EDITORIAL COMMENT

The mechanism of food allergy: what do we know today?

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Abbreviation

Th T helper

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Introduction

Food allergy is a major public health issue. Up to 8% of children and 2% of adults in westernized countries suffer from allergic reactions against various foods. Moreover, the prevalence rate for certain allergies (e.g. peanut allergy or sesame seed allergy) appears to be increasing in certain countries where these allergies were uncommon in the past.

We still need to develop better diagnostic tests and treatment methods for food allergy. Therefore, a better understanding of the pathophysiology of food allergic reactions is crucial. This editorial review will focus on our current understanding of the mechanism of food allergic reactions. It will further refer to the different topics in the articles in this section of *Current Opinion in Allergy and Clinical Immunology*.

Immunoregulation in the gastrointestinal system

Food allergy is a malfunction of the immune system in response to dietary antigens. It develops in genetically predisposed individuals when oral tolerance fails to develop normally or breaks down [1••]. Oral tolerance is the active non-response to dietary antigens administered orally.

The regular task of the immune system is to protect against dangerous pathogens. At least 90% of all pathogens use the mucosa as a portal of entry. With a surface area almost 200 times that of the skin, the mucosal surface to be protected is enormous. The gastrointestinal immune system has to discriminate between these pathogens, dietary antigens, and commensal intestinal microflora. Up to a ton of food passes through the gut every year [2], and there are many more bacteria in the gut than cells in the human body. These antigen contacts shape the immune response.

To meet the task of discrimination between pathogens, the commensal microflora and dietary antigens, the mucosal surface possesses a unique immune system that tightly controls the balance between responsiveness and non-responsiveness. It consists of an integrated network of tissues, lymphoid and non-lymphoid effector molecules such as enzymes, antibodies, chemokines and cytokines for host protection [3]. Intestinal epithelial cells are joined together by tight junctions that prevent the passage of macromolecules. On top are mucin glycoproteins lining the surface epithelium that trap pathogens and antigens from gaining access to the underlining epithelium [4••]. In addition, IgA, the most abundant immunoglobulin isotype in mucosal secretion, provides protection against microbial antigens [5].

For the proper development of mucosal barrier function and the immunoregulatory network, microbial infections, lipopolysaccharides from Gram-negative bacteria, and commensal gut microflora seem to be necessary stimuli ('hygiene hypothesis') [2,6]. T regulatory cells play an important role in this process. A number of regulatory T cells have been defined over the past few years, such as CD4+CD25+, T helper (Th) type 3 and T regulatory (Tr) type 1 cells. CD4+CD25+ cells most likely mediate their inhibition by cell–cell contact, whereas Th3 and Tr1 cells secrete transforming growth factor beta and IL-10, respectively [4••]. Suboptimal stimulatory reinforcement might contribute to the development of allergic diseases [2]. The immune system of neonates is thought to have a Th2 bias. This Th2 bias seems to diminish gradually during the first 2 years of life in non-allergic individuals. In contrast, in allergic infants, the Th2 responses increase over a similar period of time [6].

Animal studies are important for a better understanding of the immunological mechanism that underlies food allergic reactions. Currently, several animal models of food allergy are being used, including mouse, rat, swine and dog. In this issue, Knippels *et al.* (pp. 205–209) give an update on food allergy research using animal models of food allergy, including mechanistic studies, the search for new therapies as well as screening models for hazard identification of potential allergens.

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IgE-mediated food allergy

The majority of food allergic reactions are IgE-mediated. Food proteins bind to the allergen-specific IgE molecules residing on mast cells and basophils and trigger the release of mediators, such as histamine, and an acute onset of symptoms occurs. However, food-specific IgE is often present (sensitization) without clinical reactivity. Several other factors seem to influence the clinical response [7]. Although the mechanisms resulting in clinical responsiveness in food-sensitized individuals are still not completely understood, the measurement of food-specific IgE is widely used in food allergy diagnosis. The concentration of food-specific IgE correlates positively with the risk of reactions for several food allergens. Recent advances in diagnostic tests for IgE-mediated food allergy are discussed in this issue by Eigenmann (pp. 211–213).

In highly sensitized individuals, minimal amounts of the allergenic food are sufficient to elicit severe symptoms. To protect these individuals and prevent recurrent severe anaphylaxis it is important to obtain threshold doses for various food allergens that induce symptoms. Moneret-Vautrin and Kanny (pp. 215–219) have presented an update on these threshold doses and their implications for patients and the food industry.

IgE-mediated disorders affect one or more target organs, such as the skin, gastrointestinal and respiratory tracts. The reason for these distinct reactions is poorly understood. The expression of different organ-specific homing receptors, especially on T cells, are believed to play an important role. Moreover, two forms of IgE-mediated skin reaction, urticaria and atopic dermatitis, have been associated with food allergy. T cells expressing cutaneous lymphocyte antigen, a unique skin-homing receptor, are known to play an important role in atopic dermatitis. In contrast, urticaria is an acute reaction caused by activation of cutaneous mast cells. However, it was recently shown that lymphocytes expressing cutaneous lymphocyte antigen play an important role in both milk-induced skin manifestations [8].

The important role of IgE in the majority of food allergic reactions has recently been used for the development of improved therapeutic tools. It had been shown that anti-IgE therapy in patients with peanut allergy substantially increased the threshold of sensitivity to peanut on oral food challenge [9••]. Although not a cure, this effect could translate into protection against most unintended ingestions of peanuts as long as this therapy is used.

Non-IgE-mediated food allergy

A number of gastrointestinal disorders, including food protein-induced enterocolitis, allergic eosinophilic gastroenteritis, and food-protein induced enteropathy, have been associated with food hypersensitivity. The majority of these disorders are non-IgE mediated. The immunological reactions appear to involve T cells that are activated by specific food proteins. The release of Th2 cytokines by food-specific mucosal T cells and the lack of T regulatory cytokines may play a pathogenic role in the inflammatory changes in these diseases [10]. Although in the majority of food-induced gastrointestinal disorders, no specific IgE can be detected in the serum, localized IgE-mediated responses might be involved in the gastrointestinal symptoms seen in these patients [11]. The advances in pathophysiology, diagnosis and treatment in these food protein-induced gastrointestinal diseases are discussed in detail in the current issue by Heine (pp. 221–229).

Tolerance development in food allergy

Up to 8% of children in the first years of life show allergic reactions upon food ingestion. The prevalence rate then falls progressively until late childhood, after which it remains stable at 1–2% [12•]. Most infants with cows' milk allergy develop symptoms before one month of age, but become clinically tolerant to milk by 3 years of age [13]. In contrast, peanut allergy tends to persist throughout adulthood. However, it has recently been reported that up to 20% of peanut-allergic children lose their allergy [14,15]. Moreover, food allergy is one of the first manifestations of the 'atopic march', as many of these children develop asthma and allergic rhinitis later in life.

The mechanisms involved in the development of tolerance are poorly understood. However, children with persistent milk and peanut allergies appear to have IgE antibodies to distinct allergenic epitopes that are not recognized as frequently by tolerant patients [16,17•]. In the current issue, Eigenmann (pp. 211–213) discusses the relevance of epitope-specific IgE for improved diagnostic tests.

Food allergens

Despite the enormous diversity of the human diet, only a few foods are responsible for the vast majority of food allergic reactions. For systemic food allergic reactions these foods are milk, egg, peanuts, tree nuts, seeds, wheat, soy, fish and shellfish. The characterization of these allergenic food proteins has increased dramatically within the past few years [18••,19••]. The recent advances in peanut, tree nut and seed allergy will be reviewed in the other editorial review. Moreover, an update on seafood allergy will be given in the current issue by Lehrer and Ree-Kim (pp. 231–234). In addition to these food allergens, several pollen-related food allergens in fruit and vegetables cause clinical reactions, especially in the adult population. Although the majority of these reactions are limited to oral allergy symptoms,

systemic reactions have been described. Allergens eliciting these reactions belong to a few families of allergens such as Bet v 1 and profilin. Similarly, many of the plant-derived allergens resulting in systemic reactions belong to the same families of seed-storage or pathogen-related proteins. Recent findings in this complex theme on cross-reactivity between pollen and plant food as well as between 'pure' food allergens and its clinical importance are discussed in the current issue by van Ree (pp. 235–240).

Most foods in the human diet have been processed before consumption. They are harvested, dried, stored, heated, frozen, cooked, or roasted, to name only some processing methods. Processing can cause many different alterations of the food proteins. Thermal processing in particular seems to modify the allergenicity of proteins. Although it seems mostly to reduce its allergenicity, it has also been shown to increase it. In this current issue, Maleki (pp. 241–245) reviews the most recent findings on the alteration of the structure, function and allergenicity of food proteins through thermal as well as other processing events, and highlights the complexity of diagnosing food allergies.

Conclusion

Food allergy and its underlying mechanism are a very complex topic. The current issue tries to summarize recent findings with regard to the pathophysiology, diagnosis, and treatment of IgE- and non-IgE-mediated food allergy. Much of our current knowledge comes from animal studies, and recent findings are reviewed. Moreover, food allergy cannot be understood without a better characterization of the allergens that elicit clinical reactions. Recent findings on allergen modification through food processing, as well as the clinical importance of allergen cross-reactivity, are reviewed in this issue. In addition, recent advances in peanut, tree nut and seed allergy as well as seafood allergy are highlighted.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Sampson HA. 9. Food allergy. J Allergy Clin Immunol 2003; 111 (Suppl):S540–S547.
•• This excellent review gives an overview about the epidemiology, immunopathogenesis, diagnostic approaches and therapeutic intervention of food allergy.

2 Brandtzaeg PE. Current understanding of gastrointestinal immunoregulation and its relation to food allergy. Ann NY Acad Sci 2002; 964:13–45.

3 Neurath MF, Finotto S, Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. Nat Med 2002; 8:567–573.

4 Mayer L. Mucosal immunity. Pediatrics 2003; 111:1595–1600.
•• This review describes in great detail the normal mucosal immune response. It postulates how the different processes may be defective in food-allergic patients resulting in an abnormal immune response to antigen delivered by the oral route.

5 Fagarasan S, Honjo T. Intestinal IgA synthesis: regulation of front-line body defences. Nat Rev Immunol 2003; 3:63–72.

6 Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 2001; 1:69–75.

7 Sicherer SH. Food allergy. Lancet 2002; 360:701–710.

8 Beyer K, Castro R, Feidel C, Sampson HA. Milk-induced urticaria is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. J Allergy Clin Immunol 2002; 109:688–693.

9 Leung DY, Sampson HA, Yunginger JW, *et al*. Effect of anti-IgE therapy in
•• patients with peanut allergy. N Engl J Med 2003; 348:986–993.
This study describes the successful use of anti-IgE in peanut allergic patients. TNX-901, a humanized IgG1 monoclonal antibody against IgE, significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut to one equal to almost nine peanuts. This effect should translate into protection against most unintended ingestions of peanuts.

10 Beyer K, Castro R, Birnbaum A, *et al*. Human milk-specific mucosal lymphocytes of the gastrointestinal tract display a TH2 cytokine profile. J Allergy Clin Immunol 2002; 109:707–713.

11 Lin XP, Magnusson J, Ahlstedt S, *et al*. Local allergic reaction in food-hypersensitive adults despite a lack of systemic food-specific IgE. J Allergy Clin Immunol 2002; 109:879–887.

12 Wood RA. The natural history of food allergy. Pediatrics 2003; 111:1631–
• 1637.
This review provides an overview of the natural history of food allergy and provides specific information on the natural course of the most common childhood food allergies.

13 Host A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol 2002; 89:33–37.

14 Hourihane JO. Recent advances in peanut allergy. Curr Opin Allergy Clin Immunol 2002; 2:227–231.

15 Skolnick HS, Conover-Walker MK, Koerner CB, *et al*. The natural history of peanut allergy. J Allergy Clin Immunol 2001; 107:367–374.

16 Jarvinen KM, Beyer K, Vila L, *et al*. B-cell epitopes as a screening instrument for persistent cow's milk allergy. J Allergy Clin Immunol 2002; 110:293–297.

17 Beyer K, Ellman-Grunther L, Jarvinen KM, *et al*. Measurement of peptide-
• specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. J Allergy Clin Immunol 2003; 112:202–207.
This study describes that determination of epitope-specific IgE provides an additional tool to diagnose symptomatic peanut allergy, especially in children with peanut-specific IgE below diagnostic decision levels. Using SPOTs membrane, eight peptides representing the immunodominant sequential epitopes on Ara h 1, 2, and 3 were synthesized and labeled with sera from patients with symptomatic peanut allergy and patients who were sensitized but tolerant. Regardless of their peanut-specific IgE levels, the cumulative IgE binding to the peanut peptides was significantly higher in patients with peanut allergy than in tolerant patients.

18 Beyer K. Characterization of allergenic food proteins for improved diagnostic
•• methods. Curr Opin Allergy Clin Immunol 2003; 3:189–197.
This review outlines recent advantages in characterization of food allergens as well as the relevance of this knowledge for use in recently developed protein microarray technology.

19 Roux KH, Teuber SS, Sathe SK. Tree nut allergens. Int Arch Allergy Immunol
•• 2003; 131:234–244.
This review describes recent studies conducted in an attempt to identify and characterize tree nut allergens that are responsible for allergy sensitization and clinical reactions. The allergenic tree nuts discussed in this review include those most commonly responsible for allergic reactions such as hazelnut, walnut, cashew, and almond as well as those less frequently associated with allergies including pecan, chestnut, Brazil nut, pine nut, macadamia nut, pistachio, coconut, Nangai nut, and acorn.