



Review

A molecular insight of CTLA-4 in food allergy

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ABSTRACT

Food allergy is an immune provocation induced by certain food in susceptible individuals. Most of the food allergic manifestations are evident in the individual having impaired oral tolerance. In spite of worldwide prevalence, there is no permanent cure of food allergy. Food allergic reactions are complex immunological events that comprises of several immune molecules like IgE, IL-4, IL-13 and T-cells, therefore, researchers are trying to pick the correct molecule to find out pivotal therapeutic solutions. Being a key regulatory molecule in suppressing T-cells functional activities, cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) or cluster of differentiation-152 (CD-152) has contributed a novel and revolutionary dimension toward therapeutic research of several diseases. This review focuses on different immunological and mechanistic perspectives of CTLA-4 in correlation with food allergy.

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1. Introduction

Food allergic reactions are immunological disorders induced by certain food(s) in susceptible individuals. The prevalence of such reactions is encompassing several countries throughout the world. In western countries, the prevalence of food allergy is reported in 5% of children and 3–4% of adult's populations [1]. The susceptibility of any individual is determined by several factors, including genetic predisposition, dietary habits and environmental set up. But, the most appropriate answer behind the cause of food allergy is still awaited. In the susceptible individuals the impaired oral tolerance has been reported to play very important role [2]. These factors have been found to involve in induction of impaired oral tolerance and allergic sensitization to foods. The oral tolerance is a natural weapon against dietary antigens which suppress the antigen induced allergic reactions. Most of the food allergic reactions are induced by IgE mediated immediate type hypersensitivity or type I reaction, which occur within minutes to hour after food intake [3]. Along with type I reaction, late phase and non IgE mediated allergic reactions have also been reported in food allergy [4]. Due to genetic link up food allergic reactions are also referred as atopic reaction e.g., atopic dermatitis caused by egg, wheat, milk, and soy [5]. The health complications induced by allergic foods have a wide range including allergic rhinitis, bronchial asthma, atopic dermatitis and gastrointestinal disorders induced by foods like peanut, soybeans, kidney beans, red grams, green grams, eggs, and fishes,

oral allergy syndrome (OAS) induced by cherry and other foods, eosinophilic esophagitis induced corn, soy, and wheat, edema of the uvula induced by seafood, by hazelnuts, and walnuts. Recurrent aphthous stomatitis (RAS) is one of the most common oral lesions induced by milk, gluten, and other allergens, food protein-induced enterocolitis syndrome (FPIES) induced by rice and neonatal diarrhea induced by milk, soy, and grains [6]. Some time the allergic reactions occur with a high severity which may lead to a fatal outcome. These reactions are known as anaphylaxis reactions. In USA, approximately 30,000 patients come to emergency ward of the hospitals for treatment of food induced anaphylaxis. Further, about 200 food allergic patients have been reported to die due to aforesaid symptoms [7].

Food allergy is a major and increasing medical problem; however, our understanding of the immunological mechanisms of the disease is limited. Given the significant prevalence of food allergies in the recent years, in western and developing countries, therapeutic alternative to exclusion diets are strongly required. The researchers in this regimen are trying hard to find an effective and safer therapeutic option. Recent years have been very productive in foods allergic researches including immunopathogenesis of many allergic disorders, epitope mapping and its therapeutic exploitations, anti-IgE therapy and allergen-specific immunotherapy. But, still the several aspects are lacking of any pivotal therapeutic tool to combat food allergy completely. To date, avoidance of the food causing allergic manifestation in susceptible individuals is most common suggestion by clinicians. Some molecules like anti IgE, IL-4, and regulatory cells (Treg) have been considered as a potential tool for allergy treatment induced by food, but still such studies are not in their fruitful shape. In this review, an attempt has been made to highlight the functional aspects of cytotoxic T-cell lymphocyte

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antigen-4 (CTLA-4) or cluster of differentiation-152 (CD-152) in tolerance to food allergens as well as in allergic reactions and thereafter possibility of CTLA-4 as a potential target for treatment of food allergic manifestations.

2. Cytotoxic T-cell Lymphocyte Antigen-4 (CTLA-4)

There are several regulatory molecules capable to modulate different signals and maintaining homeostasis. One of such molecules is CTLA-4 or CD-152 which can transmit a negative signal to T-cells and change the fate of immune reactions. It belongs to the immunoglobulin super family and expressed on the surface of Th cells [8]. CTLA-4 may reverse the classical T-cell receptor (TCR) induced stop signal needed for appropriate interaction between T-cells and antigen presenting cells (APC) like macrophages, dendritic cells (DC) and B-cells [9]. CTLA-4 possesses similar structural properties like cluster of differentiation 28 (CD 28) and shares about 30% of the amino acid sequences [10]. The CD28 has been reported to be present within the outer membrane of T-cells. Three major structural subunits have been reported in CTLA-4 that includes an extracellular V domain, a trans-membrane domain, and a cytoplasmic tail [11]. Similar to CD28, CTLA-4 intracellular V domain has no intrinsic catalytic activity but, the YVKM motif of V domain can bind to phosphoinositide 3-kinase (PI3K), protein phosphatase 2 (PP2A) and protein-tyrosine phosphatase-2 (SHP-2) and protein-tyrosine phosphatase-3 (SHP-3) molecules [10]. The T-cell inhibition by CTLA-4 is mainly dependent on dephosphorylation of TCR proximal signaling proteins like linker for activation of T cells (LAT) and cluster of differentiation 3 (CD3) [12]. Further, T-cells signaling have been reported to get affected by CTLA-4 indirectly as it can compete with CD28 for CD86 binding [9]. The CD80 (B7-1) and CD86 (B7-2) are two subunits of B7 present on the outer membrane of APCs. The comparatively higher binding affinity of CTLA-4 to CD86 over CD28 has made it a potential therapy candidate for several diseases including food allergy [13]. Food allergic sensitization is induced by Th1 or Th2 or both, driven processes, and CTLA-4 may play a major role in suppressing sensitization or induction of oral tolerance [14]. The involvement of CTLA-4 in food allergy has opened a new dimension in food allergy research due to its high impact in the T-cells activity suppression [15,16]. The genomic regions of *CTLA-4* genes including chromosome 2q33 have been found to be associated with the development of allergy. *CTLA-4* gene polymorphisms are responsible in determination of the Th1 and Th2 balance [17]. The CTLA-4 is present within the regulatory T-cells (Treg), which is found to be involved in induction of oral tolerance and suppression of food allergy. Therefore, it is required to reveal the functional aspects of CTLA-4 in food allergy up to maximum extents, so that its role can be explored completely.

3. Regulatory T-Cells (Treg)

Treg cells are essential category of T-cells for maintaining immunological self-tolerance and immunological homeostasis in the body. In the thymus, two types of cell population generated by induction of transcription factor FOXP3, a member of the fork head-winged helix family [18]. The first cell population is FOXP3 positive (FOXP3+) while the second is FOXP3 negative (FOXP3-). The FOXP3- cells population, when reaches to peripheral system can be divided into several T-cells subtypes including Tr1, Th1, Th2, Th3 and Th17 while the FOXP3+ cell population can be further divided into natural Treg (nTreg) and induced Treg (iTreg) [19]. A diagrammatic representation for origin of Treg cells and its function is depicted in Fig. 1. The Treg-specific demethylated region, (TSDR) is a molecule used for characterization of Treg with stable FOXP3 expression. Hinz et al. [20] have carried out an experiment to

understand the fetal Treg development using this TSDR expression which indicated that both genetic and environmental set up presumably influence the development of fetal Treg cells. Further, it was elucidated that low cord blood Treg numbers may be used as a diagnostic tool for prediction of atopic dermatitis in early days of life [20]. The Treg has been reported to inhibit mast cell degranulation and anaphylaxis reactions, along with increase in secretion of IL-6 via TGF- β production [21]. Considering functional activities of FOXP3+ derived Tregs, these cell populations can be divided into two categories where, the first category primarily target T-cells and secrete suppressor cytokines, consume IL-2 and involved in cytotoxicity. The second category primarily target APCs and decrease co-stimulation and antigen presentation [22]. The CTLA-4 has been reported as an essential component for the function of nTreg cells [23]. In adults, a majority of FOXP3+ Treg expresses CTLA-4 and FOXP3+ or CTLA-4+ Treg, which may modulate CD4+ T cell activation and homing receptor expression in children [24]. Regarding the Treg cells it was reported by Duhon et al. [25] that the co localization of distinct populations of Treg cells in human blood with different Th cell subsets is mainly based on chemokine receptor expression. Although, each population has a functionally suppressive role, they may display unique patterns of pro- and anti-inflammatory cytokine production. Further, distinct populations of Treg cells can differentially express lineage-specifying transcription factors, and respond differently to antigens associated with Th1 and Th17 responses [25]. The existence of CTLA-4 with Treg is well established and it has been proved that in the absence of CTLA-4 hyper production of IgE, impaired in vivo and in vitro suppression in function of Treg cells, and down-regulation of CD80 and CD86 expression on DCs occurs [26]. CTLA-4 are known to be involved in all the three characteristic of Treg cells i.e., suppression, TCR hyposignaling, and T-cells anergy. The Treg suppression and T-cells anergy is performed by CTLA-4 external domain while TCR hyposignaling is controlled by CTLA-4 internal domain [27]. It has been reported that bacterial strain-specific induction of Foxp3+ Treg in vivo is related with protection from respiratory and oral allergic manifestations. The aforesaid study was carried out by Lyons et al. [28], which suggest the possibility of correlation of toll like receptors (TLRs) with Treg and thereafter with CTLA-4 [28].

4. Toll like receptors (TLRs) and CTLA-4

The involvement of innate immune system including DCs, epithelial cells, basophils, neutrophils, natural killer cells (NK cells) and TLRs have been reported in food allergic reactions [29]. The commensally-mediated activation of TLRs is involved in the regulation of food allergy in the intestinal mucosa [30]. Out of several types of TLRs, TLR4-dependent signals provided by commensal flora may inhibit development of peanut allergy responses by induction of food hypo responsiveness or oral tolerance [31]. It has been reported in allergy model that the TLR signals can modulate food-induced DC maturation in vitro, leading to changes in the T-cell response [32]. Recent studies explored the fact that Treg cells along with intestinal microflora may play an important role in regulation of allergic inflammation. The Treg cells markers Foxp3+, and bacterial signaling markers such as TLR-2 and TLR-4, in the duodenal mucosa of patients with food allergy has been studied by Westerholm-Ormio et al. [33] using single and double immunohistochemistry to elucidate the densities of Foxp3+ cells and TLR-2 and TLR-4 positive cells in the mucosa. Further, co localization of Foxp3 expression in CD4, CD25, and CTLA-4 cells has also been evaluated to explore the interaction between these cells. Considering aforesaid study, the increase of TLR4 cells and their correlation with TCR $\gamma\delta$ intraepithelial lymphocytes suggest a pivotal role of the innate immunity and intestinal microbiota in food

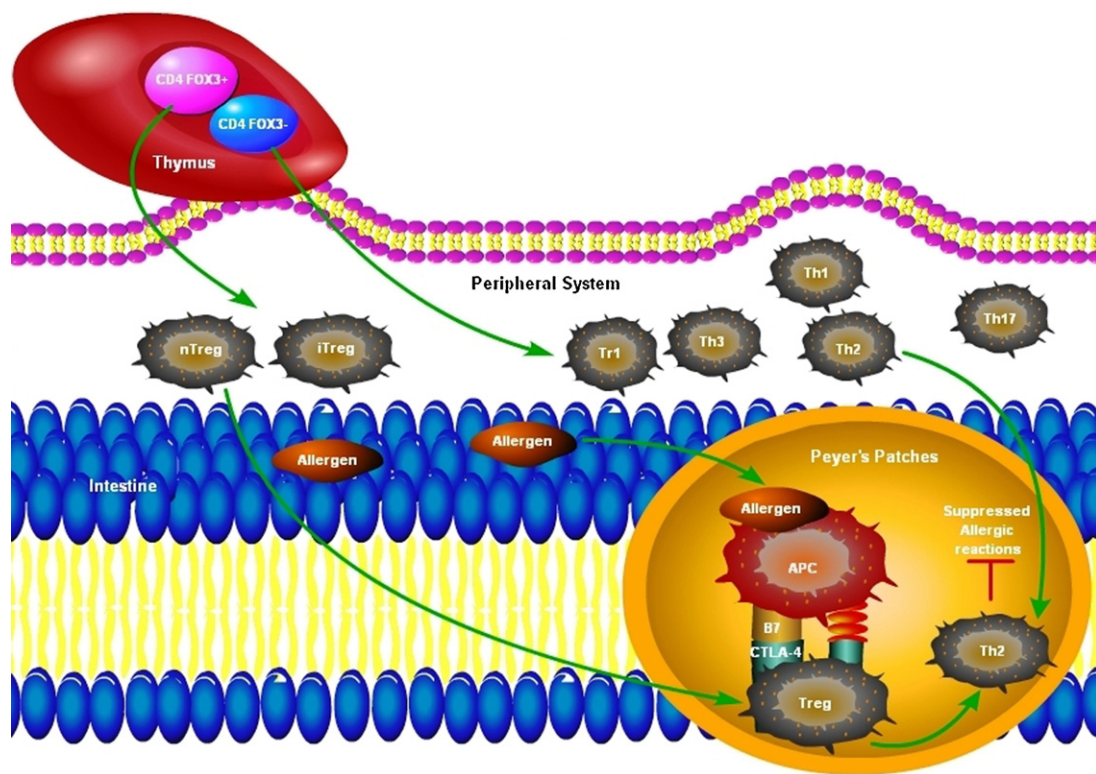


Fig. 1. A diagrammatic representation of origin of different subtypes of T-cells. The FOXP3⁺ cells population divided into Tr1, Th1, Th2, Th3 and Th17 in the peripheral system while the FOXP3⁺ cell population is divided into natural Treg (nTreg) and induced (iTreg). These Treg have ability to suppress allergic reactions and induce oral tolerance.

allergy [33]. A study has been carried out by Prescott et al. [38] to explore the association between neonatal TLR microbial recognition, function, allergy risk (maternal allergy), and prospective allergy development and it was found that maternal allergy was associated with significantly higher neonatal IL-12 and IFN- γ responses to TLR2, TLR3, and TLR4 activation, whereas TNF- α and IL-6 responses to TLR2, TLR4, and TLR5 activation were significantly higher in newborns that subsequently had allergic disease [34]. It has been reported that although, TLR4 status can influence T-cell responses and anaphylaxis severity, the nature of the influence is highly antigen- and strain-dependent [35]. Intestinal commensal bacteria promote T-cell hypo-responsiveness and down-regulate serum immunoglobulin's responses induced by food allergens through immunomodulation of the intestinal and systemic T-cell phenotype [36]. To find out the role of microbial signals in the pathogenesis of Foxp3 deficiency related diseases has been studied in Foxp3 mutant mice, which showed concurrent deficiencies in TLR signaling pathways [37].

5. Food allergens, allergen specific and non specific IgE

In food allergic manifestations the whole food is not responsible for immune provocation, but there are certain proteins which can elicit these reactions. These proteins are known as allergen or dietary antigens. Allergen possesses sequences of amino acid responsible for interaction with IgE [38]. Such sequences are known as epitopes. The epitopes can be of two types either linear or conformational based on the structure of allergens. So far, several allergens have been identified from peanut (e.g., Ara h1 and Ara h2), soybeans (e.g., Gly mBD), cow milk proteins (e.g., casein), green gram (e.g., Vig r1 and Vig r4), and kidney beans (e.g., Pha v3) and several other foods [39].

The IgE immunoglobulin is the most important immunoglobulin encountered during food allergic reactions. Based on the

stimuli received, two types of IgE can be produced in host system either nonspecific or specific to certain allergen. In case of non specific IgE production, a common stimulus to mast cells, eosinophils, basophils, T- $\gamma\delta$ -cells and cytotoxic T (Tc)-cells in presence of interleukin 4/13 (IL-4/IL-13) and CD 40 L can induce class switch to IgE in B-cells [3]. The resulted IgE are non specific in nature and possess a lesser potential as compared to that of specific IgE as depicted in Fig. 2a. Production of allergen specific IgE is a systematic and co-ordinated procedure. Following allergens exposure, Th2 cells secrete cytokines, likes IL-4, IL-5 or IL-13 [40]. In presence of CD40L and Th2 cytokines class switch to IgE take place in B-cell that results in production of allergen specific IgE [41]. Specific IgE has tremendous potential to fight against the source allergens and that is why it is implicated in the diagnostic and therapeutic aspects. The production of allergen specific IgE has been depicted in Fig. 2b. Presence of CTLA-4 can hamper the natural trend of class switching to IgE in B-cells by binding to B7 molecules as depicted in Fig. 2c. Along with IgE, the other immunoglobulins like IgG1 and IgG2a may also play important roles in food allergic reactions and production of IgE. Mice deficient in both B7-1 and B7-2 failed to generate antigen-specific IgG1 and IgG2a, indicating the role of B7 mediated signaling pathway as well as involvement of CTLA-4 molecule [42]. It has also been demonstrated in CD28-deficient mice that the basal levels of IgG1 and IgG2a has been reduced due to class switching that supports the fact that CD28/B7-1(CD80) ligand pairing might also be involved in human IgE regulation [43].

6. Mechanism of oral tolerance

Food allergy is induced by dietary antigens and most favorite place for reaction is mucosal immune system. This immune system generally exists in a state of active tolerance to dietary antigens and bacterial system. The oral tolerance to dietary antigens is induced due to participation of mucosal DCs and thereafter by Treg cells. The

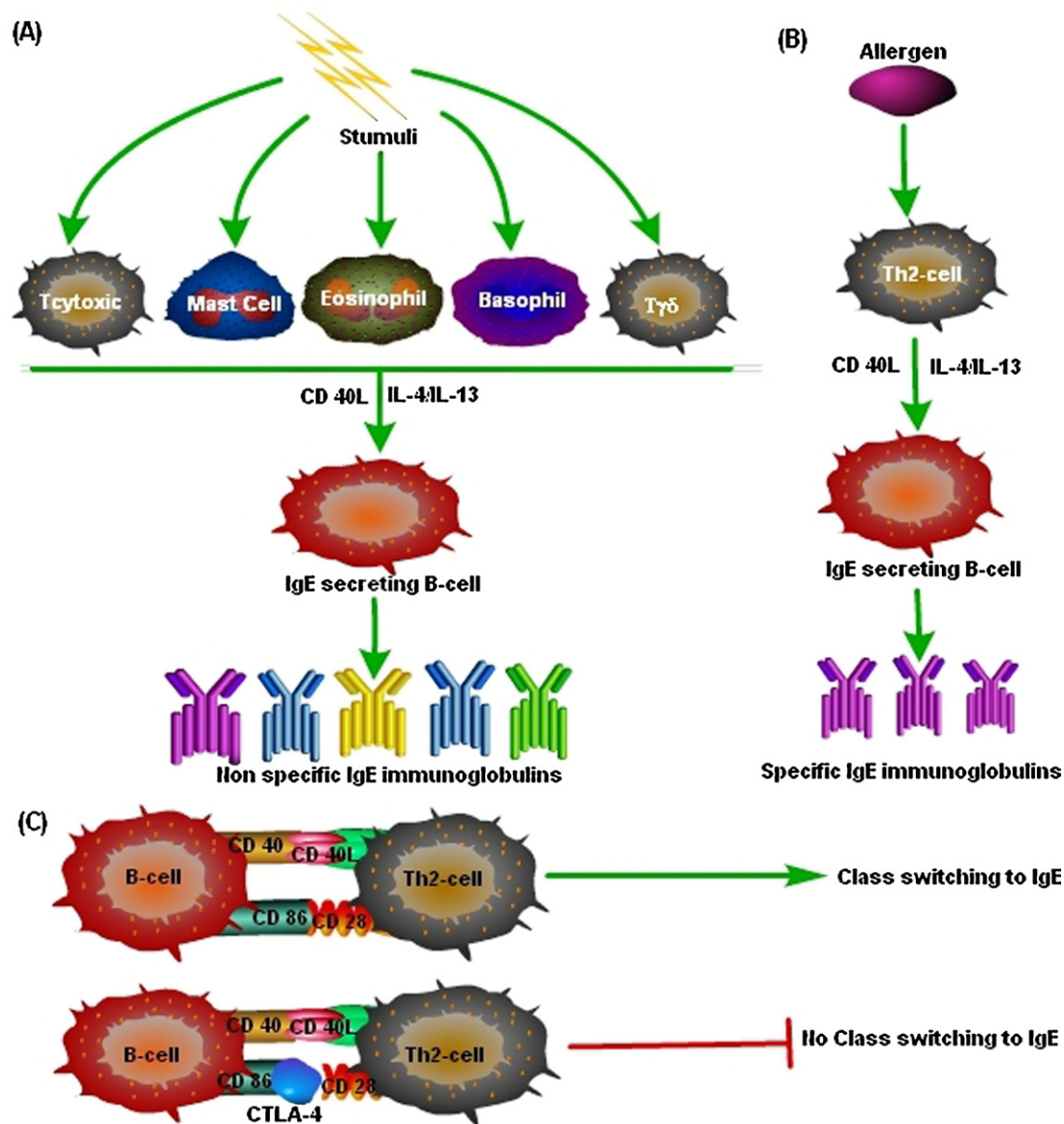


Fig. 2. A schematic diagram of formation of IgE. (A) Formation of non-specific IgE can be induced by a common stimulus in mast cells, B-cells, eosinophils, basophils, T cytotoxic (Tc) and T gamma delta (Tγδ) cells. (B) Formation of specific IgE takes place after allergen exposure that leads to induction of Th2 cells and secretion of IL-4 and IL-13. (C) CTLA-4 may lead to modulation in class switching to IgE.

prevalence of food allergy is related to the condition when immune tolerance is disrupted and a sensitizing immune response by food-specific IgE production occurs instead [44]. Oral tolerance is the state of local and systemic immune hypo- or unresponsiveness that is induced by oral administration of innocuous antigen such as food proteins. These preventive immune mechanisms are very similar to a local process that regulates responses to commensal bacteria in the large intestine and, together, mucosally induced tolerance appears to prevent intestinal disorders such as food allergy, celiac disease, and inflammatory bowel diseases [45]. Tolerance induction for food allergy (TIFA), a preventive method based on the oral tolerance property has been used as positive and radical treatment approach of food allergy. The process of oral tolerance is mediated by several immune components including cytokines like IL-10, TGF-β and IFN-γ and regulatory cells such as Treg and regulatory B-cells (Breg). Now a day, studies are going on to use IFN-γ, as an immunomodulatory biologics for tolerance induction against food allergy [46]. This tolerance response must be inhibited or bypassed to generate allergic sensitization in experimental food allergy and

this has been achieved by three main approaches first, genetic modifications, second, experimental adjuvants, and third, bypassing oral tolerance by administering the antigen through alternative routes [47]. The DCs play an essential role in regulating the balance between sensitization and oral tolerance responses to food allergens in gut mucosa. The DCs can perform these functions by controlling T-cells differentiation and activation mediated by CD28 and CTLA-4 molecules. The CD28/CTLA-4-B7 signaling pathway play influential role during the regulation of T-cell responses [48].

In non susceptible individuals, normal dietary proteins induce oral tolerance in gut mucosa as part of an active suppression of immune response induced by dietary antigens or allergens. In susceptible individuals to food allergy, impairment in oral tolerance has been well studied [49]. After having foods, it moves to stomach, where its protein contents get completely or partially digested by pepsin. Digested and partially digested proteins move to intestine where further degradation of these proteins takes place by intestinal proteolytic enzymes. Some proteins can get digested and absorbed completely, while some partially degraded proteins can

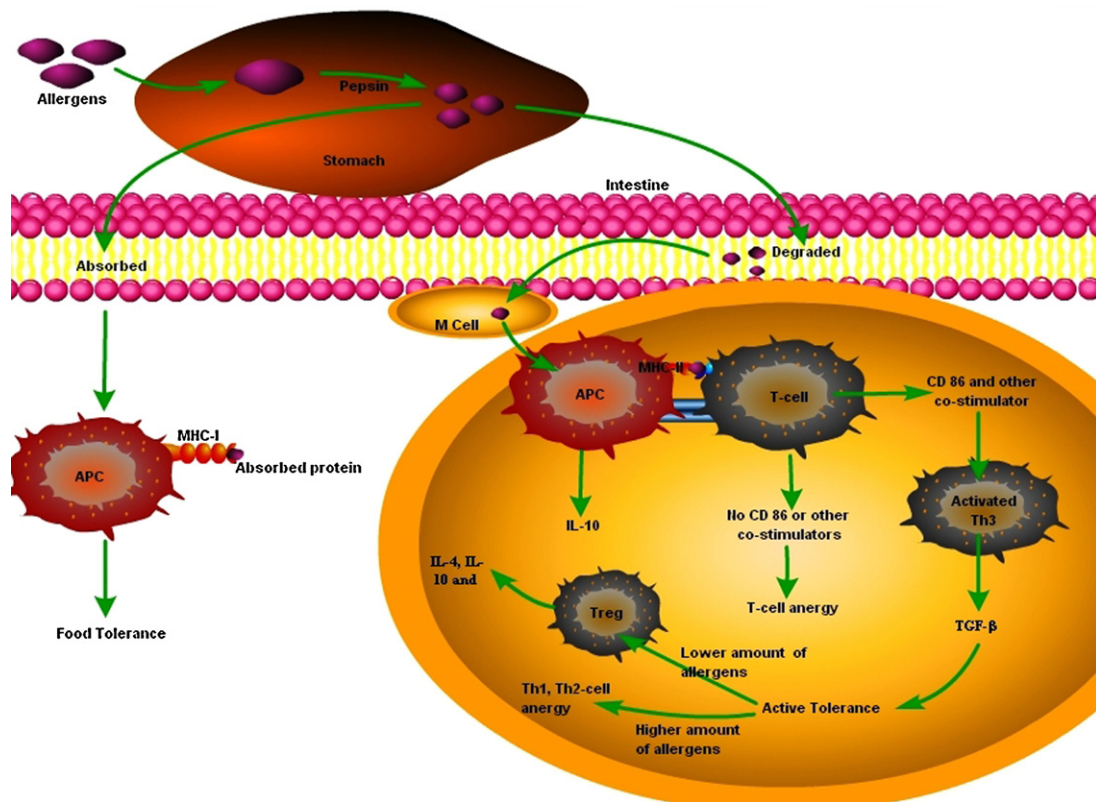


Fig. 3. A mechanistic outline of oral tolerance following dietary antigens. Food proteins get digested partially or completely. In intestine either food proteins are absorbed or degraded into smaller fragments or remain intact. The undigested food proteins are taken to APCs by M cells where fate of allergic tolerance is determined.

stay in intestine. The proteins or peptides that get absorbed by gut epithelium may get presented with MHC-I and induce healthy tolerance [50]. The undigested protein fragments get endocytosed by M cells present in intestinal mucosa. These M cells carry out these proteins from gut epithelium and release the food antigen in Peyer's patches. In Peyer's patches, DCs are the major APCs [51]. DCs endocytose the protein fragments and help in production of cytokine IL-10, (which ultimately induces Th3-cells), processing and presentation of the allergens to resident T-cells [52]. In absence of CD86 and other co-stimulatory factors, passive tolerance is induced especially via T-cells anergic specific for food, while in presence of CD86 and other co-stimulatory molecules, T-cells get activated via Th3 cytokines which results into active tolerance to specific food allergen(s) [53]. The activated T-cells produce TGF- β which suppresses B cells, macrophages and IgA production [54]. The induction of oral tolerance depends on the doses of exposed allergens. At lower dose, Th2 (IL-4/IL-10) and Th3 cytokine (TGF- β) secreting Treg plays an important role in oral tolerance induction [55]. The TGF- β triggers B cells specific for the antigen to produce IgA, which ultimately leads to oral tolerance. However at higher dose of allergens oral tolerance is induced mainly because of deletion or anergy of Th1 and Th2 cells [56]. But, sometimes higher dose of allergens may result in induction of Th3 and CD8 cells population which produce TGF- β and ultimately lead to oral tolerance. The nTreg and IL-10-producing Tr1 cells may also be responsible for homeostasis of immune tolerance and also intact immune reactions following exposure to allergens [57]. The Treg can perform their work through membrane bound TGF- β or via CLTA-4. A diagrammatic illustration of all these events has been given in Fig. 3.

7. Mechanism of food allergic sensitization

Dietary antigens or food allergens can elicit immune reactions mainly via intestinal mucosa. Most of the allergens are resistant to proteolytic enzymes and having rough and irritating properties enable them to penetrate intestinal mucosa [58]. Numerous innate immune cells including epithelium, DCs, basophils, innate lymphoid cells and others all interact to shape the adaptive Th2 immune response [59]. Mast cells are the major player in immune system and involve in both the innate and adaptive immune reactions and are widely distributed in tissues in surfaces exposed to the environment. Further, in concern of allergy, mast cells are one of the most studied cell types. Mast cells are involved in release a wide range of mediators by allergen-IgE specific triggers and sometime can also be activated by non-allergic triggers. Mast cells have also been reported as down-regulators of allergic inflammation [60]. Under normal conditions mast cells comprise 2–3% of lamina propria cells in the normal gastrointestinal mucosa [61].

Human antigen-presenting cells (APCs) bind monomeric IgE via the high-affinity IgE receptor, Fc epsilon RI (Fc ϵ RI). Although intracellular expression of the Fc ϵ RI α -chain is induced by IL-4, the up regulation of surface levels on DCs from atopic is due to enhanced expression of the Fc ϵ RI γ -chain and stabilization by binding of its ligand IgE. A characteristic function of Fc ϵ RI-bearing APCs is the specific uptake and processing of IgE-bound allergens, which is followed by T-cell stimulation [62]. Evidence for a differential regulation of the high affinity receptor for IgE, Fc ϵ RI, on the surface of atopic DCs compared with non-atopic DCs became apparent. In atopic donors, in contrast to non-atopic donors, the intracellular expression of the γ -chains of Fc ϵ RI is sufficient, thus leading to the

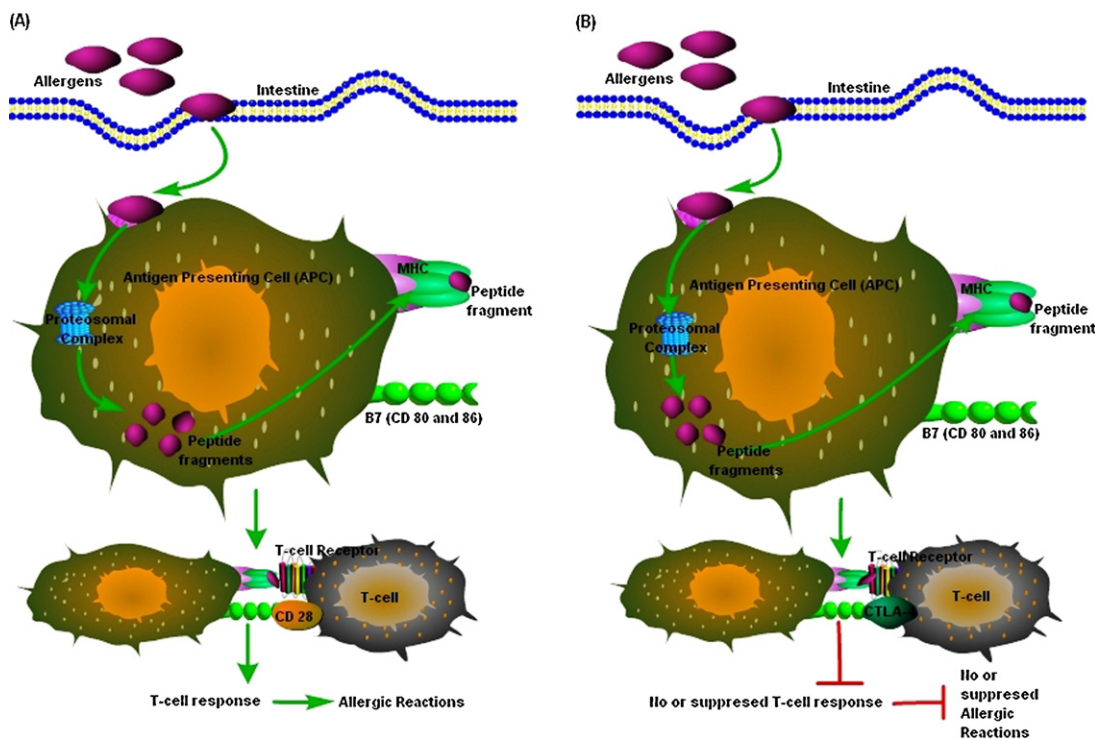


Fig. 4. A schematic outline of food induced allergic sensitization. Following exposure to allergens, endocytosis, allergen processing and presentation are performed by APCs. T helper (Th) cells recognize the allergens that lead to allergic manifestation while presence of CTLA-4 can reverse the outcomes.

assembly with the α -chain and surface expression of the receptor [63]. The IgE is the central player in the prevalence of food allergic responses. The activity of IgE is linked with a network of several proteins including two principal receptors, Fc ϵ R1 and CD23, galectin-3 and several co-receptors for CD23, like CD21 and several integrins [64]. Due to presence of Fc ϵ R1, mast cells and basophils are very crucial to food induced type I reactions. Mast cells and basophils express the complete (contain α , β , γ 1 and γ 2 subunits) high affinity IgE receptor, Fc ϵ R1. Furthermore, aggregation of the complete Fc ϵ R1 receptor results in the release of various allergic mediators that lead many of the signs and symptoms of allergic manifestations [65]. The allergens are internalized by APCs especially DCs, either by endocytosis or pinocytosis, followed by processing of allergens into peptide fragments in proteosomal complex and presentation of these fragmented peptides by MHC-II molecules [66]. These DCs possess several receptors on their outer membrane including CD86, CD80 and CD 40 [67]. The activated DCs with allergens move to Peyer's patches, where these bind to Th cells. The Th cells have several receptors on their surface including co-stimulatory molecule CD28 and CD40L [68]. The CD28 has been found to possess similar structure to that of CTLA-4. In spite of similar structure to CD28, CTLA-4 transmits an inhibitory signal to T cells [69]. Both, CTLA-4 and CD28 molecules bind to B7 molecules presented on DCs. In normal sensitization to allergens, B7 of DCs recognize CD28 of Th cells but, in presence of CTLA-4 the B7 does not get occupied by CD 28 as CTLA-4 has higher affinity to bind B7 molecules [70]. In case of CTLA-4/B7 binding, there is induced oral tolerance and suppressed allergic sensitization (Fig. 4).

8. Therapeutic perspectives of CTLA-4

Till date, therapeutic aspects of food allergy are most leaky side of allergic research as there is no permanent therapeutic solution of food allergy. However, there are a number of promising therapeutic strategies currently being investigated for the

treatment of food allergies. Several attempts including treatment of food allergy using allergen-specific approaches, such as various forms of immunotherapy, have been studied recently to find out a promising methods of desensitization. The current treatment methods included allergen immunotherapy (AIT), which may be administered in two forms, subcutaneous (SCIT), and sublingual immunotherapy (SLIT) [71]. It has been reported that oral tolerance for food antigens may be induced in two ways firstly, by initial exposure to antigen, or inherent tolerance, and secondly, by transfer of Treg, or acquired tolerance [72]. Specific oral tolerance induction (SOTI) has been reported as one of the promising treatment option for food allergy which has been found very useful in children suffering from cow milk allergy [73]. Oral therapeutic treatment with the probiotics mixture has been reported to be an effective approach as it may redirect allergen-specific Th2-polarized immune responses toward Th1-Treg responses and further, it has also been proved protective against anaphylactic reactions induced by the allergen in a murine model of food allergy [74]. Epicutaneous immunotherapy (EPIT) as a new alternative treatment of food allergy studied in peanut sensitized mice and further, it was elucidated that based on biological and physiological responses; EPIT is as efficient as subcutaneous treatment [75].

Along with immunotherapy approaches, molecular approaches like anti IgE therapy, DNA therapy, IL-4/IL-5/IL-12/IL-13 therapy, allergen specific Treg therapy, have attracted attention of researchers. Omalizumab (anti-IgE monoclonal antibodies) has been examined for the immunological changes that occurred in a group of children with significant cow milk allergy. Further, within a week of treatment, the CD4⁺ T-cell response to milk was nearly eliminated, which is suggesting anergy in, or deletion of, milk-specific CD4⁺ T cells. Over the following 3 months while the subjects remained on high doses of daily oral milk, the CD4⁺ T-cell response returned, characterized by a shift from IL-4 to IFN- γ production. Furthermore, reduced allergic sensitization or desensitization was found to be associated with reduction in milk-specific

IgE and an enhancement in milk-specific IgG4 up to some extents [76]. Thus, the use of anti-IgE monoclonal antibodies to treat food allergic reactions have raised a positive ray in molecular medicine as the anti-IgE monoclonal antibodies have been found to induce immune tolerance [77]. Further, the anti IgE therapy is used to control food allergy in which specific antibodies are used to bind IgE that make them unavailable for allergens. Anti-IgE therapy has been successfully tested in patients with food allergy, showing significant efficacy in reducing symptom scores and the use of rescue medications [78]. Although, anti IgE therapy was found effective to combat food allergy up to some extent but, some drawbacks like its high costs and long term treatment make it unapproachable for every strata of society.

The SIT has potential to alter the allergy prevalence, which has been demonstrated in allergic patients and the combination of anti-IgE and SIT have been also recommended as it has shown improved efficacy, lesser adverse effects with potential immunomodulatory effects [79]. But, still short term therapy and cost effectiveness is highly desirable. The key cytokines involved in food allergy have also attracted researchers as one of the therapeutic tools targeting IL-4 or IL-13 signaling to suppress food induced diarrhea has been well described, but still requires additional work to make it from bench work to bedside [80]. Thymus-derived Treg cells has been reported to maintain oral-tolerance and therefore evidence is growing regarding the use of adaptive Tregs in the regulation of Th1/Th2 immune responses induced due to food allergens [81].

Recent studies have explored the pivotal role of CD4+CD25+ regulatory T cells (nTreg) in the maintenance of oral tolerance to dietary antigens and further, in the regulation of the food allergic response. It has been reported that TGF- β secreting Treg (Th3) may play an important role in induction of oral tolerance in a murine model sensitized with peanut [82]. The mechanisms behind the allergic sensitization involved, mast cell and basophil suppression, enhanced level of food-specific IgG4 antibodies, suppression in the food-specific IgE/IgG4 ratio, up-regulated and expanded nTreg and iTreg cells, a shift from a Th2 to a Th1 reactions, and the development of T-cell anergy or deletion in antigen-specific cells [83].

After exploration of underneath mechanisms involving CTLA-4 in food allergy, a ray of its exploitation in therapeutics has come in light but, its use in food allergy is yet to be a reality. CTLA-4 has been targeted in several diseases as therapeutic tools. It is generally targetted by CTLA-4-Ig, a fusion protein working as antibody against CTLA-4. The fusion proteins CTLA4-Ig can be of two types based on its generation abatacept or belatacept. After thorough examinations no toxicity has been observed due to consumption of abatacept in animal models and well tolerated in non-human primates and rodents. Belatacept is a second generation form of CTLA4-Ig which has been recently approved by the Food and Drug Administration, USA [84]. Blocking CD28 interaction with B7 by the use of CTLA-4Ig might contribute to control of unbalanced immune homeostasis. It has been also reported that the CTLA-4Ig treatment can hamper the development of peanut allergy by suppressing cytokine responses, specific IgG1, IgG2a, and IgE and clinical symptoms [16]. The CTLA-4Ig therapy can be either of short term or long term, while in other allergy therapy like anti IgE therapy long term treatment is mandatory. High-dose CTLA-4-Ig has not been found to induce permanent tolerance indicating the possibility of low dose of CTLA-4Ig in treatment of food allergy [85]. It has been discussed in the earlier section that CTLA-4 signaling negatively regulates immune activation, and due to this milestone nature it may play a critical role in preventing induction or progression of allergic sensitization. To elucidate the role of CTLA-4 signaling in responses to food allergens, a murine model of peanut allergy was studied by van Wijk [16]. The outcome of this study suggests that CTLA-4 signaling is not the crucial factor in preventing

sensitization to food allergens, but plays a pivotal role in regulating the intensity of a food allergic sensitization response [16].

9. Conclusions

At present, there is no effective therapy for IgE-mediated food allergy, and patients have to rely upon food-allergen avoidance. Definitive therapies for food allergy are desperately needed as its prevalence is increasing consistently throughout the world. Considering, no treatment against food allergy, CTLA-4 can be used as one of the most relevant therapeutic options. The involvement of CTLA-4 in CD28/CTLA-4-B7 signaling pathway and recognition of B7 molecules by CTLA-4 have opened a positive conception regarding its involvement in food allergy. The CTLA-4 can be targeted at different points including class switching to IgE and induction of oral tolerance. Taken together, CTLA-4 molecule has added a new episode in food allergic research along with tremendous possibility to consider it as one of the pivotal candidates for food allergy treatment.

Conflict of interest

The authors have declared that there is no conflict of interest.

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