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Original Article

Immune suppression of food allergy by maternal IgG in murine models

Hirotaka Yamashita [a, *], Tadamasa Hayashi [a], Kenichi Saneyasu [a], Hiroki Matsuhara [a], Teruaki Matsui [a, b], Hiroyuki Tanaka [a], Naoki Inagaki [a]

[a] Laboratory of Pharmacology, Department of Bioactive Molecules, Gifu Pharmaceutical University, Gifu, Japan
[b] Department of Allergy, Aichi Children's Health and Medical Center, Aichi, Japan

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ITAM	Immunoreceptor tyrosine-based activation motifs
ITIM	Immunoreceptor tyrosine-based inhibitory motifs

ABSTRACT

Background: Most of the patients develop food allergy early in life. The factors related to parental immune condition might be one of the conceivable causes.
Methods: We reported murine models of food allergy and oral OVA tolerance. To investigate the influence of parental immune condition on infant food allergy, female and male mice with food allergy or oral tolerance were mated with each other.
Results: Food allergy was suppressed by decreased IgE production in the offspring of mice with food allergy. On the contrary, anaphylaxis for OVA was induced in the offspring of mice with oral tolerance. The suppression of food allergy being dependent on a maternal factor was revealed in the offspring after cross-mating mice with food allergy and oral tolerance. Because OVA-specific IgG, presumed to be from the allergic mother, was detected in the serum of naïve infants from mothers allergic to food, we assumed that the suppression was dependent on a specific IgG. The serum IgG purified by a G-protein column was administered before OVA sensitization in the food allergy model, and OVA-specific IgE production was found to be diminished in the administered mice. However, OVA-specific monoclonal IgG_1 and IgG_{2a} administration could not suppress food allergy. Because we detected OVA-IgG immune complex in the serum of mothers allergic to food, it might be a cause of maternal immune suppression.
Conclusions: We demonstrated that maternal specific IgG conjugated food antigen is an important factor related to the development of food allergy and acquiring tolerance.

Introduction

Owing to the change in environmental conditions, numerous allergic diseases, such as seasonal allergic rhinitis, pediatric asthma, and peanut allergy, have increased over the last 100 years.[1,2] Especially, food allergy has increased dramatically in the past few decades.[3] Based on the challenge to some foods, the prevalence of food allergy has increased from 1 to 10.8% as reported in a meta-analysis,[4] and about 5% of the children in Europe have had one or more food allergies in their lifetime.[5,6] In Japan, epidemiology of pediatric food allergy in Ogasawara Islands has shown lifetime food allergy prevalence of 8.9%.[7] The causes of increasing food allergy are considered to be genetic factors,[8–10] changes in gut microbiome,[11] sunlight and vitamin D,[12,13] (high vitamin D level is a risk factor for the development of food allergy in early infancy,[14] or infants with vitamin D insufficiency are more likely to have multiple food allergies[15]), and intake of food additives.[16] Genetic predisposition and environmental allergen exposure may be associated with the increasing prevalence of food allergy; however, these factors cannot explain the mechanisms underlying the development of food allergy.[17]

Children from asthmatic parents tend to develop asthma.[18] Similarly, parental allergy can induce allergic and non-allergic rhinitis in their offspring.[19] There is a strong familial aggregation of food allergy among family members and twin.[20,21] Maternal inflammatory cytokine levels during pregnancy were related to the cytokine levels in the offspring, and maternal IgE levels were associated with IgE levels in children.[22] Additionally, Treg number, which decreases in atopic diseases, in the cord blood was related to the risk of development of atopic dermatitis and sensitization towards food allergens during the first year of life.[23] These data indicate that allergic factors in parents affect the disposition of their

* Corresponding author. Laboratory of Pharmacology, Department of Bioactive Molecules, Gifu Pharmaceutical University, Daigakunishi 1-25-4, Gifu 501-1196, Japan.
E-mail address: hyamashita@gifu-pu.ac.jp (H. Yamashita).
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offspring. Maternal factors, such as the overall health condition during pregnancy and lactation, are attributable to the development of allergies early in life. However, reports on the association of maternal consumption of peanut, milk, and wheat during pregnancy and lactation with food allergy,[24] or with reduced odds of allergies,[25] responsible for the development of allergic diseases, are inconsistent. In this study, we revealed the association between parental (maternal) food allergy and the food allergy that developed in their offspring using murine models.

Methods

Animals

Male and female BALB/c mice, or female BALB/c-*nu/nu* mice used for obtaining monoclonal antibodies, were purchased from SLC, Inc. (Hamamatsu, Japan). The mice were housed in an air-conditioned animal room at 23 ± 1 °C temperature and 50 ± 10% humidity. Experiments were conducted following the guidelines of the Animal Experiment Committee of Gifu Pharmaceutical University.

Murine models of food allergy and oral tolerance

Murine models of food allergy and oral tolerance to food antigens[26] are shown in Figure 1B, C. In the protocol of food allergy, male and female BALB/c mice were sensitized intraperitoneally with 1 μg OVA (Sigma–Aldrich, St. Louis, MO) or PBS mixed with Imject Alum (Thermo Scientific, Rockford, IL). The mice were administered 10 mg/mouse OVA dissolved in PBS orally four times every other day to induce food allergy from 1 week after the second sensitization of OVA injection. Anaphylaxis was elicited by administration of 50 mg/mouse OVA. For the induction of oral tolerance, mice were treated with 1 mg/mouse OVA orally for 5 successive days, 1 week before the first sensitization with OVA injection. Naïve male and female mice were used as controls (Fig. 1A–C).

In murine model, a scoring system for anaphylactic symptoms such as scratching, puffiness around the eyes and mouth, diarrhea, wheezing, and death,[27,28] and changes in the rectal temperatures[29] were usually used. We evaluated food allergy by a decrease in the rectal temperature and allergic diarrhea induced by OVA intake according to our previous report.[26] The decrease in body temperature was measured as a change in 1 h from each oral OVA administration using a thermometer (KN-91, Natsume, Tokyo, Japan). Allergic diarrhea was evaluated for determining the condition of feces for 1 h after OVA administration. Severity of diarrhea was assessed by a score from 0 to 3: 0 = solid state; 1 = semi-solid form (solid containing a little liquid); 2 = slurry, and 3 = watery state.

Mating between mice allergic to food and mice with oral tolerance

Food allergy or oral tolerance to OVA was induced in five female mice, who were mated with two male mice with the same treatment. As controls, naïve male and female mice were mated. Offspring of each pair were weaned at the age of four weeks. Following weaning, food allergy was induced in female infant mice (Fig. 1D). In a cross-mating study, food allergy was induced in the female progeny from female mice with food allergy or oral tolerance or naïve mice mated with male mice with other treatment.

ELISA measurements

OVA-specific IgE, IgG_1, IgG_{2a}, and IgA levels in the blood were measured by ELISA to modify previously described reports.[30,31]

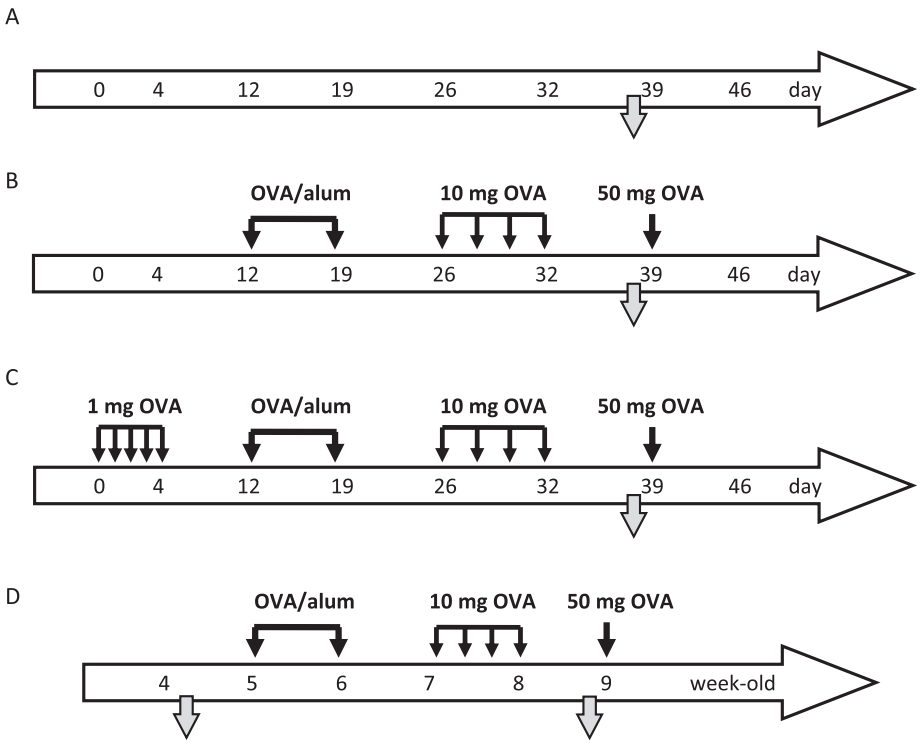

Fig. 1. Protocols for development of murine food allergy and oral tolerance models. Male and female mice were sensitized for OVA by administration of OVA/alum intraperitoneally. **(A)** Naïve female and male mice were used as controls. **(B)** Food allergy was induced in mice by oral administration of 10 mg OVA 4 times and elicited by 50 mg OVA. **(C)** Oral tolerance was induced by preliminary oral administration of 1 mg OVA for 5 successive days. **(D)** Offspring from each pair was induced for development of food allergy. **(A–C)** For measurements of immunoglobulin levels, the blood was collected from each parent at day 38, or **(D)** from offspring at 4 weeks and 8 weeks of age.

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