Symposium

Symposium on Allergy and Respiratory Diseases*

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(1) In Relation to the Factors Affecting the Genesis of Bronchial Asthma

a. Histological Changes in the Airway after Antigen Inhalation Challenge in Asthma

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Bronchial asthma is characterized clinically by paroxysmal dyspnea caused by reversible airway narrowing, physiologically by bronchial hypersensitivity, histologically by the infiltration of eosinophils and resultant destruction of the epithelium in the airway and immunologically by the increased production of IgE antibodies to environmental antigens.

This presentation is intended to examine the infiltration of inflammatory cells, especially eosinophils, in the airway mucosa and resultant changes of airway responses by antigen inhalation in allergic asthma.

1. Three phases of asthmatic responses induced by antigen inhalation and their relations to eosinophil dynamics in the airway (Fig. 1) (1).

Immediately after the inhalation of an antigen in asthmatic patients who are sensitive to the antigen, bronchospasm occurs and subsides spontaneously 30 to 60 minutes after the challenge. Three to 8 hours after the challenge airway narrowing occurs again,

in a portion of the patients. The former is called as immediate asthmatic response (IAR) and the latter is called as late asthmatic response (LAR). For several days after the challenge airway responsiveness to inhaled acetylcholine or histamine increases, showing the non-specific bronchial hypersensitivity, though no airway narrowing is observed. This response may be called as post-late phase asthmatic response (P-LAR). Eosinophils are major inflammatory cells infiltrating in the site of IgE-mediated allergic reaction. In the airway eosinophils start to accumulate 1 hour after the challenge and 6 hours after the challenge the accumulation is maximum and seems to last for several days (2, 3). In bronchoalveolar lavage which is collected after the antigen inhalation, eosinophil is increased significantly in patients who showed LAR (4). Since post-late phase airway hyperresponsiveness is observed in patients with LAR, the occurrence of airway hyperresponsiveness is considered to be dependent to the accumulation of eosinophils in the airway.

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Fig. 1. Three phases of asthmatic responses and dynamics of eosinophils after antigen inhalation in patients with asthma. AR, asthmatic response; BALF, bronchoalveolar lavage.

Chemical mediators released from mast cells by antigen challenge can be divided into 2 groups. The mediators of the 1st group are histamine, leukotriene C₄, D₄ (LTC₄, D₄), prostaglandin D₂ (PGD₂) and are spasmogenic and vasoactive. They cause immediate bronchoconstriction. The mediators of the 2nd group are platelet activating factor (PAF) and LTB₄, and are chemotactic (5). These mediators attract eosinophils to the airway. Attracted eosinophils are also activated and release PAF and LTC₄ which can cause late phase airway narrowing. Eosinophils in the tissue release their granule proteins, such as major basic protein, eosinophil peroxidase and eosinophil cationic proteins. These granule proteins are toxic to cells and tissue can cause the damage of the bronchial epithelium, which may expose irritant receptors and facilitate non-specific reflex bronchoconstriction.

2. Tissue damage by eosinophils

i) Observations of the bronchi in asthma death

Microscopic examination of section of the bronchi from patients who died from asthmatic attacks, shows extensive infiltration of eosinophils in the bronchial mucosa and in the airway lumen, and also destruction of the bronchial mucosa and

in some place its desquamation. The association of the eosinophil infiltration and destruction of the bronchial mucosa suggests that granule proteins released from infiltrated eosinophils may destroy the bronchial mucosa.

ii) Destruction of cultured tracheal rings by eosinophil granule proteins

Motojima and Gleich (6) prepared tracheal rings 1 mm thick from normal guinea pigs and cultured them for 3 days, then added eosinophil peroxidase for 15 minutes followed by addition of glucose oxidase to generate oxygen peroxide and halides. Approximately 10^{-8} M EPO caused the cessation of ciliary beatings and exfoliation of the epithelial cells. 10^{-7} M MBP also caused the similar destruction. These in vitro observations suggest that eosinophils can cause the damage of the bronchial epithelium as observed in the bronchi in asthma death.

3. Destruction of the bronchial epithelium by eosinophils (Fig. 2)

Ohashi et al.(7) carried out biopsies of the bronchial mucosa of the main bronchus from asthmatic patients and examined the specimen by electron-microscope. In normal subjects epithelial cells contact tightly each other (tight junction) and

Fig. 2. Electron microscopic photograph of the epithelium of the bronchi from biopsy specimen of patient with asthma — denuded specific granules of eosinophils are shown between epithelial cells (Oohashi). (7)

no spaces are observed between the cells. In a part of the area of the bronchial mucosa the tight junction was widened and almost always eosinophils or eosinophil granules were observed in the widened junction. Such observations suggest that eosinophils widen tight junction between epithelial cells, and such change may expose irritant receptors and cause airway hyperresponsiveness. In fact they measured airway responsiveness to inhaled acetylcholine and observed the minimal concentration of acetylcholine solution to cause 20% decrease of FEV_{1.0} was lower in patients whose tight junction in the bronchial epithelium was widened, supporting the foregoing hypothesis.

4. Creola body in the sputum after antigen challenge

Creola body was first found in the sputum of patients with severe bronchospasm and identified as fallen epithelial cells from the bronchial mucosa.

Kushima and Motojima (8) carried out mite antigen inhalation on the asthmatic patients sensitive to mite, and observed the occurrence of Creola body in the sputum. All the patients showed late asthmatic response, suggesting the accumulation of eosinophils in the airway (2). They found Creola bodies in the sputum after antigen challenge, showing the desquamation of the bronchial epithelium caused by anaphylaxis in the airway. They also found the con-

Fig. 3. Antigen-induced airway responses and eosinophil infiltration in the bronchial mucosa in guinea pigs sensitized passively or sensitized by repeated antigen inhalations. (9, 10)

centration of MBP was higher in the sputum which contained more Creola bodies, by examining the sputum which collected during naturally occurred asthmatic attacks, suggesting that MBP and other eosinophil granule proteins caused the production of Creola body.

5. Increased airway hyperresponsiveness and damage of the bronchial mucosa after antigen challenge in guinea pigs which were sensitized by repeated antigen inhalation (Fig. 3) (1, 9, 10)

Patients with allergic asthma are sensitized by the inhalation of environmental allergens, and are exposed to the allergen repeatedly. Such persistent anaphylaxis in the airway is considered to cause inflammation there, inducing airway hyperresponsiveness.

So that, Terashi and Yukawa (10) sensitized normal Hartley guinea pigs by the inhalations of 1% ovalbumin (OA) aerosols every day for 10 days. Then the animals were challenged once a week till they showed apparent attacks of dyspnea. Seven days after they showed dyspneic attacks by the inhalation of OA solution. The sensitized animals were challenge by the inhalation of OA solution, and respiratory resistance, reactivity to inhaled histamine and histological change serially after the challenge. These animals showed immediate and late airway narrowing and also increased responsiveness to inhaled histamine for 5 days. The bronchial mucosa were infiltrated with eosinophils and damaged with desquamation of the epithelium. Such histological changes were observed even 7 days after the antigen challenge.

Such observations suggest that antigen inhalation causes eosinophil accumulation in the airway and resultant destruction of the bronchial mucosa. Such inflammation in the airway causes increased responsiveness of the airway.

6. Conclusion

Inhalation of the specific antigen in allergic asthmatic patients causes infiltration of inflam-

matory cells, mainly eosinophils, and the resultant destruction of the bronchial epithelium, such as opening of tight junction between epithelial cells, causes the increase of airway responsiveness, leading to chronic asthmatic symptoms.

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