Immuno(patho)logy – hypersensitive reactions

Experimentally induced anaphylactic reaction in rabbit

Adaptive immunity vs. hypersensitivity

- Adaptive immunity
  - antigen-specific defence mechanisms that take several days to become protective and are designed to remove a specific antigen
  - develops throughout life
  - two major branches:
    - humoral immunity = production of antibody molecules (B-lymphocytes)
    - cell-mediated immunity = production of cytotoxic T-lymphocytes, activated macrophages and NK cells, + cytokines (T-lymphocytes)

- Hypersensitivity
  - immune systems cause harm to the body
  - two categories:
    - immediate (humoral) hypersensitivity
    - delayed (cytotoxic) hypersensitivity

Classification of hypersens. reactions (Gell & Coombs) – very often combinations of types!!

<table>
<thead>
<tr>
<th>Type I – immediate</th>
<th>Type II – cytotoxic antibodies</th>
<th>Type III – immunocomplexes</th>
<th>Type IV – delayed</th>
<th>Type V – stimulatory antibodies</th>
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</thead>
<tbody>
<tr>
<td>IgE-mediated</td>
<td>IgG(M)-mediated</td>
<td>antibodies against superficial antigens cause destruction of cells by complement, phagocytes or ADCC (NK-cells)</td>
<td>cell-mediated cytotoxicity</td>
<td>anti-receptor IgG</td>
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<tr>
<td>allergen binds to IgE-Fc on mastocytes and basophils, release of vasoactive mediators</td>
<td>Immunocomplexes deposited in tissues activate complement and stimulate infiltration by neutrophils (i.e., inflammation)</td>
<td>sensitized T-cells release cytokines activating destruction by macrophages or T lymphocytes</td>
<td>stimulatory or blocking IgG bind to superficial cell receptors (antagonists)</td>
<td></td>
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<tr>
<td>anaphylaxis, allergic rhinitis, asthma, eczema, food allergies</td>
<td>post-transfusion reactions, phoetal erythroblastosis, hemolytic anemia and other autoimmunities</td>
<td>vasculitides, reumatoid arthritis, SLE, glomerulonephritis</td>
<td>contact derma-titis, granulo-matous lesions (TBC, lepra, syphilis), sarcoidosis, transplantation reactions (GVHD, HuGD), T1DM, sclerosis multiplex</td>
<td>Graves’ Basedov’s thyroiditis (TSH-r activation), mya-sthenia gravis (Ach-r blockade), rare forms of T1DM (IgG r blockade)</td>
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Type I hypersensitivity

- A hypersensitivity due to excessive production of the IgE class of antibody
- Reactions between allergens and IgE bound to mast cells and basophils cause a greatly heightened inflammatory response

Allergy vs. anaphylaxis vs. atopy

- Allergy
  - inadequately increased reaction to certain environmental antigen (allergen), tolerated by majority of population
  - usually localized

- Anaphylaxis
  - generalised, life-threatening allergic reaction simultaneously affecting multiple organ systems

- Atopy
  - inherited disposition to the development of hypersensitive type I reaction

Atopy

- IgE antibodies are physiologically made in response to parasite infections
- Atopy
  - genetically conditioned disposition to ↑ IgE production in response to common pathogens or environmental antigens (i.e., allergens)
  - ↑ circulating eosinophils
  - Th1/Th2 balance shifted towards ↑ Th2 (via IL-4) stimulation of antibody formation over Th1 (via IL-2, IFN and TNF) cytotoxicity stimulation

IgE

- normal half-life 2-3 days
- mast cells and basophil bound several weeks

Classification of hypersens. reactions (Gell & Coombs) – very often combinations of types!!
Pathogenesis of IgE-mediated hypersensitivity (type I)

- Sensibilisation of B lymphocytes to the production of IgE
- Opsonisation of basophils and mast cells
  - binding of IgE to FcεRI (Ia II)
- IgE-mediated degranulation of mast cells and basophils after repeated contact with allergen
  - release of mediators
    - primary (stored in vesicles) – HISTAMINE (H₁ receptors)
    - secondary (synthesized) – PG, LTA, PAF, bradykinine, cytokines, ...
  - effects
    - vasodilatation, contraction of SMC (incl. bronchoconstriction), capillary permeability, chemotaxis, mucous secretion, platelet aggregation

Mast cell degranulation

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<th>Anaphylaxis (contrary to prophylaxis)</th>
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<td>severe, systemic, potentially fatal (i.e., shock) reaction usually following parenteral contact with allergens</td>
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<td>drugs, food, insects, environmental allergens, latex, …</td>
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<td>manifestation</td>
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<td>v.o. membranes, skin: erythema, sputhema, lichen, rash, oedema</td>
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<tr>
<td>resp. tract: bronchoconstriction, sneezing, rhinitis, nasal obstruction, irritation, coughing, wheezing, foreign body feeling</td>
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<tr>
<td>GIT: nausea, colic, diarrhea, dehydration</td>
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<td>CV system: palpitations, tachycardia, hypotension, arrhythmias</td>
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<tr>
<td>urgenital system: urine incontinence</td>
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<td>CNS: unconsciousness, convulsions</td>
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- anaphylactoid reaction:
  - IgG, immunocomplexes, anaphylatoxins or non-immune mechanisms

Allergy

- localised reaction following usually mucous membrane contact with allergen (respiratory tract, GIT), event. skin
  - atopic rhinitis
  - asthma bronchiale
  - food allergy
  - atopic dermatitis

Summary

- Anaphylaxis (contrary to prophylaxis)
- Allergy

Practicals

- repeated application of antigen (foreign serum) s.c. every 3 days

RESULTS

- (1) manifestation of anaphylactic reaction in rabbit (videorecord)
- (2) comparison of blood elements count before vs. after anaphylaxis
- (3) peripheral blood smear
- (4) calculating of the blood elements count (leukocytes, platelets, eosinophils)
Practicals I

Bürker chamber - detail

Imuno(patho)logy – hypersensitive reactions

Type II hypersensitivity

- Hypersensitivity resulting from antibodies (IgG or IgM) mistakenly reacting with normal self antigens on body cells
  - failure of immune tolerance
  - cross-reaction of antibodies against foreign antigen with body’s own

- Mechanisms
  - complement lysis
    - classical pathway → membrane attack complex (MAC) → cell lysis
  - opsonisation and activation of Fc- or C3b-receptor bearing phagocytes
    - lysosomes → cell lysis
  - antibody dependant cell-mediated cytotoxicity (ADCC)
    - NK cells attach to Fc → perforins & granzymes → caspases → apoptosis

ADCC

Transfusion reactions

- ABO incompatibility
  - anti-A, -B IgM
    - immediate, dramatic

- Other blood group antigens (Rh, Kidd, Kell, Duffy)
  - IgG
    - delayed (IgG less active in activating complement)
    - after multiple ABO compatible transfusions

- Haemolytic disease of the newborn has a similar course
  - IgM produced after delivery of the first baby clear the Rh⁺ antigen
  - memory B-cells produce anti-Rh⁺ IgG during subsequent pregnancy
**Type III hypersensitivity**
- Large quantities of soluble Ag-Ig complexes passing between endothelial cells of the blood vessels and becoming trapped on the surrounding basement membrane
- (small complexes can pass through) and cause inflammation
  - complement activation → lysis
  - chemotaxis of neutrophils → proteolysis, production of ROS and vasoactive mediators (Pg, TXA, LTA, ...)
- Localisation
  - vessels, glomerulus, synovia, choroid plexus
  - deeper in tissues

**Type IV hypersensitivity**
- Hypersensitivity resulting from cell-mediated immunity harming the body
  - antigen activates Th1-type (T_{DM}) of T₈ lymphocytes via APC (MHC-II) → cytokine production (IL-2, IF-γ, TNF, ...)
    - activation of macrophages and monocytes
  - phagocytizing cells activate T₈ lymphocytes via MHC-I → transformation to T₈ lymphocytes

**Practicals II**
- Stained with LEUKO Diff 200
- Inspection (microscopy) of blood smears

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**Haematopoiesis**
- Uncommitted stem cell gives rise to various blood cells

**Peripheral blood smear**
- Blood smear