UNIVERSITATEA DE STAT DE MEDICINĂ
ȘI FARMACIE „NICOLAE TESTEMIȚANU”
DIN REPUBLICA MOLDOVA

Immunodeficiency (primary and secondary)

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2023

Immunodeficiency

Errors of Immunity = functional/structural caused by defects in various components of the immune system (of one or more components of the immune system (humoral/cellular/mixt)

Primary (inborn errors of the immune system, genetic defect) - caused by intrinsic or congenital defects

Secondary (infections, systemic CS or other immunosuppressive drugs, malnutrition, infections, etc.)

Immunodeficiency

- Primary immunodeficiencies (PID) - inborn (inherited) errors of the immune system;
- genetic diseases.
- Around 416 IDPs are known (International Union of Immunological Societies, 2020)
- In 384 of these, the gene responsible for the disease has been identified;

- **Antibody deficiencies are the most common IDP.**
- Ex. IgA deficiency, common variable immunodeficiency (CVID) and X-linked agamaglobulinaemia

- Biological marker of humoral IDP – hypogammaglobulinaemia
- Biological marker of cellular IDP - lymphopenia

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

Quinn et al. Allergy, Asthma & Clinical Immunology (2022)

Classification of primary immunodeficiencies

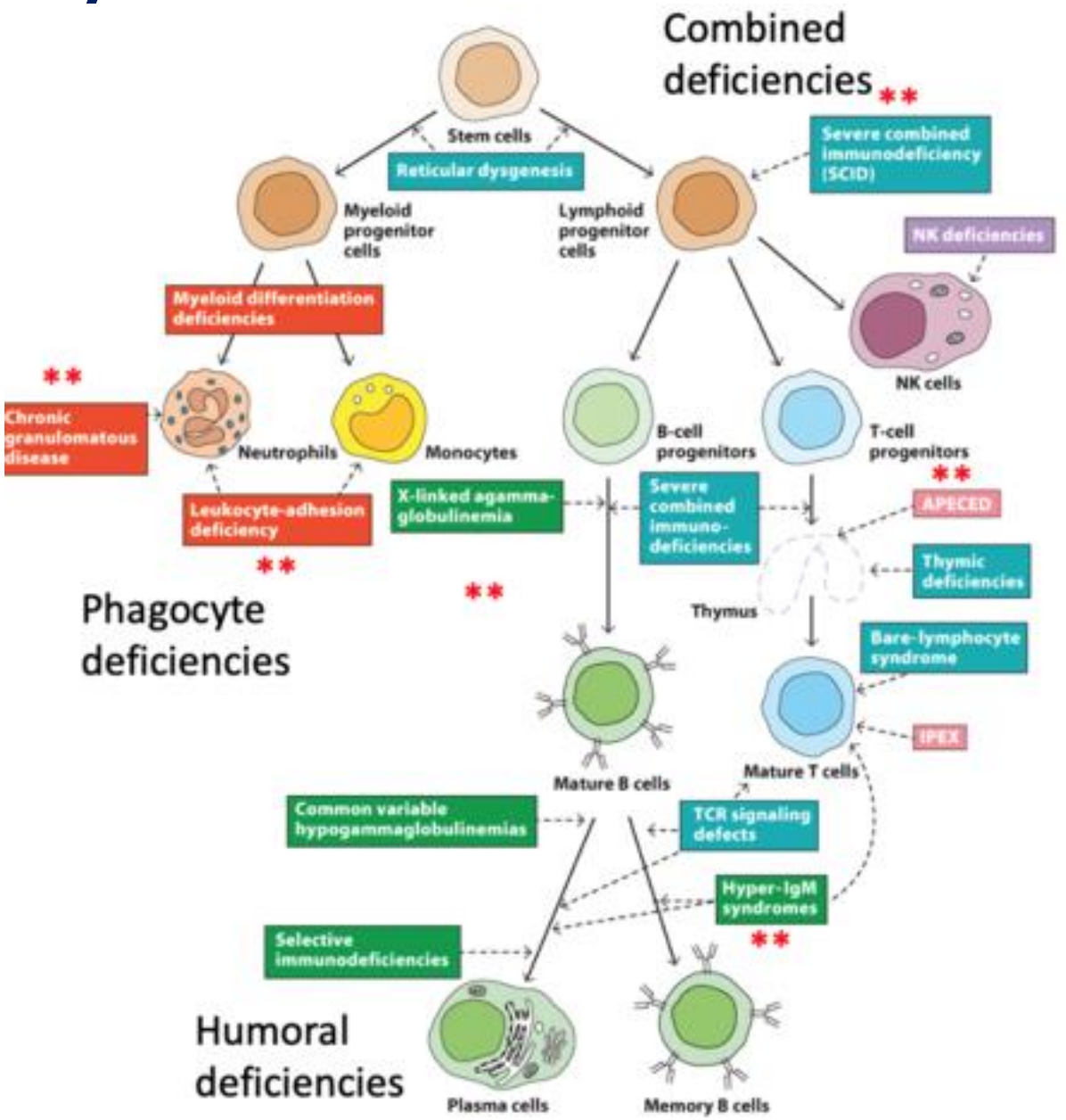
A. Stem cell defects

B. Defects in T cells

C. Defects in B cells

D. Defects in phagocytes and NK cells

E. Defects in complement system



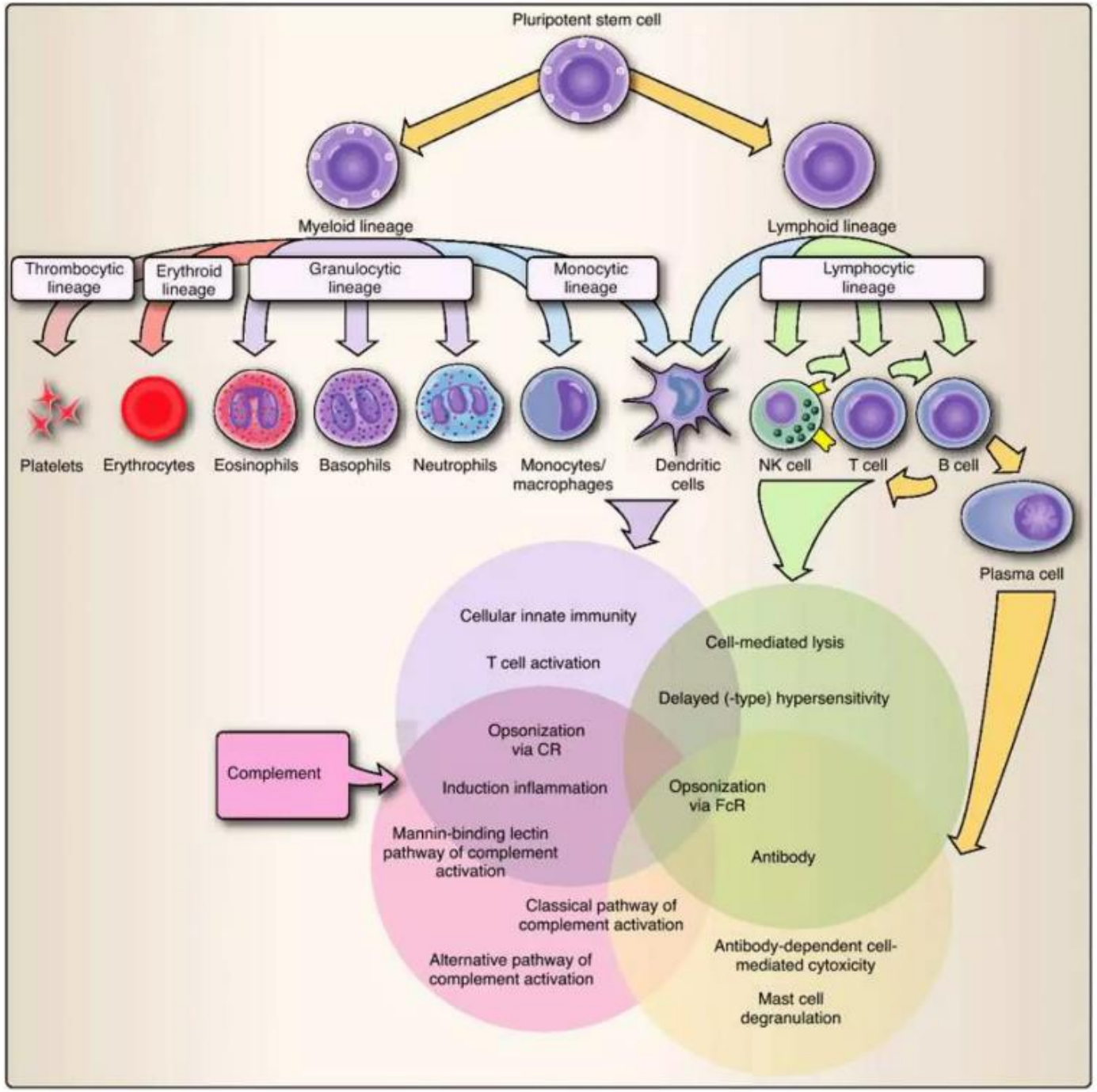
A. Stem cell defects

- Hematopoietic stem cells and lineages.

- Pluripotent stem cells in the bone marrow give rise to all five hematopoietic cell lineages:

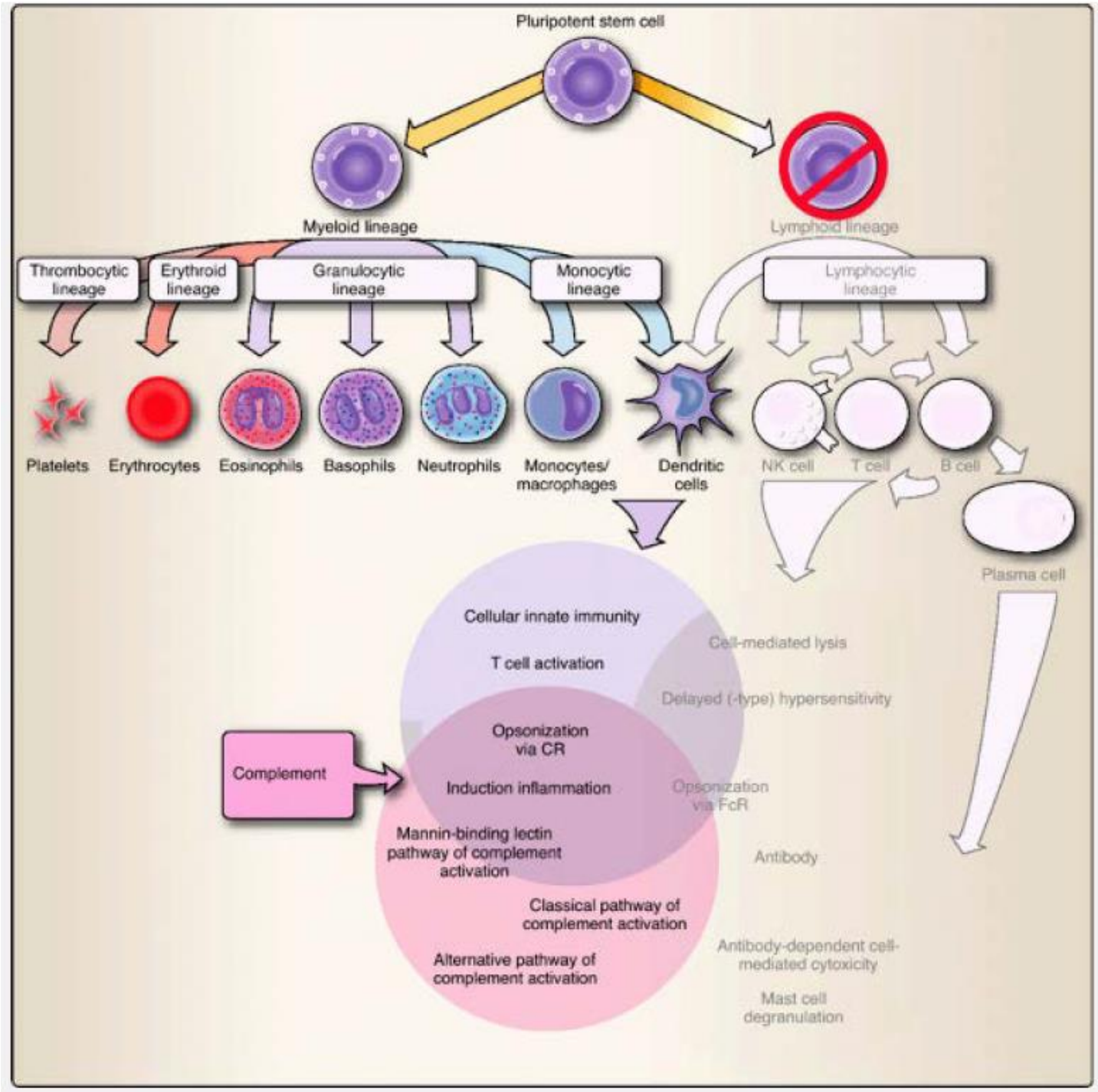
- lymphocytes,
- thrombocytes,
- monocytes,
- granulocytes,
- erythrocytes.

- both the lymphocytic and monocytic lineages produce dendritic cells.



A. Stem cell defects

- Effects of lymphoid cell lineage deficiencies.
- Defects in the lineage producing both T and B lymphocytes impair the development and/or functionality of both types of lymphocytes.
- Defects in lymphoid stem cells giving rise to both the T and B cell lineages result in defective function of both cell types.
- Individual defects may result in abnormal T and B cell numbers or functions or both.

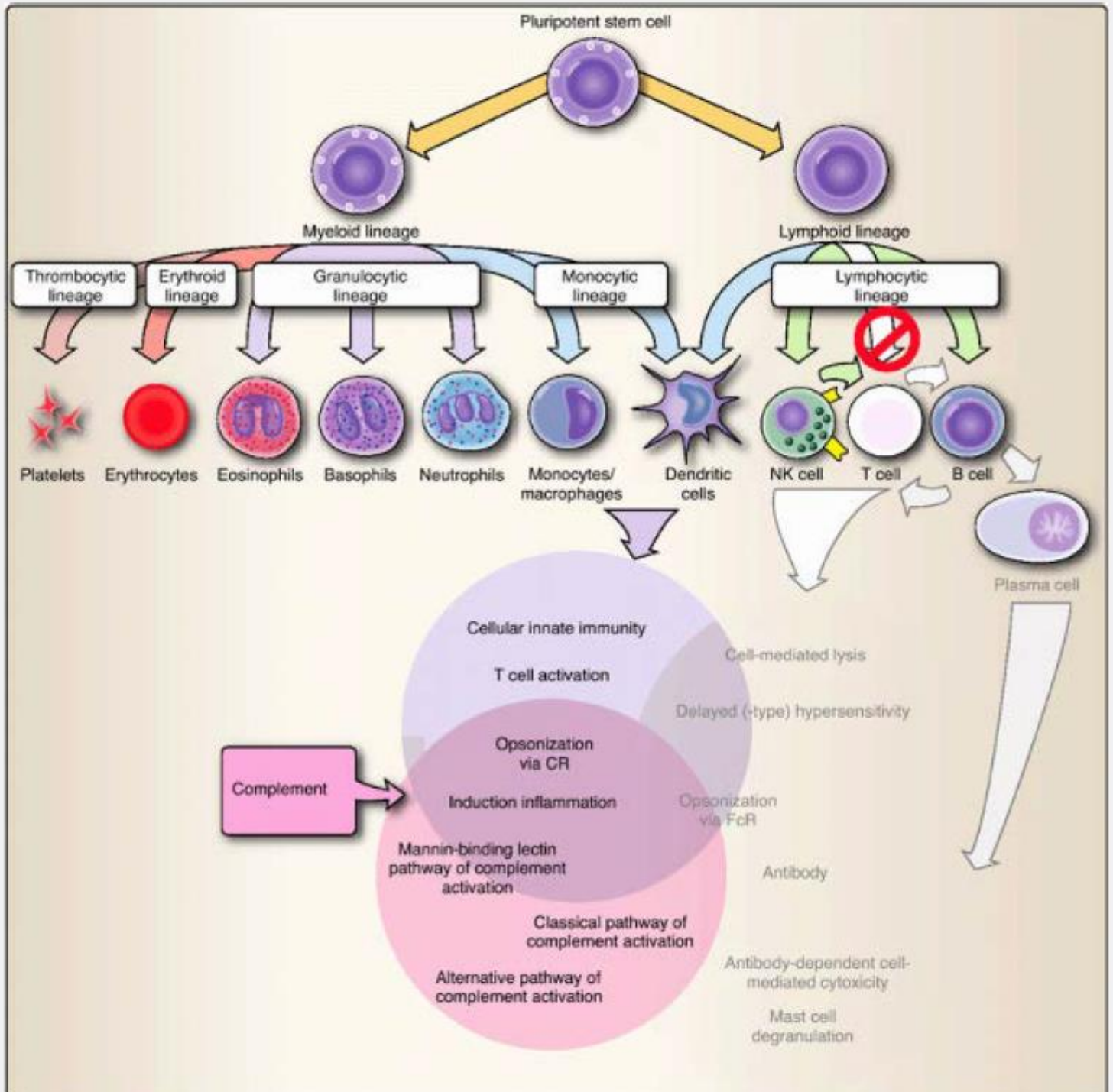


A. Stem cell defects

Disease	Inheritance	Gene	Chromosome	Consequences
Adenosine deaminase (ADA) deficiency	Autosomal-recessive	*ADA* (adenosine deaminase)	20	Very susceptible to infection; impaired purine metabolism; T- and B-cell numbers and functions decreased because of toxic metabolites; immunoglobulin levels decreased
Immunodeficiency with ataxia telangiectasia	Autosomal-recessive	*ATM* (ataxia telangiectasia mutated)	11	Increased susceptibility to infection; frequent sinopulmonary infections; DNA repair affected and variable signs, including ataxia and telangiectasia (problems with balance and widened small capillaries); occurs at varying ages and in varying functions; T-cell numbers and functions and immunoglobulin levels (especially IgG, IgA, and IgE) may decrease; B-cell numbers may be normal; autoantibodies and chromosomal abnormalities are frequently found
Purine nucleoside phosphorylase deficiency	Autosomal-recessive	*NP* (nucleoside phosphorylase)	14	Increased susceptibility to infection; impaired purine metabolism; declining T-cell numbers over time (more susceptible than B cells to accumulated toxic metabolites); declining immunoglobulin levels because of decreased T-cell help
Severe combined immune deficiency (SCID)	Autosomal-recessive	*RAG1* and/or *RAG2* (recombination-activating genes)	11	Increased susceptibility to infection; unable to rearrange DNA to form variable regions of immunoglobulins and T-cell receptors; T- and B-lymphocyte numbers/functions reduced or absent; immunoglobulin levels reduced or absent
	X-linked recessive	*IL2RG* (common cytokine receptor γ chain, a component of the receptor complexes for IL-2, IL-4, IL-7, IL-9, and IL-15)	X	Multiple effects because common γ chain is a component of receptors for several cytokines; increased susceptibility to infection; T-cell numbers and immunoglobulin levels decreased; B-cell numbers normal or increased
	Autosomal-recessive	*JAK3* (Janus kinase 3)	19	Increased susceptibility to infection; defective intracellular signaling; T-cell numbers and immunoglobulin levels decreased; B-cell numbers normal or increased
Wiskott–Aldrich syndrome	X-linked recessive	WAS (Wiskott–Aldrich syndrome)	X	Increased susceptibility to infection, especially by *Staphylococcus aureus*, develops during infancy and early childhood; T- and B-cell numbers and functions reduced, as are immunoglobulin levels; platelets abnormal and reduced in number

B. Defects in T cells

- Primary immune deficiencies intrinsic to T cells result in abnormal T cell numbers and/or functions
- Defective T cells not only reduce cell mediated immune responsiveness, but also often reduce B cell functions because of the regulatory role for T cells in B cell activation.
- Many T cell defects also cause abnormalities in B cell numbers and immunoglobulin production



B. Defects in T cells

Disease	Inheritance	Gene	Chromosome	Consequences
CD3 deficiency	Autosomal-recessive	*CD3G* or *CD3E*	11	Increased susceptibility to infection; defects in CD3γ (CD3G) or CD3ε (CD3E) proteins; variable effects on T-cell functions
DiGeorge syndrome	Autosomal-dominant or spontaneous	Unknown defects in embryonic thymic development	22 (when genetic)	Increased susceptibility to infections; T-cell numbers and functions intrinsically normal but reduced and variable owing to abnormal development of thymus from third and fourth branchial arches; variable immunoglobulin levels; deletions in chromosome 22 frequently seen; often accompanied by other defects (e.g., facial features, palate, aorta, and parathyroid glands and calcium metabolism)
MHC class II deficiencies (bare lymphocyte syndrome)	Autosomal-recessive	*CIITA* or *RFX5*	16 or 1	Increased susceptibility to infection; defective intracellular signaling; $CD4^+$ T cell numbers reduced; immunoglobulin levels decreased owing to defective T-cell help
Purine nucleoside phosphorylase deficiency	Autosomal-recessive	NP (nucleoside phosphorylase)	14	Increased susceptibility to infection; impaired purine metabolism; T-cell numbers decline over time (more susceptible than B cells to accumulated toxic metabolites); immunoglobulin levels decline because of decreased T-cell help
Transporter associated with antigen presentation (TAP) -1 or -2 deficiency	Autosomal-recessive	*TAP1* or *TAP2*	6	Increased susceptibility to viral infections and to some intracellular bacteria; decreased MHC I expression and antigen presentation; $CD8^+$ T cell numbers and functions decreased
ZAP-70 deficiency	Autosomal-recessive	*ZAP70* (ζ chain-associated protein kinase)	2	Recurrent severe infections; defective signaling from TCR; $CD8^+$ T cells absent; $CD4^+$ T cells present in normal numbers but nonfunctional

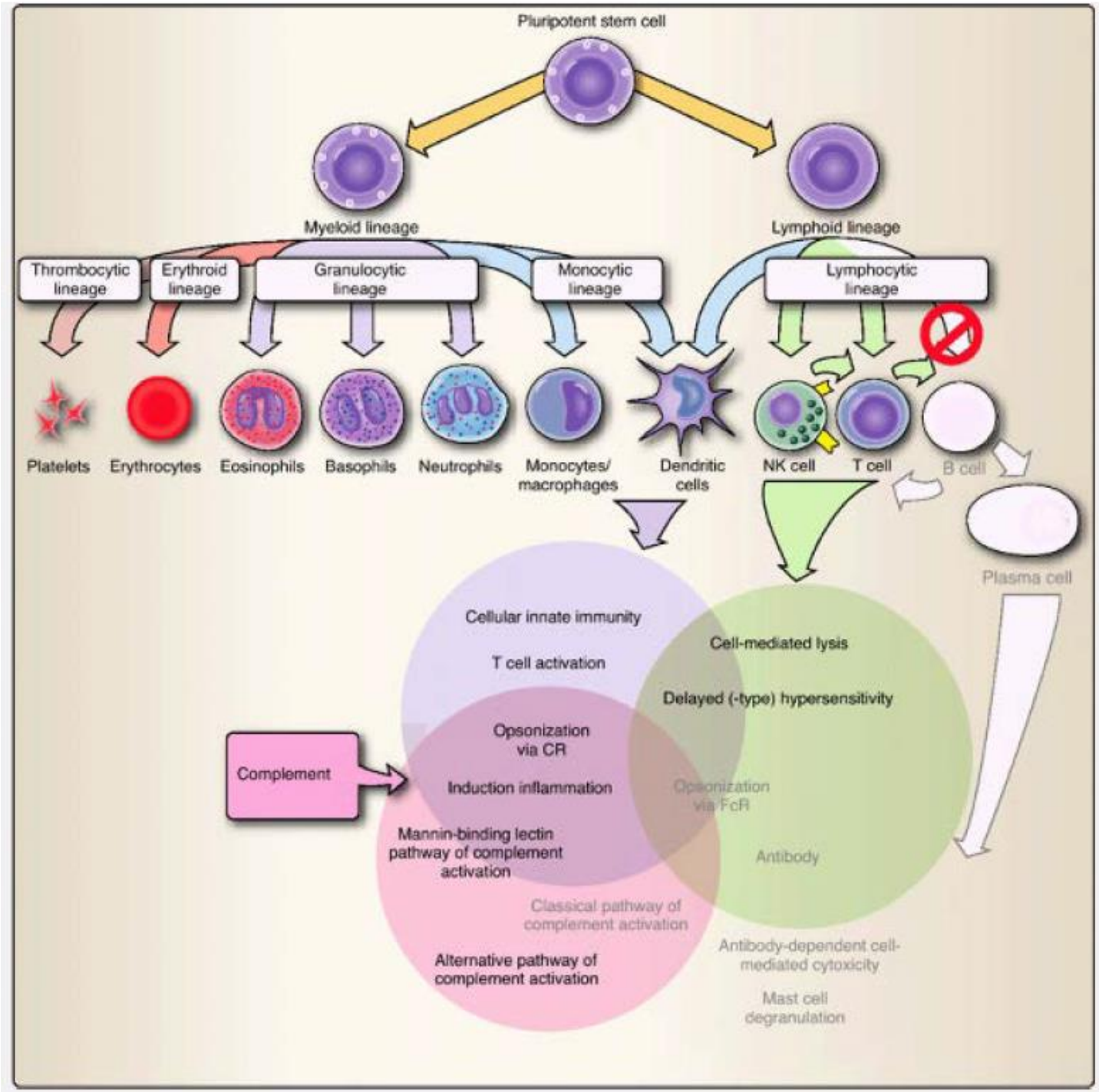
C. Defects in B cells

- B cell defects are responsible for the majority (more than 80%) of human immunodeficiency diseases

- Defective B cells affect humoral responses
- ↓ B cell numbers and/or functions,
- ↓ immunoglobulin production

- Some B cell deficiencies are characterized by abnormal production of all immunoglobulin isotypes, while others affect only one or a few.

- T cell numbers and functions are typically normal



C. Defects in B cells

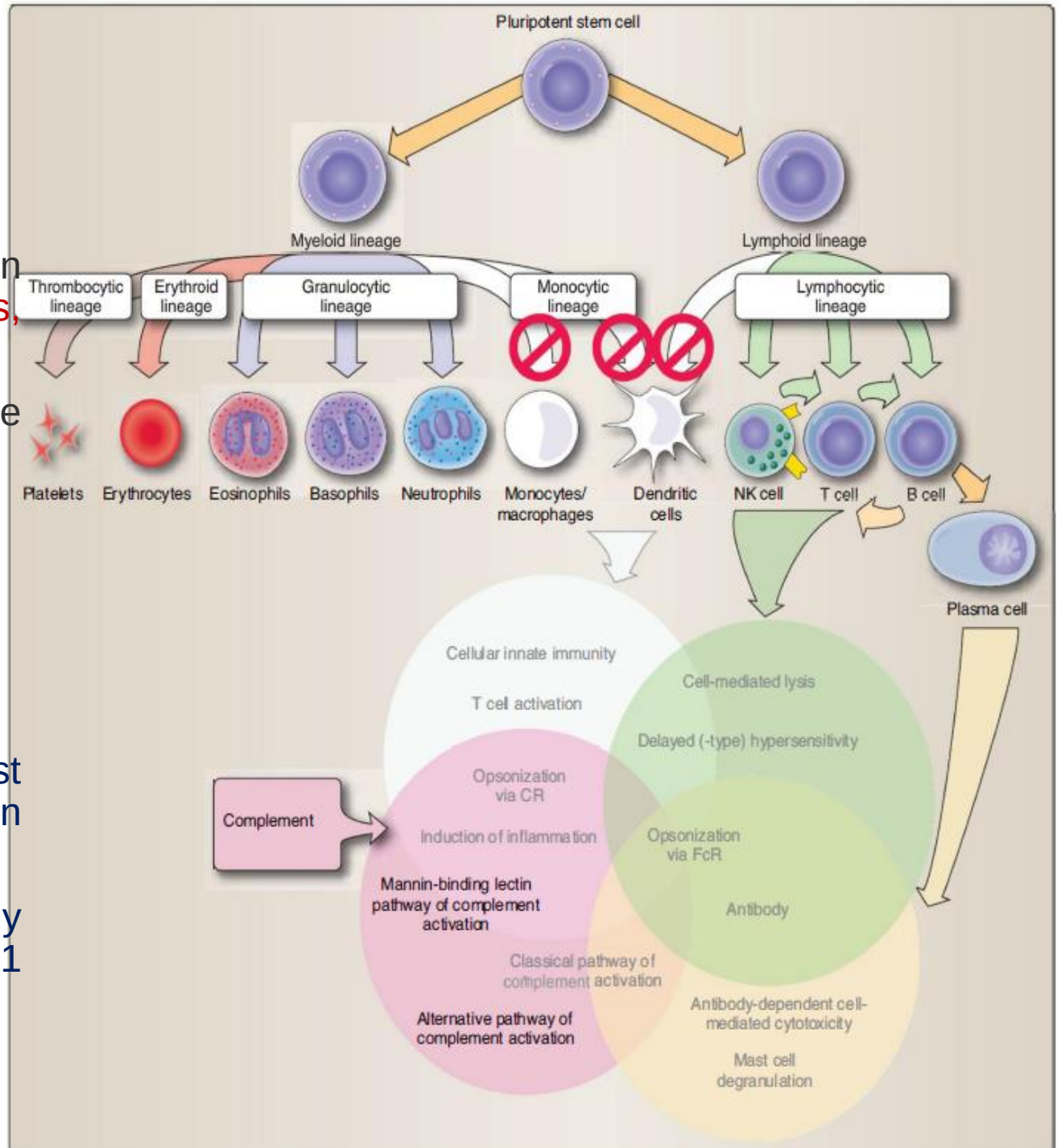
Disease	Inheritance	Gene Locus	Chromosome	Consequences
Autosomal-recessive agammaglobulinemia	Autosomal-recessive	Various genes involved in early differentiation	Various	Increased susceptibility to infection; failure in early differentiation of B cells
X-linked (Bruton) agammaglobulinemia	X-linked recessive	*BTK* (Bruton agammaglobulinemia tyrosine kinase)	X	Increased susceptibility to infection; increased susceptibility to encapsulated bacteria (e.g., *Haemophilus influenzae*, *staphylococci*, and *streptococci*); drastic decrease in B-cell numbers and immunoglobulin levels
Common variable immunodeficiency (CVI or CVID)	Multiple forms	Unknown	?	Increased susceptibility to pyogenic infection; variable symptoms; varying isotypes (or combinations of isotypes) reduced or absent
Immunodeficiency with hyper-IgM	X-linked recessive Autosomal-recessive	*CD40LG* (CD40 ligand, CD154)	X	Increased susceptibility to pyogenic infection; inability of B cells to undergo isotype switching or somatic hypermutation; elevated IgM with decreased/absent IgG, IgA, and IgE; 70% of cases because of X-linked defect
Ig heavy chain gene deletions	Autosomal-recessive	Heavy chain constant genes	14	Increased susceptibility t o infection (patients with IgG1 deficiency have increased susceptibility to pyogenic infections, whereas those with IgG2 or IgG3 are susceptible to encapsulated bacteria); various immunoglobulin isotypes absent (dependent on the affected heavy chain gene); IgG most frequently affected; B-cell numbers frequently reduced
Kappa chain deficiency	Autosomal-recessive	κ chain genes	2	Decreased or absent immunoglobulin containing κ chains; little or no effect on susceptibility to infection
Selective IgA deficiency	Multiple forms	Multiple genes	Various	Although patients with this deficiency display no increase in infections, an increased susceptibility to infections may be seen in some, especially recurrent pyogenic bacterial infections in patients also deficient in IgG2; IgA-expressing B cells decreased or absent; serum IgA reduced and often accompanied by IgG subclass deficiency; frequent allergic or autoimmune disorders; frequency of one to two per thousand individuals makes it one of the most common immune deficiency diseases

D. Defects in phagocytes and NK cells

- Immune deficiency may also result from defects in nonlymphocytic cells such as phagocytes, neutrophils, and NK cells.
- Phagocytes - key roles in innate and adaptive immune responses.
- Defects affect two major functions of these cells:

- ability to kill microbes
- interactions with other cell types

- Defects in phagocytic cells reduce the ability to ingest and degrade microbes and to engage in antigen presentation to T cells.
- Defective NK cells have the ability to kill virally infected cells and participate in development of Th1 immune responses.



D. Defects in phagocytes and NK cells

Disease	Inheritance	Gene Locus	Chromosome	Consequences
Chediak–Higashi syndrome	Autosomal-recessive	*LYST* (lysosomal trafficking regulator; also called CHS1)	1	Increased susceptibility to infection by pyogenic bacteria; defective fusion of lysosomes and phagosomes because of defect in organelle membranes; reduced ability to kill ingested microbes; decreased NK and T-cell functions; frequent albinism of eyes and skin and other defects of organelle membranes; giant granules in neutrophils and other cells
Chronic granulomatous disease (CGD)	X-linked recessive	*CYBB* (β chain of cytochrome b; also called gp91phox)	X	Increased susceptibility to infection, especially *Staphylococcus aureus*, *Salmonella enteric*, *S. typhimurium*, *Serratia marcescens*; macrophages and neutrophils affected; unable to produce superoxide metabolites
	Autosomal-recessive	*NCF1* (p47phox)	7	Increased susceptibility to infection; unable to produce superoxide metabolites for killing of ingested microbes; macrophages and neutrophils affected; NCF1 and NCF2 encode components of the NADPH oxidase complex; CYBA encodes the α chain of cytochrome b
		NCF2 (p67phox)	1	
		CYBA (p22phox)	16	
IFN-γ receptor deficiency	Autosomal-recessive	*IFNGR1* (IFN-γ receptor)	6	High susceptibility to mycobacterial infections; macrophages, neutrophils, NK cells, and Th1 cells are affected
Leukocyte adhesion defect 1 (LAD-1)	Autosomal-recessive	*ITGB2* (also known as CD18)	21	Increased susceptibility to recurrent infection by bacteria; frequent nonresolving abscesses; defective chemotaxis and adherence to endothelial surfaces by macrophages, neutrophils, and NK cells
Leukocyte adhesion defect 2 (LAD-2)	Autosomal-recessive	*GDP-fucose transporter 1*	11	Increased susceptibility to recurrent infection by bacteria and nonresolving abscesses; impaired synthesis of CD15s, a carbohydrate adhesion molecule; defects in ability of leukocytes to adhere to endothelial surfaces; reduced ability of leukocytes to move from vasculature into tissues; also causes Bombay blood group phenotype

E. Defects in the complement system

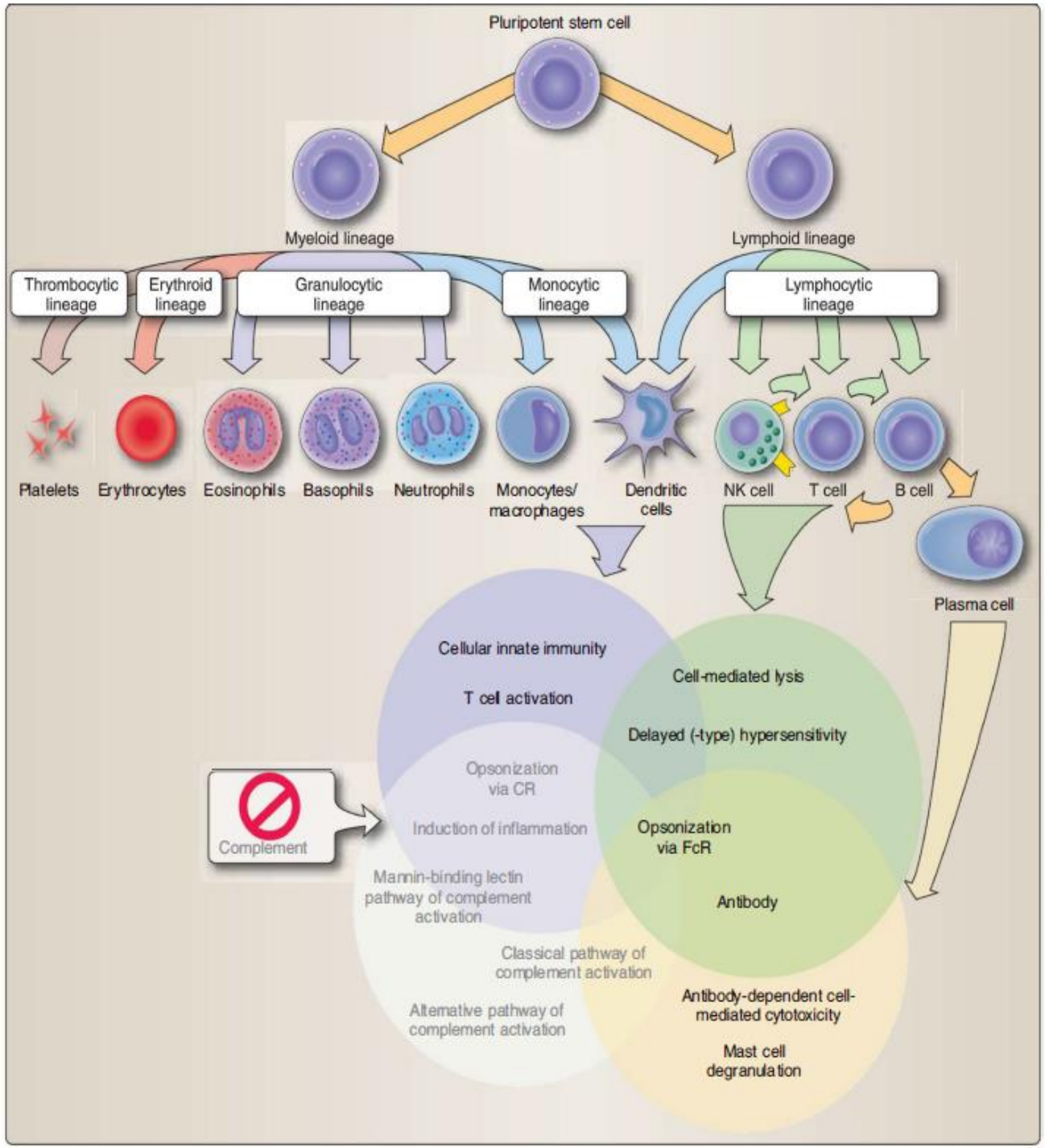
- Affect innate and adaptive immune responses

- Increase susceptibility to infection
- Increase risk of autoimmune disorders

- Defects in the classical pathway (except C3) are not associated with significantly increased susceptibility to infection except for those caused by encapsulated bacteria.

- In these infections, antibodies, complement, and neutrophils are all required simultaneously to opsonize and kill these bacteria.

- C3 deficiency results in severe problems with recurrent infection and with immune complex-mediated disease because of the central position of C3 in all three of the complement activation pathways.



E. Defects in the complement system

Disease	Inheritance	Gene Locus	Chromosome	Consequences
C1q, C1r deficiency	Autosomal-recessive	*C1QA*, *C1QB*, *C1QC* (A, B, and C chains of C1q)	1	Increased incidence of infections; systemic lupus erythematosus (SLE)-like syndromes (type III hypersensitivities; see Chapter 8); impaired removal of immune complexes
		C1R or *C1S* (C1r and C1s)	12	
C2 deficiency	Autosomal-recessive	*C2*	6	SLE-like syndromes; vasculitis; impaired removal of immune complexes
C3 deficiency	Autosomal-recessive	*C3*	19	Recurrent pyogenic infections; impaired opsonization
C4 deficiency	Autosomal-recessive	*C4*	6	Increased incidence of infections; SLE-like syndromes; impaired removal of immune complexes
C5, C6, C7 deficiency	Autosomal-recessive	*C5*, *C6*, or *C7*	9, 5, or 5	Increased susceptibility to *Neisseria*; unable to form membrane attack complex; SLE-like syndromes
C8 deficiency	Autosomal-recessive	*C8A* or *C8B* (α, β, CD8 chains)	2	Increased susceptibility to *Neisseria*; unable to form membrane attack complex; SLE-like syndromes
C9 deficiency	Autosomal-recessive	*C9*	5	Increased susceptibility to *Neisseria*; unable to form membrane attack complex
Factor H deficiency	Autosomal-recessive	*CFH* (*Factor H gene*)	1	Recurrent pyogenic infections; increased activation of alternative pathway
Factor P (Properdin) deficiency	X-linked recessive	*PFC* (properdin factor, complement)	X	Increased susceptibility to infection, particularly by *Neisseria* spp.; impaired alternative pathway; reduced stability of C3bBb convertase on microbial surfaces
Hereditary angioedema	Autosomal-dominant	*SERPING1* (C1 inhibitor)	11	Excessive spontaneous activation of classical complement pathway (especially C2) causing local inflammation; swelling of tracheal and bronchial passages that can be life threatening
Paroxysmal nocturnal hemoglobinuria	X-linked recessive	*PIGA* (phosphatidylinositol glycan)	X	Impaired synthesis of phosphatidylinositol glycan (PIG); absence of PIG prevents fixation of DAF and CD59 to the host cell membrane; unable to break down complement complexes

4 Stages of Testing for Primary Immunodeficiency

1

- History and physical examination
- CBC and differential
- Quantitative Immunoglobulin levels IgG, IgM, IgA

2

- Specific antibody responses (tetanus, diphtheria, pneumococcus)
- Lymphocyte surface markers CD3/CD4/CD8/CD19/CD56

3

- Lymphocyte proliferation studies (mitogen/antigen stimulation or skin delayed type hypersensitivity)
- Neutrophil oxidation burst (if indicated)
- Response to pneumococcal vaccine (for ages 3 and up)
- Primary Immunodeficiency gene sequencing panel

4

- Complement screening CH50, specific complement components, AH50
- Enzyme activity measurements (e.g., adenosine deaminase, purine nucleoside phosphorylase)
- Phagocyte studies (e.g., surface glycoproteins, mobility, phagocytosis)
- NK cytotoxicity studies
- Neo antigen response to test antibody production
- Other surface molecules for detailed immunophenotype (e.g., memory B cells, T/NK cell subpopulations)
- Specific protein levels (e.g., SAP, Perforin, WASp)
- Cytokine or other function receptor quantification
- IgG subclass analysis
- Genomic studies

Secondary immunodeficiency

SOURCES OF SECONDARY IMMUNE DEFICIENCY

Cause	Examples	Mechanisms
Physiologic sequelae	General malnutrition	High impact on functions with high energy requirements
	Energy metabolism	Deficiencies of amino acids crucial for energy metabolism
	Trace metal deficiencies	Deficiencies of critical cofactors
	Vitamin deficiencies	Deficiencies of critical cofactors
Therapeutic treatment	Ionizing radiation	Damages replicating cells; induces oxidative stress
	Cytotoxic drugs (including many used for cancer treatment)	Damage/kill replicating cells
	Anti-inflammatory drugs (e.g., corticosteroids)	Interfere with production of some cytokines
	Immunosuppressive drugs (e.g., cyclosporine, tacrolimus, rapamycin)	Interfere with production of some cytokines

Secondary immunodeficiency

SOURCES OF SECONDARY IMMUNE DEFICIENCY

Cause	Examples	Mechanisms
Infection	Human immunodeficiency virus (HIV)	Kills $CD4^+$ T cells, monocytes, and even $CD8^+$ T cells; the viral *nef* gene product also redirects pMHC I molecules from the cell surface and into lysosomes where they are degraded
	Epstein-Barr virus	Produces analog of interleukin-10
	Schistosoma	Secretes enzymes capable of cleaving immunoglobulins
	Herpesvirus	Inhibits MHC class I maturation within the endoplasmic reticulum
	Human cytomegalovirus (HCMV)	Interferes with transport of peptides into ER through TAP; redirects MHC class I molecules into cytoplasm rather than to cell surface
	Chlamydia	Interferes with phagocytic function by preventing fusion of phagosomes and lysosomes
	Staphylococcus	Produces toxin that kills phagocytic cells; produces protein that interferes with FcR-driven opsonization
	Yersinia	Produces toxin that kills phagocytes
	Streptococcus	Produces toxin that kills phagocytes
	Mycobacterium	Produces toxin that kills phagocytes; inhibits acidification within phagosomes by preventing fusion with lysosomes; inhibits oxidative degradation within phagosomes
	Salmonella	Inhibits oxidative degradation within phagosomes
	Leishmania	Inhibits oxidative degradation within phagosomes

Secondary immunodeficiency

SOURCES OF SECONDARY IMMUNE DEFICIENCY

Cause	Examples	Mechanisms
Cancer	Multiple myeloma	Increasingly oligoclonal immune response
	Burkitt lymphoma	Epstein-Barr virus (causative agent) produces an analog of IL-10
	Waldenström macroglobulinemia	Excessive production of immunoglobulins; increased blood viscosity
	Chronic lymphocytic leukemia (CLL)	Reduced production of immunoglobulins
	Small lymphocytic lymphoma (SLL)	Reduced production of immunoglobulins

HIV infection and AIDS

- AIDS (acquired immune deficiency syndrome) is caused by HIV (human immunodeficiency virus).
- HIV is a retrovirus that damages the cells of the body's immune system.
- People with HIV may develop opportunistic infections and various forms of cancer.

- **The Centers for Disease Control and Prevention (CDC) defines AIDS as:**

laboratory confirmation of HIV infection and CD4 + T cell count of 200 cell/ml;

or CD4+ T cell percentage of < 14;

or documentation of an AIDS-defining condition (with laboratory confirmation of HIV infection).

- Among the AIDS-defining conditions are candidiasis of the esophagus, cryptococcosis (extrapulmonary), histoplasmosis (disseminated or extrapu lmonary), Pneumocystis jirovecii pneumonia, and Mycobacterium tuberculosis infection of any site.

HIV (human immunodeficiency virus)

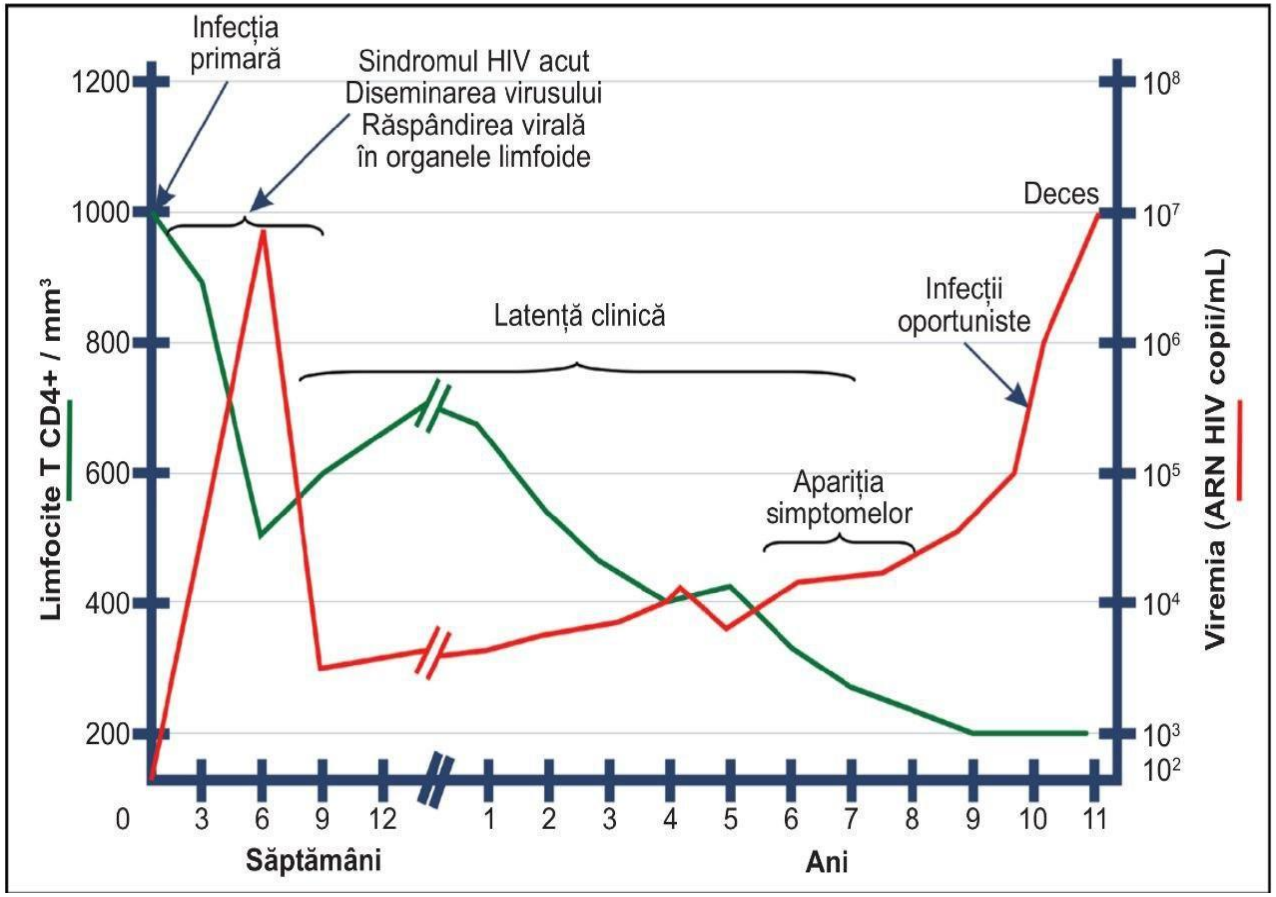
- **HIV destroys CD4+ T cells**, leading to acquired immune deficiency syndrome (AIDS).
- HIV can also infect and kill monocytes and even CD8+ T cells as the infection progresses.
- Because CD4+ T cells are so central to the development of numerous immune responses, their progressive loss produces a gradual decline in humoral and cellular responses and an increasing susceptibility to opportunistic infection that eventually becomes fatal.

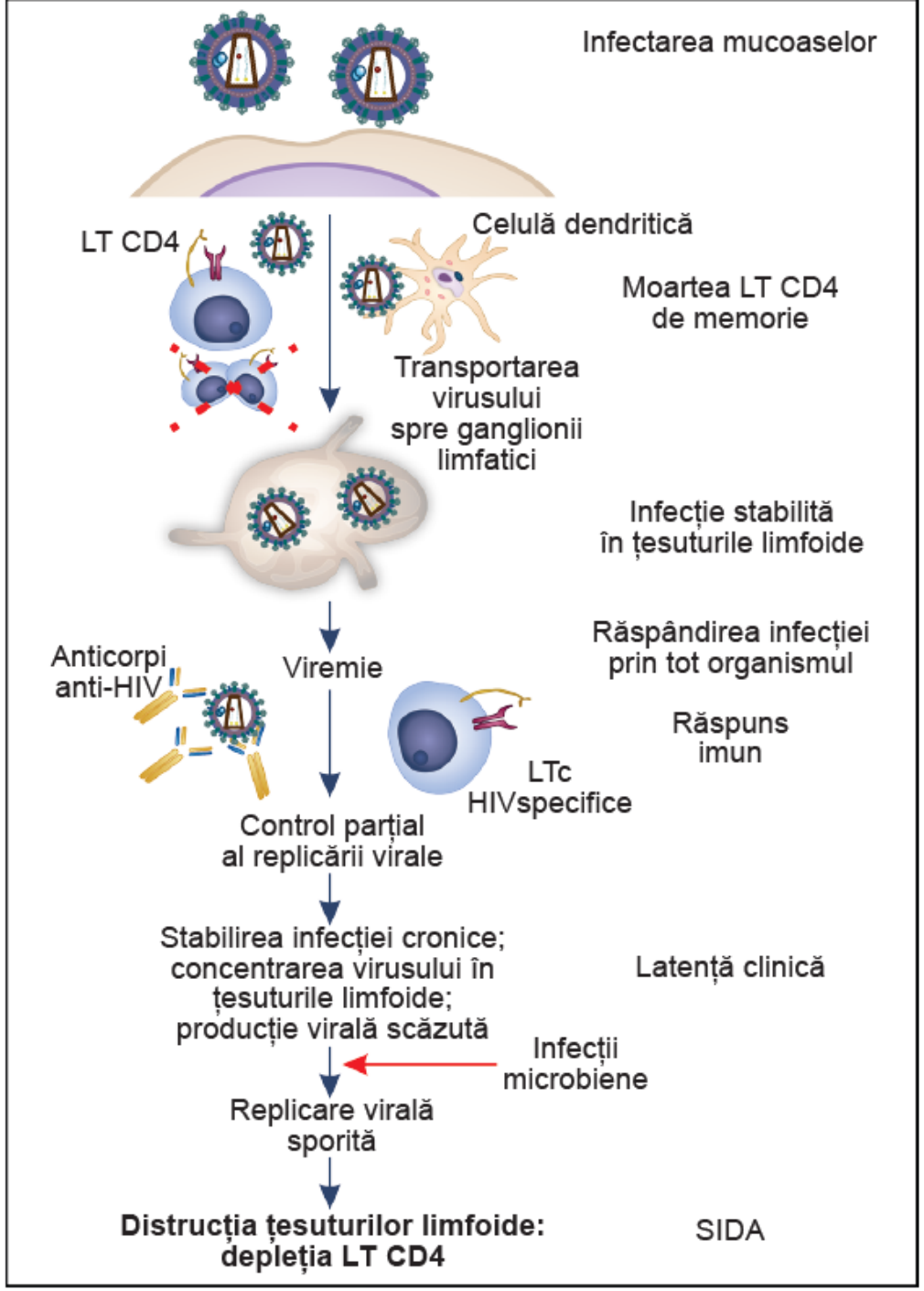
Tabelul 11.10

CATEGORII IMUNOLOGICE/CLINICE ALE INFECȚIEI HIV

Categorii imunologice (CD4)	Categorii clinice		
	A asimptomatic APG sau infecție HIV acută	**B** simptomatic (non-A, non-C)	**C** boli definitorii pentru SIDA
< 500 celule/mm^3 (>29%)	A1	B1	C1*
200-499 celule/mm^3 (14-28%)	A2	B2	C2*
< 200 celule/mm^3 (<14%)	A3*	B3*	C3*
*Categoriile A3, B3, C1, C2, C3 reprezintă definiția cazului de SIDA la adolescenții și adulții HIV pozitivi			

Evoluția infecției HIV

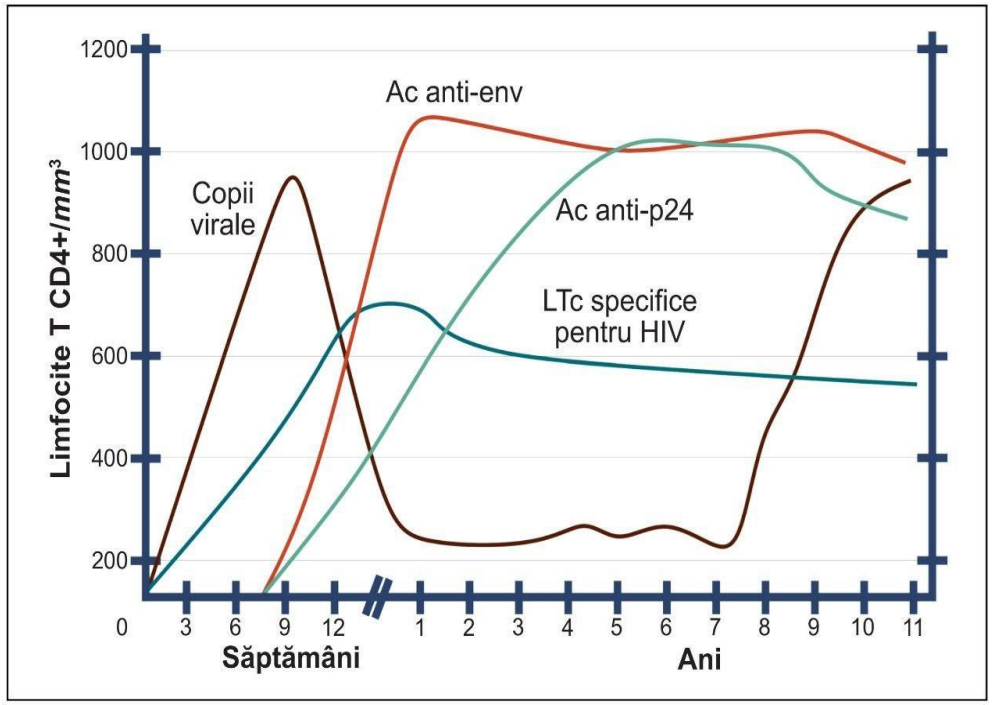


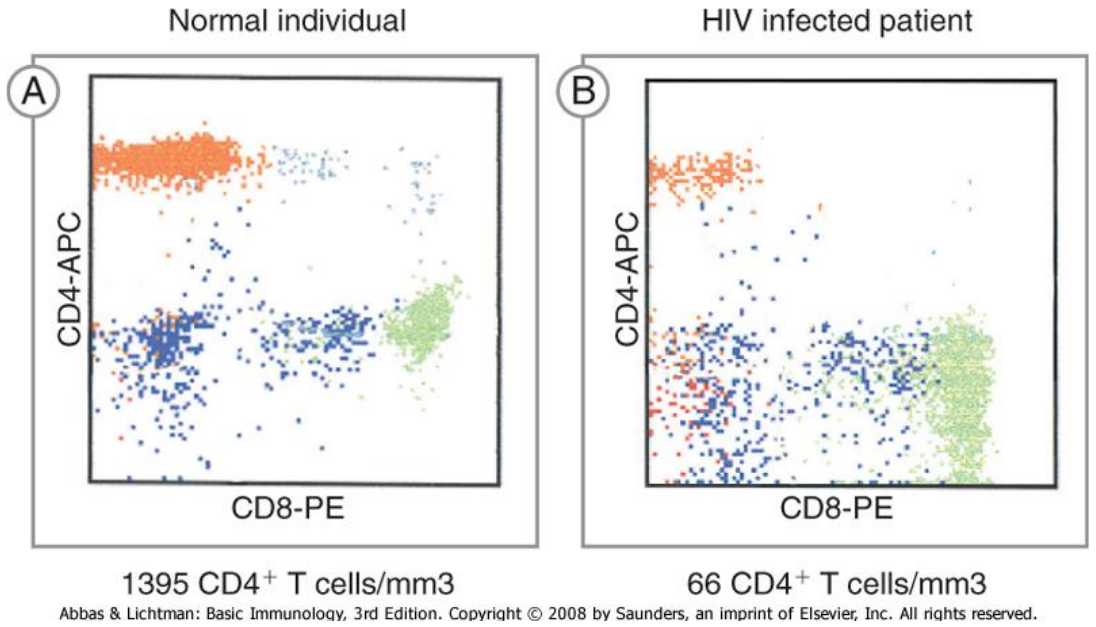


Răspunsul imun anti-HIV

Diagnosticul infecției cu HIV

- ELISA pentru gp41 (suprafață) și p24 (proteina core),
- Westernblot (confirmare) - detectarea anticorpilor anti-HIV (la 2-3 luni de la infecția inițială);
- CDC recomandă ca testele să fie + pentru cel puțin 2 dintre proteine, pentru a ↓ rezultatele fals pozitive – p24 și gp41 sau gp120 / gp160 (precursor al gp41 și gp120)
- Flowcitometrie – nr. ↓ limfocite T CD4+





Treatment of HIV infection

orientată către 5 momente cheie ale replicării virale:

- ataşarea HIV la celula gazdă;

- fuziunea HIV cu celula gazdă;

- revers-transcrierea ARN-ului viral;

- integrarea ADN-ului proviral;

- formarea de proteine virale funcţionale mediată de proteaza virală.

Terapia anti-retrovirală este inițiată când pacientul devine simptomatic sau când LT CD4+ scad sub 350/mm3