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Immunotherapy of Food Allergy: a Comprehensive Review

Christine Y. Y. Wai[1,2] · **Nicki Y. H. Leung**[1,2] · **Patrick S. C. Leung**[3,4] · **Ka Hou Chu**[1]

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Abstract Food allergy imposes a severe global health burden, and thus, there is a dire need for safe and effective treatments. Allergen-specific immunotherapy (AIT) is currently the only approach to restore immune tolerance through administrating increasing doses of allergen extracts. Unfortunately, the development of AIT for food allergies has been impeded by the frequent anaphylactic side effects during the course of treatment. The emergence of component-resolved diagnosis has greatly improved our ability to identify causative allergens and revolutionized the design of AIT. Molecular features such as IgE-binding epitopes and T cell epitopes have been elucidated in most major food allergens, inspiring the use of multiple strategies to manipulate the allergens and design safer alternatives to AIT. Although these allergen-modifying approaches are currently restricted to preclinical characterization and animal studies, the employment of these strategies has certainly paved the way for improving the safety of existing AIT. A safe and effective AIT for food allergy is not far beyond reach.

✉ Patrick S. C. Leung
psleung@ucdavis.edu

✉ Ka Hou Chu
kahouchu@cuhk.edu.hk

[1] Simon F.S. Li Marine Science Laboratory, School of Life Sciences, The Chinese University of Hong Kong, Room 201A, Science Park Road, Shatin, N.T., Hong Kong, SAR, China

[2] Department of Paediatrics, The Chinese University of Hong Kong, Shatin, Hong Kong, SAR, China

[3] Division of Rheumatology/Allergy, School of Medicine, University of California, Davis, CA 95616, USA

[4] Genome and Biomedical Sciences Facility, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA

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Abbreviations

AIT	Allergen-specific immunotherapy
APCs	Antigen-presenting cells
BSA	Bovine serum albumin
DCs	Dendritic cells
EPIT	Epicutaneous immunotherapy
FAST	Food Allergy Specific Immunotherapy
iTreg	Inducible Treg
LAP	Latency-associated protein
MHC	Major histocompatibility complex
nTreg	Naturally occurring Treg
OBOC	One-bead-one-compound
OIT	Oral immunotherapy
OVA	Ovalbumin
Ovm	Ovumucoid
PLGA	Poly(lactic-*co*-glycolic-acid)
rMet e 1	Recombinant Met e 1
SLIT	Sublingual immunotherapy
SPT	Skin prick test
TCLs	T cell lines
Th2	Type II T helper
WAS	Wiskott-Aldrich syndrome

The prevalence of adverse reactions to food was reported to approach 8% in children and 5% in adults [1]. However, these figures are likely to be inaccurate as they depend on self-reported allergies and serological profiles. Accurate food prevalence is difficult to determine and often non-reproducible due to variations in definition of allergy, study population, methodology, age, and the food allergen studied. Nevertheless, it is certain that both

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food-related anaphylaxis and the rate of hospitalization for food-induced anaphylaxis are increasing globally [2]. Affecting an estimated 520 million people worldwide, food allergy is beyond question a severe global health burden (WAO White Book 2013).

Food allergy is categorized into IgE-mediated, non-IgE-mediated type, or an intermediate type showing features of both [3]. IgE-mediated reactions are the immediate type of hypersensitivity where allergic symptoms occur within 2 h of food ingestion. Clinical manifestations of IgE-mediated reactions include acute urticarial, nausea, and systemic anaphylaxis. Non-IgE-mediated type is delayed-type hypersensitivity and believed to be cell-mediated. Common symptoms associated with cell-mediated food allergic reactions include enterocolitis and proctocolitis. The third form of allergy is the combined IgE and cell-mediated hypersensitivity, which mainly involves infiltration of eosinophils and is considered as a type of delayed hypersensitivity reaction mediated by the type II T helper (Th2) cells and eosinophilic mediator IL-5 and eotaxins [4]. The chronic condition of eosinophilic infiltration of the gastrointestinal wall mainly at the stomach and small intestine is collectively known as eosinophilic gastroenteritis (EGE), which is one major form of eosinophilic gastrointestinal disorders (EGIDs). Elevated levels of total IgE and/or food-specific IgE could be detected in some EGE patients that is accompanied by positive skin prick test to certain food allergens without the development of immediate anaphylactic symptoms [5]. These thus impose difficulties in distinguishing patients from IgE-mediated food allergy and EGID by food-specific IgE and skin prick tests.

In this review, we will focus on the IgE-mediated food allergy, which is primarily responsible for fatal anaphylactic reactions. Currently, there are no preventive medications for IgE-mediated food allergy. The primary treatment option is strict avoidance of the causal food; however, accidental ingestion is often inevitable, especially in children [6]. Therefore, the need for a safe and effective treatment for food allergies is eminent. Allergen-specific immunotherapy (AIT) is a disease-modifying approach to restore immune tolerance to the allergens by administering increasing doses of sensitizing allergens until a maintenance dose is reached. Yet, despite advances in AIT for inhalant allergens, the development of AIT for food allergies has been at a stalemate due to frequently reported anaphylactic side effects during treatment [7–12]. Unlike inhalant allergens, food allergens are subject to digestion along the gastrointestinal tract and sometimes contain more than 20 IgE-binding epitopes [13]. This has undeniably increased the risk of food allergies treated with AIT using natural allergens.

Major Food Allergens

The molecular characterizations of the allergens, such as T cell or B cell epitopes, are a key to designing safer AIT. Advances in component-resolved diagnosis have greatly enhanced our knowledge of the allergenicity of individual allergens and facilitated the design of hypoallergenic derivatives. Here, we will briefly discuss the properties of the most common food allergens (Table 1).

Peanut Allergens

Peanut allergy is the most common cause for severe food-derived anaphylaxis [14]. The severity is likely due to the high protein content in a single peanut (~ 200 mg). Thirteen peanut allergens belonging to seven protein families have now been identified. Ara h 1 is a glycoprotein belonging to the vicilin seed storage protein family [15] and is believed to have modest allergenicity due to burial of epitopes [16, 17]. Ara h 2 belongs to the 2S albumin protein family and is the dominant allergen recognized by 90–100% of peanut-allergic patients [18]. Ara h 3 and Ara h 4 were originally thought to be distinct proteins but are now believed to be isoforms of the same allergen belonging to the legumin seed storage protein family [19, 20]. Ara h 5 belongs to the profiling family and is a minor peanut allergen in low levels in peanut extracts and recognized by a minority of peanut-allergic patients [19, 21]. Ara h 6 and Ara h 7 belong to the same 2S albumin protein family and share certain homology to Ara h 2 [21]. Ara h 8 is homologous to the birch pollen allergen Bet v 1 and contributes to the cross-reactivity between birch pollen and peanut allergy [22]. Ara h 9 belongs to the lipid transfer protein family and is the dominant peanut allergen in the Mediterranean population [23, 24]. Ara h 10 and Ara h 11 are members of the oleosin structural protein family and exist in purified peanut oil bodies [25]. Ara h 12 and Ara h 13 are cysteine-rich defensin peptides. IgE reactivity to these peptides is present in only a small portion of peanut-allergic patients [26].

Tree Nut Allergens

Tree nut allergens can be classified into different groups based on their structural and functional properties [27]. The first group is the seed storage proteins, comprising 11S legumin-like proteins, 7S vicilin-like proteins, and the 2S albumins. Both the 11S legumin-like proteins and 7S vicilin-like proteins belong to the cupin protein superfamily and exist as hexamers and trimers, respectively [20]. On the contrary, the 2S albumins are small heterodimers belonging to the prolamin superfamily [28]. These three allergens are the major tree nut allergens identified from most edible tree nuts. The second group is the pathogenesis-related (PR) proteins involved in the plant defense system, including chitinases [29], PR-10 [30], and lipid transfer proteins [31–33]. The third group comprises structural proteins that are highly conserved among plants, such as profilins [34, 35] and oleosins [36].

Table 1 List of identified and characterized food allergens according to the International Union of Immunological Societies (IUIS) allergen nomenclature

Food	Allergen	Identity/protein family	Remarks	References
Peanut	Ara h 1	Vicilin		[15]
	Ara h 2	2S Albumin	Dominant peanut allergen recognized by 90–100% of patients	[18]
	Ara h 3 and 4	Legumin		[19, 20]
	Ara h 5	Profilin		[19, 20]
	Ara h 6 and 7	2S Albumins	Share sequence homology with Ara h 2	[21]
	Ara h 8	Bet v 1-homolog	Minor allergen, but contributed to the cross-reactivity between peanut and birch pollen	[22]
	Ara h 9	Lipid transfer proteins		[23, 24]
	Ara h 10 and 11	Oleosin		[25]
	Ara h 12 and 13	Defensins		[26]
Tree nuts	Cas s 5	Chitinase		[29]
	Cas s 1 and Cor a 1	PR-10		[30, 31]
	Cas s 8, Cor a 8, Jug r 3, and Pru du 3	Lipid transfer proteins		[31–33]
	Cor a 2 and Pru du 4	Profilins		[34, 35]
	Cor a 12 and Cor a 13	Oleosins		[36]
Cow's milk	Bos d 4	α-Lactalbumin		[38, 39]
	Bos d 5	β-Lactoglobulin		[38, 39]
	Bos d 6	Serum albumin		[38, 39]
	Bos d 7	Immunoglobulins		[38, 39]
	Bos d 8	Lactoferrin		[38, 39]
Egg	Gal d 1	Ovomucoid	Dominant egg allergen	[42]
	Gal d 2	Ovalbumin	Most abundant protein	[42]
	Gal d 3	Ovotransferrin		[42]
	Gal d 4	Lysozyme		[42]
	Gal d 5	Albumin	First allergen identified in egg yolk	[42]
	Gal d 6	YGP42		[43]
Fish	Group I allergens (Gad c 1, Sal s 1, Sco j 1, etc.)	Parvalbumin		[47, 48]
	Group II allergens (Gad m 2, Sal s 2)	Enolase		[58]
	Group III allergens (Gad m 3, Sal s 3)	Aldolase		[58]
	Group V allergens (Onc k 5)	Vitellogenin	Found in caviar	[52]
	Ungrouped	Collagen		[53, 54]
	Ungrouped	Aldehyde phosphate dehydrogenase		[55]
	Ungrouped	Triosephosphate isomerase		[56]
	Ungrouped	Muscle creatine kinase		[57]
Shellfish	Group I allergens (Met e 1, Pen a 1, etc.)	Tropomyosin	Major cross-reactive allergen among invertebrates	[59–61]
	Group II allergens (Pen m 2, Cra c 2, etc.)	Arginine kinase	Cross-reactivity reported among invertebrates	[65–67]
	Group III/V allergens (Lit v 3, Cra c 5)	Myosin light chain	Groups III and V are different isoforms of myosin light chain	[67, 70]
	Group IV allergens (Lit v 4, Cra c 4, etc.)	Sarcoplasmic calcium-binding proteins		[67–69]
	Group VI allergens (Cra c 6, Pen m 6)	Troponin C		[67]
	Group VII allergens (Pon l 7)	Troponin I	Unpublished data	WHO/IUIS
	Group VIII allergens (Cra c 8)	Triosephosphate isomerase		[67]

Cow's Milk Allergens

About 20% of proteins in cow's milk are whey and 80% are coagulum [37]. Whey contains globular protein including α-lactalbumin (Bos d 4), β-lactoglobulin (Bos d 5), bovine serum albumin (Bos d 6), bovine immunoglobulins (Bos d 7), and lactoferrin [38, 39]. The major allergens in the whey fraction are α-lactalbumin and β-lactoglobulin, which are involved in 80 and 76% of all allergic sensitization to cow's milk, respectively [40]. The coagulum fraction consists mainly of four individual casein proteins coded by different genes on the same chromosome: αs1-casein, αs2-casein, β-casein, and κ-casein [38]. Due to the complexity of milk proteins and polysensitization, no single allergen or particular structure has been identified in the allergenicity of milk [41].

Egg Allergens

Six major allergens were identified in hen's egg: ovomucoid (Gal d 1), ovalbumin (OVA; Gal d 2), ovotransferrin (Gal d 3), lysozyme (Gal d 4), albumin (Gal d 5), and YGP42 (Gal d 6) [42, 43]. The majority of egg allergens are found in the egg white (Gal d 1–4) except Gal d 5 and Gal d 6 which are found in the egg yolk. Two other egg proteins, lipocalin-type prostaglandin D synthase and egg white cystatin, were recently found to have IgE reactivity in egg-allergic patients, but their significance in egg allergies remains unclear [44]. While ovalbumin is the most abundant protein present in egg white, the heat stable protein ovomucoid is believed to be the dominant allergen [45].

Fish Allergens

Parvalbumin, a protein regulating calcium switching in skeletal muscle cells, was identified as the first fish allergen in the Baltic cod during the early 1970s [46–48]. Parvalbumin is recognized by 90% of fish-allergic patients [49–51] and belongs to the biggest group of food-derived allergens, the EF-hand domain family. In addition to parvalbumin, other minor allergens such as vitellogenin [52], collagen [53, 54], aldehyde phosphate dehydrogenase [55], triosephosphate isomerase [56], muscle creatine kinase [57], enolase [57, 58], and aldolase [58] have been identified in different fish species or fish-derived products such as caviar.

Shellfish Allergens

The muscle protein tropomyosin was identified as the major allergen in shrimp by three groups independently in the early 1990s [59–61] and later revealed as a pan-allergen among shellfish and other invertebrates [62, 63]. Tropomyosin is a coiled-coil secondary structure protein that belongs to the highly conserved actin filament-binding protein family. Tropomyosins are heat-stable with limited digestibility so they persist even after thorough cooking [64]. Apart from tropomyosins, other allergens have been identified in several shrimp species, such as arginine kinase [65–67], sarcoplasmic calcium-binding proteins [67–69], and myosin light chain [67, 70]. The detailed molecular features and cross-reactivity of these shellfish allergens have been reviewed elsewhere [71, 72]

Pathogenesis of Food Allergy

While normal individuals develop oral tolerance towards food proteins, food-allergic subjects mount an inappropriate IgE response to the food antigens. In such cases, food allergens are taken up by the antigen-presenting cells (APCs) and the T cell epitopes are presented to naïve T cells through the major histocompatibility complex (MHC) class II molecule. The activated T cells differentiate into Th2 cells. Th2 cells then promote a class switch in the cognate allergen-bound B cells through cell-cell interaction or cytokines (IL-4, IL-5, and IL-13). Class-switched B cells produce IgE antibodies, which rest on effector cells such as mast cells or basophils. Upon subsequent re-exposure to the same allergen, IgE cross-links the allergen on effector cells (e.g., mast cells and basophils) through the high affinity receptor FcεRI, causing degranulation. The mediators released by these cells, such as histamine, prostaglandins, and leukotrienes, are the major causes of allergic responses and anaphylactic shock. These immediate allergic symptoms can occur within minutes after allergen contact, either directly at the site of allergen exposure (i.e., mouth and intestine) or extend to other organs (i.e., skin and respiratory tract) when the allergen passes through the mucosa to the circulatory system [64, 73, 74].

Additionally, a dysregulated Th2-skewed response can be linked to functional defects in Foxp3, the key transcription factor of regulatory T (Treg) cells [1], as well as alterations in genes such as *STAT3*, *DOCK8*, or *PGM3* and genes involved in TCR signaling including *LAT*, *ZAP70*, or *RAG* [75]. A recent study also suggests a link between mutations in the Wiskott-Aldrich syndrome (WAS) gene and increased frequency of sensitization to food allergens in patients [76]. Mutations in the *WAS* gene result in WAS protein (WASP) deficiency. WASP-deficient Treg cells show increased levels of Th2 transcriptional factor *GATA3*, therefore resulting in hyper IgE phenotype and intestinal mast cell expansion in mice. It is essential to continue investigating the activation of Th2 effector responses to fully understand its mechanism and its role in food allergy.

Allergen-Specific Immunotherapy

The aim of AIT is to initially achieve desensitization (i.e., temporary increase in the threshold of effector cell activation)

and subsequently attain oral tolerance. Oral tolerance is the permanent state of unresponsiveness to the sensitizing allergen, indicating the absence of any allergen-specific response due to deletion or inactivation of T cells, or the presence of active IgG, IgA, Th1, and/or Treg responses (Fig. 1).

The initial immunological changes generated through AIT may involve decreased activity and responsiveness of effector cells, such as mast cells and basophils [77, 78]. An increase in allergen-specific IgG_4 can also be seen as early as within 1 week after the onset of AIT. This subclass of IgG antibody is generally regarded as protective as it can effectively capture the allergen before reaching the cell-bound IgE. Studies also suggest that it can downregulate IgE receptor FcεRI signaling and promote internalization of IgE in mast cells without triggering mast cell degranulation [79, 80]. Yet, the level of specific IgE typically increases in the first few months of AIT and a late decrease could only be seen when AIT is continued for extended periods of time.

Changes involving the modulation of T cell responses occur at a later stage in the course of AIT, which include a decrease in Th2 cells and release of their linked cytokines, leading ultimately to oral tolerance. These can be a result of the deletion of antigen-specific $CD4^+$ T cells when a high dosage of the antigen is administered [81]. Additionally, oral tolerance can also be achieved through the development of suppressor T cells in the gastrointestinal lymphoid tissues. This type of tolerance is independent of the naturally occurring Treg (nTreg) cells derived from the thymus. It is mediated by two different subsets of Treg cells [82, 83]. Th3 cells suppress directly through a TGF-β-dependent manner. This cytokine blocks differentiation of Th1 and Th2 cells by modifying the expression of their respective transcription factors T-bet and GATA-3 [84, 85]. It also promotes the synthesis of IgA, as well as the expansion of suppressive $CD4^+CD25^+Foxp3^+$ inducible Treg (iTreg) cells [86, 87]. iTreg cells may suppress using IL-10 which directly inhibits IgE synthesis, proliferation of Th2 cells, and cytokine production by blocking the CD2/CD28/ICOS costimulatory signaling pathway [88]. The development of these iTreg cells also depends on $CD103^+$ dendritic cells (DCs) present in the lamina propria of the intestinal tract through TGF-β, retinoic acid, and

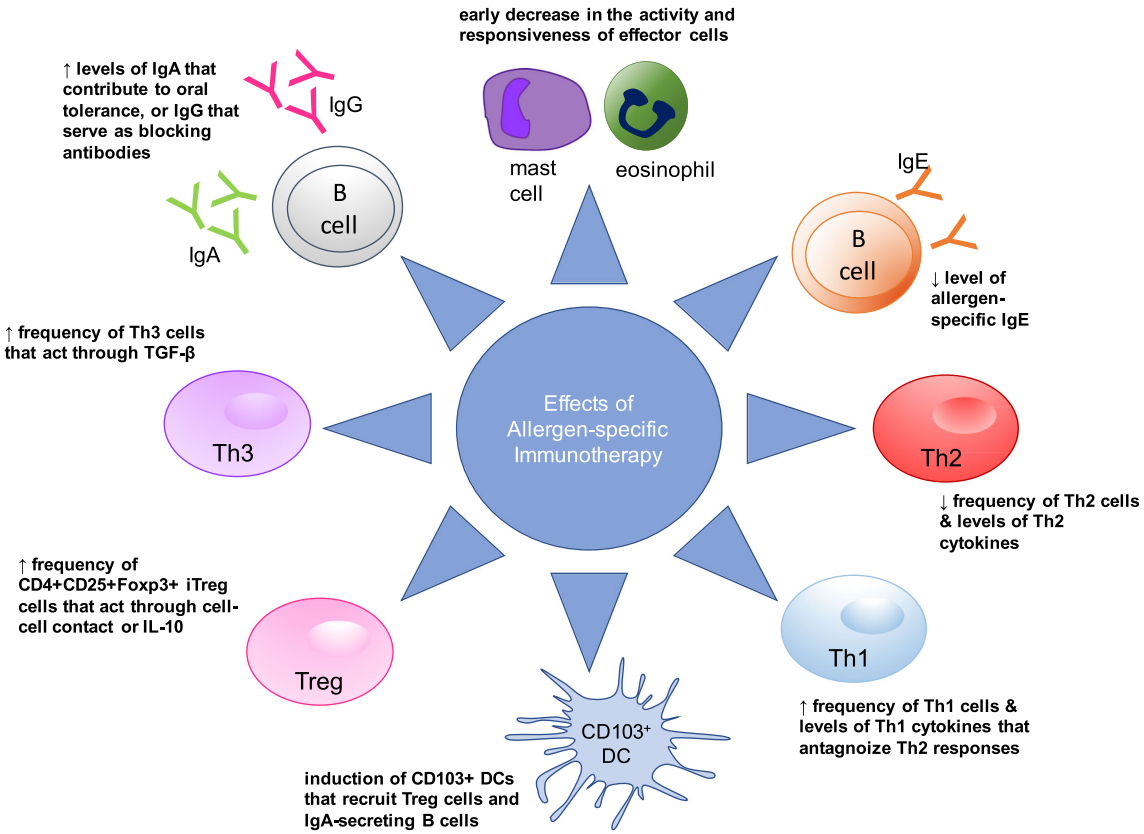

Fig. 1 Possible immunological effects of AIT. Decrease in the activity of effector cells such as mast cells, eosinophils, and basophils occur at the early stage of AIT. Level of specific IgE usually shows an early increase followed by a late decrease. Increases in frequency of Th1 cells, levels of Th1 cytokines, the generation of allergen-specific $Foxp3^+$ Treg cells, TGF-β-producing Th3 cells, and Breg cells follow subsequently and possibility antagonize the differentiation and activation of Th2 cells. The induction of $CD103^+$ tolerogenic DCs happens in parallel that could also lead to the activation of Treg cells and IgA-secreting B cells. Increase of IgA and IgG inhibitory antibody continues throughout the treatment

other factors [89]. CD103$^+$ DCs also promote IgA-secreting B cells, [90] which together with iTreg cells contribute to oral tolerance in food allergy.

In the following sections, we will discuss different AIT strategies in detail, including the use of unmodified allergens delivered via different routes (Table 2); the identification and construction of hypoallergens, T cell epitopes, mimotopes, and conjugated molecules based on immunomolecular features of the native allergen (Fig. 2); as well as their efficacies in preventing and treating food allergies in animal models and clinical trials (Table 3).

Unmodified Allergens

The first AIT was recorded in 1911 when Noon reported the use of subcutaneous injection of grass pollen extracts to treat hay fever [91]. Since then, allergen extracts have been widely used in AIT, including those targeting food allergies. Recent advances in recombinant DNA technology have prompted the use of recombinant allergens in place of whole allergen extracts. Although AIT using unmodified allergens appears to be effective for treating inhalant allergies, pioneer studies of subcutaneous immunotherapy for food allergies were considered unsafe as anaphylactic side effects were frequently observed in clinical trials of peanut AIT [92, 8]. To improve the safety of AIT for food allergies, novel methods to deliver the allergen are under investigation. The oral, sublingual, and epicutaneous routes are three major delivery routes that have been extensively explored.

Oral immunotherapy (OIT) involves daily consumption of the sensitizing allergen, typically using a start-off dose below the threshold dose, which is then followed by a gradual increase in dosage to a maintenance dose until achieving desensitization and/or tolerance. Clinical trials of OIT targeting cow's milk [93, 12, 94, 95, 9], hen's egg [96–98], and peanut [99–101] allergies demonstrated positive immunological improvements. Reduced sensitivity in skin prick test (SPT), decreased level of specific IgE, and increased level of IgG_4 and Treg cell population were consistently reported in these independent studies. Generally, OIT using native allergens has a high success rate to achieve at least partial desensitization in > 80% of subjects [102]. However, OIT with these unmodified allergens only leads to 25–40% specific oral tolerance and can also lead to adverse allergenic reactions. In a peanut OIT clinical trial, 92% of patients experienced respiratory or mild itching symptoms during the initial day of escalation [100]. All subjects experienced minor respiratory or skin reactions during home dosing, with two subjects requiring epinephrine treatment. A safe and successful establishment of permanent tolerance is yet to be accomplished in OIT.

Sublingual immunotherapy (SLIT) is considered an improvement of OIT, in that it uses allergen extracts that are usually 1000-fold less concentrated than OIT and kept under the tongue for a few minutes before spitting out or swallowing [102]. Although the exact immunological mechanisms are unclear, SLIT is believed to target the Langerhans-like dendritic cells in the sublingual mucosa that promote tolerance to allergens [103–105]. SLIT has been tested for allergen extracts of food items such as kiwi fruit [106, 107], hazelnut [108, 109],

Table 2 Different routes of allergen extract delivery in immunotherapy and their respective advantages, limitations, and possible adverse events triggered

Route of allergen delivery	Allergen types tested	Immunological effects	Adverse reactions	Limitations
Oral	Cow's milk, hen's egg, peanut, fruits, vegetables, tree nuts, etc.	Reduced sensitivity in skin prick test; increased specific IgG4 Decreased specific IgE Signs of regulatory T cell activation	Frequently occurring throughout the treatment; occasional severe systemic reactions requiring epinephrine treatment	Safety concerns Mixed results for long-term tolerance induction
Sublingual	Kiwi, hazelnut, cow's milk, peach, peanut, etc.	Reduced sensitivity in skin prick test; increased specific IgG4 Evidence of reduced basophil activation Shifted production of T_H2-type cytokine to T_H1 type	Less frequent and mostly occurring during initial dosing while fewer in maintenance; mostly local reactions	Unclear mechanism Lower efficacy compared to OIT Lack of evidence for long-term tolerance induction
Epicutaneous	Cow's milk, peanut (pilot studies)	Evidence of regulatory T cell induction Shifted production of T_H2-type cytokine to T_H1 type	Less likely and mostly local cutaneous reactions	Unclear mechanism Lack of comprehensive clinical trials

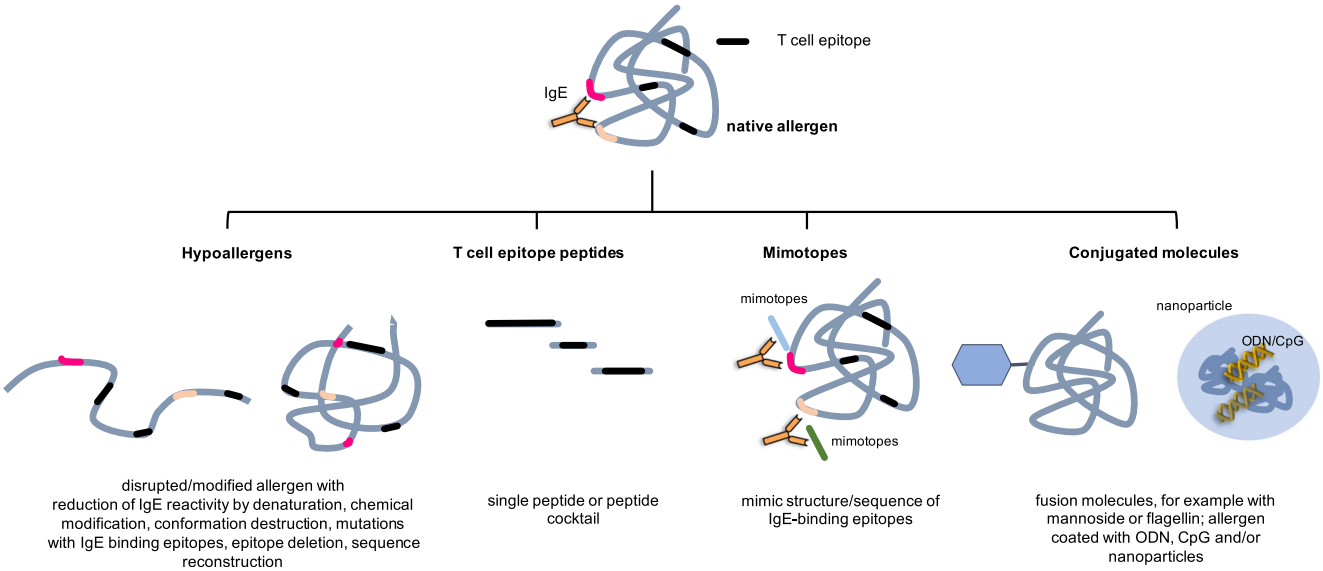

Fig. 2 Strategies for AIT modulator preparation. IgE reactivity and allergenicity of the native allergens can be abolished by manipulating or deleting the epitopes, altering the conformation by denaturation or chemical modification to construct hypoallergens. T cell epitopes that trigger $CD4^+$ T cell responses and possess T cell modulatory functions can be synthesized and delivered as a single peptide or peptide cocktail to enhance Th1 and Treg cell activities. Mimotopes that mimic the structure and/or sequence of the IgE-binding epitopes are shown to induce allergen-recognizing antibodies that might serve inhibitory functions. Conjugation of allergens with molecules with immunomodulatory functions can promote the induction of tolerogenic DCs, Treg cells, and/or Th1 cells

cow's milk [110, 111], peach [112, 113], and peanut [114, 115]. The clinical improvements reported from the above studies indicate that SLIT could reduce sensitivity in SPT and increase specific IgG_4 level as in OIT. However, Keet et al. suggested that OIT is more efficacious for desensitization than SLIT [111]. Only 1 of 10 subjects from the SLIT group passed the 8-g cow's milk challenge, compared to 8 of 10 subjects from the OIT group passing the same challenge. However, the symptoms triggered in SLIT are confined to local reactions, with the frequency of reaction varying greatly between studies, from 0.2% in hazelnut to 89% in peach. In spite of the seemingly positive clinical improvements in both OIT and SLIT, there are uncertainties concerning their safety and long-term effects. In addition, the use of OIT and SLIT is restricted in patients with more severe food-induced anaphylaxis. Strategies for improving the current protocol are needed, which might include the use of modified allergens and other relevant immunomodulatory agents, or even alternative delivery schemes.

Epicutaneous immunotherapy (EPIT) has recently emerged as an alternative allergen delivery method. Allergens enclosed in a container are delivered onto intact [116] or tape-stripped skin [117]. As the epidermis is not vascularized, EPIT prevents systemic reactions caused by circulation of allergens. Similar to SLIT, the preventive effects of EPIT are thought to be mediated through the tolerogenic Langerhans cells in the epidermis [118–120]. Preliminary studies in mouse model suggest the induction of Treg cells and a shift to Th1 milieu by EPIT [121, 122]. A recent study reported the recruitment of gastrointestinal-homing latency-associated protein (LAP) + Foxp3-Treg cells by epicutaneous application of OVA-Viaskin patches in mice sensitized and challenged intragastrically by OVA. This subset of Treg cells protects against food allergy by suppressing mast cell activation via a TGF-β-dependent manner but not IgE antibodies [123]. However, in a pilot study of EPIT in children with cow's milk allergy, only 50% of patients demonstrated an increase in cumulative tolerated dose in the oral food challenge. There was no significant increase in serum-specific IgG and IgE levels, but 25% of the recipients experienced local adverse reactions [124]. Further clinical studies are needed to monitor the safety and therapeutic efficacy of EPIT.

One main challenge towards the use of unmodified allergens in AIT lies within the optimum dosage being employed. We have recently investigated the dose-dependent safety and efficacy of AIT in a mouse model of shrimp allergy [125]. BALB/c mice were first sensitized and challenged with recombinant Met e 1 (rMet e 1) through the intragastric route. Subsequently, they were treated with low (0.01 mg), medium (0.05 mg), or high (0.1 mg) intraperitoneal injections of rMet e 1 for three times at a weekly interval. We found that despite all mice being successfully desensitized regardless of the dosage, Treg-associated regulatory mechanisms were only observed in the low or medium dosage groups. This is evident through the upregulation of Treg-associated genes and the infiltration of $Foxp3^+$ cells in the gut lymphoid tissues exclusively in these two groups of mice. These findings suggest that low-dosage immunotherapy favors the induction of local $Foxp3^+$ Treg cells and more likely to sustain long-term efficacy of AIT.

Table 3 Different experimental strategies and immunological benefits of AIT for food allergy

Strategy	Example	Immunological changes	Reference
Hypoallergen	Chemical modification	Pre-clinical stage: with marked reduction in IgE reactivity and allergenicity; able to induce blocking antibody	
	Pru p 3 (peach), Ara h 2 and Ara h 6 (peanut)		[143] [144]
	Site-directed mutagenesis		
	mAra h 2 (peanut), MEM49 (shrimp tropomyosin), parvalbumin (fish)		[134, 149, 158]
	Epitope deletion MED171 (shrimp tropomyosin)		[149]
	Sequence restructuring Fag t 1 (buckwheat)		[132]
	Conformation destruction		
	Dau c 1 (carrot), Ara h 2 (peanut)		[133, 135]
	Polyphenol sorption Peanut extract		[156]
T cell epitopes	β-Lactoglobulin (cow's milk)		
	Peptide 6 AA31–48	Prevented acute allergic skin response; lower levels of IgE, IgG_1, and IgG_{2a}; increased Treg cell %	[163]
	P1 and P2 AA67–88, AA139–153	Reduced hypersensitivity responses; no change in the levels of IgE, IgG_1, IgG_{2a}, IgA, IL-4, IL-12, IL-10, or Treg cell %	[164]
	OVA (egg white)		
	Single peptide AI-15, AA39–53	Reduced level of histamine and IgE Increased level of IgA	[167]
	Peptide mixture: AA39–53, AA147–161, AA323–343	(Cocktail) increased IFN-γ, TGF-β, and Foxp3 expression	
	Ovm (egg white)		
	SP: AA157–171 MP: 3 repeated unites of SP linked by alanine	Reduced IgE and IL-4 Increased IgA and IFN-γ	[168]
		(SP) reduced histamine; increased IgG_{2a}, IL-10, IL-12, and Treg cells	
Mimotopes	Met e 1 (shrimp tropomyosin)		
	T1–T6: AA26–45, AA46–75, AA86–105, AA146–165, AA221–240, AA251–270	Reduced IgE and Th2 cytokine expression Increased Th1 and Treg gene expression and blocking IgG2a antibody	[169]
	Met e 1 (shrimp tropomyosin)		
	Mimotope cocktail	Reduced IL-4, IL-5, and IL-13 expression; upregulated IL-10 and TGF-β expression	[196]
Conjugated molecule	Mannoside-BSA	Increased IL-10 and Treg cells	[197]
	Flagellin-ovalbumin	Reduced IL-4 and IFN-γ, increased IL-10	[198]
	Ara h 2-Fc fusion protein	Reduced allergic responses	[199]
	CpG-coated PLGA nanoparticles containing peanut extracts	Reduced IgE and Th2 cytokines, increased IgG2a and IFN-γ, offered extended protection after therapy	[201]

The frequent occurrence of adverse events during AIT with unmodified allergens, especially OIT, represents another major challenge. This thus leads to the investigations of adjunctive therapies, such as using the anti-IgE recombinant humanized monoclonal antibody omalizumab that can prevent the interaction between circulating IgE and FcεRI, to improve safety. The early off-label use of omalizumab was shown to reduce adverse reactions and enable more patients to achieve the maintenance dose in SCIT and SLIT and, more recently, in OIT [126]. In a double-blinded, placebo-controlled trial of cow's milk-specific OIT, a comparable percentage of patients passed the 10-g oral cow's milk challenge and achieved sustained unresponsiveness at 8-week after discontinuation of OIT for both omalizumab-treated and placebo-treated

groups [127]. Yet, the overall percentage of symptom-free doses during the escalation phase of OIT was 91.5% in the omalizumab-treated group, comparing to 73.9% in the placebo-treated group. In a similar study adopting a rapid oral desensitization protocol for peanut allergy, omalizumab greatly increased the median tolerated dose on the first day of rush desensitization (250 mg peanut protein for the omalizumab group versus 22.5 mg for the placebo group) [128]. Significantly more omalizumab-treated subjects could tolerate a 2000-mg maintenance dose and passed a 4000-mg cumulative dose in an open peanut oral challenge compared to the placebo-treated group. Similarly, the immunological changes were similar between the two groups. These suggest that adjunctive treatment with omalizumab has no significant effects on the outcomes of efficacy, but improvements in safety and facilitation of rapid desensitization are remarkable. It is yet noteworthy that a subset of patients could display stronger responsiveness to IgE receptor cross-linking with omalizumab treatment [129]. The identification of baseline biomarkers, such as their pretreatment basophil reactivity and/or allergen-specific to total IgE ratio, is thus essential for selection of suitable patients who will benefit from such adjunctive treatment [130].

Hypoallergens

The major obstacles in AIT, especially OIT, for food allergies are the frequent adverse side effects and prolonged treatment duration due to the low dosage restricted by the use of unmodified allergens. Alternative approaches to reduce the allergenicity while retaining the immunogenicity of allergens, such as the use of hypoallergens, are therefore promising. General strategies deployed to construct hypoallergenic food allergens involve site-directed mutagenesis within the IgE-binding epitopes, sequence restructuring, chemical modifications, disruption of allergen conformation, allergen unfolding, and more [131–135].

Since previous studies have shown that subjects allergic to raw foods can tolerate cooked foods, the use of heated allergens in AIT can promote desensitization to the native allergen in patients [136]. Heating allergens causes aggregation, which reduces their absorption and transport through the mucosal layer. It also leads to conformational changes and/or changes to a significant proportion of the IgE-binding epitopes, reducing their allergenicity sufficiently for safe use in AIT [137, 138]. It was shown that mice sensitized with heated ovalbumin (h-OVA, heated to 70 °C for 10 min) have significantly lower levels of OVA-specific IgE and mouse mast cell protease-1 (mMCP-1) upon OVA challenges compared to control mice sensitized with OVA [139]. They also displayed higher levels of specific IgG_{2a} and a prominent Th1-type immune response. The gain of desired antigenic properties of h-OVA was probably due to not only the irreversible structural changes but also the formation of a different panel of peptide fragments upon digestion compared to raw OVA. Although results from animal studies seem promising [140, 138], an open food challenge to baked egg in 236 egg-allergic children resulted in 36% reaction to the challenge, with 14% of them experiencing anaphylaxis [141]. In another baked-milk OIT therapy, only 3/14 OIT subjects reached their tolerance goal at a maintenance dose of 1.3 g per day [142]. Eight patients could not complete the therapy due to IgE-mediated side effects including anaphylaxis. It is apparent from these reports that treatments with heated molecules usually only generate desensitization but not tolerance, and heating allergens does not necessarily produce hypoallergenic proteins in all allergic patients.

While "natural" manipulation might not be sufficient in yielding hypoallergenic proteins, variants with reduced allergenicity can be generated by means of chemical modification or genetic engineering. Native allergens can be reduced and alkylated to disrupt the disulfide bonds, such as in the major peach allergen Pru p 3 [143], as well as in the peanut allergens Ara h 2 and Ara h 6, or additionally linked to glutaraldehyde to achieve structural changes in Ara h 2 and Ara h 6 [144]. These strategies could effectively produce hypoallergenic variants that have diminished IgE reactivity and allergenicity in immuno-blotting, rat basophilic leukemia (RBL) release assays, and immunization experiments. However, further studies are needed to confirm their antigenic characteristics as such modifications may cause drastic conformational changes resulting in the loss of T cell epitopes and increased risk of sensitization [145].

By inhibiting IgE/allergen cross-linking, anaphylactic side effects in AIT could be greatly reduced. In this context, the IgE-binding epitopes contain important information for constructing the relevant hypoallergens. IgE-binding epitopes of the majority of food allergens have been mapped, including α-lactalbumin (cow's milk) [146], ovalbumin (egg white) [147], Ara h 2 (peanut) [148], Pen a 1 and Met e 1 (shrimp) [149, 150], as well as Pru p 3 (peach) [151]. Modifications of the amino acid sequences within these IgE-binding epitopes to abolish IgE reactivity can therefore be achieved simply by site-directed mutagenesis. The introduction of mutations into the 10 linear epitopes of Ara h 2 at positions 20, 33, 39, 51, 58, 64, 117, 127, and 144 resulted in a hypoallergen (mAra h 2) that displayed only 29.6% IgE binding reactivity relative to wild-type Ara h 2 (wAra h 2) [152]. mAra h 2 still maintained intact T cell epitopes as it had the same peripheral blood mononuclear cell (PBMC)-stimulating ability compared to wAra h 2. On the other hand, our laboratory identified nine major IgE-binding epitopes of the major shrimp allergen Met e 1 [149]. By comparing these epitope sequences to the homologous tropomyosin sequences of four edible fish species, 49 point mutations were introduced into the nine epitopes to

construct the tropomyosin mutant MEM49. Another mutant, MED171, was constructed by deleting all the nine IgE-binding epitopes, resulting in a smaller truncated molecule of 171 amino acid residues. Both MEM49 and MED171 displayed > 70% reduction in their in vitro reactivity towards IgE of shrimp-allergic subjects compared to Met e 1. These two hypoallergens also had markedly reduced in vivo allergenicity in passive cutaneous anaphylaxis assay and immunization experiment. More importantly, mice immunized with either of the hypoallergens produced Met e 1-specific IgG_{2a} antibody that inhibited IgE of shrimp-allergic subjects and sensitized mice from binding to Met e 1. Such phenomenon is considered beneficial as these antibodies can rapidly modulate allergic reactions. The prophylactic and therapeutic efficacies of the hypoallergens in the form of DNA vaccines are now under investigation using a mouse model of shrimp hypersensitivity [153, 154].

Instead of manipulating the IgE-binding epitopes through "tailored" modifications for each food allergen, a general approach to construct hypoallergens adaptable to multiple food allergens is highly desirable. Reports have shown that polyphenols from fruits and vegetables might modulate the immune cells and pathways involved in allergic responses, thus alleviating inflammatory symptoms [155]. A recent study described a polyphenol-containing cranberry juice mixed with peanut flour that allowed sorption of polyphenols to peanut proteins to form a cranberry polyphenol-fortified peanut matrix [156]. Using basophil degranulation assay, it was found that this matrix triggered significantly less degranulation (median = 37.2%) compared to unmodified peanut flour (median = 66.1%). Peanut-allergic mice challenged with the matrix also showed significantly reduced levels of mMCP-1. These data suggest that the matrix is hypoallergenic and potentially useful for AIT targeting peanut allergy. Similar technology of food-grade quality that is economical, simple in the preparation of hypoallergens, and readily adaptable to multiple food allergens should be explored to further advance food allergy management.

Currently, most hypoallergenic food allergens are largely restricted to the early stages of construction and preclinical characterization. One major step forward in the management of food allergy is an EU-funded collaborative project initiated in 2008 Food Allergy Specific Immunotherapy (FAST) [157]. This project aims to develop safe and effective subcutaneous AIT towards fish and peach allergies using hypoallergenic proteins. Two hypoallergens of fish parvalbumin Cyp c 1 have been developed in this project. The first one is a chemically modified mutant constructed by glutaraldehyde treatment, and the second one is a calcium binding site double mutant described by Swoboda et al. in 2007 [158]. The double mutant has a ~ 100-fold reduced allergenicity. Immunization with this mutant induced IgG antibody, leading to 67–76% inhibition towards IgE of fish-allergic patients. On the other hand, five hypoallergenic variants of peach Pru p 3 are constructed in the FAST project. These include a "natural hypoallergen" rFra a 3, rPru p 3 sur (surface mutant with three amino acids mutated to alanine), rPru p 3 cys (four cysteines mutated to serine), rPru p 3 RA (reduced and alkylated Pru p 3), and glutaraldehyde-treated rPru p 3.

The first stage of the FAST project involves production of the hypoallergens under good manufacturing practice for clinical trials. The preclinical development of the double mutant of fish parvalbumin Cyp c 1 and wild-type Cyp c 1 was recently reported [159]. This fish parvalbumin mutant was found to be a stable molecule upon expression and exhibited no toxic effects when adsorbed to aluminum hydroxide. This mutant also displayed ~ 1000-fold reduction in its allergenic activity in the ImmunoCAP inhibition experiment and RBL release assay while its immunogenicity in inducing PBMC proliferation was retained. The subsequent stage of the project will involve animal studies on the efficacies of subcutaneous treatment with the selected hypoallergens through a panel of in vitro and in vivo experiments. The group recently reported that the antisera generated by immunizing mice with hypoallergenic Cyp c 1 contained IgG antibodies that block fish-allergic patients' IgE from binding to wild-type Cyp c 1 [160]. The antisera were also capable of reducing allergic responses in a murine model of Cyp c 1-induced hypersensitivity, probably by inhibiting IgE from binding to Cyp c 1 and basophil degranulation. The final stages of the project will include phase I/IIa and phase IIb clinical trials to determine safe dosages, as well as the tolerability and clinical outcome of the therapy in allergic patients through double-blind, placebo-controlled food challenge after treatment. Future reports from the FAST project are expected to provide novel strategies to replace avoidance, the standard "therapy" to food allergies, and bring our understanding of food allergy management to the next level.

T Cell Epitopes

T cell epitopes are short peptide fragments of the allergen that activate naïve T cells through the MHC class II molecules expressed on APCs [73]. These fragments lack secondary or tertiary structures and do not cross-link IgE or activate effector cells. However, they possess modulatory potential in reshaping the T cell environment from a Th2-type to a Th1- and/or Treg-dominating response. These properties make them a safe and effective therapeutic modulator ideal for AIT use as shown in successful clinical trials for cat and bee venom allergies [161, 162].

Nonetheless, there have only been a limited number of animal studies involving the investigation of T cell epitopes as immunotherapy for food allergies. Using T cell lines (TCLs) generated from cow's milk allergy patients and with

reference to previous reports, three regions of β-lactoglobulin, (regions 13–48, 91–120, and 139–162) were found to contain T cell-reactive sequences [163]. However, oral pretreatment with the peptide mixtures covering any one of the three reactive regions did not protect against the development of cow's milk allergy in mice subsequently sensitized to whey. Yet, pretreatment with a single peptide (peptide 6, AA31–48) significantly reduced acute allergic skin response, as well as levels of whey-specific IgE, IgG_1, and IgG_{2a}. Percentage of $CD4^+CD25^+Foxp3^+$ Treg cells was also significantly increased in mice pretreated with peptide 6. On the other hand, data reported by Thang and Zhao are less promising [164]. Oral delivery of any of the T cell-reactive peptides of β-lactoglobulin (P1: 22-mer, AA67–88; P2: 15-mer, AA139–153) could only reduce the severity of hypersensitivity responses. There were no changes in the levels of specific IgE, IgG_1, IgG_{2a}, and IgA; in the levels of splenic IL-4, IL-12, and IL-10; or in the percentage of Treg cells, even though the peptides were delivered frequently and for a long duration (three consecutive days per week for 4 weeks at 1 mg/peptide). The discrepancy in the degree of clinical improvement reported in the two studies might be due to the use of peptides spanning different "immunogenic" regions of β-lactoglobulin. It is also noteworthy that peptide 6 used by Meulenbroek et al. [163, 178] actually could not elicit proliferation in any of the TCLs, leaving the question of whether the observed effects are contributed by a "true" T cell determinant of β-lactoglobulin.

The T cell epitopes of two major egg allergens, OVA and ovumucoid (Ovm), were previously identified [165, 166] and applied in AIT studies in murine models. Subcutaneous injection with a single T cell peptide of OVA (15-mer, AI-15: AA39–53) or a mixture T cell epitopes (three 15-mer peptides, covering AA39–53, AA147–161, and AA329–343) effectively reduced the levels of histamine and OVA-specific IgE while increasing the level of fecal IgA [167]. A peptide cocktail could generate more pronounced effects by upregulating the expressions of Th1-linked cytokine IFN-γ and Treg-associated genes TGF-β and Foxp3 in the small intestine of treated mice. Similar effects could be observed when the T cell epitope of Ovm was delivered as treatment [168]. Two synthetic peptides containing five residues as single peptide (SP) (AA157–171) and 51 residues as a multiple peptide (MP) (three repeated units of SP linked by alanine residues) were used to treat Ovm-sensitized mice orally. Both SP and MP markedly reduced the levels of specific IgE and IL-4 while increasing the levels of fecal IgA and IFN-γ. However, only treatment with SP significantly reduced the histamine level and boosted levels of IgG_{2a}, splenic IL-10 and IL-12, as well as $CD4^+Foxp3^+$ cells.

Our laboratory identified six major T cell epitopes (20-mer long; T1–T6, AA26–45, AA56–75, AA86–105, AA146–165, AA221–240, and AA251–270) of shrimp tropomyosin Met e 1 and evaluated their therapeutic efficacy in a murine model of tropomyosin hypersensitivity [169]. These epitopes were mapped based on the proliferation and cytokine responses of spleen cells from BALB/c mice orally sensitized to Met e 1. Their epitope sequences are also similar to the reactive regions mapped on Pen a 1 using TCLs generated from shrimp-allergic subjects [170]. Similar to mice treated with the T cell epitopes of OVA and Ovm, the oral delivery of a mixture of these six Met e 1 T cell peptides also significantly reduced severity of systemic allergic symptoms, level of specific IgE, and expression of Th2 cytokines (IL-5 and IL-13) in the ileum. The effects of the treatment are limited not only to the restoration of Th1/Th2 balance and induction of Treg-like responses but also to the synthesis of IgG_{2a} antibodies that have both in vitro and in vivo inhibitory functions.

OIT using unmodified allergens represents a promising regimen in the treatment of food allergies via the induction of oral tolerance [171, 7, 102, 172, 173]. Yet, the use of intact allergens is not completely without risk [174]. From the abovementioned studies, it is clearly demonstrated that oral delivery of dominant T cell peptides, as both prophylactic and therapeutic agents, could effectively confer oral tolerance in murine models of various food allergies, making oral peptide immunotherapy (PIT) a promising strategy for treatment. While the major T cell determinants of most major food allergens, such as Ara h 1 and Ara h 2 (peanut) [175–177], αs1-casein and α-lactoglobulin (cow's milk) [178, 179], and Pru p 3 (peach) [180, 181], have been mapped, the efficacy of using these epitopes in PIT targeting these allergies has not been explored. The major obstacles in translating these identified epitopes into PIT might involve a large portion of sequences that can elicit a T cell response. For example, among the 69 20-mer overlapping peptides that span the full length Ara h 1, only four did not trigger proliferation in any of the TCLs generated from peanut-allergic patients [177]. The recognition was only 22–33% among the major respondents. A similar pattern was also found in the mapping of T cell epitopes of Pru p 3 [182]. Among the four T cell-activating regions, only Pru p $3_{61–75}$ was recognized by 50% of patients while Pru p $3_{13–27}$, Pru p $3_{34–48}$, and Pru p $3_{43–57}$ were only recognized by ~30% of patients. We suspect that a highly diverse set of HLA alleles and APCs along the digestive tract and diversity in the degree of allergen digestion in the allergic population might be the major confounding factors leading to the high diversity of T cell-activating sequences found among most food allergens [183, 64]. This therefore poses difficulties in pinpointing specific set of peptides as major immunodominant T cell epitopes for clinical use.

The use of peptide fragments of the allergens may be an alternative to the use of specific T cell epitopes for AIT. These fragments can be simply prepared by digesting the allergen extract using food-grade enzymes or pepsin. Yang et al.

demonstrated that over 85% of the egg white fragments yielded by enzymatic hydrolysis only have molecular masses of < 1.3 kDa [184]. Oral treatment with the hydrolyzed extract could effectively reduce the levels of histamine, specific IgE, and the expression of both Th2 (IL-4 and IL-13) and Th1 (IFN-γ and IL-12) cytokines in the ileum. TGF-β and Foxp3, a cytokine and transcription factor of Treg cells, respectively, were significantly upregulated. In another similar study, Kulis et al. digested the cashew proteins by pepsin, which yielded peptide fragments of 3–6 kDa in size [185]. Intraperitoneal treatment with these pepsinized extracts also helped to reduce allergic responses and Th2 cytokines, as well as induce IgG production in a mouse model with established hypersensitivity to cashew. These studies demonstrate that the use of digested allergen extract might provide enough T cell-stimulating peptides to a heterogeneous pool of patients with food allergies, therefore generating positive immunological changes in AIT.

Mimotopes

Mimotopes are peptides mimicking the IgE-binding epitopes of an antigen. They have been proposed for use in the treatment of allergic diseases as they can induce blocking antibodies against the native allergen [186–189]. Since then, mimotopes specific to several allergens have been identified through biopanning of phage-displayed libraries, but their applications were mostly limited to epitope mapping [190–194]. Wallmann et al. reported the use of a single mimotope specific to the timothy grass pollen allergen Phl p 5 for treating allergic asthma in a mouse model [195]. Mimotope-treated mice showed a decrease in eosinophil infiltration and Th2-associated cytokines IL-4 and IL-5 in the bronchoalveolar fluid. No adverse effects or changes in Phl p 5-specific T cell reactivity were observed in the treated mice. The lack of T cell epitope could be a major advantage of mimotope treatment as this can avoid T cell-mediated side effects in conventional AIT.

Nevertheless, the therapeutic effects of mimotopes in food allergies remain unclear. This is partly because a mimotope identified by the biopanning method is restricted to a single consensus epitope while most food allergens possess multiple linear epitopes [13]. Our laboratory recently reported the use of a one-bead-one-compound (OBOC) combinatorial peptide library in identifying 25 mimotopes corresponding to six immunodominant regions of the major shrimp allergen tropomyosin [196]. The therapeutic efficacy of a mimotope cocktail consisting of a mixture of these mimotopes is currently under investigation using a mouse model of shrimp hypersensitivity [153, 154].

Conjugated Molecules

One therapeutic approach in food allergy is to design fusion allergens that are directed to specific regulatory signaling pathways. For example, a mannoside-bearing bovine serum albumin (BSA) fusion protein substantially reduces anaphylactic response in a food-induced anaphylaxis mouse model [197]. The mannoside-BSA selectively targeted the C-type lectin receptor on lamina propria DCs and helped to induce oral tolerance through the expression of IL-10 and promotion of $CD4^+$ type I regulatory T cells. Another similar approach is to target toll-like receptor 5 (TLR5) on myeloid DCs with flagellin, which is a major constituent protein of bacteria flagella [198]. The flagellin-ovalbumin fusion protein could induce the expression of IL-10 by myeloid DCs and suppress IL-4 and IFN-γ secretion by ovalbumin-specific T cells.

Besides pattern recognition receptors like C-type lectin receptors or TLRs, it is also possible to target the low-affinity FcγRIIB receptor on mast cells or basophils. A peanut allergen (Ara h 2) fused to the Fc portion of human IgG_1 could ameliorate anaphylactic response in a mouse model of peanut allergy induced by whole peanut extract [199]. The aggregation and cross-linking of FcγRIIB and FcεRI by the allergen prevented degranulation and resulted in a tolerogenic signaling pathway.

Another strategy is to coat the food allergens or extract in CpG oligonucleotides and/or poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles. CpG provides an adjuvant effect to favor Th1 responses that antagonize the Th2 allergic responses. PLGA nanoparticles are biodegradable particles for oral drug delivery and stable in the gastrointestinal environment [200]. OIT with CpG-coated PLGA nanoparticles containing peanut extract was proven safe and effective in a murine model of peanut allergy [201]. Treated mice had their peanut-specific IgE and Th2 cytokine levels significantly reduced, and were protected from anaphylaxis. The treatment also boosted IgG_{2a} antibody and IFN-γ levels. Most importantly, 16 of 22 treated mice remained protected for over 4 months after therapy even peanut extracts were given periodically.

The major advantage of using the fusion allergen strategy is that the molecular characteristics such as T cell or B cell epitopes of the allergens are not required to create the fusion protein. However, it also means that the allergen would be expressed in its native form. The safety of such fusion proteins must be thoroughly investigated before clinical application.

Concluding Remarks

The fact that patients can outgrow certain food allergies suggests that oral tolerance can be acquired through effective AIT. Despite some mild anaphylactic side effects during

unmodified allergen-based OIT and SLIT, these forms of treatment do show promising results and a major step forward in the management of food allergies. Further understanding of their long-term efficacies and mechanisms will help to polish these regimens. Although the hypoallergens, T cell epitopes, mimotopes, and conjugated molecules discussed in this review are still currently at the level of preclinical characterization and animal studies, the use of these modulators in OIT and/or SLIT would further advance the safety of existing strategies. Large-scale clinical trials are much anticipated in the coming years, and effective AIT for food allergies will also soon be within reach.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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