Classification, pathogenesis and diagnostics of allergic diseases

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Of all the body’s organs, the immune system may be the most challenging to coordinate. The system is collection of individual immune cells, immune cell aggregates, immune tissues, and immune organs.
• Billions of immune cells communicate with each other.

• Functional integration of the immune system is accomplished mainly by cell-to-cell communication

• Every immune system cell is equipped with different surface molecules and is able to synthesize and release a variety of small molecules that travel to other cells and stimulate those cells to become either more active or less active.
Many common biologic mechanisms prevent immune responsiveness to harmless environmental factors and to self-antigens.

Tolerance

Immune tolerance normally ensure that immune effector cells are not activated against host tissues or innocuous agents.
Allergy: immune reaction to a non replicating (harmless) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.

In contrast to infections: symptoms are caused almost exclusively by the immune reaction, not by the „bug“ (virus, bacteria, etc.)
Allergens

- Non-reproducing foreign substances
- Mostly Proteines/Glykoproteines
  - Of animal or vegetable origin
  - Drugs/Chemicals
The allergy is **not** directed to pollen, but to proteins within pollen!

Pollen = carrier (grain) + allergen (surface) + lipids
Betula verrucosa 1
Bet v 1
Major Allergen
House dust mites' allergens are a common cause of asthma and allergic symptoms worldwide.

- *D. pteronyssinus* (European)
- *D. farinae* (American)
- feed on organic detritus, such as flakes of shed human skin

The mite's gut contains potent digestive enzymes (proteases) that persist in their feces.
Allergic to your Pet?

*Hilger C, Zahradnik E. Allergologie 2015;38:83-90*

**Can f 1 saliva**

**Fel d 1 saliva and skin**

### Table: Allergens and Allergen Source

<table>
<thead>
<tr>
<th>Spezies</th>
<th>Allergen</th>
<th>Proteinfamilie</th>
<th>UniProtKB accession No</th>
<th>Apparentes MG in kDa</th>
<th>Allergenquelle</th>
<th>Sensibilisierungsrate in %</th>
<th>In-vitro Diagnostik verfügbar</th>
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<tbody>
<tr>
<td>Katze</td>
<td>Fel d 1</td>
<td>Sekretoglobin</td>
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<td>Leber</td>
<td>14 – 23</td>
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<td>Hund</td>
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<td>Lipokalin</td>
<td>O18874</td>
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<td>Kallkrein</td>
<td>P09562</td>
<td>28</td>
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<td>Can f 6</td>
<td>Lipokalin</td>
<td>H2B3G5</td>
<td>27 – 29</td>
<td>Speicheldrüse</td>
<td>61</td>
<td>nein</td>
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Bee / Wasp Allergy

<table>
<thead>
<tr>
<th>Api m 1</th>
<th>Phospholipase $A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Api m 3</td>
<td>Saure Phosphatase</td>
</tr>
<tr>
<td>Api m 4</td>
<td>Mellitin</td>
</tr>
<tr>
<td>Api m 10</td>
<td>Icarapin</td>
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</table>

<table>
<thead>
<tr>
<th>Api m 2</th>
<th>Hyaluronidasen</th>
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<tr>
<td>Api m 5</td>
<td>Dipptidylpeptidase</td>
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<tr>
<td>Api m 12</td>
<td>Vitellogenine</td>
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</table>

<table>
<thead>
<tr>
<th>Ves v 1</th>
<th>Phospholipase $A_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ves v 5</td>
<td>Antigen 5</td>
</tr>
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</table>

| Ves v 2 | | |
|---------| | |
| Ves v 3 | | |
| Ves v 6 | | |
Types of allergic reactions
<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Time Before Clinical Signs</th>
<th>Characteristics</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Anaphylactic)</td>
<td>&lt;30 min</td>
<td>IgE binds to mast cells or basophils; causes degranulation of mast cell or basophil and release of reactive substances such as histamine</td>
<td>Anaphylactic shock from drug injections and insect venom; common allergic conditions, such as hay fever, asthma</td>
</tr>
<tr>
<td>Type II (Cytotoxic)</td>
<td>5–12 hours</td>
<td>Antigen causes formation of IgM and IgG antibodies that bind to target cell; when combined with action of complement, destroys target cell</td>
<td>Transfusion reactions, Rh incompatibility, hemolytic anemia, thrombocytopenia, granulocytopenia</td>
</tr>
<tr>
<td>Type III (Immune Complex)</td>
<td>3–8 hours</td>
<td>Antibodies and antigens form complexes that cause damaging inflammation</td>
<td>Arthus reactions, serum sickness</td>
</tr>
<tr>
<td>Type IV (Delayed Cell-Mediated, or Delayed Hypersensitivity)</td>
<td>24–48 hours</td>
<td>Antigens activate T&lt;sub&gt;C&lt;/sub&gt; that kill target cell</td>
<td>Rejection of transplanted tissues; contact dermatitis, such as poison ivy; certain chronic diseases, such as tuberculosis</td>
</tr>
</tbody>
</table>
Sensitisation
The increased PAR-2 receptor expression in bronchial epithelium from asthmatics and the increased epithelial expression upon allergen exposure possibly accounts for the higher mediator levels seen in bronchial or nasal lavages. The consequences of this epithelial cell activation for DC function remain to be determined.

A cytokine that has been spotlighted in the allergic immune response is TSLP. TSLP is a novel IL-7 like cytokine, which is produced by epithelial cells, keratinocytes, stromal cells, and mast cells. The interest in TSLP was triggered by its ability to activate human immature myeloid DCs, resulting in the induction of CD4+ T cell responses with a proallergic phenotype.

High levels of TSLP are expressed by human keratinocytes of atopic dermatitis patients, but not in other non-allergic types of skin inflammation. In situ hybridization techniques have been used to show that higher levels of TSLP are expressed in the bronchial mucosa/submucosa of asthmatic patients compared with healthy controls. In Th1-mediated pathology in inflammatory bowel diseases such as Crohn disease, TSLP mRNA was undetectable, whereas epithelial cells isolated from human healthy colon expressed TSLP constitutively.

These data suggest a role for TSLP in the induction of an allergic immune response via the stimulation of myeloid DCs. Even though TSLP has a broader spectrum of action in mice in which it stimulates the growth and differentiation of pre-B-cells, peripheral CD4+ T-cells, and myeloid DCs, the studies in mice confirm the human data. In a murine, lung-specific model, over-expression of TSLP induced allergic airway inflammation that was characterized by infiltration of eosinophils and Th2 cells. In addition, it was demonstrated that TSLP induced pro-allergic Th2 response from naïve precursors, whilst inhibiting Th1-associated (IFN-gamma) or Treg-associated (IL-10) cytokine production. Furthermore, an in vivo allergic inflammatory model revealed that TSLPR-KO mice demonstrated a profound reduction of inflammation in the lungs after OVA-sensitization.

Rescigno et al. suggested that the working spectrum of TSLP could be dose-dependent. By using MoDCs and medium from bacteria-treated epithelial cells, they showed that a narrow window of TSLP concentrations (0.07–0.15 ng/ml) inhibits IL-12 secretion (i.e. stimulate a Th2 response). When the concentrations were outside the window, DCs were able to promote IFN-c producing T-cells (i.e. stimulate a Th1 response).

Because expression of TSLP appears to be very important in the induction of a Th2 allergic immune response, the regulation of TSLP expression has been investigated recently. A role for retinoic acid signalling in the expression of TSLP was shown in epidermal keratinocytes of the mouse. In human airways, the expression of TSLP is triggered by activation of TLR3 by dsRNA, by infection with rhinovirus and by stimulation with Th2 cytokines. Regulation of TSLP expression involves NF-kappaB and IFN regulatory factor 3 (IRF-3) signalling via TLR3.

IL-4 and dsRNA have a synergistic effect on the TSLP production and suggest an amplification of Th2 inflammation via the induction of TSLP in the asthmatic airway. This is a rather surprising observation as PolyI:C stimulation and rhinovirus infection result in the induction of a Th1-type immune response.

Whether TSLP is a crucial epithelial factor in the development of allergic airway diseases like asthma and...
The immune system is highly specific and needs danger signals to become activated.

How can a harmless/innocuous substance like a pollen potentially induce an IgE mediated immune reaction?
Ability of „innocuous“ proteins to activate immune system

1. House dust mite allergen Der p1: cysteine protease cleaves tight junction protein occludin \( \rightarrow \) Increased epithelial permeability and facilitating its entry into the tissue

2. House dust mite allergen Der p2: structural and functional homology with MD-2, LPS-binding component of TLR 4 signaling complex \( \rightarrow \) facilitates signaling through direct interactions with the TLR4 complex

3. Pollen-associated lipid mediators (PALMs): When pollen grains are hydrated on the respiratory epithelia, they release allergens and eicosanoid lipids \( \rightarrow \) so-called pollen-associated lipid mediators (PALMs) \( \rightarrow \) act as stimulators of DC
The increased PAR-2 receptor expression in bronchial epithelium from asthmatics and the increased epithelial expression upon allergen exposure possibly accounts for the higher mediator levels seen in bronchial or nasal lavages. The consequences of this epithelial cell activation for DC function remain to be determined.

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Whether TSLP is a crucial epithelial factor in the development of allergic airway diseases like asthma has been investigated. TSLP expression is upregulated in asthmatic airways, and blocking TSLP signaling reduces airway inflammation. TSLP-deficient mice show reduced airway inflammation and airway hyperresponsiveness in response to allergen challenge. TSLP expression is also increased in patients with allergic rhinitis, another allergic disease, and blocking TSLP signaling reduces nasal symptoms and airway responsiveness in these patients.

In summary, TSLP is an important cytokine in the allergic immune response, and its regulation is a key target for developing therapies for allergic diseases.
Airway immune response

Air pollutants

Bacteria

Allergen

DC modulating factors
TSLP
PGE2
TGF-b
IL-10
GM-CSF

Antigen

Virus

DC

Recruitment by chemokines

Inflammatory cytokines

Lymph node

Treg cells

Th1 cells

Naïve Th cells

Th2 cells

Th17 cells

Airway immune response

TH2 polarisation is critical for the IgE production

J. van Tongeren et al. Allergy 2008: 63: 1124–1135
What drives Th2 polarisation?

- antigen dose,
- nature of the antigen,
- direct cell-to-cell interaction with APCs
- the cytokine receptors available on the naive cell
- Genetic predisposition
- enviromental factors
- gastrointestinal Flora
Hygien-Hypothesis

«Western» Lifestyle

Traditional Lifestyle

Th2
IL-4, IL-5

Allergy-Epidemic

Allergy-Prevention
Microbial exposure boosts Th1 response

Protective effect of the farm environment

Protective effect by parasite infection

Gern et al. Nature Reviews 2002
Sensitization Phase

- Allergen
- epithelial barrier
- lymph node

**DC**

**T cell (naiv)**

---

clonal expansion

**TH2**

**TH2**

**TH2**

**TH2**

**TH2**

IL-4, IL-5, IL-13, IL-31

---

**B cell**

**Ig Switch**

**Production of allergen-specific IgE**

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**Plasma cell**
<table>
<thead>
<tr>
<th></th>
<th>IgM pentamer</th>
<th>IgG monomer</th>
<th>Secretory IgA dimer</th>
<th>IgE monomer</th>
<th>IgD monomer</th>
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<tr>
<td><strong>Heavy chains</strong></td>
<td>( \mu )</td>
<td>( \gamma )</td>
<td>( \alpha )</td>
<td>( \varepsilon )</td>
<td>( \delta )</td>
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<tr>
<td><strong>Number of antigen binding sites</strong></td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<tr>
<td><strong>Molecular weight (Daltons)</strong></td>
<td>900,000</td>
<td>150,000</td>
<td>385,000</td>
<td>200,000</td>
<td>180,000</td>
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<tr>
<td><strong>Percentage of total antibody in serum</strong></td>
<td>6%</td>
<td>80%</td>
<td>13%</td>
<td>0.002%</td>
<td>1%</td>
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<tr>
<td><strong>Crosses placenta</strong></td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td><strong>Fixes complement</strong></td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
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<tr>
<td><strong>Fc binds to</strong></td>
<td>phagocytes</td>
<td></td>
<td>mast cells and basophils</td>
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<td></td>
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<tr>
<td><strong>Function</strong></td>
<td>Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor</td>
<td>Main blood antibody of secondary responses, neutralizes toxins, opsonization</td>
<td>Secreted into mucus, tears, saliva, colostrum</td>
<td>Antibody of allergy and antiparasitic activity</td>
<td>B cell receptor</td>
</tr>
</tbody>
</table>
Type-I (immediate hypersensitivity)

Antigen-Specific IgE Antibody

Mastcells

FcεRI

IgE
Cross linking of 2 Fc-IgE-RI is required for mast cell activation

Mediator release
Plasma cell (produces IgE antibody)

Mast cell (releases mediators)

IgE cross linking by antibody

Antigen (pollen)

Activation

Mast cell

Histamine and other mediators

Symptoms
Mast cell

Nature Reviews | Immunology
Activated mast cell (or basophil) produces:

- Biogenic amines (e.g., histamines)
- Lipid mediators (e.g., PAF, PGD₂, LTC₄)
- Cytokines (e.g., TNF)
- Lipid mediators (e.g., PAF, PGD₂, LTC₄)
- Enzymes (e.g., tryptase)

These mediators lead to:

- Vascular leak
- Broncho-constriction
- Intestinal hypermotility
- Inflammation
- Tissue damage
Symptoms of IgE mediated (immediatet) reaction

Eyes: Conjunctivitis

Nose: Rhinitis

Lungs: Asthma

Skin: Urticaria Angioedema
Classification of allergic reactions according to Mueller
Anaphylaxis

= potentially life threatening situation; rapid onset

Massive mediator release

different organs are involved (skin, respiratory, cardiovascular system)

most frequent cause in Switzerland: hymenoptera venom allergy, drug allergy, food allergy
Is anaphylaxis always IgE mediated???

No, Anaphylaxis may involve other mechanisms than IgE, e.g.:

- Complement activation
- IgG and IgM immune complexes
- Non-immunologic mechanisms
- Pseudo allergies (radio contrast media)
- Toxic effects of insect venom
- Non-steroidal anti-inflammatory drugs
Food Allergy
Adverse reaction Food

1. Toxic

2. Nontoxic
   A) Immune mediated
      - IgE mediated
      - Non-IgE mediated

   B) Non immune mediated (food intolerance)
      - enzymatic (e.g. lactase deficiency)
      - pharmacological (abnormal reactivity to substances e.g. amines)
      - undefined (e.g. food additive intolerance)
2 Groups of food allergy

Food sensitization develops as a consequence of crossreactivity with airborne allergens

Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

Mostly in children “real food allergy”
Oral allergy syndrome

Sensitization to heat/pepsine labile plant-derived proteins in patients with pollen allergy

Cross reactivity between homologous plant derived proteins and pollen proteins

Bet v1 → nuts, apple, kiwi

Heated normally well tolerated

Allergen cross reactivity seems to be due to IgE antibodies that recognize structurally similar epitopes on different proteins that are phylogenetically closely related or present evolutionarily conserved structures
Food allergy - crossreaktivität

**celery**-**birch**-**mugwort**-**spices** syndrome

shellfish and dust mite allergy
Food allergy - crossreactivity

Latex-fruit syndrome

Cat-pork syndrome

Fel d 2

Pig serum albumine
2 Groups of food allergy

Food sensitization develops as a consequence of crossreactivity with airborne allergens

 Mostly adults, cross reactivity

Food sensitization occurs by gastrointestinal tract (often stable proteins)

 Mostly in children “real food allergy”
Lipid transfer proteins
Role in defence against fungi and bacteria
Heat stable, begin to unfold above 95°, protein refold on cooling
More severe allergic reactions
Peanut allergy
Exercise-induced anaphylaxis (EIAn)

Non-food-dependent (EIAn)

Food-dependent (FDEIAn)

Food-specific

Non-food-specific

Tri a 19
Bee / Wasp Allergy

| Api m 1 | Phospholipase A₂ |
| Api m 3 | Saure Phosphatase |
| Api m 4 | Mellitin |
| Api m 10 | Icarapin |
| Api m 2 | Hyaluronidase |
| Api m 5 | Dipaptidylpeptidase |
| Api m 12 | Vitellogenine |
| Phospholipase A₁ | Ves v 1 |
| Antigen 5 | Ves v 5 |
| Ves v 2 |
| Ves v 3 |
| Ves v 6 |
Hymenoptera venom allergy

- The prevalence of an allergy systemic reaction after a Hymenoptera sting is estimated between 1 and 7% in Europe.

- Mortality: 200 cases per year in Europe.

- One of the most frequent causes of anaphylaxis in the adult population.

- Bee sting: 50 μg (30-140 mg) of venom proteins, after a wasp sting: 3–5 μg of venom proteins are introduced to the body of the victim.

- Toxic reaction: > 50-100 stings (in adults); > 10 stings (in children).
Local reactions after hymenoptera stings

Large local reaction = Swelling exceeding 10 cm

Not an Allergy!
Drug allergy
IgE mediated drug allergies
(immediate reactions)

<table>
<thead>
<tr>
<th>Anaphylactic IgE-mediated reactions</th>
<th>Antibiotics</th>
<th>Chemotherapy drugs</th>
<th>Monoclonal antibodies</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing, pruritus, urticaria, angioedema, laryngeal edema, rhinorrhea, conjunctivitis, shortness of breath, wheezing, bronchospasm, nausea, vomiting, diarrhea, hypotension</td>
<td>Beta-lactams</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon)</td>
<td>Rituximab, trastuzumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penicillins, cephalosporins, amino-penicillins</td>
<td>Ciprofloxacin, levofloxacin</td>
<td></td>
<td>Chronic inflammatory diseases, cancers (leukemias, breast, ovarian)</td>
</tr>
<tr>
<td></td>
<td>Fluroquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Desensitization often possible!!!
Non-IgE mediated drug allergies (immediate reactions)

Positive oral aspirin challenge. Although the mechanism of desensitization is unknown, desensitized patients tolerate aspirin and NSAIDs at pharmacological doses, and prolonged desensitization can be achieved by daily administration of aspirin or NSAIDs [29]. Protocols for aspirin and NSAID desensitization are based on the controlled progressive administration of incremental doses starting at 30 mg of aspirin and progressing to 60, 100, 150, 325, and 650 mg at 3 h intervals (Table 3). Respiratory responses are measured by forced expiratory volume at 1 s (FEV1), and a decline of 20% is considered a positive challenge. The dose is then repeated until no reaction occurs and the patient continues until reaching 325 or 650 mg. Cross desensitization is universal for all NSAIDs once desensitization has been achieved at therapeutic levels [31]. Patients who have severe gastrointestinal intolerance to aspirin and NSAIDs have been challenged with lysil-aspirin either nasally or bronchially [32,33]. Desensitization has been less successful for intolerant patients with cutaneous reactions [34].

Table 3 Desensitization to aspirin in a patient with asthma

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>180</td>
<td>81</td>
</tr>
<tr>
<td>240</td>
<td>162</td>
</tr>
<tr>
<td>330</td>
<td>325</td>
</tr>
<tr>
<td>420</td>
<td>650</td>
</tr>
</tbody>
</table>

Aspirin to be continued at 650 mg orally, twice a day. Adapted from White et al. [30].

Table 4 Desensitization to aspirin in a patient with aspirin-related urticaria-angioedema

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>20</td>
<td>0.3</td>
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<td>60</td>
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<tr>
<td>80</td>
<td>10</td>
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<td>100</td>
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<td>140</td>
<td>81</td>
</tr>
<tr>
<td>160</td>
<td>162</td>
</tr>
</tbody>
</table>

Aspirin to be continued at 162 mg once per day. Adapted from Wong et al. [5].

Figure 1 Indications, drugs, and diseases treated with rapid desensitisation

<table>
<thead>
<tr>
<th>Indications</th>
<th>Drug most frequently used</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic</td>
<td>Beta-lactams</td>
<td>Penicillins, cephalosporins, amino-penicillins</td>
</tr>
<tr>
<td></td>
<td>Fluroquinolones</td>
<td>Ciprofloxacin, levofloxacin</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>Sepsis, Meningitis, Pneumonia, Pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy drugs</td>
<td>Platins (Carboplatin, cisplatin, oxaliplatin), Rituximab, trastuzumab</td>
</tr>
<tr>
<td></td>
<td>Monoclonal antibodies</td>
<td>Primary and recurrent metastatic cancers (breast, ovarian, colon), Chronic inflammatory diseases, cancers (leukemias, breast, ovarian)</td>
</tr>
</tbody>
</table>

Anaphylactoid

Direct mast cell/basophil, complement, and leukotriene metabolism reactions

Flushing, pruritus, urticaria, angioedema, throat tightness, shortness of breath, nausea, vomiting, diarrhea, hypotension, hypertension, back and/or abdominal pain

Aspirin/NSAIDs

Cardiac protection, asthma w/ nasal polyposis, chronic inflammatory diseases (RA, Crohn's)

Vancomycin

MRSA

Chemotherapy drugs

Taxenes (Paclitaxel, docetaxel)

Primary and recurrent metastatic cancers (breast, ovarian, colon)

Pseudo-allergic reactions radio contrast media: direct membrane effects related to the osmolarity of contrast media solution
Symptoms of T cell mediated drug allergy

- Makulo-papular Exanthem
- bullous Exanthem
- Acute generalized exanthematous Pustulosis (AGEP)
- Stevens-Johnson Syndrome (SJS) toxic-epidermal Necrolysis (TEN)
- DRESS, Hepatitis, interstitial Nephritis, Pneumonitis
Chemical structure of drug molecule

No protein drugs, small molecules
1-2 kDa, haptens

Protein drugs
Large molecules >20 kDa
Haptens

Small molecules alone are not immunogenic!

Haptens = reactive chemical substances binding to a larger protein $\rightarrow$ hapten-carrier complex forms neo-antigenic determinants able to induce both a T-cell and B-cell immune response.

hapten + carrier protein $\rightarrow$ hapten-carrier complex

Not immunogenic Not immunogenic Immunogenic
p-i concept:

a) the drug binds first to the TCR (by non covalent bonds; not restricted to a HLA-allele)

or

b) the drug binds first to the HLA molecule, and the HLA-peptide-drug complex is then recognized by the TCR (HLA-class I restricted, CD8)
Hapten  p-i (TCR)  p-i (HLA)

Immune reaction  Pharmacological interaction
Contact Dermatitis
Contact Dermatitis

non-infectious reaction of the skin to external substances

Allergic contact dermatitis
T- Zell mediated immune response to contact allergens like:
- Nickel, lanolin, Peru balsam or potassium dichromate
- jewellery, medication cosmetics, dyes impregnating agents

Irritative contact dermatitis
Non immune mediated response to physical, chemical irritants and physical influences
- rubbing, pressure, heat and cold or UV rays
- water, soap, disinfectants,
Allergic Contact Dermatitis

- The reaction usually occurs 24–48 hours after contact with the allergenic substance.
- The skin is inflamed and reddened, it may swell up and blisters or papules may appear.
- These symptoms are often combined with severe itching.
- The skin reaction appears at the site of the body where the skin came into contact with the irritant, but may also spread to nearby or remote regions of the skin.
Allergic Contact Dermatitis
Diagnostics of allergic diseases
Diagnostics of allergic diseases

- Medical history
- Symptoms
- Tests
Diagnostics of allergic diseases

Typ I Hypersensitivity

Skin pricktest

Prick-to-prick Test
Diagnostics of allergic diseases

In-Vito Test and molecular allergy diagnostics

Type I Hypersensitivity

Serum IgE
Diagnostics of allergic diseases
Basophil activation Test
Conjunctival provocation tests (CPT, allergen solution)

No standardization of CPT; no grading of ocular reactions

Digital image analysis possesses the potential of being an objective evaluation method compared to the wide-spread subjective

Dogan et al. Int Arch Allergy Immunol 2014;163:59–68
Oral provocation tests

Food challenge Tests
Patch Tests
Type IV Hypersensitivity
Therapy principles
Therapy principles

1. Symptomatic therapy
   - antihistamines
   - corticosteroids
   - leukotrien antagonists
   - antiasthmatics (inhalative medication)
   - biologics (Omalizumab, anti-IgE), (Mepolizumab anti-IL5)

   Inhibition of inflammatory mediators released during effector phase:
   - anti histamines
   - mast cell stabilizers
   - leukotrien antagonists
   - anti IL-4, IL-5
   - anti IgE
   - Glucocorticoids

   - TH2
AntI IgE therapy (omalizumab)

Binding of omalizumab to the ce3 domain of IgE.

Adapted from Francés et al. 2014 Actas Dermosifiliogr. 2014;105:45-52. - Vol. 105 Num.01
Therapy principles

Allergen-specific Immunotherapy alters course of disease
Bee keepers

Systemic reactions in 45% of beekeepers with <15 bee sting / year

No/less systemic reactions in beekeepers with > 200 bee sting / year

Why???
Allergen-specific Immunotherapy

Reduktion allergischer Symptome
Calderon et al. JACI 2011;127:30-8
Radulovic et al. Allergy 2011;66:740-52

Asthma prevention
Jacobsen et al. Allergy 2007;62:943-8
Möller et al. JACI 2002; 109: 251-256
Schmitt J et al. JACI 2015;136:1511-6
Mechanisms of SIT

**A**

- **Early desensitization:** decrease in mast cell and basophil activity for degranulation and systemic anaphylaxis
- **T cell tolerance:** induction of T<sub>Reg</sub> cells suppression of Th2-Th1 cells
- **Late desensitization:** decrease in tissue mast cells and eosinophils and release of their mediators

**B**

- **Type I skin test reactivity**
- **Specific IgE**
- **Specific IgG4**

Definitions

**Allergy**: immune reaction to a non replicating (harmles) substance (protein, chemical, drug, metal), which leads to clinical symptoms like.
Atopy: genetic determined readiness to react by IgE formation to substances taken up via aerogen or gastro-intestinal routes

Sensitization: immune reaction to a foreign substance (proven in skin tests, serology, cellular tests...
Summary
Immune **tolerance** normally ensure that immune effector cells are not activated against host tissues or innocuous agents.

Allergic inflammation is characterized by **IgE-dependent** activation of **mucosal mast cells** and an infiltration of eosinophils.

Production of IgE antibody is regulated mainly by **Th2 cells**. Activated **Th2 cells trigger IgE** production in B cells through a combination of signals, including secreted cytokine (**IL-4, IL-13, IL-5**).

The fundamental strategy of **immunotherapy** for allergic diseases is to correct dysregulated immune responses by inducing peripheral allergen tolerance.