Innate and adaptive immunity

**Innate (natural) immunity**
- first line of defence
- rapid; independent of previous exposure to a pathogen
- common to all members of a species

**Acquired immunity**
- induced by previous exposure to antigens that are perceived as non-self
- specific for each antigenic substance
- memory

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**INNATE IMMUNITY**
- Microbe
- Epithelial barriers
  - Phagocytes
  - Complement
  - NK cells

**ADAPTIVE IMMUNITY**
- B lymphocytes
- T lymphocytes
- Antibodies

**Time after infection**
0 6 12

**Days**
1 2 3 4 5

Robbins
Figure 4-5 Subsets of CD4+ effector T cells. In response to stimuli (mainly cytokines) present at the time of antigen recognition, naive CD4+ helper T cells may differentiate into populations of effector cells that produce distinct sets of cytokines and perform different functions. The types of immune reactions elicited by each subset, and its role in host defense and immunological diseases, are summarized. Two other populations of CD4+ T cells, regulatory cells and follicular helper cells, are not shown.
Humoral immunity

Figure 4–6 Humoral immunity. Naive B lymphocytes recognize antigens, and under the influence of helper T cells and other stimuli (not shown), the B cells are activated to proliferate and to differentiate into antibody-secreting plasma cells. Some of the activated B cells undergo heavy chain class switching and affinity maturation, and some become long-lived memory cells. Antibodies of different heavy chain isotypes (classes) perform different effector functions, shown on the right.
Role of various parts of immunological protection

**NON-SPECIFIC (INNATE) IMMUNITY**
- Complement
- Phagocytosis

**SPECIFIC (ACQUIRED) IMMUNITY**
- Antibody
- Cellular

**Pyogenic bacteria**
- Staphylococci
- Streptococci
- Haemophilus

**Bacteria**
- Staphylococci
- Gramm-negative

**Fungi**
- Candida
- Aspergillus

**Protozoa**

**Other bacteria**
- Neisseria

**Some viruses**

- Bacterium
- Complement

**Pyogenic bacteria**
- Staphylococci
- Streptococci
- Haemophilus

**Some viruses**
- Enterviruses (polio)
- ECHO-viruses

**Most viruses**
- Cytomegalovirus
- Vaccinia
- Herpes
- Measles

**Fungi**
- Candida
- Aspergillus

**Bacteria**
- Mycobacteria
- Listeria
- Pasteurella

**Protozoa**
- Pneumocystitis

**Antibody**

**Toxin**

**Antibody layer**

**NK cell**
- IFN-α

**Virus**

**T- lymphocyte**
Immunological disorders - immunopathology

Classical subdivision:
1. Hypersensitive reactions (allergy) (hypersensitivity)
2. Autoimmune disorders
3. Immunodeficiencies

"Immunological disorders" is a chapter not any different from "Inflammation". It is not another world, other mechanisms involved. It is about inflammation which got out of the control and became useless.

Hypersensitivity and autoimmunity are exaggerated and prolonged inflammations to normal/expected stimuli or abnormal inflammations to minimal/non-existing or virtual enemies. In either way, body is harmed.

Rational subdivision:

Hyperergic immune status (excessive or autoaggressive reactions; inflammation)
- Hypersensitivity = external foreign antigens
- Autoimmunity = internal self antigens
- Both may share similar mechanisms Coombs & Cell immunopathology
- Immunodeficiencies

Hypoergic immune status (insufficient reactions), insufficient inflammation
Clinical immunology

Immunodeficiency syndromes
1. Primary

**IMMUNODEFICIENCIES**

1. **Primary Immunodeficiencies**
   - Combined immunodeficiency (ID)
     - Severe combined ID (SCID) X-linked or AR-linked
     - Adenosine deaminase def. (ADD)
     - Purine nucleoside phosphorylase def. (PNPD)
     - MHC class II deficiency
     - MHC class I deficiency (bare leucocyte syndrome)
     - Reticular dysgenesis
     - CD3g or CXD3e deficiency
     - CD8 deficiency
   - Predominantly antibody immunodeficiencies
     - X-linked agammaglobulinemia (Bruton)
     - Hyper IgM syndrome (X-linked; other)
     - IgA deficiency
     - Selective IgG deficiency
     - Transient hypogammaglobulinemia
     - Common variable ID (CVID)
     - Secretory component deficiency
     - Antibody def. with normal Ig
     - Ig heavy chain deletion
     - Kappa chain deficiency
   - Syndromes associated with ID
     - Chromosomal instability:
       - Bloom syndrome, Fanconi anemia, Seckel syndrome, Xeroderma pigmentosum, ICF syndrome, Nijmegen breakage sy.
     - Chromosomal def.:
       - Down sy., Turner sy., Chromosome 18 rings, del.
     - Hereditary metabolic defects:
       - Trascobalamin 2 deficiency, Methylmalonic acidemia, Hereditary orotic aciduria, type 1 Mannosidosis, Glycogenosis 1b, Chédiac - Higashi sy., Biotin dependent carboxylase def.

2. **Acquired Immunodeficiencies**
   - AIDS (Acquired immunodeficiency syndrome)
   - Iatrogenic (X ray, gamma radiation)
   - Acute radiation sickness
   - Idiopathic CD4+ lymphopenia

3. Syndromes associated with ID
   - ID with general growth retardation:
     - Short-limb skeletal dysplasia,
     - Cartilage-hair hypoplasia
     - Schimke immunoosseous dysplasia,
     - Dubowitz syndrome
     - Progeria (Hutchinson – Gilford sy.), ID with absent thumbs
   - ID with dermatological defects:
     - Partial albinism, Netherton sy.
     - Acrodermatitis entheropathica,
     - Dyskeratosis congenita,
     - Anhydrotic ectodermal dysplasia,
     - Papillon-Lefevre sy.
   - Other:
     - Hyper IgE syndrome,
     - Chronic mucocutaneous candidiasis
     - Hereditary or congenital hyposplenism
     - Ivermark syndrome
Immunodeficiencies in adaptive immunity

**BONE MARROW**
- Pluripotent stem cell
  - Pro-B cell
  - Pre-B cell
  - X-linked agammaglobulinemia (BTK)
  - IgM heavy chain

**THYMUS**
- ADA deficiency
- X-linked SCID (cytokine γ chain)
- DiGeorge syndrome
- MHC Class II deficiency

- Immature T cell
- T-cell receptor

**immature B cell**
- Hyper-IgM syndrome (CD40L)

**Mature B cells**
- IgM
- IgG
- IgA
- IgE

**Mature T cells**
- CD4+ T cell
- CD8+ T cell
- CD4+
Bruton’s agammaglobulinemia

- X-linked recessive defect caused by genetic mutation of B-cell specific tyrosine kinase
- B-Ly maturation disorder, arrest at the preB-stage -> Ig deficiency
- capsule-forming pyogenic bacteria (staphylococci, streptococci, pneumococci (meningitis, pyoderma, sepsis))
- **Selective IgA deficiency** - one of the most common; sporadic, familial, assoc with atopic disposition (rise IgE) + HLA B8, DR3 recurrent resp. infect.

- **Selective IgG deficiency - IgG2** - haemophilus, meningococcus, pneumococcus; respiratory tract infections

- **Hyper IgM syndrome** - X-linked or AR, mutation in CD40-ligand; arrest of B-Ly development at IgM level (switching defect)
Common variable immunodeficiency (CVID)

- A group of disorders associated with inadequate Ig production;
- Often associated with HLA A1, B8, DR3; recurrent respiratory infections
  - Arrested B-Ly maturation at pre B-Ly (no plasma cells)
  - Inrespositivity to T-Ly
  - Defective glycosylation of Ig
Wiskott- Aldrich syndrome (WAS)

- **Def.:** X-linked chromosomal defect leading to altered CD43 expression → impaired binding of actin fibres to TCR receptors in T-Ly and various receptors in Tro → defect of T-Ly & Tro functions & maturation
- **Sy:** trombocytopenic purpura, petechias
- recurrent infections, eczema

D. Wiskott – Aldrich syndrome
**Di George syndrome**

- **Etio:** 22q11 deletion syndrome; malformation of 3rd and 4th pharyngeal pouches in fetus (give rise to thymus, the parathyroids, thyroid C cells, branchiogenic structures)
- **Sy:** (A) hypoplasia of the thymus - decreased T cells (normal B cells) (recurrent viral and fungi infections)
- (B) hypoparathyroidism (hypocalcaemic tetany), facial abnormalities; congenital defects of the heart and great vessels. aortic arch malformation, hypothyroidism, esophageal atresia, underdevelopment of thymus (in 20% of cases)
Ataxia telangiectasia

**Def:** heterogenous group of AR-inherited diseases with chromosomal instability & weak DNA repair; ↑ sensitivity to radiation (! X-ray scan !) → ↑ DNA breakages (e.g. damage in Ch14 causes defect in TCR and Ig synthesis)

**Sy:** 1. progressive immunodeficiency & recurrent infectious diseases (sinusitis, pulmonary infections) 2. cerebellar ataxia; oculocutaneous telangiectasia
Severe combined immunodeficiency (SCID)

- **Def.**: group of inherited heterogenous disorders of T-Ly - thymus, lymph nodes, tonsils absent; no CD3+ Ly in blood
- **Occ.**: 1:100,000 children;
- **Etio**: various genetic defects (AR-linked gene defect for TCR and Ig, g-chain of IL2 receptor; purine metabolism dis.: defective cell division,

**different defects -> similar outcome**
(a) defect in Ig- structure
(b) defect in cytokine receptor
(c) defect in JAK-STAT signalling
Immunity defects - overview

ADA deficiency
SCID (severe combined immune deficiency)
CVID (common variable immune deficiency)
Severe combined immunodeficiency (SCID)

- **Occ:** 3-6 months of age; variable intensity
- **Sy:** infections - respiratory gastrointestinal skin - eczema
- recurrent, serious infections that are not easily treated
  - Pneumonia (Pneumocystis, Candida)
  - Meningitis
  - Sepsis - bacteriemia
- other infections, including the following:
  - chronic skin infections
  - yeast infections in the mouth and diaper area
  - diarrhea (rotavirus),
  - infection of the liver
Immunodeficiencies

Non-specific immunity failure (leucocytes, complement)

a) Defects in chemotaxia, attachment & diapedesis
b) Defects in phagocytosis & killing mechanisms
c) Defects in complement
Leukocyte adhesion deficiencies (LAD)

**LAD 1** – AR – inherited mutations in the ITGB2 (encodes CD18 - protein present in several cell surface receptor complexes in leucocytes), including integrin (lymphocyte function-associated antigen 1; LFA-1), complement receptor 3 and 4 (CR-3, CR-4)
- Neutrophils unable to adhere to and migrate out of blood vessels (so their counts can be high).
- Impairs immune cell interaction, immune recognition, and cell-killing lymphocyte functions.
- The lack of CR3 interferes with chemotaxis, phagocytosis, and respiratory burst.

**Sy:**
- **Recurrent bacterial or fungal soft tissue infections** (often apparent at birth)
- **Delayed separation of the umbilical cord, periodontal disease, elevated neutrophils,**
- **Impaired wound healing,** but not increased vulnerability to viral infections or cancer

**LAD 2** - absence of neutrophil sialyl-LewisX, a ligand of P- and E-selectin on vascular endothelium
Chediak–Higashi syndrome
Myeloperoxidase deficiency

**Chediak-Higashi syndrome**
- AR - inherited defective chemotaxis + intracellular killing of bacteria in granulocytes
- abnormal giant granules; absence of degranulation (microtubular dysfunction)
- NK- cells impaired ADCC susceptibility to infection by catalase-negative bacteria
- **Sy:** oculocutaneous albinism, photophobia, neurologic defects

**Myeloperoxidase deficiency**
- MPO converts $\text{H}_2\text{O}_2 + \text{Cl}^-$ into hypochlorous anion ($\text{OCl}^-$) stored in specific granules
- reduced O2- dependent killing in granulocytes + monocytes
- **Sy:** repetitive infections, mainly **candidiosis**
Infantile septic granulomatosis (ISG)  

- Insufficient oxidative burst (production of oxygen radicals) in presence of normal diapedesis and phagocytosis

**Etio:**
- a) lack of cytochrome $b_{558}$ in granulocyte phagosomes (X-linked recessive);
- b) lack of G6PD;
- c) defect in NADPH oxidase; defective $e^{-}$ transport through membrane for $O_{2}^{-}$ superoxid radical formation

**Sy:** Repetitive pyogenic infections
- lymphadenitis; septic abscesses in organs (*Staphylococcus, Klebsiella, Serratia, Aspergilus*)

- Catalase – negative strains (staphylococcus, haemophilus) can be killed by $H_{2}O_{2}$
<table>
<thead>
<tr>
<th>Complement proteins</th>
<th>Deficiency-associated manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C4</td>
<td>SLE, pyogenic infections (e.g., pneumococcal sepsis)</td>
</tr>
<tr>
<td>C3, FH, F1</td>
<td>Pyogenic infections, glomerulonephritis</td>
</tr>
<tr>
<td>C8</td>
<td>Infections, especially by <em>Neisseria</em> spp. (gonococci, meningococci); sclerodactyly</td>
</tr>
<tr>
<td>CR3, CR4, LFA-1</td>
<td>Gingivitis, delayed deciduation of the umbilical cord, recurrent sepsis</td>
</tr>
</tbody>
</table>
C1 inhibitor deficiency-hereditary angioedema

- a) AD - linked hereditary, b) acquired form (AAE) in cancer of the lymphatic system or as autoimmune diseases.
- C1 inhibitor (antiprotease) is degraded very quickly; can not block proteases that perpetuate vascular changes of inflammation.
- Sy: recurrent acute angioedematous swelling (hardened; white or pinkish rash) of the skin and/or mucosae) without urticaria lasting 2 to 5 days); increasing intensity over 6 to 24 hours, spontaneously subsides in 12 to 36 hours;
- Subcutaneous: face, neck, shoulders, extremities (hands, feet, arms, legs), buttocks, genitals
- Submucosal: abdominal organs: stomach, intestine, bladder; upper respiratory tract: tongue, throat, pharynx and larynx
- Glottis, hoarseness, voice loss, asphyxia.

Precipitating Factors: Trauma; physical exercise (e.g., cycling); operations: dental extractions; Fatigue; Insomnia; Stress; Infections; Menstruation; Estrogens (oral contraceptives, hormone replacement therapy); antihypertensive drugs of the ACE (angiotensin converting enzyme) inhibitors.
# Hereditary angioedemmas – diff. diagnostics

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Hereditary Angioedema (due to C1-INH Deficiency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Generally other family members are affected</td>
</tr>
</tbody>
</table>
| Clinical symptoms| • Cutaneous edemas  
                  • Painful abdominal attacks  
                  • Laryngeal edema (rare, life threatening) |
| Affected age groups| First signs in childhood and adolescence, with frequent recurrences |
| Types and causes | • Hereditary angioedema type I (HAE I) (genetic deficiency of C1-INH)  
                  • Hereditary angioedema type II (HAE II) (genetic or functional deficiency of C1-INH synthesis)  
                  • Hereditary angioedema type III (HAE III) (only affects women, unknown genetic defect) |
| Laboratory finding (in plasma) | • HAE I – low activity and concentration of C1-INH  
                  • HAE II – low activity and normal or increased concentration of C1 – INH |
| Treatment        | HAE I & II – C1-INH concentrate, danazol or stanozolol |

**SYMPTOMS OF HEREDITARY ANGIOEDEMA**

- **Head**
  - Headache, dizziness, voice alterations, possible visual alterations and signs of paralysis.
- **Throat**
  - Swelling of the airway, laryngeal edema beginning with difficulty swallowing, change in voice pitch, hoarseness, difficulty breathing and in extreme cases asphyxiation.
- **Intestinal Region**
  - Vomiting, abdominal pain, diarrhea, cramping and discomfort.
- **Bladder**
  - Burning sensation when urinating, bladder and lumbar region pain, symptoms similar to urinary tract infection.
- **Genitals**
  - Swelling of the scrotum and vulva.
- **Cutaneous Edema**
  - Sensation of tightness, pressure and swelling.
- **Extremities (Arms and Legs)**
  - Swelling, decrease in normal mobility and difficulty walking.
**Positive feedback loop syndrome**

- **strengthened positive feedback loop around C3bBb-C3 convertase consumes all available C3 (symptoms similar to primary C3 deficiency)**
- **Etio**: a) deficiency of inhibitory factors H and I (normally control C3 activation); b) antibodies against C3bBb complex (block of disassembling into C3b + Bb fragments)
- **Sy**: subcutaneous lipodystrophy, mesangio proliferative glomerulonephritis, recurrent pyogenic infections
Acquired immunodeficiency syndrome (AIDS)
A. Structure of the genome and the virion
C. AIDS

- Opportunistic infections:
  - Pneumocystis carinii
  - Toxoplasmosis
  - Mycobacteria
  - Herpes viruses: HSV, CMV, EBV

- Neurological complications:
  - Acute meningoencephalitis
  - Vacuolar myelopathy
  - Peripheral neuropathy

- HIV-associated tumors:
  - Kaposi's sarcoma
  - Malignant lymphomas: NHL

A. Time course of HIV infection:

- Acute phase
- Symptom-free interval
- ARC
- AIDS

- Helper T cells
- Cytotoxic T cells
- HIV particles
- Anti-HIV antibodies