Food allergy

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Abstract | Food allergies manifest in a variety of clinical conditions within the gastrointestinal tract, skin and lungs, with the most dramatic and sometimes fatal manifestation being anaphylactic shock. Major progress has been made in basic, translational and clinical research, leading to a better understanding of the underlying immunological mechanisms that lead to the breakdown of clinical and immunological tolerance against food antigens, which can result in either immunoglobulin E (IgE)-mediated reactions or non-IgE-mediated reactions. Lifestyle factors, dietary habits and maternal–neonatal interactions play a pivotal part in triggering the onset of food allergies, including qualitative and quantitative composition of the microbiota. These factors seem to have the greatest influence early in life, an observation that has led to the generation of hypotheses to explain the food allergy epidemic, including the dual-allergen exposure hypothesis. These hypotheses have fuelled research in preventive strategies that seek to establish desensitization to allergens and/or tolerance to allergens in affected individuals. Allergen-nonspecific therapeutic strategies have also been investigated in a number of clinical trials, which will eventually improve the treatment options for patients with food allergy.

The prevalence of food allergy has increased in recent decades and is now recognized as a substantial public health burden in developed countries, following the epidemics of asthma and allergic rhinitis that rose to prominence in the last few decades of the 20th century. Although different clinical entities are covered under the umbrella term 'food allergy', the common mechanism among all is the breakdown of clinical and immunological tolerance against ingested foods. This breakdown results in immunoglobulin E (IgE)-mediated diseases (TABLE 1) as well as non-IgE-mediated conditions, including eosinophilic oesophagitis, allergic proctocolitis and food protein-induced enterocolitis. The typical symptoms of food allergy include disturbances to the skin, respiratory tract and gastrointestinal tract as well as cardiovascular aberrations. In its most severe form, known as anaphylaxis, immediate hypersensitivity to food can involve several organ systems and induce life-threatening hypovolaemic shock and respiratory compromise.

The development of immunological and clinical tolerance represents a key mechanism to prevent chronic inflammatory diseases, such as food allergies, later in life. Tolerance is acquired, relies on antigen exposure, is antigen-specific and represents a lifelong process that starts prenatally[1]. Innate and adaptive immune responses cooperate in a coordinated fashion to mount tolerance; with regard to food antigens, tolerance requires food antigen exposure, which starts *in utero* (BOX 1). Extrinsic environmental and lifestyle factors also contribute to the manifestations and maintenance of the disease. For example, the qualitative and quantitative composition of the microbiota has been linked to food allergies[2–5].

Major advances have been achieved in basic, translational and clinical research, improving our mechanistic understanding of food allergy and enabling the development of therapeutic and preventive measures. New diagnostic tools are being developed, including recombinant allergens for *in vitro* diagnostics[6] and cellular testing[7–10]. Despite such advances, the main 'therapy' for food allergies remains strict allergen avoidance[11], which is not always possible and can lead to accidental reactions. However, exciting therapies are in clinical development, including treatment with biological therapies as well as allergen-specific therapies — such as oral, sublingual and epicutaneous immunotherapy. Prevention of food allergies remains a key challenge. To develop effective preventive measures, the contributing factors for the development of food allergies need to be defined. In this regard, several hypotheses have been developed, including the dual-allergen exposure hypothesis, the hygiene hypothesis and the vitamin D hypothesis.

This Primer provides a comprehensive overview of the recent advances in the field of food allergy in terms of mechanistic understanding, diagnostics, prevention and management. Although we discuss food allergies in paediatric and adult populations, nonallergic reactions (for example, food intolerance) or food-induced dermatitis are not discussed in detail.

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Epidemiology

Food allergens represent a major health problem, particularly in developed countries. Globally, Australia has the highest prevalence of IgE-mediated food allergy, with 10% of infants demonstrating challenge-confirmed allergies to one or more foods; by contrast, other developed areas such as Europe and the United States have prevalence estimates of 1–5%[12–16]. Estimating the prevalence of food allergies is difficult because the gold standard is the performance of a controlled food challenge, which can only be performed in specialized centres. However, even under such conditions, the prevalence remains high. Few large studies have attempted to measure the prevalence of food allergy in the same population at two time points employing the same definition of food allergy; accordingly, information about whether food allergy is truly on the rise is mostly based on surrogate measures, such as rates of anaphylaxis admissions to emergency departments[17]. However, although the proportion of cases due to food-related anaphylaxis admission is likely large (rather than, for example, insect stings), definite numbers are not available. Furthermore, inconsistencies in definition and reporting have made the prevalence of food-related anaphylaxis in the general population surprisingly difficult to assess, but it is probably between 0.5% and 2.5% in the United States[18]; general consensus is that prevalence has been steadily rising[17,19].

The population-based studies that do assess changes in prevalence of food allergy (as opposed to anaphylaxis) have primarily focused on peanut allergy, with evidence of increasing prevalence in the United Kingdom and United States[20]. The 2013 US Institute of Medicine report on the global burden of food allergy stated that although plentiful 'soft' data (for example, parental reports, school teacher surveys and medical staff surveys) indicate an increasing prevalence of food allergy, few well-designed comprehensive studies support this notion[21] (FIG. 1). Accordingly, accurate assessments of the true prevalence of food allergy are needed, and understanding whether prevalence is increasing is needed to prioritize public health efforts to address the problem[22].

Many individuals with food allergy will naturally outgrow it over time; however, the natural course highly depends on the causative allergen. Hen egg and cow milk allergy are frequently outgrown, whereas peanut and tree nut allergies tend to persist for life[23]. Indeed, the EuroPrevall birth cohort study evaluated the frequency of food allergy in 2,049 children from 9 European countries from birth until 2 years of age, showing that 69% of the children with cow milk allergy who were re-evaluated 1 year after diagnosis subsequently tolerated milk[24]. Similarly, half of the children who were allergic to hen eggs became tolerant within 1 year of the initial diagnosis[15]. By contrast, it has been shown in the Australian HealthNuts study that only 22% of children with peanut allergy at 1 year of age became tolerant by 4 years of age[25].

Mechanisms/pathophysiology

Food allergy comprises several immunological mechanisms that drive the reactions to ingested antigens. In its most common form, food allergy manifests as immediate hypersensitivity in which specific IgE antibodies bound to mast cells and basophils trigger the release of mediators that lead to very rapid physiological responses in a number of target tissues. By contrast, chronic allergic inflammatory processes primarily localized to the intestine underlie the syndromes of food protein-induced allergic proctocolitis, enterocolitis and eosinophilic oesophagitis. Although food allergen-specific IgE is occasionally present in patients affected by these conditions, T cell-driven responses, not IgE-triggered mast cell activation, are considered to be the major drivers of inflammation.

A unifying immunological theme among all of these processes is the breakdown of food-specific tolerance. The key challenge faced by the enteric immune system is to distinguish necessary and harmless food proteins and commensal enteric microbiota from potentially harmful pathogens, including helminth parasites (the effective expulsion of which depends on IgE antibodies and eosinophils)[26]. Tolerance of food antigens and inhibition of the development of allergic responses targeting them are active processes dependent on the generation of food antigen-specific regulatory T (T_{reg}) cells[27].

IgE-mediated food reactions

Absorption of the allergen through the intestinal epithelium and access to the mucosa and bloodstream where immune effector cells reside are enhanced in those with food allergy[28]. The ingested food allergens interact with IgE and its high-affinity Fc receptor (FcεRI; also known as high-affinity immunoglobulin ε receptor (FCER1)) on mast cells in mucosal tissues and on circulating basophils, leading to the activation of these cells (FIG. 2). FcεRI crosslinking triggers a signalling cascade that begins with the tyrosine protein kinase SYK, leading to the exocytosis of granules that contain preformed mediators of hypersensitivity, which include histamine, tryptase and chymase. *De novo* synthesis of lipid metabolites of arachidonic acid also occurs, including leukotrienes, prostaglandins and platelet-activating factor (PAF). These low-molecular-mass mediators elicit a range of physiological responses such as vasodilation, increased vascular permeability, activation of nociceptive nerves that mediate itch and smooth muscle constriction[29].

In the gastrointestinal tract, these physiological responses manifest as oral pruritus (itch) and angio-oedema (in which plasma accumulates in the deep dermis and subcutaneous or mucosal tissues), along with intestinal mucosal hyperaemia, increased contractility, mucus secretion and acute diarrhoea. Additionally, proteases such as tryptase can activate the complement and kinin–kallikrein cascades[30], which generate bradykinin (a mediator that increases vascular permeability). Typically, symptoms arise within minutes after food ingestion although, less commonly, they can occur several hours later. Allergen activation of mast cells and basophils additionally initiates transcription of a number of cytokines including IL-4 and IL-13 (a process that is amplified in the presence of IL-33)[31,32]; these cytokines promote the survival of pro-allergy T helper 2 (T_H2) cells and suppress T_{reg} cell function. Both mast cell degranulation and cytokine transcription can be suppressed by T_{reg} cells *in vitro*[33,34], indicating that T_{reg} cells might not only regulate the expansion of T_H2 cells but also suppress IgE-mediated mast cell activation during tolerance induction in those with food allergy.

Unlike other forms of systemic anaphylaxis (such as to insect stings or injected medicines), reactions to food are not typically associated with elevations in plasma levels of tryptase. Thus, the absence of detectable tryptase cannot be taken to exclude the possibility of anaphylaxis in a patient who has experienced an acute reaction to food. This finding probably relates to the low levels of this protease in mast cells that predominate in the intestinal mucosa and to the lack of systemic dissemination of this small amount of tryptase via the vasculature. However, food reactions have been associated with elevated plasma levels of PAF, a product of activated macrophages, along with reduced amounts of its inactivating enzyme, PAF acetylhydrolase, indicating that this lipid mediator might be a more useful clinical biomarker of anaphylaxis than tryptase[35]. Consistent with the presence of PAF, food allergen-induced basophil activation has been reported to induce the activation of platelets and formation of basophil–platelet complexes[36], providing a possible mechanistic explanation for elevated PAF in patients undergoing anaphylaxis.

Anaphylaxis. When absorbed, food allergens and the mediators released by activated mast cells and basophils are distributed systemically via the bloodstream to distant tissues; IgE-sensitized basophils and tissue-resident effector cells respond in a variety of ways. For example, plasma leak induced by histamine and arachidonic acid metabolites results in hives (urticaria, in which plasma accumulates in the superficial dermis), angio-oedema and hypotension. Angio-oedema in the intestine can cause cramp-like pain and obstruction, leading to vomiting. Laryngeal oedema has the potential to lead to complete airway obstruction and respiratory arrest. Among food allergens, peanuts, tree nuts and shellfish are most commonly associated with anaphylaxis, but severe reactions can occur with a wide range of foods, with cow milk and hen eggs being additional major triggers in young children. Additionally, some regional differences in dominant food allergens are apparent; for example, in the Mediterranean basin, fruits and vegetables that contain low-molecular-mass lipid transfer proteins (which are highly cross-reactive between foods) are the major cause of anaphylaxis[37].

One unusual form of anaphylaxis involves IgE antibodies that are produced in response to the oligosaccharide galactose-α-1,3-galactose (α-gal), which are typically introduced during tick bites. Subsequent ingestion of mammalian meat (which bears the same α-gal structure) can lead to reactions that are delayed by several hours, possibly owing to the slow absorption of complex lipids harbouring the antigen[38–40]. In another unusual form, certain murine models administered high-dose intravenous

Table 1 | **Food hypersensitivity (allergic) disorders by predominant organ affected**

Target organ	IgE-mediated disorders	Predominantly non-IgE-mediated disorders*	Non-IgE-mediated (cellular) disorders
Skin	• Generalized urticaria • Acute contact urticaria • Angio-oedema • Erythematous morbilliform rash • Flushing	Atopic dermatitis	• Contact dermatitis • Dermatitis herpetiformis
Lungs	• Allergic rhinoconjunctivitis • Acute bronchospasm	Asthma	Food-induced pulmonary haemosiderosis (Heiner syndrome)
Gastrointestinal tract	• Oral allergy syndrome • Acute gastrointestinal spasm	• Eosinophilic oesophagitis • Eosinophilic gastritis • Eosinophilic gastroenteritis	• Food protein-induced enterocolitis syndrome • Food protein-induced proctocolitis syndrome • Food protein-induced enteropathy syndrome • Coeliac disease
Cardiovascular system	• Hypotension • Dizziness and/or fainting	NA	NA
Generalized reaction‡	• Anaphylaxis • Food-associated exercise-induced anaphylaxis • NSAID-associated, aspirin-associated or alcohol-associated food-induced anaphylaxis	NA	NA
Other	• Uterine cramping and contractions • Feeling of 'pending doom'	NA	NA

IgE, immunoglobulin E; NA, not applicable. *Disorders associated with IgE hypersensitivity. ‡Involving two or more organ systems.

Box 1 | **The window of opportunity**

The window of opportunity describes a critical period in life during which environmental factors exert a lasting effect on the individual and determine an individual's susceptibility to developing allergies and certain lifestyle diseases in adult life. This period spans from intrauterine development through to at least the first 2 years in postnatal life and is referred to as the 'first 1,000 days' (www.thousanddays.org)[221]. In the past, many nations and organizations encouraged food antigen-avoidance campaigns during pregnancy and/or in early infancy to prevent the development of food allergies — a paradigm that has now substantially changed[222]. However, it remains under investigation whether proactive exposures foster the development of tolerance.
The immune system is supported in mounting strong and long-lasting adaptive immune responses by many environmental trigger, one of the most prominent of which are bacteria[223]. Recent research indicates that there are ample opportunities for early microbial encounters. Within the placental tissue, bacterial DNA and microbial (cell-wall) components are readily detectable[224] and mainly originate from the mother through the upper and lower gastrointestinal tract. The mode of delivery also determines early colonization of the neonatal gastrointestinal tract[225]. Marked differences have been detected between children born via caesarian section versus those born via vaginal delivery. Whether a causal link can be made between the development (or the protection) of chronic inflammatory diseases later in life and mode of delivery needs to be determined. The microbial 'exposome' as the sum of all these exposures is also determined by the environmental microbial situation[154]. Factors contributing to the unique pattern of bacterial exposures include housing and living conditions, the presence of pets in the household and urbanization versus living on (traditional) farms. Later in life, the colonization pattern is heavily influenced by the type, structure and composition of the food[226,227]. Exclusively or partially breastfed infants differ from formula-fed children. The major role of these microorganisms is in shaping and educating the immunological and metabolic functions of the individual.

antigen challenge can initiate an anaphylaxis response in the absence of IgE by cognate interaction with specific immunoglobulin G (IgG) antibodies bound to activating Fcγ receptors on effector cells[41,42]; there is evidence that under similar intravascular challenge, such IgG-mediated hypersensitivity reactions can arise in humans. IgG signals can activate both the classic mast cell pathway of mediator release (similar to the IgE–FcεRI-mediated reactions) and an alternative pathway that results in the production of PAF by macrophages. However, only IgE antibodies trigger histamine release by mast cells and basophils. Currently, no evidence supports a role for IgG in food anaphylaxis, which seems to be exclusively IgE-mediated, occurs only in individuals with food-specific IgE responses and is effectively inhibited by IgE blockade[43]. Indeed, reactions to enteral challenge have been shown to be fully IgE-dependent in several murine models of food allergy[44,45].

Factors regulating severity. Not all individuals with positive tests for food-specific IgE antibodies exhibit allergic reactions following ingestion. The presence of an IgE response is referred to as sensitization and is necessary but not sufficient to drive symptomatic food allergy[46]. Although the discordance between the presence of IgE and clinical sensitivity creates a diagnostic conundrum for clinicians treating patients with suspected allergy, it provides an important clue about the pathogenesis of food allergy, indicating the importance of non-IgE factors in hypersensitivity responses. These factors likely include the number and sensitivity of mast cells residing in the intestine and their threshold for IgE-induced activation as well as the sensitivity of target tissues to mast cell mediators.

Mast cells differentiate in tissues from blood-borne bone marrow-derived precursors, acquiring FcεRI and mast/stem cell growth factor receptor Kit (KIT) expression along with the formation of the granules that contain the aforementioned allergy mediators. Studies indicate that IL-9 is important in this process[47,48]. IL-9 is often produced — along with IL-4 by T_H2 cells — and is considered a T_H2 cytokine. IL-9 can induce goblet-cell metaplasia and mucus production and plays a critical part in helminth parasite expulsion[49,50]. So-called T_H9 cells have also been identified, which also produce IL-9 but with a cytokine profile that seems to be regulated by the transcription factors PU.1 (also known as SPI1) and interferon regulatory factor 4 (IRF4) rather than *trans*-acting T cell-specific transcription factor GATA3 (GATA3), which is associated with the T_H2 programme, suggesting that this is a distinct helper T cell sublineage[51,52]. Evidence supports the major source of IL-9 in the intestine is mucosal mast cells themselves, with these cells potentially acting in an autocrine manner to drive cell expansion[48]. In addition, the survival of gut-resident mast cells is enhanced by IL-4, which also reduces the threshold for activation by antigen. The responsiveness of the vascular endothelium to the vasoactive mast cell mediator histamine is also markedly enhanced by IL-4. Thus, IL-4 is tightly linked to overall atopic status (that is, the predisposition to developing allergic hypersensitivity) and T_H2 expansion; genetic variants that affect IL-4 receptor function[53] seem to modulate the severity of IgE-mediated allergic reactions.

Another key factor regulating IgE–FcεRI-mediated reactions is the strength of the concurrent IgG response to the same antigens. Specific IgG antibodies exert a strong suppressive effect on IgE-mediated mast cell and basophil activation[54]. Indeed, natural resolution of hen egg and cow milk allergy with age occurs in parallel with increasing production of IgG specific to those antigens[55,56]. Oral immunotherapy, in which allergic individuals acquire unresponsiveness following incremental ingestion of increasing doses of allergen, induces only modest decreases in specific IgE levels but potently stimulates the expansion of allergen-specific B cells and production of specific IgG antibodies[57,58]. These IgG antibodies signal via the cognate receptor FcγRIIb (also known as low-affinity immunoglobulin γ Fc region receptor II-b (FCGR2b)) to attenuate the IgE–FcεRI reaction[57,59] (FIG. 3). IgG plays a similar part in aeroallergen sensitivity[60]. A recent analysis of several large paediatric cohorts showed that although the prevalence of aeroallergen-specific IgE antibodies is quite high, the association of these antibodies with clinical sensitivity is low and the presence of IgG antibodies seems to be protective[61].

The central and peripheral nervous systems also likely exert influence on mast cell-mediated hypersensitivity reactions. Tissue mast cells reside in close proximity to and interact with neurons; signals from spinal afferents can induce mast cell mediator release[62,63]. In turn, mast cell mediators can activate neurons, and mast cell effects on secretomotor neurons have been shown to regulate mucus secretion and intestinal smooth

muscle contraction in animal models of food allergy[62]. These findings might account for the empirical observation that the severity of allergic reactions seems to be influenced by psychosocial factors. Other factors that are thought to decrease mast cell and basophil trigger thresholds (and hence increase the severity of reactions) include the ingestion of alcohol[64] and NSAIDs[65], the menstrual cycle[66], exercise and viral infections.

Non-IgE-mediated food allergy

Eosinophilic oesophagitis. Eosinophilic oesophagitis is a chronic inflammatory process characterized by epithelial hyperplasia, analogous to the skin pathology of atopic dermatitis but quite different from IgE-mediated immediate hypersensitivity (FIG. 4). The condition presents with gradual onset of gastro-oesophageal reflux, dysphagia (difficulty swallowing), food aversion,

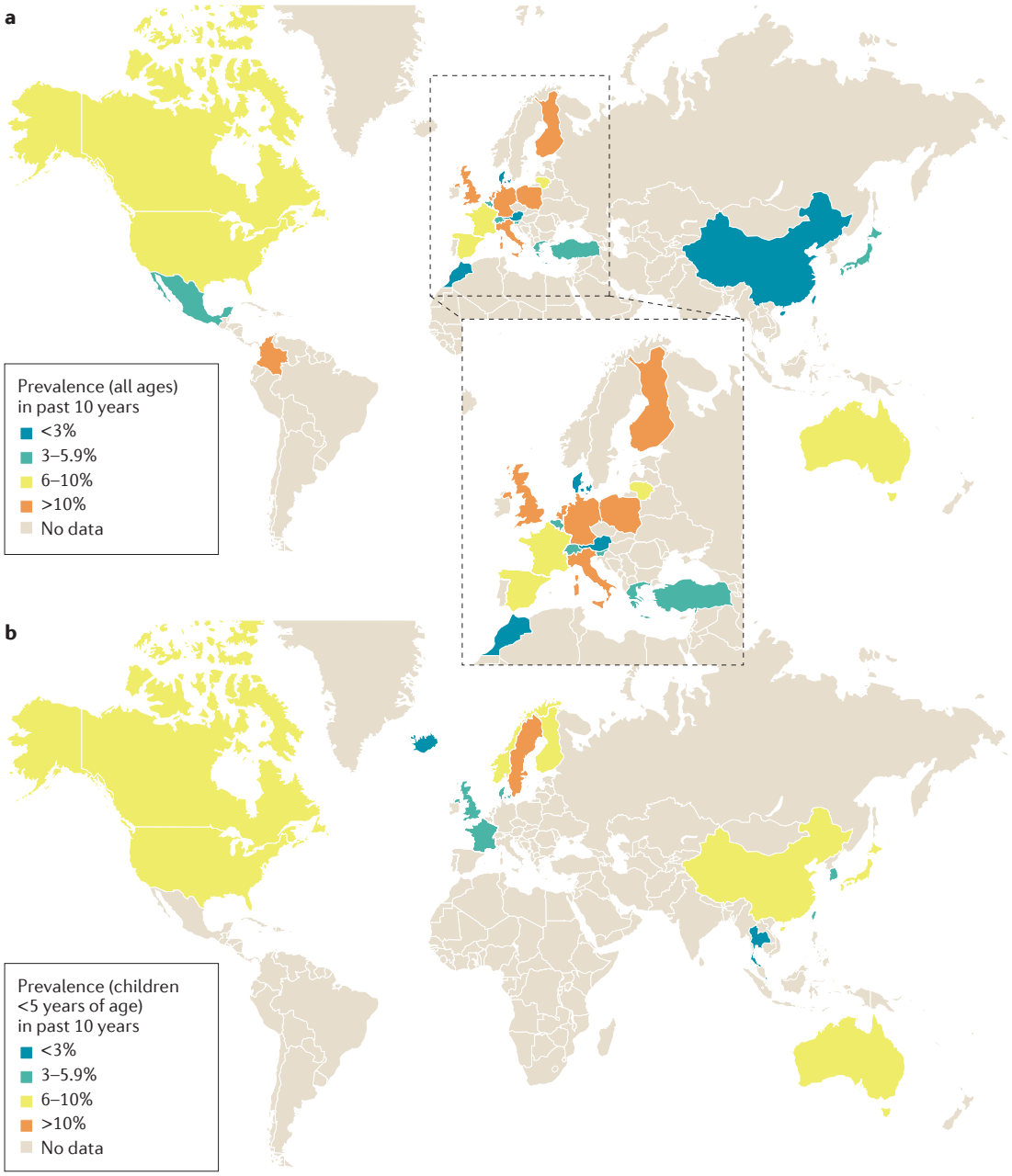

Figure 1 | **The prevalence of food allergy worldwide.** The prevalence of food allergy in all ages (part **a**; inset for clarity) and in children <5 years of age (part **b**) is shown. Substantial evidence shows global regional variation[236] of food allergy as well as changes in food allergy prevalence associated with migration. A study of 65,000 children at school entry in Australia showed that parent-reported nut allergy was twice as common in children born in Australia but of Asian descent than in white children born in Australia; however, Asian children born in Asia who then migrated to Australia in the first 5 years of life were completely protected[237]. The reasons for the regional and migratory differences in food allergy prevalence provide an opportunity to consider a hypothesis for why food allergy may be on the rise in some parts of the world and not others[20]. Based on data in REF. 21.

eosinophil-predominant mucosal infiltrates in the oesophagus and oesophageal strictures (abnormal narrowing); it is clearly driven by food allergens, and elimination diets are beneficial[67]. Although many patients with eosinophilic oesophagitis harbour food-specific IgE antibodies (and some have coexisting classic IgE-mediated allergic reactions to foods), the correlation is poor between the presence of these IgE antibodies and the inflammatory process underlying eosinophilic esophagitis. In murine models, the disease can be induced in IgE-deficient animals[68]; in humans, incomplete clinical responses to anti-IgE therapy along with correlations between higher IgG4 levels and disease activity suggest that IgG-related mechanisms are largely at play in the eosinophilic oesophagitis inflammatory response[68–71].

In addition to the eosinophil infiltrate that defines the disease, increased numbers of mast cells, plasma cells and T cells are present in the oesophageal mucosa of patients with eosinophilic oesophagitis[72]. Levels of IL-5 (produced by T_H2 cells) are elevated; this cytokine promotes eosinophil differentiation and primes eosinophils for responses to chemotactic molecules that drive their recruitment into tissues. IL-13 is also present and influences epithelial gene expression, inducing overexpression of CC-chemokine ligand 26 (CCL26) — a potent chemoattractant for eosinophils[73]. Transforming growth factor-β (TGFβ) is also present and probably drives the subepithelial fibrosis that can eventually lead to strictures[74]. Genome-wide association studies have linked the genes encoding thymic stromal lymphopoietin (TSLP), CCL26 and calpain to eosinophilic oesophagitis risk[75–78]. These associations suggest important roles for the epithelium in driving immune responses (via production of TSLP) and eosinophil recruitment (via CCL26, an eosinophil-specific chemokine), and indicate that these might be suitable targets for future therapies in eosinophilic oesophagitis. The potential role of calpain in pathogenesis is less certain, but it might exert disruptive effects on the oesophageal epithelium and disrupt barrier function[79].

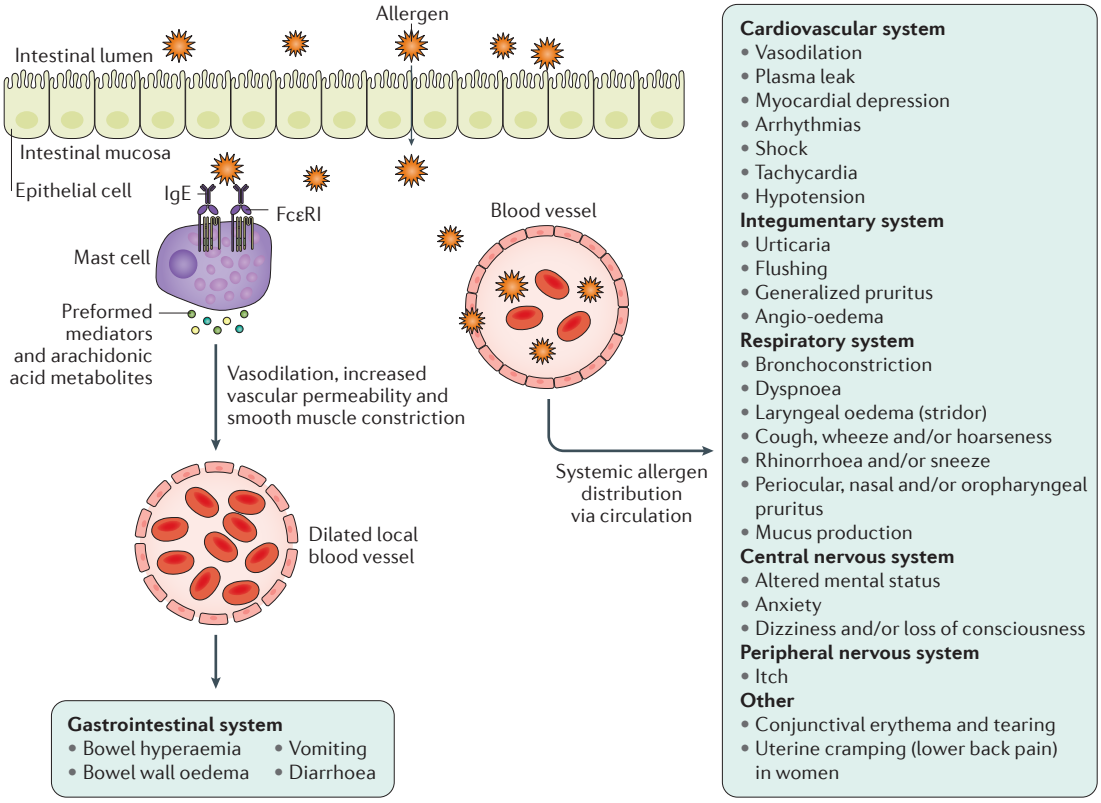

Figure 2 | **Ig-mediated reactions to food allergens.** Ingested food allergens pass through the intestinal epithelium by a variety of mechanisms — including transport through epithelial cells, passage through gaps between cells and uptake by microfold cells (which are specialized epithelial cells overlying Peyer patches) — and encounter mast cells in the mucosa. When immunoglobulin E (IgE) antibodies, which are bound to the mast cells by the high-affinity immunoglobulin ε receptor (FcεRI; also known as FCER1), recognize and bind to the allergen, receptor crosslinking occurs. This crosslinking results in the release of preformed mediators of hypersensitivity (such as histamine and the proteases tryptase and chymase) and in the activation of *de novo* synthesis of arachidonic acid metabolites, which include leukotrienes (for example, leukotriene B_4 and the cysteinyl leukotrienes of leukotriene C_4, leukotriene D_4 and leukotriene E_4), prostaglandins (for example, prostaglandin D_2) and platelet-activating factor. These mediators promote vasodilation and increased vascular permeability, which contribute to bowel wall swelling; smooth muscle contraction and mucus production also occur under the influence of these factors, resulting in vomiting and diarrhoea. When distributed systemically, the allergen and IgE-sensitized circulating basophils and tissue-resident mast cells can react, resulting in anaphylaxis (a rapid systemic allergic reaction that can cause death).

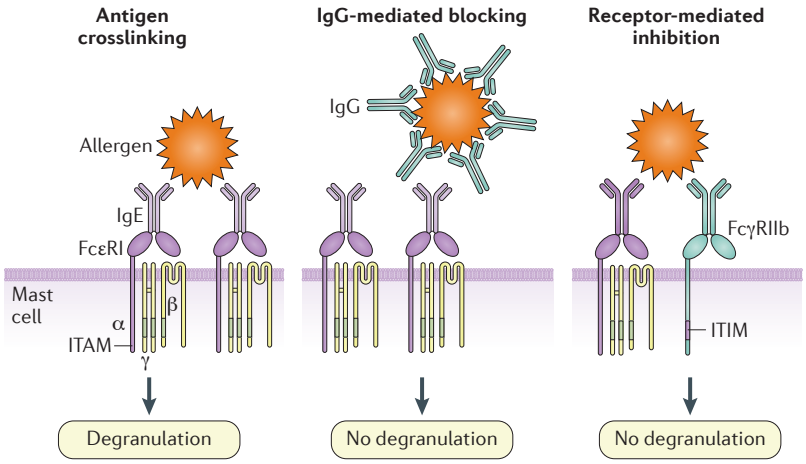

Figure 3 | **Food allergen-specific IgG antibodies counter the effects of IgE.** Immunoglobulin G (IgG) antibodies directed at food antigens arise naturally in individuals who are outgrowing food allergy or are induced through the process of oral immunotherapy. IgG antibodies against food antigens inhibit immunoglobulin E (IgE)-mediated activation of mast cells and basophils by two main mechanisms. In the first mechanism, IgG antibodies, which are present in larger quantities than IgE, bind food allergens before they encounter mast cells, masking their IgE-binding epitopes and blocking IgE binding. In the second mechanism, the allergen simultaneously binds to the IgE and IgG that are affixed to their cognate receptors (high-affinity immunoglobulin ε receptor (FcεRI; also known as FCER1) and low-affinity immunoglobulin γ Fc region receptor II-b (FcγRIIb; also known as FCGR2b), respectively) on the mast cell surface, leading to crosslinking of these receptors. The cytosolic domains of FcεRI γ-chains and β-chains harbour immunoreceptor tyrosine-based activation motif (ITAM) sequences that serve as docking sites for the activating protein tyrosine kinase, SYK (not shown). The inhibitory IgG receptor FcγRIIb contains an immunoreceptor tyrosine-based inhibition motif (ITIM) that recruits protein tyrosine phosphatases and inositol phosphatases, which counteract the activating signalling pathways triggered by SYK.

Allergic proctocolitis and food protein-induced enterocolitis. Eosinophil-predominant mucosal inflammation driven by food exposure can occur throughout the gastrointestinal tract. One of the most common forms of cell-mediated food allergy is allergic proctocolitis, which presents with rectal bleeding in otherwise well-seeming infants, often upon introduction of formula that contains cow milk proteins[80–82]. Mucosal eosinophils are abundant in these infants, but total IgE levels are normal and food protein-specific IgE is absent, consistent with a non-IgE-mediated mechanism[82].

A more-severe form of gastrointestinal reaction occurs in food protein-induced enterocolitis syndrome. Patients with this condition present with vomiting, pallor and lethargy following ingestion of specific foods, but they do not seem to have IgE sensitization to the offending food antigens despite the presence of eosinophils and T_H2 cells in the intestinal mucosa. A full picture of the pathogenesis of this disorder has yet to be worked out, but evidence exists for both T cell-mediated and neuroendocrine pathways leading to altered intestinal permeability and fluid shifts[83].

Immune responses to food antigens

The coordinated generation of food-specific IgE antibodies, induction of intestinal mast cell expansion and enhancement of macromolecular transport across the intestinal epithelium that underlie food allergy all occur under the control of allergen-specific $CD4^+$ T_H2 cells. Conversely, suppression of the food allergy phenotype requires the induction of T_{reg} cells. These two T cell responses are initiated by specialized antigen-presenting cells (APCs) that ingest and process antigens to peptides loaded onto major histocompatibility complex (MHC) class II molecules at their surface (FIG. 5). Intestinal APCs are phenotypically and functionally variable with respect to whether they induce T_{reg} cells or T_H2 cells and are subject to environmental factors[84]. Under the influence of the local commensal microbiota, pathogens, diet, metabolites and probably inherent structural features of the allergens they encounter, APCs play a key part in defining the T_{reg} and T_H2 balance (reviewed in detail in REFS 84,85).

Tolerance induction. The transit of macromolecular allergens through the gut epithelium to access mucosal APCs can occur by several processes, including paracellular diffusion, enterocyte transcytosis and passage via specialized microfold (M) cells that overlie gut lymphoid tissue (such as Peyer patches) and via transcellular goblet cell-associated antigen passages[86]. Pre-existing allergen-specific IgA or IgE antibodies can promote enterocyte or M cell transcytosis in an active uptake process mediated by the polymeric immunoglobulin receptor or CD23, which is the low-affinity IgE receptor. Epithelial cells also express MHC class II antigens and have been proposed to be functional APCs that contribute to T cell activation[87]. Specialized macrophages that express CX_3C-chemokine receptor 1 (CX_3CR1) also express the tight junction proteins typically found on epithelial cells and are, therefore, able to pass their processes through epithelial junctions to sample luminal food and bacterial antigens[88,89]. Additionally, CX_3CR1^+ macrophages produce IL-10 and promote T_{reg} cell induction.

The default pathway for food proteins penetrating the epithelium in the absence of other danger signals is the induction of tolerance. In mice, $CD103^+$ dendritic cells that have taken up food antigens in the gut mucosa migrate to mesenteric lymph nodes, where they can present to T cells. These $CD103^+$ dendritic cells express the gut-homing CC-chemokine receptor 9 and the integrin α4β7 and exhibit a default bias towards T_{reg} cell induction[90,91]. This finding is supported by their expression of aldehyde dehydrogenase, which enables the dendritic cells to metabolize vitamin A into retinoic acid, which signals via the retinoic acid receptor on T cells to induce the expression of the gut-homing receptor α4β7 and the expression of forkhead box protein P3 (FOXP3; the master transcription factor responsible for inducing and maintaining a T_{reg} phenotype[92]); retinoic acid also suppresses the production of helper T cytokines. The dendritic cells also express αvβ8 integrin, which facilitates the generation of immunosuppressive TGFβ to further enhance T_{reg} cell induction[90,93]. Once absorbed into the blood, food antigens enter the portal circulation for a first pass through the liver, where they again come into contact with tolerogenic populations of APCs, including Kupffer cells (the resident macrophages of

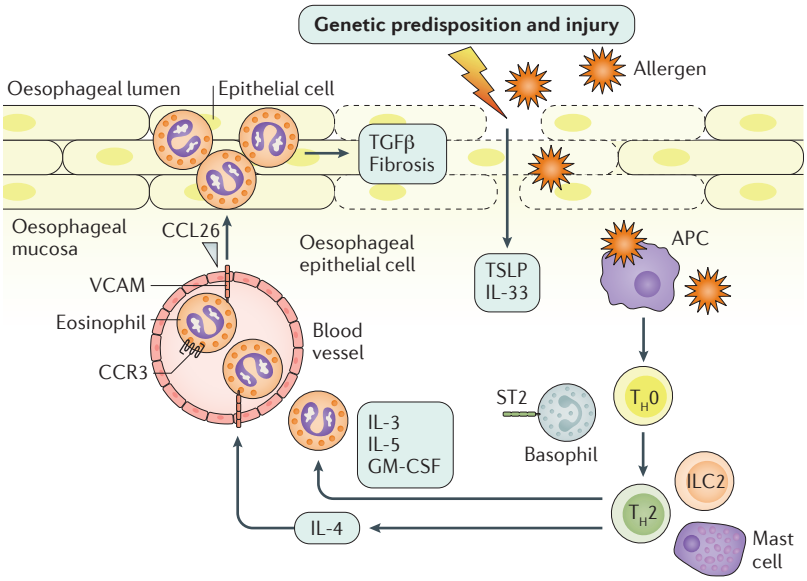

Figure 4 | **Eosinophilic oesophagitis.** Eosinophilic oesophagitis is an immune reaction not driven by immunoglobulin E response to food allergens in which a combination of genetic predisposition and injury (including from gastro-oesophageal reflux) trigger the production of thymic stromal lymphopoietin (TSLP) and IL-33 by oesophageal epithelial cells. These factors enable the penetration of food allergens. In the mucosa, TSLP and IL-33 promote type 2 cytokine production via effects on basophils (via the IL-33 receptor, ST2; also known as IL-1 receptor-like 1 (IL1RL1)) and antigen-presenting cells (APCs), which induce the differentiation of naive T helper cells (T_H0) to T helper 2 (T_H2) cells. The type 2 cytokines include IL-3, IL-5 and granulocyte–macrophage colony-stimulating factor (GM-CSF), which promote eosinophilopoiesis and prime eosinophils for migration towards chemokines. IL-4 is also produced and induces vascular cell adhesion molecule (VCAM) expression on the vascular epithelium, which facilitates rolling and eventual extravasation of eosinophils. Eosinophils sense the CC-chemokine ligand 26 (CCL26) gradient via the CC-chemokine receptor 3 (CCR3) and infiltrate the mucosa, causing tissue damage and driving fibrosis (via transforming growth factor-β (TGFβ) signalling), eventually leading to the strictures characteristic of the disease. Mast cells and type 2 innate lymphoid cells (ILC2s) are also found in the oesophageal mucosa and likely provide inflammatory mediators of inflammation and IL-4, respectively.

the liver) and liver sinusoidal endothelial cells. Children with chronic liver disease and liver-transplant recipients have an unusually high rate of new-onset food allergy, a phenomenon that implicates liver resident cells in food allergy; in these individuals, the mismatched MHC between their own T cells and the allograft hepatocytes might underlie the failure to maintain tolerance[94,95].

Tolerance breakdown. The breakdown of these physiological tolerogenic pathways can lead to a shift away from T_{reg} cell induction by $CD103^+$ dendritic cells to the generation of pro-allergic T_H2 effector cells. The full range of factors that might trigger this switch is only somewhat understood, but it likely includes the products of commensal microorganisms or those of pathogenic bacteria and viruses (that is, pathogen-associated molecular patterns (PAMPs)), injury to the intestinal epithelium and the effects of antigen exposure at other sites, particularly the skin. For example, activation of a number of receptors for PAMPs, including Toll-like receptor 2 (TLR2), TLR5, TLR7 and TLR8, has been reported to enhance the ability of dendritic cells to activate T_H2 effector cells[96–98]. In addition, the production of gut epithelial cytokines, TSLP, IL-25 and IL-33 following injury, infection or immune activation supports local T_H2 cell induction and expansion[99]; these cytokines act on dendritic cells to, for example, express OX40 ligand (OX40L; also known as tumour necrosis factor ligand superfamily member 4 (TNFSF4)), a cell-surface molecule that favours T_H2 cell differentiation[100]. Upon food allergen exposure and immune activation, the expanded T_H2 cell population arising under these conditions provides a local reservoir of IL-4, the key pro-allergic cytokine that serves to further sustain T_H2 cell responses, drive IgE switching in B cells, promote mast cell survival and enhance tissue sensitivity to the actions of mast cell mediators. Furthermore, the gut epithelial cytokines also drive the expansion of type 2 innate lymphoid cells, which lack adaptive immunological specificity but produce the T_H2-inducing cytokines IL-4 and IL-13 that block T_{reg} cell function[101].

Evidence also suggests that food-specific IgE antibodies act in a positive feedback loop to promote T_H2 cell induction and suppress T_{reg} cell induction (FIG. 5). This process occurs via food allergen-driven mast cell activation via FcεRI and the subsequent generation of IL-4 by those activated cells[102]. One of the most remarkable immunological shifts that occurs in the process of tolerance breakdown in food allergy is a reprogramming of T_{reg} cells to a T_H2 phenotype. T_{reg} cells acquire the ability to produce IL-4 while maintaining expression of $FOXP3^+$, subverting T_{reg} cell function from tolerogenic to pathogenetic[34].

Additionally, some of the forces driving tolerance breakdown might arise outside the intestine. For example, the majority of children who have food allergy also have a history of atopic dermatitis, and some evidence suggests that food allergen entry through scratched or inflamed skin leads to a breakdown of tolerance in the intestine[103] (BOX 2). In some circumstances, sensitization may occur via the respiratory route. IgE antibodies generated in response to some inhaled aeroallergens can cross-react with food antigens, giving rise to the oral allergy syndrome (TABLE 1), in which ingestion of fresh fruits and vegetables triggers pruritus restricted to the oropharynx. Similarly, sensitization to latex, which is thought to occur in part by inhalation of particles, can lead to sensitivity to a number of foods, including banana, avocado and kiwifruit[104].

Factors driving food sensitization

The induction of the T_H2 responses that drive IgE-mediated food allergy and suppression of T_{reg} responses to foods is probably determined by the integrated signals delivered by the highly complex immunomodulatory combination of commensal microbiota, their metabolites, adjuvant factors contained within food, dietary nutrients and as yet unknown molecules present in the setting of the initial encounters with the ingested food antigens. The increase in food allergy over recent decades strongly implicates environmental factors as a dominant force in determining food allergy risk[105]. The environmental influence is supported by studies in germ-free mice, which have been shown to be prone to

allergic responses to foods; studies have shown that the level of microbial diversity is a critical determinant of B cell isotype switching to IgE in the intestinal mucosa, with more-complex microbial systems suppressing IgE responses[106]. In addition to microbial diversity, the presence of specific microbial species seems to be protective. For example, in murine models, commensal bacteria isolated from genetically food allergy-prone animals confer susceptibility to allergic sensitization when transferred into wild-type (normally tolerant) recipients[107]. Reconstitution with microbiota enriched for certain *Clostridium* species promotes Foxp3$^+$ T_{reg} cell formation[106]. Some of these species influence the intestinal cytokine milieu, enhancing levels of tolerogenic IL-10 and TGFβ[108]. In humans, the intestinal microbiota present at birth influences the risk of allergic sensitization and disease in childhood, with some evidence that the high diversity of the microbiota as well as the presence of certain species of the genus *Clostridium* are protective against food allergy[3,4,109]. However, the role of *Clostridium* spp. or other specific classes of bacteria requires further evaluation as studies on this topic are still scarce. Additionally, a wide range of factors is thought to influence the composition of the infant microbiota, including the route of delivery (vaginal or caesarian section), the environment (rural or urban), diet, perinatal and postnatal antibiotic exposure, infection with viral pathogens and others[105].

In addition to expressing PAMPs, intestinal microorganisms produce immunomodulatory compounds that include short-chain fatty acids, which bind to G protein-coupled receptors (GPCRs) to modulate intestinal epithelial permeability and the induction of T_{reg} cells[110–113]. Mast cells express a number of GPCRs that bind to known endogenous mediators, including prostaglandins, cysteinyl leukotrienes, complement C3a, sphingosine-1-phosphate and antimicrobial peptides[114]. Some of these GPCRs also bind to as-yet undefined ligands[115]. One recently characterized GPCR, mas-related G-protein-coupled receptor member X2, is specific for peptides and quinolone compounds and can induce mast cell degranulation in the absence of any specific IgE[116]. Dietary nutrients might exert influences on the composition of the gut microbiome; GPCRs and other receptors might sense compounds present in the intestinal lumen and absorbed across the epithelium (such as

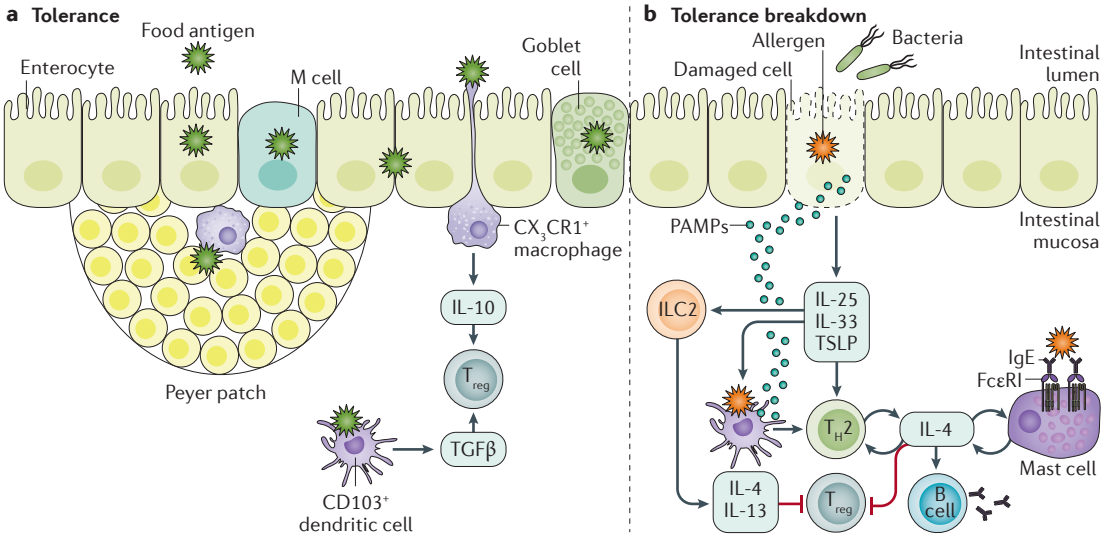

Figure 5 | **Immune tolerance and breakdown of tolerance to ingested antigens. a** | Under normal conditions, food antigens in the gastrointestinal lumen pass into the intestinal mucosa or into Peyer patches (small masses of lymphatic tissue in the ileum) by transiting between enterocytes or by active transport through enterocytes, microfold (M) cells or goblet cells. Antigens can also be sampled by specialized CX_3C-chemokine receptor 1 ($(CX_3CR1)^+$ macrophages that extend dendrites between enterocytes and into the lumen or by CD103$^+$ dendritic cells in the lamina propria. These cells induce regulatory T (T_{reg}) cells (via IL-10 production by macrophages and transforming growth factor-β (TGFβ) production by dendritic cells). **b** | Tolerance breaks down in situations in which danger signals arise, such as in the setting of exposure to certain pathogen-associated molecular patterns (PAMPs) or following epithelial damage (which leads to the expression of, for example, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)). Under these conditions, mucosal dendritic cells acquire a phenotype that favours T helper 2 (T_H2) cell priming when induced by the food antigens (now, allergens). In turn, T_H2 cells produce IL-4 that stimulates many aspects of the allergic response, including the induction of immunoglobulin E (IgE) isotype switch recombination in local B cells, mast cell expansion and, in an autocrine loop, the further expansion of the T_H2 pool. IL-4 also suppresses the function of tolerogenic T_{reg} cells and can reprogramme these cells to produce IL-4 themselves, converting them to a pathogenetic phenotype. Type 2 innate lymphoid cells (ILC2s), which are T_H2-like cells without antigenic specificity, provide another source of IL-4 as well as IL-13 that block T_{reg} cell function. In the setting of recurrent food exposure and emerging food allergen-specific IgE responses, allergen-activated mast cells residing in the gastrointestinal mucosa become an important local source of IL-4. Animal studies indicate that this mast cell-derived IL-4 is critical for the consolidation and expansion of the food-allergen-specific T_H2 response in the lamina propria and draining mesenteric lymph nodes[32,102]. FcεRI, high-affinity immunoglobulin ε receptor (also known as FCER1).

dietary nutrients). Indeed, such molecular mechanisms of 'sniffing out' allergens are now the subject of intensive investigation and will likely play an important part in determining the balance of immune sensitization versus tolerance to ingested antigens.

Diagnosis, screening and prevention

Diagnosis

Adverse reactions to foods are divided into those that are immunologically mediated (that is, hypersensitivities) and those that are nonimmunologically mediated (that is, metabolic, toxic, pharmacologic or aversive). The US National Institute of Allergy and Infectious Diseases defines food allergy as "an adverse health effect arising from an immune response that occurs reproducibly on exposure to a given food"; the definition of the European Academy of Allergy and Clinical Immunology is similar[81,117]. However, here we focus on IgE-mediated food hypersensitivities; non-IgE-mediated food hypersensitivities present a considerable diagnostic challenge owing to their delayed onset and lack of specific diagnostic laboratory tests. For these disorders, diagnosis relies primarily on the presence of a characteristic clinical history, laboratory studies to exclude other potential diagnoses and elimination diets and oral food challenges[118].

For IgE-mediated food hypersensitivities, the double-blind placebo-controlled food challenge (DBPCFC) is the gold standard for diagnosis[81,117] (see below); the accuracy of other (emerging) diagnostic procedures is generally compared with that of the DBPCFC. Although a medical history is central to the diagnosis of food allergy and critical to guiding the studies necessary for confirmation, it can only be validated by a positive DBPCFC in ~30–40% of individuals[46,81,119]. Nevertheless, in the absence of laboratory tests that accurately identify clinical reactivity to food allergens, acquisition of a detailed clinical history is of central importance; this history informs the use of selected laboratory studies and the need for a confirmatory supervised oral food challenge. Without a compelling history and laboratory studies, an oral food challenge is necessary to confirm the diagnosis; history alone or laboratory findings alone are insufficient to diagnose a patient as food-allergic[81,117].

Medical history and physical exam. A detailed medical history will help focus the evaluation of a potential food allergy. As indicated in TABLE 1, immunologically mediated food allergy reactions may result in a variety of different disorders. In addition, several distinct phenotypes of IgE-mediated food allergy are now recognized[120]. The phenotype represents the clinically relevant, observable properties of the condition without specific descriptions of its mechanism of action; by contrast, the endotype is a subtype of the condition that is defined by a distinct functional or pathobiological mechanism. The phenotype and endotype are determined by an individual's genotype, inherited epigenetic factors and exposure to environmental factors. Accordingly, when obtaining the medical history, questions should focus on obtaining information that will help such characterization — for example, the characteristics of the food (for example, cooked or raw) and the quantity suspected of eliciting the reaction, potential adjunct factors and the type of symptoms experienced.

In addition, a thorough medical history should determine the duration between ingestion and the development of symptoms, whether repeat ingestion has produced similar symptoms on other occasions and whether other factors (such as exercise, NSAID use or alcohol ingestion) occurred at or around the time of the reaction. Other important issues to clarify are how the reaction was treated and the length of time since the last reaction occurred.

Laboratory studies. Skin prick tests (SPTs) with commercial extracts or fresh foods provide a rapid method to screen patients for the presence of food-specific IgE antibodies bound to cutaneous mast cells. Food allergen extracts or fresh foods that elicit a wheal — a raised, red, itchy bump — that is ≥3 mm larger than that elicited by the negative control are considered positive and indicate the possibility that the patient experiences symptomatic reactivity to the food tested[81,117]. In general, the larger the wheal diameter, the more likely the positive test correlates with clinical reactivity to the food; a wheal diameter >10 mm indicates high likelihood of an allergic reaction[46]. Indeed, a paediatric study showed that SPTs with cow milk, hen eggs or peanuts that elicited wheal diameters >8 mm were >95% predictive of clinical reactivity[121]. However, allergen extract materials and methods of performing and recording SPT results are not standardized, leading to considerable variability in results from centre to centre. Negative SPTs largely confirm the absence of IgE-mediated allergic reactivity[119]; together with undetectable serum food-specific

Box 2 | **Food allergy and atopic dermatitis**

Atopic dermatitis (a type of allergic eczema) results from skin barrier defects. Mutations of at least two genes important in barrier function — *FLG*, which encodes filaggrin, and *SPINK5*, which encodes serine peptidase inhibitor Kazal type 5 — have been linked to atopic dermatitis and are both independently associated with food allergy[228,229]. Murine models of atopic dermatitis (by means of epicutaneous allergen application and tape stripping (to mimic the skin injury induced by scratching) or through homozygous disruption of *Flg*) have revealed a potential mechanistic basis for the connections between barrier function, allergic skin inflammation and tolerance breakdown in the gut and the skin. Both tape stripping of mouse skin and scratching of human skin disrupt skin integrity, strongly induce IL-33 production and, in the mouse model, induce intestinal mast cell expansion and increased susceptibility to food anaphylaxis[230]. The *Flg*-knockdown model revealed the importance of skin barrier function in maintaining immunological tolerance. The majority of classic food allergy develops in the first decade of life, and children with atopic dermatitis are at greatest risk[231,232]. Studies have shown a direct correlation between the age of onset and severity of atopic dermatitis with the likelihood of developing food allergy; >50% of infants developing severe eczema in the first few months of life develop classic food allergies[233,234]. Early-life eczema is frequently associated with food allergy, and approximately one in five infants with infantile eczema will go on to develop a food allergy[84]. The risk increases the earlier and more severe the onset of the eczema. Almost 50% of infants with severe eczema that becomes evident in the first 3 months of life will develop food allergy by 1 year of age[11,234,235]. Although food allergy presents in many patients as eczema, and eczema is a risk factor for food allergy development (through barrier defects and other mechanisms), food allergy itself is not necessarily a risk factor for eczema development.

Table 2 | **Food-specific IgE levels for prediction of allergic reactivity**

Allergen	Serum antibody level (kU_A/l)*	Positive predictive value (%)	Refs
Children (2–18 years of age)			
Hen egg	7	98	124
Cow milk	15	95	124
Peanut (general)	14	100	124
Peanut Ara h 2 antigen	5	96	238
Fish	20	100	124
Tree nuts	~15	~95	129
Hazelnut Cor a 9 antigen	1	90	239
Hazelnut Cor a 14 antigen	5	90	239
Soybean	30	73	124
Wheat	26	74	124
Infants (≤2 years of age)			
Hen egg	2	95	240
Cow milk	5	95	125

*kU_A/l, kilounits of allergen-specific antibody per litre.

IgE, negative SPTs exclude IgE-mediated food allergy with >95% certainty[46]. However, in those with a highly suggestive history, SPTs with the fresh food — in which the food is pricked and then the skin is pricked[122] — are needed to exclude IgE sensitivity owing to the poor stability of some allergenic proteins in some foods.

In vitro quantitative measurements of food-specific and food-component protein-specific IgE antibody levels in patient sera have been increasingly used in the past decade. These tests include ImmunoCAP (ThermoFisher), Immulite (Siemens AG) and HYTEC-288 (Hycor), and they measure the quantity of specific IgE antibodies a patient has to various potential allergens, although some between-platform variability has been noted[123]. The quantity of food-specific IgE in serum is correlated with the probability that an individual will experience an allergic reaction to a given food[124–129] and the predictive power of several allergens has been determined (TABLE 2). However, these predictive values can vary depending on the age of the individual[128] and the population under study[127]. Additionally, in some foods, such as sesame, skin testing and IgE measurements are less useful in adults than in young children because oleosins (the main allergen) are more often responsible for allergic reactivity[130]. Oleosins are highly lipophilic and nearly insoluble in saline or aqueous extracts; thus, skin and IgE tests are often falsely negative[131]. Rarely, patients with undetectable food-specific IgE (or negative SPTs) experience an allergic reaction; for these individuals, a physician-supervised food challenge is necessary to confirm the absence of clinical food allergy.

Many foods contain component proteins that are homologous to proteins in other foods and plant pollens, and in some cases, these homologous proteins are responsible for symptoms of oral allergy syndrome (TABLE 1). In this syndrome, the IgE initially directed against the plant pollen, which can induce allergic rhinitis when inhaled, cross-reacts with the homologous protein in the food when ingested, inducing pruritus of the lips, tongue, palate and oropharynx as well as mild oedema of the lips and tongue in a subset of pollen-allergic individuals. However, these homologous proteins frequently result in clinically irrelevant levels of IgE or positive SPTs to the whole food protein. Consequently, *in vitro* assays that measure component proteins, so-called component-resolved diagnostics, have been developed to enable clinicians to better identify patients with allergic reactivity to foods.

Oral food challenge. DBPCFC provides the definitive diagnosis of food allergy but is time-consuming and expensive. Expert panels have agreed that a single-blind or open food challenge might be considered diagnostic when it elicits no symptoms (negative challenge) or when objective symptoms observed in the challenge largely duplicate symptoms reported in the medical history and are supported by laboratory studies (positive challenge)[81,117]. In performing an oral food challenge, several factors must be considered on the basis of the medical history, including the form of the food (that is, cooked or raw), the matrix used for blinding (that is, the type of food or liquid used to camouflage the potential food allergen, which could affect the rate of absorption), the dosing regimen (that is, the initial and total dose), the number of doses, the time interval between doses and the duration of observation[119,132].

A variety of protocols for the DBPCFC have been used over the past 40 years, but in 2008, a group of food allergy experts from Europe and the United States proposed a standard procedure for conducting the DBPCFC[109]. Typically, suspected foods are eliminated from the diet for 7–14 days before the challenge, and medications that might interfere with the interpretation of challenge results, such as antihistamines, are discontinued. The suspected food is blinded in a matrix such that it is indistinguishable from the placebo; ideally, the active and placebo challenges should be carried out on separate days. For safety reasons, the challenge is initiated with very small amounts of food protein that are increased in a stepwise fashion, for example 1 mg, 3 mg, 10 mg, 30 mg, 100 mg and so on of food protein, until objective symptoms develop or the full challenge dose is ingested. The time interval between doses varies from 15 minutes to 30 minutes depending on the type and severity of suspected symptoms. Clinicians conducting oral food challenges must be experienced in the identification and management of anaphylactic reactions to avoid adverse implications for the patient.

Elimination diet. Elimination diets consist of avoiding specific foods on the basis of clinical history and are sometimes useful in identifying likely allergens, especially in mixed IgE-mediated and non-IgE-mediated disorders such as atopic dermatitis and eosinophilic oesophagitis[81,117]. If symptoms clear when multiple foods are removed from the diet, individual foods are added back one at a time every few days to identify the food or

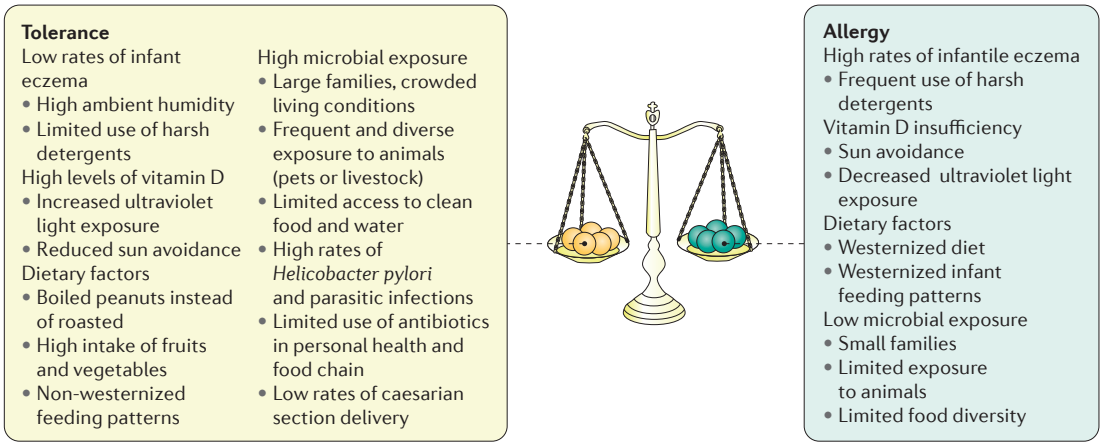

Figure 6 | **Integrating hypotheses of food allergy.** Multiple possible contributing factors have been ascribed to how food allergy develops, potentially explaining differences in prevalence in various regions of the world and offering potential avenues for preventive interventions. For example, in Australia, where highly effective anti-skin-cancer campaigns have provided dramatic declines in melanoma since the mid-1990s, high rates of vitamin D insufficiency correlate with increases in food allergy[150] and could provide a platform from which to refine food allergy prevention programmes.

foods responsible for the allergic symptoms. However, the duration of these diets should be limited, usually no more than 2–4 weeks, because long-term diets eliminating large numbers of foods have been associated with the development of malnutrition[81,133].

Prevention

In 2000, the American Academy of Pediatrics (and later the European Society for Paediatric Gastroenterology Hepatology and Nutrition and the Australasian Society of Clinical Immunology and Allergy)[134,135] recommended that infants at high risk of food allergy should delay the introduction of common allergens. The US guidelines suggested that consumption of dairy products be delayed until 1 year of age, hen eggs until 2 years of age and peanuts, nuts and fish until 3 years of age and that nursing mothers should also eliminate peanuts and tree nuts from their diets. However, these ostensibly primary preventive measures seem to have had the opposite effect; as food allergy continued to rise, evidence from observational studies suggested that delaying the introduction of allergenic foods increases the risk of developing food allergy[136,137], necessitating a revision of this strategy.

Important advances have been made over the past decade to better characterize the risk factors for developing food allergy, and current evidence suggests that the risk is multifactorial. These multiple contributing factors have recently been summarized as the '5Ds' — dry skin, diet, dogs, dribble and vitamin D — which can be ascribed to three separate hypotheses of how food allergy develops (and providing a basis on which preventive strategies could be devised, although few have been implemented at the population level)[138]. These hypotheses are the dual-allergen exposure hypothesis[139] (dry skin and diet), the vitamin D hypothesis[140] and the hygiene hypothesis[141] (dogs and dribble). At this point in time, the dual-allergen exposure hypothesis is supported by the strongest body of evidence that has resulted in changes to clinical practice and public health policy for food allergy prevention. Ongoing trials of exposure to other allergenic solids, eczema prevention[142] and vitamin D supplementation[143] are eagerly anticipated to inform further preventive strategies (FIG. 6).

The vitamin D hypothesis. The vitamin D hypothesis is supported by ecological and epidemiological evidence that suggests a role for vitamin D deficiency in the development of food allergy. For example, several studies have shown higher rates of food allergy, adrenaline autoinjector prescriptions and hospital admissions for food-related anaphylaxis in children living further from the equator than those living closer to the equator and those born in autumn or winter compared with those who were born in spring or summer (equatorial distance and seasonal birth are proxies of vitamin D levels)[144–148]. Direct evidence for a role for vitamin D stems from the HealthNuts study in Australia, which provided the first evidence that directly measured vitamin D level is associated with the risk of food allergy[149]. In that study, infants with vitamin D levels <50 nmol per litre at 1 year of age had an 11-fold higher risk of peanut allergy confirmed by oral food challenge than infants with vitamin D levels >50 nmol per litre; hen egg allergy risk was nearly 4-fold higher[149]. Some evidence suggests that vitamin D is important in the regulation of T_H cell differentiation and the induction of T_{reg} cells[150]. Indeed, vitamin D plays an important part in several immune functions, particularly in the development of effector T cell subsets. In this regard, T_H2 immune responses have been shown to be favoured under low vitamin D or vitamin D-deficient conditions[151,152,153]. Although the underlying signalling mechanisms are still not completely understood, this concept provides the foundation for further clinical studies and investigations in this area.

The hygiene hypothesis. The hygiene hypothesis postulates that a lack of exposure to microorganisms and infections in early childhood increases susceptibility to allergic disease by modulating the development of the immune system[141]. In support of this hypothesis is the observation that an allergy epidemic (encompassing asthma, rhinitis and food allergy) began in the second half of the 20th century, well before the avoidance of the ingestion of 'high-risk' foods in newborn babies was recommended. The development of allergic disease, including food allergies, is the result of complex interactions between the genetic predisposition of the individuals and environmental and lifestyle factors — food allergy is a prototypic gene × environment condition. Several lifestyle conditions have been identified that increase the risk of the development of the disease, including active and passive smoking (particularly maternal smoking during pregnancy and breastfeeding), exposure to (food) allergens, dietary habits and microbial exposures.

Microorganisms that colonize the cutaneous and mucosal surfaces of the body closely interact with the (developing) immune system. These microorganisms play a critical part in the maturation of immune responses, either in the direction of the immunological tolerance or in the direction of inflammation. For tolerance development, microbial diversity is important[154]. The more diverse the microbial pattern is, the better the tolerogenic maturation of adaptive immune responses. Real-life 'experiments' of the hygiene hypothesis are children raised and living on traditional farms[155,156], who have lower rates of allergy than city-dwelling children. Furthermore, less-diverse exposure and lower rates of colonization with particularly 'risky' bacteria (such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria* spp. and *Klebsiella* spp.) increase the risk of developing asthma[157]. Another risk factor is delivery via caesarian section, which avoids and prevents contact with beneficial vaginal microorganisms[158–160]. Indeed, observational studies have shown that factors associated with increased microbial exposure, such as exposure to pet dogs, living on a farm, childcare attendance, vaginal delivery and the presence of older siblings, might have protective effects against developing food allergy[161–163].

The dual-allergen hypothesis. The dual-allergen exposure hypothesis[139] postulates that disrupted skin barrier function in early life, as occurs in infant eczema (BOX 2), results in allergen sensitization through environmental exposure via the skin (rather than orally). However, given the trend to avoid allergenic solid foods, the opportunity to abrogate the sensitized state by oral tolerance fails and food allergy develops. Observational studies suggest that early introduction of allergenic foods reduces the prevalence of food allergy[137,149,164]. Recently, data supporting this hypothesis were reported from a randomized controlled trial investigating the early introduction of allergenic foods as primary and secondary prevention of peanut allergy in high-risk infants (that is, those with either severe early-onset eczema or hen egg allergy (confirmed by SPT screening)) in the Learning Early About Peanut allergy (LEAP) study[165].

The LEAP study was designed to induce oral tolerance to peanuts and prevent the development of peanut allergy. Infants (4–11 months of age) were randomly assigned either to consume 6 g of peanut protein per week until 5 years of age or to strictly avoid peanuts for the same period; 542 children with no SPT reactivity (that is, 0 mm wheal diameter) were randomly assigned into the study and 98 children with small wheal diameters (1–4 mm) were also entered. Children with a wheal diameter >4 mm at SPT screening were not included in the study as they were highly likely to have peanut allergy. At 5 years of age, the consumption group showed a significantly lower peanut allergy prevalence compared with the avoidance groups in both the SPT-negative (86% reduction in peanut allergy, showing primary prevention) and SPT-positive (70% reduction, showing secondary prevention) groups[165]. Furthermore, the LEAP-On study withdrew peanut consumption from all infants in the LEAP study at age 5 years and showed that the effects of early peanut introduction in infancy on the prevention of peanut allergy were both clinically and immunologically sustained after 12 months, demonstrating that these effects were not dependent on ongoing antigen exposure. Although the LEAP study looked at prevention of allergy through oral tolerance induction in a highly atopic group of individuals, a substantial proportion of enrolled participants did not have egg allergy and had only mild or moderate eczema; these subgroups responded equally well to the LEAP intervention. Although these findings hold promise, whether early peanut introduction in low-risk infants (that is, those without hen egg allergy or eczema) is effective is unclear. Additionally, the role of SPT-based screening to stratify infants for such a primary preventive measure is controversial, and the question remains whether screening and primary prevention measures should be confined only to a moderate-to-high-risk atopic group. For example, one study of 5,276 infants — who underwent SPT followed by confirmatory oral food challenges in those who screened positive — showed that 16% of the study population were high risk and would benefit from screening, but screening would miss 23% of individuals with peanut allergy at the general population level[166].

Five other trials have examined the effect of early hen egg introduction on the development of egg allergy, with mixed findings[167–171]. Although four of these studies showed reduced rates of allergy, only one achieved statistical significance in the intention-to-treat analyses, and a meta-analysis of these studies showed a favourable effect of early consumption of hen eggs in infancy on the prevention of egg allergy[167,172]. Another study, the Enquiring About Tolerance (EAT) randomized controlled trial, assessed the efficacy of early introduction of six allergenic foods to the infant while continuing to breastfeed from 4 months of age compared with 'standard' introduction at ~6 months of age. Although the prevalence of food allergy was lower in the early introduction group, statistical significance was achieved only in the per-protocol analysis. No bias could be detected to explain this discrepant result, but it is impossible to completely exclude hidden bias in the per-protocol group.

However, instrumental variable analysis of the EAT findings suggests that improved adherence explains the significant reduction in food allergy in the EAT trial per-protocol intervention group rather than bias. The EAT study did not adversely affect breastfeeding rates in the early introduction group.

Following the publication of the LEAP study, new North American NIH guidelines (endorsed by numerous professional bodies) now specifically recommend the early introduction of peanuts into the diet of infants with eczema to prevent peanut allergy[173]. Indeed, evidence of changes in infant feeding practice has already been documented[174].

Management

Strict allergen avoidance is the only causal 'therapy' for food allergy[175], which, of course, does not mitigate unintended ingestion. Patients who are at risk of severe allergic reactions must carry medication for immediate self-treatment at all times, such as an adrenaline autoinjector[176]. However, emerging therapies are being developed, including protocols of oral tolerance and desensitization to cure food allergy, which are urgently needed.

Elimination diet

To avoid the offending allergens, the patients or their caregivers have to be able to recognize unsafe food products. Allergen labelling for the most common allergens in prepackaged food is mandatory in many places throughout the world, including the European Union, the United States, Australia, Canada and Japan, and has led to improved food safety for consumers[177]. However, the unintended presence of allergens due to cross-contamination is still a problem, resulting in the widespread voluntary — unregulated — use of precautionary allergen labelling (PAL) by the food industry with phrases such as 'manufactured on shared equipment' or 'may contain'. The content of low amounts of potential allergens (such as 'nuts' and 'egg') is not regulated in many parts of the world, which leaves individuals with food allergies with considerable uncertainty. One study in the United States and Canada showed that almost half of consumers falsely believed that PAL was required by law, and 37% of respondents thought that PAL was based on the amount of allergen present, which might influence buying practices[178]. Accordingly, the determination of threshold levels of common allergens in foods is currently under investigation to inform better regulatory approaches[179]. For example, one study determined that the dose for peanut protein that elicits a reaction in 5% of allergic individuals (that is, the ED05) is 1.5 mg of peanut protein[180]; however, a single administration of 1.5 mg of peanut protein elicited objective reactions in fewer than the predicted 5% of patients with peanut allergy[180]. The process requires refinement and validation.

In venues offering non-prepackaged foods, such as restaurants and bakeries, a reported 25% of children (with food intolerance) experience an allergic reaction[181]. Although the majority of staff in bakeries reported feeling able to advise food-allergic consumers regarding a safe product choice, cow milk (>3 mg protein per serving) could be detected in one out of five products being sold as 'cow-milk-free' (REF. 181). Fortunately, the same regulation for prepackaged foods has recently been extended to non-prepackaged foods in some countries.

Self-treatment of accidental reactions

Antihistamines can be used to treat rhinitis, conjunctivitis and urticaria in mild allergic reactions. For anaphylaxis, administration of adrenaline with autoinjector devices is the current mainstay of therapy[176]. Adrenaline acts on target tissues to reverse the effects of mast cell mediators, acting on β_1-adrenergic receptors to enhance myocardial function and on β_2-adrenergic receptors to enhance bronchodilation. Adrenaline can also attenuate mast cell mediator release; in the vascular endothelium, adrenergic signals regulate nitric oxide production to modulate vascular tone and permeability. Inhaled salbutamol, antihistamines and corticosteroids are useful add-on medications to adrenaline; in particular, corticosteroids can be given to prevent delayed reactions (that is, late-phase allergic responses ≥8 hours after consumption) but are not useful as first-line treatment as they are slow-acting.

An increased risk of anaphylaxis has been reported in patients who have had an anaphylactic reaction in the past, react to small amounts of the allergen, show increased severity of their reactions, have systemic reactions to persistent food allergens (such as peanuts and tree nuts) or have bronchial asthma[182]. The prescribing physician must demonstrate the correct usage of the adrenaline autoinjector to the patient and/or their caregiver and provide written instructions. In many countries, these written instructions for emergency anaphylaxis treatment are readily available, with the physician just needing to add patient-specific details. Recognition of allergic symptoms and adequate handling is not always easy for the patient and their caregivers; however, structured patient education programmes have been shown to improve the management of anaphylaxis by increasing patients' empowerment to prevent and treat their disease[183].

Emerging immunotherapy

Patients with food allergy are always at risk of anaphylactic reactions; thus, allergen-specific and nonspecific therapies, other than elimination diets, are urgently needed.

Allergen immunotherapy is a well-known and effective treatment for venom allergy, allergic rhinitis and conjunctivitis caused by inhalant allergens; it can be administered via the subcutaneous (venom and inhalant allergens) or sublingual (inhalant allergens) route. Allergen immunotherapy for food allergy is currently under development and should be administered only in clinical trials[117,175,184]; several protocols have been described. Oral immunotherapy is the most commonly studied approach[185] and avoids the adverse effects experienced with subcutaneous application. The process involves two steps. First, the patient is desensitized. Desensitization, in which effector cells involved in a

specific immune response develop reduced reactivity or become nonreactive, relies on the regular administration of the allergen to ensure protection. Second, tolerance, in which the nonreactive state remains permanently, is established. Once a state of tolerance has been achieved, the patient can consume the food infrequently without eliciting a response[186].

The experimental designs for oral immunotherapy include giving the food allergen with starting doses low enough not to cause reactions (and lower than the threshold identified in an initial oral food challenge) and increasing the dose in regular intervals[186]. Alternatively, a fixed dose can be given for the entire study. Successful desensitization and tolerance development is still assessed by clinical observation. Unfortunately, there is no biomarker or *in vitro* test currently available that shows adequate sensitivity and specificity in this regard.

The first international phase III oral immunotherapy trial is currently being conducted for peanut allergy, aiming to bring this therapy to market (EudraCT-Number: 2015-004257-41). Sublingual immunotherapy is also under investigation and was shown to be effective in a meta-analysis on allergen immunotherapy for IgE-mediated food allergy[185]. A head-to-head study of oral immunotherapy and sublingual immunotherapy in patients with peanut allergy has shown that oral immunotherapy is more efficient but sublingual immunotherapy had fewer adverse effects[184]. A recent meta-analysis demonstrated a substantial benefit in terms of desensitization and sustained unresponsiveness; long-term follow-up of these patients is urgently awaited[185]. However, the analysis also revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving allergen immunotherapy compared with an elimination diet[185].

Epicutaneous immunotherapy is also under investigation. An early trial in patients with peanut allergy showed that peanut epicutaneous immunotherapy administration (administered via a patch containing placebo, 100 μg or 250 μg peanut protein) was associated with a modest treatment response[187]. After 52 weeks of treatment (the primary end point), the participants were able to consume 0 mg (placebo group), 43 mg (100 μg group) and 130 mg (200 μg group) of peanut protein; longer follow-up was not reported. Treatment success was higher among younger children (4–11 years of age) than in older participants (>11 years), although the study was not designed to detect an age effect[187]. Adverse effects were predominantly local patch-site and mild reactions[187]. An international phase III trial is currently being conducted (EudraCT-Number: 2015-002461-37).

Many small studies have shown the benefit of various immunotherapy protocols; however, adverse effects have been described from local oral allergy symptoms to anaphylaxis. In addition, the development of eosinophilic oesophagitis has been reported in ~3% of patients undergoing oral immunotherapy[188]. An interesting approach to reduce the adverse effects of oral immunotherapy is pretreatment with anti-IgE. Indeed, a randomized, double-blind, placebo-controlled trial of omalizumab (an anti-IgE humanized monoclonal antibody) in combination with cow milk oral immunotherapy showed markedly reduced adverse effects during oral immunotherapy escalation in those also receiving omalizumab, fewer dose-related reactions that required treatment and fewer doses of oral immunotherapy required to achieve maintenance and desensitization[189].

In another study, omalizumab enabled participants to be rapidly desensitized to peanuts within 8 weeks of oral immunotherapy; in the majority of participants, desensitization was sustained 6 weeks after withdrawal of omalizumab[190]. Finally, individually dosed intramuscular injections of omalizumab, monitored by basophil allergen threshold sensitivity, might be an effective and safe treatment for severe peanut allergy in young adolescents as add-on therapy[191]; this approach is still an off-label treatment for food allergies.

Quality of life

Patient and parental anxiety about the risk of experiencing a reaction following inadvertent food allergen ingestion contribute greatly to the quality-of-life impairments associated with food allergy. To an outsider, an individual with a life-threatening food allergy can seem unburdened and healthy. However, the appearance of normalcy can belie a considerable effect of food allergy on health-related quality of life (HRQOL). Management requires allergen avoidance, a time-consuming and potentially anxiety-provoking undertaking, and constant preparedness to recognize and treat an allergic reaction[46]. Allergen avoidance and treatment preparedness extends to every moment — with no 'time off' — enabling anxiety to build because the results of a 'mistake' could be fatal.

The effect of managing food allergy on reducing HRQOL has been defined in many studies. A systematic review showed that children with a food allergy and their families scored poorly in specific domains of HRQOL compared with normative data[192]. For the child with an allergy, affected domains were regarding body pain, physical functioning, mental health and general health as well as emotional, social and psychological quality of life. For parents, overall quality of life, social health, emotional health and effect on time were negatively affected; having a child with a food allergy also placed limitations on family activities. Studies employing generic instruments have suggested that the HRQOL limitations imparted by a food allergy are greater than those imparted by diabetes mellitus[193,194] or rheumatoid arthritis[195]. However, although generic instruments can provide insight on the scope of effects, they are not sensitive to the specific burdens associated with food allergy and cannot evaluate the effect of food allergy interventions on HRQOL. Accordingly, a number of food allergy-specific HRQOL instruments have been developed and validated for adults, adolescents and children as well as parents and caregivers[196]. Some of these instruments can discriminate the HRQOL effects of number of allergic events, the severity of the reactions or types of foods involved, indicating that they are valid and have utility in research and, potentially, patient care.

Studies using food allergy-specific instruments have identified a number of aspects of food allergy that affect HRQOL, which have implications for management. For example, the more foods avoided[197–199], or having to avoid very common foods such as cow milk and hen eggs[200], the greater the negative effect on HRQOL. More-severe past reactions are also generally associated with poorer HRQOL[198,199]. Bullying related to food allergy is common[201,202] and is associated with reduced HRQOL[203]; parental awareness and parental notification of the school about bullying can result in lasting improvements[204]. Having had a diagnostic oral food challenge generally results in improved HRQOL even if the result was positive, presumably because comfort can be gained in understanding the allergy[205,206]. Oral immunotherapy is also associated with improved HRQOL[122,207,208]. Simple educational interventions or access to knowledgeable health-care professionals can improve HRQOL[209–211]. Although disease-specific instruments have been validated to detect changes among groups of affected patients, none are yet validated for the screening or clinical management of individual patients[196]. Nonetheless, anxiety, bullying and HRQOL should be discussed and addressed in patient management[212].

Outlook

Despite many advances in both basic and translational research, the contributing factors in the breakdown of tolerance that occurs in food allergy have not been fully elucidated. It is now commonly agreed that early-life events play a critical part in the development of food allergies (BOX 1) and that environmental and lifestyle factors and dietary components contribute as well. More research is needed to understand the mechanisms of early-life events such as interaction between maternal–fetal pathways and postnatal mother–child interactions. These early-life events seem to be crucial in shaping early immune and metabolic response patterns. A firm framework linking these factors is urgently needed to provide the foundation for preventive measures. Ultimately, only effective prevention will stop the food allergy epidemic.

In terms of translational research, recent technological advances have enabled investigators to map IgE-binding 'allergenic' epitopes on different food allergens[213,214], revealing that conformational and sequential (linear) epitopes have a role in allergic reactions. For example, individuals harbouring IgE antibodies to conformational epitopes typically tolerate the allergenic food after extensive heating (baking), which at least partially alters the tertiary structure of component proteins. By contrast, those harbouring IgE antibodies to sequential epitopes continue to react to the food regardless of cooking method[215,216]. These interesting findings suggest that epitope-specific binding correlates better with clinical reactivity than quantitative IgE measurement[217], which might improve prediction of the clinical severity of reactions[218] and improve patient care.

Furthermore, the basophil activation test — in which CD63 and CD203c expression is measured following allergen stimulation of a patient's basophils *in vitro* — might provide a more-specific and sensitive surrogate for the oral food challenge[8] and enable discrimination of patients with transient cow milk or hen egg allergy who can tolerate the baked products from those with persistent allergy[219]. Although the function of CD63 and CD203c is unclear, the proteins can be used as biomarkers of basophil activation[220]. Optimal results require processing blood samples shortly after acquiring the sample[8,117], which is not practical in most clinical settings, but technical advances might soon circumvent this limitation. Another field where considerable progress has been made is the genetic and molecular characterization of allergens and their components, which has already led to improved possibilities for allergy diagnostics (component-resolved diagnostics). Together with the improvement of cellular assays, component-resolved diagnostics could greatly improve allergy diagnostics in the future.

In terms of treatment strategies, it remains unsatisfactory that, at present, the only effective treatment is strict allergy avoidance. In addition to emerging immunotherapies, biologics such as anti-IgE and anti-cytokine or anti-cytokine-receptors are promising. More and larger clinical trials are needed to fully elucidate the potential of such strategies.

Taken together, the recent advances in various areas and fields of basic, translational and clinical food allergy research set the stage for the next level of improved diagnostics, treatment and prevention. In particular, larger prospective clinical studies are required to test the new concepts in the arena of food allergies, which will propel the development and implementation of new management paradigms.

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