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Role of IgE in the development of allergic airway inflammation and airway hyperresponsiveness – a murine model.

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Increased production of immunoglobulin E (IgE) in response to common environmental antigens is the hallmark of atopic diseases such as bronchial asthma, allergic rhinitis, and atopic dermatitis (1). IgE, bound to high-affinity IgE receptors (Fc ϵ RI), triggers the activation of mast cells after cross-linking with specific antigen, resulting in the synthesis and release of a variety of proinflammatory mediators and cytokines (2, 3). IgE-dependent mast-cell activation is the central mechanism underlying immediate allergic reactions including allergen-induced bronchoconstriction, mediated through release of histamine and leukotriene D₄ (4). The role of IgE, Fc ϵ RI, and mast cells has been confirmed in animal models of anaphylaxis: systemic delivery of IgE plus specific antigen (or treatment with anti-IgE alone) causes anaphylactic reactions in normal mice but fails to trigger immediate systemic responses in mast-cell-deficient- (5–7) or Fc ϵ RI-deficient mice (8).

Bronchial asthma is characterized by reversible airway obstruction in response to allergen, chronic eosinophilic airway inflammation, and nonspecific airway hyperresponsiveness (AHR) (9–11). Increased numbers of eosinophils are found in bronchial biopsies and in the bronchoalveolar lavage (BAL) fluid of patients with bronchial asthma (12–14), and the number of eosinophils tends to correlate with severity of disease (15). The development of eosinophil infiltration appears to depend on the production of Th2-type cytokines by activated T cells. The importance of interleukin (IL)-4 and IL-5 for eosinophil accumulation has been demonstrated in various animal models (16–18), and a similar cytokine pattern has been found in the lungs of patients with allergic bronchial asthma (19, 20).

In contrast to the recognized importance of T cells, Th2-type cytokines, and eosinophils, the role of IgE in chronic or persistent airway inflammation and AHR is not well-

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defined and requires further delineation. In patients suffering from bronchial asthma, IgE levels in serum or BAL fluid are often increased and may correlate with the incidence or severity of the disease (21, 22). However, this association is not uniform. The fact that patients suffering from allergic airway disease often demonstrate increased IgE, Th2-type cytokines, and eosinophilic inflammation makes it difficult to evaluate the interrelationship or importance of IgE in the induction of airway inflammation and AHR. The mouse provides an excellent model to investigate the contribution of individual components to the development of AHR. The advanced understanding of murine immunology and the availability of genetically altered mouse strains and immunologic reagents enables such analyses. We have studied the influence of IgE on allergen-induced airway inflammation and AHR in normal and genetically altered or antibody-treated animals, following three different approaches employing passive sensitization with allergen-specific IgE or active sensitization with allergen. In all three models, IL-5-mediated eosinophilic airway inflammation appeared to be a prerequisite for the development of AHR, confirming data obtained in IL-5-deficient mice (23). In this review, we present data showing that IgE plays an important role in the induction of AHR after sensitization protocols which result in limited eosinophil airway infiltration, but is not required for eosinophilic airway accumulation or increased airway responsiveness (AR) under conditions where a more substantial eosinophilic response can be elicited.

Airway inflammation and AHR in passively sensitized mice

In patients with atopic bronchial asthma, increased IgE production and eosinophil accumulation in the airways occur simultaneously. In order to study directly the importance of allergen-specific IgE (and of other allergen-specific antibody isotypes) for the induction of airway inflammation and AHR, we generated ovalbumin (OA)-specific B-cell hybridomas to study the effects of passive sensitization with anti-OA antibodies on anaphylactic reactions, airway inflammation, and AHR in BALB/c mice (24). Administration of anti-OA IgE and IgG1, but not anti-OA IgG2a, IgG3, or anti-TNP IgE as an irrelevant control antibody, resulted in the development of passive cutaneous anaphylaxis, immediate cutaneous hypersensitivity (ICH), and systemic anaphylaxis reactions. This demonstrates the importance of IgE (or IgG1) in the induction of antigen-

induced immediate hypersensitivity and demonstrates that anaphylactic reactions can be triggered through IgG-mediated mast-cell activation, as suggested in studies of IgE-deficient mice (25).

The involvement of allergen-specific antibodies in the induction of airway inflammation and AHR was also studied. BALB/c mice were passively sensitized with anti-OA antibodies and challenged with aerosolized OA via the airways (24). AHR was determined by electrical field stimulation (EFS) of tracheal smooth-muscle segments (26). AHR developed only after passive sensitization with allergen-specific IgE or IgG1 and only after two or more airway challenges with the relevant allergen (OA), demonstrating specificity of the response. Development of increased AR was associated with increased numbers of eosinophils in the BAL fluid (~fivefold vs mice passively sensitized with TNP-IgE or TNP-IgG1 before OA airway challenge) and in isolated cells from lung digests (~fourfold). The responses are probably mediated through interaction of IgE with the high-affinity receptor for IgE, since passive sensitization plus airway challenge failed to induce AHR in Fc ϵ RI-deficient mice (unpublished data), but resulted in increased AR in passively sensitized CD23 (low-affinity receptor)-deficient mice (27). These data suggest that IgE/IgG1-mediated reactions in combination with local challenge of the airways with allergen results in eosinophilic airway inflammation, leading to altered airway function.

The impact of passive sensitization with allergen-specific IgE on T-cell function was also examined. We previously demonstrated that T cells bearing specific variable regions of the β -chain of the T-cell receptor (V β 8.1/8.2-positive T cells) regulate production of IgE and development of AHR in mice actively sensitized to OA (28). V β 8.1/8.2-positive T cells from sensitized mice are able to transfer AHR passively into naive animals (29) and account for most IL-4 production by peribronchial lymph-node (PBLN) cells (30). We analyzed PBLN T cells and found that the combination of passive sensitization with anti-OA IgE and repeated OA airway challenges resulted in a significant *in vivo* expansion of (OA-reactive) V β 8.1/8.2-positive T cells compared to nonsensitized or passively sensitized but unchallenged animals (data not shown). Furthermore, we were able to demonstrate *in vitro* enhancement of T-cell activation by allergen-specific IgE, showing that proliferative responses, cytokine production, and T-helper cell function for IgE production by B cells were increased in sensitized T cells cocultured with allergen and allergen-specific IgE (31). These data indicate that passive sensitiza-

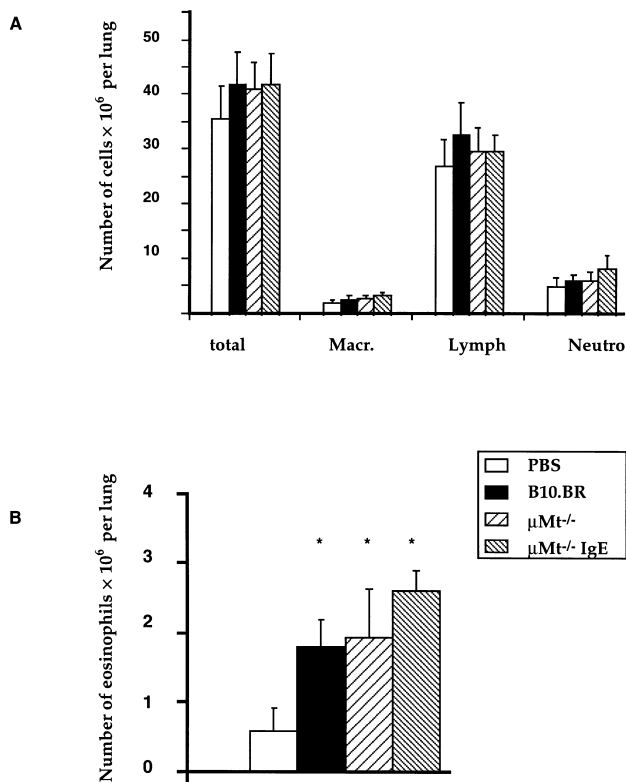


Figure 1. Airway sensitization to OA increases eosinophil infiltration in normal and in B-cell-deficient mice. Normal B10.BR ($n=12$) and B-cell-deficient mice $\mu\text{Mt}^{-/-}$ mice ($n=12$) were exposed to OA via airways for 10 days. Another group of $\mu\text{Mt}^{-/-}$ mice received anti-OVA IgE antibody treatment on days 4, 6, and 8 of 10-day protocol ($n=8$). Control animals were exposed to nebulized PBS ($n=8$). Relative numbers of different types of leukocytes isolated by lung digestion 2 days after last challenge were determined under light microscopy. Expressed are mean $\pm$ SD of percentages of different cell types. * $P<0.01$ vs PBS.

tion with allergen-specific IgE plus airway challenge enhances T-cell function, leading to increased Th2-type (IL-5) cytokine production and eosinophilic airway inflammation.

The importance of IgE and T cells in the development of AHR was directly addressed by studying the effects of passive sensitization in normal and athymic BALB/c nu/nu mice [32]. Both normal and athymic BALB/c mice developed allergen-specific ICH after passive sensitization with anti-OA IgE. This demonstrates the independence of IgE-mediated immediate reactions from T cells and shows that passively sensitized athymic mice are fully capable of generating immediate allergic responses and mast-cell degranulation. In contrast, the combination of passive sensitization with anti-OA IgE followed by local airway challenge with allergen triggered the development of AHR only in normal, but not in athymic, mice. Restoration of T cells by adoptive transfer from normals to nude mice before passive sensitization with IgE followed by airway challenge re-established the capacity

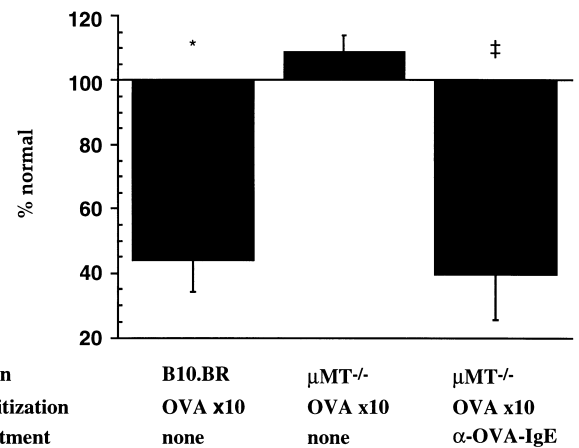


Figure 2. Anti-OA IgE is required for development of airway hyper-responsiveness after exclusive airway exposure to allergen. Groups as described in Fig. 1. Two days after last challenge, *in vitro* airway reactivity was measured by electrical field stimulation of tracheal smooth-muscle segments. Compared are frequencies leading to 50% maximal contraction, $\text{ES}_{50} \pm \text{SEM}$ in Hz, from three independent experiments. Results are expressed as percentage of control ES_{50} values (100%) in nonsensitized (PBS) animals (control ES_{50} : 4 ± 0.4 Hz). * $P<0.02$ vs PBS; ‡ $P<0.03$ vs OA-sensitized $\mu\text{Mt}^{-/-}$ mice without anti-OA IgE treatment. $\mu\text{Mt}^{-/-}$ mice receiving anti-TNP IgE during 10-day OA nebulization had ES_{50} levels similar to those of OA-sensitized, untreated $\mu\text{Mt}^{-/-}$ mice.

for development of AHR in athymic mice. Similarly, treatment of passively sensitized athymic mice with IL-5 before airway challenge restored development of AHR [32]. A significant increase in numbers of eosinophils in the lungs was observed only in passively sensitized normal, but not in athymic, mice unless they were treated with IL-5 before airway challenge. On the other hand, treatment of non-sensitized nude mice with IL-5 before airway challenge induced significant increases in eosinophil numbers in the lung tissue (~fourfold) without leading to AHR. These findings identify the requirements for allergen-specific IgE, IL-5, and repeated airway challenges with allergen in the development of AHR in this model. The data further indicate that IgE-mediated mast-cell activation by itself does not result in sufficient IL-5 production or eosinophilic airway inflammation, but that IL-5-producing T cells are required to induce airway inflammation. Cumulatively, these data indicate a critical role for IgE in the development of AHR in this model of passive sensitization.

Airway inflammation and AHR in mice sensitized via the airways

For further study of the importance of B cells and IgE in the induction of airway inflammation and AHR after active

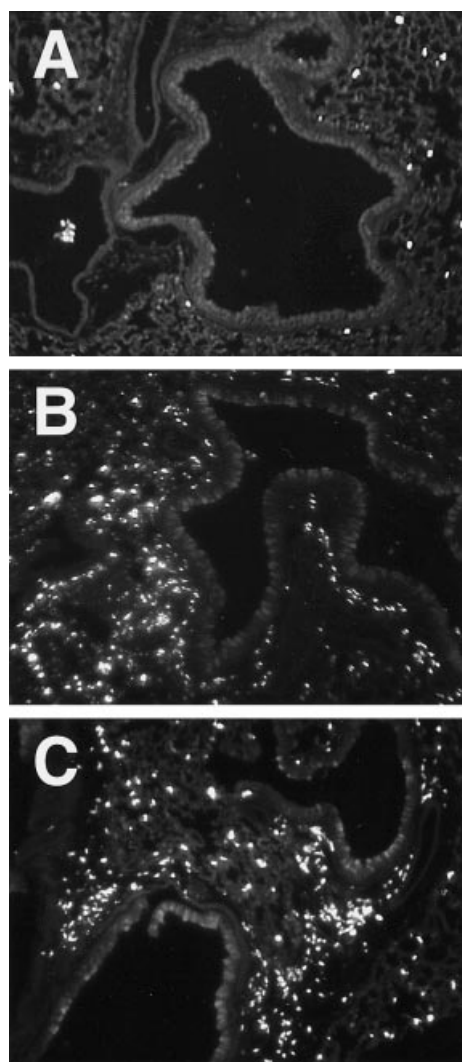


Figure 3. Eosinophil airway infiltration after systemic sensitization plus repeated airway challenge. Normal ($n=12$) and B-cell-deficient ($n=12$) mice were sensitized by intraperitoneal injection of OA/alum on days 1 and 14 followed by daily OA airway challenges on days 28–30. Control animals received only OA airway challenges ($n=8$). Lung sections were prepared and stained for eosinophils with anti-MBP antibody. Shown are central airways of nonsensitized, challenged control (A), sensitized, challenged normal (B), and sensitized, challenged, B-cell-deficient mouse (C). Note marked peribronchial eosinophilia in both B and C.

sensitization, we utilized a model of active airway sensitization (26). Mice were sensitized by nebulization with OA (1% in PBS, 20 min daily for 10 days) in the absence of adjuvant, mimicking a more natural mode of sensitization with airborne allergens. This approach results in a modest increase in production of anti-OA IgE, antigen-specific T-cell proliferative responses, increased production of IL-5 by PBLN cells, limited eosinophil accumulation in the lung tissues (~fourfold vs PBS-nebulized mice), and development of AHR (16). Treatment of mice with anti-IL-5 antibody

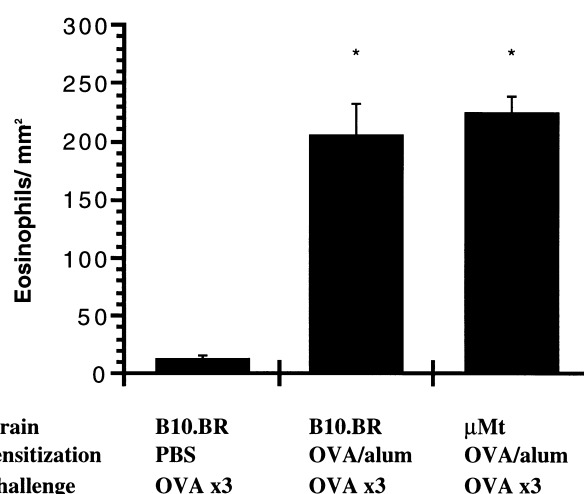


Figure 4. Peribronchial eosinophil accumulation after systemic sensitization plus repeated airway challenge. Sensitization and challenge as described in Fig. 3. Sections of peribronchial tissue were stained with rabbit anti-mouse MBP antibodies. Four sections per lung around similar-sized central airways were chosen randomly, and number of eosinophils in connecting tissue counted in blinded, computer-assisted fashion. Expressed are mean $\pm$ SD numbers of eosinophils per mm² lung tissue from three independent experiments. * $P<0.01$ vs PBS.

during airway sensitization blocks eosinophil airway accumulation and completely inhibits the development of AHR, despite elevated allergen-specific IgE serum levels and allergen-specific ICH (16). Similarly, depletion of IL-5-producing CD8⁺ T cells before airway sensitization prevents eosinophil airway accumulation and development of AHR without affecting IgE production (33). These two studies define IL-5-mediated eosinophil airway accumulation as an essential component in the development of AHR in this model of active airway allergen exposure. Treatment of mice with interferon (IFN)- γ , the main antagonist of IL-4 in the regulation of Th2-type cytokines and IgE production (34), during primary (35) or secondary (36) allergen exposure prevents the development of airway eosinophilia and AHR as well as reduces allergen-specific IgE production, implying a role for IgE in increased AR in this model.

The availability of genetically manipulated B-cell-deficient mice ($\mu\text{Mt}^{-/-}$) (37) allowed us to study directly the importance of B cells and antigen-specific IgE in the development of airway inflammation and AHR in this model of airway sensitization. Obviously, in the complete absence of antibody production, there is no contribution of IgG antibodies, as observed in IgE-deficient mice (25). Airway sensitization resulted in allergen-specific responses and allergen-driven Th2-cytokine production by isolated T cells from PBLN in both normal and B-cell-deficient B10.BR

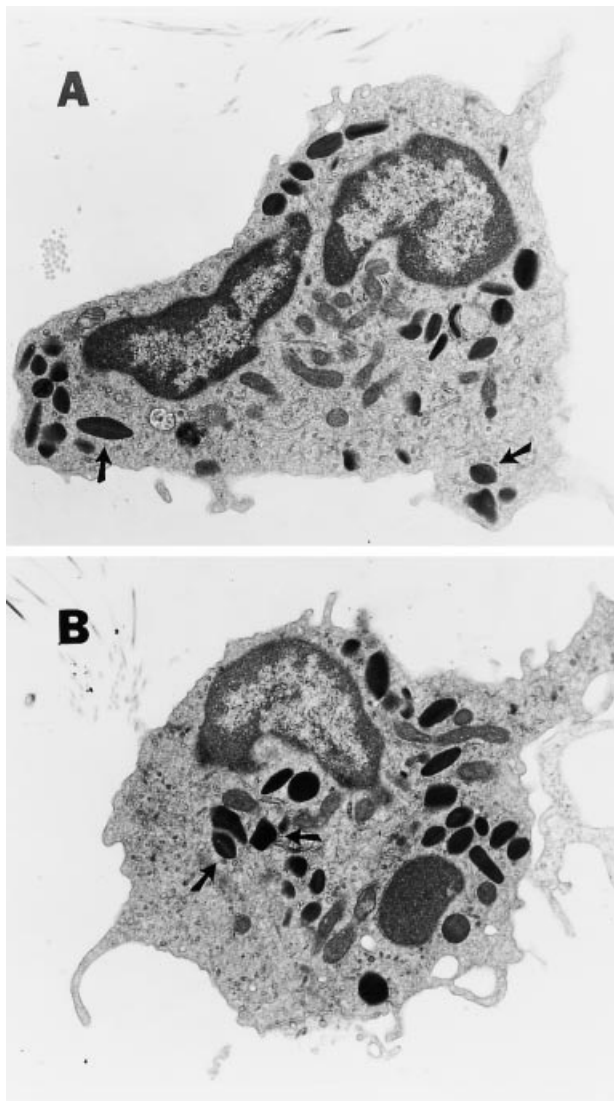


Figure 5. Eosinophil activation and degranulation. Lung sections were prepared for electron microscopy. Shown are eosinophils from sensitized and challenged normal (A) and sensitized and challenged, B-cell-deficient mouse (B). Arrows indicate granule deformation and degranulation (loss of central core, hypodensity). Note development of pseudopods.

mice (38). This demonstrates that B cells and/or IgE itself is not essential for allergen-induced T-cell activation and confirms reports showing B-cell-independent T-cell priming (39), T-cell memory (40, 41), and T-cell tolerance (42, 43). Associated with airway sensitization was a similar eosinophil accumulation in the lung tissues of both normal and B-cell-deficient mice (Fig. 1). However, AHR developed in normal, but not in the B-cell-deficient, mice (Fig. 2). Reconstitution of B-cell-deficient mice with anti-OA IgE during airway sensitization fully restored the development of AHR (Fig. 2), without leading to a significant further

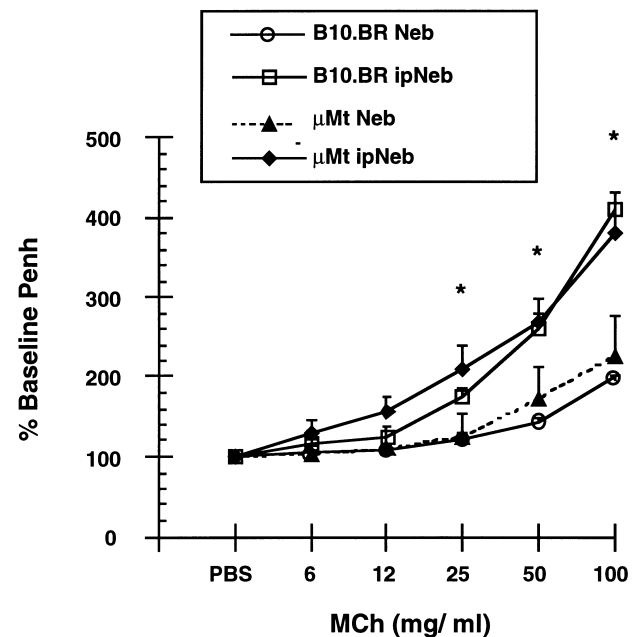


Figure 6. Development of *in vivo* airway hyperresponsiveness in normal and B-cell-deficient mice. Groups and sensitization as described in Fig. 3. Airway responsiveness to aerosolized MCh was measured in unrestrained, conscious mice. Mice were placed in main chamber of whole-body plethysmograph and exposed first to PBS, and then to increasing doses (6–100 mg/ml) of MCh for 3 min for each nebulization, followed by readings for 3 min after each nebulization. Penh (enhanced pause = pause × [peak inspiratory box flow/peak expiratory box flow]) values were determined. Expressed are means ± SEM of percent increase in Penh values compared to Penh values after PBS nebulization from three independent experiments. * $P < 0.02$ vs nonsensitized controls.

increase in eosinophil accumulation compared to airways of sensitized B-cell-deficient mice without IgE treatment (Fig. 1). Cumulatively, these data indicate the requirement for IgE in the development of increased AR by this mode of allergen exposure. B cells and IgE were not necessary for T-cell activation and eosinophilic airway inflammation after allergen exposure via the airways, but allergen-specific IgE and eosinophil infiltration of the airways together result in the development of AHR.

Airway inflammation and AHR in systemically sensitized and airway-challenged mice

The third approach utilized systemic sensitization followed by airway allergen challenge. In this model, mice were sensitized by intraperitoneal injections of OA (20 mg) emulsified in alum (2 mg) on days 1 and 14, followed by daily airway allergen challenge (1% OA in PBS, 20 min) on

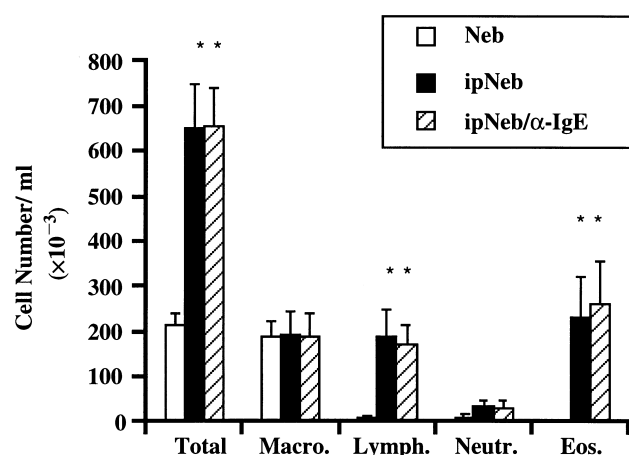


Figure 7. Cell composition of BAL fluid after anti-IgE treatment. Sensitization as described in Fig. 3. Compared are mean $\pm$ SD of total and leukocyte subsets in BAL fluid from nonsensitized but challenged (Neb, $n=10$) and sensitized and challenged BALB/c mice receiving control IgG (ipNeb, $n=14$) or anti-IgE (200 μ g ip), 2 h before each airway challenge (ipNeb/ α -IgE, $n=16$). * $P<0.01$ vs nonsensitized controls for both sensitized groups.

days 28–30. This protocol results in more marked increases in allergen-specific IgE and IgG1 production and Th2-type cytokine production, and a more robust accumulation of eosinophils in the airway (~ 20 -fold vs sham-sensitized, challenged mice) compared to the other approaches to allergen exposure (passive sensitization or exclusive airway exposure). Furthermore, sensitization and challenge in this way enabled us to detect AHR by two new approaches to measure *in vivo* airway responses: invasive measurements of lung resistance (R_L) and dynamic compliance (C_{dyn}) in response to aerosolized methacholine (MCh) in anesthetized mice and the noninvasive measurement of AR to aerosolized MCh by barometric whole-body plethysmography in conscious, spontaneously breathing mice (44). Barometric plethysmography reliably detects increased AR to inhaled MCh in allergen-sensitized mice, and the responses correlate closely to changes in R_L or intrapleural pressure, as measured by invasive techniques (45).

We utilized these techniques to study the induction of inflammatory responses and AHR in systemically sensitized and challenged B-cell-deficient mice. As observed after allergen exposure exclusively via the airways, systemically sensitized and challenged B-cell-deficient mice showed T-cell function (allergen-driven cytokine production and proliferative responses) similar to that of normal sensitized and challenged mice. An eosinophil-specific immunostaining method with rabbit anti-mouse major basic protein (MBP) was used to localize eosinophils *in situ* (16). Fig. 3 demonstrates the marked peribronchial eosinophil accumu-

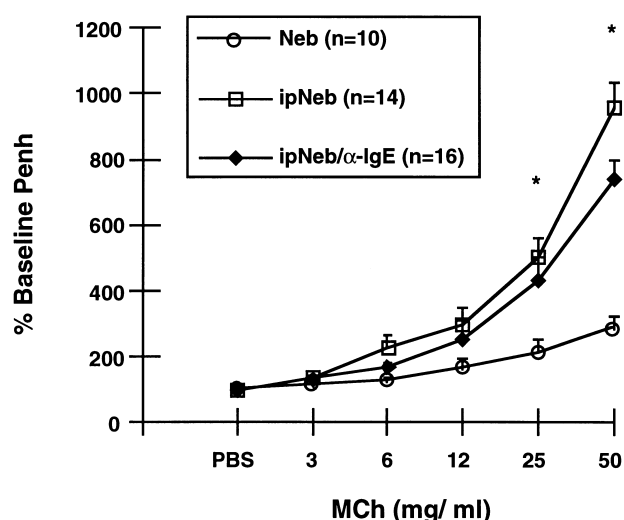


Figure 8. Anti-IgE treatment does not inhibit development of AHR. Groups as described in Fig. 7; measurement of *in vivo* airway response as described in Fig. 6. Expressed are means $\pm$ SEM of percent baseline Penh from three independent experiments. * $P<0.01$ vs Neb for ipNeb and ipNeb/ α -IgE.

lation in both normal and B-cell-deficient mice compared to nonsensitized controls, and the results were similar in both groups of mice. Numbers of eosinophils in the peribronchial region were counted with a computer-assisted program and were increased by ~ 20 -fold (Fig. 4). We studied eosinophils *in situ* by electron microscopy for signs of activation. In both normal and B-cell-deficient sensitized/challenged mice, $>90\%$ of eosinophils in the airways were activated (granule deformation, degranulation, loss of central core, pseudopods, unrounding of cells) (Fig. 5). In association with the marked eosinophilic airway inflammation and activation, both strains of mice developed *in vitro* AHR to EFS (not shown) and *in vivo* AHR to aerosolized MCh compared to nonsensitized, but challenged control mice (Fig. 6). These data indicate that the role of B cells and allergen-specific IgE (or other antibodies) in the development of AHR after systemic sensitization and repeated airway challenge is less apparent in the face of marked eosinophil infiltration and activation in the airways. These data contrast with results from Eum et al. (46), who suggested that antigen-driven migration of eosinophils to the epithelial layer of the airways and consequent development of AHR were dependent on high levels of allergen-specific IgE in a high-IgE-producing mouse strain (BP2); in their study, neither eosinophil migration nor AHR occurred in BALB/c mice. However, no explanation was given for the equivalent number of eosinophils observed in the BAL fluid of BALB/c and BP2 mice despite the absence of eosinophils in the epithelium of the former. Furthermore, it remains unclear

Table 1. Requirements for IgE in development of AHR

Mode of sensitization	Strain	Response		Dependence of AHR on	
		IgE	Eosinophils	IgE	Eosinophils
Passive	BALB/c	++	+	+++ ¹	++
Airway	BALB/c	+	+	++ ¹	+++
Systemic	BALB/c	+++	++	- ²	+++
	C57BL/6	++	+++	-	+++

¹Altered airway function detected in tracheal smooth-muscle preparations in response to electrical field stimulation.
²Altered airway function detected in tracheal smooth-muscle preparations as well as *in vivo* to inhaled MCh.

why sensitization and challenge in their study did not induce AHR in BALB/c mice, the most commonly used strain in the study of allergen-induced AHR.

To confirm the finding that IgE and, by extension, IgE-mediated mast-cell activation are not required to induce AHR after systemic sensitization and airway challenge, we investigated the importance of mast cells in the development of inflammatory airway responses in this system (47). Both mast-cell-deficient (WW^V) and normal, congenic littermates showed similar increases in allergen-specific IgE production and eosinophil infiltration in BAL fluid and in the peribronchial tissue of the lungs (~20-fold *vs* controls) after sensitization and challenge. Measurements of *in vivo* responses to aerosolized MCh revealed similar and significantly enhanced increases in R_L and decreases in C_{dyn} in both mast-cell-deficient and normal mice compared to nonsensitized but challenged controls. These data indicate that airway eosinophilic inflammation and development of AHR are independent of (IgE-mediated) mast-cell activation.

Evidence is accumulating that development of airway inflammation and/or AHR may be regulated or expressed through different mechanisms in different mouse strains (48). AHR development in BALB/c mice has been proposed to be caused by IgE-mediated mast-cell activation; in B6 mice, which are deficient in the tryptase-like mast-cell protease 7 (49) and in the secretory phospholipase A₂ (50), eosinophil infiltration might be the dominant effector event. We investigated the role of IgE in the high-IgE-responder strain, BALB/c. Due to the lack of genetic B-cell- or mast-cell-deficient BALB/c mice, we investigated the effects of treatment with a nonanaphylactogenic anti-IgE antibody (51). Intraperitoneal injection of systemically sensitized mice with anti-IgE antibody 2 h before each of the three airway challenges significantly reduced anti-OA and total IgE serum levels to <20% of sensitized/challenged controls

without affecting cytokine production by PBLN cells or eosinophil accumulation in the peribronchial lung tissue or BAL fluid (Fig. 7). However, anti-IgE antibody treatment effectively eliminated IgE-mediated immediate allergic responses: allergen-mediated *in vitro* mast-cell activation (as measured by *c-Jun* kinase activation) and *in vivo* systemic and cutaneous anaphylaxis after (intravenous or intradermal) OA injection of passively or actively sensitized BALB/c mice were completely inhibited. These results contrast with another study which suggested a closer interrelationship between IgE and eosinophilic inflammation: Coyle et al. (51) observed impaired eosinophil accumulation in sensitized BALB/c mice treated with anti-IgE antibody before a single airway challenge. It is unclear whether the use of a different allergen (house-dust mite) or a different challenge protocol (single intranasal exposure) accounts for the differences in the results of this study from our own. Measurements of *in vivo* AHR to aerosolized MCh showed significant increases in airway responsiveness in both anti-IgE-treated and control mice (receiving rat IgG) after sensitization and challenge (Fig. 8). Animals treated with anti-IgE antibody showed similar responses at all but the highest MCh concentration where AHR was slightly, but significantly, diminished compared to control mice. These data indicate the important role of IgE in allergen-mediated immediate hypersensitivity, but confirm that IgE is not required for the development of eosinophilic airway inflammation and AHR in mice systemically sensitized and challenged via the airways.

Summary

The importance of IgE in airway inflammation and development of AHR in allergen-sensitized mice has been compared and contrasted in different models of sensitization and challenge. Using different modes of sensitization in normal and genetically manipulated mice after anti-IgE treatment, we have been able to distinguish the role of IgE under these different conditions. Striking differences in the three sensitization protocols were delineated in terms of the role of allergen-specific IgE, extent of eosinophilic airway inflammation, and development of AHR (Table 1). The highest levels of IgE and eosinophil infiltration (~20-fold increases) were achieved after systemic sensitization with allergen (plus adjuvant) followed by repeated airway challenge. Passive sensitization with allergen-specific IgE followed by limited airway challenge induced a modest eosinophilic inflammatory response in the airways despite

high levels of serum IgE. Exposure to allergen exclusively via the airways also resulted in a modest serum IgE response and a limited eosinophilic inflammatory response (~fourfold increases). Under all of these conditions, inhibition of IL-5-mediated eosinophilic airway inflammation was associated with attenuation of AHR. In contrast, the differences in the responses to the different modes of allergen exposure were associated with differences in the requirements for IgE in the development of AHR (Table 1). In the two models associated with mild eosinophil infiltration (passive sensitization and exclusive airway exposure), IgE was required for the development of AHR but did not substantially enhance airway inflammation on its own. However, IgE-allergen interaction was able to enhance T-cell function *in vitro* and induce T-cell expansion *in vivo*. In mice systemically sensitized and challenged via the airways, IgE (or IgE-mediated mast-cell activation) was not required for T-cell activation, eosinophilic inflammation and activation in the airways, or development of AHR. This was most clearly seen in B-cell-deficient and mast-cell-deficient, low-IgE-responder mouse strains (B6, B10) and in anti-IgE-treated high-IgE-responder mice (BALB/c). At the same time, we confirmed the importance of IgE in the induction of immediate-type hypersensitivity (mast-cell activation, immediate cutaneous hypersensitivity, passive cutaneous and systemic anaphylaxis).

These differences were also highlighted by the means used to detect altered airway function. Passive sensitization and limited airway challenge or exclusive airway exposure to allergen over 10 days elicited changes in airway function that could be detected only in tracheal smooth-muscle

preparations exposed to EFS. In contrast, systemic sensitization followed by repeated airway challenge resulted not only in changes in the contractile response to EFS but also in increased responsiveness to inhaled MCh. Thus, these results distinguish not only the differential involvement of IgE and eosinophil numbers but also their contribution to the readouts used to monitor airway function.

Based on these studies, we conclude that IgE plays an important role in the development of airway inflammation and AHR under conditions in which limited IL-5-mediated eosinophilic airway infiltration is induced. In conditions where a robust eosinophilic inflammation of the airways is elicited, IgE (and IgE-mediated mast-cell activation) does not appear to be essential for airway inflammation and the development of AHR, detected as increased responsiveness to inhaled MCh. These findings reveal the potential importance of differential targeting in the treatment of allergic diseases with a predominance of IgE-mediated symptoms, e.g., allergic rhinitis and conjunctivitis, where anti-IgE may be an effective therapy, compared to those diseases with a predominant inflammatory component, e.g., AHR in atopic bronchial asthma, where anti-inflammatory or anti-IL-5 therapy may be more beneficial.

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