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Review

Immunopathogenesis of distant manifestation in effector phase after local airway allergy

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ABSTRACT

Allergy airway diseases are prevailing in the world's population. These are multifactor disorders in which the most important components are the genetic predisposition of the patient (atopy), modulatary effects by environmental factors, infections and irritants. The airway allergy may occur as immediate, late or dual in onset. Allergic airway reactions are not always limited to the area they originated. Some studies indicate that the relation between sensitization to aero-allergens and allergic reaction in other parts (especially dermal lesions) of the body. However, the mechanisms of distant manifestations after a local allergic reaction have not been elucidated. This review describes hypothetical molecular mechanisms of the development of systemic lesions especially at dermis in the effector phases of airway allergy, including the roles of adhesion molecles, cytokines, chemokines and several biological active mediators. The difference between reaction of distant manifestation and IgE-dependent allergic anaphylax will be briefly mentioned.

KEYWORDS: airway allergy, eosinophil, IgE, mast cell, Th1 cell, Th2 cell, cytokine, chemochine, adhesion molecule, distant manifestation

INTRODUCTION

Airway allergy is an inflammatory disorder characterized by airflow obstruction of variable degrees, bronchial hyper-responsiveness, and is caused by environmental factors and induced by a combination of genetic and environmental stimuli. Genetic studies have revealed that multiple loci are involved in the etiology of allergic diseases, which are characterized by a predominant helper T (Th)2 response [1, 2]. Allergic reactions are not limited to the area they originated, and there has been a lot of speculation on the relation between dermatitis and sensitization to aero-allergens and food allergens in humans [3, 4]. However, the mechanisms, which lead to the development of systemic element, and particularly the mechanisms of distant manifestations after a local allergic reaction have not been elucidated [5]. Possibilities of the development of cutaneous lesions in humans with food and milk allergy include locally and systemically produced cytokines, chemokines and several chemical mediators [6]. Especially, interactions between inflammatory cells and endothelial cells via adhesion molecules may play important roles in various inflammatory and immune responses [7, 8]. For example, milk-induced urticaria is associated with the expansion of T cells expressing cutaneous lymphocyte antigen (CLA) on lymphocytes in the cutaneous tissues [3], leading to the development of cutaneous lesion. On the other hand, very late antigen-4 (VLA-4), a counter receptor of VCAM-1 on endothelium, plays an important role in the migration of mainly eosinophils and lymphocytes to the sites of inflammation [9]. In addition, lymphocyte function-associated antigen (LFA)-1 on neutrophils and monocytes interacts with

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intercellular-associated molecule (ICAM)-1, a counter receptor for LFA-1, on endothelium and those cells may play a role in inflamed areas [7]. Allergic respiratory inflammation might even spread systemically to involve nonrespiratory organs. Eosinophilic enteritis and eosinophilic esophagitis are reported during pollen seasons in patients with seasonal allergic rhinitis in human [5]. Also, eosinophil-associated gastrointestinal disorders in allergic diseases including allergic asthma and rhinitis have been reported [10]. Moreover, it has been suggested that late-phase reactions are manifestations of the systemic inflammatory events, leading to pathologic response in other parts of body [5].

There are a number of reports allergen- exposed local reaction in sensitized individuals. On the other hand the systemic inflammatory events in local allergic diseases may lead to pathologic response in other parts of body [5], but the underlying pathogenesis of distant lesions of allergen-unexposed sites with or without clinical symptoms in allergic airway disorders is largely unknown. Thus, this article focused on the distant lesions such as dermis with special reference to the expression of adhesion molecules.

Immediate and late reactions in effector phase in allergic airway reaction

The aim of this article is to introduce and discuss distant manifestation, which is not allergen unexposed site, in the effector phase of airway allergy except for anaphylaxis. In this section, general information of the type of allergic reactions will be briefly introduced.

In the effector phase, allergic airway reaction of nasal/bronchial mucosa can be divided into an immediate- and/or a late-phase reaction in human with airway allergy and animal models, and some develop a late-phase reaction after a symptom-free interval [1, 11, 12] (Fig. 1).

In immediate phase mast cells increase in number in the mucosa. Stem cell factor (SCF) from several cells (e.g. fibroblast and endothelial cells) induces differentiation of mast cells from their bone marrow [13, 14]. The increased number of IgE-bearing mast cells (mucosal and connective tissue types) and basophils interacting allergens lead to a specific immunological reaction. Interleukin (IL)-4, a switch factor for IgE synthesis, and IL-5, an eosinophil growth factor are produced by helper T(Th)2 cells and IL-6 contributes to the terminal differentiation of B cells to plasma cells in the production of antibodies [15]. Mast cells and infiltrated basophils release biological active materials (e.g., leukotriens: LTs, prostaglandins: PGs, histamine, serotonin and eosinophil chemotactic factor of anaphylaxis (ECF)-A, leading to local inflammation [16]. Also tumor necrosis factor (TNF)-α produced by mast cells induces airway neutrophilia and may contribute to the airway inflammation [17].

Late allergic reaction is the allergen specific and IgE independent [1]. Recruitment of eosinophils and Th2 cells migrate into the mucosa and release several mediators such as LTs, PGs, histamine and serotonin from eosinophils [16]. Major basic protein (MBP), eosinophil derived peroxidase (EPO) and eosinophil cationic protein (ECP) from eosinophils result in tissue damages [16]. Cytokines (IL-4, IL-5, IL-9 and IL-13) from Th2 cells play a role in activity of eosinophils and increase in goblet cell hyperplasia/metaplasia and hypertrophy [1, 18]. IL-5 promotes the production of eosinophils in bone marrow [19]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) derived from several cells (e.g. T cells, macrophages, endothelial cells, fibroblast, mast cells) stimulates the proliferation and maturation of myeloid progenitors, as well as functionally activating mature neutrophils, eosinophils, and macrophages [20]. Moreover, several types of cells and mediators involved in the late phase reactions, which can also lead to priming and long-term inflammation [21]. For example, IL-23 producing CD4(+) T-cell and IL-17A producing Th-17 cells plays an important role in the development of chronic inflammatory diseases, including autoimmune diseases. The enforced expression of IL-23 in the airways significantly enhanced antigen-induced eosinophil and neutrophil recruitment into the airways [22]. The airway epithelium modulates Th2 responses through the production of a group of epithelial-derived Th2-driving cytokines, including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), which enhance Th2 inflammatory responses [23].

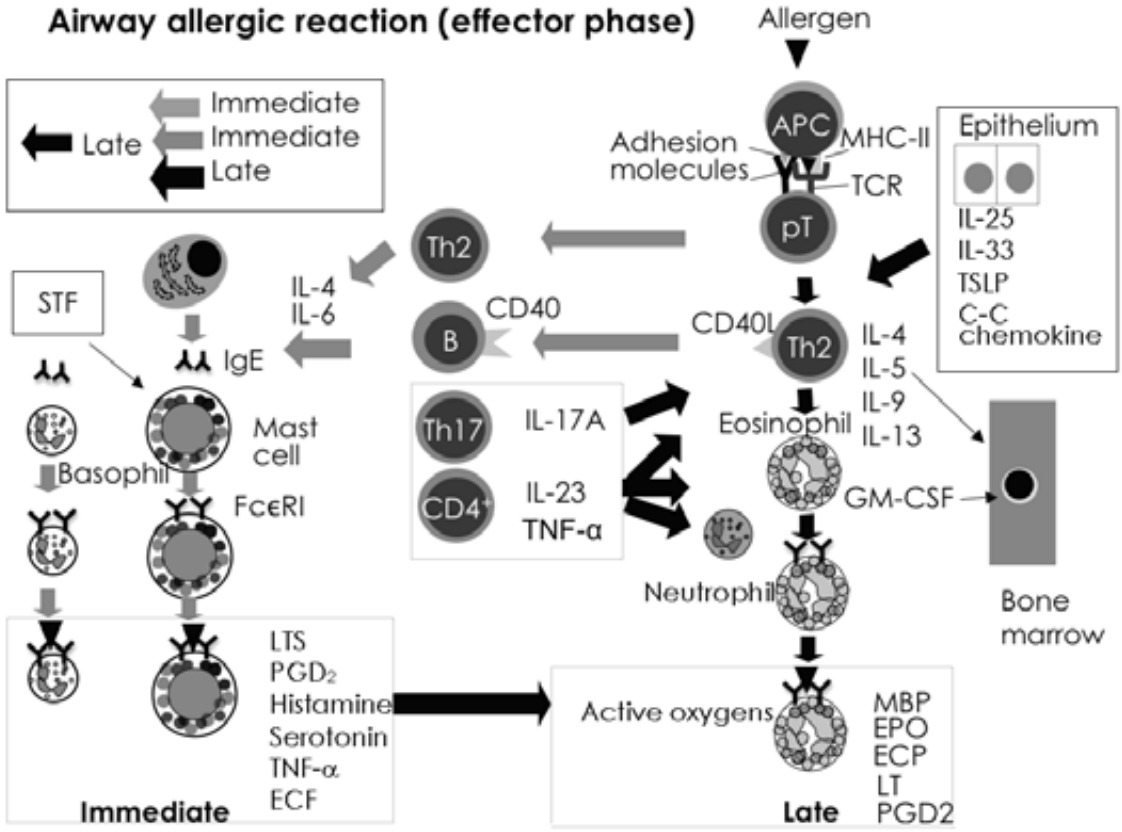

Fig. 1. Immediate and/or late allergic airway reaction in effector phase. APC: antigen presenting cell, MHC-II: major histocompatibility complex-class II, TCR: T cell receptor.

Keratinocyte-produced TSLP may represent an important factor in the link of atopic dermatitis to asthma [24]. These epithelial-derived Th2-driving cytokines execute a regulatory function of the epithelium on mucosal immunity by promoting Th2 responses [16]. Moreover epithelium stimulated with Th2 cytokines produce C-C chemochines (e.g. eotaxin, and regulated on activation normal T expressed and secreted: RANTES), which may be involved in regulation of eosinophil recurutement [25]. In addition, dendritic cells (DCs) are the professional antigen presenting cells that have the capacity to present antigen to naive-T cells and T-effector cells and DCs have an important role in the immunological outcome of the disease [26, 27].

Distant manifestation after allergen exposure in effector phase of sensitized individuals

In this section, some evidences of systemic reaction in sensitized individuals exposed allergens will be introduced.

Incorvaia *et al*. [28] have reviewed that allergic skin pathology includes disorders which are IgE-mediated, such as urticaria/angioedema, cell-mediated, such as contact dermatitis, which is typically local skin inflammation in the site where contact with the hapten takes place, or mediated by both these mechanisms, such as atopic dermatitis. On the other hand, the phenomenon of systemic propagation of allergic reactions occurs over the entire spectrum of allergic diseases [5]. For example, urticaria/angioedema and atopic dermatitis are systemic in their expression, as contact with the specific allergen in the gastrointestinal tract (as occurs for foods in both urticaria and atopic dermatitis) or the respiratory tract (as occurs for house dust mites in atopic dermatitis) is able to elicit an allergic reaction in the skin [28].

In allergic airway diseases mucosal inflammation was not restricted to the challenged organ only, but extended throughout the whole airway in

subjects with allergic rhinitis [29]. There are a lot of speculation on the relationship between atopic dermatitis and sensitization to aero-allergens and food allergens [30-32]. It is probable that aero-allergens may induce cutaneous manifestations through direct contact with the skin of sensitized persons and there is the possibility that the skin problem may reflect systemic propagation of an allergic reaction originally occurring in the respiratory mucosa [5, 33]. Brinkman *et al*. [34] demonstrated that dustmite allergen inhalation challenge can cause a flare up of skin lesions in patients with pre-existing atopic dermatitis and dust-mite sensitization in skin. Importantly, the worsening in the clinical dermatitis occurred around 24 hours after the inhalation challenge and no acute cutaneous symptoms were noted. In addition, the effect of the inhalation challenge on the skin was more pronounced in the subjects who also had asthma, as opposed to those who only had allergic rhinitis. Moreover, systemic immune activation in atopic dermatitis is supported by the observation that these patients have increased numbers of circulating activated Th2 cells, eosinophils, macrophages, and IgE. This systemic activation might facilitate local infiltration of primed T cells, eosinophils, and macrophages into the respiratory mucosa after inhalation of allergen in genetically predisposed hosts [35]. These data suggest that local allergic reaction is able to induce systemic reaction and that underlying immunological status in sensitized patients may determine the degree (severity) of allergic reaction in distant sites and different types of reaction. Moreover, quantity and quality of immune reactions at the distal site may not always identical at those of the allergen exposed site.

Hypothetical mechanisms of systemic reaction in allergen-unexposed site in effector phase in allergic airway diseases

Airway allergy may have a possibility to evoke distal lesions including dermal lesions (Fig. 2). In this section, hypothetical mechanims will be discussed.

It is well known that atopic dermatitis (frequently in association with food allergy) predates the development of asthma and allergic rhinitis by several years [35]. Most reports focuss on dermal allergic reaction or digestive organs as the primary lesions, but there are a few reports in the development of lesions in allergen-unexposed sites (e.g. dermal lesions) after the development of allergic airway lesions.

It is possible that allergen is slowly absorbed from the site of its original contact with the body (the respiratory or the gastrointestinal mucosa) into the peripheral blood [5] and it is picked up by mast cells and antigen presenting cells in various organs. This would lead to the distant-local reactions. In addition, DCs may play a crucial role not only in the induction phase but also in the effector phase [26]. We have previously demonstrated that an allergic reaction induced in the nasal or bronchial mucosa should simultaneously occur in other parts of body in late allergic models [36, 37]. This suggests that distant manifestations may occur in human patients with airway allergy.

Immediate reaction in distant tissue (dermis) of airway allergic reaction in effector phase

It is well known that anaphylactic reaction after some allergen exposure is induced systemically by immediate reaction. In this section, some evidence in distant lesions without clinical symptoms will be mentioned in a animal model of airway allergy.

There is a possibility that immediate allergic airway reaction may result in the development of immediate allergic reaction at distant various tissues. However, distant dermal lesions in immediate airway allergic reaction in experimental animal models are largely unknown other than anaphylaxis. We have reported that in late allergic rhinitis model the binding of IgE and ovalubumin (OVA) on mast cells and eosinophils outside of blood vessels in the dermis and subcutaneous tissues, resembling to the urticaria like lesions [36]. Those in the circulation may be derived from damaged venules.

Venular wall damages will result in increased permeability and leak of IgE and OVA may occur. It is probable, since vascular damage by eosinophilic venulitis was observed at the site of eosinophils adhered to endothelium of venules via

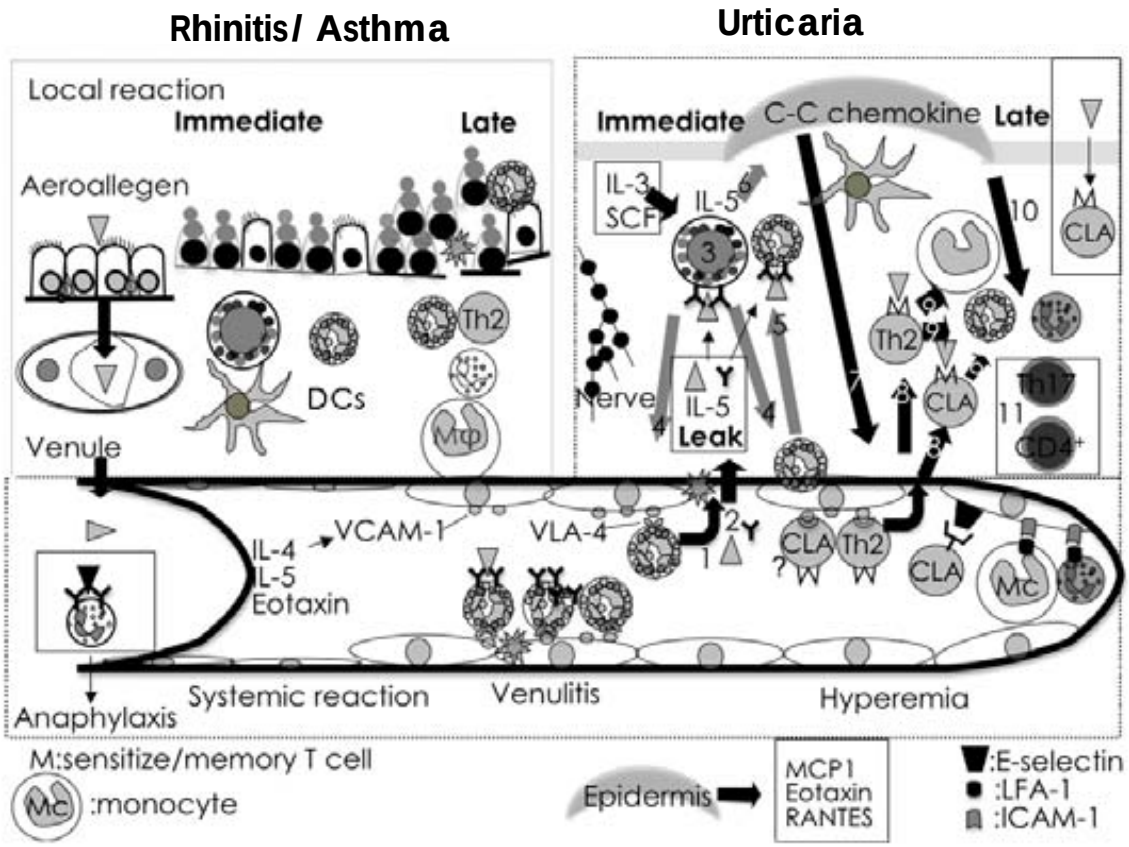

Fig. 2. Schema of hypothetic development of distant (cutaneous) lesions during the effector phases in allergic airway diseases. In immediate reaction, eosinophils attached endothelial cells (1) damage them. This cause the leak of allergen, IgE and cytokines (2) and bind of IgE and allergen on mast cells (3), resulting in release of bioactive substance (4). In addition, ECF from mast cells attract eosinophils outside of vessels (5) and again binding of allergen and IgE on eosinophils may occur. On the other hand, in late reaction (6-10), IL-5 produced from mast cells may induce C-C chemkines (6), which may attract Th2 cells and CLA^+ cells (7), and exudation of those cells may occur (8). These events activate eosinophils, neutrophils and macrophages (9). Also IL-17 from Th17 cells, other $CD4^+$ T cells and DCs (10 and 11) contribute to the development of inflammation. Before local inflammatory reaction occurs, adhesion molecules (1) (e.g. ICAM-1/LFA-1, VCAM-1/VLA-4, E-selectine/CLA-ligand) may play an important role. On the other hand, aero-allegens via skin also may play a role in the development of dermatitis. Dendritic cells (DCs) may participate not only in induction but also in maintain of inflammation.

VCAM-1 on endothelium and its counter receptor (VLA-4) on eosinophils and lymphocytes. Then, release of cytotoxic substances (e.g. eosinophil peroxidase: EP, major basic protein: MBP or active oxygens) from eosinophils may cause damages to endothelium, resulting in an increased vascular permeability [38].

Secondly, leaked IgE cross-linked on tissue mast cells with OVA results in the release of histamine, ECF-A, LTB4, LTC4, LTD4, PGD2 as well as cytokines, such as IL-5 and IL-13, which directly induce allergic symptoms [39, 40]. Although the principal cell is the mast cell, other IgE receptor-bearing cells such as the macrophage, eosinophil, and platelet might also be involved in this immediate response [39]. ECF-A may accumulate eosinophils from blood vessels to the cutaneous tissues. Thereafter, again increased production of histamine, serotonine and LTs from eosinophils and basophils may contribute to an increase in vascular permeability. IL-4 has the capacity to induce vascular leak by a direct effect on cultured

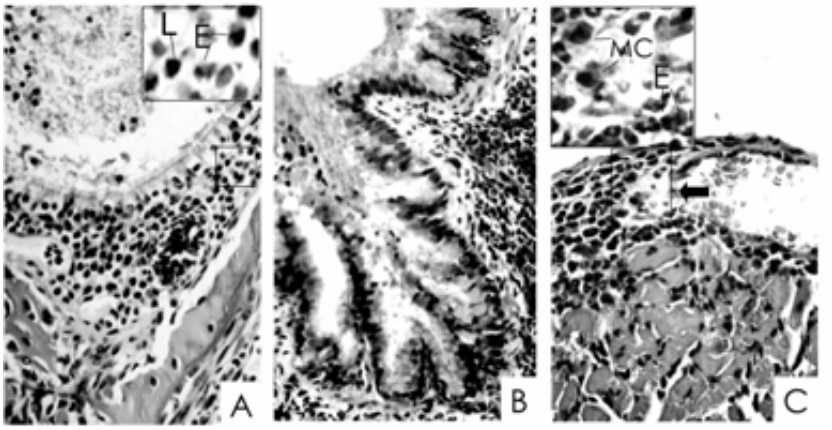

Fig. 3. Late allergic rhinitis (A and insert: enlargement of rectangle of A) and bronchitis (B) in which dominant reaction of lymphocytes and eosinophils occur. On the other hand, mast cells and eosinophils are mainly observed in and around small veins in epicardium of heart (C and insert: enlargement of rectangle of C) and an arrow in C indicates destruction of wall of vein in late allergic bronchitis.
L: lymphocyte, E: eosinophil and MC: mast cell in B and C.

endothelial cells [41]. Locally produced IgE by plasma cells outside of blood vessels may be another possibility other than leak of IgE derived from blood circulation. However, a few plasma cells were detected, suggesting their role of plasma cells is minor [36], suggesting that this possibility is less likely.

Alternatively, OVA-sensitized individuals developed the late reaction in nasal and bronchial mucous membranes at 96 hours after intranasal challenge with OVA where eosinophils and Th2 type lymphocytes [36, 37, 42] are dominant (Fig. 3A, B), whereas mast cells and eosinophils were dominant in dermis in this model. In addition, the same lesions in venules and small veins of heart (Fig. 3C, our unpublished data) as seen in dermis were observed. In addition, systemically absorbed allergen would be uptaken by every mast cell in every tissue, on the basis of the assumption that every one of these cells carries specific IgE recognizing allergens against which allergic sensitization has occurred. Thus, the presence of mast cells in tissues may determine the immunologic reaction, because immediate reaction occurs at the site in which mast cells are abundant. These suggest that different systemic manifestations may occur between airway allergy and other parts of the body in the same patients. More importantly, late reaction in terms of duration of time after allergen exposure does not coincide with the cell types and humoral factors. This suggests dissocation of reaction may occur between original sites and distant sites.

Late reaction in distant tissue (dermis) of airway allergic reaction in effector phase

There are a few reports on late reaction in distal tissues especially. Also the information of late reaction in dermal tissues in airway allergy is totally lacking. In this section, some report will be introduced and the mechanisms will be discussed in a model mouse.

It is not clear that acute and/or late local reactions in airway allergy may induce late reaction at distal tissues. Regarding the systemic manifestation in local allergy, CLA^+ ($CD45RO^+$ memory/ effector T cells) is the major T cell ligand for the vascular adhesion molecule E-selectin, is supposed to play a role in patients with allergic contact dermatitis or atopic dermatitis, and memory T cells from asthmatic individuals and patients with both asthma and atopic dermatitis express the allergen specificity [42]. In addition, ICAM-1 on post capillary venule/ LFA-1 or VCAM-1/VLA-4 on endothelium in allergic contact dermatis and atopic dermatitis, which may contribute CLA^+ T cell accumulation in dermal tissues [43].

Another possibility is the late reaction following the immediate reaction. Activated mast cells produce cytokines such as IL-5, which sitimulate epithelial cells, resulting in the production of C-C chemokines such as RANTES and eotaxin [16]. These would attract Th2 cells outside of venules and then attract eosinophils in subcutaneous tissues. On the other hand, GM-CSF produced from epithelial cells together with TNF-a from mast cells may attract neutrophils and maccrophages, which will be trapped venules, at the inflamed sites. On the other hand, Th17 cells are characterized by their IL-17 (or IL-17A), IL-17F, IL-6, TNF-α, and IL-22 expressions, which coordinate local tissue inflammation through upregulation of proinflammatory cytokines and chemokines [44]. Several events may occur as described in the section of late reaction.

Eosinophil dominant reaction without local mast cell and Th2 cell in intestinal venule in airway allergy in effector phase

In this section, the possibility of non-immunological reaction in intestine, which is evoked during the developmet of airway allergic reaction, will be introduced.

Eosinophilic venulitis without the participation of not only mast cell but also Th2 cells developed in the lamina propria in the small intestines in a model of late asthma induced OVA sensitization and challenge [37]. Eosinophils were restricted mainly within the venular lumen and attached firmly to endothelial cells expressing VCAM-1. Degranulation of eosinophils may lead to damage of venules by releasing their cytotoxic substances, but clinical symptoms such as diarrhea or softing of feces were not observed. Venulitis induced by either eosinophils itself, IgE-bound eosinophils and/or OVA-binding in IgE-sensitized eosinophils is unclear. In addition, less accumulation of Th2 cells in and around venules and less involvement of intestinal epithelial cells were observed. These suggest that clinical symptoms will be induced by more severe intestinal lesions. Taken together, eosinophilic venulitis may be the result of the sequence of systemic Th2 reaction.

Distant manifestation and anaphylaxis

As mentioned above, the mechanisms of distal lesions are unclear except for those of anaphylaxis. In this section, the difference between non-anaphylactic and anaphylactic reactions will be discussed (Fig. 4).

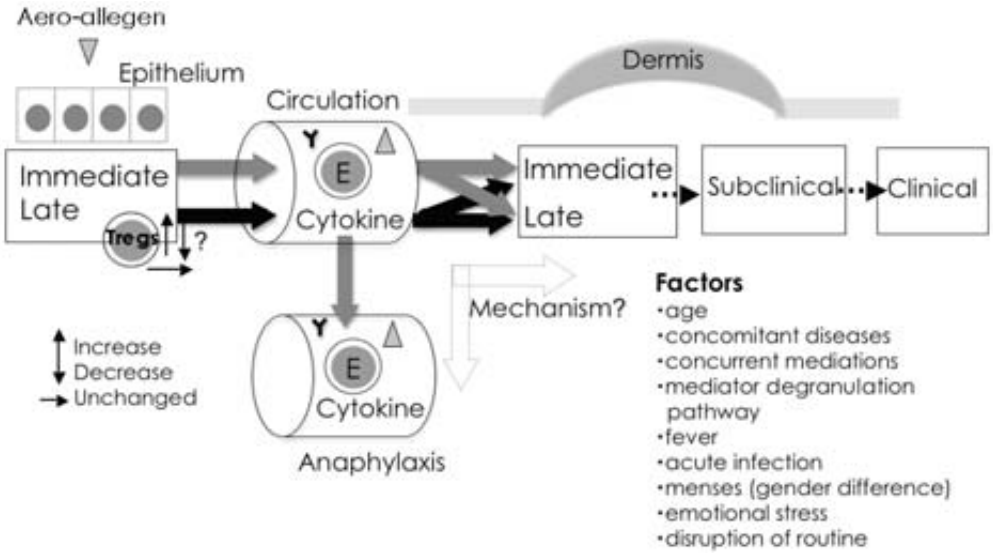

Fig. 4. Distant manifestation and allergic anaphylaxis (hypothesis). Several factors, which may be responsible for determinig the development of anapheraxis [47]. In addition, function of Tregs may, at least in part, determine disease direction. E: effector cells.

It is characterized by production of allergen-specific IgE, which binds to mast cells and initiates a cascade of molecular and cellular events that affect the respiratory tract (rhinitis and asthma), skin (dermatitis, urticaria), and multiple systems (anaphylaxis) in response to a variety of allergens including pollens, mold spores, animal danders, insect stings, foods, and drugs, in addition to immunoregulatory dysfunctions similar to those noted in highly stressed populations [45].

Systemically absorbed allergen would initially activate basophils in the circulation before reaching distant tissues and basophil activation would lead to generalized reactions resembling anaphylaxis [46]. However, the mechanisms by which determine non-anaphylaxis (sub-clinical status) or anaphylaxis (clinical symptoms) and their relationship are unknown in airway allergy. As already stated, among Th2-type cytokines, IL-4 is responsible for class switching in B cells, which results in production of allergen-specific IgE antibodies that bind to specific receptors on mast cells and basophils. One might suppose that after re-exposure to the sensitized allergen, this phase is followed by activation of IgE Fc receptors on mast cells and basophils resulting in biogenic mediator releases being responsible for the symptoms and signs of anaphylaxis.

Simons [47] has pointed out that important patient-related risk factors for severity and fatality include age, concomitant diseases, and concurrent medications, as well as other less well-defined factors, such as defects in mediator degradation pathways, fever, acute infection, menses, emotional stress, and disruption of routine.

It is well known that drug and food allergies were the most common known causes of anaphylaxis. Patients with asthma have a greater risk of anaphylaxis than those without asthma, and the risk is greater in severe than nonsevere asthma. Moreover, women are at higher risk of anaphylaxis than men, especially those with severe asthma [48]. It seems likely, since females are more sensitive to asthma compared to males in a late asthma model [49]. Alternatively, $CD4^+CD25^+$ ($FoxP3^+$) regulatory T-cells (Tregs) have been shown to be critical in the maintenance of immune responses, such as prevention of autoimmunity and hampering allergic diseases. Tregs and/or IL-10-producing Tr1 cells have been shown to be responsible for the protection of immune tolerance and intact immune reactions following exposure to allergens such as aero-allergens or food allergens [50, 51]. In this regard, both cell-cell contact through membrane bound transforming growth factor (TGF)-β or via suppressive molecules such as cytotoxic T-lymphocyte-associated antigen (CLTA) -4 and soluble cytokine- (TGF-β and IL-10) dependent mechanisms have been shown to contribute to the ability of Tregs to operate effectively, and those cells are capable of suppressing Th2 responses to allergens in health, whereas such inhibition is attenuated in allergic conditions [50, 51]. If that is the case decreased function of Treg cells may, at least in part, participate in the systemic development of allergic reaction including anaphylaxis.

In contrast, there was a significant increase in Tregs in asthmatic children [52]. Moreover, Botturi *et al*. [53] have reported tha T cell activation differs between allergic rhinitis and asthma. In asthma, a constitutive, co-receptor independent, Th1 activation and Treg deficiency is found. In addition, in allergic rhinitis, an allergen-induced Treg cell deficiency is seen, as well as an Inducible co-stimulator (ICOS)-, CD28- and CTLA-4-dependent Th2 activation and allergic asthmatics display both characteristics [54].

Thus, further study is needed to clarify the role of Tregs in distant manifestation in airway allergy, because their behavior may determine the direction of distant manifestation of airway allergy.

Alternatively, Incorvaia *et al*. [28] reviewed that systemic Th2 reaction evoked by atopic dermatitis may permit the development of airway allergy as follows. The pathogenesis of which is linked to a complex interaction between skin barrier dysfunction and environmental factors such as allergens and microbes. Especially the mutation of the skin barrier protein filaggrin is related strictly to allergen sensitization and to the development of asthma in subjects with atpic dermatitis. The altered skin barrier function results in the passage of allergens through the skin and to systemic responses. Langerhans cells in epidermis which, via their IgE FcεRI, capture the

allergens and present them to Th0 cells, leading to activation of Th2 cells. As a result Th2 cells seem to drive airway inflammation following cutaneous exposure to antigens. If that is the case, skin lesions such as atopic dermatitis under the influence of dysfunction of skin barrier will develop by allergen exposure via skin (Fig. 2) in patients with airway allergy other than the development of skin lesions induced by systemic Th2 reaction as explained in this article.

CONCLUSION

The key questions are the underlying mechanisms of distant manifestation in airway allergic reaction. The mechanisms of distant lesions may be determined by the existence of mast cells, interaction of adhesion molecules, immunological status including function of Tregs, allergic type, circulation of IgE, cytokines and several immunocompetent cells [20, 46], dose (several times of allergen exposure) and route of allergen exposure including genetic susceptibility. In addition, a systemic reaction may develop with or without clinical symptoms. Regarding the development of skin lesions evoked by allergens interacted with inflammatory cells, skin-homing may be crucial event in atopic dermatitis, mediated by the CLA receptor, which characterizes T cell subpopulations with different roles in atopic dermatitis and asthma. Another uncleared issue is the mechanisms of the difference between distant manifestation and anaphylaxis. Further studies are required to clarify these points for undestandings of pathogenesis of the development of distant lesions in airway allergy.

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