Recent advances in pathophysiology of food & cow milk protein allergy

John Sinn

Food allergies are atypical immune reactions provoked by exposure to certain food proteins; they involve complex immunological interactions and have varying symptoms, depending on whether they are predominantly immunoglobulin E (IgE) mediated, non-IgE-mediated, or result from both mechanisms. Immune programming begins in utero and during infancy, when the immature immune system is responsive to environmental conditions, and its development can be profoundly influenced by events that favor either tolerance or sensitization. Besides genetic predisposition, common factors underlying allergic sensitization include the route (eg, fetal, skin, breast milk), timing and dose of allergen exposure, environment (eg, diet, pollutants, microbes), and the tissue milieu, in particular a bias towards Th2- versus tolerogenic Th1-mediated responses (Figure 1).

Allergic reaction mechanisms

Food allergies fall into two general classes, IgE-mediated and non-IgE-mediated. IgE-mediated allergy occurs when exposure to an allergic epitope stimulates B cells to release allergen-specific IgE antibodies, which bind covalently to IgE receptors on the surface of reactive mast cells. This sensitizes the mast cells to the allergen; allergic reactions occur when re-exposure of these IgE-bound reactive cells to the sensitizing epitope causes them to release histamines.

Two types of allergens are believed to provoke IgE-mediated food allergies. Class 1 allergens (Table 1), or primary sensitizers, weigh from 10 to 70 kD and are generally stable when subjected to heat, acid, or proteases. Class 2 allergens are generally plant-derived proteins which are heat labile, cross-reactive and associated with oral allergy and latex-fruit syndromes.

From Royal North Shore Hospital and The Children's Hospital, Westmead, The University of Sydney, Australia

> ***"There is an optimal window for introducing allergenic foods to build tolerance."***
>
> *John Sinn*

Food protein antigenicity increases with molecular weight, and cooking can change the antigenicity. For example heating cow milk has no effect, superheating even increases antigenicity, whereas baked egg is less allergenic. Interestingly, roasting nuts causes the Maillard reaction, which makes proteins much less digestible and more allergenic, whereas boiling, as is common in Asian cuisine, decreases antigenicity.

Non-IgE-mediated allergies involve the concerted effects of dendritic cells, increased Th2 cell numbers, genetic makeup, and environmental factors, all of which lead to abrogation of oral tolerance and make hypersensitivity reactions more likely.

Clinical features of food allergies

IgE-mediated allergies usually manifest as immediate and acute allergic reactions within 2 hours of exposure. Reactions such as urticaria, angioedema, or anaphylaxis may develop, and are normally characterized by cutaneous, gastrointestinal, and respiratory symptoms. Major allergens implicated in such responses include cow milk, egg, soy, peanut, tree nuts, fish and shellfish. Notably, cow milk accounts for 11%–28% of these reactions and 11% of deaths due to anaphylaxis. Foods may also trigger anaphylactic reactions if ingestion is followed by exercise; physical exertion is thought to stimulate the release of mast cells and alter intestinal permeability. This type of IgE-mediated food allergy is called food-dependent exercise-induced anaphylaxis, and commonly triggered by wheat, shellfish and celery.

Oral allergy syndrome, on the other hand, results from ingesting raw fruits and vegetables and has mild oropharyngeal symptoms accompanied by pruritus and angioedema. It occurs due to primary

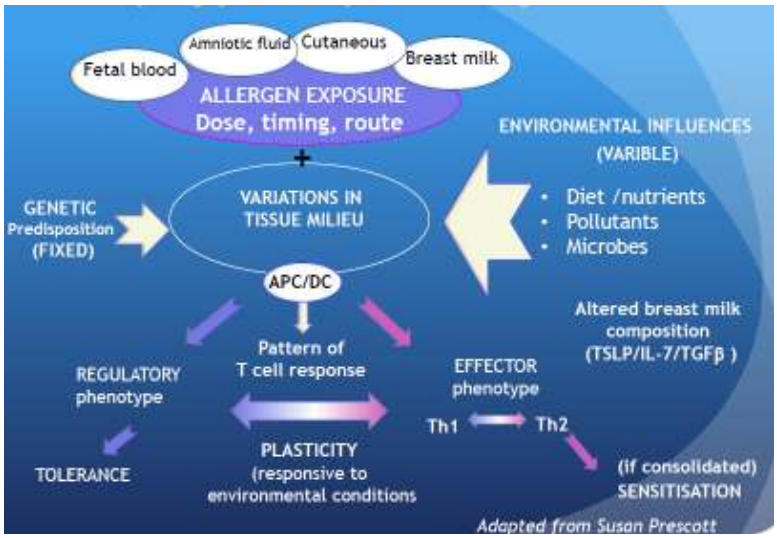

Figure 1. Underlying pathways to allergic sensitization

sensitization to pollen proteins that are homologous to food proteins, and is also known as pollen-food allergy syndrome. As with non-IgE-mediated allergy, patients may develop gastrointestinal disturbances including enterocolitis, proctocolitis, acid reflux, or constipation, due to hypersensitivity to cow milk, soy, or grains.[1,2]

Non-IgE food allergies are much harder to diagnose and treat. These include cow milk induced enteropathy; allergic eosinophilic gastroenteritis; food-protein-induced proctocolitis; food-protein-induced enterocolitis syndrome (FPIES); gastro-esophageal reflux disease (GERD); colic; and constipation. FPIES usually occurs in infants younger than 8–12 months but is also known to occur in older children with fish, shellfish, and cereals hypersensitivity. It is characterized by increased expression of TNFα and decreased expression of TGF-β. FPIES causes severe nausea, abdominal cramps, protracted vomiting and/or bloody diarrhea 1 to 3 hours after eating, anemia, abdominal distension, and failure to thrive; furthermore, 15% of patients with severe enterocolitis suffer from hypotension. Half of FPIES cases spontaneously resolve by 18 months and 90% by 36 months. Food-protein-induced proctocolitis results from the activation of non-IgE-mediated mechanisms by eosinophilic infiltration in the colon. A classic feature is passing blood-streaked stools. Severe colic, which causes infants to cry persistently, affects approximately one-third of babies, but generally subsides by age 4 months. GERD is typified by partial villous atrophy on intestinal biopsy. Cow milk allergy is responsible for approximately 40% of GERD cases and 70% of chronic constipation.

Table 1. Major IgE-mediated food allergens

Class 1	Class 2
Cow milk • Caseins • α-lactoalbumin • β-lactoglobulin • Serum albumin	**PRP group 2**: Latex, avocado, banana, chestnut, fig • Glucanase
Hen egg • Ovomucoid • Ovalbumin • Ovotransferrin	**PRP group 3**: Latex, avocado • Chitinase
Peanut • Vicillin (also lentil) • Conglutin • Glycinin	**PRP group 5**: Cherry, apple, kiwi • Thaumatin-like proteins
Soy • Glycinin • Profilin • Trypsin inhibitor	**PRP group 10**: Apple, cherry, apricot, peach, pear, carrot, celery, parsley, hazelnut • Birch Bet v1 homologs
Shrimp • Tropomyosin	**Celery-mugwort-spice syndrome**: Latex, celery, potato, pear, peanut, soybean • Birch Bet v2 homologs • Profilin
Fish • Parvalbumins	
Fruit & Vegetables: Apple, apricot, peach, plum, corn • Lipid-transfer proteins	

PRP, pathogenesis-related protein

Some food allergies result from mixed IgE and non-IgE reactions. For example, atopic dermatitis is a chronic inflammatory skin disease that causes acute and pruritic lesions. Atopic dermatitis involves IgE-mediated activation of cutaneous mast cells and late-phase infiltration of inflammatory cells such as eosinophils and T cells following exposure to common trigger foods such as egg, wheat, milk, and soy. Mixed IgE/non-IgE food allergy can also manifest as eosinophilic gastroenteropathy due to eosinophilic infiltration of the gastrointestinal tract. Patients often exhibit dysphagia, poor growth, and/or abdominal discomfort (eg, nausea and vomiting).[3]

Diagnosing food allergies

To date, there are no standard tests to confirm or eliminate a diagnosis of food allergy. Rather, physicians rely on a diagnostic workup comprising a comprehensive physical examination and medical history to determine potential trigger factors and associated symptoms, coupled with laboratory tests to provide further confirmatory evidence.

Skin-prick test (SPT) is the first-line diagnostic test for suspected food allergy; however, this may not be necessary if an oral challenge has been previously performed. Alternatively, a previously SPT may obviate oral challenge in the diagnostic paradigm. Food reactions are graded on a scale of 0–4+ or by measuring the diameter of the wheal and flare reaction. A wheal size of <4mm (0+) is interpreted as negative; wheal size 5 to 10 mm (2+) scale indicates mild sensitization; wheal size 10 to 15 mm (3+), moderate sensitivity; and wheal size >15 mm (4+) is classed as high sensitivity. The value of SPT in confirming food allergy depends upon the skill of the interpreter and the quality of allergens used. False positive results can be obtained if reagents are mixed; on the other hand, false negatives arise if the agent used is too diluted, if antihistamine was administered before the test, or if the prick is not deep enough.

Radioallergosorbent test (RAST) usually combined with SPT to diagnose food allergy. RAST is preferred if antihistamine medications cannot be avoided, as the results are not affected. An IgE level of 0.35IU/L is the threshold for predicting clinical reactivity, with lower IgE levels interpreted as absent or undetectable allergen-specific IgE; higher levels indicate presence of allergen-specific IgE. Notably, RAST has high sensitivity but relatively low specificity, therefore necessitating an adjunct test such as oral food challenge (OFC).

A new test that measures the concentration of IgE with higher sensitivity and specificity than RAST has been developed; CAP RAST (ImmunoCAP®) is useful for patients on antihistamines and for diagnosing allergen cross-reactivity. When diagnosing infancy-onset hypersensitivity to cow milk, a CAP RAST value of 2.5 KU(A)/L or greater confirms clinical reactivity with positive predictive value of 90%, in which case OFC is unnecessary.[4] In a prospective study, the high accuracy and precision of CAP RAST in diagnosing symptomatic allergy to egg, milk, peanut and fish, made double-blind, placebo-controlled OFC unecessary.[5]

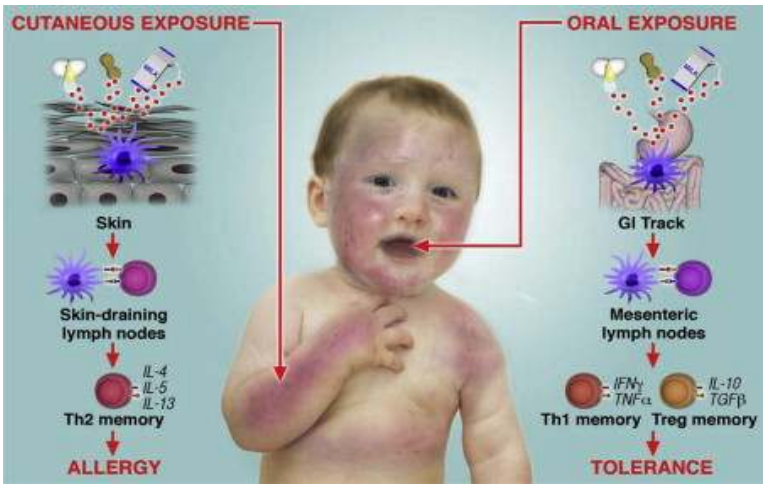

Figure 2. Cutaneous vs. oral exposure to allergens

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Preventing and treating food allergy

No one approach is favored to treat food allergy and a wide array of options have been investigated. These are united by the common aim of early acquisition of oral tolerance.

Under optimal conditions, tolerance may be induced by re-exposing patients to the culprit food. The oral route may be more effective than the cutaneous or respiratory routes, which are both implicated in promoting Th2 responses and subsequent increase in allergy sensitization (Figure 2).[6] Additionally, gastric conditions (eg, gastric pH and microflora) also influence the development of oral tolerance. Gastric pH of 2 is associated with tolerance, immuno-ignorance and reduced allergenicity, while a pH of 5 can increase the likelihood of sensitization. There is indirect evidence from murine models that the absence of gut commensal bacteria can prevent oral tolerance development and result in excessive immunological responses to allergen exposure.

The apparent benefit of allergen exposure in inducing oral tolerance has cast doubt on the policy of allergen avoidance. There is mounting evidence that avoidance is ineffective, and, rather, that there is an “optimal window” for introducing allergenic foods to build tolerance. Ideally, complementary food should be introduced between ages 4–6 months, with earlier or later exposure either increasing the risk of allergies or having no preventive effect.[7-9] More importantly, exclusive breastfeeding for the first 3 months can protect against atopic dermatitis in children with a family history of atopy.[10]

Allergen-specific treatments, such as immunotherapy, have also shown potential in managing food allergies. Immunotherapy modulates the immune response to allergenic foods. In a systematic review of five randomized controlled trials that involved 218 patients, oral immunotherapy significantly increase the likelihood of achieving complete tolerance to cow milk, compared with elimination diet (relative risk: 10.0).[11] Alternatively, allergen non-specific treatments such as anti-IgE, Chinese herbal medicine, and cytokine blockers may be future potential options to decrease food allergy.

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