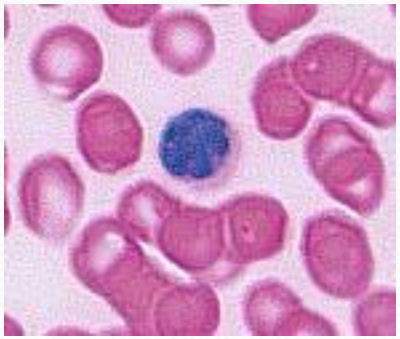
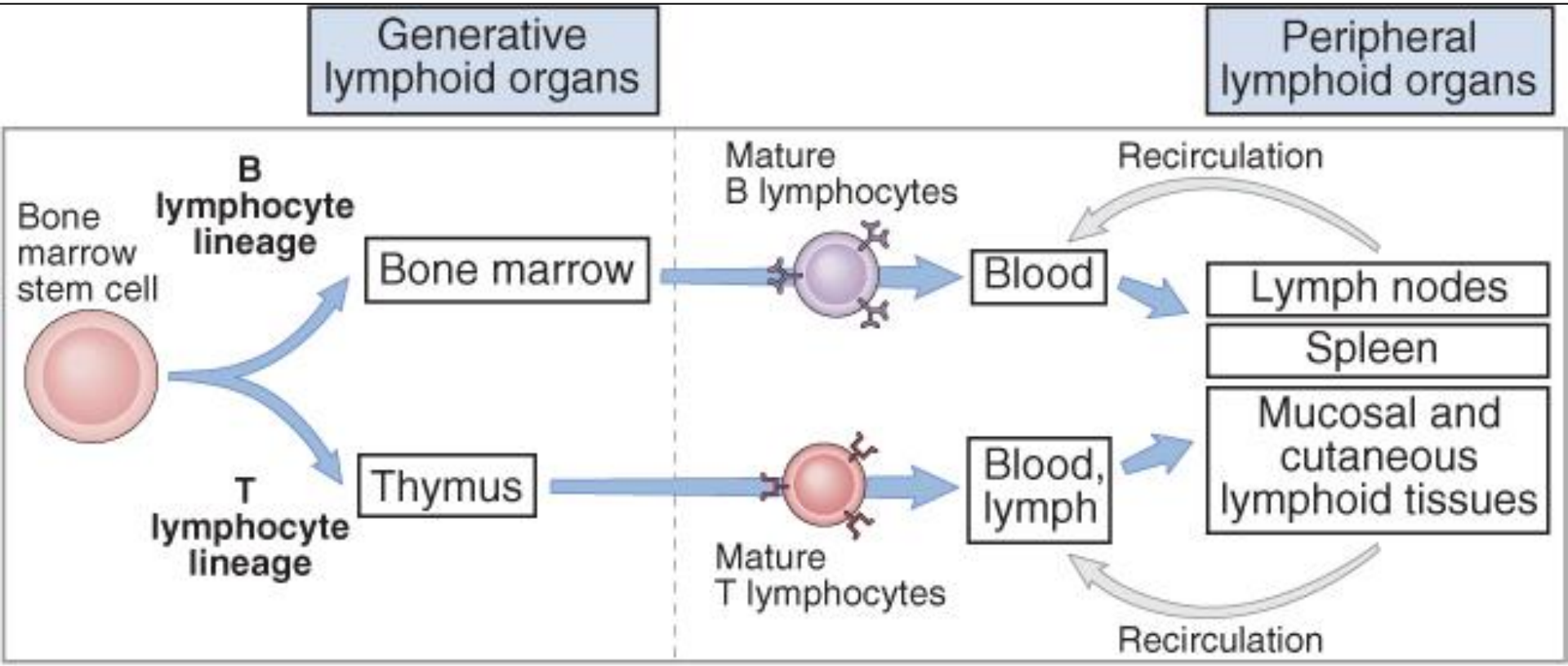
T lymphocytes

Lymphocytes

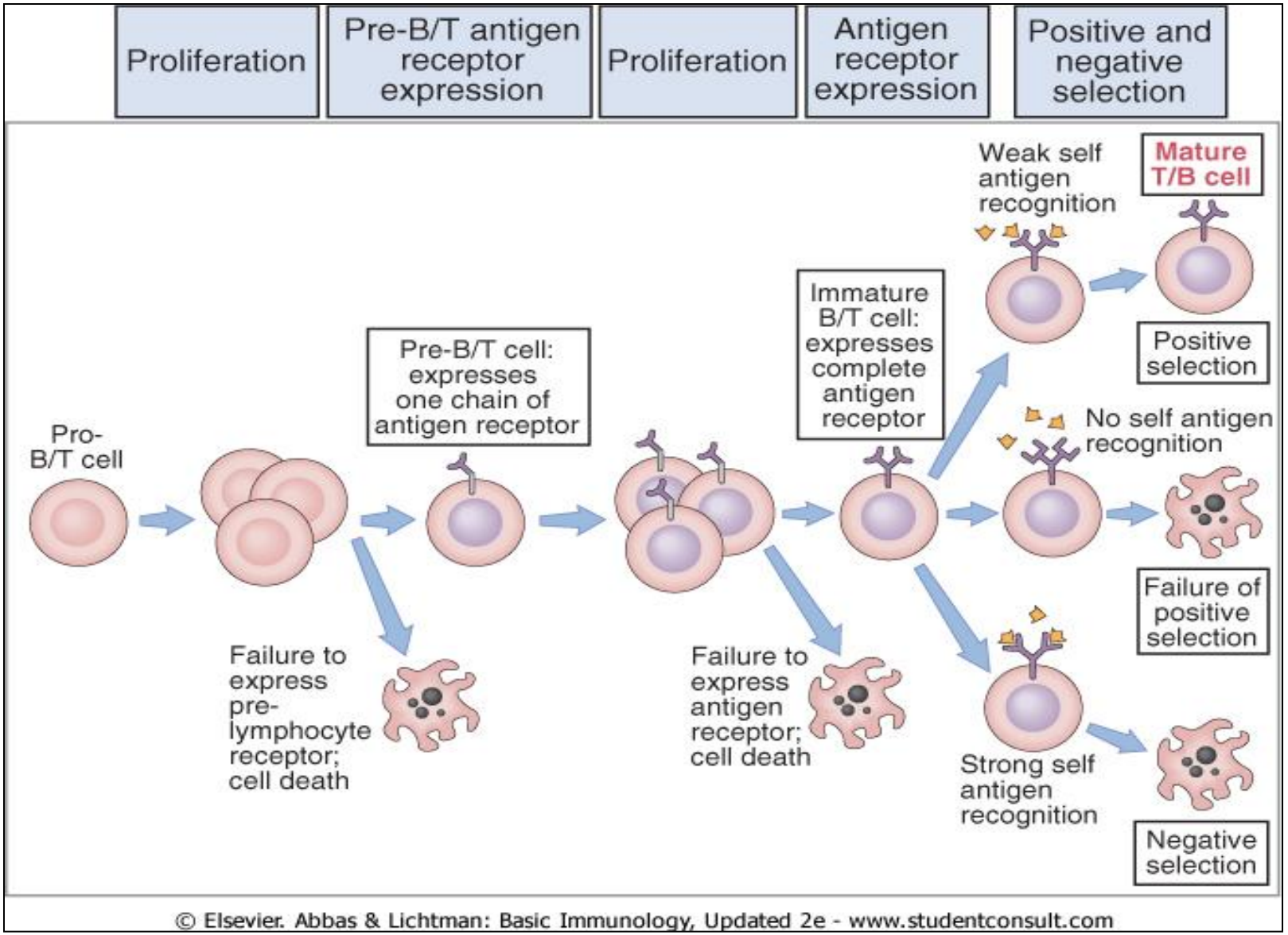


1. Lymphocytes are wholly responsible for the specific immune recognition of pathogens, so they initiate adaptive immune responses.
2. Lymphocytes are derived from bone-marrow stem cells.
3. B lymphocytes mature in the bone marrow.

   T lymphocytes mature in the thymus.



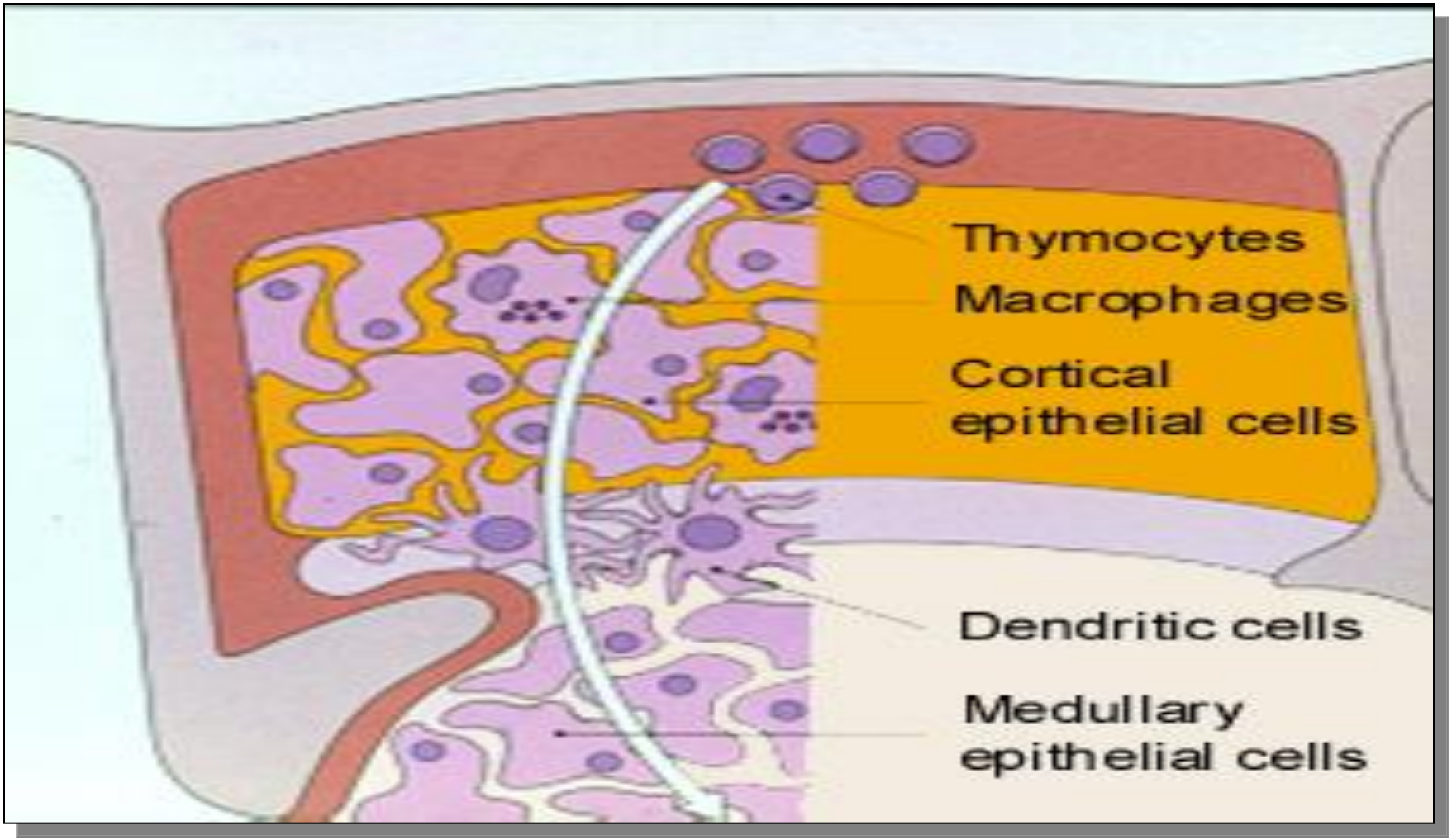
Steps in the maturation of lymphocytes



I. Ontogeny of T cells

Bone marrow	Thymus		Blood
Pro-T cell	Pre-T cell	Thymocytes	T cells

Thymus


Thymocytes
Macrophages
Cortical epithelial cells
Dendritic cells
Medullary epithelial cells

1. Factors promoting T cell development in the thymus

- Interaction of cell adhesion molecules between immature thymocytes and thymic stroma cells
- Cytokines (IL-1, IL-6, IL-7) and hormones secreted by thymic stroma cells
- Cytokines (IL-2, IL-4) secreted by thymocytes themselves
- MHC-autoantigen complex on the thymic stroma cells

2. Sequential development of thymocytes

- **Pre-T cells**

  no T cell marker expression, but TdT^+ and some of them express CD7

- **Double negative cells (DN)**

  $CD4^-CD8^{--}$; $CD2^+$, $CD5^+$, cytoplasmic $CD3^+$

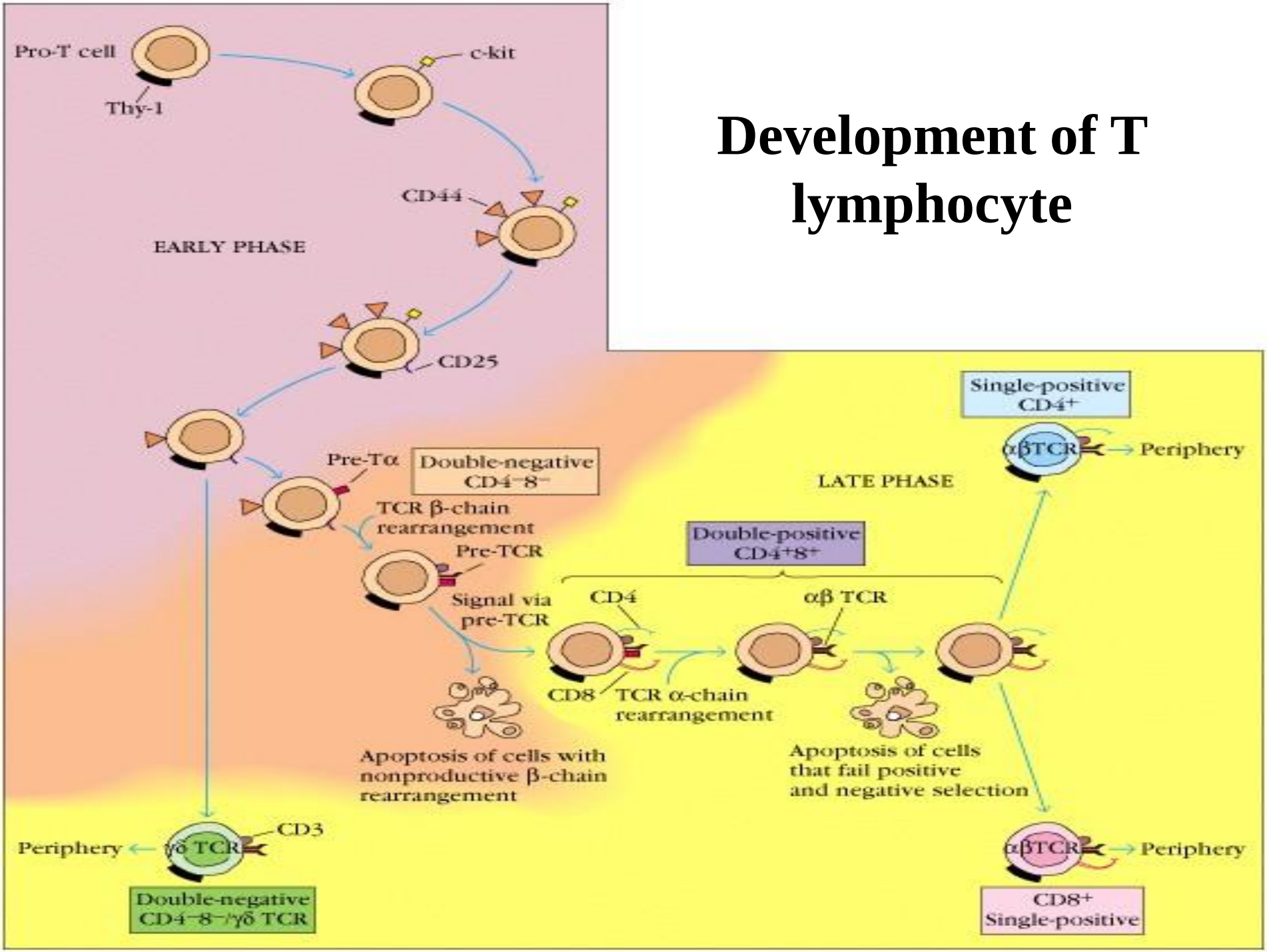
- **Double positive cells (DP)**

  $CD4^+CD8^+$, $CD1^+$, $CD3^+$, $\gamma\delta TCR^{low}$, $\alpha\beta TCR^{low}$

- **Mature T cells (single positive T cells)**

  $CD4^+$ or $CD8^+$, $CD2^+$, $CD3^+$, TCR^+

Development of T lymphocyte



3. Positive and negative selection

Positive selection

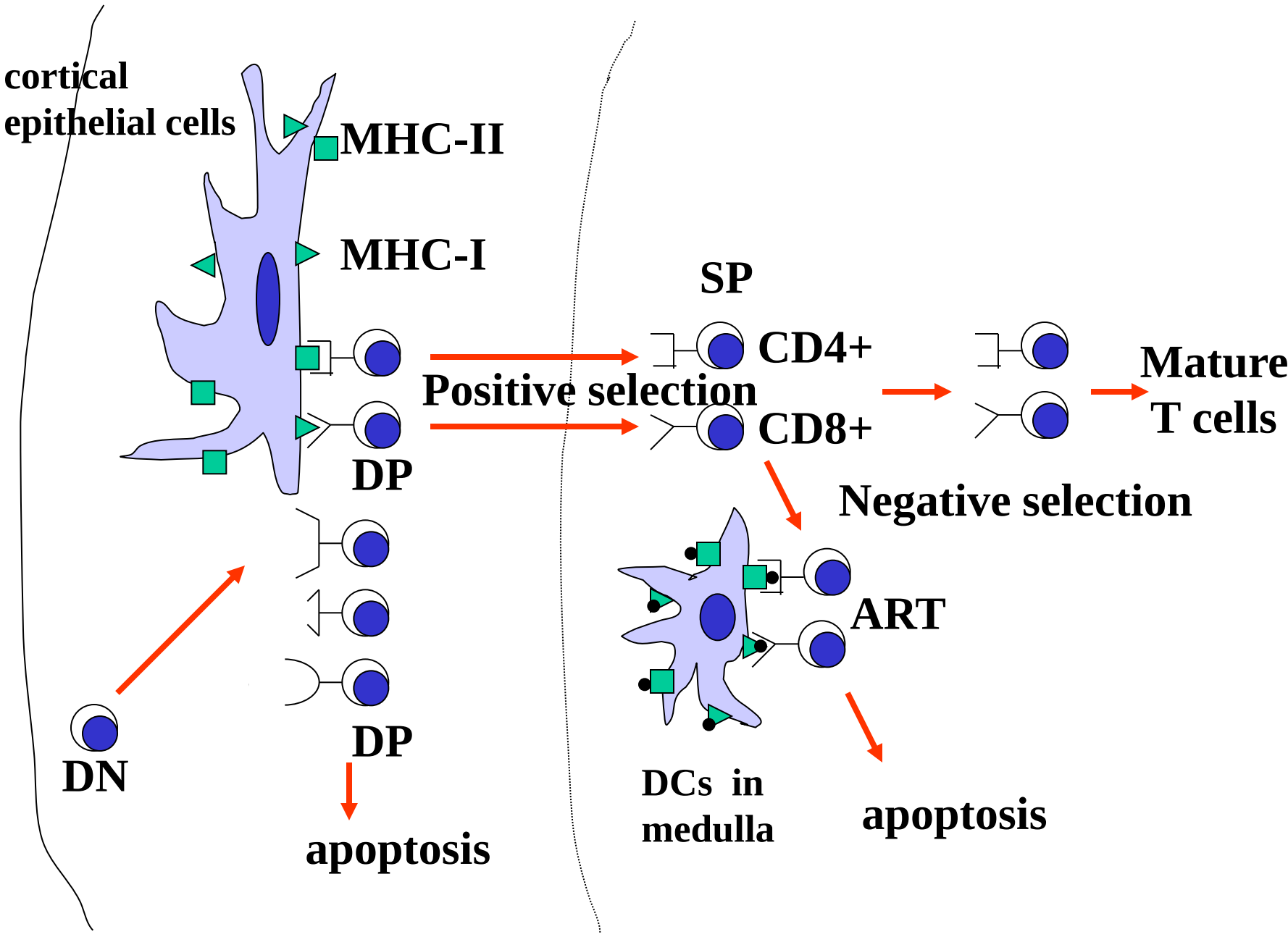
- DP cells that bind, with moderate affinity, to MHC-Ag on thymic stroma cells survive----MHC restriction
- MHC I----$CD8^+$ T cells
- MHC II----$CD4^+$ T cells

Negative selection

- Cells that bind to MHC-Ag on thymic stroma cells (or auto-reactive T cells, ART) will undergo apoptosis
- Formation of central immune tolerance

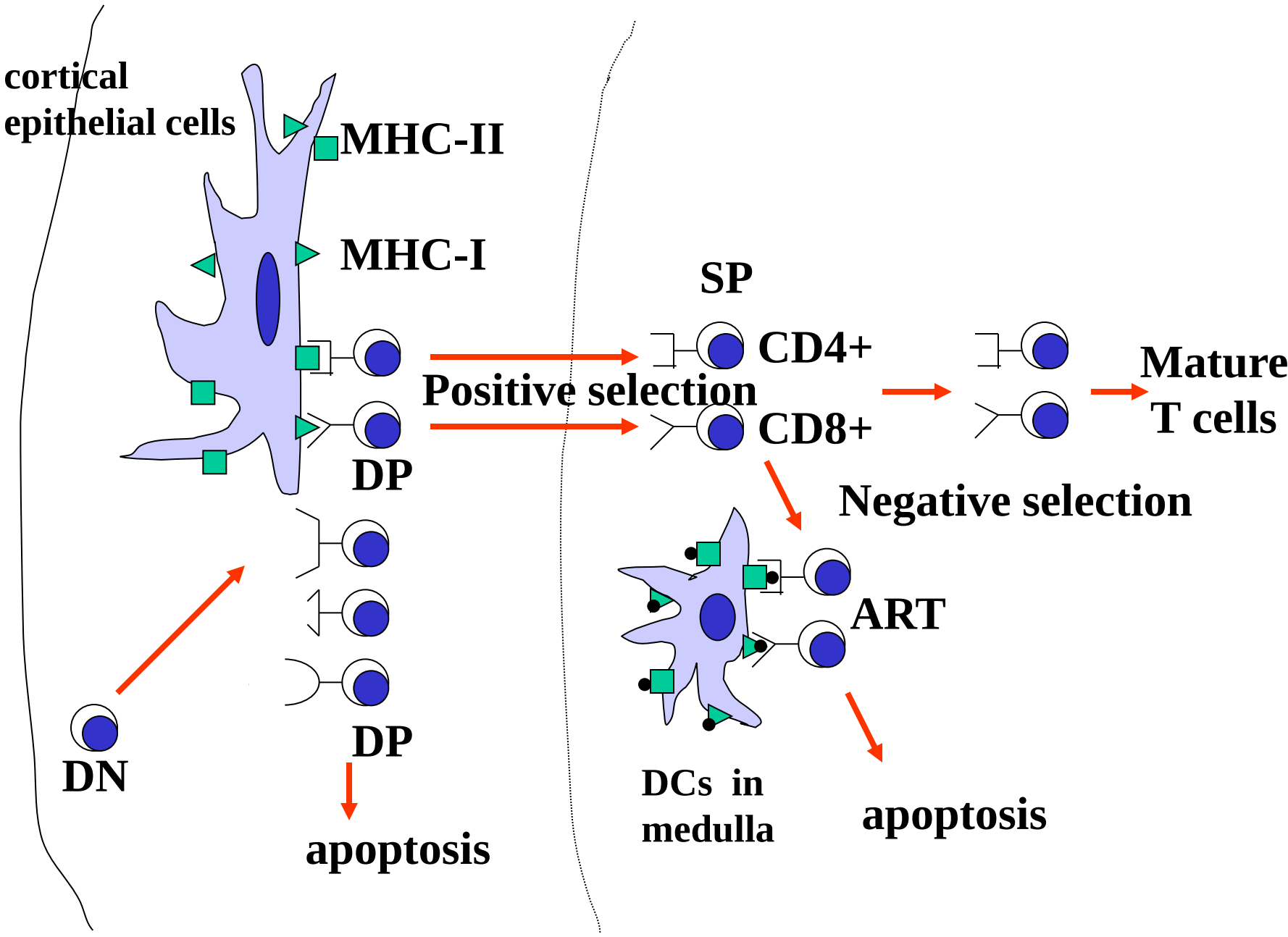
positive selection

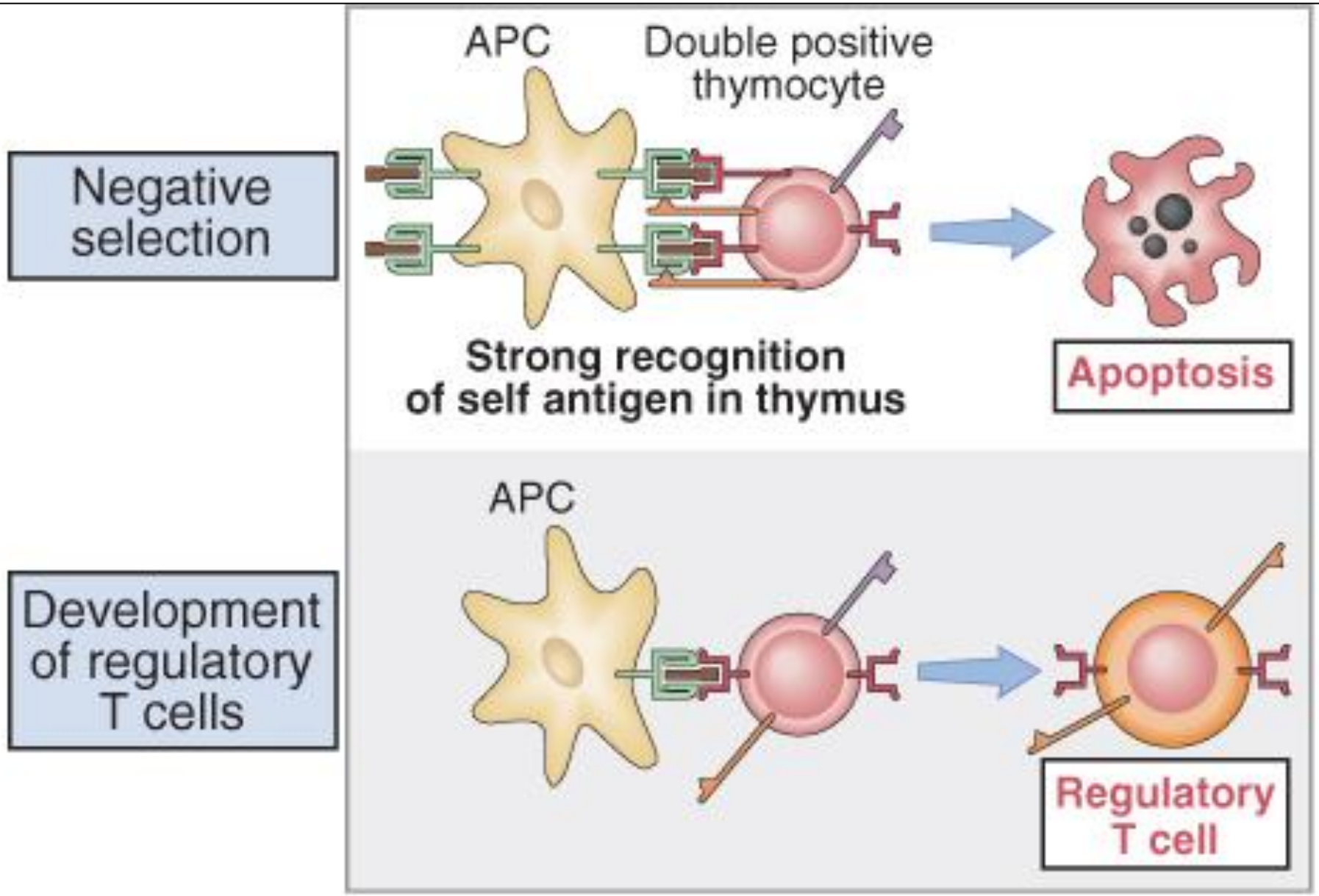
- TCR interact with self MHC→T cells develop
- TCR can not interact with self MHC→T cells apoptosis
- MHC-Ⅰ molecules select $CD8^+$T cells
- MHC-Ⅱ molecules select $CD4^+$T cells
- Presented by cortical epithelial cells
- MHC restriction

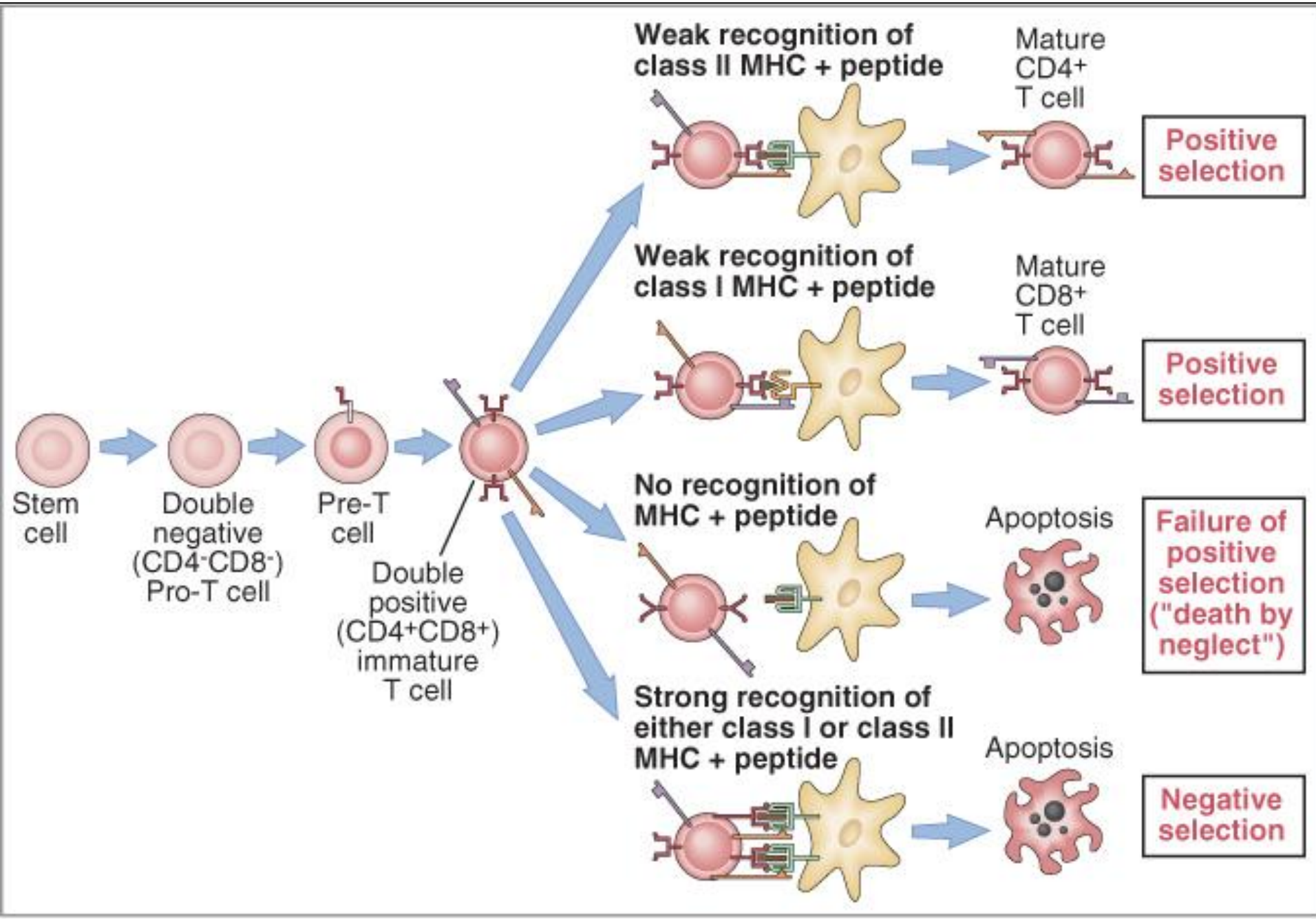

cortical
epithelial cells
MHC-II
MHC-I
DP
DP
DN
apoptosis
SP
CD4+
CD8+
Positive selection
Mature
T cells
Negative selection
ART
DCs in
medulla
apoptosis

negative selection

- High affinity TCR→Ag/self MHC→apoptosis
- Low affinity TCR→Ag/self MHC→mature
- By dendritic cells
- Clear auto-reactive T cell (ART)


cortical
epithelial cells
MHC-II
MHC-I
DP
DP
DN
apoptosis
SP
CD4+
CD8+
Positive selection
Mature
T cells
Negative selection
ART
DCs in
medulla
apoptosis





II. T cell surface markers

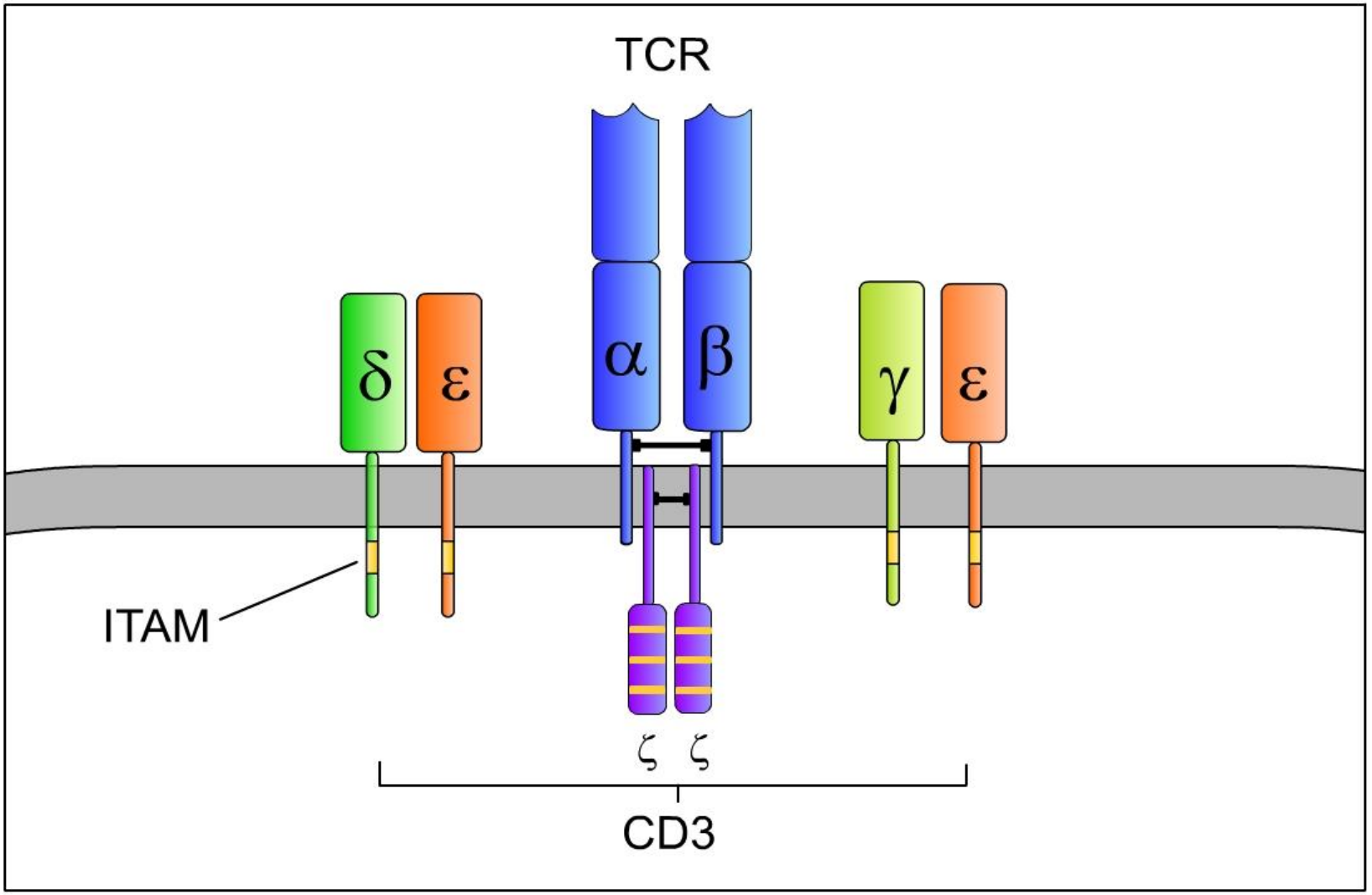
1. TCR-CD3 complex

➢ TCR

- **A heterodimer comprising an α and a β chain or a γ and a δ chain joined by a disulfide bond.**
- **Function: specific recognition of peptide-MHC complex.**

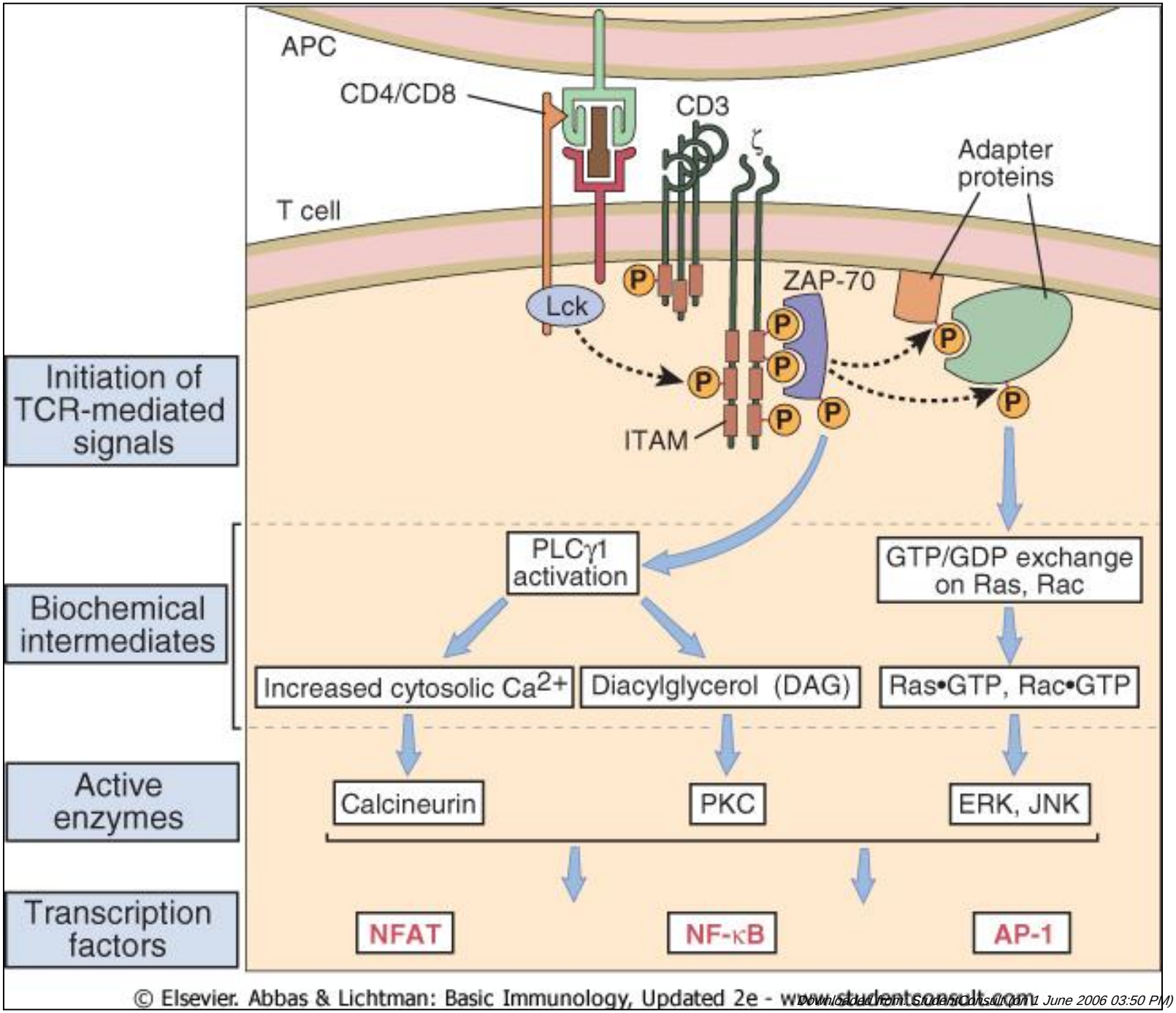
➢ CD3

- **Consists of 5 proteins that are designated as γ, δ, ε, ζ and η.**
- **Three dimers: γε, δε, ζζ (ζη)**
- **The cytoplasmic domain contains ITAM (immunoreceptor tyrosine-based activation motif) YXXL/V**
- **Function: transduction of signals that lead to T cell activation.**



TCR-CD3 complex

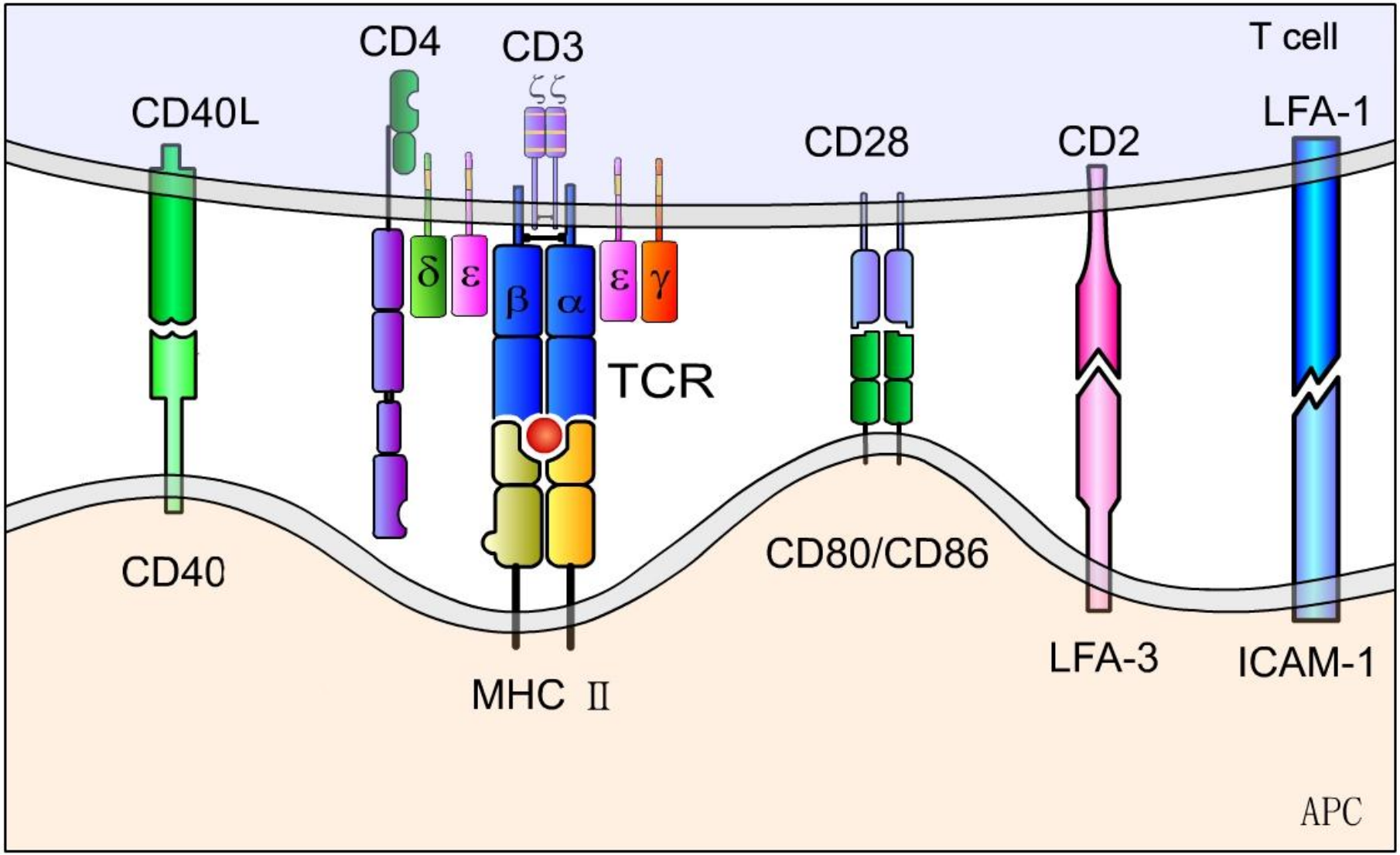
Immunology



2. CD4 and CD8 (coreceptor)

- **Function: 1) Help TCR recognition of antigen**
  2) help the TCR-CD3 signals transduction

- **CD4: MHC II Ag binding, Receptor of HIV gp120**
- **CD8: MHC I Ag binding**



Main costimulatory molecules mediating interactions between T cells and APCs

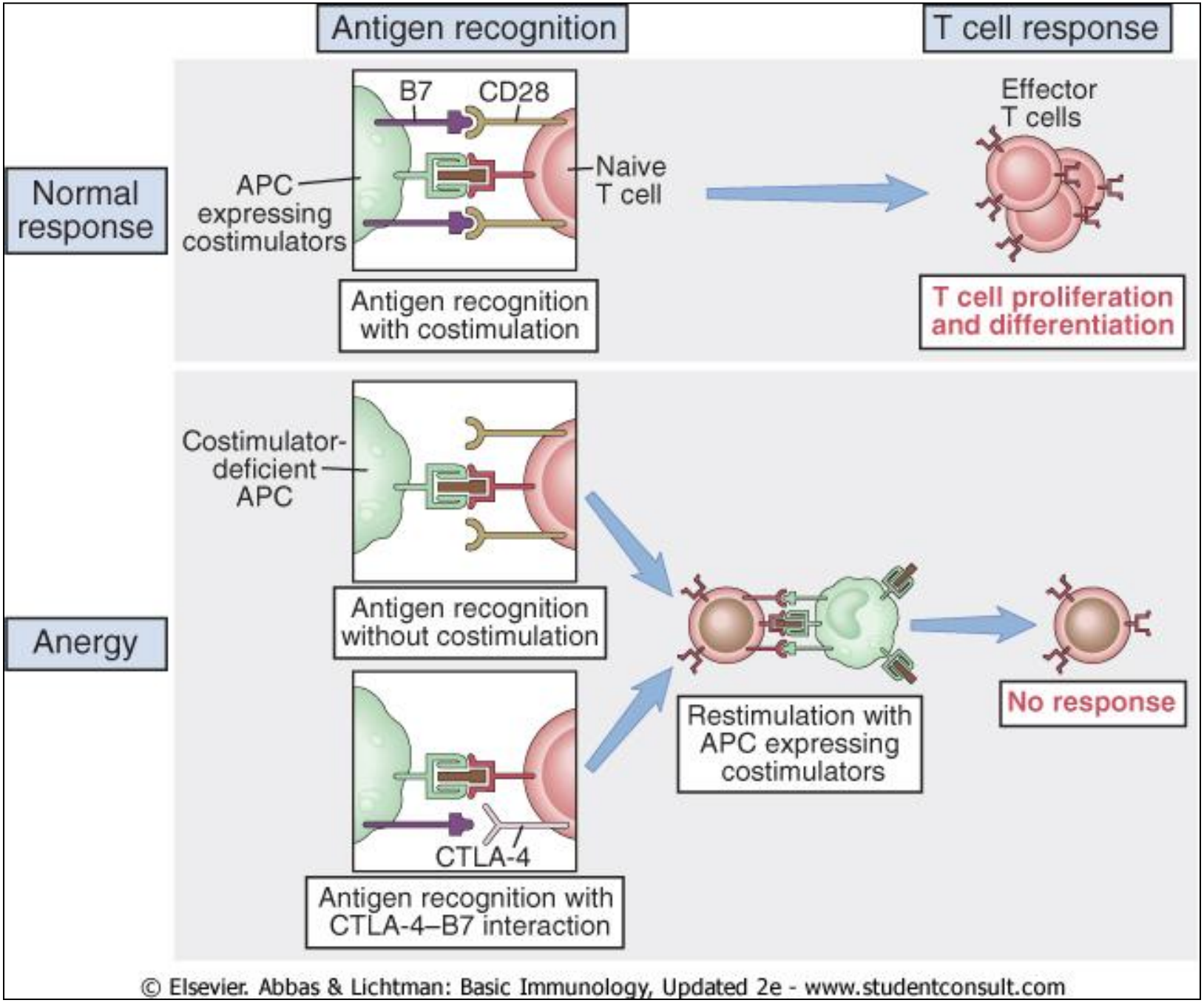
3. Co-stimulatory receptors

- **CD28: its ligands are B7 family molecules, including B7-1/2 (CD80/CD86)**

  Function: costimulation, activation of T cells

- **CTLA-4 (CD152): homodimer, homologous to CD28.**

  Function: inhibits T cell costimulation (the cytoplasmic domain contains ITIM)



- **CD40L (CD154): its receptor is CD40**
- **ICOS: expressed on activated T cells**

  ligand---B7RP-1 (mouse monocytes, B cells)； B7-H2(human)
- **CD2: SRBC receptor, LFA-2**
- **LFA-1 and ICAM-1: mediate adhesion between APC (or target cells or endothelial cells) and T cells or other leukocytes.**

4. Receptors of mitogens

- **PHA-R**
- **ConA-R**
- **PWM-R (also on B cells)**

III. T cell subsets

1. CD4$^+$T and CD8$^+$T cells
2. TCR$\alpha\beta$ T cells and TCR$\gamma\delta$ T cells
3. Th, Tc and Treg
4. Naive T cells, effector T cells and memory T cells

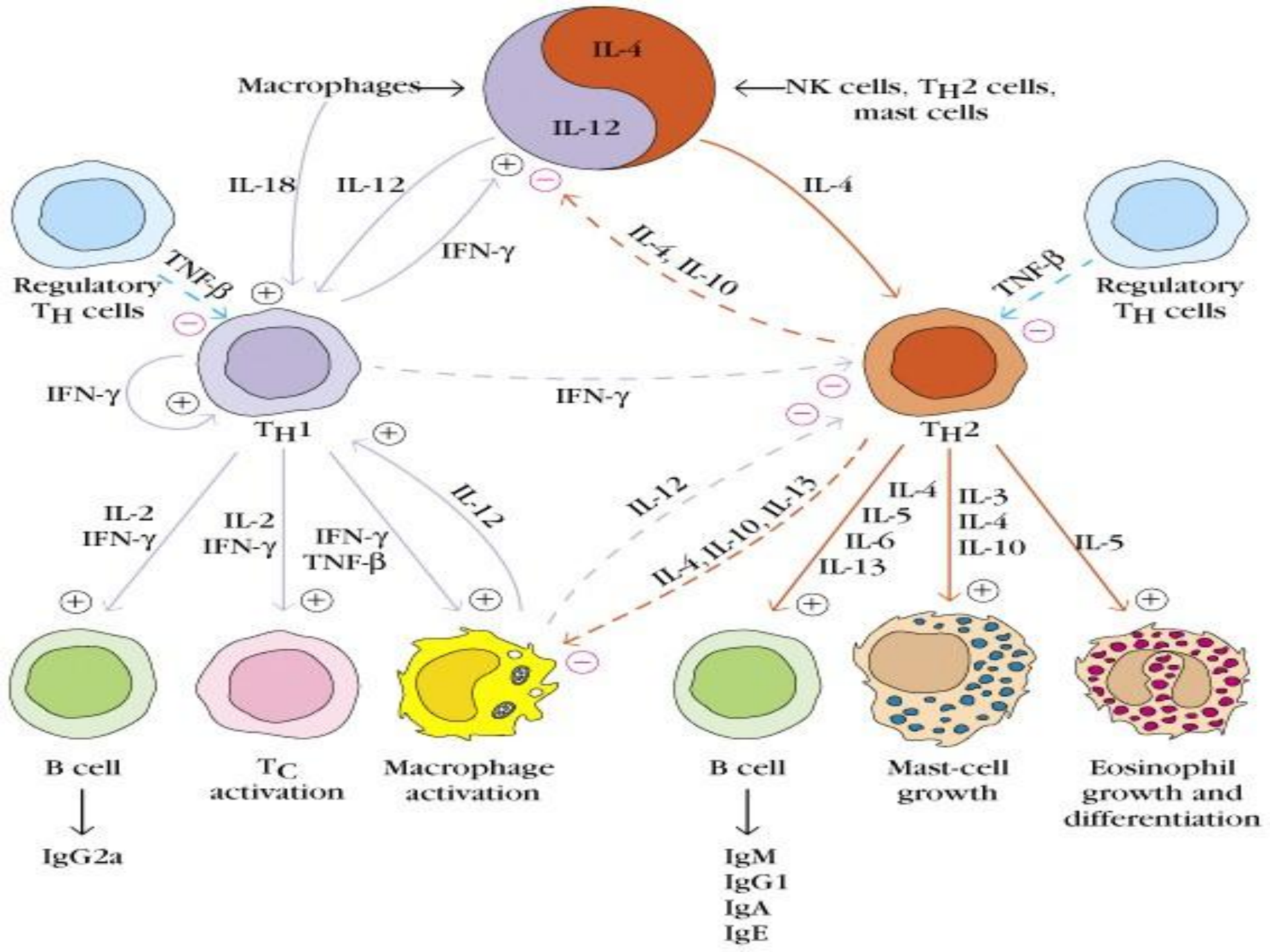
IV. Functions of T cells

1. $CD4^+$ helper T cells (Th)

Th0: T cells activated by Ag can secret many CKs in short time

Th1: produce IL-2 and IFN-γ, but not IL-4. They are chiefly responsible for cell-mediated immune responses, but can also help B cells to produce IgG2a, but not much IgG1 or IgE;

Th2: secrete IL-4, 5, 10, 13, but not IL-2 and IFN-γ, are very efficient helper cells for production of antibody, especially of IgG1 and IgE ;


IL-4
IL-12
Macrophages
NK cells, TH2 cells, mast cells
IL-18
IL-12
IFN-γ
IL-4
IL-4, IL-10
Regulatory TH cells
TNF-β
TNF-β
Regulatory TH cells
IFN-γ
IFN-γ
TH1
TH2
IL-2
IFN-γ
IL-2
IFN-γ
IFN-γ
TNF-β
IL-12
IL-12
IL-4,IL-10,IL-13
IL-4
IL-5
IL-6
IL-13
IL-3
IL-4
IL-10
IL-5
B cell
IgG2a
TC activation
Macrophage activation
B cell
IgM
IgG1
IgA
IgE
Mast-cell growth
Eosinophil growth and differentiation

2. $CD8^+$ cytotoxic T cells (CTL, Tc)

Function: directly kill target cells (cytotoxicity)

Mechanisms:

1. Cytolysis (necrosis) ------ three stages:

a. contact phase: recognition of antigen in the context of MHC class I molecules

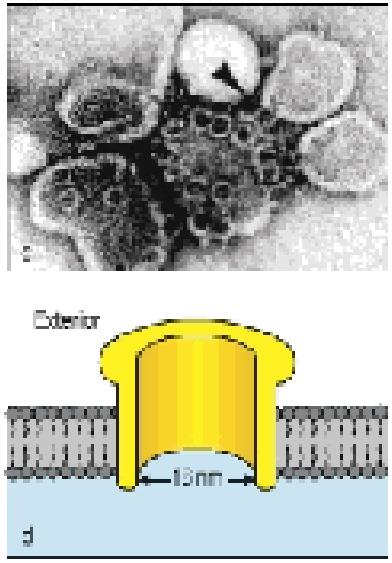
b. secretory phase: release of cytolytic granules (perforin and granzymes)

c. lysis phase: osmotic death

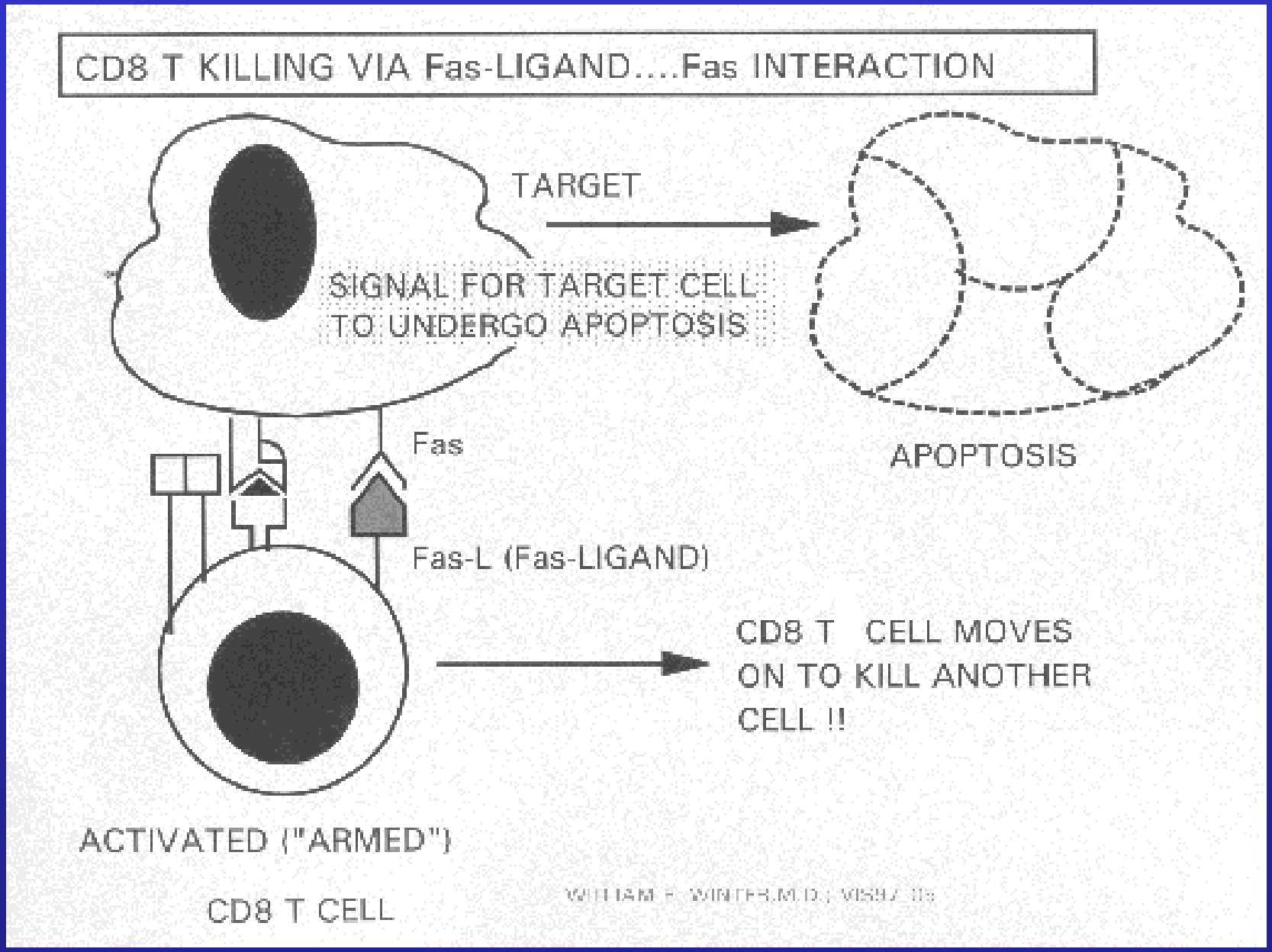
2. Cell apoptosis

a. FasL-Fas: CTLs express FasL interaction with Fas on target cells → activation of caspase 8 →apoptosis

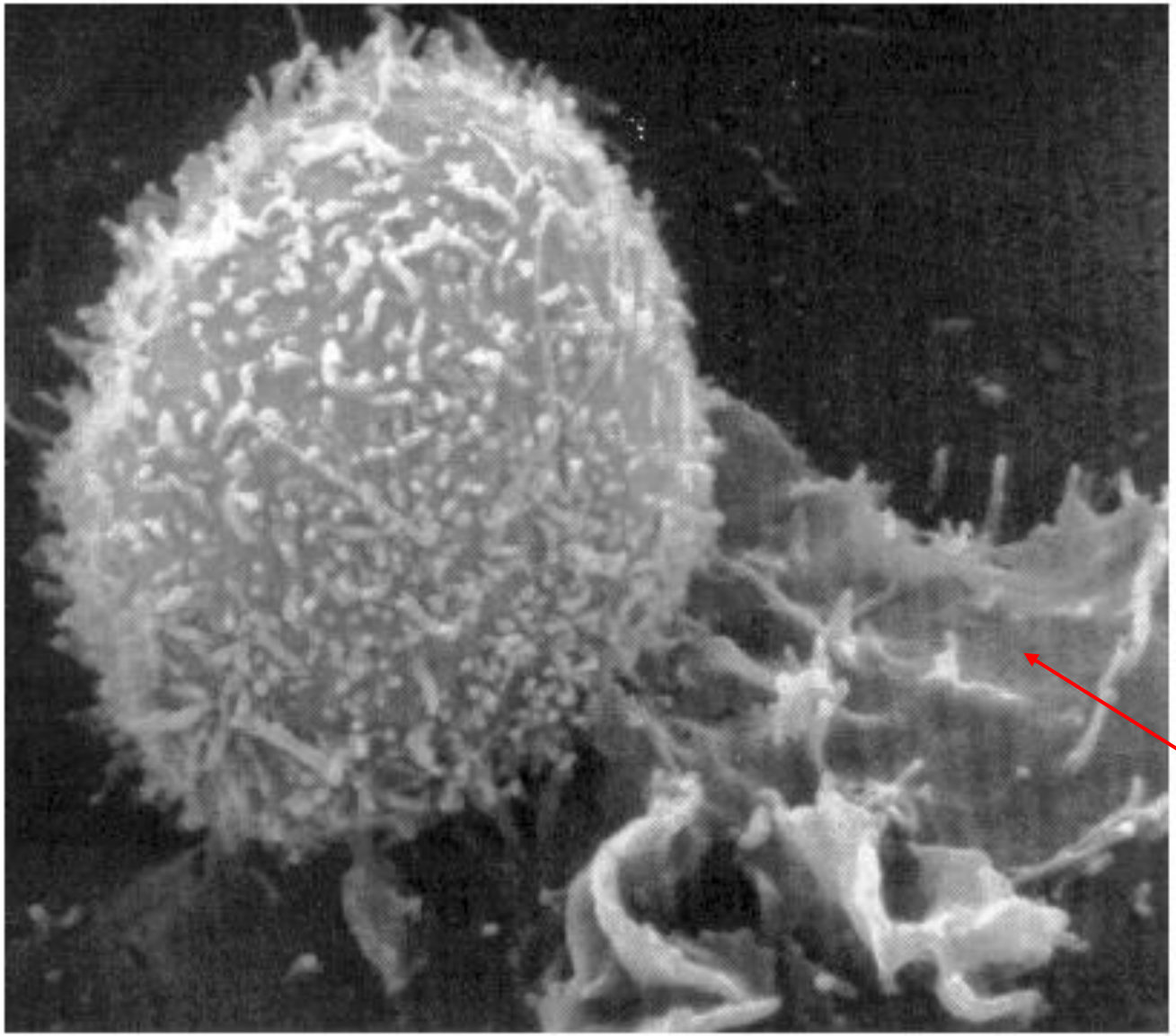
b. Granzymes →caspase 10→ apoptosis



Perforin: creates a hole in the target membrane


CD8 T KILLING VIA Fas-LIGAND....Fas INTERACTION
TARGET
SIGNAL FOR TARGET CELL
TO UNDERGO APOPTOSIS
APOPTOSIS
Fas
Fas-L (Fas-LIGAND)
CD8 T CELL MOVES
ON TO KILL ANOTHER
CELL !!
ACTIVATED ("ARMED")
CD8 T CELL

CD8 T killer cell (CTL)



"Dead"

target cell

3. Regulatory T cells (Treg)

1) $CD4^+$ $CD25^+$ Foxp3 $^+$ regulatory T cells (Treg)

Function: down-regulation of immune response by inhibiting the activation and proliferation of $CD4^+$ or $CD8^+$ T cells.

Mechanisms:

- **Direct inhibition by contacting target cells.**
- **Down-regulation of the IL-2Rα chain.**
- **Inhibition of CD80/CD86 and MHC I expression by APC, thereby inhibiting Ag presentation.**

2) nTreg

iTreg