What is Food Allergy?

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Symptoms of food hypersensitivity

Oral allergy syndrome (OAS): Itching and swelling of the mouth and oropharynx

Skin: Urticaria, activation of atopic eczema

Respiratory system: rhinitis, asthma

Gastrointestinal system: nausea, vomiting, abdominal pain, diarrhoea

Conjunctivitis

Angio-oedema

Anaphylaxis

Often from two or more organ systems
Classification of adverse reactions to food

Aversion

Food hypersensitivity

Errors of metabolism (inborn or acquired)

Food poisonings and/or infections (toxic or microbial)

Adverse reactions to food

Food allergy

IgE-mediated food allergy

Classical food allergy

Non-IgE-mediated food allergy

Inhalation-cross-reactive food allergy

Non-allergic food hypersensitivity (intolerance)

A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force.

Immunoglobulin E (IgE)
Allergens cross-links IgE and activate mast cells

IgE-antibodies bind to mast cells (sensitization)
Threshold values: Egg as an example
The technique for demonstrating absorption of unaltered fish protein was as follows: A site on the skin of the subject to be tested is passively and locally sensitized with 0.05 cc. of serum obtained from a certain fish-sensitive patient. On the following day the subject is fed 50 gm. of raw herring on an empty stomach. Development of a wheal at the sensitized site is proved to indicate absorption of fish into the circulation in an unaltered state. The phenomenon occurred in 93.8% of 65 cases tested.

In 50% of the subjects the reaction occurred within 15 min. after the fish meal; in 83.3%, within 1/2 hr.

Atopic patients and families show a lower percentage of positive reactions than normals. In a patient with hookworm disease, who failed to show a positive reaction, a true lack of permeability to unaltered proteins was demonstrated throughout the entire alimentary tract.
Allergenic activity recovered in serum of a non-allergic person after ingestion of peanuts

Dose response study

Allergenic activity determined by histamine release (% HR) using passive sensitization of basophils with a serum from a strongly peanut allergic person

Abstract #1017: C G Dirks, M H Pedersen, M H Platzer, C Bindslev-Jensen, P S Skov, L K Poulsen
Systemic absorption of biologically active peanut allergens in non-allergic volunteers following oral intake
Immunological regulation of the IgE production
Female, age: 33
Last exposure to codfish in 1970. SPT positive. Response to challenge: Asthma

Male, age: 26
Last exposure to codfish in 1988. SPT positive. Response to challenge: Asthma + G.I. symptoms

Data from TK Hansen
Sensitization phase of the allergic immune response

- Præ B
- Th0
- Allergen
- Danger signals
- IgE producing plasmacells
- IL-4, IL-13
- IL-9
- IL-3
- IL-5
- GM-CSF
- Histamin
- LTC4, LTB4
- PGD2
- PAF
- Heparin
- Tryptase
- Chymase
- Chemokiner: Eotaxin-1, -2, -3
- IL-8, RANTES
- Cytokiner: IL-3, IL-4, IL-5, TNF-a

Immature dendritic cell

Mature DC

Allergen

Danger signals

???
Differentiation of CD4+ T-cells into Th1 or Th2 cells

- IgG-response: "protecting immunity" autoimmunity
- IgE-response: "allergic phenotype" parasites

IL-1, IL-1ra, IL-6, TNF-a
IL-4
IL-10
IL-13

Macrophages, dendritic cells (DC1, DC2)

IFN-α
IL-12
IL-18

IFN-γ
IL-2

NK

CD4+ precursor

Th0

Th1

Th2

IFN-γ
IL-4

Th1 response
Th2 response

Bacteria, virus

Allergens, Parasites

IL-4
IL-5
IL-9
IL-13

mast cell

IL-2
IFN-γ

IgG-response

autoimmunity

"protecting immunity"
The Increasing Incidence of Immune Regulatory Disorders


The diagram shows the incidence of various immune disorders over time. The x-axis represents years from 1950 to 2000, and the y-axis represents the incidence of immune disorders (%) from 100 to 400. The disorders include Crohn's disease, multiple sclerosis, type 1 diabetes, and asthma.
CD4+ T-cells can be regulatory or inflammatory cells

Treg: CD4+CD25+
Constitutes 7% of CD4+
Inhibits proliferation and cytokine production..
..presumably by IL-10 (soluble) and CTLA-4 (contact)
Sensitization in Greenland

Krause TG, Koch A, Friborg J, Poulsen LK, Kristensen B & Melbye M
Increasing prevalence of atopy in the Arctic
Risk factors for becoming sensitized to foods
Food Allergy and Anaphylaxis Guidelines

Translating knowledge into clinical practice

European Academy of Allergy and Clinical Immunology
Four paradoxes in food allergy

Regional differences

Temporal changes of food allergy prevalence

Differential natural history of varying food allergies

Taxonomically related, but allergenically different foods

Poulsen LK
In search of a new paradigm: Mechanisms of sensitization and elicitation of food allergy
Allergy 60(5):549-58 (2005)
Prevalence of food allergy

A selected pediatric population (<3Y)
Reported prevalence of food hypersensitivity: 28%
Confirmed by DBPCFC: 3.9 %

E. Young, M.D. Stoneham, A. Petruckevitch, J. Barton & R. Rona
A population study of food intolerance.

Bock, SA
Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life.

A population based study of 2 x 7500 households
Reported prevalence of food hypersensitivity: 20%
Confirmed by DBPCFC: 1.4 - 1.8 %
Filaggrin mutations

The allergens - terminology

Allergenic materials
- the sources of allergens

Allergens
- IgE-binding antigens
- normally proteins

Allergen extracts
- pharmaceutical preparations of allergens for diagnosis or treatment
1. Identification of new allergenic sources

The ImmunoCAP catalog contains more than 600 different sources

Do we need more?

New allergenic sources due to climate changes?

New allergenic sources due to globalization of food markets and habits?

New occupational allergens?
Allergen research in the clinic: 3 waves

2. Identification, characterization, and cloning of single allergens

From the editorial by Stefan Vieths & Karin Hoffman-Sommergruber:

...existing allergen purification protocols were improved and expression strategies for producing recombinant allergens were evaluated and optimized. Subsequently, authentication of the highly pure protein batches were performed using state of the art methods including MALDITOF mass spectrometry, tandem mass spectrometry and N-terminal amino acid sequencing. Tertiary structures were evaluated by high resolution one-dimensional 1H NMR spectroscopy; secondary structure was evaluated by far-UV circular dichroism spectroscopy. Allergenic activity was studied by IgE ELISA, IgE immunoblotting and cellular basophil activation tests, using selected sera from a panel of food allergic subjects. In the first round, 31 allergens from ten foods including many of the EC labelling list (apple, peach, hazelnut, peanut, celery, cow’s milk, goat’s milk, hen’s egg, fish, and shrimp) were produced and purified by leading scientists in this field and for the first time characterised to a comparable extent.

131 pages, 11 original papers, 140 authors
"The golden age of new allergen discovery is over"

James D. Astwood

<table>
<thead>
<tr>
<th>Year</th>
<th>Unique sequences</th>
<th>Homologues, isoforms etc.</th>
<th>Total sequences</th>
<th>New</th>
<th>%New</th>
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<td>2000</td>
<td>180</td>
<td>400</td>
<td>580</td>
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<td>2005</td>
<td>185</td>
<td>900</td>
<td>1085</td>
<td>5</td>
<td>0.5</td>
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</table>
3. Identification of cross-reactive patterns

For each n allergens, there are n x (n-1) possible cross-reactivities!

Example: Food allergy - cross-reacting foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Crossreaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>Goat's milk, mare's milk, sheep's milk</td>
</tr>
<tr>
<td>Hen's egg</td>
<td>Eggs from goose, turkey, duck. Chicken meat. Bird feathers.</td>
</tr>
<tr>
<td>Codfish</td>
<td>Plaice, mackerel, herring other fishes</td>
</tr>
<tr>
<td>Peanut X)</td>
<td>Soy, green bean, pea</td>
</tr>
<tr>
<td>Shrimp</td>
<td>Crab, crayfish, lobster</td>
</tr>
<tr>
<td>Birch</td>
<td>Hazelnuts, apple, potato, carrot, cherry, kiwi</td>
</tr>
<tr>
<td></td>
<td>almond and other tree nuts</td>
</tr>
<tr>
<td>Wheat X)</td>
<td>Grass pollen, rye, sesame, buckwheat, oats</td>
</tr>
<tr>
<td>Banana</td>
<td>Latex, avocado, pear</td>
</tr>
</tbody>
</table>
Clinical non-relevant cross-reactions

65 grass-pollen allergics who tolerate 25 grams of 6 cereal products plus peanut were tested in skin test and specific IgE (ImmuLite® & ImmunoCAP®).

46% (SPT), 37% (ImmunoCAP) and 20% (Immulite) reacts the tolerated foods.

Martens M, Schnoor HJ, Malling H-J & Poulsen LK
The clinical relevance of in vivo/in vitro tests for cereal and peanut sensitisation in grass pollen allergic patients
Clinical and Translational Allergy 2011, 1:15
New proteins in the food chain: Is there evidence of new sensitization and allergies?

Largest increases in sensitization rates comes from allergenic sources already known to be allergens.

New sources may be allergenic, but most often this happens because of cross-reactivity to allergens already well-established in society.

Individual novel proteins can - and should - be screened for potential cross-reactivity before their entry into the food chain.

Hidden allergens and unknown cross-reactivities are probably the largest allergy-related public health problem.

New processing technologies may cause new problems.