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Review Article

Food Allergy: Immunological Mechanisms and Prevention Strategies

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Abstract

Adverse immune reaction that occurs after the ingestion of specific food is called food allergy. In 2012, World Allery Organization (WAO) and Worldwide Universities Network (WUN) conducted collaborative project to survey globally on the prevelance of food allergy and reported that 10% of prevelance to food allergy occur in below five year children in Europe, where as 7-10% observe in USA, Asia and Africa. The major food allergens to cause food allergy worldwide are Bos d 4, Bos d 5, Bos d 7, Bos d 8 (milk), Gal d 1 (egg), Gad c 1 (fish), Pen a 1 (crustacean shell fish), Cor a 8 (tree nuts), Ara h 1, Ara h 2, Ara h 3, Ara h 5 (peanut), α, γ-gliadin (wheat), Gly m 1, Gly m 4 (soybeans). In this review, immunological mechanisms involved and their prevention have been discussed. In gastrointestinal system the food allergen shows resistance to digestive enzymes, and induce sensitization and effector phase of allergy, thus stimulate inflammation by activating NF-κB pathway. Probiotics are live microorganisms which when administered in sufficient quantity which will improve the host health. These probiotic organisms have immune regulatory properties which regulates the Treg cells towards anti-inflammatory action thereby producing IL-10 cytokines thus establish tolerance to food allergen and the food allergy perhaps minimize or prevent by probiotic intervention.

Keywords: *Food allergy, Probiotics, Inflammation, NF-κB, Gastrointestinal mucosa, Immunoregulation*

Abbreviations: GALT: Gut Associated Lymphoid Tissue; TLR: Toll Like Receptor; PRRs: Pattern Recognition Receptors; IL: Interleukin; TNF: Tumor Necrosis Factor; FA: Food Allergen; Foxp3: Forkhead box p3; IKK: I Kappa B Kinase; EMSA: Electrophorotic shift Mobility Assay; IgE: Immunoglobulin E; OAS: Oral allergy syndrome; RAST: Radioallergosorbent test

Introduction

Food allergy is an adverse immune response to food proteins, affecting 7-10% of young children and 3-4% of adults [1-4]. Food allergy can be defined as "Immune-mediated adverse reaction to food" [5]. Food allergy is now recognized as worldwide problem and appears to increase, because of lifestyle changes such as change in alimentary habits, living conditions, excessive use of antibiotics contributing to immune deviation and thus development of allergy in modern times [6]. In Asia, towards cow milk (5.7%), egg (9.1%), peanut (8.1%), wheat (0.3-1%), nuts (5%), fish and shellfish (15.8%) food allergy has diagnosed [7-8]. In India, approximately 1-2% of food allergy has been observed [9]. Protein in these food acts as an allergen. Allergies occur when the body's immune system mistakenly indentifies a protein as harmful agent. In many cases proteins or fragments of proteins are resistant to digestion and those that are not broken down in the digestive process are tagged by immunoglobulin E (IgE), these tags disguise the immune system thinking that the protein as an invader which stimulates the immune cells to attack and that will manifest an allergic reaction [10]. These reactions can range from mild to severe and there is no proper cure, and which can be prevented or sensitization can be reduced [11]. Interestingly, the increased prevalence of food allergy is paralleled by an increase in the severity and spectrum of disorders involving hypersensitivity responses [12]. Allergenic reactions induced by food protein shows different disorders and symptoms in gastrointestinal system which is characterized by immediate and cellular mediated mechanism [13].

The gastrointestinal system plays a central role in immune system homeostasis, functioning as barrier against antigen. The gastrointestinal system is induced by huge amount of immune cells, like gut-associated lymphoid tissue (GALT) represents 70% of entire immune system, GALT interact in a dynamic manner to a particular stimulation, thereby modify immune response allowing either tolerance or degradation of luminal antigens, or induce both innate and adaptive immunity which implicated in very complex immune mechanisms [14]. In gastrointestinal tract the probiotics strains like Lactobacillus GG colonize and act as barrier against food induced allergenic protein and thus control the antigen to enter into the mucosa and prevent the sensitization of hypersensitive reactions [15].

Probiotics are dietary supplements containing live beneficial microorganisms that can improve the health of host when consumed at appropriate amount. WHO/FAO (2002) defines "probiotics are live microorganisms which when administered in adequate amounts confer health benefits to the host". While International Life Science Institute (ILSI) Europe, defined probiotic as "a live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits to the consumer" [16]. Probiotics along with prebiotic, which are indigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or limited number of bacteria found beneficial in initiating the burden of disorders with hypersensitivity [17]. The most common probiotics are lactic acid bacteria belonged to the genera of *Lactobacillus* and *Bifidobacterium* [18-19].

Beneficial effect of probiotics to prevent pathogenic infections, to improve inflammatory disease symptoms and to reduce the risk of food allergic disorders has been recorded [20]. Probiotics act at various levels in the gastrointestinal tract, and participate in degradation of protein antigens, enhance intestinal barrier functions, promote the development of mucosal immune system, or influence the composition of intestinal microbiota in a competitive or symbiotic manner by expressing the regulatory cells towards anti-inflammatory cyotkine IL-10 [21] and establish tolerance to defined allergen [22-23].

Types of food allergens

Some of the major food allergens are listed in Table-1, of which children affecting 7-10% and 3-4% of adults suffer with allergic disorder by intake of these protein types of food with most prevalence.

Source	Food Protien	Allergen
Milk	Casein (αs1, αs2, β, Υ1, Υ2, Υ3, κ), α-lactalbumin, β-lactoglobulin, immunoglobulin	Bos d 8, Bos d 4, Bos d 5, Bos d 7
Cod	Parvalbumin	Gad c 1
Shrimp	Tropomyosin	Pen a 1, Pen i 1, Met e 1
Soy	Conglycinin, glycinin, vicilin	Gly m 1, Gly m 4
Apple	Nonspecific lipid-transfer proteins	Mal d 1, Mal d 2, Mal d 3
Peanut	Vicilin, conglutin, glycinin	Ara h 1, Ara h 2, Ara h 3
Celery	Profilins	Api g 1, Api g 4
Wheat	Gluten	α, Υ-gliadin
Peach	Nonspecific lipid-transfer proteins	Pru p 1, Pru p 3
Hazelnut	Nonspecific lipid-transfer proteins	Cor a 8
Rice	α-amylase inhibitor	Ory s 1
Mustard	2S albumin	Sin a 1
Barley	α-amylase inhibitor	Hor v 1
Potato	Patatin	Sol t 1
Egg	Ovomucoid, Ovalbumin, Ovotransferrin	Gal d 1, Gal d 2, Gal d 3
Carrot	Pathogenesis- related protein	Dau c 1

Table 1: *Some of the food allergens mediated food allergy.*

Types of food allergy

IgE mediated disorder	Non-IgE mediated disorder
Oral allergy syndrome	Proctocolitis
Gastrointestinal anaphylaxis	Enteropathy syndrome
Allergic Eosinophilic Gastroenteritis	Allergic Eosinophilic Gastroenteritis
	Enterocolitis syndrome or FPIES
	Celiac disease

Table 2: *Some of the food allergy mediated disorders in gastrointestinal tract.*

Food allergy can be classified into three groups according to mechanism of allergic response (Table 1 and 2), can be classified as,

- IgE- mediated (classic) food allergy-a common type of allergy, which occurs shortly after eating and are called immediate type reaction. It involves type II hypersensitive reaction which is mediated by IgE antibody and sometimes involves anaphylaxis, and this type of allergy is increase in industrialized country because of reduced tolerance to allergen [7,24-25].

- Non-IgE mediated or cell mediated food allergy – it occurs some hours or days after eating the allergenic protein food and are called delayed type reaction. This type of allergy is difficult to diagnose and it involves antigenic specific Treg cell. The allergy causing food protein usually present in infant formulas such as milk and soya based products are best examples [5,7]. And it involves type III and type IV hypersensitive reaction and sometimes it causes death [25].

- IgE and/ or non-IgE mediated- a hybrid of above two types of responses. In children this type of allergy occurs with severe eczema [7,26].

Immune mechanism underlying the food allergy and the role of Treg cells

Allergy can be divided into two phases: sensitization phase and effector phase [24]. After first contact of ingested food allergen with gastrointestinal tract, the primary sensitization occurs, which will trigger the allergic response. These food allergens are stable proteins which show resistance to digestive enzymes and heat denaturation [27-29]. In allergic patients the allergy specific CD4+ TH2 cells produce IL-4, IL-5 and IL-13, which promote B-cells to produce allergy specific IgE and binds to basophils and mast cells surface. Then the effector phase takes place after initial contact with allergens, leading to activation and release of allergic substances like histamine which are responsible for symptoms, eliciting severe clinical manifestations [30].

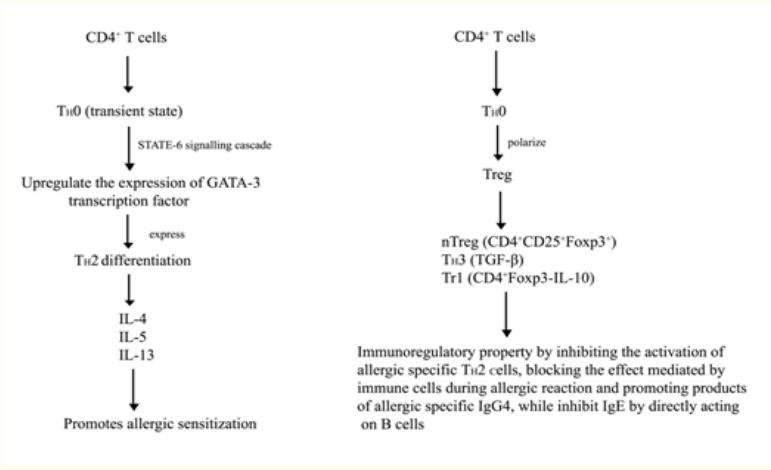

Figure 1: *The role of Treg cells in the regulation of immune mechanism by food allergy [24].*

In human, Foxp3 (forkhead box p3) protein regulate some immune cells like regulatory T cells based on the antigenic stimuli Treg cells are classified into nTreg (CD4+CD25+Foxp3+) and inducible Treg cells (iTreg). During point mutation in Foxp3 gene leads to immunodysregulation, polyendocrinopathy, enteropathy, X- linked (IPEX) autoimmune disease, which decreases the function of Treg cells in intestine by sensitization [31-32].

Conventionally Treg cells generate tolerance to self and non self antigens of food allergens. Treg cells have immunoregulatory properties which prevent misguided immune responses to allergens [33-34].

The immunoregulatory property of Treg cells are capable of suppressing sensitization phase and effector phase which play role in pathogenesis of food allergy and inhibit TH2 cells directly by enhancing TH1 cells polarization and induce the production of anti-inflammatory cytokines such as IL-10, TGF-β and inhibiting IgE by acting on B cells which would prevent allergic disorder [32,35-36].

Regulatory mechanism of inflammation induced by food allergen

The activity of inflammation is directed by signaling pathway which is induced by food allergen through the activation of TLR (Toll-like receptor), PRRs (Pattern Recognition Receptors), Inflammasome receptors which leads to production of pro-inflammatory cytokine (IL-1, TNFα). These inflammatory cytokines activates the nuclear factor-κB pathway [37]. The role of NF-κB in the inflammatory response has not reported from in vitro studies [38]. Mechanism of inflammation caused by food allergen could be elucidated as follows (Figure 2); when a food allergen (FA) reaches to the gastrointestinal mucus, FA invades the mucosal barrier and binds to specific receptor on the epithelial cell which produce the signals that can activate the enzyme I kappa B Kinase (IKK). This IKK phosphorylates the IκBα protein results in the conversion of inactive NF-κB into active NF-κB. Activated NF-κB is a heterodimer of two proteins, RelA and P50, these proteins bind to DNA at specific site and transcribe into mRNA, which interns translated into protein finally results in change in cell function by expression of some immune molecules like proIL-1 [39].

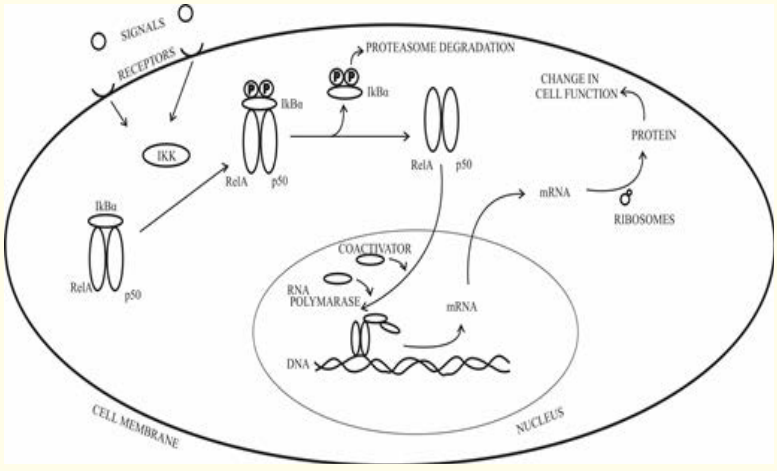

Figure 2: *Mechanism of inflammation through NF-κB pathway [38].*

This proIL-1 in presence of assembly of inflammasome turns to biologically active IL-1, which is rapidly released, leading to food allergen to cause inflammation. Manna., et al. [40] studied the regulation of NF-κB in the expression of NURR1 promoter having -585- and -576- bp, which involve in TH2 dependent hypersensitivity reaction and this was examined through EMSA (Electrophorotic shift mobility assay) in animal cell model with DNA binding ability and inflammation [40-43].

Symptoms, Clinical manifestations, prevention and treatment for some gastrointestinal disorders caused by IgE and non-IgE mediated food allergens

The main factor that induces clinical expression of gastrointestinal allergy is an imbalance of T-cell system and prevalence of TH2 response

with its cytokine pattern (IL-4 and IL-5). At gastrointestinal level, the IgE mediated allergic manifestations are caused by immune complexes. Various disorders of gastrointestinal system caused by IgE mediated food allergy are, gastrointestinal anaphylaxis [44], Allergic eosinophilic oesophagitis which is characterized by swelling of esophagus caused by massive inflammation with eosinophils [45] and Oral allergy syndrome (OAS), consist of itching and swelling of lips, oral mucosa in soft place immediately after eating fruits or vegetables [46]. The symptoms include rapid onset of nausea, abdominal pain, cramps, vomiting, diarrhea, urticaria, weight loss. The severe reactions caused by ingestion of food such as cow's milk, egg, peanut, fish, crustaceans, shellfish, pea, beef, chicken, rye, corn, soy, potatoes, oats, tomato and wheat [47]. Patients with birch-pollen hay fever may have symptoms of Oral allergy syndrome after ingesting hazelnut, apple, and carrot [1]. Diagnosis is done using biopsy of esophagus for Allergic eosinophilic oesophagitis with evidence of eosinophils infiltrating the esophageal tissue, skin prick test or IgE sera detection and RAST (Radioallergosorbent test) has been recommended. However, in case of OAS, patient's ingested cooked food did not show any symptoms as the allergens responsible which were destroyed in heating process [14,28,48]. Elimination of allergen from diet or administration of glucocorticoids ameliorates oesophageal eosinophil infiltration [49].

Probiotic interventions in life aimed to prevent atopic manifestations have been reported. In a double blinded study, oral treatment of pregnant mother and then infant with a probiotic mixture containing *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve* Bb99 and Propionibacterium freudenreichii ssp shermanii JS showed to reduce IgE-mediated allergy [50]. In a similar study, administration of *Lactobacillus reuteri* prevented the prevelance of IgE- mediated eczema and sensitization [51]. Probiotic treatment with *Lactobacillus fermentum* VRI-OO3 PCC in young children with severe atopic dermatitis showed a decrease in the severity of allergic signs [52]. Sanchez., *et al.* [53] studied the extracellular proteins secreated by probiotic bacteria which directly interact with the host mucosal cells which are responsible for their mechanism of action by using the strains of *Bifidobacterium* and *Lactobacillus.*

Non-IgE mediated or cell mediated food allergy include, Food protein enteropathy and Food protein induced enterocolitis/proctocolitis syndrome. Food protein enteropathy is an adverse reaction to food affecting mainly the children under 2-3 years age group [54], majorly the consumption of milk, soybean, and wheat. The symptoms include vomiting, diarrhea, enteropathy with protein loss, malabsorption, constipation, and poor growth. Diagnosis includes endoscopy and histology, with identification of intraepithelial lymphocytes, eosinophils and atrophy of villuses. A similar but more severe pathology is proctocolitis, enterocolitis, which present ulceration with consequent bleeding, and hemorrhagic anemia [2]. Another type of food allergy is Celiac disease with flatulence and weight loss. The common cause of disease is hypersensitivity to gluten protein wheat and diagnostic feature is flattening of villi in biopsy specimen. Gayathri and Rashmi, [55] reported the causes and molecular mechanisms involved in celiac disease development and its strategies to control and significance of reducing gluten burden in patients of celiac disease using probiotics, as it is an intestinal chronic disorder with multifactorial etiology resulting in small intestinal mucosal injuries and malabsorption. Furthermore, Jyonouchi, [11] studied that non-IgE mediated response initiated by cell mediated response to food allergen affecting the gastrointestinal mucosa in tern induce immune system and affects the gut immune homeostasis results in the adverse reaction to allergen. Where probiotic strains inhibited TH2 response and reduce IL-4, IL-5, and TNF-α, this mechanism depend on monocytes and require TH1 cytokines (IL-12 and IFN-γ) [23,35,56] and this conjugate inhibit the regulation of costimulatory molecule that leads to suppression of intestinal allergic response [57]. The main drawback of probiotics intervention is that the lactic acid bacteria colonize in gastrointestinal tract for limited period or during the time of consumption [58]. Therefore, incremental supplement as a dietary adjuvant would be promising to prevent either IgE or Non-IgE mediated allergic manifestations.

Allergic eosinophilic gastroenteritis is an IgE and/or cell mediated induced mechanism which is seen in all group of age [13], presenting symptoms like abdominal pain, irritability, intermittent vomiting, weight loss and peripheral blood eosinophilia (50%). Its diagnosis includes clinical history, endoscopy, skin prick test, and presence of inflammation and significant eosinophilic infiltration of oesophagus, stomach or small intestine [59]. Elimination of diet containing allergic protein is the only available treatment. Mishra., *et al.* [60] studied the eosinophilic infiltration into oesophagus in allergic gastroenteritis and gastroesophageal reflux was induced upon exposure of mice, they demonstrated that IL-5 has regulatory eosinophil accumulation, where as in the absence of IL-5 in anti-IL-5 treated mice, the oesophageal eosinophilia markedly reduced in oesophagus. Even though many clinical studies showed that the invervention of probiotics in preventing and managing the food allergy, the result vary depending on probiotic strain selection and/ or in model selection [61-66].

Other than the probiotics intervention in modulating the tolerance to potential antigenic food protein is by using epinephrine, antihistamine and steroids should be available to treat patient at risk for severe reaction. Prompt administration of epinephrine at the first sign of a severe action must be emphasized because delayed administration has reportedly fatal and/or near- fatal food allergic reaction [49]. Resveratrol (trans-3,41-5- trihydroxystilbene), a polyphenolic phytoalexin found in grapes and root extracts of the weed Polygonum cuspidatum, exhibits anti-inflammatory effect [40]. It suppresses NF-κB that regulates the expression of various genes involved in inflammation. This suppression of TNF- induced NF-κB was not restricted by myeloid cells (U-937), lymphoid (Jurkat), epithelial (HeLa and H4) cells.

Conclusion

Food allergy is a worldwide problem increasing globally and there is no proper data on prevalence which is reported by World Allergy Organization (WAO). Food allergy is reduced by strict avoidance of food protein in diet where as some studies showed that avoidance of food protein often leads to malnutrition. The interaction of probiotic bacteria with gastrointestinal tract develop allergy specific Treg cells which further initiates immune modulation towards anti-inflammation by increasing the production of IL-10, suppressing both sensitization and effector phase of inflammation. Careful selection of probiotic strain with prebiotics is an alternative and effective option perhaps, a promising mechanism in the prevention of food allergy.

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