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REVIEW

Food Allergy Insights: A Changing Landscape

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Abstract

The panorama of food allergies (FA) has changed profoundly in recent years. In light of recent advances in knowledge of pathogenetic mechanisms and a greater attention to the multifaceted range of possible clinical manifestations, there is a need for a critical review of past classifications. Changes in nutrition, environment and lifestyles around the world are modifying the global FA epidemiology and new FA phenotypes are also emerging. Furthermore, both biotechnological advances in this field and recent personalized therapies have improved the diagnostic and therapeutic approach to FA. Consequently, both the prevention and clinical management of FA are rapidly changing and new therapeutic strategies are emerging, even revolutionizing the current medical practice. Given the significant increase in the prevalence of FA in recent years, the objective of this review is to provide an updated and complete overview of current knowledge in its etiopathogenesis, diagnostics and therapy, useful not only for a better understanding of this frequent and complex pathology but also for practical guidance in its clinical management.

Keywords Food allergy · Oral allergy syndrome · Omalizumab · Eczema · IgE · Translational immunology

Abbreviations

FA	Food allergies
OAS	Oral allergy syndrome
DBPCFC	Double-blind placebo-controlled food challenge
Treg T	Regulatory cells
PAF	Platelet activating factor
IL-4	Interleukin-4
DCs	Dendritic cells
TGF-β	Transforming growth factor-beta
APCs	Antigen-presenting cells
TSLP	Thymic stromal lymphopoietin
IECs	Intestinal epithelial cells
ILC2s	Type 2 innate lymphoid cells
OFC	Oral food challenge
CRD	Component-resolved diagnostics
BAT	Basophil activation test
Gp53 or LAMP-3	Lysosomal-associated membrane glycoprotein-3
FAIT	Food allergen-specific immunotherapy
PR	Pathogenesis-related proteins
LTP	Lipid transfer proteins
OIT	Oral immunotherapy
EPIT	Epicutaneous immunotherapy

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Introduction

Food allergies (FA), as well as food intolerances, fall within the broader umbrella of adverse reactions to food, and in particular in the group of non-toxic reactions. They are characterized by individual susceptibility to specific foods that are harmless to most healthy individuals (Valenta et al. 2015).

FA and intolerances, although often clinically similar, are clearly different disease entities. For example, some foods, very common in our diet, such as tuna, sardines, tomatoes, spinach, sauerkraut, alcoholic drinks, contain high levels of histamine, an important vasoactive mediator of allergies; other foods, including chocolate, strawberries, pineapple, fermented cheeses, pickled or smoked fish, sausages, egg whites, contain substances that can release histamine. All of them can, therefore, cause clinical manifestations,

mimicking allergic symptoms, although their pathogenesis is not immunologically mediated. Milk intolerance, caused by lactose malabsorption, due to a deficiency of lactase, an enzyme of the brush border of intestinal epithelial cells (IECs), induces symptoms (bloating and abdominal pain with diarrhea after milk and dairy intake) that can be confused with an immunologically mediated milk allergy. Furthermore, many foods can also trigger more than one type of reaction, for example, both pharmacological and immunological (Wang and Sampson 2011).

In 2010, the US National Institute of Allergy and Infectious Diseases (Boyce et al. 2010; Burks et al. 2011) defined FA as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food; whereas, intolerances are non-immune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms. Moreover, based on the specific immunological mechanism involved, FA can be distinguished in IgE-mediated, non-IgE-mediated and mixed reactions (Valenta et al. 2015). Figure 1 schematizes the current classification of adverse food reactions. In this review, we mainly refer to IgE-mediated FA.

FA Phenotypes

Patients with FA show a great diversity in their clinical presentation, biomarker expression, natural history and therapeutic responses. Based on clinical presentation and pathobiology, different FA phenotypes and endotypes can be, therefore, recognized, exhibiting some degree of overlap between them. Patients with a specific endotype may belong to different phenotypic clusters of disease (Baker and Sampson 2018). The phenotype is the observable characteristic of the disease; while, the endotype defines the pathobiological mechanism underlying the clinical manifestations.

FA can affect different organs and systems, including gastrointestinal tract, skin, cardiovascular, respiratory and nervous systems. The variability of clinical expression is considerable, ranging from mild and localized manifestations, such as fleeting oral itching, to severe and potentially fatal reactions such as anaphylactic shock (Renz et al. 2018; Cianferoni and Muraro 2012).

Exercise-Induced Anaphylaxis

As in most allergic and autoimmune diseases, phenotype and endotype are determined by genotype, epigenetic and environmental factors (De Martinis et al. 2016; Greenhawt 2015; Gupta et al. 2016). Moreover, there are several facilitating factors able to elicit an allergic reaction when exposure occurs in the proximity of food intake, including physical exercise, menses, infections, alcohol and drugs, such as nonsteroidal anti-inflammatory drugs and antiacids. For example, urticaria or anaphylaxis can be triggered following physical exercise performed by the patient within 2–4 h from the ingestion of culprit foods (food-dependent exercise-induced anaphylaxis—FDEIA). Young people and children are more frequently affected with a female predominance. Wheat, milk, shellfish, celery and soy are the most

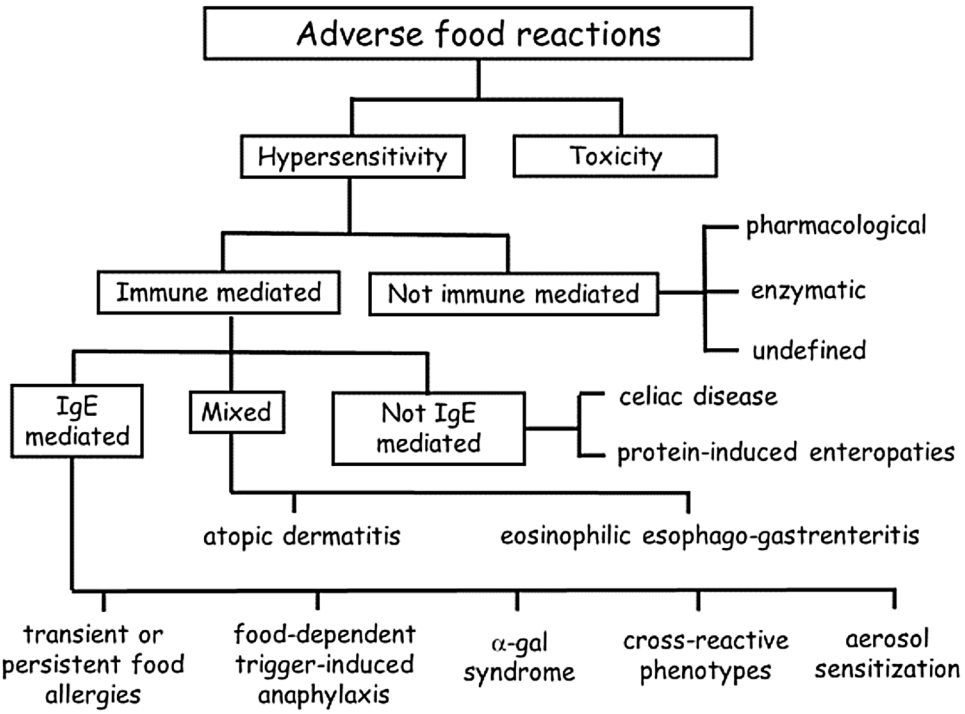

Fig. 1 Classification of adverse reactions to foods. Food allergies, unlike intolerances, are immunologically mediated reactions, Immune-mediated food reactions are also divided into IgE mediated, non-IgE mediated and mixed, different from each other both clinically and immunopathogenetically

common responsible foods. Physical exercise is believed to increase the gastrointestinal absorption of the allergen and/or lower the activation threshold of basophils and mast cells in sensitized subjects (Cianferoni 2016). It has been hypothesized that exercise enhances the absorption of allergens from the gastrointestinal tract in their improperly digested or undigested forms. Aspirin, another well-known trigger for anaphylaxis in FDEIA patients, as well as exercise, may also facilitate allergen absorption from the gastrointestinal tract (Morita et al. 2007). The identification of the culprit food, by skin prick test and serum-specific IgE antibody detection, together with the lifestyle modification to avoid exercise and other augmentation factors in the proximity of possible ingestion of a causative food, are key features in the management of this condition (Muñoz-Cano et al. 2017). The most frequent causative food is wheat; approximately 80% of the patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) have IgE reacting to omega-5 gliadin and the remaining of the patients to high-molecular-weight glutenin (HMW-glutenin). Simultaneous measurement of specific IgE to omega-5 gliadin and HMW-glutenin could be useful in diagnosing WDEIA compared with the routine diagnostic system for wheat (Morita et al. 2009; Takahashi et al. 2012).

Alpha-Gal

Another particular type of FA is the alpha-gal syndrome, initially described in 2004 in the USA, that is characterized by the onset of anaphylaxis after 3–6 h after a meat meal. It is, therefore, a late anaphylactic reaction, in the past considered an idiopathic anaphylaxis (Kuhlen 2015). The responsible allergen is the galactose-alpha 1,3 galactose carbohydrate, contained in red meat (Commins et al. 2016; Platts-Mills et al. 2015). A positive prick by prick test with raw meat is a frequent finding. Sensitization, which occurs after tick bites ("Amblyomma americanum" or "Lone star") (Araujo et al. 2016), decreases over time avoiding tick bites, as demonstrated by the possibility of reintroducing mammalian meat in the diet without symptoms. Similar anaphylactic reactions have been reported in cancer patients undergoing chemotherapy with cetuximab, due to cross-reactivity with alpha-gal (Berg et al. 2014).

Occupational Allergy

Patients can also be sensitized to food through exposure to homologous plant pollens or aerosolized food proteins (FA with aerosol sensitization) (Popescu 2015). Reactions to the involved allergens cause symptoms ranging from local manifestations to systemic reactions, triggered by aerosolized food allergens. These latter are often forms of occupational allergies that occur in patients working in the food industry. The causative foods include fish, shellfish, wheat and other cereals, fruits and vegetables. Patients may present with respiratory manifestations (asthma and allergic rhinitis), anaphylaxis or contact urticaria. A history of symptoms that occur predominantly in the workplace is suggestive (Jeebhay et al. 2019).

Pollen-Food Allergy Syndrome

The pollen-food allergy syndrome is a polysensitization to inhalant and food allergens, also known as oral allergy syndrome (OAS), since symptoms are largely localized to the oropharynx. Commonly culprit foods are raw apple, peanut, hazelnut, almond and other fruits in the Rosaceae family in patients with birch allergy; melon, kiwi and banana in patients with ragweed allergy; tomato and melon in patients with grass allergy. Pollen-food syndrome is one of the most common FA phenotypes in adults and adolescents. It occurs in patients with allergic rhinitis due to pollen hypersensitivity. In a subset of patients with pollen allergy, IgE cross-react with the homologous protein in the ingested food, inducing itching and other manifestations to the lips, tongue, palate and oropharynx. The percentage of patients with pollen allergy who suffer from OAS varies 40–60%. Pollen-food syndrome is caused by the production of specific IgE against epitopes of pollen from mostly tall trees that cross-react with epitopes of homologous proteins contained in plant foods (Lukschal et al. 2016). These homologous proteins frequently induce the production of clinically undetectable levels of IgE and often skin prick tests with the standard food allergen extract are negative. Cross-reactive IgE can be directed against thermolabile food epitopes; so, it is necessary to use raw fruits or vegetables in diagnostic tests (prick by prick) (Chinthrajah et al. 2015). The responsible IgEs are, therefore, initially directed against the pollen of a plant that, if inhaled, is able to induce allergic rhinitis. The symptoms, which arise immediately upon contact of the raw fruit (more often apple and peach) with the oral mucosa of patients with pollen allergy, include itching and oral burning, lip, tongue and palate angioedema, and sometimes abdominal pain (Werfel et al. 2015).

Latex-Food Allergy Syndrome

Latex allergy, peaked in the 1990s in the United States and Europe due to the widespread use of latex, is now reducing with the increasing use of alternative materials. However, the percentages of use of the latex gloves and the allergy associated with it remain high in some countries and in some occupations, such as health workers, catering workers and cleaning staff. Among patients with latex allergy, 30–50% of subjects show associated hypersensitivity to certain foods of plant origin, such as avocado, banana, kiwi, chestnut,

peach, tomato, white potato and pepper (latex-food allergy syndrome) (Baker and Sampson 2018; Jeebhay et al. 2019).

The natural history of the FA exhibits different patterns in children and adults (Iweala et al. 2018). While IgE-mediated allergies to cow's milk and egg, as well as to wheat and soy, tend to disappear naturally with age, atopic reactions to peanuts, walnuts, crustaceans and molluscs usually persist into adulthood. Thirty per cent of patients have more than one type of FA that develop in succession over time (Waserman et al. 2018). The appearance of a FA and its natural history, as well as the risk of systemic reactions, is conditioned by the type of culprit food (Valenta et al. 2015). For example, for milk, eggs and peanuts, the onset is usually in early childhood, but they tend to disappear over time. In other cases, especially for various types of fruit, sensitization appears belatedly and tends to progress with various types of cross-reactivity, configuring peculiar clinical patterns, such as pollen-food syndrome (Wang and Sampson 2011).

FA Epidemiology

The variability of clinical manifestations, the complexity of the diagnostic formulation, the marked influence of autosuggestion and, not least, the flourish of methods not subjected to the necessary verification of their reliability, to which unfortunately many patients often resort, have led in the past to emphasize diagnoses of "psychological intolerance to food substances", underestimating real food allergies. Anxiety disorders and psychiatric symptoms profoundly influence the subjective perception of illness by both patients and doctors, so that the double-blind placebo-controlled food challenge (DBPCFC), which is still the diagnostic gold standard, confirms the diagnosis of FA in only 45% of cases. Based on these considerations, it was long believed that adverse reactions to foods are rare diseases (Ferguson 1990).

But currently, this concept has been overcome, so that FA is now considered a major global health problem, affecting millions of people and impacting multiple aspects of patients' life. Although the real prevalence is uncertain, it is estimated that over 220 million people worldwide suffer from some form of FA (Sicherer and Sampson 2018). It is also estimated that FA affects 15 million Americans (Jones and Burks 2017). The prevalence of FA is, therefore, high and has increased in the last two decades, especially in industrialized Western countries (Berin and Sampson 2013). FA is much more common in children than in adults. In the USA, up to 8% of children and 5% of adults suffer from FA according to estimates by the Center for Disease Control and Prevention (Schussler et al. 2017). However, a considerable increasing number of elderly people also present symptoms of FA (De Martinis et al. 2017, 2019b; Sirufo et al. 2020). In Europe, 17 million people with FA are calculated and around 40% of them have had a life-threatening reaction. In particular, according to European Academy of Allergy and Clinical Immunology (EAACI) estimates (Muraro et al. 2014a), the prevalence has doubled in the last 10 years and a growing number of serious potentially lethal FA reactions have been found in children and young adults.

There is also a significant geographical variability in FA distribution that can be linked to various factors. Both the exponential growth and the geographical variability suggest the contribution of genetic, environmental and lifestyle habits (Genuneit et al. 2017). For example, the highest prevalence of IgE-mediated FA has been documented in Australia, where 10% of children have challenge-confirmed allergies to one or more foods (Caraballo et al. 2016). Moreover, an interesting study showed that among children of Asian origin, but born in Australia, the allergy to nuts was twice as common as the white children born in Australia, whereas Asian children born in Asia and emigrated to Australia by the fifth year of age were protected (Panjari et al. 2016).

It is estimated that, in industrialized western countries, substantially eight foods (wheat, cow's milk, soy, eggs, fish and shellfish, nuts and peanuts) are responsible for 90% of FA, particularly in children; however, in over 80% of cases, these allergies recover spontaneously within the first 3 years of life. Many other foods may also be implicated, in relation to eating habits, and the type of sensitization may change over time (Benedè et al. 2016). Different estimations of FA prevalences in several developing countries have been made. For example, in Mexican schoolchildren, immediate hypersensitivity reactions are mainly triggered by the consumption of shrimp and other shellfish, strawberry, chocolate, and egg (Ontiveros et al. 2016). Fruit/vegetables, seafood, and meats are the most reported allergens in Cartagena population (Marrugo et al. 2008). The most common food allergens in children from the Central American country El Salvador are milk, shrimp, chili, chocolate, and nuts (Cabrera-Chávez et al. 2018). Up to 5.5% of school-aged Chilean children suffer from FA, most frequently to walnut and peanut (Hoyos-Bachiloglu et al. 2014).

Several possible factors, therefore, contribute to FA development, potentially explaining differences in the prevalence in various world regions and also offering potential avenues for specific preventive interventions (Shroba et al. 2019). For example, in Australia, where highly effective anti-cancer skin campaigns have caused a drastic drop in melanoma since the mid-1990s, high rates of vitamin D insufficiency correlate with increased food allergy and could provide a platform to refine FA prevention programs, eventually based on diet supplementation (Sicherer and Sampson 2014; Suaini et al. 2015) as shown in other conditions (Ciccarelli et al. 2016).

Immunopathogenesis

Mechanisms Underlying Systemic and Local Manifestations

The immunological mechanism of IgE-mediated FA is the type I hypersensitivity towards a specific allergen and involves a sensitization phase, in which a first contact with the allergen induces initial immune response with tolerance rupture and specific IgE production. The route of the first food allergen contact is usually oral, but other routes of sensitization could also be involved, such as altered skin, especially in atopic dermatitis, or even the inhalation route (aerosol sensitization to food proteins). A second contact with the allergen leads to the elicitation of allergic reactions and clinical manifestations (Chinthrajah et al. 2015). Through their anchorage site on the Fc fragment, IgEs attach themselves to the specific high-affinity receptors on the membrane of tissue mast cells and circulating basophils, sensitizing them. The cytoplasm of these cells is rich in granules which contain vasoactive substances and mediators of anaphylaxis, whose prototype is histamine. These substances are released when the allergen penetrates a second time into the sensitized organism and binds to the specific IgE on the membrane of these cells, inducing cross-link and cell degranulation in the tissue and/or into the blood stream (early phase reaction) (Johnston et al. 2014). Immediately after the effector cell degranulation, the "de novo" production of leukotrienes, platelet activating factor (PAF) and cytokines, i.e., interleukin (IL)-4, IL-5 and IL-13, occurs, therefore, maintaining, supporting and feeding the allergic inflammation (Wang and Sampson 2011).

In addition to such immediate phase, there is also a late phase of the IgE-mediated allergic reaction, different from the delayed cellular hypersensitivity reactions. Various chemotactic mediators of the early phase cause attraction and modulation of other inflammatory cells. These cells, in turn activated, are involved in the maintenance and chronicization of allergic inflammation through the production of other inflammatory mediators, thus initiating the late phase of the allergic reaction (Aalberse et al. 2016).

Mast cells are essential for both local and systemic manifestations of FA. Multiple pathways of anaphylaxis are related to the early and late phases, underlying the systemic and local manifestations of FA. Initial phase responses are mainly mediated by histamine and PAF and are actively regulated by T regulatory cells (Treg) interactions (Zhang et al. 2014). Activation of neutrophils and basophils induces additional pathways if the allergen becomes accessible into the blood. The activation of macrophages by IgG can also represent an alternative pathway. The release of specific cytokines, mainly tumor necrosis factor-α, IL-31, IL-33, and IL-9, sustains late tissue inflammation (Ciccarelli et al. 2015; De Martinis et al. 2020). Systemically disseminated antigen can trigger reactions in organs distant from the gastrointestinal tract (urticaria, bronchospasm) through histamine-dependent mechanisms and PAF. Serotonin, in addition to PAF, also exerts central roles in the local gastrointestinal acute response (diarrhea) to food allergen exposure. When distributed systemically, the allergen can react with IgE-sensitized circulating basophils and tissue mast cells, resulting in anaphylaxis (severe life-threatening allergic reaction involving multiple organs and systems) (Deschildre and Lejeune 2018). Table 1 summarizes the most frequently involved organs and related symptoms in FA. Repeated exposure to the food allergen drives and perpetuates the allergic inflammation and mastocytosis, which represent the background for the development of local symptoms and gastrointestinal manifestations of FA (Chinthrajah et al. 2016).

Sensitization to Food Antigens

In the past, it was believed that a healthy person simply did not develop an immune reaction against food, but this is not the case at all. The immune system physiologically recognizes food epitopes as harmless and develops tolerance towards them. Tolerance to food antigens can be reprogrammed by inflammatory stimuli generating allergic responses (Chinthrajah et al. 2016). In some individuals, due to an abnormal relationship between the intestinal immune system and some food substances to which tolerance has not been established or stopped, FA develops (Ruiter and Shreffler 2012). Tolerance is an active and highly specific antigen-induced immune process that involves various cell types. The central cells in tolerance determinism are dendritic cells (DCs) that present food antigens to naive T cells, promoting their differentiation into $Foxp3^+$ Treg cells. These cells secrete IL-10 and transforming growth factor (TGF)-β, which suppresses allergic response through retinoic acid-dependent mechanisms (Yu et al. 2016). $Foxp3^+$ Tregs in the lamina propria are expanded by IL-10-expressing $CX3CR1^+$ macrophages, leading to the suppression of allergic sensitization in an antigen-specific manner. $CX3CR1^+$ macrophages, through a peculiar periscopic mechanism, insinuate their dendritic extensions between the epithelial gap junctions and capture directly in the lumen the food antigens. Antigens captured in the lamina propria and Peyer's patch are carried to the mesenteric lymph node by $CD103^+$ DCs, which also drive gut-homing of IgA-secreting B cells, contributing to maintain specific tolerance (Sampath et al. 2017).

Table 1 Most frequent symptoms of food allergy

Gastrointestinal	Respiratory	Cutaneous	Cardiovascular	Neurological	Other
Oral tingling, itching and swelling, nausea, bowel hyperemia and wall edema, abdominal pain, vomiting and diarrhea	Airway phlogosis, bronchospasm, mucus production, laryngeal edema, dyspnea, cough, wheeze, hoarseness, rhinorrhea, sneeze, periocular, nasal and oropharyngeal pruritus	Urticaria, Hot flushing, hives, generalized itching, angioedema	Systemic anaphylaxis: vasodilatation, Plasma leak, arrhythmias, tachycardia, myocardial depression, hypotension, shock	Anxiety, Altered mental status, paresthesia and itching, dizziness, consciousness loss	Erythema and conjunctival edema, tearing, visual fogging, uterine cramps in women

When this equilibrium breaks down, mainly due to danger signals, such as exposure to certain molecular patterns associated with pathogens or epithelial damage, a series of signal pathways, starting from the epithelium and through the production of several inflammatory cytokines that act in synergy, are triggered. IL-25 and IL-31 activate antigen-presenting cells (APCs) and induce pro-inflammatory effects (Ginaldi et al. 2015); whereas, IL-33 and thymic stromal lymphopoietin (TSLP) activate and reprogram APCs to induce lymphocyte differentiation towards Th2 rather than Treg profile and consequent IL-4 and IL-13 production and allergic sensitization (Iweala and Nagler 2019; Yu 2012). Sensitization to food allergens can also intervene in elderly subjects, favored both by the chronic inflammation that characterizes senescence and by the impaired absorptive function of the aging gut (Corazza et al. 1998; De Martinis et al. 2007).

In summary, tolerance breaks down in situations in which danger signals arise, leading to the production of inflammatory cytokines from IECs (Huang et al. 2017). As a consequence, mucosal DCs acquire a phenotype that favors Th2 cell priming when induced by food antigens that in this case function as allergens. IL-4, derived from Th2 cells, stimulates many aspects of the allergic response, including the induction of the isotypical switch in local B cells for the production of IgE, the expansion of mast cells and eosinophils, and the further expansion of the Th2 lymphocyte pool. IL-4 also suppresses the function of tolerogenic Treg cells and reprograms these cells to produce IL-4, converting them into a proallergic phenotype (Leyva-Castillo et al. 2019; Nakajima-Adachi et al. 2017). Type 2 innate lymphoid cells (ILC2s), which are Th2-like cells without antigenic specificity, and TH9 cells, which are IL-9 producing mucosal mast cells, provide another source of inflammatory cytokines (IL-4, IL-9, IL-13), blocking the function of Treg cells (Ruiter and Shreffler 2012) and driving intestinal mastocytosis in an autocrine loop (Shik et al. 2017). In the scenario of repeated allergenic stimulations and specific recurrent IgE responses to food allergens, also the mast cells of the gastrointestinal mucosa, activated by allergens, become an important local source of IL-4 (Renz et al. 2018; Sampath et al. 2017).

Skin exposure to food allergens, bypassing the normal tolerogenic default response to foods in the intestine, can promote sensitization (Cabanillas et al. 2017). Skin cytokines act on DCs to shift immunity towards Th2 allergic rather than tolerogenic responses. In turn, skin DCs induce expression of gut-homing receptors on skin Th2 differentiating cells through retinoic acid secretion (Kim et al. 2016). Therefore, both defective skin and gut barrier functions could contribute to FA induction. Clinical observations confirm that in FA the skin may functions both as a target organ and a site of primary sensitization. Atopic dermatitis is an important risk factor for FA development (atopic march)

(Sicherer and Leung 2014). Skin barrier defects contribute to allergic sensitization. The predisposition to the development of Th2-mediated diseases, including FA, has been associated with mutations in filaggrin, which is an important protein for the integrity of the skin barrier. Inflammatory cytokines, including IL-25, IL-33 and TSLP, are also released by the skin epithelium and act on DCs and other cells to divert the immune response towards Th2 allergic reactions rather than tolerogenic responses. So, it is now established that defective barrier functions in the skin, as well as in the intestine, facilitate sensitization to food allergens (Johnston et al. 2014). Furthermore, tissue-derived cytokines, in particular IL-33, also intervene in determining allergic sensitization and in triggering reactions, probably through the activation of ILC2s, that in turn produce IL-4 and IL-13. IL-33 is a pleiotropic cytokine that plays a key role in different pathological conditions, acting both as an alarmin in response to signals of tissue damage, and as an inducer of Th2 immune responses (Ginaldi et al. 2019). Signals able to initiate sensitization include intrinsic activities of food components on innate cells, such as NKT cells, and exposure to bacterial toxins (Wesemann and Nagler 2016). The intestinal microbiota can also influence the balance between tolerance and sensitization (Johnston et al. 2014; Sampson et al. 2018). The food antigen sensitization mechanisms are illustrated in Fig. 2.

The current view about the pathogenesis of FA stems from the integration of different hypotheses. The vitamin D hypothesis is based on the observation that low levels of vitamin D, which is an immunomodulator with general tolerogenic effects, increase the risk of FA (Suaini et al. 2015). According to the diet hypothesis, the infant feeding patterns in industrialized countries and the westernized diets (low intake of fruits and vegetables, and insufficient intake of vitamin A), as well as methods of food preparation, influence sensitization favoring FA. The hygiene hypothesis considers the lack of exposure to microorganisms and infections in early childhood an important risk factor for allergization. Finally, the hypotheses currently supported by the strongest body of evidence are the microbiota perturbation hypothesis (certain bacterial strains, such as *Clostridium* species and *Bacteroides fragilis*, but especially microbial diversity, promote the generation of Treg cells and increase tolerance development; while, the widespread use of antibiotics facilitates the onset of allergies) (Blázquez and Berin 2017; Iweala and Nagler 2019), and the dual-allergen hypothesis (disrupted skin barrier in early life and lack of food allergen intake with consequent environmental rather than oral exposure) (Renz et al. 2018).

The role of the microbiota in the induction of immune tolerance is a very active research area (Berin and Sampson 2013). The approach to the prevention of FA has changed following the evidence that both microorganisms and antigens can modulate the immune system (Fu et al. 2016). Early microbial encounters support immune system in mounting balanced and long-lasting adaptive immune responses. Bacterial DNA and cell wall components, mainly originated from the mother through the gastrointestinal tract, are already present in the placenta. Early colonization of the neonatal gastrointestinal tract also occurs during vaginal delivery (Diesner et al. 2016). Differences have been described in immune reactivity later in life in children born via caesarian section versus those born via vaginal delivery.

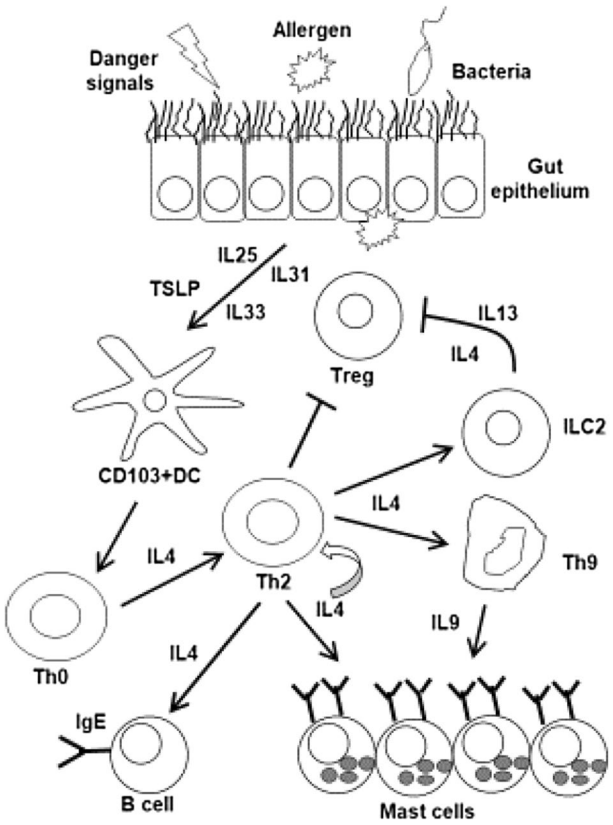

Fig. 2 Tolerance breakdown mechanisms leading to allergic sensitization. Tolerance breaks down in situations in which defective gut barrier function and danger signals (injury, allergen, bacteria) arise, leading to epithelial cell secretion of inflammatory cytokines, such as interleukin (IL)-25, IL-33 and thymic thymus lymphopoietin (TSLP). As a consequence, mucosal $CD103^+$ dendritic cells (DCs) acquire a phenotype that favors T helper 2 (Th2) cell priming and expansion when induced by food antigens (allergens). Th2 derived IL-4 stimulates isotypic switching in B lymphocytes with IgE production and mast cell expansion and sensitization, thus promoting release and accumulation of mediators of allergic inflammation. Moreover, Th2 cytokines suppress and reprogram tolerogenic T regulatory (Treg) cells to produce IL-4 themselves and, with an autocrine stimulus mechanism, promote the further expansion of the pool of the Th2 pool. Tissue-derived cytokines, via activation of Th9 and type 2 innate lymphoid cells (ILC2s), which are Th2-like cells without antigenic specificity, provide other sources of pro-allergic cytokines (IL-4, IL-9 and IL-13), further blocking the function of Treg cells and and driving intestinal mastocytosis in an autocrine loop

Environmental microbial situation, determined by living conditions, presence of pets in the house, urbanization or living on farms, contributes to the unique pattern of bacterial exposures (Huang et al. 2017). Later in life, the colonization pattern is heavily influenced by the type and composition of the food; for example, breastfed infants differ from formula-fed children. The microorganisms that normally colonize the skin and the intestine influence the development of the immune system and can promote or curb the development of immune tolerance to food (Berni Canani et al. 2015). Changes in the composition of human skin and intestinal microbiota have been correlated with FA, but the changes observed in bacterial strains are not yet clearly defined (Blázquez and Berin 2017). A protective effect of probiotic intake during pregnancy or breastfeeding has also been suggested (Garn et al. 2013).

Thus, considering that tolerance to food antigens is established early in the life, the term "window of opportunity" has recently been coined to indicate the critical period in life, from intrauterine development through to at least the first 2 years (the first 1000 days), during which environmental factors exert a lasting effect and determine individual's susceptibility to developing allergies, as well as certain lifestyle diseases, in adult life (Platts-Mills 2015; Renz et al. 2018).

Old and New Diagnostic Tools

The diagnosis of FA mainly relies on clinical history, laboratory tests to exclude other potential diagnoses, prick tests, specific serum IgE search and elimination diets followed by the reintroduction of foods (Bartuzi et al. 2017; Skypala et al. 2015).

Oral Food Challenge

An oral food challenge (OFC) is a highly accurate diagnostic test for FA, and can be performed either as an open challenge or as single and/or DBPCFC. Both for elimination diets and for food challenges, there are specific protocols to guarantee accuracy and safety (Kowalski et al. 2016). For example, in the DBPCFC, still considered the "gold standard" for diagnosing a FA, increasing doses of the suspected food allergen and placebo are given separately, even on different days, and neither the patient nor the doctor knows which one is administered. It is, therefore, a complex test that requires a long execution time and, above all, it is burdened by the risk of severe anaphylactic reactions (Kattan 2015).

In recent years, new diagnostic tools to replace the OFC or, at least, predict the risk of severe anaphylaxis, have been developed. In particular, the molecular or component-resolved diagnostics (CRD) and the basophil activation test (BAT) can contribute not only to diagnosis and prognosis formulation but also , above all, to the personalized treatment tailored on the specific patient's molecular and clinical profile (Macchia et al. 2015).

Basophil Activation Test

The BAT is an in vitro test that utilizes allergenic proteins as stimulants. This test is based on the expression of specific markers, such as CD63 and CD203c, on the surface of activated basophils. The CD63 receptor, also known as Gp53 or LAMP-3 (lysosomal-associated membrane glycoprotein-3), belongs to the tetraspanin family, poorly expressed on the surface of quiescent basophils, being predominantly present in their intracellular granules. Following cell activation, the granules and, with them, the CD63 molecule, are exposed on the surface. As a consequence, there is an increased surface expression of this marker on basophil surface, evidenced by quantitative and multiparametric flow cytometry. The result is expressed as both percentage and fluorescence intensity of $CD63^+$ and/or $CD203c^+$ basophils (Santos and Lack 2016). This test is mainly used to assess the degree of individual reactivity to a specific allergen and the definition of individual specific reactivity threshold. The negativity of this test, even if not decisive, allows for the selection of patients with a minimum risk of reaction at the provocative tests. However, it is a laboratory method that is not yet widely available (Santos and Shreffler 2017).

Component-Resolved Diagnostics

CRD, through the IgE search for specific epitopic components, allows definition of IgE-sensitization pattern at a molecular level through the use of purified, native or recombinant allergens (Heffler et al. 2018). Unlike standard tests, it, therefore, differentiates, through the recognition of responsible allergenic molecules, true sensitizations from clinically non-significant cross-reactivity, and identifies specific molecular sensitization profiles linked to different patterns of clinical severity (Cardona and Ansotegui 2016; Luengo and Cardona 2014). There are, in fact, several specific cross-reactive allergenic components in food and allergenic extracts. Prick/RAST with standard extracts lack sensitivity, indicating sensitization to a food but not to which molecule contained in it. Instead, the CRD allows to identify the culprit allergenic molecules, to determine the profile of individual reactivity and to formulate a prognostic judgment. New strategies to manage severe food allergies are required, with the goal to protect patients against the most severe accidental reactions, and CRD test is, therefore, an additional tool for assessing the risk of systemic reactions (Arasi et al. 2018).

The characterization of a growing number of new molecules with different structural and biological

characteristics is ongoing and the list of these molecules is constantly updated in the Official list of allergens by the International Union of Immunological Societies Allergen Nomenclature sub-committee of the WHO (Pomés et al. 2018). Although in vitro tests for the measurement of specific IgE against molecular components are actually useful to better identify and characterize allergic patients, the increasing number of newly discovered molecules expressing different structural and biological characteristics makes the interpretation of molecular diagnosis difficult.

Panallergens are among the most widespread specific components. They are grouped into four main families of plant food allergens: pathogenesis-related proteins (PR), profilins, lipid transfer proteins (LTP), and storage proteins (Hauser et al. 2010). Allergic reactions to fruits and vegetables can result from a primary sensitization to food or to inhalant allergens. Usually, cross-reactivity is attributable to labile allergens (e.g., PR-10 and profilins) and is associated with mild oral reactions; while, heat and proteolysis-resistant allergens, that mainly sensitize through the oral route, are associated with systemic reactions (e.g., seed storage proteins and nsLTP) (Mazzucchelli et al. 2018). For example, apple contains thermolabile allergenic molecules (epitopes) belonging to the family of not only PR-10 (Mal d1) and profilins (Mal d4), but also thermostable LTP (Mal d3). LTP Mal d3 sensitization is associated with sevenfold greater risk of anaphylaxis than Mal d 1 (Bet v 1 homologous). Mal d3 sensitization is, therefore, considered a marker of mild reactions to fresh fruit and vegetables caused by cross-reactivity with plant pollen (birch) (Chinthrajah et al. 2015). Thus, among patients with allergy to Rosacea fruits, based on CRD, it is possible to distinguish those with LTP and Bet v1/profilin sensitization and pollen allergy from those with LTP but no Bet v 1/profilin sensitization and no pollen allergy. Patients in the former group develop mainly mild symptoms (OAS), whereas those in the latter are at risk of systemic reactions (Woodfolk et al. 2015).

Given that single allergenic peanut molecules are associated with different clinical pictures, a molecular approach can be crucially useful for the diagnosis of peanut allergy too and for subsequent management. Ara h8 and Ara h5 are, respectively, PR-10 and profilin epitopes, Ara h1, 2, and 3 are storage proteins and Ara h9 belongs to the LTP group. LTPs are responsible for 60% of food and fruit allergy cases and are associated with the highest risk of serious or fatal reactions. Concerning peanuts allergy, Ara h2 is a major peanut protein, associated with severe clinical reactions; whereas, Ara h8 is a labile birch pollen homolog (Bet v1) which is not likely responsible for significant clinical reactions. Therefore, patients with elevated levels of IgE for LTP and storage proteins should be excluded from oral challenge tests (Platts-Mills et al. 2016).

Moreover, CRD also allows to predict the persistence of an AA and consequently plan the therapeutic approach. Two-thirds of egg-allergic children become tolerant within the first 5 years of life. Children with a prolonged egg allergy show elevated IgE against sequential epitopes of ovomucoid (Gal d1) and ovalbumin (Gal d2) and more often do not tolerate even cooked food (Hemmer et al. 2016). The same occurs in the allergy to cow's milk caused by sensitization to the epitope Bos d8 of casein, which is strong and stable. This diagnostic methodology applies to a growing number of foods as we deepen our knowledge of epitopes, and many CRD tests are already commercially available and widespread used (Alessandri et al. 2017).

Food Allergy Prevention in the Light of Scientific and "Real Life" Clinical Observations

In the past, the American Academy of Pediatrics (Fiocchi et al. 2006), as well as the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (Wershil et al. 2002) and the Australian Society of Clinical Immunology and Allergy (Baumgart et al. 2004), recommended delaying as much as possible the introduction of common allergens in the diet of children at high risk of FA. According to these guidelines, the consumption of dairy products should be delayed up to 1 year of age of the child, chicken eggs up to 2 years and fish, nuts and peanuts up to 3 years. These guidelines also stipulated that even breastfeeding women would remove nuts and peanuts from their diet. However, despite the strict application of these preventive measures, FA continued to increase (Keet and Wood 2014; Sicherer and Sampson 2018).

These concepts were recently revolutionized by the Learning early about peanut allergy (LEAP) Randomized trial of peanut consumption in infants at risk for peanut allergy (Du Toit et al. 2015). The study was aimed at testing the hypothesis that regular consumption of peanut-containing products, once started in childhood, would elicit a protective sustained immune response rather than an allergic reaction. The study showed that the precocious peanut introduction into the diet prevents FA development. Overall, sustained consumption of peanuts from the first 11 months of life was very effective in preventing the development of peanut allergy. The authors, therefore, concluded that the practice of excluding peanut from children diet contributed to increase incidence of peanut allergy, allowing skin exposure in the absence of intestinal tolerogenic signs following ingestion. This fundamental study and its follow-up also demonstrated an increase in peanut-specific IgG4 levels in the peanut group; while, the avoidance group had increased peanut IgE levels. Dietary recommendations

for the prevention of peanut allergy have been, therefore, updated according to the results of the LEAP study (Fleischer 2017; Greenhawt 2015). Based on these results, the new dietary guidelines recommend the introduction of peanuts to high-risk children in the first 4–6 months of life. The paradigm of food antigen avoidance during pregnancy and in early infancy to prevent the development of FA is, therefore, substantially changed, and practice guidelines and position statements from the most representative allergological scientific societies are being oriented towards the early food allergen introduction, which could be a promising prevention strategy (Ebisawa et al. 2017; Muraro et al. 2014b; Netting et al. 2017). It also seems that maternal consumption of common food allergens, such as peanuts, nuts, milk and wheat during pregnancy can reduce the risk of FA in infants (Ohsaki et al. 2018). Similarly, the introduction of greater food diversity in childhood may be associated with a reduced risk of allergic disease.

However, other studies suggest that food sensitization may instead develop during pregnancy, as the maternal–fetal interface develops a Th2- and Treg-mediated environment to protect the fetus. Undoubtedly, fetus is exposed to food allergens contained in the mother's diet, as confirmed by the presence of intact major food allergens in amniotic fluid samples, possibly giving rise to first sensitization. This early contact could explain, in some circumstances, subsequent sensitization to foods never eaten before. Maternal factors, including the impact of immune complexes, TGF-β, vitamin A, and regulatory T-cell responses, contribute to the induction of neonatal tolerance vs. development of allergic responses to maternally transferred allergens. Thus, allergen avoidance during pregnancy may be safe in certain cases (Fujimura et al. 2019; Pastor-Vargas et al. 2016).

Another large prospective randomized study (Fisher et al. 2018) found that, in addition to peanut, also the early introduction into the diet of cow's milk, eggs, sesame and wheat in potentially allergic children could be a useful prevention tool (Halken et al. 2017; Nicklaus et al. 2019). However, many questions regarding the effects of the type of allergen, dose and frequency require further consideration before recommendations can be widely applied.

The Changing Therapeutic Approach to FA

Immunotherapy

In line with what was said, even the therapeutic approach has changed. In the past, the traditional approach to FA was the careful avoidance of the culprit foods, which unavoidably condition patients to difficult and frustrating elimination diets, but what is worse, without being able at all to avoid accidental exposures leading to possible severe anaphylactic reactions. Currently, novel strategies are under investigation and in particular food allergen-specific immunotherapy (FAIT), which has been designed on the basis of our growing understanding of how desensitization to food protein antigens occurs (Henson and Burks 2012; Virkud and Vickery 2012).

The purpose of FAIT is to alter the allergic response to a food allergen, so that the patient becomes desensitized or possibly permanently unresponsive to the specific food. Alternatively, some patients may simply benefit from an increase in the threshold dose of food needed to trigger an allergic reaction (Berin and Mayer 2013). In these cases, patients may have some protection from accidental exposures and this increased safety also improves quality of life (Lanser 2015).

FAIT Methods

EAACI Guidelines on Allergen Immunotherapy (Pajno et al. 2018) established evidence-based recommendations for active treatment of IgE-mediated FA. Moreover, the latest EAACI guidelines (Muraro et al. 2018) recommend the modalities and describe the advantages and disadvantages of the various forms of FA immunotherapy tested to date: oral (OIT), sublingual (SLIT), and epicutaneous (EPIT) routes. In the OIT, a low dose of allergen (in the range of milligrams) is ingested every day. SLIT involves the administration of a liquid allergen extract under the tongue, where it is held for several minutes. Conversely, EPIT uses an adhesive containing microgram amounts of allergen to supply antigen to the surface of the skin (Tordesillas et al. 2017). In all these types of FAIT, except for EPIT, gradually increasing doses of specific allergen are delivered.

Currently, head-to-head trials of OIT versus SLIT and EPIT, aimed at verifying the effectiveness of the different immunotherapies for IgE-mediated FA, seem to indicate that OIT is more efficacious for desensitization and sustained unresponsiveness after 6-week off therapy. Notwithstanding it is associated with higher frequency of unpredictable adverse events, most of them are not severe. The rationale for OIT is that the ingestion of a food antigen determines preferential tolerance (active immune response) (Greenhawt and Vickery 2015). The patient takes a very small initial dose of the food (3–6 mg of protein) and gradually increases the dose every 2 weeks up to the maintenance dose (several months). The initial dose and dose increases are administered under clinical control, while the other daily doses are taken at home) (Renz et al. 2018). At present, OIT is recommended for persistent allergy to cow's milk, hen's egg, or peanut in children from around 4–5 years of age, on the basis of its ability to increase the threshold for clinical reactions, at least while on therapy (Chu et al. 2019). Moderate to mild allergic reactions are common especially in the initial

incremental phase of OIT (predominantly gastrointestinal disorders). However, most patients with side effects (allergic reactions) continue therapy. In a small percentage of cases of OIT, eosinophilic esophagitis develops and treatment is interrupted (Aceves 2014).

FAIT-Induced Immune Changes

The main immune changes observed during specific immunotherapy for FA are summarized in Table 2. $CD4^+$ allergen-specific T cells pass from allergic to regulatory or anergic phenotypes. As a consequence, there is an increase in the number of $Foxp3^+$ Treg cells, mainly producing TGF-β1. The shift from allergen-specific Th2 cells to other cell subsets is the key event in sustained non-response. This shift reduces the inflammatory response of tissues that encounter food allergens, thus mitigating the recruitment and activation of innate immune cells such as mast cells and basophils. Other cells are probably eliminated through exhaustion or anergic mechanisms. A decrease of allergen-specific IgE levels and an increase of allergen-specific IgG4, that compete with IgE to dampen allergic response, are also observed (Scott-Taylor et al. 2018). The immune changes that accompany desensitization take place as a progression of different events: for example, the reactivity of mast cells and basophils to degranulation is an early consequence of immunotherapy. Furthermore, the observed increase in the number of B regulatory (Breg) cells that secrete IL-10, indicates that also Breg cells may have an important role in immunotherapy. But despite the finding of these immunological modifications, further research is still needed to identify appropriate biomarkers for successful immunotherapy.

Drug Treatments

Currently, there is no definitive treatment for FA: the elimination of food allergens and the treatment of systemic reactions induced by food allergens with adrenaline remain the standard of care. Early adrenaline administration is a crucial factor in preventing death from anaphylaxis. Early treatment with adrenaline after exposure to allergens (within the first 6 min after exposure) is more effective than subsequent treatment (more than 20 min after the onset of symptoms). A first dose of insufficient and/or late adrenaline could increase the risk of biphasic reactions (recurrence of symptoms within a few hours). Adrenaline can reverse edema, urticaria, bronchospasm, hypotension and gastrointestinal symptoms within minutes (Keet 2011).

Other drugs, including antihistamines, such as diphenhydramine or more specific H1 receptor blockers, such as cetirizine, are useful for treating localized FA symptoms, for example itching and hives. Gastrointestinal symptoms can be treated with H2 receptor blockers, such as famotidine. However, all these drugs only control FA symptoms and do not influence the underlying immune disorder (Simons et al. 2015).

Personalized nutritional and/or medical interventions (Zhang et al. 2015), biologics (Bauer et al. 2015), such as omalizumab (anti-IgE), dupilumab (anti-IL-4Ra), reslizumab and mepolizumab (anti-IL-5) monoclonal antibodies, as well as intestinal microbiome reconstitution (*Clostridium fragilis*, *Lactobacillus bifidus*) (Fiocchi et al. 2012; Liu et al. 2017), are therapeutic tools that have now become part of the current strategy for treating FA.

Nutritional interventions should consider also the dietary therapy in individuals suffering FA, since this condition needs a restriction diet (avoiding the allergen) and consequently the whole nutrients involved into the food matrix that contains the allergen. For instance, children with milk allergy need adequate nutritional counseling and regular monitoring of growth and should be supplemented with calcium and vitamins A and D (Tiainen et al. 1995).

Biological Therapies

The development of knowledge of molecular processes involved in sensitization inspired the use of monoclonal antibodies as therapeutic agents in FA to block these processes. In particular, the combination with biologics may enhance safety of immunotherapy. For example, since allergic reactions are common and often severe during OIT, the use of omalizumab has been employed, in association with OIT, to increase safety. Omalizumab binds to the Fc region of IgE antibodies, blocking the IgE binding to their receptors (FcεRI) and thus preventing activation and degranulation of mast cells and basophils (De Martinis et al. 2019a; Sirufo et al. 2019). Omalizumab was originally approved for the treatment of allergic asthma, but has now been tested in other pathological conditions (De Martinis et al. 2019c; Sirufo et al. 2018) and, in combination with OIT, also for the treatment of FA. Patients initially

Table 2 Immune changes during specific food allergy immunotherapy

Decrease of allergen-specific Th2 cells
Decrease of specific IgE levels
Decreased mast cell and basophil reactivity to degranulation
Increased TGF-β and IL-10 production
IL-10 secreting Breg cell expansion
Allergen-specific $Foxp3^+$ Treg expansion
Reconversion of Th2 into Treg cells
B cell IgG4 class switching
Increase of specific IgA and IgG4 levels

Th2 T helper type 2, *Ig* immunoglobulin, *IL* interleukin, *TGF* transforming growth factor, *Breg* B regulatory, *Treg* T regulatory

receive omalizumab injections on a bi-weekly or monthly for at least 8 weeks to reduce free IgE and reduce the surface expression of FcεRI on mast cells (Vazquez-Ortiz and Turner 2016). The OIT begins after an initial period of overlap of several weeks in which both omalizumab and the food allergen are administered; thus, the biological drug is suspended. OIT plus omalizumab may allow the immune system to be desensitized to food allergens more quickly and safely than OIT alone (Fiocchi et al. 2017). However, further clinical trials are needed to confirm the safety and efficacy of omalizumab, to optimize maintenance doses and to assess the sustainability of desensitization or the establishment of tolerance. Other biologics, targeting upstream mediators of FA, could also be useful. For example, monoclonal antibodies specific for IL-5 (mepolizumab and reslizumab) have been used in some clinical studies to treat eosinophilic esophagitis. Three-monthly mepolizumab infusions resulted in decreased counts of esophageal eosinophils. Four-monthly reslizumab infusions reduced the esophageal eosinophil count by approximately 60% (Ko and Chehade 2018).

Conclusions

Tolerance is the state of healthy non-immunological responsiveness to common food antigens. Conversely, desensitization is a temporary increase in the threshold for allergen reactivity, whose mechanisms are not well understood but likely differ from those of the non-allergic permanent immune tolerance status. Immunotherapy often results in desensitization rather than in a lasting state of prolonged irresponsiveness. It is not known whether a FA patient who has been desensitized through immunotherapy will remain permanently unresponsive to that food allergen. In this case, it is rather a sustained non-response, distinct from healthy pre-allergic immune tolerance. New immunotherapies for FA have been designed on the basis of our growing understanding of how desensitization to food protein antigens occurs. However, although the enormous progress made in recent years in understanding the immunological mechanisms underlying FA, and above all, the availability of innovative diagnostic and therapeutic tools, such as immunotherapy and biological drugs targeted to important immunological checkpoints, FA still represents an evolving research field, and consequently also its management is still a changing landscape.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest.

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