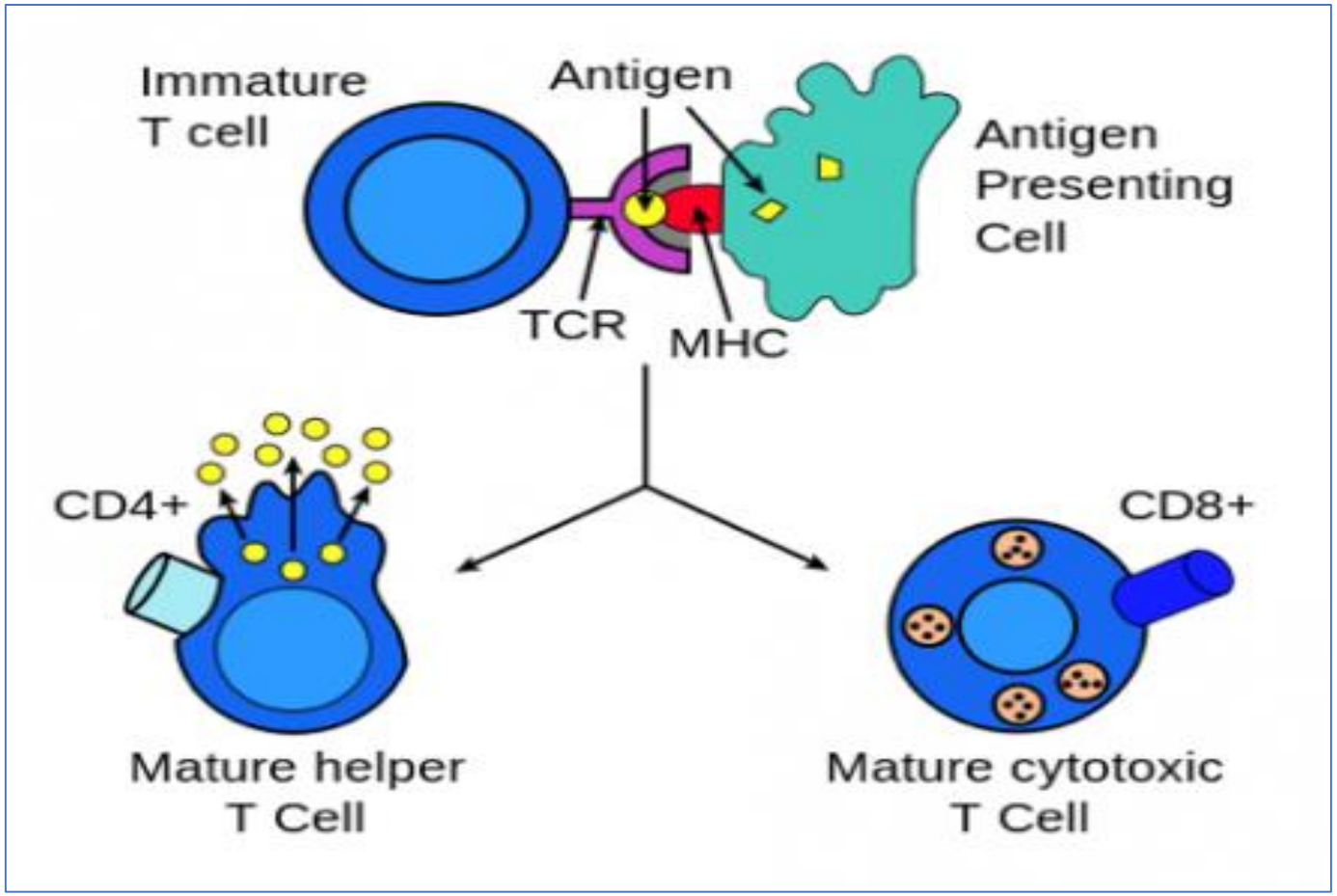
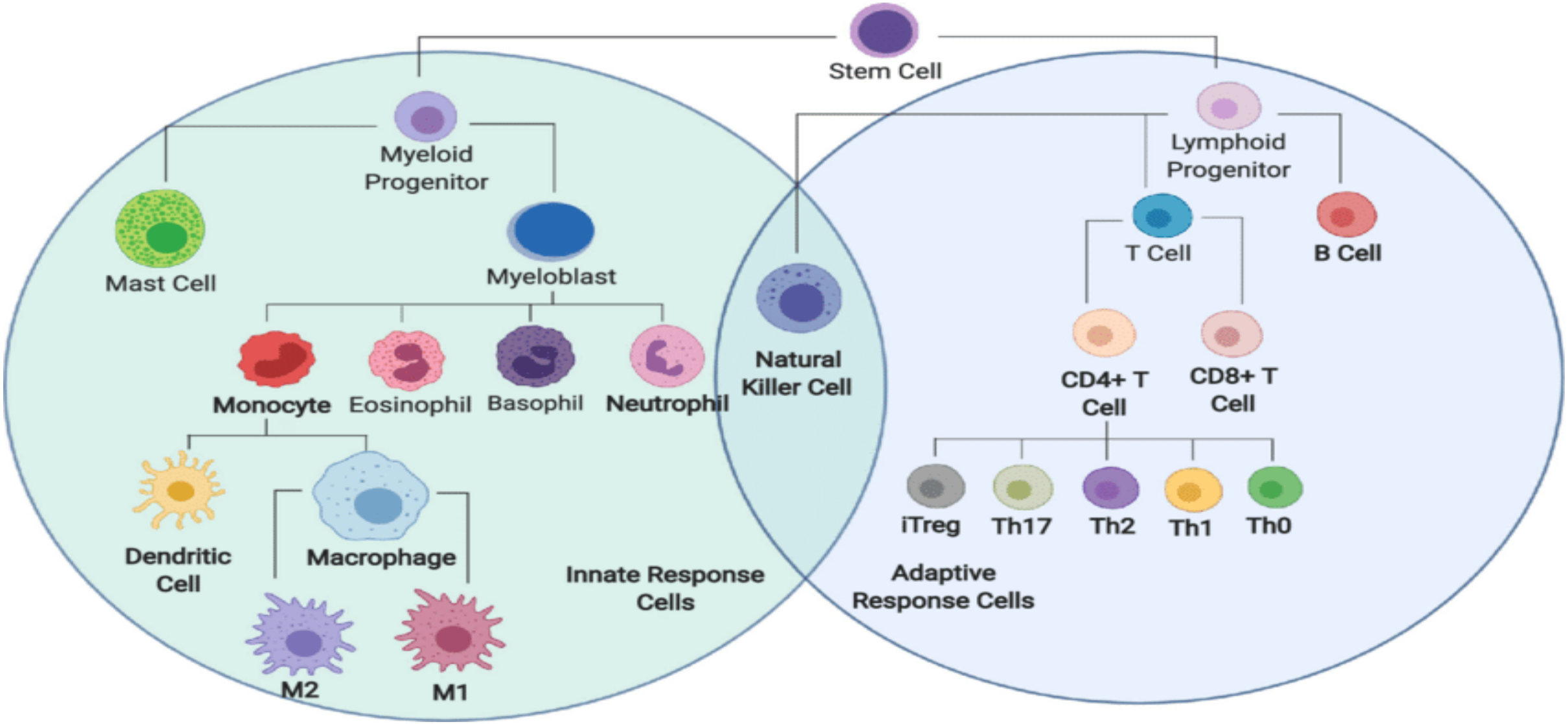
# *Cellular immune response*



# Components of Immune system

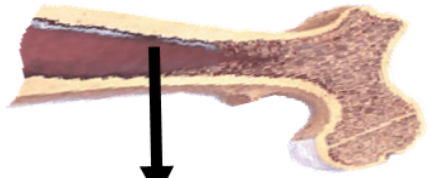


# CELLULAR IMMUNE RESPONSE

**The Immune Cellular response is a component of acquired immunity responsible for eliminating microbes that can survive in phagocytic vacuoles (optional intracellular) or in the cytoplasm of infected cells (mandatory intracellular).**

**This type of immunity is mainly achieved by T lymphocytes.**

# Hematopoietic Cells



Bone Marrow

Hematopoietic Stem Cell

Myeloid Progenitor Cell

Lymphoid Progenitor Cell

RBC

Platelet

Natural Killer Cell

Neutrophil

Eosinophil

Basophil

Monocyte

Dendritic Cell

Macrophage

Inflammation

Innate

T Lymphocytes

- Helper cells
- Regulatory cells
- Cytotoxic cells

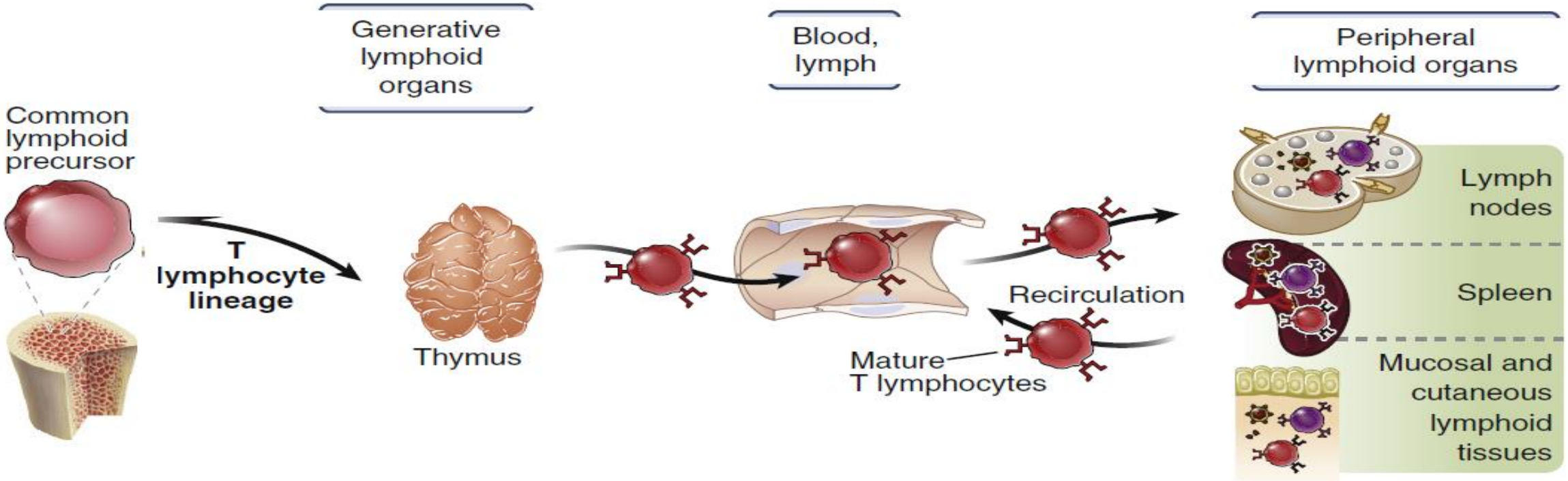
B Lymphocyte

Plasma Cell

Antibodies

Adaptive

- The precursors of T lymphocytes (TL) migrate to the thymus, where under the influence of stromal cells (IL-7) and Hassal corpuscles they differentiate into mature T lymphocytes.
- TL migration from cortex to thymic medulla is accompanied by acquisition of specific surface proteins (receptors: TCR, CD2, CD3, CD4, CD8, etc.).
- At an early stage of selection, only lymphocytes with functional TCR will survive.



- Further development of TL requires cell selection dependent on the pattern recognition of molecules of the Major Histocompatibility Complex (MHC) – negative selection and positive selection – independent processes.

- T lymphocytes, which in the medulla of the thymus recognize with high affinity their own peptides associated with MHC II (dendrite cells and epithelial cells), are exposed to a positive apoptotic signal and negative selection (death by apoptosis) ~ 5%.

- So when the connection of TL receptors to MHC is too tight, these cells will die, to avoid the formation of clones of super-reactive lymphocytes, capable of attacking their own antigenic structures.

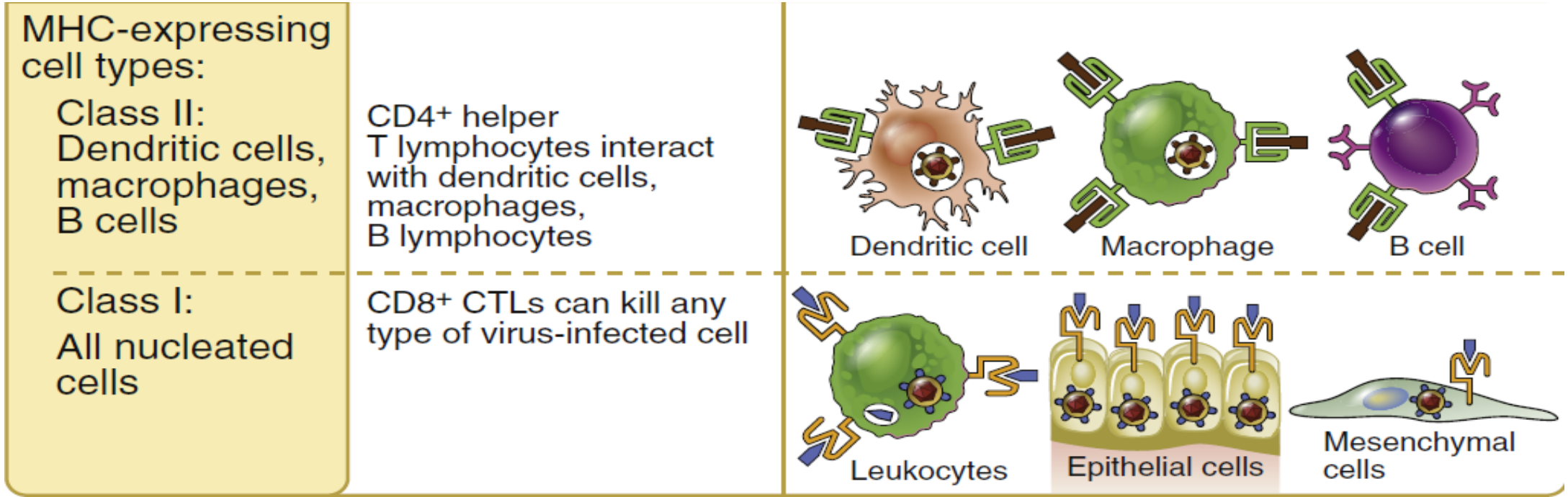
❖Positive selection:

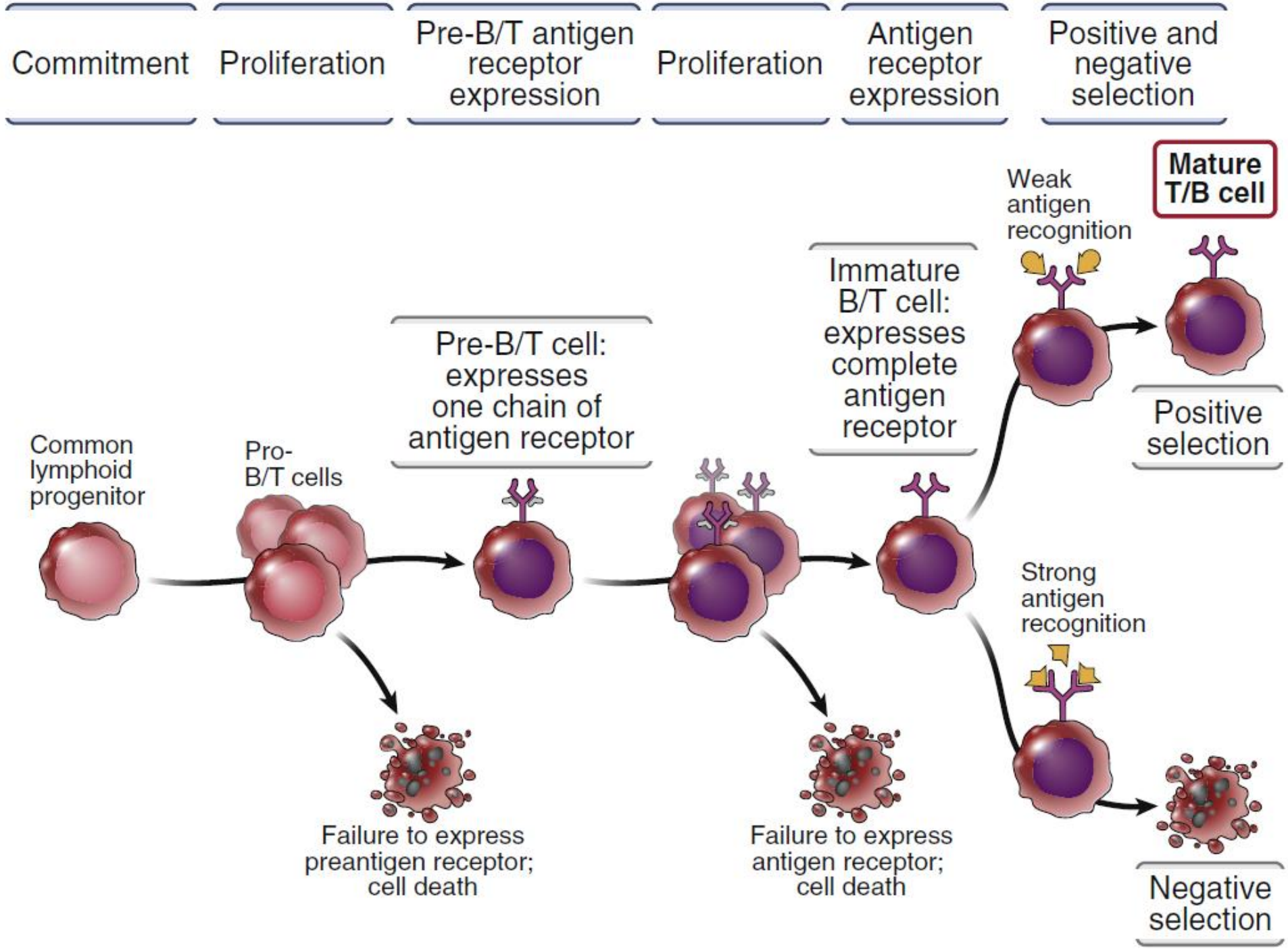
- T lymphocytes, which have a not so strong bond with MHC molecules, they are not exposed to the action of the proapoptotic signal and they will survive.
- Those capable of recognizing peptides in association with MHC I molecules lose the CD4 receptor and become TCD8+ cells.
- Those that recognize MHC II - lose the CD8 receptor and become TCD4+ cells, respectively.

P.S. Dendritic cells express both molecules: MHC I and MHC II !

Naïve CD8 cells will be activated by CMH I.

Naïve CD4 and CD8 cells will be activated by CMH II.



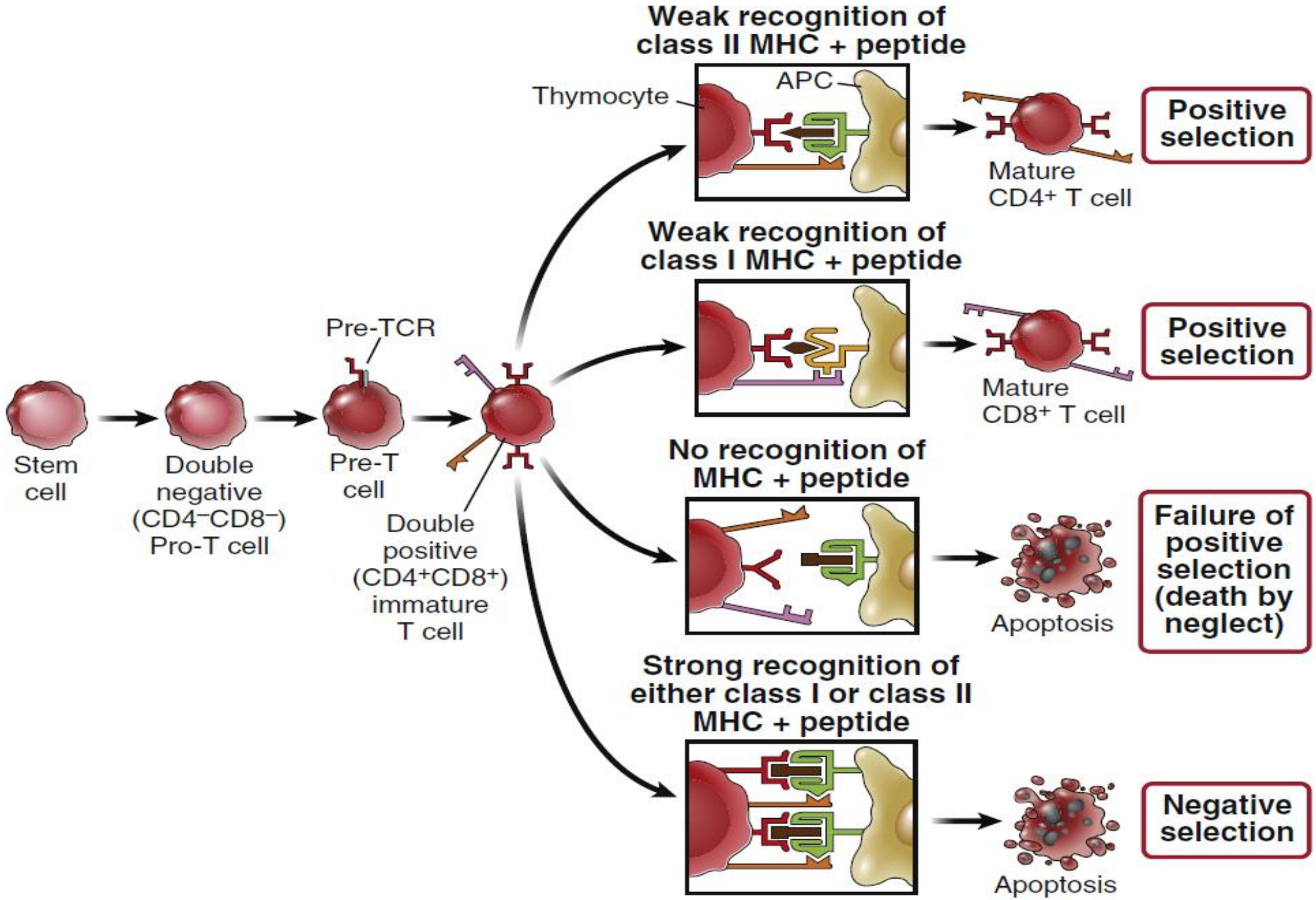

Commitment
Proliferation
Pre-B/T antigen receptor expression
Proliferation
Antigen receptor expression
Positive and negative selection
Common lymphoid progenitor
Pro-B/T cells
Pre-B/T cell: expresses one chain of antigen receptor
Failure to express preantigen receptor; cell death
Immature B/T cell: expresses complete antigen receptor
Failure to express antigen receptor; cell death
Weak antigen recognition
Mature T/B cell
Positive selection
Strong antigen recognition
Negative selection

❖Positive selection – thymus-dependent or general selection:

T lymphocytes survived in the thymus by positive selection recognize peptides expressed by APC in thymocytes.

Important: there may be a danger that these lymphocytes, leaving the thymus, will not recognize as self proteins from other organs

❖This phenomenon does not normally occur due to the presence of a protein, called protein-regulator-autoimmune, which induces the expression of several proteins, imminent and other organs (lung, kidney, etc.).


Weak recognition of class II MHC + peptide
Thymocyte
APC
Positive selection
Mature CD4+ T cell
Weak recognition of class I MHC + peptide
Pre-TCR
Positive selection
Mature CD8+ T cell
Stem cell
Double negative (CD4−CD8−) Pro-T cell
Pre-T cell
Double positive (CD4+CD8+) immature T cell
No recognition of MHC + peptide
Failure of positive selection (death by neglect)
Apoptosis
Strong recognition of either class I or class II MHC + peptide
Negative selection
Apoptosis

**Naïve B and T lymphocytes** are cells that have not yet encountered Ag.

They populate peripheral lymphoid organs, for short period of time exit in the blood circuit for recognition of Ag.

After interaction with Ag follows their activation, proliferation and differentiation into effector cells:

**B lymphocytes** – Ab producing plasmocytes.

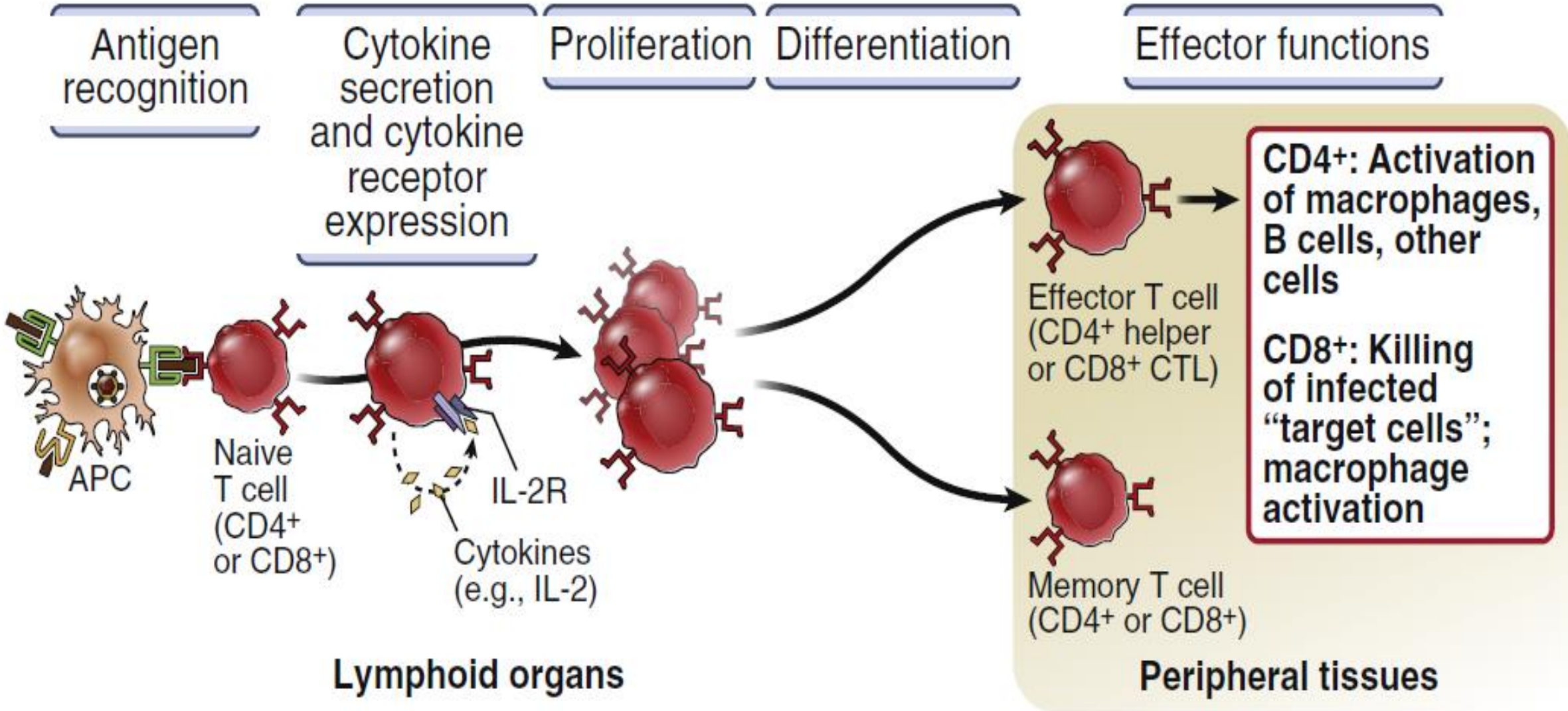
**T-helper (CD4) and T-cytotoxic (CD8) lymphocytes**

B lymphocytes account for a 10-15% share of all lymphocytes, with a short service life of 3-5 days.

T lymphocytes constitute 70% with a long lifespan (months, years).

The CD4/CD8 lymphocyte ratio is 3:2.

The normal value range of CD4 is 500 to 1500 cells/$mm^3$, CD8 - ranging from 150 to 1000/mm 3.

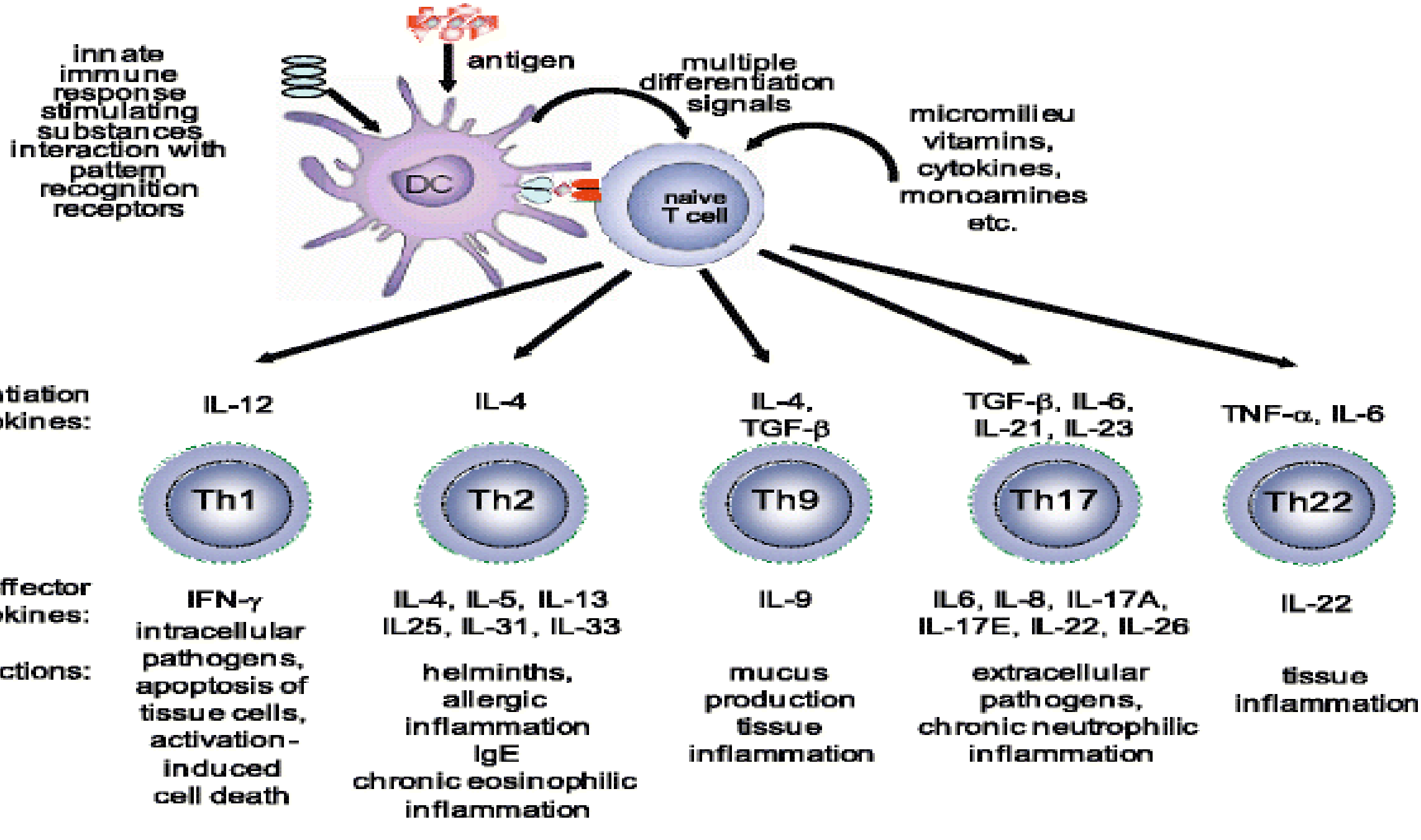

Antigen recognition
Cytokine secretion and cytokine receptor expression
Proliferation
Differentiation
Effector functions
APC
Naive T cell (CD4+ or CD8+)
IL-2R
Cytokines (e.g., IL-2)
Effector T cell (CD4+ helper or CD8+ CTL)
Memory T cell (CD4+ or CD8+)
CD4+: Activation of macrophages, B cells, other cells
CD8+: Killing of infected "target cells"; macrophage activation
Lymphoid organs
Peripheral tissues

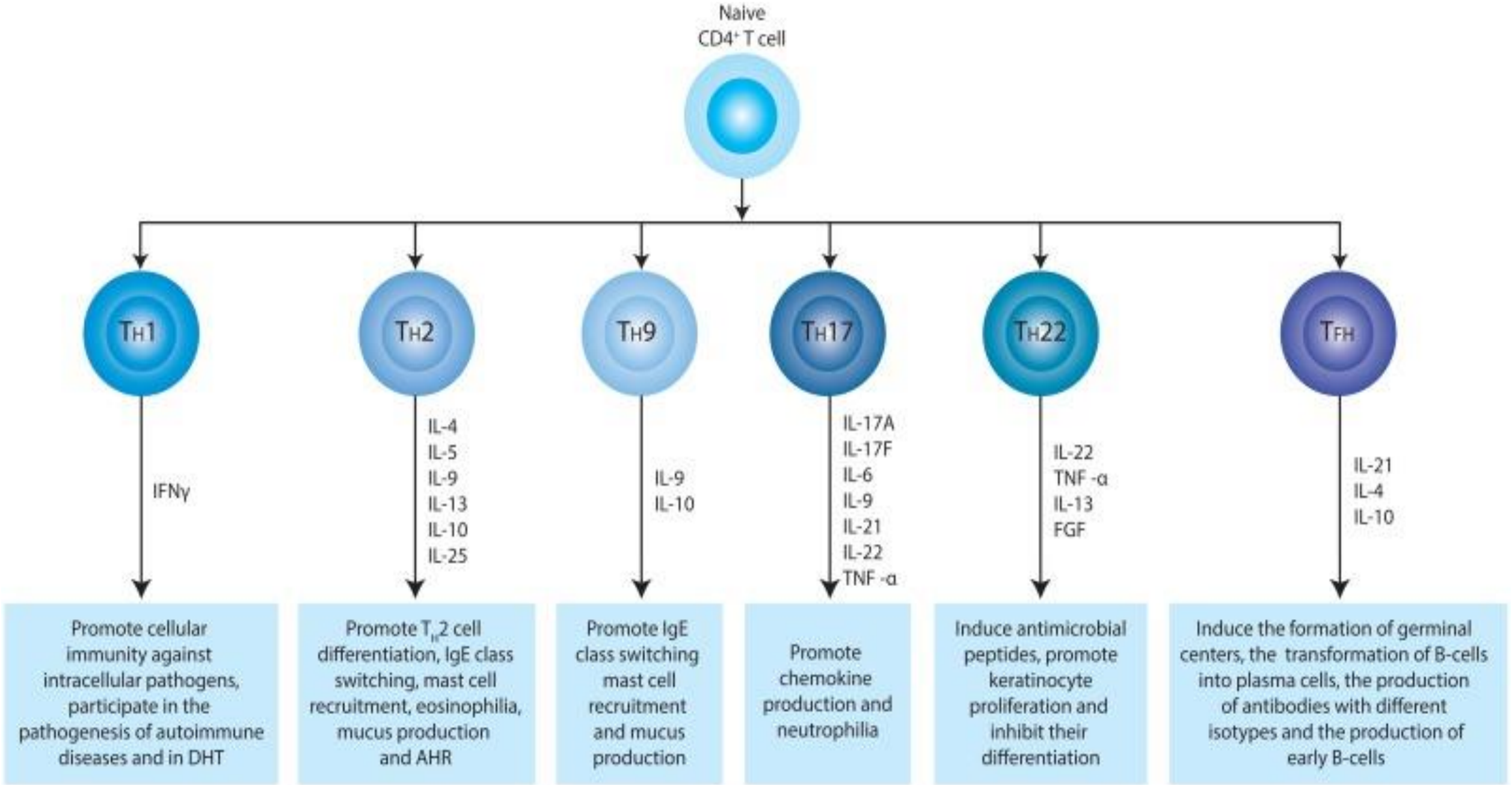
# T-helper lymphocytes:

**Cells that help other immune cells eliminate pathogens from the body:**
**Th1, Th2, Th9, Th17, Tfh (folicular helper), Treg**

**Classification criteria :**

1. **Cytokines that provide CD4 differentiation into subtypes**
2. **Transcription factors participating in lymphocyte differentiation**
3. **Cytokines that are produced and released by these T-helper subclasses**


innate immune response stimulating substances interaction with pattern recognition receptors
antigen
DC
multiple differentiation signals
naive T cell
micromilieu vitamins, cytokines, monoamines etc.
differentiation cytokines:
IL-12
IL-4
IL-4, TGF-β
TGF-β, IL-6, IL-21, IL-23
TNF-α, IL-6
Th1
Th2
Th9
Th17
Th22
effector cytokines:
IFN-γ
IL-4, IL-5, IL-13 IL25, IL-31, IL-33
IL-9
IL6, IL-8, IL-17A, IL-17E, IL-22, IL-26
IL-22
functions:
intracellular pathogens, apoptosis of tissue cells, activation-induced cell death
helminths, allergic inflammation IgE chronic eosinophilic inflammation
mucus production tissue inflammation
extracellular pathogens, chronic neutrophilic inflammation
tissue inflammation


Naive
CD4+ T cell
TH1
TH2
TH9
TH17
TH22
TFH
IFNγ
IL-4
IL-5
IL-9
IL-13
IL-10
IL-25
IL-9
IL-10
IL-17A
IL-17F
IL-6
IL-9
IL-21
IL-22
TNF -α
IL-22
TNF -α
IL-13
FGF
IL-21
IL-4
IL-10
Promote cellular immunity against intracellular pathogens, participate in the pathogenesis of autoimmune diseases and in DHT
Promote T$_H$2 cell differentiation, IgE class switching, mast cell recruitment, eosinophilia, mucus production and AHR
Promote IgE class switching mast cell recruitment and mucus production
Promote chemokine production and neutrophilia
Induce antimicrobial peptides, promote keratinocyte proliferation and inhibit their differentiation
Induce the formation of germinal centers, the transformation of B-cells into plasma cells, the production of antibodies with different isotypes and the production of early B-cells

# Why so many subclasses of T-helper lymphocytes are needed?

1. Various types of pathogens and infections.
2. Different target cells.
3. Pathogens with particularly high resistance of their breakdown by macrophages by phagocytosis.
4. Pathogens too large in size to be effectively phagocytes (eg, parasites).

**A common pattern:**

**T-helper releases various cytokines, which communicate and help other immune cells destroy and eliminate Ag from the body.**

# Th1

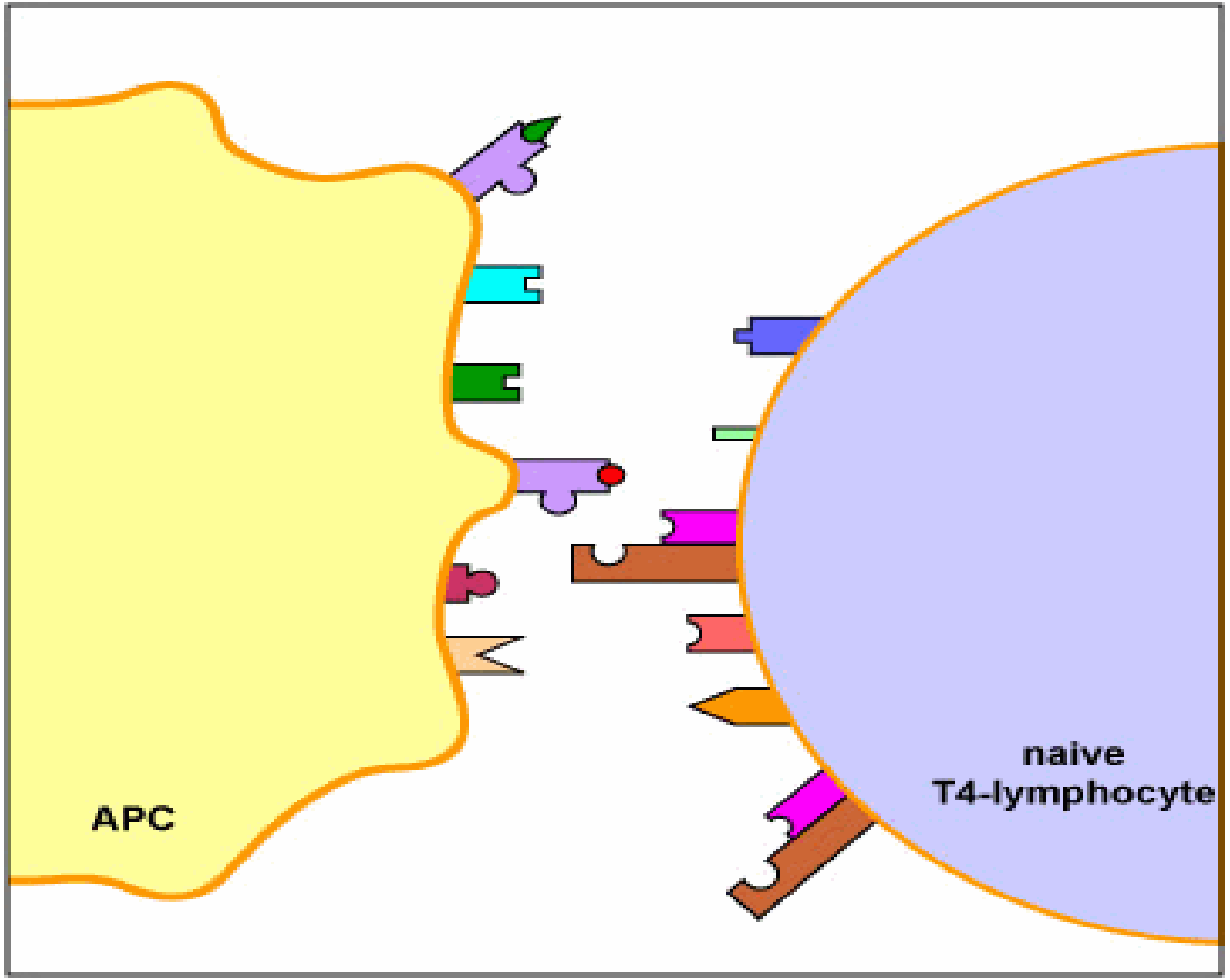
Dendritic cells (DC) and macrophages activated by intracellular pathogens lead to activation of Th-naïve lymphocytes and ensure its differentiation into Th1 via IL-12, IL-18 and type 1- INF (gamma and beta).

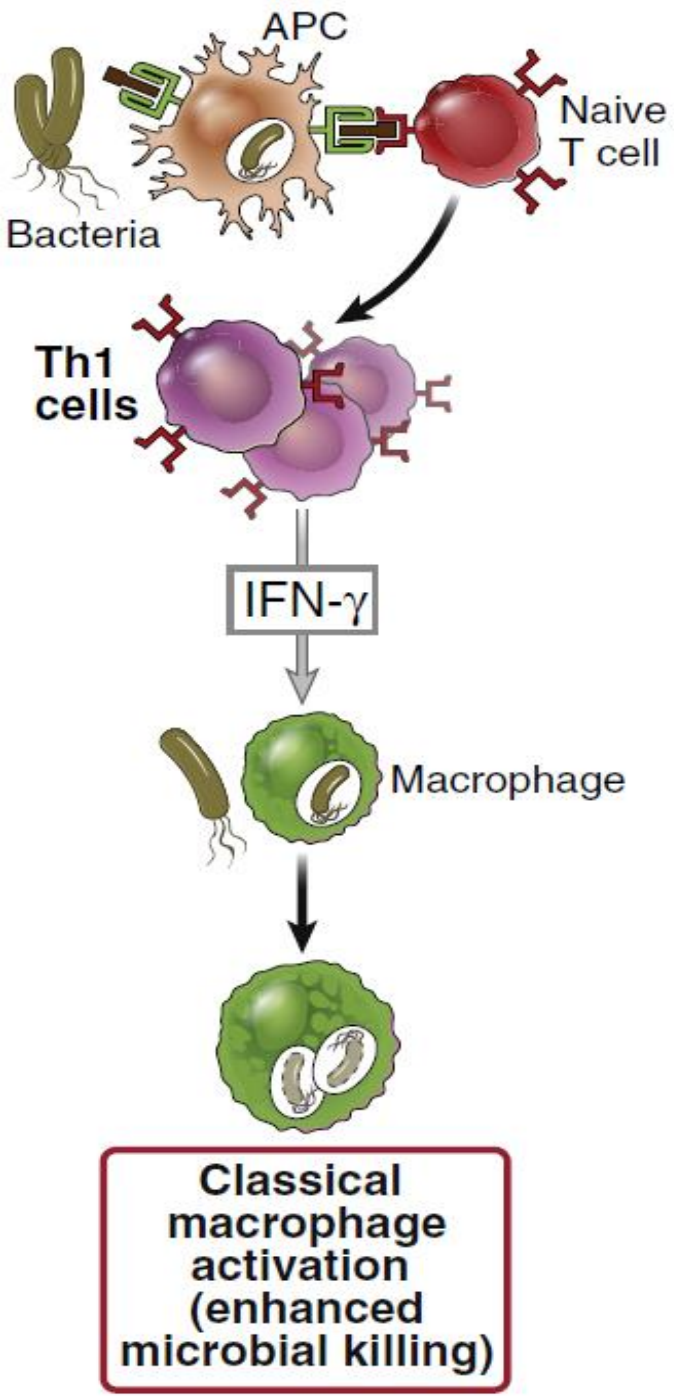
IL-18 potentiates the action of IL-12.

The transcription factor STAT4 plays an important role in the differentiation process.

STAT - Signal transducer and transcription activator 4 - transcription factor belonging to the STAT family of proteins.

Co-stimulators: CD40L-CD40R, B7-CD28, CD2-LFA3 (Lymphocyte function associated antigen-3).


APC
naive
T4-lymphocyte




# Th1

Once T-naïve is differentiated into Th1, the latter secretes INF-gamma, which activates macrophages and thus facilitates phagocytosis of the pathogen.

**INF-gamma** also stimulates the production of antibodies by plasma cells.

**IL-2 (T-lymphocyte growth factor)** released by Th1 plays a notable role in Th1 lymphocyte proliferation through its autocrine action.

**Th1 also** produces TNF-beta, a cytokine involved in inflammation related to the phagocytosis process.

# Th2

## mediates the attack of extracellular pathogens and allergens

In the attack with parasites APC (dendritic cell) releases IL-4, which provides Th-naïve differentiation into Th2.

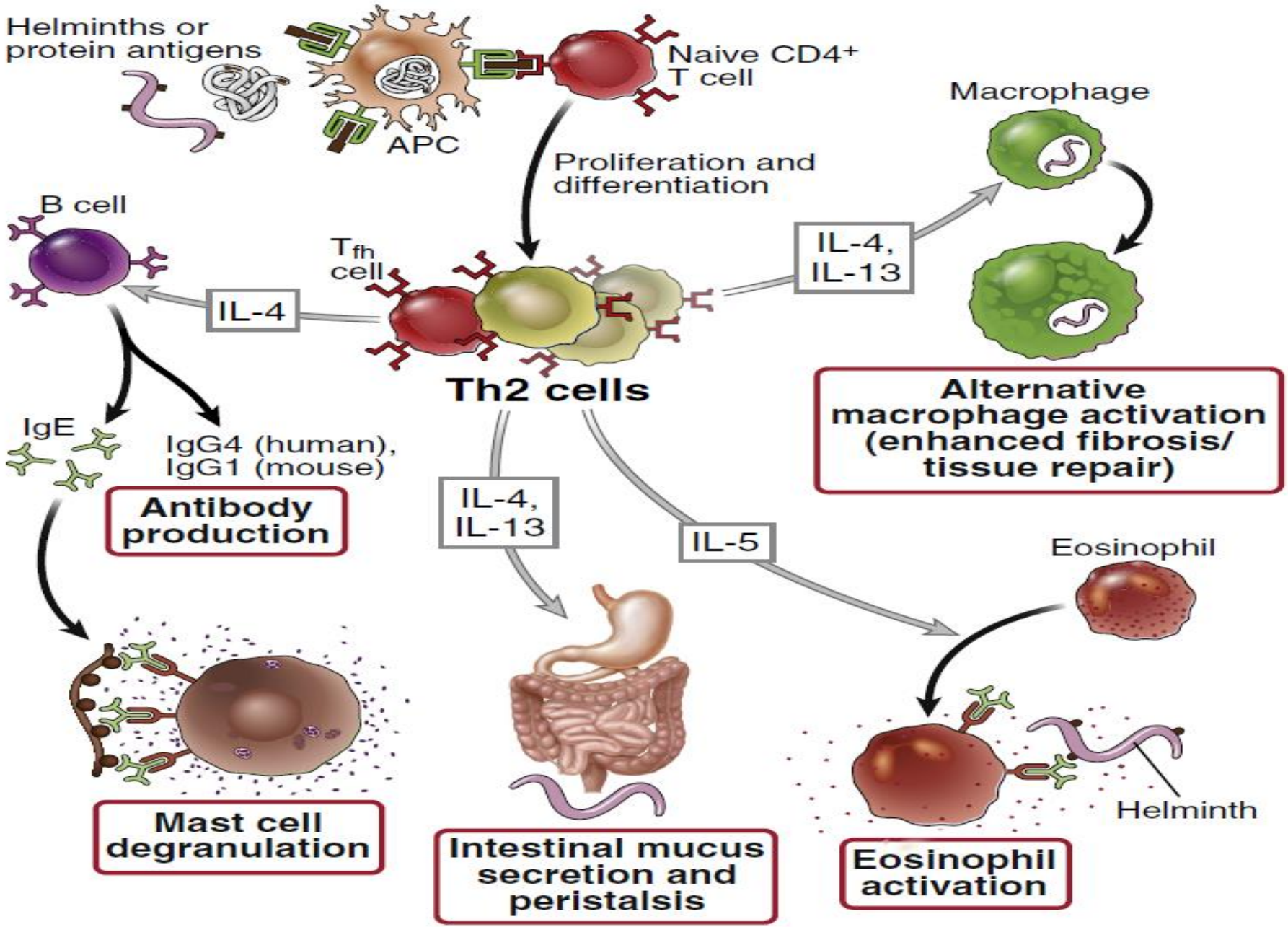
**Th2** releases cytokines IL-4, IL-5, IL-9, IL-10, IL-13.

**IL-4** stimulates B lymphocytes for IgE production.

**IL-5 and IL-9** stimulates mast cells and eosinophils.

**IL-13** stimulates mucus production in the intestinal tract.

The released IgE binds the parasite. Subsequently, mast cells and eosinophils bind to the Fc fragment of IgE covering the parasite. The enzymes released by degranulation of these cells will kill the parasite.


Helminths or protein antigens
APC
Naive CD4+ T cell
Proliferation and differentiation
Macrophage
B cell
Tfh cell
IL-4
IL-4, IL-13
Th2 cells
IgE
IgG4 (human), IgG1 (mouse)
Antibody production
Alternative macrophage activation (enhanced fibrosis/ tissue repair)
IL-4, IL-13
IL-5
Eosinophil
Mast cell degranulation
Intestinal mucus secretion and peristalsis
Helminth
Eosinophil activation

Th1-related responses are implicated in the pathogenesis of organ-specific autoimmune disorders, Crohn's disease, sarcoidosis, acute kidney allograft rejection, and unexplained recurrent abortions.

In contrast, allergen-specific Th2 responses are responsible for atypical disorders in genetically susceptible individuals. In addition, Th2-related responses play a pathogenetic role in progressive systemic sclerosis and fibrous alveolitis.

# Th17

## The name derives from IL-17 produced by these lymphocytes

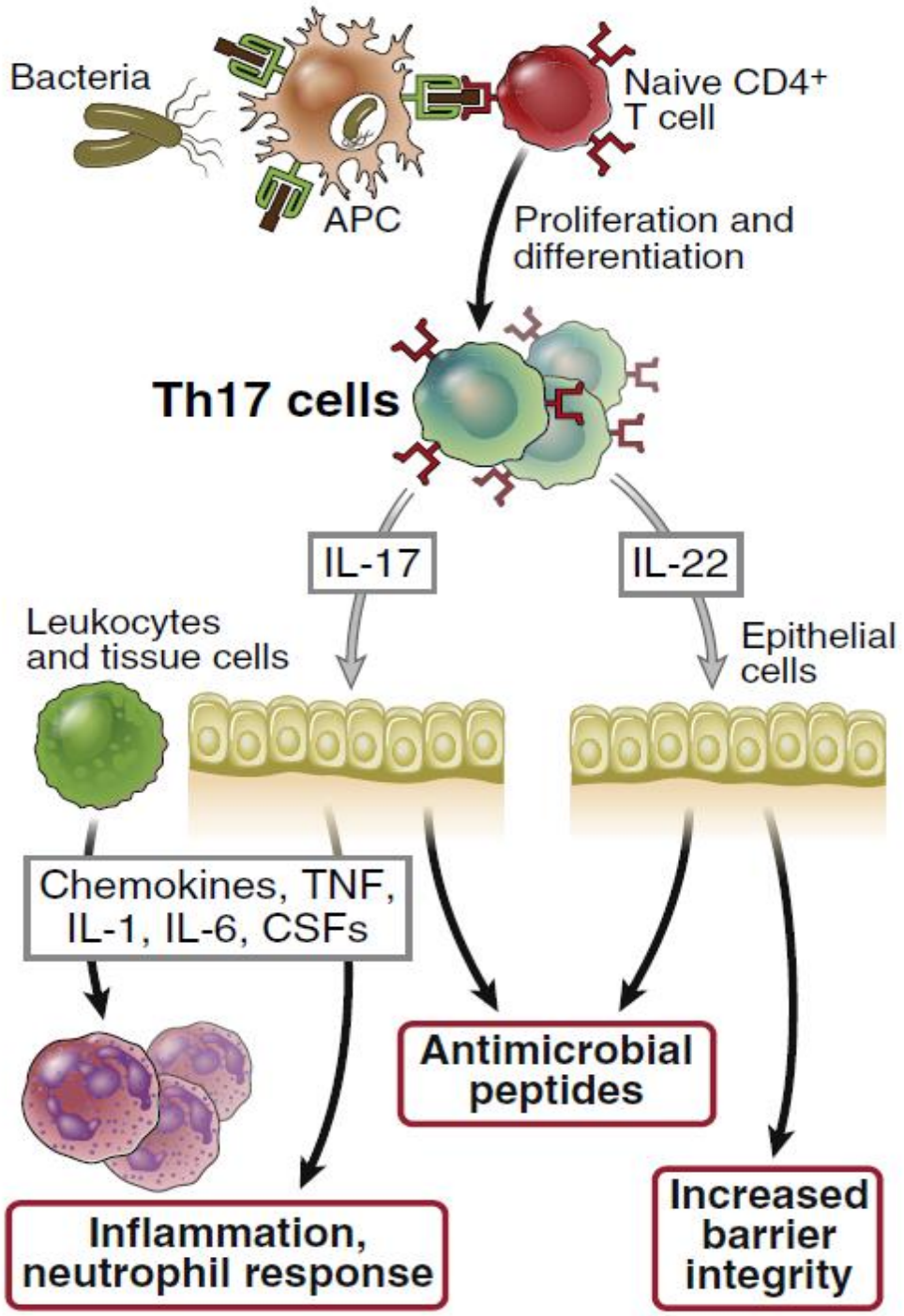
**In attack with extracellular bacteria and fungi CD will produce differentiation**

**Th-naiv in Th17 under the action of IL-6 and TGF-beta (growth transforming factor).**

**TH-17 releases IL-17 and IL-22.**

**IL-17 participates in the recruitment of neutrophils (potentially pro-inflammatory). Neutrophils must destroy extracellular bacteria and fungi, including through the phenomenon of NETosis (neutrophil death and trap formation from proteases).**

**IL-22 stimulates epithelial cells to produce antimicrobial proteins.**



# Th17

**Th17 cell-mediated inflammatory response is associated with diseases that have an important inflammatory component, such as:**

**rheumatoid arthritis**

**systemic lupus erythematosus (SLE)**

**bronchial asthma**

**Transplant rejection.**

**IL-17 acts in synergism with TNF-alpha leading to activation of genes controlling pro-inflammatory factors.**

**IL-17 binds with fibroblast, epitheliocyte and endotheliocyte receptors, causing the release of IL-8 and MCP-1 (the chemoattractant protein of monocytes).**

**Important: IL-17 and IL-22 stimulates the expression of defensins (proteins in the epidermis with antibacterial effect).**

# Th22

**Th-22 derives from plasma dendritic cells (a set of CDs circulating in plasma and lymph) under the action of IL-6 and producing large amounts of INF-type 1.**

**Transcriptional profile of Th-22 It also includes genes coding for FGF (fibroblast growth factor), IL-13, and chemokines involved in angiogenesis and fibrosis.**

**Th-22 stimulate keratinocyte proliferation and have a pathogenetic role in the evolution of psoriasis.**

## Th reg (regulatory lymphocytes) known as suppressor lymphocytes: 5-15% of T-CD4

**Once the pathogen is destroyed Th reg tempers the activity of the immune system. So, Th reg prevents autoimmune pathology.**

**Mechanisms:**

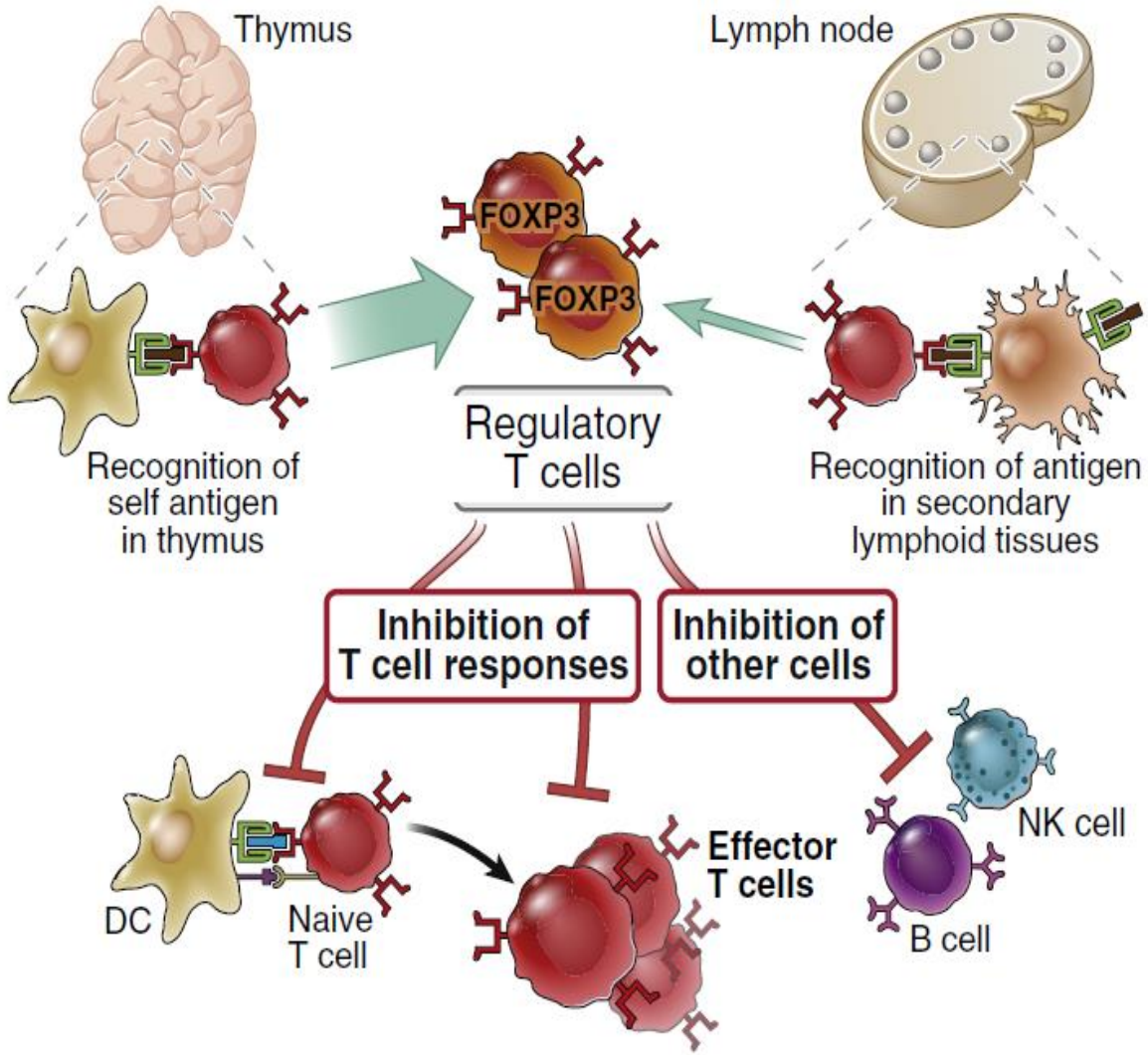
**1. Th reg produces TGF-beta and IL-10, which provide attenuation of the immune response:**

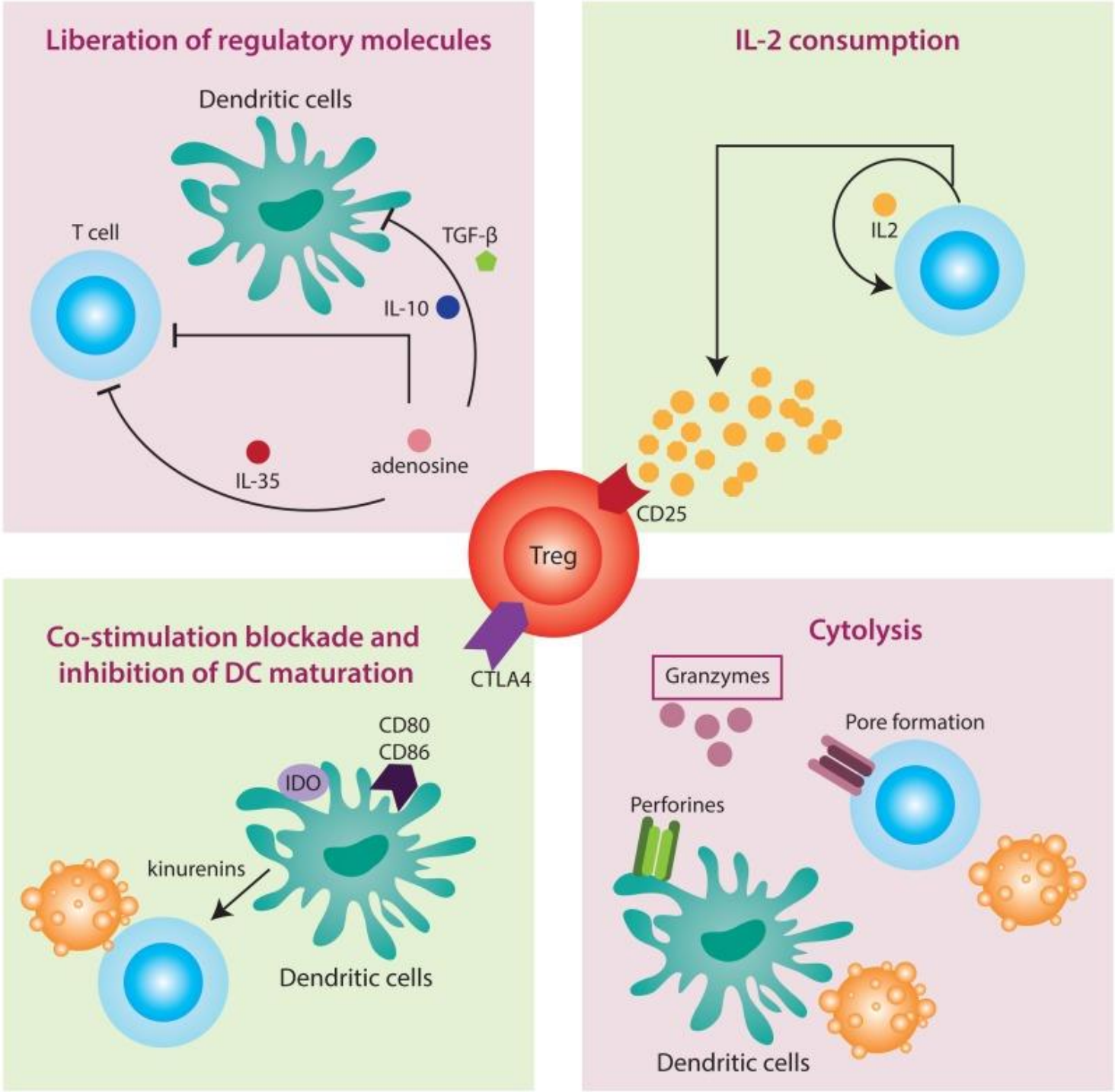
**2. IL-10 has a suppressive effect on macrophages.**

**3. TGF-beta increases the population of Th reg.**

**4. IL-10, TGF, IL-35 and adenosine inhibit the secretion of cytokines specific to phenotypes Th1, Th2 and Th17.**

**5. CD25 – receptor to IL-2. It has a competing effect with IL-2 versus effector immune cells.**






**CTLA4 –**
**cytotoxic T-lymphocyte antigen 4 - may block or remove B7 molecules made by APCs and make these APCs incapable of providing costimulation via CD28 and activating T cells.**

**Granzyme and perforin will destroy the effective immune cells.**

# Tfh: T- follicular helper cells

**Tfh has ability to express costimulatory molecules such as CD40 and ICOSL (inducible T cell costimulator molecule-ligand) at the highest level.**

- **Tfh stimulates the production of antibodies by B lymphocytes through the release of:**
- **Transcription factor BCL-6 (B-cell lymphoma 6), a protein encoded by BCL-6 genes on chromosome 3 and involved in controlling the proliferation of immature splenic dendritic cells. Increased expression of the BCL-6 gene may lead to the risk of developing non-Hodgkin's lymphoma.**
- **IL-4**
- **IL-10**
- **IL-21**

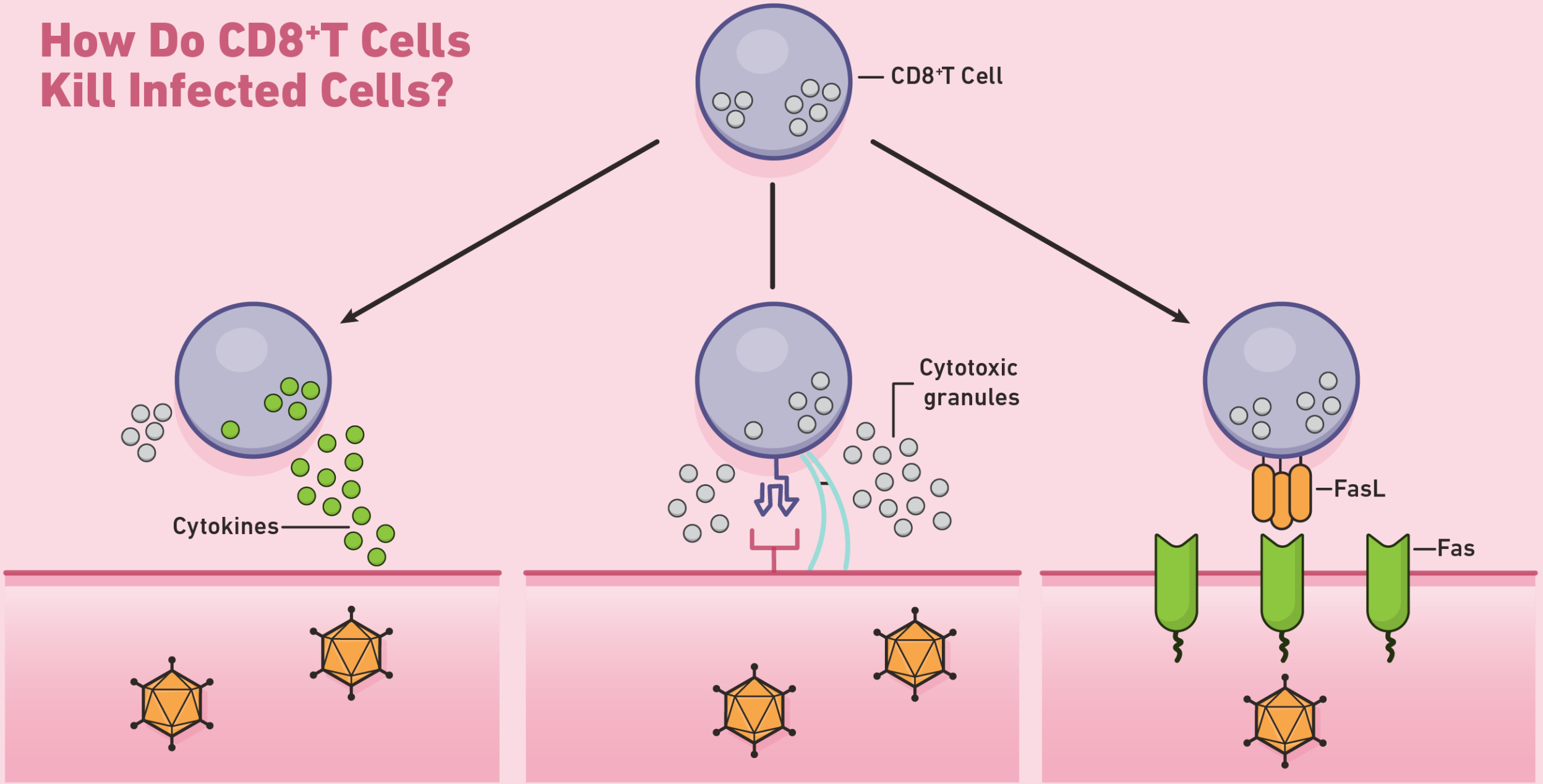
# T-CD8 lymphocytes (cytotoxic)

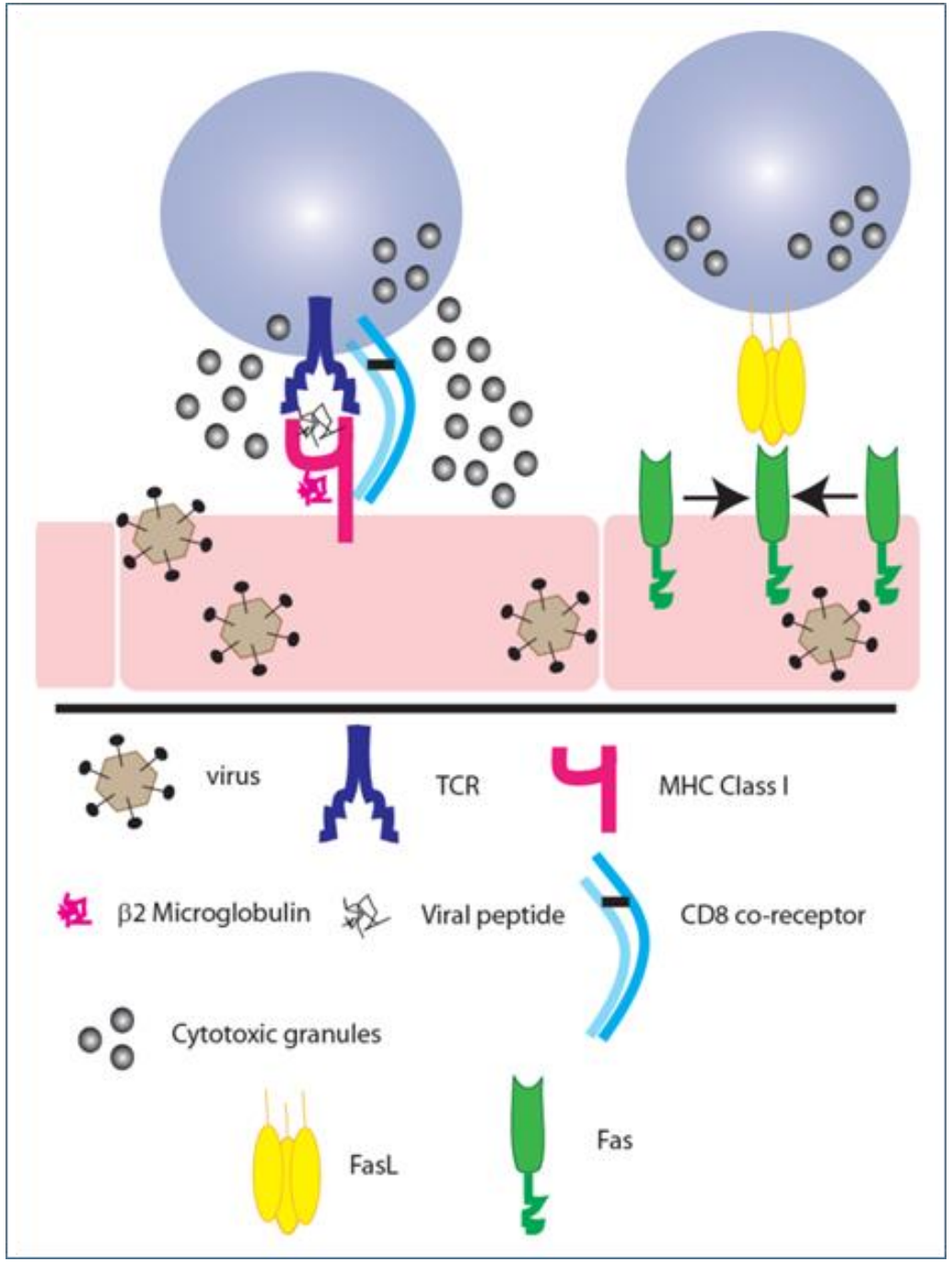
**They impose themselves within adaptive immunity through the ability to destroy cancerogenic and virus-infected cells that have expressed the non-self antigen by MHC- I, recognized by TLR and CD8 receptors.**

**The cytotoxic effect of T-CD8 is achieved by 3 basic mechanisms:**

**1. The release of perforin and lysis of the cell. Release of granzyme and apoptosis of the cell (granzyme B activates caspase-1).**
**2. Ligand expression for the Fas receptor (eg, CD95), the interaction of which will lead to the onset of apoptosis on the extrinsic pathway.**
**3. T-CD8 can also release TNF-alpha as well as IFN-γ, cytokines important in antiviral defense and control of tumor growth proliferation.**

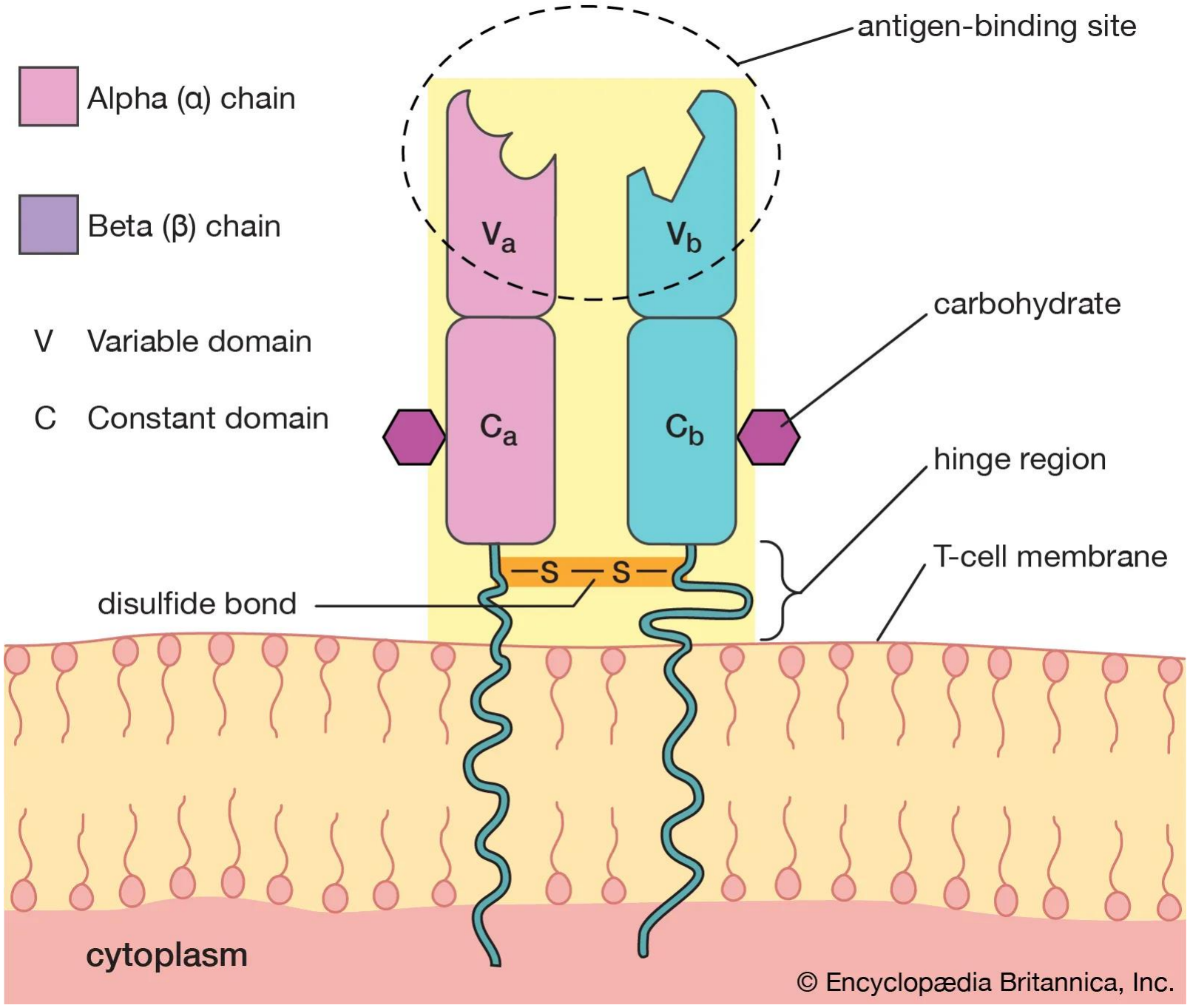
# How Do CD8⁺T Cells Kill Infected Cells?






**The complexity of interaction T-CD8 with virus-infected cell, which through MHC I expresses for T lymphocyte antigenic epitope.**

**CD8 is a dimeric costimulator.**




# T-lymphocyte antigen receptor structure - TCR

**Some professional antigen presenting cells can phagocyte infected or dead tumor cells or cellular debris, and following Ag processing, it is expressed with the MHC- I to T-CD8 lymphocytes – the cross-presentation phenomenon.**

**The main costimulatory molecule for T-CD8 is CD28.**

**The memory subset of CD8+ T cells can be classified into three distinct groups:**

1. **central memory cells,**
2. **effector memory cells,**
3. **tissue-resident memory cells.**

**1. Central memory cells are resident lymphocytes in lymphoid tissue that usually respond to secondary infections through rapid proliferation. In humans, they are phenotypically characterized by co-expression of CD127, CD27, and CD28 surface markers.**

**2. Effector memory cells circulate throughout the body ready to find out and kill target cells that match the antigen. Their proliferation and renewal activity is low.**

**3. Tissue-resident memory cells - mature cells that are "waiting" for secondary infections at the initial site of injury or invasion.**

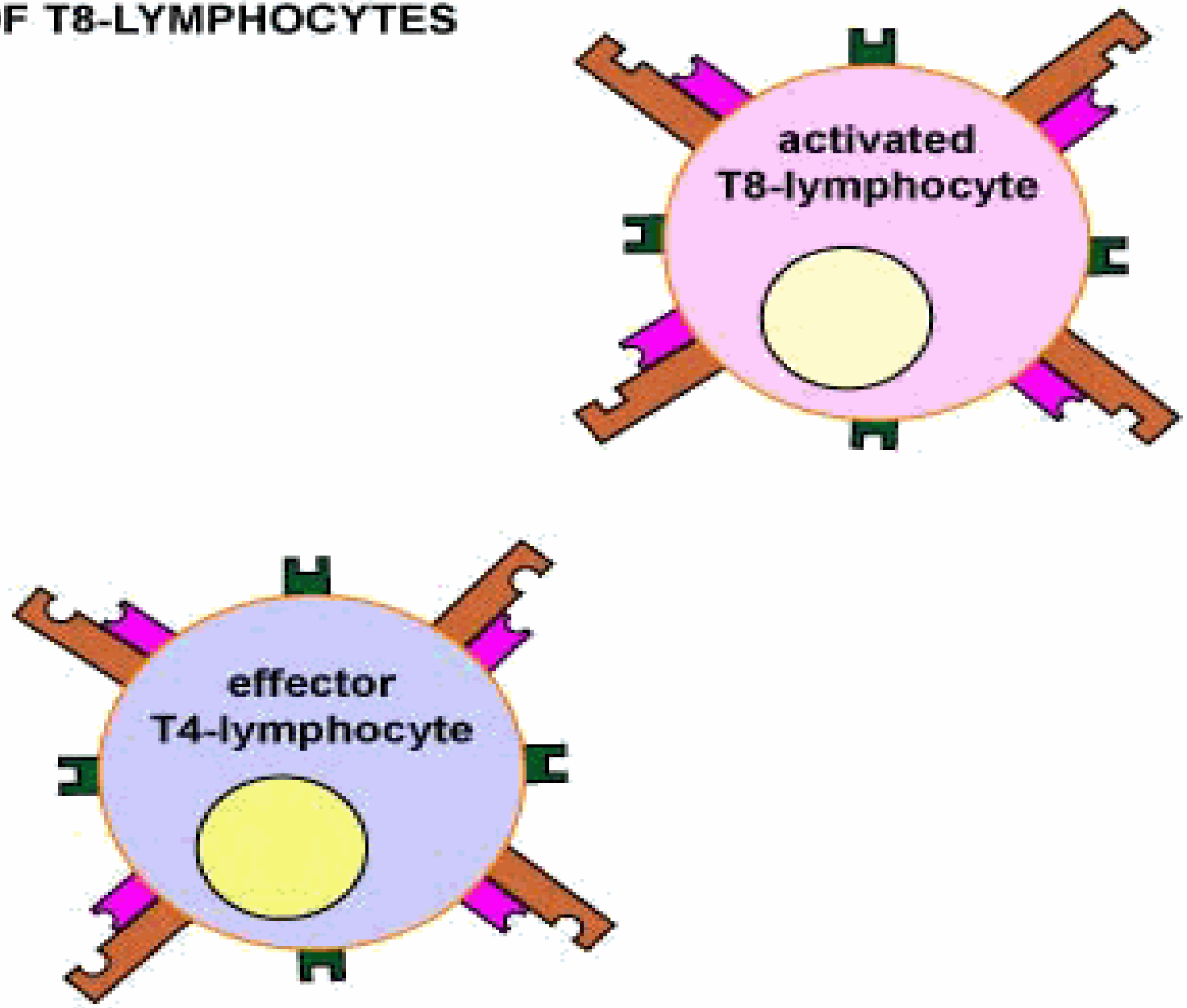
**Important:**

1. **T-CD8 may suppressively influence HIV replication in T-CD4 lymphocytes without lysis of it. T-CD8 is thought to release a virus replication inhibition factor (a protein not found in other cells, resistant to heat stress, acidosis).**

**2. T-CD8 can release a set of cytokines (IFNγ, TNFα, IL-2) and chemokines) and thus stimulate immune cell recruitment.**

**3. The uncontrolled activity of T-CD8 lymphocytes may contribute to autoimmune responses against healthy cells.**

## INTERLEUKIN-INDUCED PROLIFERATION OF T8-LYMPHOCYTES




**There may be important cooperation between T-CD8 and T-CD4 as increasing the proliferation capacity of CD8 by IL-2 released by CD4.**

**In the same time, IL-2 release by nearby CD4 cells is stimulated by IL-2 released by CD8.**

# Important:

**Immunological memory** – The ability of the immune system to achieve a faster, more intense and more effective response to repeated meetings with the same Ag.

**Tolerance** – absence of immune response to own antigens (self). It is determined by the inactivation and elimination of autoreactive lymphocytes in the process of maturation of T and B lymphocytes.

# Important

## Cytokines:

■ Cytokines are molecules that allow different cells to communicate with each other in producing a reaction.

♦ Cytokines bring together a heterogeneous group of molecules: interleukins (IL), lymphokines, monokines, interferons (IFN), colony stimulating factors (CSF), tumor necrosis factors (TNF), etc.

## Important - Cytokines:

- Cytokines allow immune cells to multiply and differentiate (eg, IL-2 is a growth factor of T lymphocytes, and IL-4 stimulates B lymphocytes and their differentiation into Ig-producing plasmocytes).

- Cytokines act on cells via membrane receptors, which are not always active. Their expression may be induced by another cytokine (e.g., IL-1 induces the IL-2 receptor on T and B lymphocytes).

- Cytokine receptors are also present on other cells of the body.

# T Cell-Mediated Diseases

## Exaggerated T- cell immune response

- autoimmunity and
- exaggerated or persistent responses to environmental antigens.

**Mechanisms:**

In different T cell–mediated diseases, tissue injury is caused by inflammation induced by cytokines that are produced mainly by CD4+ T cells or by killing of host cells by CD8+ CTLs

examples:

- Contact dermatitis
- Multiple sclerosis
- Psoriasis
- T1 DM
- tuberculosis

## Deficiency of T –cell immune response

- Defects in T cell maturation
- Defects in T cell proliferation and differentiation
- Defects in T cell activation

Examples:

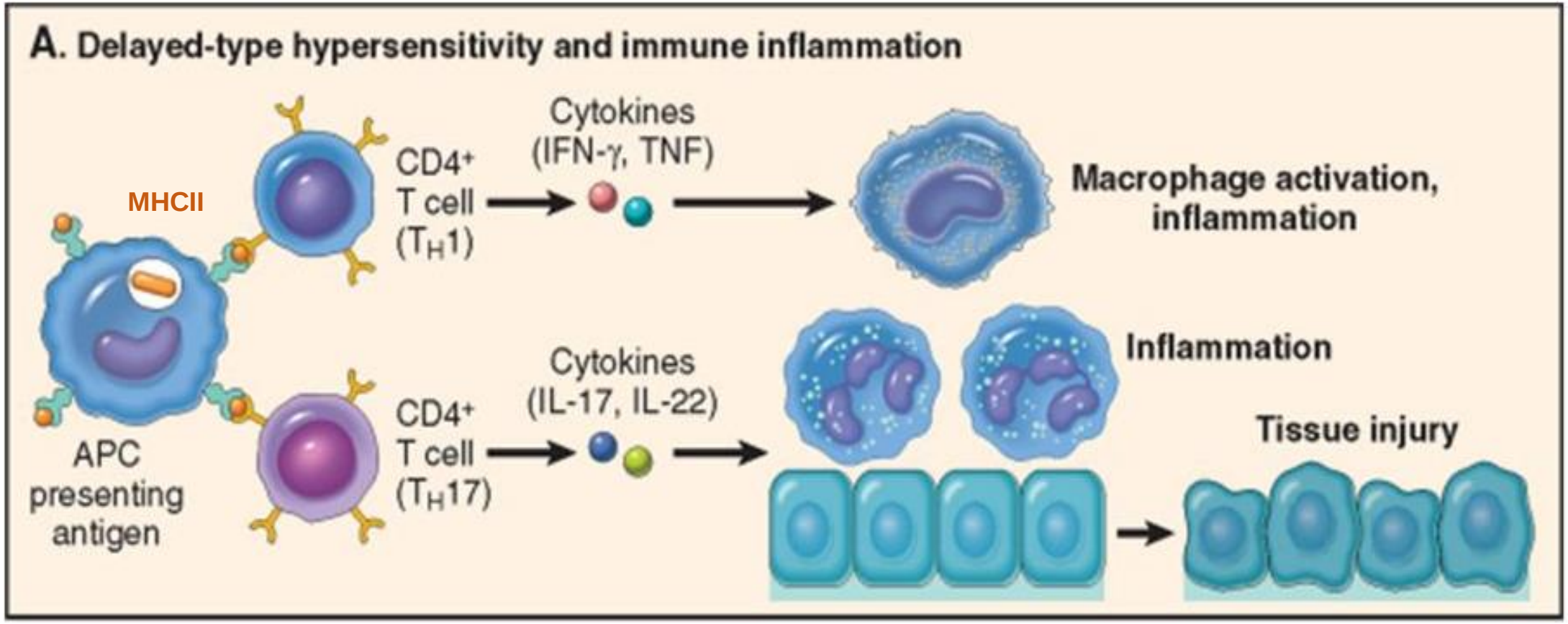
Congenital defects:

- Severe combined immunodeficiency (SCID)
- DiGeorge syndrome
- Common variable immunodeficiency (CVID)
- Bare lymphocyte syndrome

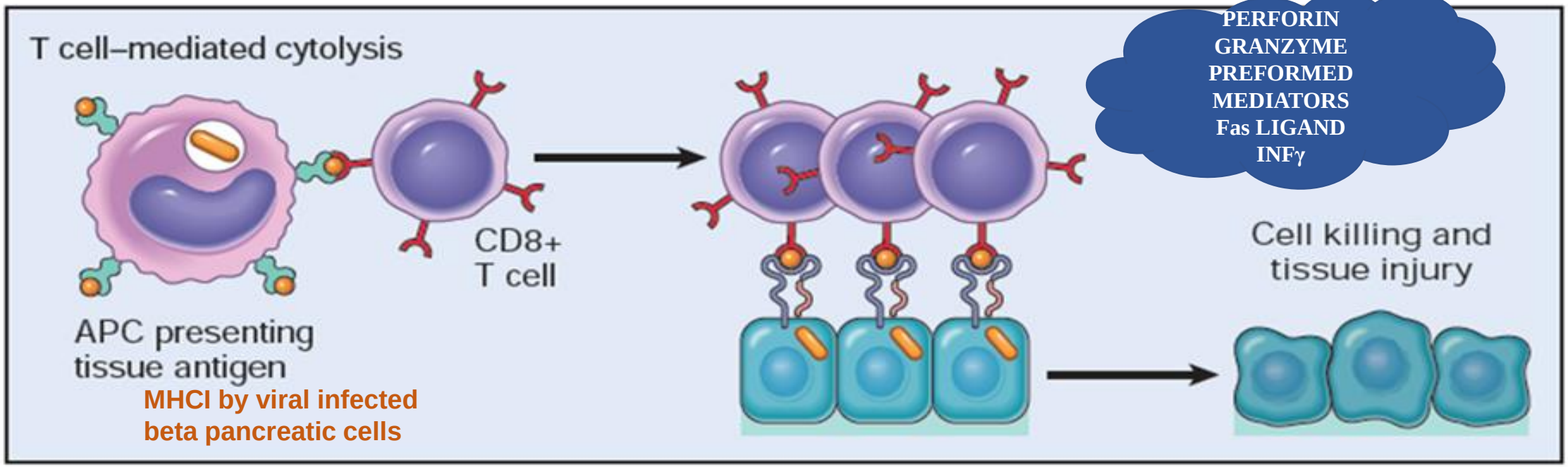
Acquired defects:

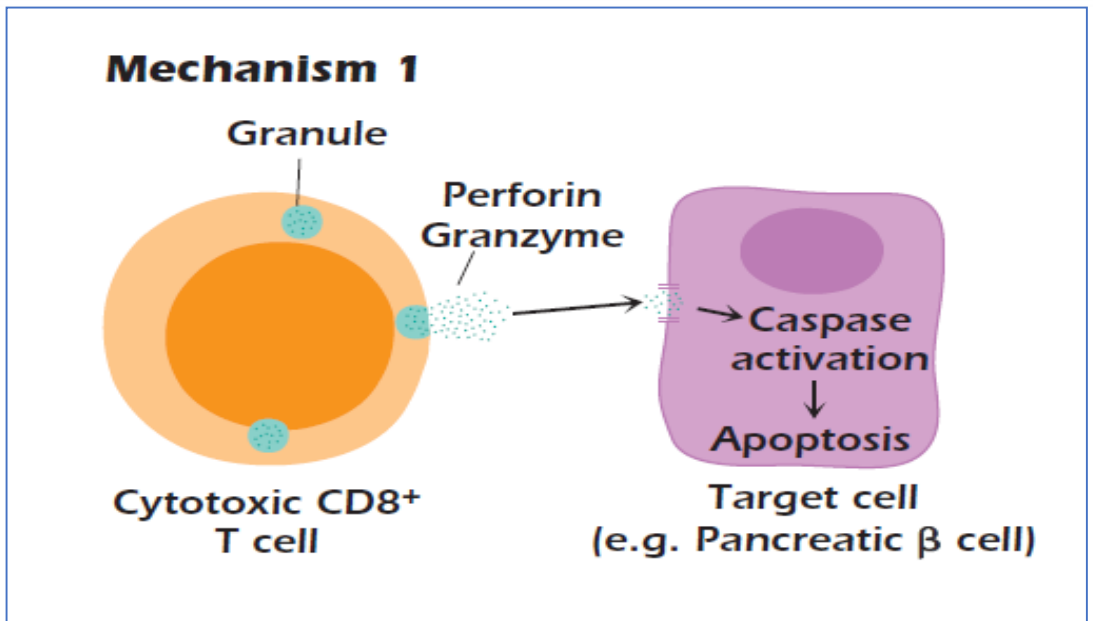
- Human immunodeficiency virus

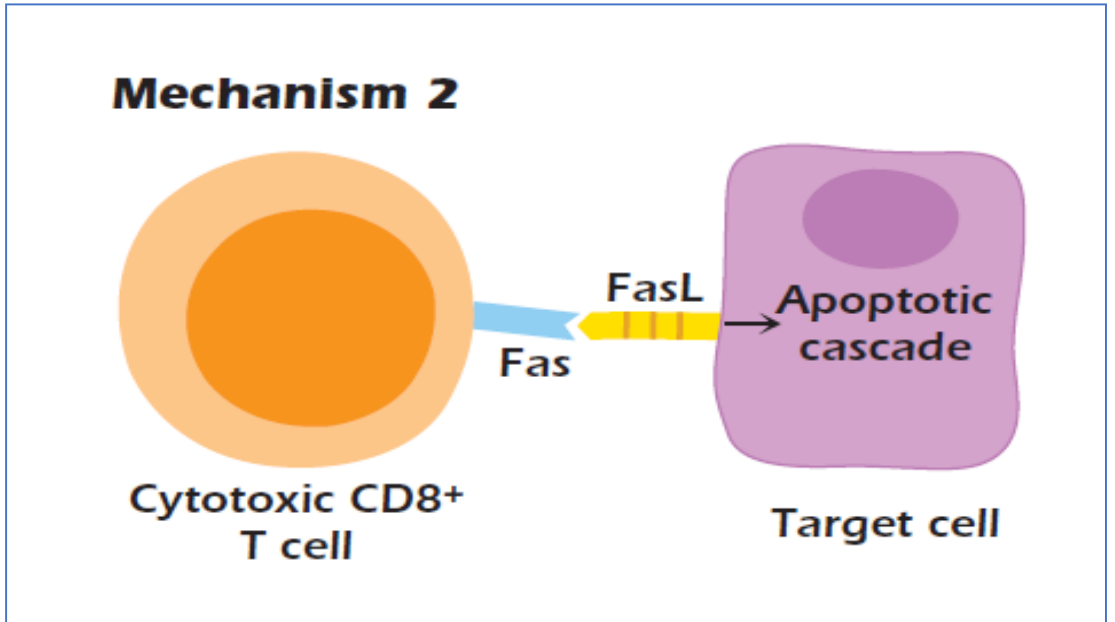
# CD4+Tcell – mediated inflammatory reaction



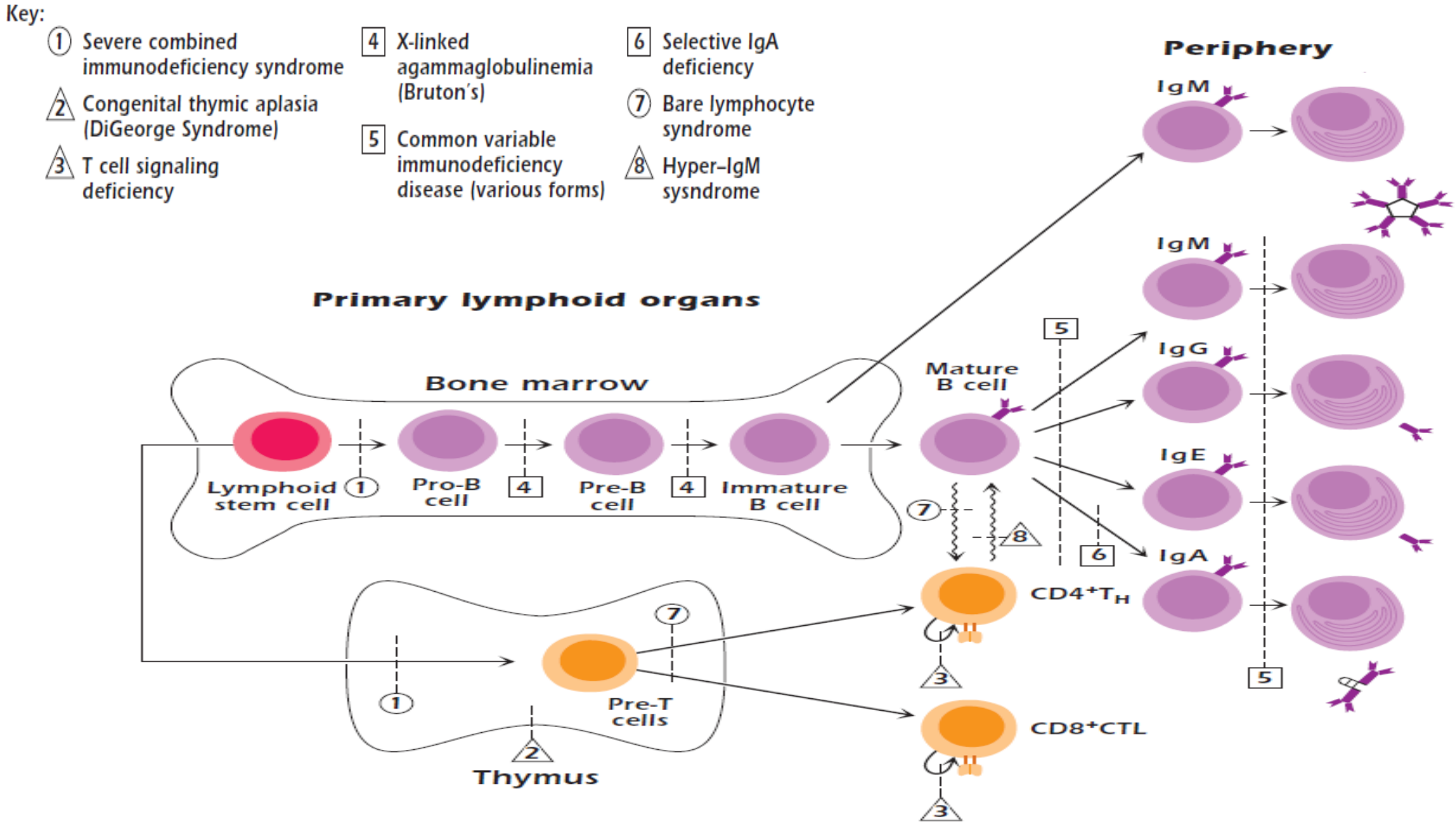
# CD8+ T cell –mediated cytotoxicity



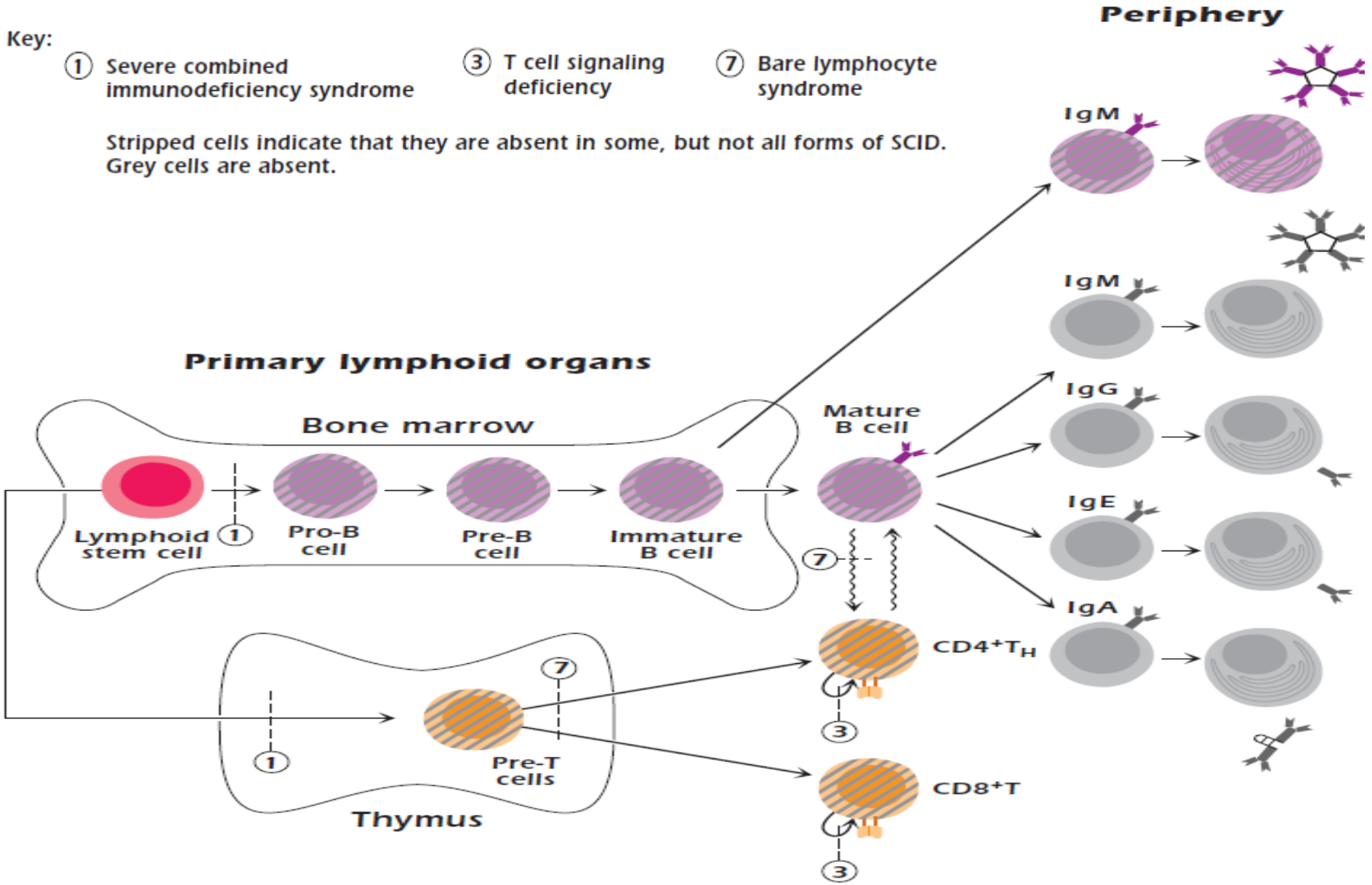
# _T-cell immunodeficiency disorders



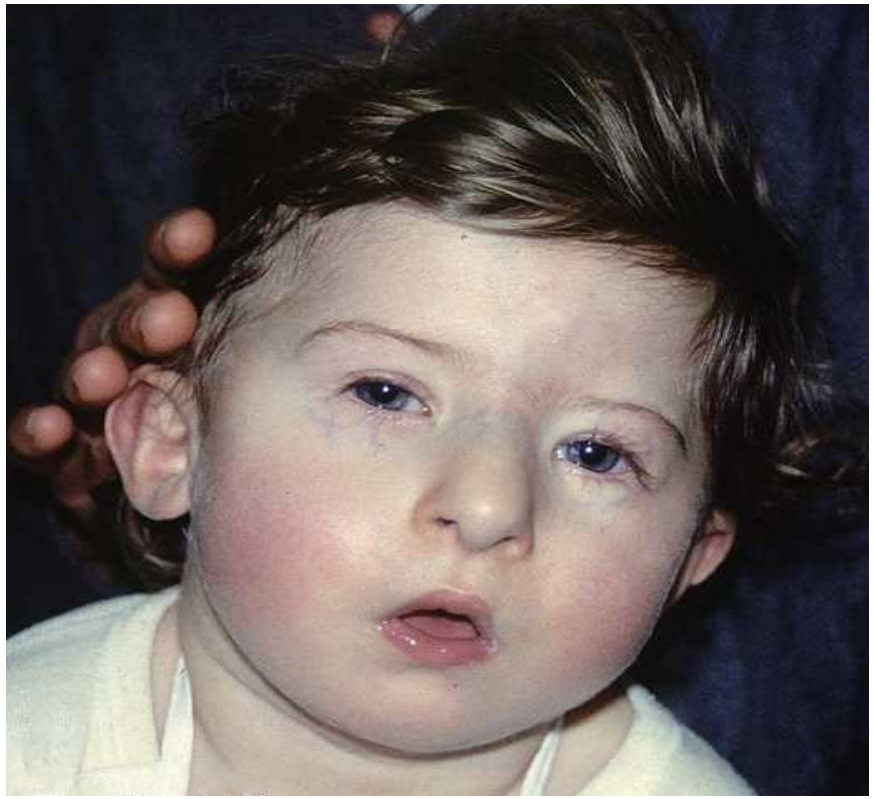
# *Severe combined immunodeficiency syndrome* (SCIDS)

- **David Vetter from Texas, was a sufferer of severe combined immunodeficiency (SCID), a hereditary disease which dramatically weakens the immune system. He was called *'the boy in the bubble.'***
- **He died in 1984 (at 12 years) after a bone marrow transplant went terribly wrong.**

# *Severe combined immunodeficiency syndrome* (SCIDS)

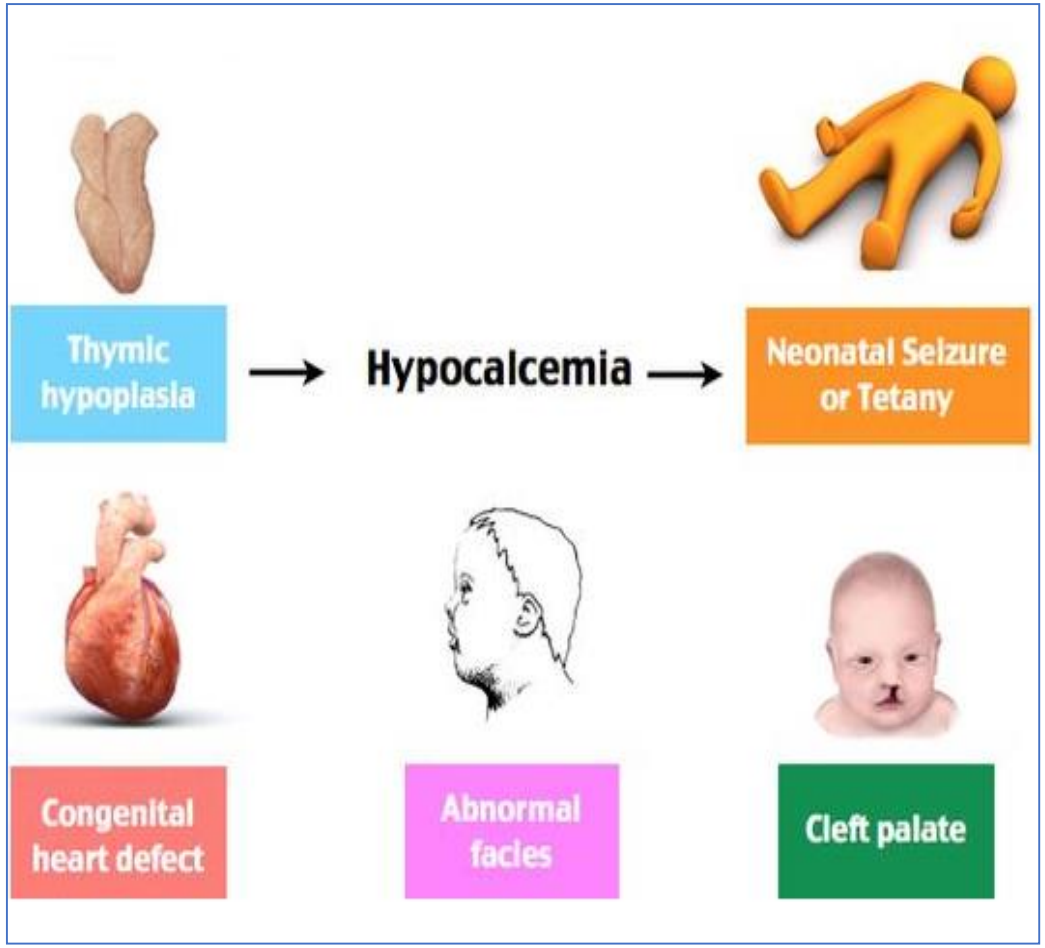


# Primary cell mediated immunodeficiency syndrome. DiGeorge syndrome



- **Defect embryonic development before 12th week of gestation, thymus, parathyroid gland, and parts of the head, neck, and heart are developing.**
- **Defects of a gene on chromosome 22 (22q11)**
- **Causes mostly due to extrinsic teratogens.**

# Primary cell mediated immunodeficiency syndrome. DiGeorge syndrome




## CATCH-22

**C**ardiac abnormalities

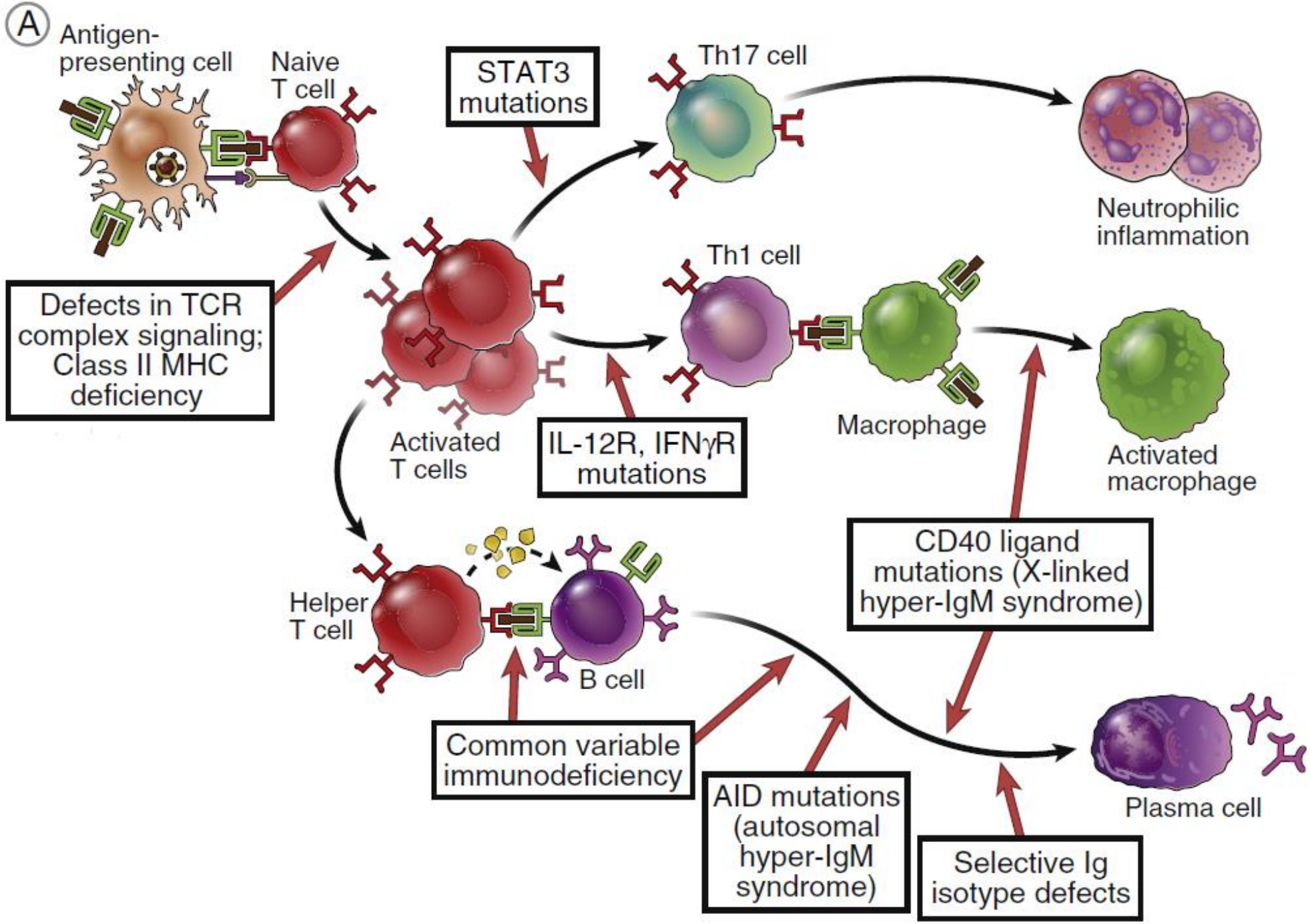
**A**bnormal facies

**T**hymic absence/abnormality, **T** cell abnormality

**C**left palate

**H**ypocalcemia

Chromosome **22**


A
Antigen-presenting cell
Naive T cell
STAT3 mutations
Th17 cell
Neutrophilic inflammation
Defects in TCR complex signaling; Class II MHC deficiency
Th1 cell
Activated T cells
IL-12R, IFNγR mutations
Macrophage
Activated macrophage
CD40 ligand mutations (X-linked hyper-IgM syndrome)
Helper T cell
B cell
Common variable immunodeficiency
AID mutations (autosomal hyper-IgM syndrome)
Selective Ig isotype defects
Plasma cell

# Congenital Disorders related with defect T – cell activation and differentiation

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 |
| Common variable immunodeficiency | Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems | Mutations in receptors for B cell growth factors, costimulators |
| Defective class II MHC expression: the bare lymphocyte syndrome | Lack of class II MHC expression and impaired $CD4^+$ T cell activation; defective cell-mediated immunity and T cell–dependent humoral immunity | Mutations in genes encoding transcription factors required for class II MHC gene expression |
| Defects in T cell receptor complex expression or signaling | Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell-mediated immunity | Rare cases due to mutations or deletions in genes encoding CD3 proteins, ZAP-70 |
| Defects in Th1 differentiation | Decreased T cell–mediated macrophage activation; susceptibility to infection | Rare cases due to mutations encoding the receptors for IL-12 or interferon-γ |
| Defects in Th17 differentiation | Decreased T cell–mediated inflammatory responses; mucocutaneous candidiasis, bacterial skin abscesses | Rare cases due to mutations in genes encoding STAT3, IL-17, IL-17R |
| X-linked lymphoproliferative syndrome | Uncontrolled EBV-induced B cell proliferation and CTL activation; defective NK cell and CTL function and antibody responses | Mutations in gene encoding SAP (an adaptor protein involved in signaling in lymphocytes) |

ZAP70 is a kinase involved in TCR signaling; and TAP proteins transport peptides for presentation by class I MHC molecules.

# Human Immunodeficiency Virus

**Human immunodeficiency virus (HIV) is a retrovirus that infects cells of the immune system, mainly CD4+ T lymphocytes, and causes progressive destruction of these cells.**

**Acquired immunodeficiency syndrome (AIDS) was first recognized as a distinct entity in the 1980s.**

**AIDS is caused by infection with HIV.**

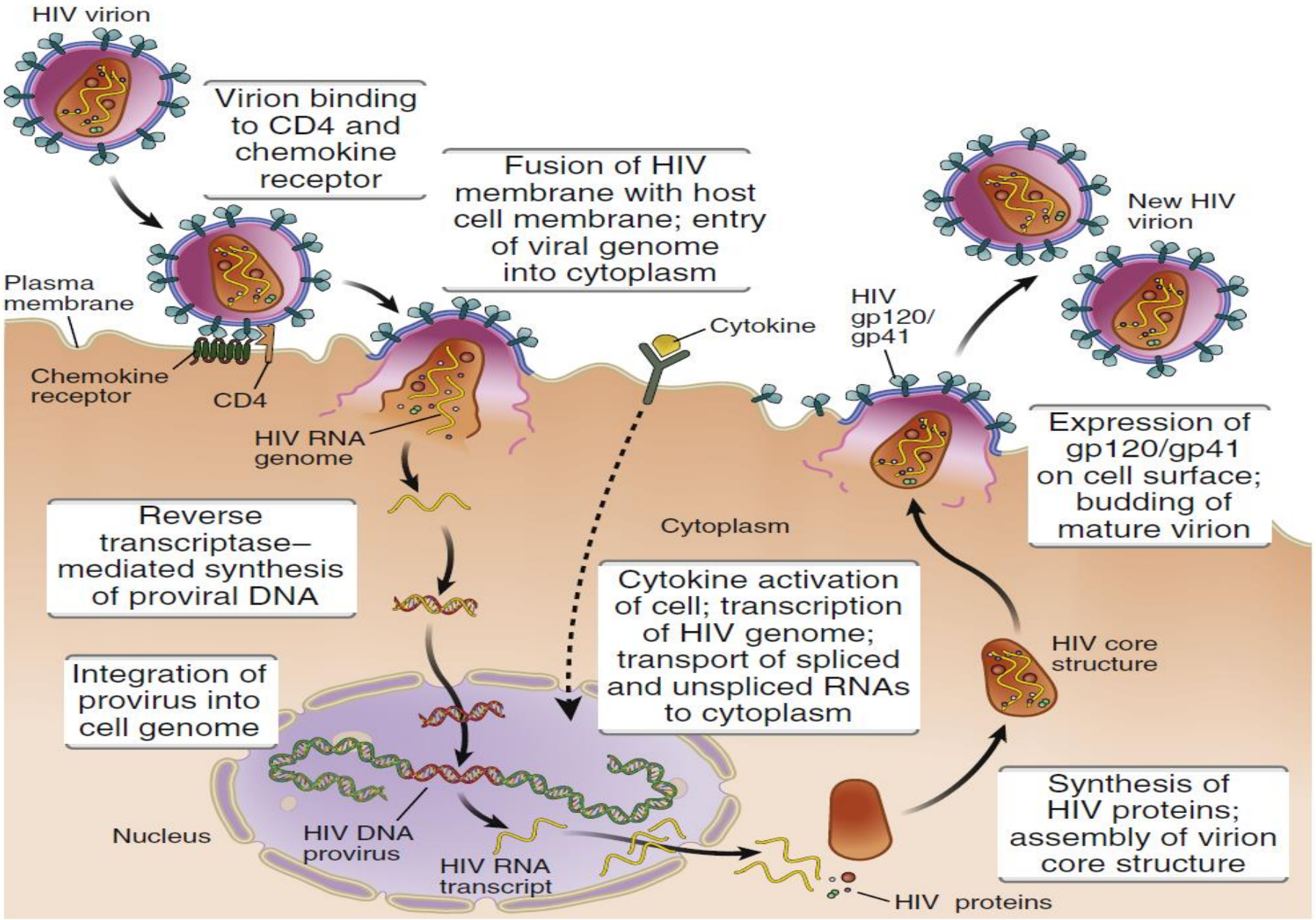
**Of the estimated 35 million HIV-infected people worldwide, about 70% are in Africa and 20% in Asia. More than 25 million deaths are attributable to HIV/AIDS, with 1 to 2 million deaths annually.**

**The life cycle of HIV consists of the following sequential steps:**

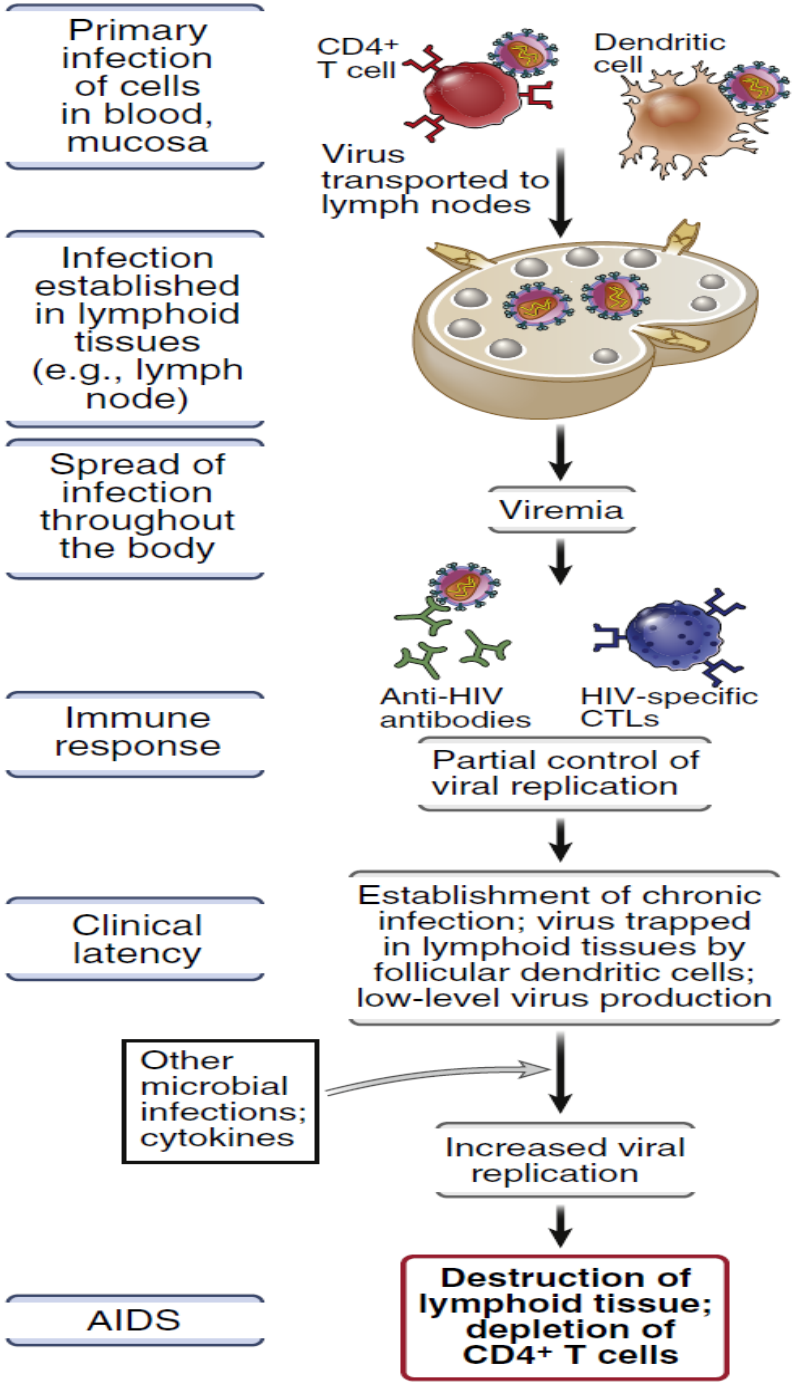
1. **infection of cells,**
2. **production of a DNA copy of viral RNA and its integration into the host genome,**
3. **expression of viral genes, and**
4. **production of viral particles.**

**The major cell types that may be infected by HIV are CD4+ T lymphocytes, macrophages, and dendritic cells at sites of entry through epithelia; in lymphoid organs such as lymph nodes; and in the circulation.**

# Life cycle of human immunodeficiency virus (HIV).



# Pathogenesis of disease caused by human immunodeficiency virus (HIV)




**Mechanisms of CD4+ T-cell depletion:**

- **Production of virus in the T cells is itself a cause of cell lysis.**
- **The infected cell seems to be intrinsically more susceptible to apoptosis.**
- **Cytotoxic T lymphocytes (CTLs) specific for virally infected cells may kill at least some of the infected cells.**
- **Uninfected CD4+ T cells may also be killed in an antibody-dependent cell-mediated cytotoxicity (ADCC)–like mechanism as a result of binding of soluble gp120 and anti-gp120 antibody to their surface CD4 molecules.**
- **Cells physically close to infected cells (bystander cells) have also been shown to undergo cell death.**

# Clinical manifestations of AIDS

**Infections:** frequently disseminated

- Fungal: candidiasis, cryptococcosis, histoplasmosis, coccidioidomycosis, cryptosporidiosis
- Parasitic: toxoplasmosis, pneumocystis, cryptosporidiosis, isosporiosis
- Bacterial: mycobacteriosis, including atypical; salmonella
- Viral: cytomegalovirus, herpes simplex virus, progressive muti-focal leukoencephalopathy

**Malignancies**

- Sarcoma: Kaposi sarcoma
- Lymphoma: Burkitt lymphoma, diffuse large B-cell lymphoma, effusion-based lymphoma, primary CNS lymphoma
- Carcinoma: invasive cancer of uterine cervix

**General conditions**

- HIV encephalopathy and dementia
- Wasting syndrome
- $CD4^+$ T-cell count $<200/\mu L$ (is AIDS defining)

# Thank you for your attention

From left: B lymphocyte; Eosinophil; Platelet; Neutrophil; Macrophage; T lymphocyte; Monocyte; NK cell; Dendritic cell; Basophil; Mast cell