Pathomechanisms in Hypersensitivity

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Turn of the 19th century: Infectious diseases

- Pocks
- Diphtheria
- Tuberculosis
- Cholera
- Polio
- Tetanus
Diphteria: a major health threat

Corynebacterium diphteriae (Klebs-Loeffler bacillus) produce phage-encoded toxin

E. von Behring and S. Kitasato (1890): passive immunotherapy with antitoxin

Deaths per 100,000

Year

Diptheria Vaccine
Introduced 1949
Antitoxin was the first major success of therapeutic immunology
...soon reports of side effects upon antitoxin

Death-rate after passive immunotherapy with „Antitoxin“

1890: 60 %
1894: 30 %
1910: 10 %

In: Reports of the Metropolitan Asylums in 1910
Vienna: Clemens Freiherr von Pirquet
HARMFUL EFFECTS OF SERUM TREATMENT

1. Delayed
   serum sickness
devlops after one week: fever, joint pains, rashes

2. Immediate
   sudden collapse, sometimes followed by rapid death. Anaphylaxis.
Novel Doctrine

*Specific interaction* of pathogen and organism determines disease course

Repeated application – reaction between allergen and antibody

**Diagnosis for (hyper-)immune state**

Intracutaneous inoculation of antigen:

- Pirquet test for tuberculosis
- Schick test for diphtheria

**Definition of „Allergy“ and Allergen**

(allos – changed; ergos – action).

*In: Münchner Med. Wochenschrift 1906*
Dept. of Juvenile Medicine in Vienna, University Vienna
Hypersensitivity – an immune reaction

1.) Sensitization phase

2.) Memory phenomena

I. Immediate type reaction: „Allergy“
   - IgE

II. Cytotoxic reaction
   - IgM, IgG

III. Immune complex reaction
   - IgG, IgA

IV. Delayed type reaction


1. \(\text{IgE}\) 1966/67 T&K. Ishizakas, S.G.O. Johannsson

1974: H. Metzger et al.

Immediate type reaction

Turn of the 20th century: allergic diseases

- Birch pollen
- Grass pollen
- Weed pollen
- Milk
- Fish
- Venom
- Dander
- Harmless agents
Symptoms

Rhinocconjunctivitis
OAS
Urticaria
Asthma bronchiale
Anaphylactic shock
Immediate type reaction: „Allergy“

What is special about allergen molecules?
Effector phase:
Multivalent antigen crosslinks bound IgE....

## Many allergens are multimers

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Reference Details</th>
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<td>ABA-1</td>
<td>Xia et al. Parasitology 120: 211. 2000.</td>
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</table>
Also B-cell triggering depends on epitope display

Schöll et al, J. Immunol. 2005
Isotype switch supported by cytokines

**Isotype Switch**

- **Receptor Recycling**
- **HLA II mit Allergen-Peptid**
- **Endozytose**
- **Lysosomaler Verdau**
- **Präsentation**

**Variable Domains Segments**
- IgM
- IgD
- IgG3
- IgG1
- IgA1
- IgG2
- IgG4
- IgE
- IgA2

**Constant Domains Segments**

**Looping out**

- **Schnitt**

**Schnitt**
IL4 and IL-13 are switch factors for IgE

Programmed and sources of preformed IL-4 and IL-13:
- CD4+ Th-cells
- Basophils, eosinophils, mast cells  
  \[(Mohr \textit{et al}., JI 2005)\]
- CD1-restricted gammmadelta T-cells  
  \[(Russano \textit{et al}, JACI 2006)\]

Sources of early IL-4:
- conventional, naive CD4+  
  \[(Noben-Trauth \textit{et al}, JI 2000)\]
- Basophils  
  \[(Koh \textit{et al}, Blood 2006)\]
- TLR-activated DCs inhibit early IL-4 by CD4 T cells  
  \[(Sun \textit{et al}, JI Feb. 2007)\]
Take home: Allergens can trigger

...if they present several identical epitopes

Schöll et al, J. Immunol. 2005
Respiratory allergens

Non-degrading
Natural factors:
Pollen carry lipid mediators with „adjuvant properties“: PALMs


Pollution – Nitrogen oxides and ozone:
Nitration of allergens enhances allergenic potential

Gruijthuijsen et al, Int Archs Allergy Imm. 2006
Food allergens

Degrading: pH and enzymes
Food allergens must stay intact

Stability during transit

Untersmayr et al, JACI 2003; Schöll et al. Am J Clin Nutr 2005
Peptic digestion is pH-dependent

The gate-keeping function of the stomach depends on acid.

- Non-digested
- Acidic gastric juice: digested
- Hypoacidic: non-digested

- PPIs
- H2-blocker
- Sucralfate
Food allergens resist or **persist**
Diagnosis in Allergy

- Anamnesis
- Serology
- Skin test
- Food: Provocation test: DBPCFC

Therapy

- Allergen-avoidance
- Antihistamines
- Beta-Mimetics for Asthma
- Glucocorticoids
**Allergen immunotherapy**

**Subcutaneous immunotherapy (SIT)**
- **1911** in EU  *(Noon & Freeman, Lancet 1911)*
- **1915** in US  *(Cooke, Laryngoscope 1915)*
- Current standard of care: rhinitis, asthma, venom

**Sublingual immunotherapy (SLIT)**
- > 20 double blind, placebo-controlled studies confirm clinical efficacy in rhinitis  *(Canonica & Passalacqua, JACI 2003)*

**Oral immunotherapy**
- **2005** no published data to support clinical efficacy.

*Medical Policy & Technology Assessment Committee (MPTAC) Review*
(04/18/2005; http://medpolicy.unicare.com)
Mechanisms I.

• Activation of Tregs

Clark & Cupper, JID 2005:
„Immature dendritic cells are polarized by the binding of type 1, type 2, or regulatory PAMP and differentiate into mature dendritic cells that induce the formation of Th1, Th2, or T regulatory T cells, respectively. In general, viral-associated PAMP give rise to Th1 responses, and PAMP from parasitic organisms favor Th2 responses…“
Mechanisms II.

- (Trapping and) Blocking antibodies: IgG1, IgG4
R.R.A. Coombs & P.H.G. Gell
defined „Hypersensitivity reactions“ in 1963

I. Immediate type reaction
   IgE

II. Cytotoxic reaction
   IgM, IgG

III. Immune complex reaction
   IgG, IgA

IV. Delayed type reaction

II. Cytotoxic reaction

Diseases:

- Thrombocytopenic purpura
- Immune-hemolytic anemia
Disease type I:

- Arthus reaction: preformed IgG - local precipitation and inflammation

Examples:

Vaccination and farmer lung
Disease type II:

- Serum sickness: patient slowly forms IgG - systemic precipitation and inflammation

Examples:

Passive immunotherapy with serum or antibodies
Delayed type reaction

- **Allergens:**
  - anorganic molecules,
  - metal ions, peptides

- **T-cells:**
  - cytotoxic and
  - strong inflammatory component

Direct destruction by cytotoxic cells
Combined hypersensitivity reactions

**Atopic dermatitis:** Type I and Type IV

IgE and T-lymphocytes

**Atopy:** genetic predisposition for IgE production

and chronic eczema

Exacerbation upon exogen triggers, e.g. food
Combined hypersensitivity reactions

• **Celiac disease:** Type III and IV

**Symptoms**
- growth inhibition
- Fe-deficiency
- Hypocalcemia
- Osteomalacia, tetany
- Hypoproteinemia, edema
- Diarrhoea
Celiac disease

• Exogen trigger: Gluten
• Endogen factor: tTG (tissue transglutaminase)
• Genetic predisposition
Pathophysiology of celiac disease

Nutritional uptake of gluten

Gastrointestinal digestion

gluten peptides

tTG

desamidated gluten peptides

Type IV

Effector T-cells

T-cells

IL-2

activation of T-helper cells

Type III

IgA, IgG

B-cells

CELIAC patients:

HLA-DQ2, DQ8, DR4
mites
pollen
food
gluten
drugs
cosmetics
harmless agents
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