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Allergy and hypersensitivity

Mechanisms of allergic disease

Editorial overview

Cezmi A Akdis

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Cezmi A Akdis

Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22, CH-7270 Davos, Switzerland

E-mail: akdisac@siaf.unizh.ch

Cezmi A Akdis is Professor of Immunology and Director of the Swiss Institute of Allergy and Asthma Research (SIAF). He is the chairman and coordinator of the Scientific Programme Committee of the European Academy of Allergology and Clinical Immunology (EAACI) and Assembly Member of the Global Allergy and Asthma European Network (GA²LEN). His research interests include: mechanisms of peripheral tolerance to allergens; effector mechanisms of allergic inflammation; mechanisms of curing allergy and asthma; and the development of better vaccines for the curative treatment of allergy.

Introduction

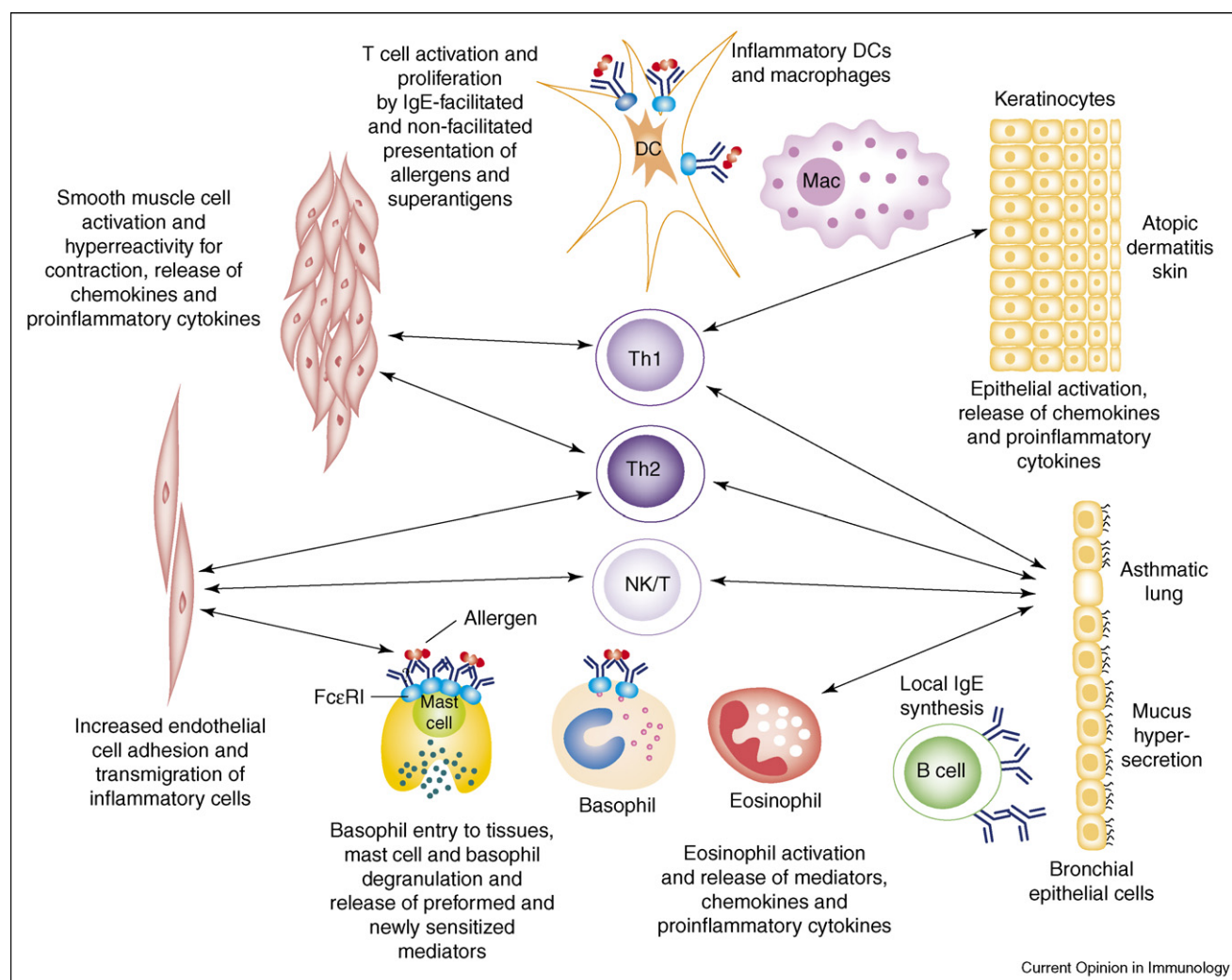
The immune system is a highly interactive network that makes its decisions based on input from all organs, tissues, infections, normal flora bacteria, and many or even any environmental agents. General rules of immunity versus tolerance as well as co-evolutionary development apply to the allergen-specific immune response, because rules for regulators and effectors of this have probably been developed in a co-evolutionary manner with helminths, mites, insect venoms, foods and other allergens. IgE sensitization against allergens showed a steep increase of up to 50% in the population together with an increase in clinical allergic disease of up to 30% in some communities, particularly during the past three decades; reasons for these epidemics, underlying mechanisms and novel treatment approaches will be intensely investigated and reported in this issue of the journal.

What makes a protein an allergen?

In diseases that involve the immune system such as allergy, autoimmunity, transplantation rejection, cancer and infections, antigens are either the direct or the indirect cause of the disease and can be targeted for the treatment [1]. Investigation of what makes a protein an allergen has been a prerequisite for understanding allergic disease to develop strategies for immune intervention. Allergens are almost always proteins, but not all proteins are allergens. A protein that has allergenic activity should display two properties: induction of the IgE response, which involves the sensitization phase including T cell, B cell and dendritic cell cooperation, and induction of a clinical response to the same or similar protein on subsequent exposures, which involves immediate- and late-phase responses [2] (see Figure 1). However, this simplistic description avoids the more complex issues during the first confrontation of the allergens with the immune system, including the biochemical properties of the allergen, other innate immune response stimulating substances around the allergen at the time of exposure (within the same extract or co-exposure with an infection or a vaccine), stability of the allergen in the tissues, digestive system, skin or mucosa, and finally dose and time of stay in lymphatic organs during the interaction with the immune system (see Box 1).

More than 1000 allergen sequences have been identified from various sources. Despite increasing knowledge of the structure and amino acid sequences of the identified allergens, only a few biochemical characteristics can be associated with allergenicity. For example, characteristics that predispose some food proteins to become allergens include: the abundance of the protein in the food, high numbers of linear IgE binding epitopes, and the resistance of the protein to digestion and processing of the food [3]. Currently, studies investigating allergenic properties generally focus on

Figure 1



Factors that lead to allergic inflammation include activation and migration of Th2 cells, eosinophils, Th1 cells, NKT cells and inflammatory dendritic cells (DCs) in the submucosal tissue of the bronchi. Type 1 hypersensitivity reactions, characterized by mast cell degranulation and basophil entry into submucosal tissue followed by degranulation, and type IV hypersensitivity responses with a contribution of T cells and NKT cells efficiently cooperate. This induces the activation of resident tissue cells such as smooth muscle cells, fibrocytes, macrophages and epithelial cells, release of proinflammatory cytokines and chemokines, and an increase in bronchial hyperresponsiveness. A ping-pong effect between migrating inflammatory cells and resident tissue cells with multiple proinflammatory cytokines and chemokines augments the inflammation. Local IgE production by B cells, the role of NKT cells, basophil entry into tissues and strong eosinophil predominance are features of asthma that have not been demonstrated in atopic dermatitis.

soluble proteins, despite the fact that natural exposure normally occurs to insoluble and aggregated particulate forms of many allergens that might have different properties.

Allergy epidemics and hygiene

The increasing prevalence of allergic disease in the past decades seems to be associated with the westernized lifestyle, but the underlying mechanisms are not completely understood. Extensive epidemiological studies under certain circumstances of lifestyles have provided

some insight into possible reasons for the so-called 'allergy epidemics'. The 'hygiene hypothesis' is one of the main propositions to explain this. Epidemiological and clinical data support the hygiene hypothesis as a cause of both allergic and autoimmune diseases [4]. Its role in other immunologic diseases, such as transplantation tolerance, chronic infections and cancer, has not been studied intensely to date. A major theory regarding its mechanisms of action deals with immune regulation [5]. Infectious agents stimulate a large variety of regulatory and suppressor cells; they intervene through components

Box 1 What makes an allergen an allergen**Evidence for distinct structural features of allergens**

Allergens belong to few protein families: Several allergens, particularly plant and food allergens, belong to very few of the thousands of known protein families [47].

Cavities and tunnels that bind ligands and other structural features that provide allergen stability: Some members of allergen families such as parvalbumin, casein, lactoglobulin, non-specific lipid transfer proteins and Bet v 1 homologues have cavities and tunnels. These are able to bind metal ions, steroids or lipid ligands [48]. Ligand binding might provide resistance to proteolysis and thermal stability, leading to increased accessibility to the immune system. Some allergen families possess compact molecules that have a high level of disulphide bond formation, such as prolamin superfamily and chitinases [49]. Some food allergens such as casein and prolamine are thermostable and do not change their structure (IgE epitopes) upon heating [50].

Interaction with membranes and other lipids: Eucaryotic cell membrane and lipid binding activity is a common feature for theumatin-like proteins, phospholipases and lipid transfer proteins [51,52].

Repetitive structures and aggregation: Tropomyosins express series of up to 40 heat-stable repetitive IgE-binding heptads [53]. Glycation reactions, which occur during roasting of peanuts, might be responsible for the apparent increase in allergenic activity [54].

IgE and T-cell epitope sharing between allergen families: The large extent of cross-reactivity among several allergen families is a well-known feature, which has implications in diagnosis and treatment [47,55].

Other features of allergens that might contribute to allergenicity

Dose: The abundance of certain allergens inside the extract is a common feature [3].

Suppression of local defenses: House dust mite Der p 1 suppresses local defenses of the lung by inactivating elastase inhibitors [56].

Induction of proinflammatory mechanisms: House dust mite allergens induce proinflammatory cytokines from respiratory epithelial cells; the cysteine protease allergen Der p 1 activates protease-activated receptor (PAR)-2 and inactivates PAR-1 [57].

Activation of airway epithelial cells: Der p 1 and Der p 5 activate human airway epithelial cells by protease-dependent and protease-independent mechanisms [58].

Transepithelial allergen delivery: Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions [59].

Spreading factor: The presence of hyaluronidase, the spreading factor in venoms, may increase allergen exposure to immunologic organs [60].

Chemotaxis and activation of eosinophils: Chemotaxis and activation of human peripheral blood eosinophils is induced by pollen-associated lipid mediators [61].

Regulation of dendritic cells: Pollen-associated lipid mediators regulate dendritic cells [62].

Cell toxic substances: Direct cell toxic substances, such as mellitin and phospholipases, exist in insect venoms [63].

that are not recognized as antigens, but bind to specific receptors on cells of the immune system. Recently, attention has been drawn to the Toll-like receptors [6] and T cell, immunoglobulin, mucin domain-containing molecules (TIM) present on T cells, which could express the function of the virus receptor (as in the case of the hepatitis A virus and Tim-1, reviewed by Umetsu and DeKruyff in this issue) [7].

The hygiene hypothesis poses several questions concerning the nature of protective infectious agents, the timing of their involvement and the mechanisms of protection. The review by Vercelli in the issue of *Current Opinion in Immunology* discusses the current status regarding the mechanisms of the hygiene hypothesis. A unifying concept for the hygiene hypothesis has not yet emerged, and might not emerge; however, various aspects of the complex interplay between immune responses of the host, and the type, dose and variety of the exposed microorganism have been suggested. Several questions remain unsettled concerning the nature of protective exposures and infections, many aspects of the mechanisms of protection, the spectrum of diseases in the scope of the hypothesis, and the difference between triggering and protective infections. Although there is potential for the development of novel preventive and therapeutic strategies, to date practical implications cannot be deduced from these findings.

Immune response or no response to allergens

Co-evolutionary development of the immune system together with infections and non-infectious environmental proteins (allergens) has generated biologically relevant thresholds and has caused major directions to be taken by the immune system. With few exceptions, the immune response against acute viral infections is directed towards complete neutralization of the microorganism. In contrast, the immune response to chronic non-cytopathic viruses (hepatitis B virus, hepatitis C virus and HIV), commensal bacteria, helminths and allergens shows different intensities depending on the dose, localization and innate immune response-stimulating properties of the microorganism as well as on the response thresholds of the host.

There are obviously several essential differences between allergen exposure and acute infections. One of the main differences is that allergen exposure persists for the entire life of a patient (mites) or repeats at a certain time of every year (pollens), except in the case of food and latex allergy and insect venoms. Another important difference is that innate immune response-stimulating substances such as Toll-like receptor-ligands exist in allergens, but in much lower quantities compared with acute infections. Allergens are exposed to the mucosal immune system together with proteins and innate immune response-stimulating substances of commensal

bacteria [8]. The human intestinal upper respiratory and the genital mucosa are colonized by a large number of microorganisms that inhabit the intestinal tract and that support a variety of physiological functions. The stepwise microbial colonization of the intestine begins at birth and continues during the early phases of life to form an intestinal microbiota that is different in each individual. This process facilitates the formation of a physical and immunologic barrier between the host and the environment, helping the gastrointestinal tract to maintain a disease-free state. Probiotics are viable microbial food supplements that are thought to have a beneficial impact on human health [9]. As shown in the second part of [Box 1](#), the direct tissue destructing capacity of allergens has been demonstrated, but again in much lower levels compared to acute infections. As reviewed by [M Akdis](#) in this issue, the default healthy immune response to allergens is expected to be no response; however, detectable T-cell and antibody (particularly IgG₄ and IgG₁) responses have been demonstrated in sensitized but clinically healthy individuals. If an immune response develops, the immune system shows allergen-specific tolerance by using multiple mechanisms in order to keep the intensity of the inflammation low and tissue destruction small.

Multifacets of ignorance and regulation of allergen-specific immune responses

The overall evaluation of the studies regarding the control of T- and B-cell responses against allergens suggests that immunological ignorance and active suppression are not entirely distinct, but rather represent linked mechanisms of peripheral tolerance [10]. Immunological ignorance suggests that T cells ignore self or foreign antigens that stay strictly outside secondary lymphatic organs or reach them only for a short period of time and below a minimal quantitative threshold [11]. As discussed above, the most common features of proteins that make them allergens are their high expression (dose), their structural features and related factors in the tissues, and their resistance to digestion (stability) ([Box 1](#)) to overcome immunological ignorance.

The mucosal surfaces of the respiratory, the gastrointestinal and the genital tract, which cover a total of 300 m² in contact with external environment, represent major sites of antigen exposure. Discrimination between pathogenic antigens, towards which a protective immune response has to be established, and harmless antigens, such as food, airborne antigens or the commensal bacterial flora that should be ignored, is the most challenging task of the mucosal immune system. Induction of mucosal tolerance or immunological ignorance of environmental harmless proteins as well as infectious agents by secretory IgA antibodies are two main mechanisms [12] (see [Figure 2](#)). Allergen-specific T regulatory (T_{Reg}) cells, reviewed by [Akdis](#), [Umetsu](#) and [DeKruyff](#), and

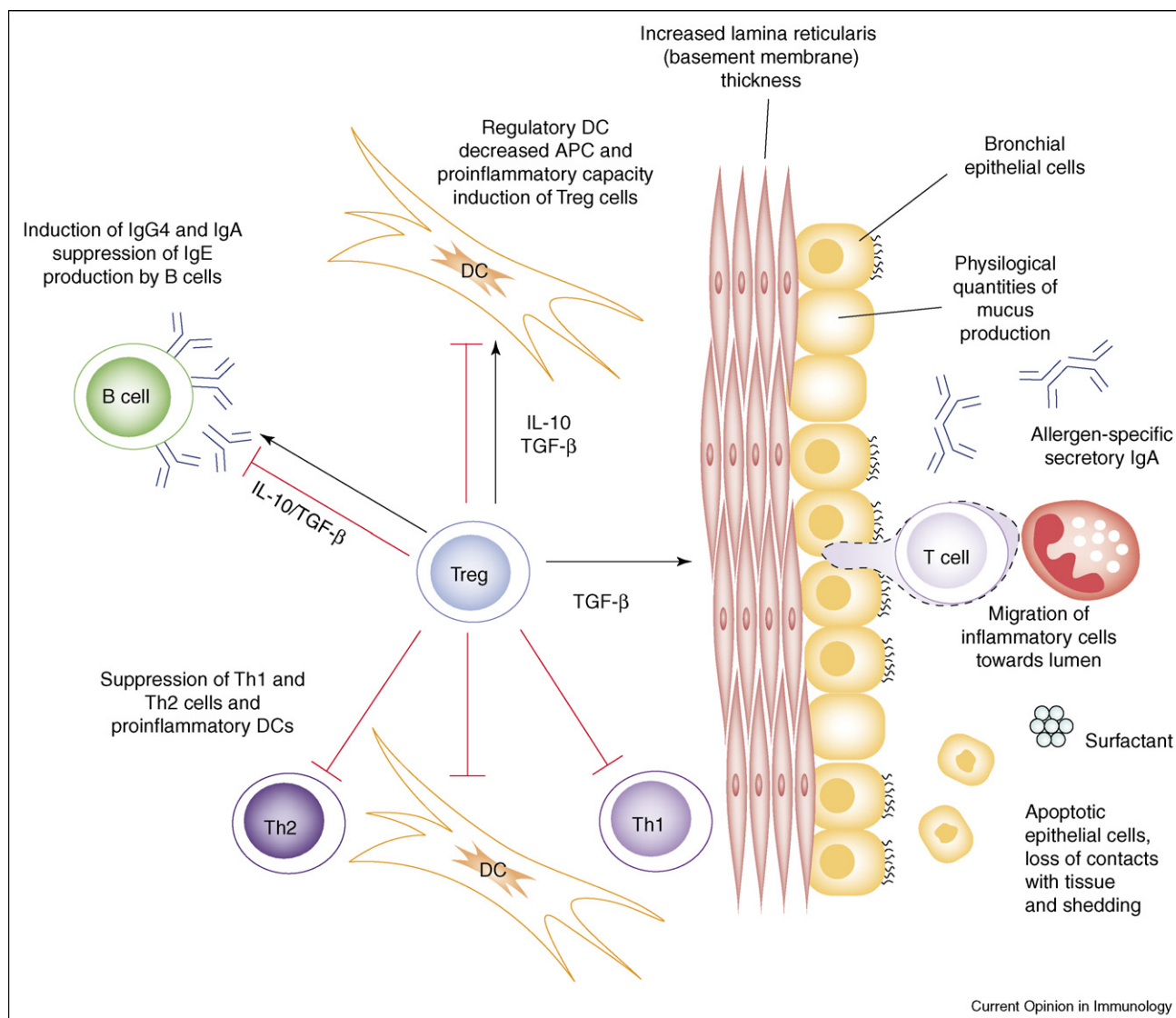
[Larché](#) in different contexts, represent the dominant T-cell subset against mucosal allergens in the healthy immune response and after allergen-specific immunotherapy (SIT) [13]. They not only suppress allergen-specific immune response development but also directly or indirectly regulate B cells by induction of IgG₄ by interleukin (IL)-10 and IgA by transforming growth factor (TGF)- β . In addition, they suppress mast cells, basophils, eosinophils and resident tissue cells, and contribute to the maintenance of peripheral tolerance as well as down-regulating thresholds of proinflammatory events in the tissues [10].

The association between serum and mucosal secretory IgA levels and development of allergy has been recently questioned. Antigen-specific secretory IgA antibodies in the gut were decreased in a mouse model of food allergy, suggesting a role for secretory IgA in ignorance to food antigens. Peyer's patch CD3⁺ cells were primarily involved by favoring IgA production through the release of IL-10 and TGF- β , and low IL-10 production in Peyer's patches favored the symptoms of food allergy [14]. Allergen-specific secretory IgA was found to protect sensitized children from development of allergic symptoms during the first two years of life, suggesting a possible ignorant role of secretory IgA against allergens [15]. In addition, increases in allergen-specific IgA has been reported in SITs performed via sublingual or subcutaneous routes [16,17].

Remodeling in asthma, which might be the consequence of excessive repair processes following repeated airway injury, includes increased deposition of several extracellular matrix proteins in the reticular basement membrane and bronchial mucosa, as well as increases in airway smooth muscle mass, goblet-cell hyperplasia and new blood vessel formation [18]. Consequently, the airway wall in asthma is usually characterized by increased thickness and markedly and permanently reduced airway calibre. A major T_{Reg} cytokine, TGF- β , is a potent regulator of fibroblast and myofibroblast function and controls the production of several extracellular matrix proteins, including collagens, proteoglycans and tenascin [19]. Other potential sources of TGF- β include eosinophils, macrophages, mast cells, neutrophils, endothelial and epithelial cells, as well as smooth muscle cells and the fibroblasts themselves [19].

Airway remodeling might represent a continuum from inflammation to scarring, but it could also be a protective response to altered airway immunology caused by ongoing cellular activation and tissue damage. The thickening of the subepithelial lamina reticularis (basement membrane) in bronchial asthma has been related to an increase in fibroblasts in correlation with TGF- β expression. Treatment of mice with anti-TGF- β antibody in the allergic lung inflammation model significantly reduced

Figure 2



Factors that could play a role in down-regulation of asthmatic inflammation. First, allergen ignorance related factors: increased basement membrane thickness that acts as a physical barrier between allergens and the immune system cells, mucosal IgA production against allergens, and mucus production in physiological quantities. Second, inflammatory cell and cytokine clearance related factors: clearance of airway tissue inflammatory cells by migration towards lumen, and induction of bronchial epithelial cell apoptosis and shedding. Third, suppression of inflammation: generation of regulatory dendritic cells (DCs) that have decreased proinflammatory and antigen-presenting cell (APC) capacity, production of T_{Reg} cells that directly or indirectly suppress effector cells and inflammatory DCs and induce IgG₄ and IgA production by B cells, and generation of other suppressor cytokines released from tissue-infiltrating cells and resident tissue cells, as well as the suppressor role of surfactants that contribute to multiple suppressor mechanisms that control allergic inflammation.

peribronchiolar extracellular matrix deposition, airway smooth muscle cell proliferation, and mucus production in the lung [20]. There is clear evidence that lamina reticularis thickening starts early in asthma, even at the time of first diagnosis [21], which suggests that a barrier between activated epithelium or mucosal allergens and inner tissues (i.e. immune system cells) occurs with the aim of down-regulation of the allergen-induced inflammatory response. It appears that the immune system

naturally tries to decrease allergen burden before the initiation of a visible disease, and continues to do so during allergic inflammation. These mechanisms resemble features of immune response to chronic helminth infections in order to decrease the antigenic burden of the helminths and to mechanically keep them away from tissues (e.g. keeping them in fibrous sacks etc.). It is generally accepted that the cyst stage of helminths occurs with the contribution of both tissue factors and parasite

factors [22]. The efforts of the immune system and lung fibroblasts to increase lamina reticularis thickness might indeed aim to make a mechanical barrier between the allergens (mites and pollens) and the submucosal tissues, particularly the immune system.

Development of the IgE response to helminths has been commonly observed, although there is no typically accompanying allergic disease. Even though helminths themselves are strong Th2 inducers, there is increasing evidence that helminth infections can protect the host against Th2-mediated allergic pathologies. Parasite infection does not prevent allergen sensitisation, but restricts the Th2 effector phase responsible for inflammation most probably related to T_{Reg} cell activity [5]. IL-10-producing B cells were suggested as an underlying mechanism for the prevention of anaphylaxis during *Schistosoma mansoni* infection, suggesting the control of mast cell degranulation threshold by IL-10 [23]. Helminth infections are also accompanied by high levels of helminth-specific IgG₄ as a link for IL-10, peripheral tolerance and suppression of allergic reactions [24].

Taken together, increased subepithelial lamina reticularis thickness [21], mucosal IgA production [15], bronchial epithelial cell shedding [25], and mucus production represent mechanisms regulated by the immune system that attempt to decrease the amount of allergen exposure (wash-away effect); these might play a role in immunological ignorance. In addition, suppressor role of surfactant [26] and transmigration of inflammatory cells away from the tissues towards the lumen might have anti-inflammatory and tissue-protective roles *in vivo*. Rapid and efficient clearance of airway tissue inflammatory cells through transepithelial migration to the lumen is central to the resolution of inflammation [27]. Interestingly, bronchoalveolar lavage cell counts have been thought to be a surrogate marker of inflammation. This might lead to a false identification of drugs that could be beneficial by increasing transepithelial migration of inflammatory cells to lumen (wash-away effect) (Figure 2).

Early and late phases of allergen-specific immune response

Differentiation and clonal expansion of T helper 2 (Th2) cells occurs in response to common environmental antigens (see Figure 1). Cytokines such as IL-4 and IL-13 induce immunoglobulin class switching to IgE and expansion of naïve B-cell populations, as well as further clonal expansion in IgE-expressing memory B cells [28]. The unequal susceptibility to activation-induced cell death between Th1 and Th2 cells that controls the T cell fate might eventually cause an imbalance in Th cell subsets leading to a peripheral blood Th2 response in polyallergic and atopic individuals [29]. This is often associated with increases in total IgE in the serum and

peripheral blood, and sometimes tissue eosinophilia. In monoallergic forms of allergic disease (i.e. insect venom allergy), allergen-specific Th2 and IgE responses are confined to the single allergen, serum total IgE is not increased, and eosinophilia is not observed [30]. These two types of allergic disease as well as non-IgE-associated types of asthma and dermatitis show differences in immune mechanisms [30]. Some epidemiological factors are different, such as sex and age of onset, but clinical features are not distinguishable [31].

IgE sensitizes mast cells and basophils by binding to the high-affinity receptor for IgE (FcεRI) expressed on their surface. Upon crosslinking of the IgE–FcεRI complexes by allergen, mast cells and basophils degranulate to release vasoactive amines (principally histamine), lipid mediators (prostaglandins and cysteinyl leukotrienes), cytokines and chemokines, all of which characterize the immediate phase of the allergic reaction [2]. Histamine is one of the key factors of the immediate phase of the allergic reaction, and regulates dendritic cells, T cells and antibody isotypes via four distinct histamine receptors (HR). HR2 acts as an anti-inflammatory and anti-allergic receptor, whereas HR1, HR3 and HR4 show proinflammatory effects [32,33]. In this issue, Grimbaldston *et al.* review novel effector and potential immunoregulatory roles of mast cells. They state that mast cells are not only associated with type-1 hypersensitivity reactions but also play a role in chronic inflammation and tissue remodelling and even display immune regulatory roles. IgE also binds FcεRI on the surface of dendritic cells and monocytes, and also binds to the low-affinity IgE receptor FcεRII (CD23) on the surface of B cells. This enhances the uptake of allergen by these antigen-presenting cells and the subsequent presentation of allergen-derived peptides to specific CD4⁺ T cells, which drive the late phase of the allergic reaction [34]. Treatment with anti-IgE-monoclonal antibody significantly reduces allergen-induced late-phase responses, demonstrating the role of IgE in enhancing T-cell responses to allergen [35].

In chronic allergic inflammations of lung and skin, the subepithelial tissue turns into a secondary lymphoid organ-like tissue with the infiltration of T cells, dendritic cells and B cells. Activated T cells interact with resident tissue cells as well as with other migrating inflammatory cells. They activate bronchial epithelial cells, smooth muscle cells, macrophages, fibroblasts in the asthmatic lungs, and epidermal keratinocytes in the allergic skin. Resident tissue cells contribute to inflammation by secretion of pro-inflammatory cytokines and chemokines [30]. Production of IFN-γ and TNF-α together with expression of FAS-ligand by Th1 cells leads to epithelial cell activation followed by apoptosis, and compromises barrier function of epithelial cells in the lungs and the skin [30]. It involves two stages. First the pro-inflammatory stage takes place, with the activation of epithelial cells and the

release of chemokines and pro-inflammatory cytokines [36]. This is followed by the eventual death of keratinocytes and bronchial epithelial cells, which leads to a visible pathology including epithelial desquamation in asthma and epidermal spongiosis in eczema. However, it represents an anti-inflammatory stage because the highly active and proinflammatory epithelial cell dies and its contacts with the inner tissue are broken (Figure 2). The important role of TNF- α in the pathogenesis of asthma is now coined by clinical studies of TNF- α antagonists [37]. As reviewed by Umetsu and DeKruyff in this issue, there has been much progress in understanding the complex interaction of effector T cells, NKT cells, other effector cells, resident tissue cells and T_{Reg} cells in asthma. Although it is not a common feature, neutrophilic inflammation occurs in severe cases of asthma and at the early phase of mice models. Th17 cells that are thought to regulate chronic neutrophilic inflammation have not been intensely investigated in allergic disease to date [38].

Novel curative treatment strategies

Allergen-SIT faces several problems related to the content of the vaccine, type of the adjuvant, route of application, long duration of treatment, side effects and limited efficacy [39]. Currently, allergen-SIT is performed using vaccines based on allergen extracts, which might contain allergens as well as non-allergenic or even toxic proteins. In addition, many extracts derived from natural materials contain innate immune response triggering substances, such as lipopolysaccharide, which is detectable and can be eliminated. However, lipopolysaccharide accompanies several other innate immune response triggering substances that are not detectable by conventional methods. Furthermore, administration of allergen extracts can cause severe, often life-threatening, anaphylactic reactions as well as new IgE sensitization to other antigens contained in the extract. Many of the problems associated with the use of natural allergens and extracts for the diagnosis and treatment of allergy can be overcome by using recombinant allergens. Another important issue to be solved is that current protocols of allergen-SIT require at least three years of clinical treatment, and efficacy is questionable in certain cases. In this issue of *Current Opinion in Immunology*, Cramer and Rhyner review novel strategies based on technological developments in engineering of recombinant allergens to overcome these problems. Recent developments in the area are the protective effect of non-IgE binding fusion allergens [40,41], use of recombinant Bet v 1 and its derivatives in birch pollen allergy [42], use of five recombinant grass pollen allergens [43], and intralymphatic SIT [44].

The question remains whether the concept of successful preventive vaccines against infections is applicable to allergen-SIT vaccines for the treatment of allergy. Anti-infection vaccines that are efficient protect via protective antibodies [45]. In contrast, vaccines that are not

protective activate T-cell responses. The persistence of the vaccine antigen to maintain sufficient numbers of activated effector T cells is crucial and does not always happen [46]. In this issue, Larché reviews direct T-cell targeting in the treatment of allergy and asthma. Whether the induction of a strong non-IgE (IgG₁, IgG₂) isotype antibody response or induction of peripheral T-cell tolerance together with non-inflammatory IgG₄ and IgA isotype antibodies would lead to more efficient SIT vaccines is still under debate, although the analysis of natural immune response supports the latter. In the case of successful anti-infection vaccines, a complete viral clearance or toxin neutralization occurs via complement-activating antibodies. However, allergen exposure continues life-long and induction of complement activation might also lead to immune pathology.

Conclusions

Extensive progress has been made in understanding of mechanisms of allergic disease with the complex interaction of effector T cells, NKT cells, other effector cells, resident tissue cells and T_{Reg} cells. As observed in natural immune responses in healthy individuals, peripheral T-cell tolerance is the key immunological mechanism in healthy immune response to allergens. Changes in the fine balance between allergen-specific T_{Reg} and Th2 and/or Th1 cells are crucial in the development and also the treatment of allergic diseases. In addition to the treatment of established allergy, it is essential to consider prophylactic approaches before the initial sensitization takes place. By the application of the recent knowledge in peripheral tolerance mechanisms, more rational and safer approaches are awaiting for the treatment, prevention and cure of allergic diseases.

Acknowledgments

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References

1. Akdis CA, Akdis M, Trautmann A, Blaser K: **Immune regulation in atopic dermatitis.** *Curr Opin Immunol* 2000, **12**:641-646.
2. Larche M, Akdis CA, Valenta R: **Immunological mechanisms of allergen-specific immunotherapy.** *Nat Rev Immunol* 2006, in press.
3. Bannon GA: **What makes a food protein an allergen?** *Curr Allergy Asthma Rep* 2004, **4**:43-46.
4. Bach JF: **The effect of infections on susceptibility to autoimmune and allergic diseases.** *N Engl J Med* 2002, **347**:911-920.
5. Maizels RM: **Infections and allergy — helminths, hygiene and host immune regulation.** *Curr Opin Immunol* 2005, **17**:656-661.
6. Kawai T, Akira S: **Pathogen recognition with Toll-like receptors.** *Curr Opin Immunol* 2005, **17**:338-344.
7. Umetsu SE, Lee WL, McIntire JJ, Downey L, Sanjanwala B, Akbari O, Berry GJ, Nagumo H, Freeman GJ, Umetsu DT et al.: **TIM-1 induces T cell activation and inhibits the development of peripheral tolerance.** *Nat Immunol* 2005, **6**:447-454.

8. Feleszko W, Jaworska J, Hamelmann E: **Toll-like receptors — novel targets in allergic airway disease (probiotics, friends and relatives).** *Eur J Pharmacol* 2006, **533**:308-318.
9. Strobel S, Mowat AM: **Oral tolerance and allergic responses to food proteins.** *Curr Opin Allergy Clin Immunol* 2006, **6**:207-213.
10. Akdis M, Blaser K, Akdis CA: **T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases.** *J Allergy Clin Immunol* 2005, **116**:961-968.
11. Zinkernagel RM, Ehl S, Aichele P, Oehen S, Kundig T, Hengartner H: **Antigen localisation regulates immune responses in a dose- and time-dependent fashion: a geographical view of immune reactivity.** *Immunol Rev* 1997, **156**:199-209.
12. Macdonald TT, Monteleone G: **Immunity, inflammation, and allergy in the gut.** *Science* 2005, **307**:1920-1925.
13. Akdis M, Verhagen J, Taylor A, Karamloo F, Karagiannidis C, Cramer R, Thunberg S, Deniz G, Valenta R, Fiebig H *et al.*: **Immune responses in healthy and allergic individuals are characterized by a fine balance between allergen-specific T regulatory 1 and T helper 2 cells.** *J Exp Med* 2004, **199**:1567-1575.
14. Frossard CP, Hauser C, Eigenmann PA: **Antigen-specific secretory IgA antibodies in the gut are decreased in a mouse model of food allergy.** *J Allergy Clin Immunol* 2004, **114**:377-382.
15. Bottcher MF, Haggstrom P, Bjorksten B, Jenmalm MC: **Total and allergen-specific immunoglobulin A levels in saliva in relation to the development of allergy in infants up to 2 years of age.** *Clin Exp Allergy* 2002, **32**:1293-1298.
16. Bahceciler NN, Arikian C, Taylor A, Akdis M, Blaser K, Barlan IB, Akdis CA: **Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites.** *Int Arch Allergy Immunol* 2005, **136**:287-294.
17. Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszczyk M, Blaser K, Akdis AC: **IL-10 and TGF- β cooperate in regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy.** *Eur J Immunol* 2003, **33**:1205-1214.
18. Bousquet J, Jacot W, Vignola AM, Bachert C, Van Cauwenberge P: **Allergic rhinitis: a disease remodeling the upper airways?** *J Allergy Clin Immunol* 2004, **113**:43-49.
19. Schmidt-Weber CB, Blaser K: **Regulation and role of transforming growth factor-beta in immune tolerance induction and inflammation.** *Curr Opin Immunol* 2004, **16**:709-716.
20. McMillan SJ, Xanthou G, Lloyd CM: **Manipulation of allergen-induced airway remodeling by treatment with anti-TGF- β antibody: effect on the Smad signaling pathway.** *J Immunol* 2005, **174**:5774-5780.
21. Laitinen LA, Laitinen A, Haahtela T: **Airway mucosal inflammation even in patients with newly diagnosed asthma.** *Am Rev Respir Dis* 1993, **147**:697-704.
22. Kim SK, Boothroyd JC: **Stage-specific expression of surface antigens by *Toxoplasma gondii* as a mechanism to facilitate parasite persistence.** *J Immunol* 2005, **174**:8038-8048.
23. Mangan NE, Fallon RE, Smith P, van Rooijen N, McKenzie AN, Fallon PG: **Helminth infection protects mice from anaphylaxis via IL-10-producing B cells.** *J Immunol* 2004, **173**:6346-6356.
24. Fischer P, Bonow I, Supali T, Ruckert P, Rahmah N: **Detection of filaria-specific IgG4 antibodies and filarial DNA, for the screening of blood spots for *Brugia timori*.** *Ann Trop Med Parasitol* 2005, **99**:53-60.
25. Trautmann A, Kruger K, Akdis M, Muller-Wening D, Akkaya A, Brouckeban EB, Blaser K, Akdis CA: **Apoptosis and loss of adhesion of bronchial epithelial cells in asthma.** *Int Arch Allergy Immunol* 2005, **138**:142-150.
26. Borron PJ, Mostaghel EA, Doyle C, Walsh ES, McHeyzer-Williams MG, Wright JR: **Pulmonary surfactant proteins A and D directly suppress CD3⁺/CD4⁺ cell function: evidence for two shared mechanisms.** *J Immunol* 2002, **169**:5844-5850.
27. Erjefalt JS, Uller L, Malm-Erfjelt M, Persson CG: **Rapid and efficient clearance of airway tissue granulocytes through transepithelial migration.** *Thorax* 2004, **59**:136-143.
28. Romagnani S: **Immunologic influences on allergy and the TH1/TH2 balance.** *J Allergy Clin Immunol* 2004, **113**:395-400.
29. Akdis M, Trautmann A, Klunker S, Daigle I, Küçüksezer UC, Deglmann W, Disch R, Blaser K, Akdis CA: **T helper (Th) 2 predominance in atopic disease is due to preferential apoptosis of circulating memory/effector Th1 cells.** *Faseb J* 2003, **17**:1026-1035.
30. Akdis CA, Blaser K, Akdis M: **Apoptosis in tissue inflammation and allergic disease.** *Curr Opin Immunol* 2004, **16**:717-723.
31. Schmid-Grendelmeier P, Simon D, Simon H-U, Akdis CA, Wüthrich B: **Epidemiology, clinical features, and immunology of the "intrinsic" (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis).** *Allergy* 2001, **56**:841-849.
32. Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OAR, Malolepszy J, Zak-Nejmark T, Koga R, Kobayashi T, Blaser K *et al.*: **Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors.** *Nature* 2001, **413**:420-425.
33. Jutel M, Watanabe T, Akdis M, Blaser K, Akdis CA: **Immune regulation by histamine.** *Curr Opin Immunol* 2002, **14**:735-740.
34. Robinson DS, Larche M, Durham SR: **Tregs and allergic disease.** *J Clin Invest* 2004, **114**:1389-1397.
35. Fahy JV: **Reducing IgE levels as a strategy for the treatment of asthma.** *Clin Exp Allergy* 2000, **30**(Suppl 1):16-21.
36. Klunker S, Trautmann A, Akdis M, Verhagen J, Schmid-Grendelmeier P, Blaser K, Akdis CA: **A second step of chemotaxis after transendothelial migration: keratinocytes undergoing apoptosis release IFN- γ -inducible protein 10, monokine induced by IFN- γ , and IFN- γ -inducible α -chemoattractant for T cell chemotaxis toward epidermis in atopic dermatitis.** *J Immunol* 2003, **171**:1078-1084.
37. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, Bradding P, Brightling CE, Wardlaw AJ, Pavord ID: **Evidence of a role of tumor necrosis factor alpha in refractory asthma.** *N Engl J Med* 2006, **354**:697-708.
38. Harrington LE, Mangan PR, Weaver CT: **Expanding the effector CD4 T-cell repertoire: the Th17 lineage.** *Curr Opin Immunol* 2006, **18**:349-356.
39. Akdis CA: **Future of allergen-specific immunotherapy: better understanding of the mechanisms, novel treatments, and long-term cure.** *Immunol Allergy Clin North Am* 2006, **26**:13-22.
40. Kussebi F, Karamloo F, Rhyner C, Schmid-Grendelmeier P, Salagianni M, Mannhart C, Akdis M, Soldatova L, Markovic-Housley Z, von Beust BR *et al.*: **A major allergen gene-fusion protein for potential usage in allergen-specific immunotherapy.** *J Allergy Clin Immunol* 2005, **115**:323-329.
41. Karamloo F, Schmid-Grendelmeier P, Kussebi F, Akdis M, Salagianni M, von Beust BR, Reimers A, Zumkehr J, Soldatova L, Housley-Markovic Z *et al.*: **Prevention of allergy by a recombinant multi-allergen vaccine with reduced IgE binding and preserved T cell epitopes.** *Eur J Immunol* 2005, **35**:3268-3276.
42. Gafvelin G, Thunberg S, Kronqvist M, Gronlund H, Gronneberg R, Troye-Blomberg M, Akdis M, Fiebig H, Purohit A, Horak F *et al.*: **Cytokine and antibody responses in birch-pollen-allergic patients treated with genetically modified derivatives of the major birch pollen allergen Bet v 1.** *Int Arch Allergy Immunol* 2005, **138**:59-66.
43. Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O: **Allergen-specific immunotherapy with recombinant grass pollen allergens.** *J Allergy Clin Immunol* 2005, **116**:608-613.
44. Johansen P, Haffner AC, Koch F, Zepter K, Erdmann I, Maloy K, Simard JJ, Storni T, Senti G, Bot A *et al.*: **Direct intralymphatic injection of peptide vaccines enhances immunogenicity.** *Eur J Immunol* 2005, **35**:568-574.

45. Zinkernagel RM: **Maternal antibodies, childhood infections, and autoimmune diseases.** *N Engl J Med* 2001, **345**:1331-1335.
46. Kaufmann SH: **Envisioning future strategies for vaccination against tuberculosis.** *Nat Rev Immunol* 2006, **6**:699-704.
47. Crameri R: **Allergy diagnosis, allergen repertoires, and their implications for allergen-specific immunotherapy.** *Immunol Allergy Clin North Am* 2006, **26**:179-189.
48. Breiteneder H, Mills EN: **Molecular properties of food allergens.** *J Allergy Clin Immunol* 2005, **115**:14-23.
49. Diaz-Perales A, Sanchez-Monge R, Blanco C, Lombardero M, Carillo T, Salcedo G: **What is the role of the hevein-like domain of fruit class I chitinases in their allergenic capacity?** *Clin Exp Allergy* 2002, **32**:448-454.
50. Chakravarty S, Varadarajan R: **Elucidation of determinants of protein stability through genome sequence analysis.** *FEBS Lett* 2000, **470**:65-69.
51. Hira T, Hara H, Tomita F, Aoyama Y: **Casein binds to the cell membrane and induces intracellular calcium signals in the enteroendocrine cell: a brief communication.** *Exp Biol Med (Maywood)* 2003, **228**:850-854.
52. Buhot N, Douliet JP, Jacquemard A, Marion D, Tran V, Maume BF, Milat ML, Ponchet M, Mikes V, Kader JC *et al.*: **A lipid transfer protein binds to a receptor involved in the control of plant defence responses.** *FEBS Lett* 2001, **509**:27-30.
53. Brown JH, Kim KH, Jun G, Greenfield NJ, Dominguez R, Volkmann N, Hitchcock-DeGregori SE, Cohen C: **Deciphering the design of the tropomyosin molecule.** *Proc Natl Acad Sci USA* 2001, **98**:8496-8501.
54. Maleki SJ, Chung SY, Champagne ET, Raufman JP: **The effects of roasting on the allergenic properties of peanut proteins.** *J Allergy Clin Immunol* 2000, **106**:763-768.
55. Linhart B, Valenta R: **Molecular design of allergy vaccines.** *Curr Opin Immunol* 2005, **17**:646-655.
56. Brown A, Farmer K, MacDonald L, Kalsheker N, Pritchard D, Haslett C, Lamb J, Sallenave JM: **House dust mite Der p 1 downregulates defenses of the lung by inactivating elastase inhibitors.** *Am J Respir Cell Mol Biol* 2003, **29**:381-389.
57. Asokanathan N, Graham PT, Stewart DJ, Bakker AJ, Eidne KA, Thompson PJ, Stewart GA: **House dust mite allergens induce proinflammatory cytokines from respiratory epithelial cells: the cysteine protease allergen, Der p 1, activates protease-activated receptor (PAR)-2 and inactivates PAR-1.** *J Immunol* 2002, **169**:4572-4578.
58. Kauffman HF, Tamm M, Timmerman JA, Borger P: **House dust mite major allergens Der p 1 and Der p 5 activate human airway-derived epithelial cells by protease-dependent and protease-independent mechanisms.** *Clin Mol Allergy* 2006, **4**:5.
59. Wan H, Winton HL, Soeller C, Tovey ER, Gruenert DC, Thompson PJ, Stewart GA, Taylor GW, Garrod DR, Cannell MB *et al.*: **Der p 1 facilitates transepithelial allergen delivery by disruption of tight junctions.** *J Clin Invest* 1999, **104**:123-133.
60. Girish KS, Kemparaju K: **Inhibition of Naja naja venom hyaluronidase: role in the management of poisonous bite.** *Life Sci* 2006, **78**:1433-1440.
61. Plotz SG, Traidl-Hoffmann C, Feussner I, Kasche A, Feser A, Ring J, Jakob T, Behrendt H: **Chemotaxis and activation of human peripheral blood eosinophils induced by pollen-associated lipid mediators.** *J Allergy Clin Immunol* 2004, **113**:1152-1160.
62. Traidl-Hoffmann C, Mariani V, Hochrein H, Karg K, Wagner H, Ring J, Mueller MJ, Jakob T, Behrendt H: **Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization.** *J Exp Med* 2005, **201**:627-636.
63. Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN: **Diagnosis of Hymenoptera venom allergy.** *Allergy* 2005, **60**:1339-1349.

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