FACS analysis 48 h after TNP-BSA administration. Shown is a representative CD25 versus CD69 staining of CD4⁺ T cells from five independent experiments.

administration in TNP-IgE mice (TNP-BSA 28.0 ± 9.8 versus BSA $2.1 \pm 1.0 \times 10^4$ at 48 h, $n = 8$ mice in each group, $P < 0.01$) (Fig. 1b). In contrast, the number of eosinophils, neutrophils or macrophages was not significantly increased in TNP-IgE mice and WT mice at 48 h after TNP-BSA administration (Fig. 1b). FACS analysis revealed that the majority of lymphocytes in BALF of TNP-BSA-administered TNP-IgE mice were CD4⁺ T cells ($60.2 \pm 10.4\%$, $n = 6$) (Fig. 1c,d). The number of CD8⁺ T cells and B cells was also slightly increased in TNP-BSA-administered TNP-IgE mice (Fig. 1c,d). Although approximately 25% of CD4⁺ T cells exhibited an activated phenotype (CD25⁺ CD69⁺)

(Fig. 1e), the levels of IL-4, IL-5 and IFN- γ in the BALF were still undetectable after TNP-BSA administration in TNP-IgE mice (data not shown). Histological analysis showed that the intranasal administration of TNP-BSA also induced lymphocyte recruitment in the perivascular and peribronchial spaces of the lung in TNP-IgE mice (data not shown).

IgE cross-linking does not enhance airway reactivity to methacholine

Next, we examined the effect of IgE cross-linking on airway reactivity to methacholine in TNP-IgE mice. TNP-BSA or BSA was

administered intranasally to TNP-IgE mice and WT mice and, 48 h later, the airway reactivity to aerosolized methacholine was measured by whole body plethysmograph. The intranasal administration of TNP-BSA did not increase airway reactivity to methacholine in TNP-IgE mice as compared with BSA administration ($n = 5$ in each group) (Fig. 2). As anticipated, TNP-BSA did not increase airway reactivity to methacholine in WT mice and the airway reactivity was comparable to that in TNP-BSA-administered TNP-IgE mice (data not shown). These results indicate that IgE cross-linking is not sufficient for the induction of airway hyperreactivity in this system.

Cyclooxygenase inhibitor prevents IgE-induced CD4⁺ T cell recruitment into the airways

We then determined which mediators are involved in IgE-induced CD4⁺ T cell recruitment into the airways. Because it has been suggested that prostaglandin D₂ (PGD₂) from mast cells is involved in CD4⁺ T cell recruitment [26], we examined the effect of acetylsalicylic acid on the IgE-induced CD4⁺ T cell recruitment in TNP-BSA-administered TNP-IgE mice. As shown in Fig. 3, the number of CD4⁺ T cells in BALF in TNP-BSA-administered TNP-IgE mice was significantly decreased by acetylsalicylic acid (acetylsalicylic acid (6 mg) 3.9 ± 1.0 versus saline $18.3 \pm 5.4 \times 10^4$, $n = 5$, $P < 0.01$). The number of CD8⁺ T cells in BALF tended to be decreased by acetylsalicylic acid but the differences were not statistically significant (Fig. 3b). On the other hand, a cysteinyl leukotriene 1 receptor antagonist pranlukast did not decrease the number of CD4⁺ T cells and CD8⁺ T cells in BALF in TNP-BSA-administered TNP-IgE mice (data not shown). In addition, the administration of neutralizing antibody to TNF- α did

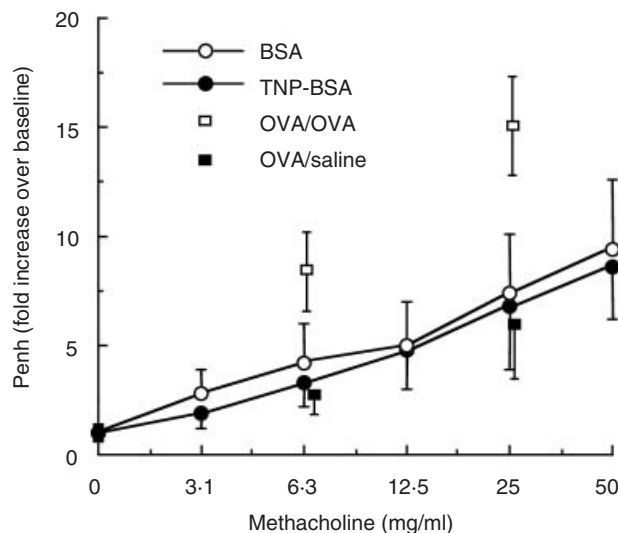


Fig. 2. IgE cross-linking does not induce airway hyperreactivity. TNP-BSA or BSA was administered intranasally to TNP-IgE mice. Forty-eight hours after TNP-BSA or BSA administration, airway reactivity was measured using a Buxco system where mice were exposed to increasing concentrations of aerosolized methacholine (3.1–50 mg/ml). Airway reactivity was expressed as enhanced pause (Penh) values for each concentration of methacholine over baseline response. As controls, OVA-sensitized BALB/c mice were challenged three times with the inhaled OVA or saline, and 24 h later airway reactivity to aerosolized methacholine was measured. Data are means $\pm$ s.d. for five mice in each group.

not decrease the number of CD4⁺ T cells and CD8⁺ T cells in the BALF in TNP-BSA-administered TNP-IgE mice (data not shown). Taken together, these results suggest that prostaglandins are involved in IgE-induced CD4⁺ T cell recruitment into the airways.

IgE cross-linking enhances Th2 cell-mediated eosinophil recruitment into the airways

Finally, we studied whether IgE-dependent mast cell activation contributed to Th2 cell-mediated eosinophil recruitment into the airways by the adoptive transfer system of antigen-specific Th2 cells to TNP-IgE mice. OVA-specific Th2 cells prepared from DO11.10 mice were transferred to TNP-IgE mice or WT mice, and 2 days later the mice were challenged with the inhaled OVA or saline (as a control) for 20 min. TNP-BSA or BSA was then administered intranasally to the mice and the number of eosinophils and OVA-specific CD4⁺ T cells (KJ1-26⁺ CD4⁺ cells) in BALF was counted at 48 h after TNP-BSA or BSA administration. Without the cell transfer of OVA-specific Th2 cells, the inhaled OVA did not significantly induce eosinophil recruitment into the airways in TNP-IgE mice or WT mice (data not shown). When OVA-specific Th2 cells were transferred to WT mice and TNP-IgE mice, the inhaled OVA similarly induced eosinophil (Fig. 4a) and OVA-specific CD4⁺ T cell (Fig. 4b) recruitment into

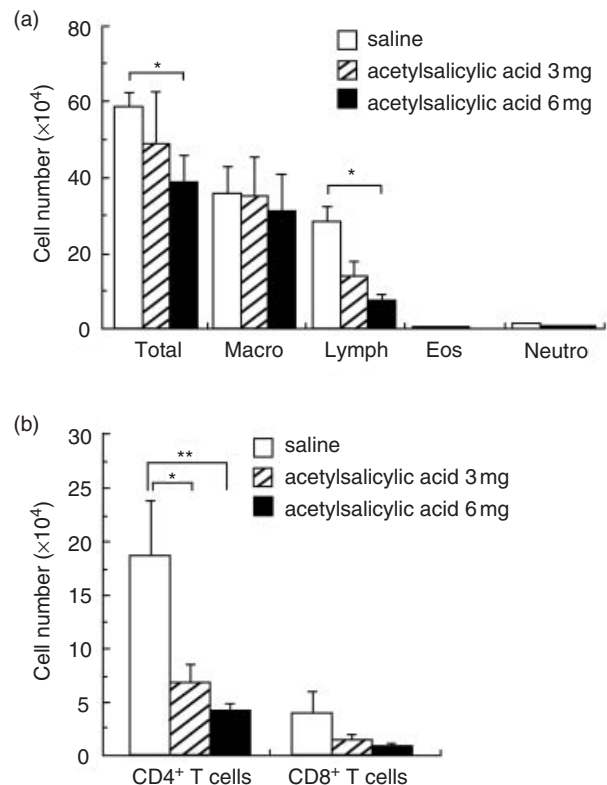


Fig. 3. Acetylsalicylic acid inhibits IgE-induced CD4⁺ T cell recruitment into the airways. TNP-IgE mice were injected intraperitoneally with acetylsalicylic acid (3 mg or 6 mg/mouse) or saline (as a control), and 30 min later TNP-BSA was administered intranasally to the mice. The number of lymphocytes, eosinophils, neutrophils and macrophages in BALF was counted 48 h after the TNP-BSA administration (a). The number of CD4⁺ and CD8⁺ T cells in BALF was also analysed by FACS (b). Data are means $\pm$ s.d. for five mice in each group, * $P < 0.05$, ** $P < 0.01$.

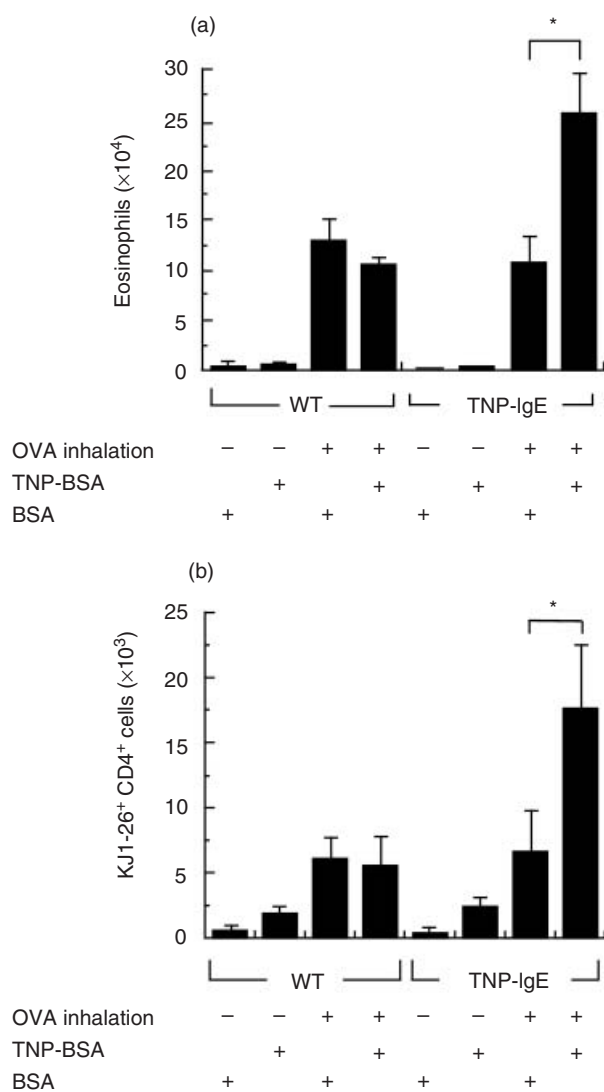


Fig. 4. IgE cross-linking enhances Th2 cell-mediated eosinophil recruitment into the airways. OVA-specific Th2 cells were prepared and transferred to TNP-IgE mice or WT mice as described in the Methods. Two days later, the mice were challenged with the inhaled OVA or saline (as a control) for 20 min. TNP-BSA or BSA was then administered intranasally to the mice, and the number of eosinophils (a) and OVA-specific CD4⁺ T cells (CD4⁺ KJ1-26⁺) (b) in BALF was counted 48 h after TNP-BSA or BSA administration. Data are means $\pm$ s.d. for eight mice in each group, * $P < 0.01$.

the airways in both mice. On the other hand, intranasal administration of TNP-BSA alone did not induce eosinophil recruitment into the airways in TNP-IgE mice or WT mice even when Th2 cells were transferred to these mice (Fig. 4a). Interestingly, TNP-BSA administration significantly enhanced OVA-induced eosinophil ($n = 8$, $P < 0.01$) (Fig. 4a) and OVA-specific CD4⁺ T cell ($n = 8$, $P < 0.01$) (Fig. 4b) recruitment into the airways in TNP-IgE mice but not in WT mice. FACS analysis revealed that the majority of OVA-specific CD4⁺ T cells in the BALF exhibited an activated phenotype (data not shown). These results suggest that IgE-dependent mast cell activation enhances Th2 cell-mediated allergic airway inflammation by recruiting Th2 cells into the airways.

DISCUSSION

In this study, we show that using IgE transgenic mice without antigen sensitization, IgE cross-linking by a relevant antigen directly induces CD4⁺ T cell recruitment into the airways in a prostaglandin-dependent manner (Figs 1 and 3). We also show that, although IgE cross-linking alone does not induce eosinophil recruitment into the airways, IgE cross-linking significantly enhances Th2 cell-mediated eosinophil recruitment into the airways (Fig. 4). Therefore, these results indicate that IgE-dependent mast cell activation enhances Th2 cell-mediated allergic airway inflammation by recruiting Th2 cells into the airways.

In a previous study [22], we showed that mast cells in ear skin of TNP-IgE mice were heavily loaded with TNP-specific IgE as detected by immunohistochemical staining. In contrast, such IgE-loaded mast cells were undetectable in WT mice even though the comparable numbers of mast cells existed in ear skin of TNP-IgE mice and WT mice. We also found that the epicutaneous application of picryl chloride carrying a TNP group induced an immediate cutaneous reaction in TNP-IgE mice but not in WT mice. Moreover, using peritoneal mast cells, we found that IgE bound to Fc ϵ RI on c-kit⁺ mast cells in TNP-IgE mice. Therefore, it is suggested that intranasal administration of TNP-BSA induces mast cell activation through the cross-linking of Fc ϵ RI in TNP-IgE mice. However, it is still possible that Fc ϵ RI on basophils and eosinophils [27,28] as well as other IgE receptors including CD23 and Fc γ receptors [29] may be involved in TNP-BSA-induced CD4⁺ T cell recruitment in TNP-IgE mice.

We show that IgE cross-linking principally induces CD4⁺ T cell recruitment into the airways and thus enhances Th2 cell-mediated eosinophilic airway inflammation by recruiting Th2 cells into the airways. This implies that both antigen-specific IgE antibody on mast cells and antigen-specific Th2 cells cooperate synergistically to induce antigen-induced eosinophilic airway inflammation in asthma. Our findings are consistent with the previous observations that using mast cell-deficient mice, the role of mast cells in antigen-induced eosinophil recruitment into the airways can be detected only in the situation in which mice were weakly sensitized and challenged with antigens and thereby subsequent Th2 cell-mediated eosinophil recruitment was modest [19].

We demonstrate that, however, IgE-dependent mast cell activation alone is not sufficient for the induction of eosinophil recruitment into the airways (Fig. 1) or the induction of AHR (Fig. 2). In contrast to the convincing function of IgE and mast cells in the early phase reaction [30], the roles of IgE in allergic airway inflammation and AHR in the late phase are still controversial. In the previous study using IgE-deficient mice, it was demonstrated that the features of asthma, including eosinophil infiltration into the airways and AHR in the late phase, can be elicited in the absence of IgE [14], suggesting that IgE is not essential for the induction of allergic airway inflammation. On the other hand, in a previous study with the mice sensitized passively with antigen-specific IgE followed by the corresponding antigen challenge, it has been reported that antigen-induced mast cell activation induces eosinophil recruitment into the airways and induces AHR [31]. Interestingly, in their study it was reported that the repeated antigen challenges are required for the induction of eosinophilic airway inflammation and AHR in the passively sensitized mice [31]. Therefore, it is possible that antigen-specific T cells may be activated during the period of antigen

challenges and that these activated T cells may contribute to the induction of eosinophilic airway inflammation and AHR. This notion is in agreement with our finding that IgE cross-linking by antigens significantly induces eosinophilic airway inflammation only when antigen-specific Th2 cells are activated simultaneously by antigens (Fig. 4).

We have also found that IgE-induced CD4⁺ T cell recruitment into the airways is significantly decreased by a cyclooxygenase inhibitor acetylsalicylic acid (Fig. 3) but not by a cysteinyl leukotriene 1 receptor antagonist pranlukast (data not shown), suggesting that prostaglandins are involved in IgE-induced CD4⁺ T cell accumulation in the airways. Moreover, our findings that CD4⁺ T cells are accumulated preferentially into the airways (Fig. 1d) suggest that the IgE-induced CD4⁺ T cell recruitment is not due simply to an increase of vascular permeability. In this regard, it has been shown that PGD₂ is the major cyclooxygenase metabolite produced by mast cells in response to antigen challenge [32]. In addition, the importance of PGD₂ in allergic airway inflammation has recently been demonstrated by using mice deficient in PGD₂ receptor, DP [33]. More recently, it has been shown that PGD₂ also induces chemotaxis of Th2 cells through a novel PGD₂ receptor, chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) [26]. Therefore, it is suggested that PGD₂ may be involved in IgE-induced CD4⁺ T cell recruitment into the airways.

On the other hand, because it has also been shown that thromboxanes are involved in the accumulation of lymphocytes in the airways of a guinea pig asthma model [34], other prostanoids such as thromboxanes might be involved in IgE-induced CD4⁺ T cell recruitment in TNP-IgE mice. It is also possible that acetylsalicylic acid may directly decrease the CD4⁺ T cell recruitment by inhibiting adhesion of T cells to the endothelium [35].

Although it has been shown that mast cell mediators induce short-term AHR [36], our results suggest that IgE cross-linking alone does not significantly induce persistent AHR. A previous study also showed that anti-IgE antibody treatment of sensitized mice prevented systemic anaphylactic reactions, but failed to affect the development of persistent AHR associated with airway inflammation [37]. On the other hand, some studies revealed that IgE and mast cells were necessary for AHR associated with airway inflammation 24 h after antigen challenge [18,19]. The differences in the role of mast cells in the development of AHR may be explained by the differences in the relative contribution to AHR of activated T cells and their cytokines such as IL-13 [2] and eosinophils [7,37]. In addition, in the cell transfer experiments, we found that WT and TNP-IgE mice that had received OVA-specific Th2 cells and subsequent inhaled OVA challenge showed no significant increase in airway reactivity to methacholine even after TNP-BSA administration. It is consistent with the previous findings that AHR associated with mild airway eosinophilia induced by passive sensitization with IgE or exclusive airway sensitization and challenges with antigens could be detected only by *in vitro* airway smooth muscle contraction to electrical field stimulation but not by *in vivo* hyperresponsiveness to inhaled methacholine [31,38].

In summary, we have shown that IgE cross-linking by antigens of mast cells induces CD4⁺ T cell recruitment into the airways and consequently enhances Th2 cell-mediated eosinophil recruitment into the airways. Although the molecular mechanisms underlying this phenomenon remains to be determined, our results show a novel relationship between IgE-dependent mast cell activation

and Th2 cell-mediated allergic inflammation in the late-phase allergic airway responses.

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