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Immuno pathogenesis of food protein- induced enterocolitis syndrome (FPIES)

Abstract

Food protein -induced enterocolitis syndrome (FPIES) is a type of cell-mediated, non-IgE mediated, food allergy reactions characterized by repetitive vomiting in 1-4 hours after consuming specific food allergens. It has been long thought to be cellular immunity-mediated disorder by clinical and laboratory findings. Immune mechanism of FPIES has not been well defined so far. Food protein-specific T lymphocytes become activated and proliferate when they come across specific food proteins in the intestinal lumen. Consequently, they release intensively proinflammatory cytokine TNF-α and mildly IFN-γ plus low TGF-β in this cytokine storm. The proinflammatory cytokine storm helps TNF-α affect on intestinal epithelial cells, on where decrease expressions of TGF-β receptor type I, causing local intestinal inflammation and barrier permeability interruption. Understanding of immune mechanism (immuno-pathogenesis) of cellular immune-mediated reaction to foods, like FPIES, it will help to understand FPIES better and manage this disease properly.

Keywords: food protein-induced enterocolitis syndrome, food allergy, TNF-α, TGF-β

Volume 6 Issue 3- 2018

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Received: May 07, 2018 | **Published:** May 29, 2018

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a type of cell-(non-IgE) mediated food allergy reactions described by repetitive vomiting in 1-4 hours after consuming a specific food allergen.[1–3] It has been long thought to be cellular immunity-mediated disorder by clinical and laboratory findings. However, immune mechanism of FPIES has still not been well defined.[4–6]

The default response of intestinal mucosal immune system against the specific food proteins is to develop tolerance by means of T-reg (CD4+-CD25+) cells. This normal/physiologic response was well demonstrated in resolved cow's milk (CM)-FPIES patients and subjects tolerant to CM.[7] In this manuscript, firstly the way of normal immune system response, then the mechanism of tolerance and FPIES disease development is told, respectively. The immune mechanism of the FPIES disease under four different subtitles is to be discussed in the light of recent literature.

Normal-physiologic immune response to food allergens: tolerance development

When food allergens arrive into intestinal lumen in healthy subjects, if intestinal epithelial barrier intact, macrophages under the epithelial cells captures allergens and present them to CD103+ dendritic cells. Dendritic cells process these allergens and as usual they drain into regional lymph nodes, where they present allergens as peptides to the naïve CD4+ T cells. During this process, released cytokines such as TGF-β and IL-10 help turn naïve cells into T-reg cells. These cytokines also make B-cells produce specific IgA to these food allergens, instead of IgE isotype.[4]

Similar response occurs in patients when the FPIES resolves and the patient become tolerant**.** In resolved CM-FPIES patients with negative oral food challenge (**OFC**) result, higher serum IL-10 was detected. Significantly higher IL-10 levels in patients with resolved CM-FPIES suggest that expression of IL-10 could be linked with the tolerance development.[4] Consistently, in an 8-month-old patient having rice-FPIES (i.e., the patient had acquired tolerance to rice) with negative (tolerant) provocation, an increase in IL-10 expression of T-cells was shown after rice provocation 6 months later after a positive challenge.[8–10]

I- Abnormal immune response: cell–mediated type of food allergy development

Food protein-specific T lymphocytes become activated and proliferate when they come across specific food proteins in the intestinal lumen. As a result, food allergens arrive into intestinal lumen in these subjects, where intestinal barrier inflamed/damaged, allergens in large amount go through between epithelial cells themselves instead of captured by macrophages. When CD103+dendritic cells process these allergens, they express OX-40L and drain into regional lymph nodes, where they present allergens as peptides to the CD4+ T cells expressing CD40. During this process, released cytokines such as IL-4, IL-5 and IL-13 activate TH2-mediated immune response. IL-4 also makes B-cells produce specific IgE against these food allergens, instead of IgA isotype.[4–6]

TH2-mediated immune response was demonstrated after ingestion of causative foods, an increase in interleukin IL-4 and a decrease in IFN-γ expression detected in early-onset FPIES. After stimulation with CM protein, peripheral blood T cells of these patients also produce cytokine IL-5.[4–6] In non-IgE mediated food allergy, TNF-α, IL-6, and TH2 cytokines (IL-4, IL-5, and IL-13), but not IFN-γ or IL-17, were found to be amplified in the supernatant from CM protein-stimulated peripheral blood mononuclear cells (PBMNC) cultures of Japanese infants.[11–13] In rice-FPIES cases with positive OFC, increase in IL-4 and decrease in IFN-γ expressions after a positive provocation test with rice (i.e. rice triggered an FPIES attack).[8–10]

The role of cellular immune system in FPIES immuno-pathogenesis: CD103+- dendritic cells

As mentioned above, CD103+ dendritic cells play an important role in migration/processing of food allergens into peptides and

presenting them to naïve T cells. This role of dendritic cells was shown in FPIES patients' dendritic cells by increased HLA-DR expression and maturation, improving their antigen presentation capability.[14] For instance; dendritic cells of FPIES cases demonstrated a notably increase in the HLA-DR molecule expression when encounter to sole or tuna extracts (fish-induced FPIES) than control group expression.[15]

Peripheral blood mononuclear cells (PBMNCs)

In patients having FPIES, encounter of PBMNCs with fish extracts stimulated significantly higher amounts of TNF-α and mildly increased IL-6 than in control ones.[15] Accordingly, in patients with CM-FPIES, PBMNCs showed incomplete TGF-β responses upon milk protein casein stimulation. This type of deficient response might have a significant role in the pathophysiology and could be utilized as a possible marker of resistant CM-FPIES cases**.**[7]

Other innate immune cells (neutrophils, eosinophils, phagocytes and mast cells)

In acute phase of FPIES, neutrophilic leucocytosis is observed in peripheral blood smear. Also, neutrophilia is detected in gastric aspirate, stool mucus and in intestine biopsies from FPIES cases. Increased serum IL-8 levels, unspecific stress response or the side effect of steroid use in FPIES patients were considered to participate in neutrophilia.[16]

Conspicuous and mild eosinophilia is seen in early-/late-onset FPIES patients, respectively. Eosinophilia in infantile FPIES at onset reported to be transient and could indicate good prognosis.[12] Eosinophil increase in intestinal biopsies has been detected from FPIES patients. Increase in fecal eosinophil-derived neurotoxin (**EDN**) after intake of the causative food allergens indicates the role of eosinophils in the disease.[17] CD69 expression on eosinophils was demonstrated after acute FIPES reactions.[18] In contrast, eosinopenia after OFC, mimicking FPIES attack, has been reported.[16]

As told above, phagocytic cells (macrophages) may have an active role in the development of FPIES and their calprotectin production found to be increased and detected in feces.[17]

Mast cells in the body are always observed around any inflamed tissue. After cytokine storm (TNF-α) in intestinal lumen, intestinal epithelial barrier got inflamed and damaged. The role of mast cells has recently drawn attention. In this environment, TH9 cells release IL-9, which is a growth factor for mast cells, and contribute to accumulate mast cells under the intestinal barrier.[4] This is consistent with elevated basal tryptase levels in FPIES patients.[19] After barrier damaged, high amount of food allergens penetrates into lamina propria and epithelial cells produce IL-33. It supports acute response to food allergens by affecting directly on mast cells and augmenting IgE-mediated reaction.[4–19] Elevated casein-specific IL-9 release from T-cells was found in CM-FPIES patients compared with IgE-mediated milk allergy cases.[6] Cytokine IL-9 is thought to contribute to FPIES pathogenesis by rising intestinal mast cell counts and changing intestinal permeability.

II- The role of cytokine response against food allergens in FPIES

During cellular interaction with food allergens, increased amount of TNF-α is released in the intestinal lumen. In this microenvironment, balance of TNF-α/TGF-β1 cytokines released from activated T-lymphocytes is important to develop intestinal barrier damage.[20] Proinflammatory cytokines (TNF-α, IFN-γ) are known to contribute the barrier damage in the intestine. When large amount of food allergens enter into lamina propria, TH2 cytokines (IL-4, IL-5 and IL-13) are released and they make B-cells produce IgE antibodies.[21–23]

An association among increased TNF-α, decreased TGF-β RI expression and intestinal villous atrophy was demonstrated in intestinal biopsies.[6] Increased TH2 cytokine concentrations were studied by Caubet et al.[6] in CM– FPIES patients**.**[6] TH2/TH1 cytokine concentrations and change in their serum level in time from 0-72 hours after OFC and FPIES attack were well studied.[11]

III- Epithelial barrier dysfunction (Damage/ Inflammation) in FPIES

While food allergens come across sensitized T-cells in intestinal lumen, a cytokine storm (TNF-α) occurs and end up with epithelial barrier dysfunction. This inflammatory characteristics of intestinal mucosa of duodenum and jejunum was demonstrated with increased edema, variable villus atrophy, intraepithelial lymphocytes, CD4+-T cells, IgM- IgA producing plasma cells, mast cells and eosinophils.[7,15] Epithelial barrier dysfunction (damage / inflammation) in FPIES is the distinguishing feature of FPIES from other non-IgE mediated, cellular immunity-mediated food allergy types such as allergic proctocolitis and enteropathy.[24]

An interruption of the epithelial barrier function, an increased food allergen entrance to the submucosa, and following allergen-specific lymphocyte activation could be clarified by poor TGF-β reactions. TGF-β is known to control the intestinal epithelial integrity by preserving and recuperating the barrier role of human enterocytes. TGF-β is also type of cytokine that causes T-cell inhibition and supports B-cell switching to isotype IgA antibody production.[6] Poor TGF-β1 release and the low expression of TGF-β receptor type I on the epithelial cells and PBMNCs in the lamina propria were also demonstrated in duodenal biopsies from most of the FPIES cases as well.[25]

IV- The role of humoral immune system in FPIES immuno-pathogenesis

Humoral immune system reactions in FPIES patients are known by a scarcity of specific antibody production including all immunoglobulin classes/isotypes. For example: cases with CM-FPIES have low serum titers of casein specific IgA/IgG/IgG4.[25] Low serum levels of casein specific IgG4 and IgA would elucidate the responses happening in FPIES owing to weakened neutralization capacity of intestinal micro-environment. Both IgG4 and IgA isotype demonstrate allergen-specific suppressive action in ex *vivo* and *in vitro* biologic assays e.g. basophil histamine release.[7] IgG4 antibodies attach complement weakly and could play a preventive role in rivaling with other subclasses that could trigger complement pathway. Comparatively short of IgG4 level in FPIES cases might be implicated in the pathogenesis.

Consistent with the low serum casein specific IgA, the PBMNCs from the same cases confirm TGF-β incomplete reactions after stimulation with casein which might have a significant role in FPIES pathophysiology. Bearing in mind the relatively vital role of IgA, it is assumed that the major regulatory cytokine for this antibody class (IgA) is TGF-β. It might take part in the pathophysiology of FPIES by stimulating B-cells to make IgA isotype switch.[6,7]

Citation: Özdemir Ö. Immuno pathogenesis of food protein- induced enterocolitis syndrome (FPIES). *MOJ Immunol.* 2018;6(3):86–88.
DOI: 10.15406/moji.2018.06.00199

Specific IgE antibody production is also usually not found in FPIES patients. It is tempting to hypothesize that specific IgE antibody produced in the intestinal mucosa might have a role in the allergen uptake and local inflammation. If specific IgE antibodies to food allergens detected in FPIES cases, food tolerance development is thought to be delayed and clinical picture of FPIES to be persistent.[6]

Conclusion

In the pathogenesis, food protein-specific T lymphocytes become activated and proliferate when they come across specific food proteins in the intestinal lumen. Consequently, they release intensively proinflammatory cytokine TNF-α and mildly IFN-γ plus low TGF-β in this cytokine storm. The proinflammatory cytokine storm helps TNF-α affect on intestinal epithelial cells, on where decrease expressions of TGF-β receptor type I, causing local intestinal inflammation and barrier permeability interruption. Understanding of immune mechanism (immuno-pathogenesis) of cellular immune-mediated reaction to foods, like FPIES, it will help to understand FPIES better and manage this disease properly.[26]

Acknowledgements

None.

Conflict of interest

The author declares that there is no conflict of interest.

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