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Birch Pollen-Related Food Allergy: An Excellent Disease Model to Understand the Relevance of Immunological Cross-Reactivity for Allergy

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1. Introduction

According to the position paper from the European Academy for Allergy and Clinical Immunology (EAACI) "food allergy" summarizes immune-mediated, non-toxic adverse reactions to foods (Figure 1)(Bruijnzeel-Koomen et al., 1995). The most common form of food allergy is mediated by immunoglobulin (Ig)E antibodies and reflects an immediate-type ("Type 1 hypersensitivity") reaction, i.e. acute onset of symptoms after ingestion or inhalation of foods. IgE-mediated food allergy is further classified into primary (class 1) and secondary (class 2) food allergy. This distinction is based on clinical appearance, the predominantly affected group of patients (children or adults), disease-eliciting food allergens and the underlying immune mechanisms. Primary (class 1) or "true" food allergy starts in early life and often represents the first manifestation of the atopic syndrome. The most common foods involved are cow's milk, hen's egg, legumes (peanuts and soybean), fish, shellfish and wheat. Of note, allergens contained in these foods do not only elicit allergic reactions in the gastrointestinal tract but often cause or influence urticaria, atopic dermatitis as well as bronchial obstruction. With a few exceptions (peanut and fish) most children outgrow class 1 food allergy within the first 3 to 6 years of life.

Secondary (class 2) food allergy describes allergic reactions to foods in mainly adolescent and adult individuals with established respiratory allergy, for example to pollen of birch, mugwort or ragweed. This form of food allergy is believed to be a consequence of immunological cross-reactivity between respiratory allergens and structurally related proteins in the respective foods. In principle, the recognition of homologous proteins in foods by IgE-antibodies specific for respiratory allergens can induce clinical symptoms. Foods inducing allergic reactions in the different groups of patients vary according to the manifested respiratory allergy. Different syndromes have been defined, such as the birch-fruit-hazelnut-vegetable syndrome, the mugwort-celery-spice syndrome or the latex-shrimp syndrome.

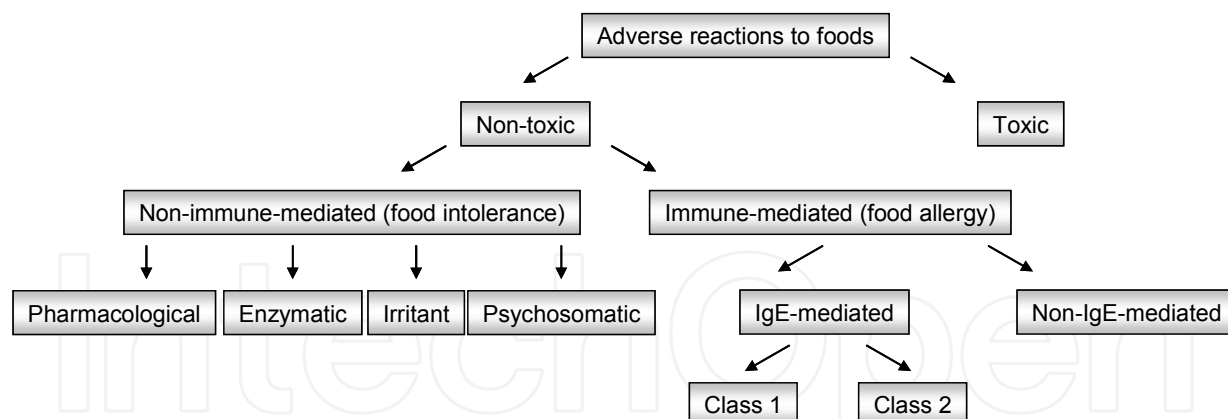


Fig. 1. Classification of adverse reactions to foods according to the pathophysiology (Bruijnzeel-Koomen et al., 1995). Adverse reactions to foods comprise toxic and non-toxic reactions. The latter reactions are either non-immune-mediated or immune-mediated. IgE-mediated reactions constitute type I hypersensitivity while non-IgE-mediated reactions are suspected to be mediated by IgG or IgM immune complex reactions (type III hypersensitivity) or cell-mediated delayed-type reactions (type IV hypersensitivity).

2. Immune mechanisms underlying IgE-mediated allergy

IgE-mediated allergy develops upon contact with an allergenic protein leading to sensitisation. The allergen is absorbed through the mucosal membrane of the respiratory or the gastrointestinal tract or the skin and can enter tissues through disrupted epithelium and gain access to antigen-presenting cells (APC), most importantly dendritic cells, which takes up allergen and migrate to lymph nodes. There they present small peptide fragments resulting from allergen processing bound to major histocompatibility complex (MHC) class II molecules to naïve CD4⁺ Th lymphocytes. Depending on key cytokines present during the initial interaction with APC naïve CD4⁺ cells differentiate into five different (and maybe more) “classical” effector cell subsets, Th2, Th1, Th17, Th22 cells and induced regulatory T (Treg) cells (Figure 2). The presence of interleukin (IL)-4 promotes T cell differentiation towards allergen-specific Th2 cells that produce high amounts of the signature cytokines IL-4, IL-5, IL-9 and IL-13 but little or no interferon- γ (IFN- γ). IL-4 is the major switch factor for IgE synthesis in B cells. The presence of IL-12 and IL-27 during T cell priming fosters the differentiation of Th1 cells that produce high amounts of the signature cytokine IFN- γ , which is a potent antagonist of IL-4 and inhibits the differentiation of Th2 cells. Human Th17 cells differentiate in the presence of IL-1 β and IL-23. This subset synthesizes the signature cytokines IL-17a, IL-17f, IL-22 and IL-21. Th17 cells are important for the defence against extracellular bacteria and fungi and play a role in inflamed skin in atopic dermatitis. Moreover, Th17 cells have been shown to be involved in initiation and augmentation of inflammation in the airways and in the gut mucosa. Th22 cells produce IL-22 but not IL-17 and differentiate in the presence of IL-6 and TNF- α (Duhon et al., 2009). IL-22 is a growth factor for keratinocytes and Th22 cells have been considered to have a role in protective and regenerative epithelial cell responses (Eyerich et al., 2009). Induced Treg cells suppress the differentiation and effector phases of other T cell subsets either by cell-cell contact and/or by IL-10 and/or TGF- β . Different subsets of Treg cells have been described. So-called Th3 cells producing high amounts of TGF- β have been implicated as mediators of oral tolerance.

The term “Tr1 cells” was proposed for all IL-10-producing regulatory T cell populations that are induced by IL-10. Additional subsets of Treg cells may exist as well as additional subsets of effector cells, e.g. the more recently described Th9 (Veldhoen et al., 2008, Wong et al., 2010). In addition, evidence accumulates that there is a significant degree of overlap and plasticity between the different subsets of CD4⁺ T effector and regulatory lymphocytes.

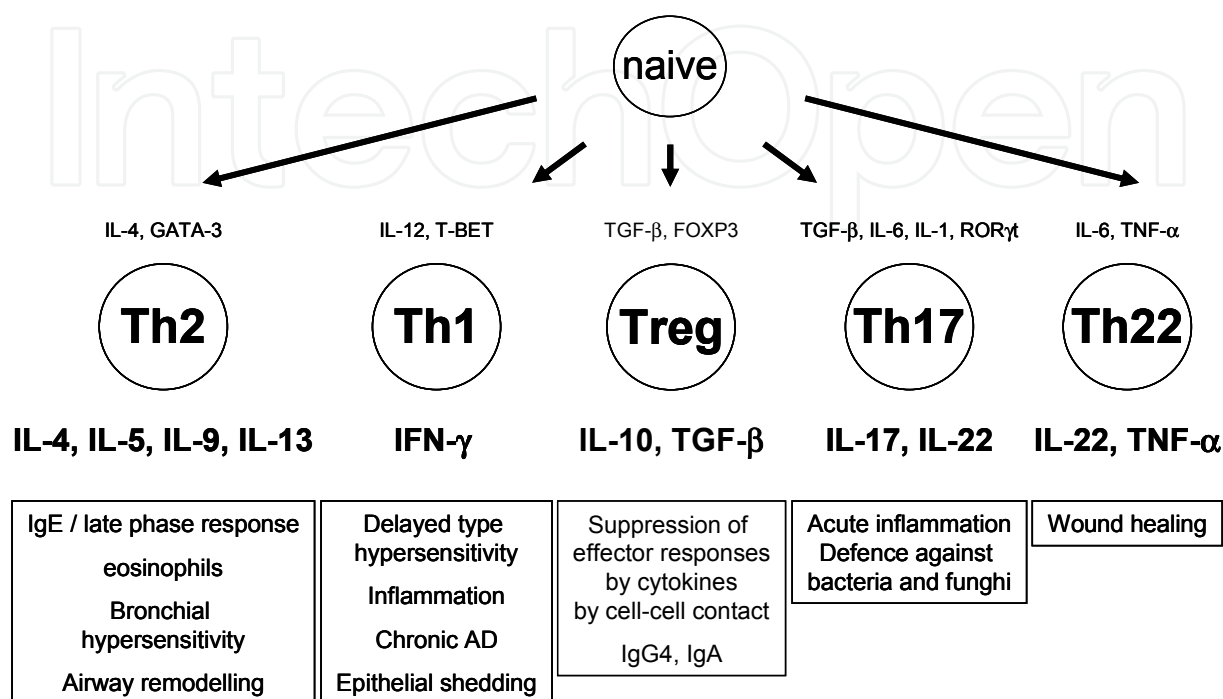


Fig. 2. Classical CD4⁺ T cell subsets and their role in IgE-mediated allergy. Naïve CD4⁺ T lymphocytes differentiate into different subsets directed by cytokines in the microenvironment during their activation *via* the T cell receptor. The presence of high concentrations of IL-4 promotes the induction of Th2 cells, IL-12 of Th1 cells, TGF- β Treg cells, TGF- β and IL-6 and/or IL-1 Th17 cells and IL-6 and TNF- α Th22 cells. The different subsets are characterized by the expression of different transcription factors (GATA-3, T-bet, Foxp3, ROR γ t). The transcription factor of Th22 cells has not yet been identified. Upon activation the different subsets of CD4⁺ effector cells produce different signature cytokines and thereby exert different effector functions.

IgE-mediated disorders result from an aberrant Th2-dominated response to allergens due to ineffective counter-regulation by allergen-specific Th1 and Treg cells. The overshooting allergen-specific Th2 response promotes the production of allergen-specific IgE antibodies which subsequently are bound to the high affinity receptor (Fc ϵ RI) on the surface of effector cells such as mast cells and basophils (Figure 3). Cross-linking of IgE by allergen induces effector cell activation and the release of preformed mediators, most importantly histamine, which cause immediate allergic symptoms. After 6-48 hours late phase reactions occur which are mediated by eosinophils and allergen-specific T cells that have migrated to the site of inflammation. Allergen-IgE-complexes bind to low affinity IgE receptors (Fc ϵ R2, CD23) expressed on lymphocytes, monocytes, macrophages and platelets. Receptor-mediated endocytosis of allergens *via* Fc ϵ R2 is an important way of allergen uptake by B lymphocytes which is thought to increase allergic responses by promoting Th2 responses.

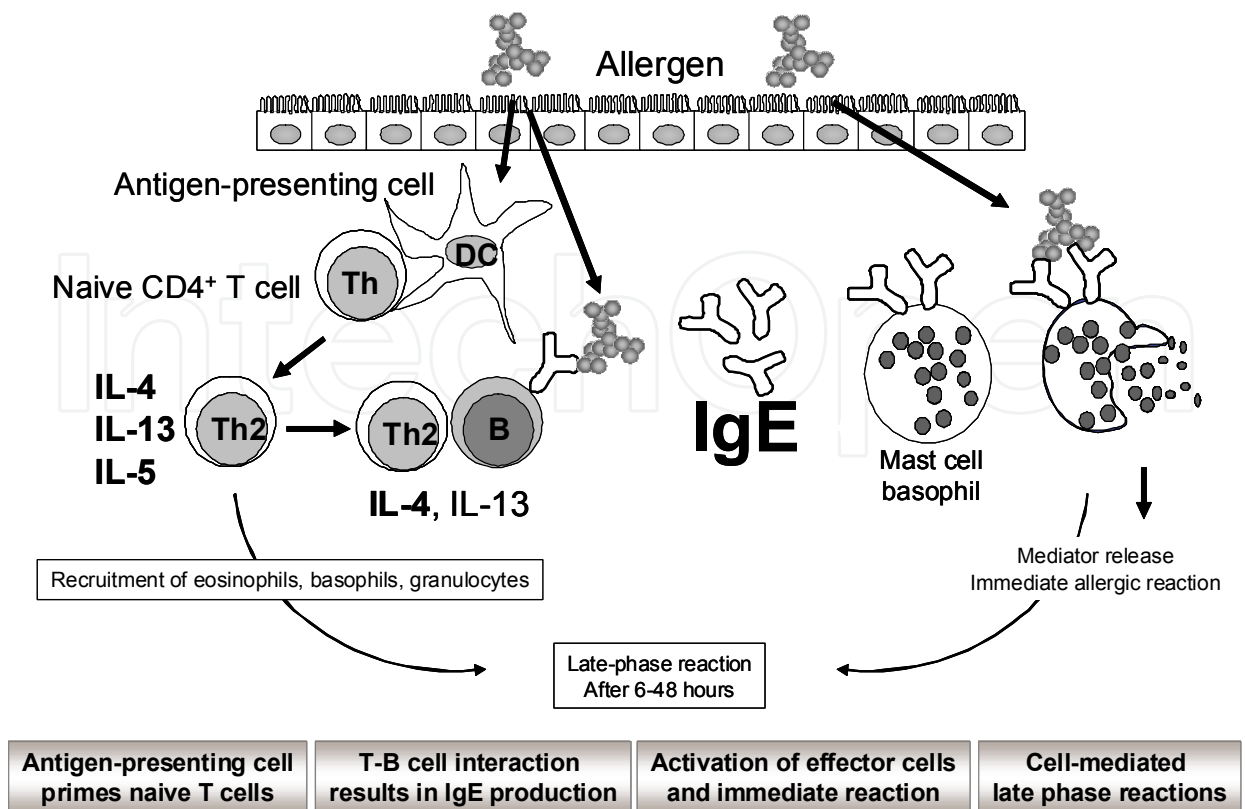


Fig. 3. The pathophysiology of IgE-mediated allergy. Allergens enter the human body through mucosal sites, e.g. in the respiratory or gastrointestinal tract, or via the skin. Antigen-presenting cells, most importantly dendritic cells (DC), take up allergens and migrate to lymph nodes where they present allergens to naïve CD4⁺ T helper (Th) cells. In atopic individuals, the majority of allergen-specific T cells differentiate into Th2 cells producing high amounts of the signature cytokine IL-4. Interaction of Th2 cells and B cells leads to the production of IgE antibodies which are bound on the surface of effector cells. Upon repeated allergen encounter, these effector cells are activated and release preformed mediators, most importantly histamine, causing immediate allergic symptoms. After 6-48 hours cell-mediated late phase reactions in target organs can occur because different types of granulocytes and allergen-specific T cells have migrated to inflammatory sites.

3. Birch pollen-related food allergy: Clinical appearance

Birch pollen is one of the most common causes of rhinoconjunctivitis and allergic asthma in Northern and Central Europe and North America (Lin et al., 2002, Stevens et al., 2003). Already in 1948 it has been recognized that birch pollen-allergic patients tend to develop allergic reactions to fruits and vegetables in addition to seasonal respiratory symptoms (Juhlin-Dannfelt, 1948). An association between birch pollinosis and allergic reactions to diverse foods was first demonstrated in the late seventies (Hannuksela and Lahti, 1977). In this report, more than 380 Finish patients with various atopic disorders were tested for allergic reactivity to common fruits and vegetables. Of the patients with hypersensitivity to birch pollen, 36% showed immediate positive responses to fresh fruits and vegetables whereas such reactions were rare among patients without allergy to birch pollen. One year later a correlation between birch pollen allergy and allergic symptoms to nuts, apple, peach,

cherry, pear, plum, carrot and new potato was reported in 1120 adult Swedish patients (Eriksson, 1978). A subsequent interrogation of 600 patients with pollen allergy again confirmed that hypersensitivity to various nuts, fruits and roots was reported more often by patients with (70%) than by patients without birch pollen allergy (19%) and that grass pollen allergy negatively correlated with food hypersensitivity (Eriksson et al., 1982).

Approximately, 100 million people suffer from birch pollen allergy worldwide and approximately 70% of these individuals develop birch pollen-related food allergy. Therefore, this secondary food allergy has to be regarded as one of the most common plant food allergies in adolescent and adult individuals today. Interestingly, birch pollen-related food allergy is perennial in more than 80% of the affected individuals, i.e. affecting the patients also outside of the birch pollen season (Geroldinger-Simic et al., 2011). Around 40% of the patients suffer from more severe symptoms during the pollen season as compared to the pollen-free time period. The most frequent triggers of birch pollen-related food allergy are stone-fruits (apple, peach) and hazelnuts. In addition, particular vegetables (celery, carrot), peanuts and soy products can also induce allergic reactions in birch pollen-allergic patients (Asero et al., 1996, Eriksson et al., 1982, Geroldinger-Simic et al., 2011, Ghunaim et al., 2005, Osterballe et al., 2005). In the majority of patients allergic reactions to these foods manifest as contact urticaria of the oral mucosa (oral allergy syndrome, OAS). Typical symptoms comprise itching of the lips, tongue and throat, sometimes accompanied by oedema of the lips and tongue and occur within minutes after contact with the food (Ortolani et al., 1988). Many patients also describe itching in their ears. Usually, these reactions disappear within 20-30 minutes. In addition to OAS which is confined to the site of allergen exposure, systemic and more severe IgE-mediated reactions such as urticaria, asthma or anaphylactic shock may occur occasionally. In particular, the consumption of soy-containing food products which contain the Bet v 1-homologous protein Gly m 4 have been described to trigger anaphylactic reactions such as swollen tongue, angioedema, urticaria, rhino-conjunctivitis and/or hypotension within 15-30 min after consumption (Kleine-Tebbe et al., 2002, van Zuuren et al., 2010). However, several patients experiencing severe systemic reactions to soy-products were found to show IgE-reactivity to seed storage proteins in soy which are primary food allergens and also likely candidates to cause the observed severe soy allergy (van Zuuren et al., 2010).

4. Birch pollen-related food allergy: Involved allergens

Birch pollen contains one major allergen, Bet v 1, which is recognized by IgE antibodies from more than 90% of birch pollen-allergic patients (Geroldinger-Simic et al., 2011). Bet v 1 belongs to the pathogenesis-related (PR) 10 protein family. Other members of this protein family have been identified in different foods, such Mal d 1 in apple, Pru p 1 in peach, Pru av 1 in cherry, Pyr c 1 in pear, Cor a 1 in hazelnut, Api g 1 in celery, Dau c 1 in carrot, Gly m 4 in soybean, (all summarized in (Bohle, 2006), Vig r 1 in mungbean (Mittag et al., 2005), Ara h 8 in peanut (Mittag et al., 2004), Act d 8 in kiwi (Oberhuber et al., 2008) and jackfruit (Bolhaar et al., 2004). Although birch pollen contains additional minor allergens, e.g. Bet v 2 (birch profilin), that have homologous proteins in various foods, IgE antibodies specific for Bet v 1 seem to be most relevant for clinical reactions against birch pollen-related foods since a large number of birch pollen-allergic patients with food allergy is exclusively sensitized to the major birch pollen allergen (Geroldinger-Simic et al., 2011).

The identification of the genes encoding various different Bet v 1-homologs in a great variety of food (Table 1) allowed their production as recombinant proteins (Table 1) which were employed to analyse structural and immunological characteristics.

Food	Bet v 1-homolog	GeneBank Acct. No.	Sequence identity (%)
Apple	Mal d 1	AJ417551	56
Hazelnut	Cor a 1	AF136945	67
Nectarine/Peach	Pru p 1	DQ251187	73
Kiwi	Act d 8	AM489568	53
Carrot	Dau c 1	AF456481	37
Apricot	Pru ar 1	U93165	56
Cherry	Pru av 1	U66076	59
Pear	Pyr c 1	AF057030	57
Peanut	Ara h 8	AY328088	46
Celery	Api g 1	Z48967	41
Soybean	Gly m 4	X60043	45
Strawberry	Fra a 1	Q256S2	53
Raspberry	Rub I 1	Q0Z8U9	55

Table 1. Bet v 1-homologs in birch pollen-related foods

Bet v 1-related food proteins display the typical Bet v 1-fold due to their high amino acid sequence similarity with Bet v 1 (Radauer et al., 2008). The highly similar tertiary structure explains why IgE-antibodies specific for conformational epitopes of Bet v 1 can cross-react with its food homologs. In addition to Bet v 1-specific IgE antibodies, Bet v 1-specific T lymphocytes cross-react with related food allergens. This fact has been demonstrated in *in vitro* experiments by employing Bet v 1-specific T cell clones that had been isolated from the blood of birch pollen-allergic patients. The clones were stimulated with recombinant Bet v 1-related food allergens and proliferative and cytokine responses were assessed (Bohle et al., 2003, Bohle et al., 2005, Fritsch et al., 1998). Several Bet v 1-specific clones proliferated in response to different food allergens and produced similar cytokine patterns as compared to stimulation with Bet v 1. In particular, T cells specific for the immunodominant T cell-activating region Bet v 1₁₄₂₋₁₅₆ which is located in a highly conserved amino acid region of the major birch pollen allergen responded to several Bet v 1-related food allergens (Jahn-Schmid et al., 2005). The cellular cross-reactivity is due to the high amino acid sequence similarity between Bet v 1 and its food homologs in this region. In addition to the C-terminal T cell epitope located within Bet v 1₁₄₂₋₁₅₆ (Figure 4), the major birch pollen allergen contains other relevant T cell activating regions spreading its entire amino acid sequence (Jahn-Schmid et al., 2005). Most T cell-activating regions that have been identified in Mal d 1, Cor a 1 and Api g 1 match the amino acid sequences of these epitopes (Bohle et al., 2003, Bohle et al., 2005, Fritsch et al., 1998). Thereby, the receptor of a Bet v 1-specific T cell can cross-react with a peptide derived from antigen-processing of Bet v 1-related food allergens.

Bet v 1	GVFNYETETTSVIPAAARLFKAFILDGDNLFPKVAPQAISSVENIEGNGGPGTIKKISFPE	60
Mal d 1	GV+ +E E TS IP +RLFKAF+LD DNL PK+APQAI E +EGNGGPGTIKKI+F E	60
Cor a 1	GVF YE E TSVIP ARLFK+F+LD DNL PKVAPQ +S EN+EGNGGPGTIKKI+F E	59
Pru p 1	GVF YE+E TS IP RLFKAF+LD DNL PK+APQAI E +EG+GGPGTIKKI+F E	61
Act d 8	G Y+ E S I A ++FKAF+LDGD + PK P AI+ V+ +EG+GG GTIK +F E	61
Dau c 1	G ++ E TS + A ++F +LD D + PK A A SVE-++G+GG GT++ I+ PE	59
Pru ar 1	GVF YE+E TS IP RLF AF+L DNL PK+APQAI E +EG+GGPGTIKKI+F E	60
Pru av 1	GVF YE+E TS IP RLFKAF+LD DNL PK+APQAI E +EG+GGPGTIKKI+F E	60
Pyr c 1	G++ +E E TS IP RLFKAF+LD DNL PK+APQAI E +EGNGGPGTIKKI+F E	60
Ara h 8	GVF +E E TS +P A+L+ A + D D++ PK+ + SVE +EGNGGPGTIKK++ E	59
Api g 1	GV + E TS + A ++F+ F++D D + PK AP A SVE-I+G+GGPGT+K I+ P+	59
Gly m 4	GVF +E E S + A L+KA + D DN+ PK-A + SVEN+EGNGGPGTIKKI+F E	59
Fra a 1	GV+ YE E TS IPA +LFKAF+LD DNL PK+APQA+ E +EG+GGPGTIKKI+F E	61
Rub i 1	TSVIP +LFKAF+LD DNL PK+APQA+ SVE IEG+GG GT+KKI E	61
Bet v 1	GFPFKYVKDRVDEVDHTNFKYNYSVIEGGPIGDTLEKISNEIKIVATPDGGSILKISNKY	120
Mal d 1	G + YVK R+D +D ++ Y+Y++IEG + DT+EKIS E K+VA G +I IS+-Y	119
Cor a 1	G FKY+K +V+E+DH NFKY YS+IEGGP+G TLEKIS EIK+ A P GGSILKI++K	120
Pru p 1	G + YVK ++D +D N Y+Y++IEG +GD LEKIS E K+VA+P GGSI+K ++ Y	121
Act d 8	G K VK R+D +D NF Y+YS+IEGG + D E IS IKIVATPDGG I K + Y	120
Dau c 1	G P + R D V+ Y+ +VI+G + +E I + +V T DGGSI K + +	119
Pru ar 1	G + YVK ++D +D N Y+Y++IEG +G+ LEKIS E K+VA+P GGSI+K ++ Y	120
Pru av 1	G + YVK ++D +D N+ Y+Y++IEG +GDTLEKIS E K+VA+P GGSI+K ++ Y	120
Pyr c 1	G + YVK RVD +D ++ Y Y++IEG + DT+EKIS E K+VA+ G +I IS+-Y	119
Ara h 8	K++ +V+ +D N+ YNYSV+ G + T EKI+ E K+V P+GGSI K++ KY	119
Api g 1	G P + R+D V+ ++YSVI+G + +E I N + +V T DGGSI K + +	119
Gly m 4	K+V +++ +D N Y+YSV+ G + DT EKI+ + K+VA P+GGS K++ KY	119
Fra a 1	G + YVK ++ +D N Y+YS+IEG + + +EKI E K+V+ P GG+I+K ++KY	121
Rub i 1	G YVK ++D +D NF Y+YS+ EG +GD +EKIS EIK+VA+ GSI+K ++ Y	110
Bet v 1	HTKGDHEVKAEQVKASKEMGETLLRAVESYLLAHSDAY	159
Mal d 1	HTKG+ E+K E VK KE L + +ESYL H DAYN	158
Cor a 1	HTKG+ + E++KA KE L +AVE+YLLAH DAY	159
Pru p 1	HTKGD E+K E VKA KE L + +E+YL H DAYN	160
Act d 8	K D +V E++KA KE + + VE+YLLA+ D	157
Dau c 1	HTKGD V E +K + L +A+E+YL+A+	153
Pru ar 1	HTKGD E+K E VKA KE L + +E+YL H DAYN	159
Pru av 1	HTKG+ E+K E VKA KE L + +E+YL H DAYN	159
Pyr c 1	HTKGD E+K E VKA KE L + +ESYL H DAYN	158
Ara h 8	HTKGD + E++K K GE L RA+E Y+LA+ Y	157
Api g 1	HTKGD V E +K + E L +A+E+YL+A+	153
Gly m 4	TKGD E +++K K + L +A+E+YLLAH D-YN	157
Fra a 1	HTKGD E+K E VKA KE L + +E YL H YN	160
Rub i 1	H KG E+K EQVK KE L +	136

Fig. 4. Sequence alignment of Bet v 1-related food proteins and Bet v 1. Similar amino acid residues are indicated by +. The immunodominant T cell epitope in the C-terminus of Bet v 1 is underlined.

Resistance to gastrointestinal degradation and to heat treatment is considered to be an important characteristic of food allergens and was investigated by employing recombinant Bet v 1-related food allergens. Simulated gastrointestinal degradation of Mal d 1, Api g 1 and Cor a 1 revealed that these proteins were completely fragmented within a few minutes

of exposure to pepsin, the most prominent gastric protease (Kopper et al., 2004, Schimek et al., 2005, Schulten et al., 2011). Proteolytic degradation of Bet v 1-homologous food allergens into small fragments leads to the loss of their IgE-binding capacity because most IgE-epitopes of Bet v 1 are conformational epitopes depending on the tertiary protein structure (Mittag et al., 2006, Neudecker et al., 2003, Scheurer et al., 1999). The rapid and complete degradation of Bet v 1-homologous food allergens explains why systemic IgE-mediated reactions rarely occur after consumption of birch pollen-related foods. At the site of contact with fresh foods, i.e. the oral mucosa, local IgE-mediated immediate allergic reactions are induced by intact food allergens. After swallowing Bet v 1-related food allergens are rapidly degraded in the stomach and cannot be absorbed into the blood stream in a form capable of inducing IgE-mediated effector cell activation. As a consequence, systemic allergic reactions to birch pollen-related foods are rare. However, there are exceptions to this process, for example, the so-called “bio-bar syndrome”. This syndrome describes occasional anaphylactic reactions in patients with birch pollen allergy that occur after the consumption of fruit and vegetable smoothies. These drinks are usually prepared from fresh apple and/or raw carrot and drunk very rapidly at so-called bio-bars. We recently found a possible explanation for this phenomenon by performing *in vivo* absorption assays in an animal model (Schulten et al., 2011). We observed that the pH value in the stomach of rats rises to 5 after allergen administration. Similarly, administration of a peanut-based meal initially neutralized the gastric pH value of piglets to approximately 7, which was subsequently acidified by HCl secretion (Kopper et al., 2006). The high pH value renders pepsin inactive. Consequently, Bet v 1-homologous food allergens were not degraded by the protease and could be detected in the rat serum after a time period of 2 hours (Schulten et al., 2011). Deduced from these *in vivo* results from animal models we propose that rapid drinking of freshly prepared smoothies on an relatively empty stomach of birch pollen-allergic individuals will rise the gastric pH value and prevent immediate pepsinolysis of food allergens. Thereby, a dose of IgE-reactive Bet v 1-related food allergens can be absorbed which is sufficient to subsequently cause systemic anaphylaxis. The same cascade of events may also explain the severe anaphylactic reactions observed in birch pollen-allergic patients after ingestion of soy-based foods, in particular soy milk, containing the Bet v 1-homolog Gly m 4 (Kleine-Tebbe et al., 2002).

Recombinant Bet v 1-related food allergens were also employed to investigate the effects of heat treatment on these proteins. Exposure to high temperatures demolishes their 3-dimensional structure, thereby reducing their capacity to bind IgE and consequently, to induce IgE-mediated effector cell activation (Bohle et al., 2006). This biochemical behaviour explained why typically, only fresh fruits and vegetables induce immediate allergic symptoms whereas cooked birch pollen-related foods are usually tolerated by birch pollen-allergic patients.

In summary, Bet v 1-related food allergens lack typical features of primary food allergens, i.e. resistance to gastrointestinal degradation and heat treatment. Therefore, they are considered to be secondary or incomplete food allergens, i.e. incapable of initiating an allergic sensitization in an individual by themselves. However, due to their structural similarity with Bet v 1 and to the high amino acid sequence identity between the major birch pollen allergen and its dietary homologs these proteins can induce allergic symptoms when cross-reactive Bet v 1-specific IgE antibodies and T cells are present in allergic patients. IgE-mediated symptoms appear as OAS immediately after contact with the respective fresh foods in the majority of patients. The activation of Bet v 1-specific T cells by Bet v 1-related

food allergens may induce late phase responses in target organs in a minority of birch pollen-allergic patients, for example a worsening of atopic eczema occurring 12-48 hours after consumption of birch pollen-related foods (Bohle et al., 2006, Werfel et al., 1999). In biopsies of such flare ups Bet v 1-specific T cells have been detected (Reekers et al., 1999). This finding indicated that after ingestion and gastrointestinal proteolysis of Bet v 1-related food allergens fragments thereof were absorbed into the blood and induced the activation of Bet v 1-specific T cells. Indeed, several fragments of Bet v 1-homologous food allergens were identified after simulated gastrointestinal degradation that contained T cell activating regions and induced the proliferation and cytokine synthesis of Bet v 1-specific T cell clones *in vitro* (Schimek et al., 2005). *In vivo*, Bet v 1-specific T lymphocytes activated by such cross-reactive peptides may migrate into target organs such as the skin and exert local effector functions, e.g. a worsening of atopic eczema.

Of note, T cell-mediated symptoms induced by Bet v 1-related food allergens can occur independently from IgE-mediated reactions. This means that patients who do not experience an OAS when consuming birch pollen-related foods may still suffer from flare-ups of their atopic eczema several hours after ingestion. For example, when birch pollen-allergic patients were challenged with cooked birch pollen-related foods, these individuals did not experience immediate symptoms but T cell-mediated late phase reactions (Bohle et al., 2006). Together, biochemical and immunological data gained with recombinant Bet v 1-homologous food allergens provide an explanation for this clinical observation. Allergen-recognition differs between IgE antibodies and allergen-specific T cells. In contrast to IgE antibodies which often recognize conformational epitopes depending on the tertiary structure of an allergen T cells recognize small linear peptides generated during antigen processing of proteins (Figure 5). Cooking of Bet v 1-homologs leads to their loss of IgE-binding. Nevertheless, heat-denatured Bet v 1-related food allergens are taken up and processed by antigen-presenting cells and thereafter, presented to T lymphocytes.



Fig. 5. Antigen-recognition by B and T lymphocytes. Antibodies (indicated as Y) produced by plasma cells often recognize conformational epitopes that depend on the tertiary structure of proteins. The amino acid residues forming the epitope are not neighbouring residues in the primary sequence. In contrast, linear T cell epitopes highlighted as black lines within the amino acid sequence consist of neighbouring amino acid residues.

What may be the consequence of T cell activation by ingested Bet v 1-related food allergens? In allergic individuals, allergen-specific T cells were shown to be long-lived and to exist for several years (Bohle et al., 1998, Wedderburn et al., 1993). In order to survive, specific memory T cells seem to require repeated contact with antigen. The ingestion of pollen-related food proteins capable of activating pollen-specific T lymphocytes may represent one way to stimulate these cells, in particular outside of the tree pollen season. In our studies the majority of the food allergen-reactive Bet v 1-specific TCC were Th2-like and synthesized high levels of IL-4 in response to the food allergens (Bohle et al., 2003, Bohle et al., 2005, Fritsch et al., 1998). Therefore, the perennial uptake of pollen-related food could stimulate the survival of T cells and ongoing IL-4 synthesis and thereby contribute to the typical maintenance of high levels of pollen-specific IgE also outside of the tree pollen season. A summary of the consequences of consumption of Bet v 1-related food allergens is provided in Figure 6.

5. Bet v 1 is the primary sensitizer in birch pollen-related food allergy

Clinical, immunological and biochemical data support that birch pollen-related food allergy is a secondary food allergy and results from primary respiratory sensitization to the major birch pollen allergen and subsequent immunological cross-reactivity. From the clinical point of view, the majority of patients develop food-induced allergic symptoms after the onset of respiratory allergy (Geroldinger-Simic et al., 2011). Furthermore, a high number of birch pollen-allergic patients shows IgE-reactivity to Bet v 1-related food allergens without developing clinical reactions to the respective foods whereas only very few food-allergic individuals display IgE-reactivity to Bet v 1-homologous food allergens in the absence of Bet v 1-specific IgE antibodies (Flinterman et al., 2006, Moneo et al., 1999). Finally, patients suffering from allergic reactions to stone-fruits and hazelnuts in birch-free areas are not sensitized to Bet v 1-homologous food allergens but to other plant food allergens, e.g. non-specific lipid transfer proteins (Fernandez-Rivas et al., 2008, Fernandez-Rivas et al., 2006).

Immunologically, Bet v 1 not only cross-reacts with its related dietary proteins but the major birch pollen allergen dominates the IgE and T cell reactivity to its homologs. For example, pre-incubation of patients' sera with Bet v 1 totally abolishes their IgE-binding to Mal d 1 and Api g 1 whereas pre-incubation of the same sera with Bet v 1-related food allergens reduces IgE-binding to the major birch pollen allergen to only around 50% (Bohle et al., 2003, Kinaciyan et al., 2007). These experimental findings indicate that Bet v 1 contains most IgE-epitopes of its food homologues and binds IgE with higher affinity. Thus, it may be concluded that Bet v 1 initiated the production of specific IgE antibodies *in vivo*. Similar to the IgE level, experimental *in vitro* approaches revealed that Bet v 1 dominates the T cell response to its food-homologs. When T cells reactive with Bet v 1-related food allergens were isolated from the peripheral blood of allergic patients and re-stimulated with either the food allergen or Bet v 1, most cultures responded stronger to the major birch pollen allergen (Bohle et al., 2003, Bohle et al., 2005, Fritsch et al., 1998). This finding indicates that T cells which respond to stimulation with Bet v 1-related food allergens are cross-reactive, Bet v 1-specific clonotypes. Again, these observations support that Bet v 1 was the initial stimulus for an allergic response in birch pollen-related food allergy.

Biochemically, the high susceptibility of Bet v 1-homologous dietary allergens to proteolytic degradation in the stomach and small intestine prevents them from reaching the gut-associated lymphoid tissue (GALT) in an intact form. Therefore, Bet v 1-homologous food allergens are considered to be incapable of sensitizing an individual by themselves after

being taken up through their natural route of exposure. In contrast, the major birch pollen allergen is inhaled and thereby not exposed to the harsh conditions of the gastrointestinal tract. Bet v 1 reaches the respiratory tract in an immunological active form where it can induce IgE-production. Together, clinical and experimental observations support that the major birch pollen allergen is the primary sensitizer in birch pollen-related food allergy.

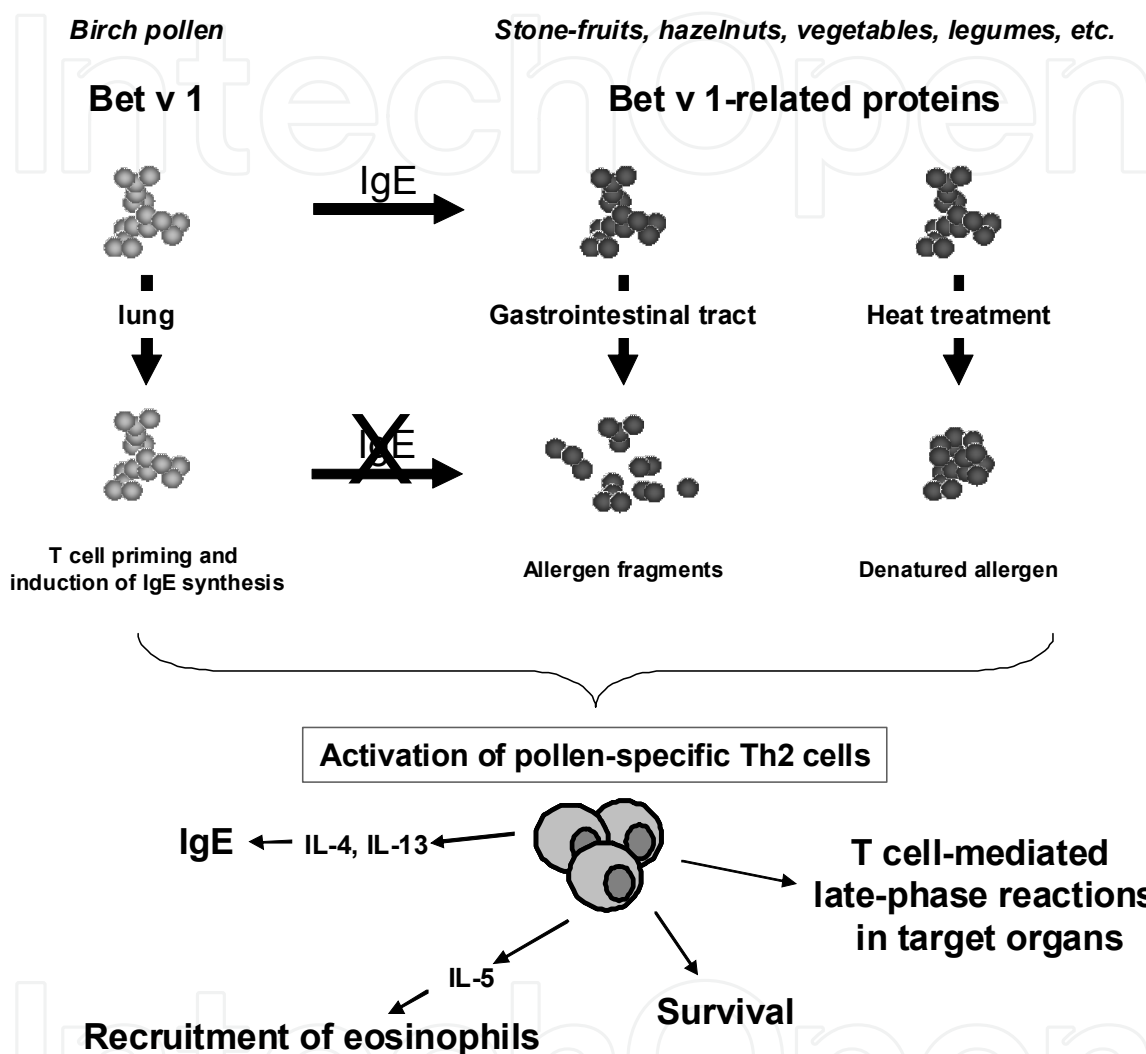


Fig. 6. Proposed pathophysiology of pollen-related food allergy. Bet v 1 initiates respiratory sensitization. Bet v 1-specific IgE antibodies recognize structurally related dietary proteins in various foods which may cause clinical reactions, often directly at the site of allergen contact, e.g. the oral mucosa. After ingestion Bet v 1-related food homologs are degraded when passing through the intestinal tract. Cooking of the respective foods also denatures Bet v 1-related food allergens. The destruction of their 3-dimensional structure leads to the loss of IgE-binding capacity of Bet v 1-homologous food proteins. Nevertheless, allergenic fragments after gastrointestinal degradation as well as heat-denatured Bet v 1-related allergens are still capable of activating Bet v 1-specific T lymphocytes. Upon activation, Bet v 1-specific T cells proliferate and produce cytokines. They also migrate to different target organs where they may exert clinical late-phase reactions, e.g. the worsening of atopic eczema in the skin. Possibly, activation of pollen-specific Th2 cells by ingested food proteins also contributes to their survival and longevity in allergic patients.

Interestingly, a few food-allergic patients have been identified to bear IgE antibodies specific for Bet v 1-related food allergens, e.g. Cor a 1 in hazelnut, without being sensitized to the major birch pollen allergen (Flinterman et al., 2006). This finding suggested that a non-pollen-related route of sensitization to the Bet v 1-homologous hazelnut allergen may be possible. Along these lines, we previously found evidence for a potential sensitizing capacity of Cor a 1 based on the identification of T cell clones that did not cross-react with Bet v 1 (Bohle et al., 2005). However, in simulated gastrointestinal degradation assays pure Cor a 1 lost its IgE-binding ability within a few seconds of incubation with pepsin (Schimek et al., 2005). This discrepancy tempted us to investigate whether the natural matrix embedding Cor a 1 may contribute to its sensitizing capacity. Actually, in simulated gastrointestinal degradation assays, we found that the presence of hazelnut extract protected Bet v 1-related food allergens from gastric proteolysis (Schulten et al., 2011). Since Cor a 1 has been demonstrated to be relatively resistant to simulated degradation by the intestinal protease trypsin (Schimek et al., 2005) we conclude that hazelnuts which provide a food matrix rich in carbohydrates and proteins under certain circumstances may contribute to a sensitizing capacity of the major hazelnut allergen independently from respiratory sensitization to Bet v 1. Most patients showing IgE-reactivity to Cor a 1 but not to Bet v 1 were children (Flinterman et al., 2006). Therefore, the still immature gastrointestinal tract of children may be such an additional precondition for a possible sensitization to Cor a 1.

6. Treatment strategies for birch pollen-related food allergy

6.1 Specific immunotherapy with birch pollen

Together, clinical and immunological observations provide strong evidence that birch pollen-related food allergy is a consequence of cross-reactivity between Bet v 1 and its dietary homologs. Thus, one would assume that successful allergen-specific immunotherapy (SIT) of birch pollen allergy might concomitantly cure birch pollen-related food allergy. SIT consists of a series of continuous administration of increasing doses of allergen extracts to the allergic patient in order to induce clinical tolerance (1993) and is currently the only causative treatment for IgE-mediated allergy that results in long-term clinical tolerance to allergens. Various studies have shown that successful SIT alters the allergen-specific immune response (Larche et al., 2006). In general, SIT induces high levels of allergen-specific IgG antibodies, in particular IgG4, which are considered as “blocking” antibodies because they compete with IgE for allergen-binding and thereby impair IgE-mediated reactions, e.g. allergen-induced activation of basophils and mast cells or IgE-facilitated allergen uptake and presentation to T cells (James et al., 2011, Nouri-Aria et al., 2004, van Neerven et al., 1999, Wachholz et al., 2003). At the T cell level it has been demonstrated that SIT induces a shift from the disease-eliciting T helper (Th) 2- towards a Th1-like response and regulatory CD4⁺ T (Treg) cells that actively suppress proliferation and cytokine production of allergen-specific effector T cells (Akdis et al., 1998, Bellinghausen et al., 1997, Ebner et al., 1997, Jutel et al., 2003). In addition to the modulation of the adaptive immune response to allergens, SIT also modulates the function of APC and effector cells (Larche et al., 2006), e.g. reduction of the number of mast cells and their ability to release mediators. The recruitment of eosinophils and neutrophils to sites of allergen exposure is also reduced during SIT.

An overview on the immune mechanisms operative during successful SIT is given in Figure 7. However, it is still not clear which of these immune mechanisms actually translate(s) into

clinical tolerance of patients, i.e. improvement of symptoms, and whether one or more of these mechanisms fail those individuals who are not cured by SIT.

SIT with birch pollen has been proven efficient for the treatment of birch pollinosis (Bodtger et al., 2002, Cirila et al., 1996, Winther et al., 2000). However, the clinical benefit of SIT with birch pollen on birch pollen-related food allergy is still debated. Whereas a few studies have described that patients improved their clinical symptoms to birch pollen-related foods after birch pollen-SIT (Asero, 1998, 2003, 2004) others have reported limited curative effects of birch pollen-SIT on birch pollen-related food allergy and some patients even developed allergic reactions to foods during the course of therapy (Bucher et al., 2004, Herrmann et al., 1995, Modrzynski et al., 2002, van Hoffen et al., 2011). It has to be stressed that at present a prospective study investigating food allergic reactions in a sufficient number of birch pollen-allergic patients before and during birch pollen-SIT by means of double-blind placebo controlled food challenges (DBPCFC) is lacking. Nevertheless, the majority of clinicians observe that only approximately one third of birch pollen-allergic patients undergoing birch pollen-SIT concomitantly improve birch pollen-related food allergy. Thus, no effective treatment for this secondary food allergy exists at present. However, because of its high prevalence and the impaired quality of life of the affected individuals, there is a need for an efficient treatment strategy for birch pollen-related food allergy.

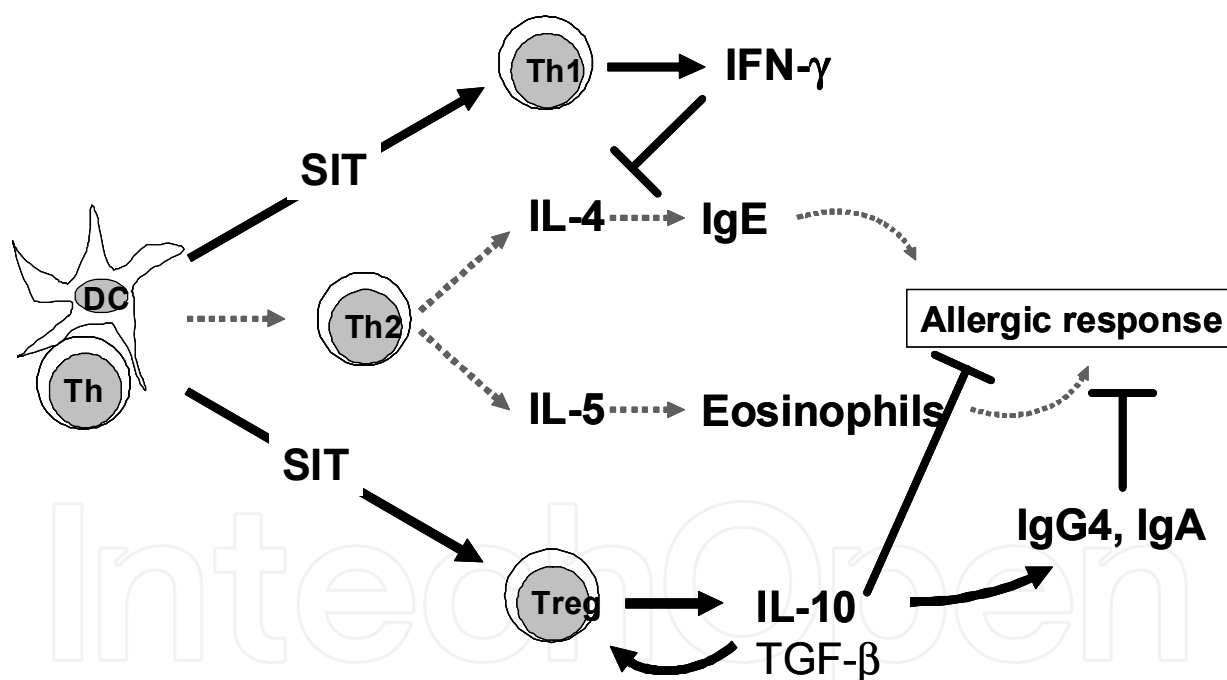


Fig. 7. Immune mechanisms operative during allergen-specific immunotherapy (SIT). An overshooting allergen-specific Th2 response causes allergic diseases. Th2 cells produce IL-4 that triggers B cells to produce allergen-specific IgE antibodies. Th2 cells also synthesize IL-5, which activates eosinophils. IgE and eosinophils mediate the immediate allergic response. SIT induces immune deviation, i.e. the switch from Th2 towards Th1-like cells which produce high levels of IFN- γ , a potent antagonist of IL-4. SIT also promotes the induction of regulatory T (Treg) cells which produce IL-10 and/or TGF- β . These immunosuppressive cytokines induce the production of allergen-specific IgG4 and IgA antibodies which may compete with IgE for allergen-binding ("blocking antibodies"). IL-10 promotes further induction of regulatory T cells.

Sublingual immunotherapy (SLIT) has been demonstrated to be an effective and safe alternative for conventional subcutaneous SIT of birch pollen allergy (Horak et al., 1998, Khinchi et al., 2004, Mauro et al., 2007). Similar to subcutaneous immunotherapy SLIT induces allergen-specific IgG1 and IgG4 antibodies and a modulation of the allergen-specific T cell response (O'Hehir et al., 2009, Scadding et al., 2010). Moreover, SLIT induced increased Foxp3⁺ cells - presumably regulatory T cells - in the sublingual epithelium (Scadding et al., 2010). Speculating that sublingual administration, directly at the site of food-induced allergic symptoms, instead of subcutaneous injections might improve the therapeutic benefit on birch pollen-related food allergy, we have evaluated the effects of SLIT with birch pollen extract on apple allergy in birch pollen-allergic individuals (Kinaciyan et al., 2007). The clinical efficacy of birch pollen SLIT was assessed by means of nasal provocation tests with birch pollen extract and double-blind placebo-controlled food challenges with Golden Delicious apples before and after 1 year of treatment. Nine patients improved in nasal provocation tests to birch pollen and were therefore considered as successfully treated. However, only very few of the nine patients concomitantly improved allergic reactions to apple in double-blind placebo-controlled food challenges. To understand this limited curative effect of birch pollen-SLIT on associated apple allergy, Bet v 1- and Mal d 1-specific antibody and T cell responses were analysed in the successfully treated individuals. All patients developed significantly increased Bet v 1-specific IgG4 antibody levels after 1 year of SLIT. Interestingly, Mal d 1-specific IgG4 antibody levels did not increase significantly in parallel (Kinaciyan et al., 2007). At the T cell level, a significant reduction of Bet v 1-specific T cell proliferation after 4 and 52 weeks of SLIT was found (Bohle et al., 2007). This reduced allergen-specific T cell response could be referred to the induction of IL-10-producing regulatory T cells in the early phase and the switch from Bet v 1-specific Th2 cells towards more Th1 cells in the late phase of SLIT. However, no similar modulation of the Mal d 1-specific T cell response was observed. Together, these findings suggested that birch pollen SLIT induced the characteristic immune mechanisms operative during SIT, such as blocking antibodies, peripheral tolerance, regulatory T cells and immune deviation, specific for Bet v 1 but not for its highly cross-reactive homologue in apple. Along these lines, a more recent study demonstrated that conventional subcutaneous SIT with birch pollen also failed to induce food-reactive IgG4 antibodies (van Hoffen et al., 2011). The sera from 10 birch pollen-allergic patients with associated allergy to hazelnut were investigated for Bet v 1- and Cor a 1-specific IgG4 antibodies before, after 3, 6, 9 and 12 months of birch pollen-SIT. Again, the significant increase of Bet v 1-specific IgG4 antibody titers was not paralleled by a significant increase of Cor a 1-reactive IgG4 antibody levels. Nevertheless, after three months of treatment the sera contained significantly enhanced Cor a 1-reactive IgG levels and the sera obtained after 1 year of treatment showed IgE-blocking capacity in facilitated antigen-binding (FAB) assays (Shamji et al., 2006). Still, SIT with birch pollen extract did not result in clinical improvement of hazelnut allergy in these patients as analyzed by means of double-blind placebo-controlled food challenges at inclusion and after 1 year of treatment (van Hoffen et al., 2011).

Together, these studies imply that the limited clinical effect of SIT with birch pollen may be due to a failure of the induction of cross-reactive IgG and T cell responses. However, it needs to be pointed out that so far in relatively low numbers of birch pollen-allergic individuals were assessed for their antibody and T cell responses to Bet v 1-homologous food allergens during birch pollen-SIT or SLIT. Therefore, we analysed IgG responses

specific for Bet v 1, Mal d 1 and Cor a 1 in sera from 49 patients who received birch pollen SIT for 1-3 years and developed Bet v 1-specific IgG4 antibodies. Interestingly, only around 33% of these individuals developed food-reactive IgG4 antibodies. Food-reactive antibodies in general increased later during the course of therapy as compared to Bet v 1-specific IgG4 antibodies and blocked IgE binding to Bet v 1-related food allergens. Similarly, only a limited number of birch pollen-allergic patients developed food-reactive IgG1 antibodies after subcutaneous administration of a recombinant hypoallergenic variant of Bet v 1 (Niederberger et al., 2007). In a recent study including more than 200 birch pollen-allergic individuals we observed that patients tolerating birch pollen-related foods showed higher ratios of serum allergen-specific IgG4/IgE antibody levels than patients with food allergy (Geroldinger-Simic et al., 2011). These naturally occurring allergen-specific IgG4 antibodies were capable of blocking IgE-binding to Bet v 1-related food allergens. These data indicate that the presence of allergen-specific IgG4 antibodies which compete with IgE for allergen-binding may be important for the development of food tolerance. Therefore, SIT or SLIT should induce such antibodies. However, treatment with birch pollen does not effectively induce food-reactive IgG4 antibodies in every patient. Therefore, we propose that vaccines for the treatment of birch pollen-related food allergy should contain the disease-eliciting food allergens. Previously, a randomized, double-blind, placebo-controlled study has demonstrated significant increases in tolerance to hazelnut after sublingual administration of hazelnut extract (Enrique et al., 2005). Tolerance induction was accompanied by increased IgG4 antibody and IL-10 levels after immunotherapy in only the active group. Thus, SLIT with Bet v 1-associated food allergens may be a promising approach for treatment of birch pollen-related food allergy.

Finally, it is an interesting immunological finding that a high number of birch pollen-allergic patients show food-reactive Bet v 1-specific IgE antibodies but fail to develop cross-reactive IgG antibodies during treatment with birch pollen despite developing high levels of Bet v 1-specific IgG antibodies. Therefore, birch pollen-related food allergy is an interesting model to study the question how cross-reactivity of structurally related allergens can cause allergy whereas the immunomodulation of the allergen-specific response in SIT-treated patients who improve their pollinosis does not concomitantly translate into clinical tolerance to associated foods.

6.2 Future concepts for treatment of birch pollen-related food allergy

Although rarely life-threatening birch pollen-related food allergy is highly prevalent and often causes perennial discomfort. Furthermore, this secondary food allergy prevents birch pollen-allergic patients from consuming a great variety of fresh fruits and vegetables which contain vitamins and are considered to be healthy. This situation demands for effective treatment which at present does not exist. Recent developments in the treatment of food allergy suggest oral immunotherapy (OIT) with the disease-eliciting food as an interesting option (Nowak-Wegrzyn and Sampson, 2011). Indeed, results from a double-blind placebo controlled study in peanut-allergic children demonstrated that OIT with peanut induced desensitization and concurrent immune modulation (Varshney et al., 2011). In contrast to the placebo group, the actively treated OIT group showed significant reductions in skin prick reactivity to peanut and significant increases in peanut-specific IgG4 antibodies. Furthermore, the ratio of FoxP3^{hi}: FoxP3^{intermediate} CD4⁺CD25⁺ T cells increased in peanut OIT subjects suggesting the induction of regulatory T cells. Similar approaches might be

feasible for the treatment of birch pollen-related food allergy. Recently, it was observed that continuous consumption of small amounts of apple induces clinical tolerance in birch pollen-allergic patients with apple allergy (Kopac et al., 2010). In this study, 21 patients daily consumed small amounts of apple, doubling the dose every two weeks. After a regular exposure of in average 22 weeks, 16/21 patients tolerated a complete apple without developing any signs of an OAS. This desensitization was paralleled by a decrease of intradermal reactivity to Mal d 1. This preliminary study indicates that OIT may be a possible approach to treat birch pollen-related apple allergy.

Novel concepts for allergy vaccines for SIT include the use of recombinant allergens instead of crude extracts containing a mixture of allergenic and non-allergenic proteins of an allergen source (Valenta et al., 2011). Although progress has been made to improve the quality and standardization of protein extracts the use of allergen extracts for SIT still bears some disadvantages. The complex protein mixture makes it difficult to determine the exact content of single allergens. Due to the production process the concentration of individual allergens may vary between different batches. Highly labile allergens might even be totally lost during the production process and not be present in the extract. The availability of recombinant allergens with the same immunological characteristics as their natural counterparts can overcome several of these disadvantages. Briefly, recombinant allergens can be produced as molecules with known molecular, immunologic and biological characteristics in consistent quality and unlimited amounts. Thus, the content of individual allergens in a vaccine can precisely be formulated and the potential loss of allergens destroyed during the production process of allergen extracts can be excluded. Regarding the treatment of birch pollinosis, recombinant Bet v 1 has been demonstrated to be as effective as birch pollen extract (Pauli et al., 2008). As discussed above, we propose that vaccines for the treatment of birch pollen-related food allergy should contain the disease-eliciting dietary allergens. Bet v 1-related proteins are known to be easily degraded during the procedures applied for the production of protein extracts. Since the most important and frequently recognized Bet v 1-related food allergens are available as recombinant proteins (Table 1), these proteins should be employed as active component in future vaccines for SIT or SLIT of birch pollen-related food allergy.

In addition to producing well-defined batches of recombinant wild-type allergens with identical features to their natural counterparts, the recombinant DNA technology also offers the possibility to selectively modify certain properties and functions of allergenic proteins (Mutschlechner et al., 2009). Diverse modifications of allergens can be genetically engineered, e.g. variants with reduced IgE-binding capacity, multi-mers of single allergens or hybrids consisting of different allergens. Furthermore, allergens can be genetically fused with proteins that promote immune responses which counter regulate the disease-eliciting Th2-dominated immune response in allergic individuals and may therefore, improve the efficacy of SIT (Bohle et al., 2004, Gerstmayr et al., 2007). All these approaches may also be employed to develop an effective treatment strategy for birch pollen-related food allergy.

We have recently sublingually administered recombinant Mal d 1 to 18 birch pollen-allergic patients with associated apple allergy. The recombinant apple allergen was well tolerated by the individuals and no severe side-effects were observed. This approach may be regarded as a first proof-of-concept for the applicability of recombinant Bet v 1-related food allergens for SLIT. Certainly, several questions regarding the optimum content of a vaccine to treat birch pollen-related food allergy remain open. Most patients react to more than one food and it

remains to be determined whether all individual food allergens should be employed for treatment. Moreover, it remains to be investigated whether the vaccine should contain food allergens with or without Bet v 1.

7. Conclusion

Birch pollen-related food allergy is a relevant allergic disease that affects the vast majority of birch pollen-allergic patients and strongly impairs their quality of life. Currently, no effective therapy for this form of food allergy is available. The detailed investigation of the allergic response to Bet v 1-homologous food allergens has provided evidence that birch pollen-related food allergy results from immunological cross-reactivity of the major birch pollen allergen and structurally related dietary proteins. However, it is somehow astonishing that successful SIT or SLIT of birch pollinosis accompanied by the modulation of the Bet v 1-specific immune response does not effectively cure birch pollen-associated food allergy in parallel. Primary sensitization to the major birch pollen allergen and subsequent cross-reactivity can cause food allergy. However, the immunomodulation of Bet v 1-specific antibody and T cell responses during SIT with birch pollen does not concomitantly modulate reactivity to the respective food allergens. Thus, birch pollen-related food allergy is an interesting model to learn more about the consequence of immunological cross-reactivity between related allergens in different sources. The detailed analysis of the immune mechanisms failing in patients who do not improve pollen-associated food allergy during SIT with birch pollen will help to improve the treatment and to develop an efficient therapy for birch pollen-related food allergy.

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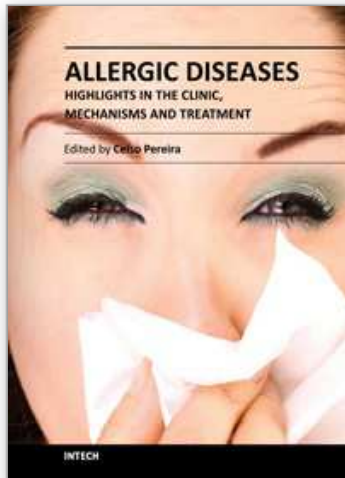
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