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REVIEW

BIOTECHNOLOGY IN CONTROLLING FOOD ALLERGY

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SUMMARY

Allergy to food is the hypersensitivity of the immune system when contacting to proteins or components in food. The incidence of food allergy continuously increases year by year particularly in industrial countries, and by now has become a serious problem worldwide since every protein-containing food can cause allergic reactions. Food allergy can affect 1 - 2% of the adult population and up to 8% of children population. The most common food allergy is the type I reaction which is mediated by Immunoglobulin I. Responses to food are varied from skin reactions to anaphalytic shocks which can lead to death. Food allergy is mainly treated by systematic medication or removal and/or avoidance of the causal food. Another promising solution for allergic patients is the development of hypoallergenic food. Hypoallergenic foods can be produced via (1) food processing or by selection or (2) development of hypoallergenic primary materials. Selection and breeding of low-allergenic variety is the conventional strategies to produce hypoallergenic food. Additionally, biotechnology offers a quicker and more efficient strategy to develop such food by gene silencing. Antisense and RNA interference-induced gene silencing are two common strategies to remove undesired proteins from plant-derived foods. Hypoallergenic rice, soybean, peanut, apple and tomato are good examples supporting the feasibility of biotechnology in reducing food allergy.

Keywords: *Aantisense, food allergy, gene silencing, hypoallergenic food, RNA interference*

FOOD ALLERGY

What is food allergy?

The term "allergy" derives from the Greek words "*allos*" and "*ergon*" meaning "other" and "action", respectively (Glossary of Allergy Terms, Asthma and Allergy Foundation of America; www.aafa.org). Thus, food allergy is an inappropriate reaction by the body's immune system to the ingestion of a food that in the majority of individuals causes no adverse effects (Mekori, 1996; Bruijzeel-Koomen *et al.*, 1995).

Allergy to foods can be an important nutritional problem for humans since any food source containing proteins has the potential to elicit allergic reactions (Sampson, 1999a/b; 2004). Allergic responses may occur on the skin (eczema, dermatitis or hives), in the respiratory tract (shortness of breath, rapid breathing or asthma) or the gastrointestinal tract (oral allergy syndrome (OAS), abdominal pain or diarrhea) (Fig. 1A). Allergic reactions sometimes are severe and can even cause an anaphylactic shock, which may be lethal (Bruijzeel-Koomen *et al.*, 1995; Helm, Burks, 2000; Kagan, 2003).

The occurrence of food allergies continues to increase year by year, especially in industrial countries. General surveys in the American population reported that as many as 25 - 30% households consider at least one family member to have a food allergy (Atkins, James, 2007). This high rate was not supported by subsequent studies; however, the actual prevalence of food allergies is believed to be around 1 - 3.7 % in adults and up to 6 - 8% in children (Helm, Burks, 2000; Vieths *et al.*, 2002; Wood, 2003; Sampson, 2004; Madsen, 2005; Mills, Breiteneder, 2005; Atkins and James, 2007). Changes in life style including food consuming pattern, child vaccination, housing insulation, hygiene,... are thought to be the major reasons for this high prevalence.

Mechanism of IgE-mediated food allergies

Most cases of food allergies are type 1 allergic reactions mediated by immunoglobulin E (IgE)

(Roitte *et al.*, 1993). This type of reaction affects around 10 - 25% of the population in industrial countries (Mekori, 1996); however the prevalence in a selected population is even higher, for instance about 69.4% of Berlin food allergic population (Madsen, 2005) or 70 - 85% of atopic eczema/dermatitis patients in Sweden (Bardana, 2004). Especially, children are normally more affected by IgE-mediated food allergies than adults (Bock, 1987; Sampson, 1990). The interaction between an allergen and the immune system involves a sequence of reactions with a large number of cytokines. When an allergen enters the body, it is recognized by Antigen Presenting Cells (APCs) and subsequently processed into peptides which later interact with the naive TH_0 cells and modified them to antigen-specific TH_2 cells (Fig. 1B). Such antigen-specific cells produce a number of cytokines, especially IL-4, IL-10, and IL-13. IL-4 and IL-10 inhibit the formation of TH_1 cells while IL-4 and IL-13 stimulate B cells to produce a huge amount of allergen-specific IgEs. Secreted IgE will attach to high-affinity IgE receptors (FcεRI) of mast cells, basophilis and eosinophilis. During the second contact, the allergens will bind to specific IgEs on the surface of mast cells, basophilis and eosinophilis, leading to the degranulation of these cells and release of inflammatory mediators including histamine, leukotriens and cytokines. Those mediators cause allergic symptoms on the skin, in the respiratory and the gastrointestinal tracts (Roitt, *et al.*, 1993; Jeurink, Savelkoul, 2006; Larché *et al.*, 2006).

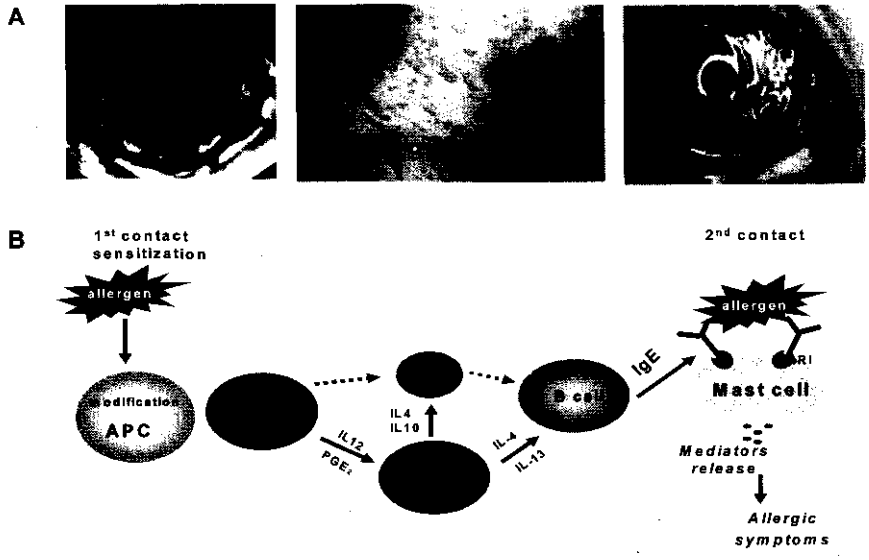

Figure 1: A. Imagination of food allergy. From left to right: Oral allergy syndrom (OAS), urticaria and conjunctivitis; **B.** Mechanism of IgE-mediated allergic reactions (modified from Larché *et al.*, Immunology, 2006). The recognition of allergens by APC will activate naive TH_0 cells to become allergen-specific TH_2 cells. The balance of TH_1-TH_2 will be changed, resulting in the overproduction of TH_2. TH_2 produces various inteleukins including IL-4 and IL-13 to stimulate overproduction of allergen-specific IgEs. IgEs subsequently bind to mast cells via high-affinity IgE receptors (FcεRI). During the second contact, the allergen will be cross-linked to the specific IgE on the surface of mast cells, resulting in the release of inflammatory mediators such as histamine. Allergic symptoms will subsequently develop. Linear arrows: positive effect; dashed arrows: negative effect.

APPROACHES TO REDUCE FOOD ALLERGY

Since any proteins in foods can be the source of allergens, food allergy represents a nutritional problem for humans and causes a high burden on the economy. It is estimated that approximately 45

millions of Euros were spent for allergy treatment in Western Europe in the year of 2004 (Gilissen *et al.*, 2006). Additionally, the reduction in "quality of life" of allergic patients themselves and their relatives is hardly quantified in terms of money.

Food avoidance

The simplest way to eliminate food allergy is the avoidance of the causing food. However, many allergenic proteins are pan-allergens, which can bind to IgE antibodies of different pollen and food allergic patients (Aalberse *et al.*, 2001; Rodriguez, Crespo, 2002; Ferreira *et al.*, 2004). Therefore, elimination of a number of foods in the diet is impossible, especially for children. Additionally, long-term elimination of foods probably leads to nutritional disorders, reducing life quality of patients and their family members, and severely restricting their social activities and causing isolation.

Medications and vaccination

A specific immunotherapy (SIT) to inhalant allergens has proven to be highly successful in preventing the development of allergic reactions. Injection of a predicted allergen over a long period of time gradually alters the immune response, in which the number of allergen-specific TH_2 cells decreases while the number of TH_1 cells increases. Subsequently, sensitivity to a certain allergen will be reduced (Bousquet *et al.*, 1998; Wachholz *et al.*, 2002; Weiss *et al.*, 2006; Larché *et al.*, 2006). This process was successfully applied against grass, ragweed, mountain cedar or birch pollen allergies (Wachholz *et al.*, 2002; Mahler *et al.*, 2004; Niederberger *et al.*, 2004; Weiss *et al.*, 2006). Successful SIT against food allergy was shown only in animal model systems (Roy *et al.*, 1999; Takagi *et al.*, 2005) and is not widely recommended in humans as stable extracts from plant foods standardized for the relevant allergens are limited and severe side effects may occur (Enrique, Cisteró-Bahíma, 2006; Nieuwenhuizen, Lopata, 2005). However, it was shown that SIT against some pollen allergens which exhibit cross-reactivity with food allergens may remove symptoms caused by these food allergens, e.g SIT against birch pollen reduced the OAS to apples and hazelnuts (Hansen *et al.*, 2004; Bucher *et al.*, 2004). Antihistamine treatment may decrease symptoms by inhibiting the histamine release of mast cells (Leurs *et al.*, 2002; Simons, 2004). Beside these approaches, anti-IgE therapy was shown to reduce severe allergic asthma in peanut-allergic patients (Leung *et al.*, 2003). Blocking the invasion of cytokines (IL4, IL5, IL9 or IL13) by appropriate antibodies has been clinically tested but has not yet been commercially recommended for food allergic patients (Nieuwenhuizen, Lopata, 2005). Additionally, a natural therapy using Chinese herbal formulas showed promising results in down-regulating TH_2- and IgE-responses and thereby reducing the allergic symptoms as shown in murine models for peanut allergy (Li *et al.*, 2001; Srivastava *et al.*, 2005).

Hypoallergenic food

Alternative to food avoidance, the development of hypoallergenic food is promising to improve life quality of allergic patients. Such foods can be produced through (1) the elimination or destruction of allergenic epitopes or (2) the development of hypoallergenic primary materials. A number of processing technologies such as chemical or biochemicals (hydrolysis using proteases, peroxidases, cellulases) or physical (heating or extraction) strategies are investigated to reduce allergenic proteins in food products.

Food processing

Brenna *et al.* (2005) described a chemical removement of peels from apricots to a reduction of allergenic potential in final products. The commercially available "Fine rice" is produced by protease digestions of the major allergenic globulin in rice grains (Watanabe *et al.*, 1990). Similarly, allergens from soybean, roasted peanut or wheat flour might be reduced by hydrolysis using protease, peroxidase or a mixture of peroxidase and cellulase (Yamanishi *et al.*, 1996; Chung *et al.*, 2004; Watanabe *et al.*, 2000). These enzymes can digest the folding structure of proteins leading to destruction of the IgE-binding epitops of putative allergens. Nevertheless, only a certain number of allergens can be digested via enzymatic hydrolysis and a large number of allergens are indigestible or difficult to modify under normal food processing conditions (Vieths *et al.*, 1996).

Selection and breeding

Selection and breeding are conventional methods to obtain hypoallergenic primary materials. As shown in the EU-SAFE project, allergenicity of a large number of apple cultivars and genotypes were

analyzed within apple allergic population (Gilissen *et al.*, 2006). Clinical analysis revealed a significant difference in allergenic potential with a factor of thirty. The genetic basis of this difference in allergenicity was also demonstrated within this project. This would allow the crossing between different apple cultivars to produce a hypoallergenic one with improved agronomic characteristics. Selection and breeding of hypoallergenic cultivars is not restricted to apple and can be applied to other crops with diverse genotypes. One disadvantage of this strategy is time-consuming and requires a large scale of plant material for selection.

Genetic engineering

Genetic engineering is the modern way to manipulate directly one organism's genome. Thus, genetic engineering offers a quicker way to produce hypoallergenic food by silenced genes coding for allergens. Gene silencing can be achieved by several methods including antisense and RNA interference (RNAi) followed these major steps: (i) identification and isolation of genes coding for allergens plant sources; (ii) insertion of partial or full length nucleotide sequences of these genes into appropriated vectors (iii) stable transformation of these constructs into plant cells and (iv) analysis the expression of allergens and its efficiency in reducing allergenic potential *in vitro* and *in vivo* of transformed products.

Reduction of allergenic proteins by antisense approach

Rice is a cereal which is widely produced and consumed in Asia countries. Sensitivity to rice is mainly associated with 14 - 16 kDa proteins. cDNA clones encoding these allergenic proteins were isolated from a appropriated cDNA library and cloned in antisense orientation into a plant transformation vector (Tada *et al.*, 1996). The antisense approach repressed the expression of these allergenic genes, leading to a reduction up to 80% in accumulation of the allergenic 14 - 16 kDa protein. The high levels of reduction observed were stably inherited in at least three generations. Similarly, the antisense-induced gene silencing was also used to prevent the accumulation of Gly m Bd 30 K, a major allergen in soybean (Herman *et al.*, 2003). Western analysis using either polyclonal raised against Gly m Bd 30K protein or pool sera of soybean allergic patients exhibited no residual of this protein in transgenic seeds. However, in both cases, functional analysis such as triggerring of effector cells to quantify the allergenic potential of transgenic materials was not demonstrated.

Reduction of allergenic proteins by RNAi approach

RNA interference or RNAi is an ancient part of the antiviral system found animals and plants (Voinnet *et al.*, 2001). RNAi was first described by Fire *et al.* (1998) who later won the 2006 Medical Nobel prize for this discovery. From then on, RNAi become an efficient tool to silence target genes in many organism. Normally, an RNAi gene construct consist of an inverted repeat of a fragment of target gene sequence separated by an intron (Fig. 2). The introduction of such constructs will form so called small interfering RNAs (siRNAs), which can initiate the degradation of viral RNA or endogenous mRNA by base-pairing interactions with homologous sequences (Fire *et al.*, 1998). Compared to other strategies, RNAi has been shown to be most efficient leading to almost 100% inhibition of endogenous transcripts accumulation (Smith *et al.*, 2003; Wesley *et al.*, 2003).

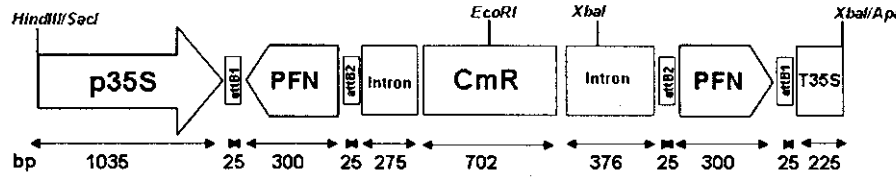

Figure 2. Imagination of an RNAi constructs used to silence a tomato allergen (Le *et al.*, JACI 2006b).

Following RNAi strategy, Le *et al.* (2006a/b) and Lorenz *et al.* (2006) described a strategy to produce hypoallergenic tomato fruits. On the basis of the isolation of two tomato allergens Lyc e 1 and Lyc e 3 (the official name of two tomato allergens, profilin and lipid transfer protein according to the International Union of Immunological Societies), RNAi constructs were designed coding nucleotide

sequences of either Lyc e 1 or Lyc e 3. Subsequently, these constructs were introduced into tomato plants via *Agrobacterium*-mediated transformation. With Northern blotting, the effect of RNAi-induced gene silencing was revealed by means of a strong reduction in Lyc e 1 or Lyc e 3 transcripts. Reduction of expression of these allergens was subsequently by immunoblotting. In wild type tomato fruits, strong bands were detected with specific antibodies raised against Lyc e 1 or Lyc e 3 at the expected apparent molecular weight but absence in transgenic fruits. The amount of residual Lyc e 1 or Lyc e 3 was subsequently quantified by immunological analysis (ELISA inhibition assay or histamine release assay). A ten-fold-decrease in Lyc e 1 abundance and up to one hundred-fold reduced were obtained in transgenic fruits. Additionally, these authors included the first *in vivo* clinical analysis (skin prick test) with transgenic fruits. Skin prick test is a fast clinical analysis and easy to perform (Fig. 3A). It reflects the reactivity of mast-cell-bound IgEs, which fulfill a major role in type I allergic reactions. A decrease in allergenic protein expression by RNAi silencing led to the reduction in allergenic potential of transgenic tomato fruits (Fig. 3B). Skin prick tests showed a partial reduction in skin reactivity, approximately 20 - 80% with Lyc e 3-silenced fruits and 16 - 61% with Lyc e 1-silenced fruits. Le *et al* explained the less impressive reduction in skin reactivity by the non mono-sensitive to one single allergen of tomato sensitive patients involved. Additionally, the heritability and stability of RNAi gene silencing were confirmed at T1 and T2 generations of green-house grown transgenic plants (Lorenz *et al.*, 2006). RNAi has also been used to reduce the accumulation of peanut and apple allergens (Herman *et al.*, 2003; Gilissen *et al.*, 2005). Immunoblots revealed significant reduction in the content of allergenic proteins in these plants. Further, the allergenic potency was verified by means of IgE binding capacity in peanuts or apple leaves. However, further functional tests such as the ability to trigger mast cell were still missing in case of transgenic peanuts and only apple leaves were performed skin prick test. Nevertheless, the examples of silenced peanut, apple and tomato supported the feasibility of producing hypoallergenic food via RNAi-mediated gene silencing. Additionally, RNAi technology might allow simultaneous silencing of multigene families (homology-based silencing of related genes) and of multiple target genes (chimeric RNAi) in a cell and organ specific manner. Le *et al.* (2006a/b) demonstrated the silencing of more than one member of a multigene family when introducing RNAi constructs containing cDNAs of one homologous isoform. RNAi approach was shown to be an efficient and applicable approach to produce hypoallergenic food since RNA interference is a natural and widespread mechanism of gene regulation in living organism.

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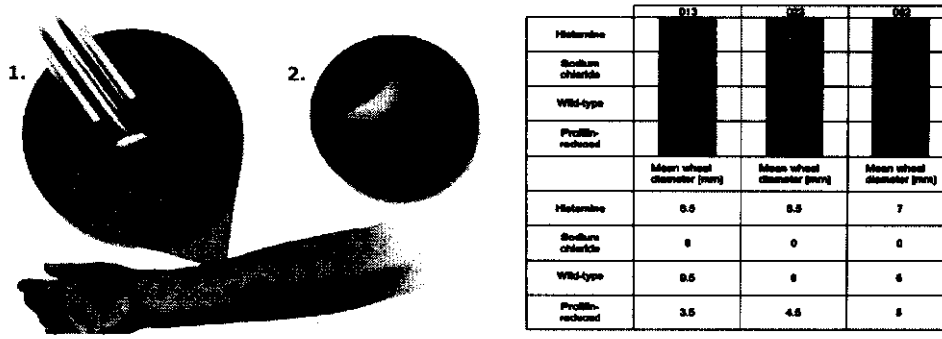

Figure 3: A. Imagination of skin prick testing. 1: introduce of allergens into the patient's skin. 2: analyse the allergic reaction by means of wheal diameter. **B.** Results of skin prick testing of tomato sensitive patients (013, 023 and 002) using native and Lyc e 1-silenced fruits (Le *et al.*, JACI, 2006b). The *in vivo* clinical analysis revealed a decrease in skin reactivity of transgenic tomato fruits indicating a reduction in allergenic potency.

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VAI TRÒ CỦA CÔNG NGHỆ SINH HỌC TRONG KIỂM SOÁT DỊ ỨNG THỰC PHẨM

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Viện Công nghệ sinh học

TÓM TẮT

Dị ứng với thực phẩm hiện đang là một trong những vấn đề dinh dưỡng cấp thiết, bởi tất cả các thực phẩm có chứa protein đều có thể là tác nhân gây dị ứng. Dị ứng thực phẩm thường gặp nhất là type I do immunoglobulin E xúc tác phản ứng mẫn cảm. Biểu hiện lâm sàng của dị ứng thực phẩm khá đa dạng, từ nổi mày đay, ngứa ran, đau bụng, khó thở cho tới sốc phản vệ và có thể dẫn tới tử vong nếu không được cấp cứu kịp thời. Dị ứng thực phẩm hiện nay không có thuốc đặc trị. Do vậy, đối với người bị dị ứng, hạn chế sử dụng thực phẩm có chứa chất gây dị ứng hoặc sử dụng các thực phẩm không gây dị ứng là giải pháp hữu hiệu duy nhất . Thực phẩm không gây dị ứng là những thực phẩm không có chứa một hoặc vài protein gây dị ứng đã biết. Loại thực phẩm như vậy có thể được sản xuất bằng cách (1) sơ chế các nguyên liệu ban đầu (food processing) nhằm phân hủy các protein dị ứng hoặc (2) sử dụng các nguyên liệu không gây dị ứng. Chọn lọc và lai giống là phương pháp công nghệ sinh học truyền thống để tạo các nguyên liệu không dị ứng. Giải pháp công nghệ sinh học hiện đại là gây bất hoạt các gen mã hóa cho những protein gây dị ứng (gene silencing), từ đó loại được các protein không mong muốn này. Cho tới nay, antisense và RNAi là những phương pháp thường được sử dụng để ức chế biểu hiện của gen và đã tạo nên những dòng lúa, đậu nành, táo và cà chua không gây dị ứng. Đặc biệt, RNAi là phương pháp có khả năng ức chế gen cao hơn, gây bất hoạt đồng thời nhiều đồng phân khác nhau của một họ gen hoặc nhiều gen khác nhau, mở ra một giải pháp mới nhằm hạn chế dị ứng thực phẩm cũng như nâng cao chất lượng cuộc sống cho các bệnh nhân bị dị ứng.

Từ khóa: *Antisense, dị ứng thực phẩm, bất hoạt gene, RNA interference, thực phẩm không dị ứng*

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