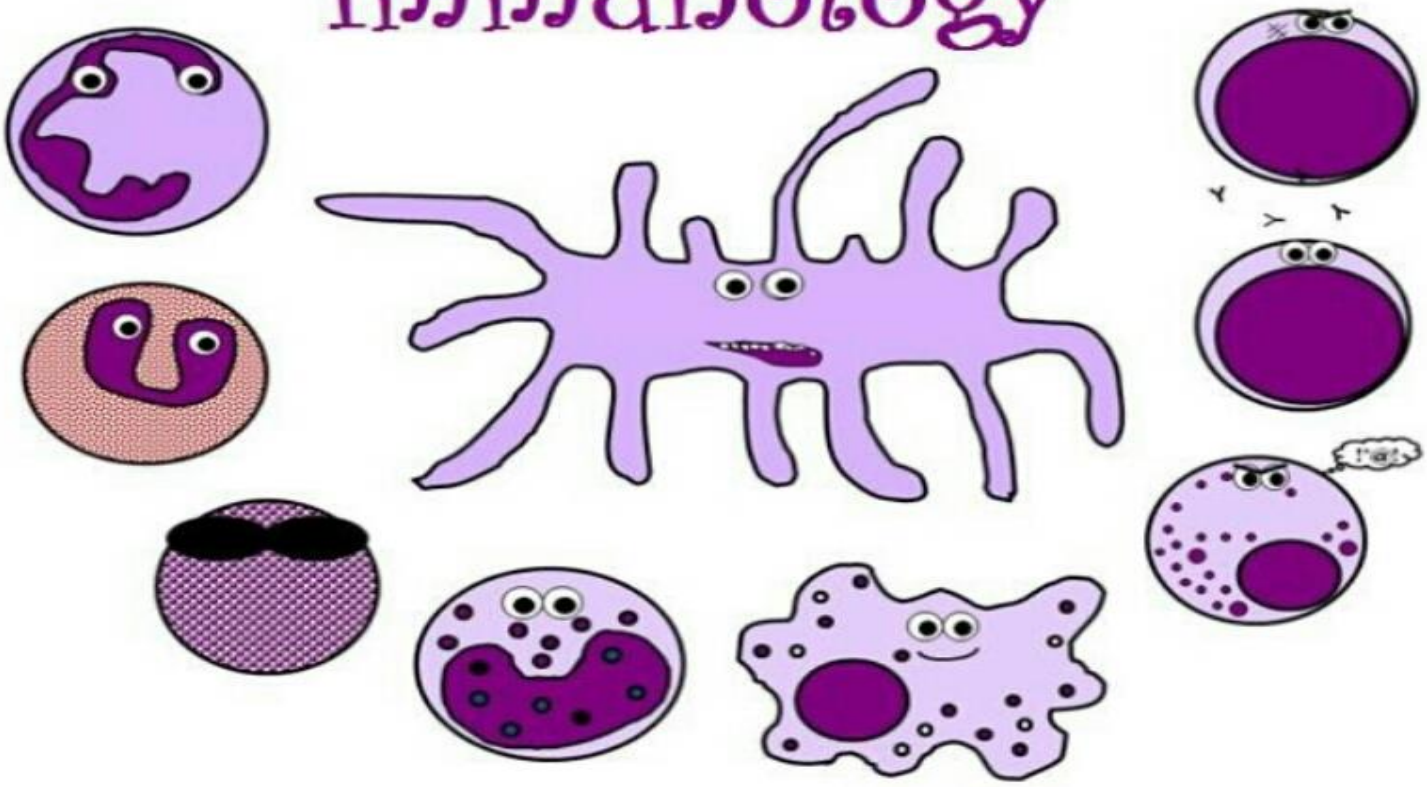
Immunology



Lecture: 7
Subject: Cellular immunity
Edited by: Sally Alsadi

Adaptive Immunity
Cellular Immunity

Mohammad Altamimi, MD, PhD
Jordan University
Faculty of Medicine

Objectives

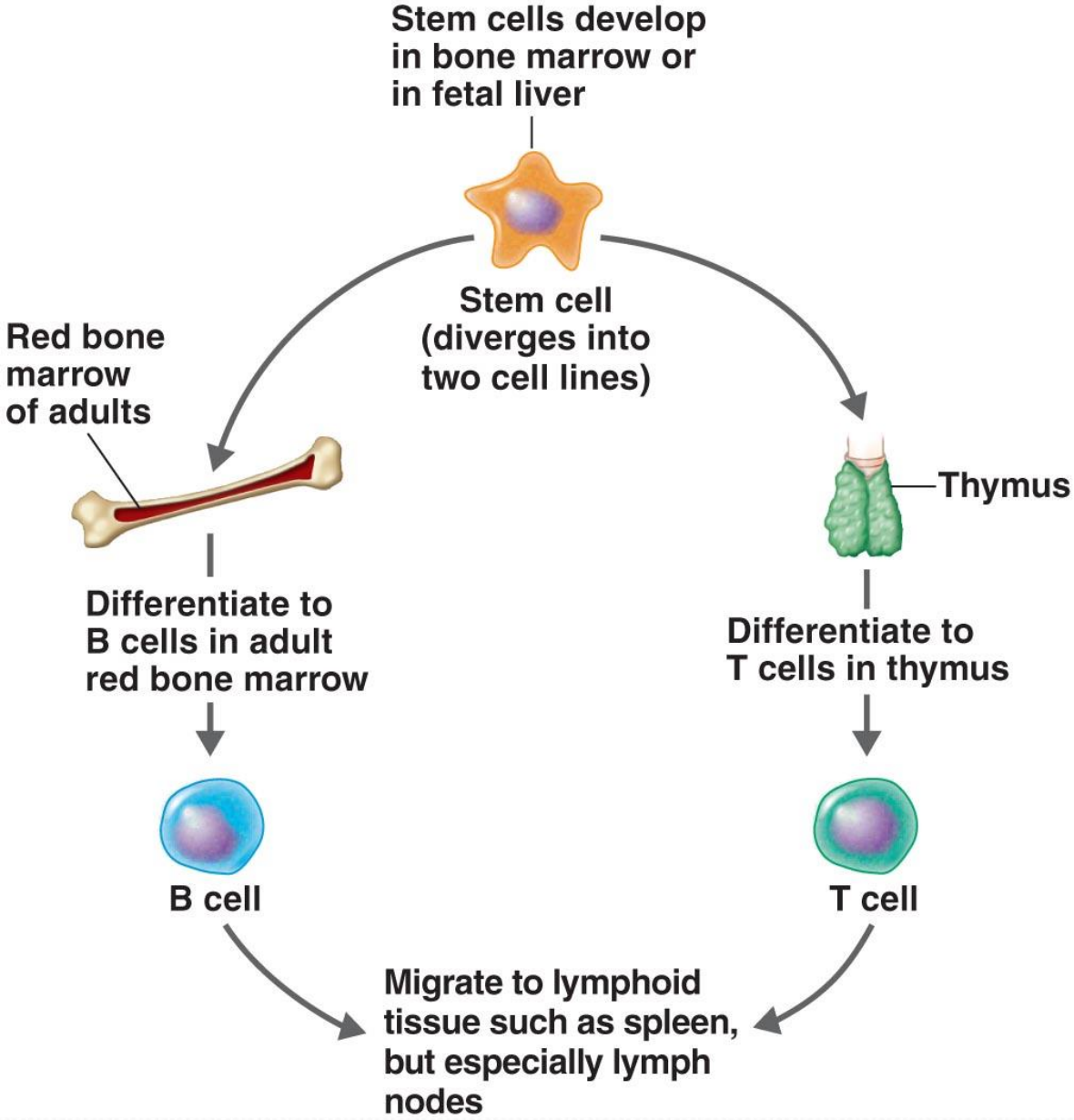
- Explain the principles of adaptive immunity
- Introduce the immune cells that mediate adaptive immunity and their specific roles
- Discuss the differences between cell-mediate immunity and humoral immunity
- Explain what interactions are required for activation of T cells and B cells
- Discuss the stages of cellular and humoral immunity
- Discuss immunological memory and outline the differences between primary and secondary responses
- Compare and contrast the innate and adaptive immune response

Adaptive Immunity

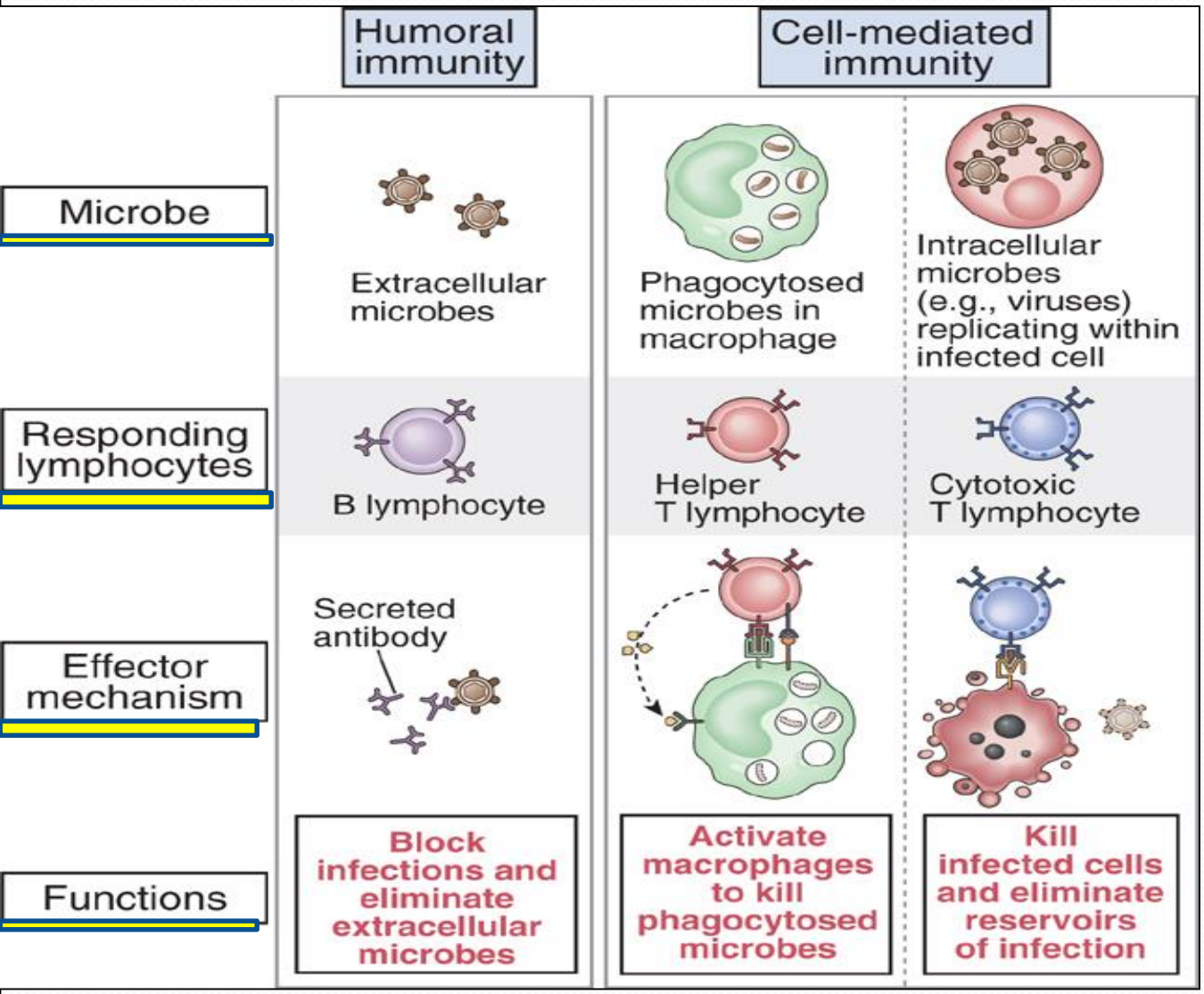
- **Adaptive immunity**:
  - Induced resistance to a specific pathogen
  - Learnt by experience
  - Confers pathogen-specific immunity
  - Enhanced by second exposure
  - Has memory
  - Is poorly effective without innate immunity

1. **Humoral immunity:** B cells and antibodies
2. **Cellular immunity:** Due to T cells and cytokines

Dual Nature of Adaptive Immunity



Types of Adaptive Immunity



T-cells :

->ingest intracellular microbes "*ingested by macrophages*"

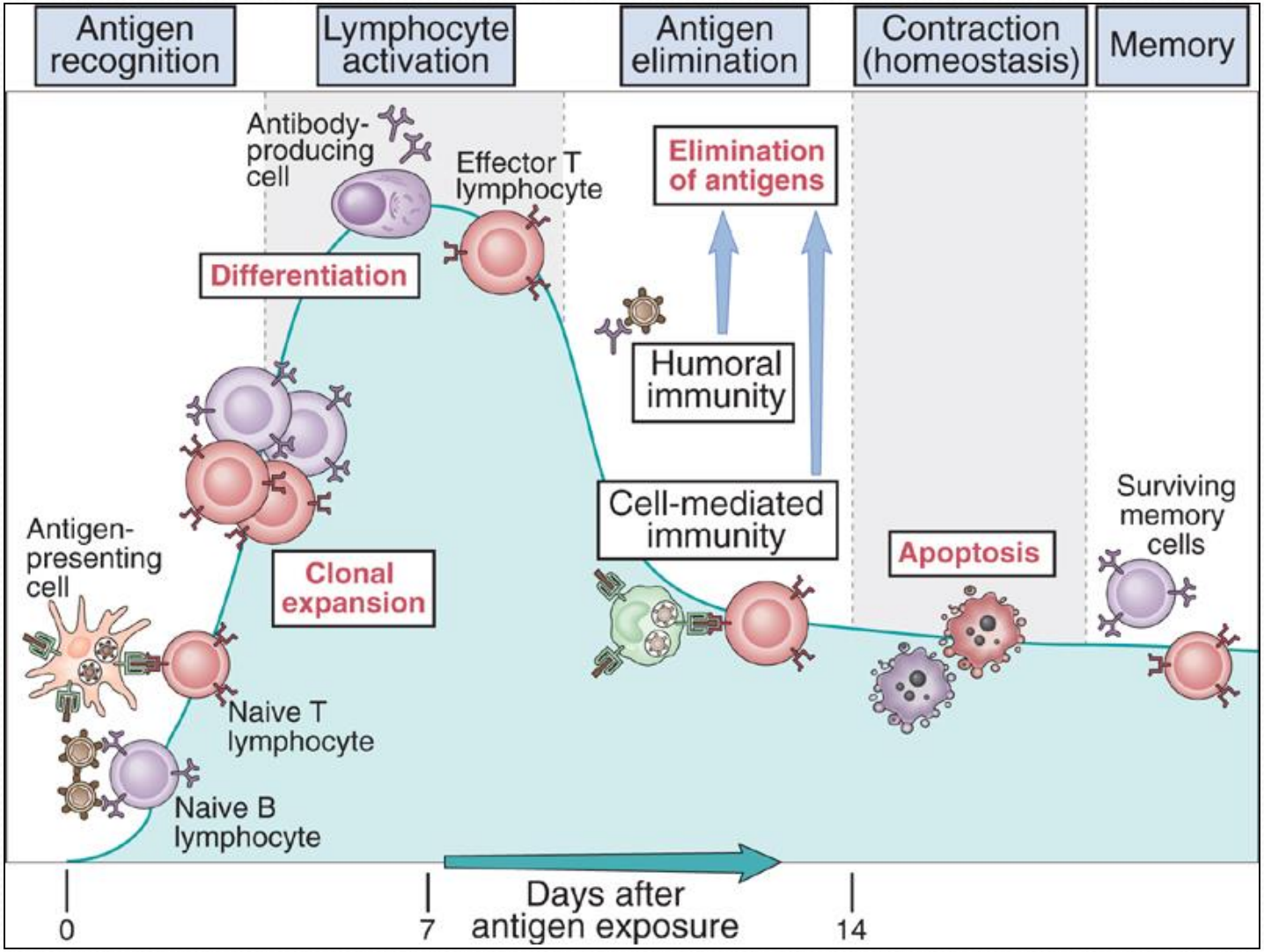
->attack viruses "*that bind to receptors of cells and replicate inside the cytoplasm*"

Remember :

***part of infected viruses life is outside the cells "*considered as exogenous antigen*" and the other life is inside the cell "*endogenous antigen*".**

***B-cell dependent T-cell activation "*T-cell induces B-cells to produce Abs*".**

Phases of Adaptive Immune Responses



Cellular Immunity

T Cells and Cellular Immunity

- This type of immunity is performed by T cells to compate infection by intracellular microbes
- Intracellular infections include:
  - Microbes ingested by macrophage that resist microbicidal activity of macrophage
  - Viruses that binds to cells receptors and replicate in the cytoplasm of these cells
- T cells help B cells to produce antibodies
- T cells interact with other cells of the immune system
- Types of T cells:
  1. Helper T cells *" co-receptor=CD4"*
  2. Cytotoxic T cells *"co-receptor=CD8>>killing"*
  3. Regulatory T cells *"co-receptor=CD25>>mostly are repressors to T-cells after activation"*

Stages of Cellular Immunity

1. Antigen processing and presentations **(APC's and MHC's)**
2. T cells recognize and bind to Ag by T-cell receptors **(TCRs)**
3. Activation and signaling
4. Clonal expansion and differentiation of T cells
5. Effector functions
6. Shut down of immune response and formation of T memory cells

1. Antigen Processing and Presentation

- Naïve T cells can not recognize antigens directly before processing *"by APCs"*

- The antigens need to be **processed and displayed by MHC molecules** on professional antigen presenting cells
- For details see lecture on antigen presentation and processing

>Most common APC is a dendritic cell also macrophage ingests an intracellular pathogen -> peptides fr. pathogen presented on MHC class II and MHC class I molecules <<1-short peptide 9-13 residues "not exceed 30" 2-only one peptide for each MHC molecule>>. ->Antigen combined with MHC will be bound to TCRs <<so,TCRs responsible for binding of Antigen-MHC complex>>

2. Recognition and Binding

- Naieve T cells circulate through peripheral lymphoid organs
- T cells posses specific receptors that bind antigen ligands on APCs these receptors called **TCR**
- TCRs bind epitopes associated with a MHC protein
- **Adhesion molecules** strengthen the binding of T cells to APCs through integrins, selectins, LFA (leukocyte function-associated antigen)-1, CD2 adhesion molecules

->primary binding of MHC to TCRs
->secondary binding to strengthen T-cells -APCs binding adhesion molecule
Remember :
Selectins and integrins are cell-adhesion molecules utilized during inflammation
->selectin >>initial binding of WBCs
->integrins >>firm adhesion *"stage 3"*

T-cells :

->Adhesion molecules:

-CD2 -LFA.1 –integrin/selectin –CD28

->Antigen recognition :

TCRs + co-receptor :CD4 or CD8

->Signaling , activation molecules :

-CD3.zeta -co.receptors “CD4,CD8” -CD45,CD2 <<CD45=leukocyte markers CD2=adhesion + signaling molecule>>

->Co-activation/co-stimulation molecules “CD28”

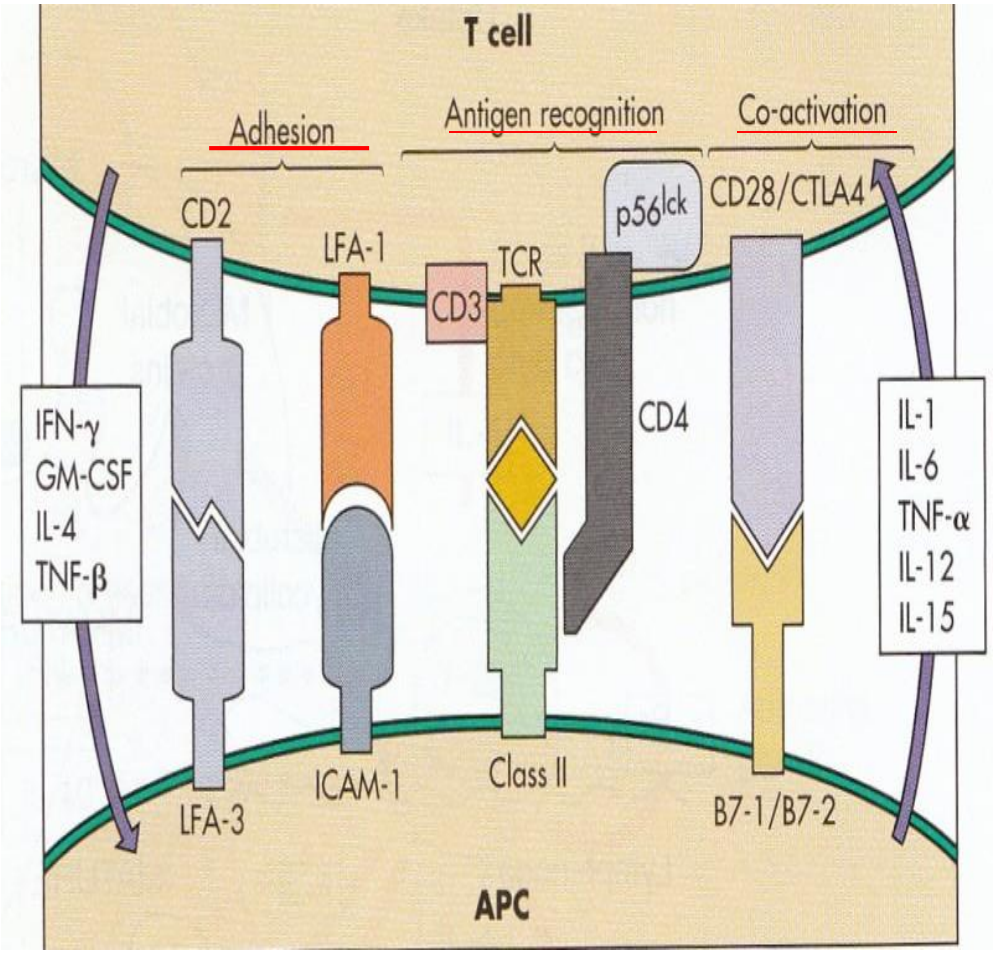
APCs :

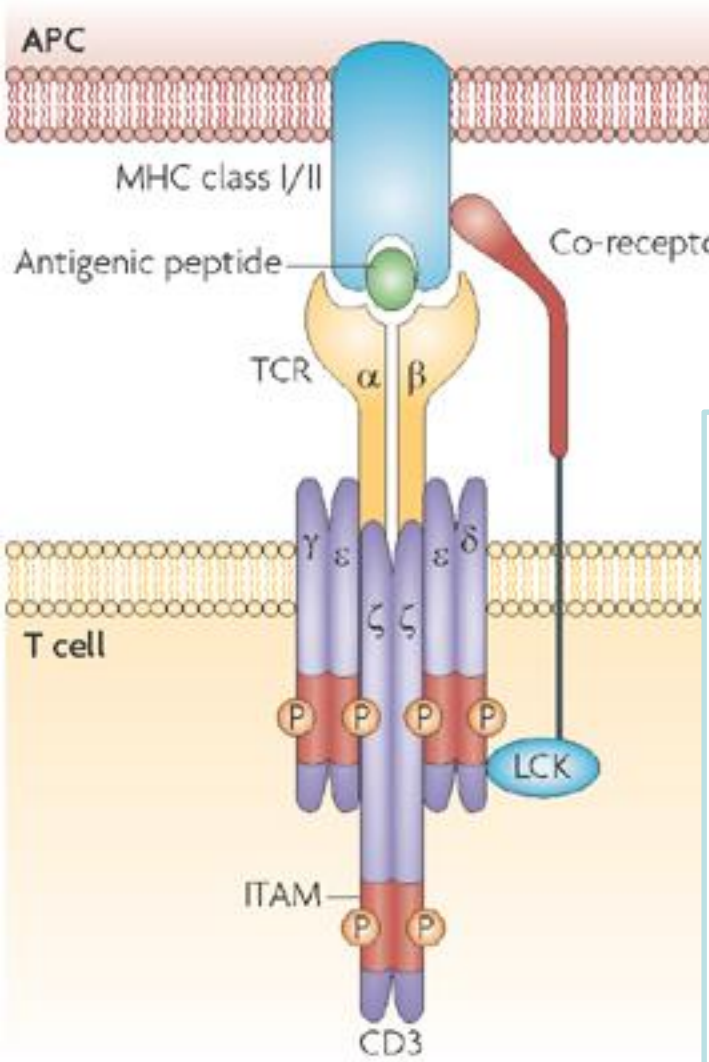
->ICAM-1 that is bound to LFA-1 on T-cell.

->B7 that is bound to CD28 ON T-cells

>>Co-stimulation=B7-CD28<<

>>Co-stimulation is considered as 2nd signal<<





◆ Antigen recognition by TCR +certain molecules provide Stimulatory signal **(Signal 1)** to the T cell ◆Binding of B7 molecule on APC with CD28 molecule on T cell provides Co-stimulatory signal **(Signal 2)** to the T cell.

Signaling and activation of T-cells are 4 groups: Why?

->to ensure that T-cell is not activated until the presence of proper signaling <<*no auto-immune disease*>>

A- Signal 1

-T.cell binding

1- CD3-zeta

2-CD4-CD8 "co-receptors"

3-CD45-CD2

B- Signal 2

-Co-stimulation

4-B7/CD28.

When T cells receive both Stimulatory (Signal 1) and Co-stimulatory (Signal 2) signals they are activated (clonal activation)

◆If the T cells receive only the Stimulatory signal without Co-stimulatory signal, they are permanently inactivated (clonally anergy "anergized") >>same thing happens with B-cell.

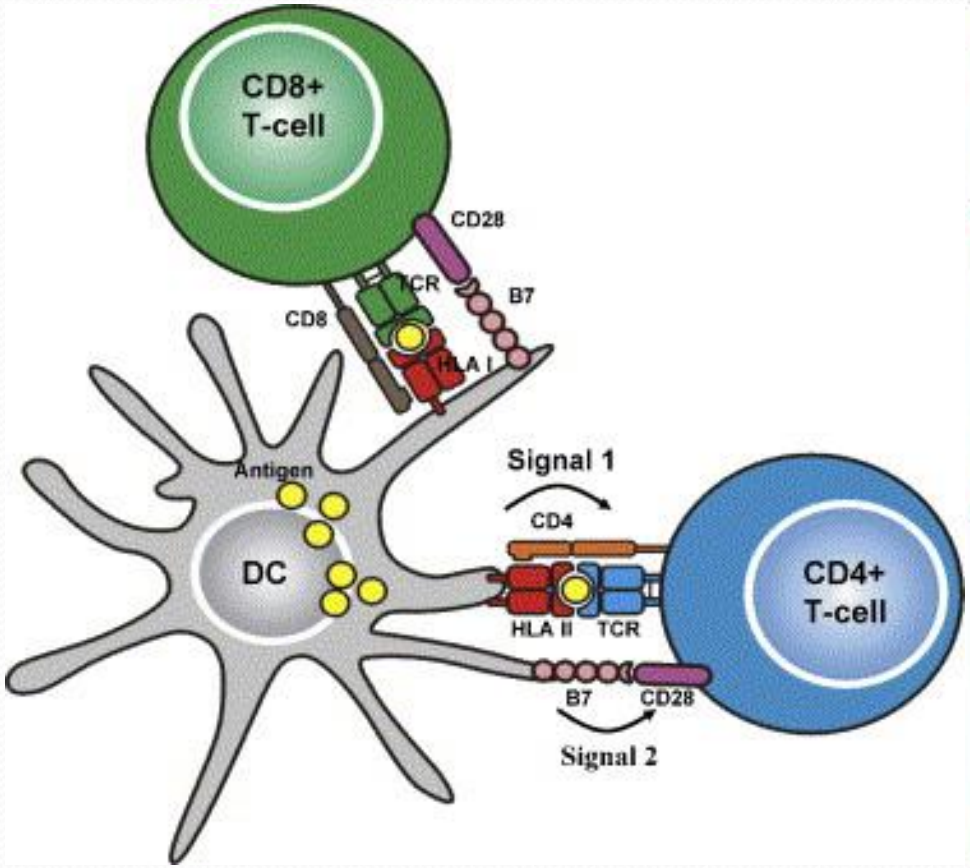
<<REMEMBER :the signaling pathway in the immunoglobulin/antibody is via alph+beta signaling>>

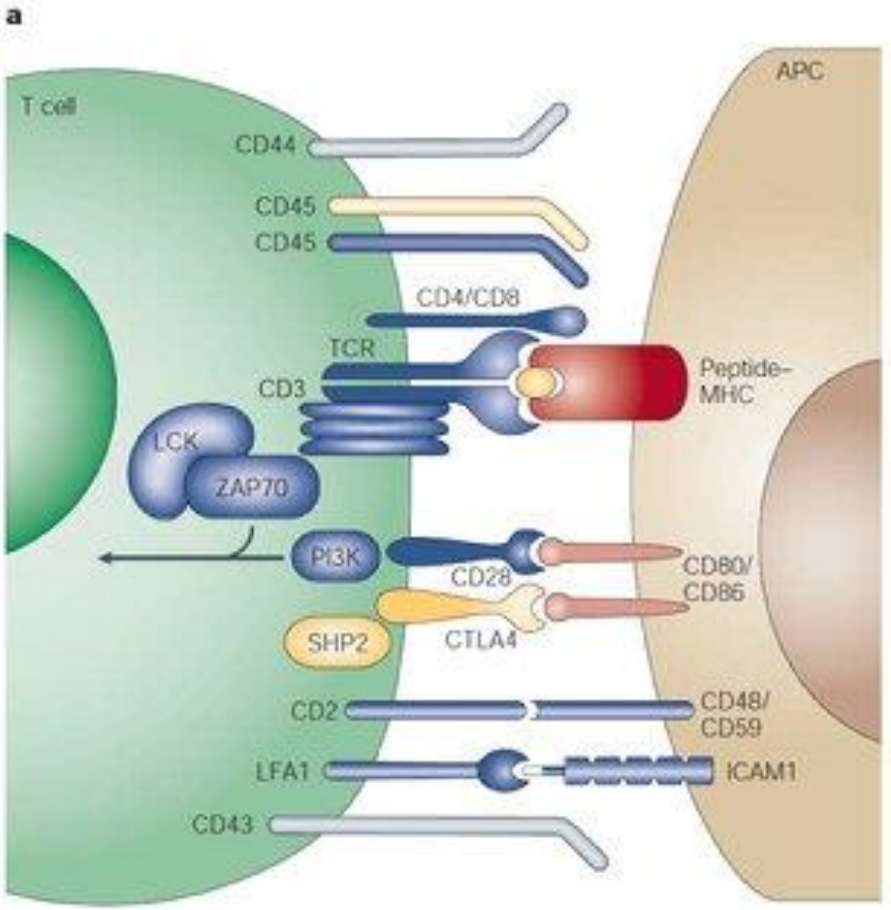
◆Activated T cells start to proliferate, synthesize and secrete IL-2 and express IL- 2 receptors on cell surface>>proliferation+ differentiation of T-cells

◆After several divisions they differentiate to effectors and memory T cell populations

3. Signaling and Activation

1. MHC + antigen – TCR binding and activation of CD3 and ζ (zeta) do the function of signaling (**TCR complex**)
2. co receptors including CD4 and CD8 play role in signaling
3. Other accessory molecules including CD45 and CD2 participate in signaling
4. Costimulatory signal
   - B7 on APC interacts with CD28 on lymphocyte
   - Receptors for costimulation recognize second signal provided by APCs
   - With out costimulation T cells remain **not active** (anergy)


CD8+
T-cell
CD28
TCR
B7
CD8
HLA I
Antigen
DC
Signal 1
CD4
HLA II
TCR
CD4+
T-cell
B7
CD28
Signal 2

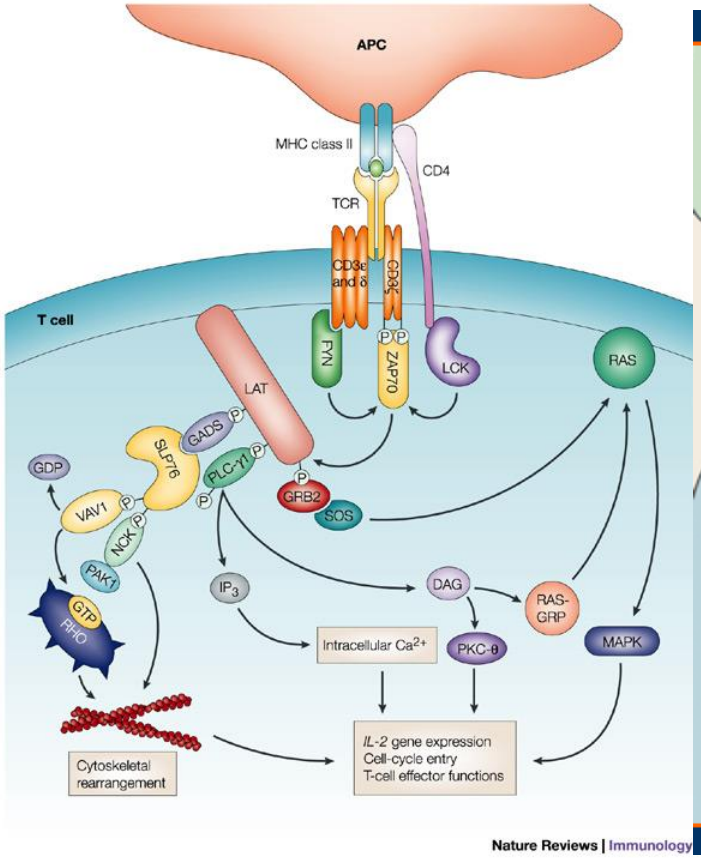

a
T cell
APC
CD44
CD45
CD45
CD4/CD8
TCR
CD3
Peptide–
MHC
LCK
ZAP70
PI3K
CD28
CD80/
CD86
SHP2
CTLA4
CD2
CD48/
CD59
LFA1
ICAM1
CD43

T cell Activation

1. Antigen recognition, primary and secondary signaling leads to T cells activation
2. Release of biochemical mediator and active enzymes that end by activation of transcription factors
3. This results in influx of calcium into the cell
4. Calcium activates calcineurin
5. Calcineurin activates gene for IL-2 and its receptor necessary for T cells proliferation and differentiation and cytokine release

Calcineurin:
->starts to secrete IL-2
–starts to put IL-2 receptors on the T-cell surface.

Details are not included



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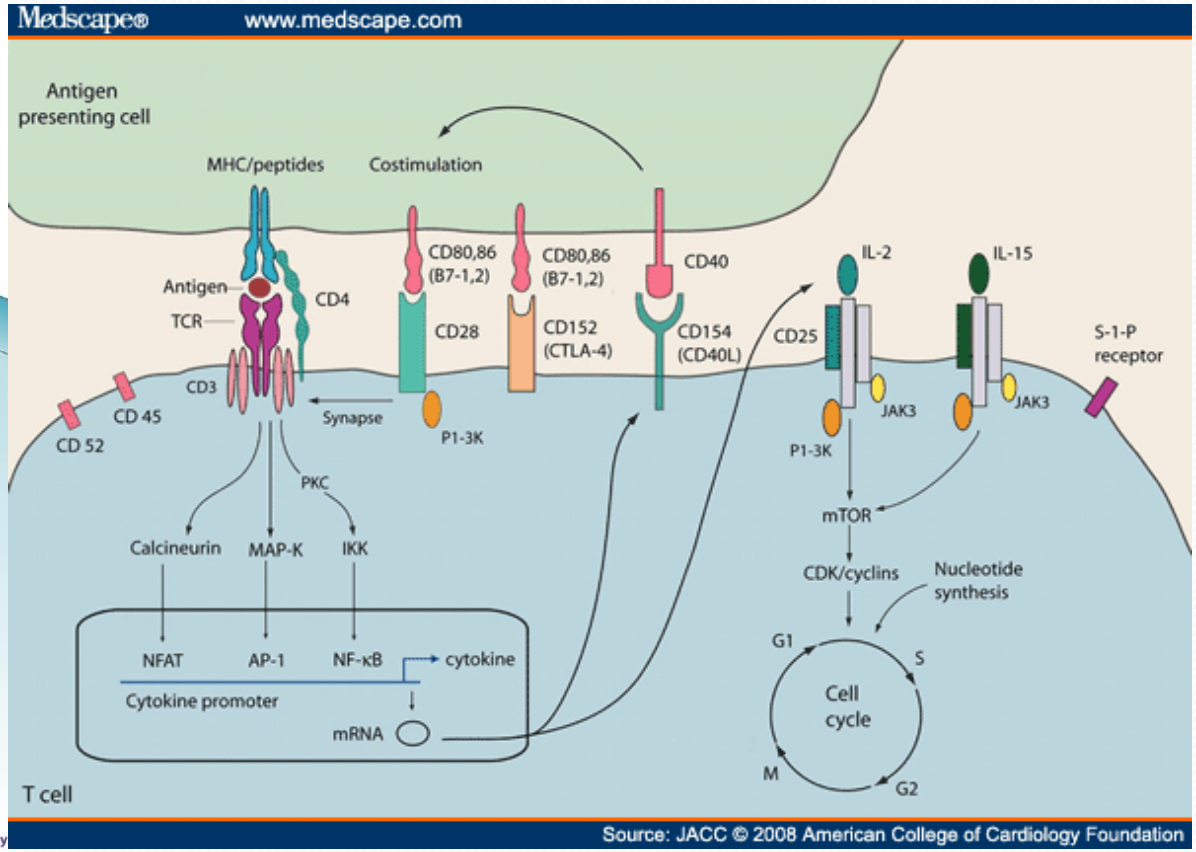
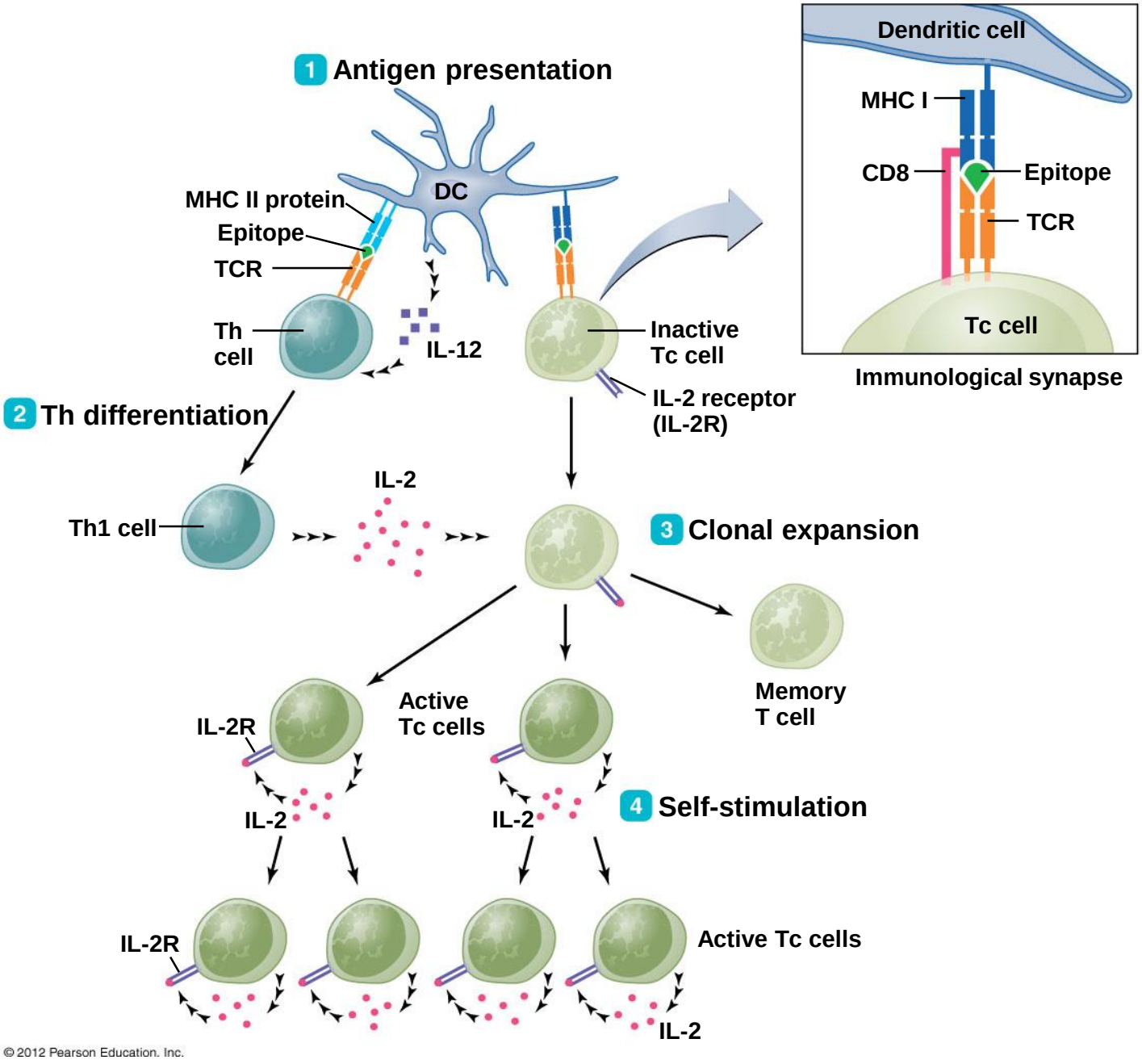


4. Proliferation and Differentiation

- As a result of T cells activation and Interleukins secretion T cells start to proliferate resulting in expansion of **antigen specific cells** or clones (1-2 days)*<<clonal expansion of cells that recognize the antigens>>*
- after 4-5 days T cells differentiate and expand to yield enough numbers of **functional T cells (effectors cells)**
- These cells leave the peripheral lymphoid tissue and migrate to site of infection
- A small subset of T cells will **differentiate into memory T cells**


1 Antigen presentation
DC
MHC II protein
Epitope
TCR
Th cell
IL-12
Inactive Tc cell
IL-2 receptor (IL-2R)
Dendritic cell
MHC I
CD8
Epitope
TCR
Tc cell
Immunological synapse
2 Th differentiation
Th1 cell
IL-2
3 Clonal expansion
Memory T cell
IL-2R
Active Tc cells
IL-2
IL-2
4 Self-stimulation
IL-2R
Active Tc cells
IL-2
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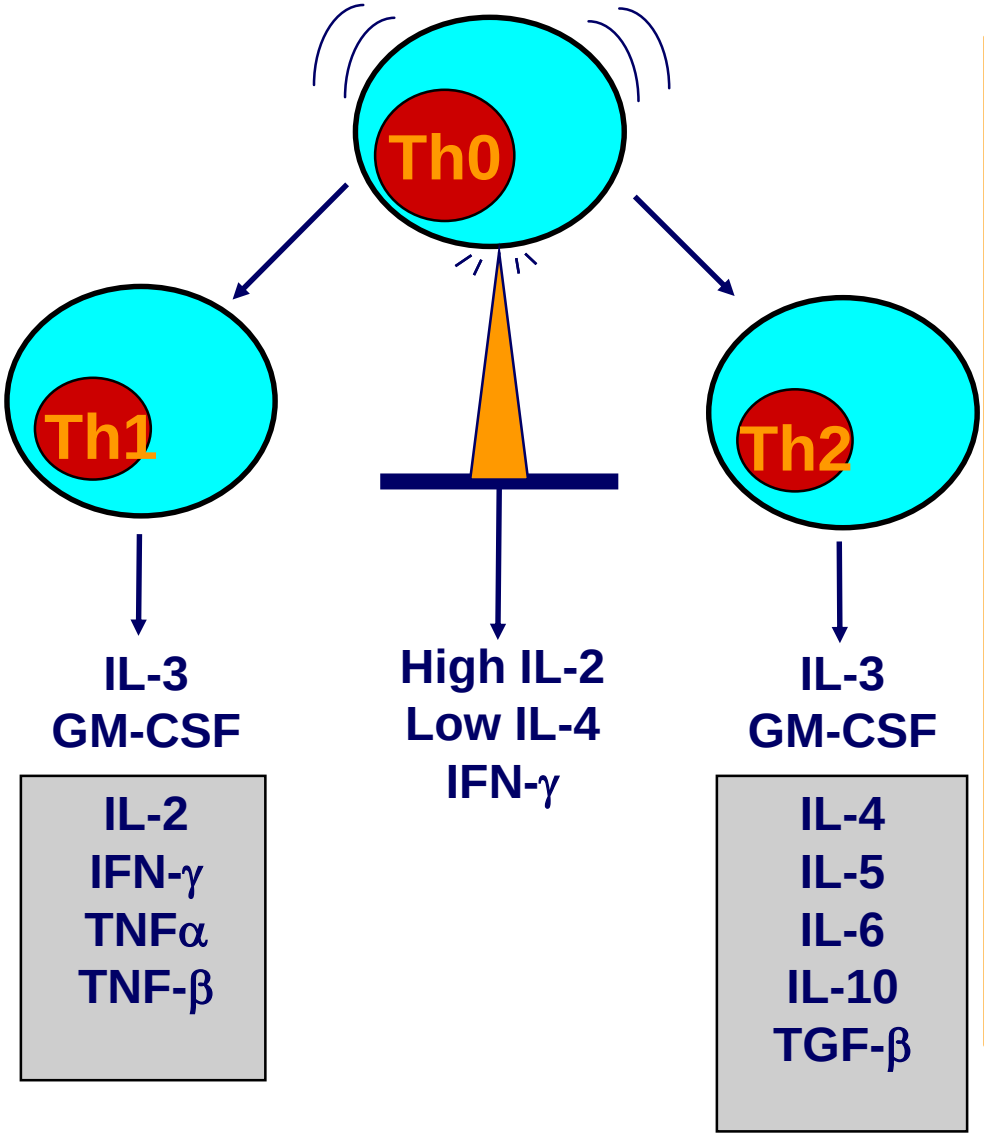
5. Effector Mechanisms

- Effector mechanisms are responsible of the final killing of microbes
- The main effector function of T cells include:

1. Activation of macrophage
2. Activation of cytotoxic T cels
3. Activation of B cells and humoral response

Cytokine profile of inflammatory T cell subsets



◆ With influence of cytokines :IL- 12 from APCs, TH cells differentiate to <u>TH1 cells</u>

◆ TH1 cells release cytokines :interferon- gama (IFN- g)

◆ IFN-g activates macrophages that phagocytose and eliminate intracellular pathogens “macrophages + cell-mediated immunity”

◆ With the influence of IL-4 TH cells differentiate to TH2 cells

◆ Cytokines from TH2 cells help B cell activation>>IgE release + activate eosinophils

◆ Thus TH2 cells regulate humoral immunity

Conclusion :

->Effector cells that mediate CMI "cell-mediated immunity" include TH cell subsets (TH1,TH2, TH17), cytotoxic cells (CTL, NK cells), and cytokine-activated macrophages

->CMI effector T cells work in concert with cells of the innate immune system (dendritic cells, macrophages) and are dependent on them for antigen presentation and/or production of cytokines that drive TH cell differentiation

->CMI effector macrophages and NK cells work in concert with antibodies from B cells to recognize antibody-coated cells and eliminate them.

T Helper Cells

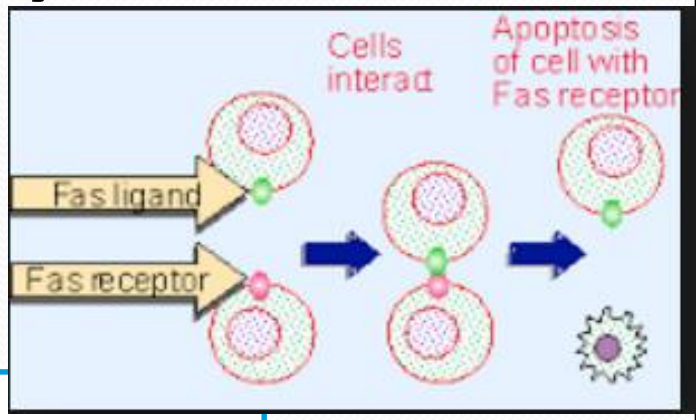
- **$CD4^+$ or T_H cells**
  - T_H cells produce cytokines and differentiate into
    - T_H1
    - T_H2
    - T_H17 *"new "*
    - Memory cells
- TH1 produces IFN-gamma which activates cells related to cell-mediated immunity, macrophages, and Abs
- TH2 activate eosinophils and B cells to produce **IgE**

->TH1>>IFN-g>>activation of macrophages
->TH2>>cytokines/IL-2>>eosinophls +B-cells activation

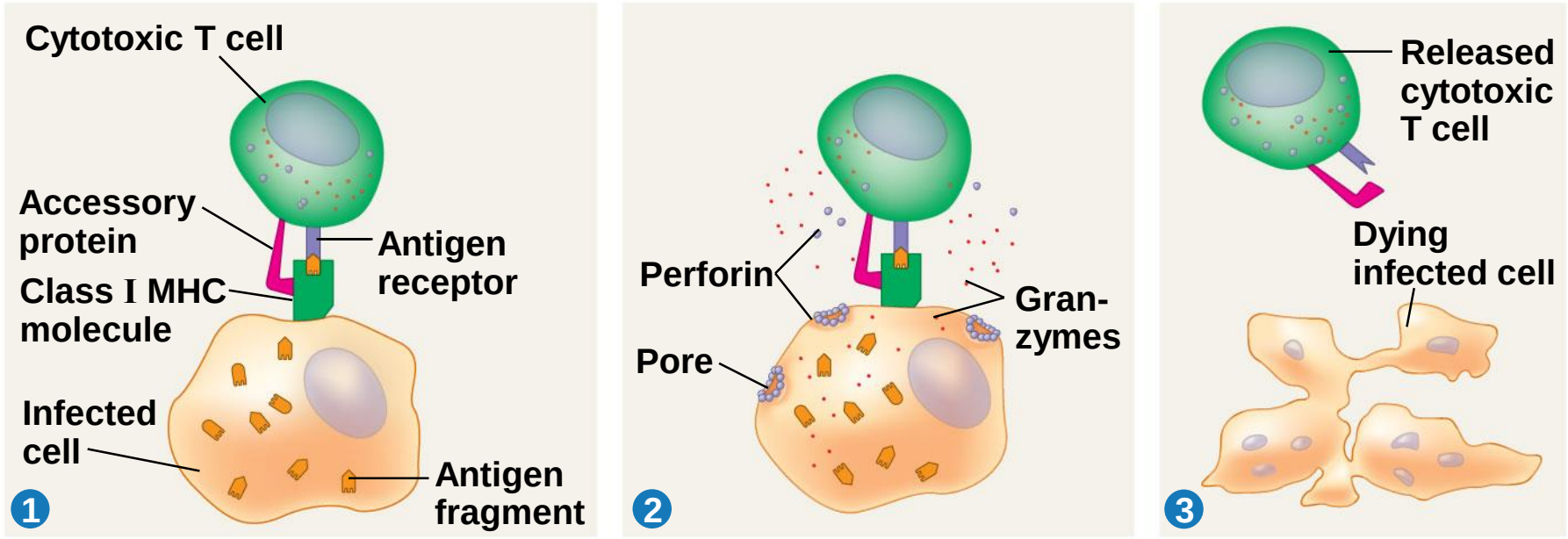
T Cytotoxic Cells *"directly kill micro-organisms"*

- **$CD8^+$** or **T_C** cells
- Target cells are self carrying **endogenous antigens**
- Activated into **cytotoxic T lymphocytes (CTLs)**
  - CTLs recognize Ag + **MHC I**
  - Induce **apoptosis** in target cell
- Cytotoxic T cells kills microorganism by:
  - Perforins
  - Granzymes – degrading enzymes
  - Fas-Fas Ligand interaction - apoptosis
  - Antibody dependent cellular cytotoxicity

"Natural-killer cells + plasma cells >>Abs for labeling Ags"



types of apoptosis :
1- antibody-dependent "for cells that are old enough to be killed"
2-fas-fas ligand interaction :
induce apoptosis for old+micro-organisms "



6. Shut down of Immune Response and Formation of T Memory Cells

No shut-down >>auto-immune disease.

- T_{reg} cells (have CD4 and CD25 on surface): Suppress T cells against self and shut down the T cells immune response after the microbe is eradicated
- As the infection is cleared proliferated immune cells are deprived of survival factors and the cells die by programmed cells death (**apoptosis**)
- A fraction of antigen-activated T cells differentiate into long lived memory T cells
- **Memory T cells** do not produce any cytokines and they do not kill microorganism, they recognize the same antigen if it enters the body again and activate the immune response faster in the second attack of microorganism **"5-7 days for adaptive immunity activation is not needed at the 2nd exposure"**