Immune disorders

- immunity & immune disorders - extreme importance (comparable to bacteriology at the early 20th cent.)
- new diseases, immunological etiology in "old" diseases, immunotherapy - considerable amount of medical information
- immune system - important for survival
- increased or decreased immunity - disease
Introduction

- humoral & cellular immunity
- **B-lymphocytes** - plasma cells - Ig A, M, G, E, D
- lymph nodes - cortex - germinal centers

- **T-lymphocytes** (60-70% in peripheral blood)
- lymph nodes - paracortex
- subspecialization (helper, suppressor, killer, natural killer)
Introduction

- Macrophages
- **Antigen-presenting cells** - dendritic cells, Langerhans cells (skin)
- MHC system
- HLA complex antigens - ability to recognize own Ag from foreign ones
- importance in transplantation - rejection (destruction of the graft by host)
1. Immune mechanisms of tissue damage

- immune response (both humoral & cellular)
- Ag (both exogenous & endogenous)
- inappropriate - hypersensitive reaction
- allergy - 4 types
I. Anaphylactic type

- quickly developing after contact of Ag (allergen) with Ab
- previous exposition!
- B-cells - IgE
- mediated through histamine, leucotriens, prostaglandins (granules of mast cells & basophilic leucocytes)
- increase of vascular permeability, vasodilatation, bronchoconstriction, increased mucoproduction
- **local reaction** - skin or mucosa
  - bee sting, food allergy, hay fever (pollinosis), asthma bronchiale, urticaria (hives)
  - familiar predisposition - atopy

- **systemic reaction**
  - parenteral administration of Ag (e.g. antiserum, drug-ATB) - systemic anaphylaxis -> anaphylactic shock
  - minutes - itching, rush, redding of skin
  - breathing problems, abdominal pain, vomiting, diarrhea
  - during several min - death due to collapse of circulation
Pathogenesis of type I hypersensitivity

Goldsy RA et al. Immunology 5th Ed, 2003, p 363
Type II hypersensitivity

Unlike Type I reactions, Type II hypersensitivity is caused by direct antibody-mediated cell damage or lysis. The actual mechanisms underlying cell destruction are multiple.

**Type II hypersensitivity**

(antibody-dependent cytotoxicity)

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**Complement-dependent red blood cell lysis.** Occurs for example in haemolytic transfusion reactions (HTR) caused by ABO incompatibility.

**Antibody-dependent red blood cell degradation.** Occurs as the result of binding of antibodies to the red cell membrane that fail to activate complement but promote macrophage uptake as in HDN caused by Rh incompatibility.

**Antibody-dependent cell-mediated cytotoxicity (ADCC).** Occurs as a result of cytotoxic antibodies become fixed on the surface of effector cells and subsequent antigen binding induce perforin-dependent or granzyme-dependent cell lysis of the cell bearing the antigen.
Type III hypersensitivity

- Caused by antibody-antigen complexes.
- When significant quantities of such immune complexes are formed, they can deposit in tissues and lead to a tissue reaction which is initiated by complement activation and leads to mast cell degranulation, leukocyte, predominantly neutrophil, chemotaxis and an inflammatory reactions caused by the activation of these cells.
Type III hypersensitivity

- activation of complement and accumulation of polymorphonuclear leucocytes
- acute inflammation of tissues
- Systemic response:
  - e.g. serum sickness - repeated exposure to animal (equine) serum (antitetanic) - fever, weakness, generalised vasculitis with edema and erhytema, arthritis and glomerulonephritis
  - immununcomplexes are deposited in tissues - inflammation
- vessel wall - acute necrotizing vasculitis (fibrinoid necrosis) - thrombosis - ischemic necrosis
- vessel wall replaced by smudgy, pink material
- local form of IS:
  - *Arthus reaction* (animal model - skin lesion) - localized area of tissue necrosis resulting from immune complex vasculitis - farmer's lungs (molds on hay)
  - some types of glomerulonephritis

- systemic lupus erythematoses (SLE)
Pathogenesis of type III hypersensitivity (right) & time course of serum sickness (below)

Goldsy RA et al. Immunology 5th Ed, 2003, p 381-2
IV. Delayed type of hypersensitivity (tuberculin-type) - cell mediated

- Type IV hypersensitivity reactions are caused by activated TH1 cells that are activated by intracellular pathogens, including bacteria, fungi and protozoa, as well certain chemicals (hair dyes, nickel salts) leading to clonal expansion and differentiation of antigen-specific cells into TH1 clones.
- frequently granulomatous reaction (epithelioid cells)
- TBC, syphilis, leprosy
  - e.g. tuberculin reaction - Mantoux test
  - person previously exposed to TBC develops after intradermal injection of Ag skin induration
  - manifestation after 8-12 h, maximum 2-7 weeks
- contact dermatitis
Pathogenesis of type IV hypersensitivity

(a) sensitisation phase

bacteria
APC

TH1 cells
DTH Cells:
TH1

(b) effector phase

IFN-γ
TNF-β

TH1 cells
Resting
Macrophage
Activated
Macrophage

APCs: Macrophages

TH1 products: IFN-γ, TNF-β, IL-2, IL-3, IL-8, MCAF, MIF

Macrophage activation: MHC cl II, TNF receptor, oxygen radicals, nitric oxide

Goldsy RA et al. Immunology 5th Ed, 2003, p 384
Transplantation rejection

- transplantation:
  - autologous (own)
  - homologous (alogenic) - human tissue
  - heterologous - animal tissue (pig skin, ovine pericardium)
- both humoral and cellular immunity - HLA system
Rejection reactions (e.g. renal graft)

- **hyperacute** (Ab mediated) - widespread arteriolitis, arteritis, thrombosis - ischemic necrosis (minutes-hours)
- **acute** (cell mediated) - lymphocytic infiltration, vasculitis, tubulitis, edema (days-months) - biopsy!!! (days-months)
- **chronic** - vascular changes - sclerosis, intimal fibrosis (months-years)
Graft versus host disease (GVHD)

- GVHD is the principal limitation to allogenic bone marrow transplantation. Although rare, GVHD can also occur after solid organ transplantation.
- GVHD occurs when donor immunocompetent T cells recognize immuno-incompetent recipient tissues as foreign and attempt to destroy them, and is usually associated with reduced levels of immunosuppression.
- The skin (dermatitis), liver (hepatitis), and GI tract (enteritis) are the main target organs of GVHD. Lung involvement can also occur.
- GVHD can manifest as an acute or chronic disease process. Acute GVHD can occur as early as the 7th to 10th posttransplant day or as late as 80 days after transplantation. Subclinical GVHD also occurs but is difficult to diagnose.
GVHD
Autoimmune diseases
Fig. 9.42 Interactions between genetic and environmental factors are important in the aetiology of autoimmune diseases.
<table>
<thead>
<tr>
<th>HLA association</th>
<th>Disease</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>Ankylosing spondylitis</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Reiter's disease</td>
<td>37</td>
</tr>
<tr>
<td>DR2</td>
<td>Goodpasture’s syndrome</td>
<td>16</td>
</tr>
<tr>
<td>DR3</td>
<td>Sicca syndrome</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Addison’s disease</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Hashimoto’s thyroiditis</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>3</td>
</tr>
<tr>
<td>DR4</td>
<td>Insulin-dependent diabetes mellitus</td>
<td>6</td>
</tr>
</tbody>
</table>
Fig. 9.41  Ways in which peripheral tolerance might be overcome to produce autoimmune responses.
<table>
<thead>
<tr>
<th>Self-antigen</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone receptors</strong></td>
<td></td>
</tr>
<tr>
<td>TSH receptor</td>
<td>Hyper- or hypothyroidism</td>
</tr>
<tr>
<td>Insulin receptor</td>
<td>Hyper- or hypoglycaemia</td>
</tr>
<tr>
<td><strong>Neurotransmitter receptor</strong></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine receptor</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td><strong>Cell adhesion molecules</strong></td>
<td></td>
</tr>
<tr>
<td>Epidermal cell adhesion molecules</td>
<td>Blistering skin diseases</td>
</tr>
<tr>
<td><strong>Plasma proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Factor VIII</td>
<td>Acquired haemophilia</td>
</tr>
<tr>
<td>β₂ Glycoprotein I and other anticoagulant proteins</td>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td><strong>Other cell surface antigens</strong></td>
<td></td>
</tr>
<tr>
<td>Red blood cells (multiple antigens)</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thrombocytopenic purpura</td>
</tr>
<tr>
<td><strong>Intracellular enzymes</strong></td>
<td></td>
</tr>
<tr>
<td>Thyroid peroxidase</td>
<td>Thyroiditis, probable hypothyroidism</td>
</tr>
<tr>
<td>Steroid 21-hydroxylase (adrenal cortex)</td>
<td>Adrenocortical failure (Addison’s disease)</td>
</tr>
<tr>
<td>Glutamate decarboxylase (β cells of pancreatic islets)</td>
<td>Autoimmune diabetes</td>
</tr>
<tr>
<td>Lysosomal enzymes (phagocytic cells)</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Mitochondrial enzymes (particularly pyruvate dehydrogenase)</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td><strong>Intracellular molecules involved in transcription and translation</strong></td>
<td></td>
</tr>
<tr>
<td>Double stranded DNA</td>
<td>Systemic lupus erythematosus (SLE)</td>
</tr>
<tr>
<td>Histones</td>
<td>SLE</td>
</tr>
<tr>
<td>Topoisomerase I</td>
<td>Diffuse scleroderma</td>
</tr>
<tr>
<td>Amino-acyl t-RNA synthases</td>
<td>Polymyositis</td>
</tr>
<tr>
<td>Centromere proteins</td>
<td>Limited scleroderma</td>
</tr>
<tr>
<td>Microbial antigen</td>
<td>Self-antigen with similar structure</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Group A streptococcal M protein</td>
<td>Antigen found in cardiac muscle</td>
</tr>
<tr>
<td>Bacterial heat shock proteins</td>
<td>Self heat shock proteins</td>
</tr>
<tr>
<td>Coxsackie B4 nuclear protein</td>
<td>Pancreatic islet cell glutamate decarboxylase</td>
</tr>
<tr>
<td>Campylobacter jejuni glycoproteins</td>
<td>Myelin-associated gangliosides and glycolipids</td>
</tr>
<tr>
<td>DNA J heat shock protein from Escherichia coli</td>
<td>HLA-DR β chain subtypes containing the rheumatoid arthritis ‘shared epitope’</td>
</tr>
</tbody>
</table>
2. Autoimmune diseases

- immune system reacts against own Ag
  - **A. Organ specific**
    - Hashimoto's thyroiditis (thyreoglobulij)
    - Graves-Basedow disease (TSH)
    - chronic atrophic gastritis - pernicious anemia
    - DM type I.
  - **B. Systemic (multiorgan)**
    - affection of vessels and/or connective tissue, variable symptomatology
      - systemic disorders of connective tissue (collagenosis)
      - rheumatic fever
Systemic lupus erythematosus (SLE)

- febrile inflammatory multisystemic disease - variable symptomatology
- females (F:M = 10:1), 2.-3. decade
- most often affected: skin, kidneys, serosal membranes, joints, heart
- several types of Ab - namely antinuclear Ab
- formation of immunocomplexes
- histologically - predominantly necrotizing vasculitis
- LE cells (fagocytosis of hematoxylin bodies - destroyed nuclei of cells) - lab test
Symptomatology

- **Skin** - facial exantema (butterfly) - cheeks + radix of the nose
- **Pleura + pericardium** - serous and fibrinous exudation - fibrosis
- **Heart** - pericarditis
  - endocarditis Libman-Sacks (verrucous) - nonbacterial thrombotic endocarditis
  - both sides of the valve
- **Kidneys** - various forms of Glnf
- **Joints** - swelling, inflammation
- **Spleen** - thickening of the capsule (serositis)
  - concentric perivascular fibrosis (onion-like)
Typical clinical presentation

- young female, butterfly-shaped exantema of the face
- febrile, joint pain, pleuritic pain, photophobia
- ANCA+
- !!!CAVE!!! frequently atypical symptomatology
- clinical course:
  - progressive - death
  - recurrences and remissions - years or decades
- treatment: steroids, immunosuppression
Rheumatoid arthritis (RA)

- symmetric chronic inflammation of the joints
- non-purulent productive synovitis - pannus (granulation tissue)
- destruction of cartilage - progressive impairment of function
- rather frequent: females 0.5-4%, males 0.1-1.3% (F:M=3-5:1)
- usually young adults
- pathogenesis - both humoral and cellular immunity
- increased Ig in serum
- "rheumatoid factor"
- clinically:
  - symetric inflammation of small joints (hands and feet), later also ankle, wrist, elbow, shoulder, jaws
  - only rarely hips
  - deformation and loss of function of joints
  - sometimes formation of subcutaneous nodules (2-3 cm in diam.) - rheumatoid nodules
Rheumatoid Arthritis

Inflamed membrane and swollen joint

Eroded cartilage and narrowed joint space
Special forms of RA

Juvenile RA (Still’s disease) - age 1-3 y.
• RA + fever, hepatosplenomegaly, lymphadenopathy

Felty's disease
• RA + splenomegaly + leukopenia
Systemic sclerosis (SS)-sclerodermia

- interstitial tissue of various organs - inflammation and fibrosis
- in 95% skin (scleroderma)
- sometimes visceral lesions (GI tract, lungs, kidneys, heart, muscles) = most important
- F:M=3:1
- any age (childhood - old age), mainly 3.-5. decade, rare
- histologically:
  - sclerosis of collagen (loss of filamentous structure, homogenization, hyalinization, no nuclei)
• skin - fingers - progression proximally
• first edema, than sclerosis of collagen, atrophy of epidermis, loss of skin adnexa
• skin is dry, with smooth surface, shiny, thin - ulceration
• loss of elasticity, rigidity
• spontaneous amputations, mask face
GI tract
- namely esophagus - atrophy and fibrosis of the wall - problems with swallowing

Locomotory apparatus
- loss of mobility, rigidity

Lungs
- interstitial fibrosis

Heart
- interstitial fibrosis of myocardium

Vessels
- Raynaud's phenomenon - polyarteritis nodosa
Polymyositis (dermatomyositis)

- symmetrical muscle weakness, pain, swelling, atrophy
- 2 peaks of incidence - 5-15 y., 50-60 y.
- frequently combination with other systemic diseases - overlap syndromes, vasculitis
- mixed connective tissue disease
Polymyositis (dermatomyositis)

Histologically
- inflammation (lymphocytes, plasma cells, histiocytes)
- atrophy, necrosis, disappearance of muscle fibres, replacement by fibrous tissue and fat
- usually starts proximally (shoulder, pelvis) - distal progression
- in 10-20% combination with malignant tumors - ca lungs, GIT (males) or ca breast, ovary (females)
Sjögren's syndrome

- dry eyes (keratoconjunctivitis sicca) - corneal lesions
- dry mouth (xerostomia)
- caused by loss of salivary and lacrimal glands - immunologically induced inflammation
- only salivary glands - benign lymphoepithelial lesion (myoepithelial sialoadenitis) - see Mikulicz's sy
- salivary glands + lacrimal glands - sicca syndrome
- combination with other autoimmune disorders (RA - 60%) - Sjögren's sy - 1933
- involvement of glands of other systems (nose, pharynx, vagina)
- histologically:
  - lymphoid infiltrates, atrophy - loss of parenchyma
- mostly females, over 40 y.
- Dx. based on histology (excision of minor salivary gland)

- Mikulicz's syndrome
- bilateral swelling of lacrimal glands, parotis and submandibular glands
- various etiology (leukemia, lymphoma, syphilis, TBC) + cases with unknown etiology - Mikulicz’s disease
Polyarteritis (periarteritis) nodosa

- necrotizing inflammation of the wall of middle sized and small arteries - necrotizing vasculitis
- deposition of immunocomplexes (similar to Arthus's phenomenon)
- often segmentally (uninvolved skipped areas) - thrombosis - infarctions
- variable clinical presentation - most frequently kidneys, heart, liver, GIT (perforation!), lungs rarely!
Polyarteritis (periarteritis) nodosa

- histologically:
  - fibrinoid necrosis (eosinophillic), infiltration by neutrophillic leucocytes, microaneurysms - rupture or thrombosis - infarction
  - healing by scar (fibrous tissue)
  - M:F=2:1 (!predominance of males!)
  - Dx. based on histology - diagnostic excision
Wegener's granulomatosis

- rare
- acute necrotizing arteritis (similar to polyarteritis nod.) - kidneys, respiratory tract (lungs), spleen
- acute granulomatous inflammation, necrotizing - namely respiratory tract (nose, paranasal sinuses, larynx, trachea, bronchi, lungs)
- necrotizing progressive Glnf. - in the past fatal, today cytostatics
Immunodeficiency
Fig. 9.20  Infections with certain micro-organisms are characteristic of various forms of immunodeficiency.
Fig. 9.23 Inherited complement deficiencies are associated with characteristic clinical syndromes.
Immunodeficiency

- Classification according altered mechanisms
  - Defects of non-specific immune response (phagocytosis, complement)
    - Syndrome of lazy leucocytes – Defects of chemotactic factors, defect of migration, leucocytic adhesion, chronic granulomatosis
  - Defects of specific immune response (antibody, T cell and combined)

- Classification according causation:
  - Primary immunodeficiency states
  - B. Secondary immunodeficiency states / chronic inflammation, tumors, metabolic diseases
Fig. 9.19 Clinical presentation in patients with primary antibody deficiency, irrespective of age.
Fig. 9.24 Commoner causes of secondary immunodeficiency.
Clinical symptoms

- Increased tendency to infection – prolonged course, recurrences,
- Worse answer on ATB
- Childhood diarrhea, small growth
- Skin, mucoses: eczema, pyodermia, candidosis...
- Neutropenia, lymphopenia, anemia
- Less usual pathogen, opportunistic microorganisms
Antibody immunodeficiency

- Decreased resistency against bacteria (not viruses and fungi)
- Varying forms depending on B cell maturation
- Decreased Ab levels

Cellular immunodeficiency

- Frequent autoimmunities
- Recurrent fungal skin infections
- B lymphocytes are normal
A. Primary immunodeficiency states

Isolated deficiency of IgA
- most frequent (1:700)
- recurrent sinopulmonary infections, diarrhea

Common variable immunodeficiency
- Hypogammaglobulinemia (frequent respiratory dis.)

Severe combined immunodeficiency
- X-linked or autosomal recessive (B and T lymphocytes)
X-linked agammaglobulinemia (Bruton's disease)
- inability of pre-B cells to differentiate into mature B-cells
- decrease in circulating B-cells, no germinal centers in LN, rudimentary Peyer's patches
- recurrent bacterial infections (H. influ., Str. pneumon., Staph. aur.)
Thymic hypoplasia (DiGeorge's syndrome)

- congenital malformation of 3rd and 4th branchial pouches
- vulnerability to viral, fungal and protozoal infections
B. Secondary immunodeficiency states

- more common
- in malnutrition, infection, cancer, renal disease, malignancies
- patients treated by immunosuppressive drugs
- Stress
- Old age
- AIDS
Acquired immunodeficiency syndrome (AIDS)

- viral etiology (HIV, RNA retrovirus)
- severe immunosupression - opportunistic infections, secondary tumors, neurologic symptoms
- first recognized 1981 - Los Angeles - pneumocystic pneumonia in 5 young homosexuals - 2 died
- Pneumocystis carinii (interstitial pneumonia in premature infants)
- onset of epidemic
- 1998 - 33,4 million of infected (22,5 in sub-Saharan Africa)
- number of both infected and ill patients increases - USA, Africa (2/3 of all cases in the world), Southeast Asia (Thailand, India, Indonesia)
Transmission

- **1. sexual contact** (lymphocytes in semen)
- **2. parenteral** - blood + derivates, drug abusers sharing needles
- **3. mother-to-infant** - transplacental, intrapartum, breast-feeding

**HIV cannot be transmitted by casual personal contact !!!**

**No transmission from patient to doctor (and vice versa) by casual contact !!!**

**Prevention of injury - needle sticks, etc.; operation or autopsy - special precautions**
Epidemiology - 6 risk groups

1. homosexual males (60%)
2. intravenous drug abusers (24%)
3. hemophiliacs (1%)
4. other blood recipients (2%)
5. heterosexual partners of other high-risk groups members
6. children of parents from groups 1.-3.
HIV-1 and HIV-2 - closely related
long incubation period
tropism for lymphocytes and nervous system
immunosupression - CD4+ T-cells (helpers)
slowly progressive fatal outcome
Opportunistic infections in AIDS

- **protozoal** (pneumocystosis-lungs; toxoplasmosis-lungs or CNS)
- **fungal** (candidiasis-GIT, respiratory tract; cryptococciosis-CNS; histoplasmosis-disseminated)
- **bacterial** (mycobacteriosis-frequently atypical; nocardiosis-lungs, CNS)
- **viral** (CMV-lungs, GIT, kidneys, CNS; HSV; varicella-zoster; slow viruses)
"Typical" patient in the USA

- young male homosexual or drug abuser
- fever, weight loss, diarrhea, generalized lymphadenopathy, multiple opportunistic infections, neurologic disorders, secondary neoplasm(s)

"Classical" clinical course

- after infection 4-7 W -> seronegative period -> seroconversion -> long latency (2-5 Y) -> lymphadenopathy -> AIDS-related complex (ARC - fever, weight loss, diarrhea) -> AIDS

- no vaccine, no drugs, only prevention
- AIDS - 100% mortality
Neoplasms in AIDS

- Kaposi's sarcoma (sarcoma idiopathicum hemorrhagicum multiplex) - related to HSV infection
- non-Hodgkin's ML (Burkitt's or immunoblastic)
- primary ML of CNS
- invasive ca of uterine cervix
AIDS and oral cavity

- 75% patients have orofacial diseases
  - infections
  - tumors
  - cervical lymphadenopathy
AIDS – oral infections

- **Fungal**
  - trash or other forms of candidosis
  - 70% patients
- **Viral**
  - HSV stomatitis
  - EBV – hairy leukoplakia
- **Bacterial**
  - gingivitis + periodontitis
AIDS – hairy leukoplakia

- almost unique to AIDS !!!
- EBV virus
- lateral borders of tongue
- soft white painless area with corrugated surface
- Mi: hyperkeratosis + koilocytes
- No premalignant lesion
- indicator of low immune status → poor prognosis
- may regress spontaneously
AIDS - tumors

- 50% patients
- **Kaposi’s sarcoma** – HSV 8
  - purplish bleeding area or nodule on palate
  - **Mi:** vascular tumor - minute proliferating blood vessels
- **Non-Hodgkin lymphomas**
  - painless swelling of palate + gingiva
  - **Mi:** high grade B cell lymphomas