Reviewer's report

Title: Rhinosinusitis derived Staphylococcal enterotoxin B plays a possible role in the pathogenesis of food allergy

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Reviewer: Harumi Jyonouchi

Reviewer's report:

Comments:

Introduction (Background)

Page 3, the first paragraph:
- Probably 2nd sentence is unnecessary.
- 3rd sentence: abdominal inconvenience do you mean abdominal discomfort?
- 4th sentence: I assume that the authors meant?
- Avoidance of offending food is the only effective therapeutic measure currently.
- 5th sentence: I think that the authors meant;
- FA are prevalent irrespective with sex, ethnicity, age, and social/economic class and imposes a heavy burden on health care expenditure and global economy.

Page 3, the 2nd paragraph:
- The first sentence: may consider revise the sentence such as written below:
- Although etiology of FA is still not well understood, significant progress has been made for the recent few years with regard to molecular mechanisms of FA.
- 3rd, 4th, 5th sentences: not clearly written (you need to discuss in relation with FA). Please revise.

Page 4, the 1st paragraph:
- Please correct several typo- or grammatical errors.
- 3rd sentence; probably unnecessary.
- It seems that the authors want to state:
- Antigen-independent, polyclonal T cell activation by SEB can worsen inflammatory condition in both Th1 mediated and Th2 mediated diseases including chronic rhinosinusitis. Thus controlling staphylococcal colonization or infection may have therapeutic implications in these conditions. It is reported that prophylactic antibiosis for Staphylococcus aureus revealed protective effects in atopic dermatitis. However, a role of superantigens in FA is not well understood.

Page 4, the 2nd paragraph:
- 2nd sentence: please clarify better.
- 3rd and 4th sentences: The authors meant as follows?
- Our previous studies in rodents revealed that concurrent oral administration of SEB and food antigens (by gavage feeding?) induces IgE-mediated reactivity to food antigens in intestinal mucosa.
- Hypothesis needs to be stated first and then explain how the prospective study was designed using what kind of outcome measures. The last sentences are explanation of obtained results and should be deleted or very simplified such as â€œ The obtained results in this prospective study did support a role of SEB in development or aggravation of FA in CRS patients.

Methods â€œ overall please consider further editing in terms of English writing.

Page 6
Study Subjects Â it is hard to believe that all the CRS-FA patients are not sensitized with common aeroallergens like dust mite. Secondary to persistent CRS symptoms, a diagnosis of allergic rhinitis may be difficult without prick skin testing. Also atopic or non-atopic asthma is a common complication in CRS patients. No asthma diagnosed in the all the CRS study subjects?
Skin prick test Â Prick skin test?
Extract of each fresh food Â extract of each unprocessed food?
Oral challenge test
One of the positive antigens from the skin test â one of the food allergens that the study subject revealed positive prick skin test reactivity?
10 common food allergens â it sounds like that these are used in prick skin testing. The symptoms of food allergy attack are closely observed â the study subjects were closely monitored for 4 hours following oral challenge in the facility where treatment of anaphylaxis was readily available.

Cytokine and antigen-specific IgE assessment: Serum levels of cytokine and allergen-specific IgE levels? Some sentences are unclear and editing is recommended.

Page 10
Antigen-specific T cell proliferation assay: (CD4+ cells are not purified)
1st paragraph;
an antigen with the largest wheal area in the skin prick test â an food allergen to which the study subject revealed the most significant prick skin test reactivity?
For intracellular cytokine staining, how many hours are cells incubated? (Usually 6-24h)

Results â again please consider through editing (English writing). Please delete redundant description of methodology or rationale. The results section should present just results only.

Page 13
The results of DBPC oral challenge test
EFSS attenuated allergic reactions to food allergens in oral challenge test?
Some sentences are redundant and should be deleted â please just describe results only.

Page 14
Serum IFN-Î³ levels: please check the scale of Fig. 1-C. Normal control healthy individuals seldom reveal IFN-Î³ levels higher than 50 pg/mL; usually 1-20 pg/ml in most of the papers published.

Page 15
Antigen specific T cell responses: More precise, accurate description of results is recommended such as written below:
When cultured with food allergens or SBE, PBMCs from CRS-FA patients produced higher levels of IL-4 (Fig. 3-A) than cells cultured without stimuli. PBMCs with stimulated with food allergen plus SBE revealed the highest IL-4 production. PBMCs from FA patients also revealed increase in IL-4 production with food allergen. However, FA PBMCs were less responsive to SBE than CRS-FA cells and concurrent cultures of SBE+food allergen did not further augment IL-4 production in FA patients?
Intracellular cytokine staining: Intracellular cytokine staining does not necessary directly reveal T cell proliferative responses. It is more accurate to say that these assays reflect frequency of IL-4 or IFN-Î³ expressing cells.
The results seem to indicate that CRS-FA PBMCs reveal significant increase in IL-4+ cells (if double stained with CD4, it can be described as IL-4+ CD4+ cells) with SBE+food allergen than SBE or food allergen alone. There might be a typo-error in % of IL-4+ cells in FA PBMCs following SBE stimuli; it looks like that SBE substantially decreased frequency of IL-4+ cells.

Page 16
The first few sentences should be stated in the method section or footnote of Table 6. I assume that Table 6 present the data obtained from CFS-FA patients but it is unclear how reduction of symptoms scores is calculated. Please clarify.

Discussion â€” Again please consider further editing in English writing. Multiple grammatical errors are noticed and several sentences need to be rewritten for better clarification.

Page 17:
1st paragraph: Simply summarize the conclusion of results.

Description of mechanisms of action of SBE is redundant in the introduction. Please simplify. It is better to concentrate on describing how SBE contained in sinus secretion can potentially affect gut mucosal immune responses.

Page 18
1st paragraph: Weal formation is generally regarded to reflect rapid increase in vascular permeability triggered by histamine. It is not clear how wheal formation quantitatively correlates with IgE levels bound to
mast cells. Recommend simplifying the sentences just describing that FESS appeared to have significantly attenuated prick skin test reactivity to food allergens. It is ideal to test if there is any change of reactivity to other aeroallergens, since SBE in the upper airway can also potentially aggravate prick skin test reactivity to common aeroallergens such as dust mite.

2nd paragraph:
Partial relieve of the clinical symptoms Â you mean partial relief?
This paragraph is not well structured. Revising the sentences will be helpful just concentrating on the results supporting the effects of FESS for attenuation of FA.

Page 19
1st paragraph. All the data indicates colonization of Staph. aureus. It is unclear if it can be said as infection.

2nd paragraph. It is better to describe that SBE can cause polyclonal T cell activation and depending on the pre-existing inflammatory condition, either Th1- or Th2- mediated inflammatory condition can be aggravated.

Last sentences: IL-5 does not facilitate IgE production.

Page 20
1st paragraph. It is better to simply emphasize the results which indicate attenuation of Th2 responses to food allergens. Then should point out the possibility that this improvement can be associated with reduction of Staph. colonization after FESS.

2nd paragraph and continued discussion with Treg cells on Page 21. Discussion is unclear. Lack of the effects of SBE on PBMCs from FA patients does not support their speculation. These CRS+FA patients may have genetic predisposition to respond rigorously to SBE and by bystander effect, their Th2 responses to food allergens may be further augmented as one possible explanation. There may be other possibilities as well. This portion of discussion is hard to follow.

Page 21
2nd paragraph Â it should be placed in the first part of discussion or in the introduction.