# Congenital and Acquired Immunodeficiencies

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# Immunodeficiency Diseases

- The normal function of the immune system is to defend individuals against infections and certain cancers.
- **Diseases caused by impaired immunity are called immune deficiency diseases.**

# Immunodeficiency Diseases

1. Congenital (Primary) Immunodeficiencies
2. Acquired (Secondary) Immunodeficiencies

# Congenital (Primary) Immunodeficiencies

- Some of these diseases are caused by genetic anomalies in one or more components of the immune system, which are called innate (primary) immune deficiencies.

# Acquired (Secondary) Immunodeficiencies

- Other disorders in the immune system occur as a result of **treatments** that cause no or insufficient function in various components of the immune system, **nutritional disorders** and **infections**, which are called acquired (secondary) immune deficiencies.

# Congenital (Primary) Immunodeficiencies

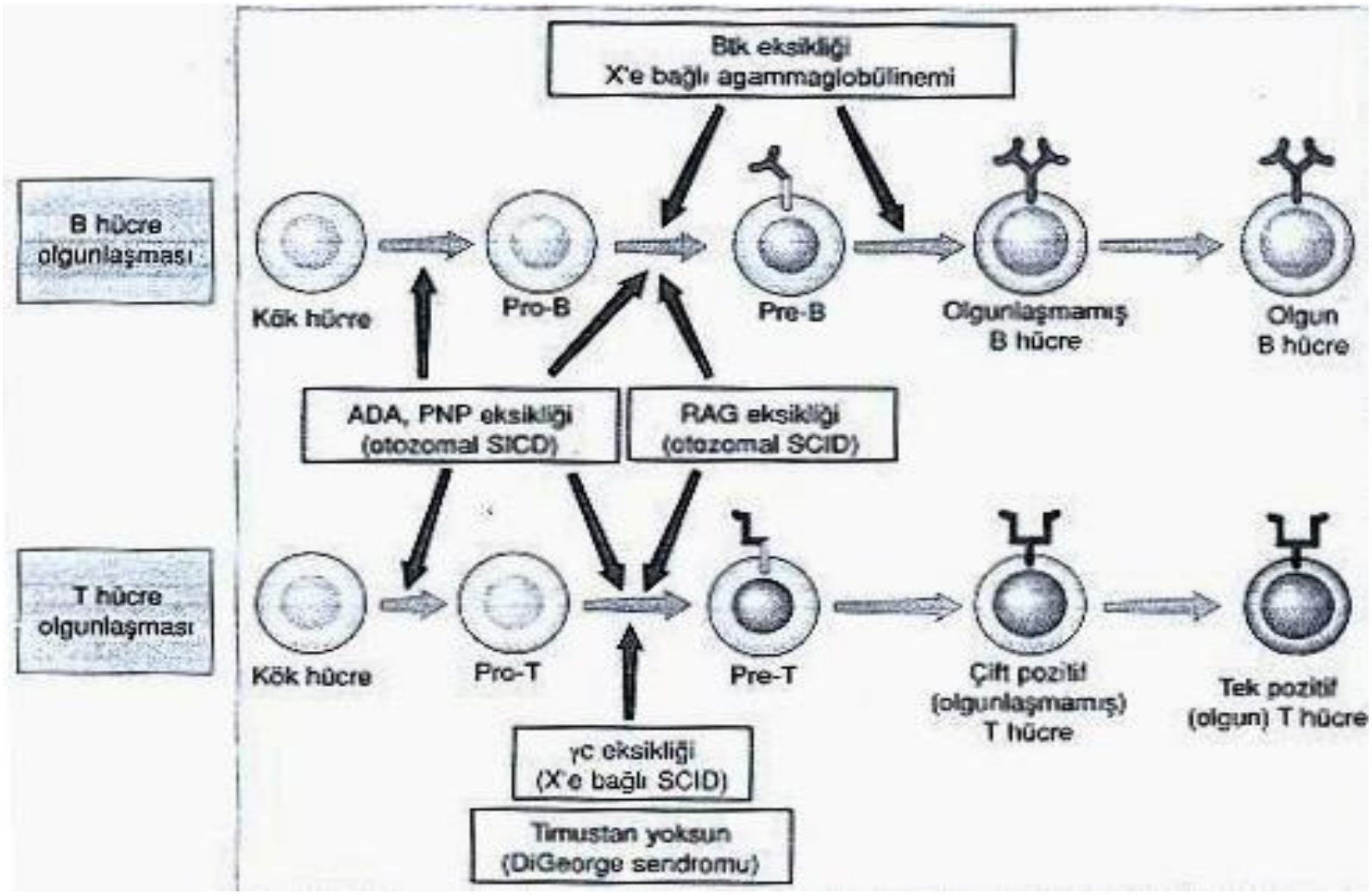
- Common to all congenital immune deficiencies characteristic is the development of complications related to infection.
- Different congenital immunodeficiency diseases have different clinical and pathological features.
- **Some of these diseases appear immediately after birth and are fatal if the immunological deficiency is not corrected.**

# Features of immunodeficiency diseases

| Type of immunodeficiency | Histopathologic and laboratory abnormalities | Common infectious consequences |
|---|---|---|
| B cell deficiencies | Absent or reduced follicles and germinal centers in lymphoid organs<br>Reduced serum Ig levels | Pyogenic bacterial infections |
| T cell deficiencies | May be reduced T cell zones in lymphoid organs<br>Reduced DTH reactions to common antigens<br>Defective T cell proliferative responses to mitogens *in vitro* | Viral and other intracellular microbial infections (e.g., *Pneumocystis jiroveci*, atypical mycobacteria, fungi)<br>Virus-associated malignancies (e.g., EBV-associated lymphomas) |
| Innate immune deficiencies | Variable, depending on which component of innate immunity is defective | Variable; pyogenic bacterial infections |

# Deficiencies in Maturation of Lymphocytes

- Most congenital immune deficiencies are the result of genetic abnormalities that interrupt the maturation of B lymphocytes, T lymphocytes, or both.
- Diseases that are deficient in both the B and T cell arms of the adaptive immune system are classified as **severe combined immune deficiency (SCID).**


B hücre olgunlaşması
Btk eksikliği
X'e bağlı agammaglobülinemi
Kök hücre
Pro-B
Pre-B
Olgunlaşmamış B hücre
Olgun B hücre
ADA, PNP eksikliği (otozomal SICD)
RAG eksikliği (otozomal SCID)
T hücre olgunlaşması
Kök hücre
Pro-T
Pre-T
Çift pozitif (olgunlaşmamış) T hücre
Tek pozitif (olgun) T hücre
γc eksikliği (X'e bağlı SCID)
Timustan yoksun (DiGeorge sendromu)

# Severe Combined Immune Deficiencies

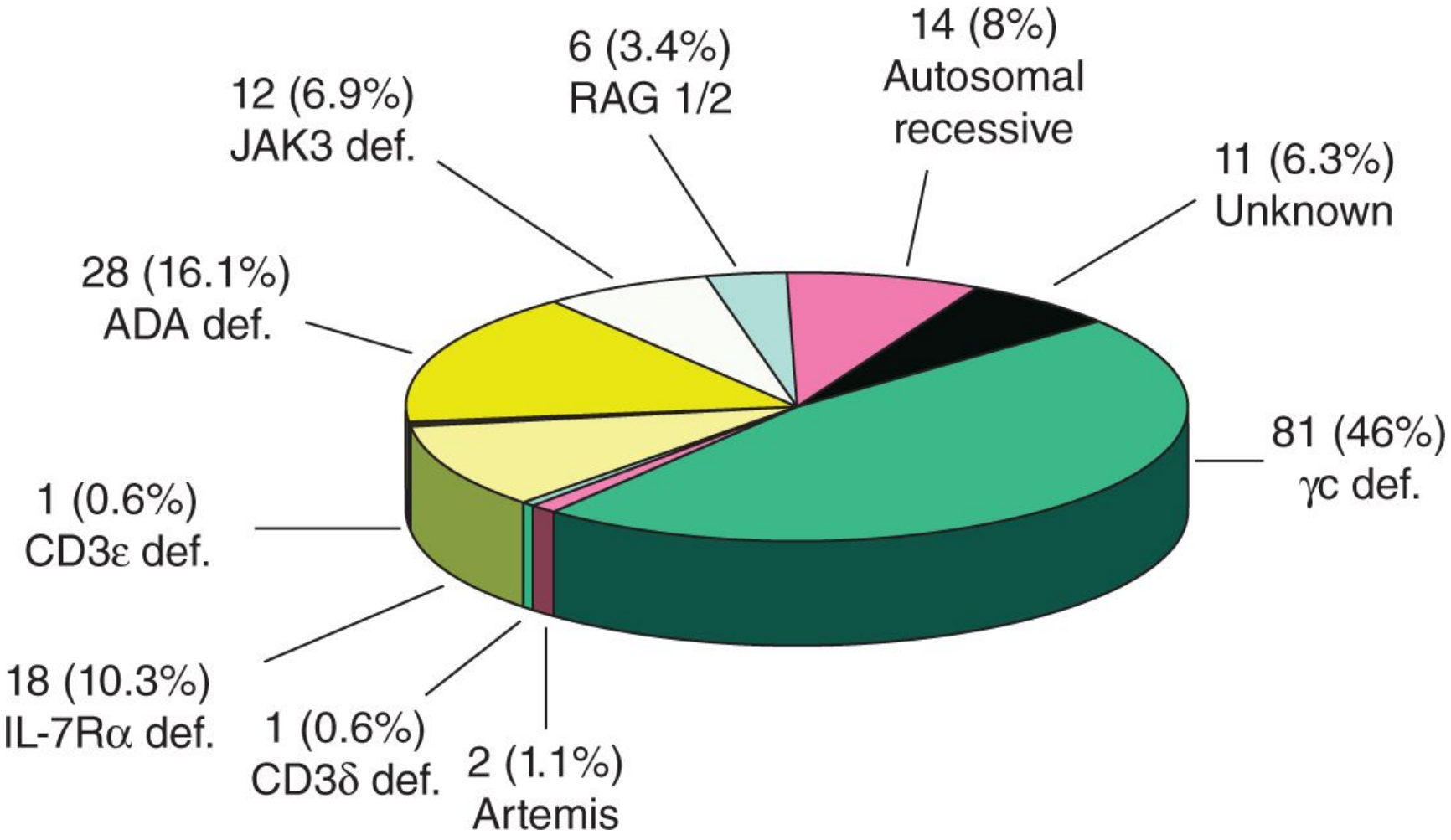
- Severe Combined Immunodeficiency Syndrome; It represents a group of diseases characterized by **disorders in the development and functions of T and B lymphocytes and natural killer cells.**
- It constitutes the most severe form of primary immunodeficiency syndromes.

# Severe Combined Immune Deficiencies

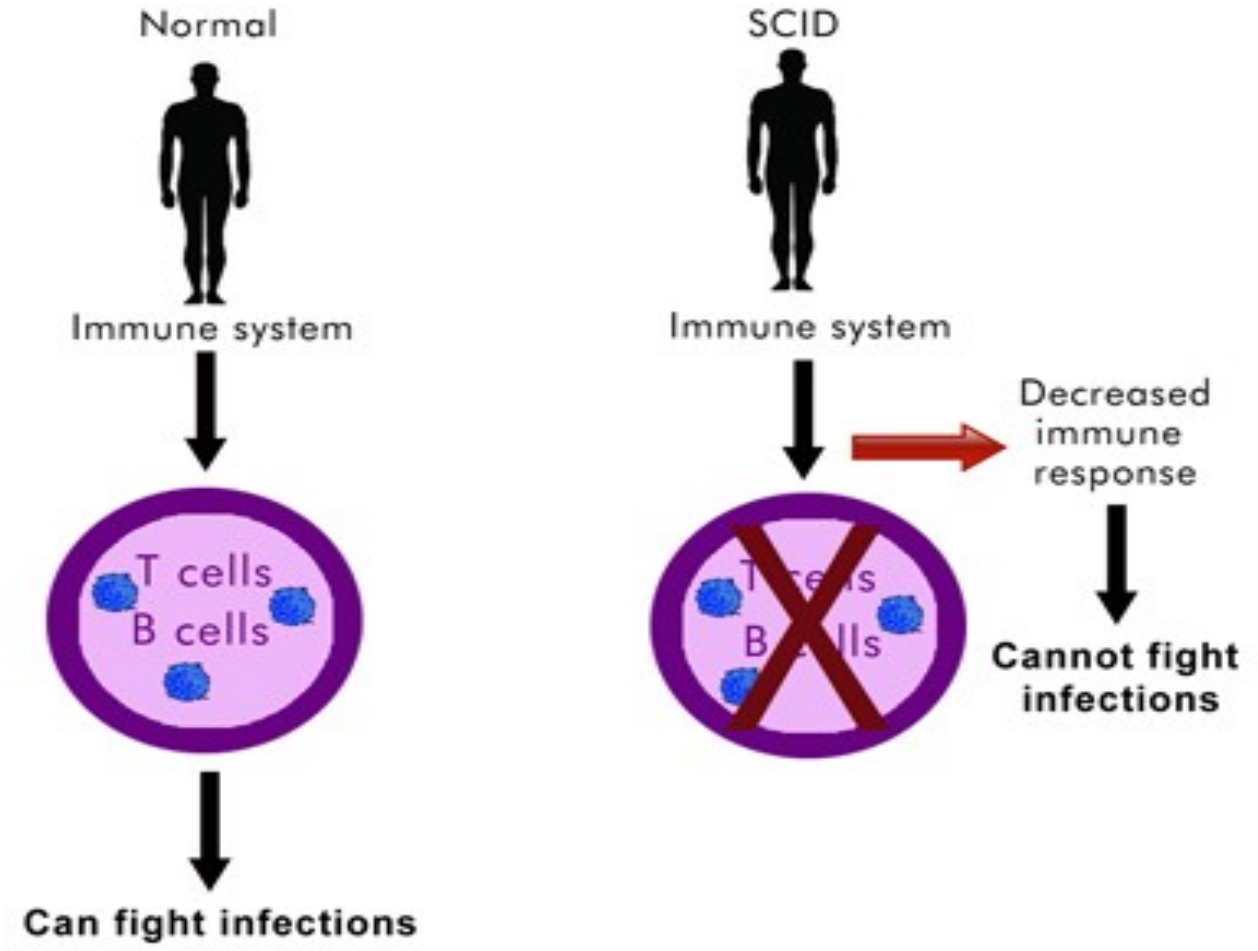
- Severe combined immunodeficiency is characterized by life-threatening opportunistic **bacterial, viral (especially cytomegalovirus, parainfluenza and rotavirus) and fungal (Pneumocystis pneumoniae, Candida, Aspergillus) infections** which usually occur in the first year of life.

# Severe Combined Immune Deficiencies

- Early diagnosis is vital for these patients.
- While these infections usually involve the **respiratory tract and gastrointestinal tract, meningitis, arthritis, and urinary tract infections** can also be seen.


12 (6.9%)
JAK3 def.
6 (3.4%)
RAG 1/2
14 (8%)
Autosomal
recessive
11 (6.3%)
Unknown
28 (16.1%)
ADA def.
81 (46%)
γc def.
1 (0.6%)
CD3ε def.
18 (10.3%)
IL-7Rα def.
1 (0.6%)
CD3δ def.
2 (1.1%)
Artemis

# SEVERE COMBINED IMMUNODEFICIENCY (SCID)

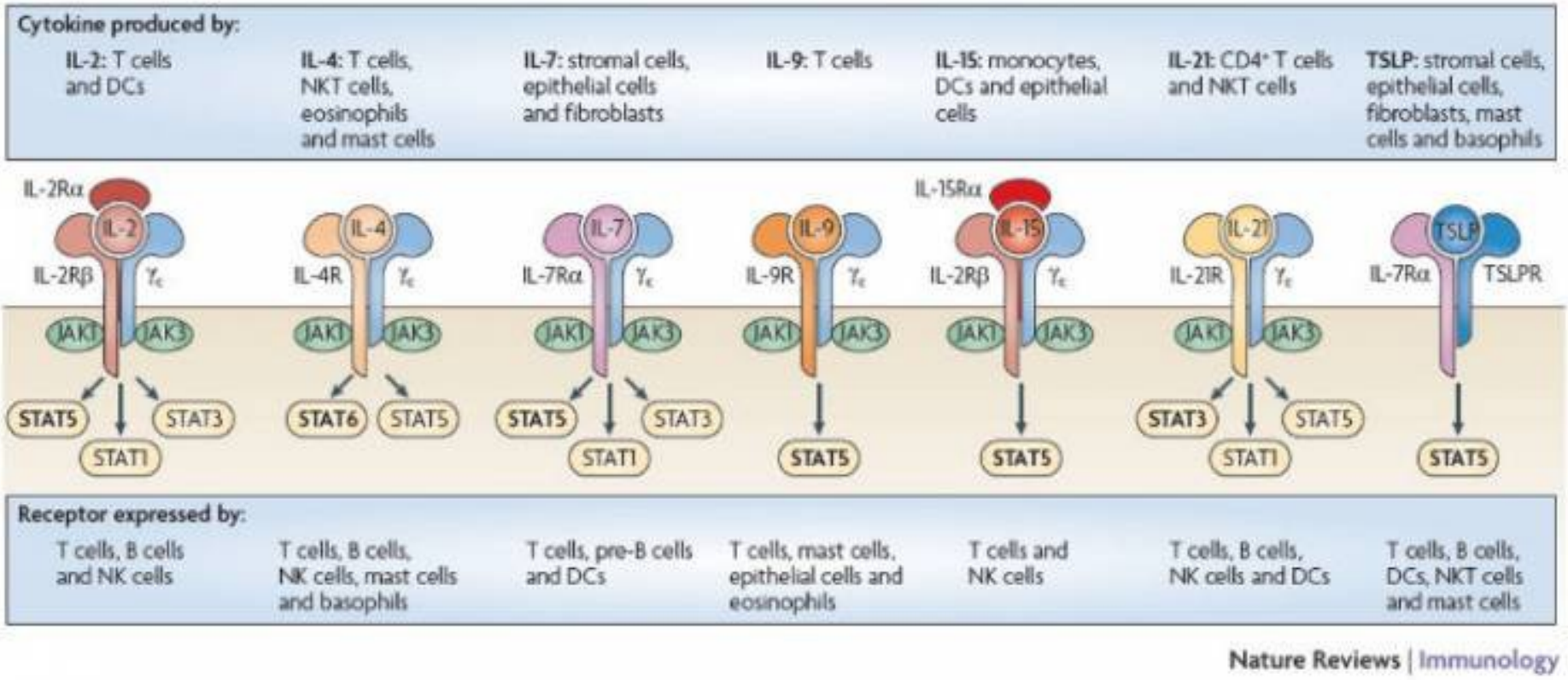


# Severe Combined Immunodeficiencies

About 50% of severe X-linked combined immunodeficiency cases are caused by mutations in a signaling subunit of the cytokine receptor and **affect only boys.**

– **This subunit is called the common γ chain (γc), because it is the common chain that enters the structure of many cytokine receptors such as IL-2, IL-4, IL-7, IL-9 and IL-15**.

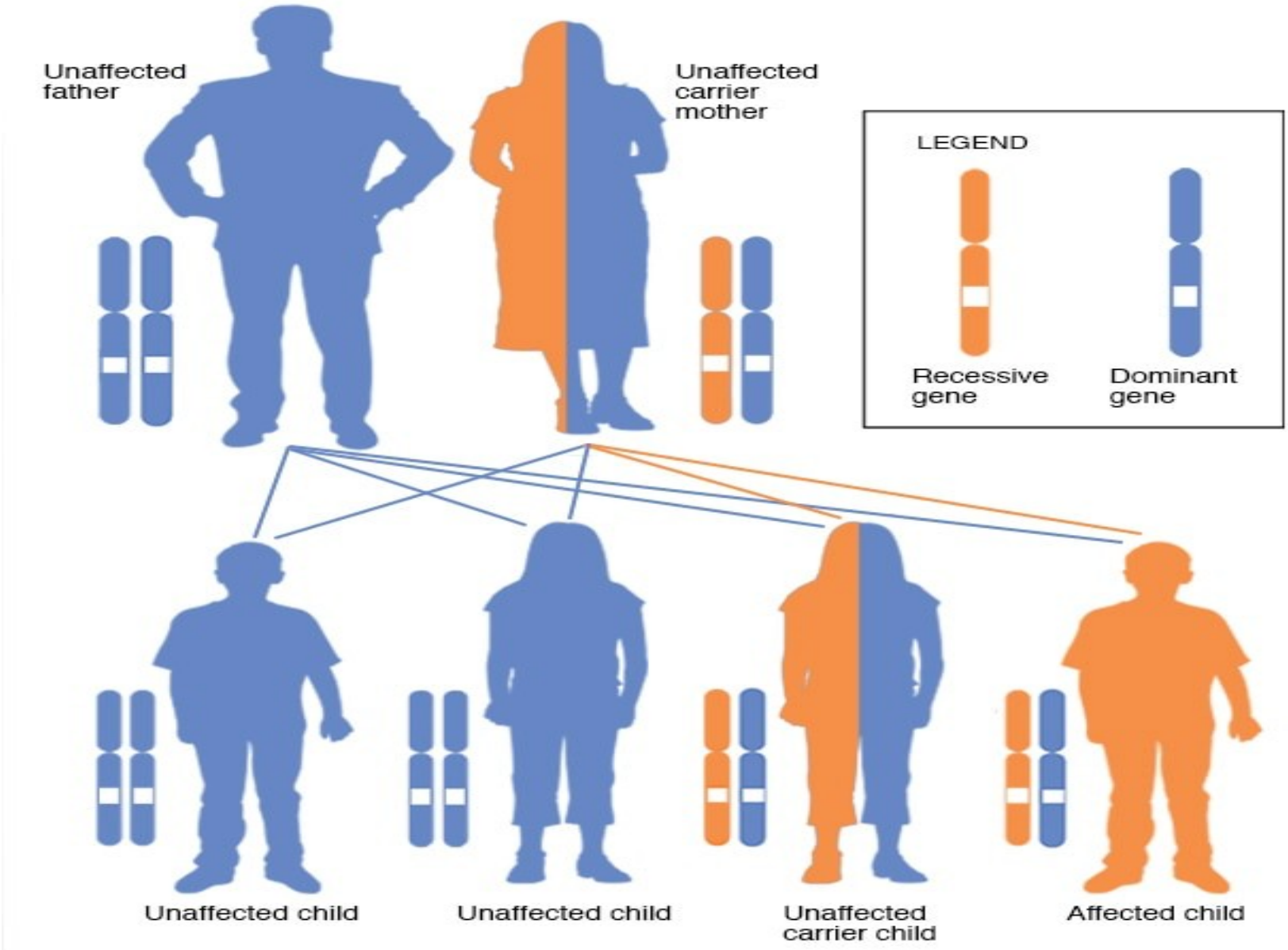
# The common gamma chain and X-SCID

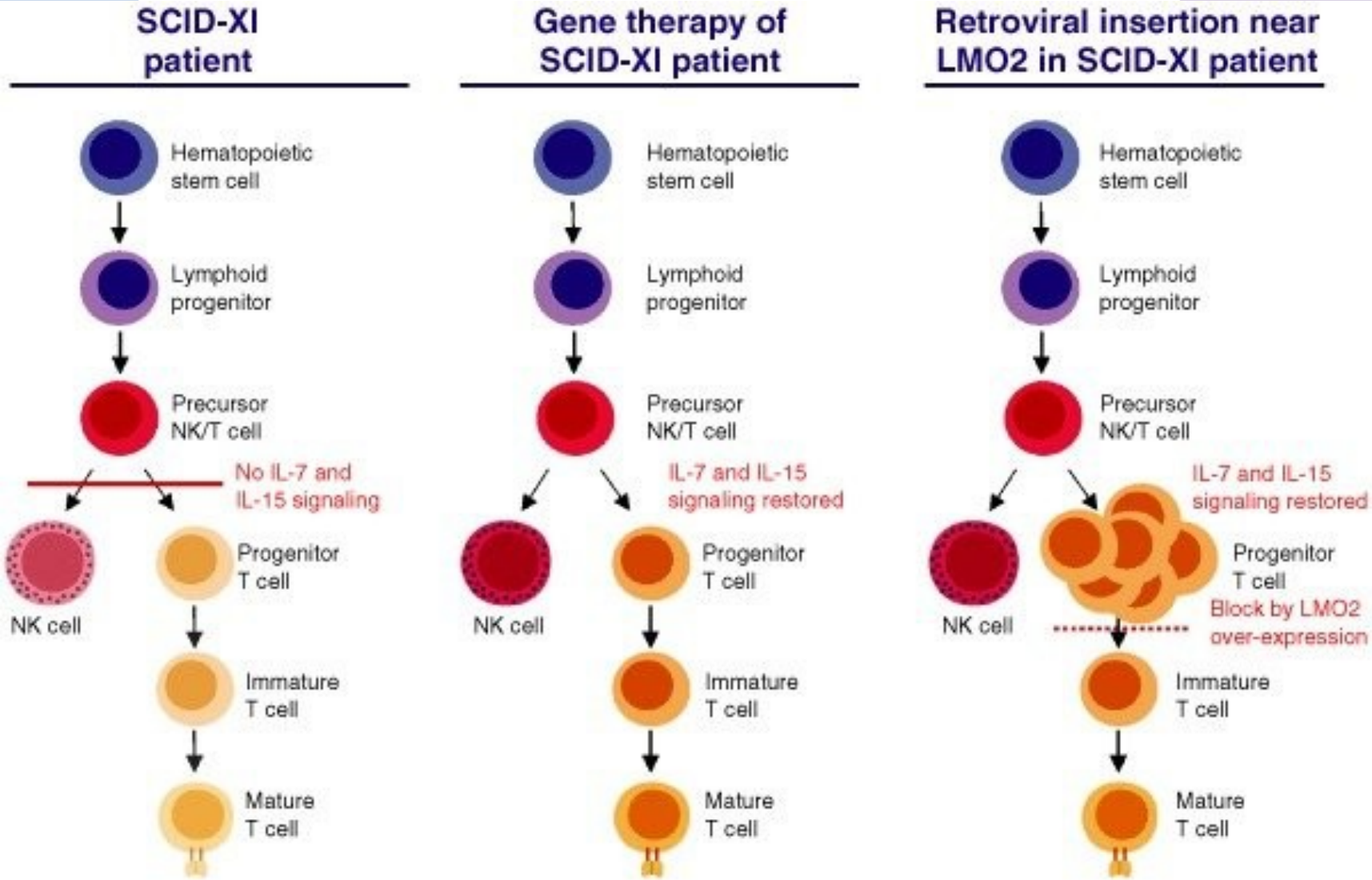



Rochman Y, Spolski R, & Leonard WJ (2009)

- When the γc chain fails to function, immature lymphocytes at the pro-T cell and pro-B cell stage cannot proliferate even in the presence of a major growth factor for these cells, such as IL-7.

– **As a result of this deficiency, a significant decrease in the number of mature T cells, deficiency in cell-mediated immunity and incomplete humoral immunity occur.**



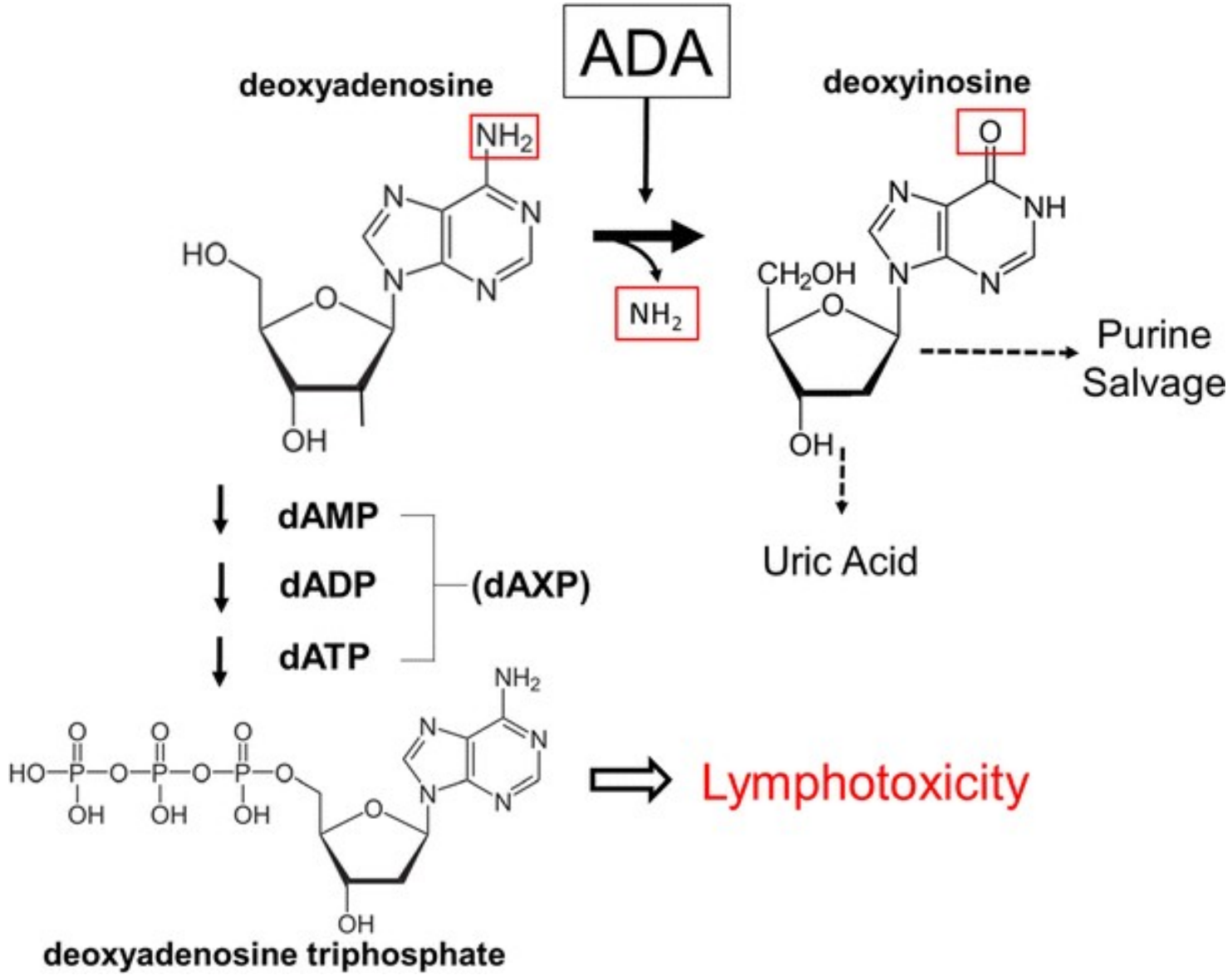

SCID-XI patient
Hematopoietic stem cell
Lymphoid progenitor
Precursor NK/T cell
No IL-7 and IL-15 signaling
NK cell
Progenitor T cell
Immature T cell
Mature T cell
Gene therapy of SCID-XI patient
Hematopoietic stem cell
Lymphoid progenitor
Precursor NK/T cell
IL-7 and IL-15 signaling restored
NK cell
Progenitor T cell
Immature T cell
Mature T cell
Retroviral insertion near LMO2 in SCID-XI patient
Hematopoietic stem cell
Lymphoid progenitor
Precursor NK/T cell
IL-7 and IL-15 signaling restored
NK cell
Progenitor T cell
Block by LMO2 over-expression
Immature T cell
Mature T cell

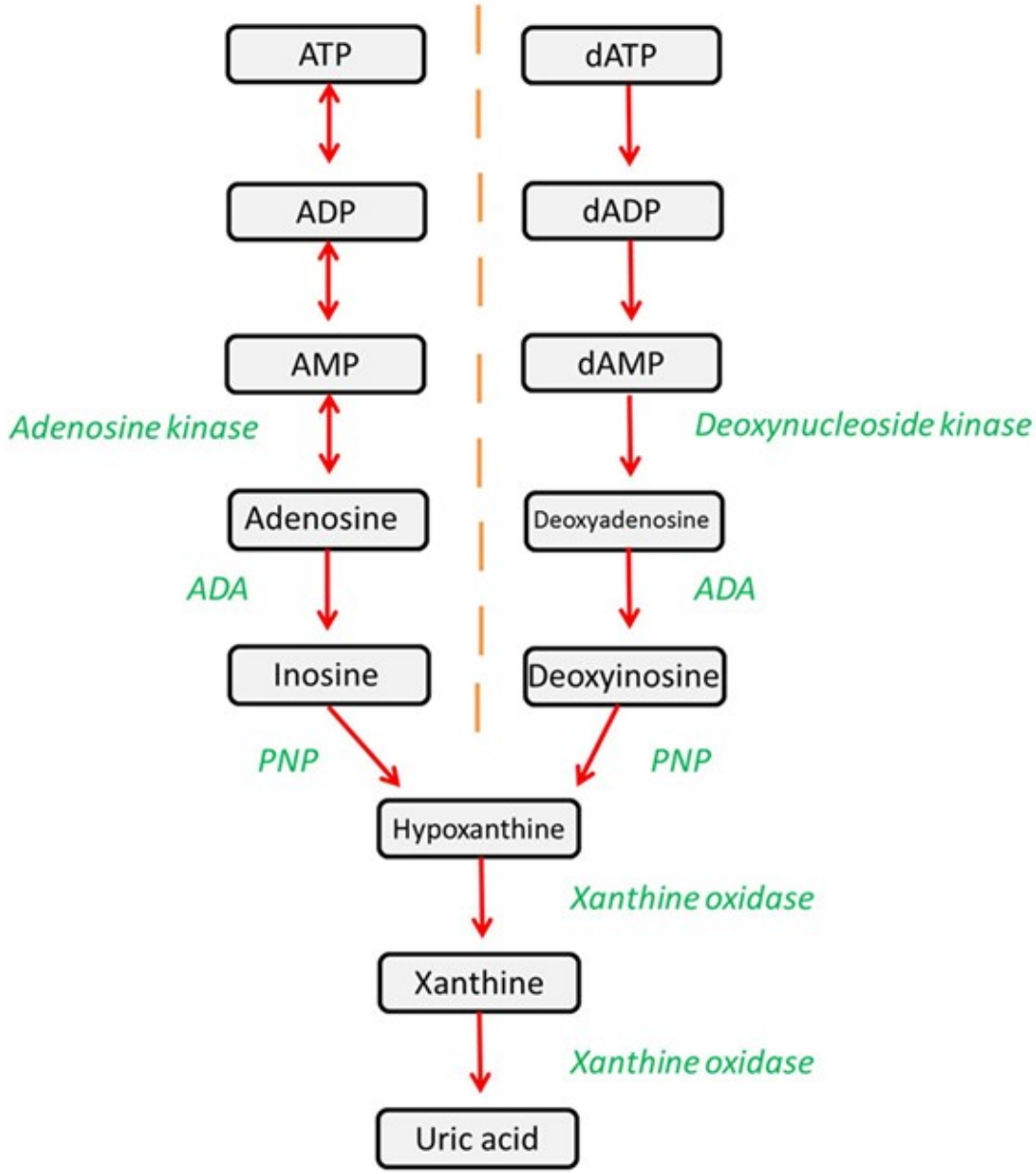
# ADA (Adenosine deaminase) Deficiency

- ADA is an enzyme involved in purine metabolism in cells.
- It catalyzes the **breakdown of adenosine to inosine.**
- Although it is found in all mammalian cells, it is known that **it primarily functions in immune system cells.**

# ADA (Adenosine deaminase) Deficiency

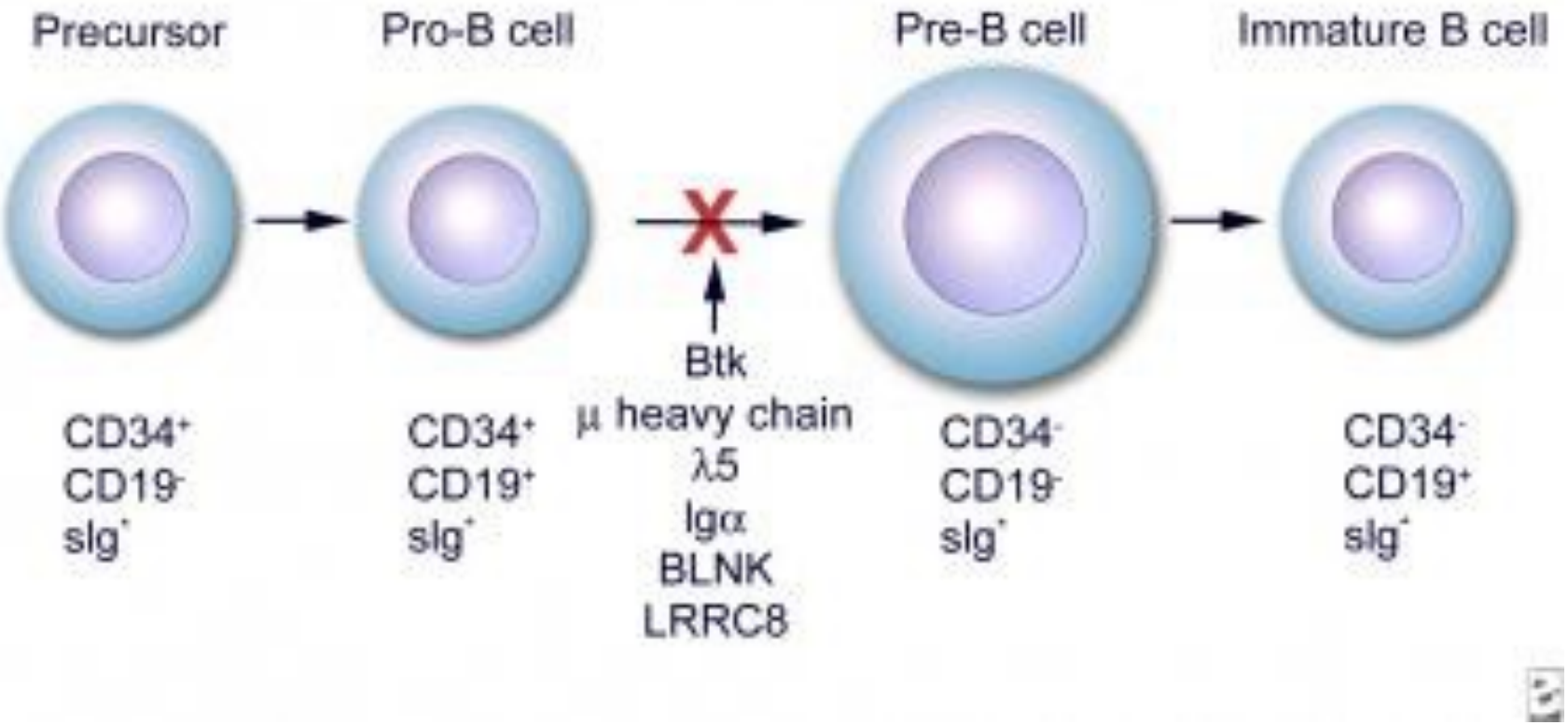
- ADA deficiency leads to accumulation of toxin purine metabolites in actively proliferating cells and stops T cell maturation.
- Patients do not have NK cells in addition to T and B lymphocytes in the circulation.


ADA
deoxyadenosine
deoxyinosine
NH2
O
NH
HO
CH2OH
OH
NH2
Purine
Salvage
Uric Acid
dAMP
dADP
dATP
(dAXP)
HO
OH
deoxyadenosine triphosphate
Lymphotoxicity

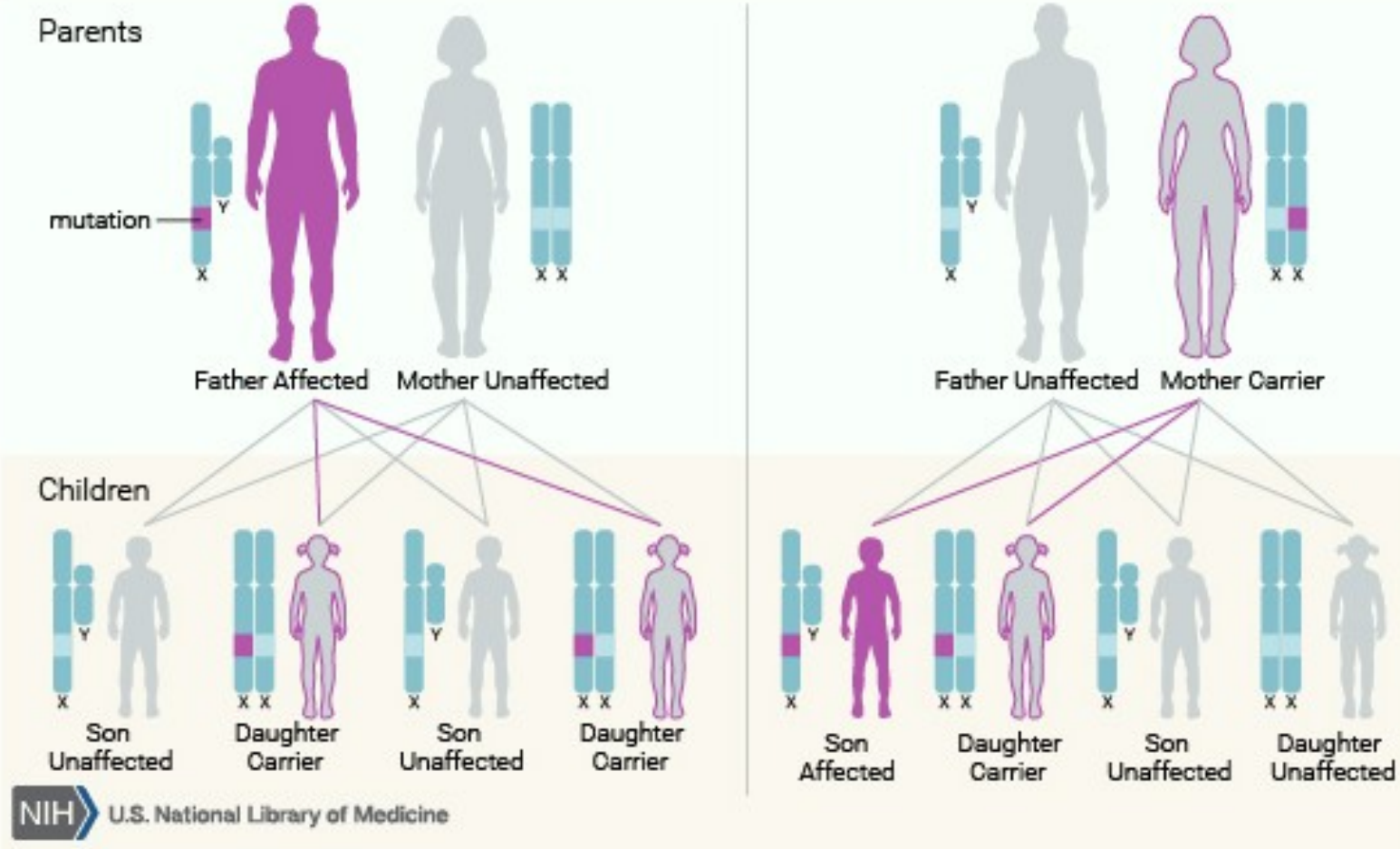

ATP
dATP
ADP
dADP
AMP
dAMP
Adenosine kinase
Deoxynucleoside kinase
Adenosine
Deoxyadenosine
ADA
ADA
Inosine
Deoxyinosine
PNP
PNP
Hypoxanthine
Xanthine oxidase
Xanthine
Xanthine oxidase
Uric acid

# B Cell Immunodeficiencies

- The most common clinical syndrome that occurs with **interruption in B cell maturation** is **agammaglobulinemia** inherited by the X chromosome.
- The disease is due to a mutation in the gene encoding **B cell tyrosine kinase (Btk)**. The enzyme gene is on the X chromosomes.
- **Women who carry the Btk mutant allele on one of their X chromosomes are carriers of the disease**, and their sons with abnormal X chromosomes will get the disease.


Precursor
Pro-B cell
Pre-B cell
Immature B cell
CD34+
CD19-
sIg-
CD34+
CD19+
sIg-
Btk
μ heavy chain
λ5
Igα
BLNK
LRRC8
CD34-
CD19-
sIg-
CD34-
CD19+
sIg-

# X-Linked Recessive

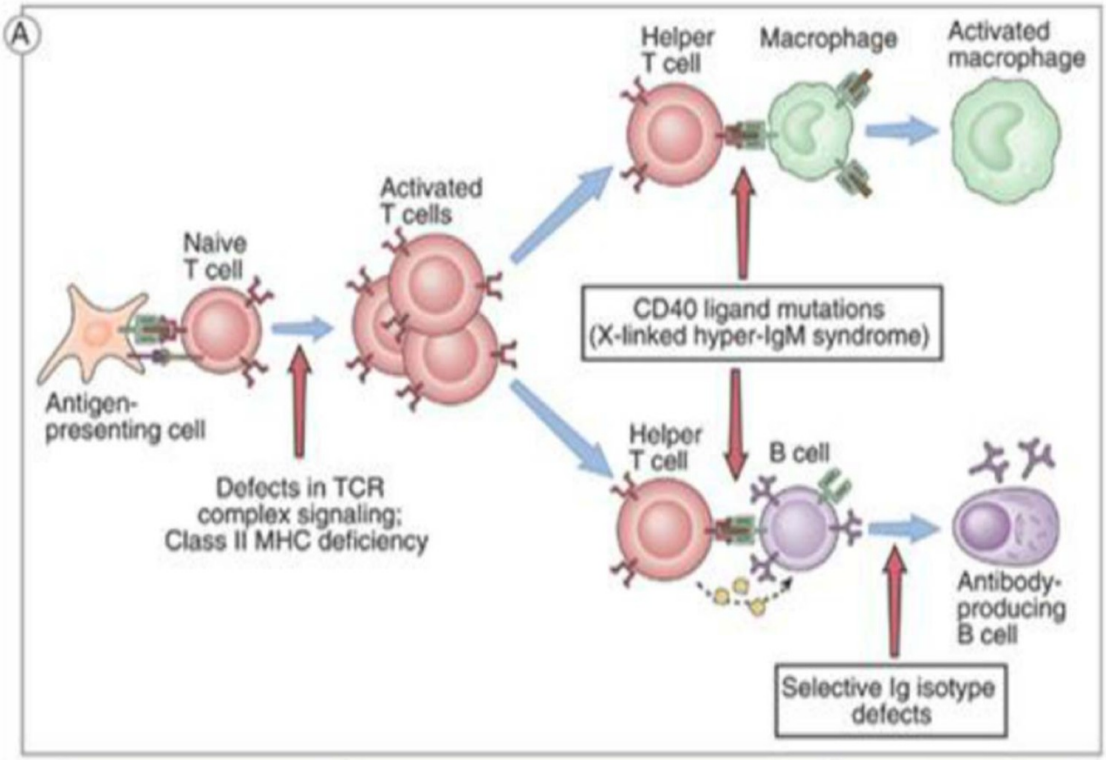


# Defects in Activation and Functions of Lymphocytes

- X-linked hyper-IgM syndrome is characterized by a defect in **B cell heavy chain isotype conversion** resulting in severe deficiency in cellular mediated immunity against intracellular microorganisms.
- **The disease is caused by mutations in the CD40 ligand.** CD40 ligand is a protein found in T helper cells that binds CD40 in B cell and macrophages
- It provides T-cell dependent activation of B cells and macrophages.

- Common variable immune deficiency (CVID) is a heterogeneous group of diseases.
- **These diseases are characterized by a weak antibody response to infections and a decrease in serum levels of IgA and IgE, often IgG.**
- While the IgM level may remain low, it remains high in most cases.

- Focus on defects related to impaired helper TcR function
- These defects impair B cell, macrophage activation




B

| Disease | Functional Deficiencies | Mechanisms of Defect |
|---|---|---|
| X-linked hyper-IgM syndrome | Defects in helper T cell–dependent B cell and macrophage activation | Mutations in CD40 ligand |
| Selective immunoglobulin isotype deficiencies | Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems | Unknown; may be defect in B cell differentiation or T cell help |

# T Cell Immunodeficiencies

- DiGeorge syndrome, on the other hand, is caused by the developmental **deficiency of the thymus** and creates a deficiency in T cell maturation. Bone marrow transplantation is the most common treatment.

## Severe combined immunodeficiency (SCID)

| Disease | Functional deficiencies | Mechanism of defect |
|---|---|---|
| X-linked SCID | Markedly decreased T cells; normal or increased B cells; reduced serum Ig | Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals |
| Autosomal recessive SCID due to ADA, PNP deficiency | Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency | ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes |
| Autosomal recessive SCID due to other causes | Decreased T and B cells; reduced serum Ig | Defective maturation of T and B cells; may be mutations in *RAG* genes and other genes involved in VDJ recombination or IL-7R signaling |

## B cell immunodeficiencies

| Disease | Functional deficiencies | Mechanism of defect |
|---|---|---|
| X-linked agammaglobulinemia | Decrease in all serum Ig isotypes; reduced B cell numbers | Block in maturation beyond pre-B cells, because of mutation in Bruton tyrosine kinase (BTK) |
| Ig heavy-chain deletions | IgG1, IgG2, or IgG4 absent; sometimes associated with absent IgA or IgE | Chromosomal deletion involving Ig heavy-chain locus at 14q32 |

## T cell immunodeficiencies

| Disease | Functional deficiencies | Mechanism of defect |
|---|---|---|
| DiGeorge syndrome | Decreased T cells; normal B cells; normal or decreased serum Ig | Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia |



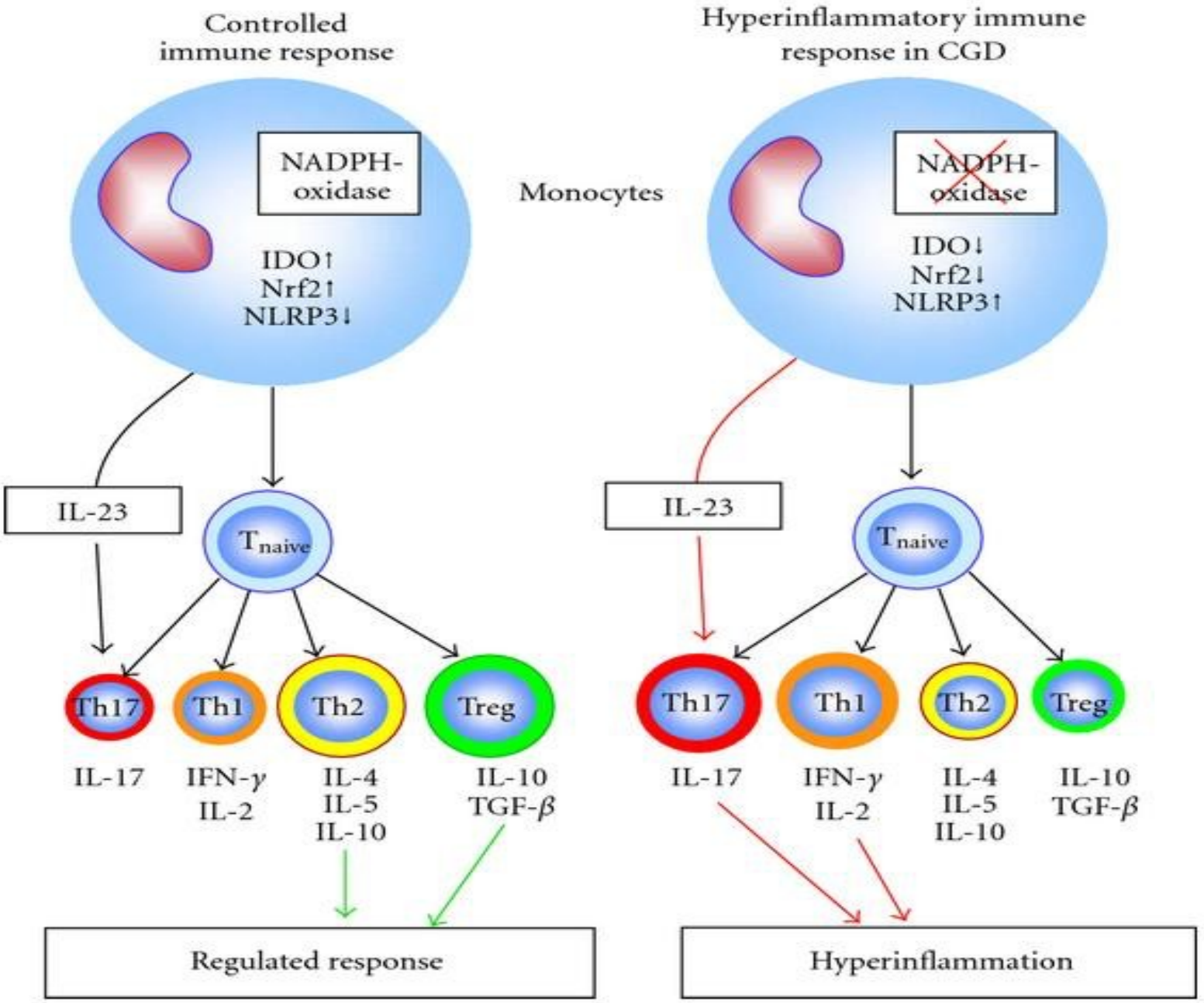
Fig. 12-3

# Deficiencies in Innate Immunity

In the two components of innate immunity; **phagocytosis** and **complement system** abnormalities are important causes of immune deficiency.

The phagocyte oxidase enzyme mutation, which catalyzes microbicidal reactive oxygen intermediates in lysosomes, causes **chronic granulomatous disease.**

- The phagocyte oxidase enzyme mutation, which catalyzes microbicidal reactive oxygen intermediates in lysosomes, causes **chronic granulomatous disease.**
- As a result, **neutrophils and macrophages cannot kill the phagocytosed microorganisms.**


Controlled immune response
Hyperinflammatory immune response in CGD
Monocytes
NADPH-oxidase
IDO↑
Nrf2↑
NLRP3↓
NADPH-oxidase
IDO↓
Nrf2↓
NLRP3↑
IL-23
IL-23
Tnaive
Tnaive
Th17
Th1
Th2
Treg
Th17
Th1
Th2
Treg
IL-17
IFN-γ
IL-2
IL-4
IL-5
IL-10
IL-10
TGF-β
IL-17
IFN-γ
IL-2
IL-4
IL-5
IL-10
IL-10
TGF-β
Regulated response
Hyperinflammation

- The immune system tries to compensate for this deficiency by calling more macrophages to the environment and activating T cells, which stimulates the activation of more phagocytes, as it fails to kill the microorganisms.
- Therefore, phagocyte accumulation occurs, but **microorganisms cannot be effectively eliminated**.
- This accumulation causes the **granuloma-like formation** that gives the disease its name.

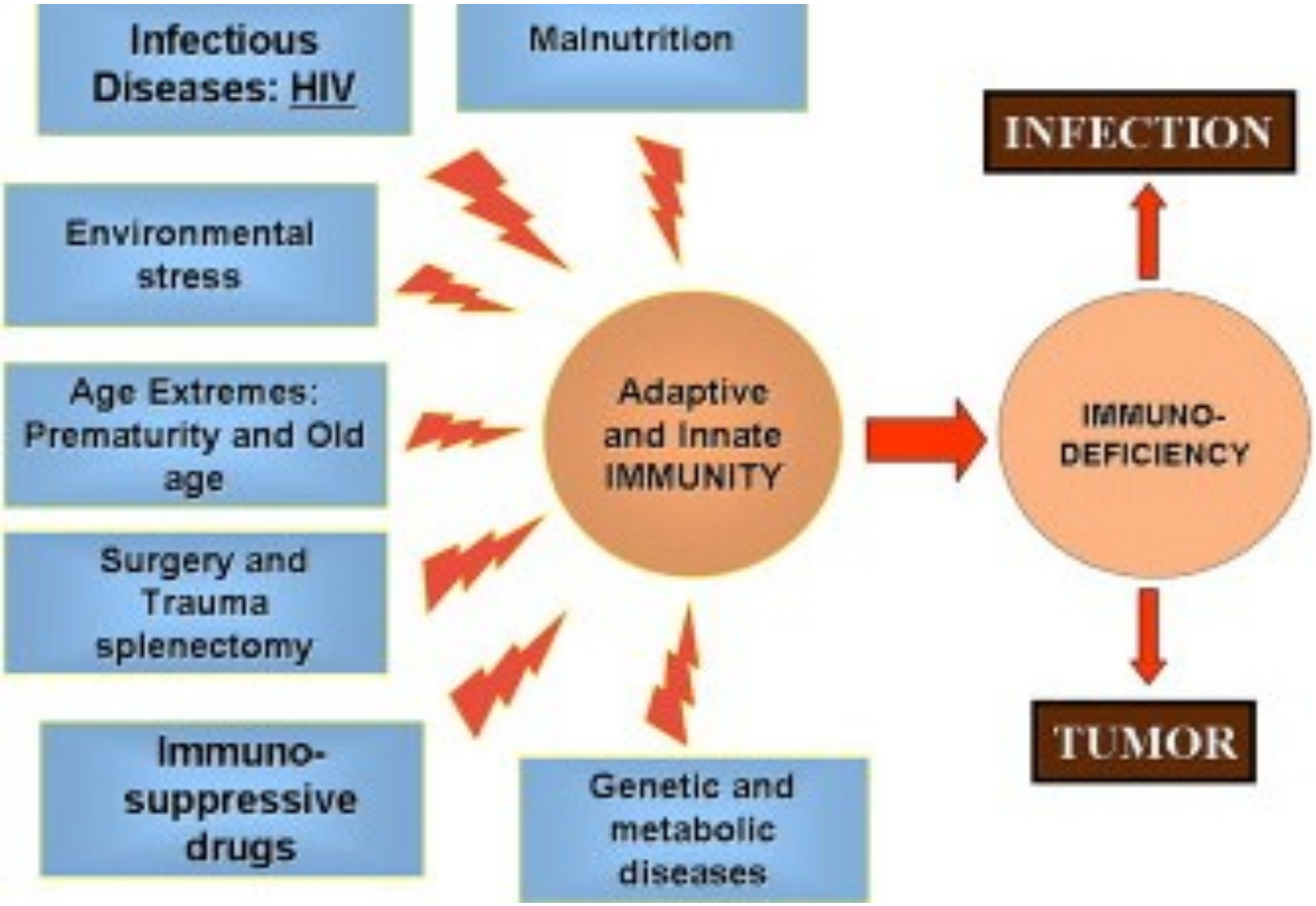
# Deficiencies in Innate Immunity

- Mutation of genes encoding enzymes or integrins required for ligand expression for selectin causes leukocyte adhesion deficiency. Integrin and selectin are involved in the adhesion of leukocytes to other cells.
- As a result of these mutations, **leukocytes cannot bind strongly to the vascular endothelium and cannot accumulate at the infection site.**

# Acquired (Secondary) Immunodeficiencies

- Immune system deficiencies can often develop due to non-genetic but acquired abnormalities during life.
- **The most important of these abnormalities is HIV infection.**
- Protein-calorie malnutrition actually results in deficiencies in all elements of the immune system and is the most common cause of immune deficiency in underdeveloped countries.

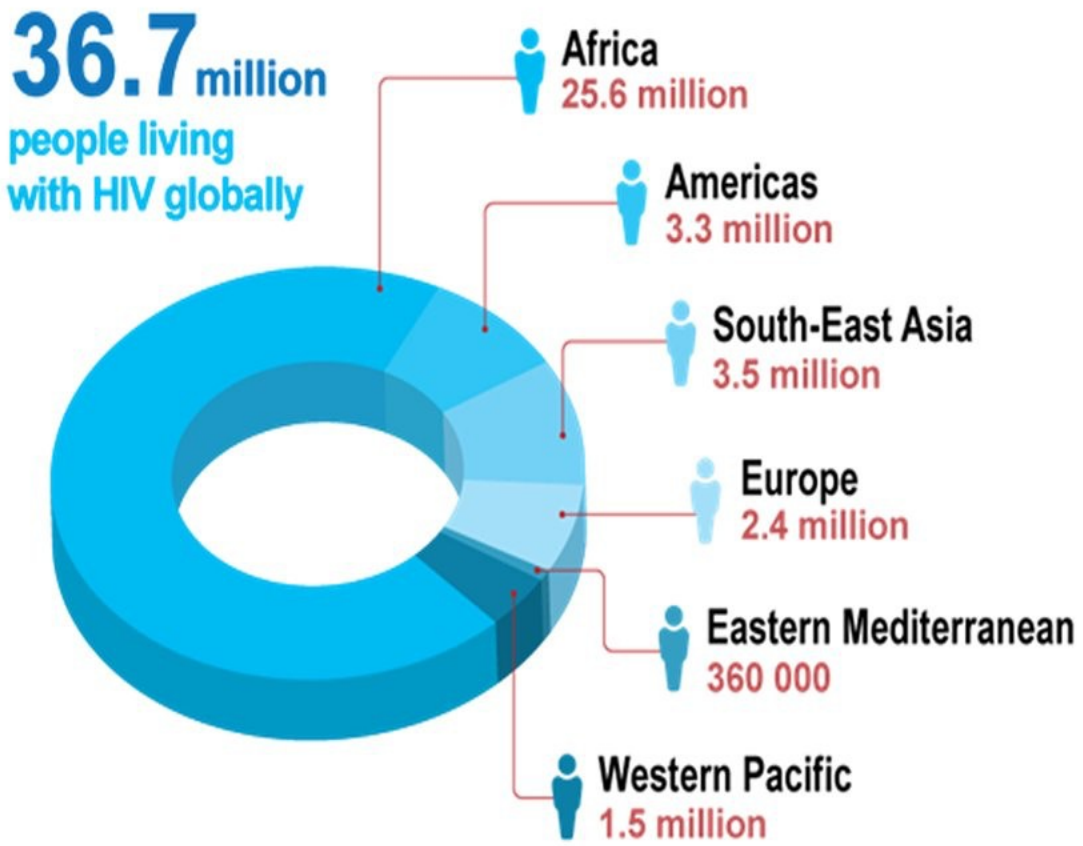
- **Cancer treatment with chemotherapeutic agents** and radiotherapy damages proliferating cells, including bone marrow progenitor cells and mature lymphocytes, and causes immune deficiency.
- Other treatments (for example, to **prevent graft rejection**) are arranged to suppress the immune response.
- Therefore, immunodeficiency is a common complication of such treatments.


Infectious Diseases: HIV
Malnutrition
Environmental stress
Age Extremes: Prematurity and Old age
Surgery and Trauma splenectomy
Immuno-suppressive drugs
Genetic and metabolic diseases
Adaptive and Innate IMMUNITY
IMMUNO-DEFICIENCY
INFECTION
TUMOR

# Acquired Immunodeficiency Syndrome (AIDS)

- AIDS is an infection caused by the human immunodeficiency virus (HIV).
- It is estimated that more than 35 million people in the world are infected with the HIV virus and more than 3 million deaths occur each year due to this disease.

# Global estimates by WHO region



# CD4 reseptörü taşıyan ve HIV in infekte ettiği başlıca hücreler

- Kan monositleri
- Doku makrofajları
- T lenfositleri
- NK lenfositleri
- Dendiritik hücreler
  - epiteliyal Langerhans hücreleri
  - lenf nodundaki folliküler dendritik hücreler
- Hematopoyetik stromal hücreler
- Beyin mikroglial hücreleridir

<u>$CD4^+$ yardımcı T-lenfositlerin 5 alt tipi var</u>

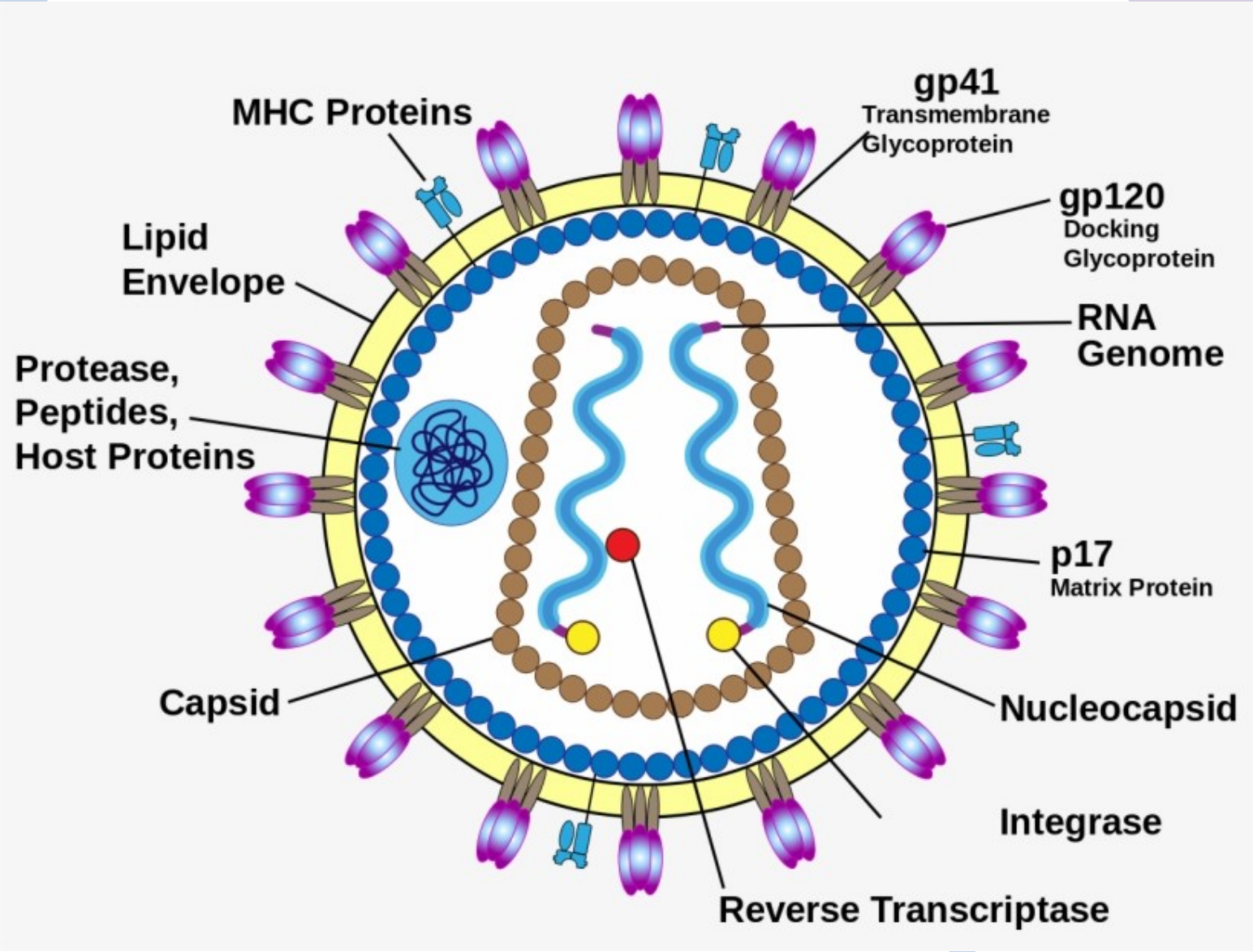
- **Th1** hücresel yanıt, sitotoksik CD8+ lenfosit yanıtının yönetilmesi
- **Th2** humoral yanıt, sitotoksik lenfosit cevabını azaltır ve antikor yapımını artırır
- **Th17** mukozal imüniteyi destekler
- **Treg** CTL baskılayarak etki eder
- **Tfh** folliküler helper humoral cevabın merkezinde yer alır

TH1 cevabı baskın olan bireyler daha uzun yaşarlar. AIDS evresinde TH1 cevabı TH2'ye dönüşür

Uzun süreli nonprogresör kalan bireylerde daha yüksek TH17 hücre düzeyleri saptanmıştır

# Human Immunodeficiency Virus (HIV)

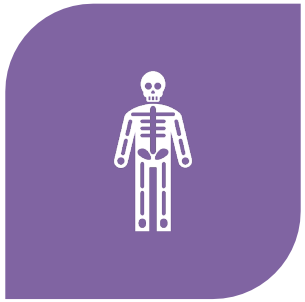
- HIV is a retrovirus that infects immune system cells, usually **CD4+ T lymphocytes**, and causes severe damage to these cells.
- The infectious HIV particle contains single-stranded RNA within the protein capsid. The viral capsid is surrounded by a lipid cover derived from host cells.
- **Viral RNA encodes structural proteins, various enzymes, and proteins that regulate the transcription of viral genes and the life cycle of the virus.**


MHC Proteins
gp41
Transmembrane
Glycoprotein
gp120
Docking
Glycoprotein
Lipid
Envelope
RNA
Genome
Protease,
Peptides,
Host Proteins
p17
Matrix Protein
Capsid
Nucleocapsid
Integrase
Reverse Transcriptase

# The life cycle of HIV consists of the following steps:

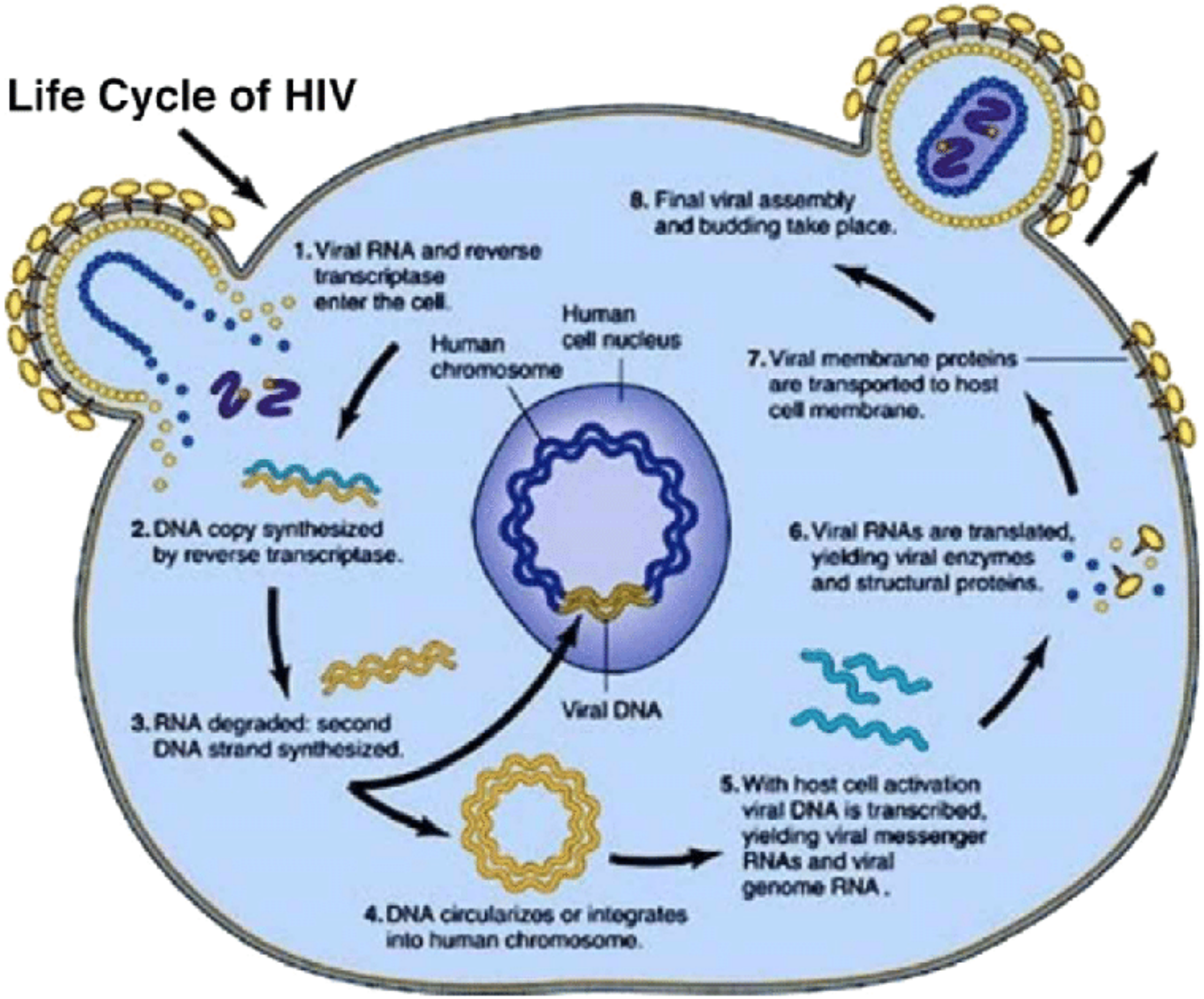
INFECTION OF CELLS

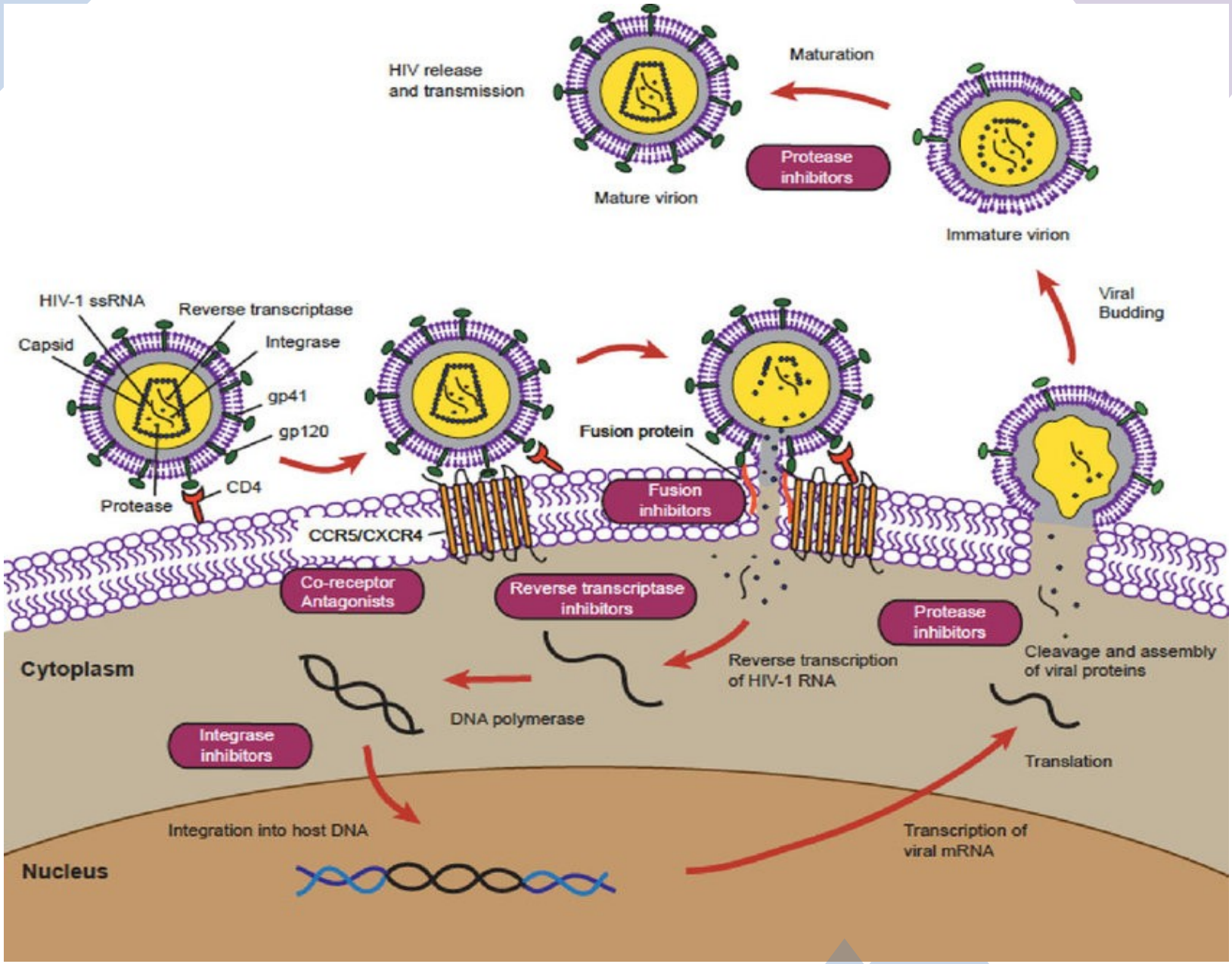
PRODUCTION OF VIRAL DNA AND INTERACTION WITH THE HOST GENOME



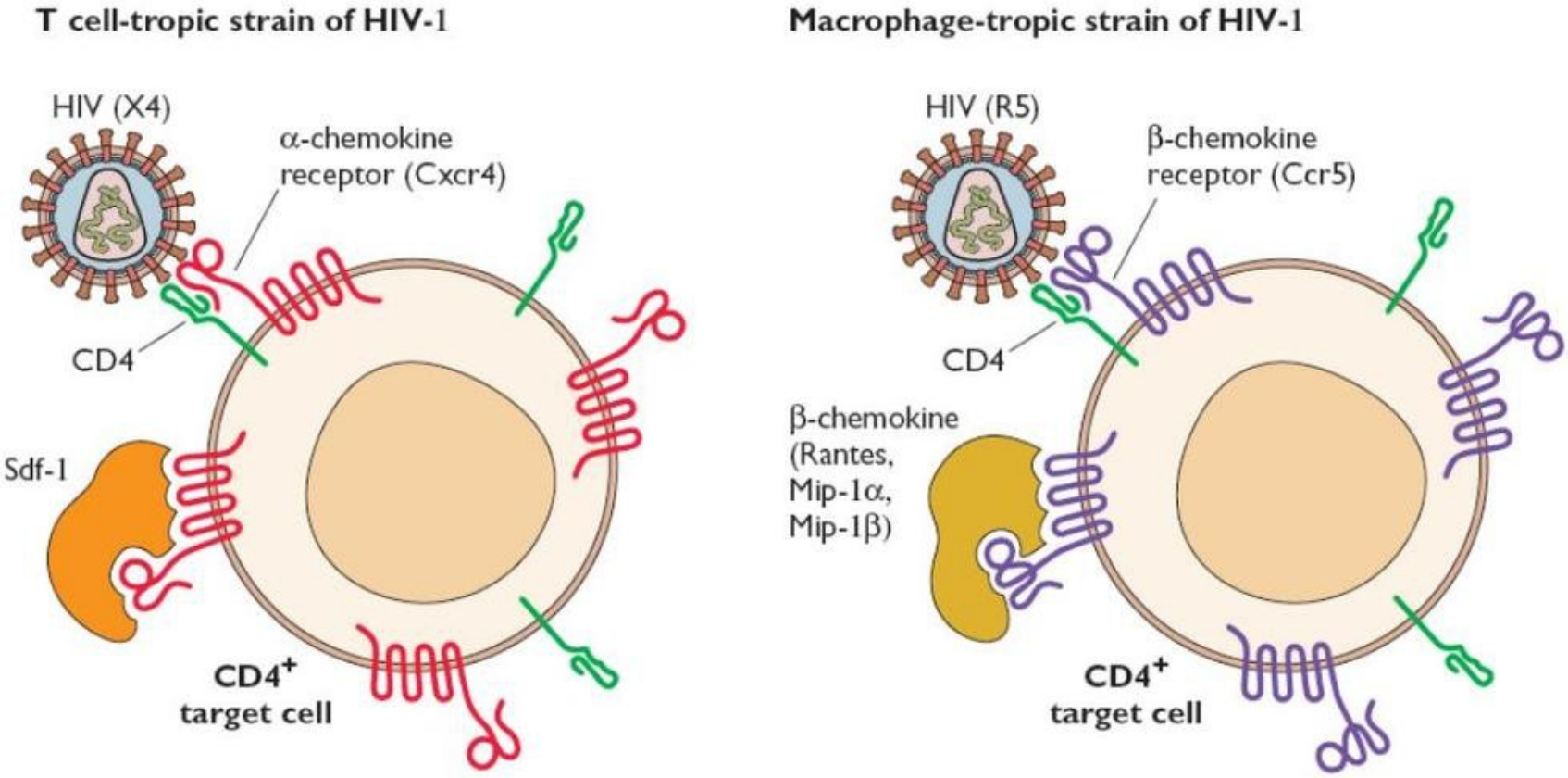
EXPRESSION OF VIRAL GENES AND PRODUCTION OF VIRAL PARTICLES

# Life Cycle of HIV




HIV release
and transmission
Maturation
Protease
inhibitors
Mature virion
Immature virion
Viral
Budding
HIV-1 ssRNA
Reverse transcriptase
Capsid
Integrase
gp41
gp120
CD4
Protease
Fusion protein
Fusion
inhibitors
CCR5/CXCR4
Co-receptor
Antagonists
Reverse transcriptase
inhibitors
Protease
inhibitors
Cytoplasm
Reverse transcription
of HIV-1 RNA
Cleavage and assembly
of viral proteins
DNA polymerase
Integrase
inhibitors
Translation
Integration into host DNA
Transcription of
viral mRNA
Nucleus

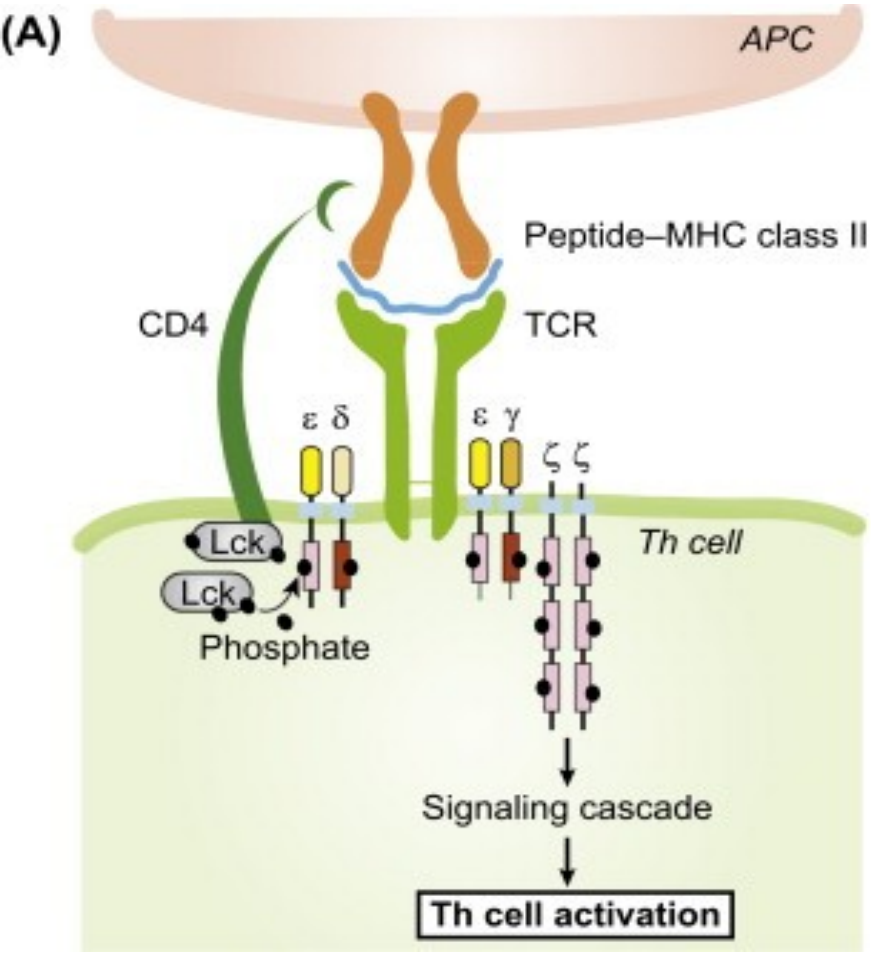
# Co-receptors

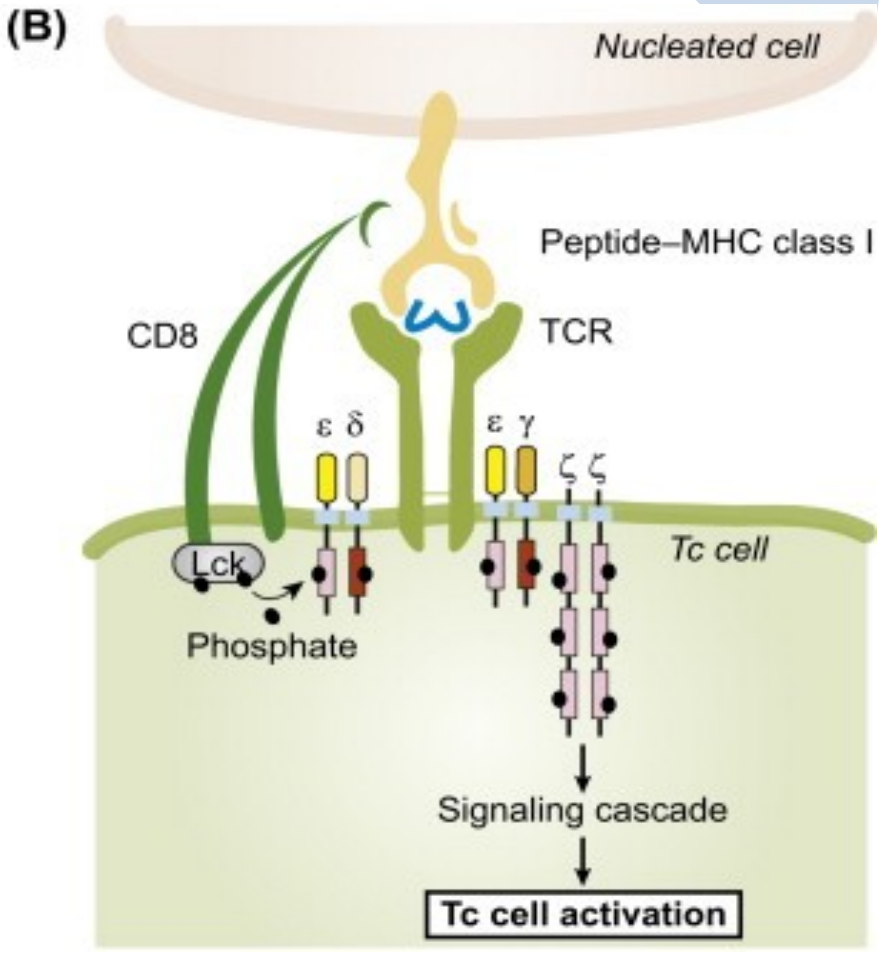


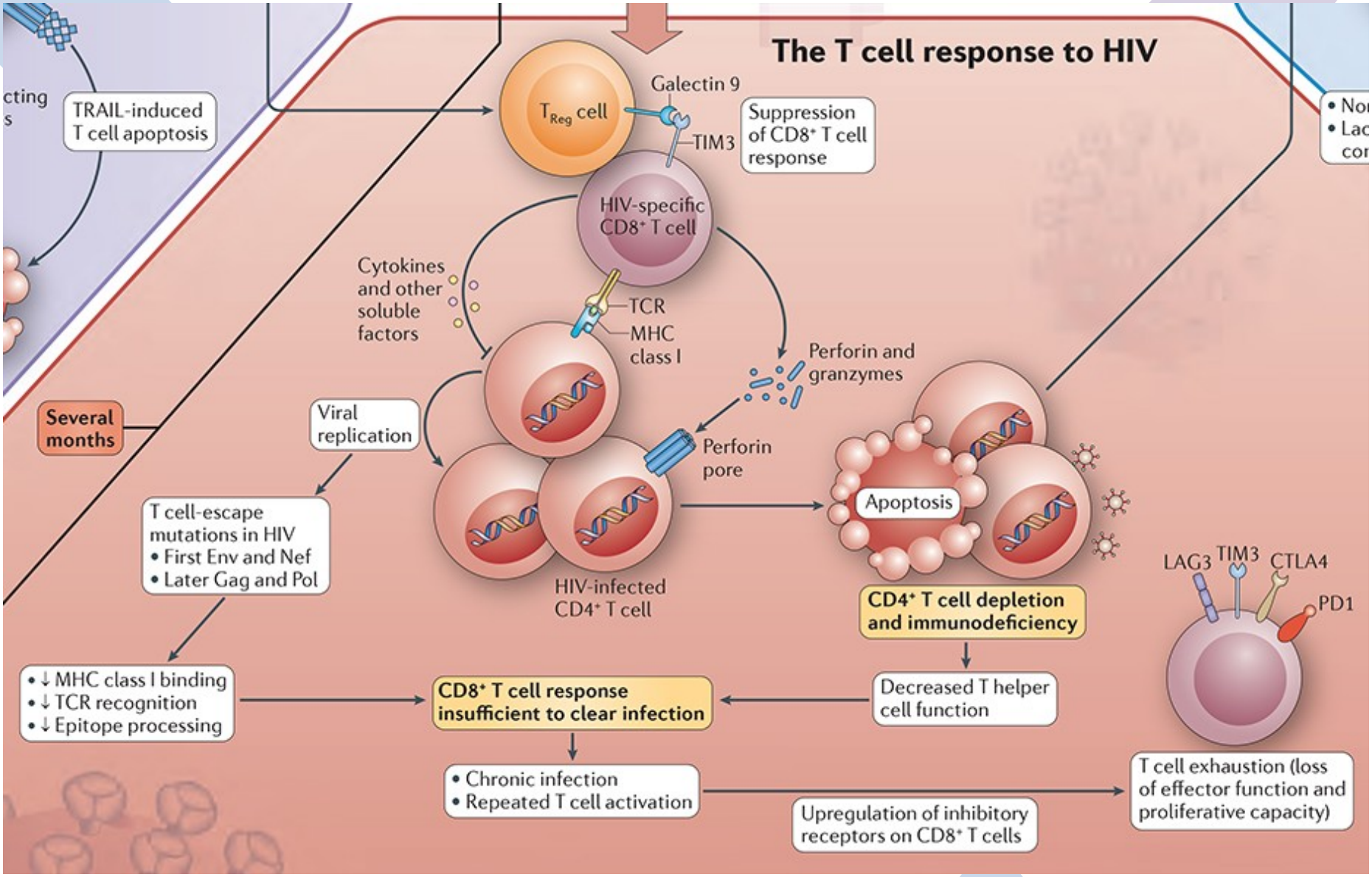
- HIV infects immune system cells through a major envelope glycoprotein called gp120, which it does so by binding specifically to chemokine receptors (CXCR4 and CCR5) and CD4 in human cells.
- Thus, the virus infects only cells expressing CD4 and these chemokine receptors.
- **The major cell type that can be infected with HIV is CD4 T lymphocytes, but macrophages and dendritic cells are also infected with the virus.** Different cell populations may use different chemokine receptors to bind to different strains of the virus.

- After binding to the cell receptor, the viral membrane fuses with the host cell membrane and the virus enters the cell cytoplasm.
- Here, the virus disrupts its own structure with the viral **protease** it contains and viral RNA is released into the cell.
- A DNA copy of the viral RNA is made by the viral **reverse transcriptase** enzyme, and the DNA integrates into the host cell's DNA through the activity of the **integrase** enzyme.
- This integrated viral DNA is called **provirus**.

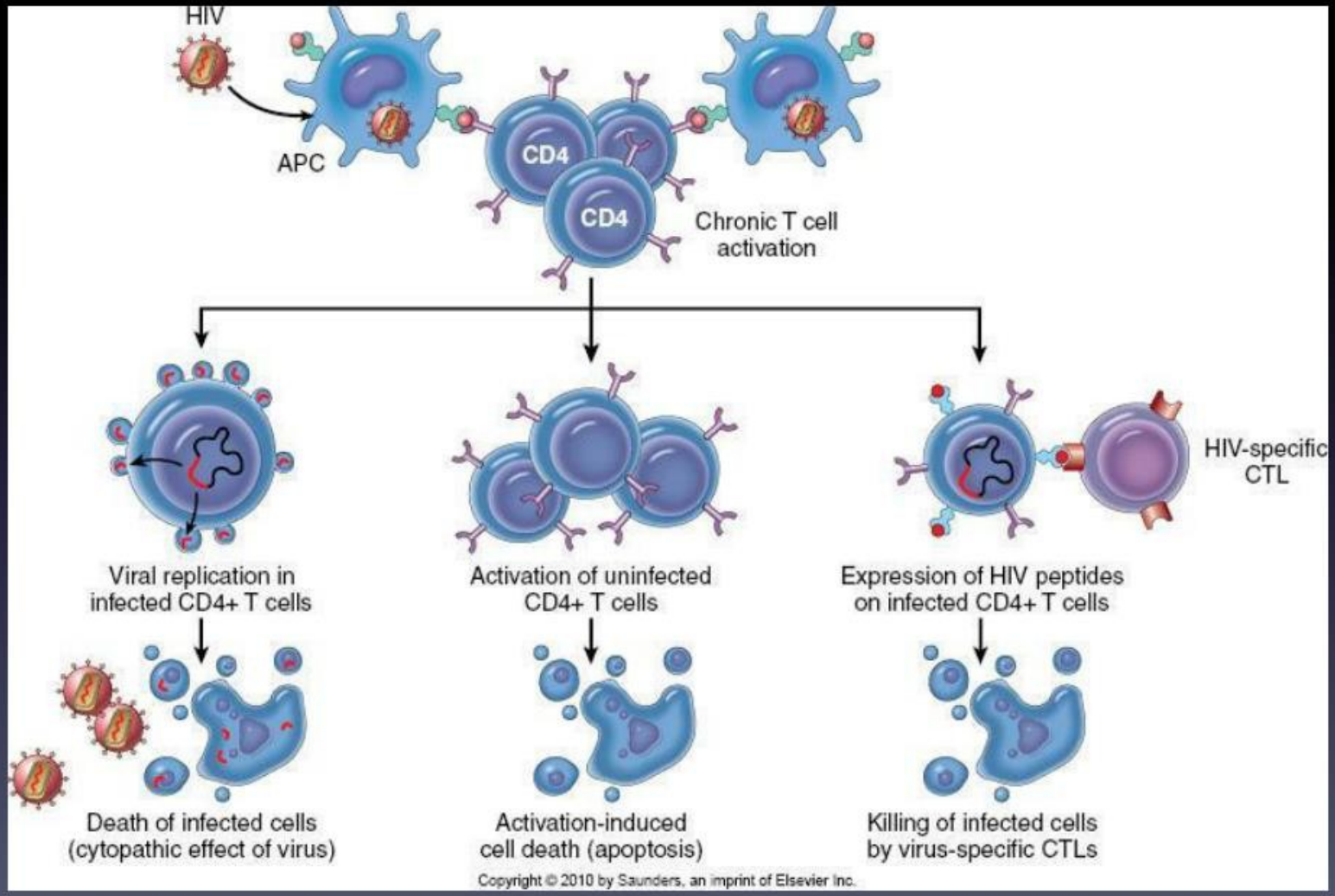
- **If an infected T cell, macrophage, or dendritic cell is activated by external stimuli**, such as another infectious microorganism, the **cell produces intense cytokines and responds to stimuli by initiating transcription of its own gene**.
- The unfortunate consequence of this normal response is that activation of **cells also activates the provirus, leading to the production of viral RNAs and later proteins.**

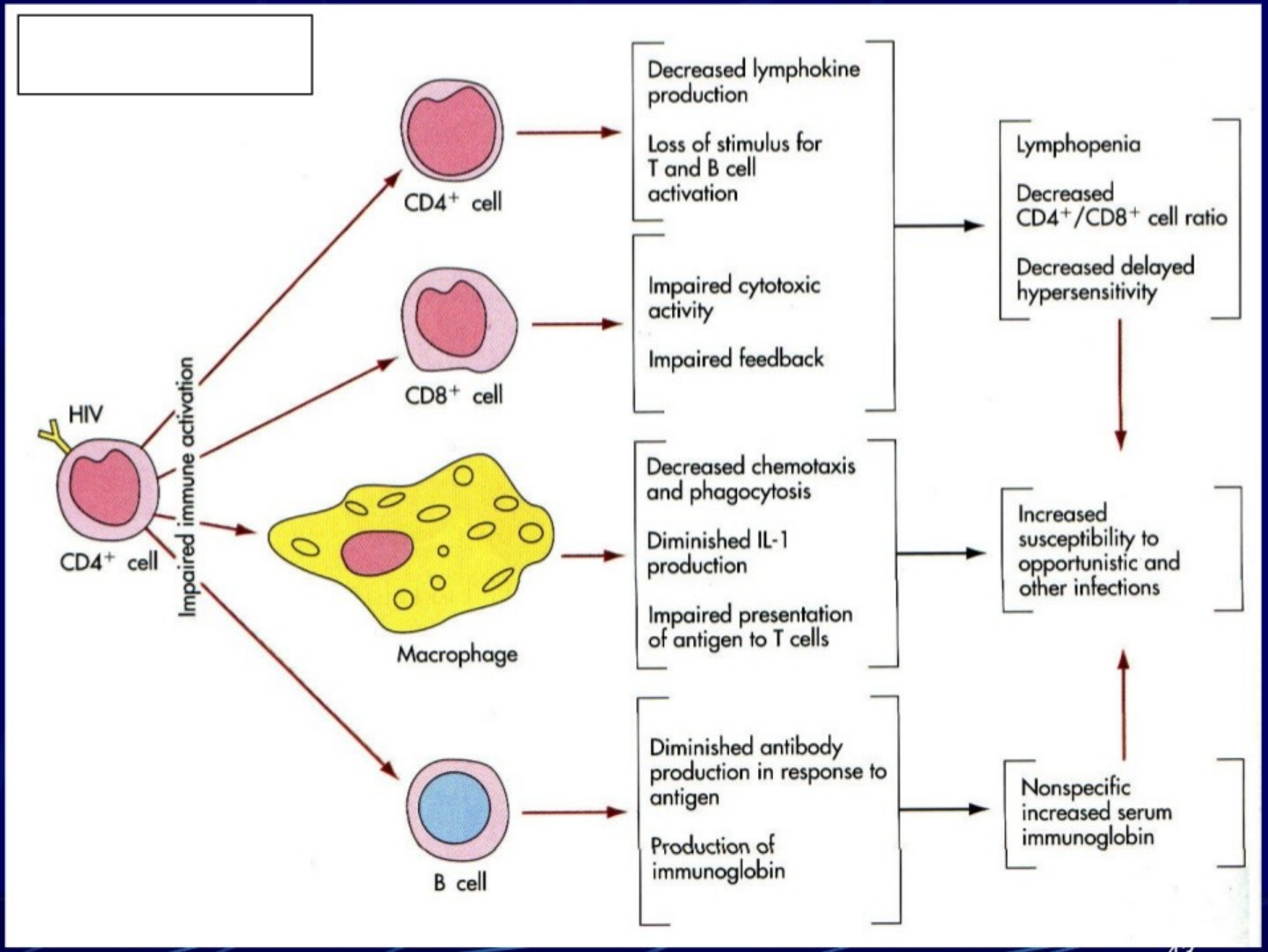

(A)
APC
Peptide–MHC class II
CD4
TCR
ε δ
ε γ
ζ ζ
Lck
Lck
Phosphate
Th cell
Signaling cascade
Th cell activation


(B)
Nucleated cell
Peptide–MHC class I
CD8
TCR
ε δ
ε γ
ζ ζ
Lck
Phosphate
Tc cell
Signaling cascade
Tc cell activation


The T cell response to HIV
TRAIL-induced T cell apoptosis
$T_{Reg}$ cell
Galectin 9
TIM3
Suppression of CD8⁺ T cell response
HIV-specific CD8⁺ T cell
Cytokines and other soluble factors
TCR
MHC class I
Perforin and granzymes
Several months
Viral replication
Perforin pore
Apoptosis
T cell-escape mutations in HIV
• First Env and Nef
• Later Gag and Pol
HIV-infected CD4⁺ T cell
CD4⁺ T cell depletion and immunodeficiency
LAG3
TIM3
CTLA4
PD1
• ↓ MHC class I binding
• ↓ TCR recognition
• ↓ Epitope processing
CD8⁺ T cell response insufficient to clear infection
Decreased T helper cell function
• Chronic infection
• Repeated T cell activation
Upregulation of inhibitory receptors on CD8⁺ T cells
T cell exhaustion (loss of effector function and proliferative capacity)

# Mechanism of CD4 T cell depletion in HIV infection




HIV
CD4+ cell
Impaired immune activation
CD4+ cell
CD8+ cell
Macrophage
B cell
Decreased lymphokine production
Loss of stimulus for T and B cell activation
Impaired cytotoxic activity
Impaired feedback
Decreased chemotaxis and phagocytosis
Diminished IL-1 production
Impaired presentation of antigen to T cells
Diminished antibody production in response to antigen
Production of immunoglobin
Lymphopenia
Decreased CD4+/CD8+ cell ratio
Decreased delayed hypersensitivity
Increased susceptibility to opportunistic and other infections
Nonspecific increased serum immunoglobin

# Human Immunodeficiency virus (HIV)

Thus, the virus forms its nucleus, migrates to the cell membrane, acquires a lipid envelope from the host and is ready to spread as an infectious viral particle ready to infect another cell.

t is possible for the integrated HIV provirus to remain latent in infected cells for months or years, hiding from the patient's immune system.

HIV-1 is the cause of the majority of AIDS cases. HIV-2, a virus associated with it, appears to be the cause of the disease in some cases.

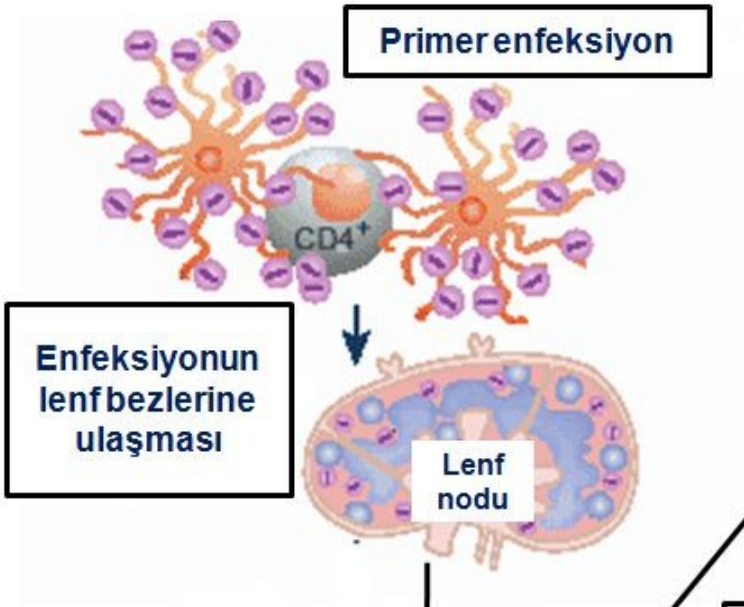
# AIDS PATHOGENESIS

- HIV creates a latent infection of immune system cells and can be reactivated to produce infectious virus.
- **This viral production not only causes death of infected cells but also kills non-infected lymphocytes with the activity of cytotoxic T cells**, and then immunodeficiency and AIDS clinic develops.
- **HIV infection is transmitted through sexual intercourse, the use of contaminated needles in intravenous drug users, transplacental transmission, or transfusion of infected blood and blood products.**

# AIDS PATHOGENESIS

1. After infection, when the virus is detected in the blood, there may be a short-lived acute viremia and the host responds as with any mild viral infection.
2. The virus infects blood CD4 T cells, dendritic cells and macrophages, epithelial entry sites, and most lymphoid organs such as lymph nodes.
3. Dendritic cells capture the virus when it enters the epithelium and transport the virus to the peripheral lymphoid organs, where it infects T cells.
4. The integrated provirus can be activated by another infection, causing the production of viral particles and the spread of the infection.

# Patogenez

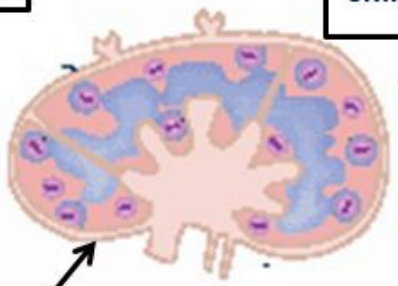



Yoğun viremi

Lenfoid organlara yayılım

HIV-özgül immun yanıt

Virus tutulur ve kronik persistan enfksiyon gelişiş



Sitokin salınımı

CD4+ T lenfosit devrinin hızlanması

Virus çoğalmasının kısmi kontrolü (immunolojik)

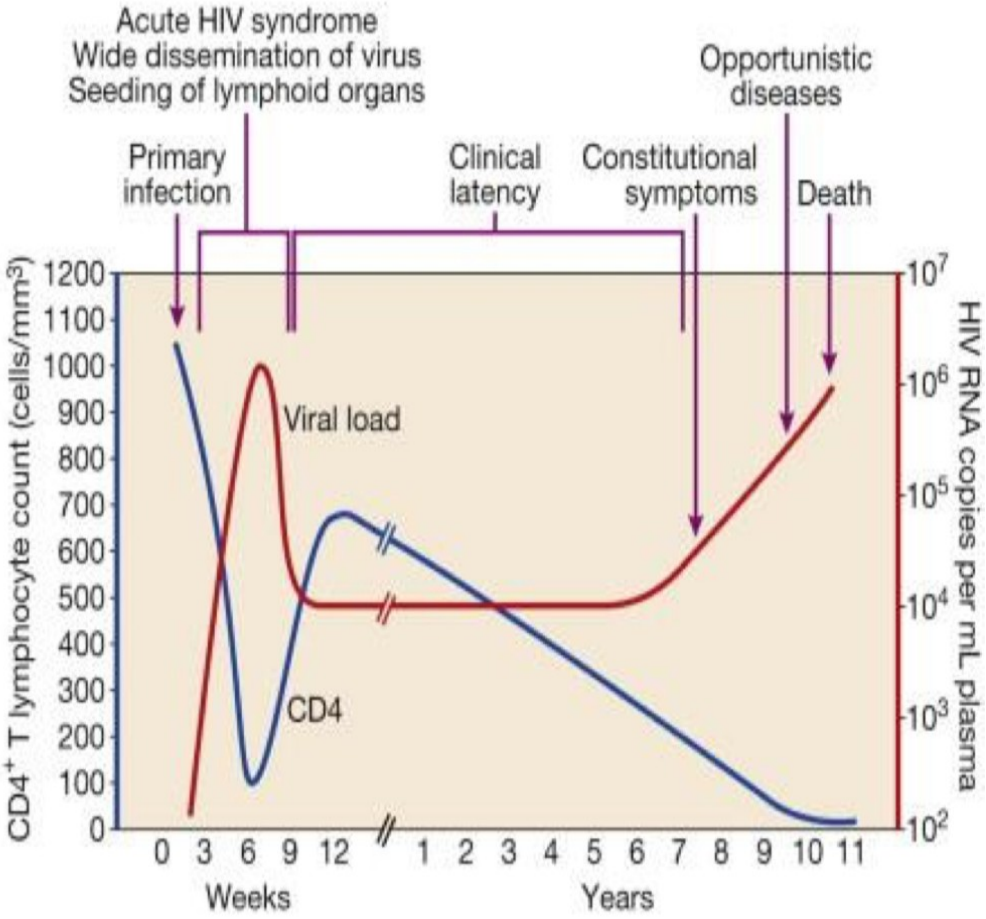
Virus çoğalmsının hızlanması

İmmun sistemin bozulması

# İmunopatogenez

- Akut infeksiyonda doğal bağışık yanıt patojene karşı ilk savunma hattıdır

- Anatomik bariyerin aşıldığı bölge mukozal yüzeylerdir
  - Genital
  - Rektal
  - Oral
  - Plasental



- ✓ Activated **CD4 T cells are the main source of infectious viral particles** during the course of HIV infection; **Dendritic cells and macrophages are the reservoir of infection.**
- ✓ **Depletion of CD4 T cells after HIV infection is associated with the cytopathic effect of the virus.**

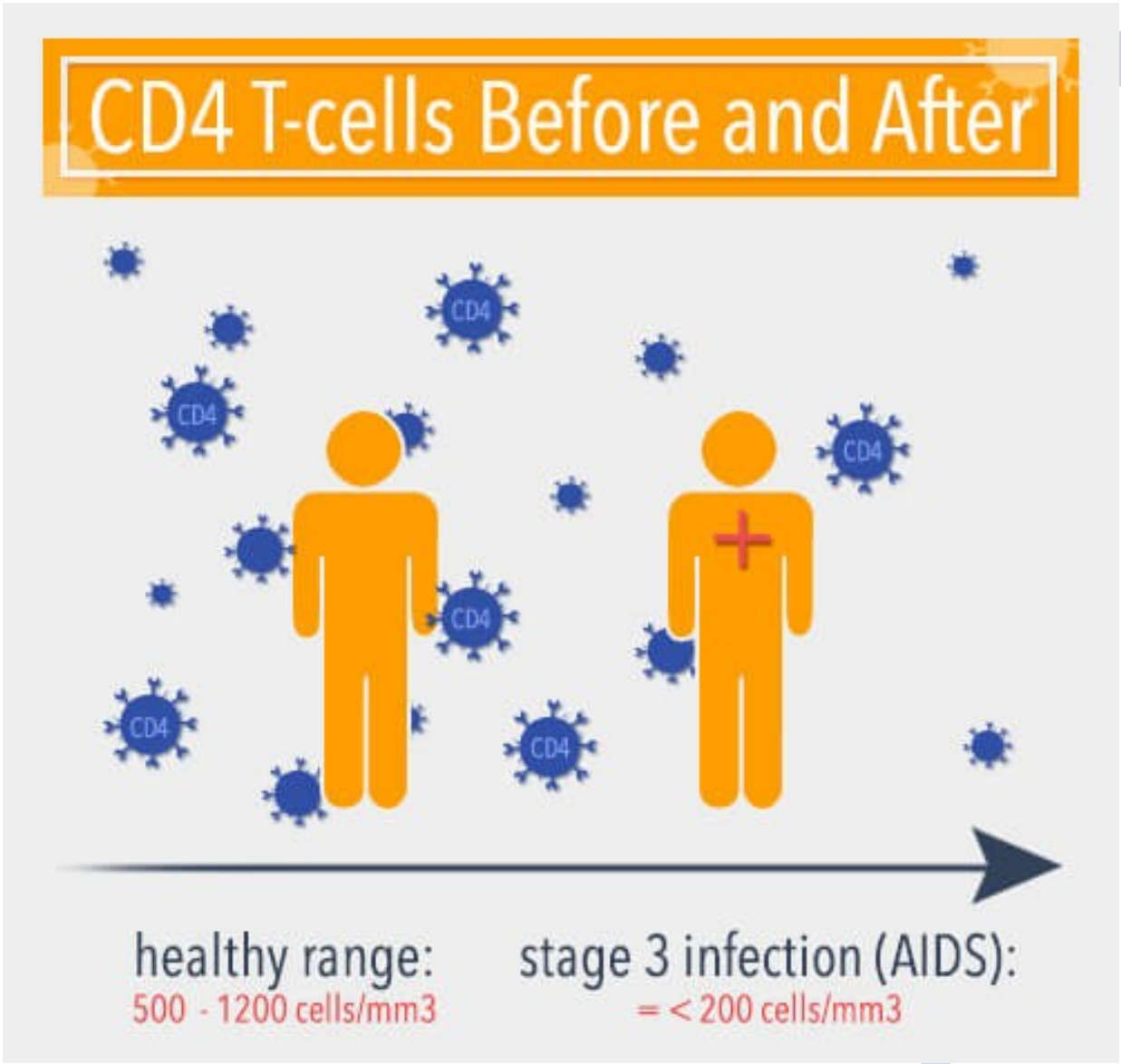
  After the production of viral particles, the death of non-infected cells with the cytopathic effect causes a decrease in the number of T cells.

# Clinical Symptoms of AIDS

- The clinical course of HIV infection is characterized by immunodeficiency.
- Associated with the early onset of viremia after HIV infection, patients may experience a mild acute illness accompanied by fever and malaise.
- This disease state regresses in a few days and the latent period of the disease begins.

# Clinical Symptoms of AIDS

- During the latent period, there is usually a continuous loss of CD4 T cells in lymphoid tissues and the structure of the lymphoid tissue is disrupted.
- As AIDS becomes chronic, **the body becomes predisposed to infections and certain cancers as a primary consequence of immune deficiency.**


CD4 T-cells Before and After
CD4
CD4
CD4
CD4
CD4
CD4
healthy range:
500 - 1200 cells/mm3
stage 3 infection (AIDS):
= < 200 cells/mm3

# HIV

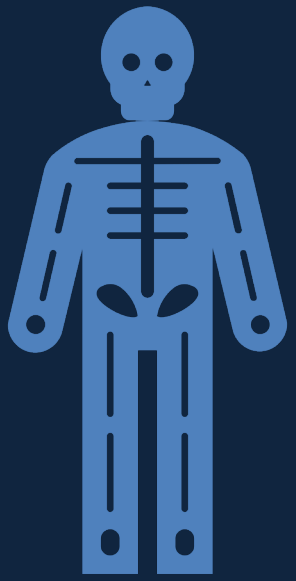
- Infections with viruses normally fought by T-cell-mediated immunity, fungi such as Pneumocystis carinii, and intracellular microorganisms such as atypical mycobacteria are common in patients.
- Some microorganisms are present in the body, but they do not infect healthy individuals with a healthy immune system.
- These microorganisms seize the opportunity to **cause infection in individuals with immune deficiency**, which are called **opportunistic infections.**

# Human Immunodeficinecy Virus (HIV)

- AIDS patients are at risk for extracellular bacterial infections because **the helper T cell-dependent antibody response to bacterial antigens is impaired.**

- Patients may also be predisposed to cancers caused by oncogenic viruses.
- **The two most common types of cancer are B-cell lymphoma, caused by the Epstein Barr virus, and Kaposi's sarcoma, caused by the herpes virus.**
- AIDS patients in the advanced period experience serious weight loss due to the change in metabolism and decreased calorie intake, that is, they are caught in Wasting syndrome.
- Some AIDS patients develop a dementia due to an infection of the macrophages (microglia) in the brain.

# Human Immunodeficinecy Virus (HIV)



- The immune response against HIV is insufficient to control the spread and pathological effect of the virus. Infected individuals produce antibodies and CTLs against viral antigens, and this response is sufficient to limit early acute HIV syndrome.
- **However, these immune responses often cannot prevent the chronic progression of the disease.**

- Antibodies against envelope glycoproteins such as GP120 are ineffective because **the virus rapidly mutates the gp120 region**, which is the target of many antibodies.
- CTLs are ineffective in killing infected cells in chronic AIDS because **the virus inhibits the expression of MHC class I molecules** by infected cells.
- The immune response to HIV reverses the spread of the infection.

# Treatment and Vaccination Strategies

- The current treatment goal of AIDS is to control the proliferation of HIV and the infectious complications of the disease.
- **Drug mixtures that inhibit the activity of viral reverse transcriptase, protease and integrase enzymes are currently applied in the early stages of infection** and provide considerable benefit. This treatment is called highly active antiretroviral therapy.

# Treatment and Vaccination Strategies

- Effective vaccine development is needed to control HIV worldwide.
- A successful vaccine should be able to induce an innate immune response, a high titer of neutralizing antibodies, a strong T-cell response, and a strong mucosal immunity. Another aspect is to provide protection against all subgroups of HIV.