The immune system and its diseases

Gunnar Houen
Professor, Dr. scient.
Statens Serum Institut
Immune system diseases

- Allergy
- Alloimmunity
- Autoimmunity
- Cancer (% ?)
- Immune deficiency
- Infection
- Inflammation
- Intolerance
Infections

- Acute → resolved infection
  - Chronic infection
    - Latent infection
      - Re-activated infection
## Inherited Immunodeficiencies

<table>
<thead>
<tr>
<th>Name of Deficiency Syndrome</th>
<th>Specific Abnormality</th>
<th>Immune Defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocyte deficiencies</td>
<td>Many different</td>
<td>Loss of phagocyte function</td>
<td>Extracellular bacteria and fungi</td>
</tr>
<tr>
<td>Complement deficiencies</td>
<td>Many different</td>
<td>Loss of specific complement components</td>
<td>Extracellular bacteria especially <em>Neisseria</em> spp.</td>
</tr>
<tr>
<td>Natural killer (NK) cell defect</td>
<td>Unknown</td>
<td>Loss of NK function</td>
<td>Herpes viruses</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndrome</td>
<td>SH2D1A mutant</td>
<td>Inability to control B cell growth</td>
<td>EBV-driven B cell tumors</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Gene with PI 3-kinase homology</td>
<td>T cells reduced</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Bloom’s syndrome</td>
<td>Defective DNA helicase</td>
<td>T cells reduced Reduced antibody levels</td>
<td>Respiratory infections</td>
</tr>
</tbody>
</table>

*Figure 11-8 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)*
Herpesvirus(es)
## Human herpesvirus diseases

<table>
<thead>
<tr>
<th>Name(s)</th>
<th>Target cell(s)</th>
<th>Primary disease(s)</th>
<th>Secondary disease(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV1 Herpes Simplex Virus 1</td>
<td>Epithelial, neurons</td>
<td>Orofacial/genital ulcers</td>
<td>Unknown</td>
</tr>
<tr>
<td>HHV2 Herpes Simplex Virus 2</td>
<td>Epithelial, neurons</td>
<td>Orofacial/genital ulcers</td>
<td>Unknown</td>
</tr>
<tr>
<td>HHV3 Varicella Zoster Virus</td>
<td>Epithelial, neurons</td>
<td>Chickenpox</td>
<td>Shingles</td>
</tr>
<tr>
<td>HHV4 Epstein Barr Virus</td>
<td>Epithelial, B cells</td>
<td>Mononucleosis</td>
<td>Lymphomas, NPC, SLE, RA</td>
</tr>
<tr>
<td>HHV5 Cytomegalovirus</td>
<td>Epithelial, leukocytes</td>
<td>Mononucleosis-like</td>
<td>Lymphomas, SLE</td>
</tr>
<tr>
<td>HHV6 Roseola Virus</td>
<td>T cells, neurons</td>
<td>Roseola</td>
<td>Unknown</td>
</tr>
<tr>
<td>HHV7</td>
<td>T cells</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>HHV8 Kaposi Sarcoma Virus</td>
<td>T cells, B cells</td>
<td>Unknown</td>
<td>Kaposi sarcoma, lymphoma</td>
</tr>
</tbody>
</table>

NPC: nasopharyngeal cancer, SLE: systemic lupus erythematosus, RA: rheumatoid arthritis
Influenzavirus

- (Zoonoser)
Zoonoser - Ebolavirus
Infection/inflammation

- Inflammation
  - pain (dolor), heat (calor), redness (rubor), swelling (tumor), loss of function (functio laesa)

- Infectious inflammation
  - immune inflammation

- Autoimmune inflammation
Infection-related diseases

- Septic shock syndrome (+)
- Allergy (+)
- Autoimmunity (-/+)
- Stomach ulcer (-/+)
- Immune deficiency (-)
- Cancer (-)
- Neurodegeneration (?)
- ......
Allergy

- IgE
- Allergens
- Pollen

- Hygiene hypothesis
- Infections ↓ ~ allergy
Stomach ulcer and infections

- Helicobacter pylori
- NSAIDs
- Gastritis
- Stomach cancer
- Stomach lymphoma
- MALT
Autoimmune diseases

- **Organ specific**
  - Only one organ involved
  - Organ specific autoantigens
  - Intracellular autoantigens
  - Viruses (bacteria) ?

- **Systemic rheumatic**
  - Connective tissue involved
  - Several/many tissues involved
  - Common autoantigens
  - Extracellular autoantigens
  - Bacteria ?
# Inherited immunodeficiencies

<table>
<thead>
<tr>
<th>Name of deficiency syndrome</th>
<th>Specific abnormality</th>
<th>Immune defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immune deficiency</td>
<td>ADA deficiency</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>PNP deficiency</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>X-linked scid, (\gamma_c) chain deficiency</td>
<td>No T cells</td>
<td>General</td>
</tr>
<tr>
<td></td>
<td>Autosomal scid DNA repair defect</td>
<td>No T or B cells</td>
<td>General</td>
</tr>
<tr>
<td>DiGeorge's syndrome</td>
<td>Thymic aplasia</td>
<td>Variable numbers of T and B cells</td>
<td>General</td>
</tr>
<tr>
<td>MHC class I deficiency</td>
<td>TAP mutations</td>
<td>No CD8 T cells</td>
<td>Chronic lung and skin inflammation</td>
</tr>
<tr>
<td>MHC class II deficiency</td>
<td>Lack of expression of MHC class II</td>
<td>No CD4 T cells</td>
<td>General</td>
</tr>
</tbody>
</table>
# Inherited Immunodeficiencies

<table>
<thead>
<tr>
<th>Name of Deficiency Syndrome</th>
<th>Specific Abnormality</th>
<th>Immune Defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiskott–Aldrich Syndrome</td>
<td>X-linked; defective WASP gene</td>
<td>Defective anti-polysaccharide antibody and impaired T-cell activation responses</td>
<td>Encapsulated extracellular bacteria</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>Loss of Btk tyrosine kinase</td>
<td>No B cells</td>
<td>Extracellular bacteria, viruses</td>
</tr>
<tr>
<td>X-linked hyper IgM Syndrome</td>
<td>Defective CD40 ligand</td>
<td>No isotype switching</td>
<td>Extracellular bacteria, <em>Pneumocystis carinii</em>, <em>Cryptosporidium parvum</em></td>
</tr>
<tr>
<td>Common Variable Immunodeficiency</td>
<td>Unknown; MHC-linked</td>
<td>Defective IgA and IgG production</td>
<td>Extracellular bacteria</td>
</tr>
<tr>
<td>Selective IgA</td>
<td>Unknown; MHC-linked</td>
<td>No IgA synthesis</td>
<td>Respiratory infections</td>
</tr>
</tbody>
</table>

*Figure 11-8 part 2 of Immunobiology, 6/e. © Garland Science 2005*
## Inherited Immunodeficiencies

<table>
<thead>
<tr>
<th>Name of deficiency syndrome</th>
<th>Specific abnormality</th>
<th>Immune defect</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagocyte deficiencies</td>
<td>Many different</td>
<td>Loss of phagocyte function</td>
<td>Extracellular bacteria and fungi</td>
</tr>
<tr>
<td>Complement deficiencies</td>
<td>Many different</td>
<td>Loss of specific complement components</td>
<td>Extracellular bacteria especially <em>Neisseria</em> spp.</td>
</tr>
<tr>
<td>Natural killer (NK) cell defect</td>
<td>Unknown</td>
<td>Loss of NK function</td>
<td>Herpes viruses</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndrome</td>
<td>SH2D1A mutant</td>
<td>Inability to control B cell growth</td>
<td>EBV-driven B cell tumors</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Gene with PI 3-kinase homology</td>
<td>T cells reduced</td>
<td>Respiratory infections</td>
</tr>
<tr>
<td>Bloom's syndrome</td>
<td>Defective DNA helicase</td>
<td>T cells reduced Reduced antibody levels</td>
<td>Respiratory infections</td>
</tr>
</tbody>
</table>

*Figure 11-8 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)*
Inherited immunodeficiencies

**CLASSICAL PATHWAY**
- C1, C2, C4
- Deficiency leads to immune-complex disease

**MB-LECTIN PATHWAY**
- MBL, MASP1, MASP2, C2, C4
- Deficiency of MBL leads to bacterial infections, mainly in childhood

**ALTERNATIVE PATHWAY**
- Factor D, Factor P
- Deficiency leads to infection with pyogenic bacteria and *Neisseria* spp., but no immune-complex disease

---

C3 convertase

C3b deposition

C3

Deficiency leads to infection with pyogenic bacteria and *Neisseria* spp. Sometimes immune-complex disease

Membrane-attack components

C5, C6, C7, C8, C9

Deficiency leads to infection with *Neisseria* spp. only

---

*Figure 11-13 Immunobiology, 6/e. (© Garland Science 2005)*
Acquired immunodeficiencies

- Infection e.g. EBV, CMV, HTLV, AIDS (Kaposis sarcoma)
- Malnutrition
- Chemotherapy
- Radiation (therapy)
- Burns
- Biological drugs
NOMA

- Cancrum oris/gangrenous stomatitis
- Malnutrition
- *Fusobacterium necrophorum*, *Prevotella intermedia*, *Borrelia vincentii*, *Porphyromonas gingivalis*, *Tannerella forsynthesis*, *Treponema denticola*, *Staphylococcus aureus*, *Streptococcus spp*
Targets of infectious diseases

- Any organ and tissue can be targeted by an infectious disease

- Many infectious diseases are not yet recognized as such

- T and/or B cell mediated immune responses (often more deleterious than the infection itself)
Infections by organ

- Gastro-intestinal
- Urogenital
- Respiratory
- CNS
- Peripheral nerve system
- Blood
- Muscle
- Skin
- Connective tissue
- Joints
Immune evasion

- Immune evasion ~ natural selection
- Ag drift
- Ag shift
- Ag camouflage
- Ag downregulation
- "Hiding"
- C’ inactivation
- Ag shedding/Ab neutralization
- "Self defence" = attack
### Immune evasion strategies

<table>
<thead>
<tr>
<th>Viral strategy</th>
<th>Specific mechanism</th>
<th>Result</th>
<th>Virus examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of humoral immunity</td>
<td>Virally encoded Fc receptor</td>
<td>Blocks effector functions of antibodies bound to infected cells</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Virally encoded complement receptor</td>
<td>Blocks complement-mediated effector pathways</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Virally encoded complement control protein</td>
<td>Inhibits complement activation by infected cell</td>
<td>Vaccinia</td>
</tr>
<tr>
<td>Inhibition of inflammatory response</td>
<td>Virally encoded chemokine receptor homolog, e.g., R-chemokine receptor</td>
<td>Sensitizes infected cells to effects of β-chemokine: advantage to virus unknown</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Virally encoded soluble cytokine receptor, e.g., IL-1 receptor homolog, TNF receptor homolog, interferon-γ receptor homolog</td>
<td>Blocks effects of cytokines by inhibiting their interaction with host receptors</td>
<td>Vaccinia, Rabbit myxoma virus</td>
</tr>
<tr>
<td></td>
<td>Viral inhibition of adhesion molecule expression, e.g., LFA-1 ICAM-1</td>
<td>Blocks adhesion of lymphocytes to infected cells</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td></td>
<td>Protection from NFκB activation by short sequences that mimic TLFs</td>
<td>Blocks inflammatory responses elicited by IL-1 or bacterial pathogens</td>
<td>Vaccinia</td>
</tr>
<tr>
<td>Blocking of antigen processing and presentation</td>
<td>Inhibited MHC class I expression</td>
<td>Impairs recognition of infected cells by cytotoxic T cells</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Inhibition of peptide transport by TAP</td>
<td>Blocks peptide association with MHC class I</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Immunosuppression of host</td>
<td>Virally encoded cytokine homolog of IL-10</td>
<td>Inhibits TNF-1 lymphocytes and reduces interferon-γ production</td>
<td>Epstein–Barr virus</td>
</tr>
</tbody>
</table>

*Figure 11-5 Immunobiology, 6/e. (© Garland Science 2005)*
Host pathogen relations

- MHC I ↓ ~ NK attack

- Chronic viral infection ~ MHC I ↓ ~ NK attack ? ~ autoimmunity

- Pathogen killing

- Host killing

- Survival of the fittest ? Both !
Pathogen detection

- Microscopy
  - direct
  - staining
  - IIF
- Culture
- PCR
- Sequencing
- Immunoassays
- MS
DNA, RNA assays

- PCR
- Arrays
- ELOSA
- Sequencing
- MS
Antibody assay methods

- Immunofluorescence
- Immunoassay (ELISA, FLISA, ...)
- Immunoblot (line blot, western blot)
- Immunodiffusion
- Immunoprecipitation
- Immuno .......
- Ab class, isotype, konc., affinity
T cell assay methods

- Fluorescence activated cell sorting
- Elispot
- Cytokine (release) assays
- CTL assays
Therapy

- Antibiotics
- Immunomodulation
- Surgery
- Vaccines
Vaccines

- Passive/active
- Preventive
- Therapeutic
- Live, attenuated, subunit, conjugated, (DNA), (peptide)
Prevention of infections

- Hygiene
- Nutrition
- Avoidance (isolation)
- Vaccination
- Prophylaxis
- Treatment
## Vaccination programme

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>24 mos</th>
<th>4-6 yrs</th>
<th>11-12 yrs</th>
<th>13-18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B¹</td>
<td></td>
<td>Hep B #1 only if mother HBsAg (-)</td>
<td>Hep B #2</td>
<td>Hep B #3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hep B series</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, Tetanus, Pertussis²</td>
<td></td>
<td></td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DTaP</td>
<td></td>
<td>Td</td>
</tr>
<tr>
<td>Haemophilus influenzae Type b²</td>
<td></td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IPV</td>
<td></td>
<td>IPV</td>
</tr>
<tr>
<td>Inactivated Polio⁴</td>
<td></td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IPV</td>
<td></td>
<td>IPV</td>
</tr>
<tr>
<td>Measles, Mumps, Rubella²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MMR #1</td>
<td>MMR #2</td>
<td>MMR #2</td>
<td>MMR #2</td>
<td>MMR #2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Varicella</td>
<td></td>
<td>Varicella</td>
<td></td>
<td>Varicella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal⁷</td>
<td></td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td>PCV</td>
<td>PPV</td>
<td>PCV</td>
<td>PCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis A series</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Influenza (yearly)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vaccines below this line are for selected populations.
MHC associations and infection

- MHC I (HLA A, B, C)

- MHC II

- Predisposition

- Protection
Gene polymorphisms and infection

- MHC I, II
- Cytokines
- Cytokine receptors
- Lymphocyte signalling ligands
- Lymphocyte signalling receptors
- C’
- Predisposition, protection
Autoimmunologi

Gunnar Houen

"Horror autotoxicus" Paul Ehrlich
Immune system

- Destruction and clearance of foreign pathogens/antigens
- Innate
- Adaptive
- Self tolerance
Infection/autoimmunity

Self | Immune system | Non self

Autoimmunity | Infection
Self tolerance

- Innate tolerance
- Central tolerance
- Peripheral tolerance
- Negative selection
- T reg ?
Innate immune system

- PAMPas
- Complement C’
- IgM ?
- NK cells
- Neutrophil granulocytes N
- Macrophages M
Innate tolerance

- Evolution
- Ignorance
- Conformation
- Separation
- C’ regulatory proteins
- Inhibitors
- Removal