Chapter 3: IgE in the intestine and food allergy

Eva Untersmayr-Elsenhuber
Department of Pathophysiology and Allergy Research
Medical University Vienna
Topics of lecture

- Intestinal disorders and IgE antibodies
- The pathophysiology of food allergy
- IgE and intestinal parasite infections and its relation to allergic diseases
- Intestinal IgE interaction partners
IgE and the intestine

- **Food allergy**

- **Parasite infections**
  IgE enhances parasite clearance
  Gurish MF et al J Immunol 2004

  IgE in stool

- **IBD**
  Increased IgE and auto-IgE Abs in CD
  Huber A et al Int Arch Allergy Immunol 1998

  Food allergy due to chronic inflammation

- **Gastrointestinal tumors**
  Participation of IgE in tumoricidal activities
  Jensen-Jarolim E et al Allergy 2008
Nomenclature of food adverse reactions

Food hypersensitivity

Food allergy
- immunologically mediated response
  - IgE-mediated food allergy
  - Non-IgE mediated food allergy

Non-allergic food hypersensitivity

Johansson SG et al. EAACI position paper 2001
Non-IgE mediated food allergy

Celiac disease 1:2000 children affected

Exogenous trigger: gluten

H₂O electrolytes

Mucosa in celiac disease

Endogenous trigger: tTG

Jensen-Jarolim E. Gastointestinaltrakt. Springer Verlag
Pathophysiology of celiac disease

- Ingested gluten
- Auto-antigen: tTG
- Genetic predisposition: MHC class II antigens HLA DQ2, HLA DQ8

Meresse B et al. Mucosal Immunology 2009
Dermatitis herpetiformis Duhring

subepidermal immunocomplexes 30% of the patients

subepidermal vesicles, neutrophils, microabscesses, depots of IgA, C3
Type IV hypersensitivity reaction

- anorganic molecules, metals, proteins
- only cell-mediated by Th1 and cytotoxic T-cells

Testing with atopic patch test, first reading after 24-48h, again 72h
Atopic dermatitis

IgE associated/cell-mediated (delayed onset/chronic)

Association with food in approx. 35% of children with moderate-to-severe rash

Age distribution: infant > child > adult

Most common causal foods: major allergens, particularly egg, milk

Typically resolves with age

Eosinophilic gastroenteropathies

Symptoms vary due to site(s)/degree of eosinophilic inflammation
- Esophageal: dysphagia, pain, generalized: ascites, weight loss, edema, obstruction
- Pathophysiology: IgE and cell-mediated; mediators that home and activate eosinophils (eotaxin, IL-5)
- Multiple causal food allergens; course of disease: persistent
Dietary protein enterocolitis/proctitis

Mainly in infancy, usually resolves with age

Cell-mediated, with increased TNF-α response, decreased response to TGF-β (enterocolitis) or eosinophilic inflammation (proctitis)

Causal foods: cow’s milk (even through breast feeding), soy, rice, oat

Symptoms of chronic allergen exposure: emesis, diarrhea, poor growth and lethargy
Re-exposure after restriction: emesis, diarrhea and hypotension (15%) 2 h after ingestion
Mucus-laden, bloody stools in infants
Nomenclature of food adverse reactions

Food hypersensitivity

Food allergy
- Immunologically mediated response
  - IgE-mediated food allergy
  - Non-IgE mediated food allergy

Non-allergic food hypersensitivity

Johansson SG et al. EAACI position paper 2001
**Epidemiology**

Self-reported allergy to milk, egg, peanut and seafood: 3-35%

Studies with OFC → 1%-10.8%
Fruits and tree nuts 0.1%-4.3%
Vegetables 0.1%-1.4%

Peanut allergy in children has doubled, 1% of school age children

*Sicherer SH, Sampson HA. JACI 2007*

CDC report: 18% increase of childhood food allergy from 1997-2007

*Branum AM et al. NCHS Data Brief 2008*

<table>
<thead>
<tr>
<th>Food-allergy rates in North America</th>
<th>Infant/child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2.5%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Egg</td>
<td>1.5%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Peanut</td>
<td>1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Fish</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Shellfish</td>
<td>0.1%</td>
<td>1%</td>
</tr>
<tr>
<td>Wheat, soy</td>
<td>0.4%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Overall</td>
<td>5%</td>
<td>3-4%</td>
</tr>
</tbody>
</table>

*Sicherer SH, Sampson HA. JACI 2010*
Hospitalisation due to food allergy

Average number of hospital discharges/year among children (under 18 years) with diagnosis „food allergy“ in the United States 1998-2006

http://www.cdc.gov/nchs/data/databriefs/db10_fig4.gif
Hospital admission rates in Australia

Data from Australian national hospital morbidity data
erate per million population

Mullins RJ. MJA 2007
Symptoms of food allergy

- **Local:** Oral allergy syndrome, angioedema, gastrointestinal pain, nausea, vomiting, diarrhea

- **Systemic:** Urticaria, angioedema, eczema, rhinitis, asthma, anaphylaxis

- **Unclear correlation:** Migraine, arthritis, fatigue, behavioral disorders
Oral allergy syndrome

Pruritus, mild edema confined to oral cavity
Uncommonly progresses beyond mouth (~7%)
or anaphylaxis (1-2%)
Might increase after pollen season

Sensitization to pollen proteins by the respiratory route → IgE Abs bind homologous, typically labile food proteins (e.g. Bet v1 in birch and Mal d1 apple)

Typical age: adult > young > child (onset after established pollen allergy)

Raw fruit/vegetables (tolerated in cooked forms)

Might be long-lived and vary with season
Urticaria/angioedema

Triggered by ingestion or direct skin contact (contact urticaria)

Food commonly causes acute (20%), but rarely chronic urticaria (2%)

Typical age: children > adults

Major allergens are the main triggers

Natural course is depending on food
Rhinitis, asthma

Symptoms accompany a food induced allergic reaction rarely isolated or chronic symptom might be triggered by inhalation of aerosolized food proteins

Infant/child>adults, except occupational disease (eg. baker’s asthma)

Main triggers: general: major allergens occupational: wheat, egg, seafood

Natural course: Depending on food
Anaphylaxis

Rapidly progressive (10-100 min after meal), multiple organ system reaction, which can include cardiovascular collapse due to massive release of mediators (histamine), mast cell tryptase levels are not always elevated, key role of PAF

In the US: 29,000 anaphylactic reactions after food ingestion, 125-150 lethal  


Can occur at any age

<table>
<thead>
<tr>
<th>Age</th>
<th>0-5</th>
<th>5-10</th>
<th>10-15</th>
<th>15-20</th>
<th>20-25</th>
<th>25-30</th>
<th>30-35</th>
<th>35-40</th>
<th>40-45</th>
<th>45-50</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanuts</td>
<td>2</td>
<td></td>
<td>4</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts</td>
<td></td>
<td></td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>walnuts</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shellfish</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>other</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most common triggers: Peanut, tree nuts, shell fish, fish, milk, eggs

Triggers of anaphylaxis

- Campari
- Banana
- Caviar
- Peanuts and tree nuts
- Eggs
- Snails
- Camomille
- Fish
- Avocado
- Shellfish
- Milk
**Exercise-induced anaphylaxis**

Food triggers anaphylaxis only if ingestion followed temporally by exercise.

Immunopathology: Exercise is presumed to alert gut absorption, allergen digestion, or both.

Onset more commonly later childhood/adult.

Main triggers: wheat, shellfish, celery.

Seem to persist.

IgE-mediated food allergy

Diesner SC. MD thesis MUW 2007
Oral tolerance versus sensitization

GI tract largest surface area in human body

Enormous quantities of antigens → suppression of immune reactions to food and harmless foreign commensal organisms
Central role: APC (IEC, DC), regulatory T-cells (Th3 cells, T\textsubscript{R}1 cells, CD4\textsuperscript{+}/CD25\textsuperscript{+} reg. T cells, \(\gamma\delta\)T cells)

T cell anergy, clonal deletion, T reg. cell induction

\(\Rightarrow\) Tolerance in the intestine 11.11.2010
Dr. Franziska Roth-Walter
Characteristics of food allergens

- Glycoproteins
- Low dose → activation of IL4-producing CD4-T-cells
- Low molecular weight (10-70 kDa) → diffusion through epithelia facilitated
- Solubility
- Stability to head, acid, proteases
- Some are enzyme inhibitors
- Abundance in food

Sensitization to food proteins

Class II. Pollen-associated food-allergens
“Non-sensitizing elicitors”
digestion-labile

Class I. „true“ food-allergens
digestion-resistant
„Non-sensitizing“ elicitors

Cross-reactivity between food and pollen allergens

Typical example Bet v1
cross-reactivity with other PR-10
(pathogenesis-related proteins) in >30% of the patients:

<table>
<thead>
<tr>
<th>Food</th>
<th>Allergen</th>
<th>Cross-reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>Mal d1</td>
<td>58%</td>
</tr>
<tr>
<td>Cherry</td>
<td>Pru av1</td>
<td>59%</td>
</tr>
<tr>
<td>Apricot</td>
<td>Pru ar1</td>
<td>60%</td>
</tr>
<tr>
<td>Pear</td>
<td>Pyr c1</td>
<td>57%</td>
</tr>
<tr>
<td>Celery root</td>
<td>Api g1.01</td>
<td>40%</td>
</tr>
<tr>
<td>Carrot</td>
<td>Dau c1</td>
<td>38%</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a1</td>
<td>67%</td>
</tr>
<tr>
<td>Soybean</td>
<td>Gly m4</td>
<td>48%</td>
</tr>
</tbody>
</table>

Radauer et al. BMC Evolutionary Biology 2008
## Other pollen – food cross-reactivities

### Profilins

Recognized by 20% of the pollen allergic patients, high cross-reactivity between profilins in pollen and vegetable food

<table>
<thead>
<tr>
<th>Pollen Allergen</th>
<th>Food Allergen</th>
<th>Sensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birch</strong> Bet v2</td>
<td><strong>Apple</strong> Mal d4</td>
<td>82%</td>
</tr>
<tr>
<td>(Grass Phl p11, Phl p12)</td>
<td>(Mugwort Art v4)</td>
<td></td>
</tr>
<tr>
<td><strong>Cherry</strong> Pru av4</td>
<td><strong>Cherry</strong> Pru av4</td>
<td>76%</td>
</tr>
<tr>
<td><strong>Apricot</strong> Pru ar1</td>
<td><strong>Apricot</strong> Pru ar1</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Pear</strong> Pyr c4</td>
<td><strong>Pear</strong> Pyr c4</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Celery root</strong> Api g4</td>
<td><strong>Celery root</strong> Api g4</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Peanut</strong> Ara h5</td>
<td><strong>Peanut</strong> Ara h5</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Hazelnut</strong> Cor a2</td>
<td><strong>Hazelnut</strong> Cor a2</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Soybean</strong> Gly m3</td>
<td><strong>Soybean</strong> Gly m3</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Tomato</strong> Lyc e1</td>
<td><strong>Tomato</strong> Lyc e1</td>
<td>78%</td>
</tr>
<tr>
<td><strong>Bell pepper</strong> Cap a2</td>
<td><strong>Bell pepper</strong> Cap a2</td>
<td>77%</td>
</tr>
</tbody>
</table>

Sensitization to almost any fruit and vegetable possible

Birch pollen related food not only Bet v1 family but also profilins

Mugwort pollen associated food allergy (celery, carrot, camomilla, spices)

Food allergy in grass pollinosis patients

*Vieths S et al. Ann NY Acad Sci 2002*
The role of carbohydrates in food allergy

CCD are classically considered as a potential source of positive in vitro results without clinical significance. Low binding affinity may be induced due to everyday contact with plant material.

Glycosylated Ara h1 but not the deglycosylated form act as Th2 adjuvant by activating dendritic cells to drive maturation of Th2 cells.

Ara h1 acts as ligand for DC-SIGN (DC-specific intercellular adhesion molecule), which also interacts with schistosome glycoprotein → Th2 responses induced.

Urticaria, angioedema, anaphylaxis 3-6h after beef, lamb, pork ingestion → pos. skin tests and IgE to galactose- α-1, 3-galactose, ie. Carbohydrate moiety of glycoproteins → first evidence for clinical symptoms!
True food allergens

Characterized by their stability to heat and proteases

Peanut allergen Ara h2, β-lactoglobulin in cow’s milk → triggers of severe allergic reactions

90% of all severe food allergic reactions against a small number of allergens

→ Declaration of milk, fish, eggs, peanuts, nuts, crustaceans, celery, soybeans, sesame seeds, mustard, and products thereof on food products since January 1, 2005 in the European Community since January 1, 2006 in the United States

www.cfsan.fda.gov/~dms/alrgact.html

→ Introduction of SGF experiments for food safety testing

Astwood JD et al. Nat Biotechnol 1996
http://usinfo.state.gov/products/pubs/biotech
Physiological gastric digestion

The major gastric protease pepsin is produced by chief cells of gastric glands

Secreted into gastric lumen as inactiv proenzyme Pepsinogen
At low pH levels → disruption of electrostatic interactions between N-terminal prosegment and active enzyme
→ Substrate-binding cleft with 2 active-site aspartates accessible
→ Protein cleavage
In vitro digestion experiments

Pepsin
pH 2

Food proteins

Stomach is gate keeper for typical food allergens

Milk
Fish
In vitro digestion at elevated pH

Allergen digestion is impaired under hypoacidity
Hypoacidity of the stomach

Physiological: Newborns

Atrophic gastritis

Pharmacological:

• Antacids
• H2 receptor blockers
• Proton pump inhibitors
The role of gastric digestion in food allergy

Experimental as well as human studies indicate that impairment of gastric digestion represents risk factor for:

- Sensitization towards regular, digestion-labile constituents of the daily diet
- Development of food allergy only if proteins are ingested under acid-suppression
- Allergic reactions towards minute amounts of allergens
- Changes in previously established LOAEL or NOAEL

Untersmayr E, Jensen-Jarolim E. JACI 2008
The effect of food preparation

Peanut allergy: effect of preparation on allergenicity
China: boiled or fried → lower prevalence
Western countries: Roasting → high temperatures → Maillard reaction → increased stability and allergenicity

Maleki SJ et al JACI 2003
Beyer K et al. JACI 2001

Emulsification (eg. peanut butter) increases allergenicity through adjuvant effect
Sicherer SH, Sampson HA. JACI 2007

Heat denaturation (baking) of milk and egg allergens → can be tolerated in 70-80% of young allergic children
IgE to conformational epitopes

Nowak-Wegrzyn A et al. JACI 2008
Lemon-Mule H et al. JACI 2008
Diagnosis of food allergy

detailed case history

• Reactions timely related with exposition

• No symptoms if food is avoided

• Family history regarding atopic disorders

• Known allergies

• Diet diary
Serological and skin testing

- Total IgE: PRIST > 100 kU/L
- Specific IgE: CAP
- Component-resolved diagnosis
- Histamin release tests
- Skin prick tests with extracts
- Prick-to-prick tests with fresh food
Provocation tests

Open Challenges:
• Allergen avoidance and re-introduction

Blinded Provocations:
• single blinded
• Double-blind, placebo-controlled
Food Challenge

Gold standard of food allergy diagnosis
Provocations with increasing concentrations of food and placebo
ONLY in facilities with ER equipment
4-6h observation after tests
For determination of threshold levels (NOAEL, LOAEL) especially in children

Standardisation of test substances!!
Therapy of food allergy

- Avoidance of causal food
  Education about label reading, cross-contact, ..
- Food-labeling regulations
- Medication: self-injectable epinephrine, steroids, antihistamins
- Oral immunotherapy gradually increased allergens doses towards maintenance dose
- Immunotherapy with cross-reactive pollen allergens: limited efficacy for cross-reactive food allergens
- Chinese herbs: Food allergy herbal formula-2
- Anti-IgE therapy

Jones SM et al. JACI 2009
Hofmann AM et al JACI 2009
Narisety Sd et al JACI 2009
Kinaciyan T et al. JACI 2007
Srivastavsa KD et al. JACI 2009
IgE and intestinal parasite infections

IgE via the high affinity receptor Fc\(\varepsilon\)RI on eosinophils → defence against parasites


IgE enhances parasite clearance and regulates mast cell responses in mice infected with *Trichinella spiralis*

Gurish MF et al. J Immunol 2004

Diseases with elevated levels of IgE antibodies an increased intestinal trans-epithelial transport of IgE → detectable amounts of IgE in stool

Allergy treatment with *Trichuris suis*?

Unlike allergy, parasite infections are common in low-income countries → Hypothesis: Immune systems evolved to silence parasite infections → imbalance in Westernized countries due to their absence

*Wickelgren I. Science 2004*  
*Schubert C. Nat Med 2004*

Studies on antihelminthic therapy reported increases in allergen skin sensitization

*Lynch NR et al. JACI 1993*  
*Van den Biggelaar AH et al J Infect Dis 2004*  
*Flohr C et al. Clin Exp Allergy 2009*

In the 1990s: 3 clinical studies on efficacy of live ova ingestion from *Trichuris suis* for Th1-mediated Crohn’s disease and Th2-mediated Ulcerative colitis

*Summers RW et al. Am J Gastroenterol 2003*  
*Summers RW Gastroenterology 2005*  
*Summers RW Gut 2005*

Randomized, double-blind, placebo-controlled clinical trial of *Trichuris suis* ova therapy for therapy of allergic rhinitis showed no therapeutic effect

*Time-point of treatment before pollen season? Differences in study groups? Low numbers of doses?*  
*Bager P et al. JACI 2010*
Local IgE production

Allergens drive class switch to IgE in nasal mucosa in allergic rhinitis patients

Class switch to IgE in bronchial mucosa of atopic and nonatopic asthma patients

Takbar P et al JACI 2007

B-cell-derived IgE production increased in intestinal juice and in feces of adults and children with food allergy

Andre F et al. Allergy 1995
Kolmannskog S et al. Int Arch Allergy Appl Immunol 1986
Kolmannskog S et al. Int Arch Allergy Appl Immunol 1985

In the duodenum IgE-positive cells are increased in adults with food allergy

Lin XP et al. J Allergy Clin Immunol 2002

Increased levels of epsilon germ-line and IL-4 transcripts in caecal mucosa from patients with food allergy → suggest local production of IgE in intestine that might be of importance for inflammatory reactions in the GI tract

Coeffier M et al. Allergy 2005

Immunoglobulin class switching to IgE and IgE production in the oesophageal mucosa of patients with eosinophilic oesophagitis

Vicario M et al. Gut 2010
Intestinal IgE binding partners

CD23

εBP

Kaiserlian D et al. Immunology 1993
Intestinal εBP expression

Wide tissue distribution and expression on various cell types → multifunctional role in cell growth regulation, cell adhesion and tumor metastases

Intestinal distribution pattern
- downregulation in inflammation
- elevated expression in colon cancer influencing neoplastic progression

Dumic J et al. Biochim Biophys Acta 2006
Moutsatsos IK et al. Proc Natl Acad Sci U S 1987

Low affinity IgE receptor CD23

CD23 expression on intestinal epithelial cells is elevated in inflammations eg. CD, food allergies

Kaiserlian D et al. Immunology 1993

IL-4 dependent IgE shuttling through the intestinal epithelium

Yu LC et al. Gastroenterology 2001

IgE/CD23 shuttle mechanism responsible for transepithelial food allergen uptake and protection of antigens from degradation during this transport

Bevilacqua C et al. Int Arch Allergy Immunol 2004

FcεRI expression pattern in enterocytes
Epithelial FcεRIα binds IgE

Receptor detection

Passive sensitization with IgE

Red: FcεRIα  green: monoc., humanized anti-NiP IgE, blue: DAPI staining of nuclei
FcεRI expression pattern in Paneth cells
Function of epithelial FcεRI

Enterocytes
- Antigen presentation capacity?
- Signalling?
- IgE Shuttling?

Paneth cells
- Secreted FcεRI α-chain?

MHC class II

Untersmayr E et al. PLoS One 2010

http://anatomy.iupui.edu/courses/histo_D502/D502f04/Labs.f04/digestive%20II%20lab/s55.40x.1.jpg
http://www.siumed.edu/~dking2/erg/images/GI112.jpg
Literature


Thank you for your attention!