Chapter 1

Introductory Chapter

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1. Introduction

Recently, a clear definition was provided by National Institute of Allergy and Infectious Diseases (NIAID) for the food allergy in which it is defined as the usually an extreme immune response against the specific proteins in food. The immune reactions triggered by these allergenic proteins are started immediately after consuming an allergic food or lately after 2–3 days. The immune response can be acute and deadly in some cases and happens in minutes, causing angioedema, throat or tongue swelling, obstruction of respiratory airways secondary to swelling, and rapid fall of blood pressure, which are indicative of a dangerous life-threatening immune reaction called anaphylaxis. The only way to effectively control an anaphylaxis shock is to give an epinephrine (adrenaline) shot to the patient as soon as possible. But some common symptoms which the patients with food allergy experience after an allergen challenge are moderate, including gastrointestinal hypersensitivity, urticaria, itchy rashes, edema in different tissues/organs, rhinitis, and chronic asthma-like reactions.

However, one should bear in mind that the food allergy is differed by its mechanism of action and the initial factors involved in the onset of the symptoms from the food intolerance. The food allergy is generally an IgE-mediated immune response but food intolerance is a difficulty in digesting a specific food or compound within a food. For instance, some people cannot digest lactose, which is usually found in milk, because they have insufficient or no activity of lactase or suffer from completely absence of the lactase, an enzyme that breaks lactose to smaller carbohydrates. This is a typical food intolerance, which is unrelated to the immune system and in comparison to reactions triggered by food allergy, and is characterized by less acute clinical manifestations such as stomach ache, headache, irritable bowel, hives (urticaria), cough, runny nose, and feeling unwell.

Food allergy is more frequent among children than in adults by which most cases of food allergy occur during first 5 years of life and disappear later spontaneously. It was proposed

that the patients, who the onset of symptoms occurs in earlier ages, are more likely to maintain their allergy to foods until their later ages. The cow's milk, peanuts, and tree nuts are three most usual causes of food allergy among children while shellfish, fruits, and vegetables are three most common causes of the food allergy among adults. However, millions of people involved in food allergy worldwide in which the globalization, transportation of new foods to the nonnative countries, increased consuming of processed foods, and production of enriched foods by food-derived proteins such as gluten or the soy proteins are the factors supporting the increasing trend of food allergy. Based on epidemiologic studies, the overall prevalence of food allergy varies between 1 and 10% of the population. In a survey based on tens of thousands medical records in the USA, the prevalence of food allergy estimated 8% among children, 3% of which experience severe immune responses. In the USA, about 12 millions of people have a type of food allergy. Surprisingly, despite the substantial progress in our knowledge about healthy nutrition and, therefore, noticeable improvements in the health and hygiene standards of the food processing and enrichments, the prevalence of food allergy has been increased continuously in recent years. In the USA, the prevalence of food allergy among children aged 0–17 has been increased from 3.4% in 1997–1999 to 5.1% in 2009–2011, showing a 50% increase in frequency. In this regard, the food allergy is not a simple and negligible health issue by considering the fact that it can impose the heavy costs to the national health budget. In the USA, the healthcare system pays annual $24.8 billion for the food allergy.

The pathogenesis of allergic responses in food-sensitive patients from an immunologic perspective is relatively well characterized in recent years but the precise primary mechanism which initiates the immune reaction against some allergenic proteins within foods in some people but not in others remains to be elucidated. Food allergies can be classified into three main categories based on their primary mechanism of initiation including 1. The pathogenic and allergic responses by which mediated by IgE production, 2. The responses which is composed of the mixed IgE- and T cells-mediated reactions, and 3. The allergic reactions unrelated to the IgE production and mediated by allergen-specific T cells.

Generally, food allergy can be considered as the atopic disorder. Progression of atopic disorders is occurred first during infancy or early childhood, clinically is being manifested as the atopic dermatitis, in a form of a phenomenon called atopic march. The emergence of an atopic disease (such as atopic dermatitis) in a patient has been associated tightly with the later progression of allergic disorders such as food allergy, allergic rhinitis, and allergic asthma. Furthermore, nonatopic illnesses such as celiac/coeliac disease or gluten sensitivity are being initiated by the completely distinct mechanisms, although again the immune system is involved. In fact, celiac disease or gluten sensitivity is a type of food intolerance not food allergy in which IgE has no role in their pathogenesis but other antibodies such as IgA and IgG does. In celiac disease, delayed cell-mediated hypersensitivity drives the immune system reactions in small intestine after digesting a gluten-containing food by a genetically predisposed individual, causing the chronic intestinal inflammation and enteropathy that result in leaky gut. However, the abnormal mixed IgE- and cell-mediated immune responses are responsible for 14–37% cases of the food allergy, making this category the most frequent type of the food allergy. The food allergies with the IgE as the only causative mechanism comprise 0.4–10% of the food-allergic cases, ranked as the second prevalent type of food allergy.

IgE-mediated immune responses usually occur rapidly in minutes and causes severe and acute clinical manifestations. However, this type of food allergy varies in different countries in order to the type of the food responsible for allergenic reactions. In most of the Asian countries, shellfish is the most frequent cause of the food allergy, whereas the wheat allergy is infrequent. Initially, food-sensitized individuals, in their subsequent exposure to that food, experience severe and immediate responses that are driven by IgE. Food allergen-specific IgE molecules are attached to the specific receptors on the effector cells such as basophils and mast cells then the allergens can bind to these receptor-bound IgE molecules, leading the cells for degranulation and release of abundant amounts of inflammatory mediators such as histamine, TNF-α, IL-4, and IL-13. Histamine is one of the key mediators in IgE-mediated allergic responses, makes the capillaries permeable to the immune cells, causes the bronchoconstriction, smooth muscle cells contraction, mucus release, and urticaria and has a key role in initiating the anaphylaxis. Mast cells contribute not only in the immediate phase of allergic responses by mass-degranulation of their inflammatory mediators like histamine and serotonin but also contribute in late-phase immune response by cytokine production, antigen presenting, and T cell priming. After an immediate phase of allergic response against an allergen food, the later phase of immune response is triggered and maintained by production of leukotrienes and cytokines such as IL-4, IL-5, and IL-13. A broad range of organ-specific and systemic clinical manifestations occur during an IgE-mediated allergic response against an allergen food. The organ-specific manifestations comprise the gastrointestinal, oral, skin, and respiratory symptoms, while the systemic manifestations include hypotension, hypothermia, and anaphylactic reactions.

Mixed immune pathways-mediated food allergy is frequently occurred in food allergen-sensitized individuals, characterized by atopic symptoms which are mostly the exacerbated atopic dermatitis after exposure to an allergenic food or in some cases gastrointestinal allergic reactions such as eosinophilic oesophagitis. The immune system in mixed food allergies acts through both IgE-mediated pathway and cell-mediated delayed hypersensitivity. The activation of T helper 2 (T_H2) cells has a central role in triggering the delayed hypersensitivity against allergenic foods.

The last type of the food allergy is mediated through non-IgE-related pathways, largely driven by the action of allergen-specific T cells. In non-IgE-mediated food allergy, (initiated by allergen-specific T cells), the most common clinical symptoms are more occurred within the gastrointestinal tract rather than in other organs such as respiratory system or skin. Generally, infants and toddlers are involved in this type of food allergy, which results in some specific types of enteropathy and enteric inflammation such as the food protein-induced enterocolitis syndrome, food protein-induced proctocolitis, and food protein enteropathy, and their etiologies have been remained unknown to date.

As an alternative viewpoint, regarding the time required for onset of symptoms, the food allergies can be classified into two groups including those mediated by rapid immune responses in which the mast cells, basophils, and IgE play main role and those mediated by delayed immune responses in which the basophils, T cells, and eosinophils are responsible for chronic allergic inflammation and late-phase immune reactions.

However, the mechanism by which the host's immune system develops the tolerance (healthy reaction) or sensitization (allergy) against a food has been partially elucidated. A subtype of dendritic cells (DCs) classified as the $CD103^+$ DCs are the key cells concerting the immune system tune against the food allergens, leading the immune responses either toward a tuned (healthy) or a false response (allergy). DCs sample the food allergens thorough the epithelial cell barrier of the gut. Other antigen presenting cells such as macrophages help the DCs for antigen sampling. Then these antigen activated DCs migrate from the lamina propria toward a secondary lymphoid tissue and there prime the naïve T lymphocytes to differentiate into $FOXP3^+$ regulatory T (T_{reg}) cells. These primed and antigen-specific T_{reg} cells are main immune cells responsible for tolerance against food allergens. In addition, $CD103^+$ DCs also involved in triggering the naïve $CD4^+$ T cell to polarize into $FOXP3^-$, IL-10-secreting T cells which are called type 1 regulatory T cells (Tr1 cells). Tr1 cells have also critical role in dampening the immune response against food antigens. The DC-mediated polarized T cells contribute in suppressing the immune reaction against food allergens and induce the IgA production by B cells. In contrast, during the sensitization process, $CD103^+$ DCs shift the immune system toward a cascade of responses directed by T_H2 cells. In sensitized patients, the food allergens trigger inflammatory responses mediated by gut epithelial cells via producing the thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These cytokines affect the DCs, empowering them to deviate the polarization of naïve T cells toward the T_H2 cells rather than the T_H1 cells. Then T_H2 cells induce the class-switching of B cells to produce allergen-specific IgE followed by subsequent responses by effector cells (mast cells, basophils) which is end in the food allergy.

There have been a series of diagnostic methods, some of them developed decades ago but until recently have been remained reliable enough although in some cases they give false positive or false negative result. However, the medical history and physical examination are the first line approach for medical diagnosis of food allergy in which some disorders such as the history of an atopic disease can guide the physician toward a proper diagnosis. In addition, a method based on step-by-step removing the nonallergic food from the dietary regimen until reaching the food causing the allergic response is the only fully reliable method of identifying the original cause of the food allergy. An accurate and generally accepted variant of the method called oral food challenge (OFC) has been developed but it could not be used extensively thus far due to requirement of intensive laboratory resources, its time-consuming procedures and the risk of undergoing anaphylactic reactions. The serologic tests such as measuring the total IgE and allergen-specific IgE, skin tests such as skin prick test, intradermal skin test, and atopy patch test can also help for diagnosis, though these tests indicate only the sensitization not a clinical food allergy. There are also two novel highly accurate diagnostic tests including the component-resolved diagnosis and basophil activation test although yet are being in the developing process in research settings.

The management and treatment methods for food allergy are mostly based on avoidance or elimination of the allergenic food from the dietary regimen. Currently, the only method whose effect can last for long time is known as the allergen-specific immunotherapy (SIT). In the SIT method, the allergen food is usually administered orally to the patient in a controlled manner in order to relieve the food allergy, which is called antigen desensitization. However,

other desensitizing immunotherapy methods are also developed and done by introducing the allergen food to the immune system via other routes of administration like sublingual or skin. In the sublingual immunotherapy (SLIT) method, first, a very small amount of the allergen food is placed under the tongue, maintained for minutes then the amount of allergen is increased gradually over the several days or weeks. The results of using SLIT or oral immunotherapy (OIT) have been very promising, making the immune system tolerant to the allergen food in gram amounts. Other therapies mainly relied on mitigating the symptoms such as the anti-IgE monoclonal antibodies, anti-histamines, anti-leukotrienes, and epinephrine. For targeting the non-IgE-mediated but T-cell-dependent food allergies, there are also some symptomatic treatments such as the steroids and anti-IL5, inhibiting the T cells activation. In additidon, some studies suggest that the early introduction of potentially allergenic food may prohibit or decrease the chance for emergence of food allergy. Other studies suggest also a preventive and protective role of vitamin D against food allergy.

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