

(別紙) 研究成果の概要 (英文)

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| Title of research project | Studies on difference in the mechanisms between food allergy and oral tolerance and the mechanisms of anaphylactic reactions induced by food allergens |
| Research project number | (1705) |
| Research period | FY 2017– 2018 |
| Name of principal research investigator (PI) | Hiroshi Kido |

Abstract/Summary

We had conducted two projects. Project 1: Studies on difference in the mechanisms between food allergy and oral tolerance. Project 2: Studies on mechanisms of anaphylactic reactions. In project 1, we found biomarkers which indicate difference in the processes between food allergy induced by eczema and natural oral tolerance. In the maturation of natural oral tolerance in early infancy, we identified typical immunoglobulin class-switching patterns, IgM→IgG3→IgG1→IgG2→(IgG4), and IgM→low affinity IgE. Once infants developed eczema in the process of natural oral tolerance, class-switching (IgG1→IgG2→IgG4) was inhibited and class-switching (IgG1→high affinity IgE) was appeared. In the oral immunotherapy against severe food allergy in childhood, we found class-switching (IgG1→IgG2→high affinity IgG4) and change from high affinity IgE to low affinity IgE. These results suggest that immunoglobulin class-switching and allergen-affinity detections are useful for monitoring the processes of food allergy and oral tolerance. Project 2: Studies on mechanisms of anaphylactic reactions. Symptoms of food allergy are known to differ depending on the causative antigens; buckwheat, peanuts, and crustaceans are reportedly prone to cause severe anaphylaxis. However, it remains unknown why some food antigens cause anaphylaxis and some others do not. In this study, we focused on the affinity of the antibody to the antigen molecule as one of the mechanisms causing anaphylaxis, and the mechanism of high affinity antigen-specific IgE production was determined by multiple directions. (1) We examined the effect of TSLP, which plays an important role in epicutaneous sensitization, on proteolytic enzyme activity in the phagosome of antigen-presenting cells. As a result, a decrease in enzyme activity was observed, but the detailed mechanism remained unknown. (2) We examined the effect of various cytokines on the expression of AICDA, an enzyme that induces both class-switching and somatic hypermutation in B cells, and found that IL-4 and TSLP enhance the expression of AICDA. 3) The affinity of IgE antibodies in patients with IgE-dependent food allergy with and without anaphylaxis is examined. (4) We established a hen's egg allergy mouse model induced by epicutaneous sensitization. The hypothermia after antigen administration, IgE antibody titer, splenocyte Th2 cytokine production and skin permeability in this mouse model were all correlated with the expression of IL-33 in the local skin site, and the expression of IL-33

was age-dependent; older mice developed more severe reactions.

At present, it has not been possible to directly prove why the affinity of some foods is high. However, we established a system to measure the activity of degradative enzymes in the endosome of antigen-presenting cells using different foods, and a food allergy model based on mouse epicutaneous sensitization.

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1. List of papers published on the basis of this research

1. Irahara M, Shinahara W, Sugimoto M, Ogawa Y, Shitukawa K, Kubota K, Yang L, **Ohya Y**, Saito H, Kagami S, Arisawa K, **Kido H**. Trajectories of class-switching-related egg and cow's milk allergen-specific immunoglobulin isotype formation and its modification by eczema with low- and high-affinity immunoglobulin E during early infancy. *Immun Inflamm Dis*. 2019;7: 74-85. doi;10.1002/iid.3.245
2. **Matsumoto K**, Mori R, Miyazaki C, **Ohya Y**, **Saito H**. Are both early egg introduction and eczema treatment necessary for primary prevention of egg allergy? *J Allergy Clin Immunol* 2018;**141**:1997-2001.

2. List of presentations based on this research

1. **Kido H**. Different modes of immunoglobulin class-switching from allergen-specific IgG1 to low and high affinity IgE in the development of oral tolerance and food allergy. 67th Japanese Society of Allergology. 2018/6/22-24. Tokyo
 2. **Kido H**, Irahara M, Sasaki Y. Differential immunoglobulin class switching in the productions of allergen-specific low and high affinity IgE in the development of pediatric food allergy. 66th Japanese Society of Allergology. 2017/6/18. Tokyo
3. The number and summary of patents and patent applications
None.
 4. Others (awards, press releases, software and database construction)

Awards

1. **Kido H**. Best Presentation award. Japanese Society of Pediatric Allergy and Clinical Immunology. 2017/11/19.

2. **Kido H.** Best Presentation award. Japanese Society of Allergology. 2017/6/16-18.