



ELSEVIER

SCIENCE @ DIRECT®

Food products and allergy development, prevention and treatment

Adrian W Zuercher¹, Rodolphe Fritsché¹, Blaise Corthésy² and Annick Mercenier¹

In westernized countries allergic diseases have reached epidemic proportions. Food is frequently a perpetrator of allergy but, in turn, modified food and selected food ingredients can become valuable intervention tools in the fight against allergy. There are two basic approaches towards mitigation of food allergy through nutrition: to reduce the allergenicity of raw food materials by physical, chemical or genetic methods or to influence host immunity towards a non-allergic state using various food ingredients. Dietary intervention for the prevention and therapy of allergy is an emerging field where initial findings from animal studies are now being validated in human trials. Nevertheless, to consolidate the utility of such interventions, more pre-clinical and clinical studies remain necessary.

Addresses

¹ Allergy Group, Nutrition and Health Department, Nestlé Research Center, Vers-chez-les-Blanc, CH-1000 Lausanne 26, Switzerland

² Research and Development Laboratory, Division of Immunology and Allergy, Département de Médecine Interne Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Corresponding author: Mercenier, Annick (annick.mercenier@rdls.nestle.com)

Current Opinion in Biotechnology 2006, 17:1–6

This review comes from a themed issue on Food biotechnology
Edited by Michiel Kleerebezem

0958-1669/\$ – see front matter
© 2006 Elsevier Ltd. All rights reserved.

DOI 10.1016/j.copbio.2006.01.010

Introduction

With a prevalence of 20% to 30% in the population of developed countries, allergy-related diseases (including atopic dermatitis, rhinitis and asthma) are nowadays recognized as an epidemic [1]. In addition to genetic predisposition ('atopy'), marked changes in alimentary habits (the appearance of exotic foods, industrial processing, and reduced consumption of fermented foods), differences in living conditions between industrialized and developing countries, exposure to pet and farm animals, and excessive use of antibiotics could all contribute to immune-deviation and thus to the development of allergy [2]. The gut microbiota has also been evoked to exert a strong impact on the immunophysiological func-

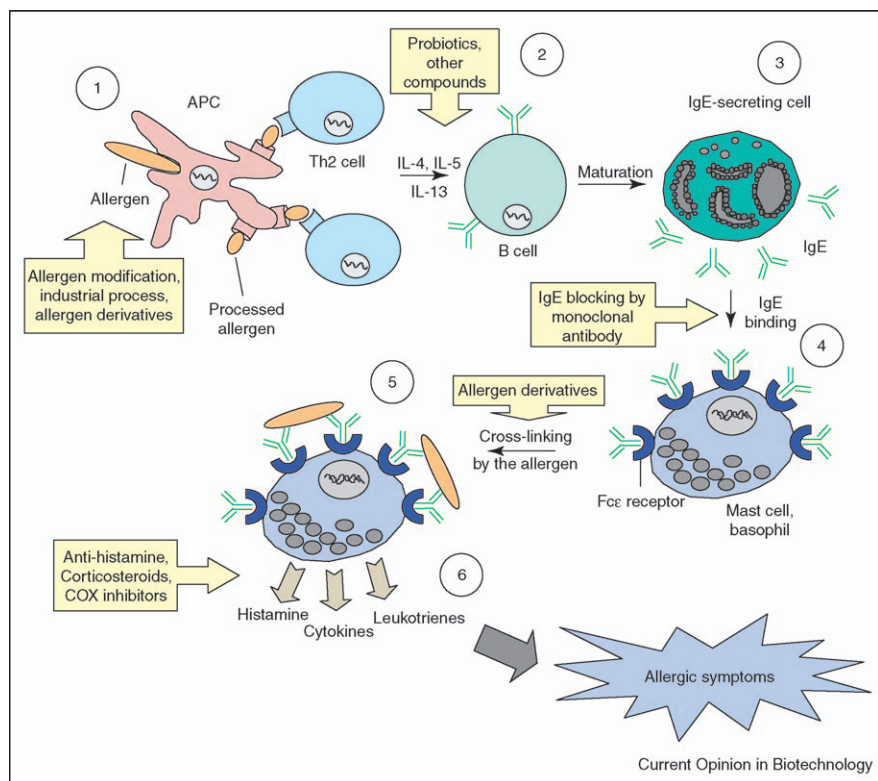
tioning of the epithelium. This highly complex and diverse microbial community helps to maintain the intestinal barrier and immune homeostasis that needs to be established after birth and during the first years of life [3].

Allergy is an inappropriate functioning of the immune system associated with the dominance of a particular type of T lymphocytes, referred to as T helper 2 (Th2) cells. Th2 cells typically secrete a selection of immune messengers, known as interleukin (IL)-4, IL-5 and IL-13. The allergic reaction is often marked by the production of immunoglobulin E (IgE), this antibody isotype being responsible for sensing the allergen and triggering allergic reaction when bound to receptors on target mast cells and basophils. Figure 1 describes the successive activation steps that ultimately lead to the release of chemical mediators causing allergic manifestations and symptoms. Even though not pathogenic on their own, allergic substances entering the body through the skin, the airways or the gut are recognized by the immune system as foreign compounds.

Up to 5–6% of young children and 2–4% of adults suffer from clinical symptoms of food allergy (Figure 2) [4,5]. Among them, many have IgE-mediated food allergy, a condition that may lead to a fatal outcome or to life-threatening conditions such as anaphylactic shock (49% of life-threatening cases), systemic reactions (33%), laryngeal angioedema (13%) or acute asthma (5%) [6]. In developed countries, the foods most commonly responsible for allergic reactions are referred to as 'The Big Eight' and include eggs, peanuts, milk, tree nuts, fish, shellfish, wheat, and soy. It is thought that the natural way for the body to prevent allergy development against food is through the induction of immunological tolerance towards antigens delivered via the oral route ('oral tolerance'). It has been shown that induction of oral tolerance is dependent on the age of the host, the dose of antigen administered and the nature of the antigen [7]. The mechanisms behind oral tolerance to food proteins are not yet fully understood, but T lymphocytes play a central role in allergen recognition and for regulating the immune response in this process. In particular, T regulatory cells are able to modulate the response of several immune cells, such as B cells and T-helper lymphocytes (Th1, Th2).

Although promising prophylactic and therapeutic treatments have been explored in humans and animal models

Figure 1



The allergic cascade: schematic representation of the major cellular and molecular players involved in the onset of allergic reactions. In an atopic person (i.e. a person prone to develop allergy owing to his genetic background), on entering the body the allergen is internalized by antigen-presenting cells (APCs; 1) and processed into peptides that upon presentation on the APC (1) lead to activation of T-helper cells of the type 2 (Th2). The secretion of particular interleukins (2) primes B cells to mature into plasma cells producing immunoglobulin E (IgE; 3), which are subsequently bound by specific Fc ϵ receptors present on the surface of mast cells or basophils (4). Cross-linking of IgE by the allergen (5) following a second exposure triggers the release of several mediators (6), which in the physiological context promote the onset of allergic symptoms. Boxes with an arrow indicate the possible steps where intervention to perturb the allergic cascade has proven successful. Examples of compounds with anti-allergic potential are listed in Table 1. COX, cyclooxygenase, involved in the production of leukotriene mediators.

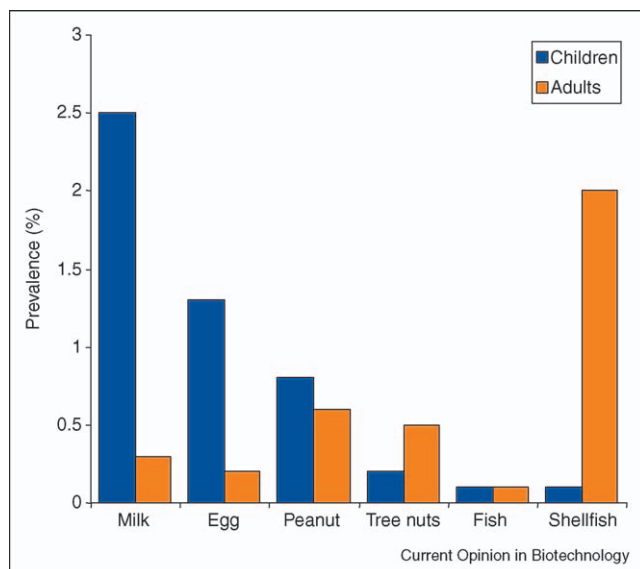
over the past few decades, the only common intervention in the case of food allergy is the eviction diet or strict avoidance of the allergen. Novel strategies addressing the problem include total or partial destruction of allergens in food by heat, high pressure, chemical treatment, enzymatic digestion or by genetic engineering. Alternatively, it can be attempted to modulate the host immune system with the objective of preventing allergen-specific sensitization without altering the immunocompetence towards harmful antigens. In this review we highlight recent approaches towards mitigation of allergy either by modification of the allergen or modification of host immunity.

Modification of food allergens: milk and beyond

The principle of reducing the allergenicity of food proteins by enzymatic hydrolysis and heat processing has been effectively demonstrated and commercially applied for the use of cow's milk in hypoallergenic (HA) infant formulas. Depending on whether primary or secondary

prevention of cow's milk protein allergy (CMPA) is attempted, the approaches with HA formulas are different. When infants are already sensitized, minute amounts of cow's milk protein can trigger an allergic reaction and it is generally agreed that only so-called extensively hydrolyzed hypoallergenic formulas (eHF) or amino acid formulas can be given to infants with established CMPA (secondary prevention). By contrast, for primary prevention in non-sensitized at risk infants (i.e. infants of atopic parents or with atopic siblings), infant formulas with reduced allergenicity are recommended by national and international pediatric expert societies [8[•]]. Partially hydrolyzed formulas (pHF) are sufficiently reduced in allergenicity to not sensitize at-risk infants, but retain sufficient immunogenicity for deviating the immune system to a hyporesponsiveness (i.e. oral tolerance) against cow's milk proteins. Breast-feeding is important in early allergy prevention, but it is not yet fully clear if minute amounts of food antigens in the mother's milk may account for induction of oral tolerance to these antigens.

Figure 2



Prevalence of food allergies in children and adults in the USA.
(Figure drawn using data from Sampson [5].)

When breast-feeding cannot take place, it is generally recommended to administer hypoallergenic infant formulas for prevention of food allergy. Oral tolerance induction to dietary proteins has been extensively investigated with intact antigens [7]. It was further shown in animal models that pHF's are able to induce oral tolerance to intact cow's milk proteins, whereas eHF's are unable to achieve this. This was established by measuring the levels of IgE and intestinal mast cell responses [9].

Several clinical studies showed that allergen-reduced infant formulas (pHF or eHF) can be used as alternatives or to supplement breast milk for allergy prevention in at-risk infants. Although additional prospective studies are needed to compare pHF and eHF, the use of these formulas in the general infant population should be considered, taking into account cost and long-term benefits [8•].

Using a different strategy, it has been attempted to eliminate — or at least to down-modulate — the expression of food allergens in plants by genetic engineering. The principle was first established by silencing expression of Lol p 5, the major allergen of rye grass, with an antisense approach [10]. Serum IgE of pollen-allergic patients showed reduced reactivity with extracts of 'allergen-silenced' grass pollen. More directly relevant to food allergy, accumulation in the seeds of one of the major soybean allergens (Gly M Bd 30 K) was successfully attenuated by transgene-induced gene silencing [11]. Similarly, using RNA interference Gilissen *et al.* [12•] demonstrated that expression of the major apple allergen

Mal d 1 was reduced in apple plantlets transformed with intron RNA containing a Mal d 1 inverted repeat. In extracts of these plantlets, Mal d 1 was barely detectable and the reactivity of engineered plantlet extracts was reduced in skin prick testing. Finally, 'post-translational gene silencing' (antisense) was proven to be effective for silencing Ara h 2, a major allergen of peanuts [13]. Several further techniques (e.g. reduction of allergenicity by point-mutation of the allergen's IgE-binding site [14]), have been applied and might, in theory, be applied to food allergens. All these genetic approaches towards allergen-free foods may represent a specific and causal strategy to avoiding allergen contact. However, approaches that only reduce rather than completely eliminate allergen expression might not satisfy the needs of an allergic consumer, as often minute amounts of allergen suffice to trigger allergic reactions. Moreover, the commercial viability of allergen-knockout products will depend on all other characteristics of the engineered plants, most notably preservation of nutritional value and flavor and, last but not least, the general acceptance of 'knockout foods' by the consumer.

Modification of the host immune system: probiotics and beyond

Probiotic bacteria have a long tradition as health-preserving and/or health-promoting food additives. Their beneficial effects on gut homeostasis and immune functions are increasingly better documented and various strains are delivered in foods (mainly in fermented milk-based products) or as food supplements. They hold potential for the prevention or treatment of a variety of medical conditions and successful clinical evaluation in several specific diseases of the gastro-intestinal tract, such as rotavirus-associated diarrhea or pouchitis, has been reported (reviewed in [15]).

A few intervention studies aimed at the prevention of atopic manifestations with probiotics have been reported. Probably the most accurately documented is a study in which *Lactobacillus rhamnosus* strain GG (LGG) was given pre-natally for 2–4 weeks before delivery to pregnant women with allergy risk factors, followed by a 6 month treatment of the newborns. Follow-up after 1 year revealed a prevalence of atopic eczema of 46% in the untreated group versus 23% in the probiotic-treated group, corresponding to a drop in relative risk to 0.51 owing to treatment [16•]. At 4 years of follow-up, the risk was still reduced to 0.57 [17]. However, all other objective parameters of allergic disease, such as allergen-specific skin-prick testing or IgE plasma levels were not influenced by the probiotic treatment. Anti-allergic effects have also been ascribed to Gram-negative probiotics. Colonization during the first week of life with a probiotic *Escherichia coli* strain (O83:K24:H31) resulted in significantly reduced allergy prevalence 10 (study in pre-term infants) or even 20 years later (full-term infants) [18].

The capacity for therapeutic, rather than preventive, intervention against allergy with probiotics has been tested in a limited number of clinical trials. In a recent study, 230 babies (<12 months) with suspected cow's milk allergy were randomized to receive either LGG, a mix containing LGG and three other probiotics or a placebo for 4 weeks. Another four weeks after the end of treatment, parameters of allergy with emphasis on symptoms of the atopic eczema/dermatitis syndrome were recorded. Reduction of the dermatitis scores (Scoring of Atopic Dermatitis, SCORAD) was noted in all groups, but a significant difference ($p = 0.036$) between the LGG and placebo groups was only noted if allergy was IgE-associated [19]. Similarly, elevated fecal IgA and a trend to reduced levels of mediators of allergic inflammation (such as α -antitrypsin, tumor necrosis factor- α or eosinophil cationic protein) were noted in the LGG group [20]. A similar study in Australia yielded even clearer results, using a different *Lactobacillus* strain (*Lactobacillus fermentum* VRI-003 PCC), longer treatments (8 weeks) and longer follow-up (16 weeks) of the infants [21^{*}].

Allergy therapy and prevention with probiotics have shown encouraging results in first human clinical trials. However, the body of evidence remains narrow at present, with data mainly from studies in infants with cow's milk allergy and with a reproducible effect on SCORAD

only. Although it might be argued that relief of symptoms is the most important and for the patient the only relevant parameter, it is not possible to deduce from these data possible mechanisms of symptom relief. This research area is currently being extended to respiratory allergens.

In addition to probiotics, a large number of compounds that might be applied in combination with food have been tested for their efficacy in allergy prevention or therapy both *in vitro* and in animal models as well as in first human clinical trials. A selective, non-exhaustive list of such compounds is provided in Table 1 and possible intervention points along the allergic cascade can be deduced from Figure 1. For example, protection against peanut-induced anaphylaxis was achieved by subcutaneous treatment with a mixture of peanut allergen and heat-killed *Listeria monocytogenes* in dogs [22]. Reduction in allergen-specific IgE and a drop in IL-5 and IL-13 production were accompanied by increased levels of interferon- γ and a limited effect on body temperature, allergy scores, and histamine release — indicative of immune suppression within the vaccinated dogs. Similarly, deliberate or environmental exposure to *Mycobacterium vaccae* appears to lead to a reduction of the allergic reactions associated with asthma and eczema [23], both in humans and in animal models. So far, no attempts to use such bacterial strains in the context of food allergy have been reported. The use of bacterial components such as lipoglycans [24], lipopoly-

Table 1

Compounds with anti-allergic potential (probiotics not included).

Compound	Origin	Effect	Model	Selected references
Non-probiotic bacteria	<i>Listeria monocytogenes</i>	↓ Symptoms ^a ; IgE	Dog	[22,23]
	<i>Mycobacterium vaccae</i>	↓ Eosinophilia	Mouse	
Lipoglycans	<i>Mycobacterium</i>	↓ Airway disease	Mouse	[24]
		↓ Eosinophilia		
Lipopolysaccharide	Gram-negative bacteria (e.g. <i>Bacillus fragilis</i>)	↓ Specific IgE	Human	[25,26]
		↓ Th2 cytokines	Mouse	
		↓ Eosinophilia		
CpG-containing DNA	Bacteria	↓ Th2 proliferation	Human (<i>in vitro</i>)	[27,28]
		↓ Eosinophilia		
Carrageenan	Seaweed polysaccharide	Adjuvant of oral tolerance	Mouse	[32]
Herbal extracts	Green tea (anti-oxidant)	↓ Anaphylaxis	Mouse	[33]
		↓ IgE		
		↓ Th2 cytokines		
n-3/n-6 PUFA	Fish oil	↓ SPT to egg	Human	[34,35]
		↓ SCORAD	Mouse	
		↓ Cytokines		
FIP-fve	<i>Flammulina velutipes</i>	↓ IgE	Mouse	[36]
		↑ Th1 cytokines		
Anti-oxidants	Vitamin C or E	↓ Risk of wheeze/eczema	Human	[37,38]
Fructo- and galacto-oligosaccharide	Various plants	↓ IgE	Human/mouse	[39]

^aSymptoms: vomiting, swelling, naso-ocular signs, pallor of oral mucosa, lethargy, diarrhea, anaphylaxis. Abbreviations: FIP-fve, fungal immunomodulatory protein fve; n-3/n-6 PUFA, n-3/n-6 polyunsaturated fatty acid; SPT, skin prick test; SCORAD, Scoring of Atopic Dermatitis.

saccharides [25,26] or CpG-containing DNA [27,28] might be another valid approach towards immunomodulation of the host. However, further studies are required to assess their potential in food, particularly the mode of delivery in active form to the gut immune system. Mechanistically, Toll-like receptors on antigen-presenting cells and intestinal epithelial cells are critically involved in sensing the various bacterial components, possibly leading to the induction of T regulatory cells with the ability to produce suppressive cytokines such as IL-10 and transforming growth factor- β [29,30]. Detailed mechanistic aspects have been covered recently in an excellent review by Priault and Nagler-Anderson [31].

In terms of food-related products, promising pre-clinical data have been obtained with oral administration of the seaweed polysaccharide carrageenan in β -lactoglobulin-sensitized mice [32] or a Chinese herbal medicine formula (FAHF-2) in peanut-sensitized mice [33]. Animals were protected for several weeks from anaphylaxis following challenge, an effect associated with a reduction in allergen-specific IgE and downregulation of IL-4, IL-5 and IL-13. A similar deviation of the immune response has been observed using dietary lipids rich in n-6 polyunsaturated fatty acid (PUFA), n-3 PUFA, and saturated fatty acids [34,35] or even using an immunomodulatory protein from the edible mushroom *Flammulina velutipes* [36]. Likewise, antioxidants such as vitamin A and E or flavonoids [37,38] have been successfully tested in allergy models. These results are encouraging, but often reports on their evaluation have remained anecdotal to date. Therefore, they will need to be very critically scrutinized through controlled clinical trials in humans. In addition, most of these studies did not attempt to evaluate the best lifetime window for intervention, which could substantially impact on the potential efficacy of these ingredients.

Conclusions

In the future, to enable the hypothesis-driven search for food ingredients with preventive/therapeutic effect and to determine to what extent immune deviation can be counterbalanced at different periods of life (i.e. at different stages of immune maturity/competence), it will be important to further elucidate the mechanisms of food allergy development. Moreover, data on interventions beyond infancy and for other types of allergy (particularly respiratory allergy) remain scarce and more pre-clinical and clinical work is warranted to consolidate the initial positive findings. This should include the definition of more reliable biomarkers, the development of *in vitro* models with good predictive power to facilitate the search for candidate ingredients, and the elaboration of *in vivo* models that more accurately reflect the human situation.

Acknowledgements

The authors wish to thank Beat Mollet and Guénolée Priault for critical comments on the manuscript.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. **Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee.** *Lancet* 1998, **351**:1225-1232.
2. von Mutius E: **Influences in allergy: epidemiology and the environment.** *J Allergy Clin Immunol* 2004, **113**:373-379.
3. Isolauri E, Rautava S, Kalliomaki M, Kirjavainen P, Salminen S: **Role of probiotics in food hypersensitivity.** *Curr Opin Allergy Clin Immunol* 2002, **2**:263-271.
4. Osterballe M, Hansen TK, Mortz CG, Host A, Bindslev-Jensen C: **The prevalence of food hypersensitivity in an unselected population of children and adults.** *Pediatr Allergy Immunol* 2005, **16**:567-573.
5. Sampson HA: **Update on food allergy.** *J Allergy Clin Immunol* 2004, **113**:805-819.
6. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G: **Epidemiology of life-threatening and lethal anaphylaxis: a review.** *Allergy* 2005, **60**:443-451.
7. Strobel S, Ferguson A: **Immune responses to fed protein antigens in mice. 3. Systemic tolerance or priming is related to age at which antigen is first encountered.** *Pediatr Res* 1984, **18**:588-594.
8. Hays T, Wood RA: **A systematic review of the role of hydrolyzed infant formulas in allergy prevention.** *Arch Pediatr Adolesc Med* 2005, **159**:810-816.
- A comprehensive review on the use of partially and extensively hydrolyzed milk formula for allergy prevention.
9. Fritsche R, Pahud JJ, Pecquet S, Pfeifer A: **Induction of systemic immunologic tolerance to β -lactoglobulin by oral administration of a whey protein hydrolysate.** *J Allergy Clin Immunol* 1997, **100**:266-273.
10. Bhalla PL, Swoboda I, Singh MB: **Antisense-mediated silencing of a gene encoding a major ryegrass pollen allergen.** *Proc Natl Acad Sci USA* 1999, **96**:11676-11680.
11. Herman EM, Helm RM, Jung R, Kinney AJ: **Genetic modification removes an immunodominant allergen from soybean.** *Plant Physiol* 2003, **132**:36-43.
12. Gilissen LJ, Bolhaar ST, Matos CI, Rouwendal GJ, Boone MJ, Krens FA, Zuidmeer L, Van Leeuwen A, Akkerdaas J, Hoffmann-Sommergruber K et al.: **Silencing the major apple allergen Mal d 1 by using the RNA interference approach.** *J Allergy Clin Immunol* 2005, **115**:364-369.
- A recent example showing that silencing of the major apple allergen results in reduced skin-prick reactivity and IgE binding.
13. Dodo H, Konan K, Viquez O: **A genetic engineering strategy to eliminate peanut allergy.** *Curr Allergy Asthma Rep* 2005, **5**:67-73.
14. Ferreira F, Ebner C, Kramer B, Casari G, Briza P, Kungl AJ, Grimm R, Jahn-Schmid B, Breiteneder H, Kraft D et al.: **Modulation of IgE reactivity of allergens by site-directed mutagenesis: potential use of hypoallergenic variants for immunotherapy.** *FASEB J* 1998, **12**:231-242.
15. Bergonzelli GE, Blum S, Brüssow H, Cortes-Thoulaz I: **Probiotics as a treatment strategy for gastrointestinal diseases?** *Digestion* 2005, **72**:57-68.
16. Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E: **Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial.** *Lancet* 2001, **357**:1076-1079.
- Prophylactic intervention with a probiotic resulted in a lower prevalence of atopic dermatitis in at-risk infants.
17. Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E: **Probiotics and prevention of atopic disease: 4-year follow-up**

6 Food biotechnology

- of a randomised placebo-controlled trial. *Lancet* 2003, **361**:1869-1871.
18. Lodinova-Zadnikova R, Cukrowska B, Tlaskalova-Hogenova H: **Oral administration of probiotic *Escherichia coli* after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years).** *Int Arch Allergy Immunol* 2003, **131**:209-211.
 19. Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M: **Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial.** *Allergy* 2005, **60**:494-500.
 20. Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E: **Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants.** *Pediatr Allergy Immunol* 2005, **16**:65-71.
 21. Weston S, Halbert A, Richmond P, Prescott SL: **Effects of probiotics on atopic dermatitis: a randomised controlled trial.** *Arch Dis Child* 2005, **90**:892-897.
- Clinical study in at-risk infants showing significant reduction of the atopic dermatitis score after consumption of probiotics.
22. Frick OL, Teuber SS, Buchanan BB, Morigasaki S, Umetsu DT: **Allergen immunotherapy with heat-killed *Listeria monocytogenes* alleviates peanut and food-induced anaphylaxis in dogs.** *Allergy* 2005, **60**:243-250.
 23. Zuany-Amorim C, Manlius C, Trifilieff A, Brunet LR, Rook G, Bowen G, Pay G, Walker C: **Long-term protective and antigen-specific effect of heat-killed *Mycobacterium vaccae* in a murine model of allergic pulmonary inflammation.** *J Immunol* 2002, **169**:1492-1499.
 24. Sayers I, Severn W, Scanga CB, Hudson J, Le Gros G, Harper JL: **Suppression of allergic airway disease using mycobacterial lipoglycans.** *J Allergy Clin Immunol* 2004, **114**:302-309.
 25. Bashir ME, Louie S, Shi HN, Nagler-Anderson C: **Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy.** *J Immunol* 2004, **172**:6978-6987.
 26. Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A *et al.*: **Environmental exposure to endotoxin and its relation to asthma in school-age children.** *N Engl J Med* 2002, **347**:869-877.
 27. Farkas L, Kvale EO, Johansen FE, Jahnsen FL, Lund-Johansen F: **Plasmacytoid dendritic cells activate allergen-specific TH2 memory cells: modulation by CpG oligodeoxynucleotides.** *J Allergy Clin Immunol* 2004, **114**:436-443.
 28. Horner AA, Raz E: **Immunostimulatory sequence oligodeoxynucleotide-based vaccination and immunomodulation: two unique but complementary strategies for the treatment of allergic diseases.** *J Allergy Clin Immunol* 2002, **110**:706-712.
 29. Adams VC, Hunt JR, Martinelli R, Palmer R, Rook GA, Brunet LR: ***Mycobacterium vaccae* induces a population of pulmonary CD11c+ cells with regulatory potential in allergic mice.** *Eur J Immunol* 2004, **34**:631-638.
 30. Mohamadzaheh M, Olson S, Kalina WV, Ruthel G, Demmin GL, Warfield KL, Bavari S, Klaenhammer TR: **Lactobacilli activate human dendritic cells that skew T cells toward T helper 1 polarization.** *Proc Natl Acad Sci USA* 2005, **102**:2880-2885.
 31. Prioult G, Nagler-Anderson C: **Mucosal immunity and allergic responses: lack of regulation and/or lack of microbial stimulation?** *Immunol Rev* 2005, **206**:204-218.
 32. Frossard CP, Hauser C, Eigenmann PA: **Oral carrageenan induces antigen-dependent oral tolerance: prevention of anaphylaxis and induction of lymphocyte anergy in a murine model of food allergy.** *Pediatr Res* 2001, **49**:417-422.
 33. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, Goldfarb J, Sampson HA, Li XM: **The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy.** *J Allergy Clin Immunol* 2005, **115**:171-178.
 34. Albers R, Bol M, Bleumink R, Willems A, Blonk C, Pieters R: **Effects of dietary lipids on immune function in a murine sensitisation model.** *Br J Nutr* 2002, **88**:291-299.
 35. Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL: **Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial.** *J Allergy Clin Immunol* 2003, **112**:1178-1184.
 36. Hsieh KY, Hsu CI, Lin JY, Tsai CC, Lin RH: **Oral administration of an edible-mushroom-derived protein inhibits the development of food-allergic reactions in mice.** *Clin Exp Allergy* 2003, **33**:1595-1602.
 37. Hoppp U, Rinne M, Salo-Vaananen P, Lampi AM, Piironen V, Isolauri E: **Vitamin C in breast milk may reduce the risk of atopy in the infant.** *Eur J Clin Nutr* 2005, **59**:123-128.
 38. Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A: **Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life.** *Am J Respir Crit Care Med* 2005, **171**:121-128.
 39. Fanaro S, Boehm G, Garssen J, Knol J, Mosca F, Stahl B, Vigi V: **Galacto-oligosaccharides and long-chain fructo-oligosaccharides as prebiotics in infant formulas: a review.** *Acta Paediatr Suppl* 2005, **94**:22-26.