

FOOD ALLERGIES IN RESPIRATORY SENSITIZATION

¹Siberian State Medical University, 2 Moscovski tr., Tomsk, 634050, Russia

Author Information

✉ **Author for correspondence:** Klimov Vladimir V. Tel. +7-906-950-63-35. E-mail: klimov@mail.tomsknet.ru

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Abstract

The review is focusing on the uncommon route of food sensitization through the unified airway. Food allergies represent a real challenge in the face of modern civilization, taking into account a high prevalence and increased morbidity rates of this pathology. Current literature sources exhibit the problem of airway-related food allergies is underestimated. We describe immune responses to food allergens, which proceed in the respiratory tract, and the fate of shaped memory T cells and B cells. Many questions of food allergies in the total and airway-related mechanism of the pathology, in particular, remain poorly understood. Hopefully, future research will elucidate the problem that is at the cutting-edge.

Keywords: food allergens; sensitization routes; allergic rhinitis; asthma; food allergy

Abbreviations

Th2	type 2 helper T cells
TSLP	thymic stromal lymphopoietin
mDC-1	type 1 myeloid (conventional) dendritic cell
Tfh	follicular helper T cell
ILC2	group 2 innate lymphoid cell

TLR	toll-like receptor
PRR	pattern recognition receptor
PAMP	pathgen-associated molecular pattern
DAMP	damage-associated molecular pattern
APC	allergen-presenting cell
HLA	human major histocompatibility complex
FcεRI	type 1 Fc-receptor for IgE

Introduction

Food allergy is a pathologic process associated with food eating when the immune system responds to nutrients as allergens and develops allergic inflammation in the gut, unified airway, skin, and even genitourinary tract. Food allergies may develop in different phenotypes such as Th2-high (IgE-dependent), Th2-low, IgE-independent, and immune system-independent phenotypes. Atopic sensitization due to IgE overproduction is prevalent. Food allergy and food intolerance are two distinct conditions but are commonly confused because they occasionally share similar symptoms. In developed countries, self-reported prevalence of food allergies makes up 3% through 7,5% in adults [Waserman 2018; Sicherer 2017], whereas food intolerance affects more than half the world's population not causing severe reactions. Systemic food anaphylaxis is a severe life-threatening form of food allergies, which occurs in selected atopic individuals and has no reliable predictive biomarkers [Beck 2019; Reber 2017]. For example, in Ontario, Canada, morbidity from food anaphylaxis in 1999-2011 was 12 cases [Waserman 2018].

Allergenicity of food allergens and routes of sensitization to them

There are four routes of IgE-dependent sensitization to food allergens: (1) gastrointestinal; (2) respiratory; (3) transcutaneous [Kelleher 2020; van Splunter 2020; Wang 2016], and (4) rare genitourinary [Allam 2015]. Accordingly, clinical manifestations are localized in the same target organs, including cardiovascular and central nervous systems, if anaphylaxis occurs [Tomar 2020; Beck 2019; Wang 2016; Skypala 2019]. Not all food proteins are allergens, therefore subject to allergenicity of food allergens is very important. Allergenicity is the allergen's ability to induce a non-adequate adaptive immune response, characterized by the overactivation of the immune system, absence of protective effect, and development of allergic inflammation and possible own tissue damage instead. Allergenicity is evaluated by many methods such as bioinformatics analysis, serological assays, mass spectrometry, cell experiments, animal models, etc. [Pali-Schöll 2019; Fu 2019; Hayes 2018]. There are some families and three classes of food

allergens [Jeebhay 2019]. Class 1 food allergens (cow's milk, peanut, hen's egg, etc.) are oral allergens that cause sensitization via the gastrointestinal tract and display severe clinical symptoms. Class 2 food allergens (e.g., birch) are aeroallergens that evoke sensitization via the respiratory tract and exert not severe cross-reactions termed "oral allergy syndrome," or "pollen food allergy syndrome" [Carlson 2019; Valenta 2015]. Class 3 food allergens (e.g., small food proteins, additives, and contaminants) not having the capacity of cross-reactivity, which sensitize via the unified airway or skin and frequently cause occupational allergies [Jeebhay 2019].

Food protein allergenicity depends on many factors: antigenic structure (multiple epitopes capable of linear IgE binding), molecular weight lower than 70 kDa, stability, solubility in water, interaction with lipids, abundance in food, biochemical characteristics of proteins allowing to pass the extremes of food processing and proteolysis by digestive enzymes, combination with adjuvants in food, ability to promote the production of high levels of allergen-specific IgE and high-affinity allergen-specific IgE, pathologic imbalance in the target organ's microbiota, damaged mucosal barriers, decreased enzyme secretion, deficiency in sIgA, atopic predisposition of a person, etc. [De Angelis 2019; Verhoeckx 2015].

"The Big Eight" food allergens cause about 90% of all food-allergic reactions. They are cow's milk, hen's eggs, peanuts, tree nuts, soy, wheat, fish, and crustacean shellfish. Food allergies to cow's milk, egg, and wheat often are outgrown as grown-up children acquire allergen tolerance, whereas allergies to peanuts, tree nuts, fish, and shellfish commonly persists over a lifetime exhibiting the high association with anaphylaxis [Waserman 2018; Valenta 2015; Koenig 2021].

Sensitization to a food allergen through the unified airway

The new or second sensitization to food allergens may happen if they come by inhalation promoting food allergies, asthma, allergic rhinitis, atopic dermatitis, and systemic anaphylaxis development. Food allergic reactions by inhalation more frequent occur in individuals already sensitized to the food, generally by ingestion. The recurrence, however, can appear due to *de novo* sensitization through inhalation. The dual-allergen exposure hypothesis postulates that early oral exposure to food allergens induces tolerance, whereas exposure at non-gastrointestinal sites, such as the skin or respiratory tract, results in food sensitization and allergy development [Smeekens 2019; Kulis 2021; Du Toit 2018]. The gut has a potent tolerogenic network, which consist of pro-tolerogenic cells and molecules due to the specific autonomous enteric nervous system and mucosal immune system [Mittal 2017; de Oliveira 2021]. The gut is a zone of

allergen tolerance. On the whole, food allergy is often a series of allergic episodes, does not look like a typical atopic disease, and represents a known exception to the rule conceived by evolution.

More commonly reported inhaled food allergens are wheat flour, seafood (preferentially, crustaceans), soy, peanut, hen's egg, and milk [Ramirez 2009]. The exposure to food allergens may proceed at home, in schools, restaurants, grocery stores, commercial flights, and occupational environments. Inhalation of food allergen depends on its airborne presence. Food processing, such as boiling, steaming, or frying, can release significant quantities of food allergens and promote the inhalation route of sensitization [Ramirez 2009]. However, the respiratory route appears not to be isolated and is combined with gastrointestinal and transcutaneous sensitization to food allergens, though the airway route in food allergies is still underestimated.

On the one hand, many food allergens are found in household dust [Hindley 2019; Trendelenburg 2018], and many food allergens causing occupational allergies act as primary sensitizers through inhalation, with no evidence of cross-reactivity to other common inhalant allergen sources [Jeebhay 2019]. On the other hand, food sources contain food products (cereals, plants/vegetables/fruits/spices, seeds, herbal teas, mushrooms, seafood, and farm products), additives (colorants, thickening agents, sulfites, and enzymes), and food contaminants (mites, insects, fungi, and parasites) [Jeebhay 2017; James 2007]. These agents commonly represent proteins (>10 kDa) derived from food sources, which may act as respiratory sensitizers through the unified airway [Jeebhay 2019].

Food allergens penetrate the body via the unified airway route, get into the nasal and lung submucosae, where the immune system responds to these allergens. Researchers demonstrated the peanut allergens triggered IL-33 and thymic stromal lymphopoietin (TSLP) synthesis in primary human nasal or bronchial epitheliocytes and stimulated maturation and migration of peanut-specific nasal/lung mDC-1 cells to draining lymph nodes. In addition, inhalational exposure to peanut and indoor dust induced peanut-specific Th2 cell differentiation and accumulation of Tfh cells in draining lymph nodes, which were associated with increased B cells numbers and peanut-specific IgE and IgG1 production [Smeekens 2019].

In response to a food allergen (see Fig. 1), epitheliocytes produce alarmins (danger signal), IL-25, IL-33, and TSLP, which upregulate group 2 innate lymphoid (ILC2) cells, dendritic (DCs) cells, and type 2 helper T (Th2) cells. Pro-immunogenic neuropeptide neuromedin U promotes ILC2 cells [Zheng 2021; Wallrapp 2017; Pasha 2019]. Conversely, endogenous neuropeptide calcitonin-gene-related peptide (CGRP) is a critical negative regulator

of ILC2 responses *in vivo* [Wallrapp 2019; Nagashima 2019]. The alarmins are essential stimulators of type 2 immunity, as they lead to the production of IL-5, IL-9, and IL-13, but they can participate in the IgE-independent pathway of allergic inflammation [Yamauchi 2019; Pasha 2019]. Toll-like receptors (TLRs) related to pattern recognition receptors (PRRs) bind to pathogen-associated molecular (PAMP) patterns or damage-associated molecular (DAMP) patterns, and after signaling, promote the release of alarmins, the synthesis of cytokines, and development of pyroptosis, creating the link between adaptive and innate immunity.

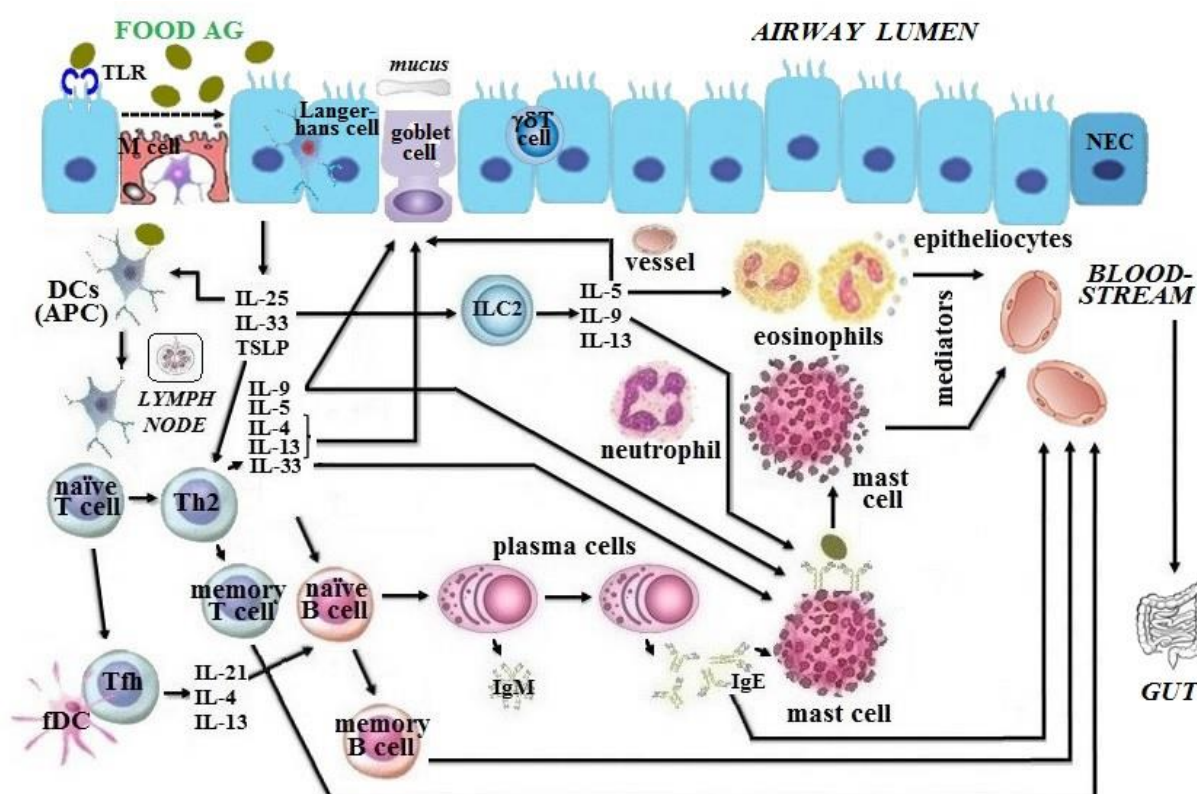


Fig.1. Sensitization to a food allergen through the unified airway

See description in the text. AG - allergens, DCs - dendritic cells, APC - allergen-presenting cells, Th2 - type 2 helper T cells, Tfh - follicular helper T cells, fDC - follicular dendritic cells, ILC2 - group 2 innate lymphoid cells, NEC - neuroendocrine cells, TLR - toll-like receptors

A food allergen that passes the epithelial barriers is processed by dendritic cells (DCs), allergen-presenting (APC) cells, which in turn migrate to draining lymph nodes, where they present allergen-derived peptides on HLA class II molecules to naïve T cells. The naïve T cells differentiate into Th2 cells and follicular helper T (Tfh) cells. Th2 cells produce type 2 cytokines such as IL-4, IL-5, IL-9, IL-13, IL-33 and drive allergic response [Drazdauskaitė 2021; Schoos 2020; Eiwegger 2019; Sampath 2019]. Tfh cells produce IL-21, IL-4, IL-13, which promote IgE

class switch recombination in B cells, plasma cell maturation, and allergen-specific IgE production. The IgE antibodies may contribute to the allergic inflammation in the unified airway, e.g., in allergic rhinitis or asthma. In this case, the allergen-specific IgE antibodies bind to FcεRI molecules on mast cells and basophils, resulting in their degranulation and allergic inflammation development due to histamine and other mediators of innate effector cells. Simultaneously, shaping two types of allergen-specific memory cells, (1) memory T cells and (2) memory B cells, occurs. These memory cells and IgE antibodies get into the bloodstream and then into the gastrointestinal tract.

Oral tolerance, an antipode of food allergies and a form of allergen tolerance, is a physiologic process of nutrient absorption with no adverse reaction. However, oral tolerance depends on multiple factors, which can maintain or destabilize it under the everyday entry of food proteins, dynamic gut microbiota, changing signals from neuro molecules, and continuous trafficking of pro-inflammatory cells and molecules [Olivera 2021]. Furthermore, it is unknown if feeding allergens can also induce true immune tolerance after generating a memory immune response [Tordesillas 2018].

Co-influence of respiratory and food allergies

Different forms of allergies affect approximately one-third of the world's population in Europe, and the rates are growing. There is a tendency for several allergic diseases to be present in the same individual simultaneously [Klimov 2019]. In the epidemiological study, allergic rhinitis occurred in 46,4%, asthma was in 11,2 %, and allergic multimorbidity was diagnosed in 9.7% compared with a single allergic disease in 43,4%. The current study's findings indicated an association between food allergies and the presence of at least one allergic disease [Skoczylas 2020].

However, isolated allergic rhinitis and asthma are not inherent in food allergic reactions, but respiratory symptoms may be part of anaphylaxis. Most asthmatic reactions to inhaled food allergens are described in occupational settings [Emons 2018]. In the workplaces, 372 different potential causative allergens were identified, including seafood, wheat flour, and hen's eggs that might lead to asthma. Workers exposed to inhaled egg allergens developed rhinitis and asthma first and subsequently other allergic symptoms to the ingested egg. Subjects who inhaled wheat flour developed asthma with or without wheat ingestion [Emons 2018].

Food allergy is frequently underestimated in association with asthma, but food allergy has been shown to trigger or exacerbate bronchial obstruction in asthma. There were reported that

34–78% of 82 asthmatic patients in Taiwan had food-related symptoms. Foods most commonly linked with their complaints were crab (67.9%), cow's milk (53.6%), shrimp (50%), and other food allergens [Wan 2016]. 1722 children between 0 and 14 years old in Sichuan province, China, were enrolled in this study. 59.7% of children were allergic to at least one allergen, comprising 24.9% to aeroallergen and 38.8% to a food allergen, respectively, whereas 36.28% of children were allergic to both aeroallergen and food allergen. Also, there have been revealed that milk, egg, and house dust mites were the most common allergens. However, an analysis of the pattern of food allergen and aeroallergen sensitization was invaluable to the effective diagnosis and treatment of allergic diseases [Liu 2020].

In the study of 200 patients in Iraq in which skin prick testing was conducted, it has been found that 46% of allergic rhinitis cases were caused by foods, including cumin (88.98%), tea (62.96%), pepper (59.25%), almond (51.85%) and other food allergens [Abdullah 2020]. 252 patients with asthma, allergic rhinitis, and combined pathology in north India participated in the study. The prevalence of food sensitization based on specific IgE to respective foods was 17% with cereals and legumes [Chandni 2019]. Among 258 patients in Mexico included in the study, the most common underlying condition was allergic rhinitis (59 %). The prevalence of food sensitization (preferably to soybeans) was 40 % [Bedolla-Barajas 2017].

In the clinical study of a case of a 38-year-old mold-allergic patient, it has been demonstrated that prior sensitization to mold aeroallergens might explain severe food reactions to cross-reacting homologs mushroom proteins. In addition, there was a well-recognized relationship between sensitization to airborne molds and allergy to mushrooms ingestion [Gabriel 2015]. In another clinical study of a series of six patient cases with immediate occupational allergy (allergic rhinitis, asthma, and urticaria) to buckwheat, it has been revealed that patients had anaphylaxis after ingestion of food that contained buckwheat [Jungewelter 2020].

So, food allergy and non-enteric atopic diseases often coexist, and they are interconnected beyond the presence of simple comorbidity [Emons 2018].

Conclusions

Food allergy is a challenge inherent in our civilization that may develop in different phenotypes such as Th2-high (IgE-dependent), Th2-low, IgE-independent, and immune system-independent phenotypes and by distinct pathogenic mechanisms and routes of sensitization. The airway route is described [Ramirez 2009; Jeebhay 2019; Smeekens 2019] but underestimated. Food allergens

penetrate the body through the unified airway route, get into the nasal and lung submucosae, where the immune system responds to these allergens, and then established memory cells and IgE antibodies come via the bloodstream to the gastrointestinal tract [Smeekens 2019]. According to the current literature sources, food allergy and non-enteric atopic diseases like allergic rhinitis and asthma often coexist in the context beyond the presence of simple comorbidity [Emons 2018].

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