Academic lectures for general medicine students – 3rd Year
2004-2015

GENERAL PATHOPHYSIOLOGY

IMMUNOLOGY
CLINICAL PATHOLOGY 1

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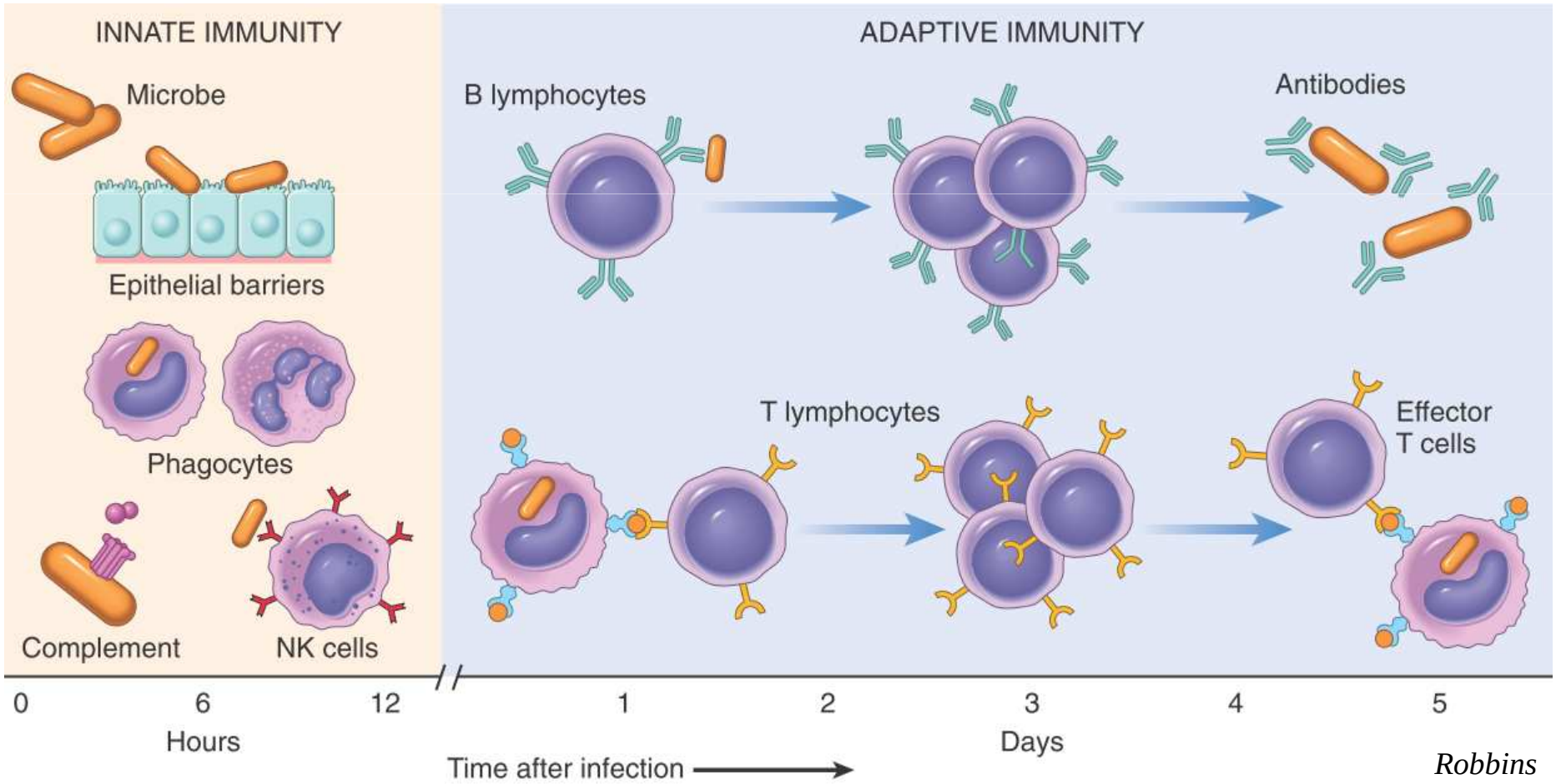
Innate and adaptive immunity

Innate (natural) immunity

- *first line of defence*
- *rapid; independent of previous exposure to a pathogen*
- *common to all members of a species*

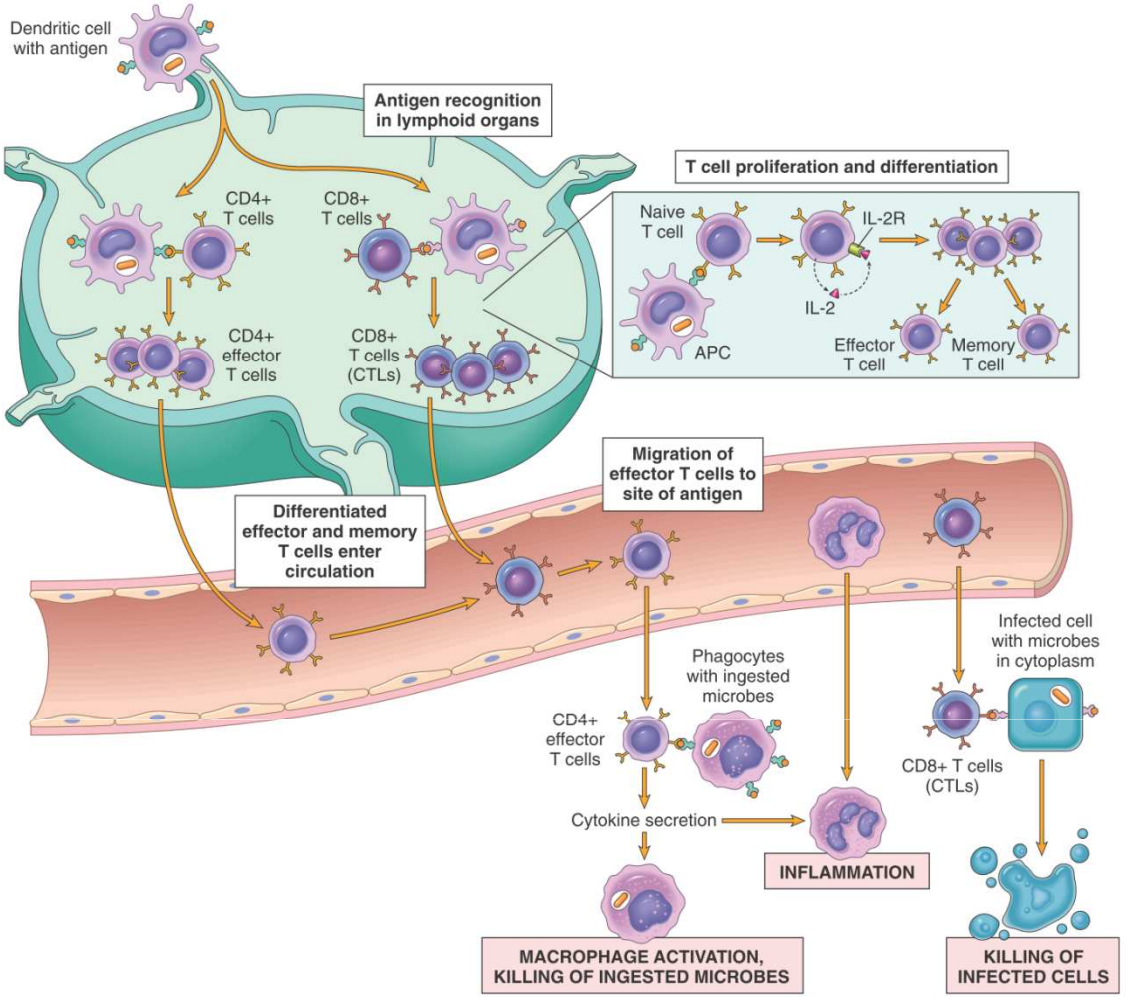
Acquired immunity

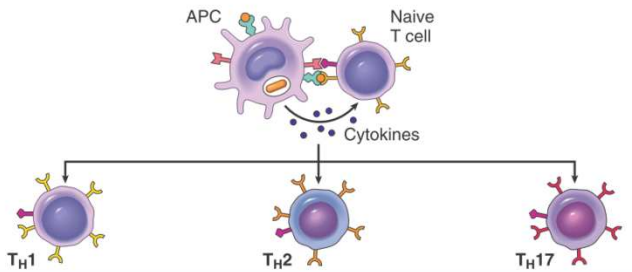
- *induced by previous exposure to antigens that are perceived as non-self*
- *specific for each antigenic substance*
- *memory*



Robbins

Celullar immunity





	T_H1	T_H2	T_H17
Cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22, chemokines
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunologic reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Immune-mediated chronic inflammatory diseases (often autoimmune)	Allergies	Immune-mediated chronic inflammatory diseases (often autoimmune)

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

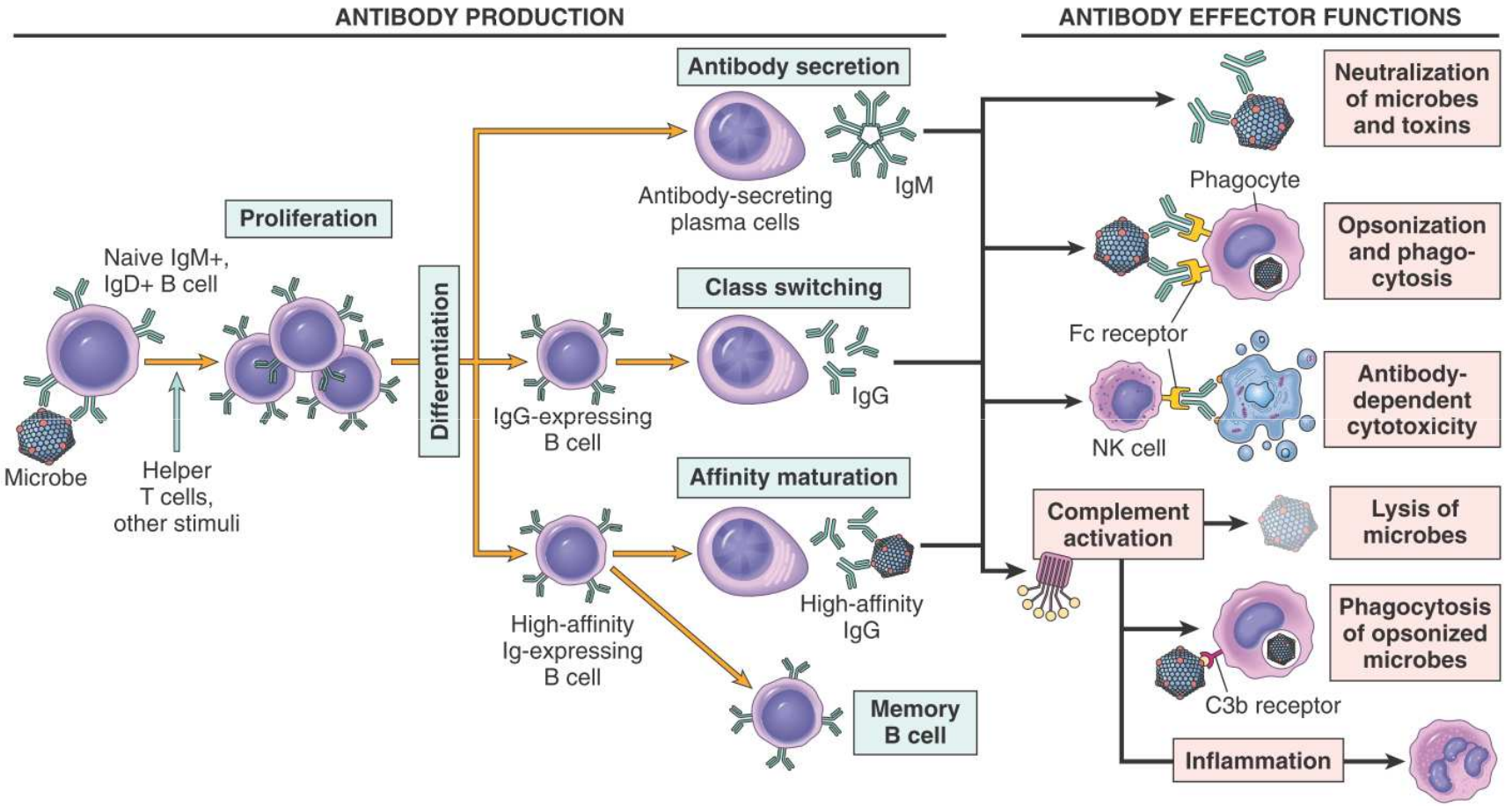
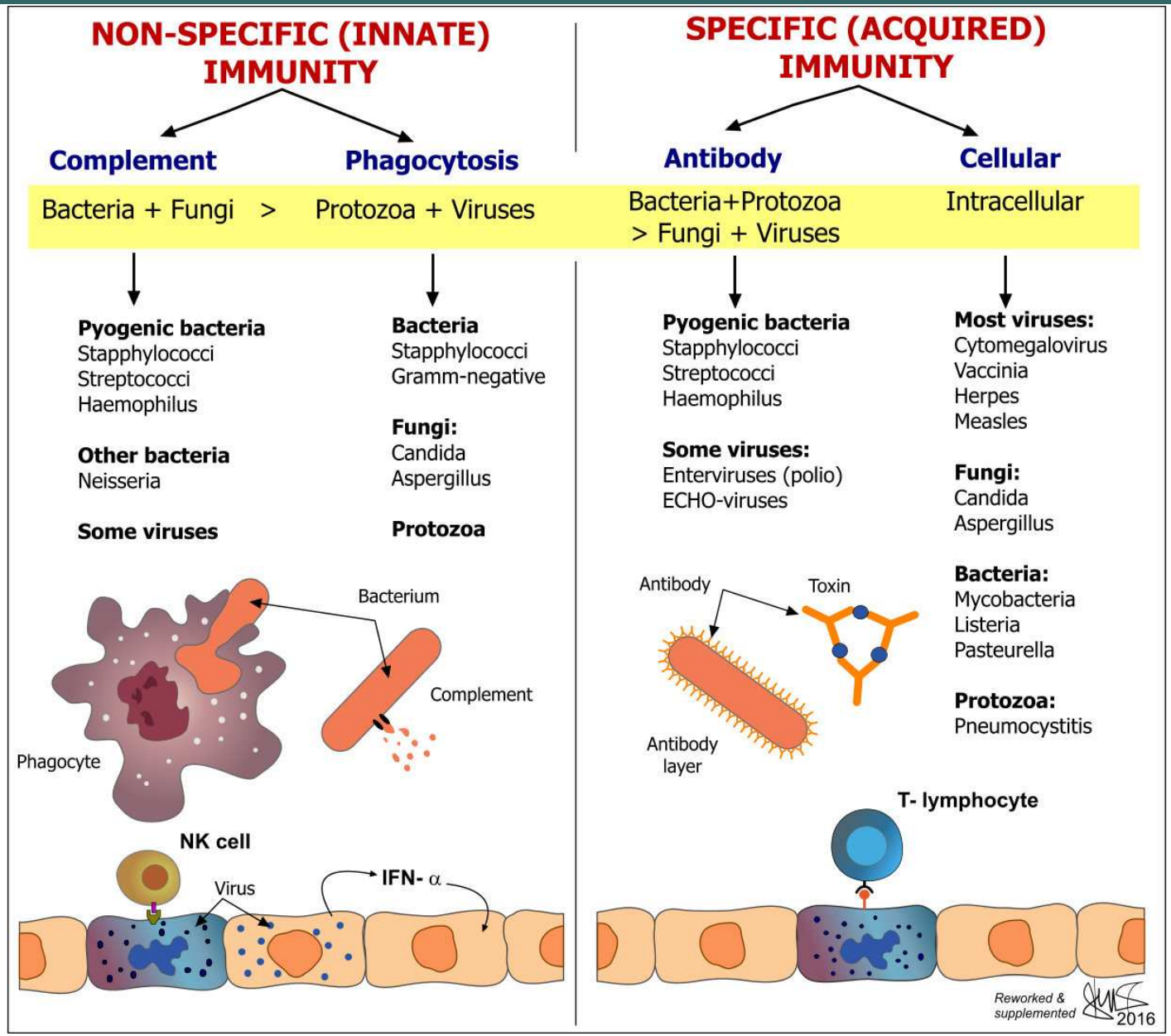


Figure 4–6 Humoral immunity. Naive B lymphocytes recognize antigens, and under the influence of helper T cells and other stimuli (not shown), the B cells are activated to proliferate and to differentiate into antibody-secreting plasma cells. Some of the activated B cells undergo heavy chain class switching 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



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 inflmmations 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 autoagressive reactions; inflammation)

→ Hypersensitivity = external foreign antigens

→ Autoimmunity = internal self antigens

Both may share similar mechanisms Coombs & Cell immunopathology

Hypoergic immune status (insufficient reactions), insuficient inflammation

→ Immunodeficiencies

Clinical immunology **3**

Immunodeficiency syndromes

IMMUNODEFICIENCIES

1. Primary

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

Predominantly celullar immunodeficiencies
- Wiskott-Aldrich syndrome
- Ataxia teleangiectatica
- DiGeorge syndrome

Syndromes associated with ID
- Hereditary metabolic defects:

Trascobalamin 2 deficiency, Methylmalonic acidemia, Hereditary orotic aciduria, type 1 Mannosidosis, Glycogenosis 1b, Chédiac - Higashi sy., Biotin dependent carboxylase def.

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.

- Hypercatabolism of Ig: Familial, Intestinal lymphangiectasia

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

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

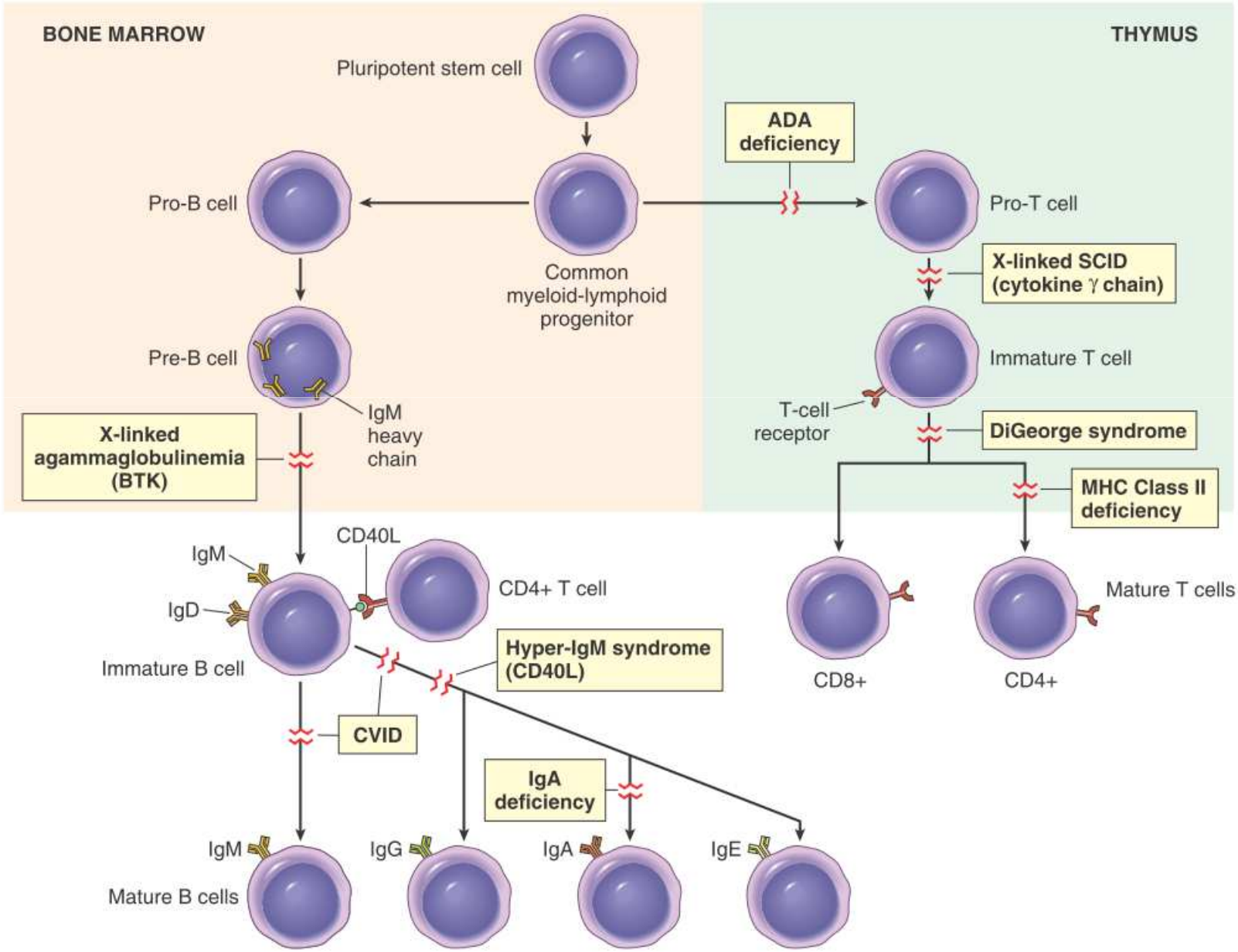
- ID with dermatological defects:

Partial albinism, Netherton sy. Acrodermatitis entheropathica, Dyskeratosis congenita, Anhydrotic ectodermal dysplasia, Papillon- Lefevre sy.,

- Other:

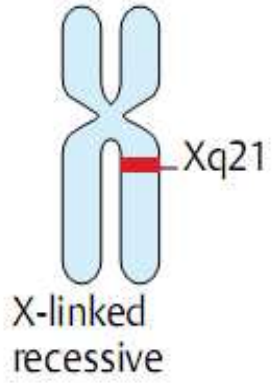
Hyper IgE syndrome, Chronic mucocutaneous candidiasis Hereditary or congenital hyposplenism Ivermark syndrome

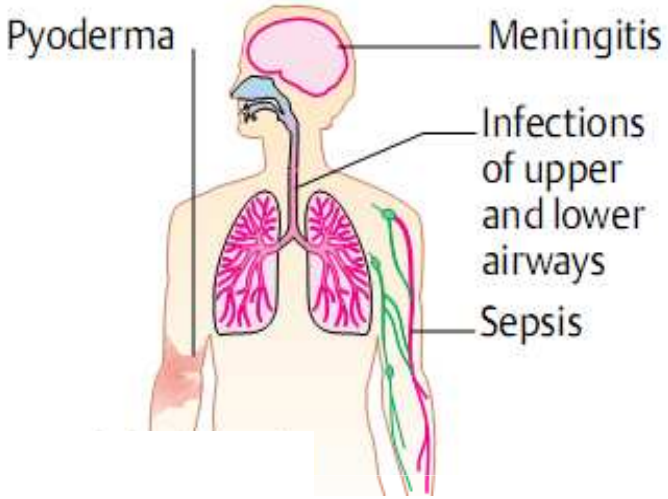
Immunodeficiencies in adaptive immunity

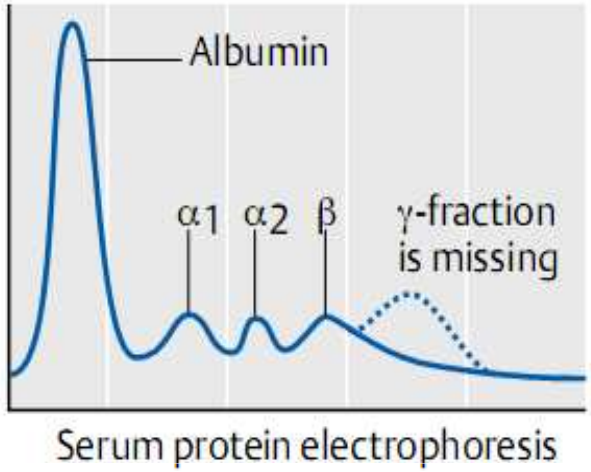


Bruton's agammaglobulinemia

HUMORAL





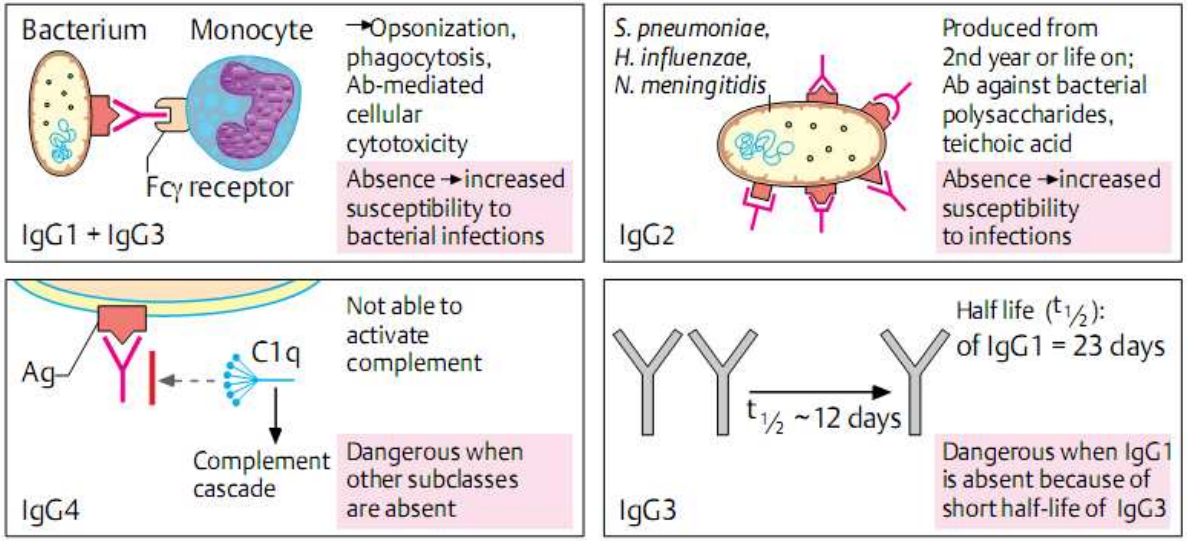


- X - linked recessive defect caused by genetic mutation of B-cell specific tyrosine kinase
- B-Ly maturation disorder, arrest at the preB-stage -> Ig defitiency
- capsule-forming pyogenic bacteria (staphylococci, streptococci, pneumococci (meningitis, pyoderma, sepsis)

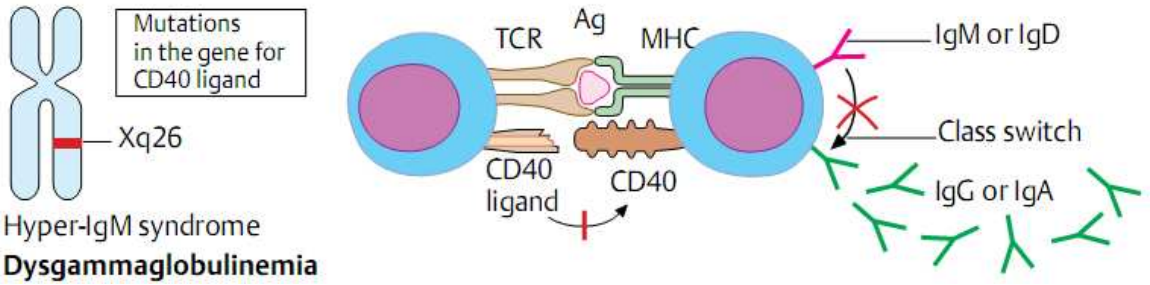
Hypo (Dys)-gammaglobulinemia

HUMORAL

- **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)



1. Selective IgG subclass defects/properties of IgG subclasses



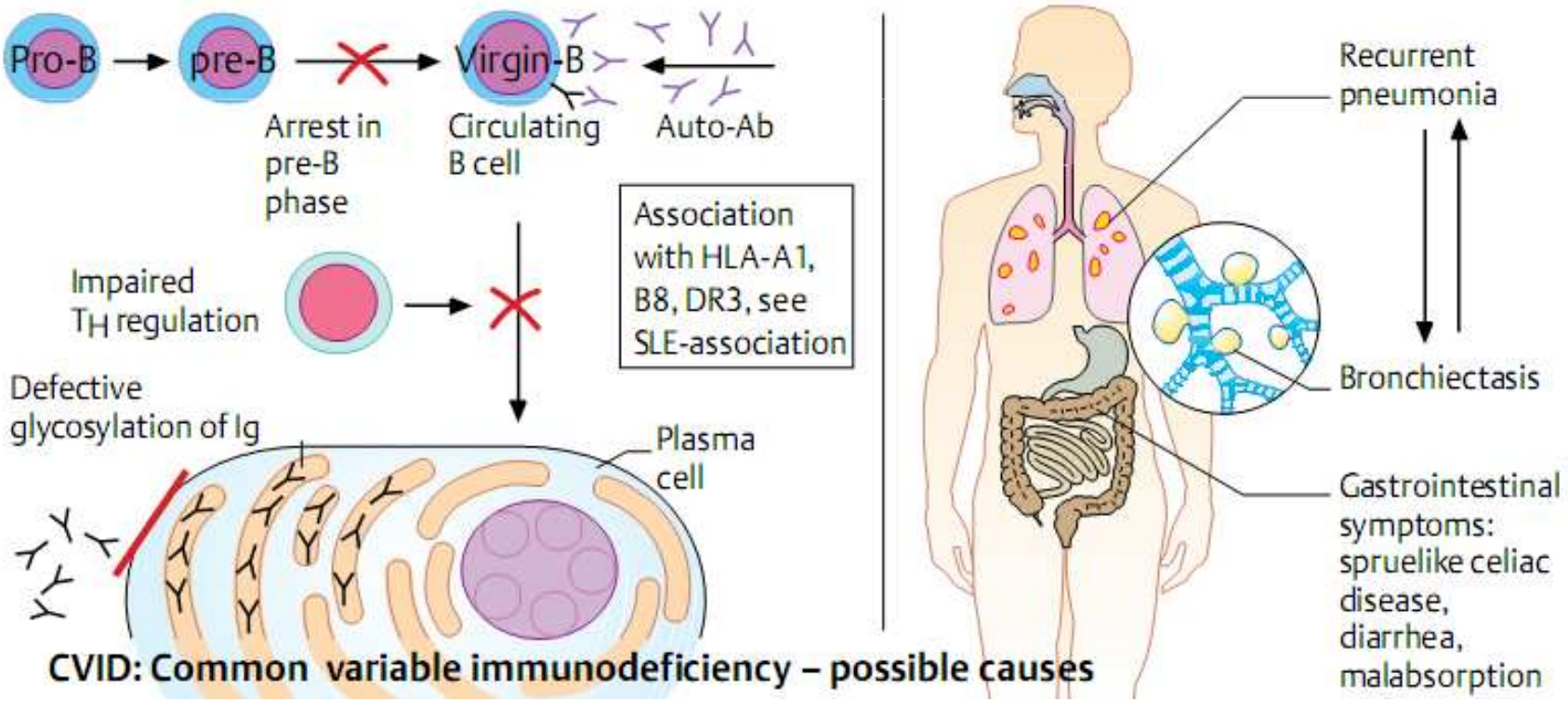
2. Hyper-IgM syndrome

B. Dysgammaglobulinemia

Common variable immunodeficiency (CVID)

CELLULAR

- group of dis. assoc. with inadequate Ig production;
- offten assoc. with HLA A1, B8, DR3; reccurent resp. infections
  - Arrested B-Ly maturation at pre B-Ly (no plasma cells)
  - Inrespositivity to T-Ly
  - Defective glycosylation of Ig

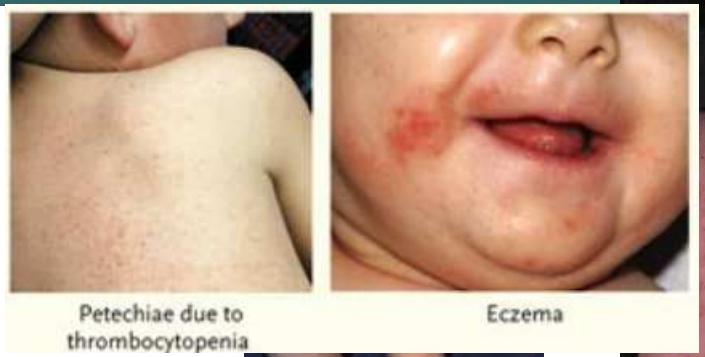


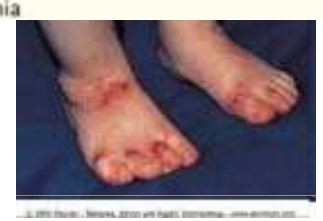
CVID: Common variable immunodeficiency – possible causes

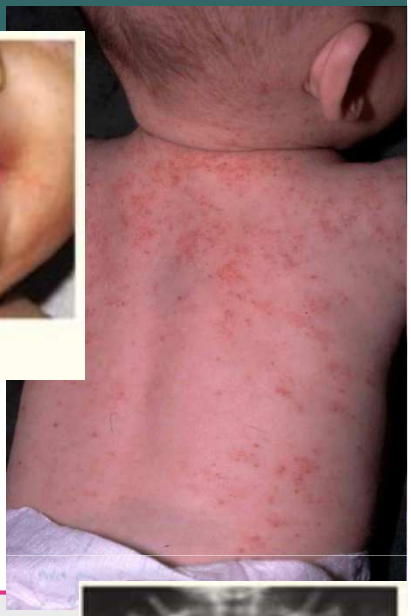
Wiskott- Aldrich syndrome (WAS)

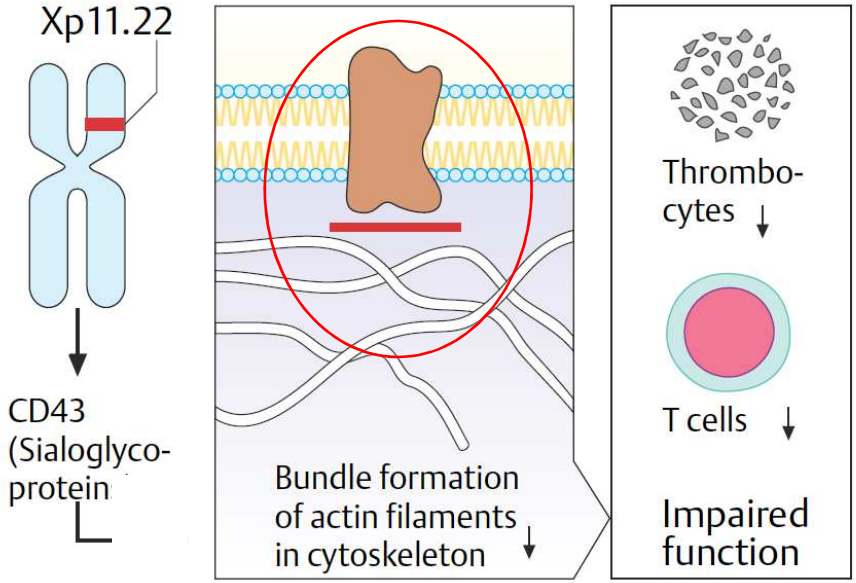
CELLULAR

- 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

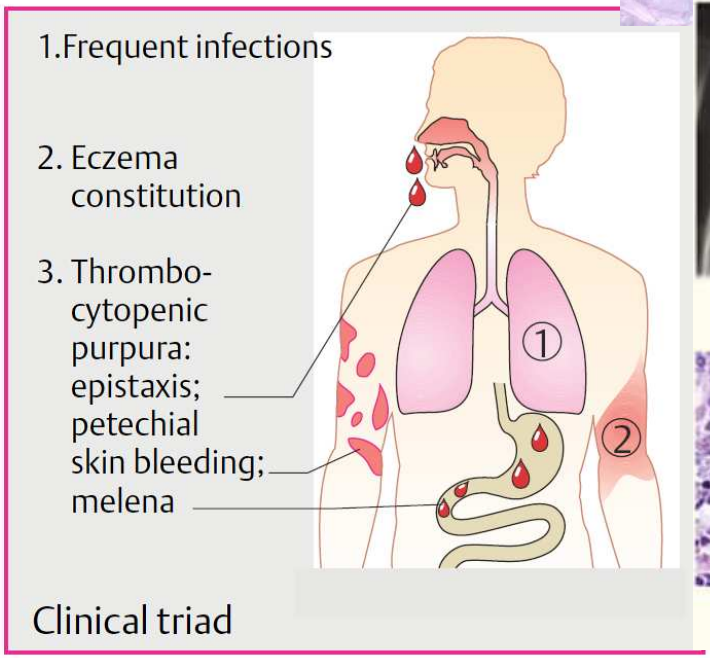


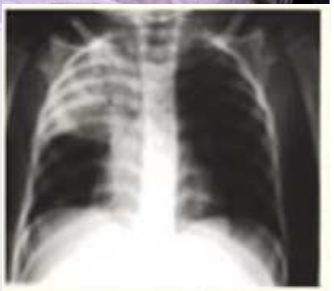




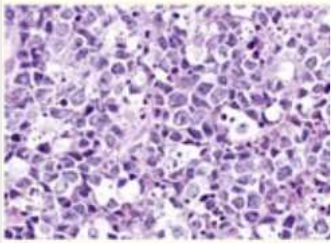


D. Wiskott – Aldrich syndrome





Pneumonia and other infections

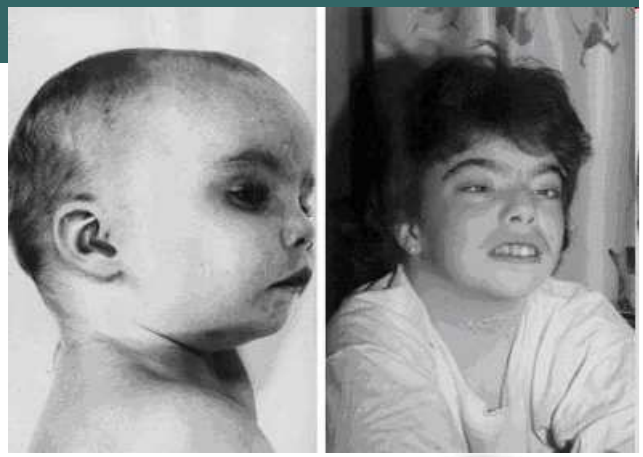


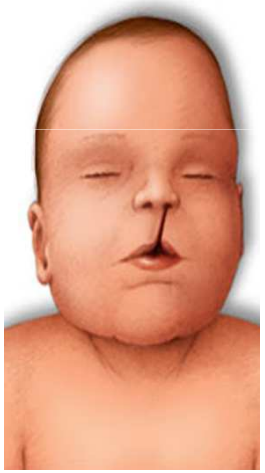
B-cell lymphoma and other cancers

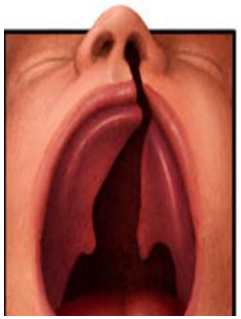
CELULLAR

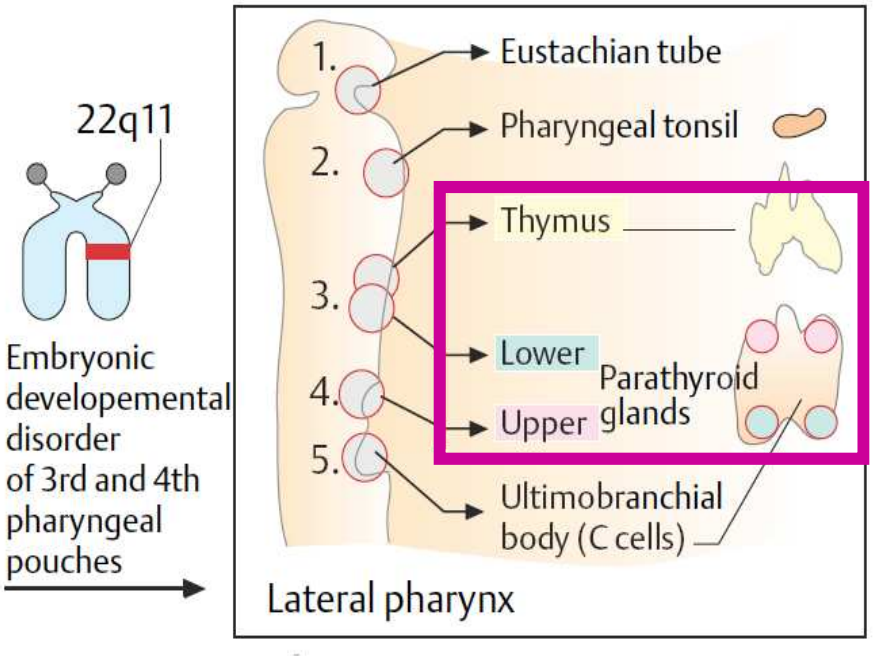
Di George syndrome

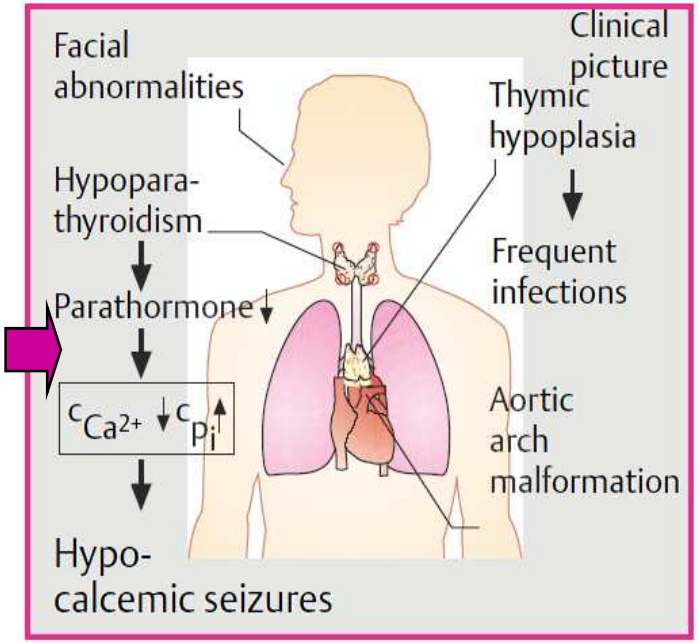
- **Etio:** 22q11 deletion syndrome; malformation of 3rd and 4th pharyngeal pouches in fetus (give rise to thymus, the parathyroids, thyroid C cells, brianchiogenic structures)
- **Sy:** (A) hypoplasia of the thymus - decreased T cells (normal B cells) (**recurrent viral and fungi infections)**
- **(B)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







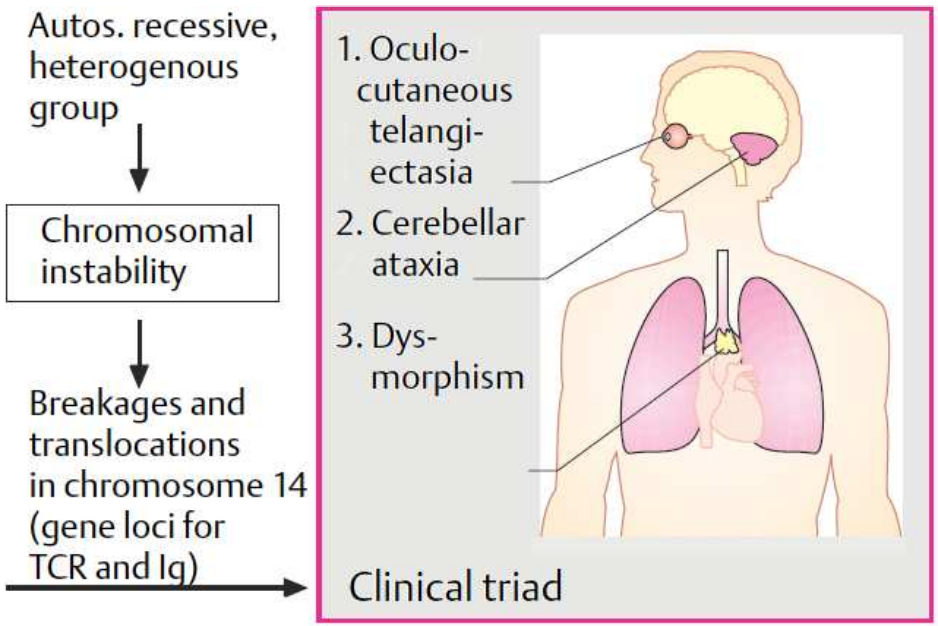


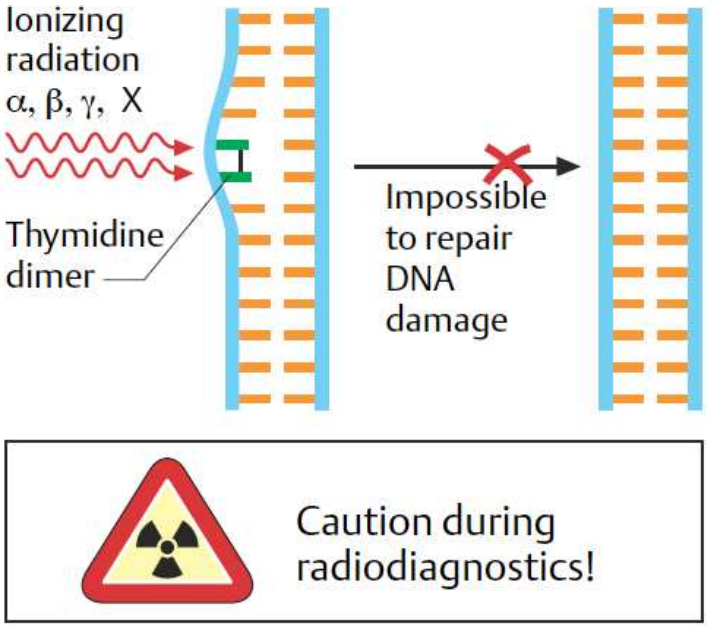


Ataxia teleangiectasia

COMBINED

- Def: heterogenous group of AR- inheredited 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 & reccurent infectious diseases (sinusitis, pulmonary infections) 2. cerebellar ataxia; oculocutaneous teleangiectasia

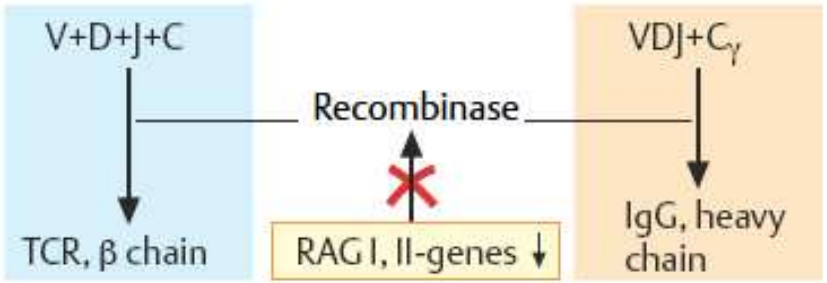


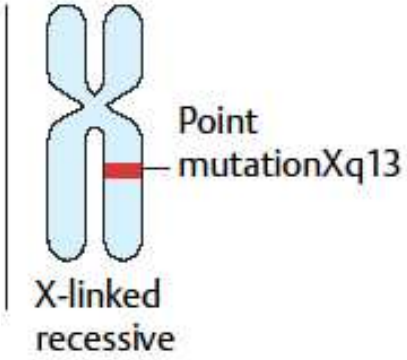


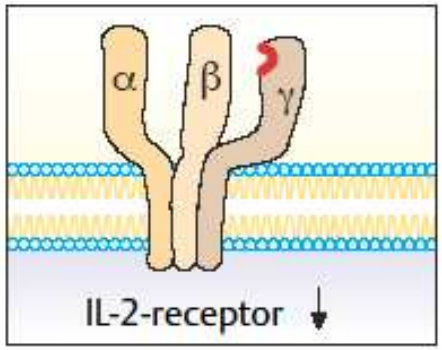
Severe combined immunodeficiency (SCID)

COMBINED

- **Def.:** group of inherited heterogenousdisorders 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,

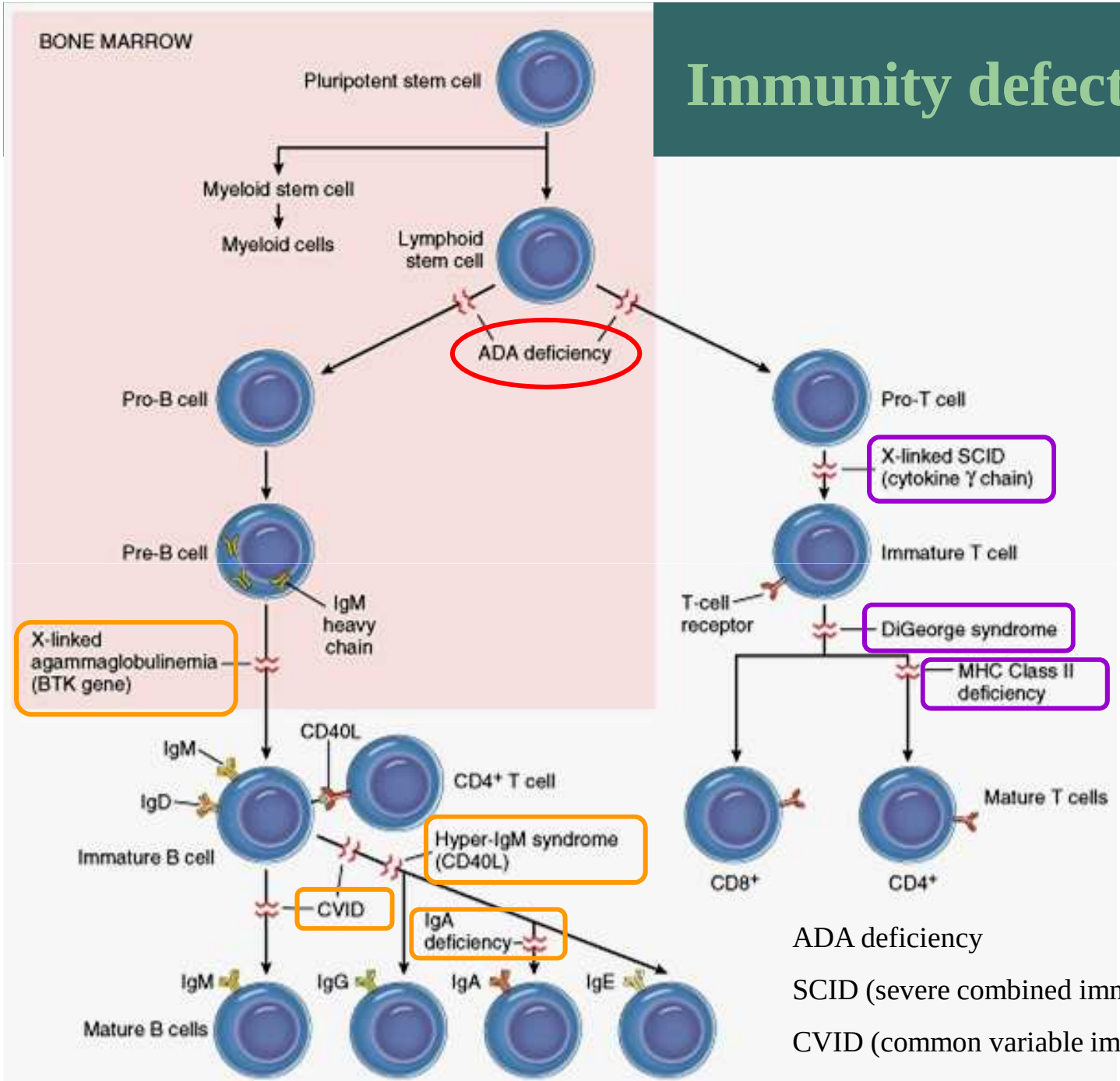






different defects -> similar outcome
(a) defect in Ig- structure
(b) defect in cytokine receptor
(c) defect in JAK-STAT signalling

Immunity defects - overview



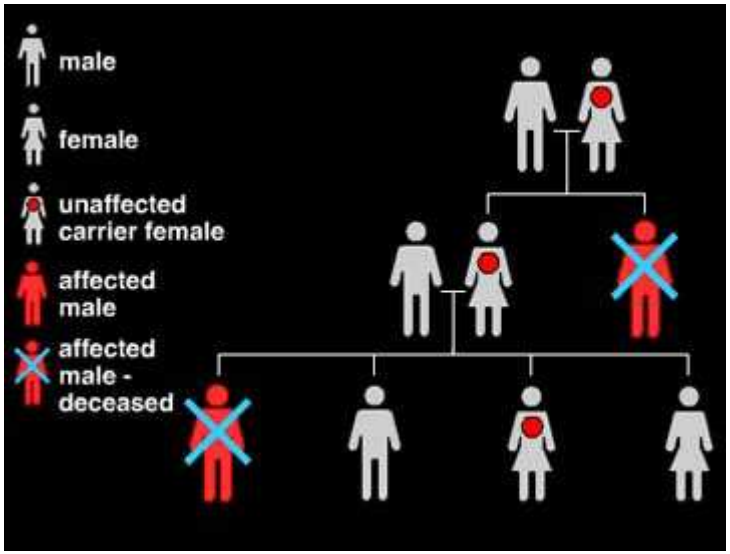
ADA deficiency

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



Clinical immunology **3**

Immunodeficiencies

Non-specific immunity failure (leucocytes, complement)

a) Defects in chemotaxia, attachment & diapedesis

b) Defects in phagocytosis & killing mechanisms

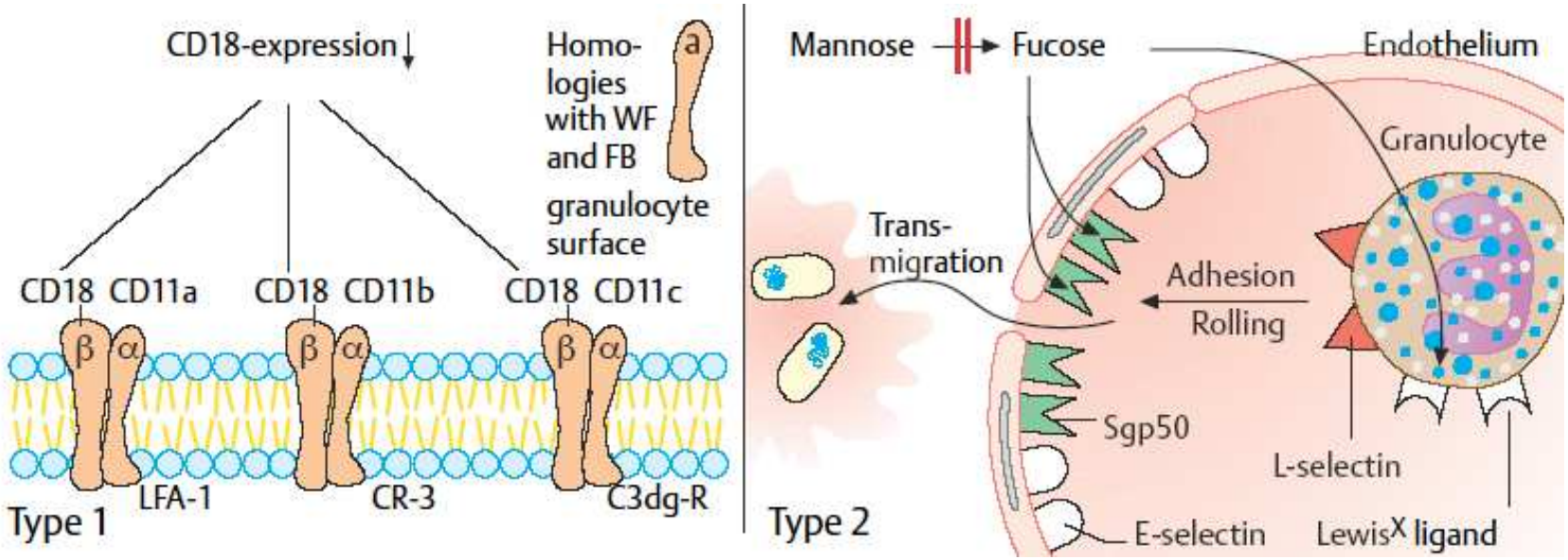
c) Defects in complement

Leukocyte adhesion deficiencies (LAD)

GRANULOCYTE

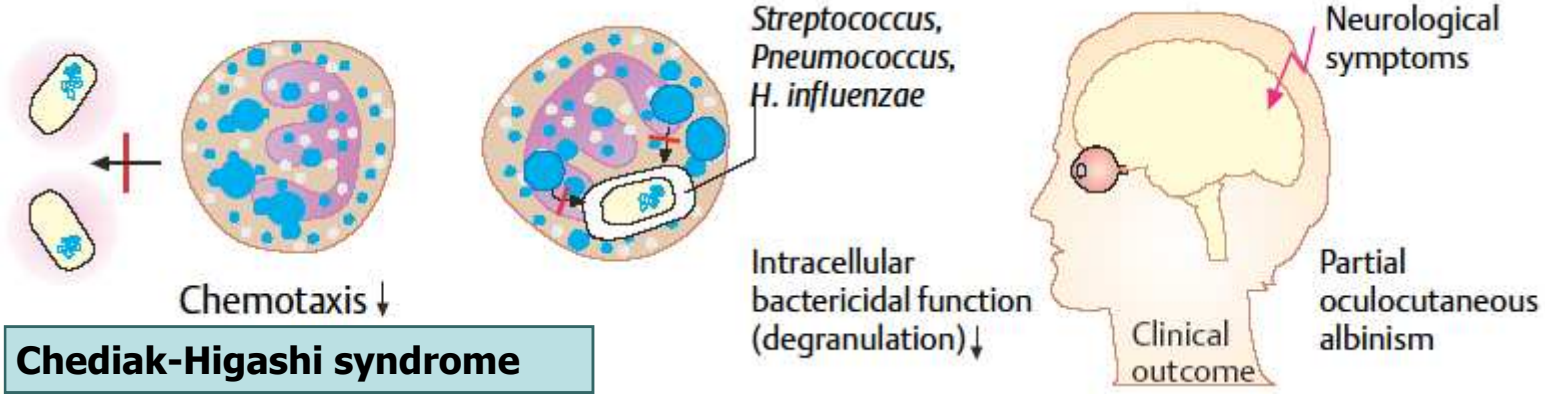
- **LAD 1 –** AR – inherited mutations in the ITGB2 (encodes **CD18** - protein present in several cell surface receptor complexes in leucocytes), including integrin (lymphocyte function-associated antigen 1; LFA-1), complement receptor 3 and 4 (CR-3, CR-4)
  - neutrophils unable to adhere to and migrate 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



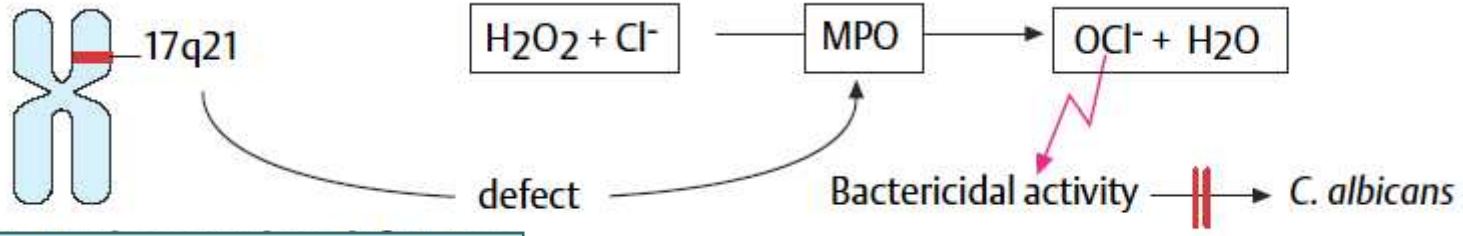
Chediak – Higashi syndrome
Myeloperoxidase deficiency

GRANULOCYTE



Chediak-Higashi syndrome

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



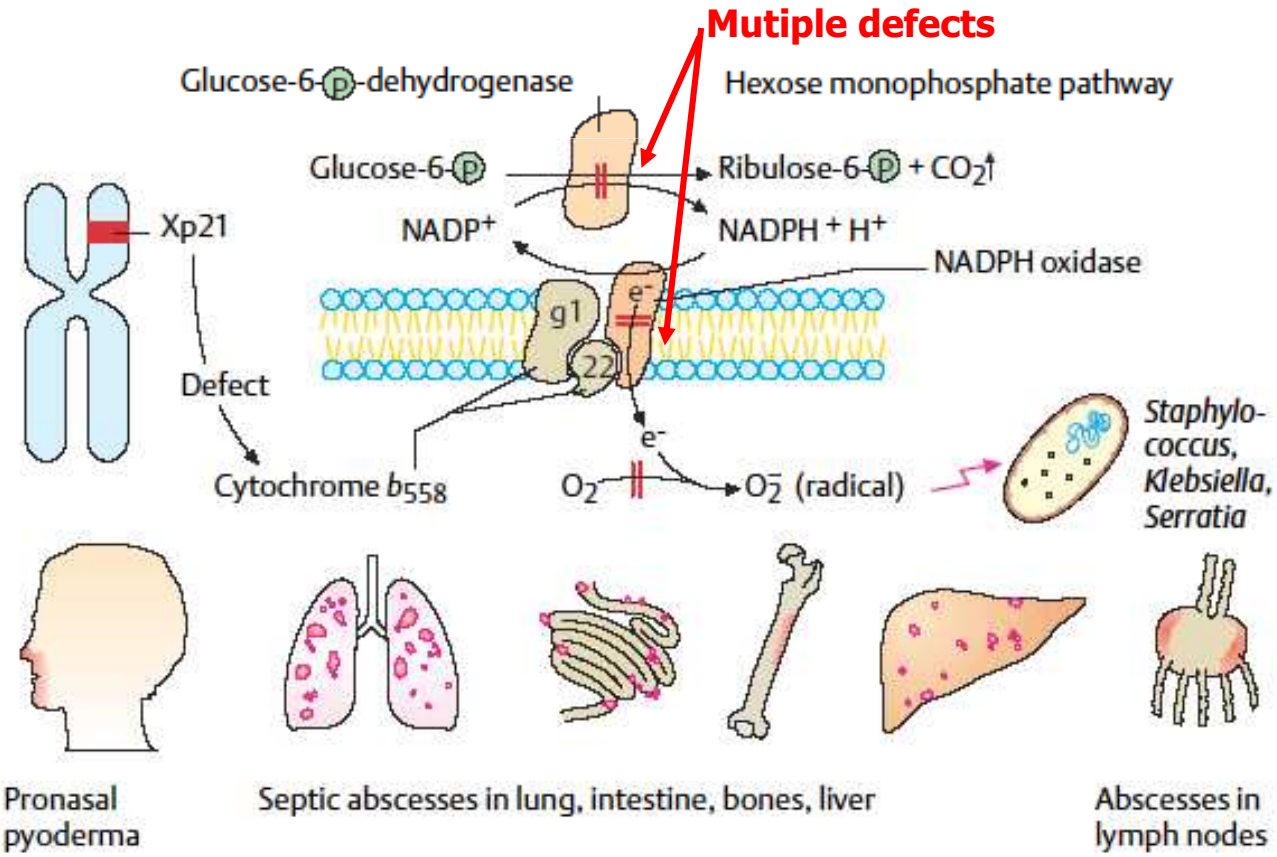
Myeloperoxidase deficiency

- MPO converts H_2O_2 + Cl into hypochlorous anion (OCl-) stored in specific granules
- reduced O2- dependent killing in granulocytes + monocytes
- **Sy:** repetitive infections, mainly **candidiosis**

Infantile septic granulomatosis (ISG) GRANULOCYTE

- Insufficient oxidative burst (production of oxygen radicals) in presence of normal diapedesis and phagocytosis
- **Etio:** a) lack of cytochrome *b*558 in granulocyte phagososmes (X-linked recessive); b) lack of G6PD; c) defect in NADPH oxidase; defective e^- trasport through membrane for $.O^-_2$ superoxid radical formation

- **Sy:** Repetitive **pyogenic infections** lymphadenitis; septic abscesses in organs (*Staphylococcus, Kebsiella, Serratia, Aspergilus)*
- Catalase – negative strains (staphylococcus, haemophillus) can be killed by H_2O_2



Complement deficiencies

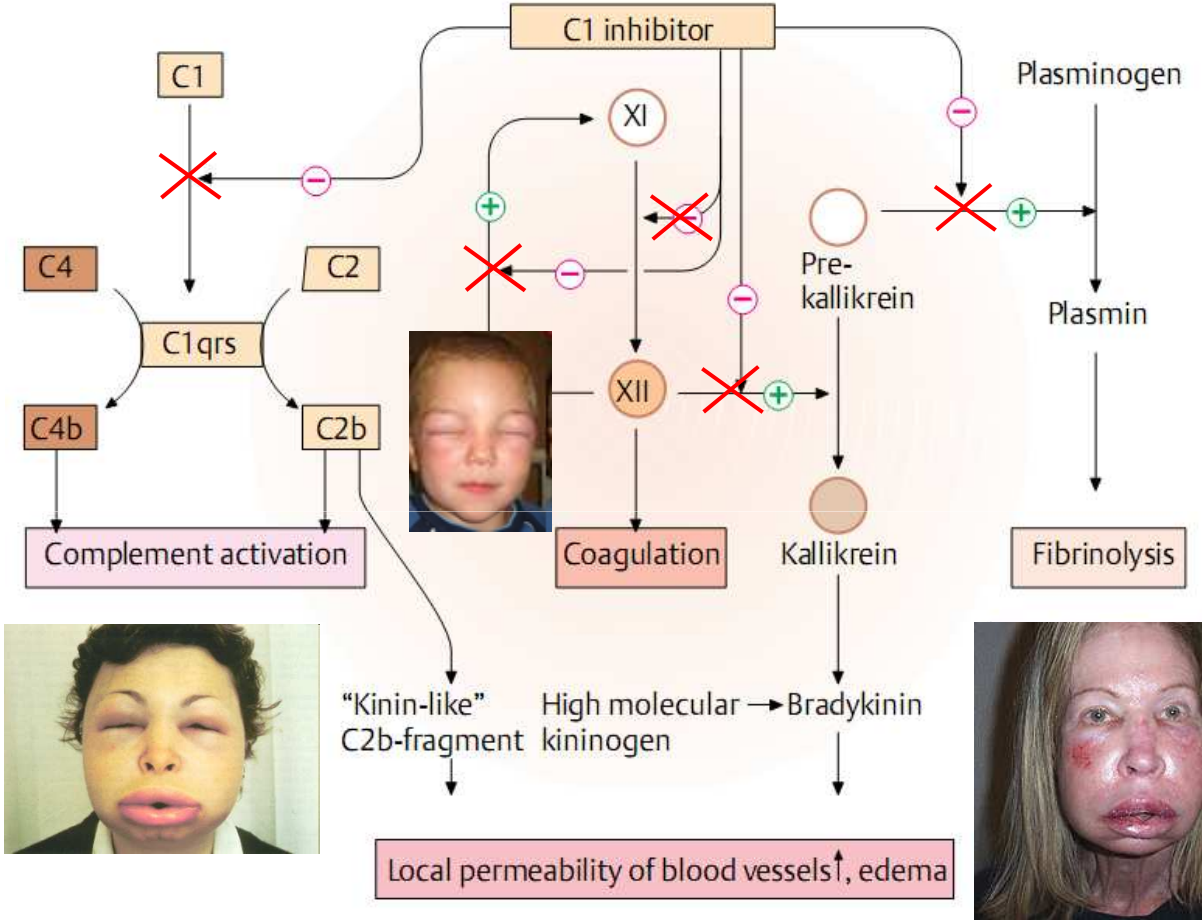
COMPLEMENT

Complement Deficiencies	
Complement proteins	**Deficiency-associated manifestations**
C1-C4	SLE, pyogenic infections (e.g., pneumococcal sepsis)
C3, FH, F1	Pyogenic infections, glomerulonephritis
C8	Infections, especially by *Neisseria* spp. (gonococci, meningococci); sclerodactyly
CR3, CR4, LFA-1	Gingivitis, delayed deciduation of the umbilical cord, recurrent sepsis

C1 inhibitor deficiency-hereditary angioedema

COMPLEMENT

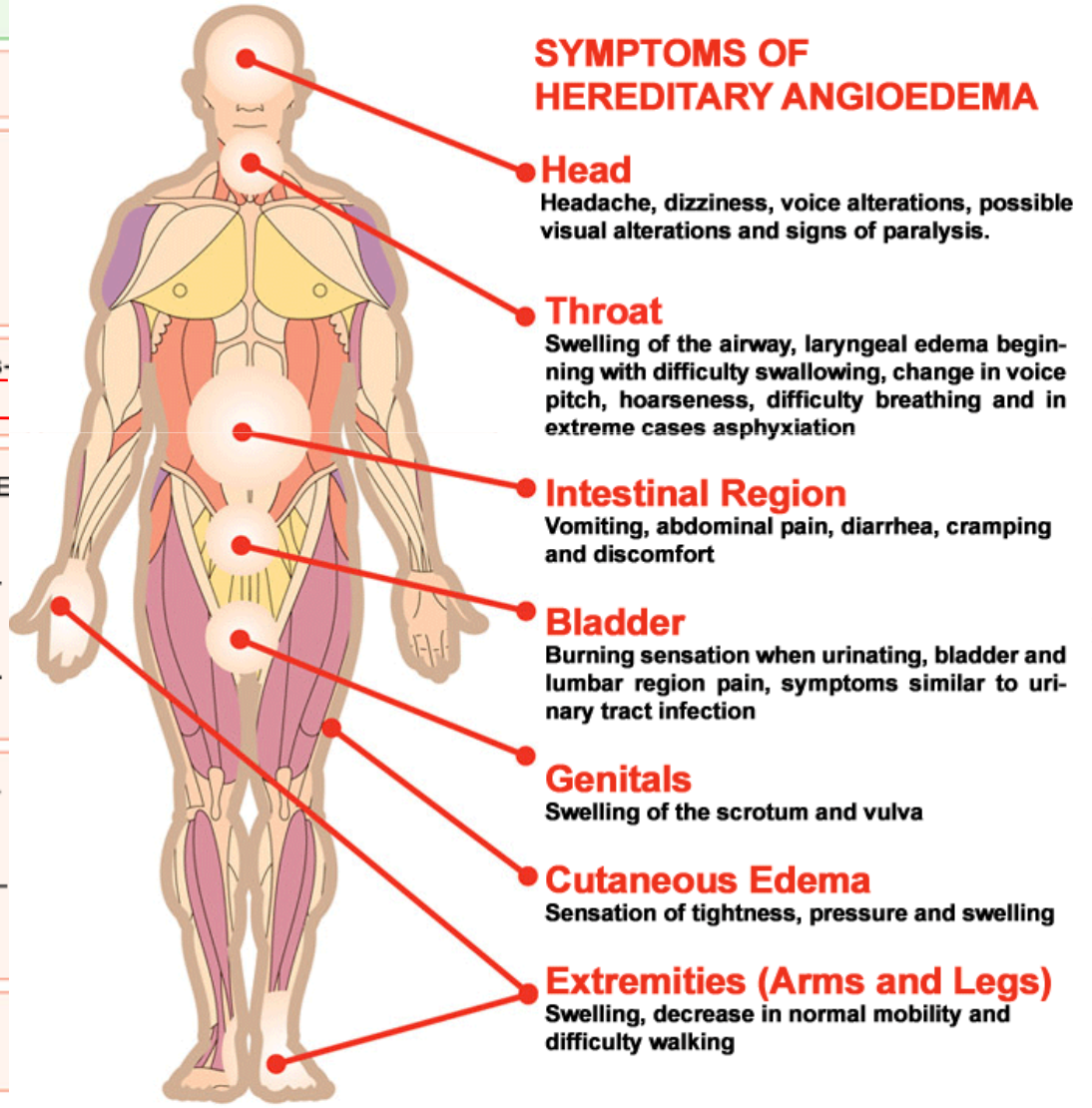
- a) AD - linked hereditary, b) acquired form (AAE) in cancer of the lymphatic system or as autoimmune diseases.
- C1 inhibitor (antiprotease) is degradated very quickly; can not block proteases that perpetuate vascular changes of inflammation
- **Sy:** recurrent acute angio-edematous swelling (hardened; white or pinkish rash) of the skin and/or mucosae) without urticaria asting 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

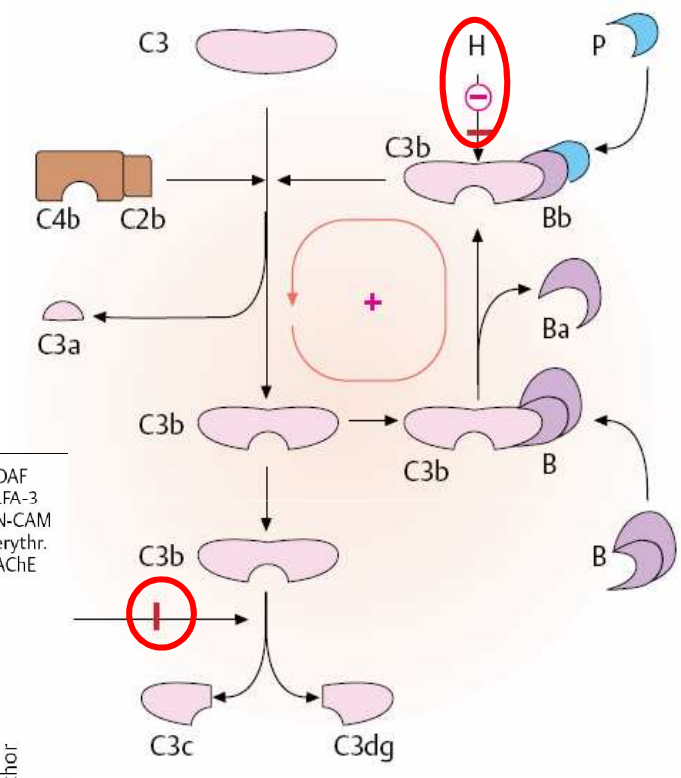
Hereditary angioedemas – diff. diagnostics

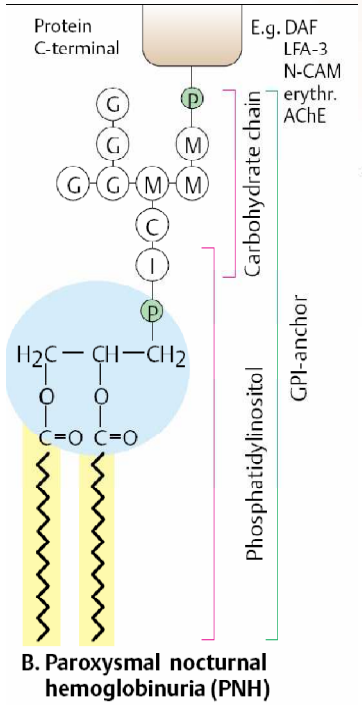
Signs & Symptoms	Hereditary Angioedema (due to C1-INH Deficiency)
Family history	Generally other family members are affected
Clinical symptoms	Cutaneous edemas Painful abdominal attacks Laryngeal edema (rare, life threatening)
Affected age groups	First signs in childhood and adolescence, with frequent 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



Positive feedback loop syndrome

- strenghtened 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, mesangioproiliferative glomerulonephritis, recurrent pyogenic infections



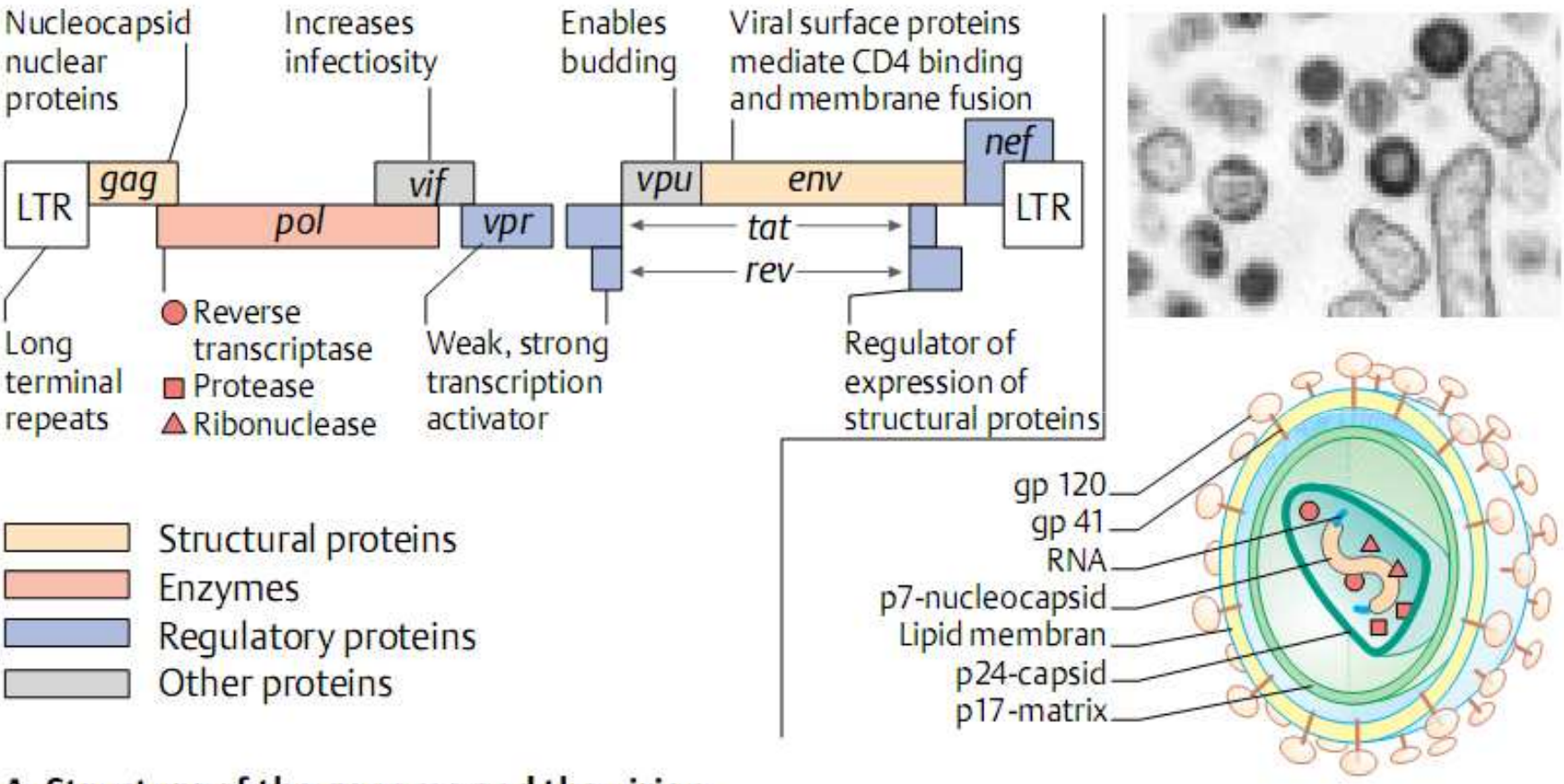


B. Paroxysmal nocturnal hemoglobinuria (PNH)

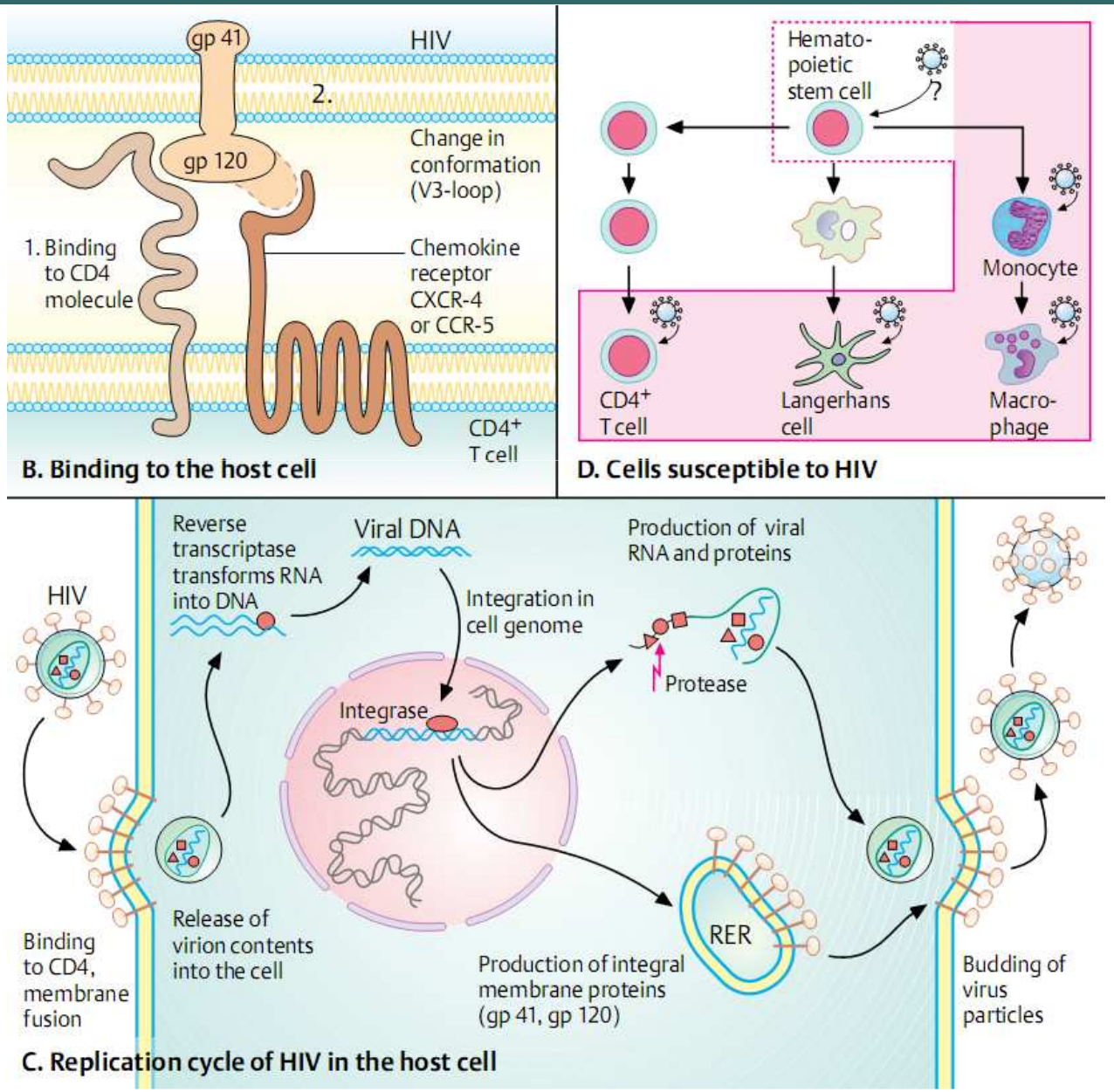
Clinical immunology **4**

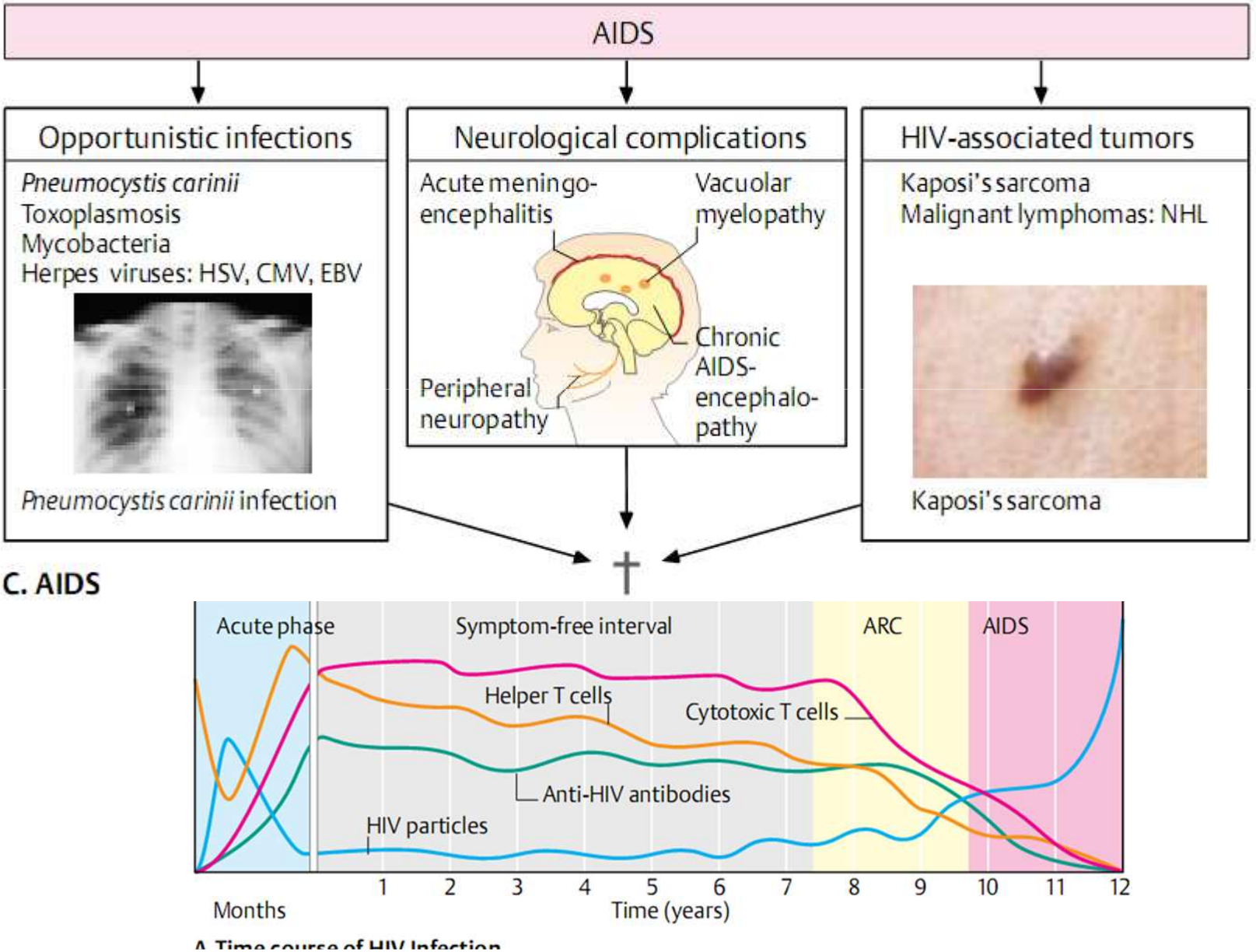
Acquired immunodeficiency syndrome (AIDS)

HIV virus



A. Structure of the genome and the virion


gp 41
HIV
2.
gp 120
Change in conformation (V3-loop)
1. Binding to CD4 molecule
Chemokine receptor CXCR-4 or CCR-5
CD4+ T cell
B. Binding to the host cell
Hemato-poietic stem cell
?
Monocyte
CD4+ T cell
Langerhans cell
Macro-phage
D. Cells susceptible to HIV
HIV
Reverse transcriptase transforms RNA into DNA
Viral DNA
Integration in cell genome
Integrase
Production of viral RNA and proteins
Protease
Binding to CD4, membrane fusion
Release of virion contents into the cell
RER
Production of integral membrane proteins (gp 41, gp 120)
Budding of virus particles
C. Replication cycle of HIV in the host cell


AIDS
Opportunistic infections
Pneumocystis carinii
Toxoplasmosis
Mycobacteria
Herpes viruses: HSV, CMV, EBV
Pneumocystis carinii infection
Neurological complications
Acute meningo-encephalitis
Vacuolar myelopathy
Chronic AIDS-encephalo-pathy
Peripheral neuropathy
HIV-associated tumors
Kaposi's sarcoma
Malignant lymphomas: NHL
Kaposi's sarcoma
C. AIDS
Acute phase
Symptom-free interval
ARC
AIDS
Helper T cells
Cytotoxic T cells
Anti-HIV antibodies
HIV particles
1 2 3 4 5 6 7 8 9 10 11 12
Months
Time (years)