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*J Immunol* 2000; 164:3855-3861; doi: 10.4049/jimmunol.164.7.3855
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An Essential Role of Mast Cells in the Development of Airway Hyperresponsiveness in a Murine Asthma Model

Tetsuto Kobayashi,* Toru Miura,* Tomoko Haba,* Miyuki Sato,* Isao Serizawa,* Hiroichi Nagai,† and Kimishige Ishizaka‡

Immunization of BALB/c mice with alum-adsorbed OVA, followed by three bronchoprovocations with aerosolized OVA, resulted in the development of airway hyperresponsiveness (AHR) and allergic inflammation in the lung accompanied by severe infiltration of eosinophils into airways. In this murine asthma model, administration of monoclonal anti-IL-5 Ab before each Ag challenge markedly inhibited airway eosinophilia, but the treatment did not affect the development of AHR. Immunization and aerosol challenges with OVA following the same protocol failed to induce AHR in the mast cell-deficient W/W<sup>v</sup> mice, but induced AHR in their congenic littermates, i.e., WBB6F<sub>1</sub> (+/+) mice. No significant difference was found between the W/W<sup>v</sup> mice and +/+ mice with respect to the IgE and IgG1 anti-OVA Ab responses and to the airway eosinophils after Ag provocations. It was also found that reconstitution of W/W<sup>v</sup> mice with bone marrow-derived mast cells cultured from normal littermates restored the capacity of developing Ag-induced AHR, indicating that lack of mast cells was responsible for the failure of W/W<sup>v</sup> mice to develop Ag-induced AHR under the experimental conditions. However, the OVA-immunized W/W<sup>v</sup> mice developed AHR by increasing the frequency and Ag dose of bronchoprovocations. The results suggested that AHR could be developed by two distinct cellular mechanisms. One would go through mast cell activation and the other is IgE/mast cell independent but an eosinophil/IL-5-dependent mechanism. The Journal of Immunology, 2000, 164: 3855–3861.

Bronchial asthma is a syndrome whose common pathogenic expression is inflammation of the airways which causes airway hyperresponsiveness (AHR). In the case of allergic asthma, the airway wall is infiltrated by Th2 cells (1, 2), eosinophils (1–3), and mast cells (2–4) and the AHR is considered to be the result from the combination of submucosal edema, infiltration of airway epithelium with eosinophils and lymphocytes, damage of epithelial cells, and the direct effect of mediators derived from mast cells and eosinophils. To analyze cellular mechanisms underlying allergic inflammation and AHR, murine models have been introduced. In these models, Ag inhalation into sensitized mice was shown to induce AHR and allergic inflammation with severe infiltration of eosinophils in airways. Several groups of investigators have established murine models to elucidate cellular and cytokine requirements for the inflammation of airways. These studies attracted increasing interest in the involvement of eosinophils and IL-5 in the pathogenesis of asthma (5, 6). Foster et al. (7) have shown that IL-5 deficiency abolished Ag-induced eosinophilia and the development of AHR. In contrast, Corry et al. (8) reported that in their murine model, administration of monoclonal anti-IL-5 before Ag challenge markedly suppressed airway eosinophilia but did not affect the development of AHR.

It is well established that cross-linking of IgE Abs on mast cells by Ag triggers the release of chemical mediators which cause immediate allergic reactions (9–11). However, the role of mast cells in the late phase response is not clear, except that the activation of mast cells leads to the synthesis of IL-4, IL-5, and TNF-α which have a potential role in causing inflammation (12, 13). The present experiments were undertaken to determine possible roles of mast cells in the development of Ag-induced AHR by making a comparison between mast cell-deficient W/W<sup>v</sup> mice and their congenic littermates. The results show that when the two strains are immunized with OVA and exposed to aerosolized Ag under exactly the same protocol, W/W<sup>v</sup> mice fail to develop AHR whereas their congenic littermates do. The experiments also demonstrate that reconstitution of W/W<sup>v</sup> mice with bone marrow-derived cultured mast cells restores the ability to develop AHR, indicating that the lack of mast cells in the W/W<sup>v</sup> strain is responsible for failure of the strain to develop AHR.

Materials and Methods

Materials

Crystalline OVA was purchased from Seikagaku (Tokyo, Japan). Biotinylation of OVA was conducted using a biotinylation kit (Amersham, Arlington Heights, IL). Standard mouse anti-OVA serum was obtained by immunization of BDF<sub>1</sub> mice with aluminum hydroxide gel (alum)-adsorbed OVA. After several booster injections of alum-adsorbed OVA, a pooled antiserum was obtained. Rat anti-mouse IL-5 mAb TRFK-5 (14) and rat IgGl, R3-34 were obtained from PharMingen (San Diego, CA). Alkaline phosphatase-coupled rabbit anti-mouse IgG1 was purchased from Zymed (San Francisco, CA). Anti-mouse IgE mAb 6HD5 (15) was purchased from Yamasa (Tokyo, Japan). Alkaline phosphatase-coupled rabbit anti-mouse IgG1 was purchased from Dainabo (Osaka, Japan).
Male BALB/c mice, mast cell-deficient WBB6F1/W/W' mice, and their congenic normal littermates, i.e., WBB6F1/+ , were purchased from Japan SLC (Shizuoka, Japan). They were housed under specific pathogen-free conditions, and five to seven mice in a group were immunized by an i.p. injection of 10 μg OVA adsorbed to 1 mg alum. A booster injection of the same dose of alum-adsorbed OVA was given 5 days later. Unimmunized control mice received saline.

Ag bronchoprovocation

Twelve days after primary immunization, both the immunized and unimmunized mice were exposed to aerosolized Ag. Aerosolization of OVA was performed using a nose-only aerosol chamber adapted for mice. Animals were exposed for 10 min to 5 mg/ml OVA aerosolized by an ultrasonic nebulizer (NE-U12; Omron, Tokyo, Japan) driven by a vacuum pump. The Ag bronchoprovocation was repeated on days 16 and 20 under the same conditions. In some experiments, both W/W' and +/+ mice were immunized and exposed to the aerosolized OVA (10 mg/ml) for 30 min three times per day. In these groups, the Ag bronchoprovocation was repeated every second day from days 12 to 20 under the same conditions.

Determination of airway reactivity

Twenty-four hours after the final aerosol exposure, bronchoconstriction was measured according to the method of Konzett and Rössler (16). Mice were anesthetized by an i.p. injection of sodium pentobarbital (50 mg/kg), and the tracheas were surgically exposed, cannulated, and connected to a rodent ventilator (model 683; Harvard Apparatus, South Natick, MA) and a bronchospasm transducer (model 7020; Ugo Basile, Comerio-Varese, Italy). Animals were mechanically ventilated with air at 60 strokes/min, with a stroke volume of 0.6 ml. A paralytic agent, pancuronium bromide, 0.1 mg/kg, was administered to eliminate spontaneous respiration. After a stable baseline airway pressure was established, acetylsalicylic acid was injected i.v. in a volume of 1 μl/g of mouse/dose, starting with 31.3 μg/kg, and increasing the concentration 2-fold for each subsequent dose. Bronchoconstriction was recorded on a flatbed recorder (model FBR-252A; TOA Electronics, Tokyo, Japan). Bronchoconstriction (percent) represents the respiratory overflow volume provoked by acetylsalicylic acid as a percentage of the maximal overflow volume (100%) obtained by totally occluding the tracheal cannula. In some experiments, airway reactivity was expressed by the area under the dose-response curve (AUC) of bronchoconstriction against the acetylsalicylic acid concentration.

Examination of bronchoalveolar lavage fluid (BALF)

Immediately after the measurement of airway reactivity to acetylsalicylic acid, BALF was collected by lavaging whole-lung three times with 0.7-ml aliquots of physiological saline containing 0.1% BSA via the tracheal cannula while gently massaging the thorax. The BALF recovered from one mouse was pooled, centrifuged, and the cells were resuspended in 100 μl saline containing 0.1% BSA. Cell numbers were determined using a hemocytometer, and cell smears were mechanically ventilated with air at 60 strokes/min, with a stroke volume of 0.6 ml. A paralytic agent, pancuronium bromide, 0.1 mg/kg, was administered to eliminate spontaneous respiration. After a baseline stable airway pressure was established, acetylsalicylic acid was injected i.v. in a volume of 1 μl/g of mouse/dose, starting with 31.3 μg/kg, and increasing the concentration 2-fold for each subsequent dose. Bronchoconstriction was recorded on a flatbed recorder (model FBR-252A; TOA Electronics, Tokyo, Japan). Bronchoconstriction (percent) represents the respiratory overflow volume provoked by acetylsalicylic acid as a percentage of the maximal overflow volume (100%) obtained by totally occluding the tracheal cannula. In some experiments, airway reactivity was expressed by the area under the dose-response curve (AUC) of bronchoconstriction against the acetylsalicylic acid concentration.

Determination of IgE and IgG1 Abs

Mouse sera were obtained 20 days after primary immunization and anti-OVA IgE and IgG1 Abs in the sera were measured by ELISA. The methods for the measurement of IgE and IgG1 Abs were essentially the same as those described by Tomura et al. (18). Briefly, microtiter plates were coated with 3 μg/ml of monoclonal anti-mouse IgE. After blocking with Superblock (Pierce, Rockford, IL) and washing with TBST, appropriate dilutions of serum samples in TBST containing 1% BSA were added to the plate. IgE Abs bound to the plates were determined using biotinylated OVA, alkaline phosphatase-streptavidin conjugate (Zymed, San Francisco, CA), and alkaline phosphatase colorimerizing kit (APMAK; Dako Japan, Kyoto, Japan). The IgG1 Abs bound to the plates, coated with 20 μg/ml OVA, were quantitated by ELISA using alkaline phosphatase-coupled rabbit anti-mouse IgG1 and phosphatase substrate system (Kirkegaard & Perry Laboratories, Gaithersburg, MD). The IgE and IgG1 Abs titers in the samples were related to a pooled serum standard containing 112 μg/ml of IgG1 anti-OVA Abs and 762 ng/ml of IgE anti-OVA Abs in 100,000 units.

Histological studies

Lungs were fixed with 10% Formalin, and the tissues were embedded in paraffin. Sections (5 μm) were stained with hematoxylin and eosin for light microscopic examinations. To examine the presence and distribution of tissue mast cells, lung tissues were fixed in Carnoy’s fixative and sections were stained with toluidine blue (19).

Statistical analysis

Homogeneity of variance was tested by the F test. Student’s t test was applied in cases in which the variance was homogeneous, whereas the Aspin-Welch’s test was applied when the variance was heterogeneous. A p value of <0.05 was considered to be significant. Values for all measurements were expressed as means ± SE.

Results

Establishment of murine asthma model

Experiments were conducted to establish a mouse model of developing AHR. BALB/c mice were immunized with alum-adsorbed OVA and exposed to OVA aerosol. Determination of airway reactivity to acetylsalicylic acid indicated that the mice immunized with OVA demonstrated a marked bronchoconstriction in response to 0.5–1 mg/kg of acetylsalicylic acid, whereas the airway of unimmunized control mice barely responded to the same doses (Fig. 1a). It was also found that the mice immunized with alum-adsorbed OVA but received saline inhalation exhibited the airway reactivity comparable to that observed in unimmunized but OVA-aerosolized mice (results not shown). As expected, sera of the immunized and OVA-challenged mice contained a substantial concentration of both IgE (18759 ± 3648.1 U) and IgG1 (16918.5 ± 1214 U) anti-OVA Abs, but neither of the Abs was detectable in the sera of unimmunized control mice.

Microscopic examination of the nucleated cells in BALF, taken immediately after the airway reactivity assay, showed a marked increase in eosinophils in the airway of immunized mice but not of unimmunized control mice (Fig. 1b). It was also found that BALF of the immunized mice contained both IL-4 (17.42 ± 4.44 pg/ml) and IL-5 (121.75 ± 24.19 pg/ml). Neither IL-12 nor IFN-γ was detected in BALF from the immunized and unimmunized mice.

In view of accumulated evidence for the involvement of eosinophils in allergic inflammation, which may cause AHR (1–3, 20, 21), we determined the possible effects of anti-IL-5 mAb in suppressing the development of allergic inflammation and AHR in aerosolized mice. Three groups of BALB/c mice were immunized with OVA and then challenged three times with aerosolized OVA. Two groups of the immunized mice received i.p. injections of either 3 or 30 μg of anti-IL-5 two hours before each OVA challenge, whereas the third group received i.p. injections of 30 μg of irrelevant rat IgG1 as a control. As expected from the previous observations of Corry et al. (8), administration of 30 μg of anti-IL-5 resulted in marked reduction in eosinophil number in BALF.
Results of histological examination of lung tissues paralleled the number of eosinophils in BALF. In control mice, which received the irrelevant Ab, a large number of eosinophils were found in the peribronchial regions of the lung, but infiltration of eosinophils into the regions was markedly suppressed by the injections of 30 mg of anti-IL-5. Despite the reduction in eosinophil numbers in BALF and lung tissues to about 10%, airway reactivity to acetylcholine in the anti-IL-5-treated mice was not significantly different from that of the control animals which received irrelevant Ab (Fig. 2b). These results indicated that in our murine model, some cellular responses other than infiltration of eosinophils may play a critical role in the development of AHR.

Role of mast cells in airway hyperresponsiveness

To determine possible roles of mast cells in the development of Ag-induced AHR, comparisons were made between mast cell-deficient W/Wv mice and congenic littermates (+/+ mice). They were immunized with alum-adsorbed OVA and challenged with aerosolized OVA three times, following exactly the same protocol employed for BALB/c mice. Measurement of IgE and IgG1 anti-OVA Abs in the sera of the immunized mice, taken at day 20, showed no significant difference between the W/Wv and +/+ mice in the Ab responses (Fig. 3a). However, determination of airway reactivity to acetylcholine showed a clear difference between the two strains. As shown in Fig. 3b, immunization and challenges with aerosolized OVA induced AHR to acetylcholine in +/+ mice but failed to generate AHR in W/Wv mice. The results were confirmed by measuring the AUC of bronchoconstriction. Although the airway of W/Wv mice gave a weak response to 4 mg/kg of acetylcholine, no significant difference was observed in the AUC between immunized and unimmunized groups of W/Wv mice. As expected, there was a significant difference ($p < 0.05$) in the AUC between the immunized groups of the two strains. However, the bronchoprovocation with aerosolized OVA appears to induce allergic inflammation in the OVA-primed W/Wv mice. Examination of nucleated cells in the BALF of the mast cell-deficient mice showed a marked increase in eosinophils, comparable in extent to that observed in aerosolized +/+ mice (Fig. 4a). Histological examination of lung tissues showed that infiltration of eosinophils in peribronchial tissues in the W/Wv mice was comparable to that observed in +/+ mice. It was also found that BALF from the two strains contained comparable concentrations of IL-4 and IL-5 (Fig. 4b).

To confirm that the lack of mast cells in W/Wv mice is responsible for failure of the development of AHR in this strain, we determined the effect of reconstitution of W/Wv mice with mast cells. Twenty million mast cells developed from bone marrow cells of +/+ mice were transferred into each W/Wv mouse, and the recipients were immunized with alum-adsorbed OVA 4 wk after cell transfer. Histological examinations of lung tissues confirmed the presence of mast cells in the tissues of mast cell-reconstituted W/Wv and +/+ mice, whereas mast cells were not detected in W/Wv mouse tissue (Fig. 5). The number of mast cells in the lung of mast cell-reconstituted W/Wv mice was about one-half that of +/+ mice. As expected, IgE and IgG1 anti-OVA Abs formed by...
the reconstituted animals were comparable to those of W/W\(^v\) mice immunized with the same dose of alum-adsorbed OVA. To determine the effect of mast cell reconstitution on the development of AHR, seven mice, each of \(1/1\), W/W\(^v\), and those reconstituted with mast cells were immunized with OVA and then challenged three times with aerosolized OVA. Determination of bronchoconstriction to acetylcholine, shown in Fig. 6\(a\), confirmed that immunization and Ag challenge failed to induce AHR in W/W\(^v\) mice; however, reconstitution with mast cells restored the responsiveness of the airways. The extent of AHR to acetylcholine in the reconstituted mice was comparable to that observed in \(1/1\) mice. Differences between AUC values in W/W\(^v\) mice and those in the reconstituted mice were statistically significant (Fig. 6\(a\)). Microscopic examination of the BALF of W/W\(^v\) mice and the reconstituted mice indicated that the presence of mast cells in the lung did not affect the Ag-induced influx of eosinophils into the airways (Fig. 6\(b\)).

The results described above are in conflict with recent observations by Takeda et al. (22), who have shown that immunization of W/W\(^v\) mice with OVA followed by aerosolized OVA challenge induced AHR. In their experiments, no difference was observed between W/W\(^v\) mice and \(+/+\) mice in the development of AHR, as determined by airway resistance and dynamic compliance after inhalation of methacholine. In view of these findings, we determined as to whether the AHR could be induced in W/W\(^v\) mice by changing the protocol of Ag challenge. Both W/W\(^v\) and \(+/+\) mice were immunized with alum-adsorbed OVA on days 0 and 5, and the animals were exposed to aerosolized OVA for 30 min three times per day. Ag exposure was performed every other day from days 12 to 20. Control unimmunized mice also received aerosolized OVA under the same protocol. As shown in Fig. 7, determination of bronchoconstriction to acetylcholine on day 21 clearly showed AHR in W/W\(^v\). Under the experimental conditions employed, there was no significant difference between the W/W\(^v\) and \(+/+\) mice in the AUC. Histological examination of lung tissues of the W/W\(^v\) mice employed in the experiment confirmed the lack of mast cells. The results indicated that AHR could be induced by frequent bronchoprovocations in the mast cell-deficient mice.

**Discussion**

In the present experiments, we described a murine model for developing AHR by immunization of BALB/c mice with alum-adsorbed OVA on days 0 and 5, followed by three bronchoprovocations with aerosolized OVA between days 12 and 20. The immunization regimen employed in the system was essentially the same as that employed by Kung et al. (17), who have demonstrated marked eosinophilic infiltration in airways by Ag bronchoprovocation on day 12. In our experience, three bronchoprovocations were required to induce AHR in these mice.

Murine models for aeroantigen-induced eosinophilic inflammation and AHR have been described by several investigators. One of the characteristics of the present model is the proportion of cellular...
components in BALF. When BALB/c mice were immunized and aerosol challenged under the protocol described in Materials and Methods, BALF contained 1.5–2.0 $\times 10^6$ eosinophils, which represented nearly 80% of total BALF cells. Similar results were obtained when $+/+$ mice were immunized and challenged with aerosolized OVA by the same protocol (Fig. 4a). The proportion of eosinophils in BALF may differ depending on mouse strains, immunization regimen, and frequency of Ag challenge. Nagai et al. (23) immunized BALB/c mice and $+/+$ mice with 50 μg of alum-adsorbed OVA on days 0 and 12 and aerosolized three times with OVA, but the number of eosinophils in BALF was in the order of $1–3 \times 10^5$, which comprised 40–50% of the total cells in BALF. Similarly, Takeda et al. (22) immunized BALB/c mice and $+/+$ mice with 50 μg of alum-adsorbed OVA on days 0 and 12 and aerosolized three times with OVA. The number of eosinophils in BALF was $3 \times 10^3$, which comprised 50% of the total cells. On the other hand, Corry et al. (8) immunized BALB/c mice by four weekly injections of alum-adsorbed OVA, gave two to three Ag challenges with a high concentration of aerosolized OVA, and obtained 2 to $3 \times 10^6$ eosinophils in BALF. Thus, the major reason for the predominance of eosinophils in BALF in our system appears to be related to the immunization regimen. It has been believed that eosinophils play a dominant role in allergic inflammation (1–3, 20, 21). In our system, however, the number of eosinophils in BALF did not correlate with the development of AHR. Administration of 30 μg of anti-IL-5 mAb before each Ag challenge markedly inhibited airway eosinophilia, but the treatment did not affect the development of AHR (Fig. 2b). Similar results were reported by Corry et al. (8) and Nagai et al. (23), who have established murine models of AHR in BALB/c mice. The present experiments also indicated that eosinophil infiltration in the airway was comparable in BALB/c and $+/+$ mice when they were immunized and challenged with aerosolized OVA under the same protocol (cf Fig. 1b vs Fig. 4a). However, bronchoconstriction induced in BALB/c mice by 0.5–1 mg/kg acetylcholine was much more than that observed in the $+/+$ mice (cf Fig. 2a vs Fig. 3b), indicating the lack of parallelism between AHR and eosinophil infiltration depending on mouse strains.

An important finding obtained in the present experiments was clear evidence for the role of mast cells in the development of Ag-induced AHR. It was found that W/W$^v$ and $+/+$ mice were comparable in IgE and IgG1 Ab responses. After three times of bronchoprovocation with OVA aerosol, $+/+$ mice showed AHR to acetylcholine, whereas W/W$^v$ mice failed to do so (Figs. 3b and 6a). It is known that W/W$^v$ mice have several genetic defects, including lack of mast cells (24). However, the present experiments showed that reconstitution of W/W$^v$ mice with $+/+$ mouse-derived cultured mast cells restored the capacity of developing

[FIGURE 5. Histology of the lung in mast cell-reconstituted W/W$^v$ mice. Mast cells are visualized in lung that were fixed in Carnoy’s fixative and stained with toluidine blue. a, Mast cell-deficient W/W$^v$ mice. b, $+/+$ mice. c, Mast cell-reconstituted W/W$^v$ mice. Magnification, $\times 100$.]

[FIGURE 6. AHR to acetylcholine expressed by AUC (a) and cellular composition in BALF (b) in W/W$^v$ mice, those reconstituted with mast cells (W/W$^v$ + BMMC), and $+/+$ mice. Results are expressed as means ± SE for each group. In a, differences in the AUC between the OVA/OVA group ($n = 7$) and saline/OVA group ($n = 5$) in each strain were evaluated. A significant difference ($p < 0.05$) was also obtained between the OVA/OVA groups of W/W$^v$ and W/W$^v$ + BMMC.]

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into airways, is Th2 cells rather than mast cells. Marked eosinophilic response in W/W^v mice, which failed to develop AHR, also indicates that infiltration of eosinophils into the airways is not sufficient for the development of AHR. Previous studies suggested that eosinophil activation rather than accumulation in local tissues correlated with increased airway reactivity (27). One might speculate that some of the mast cell-derived mediator(s), such as platelet-activating factor (28, 29), may be involved in activation/degranulation of eosinophils. It has been predicted that mast cell-derived mediators such as platelet-activating factor (30, 31), leukotrienes (31, 32), thromboxane A_2 (33), and tryptase (34, 35) have the capacity to increase airway reactivity. The present experiment indicating a clear difference between W/W^v and +/+ mice in the development of AHR suggests that some of the mast cell-derived mediators are involved in the development of AHR in our system.

Failure of W/W^v mice to develop AHR in our present experiment appears to conflict with the findings by Takeda et al. (22), who demonstrated no significant difference between W/W^v and +/+ mice in the development of Ag-induced AHR. However, the discrepancies are probably due to differences in the immunization regimen for sensitization and the protocol of bronchoprovocation employed in the two experiments. In our experiment as well, AHR could be developed in W/W^v mice by increasing the frequency and Ag dose for bronchoprovocation (cf Fig. 7). It is obvious that under this experimental condition, AHR could develop without participation of mast cells.

Conflicting results have been reported on the possible role of IL-5/eosinophils and IgE in the development of AHR. Corry et al. (8) and Nagai et al. (23) as well as our present experiments clearly showed that administration of anti-IL-5, which blocked the Ag-induced release of eosinophils from bone marrow (36) and markedly diminished eosinophil infiltration in the lung, failed to affect the development of Ag-induced AHR. In these systems, there is no clear evidence that IL-5/eosinophils play a major role in the development of AHR. In contrast, Foster et al. (7) have shown that the IL-5 gene-deficient mice failed to develop AHR. Furthermore, Hogan et al. (37) claimed that immunization of IL-4-deficient mice with OVA and subsequent challenge with aerosolized OVA resulted in the development of AHR. Since the IL-4-deficient mice failed to form IgE or IgG1 Abs, these experiments indicated that AHR could be induced in the mouse without participation of the IgE/mast cell system. This idea is supported by more recent experiments by Lee et al. (38), who have generated transgenic mice which constitutively express IL-5 in the lung epithelium. The airway expression of IL-5 resulted in the accumulation of eosinophils in the peribronchial area, eosinophil infiltration of the airways, and development of AHR in the absence of aerosolized Ag challenge.

The most likely explanation for the conflicting results described above is that AHR could be induced by at least two distinct cellular mechanisms. One would go through the IgE-dependent activation of mast cells, which initiates a sequence of events that can induce AHR, whereas the other mechanism is an eosinophil- and IL-5-dependent process in which participation of IgE/mast cells is not required. A fundamental question remaining to be answered is which mechanism is predominant in human asthma, which is a syndrome caused by inflammation of the airways. In some asthmatic patients, AHR may be caused by the IL-5- and eosinophil-dependent mechanism alone. In typical allergic asthma, however, we suspect that both the IgE-dependent and IgE-independent activation events take place in concert, and the mast cell/IgE system probably plays a key role in the development of AHR.

References


