

## Immunology – lecture 10 (Lippincott's Immunology, chapter : Hypersensitivity reactions)

### Hypersensitivity

#### Hypersensitivity – allergy immunodeficiency

Deficiency of **regulatory function** immune system  
Occasionally even healthy immune system react not correctly – hyperactively  
1963 – **Coombs a Gell** classification  
acc.to the type of ethiological immune mechanism  
Worldwide , influenced  
Sensitivity is – individual (genetic,exposition – smoking, home pets)  
*immunological base of some clinical sy is not always clearly defined – intolerance, opium, intoxication by sea fruits - dif.dg*

#### Terms

- **Allergy** – disease, during which the immune reaction to the antigen (allergen) is based on **inflammation of tissues** that leads to the changes of the function **without elimination of antigen**
- **Allergen** – antigen starting allergic reaction – chemicals – natural or synthetic
- Different types of chemicals – different mechanism of allergy
- **HyperSenzitivita** – too strong answer to antigen
- **Exposition to allergen**
- **Types and phases of allergic reactions**
- **Atopic** – person prepared to react in allergic – hypersensitive way via IgE

Excessive or inappropriate immune responses sometimes lead to host tissue damage resulting from prolonged or repeated antigen exposure. These reactions, called *hypersensitivity reactions*, cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in **inflammation**. These reactions are classified into four **hypersensitivity types** depending upon the mechanism(s) that underlie the tissue damage.

#### Types of allergic-hypersensitive reactions

Acc. Coombs and Gell – based on immunological mechanisms  
4 types:  
1. type – early reaction, atopy  
2. type – cytotoxic reaction  
3. type – reaction from immunocomplexes  
4. type – delayed type hypersensitivity reaction - DTH  
• Possibility of existence of several reactions together

#### Immunological way

- 1) **IgE-mastocyt-mediators**  
- early *reaction (type 1)*
- 2) **IgG or IgM-complement-neutrofil**  
- *cytotoxic reaction (type 2)*  
- *reaction from immunokomplexes (type 3)*
- 3) **Sensibilised effektor Tlymohocyte - TDH**  
delayed hypersensitivity – lymfokines
- *delayed type, cell reaction (type 4)*

#### Phases of hypersensitive reactions

##### A) Sensibilisation:

Exposition to antigen induce stage (with specific antibodies or sensibilised lymphocytes), that is clinically seen only after the next exposition to the same antigen – the time of sensibilisation is not always known

##### B) Fase of activity:

- reexposition,
- binding of specific effectors (Ab, cells)
- production and release of cytokines,
- clinical symptomatology

Hypersensitivity type I – (Allergic reactions, Atopy, Asthma) - also called **immediate hypersensitivity** reactions are rapid, occurring within minutes of exposure to an antigen, and

always involve IgE-mediated degranulation of basophils or mast cells.

## 1.type – early reaction – atopic (4 fázy)

### Sensibilisation

Exposition to antigen results in antibody answer – synthesis of specific IgE antibodies

Why and when IgE and atopy?

Way of enter – the same

Type of molecule – the same

The size of the dose is important  
– very small amount of Ag

General characteristic of immunity – past contacts, stimulation of immunity, exposition to ag in postnatal period (type Th1 or Th2, theory of hygiene)

## 1.type – early reaction (4 fázy)

cont

- IgE adhere by their Fc fragment on the surface of mastocytes, that are in circulation
- Second exposition to ag (10-14 days later) –
  - immediate bound to Fab fragment of IgE present on mastocytes,
  - degranulation of vasoactive amines (histamín, sérotonín), lipid mediators, chemotactic substances
- Clinical symptomatology caused by effect of mediators (smooth musles contraction, vasodilatation, increased vessel permeability, bronchospasm, oedema, anaphylactic shock)
- Allergy to drugs, molds, insect bite
- Tested by – i.c. application

Hypersensitivity type I : Mechanism: Cross-linking of FcRa-bound IgE antibodies on mast cells cause degranulation and release of vasoactive amines (e.g., histamine) resulting in smooth muscle contraction, vasoconstriction, and vasodilation of capillary endothelium.

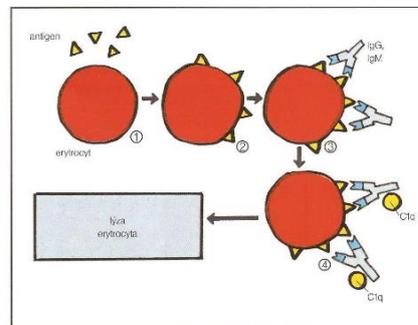
**Type II hypersensitivity reactions** are initiated by the interaction of antibody (IgM or IgG, not IgE) with cell membranes or with the extracellular matrix. Complement may also be involved. The antigens that are recognized may be intrinsic to the cell membrane or extracellular matrix, or they may be exogenous molecules, such as a drug metabolite adsorbed onto the cell membrane or extracellular matrix.

## 2.type – cytotoxic reaction

- Antibodies **against antigens on the surface of self cells or tissues** as the result of
  - deficiency of tolerance
  - cross reactivity of antibodies against exogenous antigens, that have similar structure as self cell superficial structures
  - bound of foreign antigens on the surface of self cells
- Mechanism of destruction: **opsonisation of antigen on the surface of the cell with IgG**, NK cells are bound by Fc fragment of antibody and cause lysis of cell, **activation of complement and lysis of the cell**
- Examples:

Pemfigus – IgG antibodies react with intracellular substances between epidermal cells

Haemolytical anaemia – ex.: PNC, Goodpastureov sy , Morbus hemolyticus neonatorum, posttransfusion reaction, cold aglutinins, early rejection of graft



Drug induced haemolytical anaemia: Antigen (PNC) is bound on erythrocytes. Antibodies IgG/IgM are specifically bound that activates C1q leading to lysis of the cell - haemolysis

**Hypersensitivity type II - Erythroblastosis fetalis, Goodpasture's syndrome, autoimmune hemolytic anemia**

**Hypersensitivity type II – mechanism:** IgM or IgG antibody binds to epitopes on cells or other tissue components promoting phagocytosis, antibody dependent cell-mediated cytotoxicity, antibody-mediated function disruption (receptor blocking), or complement mediated lysis.

## ***Hypersensitivity type II - Interaction of antibody with cells***

Cell-surface or extracellular matrix epitope binding by antibodies (usually IgM or IgG) results in a conformational change in the Fc portion of the antibody molecule. The conformational change in the Fc portion of the antibody molecule is recognized by cellular FcRs and by complement, and several immune-mediated destructive mechanisms may then come into play, targeted upon the site(s) of antibody binding.

### **1. Antibody-dependent cell-mediated cytotoxicity (ADCC)**

This is complement independent but requires the cooperation of leukocytes. FcR-bearing cells [e.g., monocytes, neutrophils, eosinophils, and natural killer (NK) cells] bind to cells that have IgG or IgM antibodies bound to surface epitopes on a cell.

### **2. Complement**

Complement activated by IgM and IgG antibodies generates active components of the classical pathway, namely, C3b and C4b.

These components are then deposited on the surfaces of antibody-coated cells or extracellular matrix to function as **opsonins**.

Phagocytes recognize bound antibody through their FcRs and bound complement components through their complement receptors. In this manner, both complement and antibody function as opsonins to increase phagocytosis and the destruction of microorganisms

### **3. Blood group antibodies**

These exemplify type II hypersensitivity reactions. Hemolytic anemias may result from the binding of IgM antibodies to carbohydrate structures on erythrocytes (notably anti-A or anti-B antibodies) resulting in their phagocytosis and in the presence of complement, their rapid lysis (hemolysis). Antibodies (IgG to certain protein molecules on erythrocytes [e.g., Rh factor(s)]) do not activate complement; erythrocytes are destroyed by phagocytosis.

## ***Hypersensitivity type II - Interaction of antibody with the extracellular matrix***

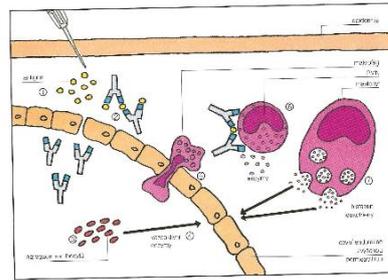
Antibodies that bind to extracellular matrix proteins (e.g., basement membrane) may activate the classical pathway of complement, generating anaphylotoxins (e.g., C5a, C4a, C3a, in descending order of potency, not in order of appearance) that recruit neutrophils and monocytes. FcR engagement with the bound antibody results in the release of reactive oxygen intermediates, resulting in inflammation and tissue injury .

## ***Hypersensitivity type II - Antibody-mediated disruption of cellular function***

Sometimes antibodies bind to cell surface receptors without activating complement or binding to FcRs. This binding blocks the receptor's ability to interact with its natural ligand . The antibody-receptor interaction may be stimulatory (e.g., Graves disease) or inhibitory (e.g., insulin-resistant diabetes, myasthenia gravis) to the receptor's signaling pathway(s).

### 3.type hypersensitivity from immunocomplexes

- Circulating antibodies produce in time of sensibilisation react with free antigen (present in blood in time of reexposition) that leads to the production of circulating immunocomplexes (CIK)
- They are usually eliminated by macrophages
- The disease starts if CIK are deposited in tissue and/or if complement is activated (production of anaphylotoxins and chemoattractants)
- Usually after chronic exposition of antigen – longlasting load of macrophages (chronical streptococcal infection, autoimmune diseases, LE, allergic alveolitis)
- Depends on the type of Ag and Ab and size of immunocomplexes (small are in circulation, big are eliminated by macrophages, medium can be deposited)



Arthus reaction – local reaction of immunocomplexes – test for existence or risk of the 3rd type of hypersensitivity (serum serum disease)

Injected antigen + IgG = IK — activation of complement, aggregation of thrombocytes, release of mediators, increase of permeability of vessels, local oedem, PMNL

Value of CIK – activity of the disease (40j normal value)

**Hypersensitivity type II – mechanism:** serum activate complement and attract neutrophils that release lytic molecules.

### Type III Hypersensitivity

Circulating antigen-antibody complexes may lead to inflammation at their sites of deposition, often resulting in blood vessel inflammation (**vasculitis**). Immune complexes may cause injury resulting from the interaction with exogenous (e.g., microbes, viruses or chemically modified self proteins) or endogenous antigens (e.g., serum proteins). Type III reactions may occur locally or systemically.

#### *Type III Hypersensitivity - Localized reactions*

Localized type III hypersensitivities, also known as **Arthus reactions**, result from acute immune complex vasculitis causing tissue necrosis. These reactions are elicited four to six hours after the intradermal introduction of a small amount of antigen. Antibody diffuses from the vasculature to form large immune precipitates that activate complement to induce a painful localized edematous inflammatory lesion. Lesions range from necrotizing vasculitis with polymorphonuclear cell infiltration to the formation of a sterile abscess.

#### *Type III Hypersensitivity - Systemic reactions*

Systemic immune complex disease, in some cases termed **serum sickness**, occurs with the wide dissemination of antigen-antibody complexes throughout the body. Very large immune complexes are rapidly cleared from the body by phagocytic cells and are relatively harmless. Smaller, circulating immune complexes have less chance to be seen by phagocytes and remain in the circulation longer. These complexes have the greatest pathologic consequences.

#### -- Exogenous antigens

Administered either in large amounts or for a prolonged period of time, these may induce antibody responses. Soluble antigen-antibody complexes immobilized along the endothelium activate complement to cause vascular injury. Complement components (e.g., C5a, C4a, and C3a) attract polymorphonuclear cells to the site, and these cells exacerbate the vascular injury. Serum sickness used to be solely a consequence of treatment with animal-derived antisera.

Before the advent of antibiotics, sera from immunized animals were often administered to human patients to ameliorate infection or the effects of bacterial toxins, such as diphtheria toxin. Horses were commonly immunized with heat-inactivated toxin (called a toxoid). Intravenously administered horse

antiserum is very efficient at neutralizing the harmful effects of bacterial toxins. Horse serum proteins persist in the patient's circulation and, unfortunately, are very good immunogens in humans. After 7 to 10 days, patients may develop symptoms of immune complex disease, corresponding to the advent of a primary antibody response to horse serum proteins. Serum sickness is a self-limiting disease, because the foreign antigen (antiserum) is cleared from the body.

#### 4. type - delayed type hypersensitivity

- 1.- 3. type are expressed within minutes after reexposure (20 minutes – to several hours)
- 4. type
  - after more than 12 hrs
  - late type – there are 4 clinical subtypes
  - a) Jones Mote
  - b) contact allergy
  - c) tuberculin reaction
  - d) granulomatous reaction

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**Type IV Hypersensitivity mechanism:** Cell-mediated, antibody independent. Release of mediators by sensitized CD4+ T cells provoke tissue destruction by mononuclear cells. CD8+ T cells known as cytotoxic T lymphocytes (CTL) may kill chemically modified host cells and cells that display disparate MHC molecules.

**Type IV hypersensitivity reactions** result from the interaction of T cell-initiated inflammation and do not involve antibody. Inflammatory responses result from the manner in which T cells encounter and respond to antigen. CD4+ T cells may be sensitized and respond to topically applied antigen (**contact dermatitis, CD**, also called contact sensitivity), by antigen injected antigen [delayed (-type) hypersensitivity, DTH]. Alternatively, CD8+ T cells may encounter cell-surface antigen and directly cause the lysis of that cell (CTL).

#### **Type IV Hypersensitivity - Contact dermatitis**

Chemically reactive substances may be absorbed through the epidermis, where they bind to proteins. Potential **contact sensitizers** include synthetic chemicals, plant products, and certain metals (e.g., nickel). Generally, contact sensitizers are, by themselves, too small (<10,000 daltons) to be recognized by the immune system. Contact sensitizers interact with self proteins to form immunogenic **neoepitopes** or **neoantigens** on these proteins. Immunologists often refer to substances that are immunogenic only when bound to another molecule as **haptens**. First acute exposure to a contact sensitizer often occurs without apparent incident but serves to

immunize the immune system. After seven or more days, reexposure or chronic exposure elicits a localized inflammation of the dermis. Clinical signs, like those seen for DTH, typically appear 24 to 72 hours after reexposure.

**Delayed (-type) hypersensitivity (DTH)** responses occur in sensitized individuals upon nontopical reencounter with antigen. In general, Type IV DTH hypersensitivity responses are stimulated by intracellular parasites such as bacteria (e.g., *Mycobacterium tuberculosis*, *M. leprae*, *Leishmania monocytogenes*), fungi (e.g., *Candida albicans*), and some viruses (e.g., mumps virus, a paramyxovirus). DTH responses occur upon reexposure to the stimulating antigen. Reexposure generally must occur more than one week after the initial antigenic encounter (Fig. 14.13). Like contact dermatitis responses, DTH responses are delayed, occurring 24 to 72 hours after restimulation. Unlike contact dermatitis responses, DTH responses are not limited to the dermis but can occur at almost any anatomical site in the body.

### **Clinical Application**

#### **Mantoux test (see Immunology practical - week 10)**

**Tuberculosis (TB)** is a potentially severe contagious disease caused by *Mycobacterium tuberculosis*. TB is spread from person to person through the air. More than 2 million people worldwide die from TB each year. Among people older than 5 years of age, TB disease is the leading cause of death due to infectious disease around the world. The Mantoux skin test is a useful screening test to identify people who have been infected with TB. It involves injection of 5 TU (tuberculin units) of purified protein derivative (tuberculin), usually 0.1 mL, intradermally. Induration (swelling) is assessed at 48 to 72 hours. The induration is due to cell infiltration and occasionally vesiculation and necrosis. A positive response is an example of type IV hypersensitivity (DTH) and indicates that the subject has had prior exposure to *M. tuberculosis*.

#### **Sources:**

Lippincott's Illustrated reviews Immunology

Immunology lecture [https://www.jfmed.uniba.sk/fileadmin/jlf/Pracoviska/ustav-mikrobiologie-a-immunologie/9\\_imm\\_lect\\_hypersensitivity.pdf](https://www.jfmed.uniba.sk/fileadmin/jlf/Pracoviska/ustav-mikrobiologie-a-immunologie/9_imm_lect_hypersensitivity.pdf)