



Review

Molecular mechanisms of IgE mediated food allergy

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ABSTRACT

The purpose of this review is to collate current knowledge and recent advances in molecular mechanism behind the immediate type hypersensitivity of foods. Food allergy is a growing concern of human health in developed as well as developing countries now days. Food allergic reactions are mostly IgE mediated and also known as immediate type hypersensitivity or type I reaction. This review encompasses a wide range of molecular events during IgE mediated reactions like primary exposure of allergens, processing of allergens by antigen presenting cells, role of transcription factors like GATA-3, STAT-6, NF-AT, c-maf, c-kit and NF- κ B, Treg cells, toll like receptors, cytokines and chemokines, class switch to IgE, Fc ϵ R1 receptor, priming of IgE on mast cells or basophils, signaling events followed by secondary exposure of allergens, degranulation and release of mediators like leukotrienes, histamines, prostaglandins, β -hexosaminidase and ultimately anaphylaxis. This review may be helpful to beginners as well as experts working in the field of allergy and immunology because of the stepwise explanations of molecular mechanisms involved in IgE mediated reactions.

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1. Introduction

Food allergy is an immune provocation by food in susceptible individuals that affects up to 6% of young children and 3%–4% of adults [1].

The prevalence of IgE-mediated food allergy is 5–8% among newborn and young children under the age of 5 years [2]. It covers a range of health complications like anaphylaxis, nasobronchial allergy, pollen food syndrome or oral allergy syndrome (OAS), food-protein-induced enterocolitis syndrome, food-induced proctocolitis, eosinophilic gastroenteropathies and atopic dermatitis [3–9]. The term “Big Eight” has been recognized for the eight most allergenic foods *i.e.*, peanut, soybeans, egg, milk, fish, seafood, wheat and tree nuts, which are responsible for the majority of food allergic reactions throughout the globe reported by the Food and Agriculture Organization (FAO) and the

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World Health Organization (WHO). The majority of food allergic reactions are mainly caused by immunoglobulin E (IgE) mediated hypersensitivity reactions [10]. The IgE mediated reactions or type I reactions are also known as immediate type hypersensitivity as it occurs within minutes to hours after the exposure of foods in susceptible individuals. However, food allergic reactions are not limited to IgE mediated reactions only as non-IgE mediated allergic reactions, IgG mediated reactions, both IgE and IgG mediated reactions or immune complex mediated responses may also occur. In non-IgE mediated responses, adverse reactions are mediated by an immune response other than IgE which has been reported in children with cow milk allergy (CMA) where allergic reactions are mediated by IgG [11]. Immune complex mediated reactions are jointly performed by IgE, IgG and IgA antibodies which are found rarely in asthma and eczema patients.

The IgE mediated responses are the easiest to diagnose among food allergy because of its high prevalence. Since, the majority of food allergic reactions are IgE mediated; molecular mechanisms behind these reactions need a thorough examination and explanation. This review is devoted to the recent developments in the area of molecular mechanism behind IgE mediated food allergic reactions.

2. Food allergens and their epitopes

Food allergens are usually food proteins capable of eliciting allergic symptoms in predisposed individuals, including severe, even life-threatening allergic reactions. These proteins are from our daily dietary intake and they are often difficult to avoid. These food allergens may be from plants or animal food sources [12]. In plant food the most abundant allergens are peanut (Ara h1, Ara h2 and Ara h3) followed by soybeans (soy alb-1 and soy alb) [13]. Common animal foods having allergenic proteins are eggs, cow's milk, shellfish and fish. The most abundant milk proteins are α S1-, α S2-, β -, and κ -caseins, α - and β -lactoglobulin [14]. Due to high protein contents legumes contribute a major proportion among allergenic foods [15–20].

Allergens are specific antigens having the capacity to elicit IgE mediated reactions. The allergenic proteins have certain site(s) which can recognize the specific antibody to provoke immune response called epitope. The epitopes are either linear or conformational. Knowledge about IgE epitopes is also useful for better understanding of the pathogenesis and tolerance induction of food allergy reactions.

3. Immunoglobulin E (IgE), mast cells and basophils in food allergy

The IgE, or immunoglobulin E, mainly associated with allergic reactions is one of the five immunoglobulins produced by the immune system [12]. The IgE antibodies are majorly found in the lungs, skin and mucous membranes. IgE antibody levels are often high in people suffering from allergic symptoms. They cause the body to react against foreign substances such as pollen, fungal spores, food allergens and animal dander. However, total IgE level exceeding 100 kU/L is highly suggestive of allergy in adults and in some people the level may go up to 2500 kU/L. Total IgE test in allergy has a good predictive value in children less than 3 years of age and may be used as a screening test in this group [21]. Due to the high impact of IgE in food allergy, the total and specific IgE are useful tool to diagnose allergic patients. Specific IgE value more than 0.35 kUA/L can be considered important regarding the prevalence of allergy due to any food [22].

Mast cells were first time identified by Paul Ehrlich in 1878 in human connective tissues on the basis of the metachromatic staining properties of their cytoplasmic granules [23]. Mast cells arise from pluripotent hematopoietic cells (CD34+, CD13+, and CD117+ cells) in the bone marrow and found at perivascular sites in tissues which directly get exposed to the environment and function as first line of defense and also known as innate or adaptive immune cells [24,25]. After activation mast cells release cytokines, chemokines, proteases, leukotrienes,

and bioactive polyamines [26]. Mast cells also possess high-affinity immunoglobulin (Ig) E receptors (Fc ϵ RI) that participate in the allergic reactions.

Basophils are another leukocyte type containing cytoplasmic granules that stain with basophilic dyes constituting less than 1% of peripheral blood contributing their similarity to mast cells, and also termed as circulating mast cells [27]. Like mast cells, basophils also possess high-affinity IgE receptors Fc ϵ RI [28]. Basophilic activation test is very common test for prediction of food allergy in susceptible patients [29].

4. Transcription factors: key regulators

Transcription factors are key molecules involved in the determination of Th1/Th2 balance. The shift toward Th2 determines allergic responses, while Th1 cytokines are supposed to suppress these reactions. Many important transcription factors like signal transducer and activator of transcription 6 (STAT6), trans-acting T-cell-specific transcription factor GATA-3, T-bet, NFAT, transcription factor Maf or c-maf, mast/stem cell growth factor receptor (SCFR) also known as proto-oncogene c-Kit and NF- κ B are actively involved in Th1/Th2 balance.

STAT-6 plays an important role in signal transduction pathway used by interleukin-4 (IL-4) and interleukin-13 (IL-13) as well as in class switch to IgE and Th2 cytokine production [30–32]. It has been reported that mice deficient in STAT6 show reduced IL-4-mediated functions [33]. STAT6 also regulates the production of Th2 cytokines through CD4+ as well as CD8+ T cells, which indicates its vital role in allergic reactions [34]. It has been reported that IL-13, having very similar biological activities to IL-4, can also account for the development of allergic response in the absence of IL-4 in the same pathway, using STAT6 activation [35].

The suppressor of cytokine signaling (SOCS) proteins, especially SOCS-2 regulates cytokines like IL-4 which is a major driver of allergic diseases [36]. Suppressor of cytokine signaling-1, an IL-4-inducible gene in macrophages has been recently identified but its functional role in mast cells and food allergy is yet to be explored [37].

GATA-3 is a trans-acting T-cell-specific transcription factor in humans encoded by the GATA3 gene [38]. The GATA-3 contains two GATA-type zinc fingers and regulates T cell development [39]. GATA-3 promotes the secretion of IL-4, IL-5, and IL-13 cytokines from activated Th2 cells [40]. It has been reported that GATA-3 along with T-bet plays an important role in the shift of Th2 or Th1 reactions [41]. The GATA-3/T-bet ratio is an important aspect while looking at Th2 shift or allergic manifestation.

Transcription factor musculoaponeurotic fibrosarcoma oncogene Maf (c-Maf or V-maf) is a transcription factor encoded by the MAF gene in human [42]. It has been reported that IL-4 gene transcription is critically regulated by c-Maf [43]. IL-4 is important in the food allergic reactions as it enhances the differentiation of naive CD4+ T cells into IL-4-producing Th2 cells. It has been shown that in c-maf $^{-/-}$ mice, CD4+ T cells had significantly reduced capacity of IL-4 production, while the levels of IL-13 and IgE were normal [44]. The direct correlation of IL-4 with c-maf gave a clue to use c-maf for diagnostic as well as therapeutic purpose.

Mast/stem cell growth factor receptor (SCFR, proto-oncogene c-Kit or tyrosine-protein kinase Kit or CD117) is encoded by the KIT gene in humans. The c-kit proto-oncogene produces the receptor for stem cell factor (CD117). Multiple transcript variants encoding different isoforms have been found for c-kit [45]. The Asp816Val is a well-characterized product of the c-kit proto-oncogene due to point mutation within exon 17. This is highly evident in the patients with mastocytosis [46]. These receptors activate mast cells for IgE-dependent activation, and improve the probability of anaphylaxis in patients with mastocytosis. The Asp816Val mutation opens a new dimension to our understanding regarding the susceptibility of any individual as it is associated with a history of anaphylaxis in the general population [47].

The nuclear factor of activated T cells (NFAT) transcription factors may play an important role in allergic events especially in the Ca^{++} signaling during the degranulation of mast cells. Its role in protein kinase C (PKC) activation has been revealed but complete exploration regarding its involvement in food allergy is yet to be done [48]. Regulation of expression of cytokines and other genes in eosinophils by subtypes of NFAT, like NFATp and NFATc has been reported but such studies regarding mast cells are still elusive [49]. The other sub types of NFAT i.e., NFATc1 and NFATc2 get accumulated in memory CD4^{+} T cells, indicating their roles in early activation following antigen attachment [50]. The above reports regarding the NFAT indicate its probable higher impact in food allergy.

Nuclear factor κB (NF- κB) together with STAT-6 plays an important role in the class switch to IgE. For class switching to IgE, CD40 and IL-4 are important factors. It has been reported that NF- κB also helps in the activation of co-stimulatory molecules CD40 and CD 154 while STAT-6 activates IL-4 binding to the high-affinity chain of the IL-4 receptor [51]. Several other transcription factors are involved in the IgE mediated reactions but their roles in food allergy are yet to be explored.

5. Role of T regulatory cells in food allergy induction

One of the primary sites for food allergic reactions is gut mucosa, which is a blend of several types of cells including regulatory T cells (Treg). Treg cells can be divided into three major subtypes, FoxP3 + Treg cells which are naturally occurring in thymus, Th3 and Tr1 cell subtypes are found in the peripheral blood and also known as adaptive Tregs. Naturally occurring Treg cells secrete both IL-10 and TGF- β , while Th3 and Th1 cells secrete IL-10 and TGF-beta respectively. Recent studies unravel the role of Treg as one of the important cells in the induction of oral tolerance as well as oral sensitizations [52]. Tolerance induction is a normal immune pathway carried out in the gut after exposure of allergens. The type of tolerance induced is dependent on the doses of allergen fed. Oral tolerance may develop either because of T cells anergy or induction of Treg cells [53]. The Treg cells are originated from the thymus and express the transcription factor forkhead box P3 (FoxP3) and are also referred as $\text{CD4}^{+}\text{CD25}^{+}\text{Foxp3}^{+}$ cells [54]. A mutation of FoxP3 in children has been found to induce high Th2 responses as well as high IgE levels which indicate that the higher the level of Treg cells, the lower the chance of food allergy [55]. The constitutive $\text{CD4}^{+}\text{CD25}^{+}$ regulatory T cells alleviate clinical signs of immediate type hypersensitivity to dietary food allergen by modulating the priming of allergen-specific T and B cell responses during oral sensitization and enhancing mast cell degranulation [56].

The role of CD28-B7 co-stimulation in allergen-induced cytokine release by bronchial mucosa from patients with moderately severe asthma revealed the importance of co-stimulatory molecules like CD80 and CD86 [57]. The CD28/CTLA-4-B7 signaling pathway has been found to involve in allergic sensitization as well as tolerance induction to orally administered peanut proteins. The T cells have CD28, while Treg have cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) as the counterpart of the CD28. The CD80 and CD86 are two subunits of B7 which is involved in the binding of CD28 to T cells and APCs. Recently, it has been reported that the CD80 is involved in the food tolerance and not CD86 [58]. Intranasal delivery of the cytoplasmic domain of CTLA-4 has been found to prevent allergic inflammation [59]. However, it has also been reported that CTLA-4 signaling is not crucial in preventing sensitization to food allergens, but it can be useful in the regulation of the intensity of a food allergy [60].

6. Role of toll-like receptor (TLRs) in food allergy

The role of commensal-mediated activation of toll-like receptors (TLRs) involved in the regulation of physiological and pathophysiological processes of the intestinal mucosa [61]. Recent studies have added a new dimension to probable role of TLRs in food allergy. It has been found that TLRs are involved in some of the food allergic

reactions. The TLR4-dependent signals provided by the intestinal commensal flora inhibit the development of allergic responses to food allergens [62]. The increased TLR4 cells and their correlation with TCR gamma delta intraepithelial lymphocytes suggest its role in the innate immunity and intestinal microbiota in food induced allergic reactions [63]. The TLR signals modulate peanut-induced DC maturation *in vitro*, leading to changes in the T-cell response to peanut. But, effects of TLRs need to be confirmed *in vivo* which might constitute another alternative for diagnostics as well as therapeutics. An increased rather than decreased perinatal TLR response has been shown to be associated with allergic diseases [64,65]. Further studies are needed to determine how these responses track in the postnatal period and whether this relative hyper responsiveness is a product of intrauterine influences, including maternal atopy, functional genetic polymorphisms, or both. The nature of the influence is highly antigen and strain dependent in the T-cell responses and anaphylaxis severity linked with TLR-4 [66]. But, several studies raised question over the involvement of TLRs in food allergy as in the Italian cohort, no evidence of correlation between TLR-2 or TLR-4 polymorphism and eczema or food allergy incidence was found [67]. Further studies are needed to clarify the possible role of different TLRs in food induced allergic diseases.

7. Exposures of allergen and allergic reaction

7.1. Primary exposure of allergens

Allergens have enzymatic or irritating factor that helps them to penetrate the mucosa. After primary exposure, food allergens are captured by antigen presenting cells especially dendritic cells (DCs) of lamina propria in intestine [68]. The allergens are internalized by DCs due to receptor-mediated endocytosis process, macropinocytosis, or phagocytosis or by incorporation of microvesicles shed from the surface of neighboring cells, and by their interaction with nanovesicles or exosomes with a size less than 100 nm [69]. The allergens are detected by ubiquitin, a 76-residue protein that is highly conserved in all eukaryotes. This is present within the cytosol of DCs. The selective attachment of ubiquitin to allergens is the initial signal for targeted protein degradation [70]. These ubiquitinated allergens move to proteasomal complex and ultimately get degraded to peptide fragments [71]. The degraded peptide fragments are presented by major histocompatibility complex class-II (MHC-II) and recognized by naïve CD4^{+} T cells. The T helper cells or CD4^{+} T cells, have been divided into two broad classes Th1 and Th2, basically classified on the type of cytokines they produce. These CD4^{+} T cells differentiate into Th2 cells especially in the presence of adequate amount of IL-4 [72]. The differentiated Th2 cells secrete cytokines IL-4 and IL-13 which induce class switching to IgE. The class switching of immunoglobulin is a biological phenomenon that changes a B cell's production of antibody from one class to another (Fig. 1). Class switching causes change in the constant region portion of the antibody heavy chain, but the variable region of the heavy chain stays the same, which does not affect antigen specificity [73]. The B cell activation signal and class switching to IgE are mainly induced by IL-4 and IL-13 (signal 1) and interaction of CD40 on B cells and CD40-ligand (signal 2) on Th2 cells. Both these signals transduce their signal by activation of the Janus family tyrosine kinases JAK1 and JAK3 which ultimately lead to phosphorylation of the transcriptional regulator STAT-6 [74]. It has been reported that mice lacking functional IL-4, IL-13, or STAT6 showed impaired $\text{T}_{\text{H}2}$ responses and IgE class switching [75]. Th1 cytokine IFN- γ was found to inhibit these events. Patient with the X-linked hyper IgM syndrome have a deficiency of CD40 ligand, a condition in which patients are unable to produce IgG, IgA or IgE [76].

After activation by allergens, the subset of CD4^{+} T-lymphocytes produces a spectrum of cytokines like IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 that cause induction of serum IgE levels and eosinophils, which, in turn, mediate the clinical symptoms [77–79]. The abundance of IL-4- and IL-5-producing cells in bronchial biopsies and in the periphery

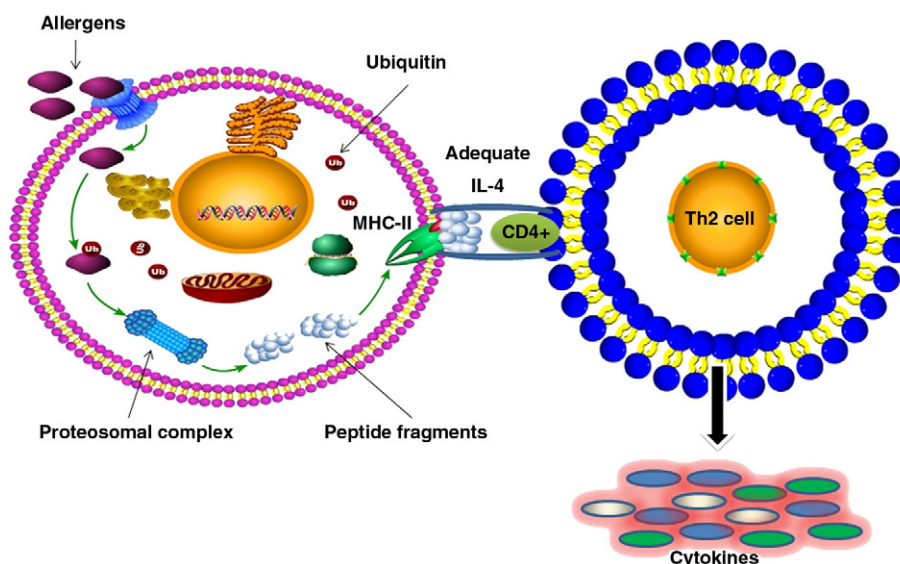


Fig. 1. Primary exposure of allergens: production of cytokines by allergen specific T-cells.

of atopic individuals with specific IgE for common environmental aeroallergens illustrates the involvement of this functional subset of CD4⁺ T cells in allergic diseases [80]. Chronic exposure of the patients with food allergy to a given food allergen induces the levels of IL-4 and IL-5. The 27.85 pg/ml mean serum IL-4 level has been reported in atopic patients while 13.26 pg/ml in non-atopic subjects with chronic gastritis and 4.3 pg/ml in patients with functional dyspepsia. The level of serum IL-5 has been reported within a range from 0 to 111.3 pg/ml with a mean value of 7.43 pg/ml in allergic patients [81]. To find out the role of IL-4 in food allergy, IL-4 deficient BALB/c mice were sensitized and challenged with ovalbumin. These mice have shown impaired class switching due to IL-4 deficiency [82]. Another pathway involving IL-13 has been reported in peanut-induced allergy which is mediated through a mast cell-IgE-FcεRI-IL-13 pathway [83]. IL-13 may also induce esophageal remodeling by an eosinophil-independent, IL-13 α-2 inhibited pathway [84]. Recently discovered IL-17 has also been found to be involved in food allergy and the subtype IL-17E but not IL-17A is associated with allergic sensitization. The IL-17A is involved in inflammation and IL-17E is able to induce Th2 cytokine production and eosinophils counts [85]. The thymic stromal lymphopoietin (TSLP) polymorphisms have been reported to be associated with the development of multiple allergic disorders in humans, indicating the involvement of TSLP in the regulation of Th2 cytokine-associated inflammatory diseases and in the activation of the development and maturation of early-stage basophils in the bone marrow [86]. The interferon-γ, a Th1 cytokine, acts in conjunction with Th2 cytokines like IL-4, IL-13, and IL-5 in maintaining chronic allergic inflammation [87].

The IgE immunoglobulin attaches with FcεRI (Fragment, crystallizable epsilon region R1) of mast cells or basophil cells (Fig. 2). FcεRI is an IgE receptor in human and is composed of four subunits α, β, γ1 and γ2 [88]. The α and β subunits are found to be involved in attachment of IgE, while γ1 and γ2 are involved in phosphorylation process. The FcεRI is found on epidermal Langerhans cells, eosinophils, mast cells and basophils, due to its cellular distribution on several cell types.

7.2. Secondary exposure of allergens

Immunoglobulin (Ig) E and its cell surface receptors, the high affinity receptor FcεRI and the low affinity receptor FcεRII (CD23), are key components of immediate-type allergic reactions [89]. IgE activates the allergic cascade effectively via the high affinity receptor, FcεRI, on blood- and tissue cells. As a member of the immunoglobulin receptor superfamily, FcεRI consists of a ligand-binding immunoglobulin

domain-containing protein (α-chain) which binds the Fc-part of IgE and signaling subunits that regulate cellular activation (β- and γ-chains) [90]. Humans express a tetrameric FcεRI (FcεRIαβγ2) on mast cells and basophils and a trimeric form (FcεRIαγ2) on antigen presenting cells [91]. The FcεRI expression is regulated by IgE since binding of monomeric IgE to FcεRIα stabilizes the receptor at the cell surface as an IgE–FcεRI complex [92,93]. After the allergen–IgE–FcεRI complex formation, immunoreceptor tyrosine activation motifs (ITAMs) of FcεRI play a very critical role in mast cell signaling [94,95]. In food allergy, a non-intrinsic tyrosine kinase pathway occurs, which is different from the intrinsic tyrosine signaling pathway. ITAMs are responsible for initiation of signaling events due to the presence of specific tyrosine residue sequence, which has the capability to get phosphorylated after cross-linking of allergens on IgE–FcεRI complex. These activated ITAMs can provide docking sites to several molecules of Src kinases family including Lyn and Syk and probably Fyn [96–98]. The role of other Src kinases in food allergy is yet to be explored. The phosphorylation of these Src kinases molecules may lead to induction of either linker of T cell activation (LAT) or linker of non-T-cell activation or both; but the best answer is still awaited. These activation linkers may open the site for involvement of several molecules including SLP76, Grb2, Vav, Gads, Sos, PLCγ, PI3K and GNEF in allergen induced mast cell signaling, although a thorough explanation is still required to explain their critical functions in food allergy [99–101]. DAG and IP3 molecules are found to be induced by PLCγ and PI3K that cause Ca⁺⁺ release from intracellular repository

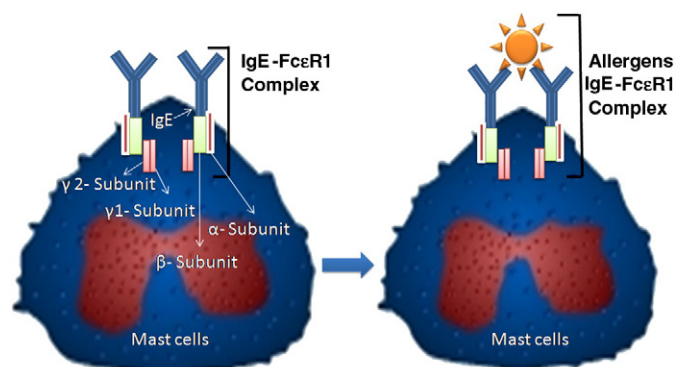


Fig. 2. Priming of IgE on mast cells.

including endoplasmic reticulum, which ultimately leads to mast cell degranulation [102]. The Hck, a tyrosine kinase has been reported to show positive regulation of mast cell degranulation by inhibition of Lyn and by phosphorylation of FcεRI [103]. A brief outline of probable mechanistic pathway that occurs during allergen induced mast cell degranulation is given in Fig. 3.

7.3. Mediators release and symptoms

Prostaglandins, cytokines, leukotrienes, histamine, slow reacting substance of anaphylaxis (SRS-A), heparin, platelet-activation factor (PAF), eosinophil chemotactic factor of anaphylaxis, proteolytic enzymes and other mediators are secreted by degranulated mast cells or basophils [12]. These mediators may cause smooth muscle dilation, capillary disruption, local swelling and other allergic symptoms. In some individuals, these reactions may occur very vigorously leading to anaphylaxis or sometimes death.

Histamine acts on histamine 1 (H1) and histamine 2 (H2) receptors to cause contraction of smooth muscles of the airway and gastrointestinal (GI) tract, increases vasopermeability and vasodilation, enhances mucus production, pruritus, cutaneous vasodilation, and gastric acid secretion [104]. Tryptase is a major protease released by mast cells, though its exact role is uncertain, but it can cleave complement pathway components namely C3, C3a as well as C5 [105]. Tryptase is found in all human mast cells and some other cells and is a good marker of mast cell activation. Proteoglycans include heparin and chondroitin sulfate. Though, the role of the latter is unknown, heparin seems to be important in storing the preformed proteases and may play a role in the production of α -tryptase [106,107]. An eosinophilic chemotactic factor of anaphylaxis causes eosinophil chemotaxis while an inflammatory factor of anaphylaxis results in neutrophil chemotaxis. Eosinophils release eosinophil major basic protein (EMBP) and, together with the activity of neutrophils, can cause significant tissue damage in the later phases of allergic reactions. Degranulation fluids also contain IL-4 that stimulates and maintains Th2 cell proliferation and switches B cells to IgE synthesis [108]. The IL-5 is a key molecule in the maturation, chemotaxis, activation, and survival of eosinophils. The IL-5 primes basophils for histamine and leukotriene release while IL-6 promotes mucus production. The IL-13 cytokine has many of the same effects as IL-4. Tumor necrosis factor- α activates neutrophils, increases

monocyte chemotaxis, and enhances production of other cytokines by T cells [109].

8. Molecular mechanisms for activation of innate immunity by food allergens

Along with acquired immunity, the role of innate immunity has been also important in food allergy. The innate immunity involved in food allergy encompasses several cells and their receptors including DCs, epithelial cells, basophils, nuocytes, NK cells and TLRs. Allergens can directly interact with DCs through pattern recognition receptors [110]. Epithelial cells play a vital role as they have sites of allergen entry into the body and also have close interaction with DCs *in situ*. Epithelial cells secrete TSLP, a cytokine after exposure of allergens which stimulates DCs to produce the Th2 cell-attracting chemokines and cytokines. Due to its adjuvant like properties, it is also referred as natural adjuvant [111]. The role of basophil is not limited to acting as an effector cells and degranulation during food allergy, but it can also act as APCs in the induction of Th2 responses, which have been evident in papain and ovalbumin [112]. The invariant natural killer T (iNKT) cells have also been reported to be involved in food allergy but, limited to the allergens with sphingolipids nature. The iNKT cells have found to proliferate and secrete Th2-type cytokine secretion after allergen exposure [113]. The nuocytes or natural helper cells or innate immune cells initially discovered in mice have been found to be engaged in allergic reactions *via* induction of Th2 responses. These cells are stimulated by IL-25 and IL-33. The stimulated nuocyte secretes cytokines IL-5 and IL-13 [114]. The role of TLRs in the food allergy has also been gaining acceptance and has been discussed in Section 6.

9. Molecular therapeutics of food allergy

At present, there are no recognized treatments for food allergies, and avoidance of allergic foods by susceptible individuals is the only preventive approach. Efforts have been made on several key molecules like IgE, cytokines and Tregs involved in allergic reactions as therapeutic target to find out solution of this global health concern.

As IgE is the major player in immediate type I food allergic reactions, a humanized anti-IgE monoclonal antibody was prepared which could bind FcεRI receptor of mast cells and block the receptor sites for other

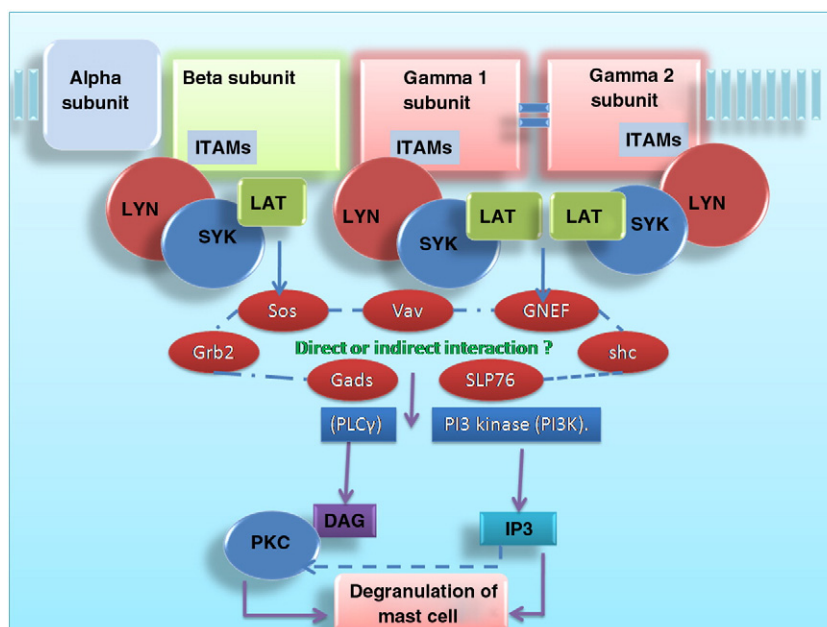


Fig. 3. Signaling in basophil and mast cells.

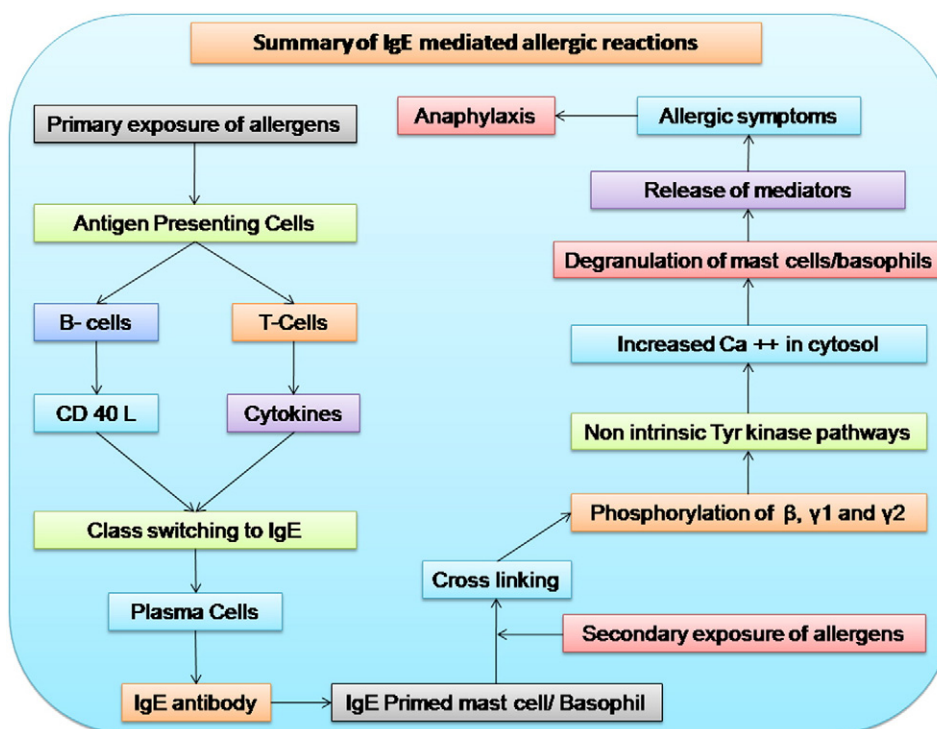


Fig. 4. Summary.

IgE and ultimately stop the allergic reactions. The example of humanized anti-IgE monoclonal antibody is omalizumab which is used in allergic asthma treatment. Anti-IgE therapy has been found to be helpful in reducing the concentration of circulating free IgE, blocking IgE binding to both FcεRI and CD23, and also down regulating the surface FcεRI on mast cells, and basophils [115].

Being key cytokines in food allergic reactions, IL-4 and IL-13 are hot choices for researchers as therapeutic tools [116]. It has been reported that production of IL-12 by Peyer patch-dendritic cells is critical for the resistance to food allergy. Therefore, by delivering an allergen in the presence of IL-12, allergic reactions could be controlled [117]. Several studies are going on in this regard but, a fruitful outcome is yet to be reality.

Treg can be used in the elevation of oral tolerance limit and reduction of sensitization to food allergy. Overcoming food allergy through acquired tolerance conferred by transfer of Tregs in a murine model has been reported but, how feasible this approach will be in humans is yet to be explored [118].

10. Conclusions

An outline of all the events encountered during the food induced allergic reactions is given in Fig. 4. The TLRs, nuocytes, CTLA-4 and other molecules need extra attention to clarify their basic mechanisms in this disease. Food allergy is a complex story, which is yet to be unraveled completely. Proper understanding of exact molecular mechanism behind its prevalence is highly required to find out an efficient therapeutic approach to combat the food allergy.

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