

Pathological Mechanisms Underlying IgE-mediated Food Allergy

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Abstract. Food allergy is an immune disease triggered by abnormal immune responses against harmless antigens that enter through our gut lumen. There are two major pathways that contribute to the food allergic symptoms: IgE-mediated and non IgE-mediated. Among all food allergy cases that have already been discovered, IgE-mediated mechanisms are responsible for over 80-90% of the cases. The IgE-mediated mechanisms include epithelium damage, T helper 2 cell induction, IgE antibody production, and the final symptoms caused by the effector cells. We also discovered that there may exist a potential relationship between B cell metabolism and the IgE production, which ultimately leads to food allergy. At the same time, since more and more people now enjoy more diverse food sources, issues regarding food allergy are outbursting these years as people's exposure to different food proteins and antigens rapidly increase. It is shown that the United States government is losing billions dollars annually to cover the lost caused by food allergy. Given the worldwide prevalence of the food allergy and the increasingly unhealthy lifestyles of many people, it is highly crucial for us to understand the fundamental mechanisms underlying the IgE-mediated food allergy, which is the most common and influential pathway that risks millions of lives. Therefore, this Review goes over the basic mechanisms underlying the IgE-mediated food allergy, namely how epithelium damage, T helper 2 cell induction, IgE antibody production, effector cell activation, and B cell metabolism lead to the final symptoms of food allergy.

Keywords: Food allergy, IgE, Antibody, Immunoglobulin, T helper cell, B cell, Cytokine, Class switch recombination.

1. Introduction

Food allergy and its pathological symptoms are the results of the immune response that falsely recognizes and fights food antigens as harmful pathogens [1]. Exposure to specific food, especially those containing large amounts of proteins such as peanut and seafood, can trigger clinical symptoms such as gastrointestinal disorders, airway inflammation, atopic dermatitis, oral allergy syndrome, and urticaria [1].

Nowadays, food allergy has become one of the commonest and most costly disease in the world [1]. Based on an epidemiological study that investigated 333,200 children in the United States, the food allergy prevalence was found to be approximately 6.7% [1]. Such an astonishing prevalence becomes a huge burden on the US healthcare budget. Based on the survey, food allergy is costing the government 24.8 billion dollars annually [1]. Even worse, the global prevalence of food allergy seems to increase in the 21st century. For instance, the number of food allergy related deaths in Australia increased by 9.7% per year between 1998 and 2012, and British healthcare system reports that the food allergy related hospital admissions has increased by 137% for children under 18 years old [1]. Environmental influences are believed to play a huge role in such an increase [2]. A popular theory seeks to explain such an increase in the food allergy prevalence by building a connection between food allergy and microbes [1, 3]. Some researchers believe that the microbial antigens, especially the ones that enter our gut, help stimulate T helper 1 cell (Th1), thus maintaining the homeostasis of the immune system and prevents food allergy [2, 3]. Based on this theory, since the Western world has become cleaner and developed a healthier lifestyle, the number of the potential microbes that enter our body is decreasing, thus weakening our immune system's capability to prevent food allergy [1].

Due to the increasing prevalence and danger of the food allergy, effective treatments and methods of prevention are in urgent demand. It's also highly crucial to understand the basic mechanism

underlying the food allergy for future development of new clinical therapies. This Review summarizes the mechanisms of IgE-mediated food allergy.

2. IgE mediated food allergy

IgE mediated food allergy is the most common source of food allergy, causing over 80-90% of the food allergy cases worldwide [1]. In addition, it is also the cause of food allergy that has been investigated and researched the most. Therefore, the mechanisms of IgE mediated food allergy have already been discovered, and a series of effective diagnosis tools and therapies have been designed. In this section, we will review the basic mechanisms underlying the IgE mediated food allergy, including the epithelial barrier damage, the Th2 cell induction, the IgE production, and the effector cell induction:

2.1 Epithelial Barrier Damage

The entry of food antigen into the gut initiates the allergy immune response [1]. Any food antigen that enters the gut lumen will be captured by passing through epithelial cells [2]. Assisted mechanisms are utilized at this stage to help transport antigens through the epithelial barriers [2,3]. Specialized cells such as microfold cells, dendritic cells (DCs), and macrophages, along with mechanisms such as diffusion and active transport, assist the passage of food antigens through the epithelial barrier [2,3]. Normally, the food antigens recognized by special antigen presenting cells without pro-inflammatory signals will promote tolerance, which identifies food antigens as harmless antigens, thus releasing chemical mediators such as interleukin 10 (IL10) [3]. These chemical mediators then produce transforming growth factor beta (TGF β), which transforms naive T cells into regulatory T cells, hence preventing the production of IgE and the food allergy [3]. For instance, CD103⁺ DCs, a vital dendritic cell involved in the process of antigen capturing and presenting, directly capture the food antigens from the gut lumen and produce TGF β and retinoid acid [2,3]. These two chemical mediators help transforming naive T cells into regulatory T cells. Also, CD103⁺ DCs may transform native CD4⁺ T cells into FOXP3⁻, IL-10 secreting T cells, which induces normal immune pathway and recognition, thus preventing allergy [2,3].

On the other hand, the integrity of the epithelial barrier, the initiation site of the immune pathway, may be damaged and compromises, resulting in the initiation of food allergy [2,3]. Damaged epithelial cells promote the release of pro-inflammatory epithelial cytokines such as IL-25, IL-33, and thymic stromal lymphopoeitin (TSLP) [2]. These pro-inflammatory chemical mediators prompt the activation of the allergic immune response pathway by signaling to antigen presenting cells at the epithelial barrier [2]. As a result, the antigen-presenting cells will recognize harmless, benign food antigens as potential threats and thus triggering further immune responses [2].

2.2 T helper 2 cells induction

In the absence of pro-inflammatory cytokines, the CD103⁺ dendritic cells may capture the food antigens from the gut lumen and transfer them to the lymph node, where the DCs present the harmless food antigens to naive T cells with MHC 2 [3]. Meanwhile, the chemical mediators, namely the TGF β and retinoid acid, released by the CD103⁺ dendritic cells prompt the transformation and expression of T regulatory cells [3]. For instance, retinoic acid induces T regulatory cell expression of integral $\alpha 4\beta 7$, leading to the migration of T regulatory cells to the gut lumen where they help maintain the homeostasis and prevent allergy [3].

On the other hand, the release of pro-inflammatory chemical mediators such as IL-33 and IL-25 by compromised epithelial cells promote the reduction of such tolerance against the food antigens [2,3]. These chemical mediators activate and influence the antigen presenting cells, thus further promoting the induction of the T helper 2 cells, which then trigger the production of IgE and the final clinical symptoms [2,3]. The activated dendritic cells recognize the food antigens as threats and express surface OX40L [2]. After their migration to the lymph node, the dendritic cells expressing

OX40L interact and bind with the OX40 on the naive T cells [2]. As a result, the interaction between OX40L and OX40 eventually accounts for the differentiation between the induction of T regulatory cells and Th2 cells [2]. Th2 cells are promoted from naive T cells due to the interaction between OX40L and OX40, which originates from the damaged epithelial barrier [2,3].

At the same time, the type 2 innate lymphoid cells (ILC2) are also believed to play a crucial role in the induction of Th2 cells [2,3]. Yet, ILC2 is able to induce Th2 cells in the absence of antigens [2]. Receiving the pro-inflammatory cytokines from the compromised epithelial dendritic cells, the ILC2 promote a Th2-mediated immune response pathway against the food antigens by releasing Th2 cytokines, such as IL-4 and IL-13 [2]. The secretion of these Th2-type cytokines suppress the transformation of T regulatory cells, hence improving the Th2-mediated immune response against the food antigens and leading to food allergies [2,3].

2.3 IgE antibody production

The development of T regulatory cells further increases the release of suppressive cytokines such as IL-10 and TGF β , which prevent the activity of effector cells and food allergy [3]. Furthermore, the migration of T regulatory cells to the gut with the help of retinoic acid and $\alpha 4\beta 7$ also increases the direct interaction and being between the effector cells and the T regulatory cells [3]. The CTLA-4 protein on the T regulatory cell can bind to effectors to suppress their activity [3].

Conversely, Th2 cells can migrate out of the lymph nodes into the lamina propriator, where they decrease pro-inflammatory cytokines such as IL-13 and IL-5 to promote pro-inflammatory effector cells such as basophils and eosinophils [3]. More importantly, Th2 cells can also release IL-4, which promotes the production of IgE antibody by the B cells [2,3].

The switch and balance between IgG-producing B cells and IgE-producing B cells mainly depends on a class-switch recombination (CSR) system that responds to the different cytokine signals by suppressing specific transcriptional switches [4]. Normally, B cells are not able to switch the type of antibody produced since they are regulated by checkpoints TNF receptor associated factor 2/3 (TRAF2 and TRAF3) [5]. These checkpoints restrain the differentiation and the CSR system of B cells in the absence of external stimulations such as Th2-type cytokines [5]. Experiments also show that the removal of TRAF2 and TRAF3 stimulates the activation of the CSR system, furthering proving the function of the TRAF2 and TRAF3 checkpoints [5]. Therefore, B cells are able to maintain a balance regarding the type of antibodies they produce since they cannot switch back and forth between the production of different antibodies without outside stimulus [5].

However, when external stimulus, including Th2-type cytokines, are accepted by the B cells, the transcription of B cells will be altered and the CSR will be activated [4]. It is found that the genes encoding the C regions of IgG and IgE are located downstream and regulated by specific switches. Researches discovered that T cells contribute to the CSR system through cytokine production [4]. For instance, Th2 cells produce IL-4, which is found to have a positive correlation with the production of IgE. Therefore, although the exact mechanisms regarding how cytokines alter the switches of the B cell genes remain unknown, we can suggest that whether B cell produces IgG or IgE heavily relies on the Th1/Th2 dichotomy and is supported by high B cell metabolic activity. In other words, having more Th1 suppresses IgE and food allergy, while expressing more Th2 and enhancing metabolic level increases IgE production and allergic symptoms.

Interestingly, researches suggest that another type of cell, the follicular Th cells (T_{fh}), is playing a highly crucial in the balance of B cell switches [4]. T_{fh} cells effectively suppress IgE responses by producing IL-21, a cytokine that indirectly interrupts IgE production through inducing the function of other anti-IgE cytokines, such as IFN- γ [4]. As a result, IgE production is highly complex and sensitive since it is very likely to be a complicated balance system in which multiple factors affect the final output of IgE antibody [4]. When it comes to food allergy, only the right Th2-type cytokines, especially IL-4, can monitor the transcriptional switches of the B cells and change them into producing IgE, causing further allergic reactions [4].

Lastly, the effect of B cell metabolism is often neglected in the IgE production, but increasing evidences suggest that B cell metabolism must have played a highly significant role in assisting and even directly causing IgE production [6,7]. Latest researches discover that B cells undergo a change of tendency of energy sources when activated by Th2-type cytokines [6]. Activated B cells switch from their reliance on glucose as their primary energy source towards fatty acids with the help of the transcriptional regulator Blimp1 [6]. This essentially means that glycolysis is skipped in activated B cells, since fatty acids are only used in the oxygen-dependent part of cellular respiration [6]. Although the exact purpose of such a change of energy source has not been investigated yet, we can assume that B cells may want a quicker, more efficient energy source, or they need to save the glucose for other purposes, such as to make up the nutrient deprivation, a highly common phenomenon in most activated B cells. Another noteworthy event that takes place in all activated B cells is their highly active amino acid metabolism [6]. A substantial amounts of amino acids is required for not only the production of antibodies, but also the activation of other crucial factors that help complete the production of antibodies [6]. For instance, mTORC1 is a significant protein complex supported by high levels of amino acids that helps promote the antibody production and fuel other extensively active cellular activities, such as glucose uptake and cell growth [6]. These events are highly important since they account for most of the extra fuel required by the antibody production [6]. In other words, without the highly active amino acid metabolism, the B cells may not even manage to switch and produce the IgE antibodies. In fact, there may even exist a cause-and-effect relationship between the B cell metabolism and the antibody production. It is clearly observed that B cells require more fuel than usual once they initiate antibody production. Therefore, those that fail to switch the energy source and increase their amino acid metabolism may also fail to switch and produce the IgE antibodies. Although there's no direct evidence supporting such a hypothesis yet, B cell metabolism, in addition to Th2-type cytokine activation, may be playing a much more direct and important role in the IgE production that we previously assume [6, 7].

2.4 Effector cells induction and functions

In the presence of cytokines released by T regulatory cells, B cells can produce IgA antibodies, which are believed to maintain tolerance and suppress effector cell activity [3]. IgA antibody level is tightly associated with desensitization, a process by which the patients gradually reduce their allergy symptoms, thus maintaining normal tolerance against the food antigens in the absence of IgE antibodies [3].

However, when pro-inflammatory cytokines are secreted from compromised epithelial DCs and Th2 cells, B cells switch into the production of food-specific IgE, promoting sensitization and food allergy [2,3]. The IgE antibodies produced by the affected B cells can bind to the FcεRI receptors found on mast cells and basophils [2]. The interaction between food-specific IgE and effector cells then prompt the secretion of preformed chemical mediators into circulation, thus resulting in allergic symptoms that simultaneously take place all over the body [2].

Some of the most important chemical mediators released by the IgE-effector complex are histamine, tryptase, platelet activating factor, leukotrienes, and prostaglandins [2,3]. Histamine plays a very important role in triggering the clinical symptoms of anaphylaxis [2]. Histamine-mediated reactions often takes place rapidly after the release of histamine from the activated effector cells [2]. Histamine interacts with the H1 and H2 receptors, leading to vasodilation, increased heart rate, increased cardiac contraction, and lower blood pressure [2]. The accumulation of these effects can eventually lead to severe heart disease [2]. Tryptase, a mediator released by activated mast cells, usually leads to allergic reaction 60-90 minutes after the initial release [2]. Tryptase can cause severe angioedema, an allergic symptom that causes swelling underneath the skin, by activating the contact system [2]. Platelet activating factor is another crucial anaphylaxis mediator [2]. Platelet activating factor leads to increased vascular permeability, degranulation of eosinophils and neutrophils, and severe bronchoconstriction [2]. Therefore, platelet activating factor released by the affected effector cells account for the difficulty breathing of the allergy patients [2, 3]. Leukotrienes, unlike the

previous three mediators, are lipid mediators [1]. They have a rather slower onset time from the initial release. They often slowly result in smooth muscle contraction and increasing vascular permeability after the intake of food antigens [1]. Leukotrienes also help producing more pro-inflammatory cytokines, therefore further promoting other mediators and the allergic reaction [2, 3]. Finally, prostaglandins are also lipid mediators released from activated mast cells [1, 2]. They have a huge impact on the heart and lung function of the patient [1]. The release of prostaglandins usually result in bronchoconstriction, peripheral vasodilation, and artery vasoconstriction [1]. The accumulation of prostaglandins can therefore lead to severe, life-threatening allergic reactions for the patients [1, 2]. Furthermore, prostaglandins, similar to the leukotrienes, help recruit other pro-inflammatory cells, thus enhancing the secretion of histamine and the overall immune response against the food antigens [2,3].

3. Discussion

Indeed, food allergy is a disease underestimated by many people, including some researchers. Although the basic mechanisms underlying the IgE-mediated food allergy have already been discovered, there are still many mysteries regarding other crucial factors that contribute to the causes of food allergy [1]. For instance, the effect of B cell metabolism, the non-IgE mediated food allergy, and many other cellular activities remain unknown [1, 6]. As a result, suitable treatments cannot be designed and hundreds of thousands of patients are still suffering from allergic symptoms, to which they can't do anything but merely removing the allergic product, which is highly ineffective [1].

In addition, food allergy is costing the government billions of dollars annually, putting a huge burden on the economic budget [1]. At the same time, it affects millions of people across the nation who suffer from allergic symptoms and even death threats. Therefore, it will be more and more significant for us to understand the mechanisms of food allergy and design appropriate treatments that can effectively prevent and even cure food allergy.

References

- [1] Ian R. Mackay, Fred S. Rosen. Allergy And Allergic Disease. The New England Journal of Medicine. Vol. 344 (2001) No. 1, p. 30-37.
- [2] Sara Anvari, Jennifer Miller, Chih-Yin Yeh, et al. IgE-Mediated Food Allergy. Clinical Reviews in Allergy and Immunology. Vol. 57 (2019), p. 244-260.
- [3] Wong Yu, Deborah M. Hussey Freeland, Kari C. Nadeau. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. Vol. 16 (2016) No. 12, p. 751-765.
- [4] Zhangguo Chen, Jing H. Wang. How the Signaling Crosstalk of B cell Receptor (BCR) and Co-Receptors Regulates Antibody Class Switch Recombination: A New Perspective of Checkpoints of BCR Signaling. Front. Immunol. Vol. 12 (2021).
- [5] Alba Azagra, Ester Marina-Zárate, Almudena R. Ramiro, et al. From Loops to Looks: Transcription Factors and Chromatin Organization Shaping Terminal B cell Differentiation. Trends in Immunology. Vol. 41 (2020) No. 1, p. 46-60.
- [6] Iwan G. A. Raza, Alexander J. Clarke. B Cell Metabolism and Autophagy in Autoimmunity. Front. Immunol. Vol. 12 (2021).
- [7] Christopher D.C. Allen. Features of B Cell Responses Relevant to Allergic Disease. J Immunol. (2022), p. 257-266.