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Preparation of an allergen-specific immunomodulator by phosphorylation of a major buckwheat globulin allergen, Fag e 1, with diminished IgE response *via* Tfh cell activation

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Abstract

Fag e 1 is a 22 kDa globulin found in common buckwheat (*Fagopyrum esculentum*) and it is known to be one of the major allergens causing severe allergic symptoms. In this study, we successfully obtained recombinant Fag e 1 using the *Pichia* expression system and prepared an allergen-specific hypoallergenic agent by the controlled dry-heating phosphorylation of Fag e 1 (P-Fag e 1). Then, we investigated if P-Fag e 1 can be useful as an immunomodulator in Fag e 1-sensitized mice. For this, P-Fag e 1 was orally administrated into Fag e 1-sensitized mice for 6 weeks, and then these mice were challenged with Fag e 1. We observed a significant reduction in the histamine release in addition to diminished production of total as well as specific IgE in the P-Fag e 1-treated mice. In contrast, total IgA level increased by the treatment with P-Fag e1. The levels of the IL-4 cytokines from both spleen and Peyer's patches were significantly decreased in P-Fag e 1 treated mice. Additionally, the population of T follicular helper cells (Tfh cells) was increased in the P-Fag e 1 treated group. The suppression of IgE production in the Fag e1 treated group might be due to the enrichment of the Tfh cells and IgA production. Therefore, it could be proposed that P-Fag e 1 is an allergen-specific immunomodulator in mice allergic to Fag e 1.

Keywords : buckwheat, Fag e 1, immunomodulator, *Pichia* expression system, phosphorylation

I Introduction

A number of clinical studies have shown evidence that oral immunotherapy can be safely and effectively used for patients with food allergy. Immune tolerance is a mode of oral immunotherapy that is used for these patients. One of the widely accepted mechanisms explaining the role of immune tolerance is isotype switching. Mature B cells show antibody class-switching as a response to antigenic stimulation and presence of co-stimulatory signals[1)]. Class-switching also occurs in B cells that secrete allergen-specific IgG_4 instead of IgE leading to inhibition of binding between the allergen and IgE on the mast cells and basophils[2)]. In addition, T follicular helper cells (Tfh cells) which are a subset of T cells support the functions of B cells. These cells also produce IgA and IL-21 cytokines which are responsible for reducing the allergenicity[3, 4)]. However, oral administration of food allergens is associated with IgE-mediated and anaphylactic symptoms[5)]. Therefore, the development of effective and safer tolerogens is urgently needed.

Recently, allergen-specific immunotherapy has become a tool for prevention and treatment for many diseases[6)]. The benefits of allergen-specific immunotherapy include reduction of disease severity leading to decreased drug usage as well as prevention of future sensitizations during long-term treatments. It also improves the safety and efficacy of the future treatments[7)]. The functional properties of proteins can be further improved by chemical modification and this method

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