Adaptive Immunity
Cellular Immunity

Immunology Lecture 8

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Objectives

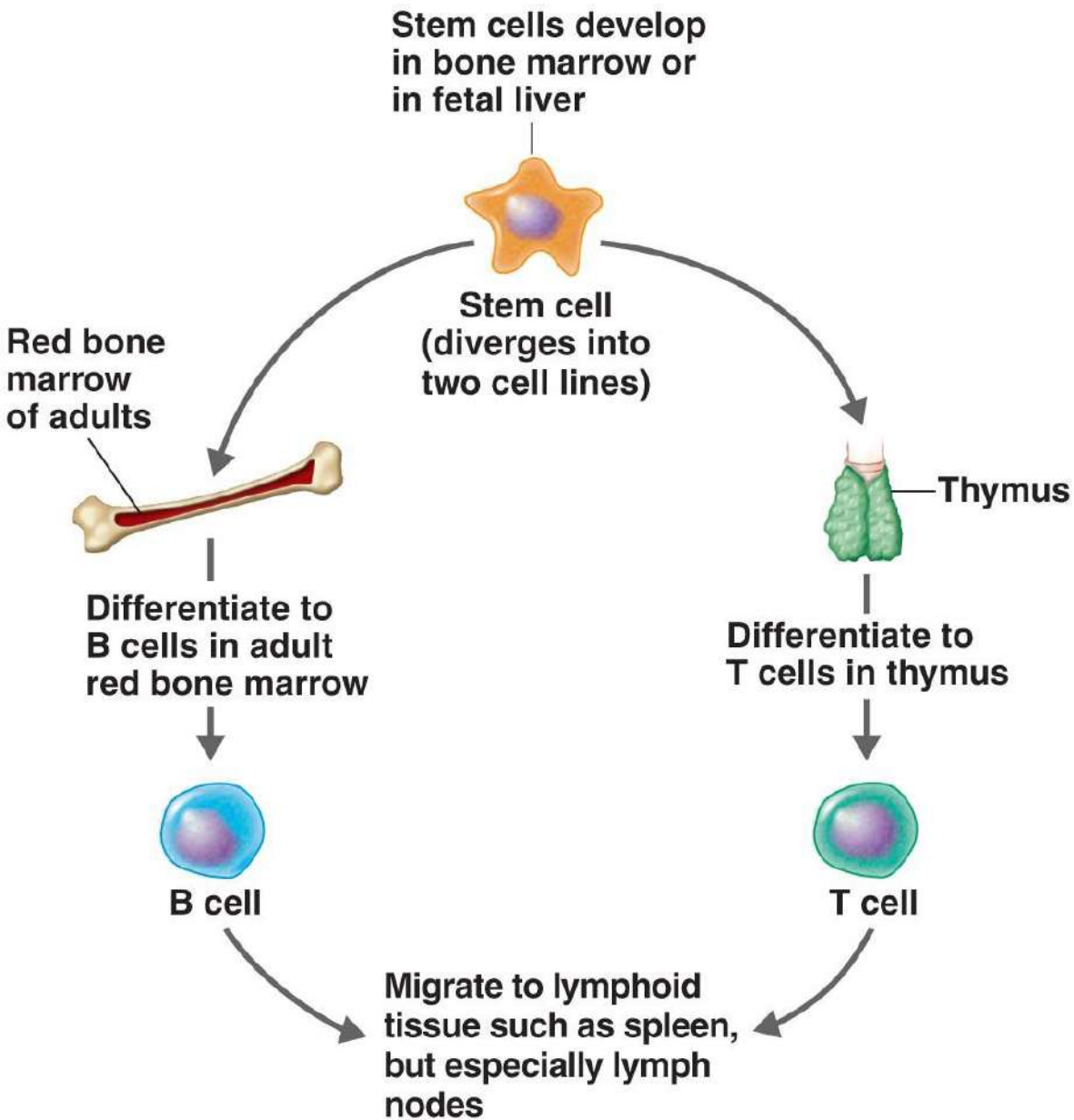
- Explain the principles of adaptive immunity
- Introduce the immune cells that mediate adaptive immunity and their specific roles
- Discuss the differences between cell-mediate immunity and humoral immunity
- Explain what interactions are required for activation of T cells and B cells
- Discuss the 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

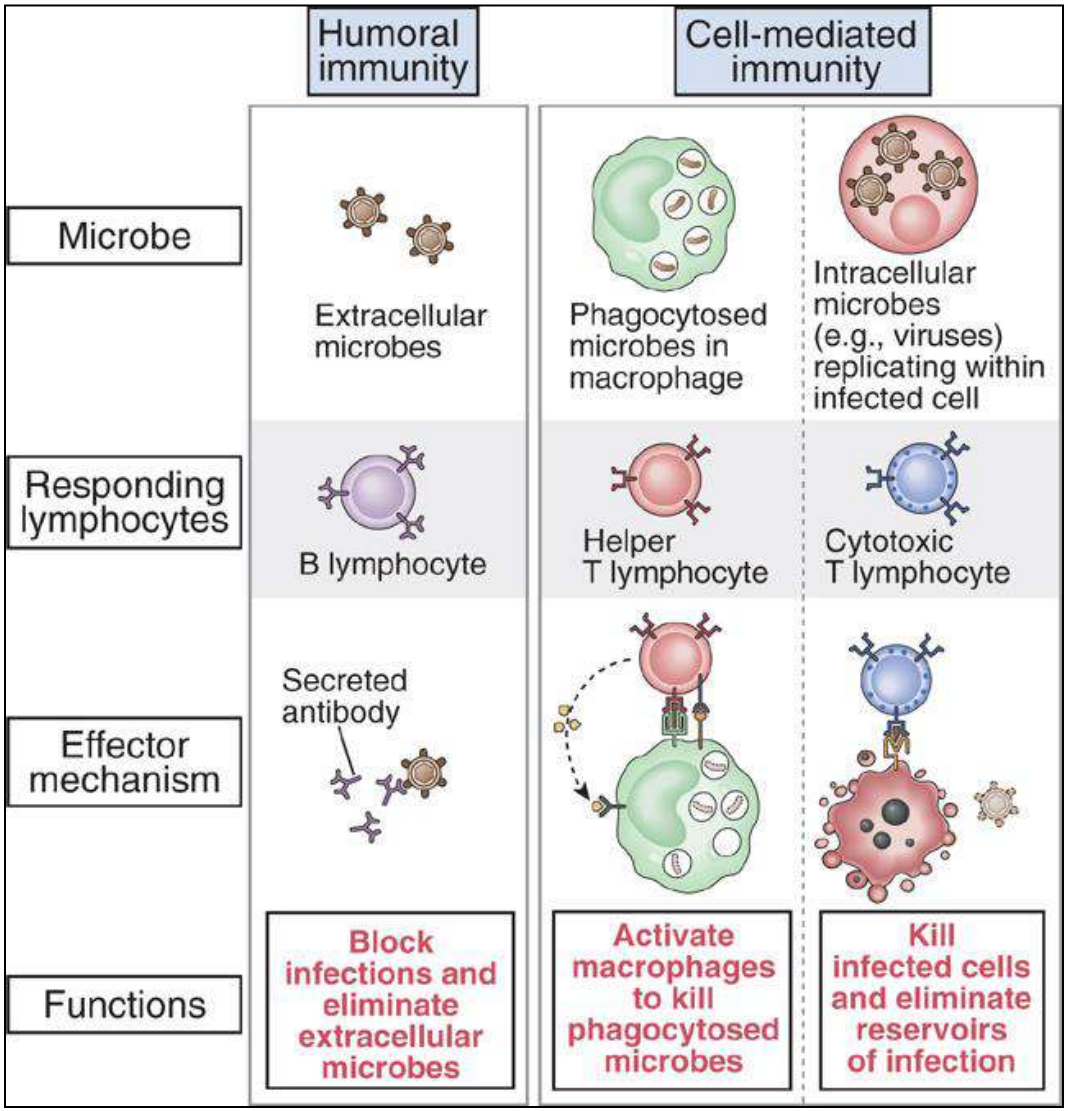
- **Adaptive immunity**:
  - Induced resistance to a specific pathogen
  - Learnt by experience
  - Confers pathogen-specific immunity
  - Enhanced by second exposure
  - Has memory
  - Is poorly effective without innate immunity

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

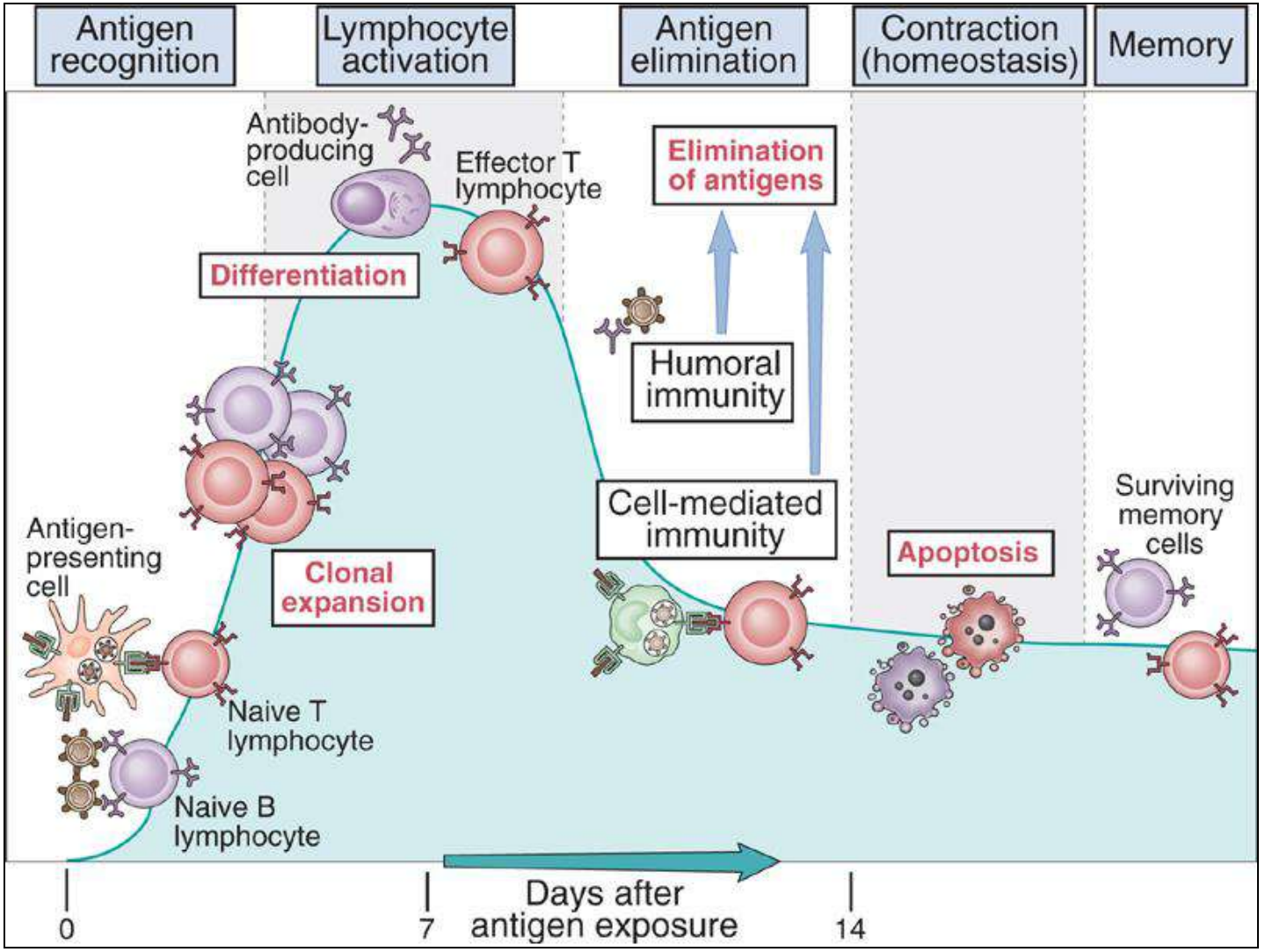
Dual Nature of Adaptive Immunity



Types of Adaptive Immunity



Phases of Adaptive Immune Responses



Cellular Immunity

T Cells and Cellular Immunity

- This type of immunity is performed by T cells to combat 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
  2. Cytotoxic T cells
  3. Regulatory T cells

Stages of Cellular Immunity

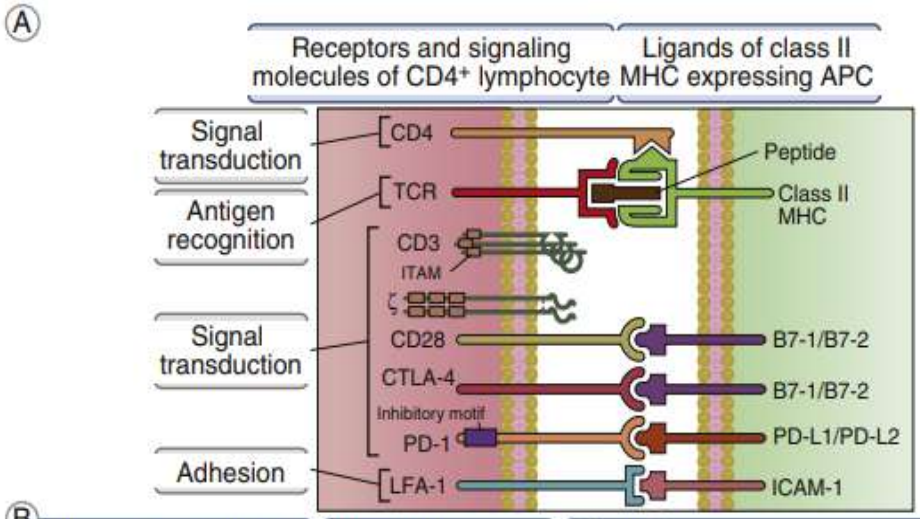
1. Antigen processing and presentations (APC's and MHC's)
2. T cells recognize and bind to Ag by T-cell receptors **(TCRs)**
3. Activation and signaling
4. Clonal expansion and differentiation of T cells
5. Effector functions
6. Shut down of immune response and formation of T memory cells

1. Antigen Processing and Presentation

- Naïve T cells can not recognize antigens directly before processing
- 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

2. Recognition and Binding

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



B

Surface molecules of T lymphocytes	Function	Ligand	
		Name	Expressed on
TCR	Antigen recognition	Peptide-MHC	All T cells
CD3		None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen-presenting cells
CD8	Signal transduction	Class I MHC	All nucleated cells
CD28	Signal transduction (costimulation)	B7-1/ B7-2	Antigen-presenting cells
CTLA-4	Negative regulation	B7-1/ B7-2	Antigen-presenting cells
PD-1	Negative regulation	PD-L1/ PD-L2	Antigen-presenting cells, tissue cells, tumor cells
LFA-1	Adhesion	ICAM-1	Antigen-presenting cells, endothelium

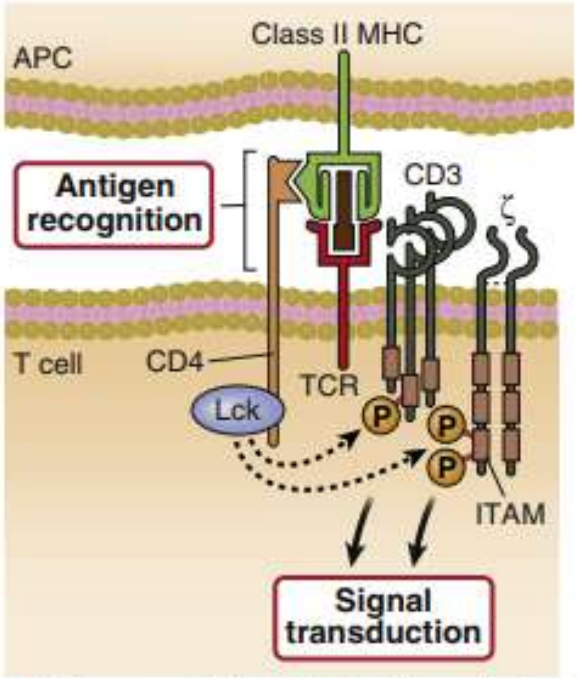
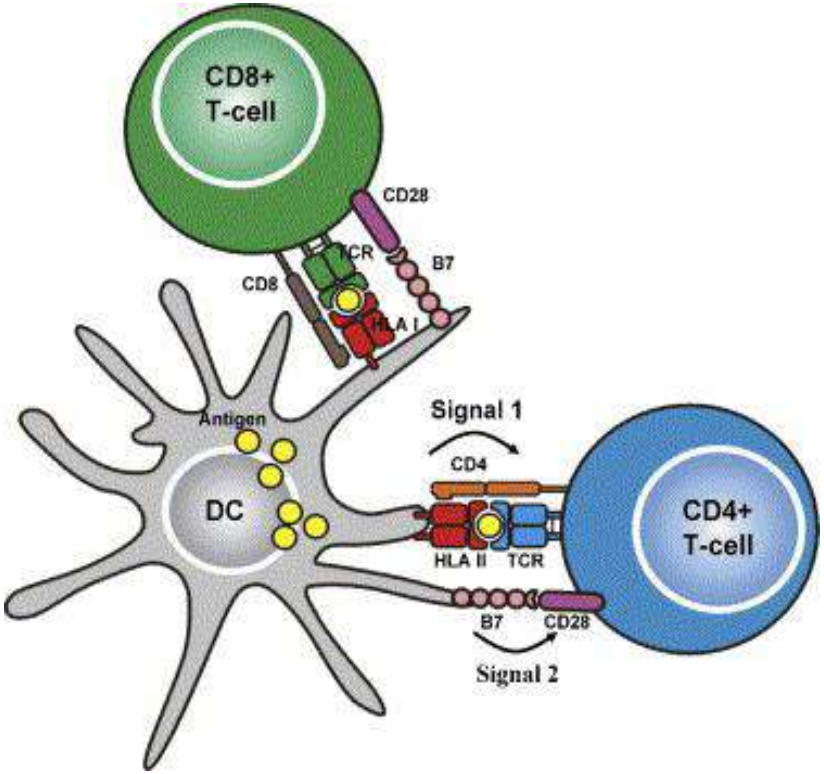


Fig. 5.5 Antigen recognition and signal transduction during T cell activation. Different T cell molecules recognize antigen and deliver biochemical signals to the interior of the cell as a result of antigen recognition. The CD3 and ζ proteins are noncovalently attached to the T cell receptor *(TCR)* α and β chains by interactions between charged amino acids in the transmembrane domains of these proteins (not shown). The figure illustrates a CD4+ T cell; the same interactions are involved in the activation of CD8+ T cells, except that the coreceptor is CD8 and the TCR recognizes a peptide–class I MHC complex. *APC,* Antigen-presenting cell; *ITAM,* immunoreceptor tyrosine-based activation motifs; *MHC,* major histocompatibility complex.

3. Signaling and Activation

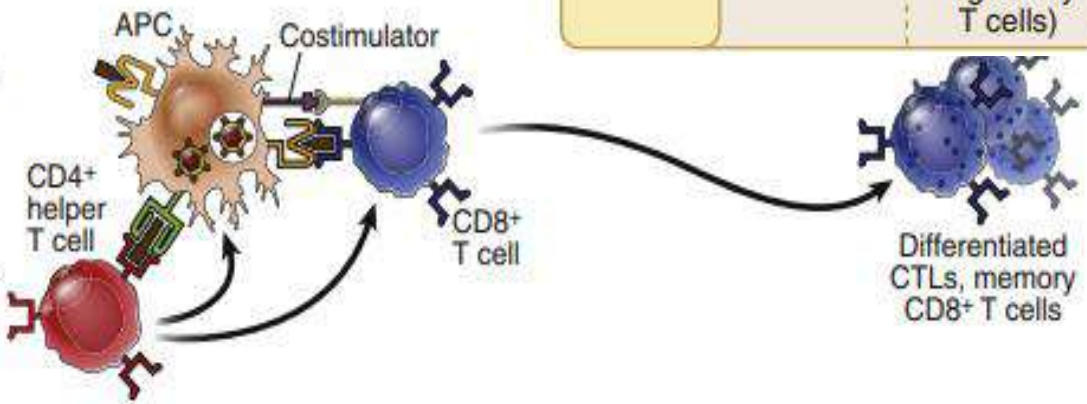
1. MHC + antigen – TCR binding and activation of CD3 and ζ (zeta) do the function of signaling (**TCR complex**)
2. co receptors including CD4 and CD8 play role in signaling
3. Other accessory molecules including CD45 and CD2 participate in signaling
4. Costimulatory signal
   - B7 on APC interacts with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



Name	B7-1 (CD80)	B7-2 (CD86)	ICOS-L (CD275)	PD-L1 (B7-H1, CD274)	PD-L2 (B7-DC, CD273)
Ligands on APCs and other cells					
Receptors on T cells					

Name	CD28	CTLA-4	ICOS	PD-1
Major function	**Activation** (naive T cells)	**Inhibition** (mediates suppressive function of regulatory T cells)	**Activation** (follicular helper T cells in antibody responses)	**Inhibition**

CD4+ helper T cells produce molecules that stimulate CTL differentiation

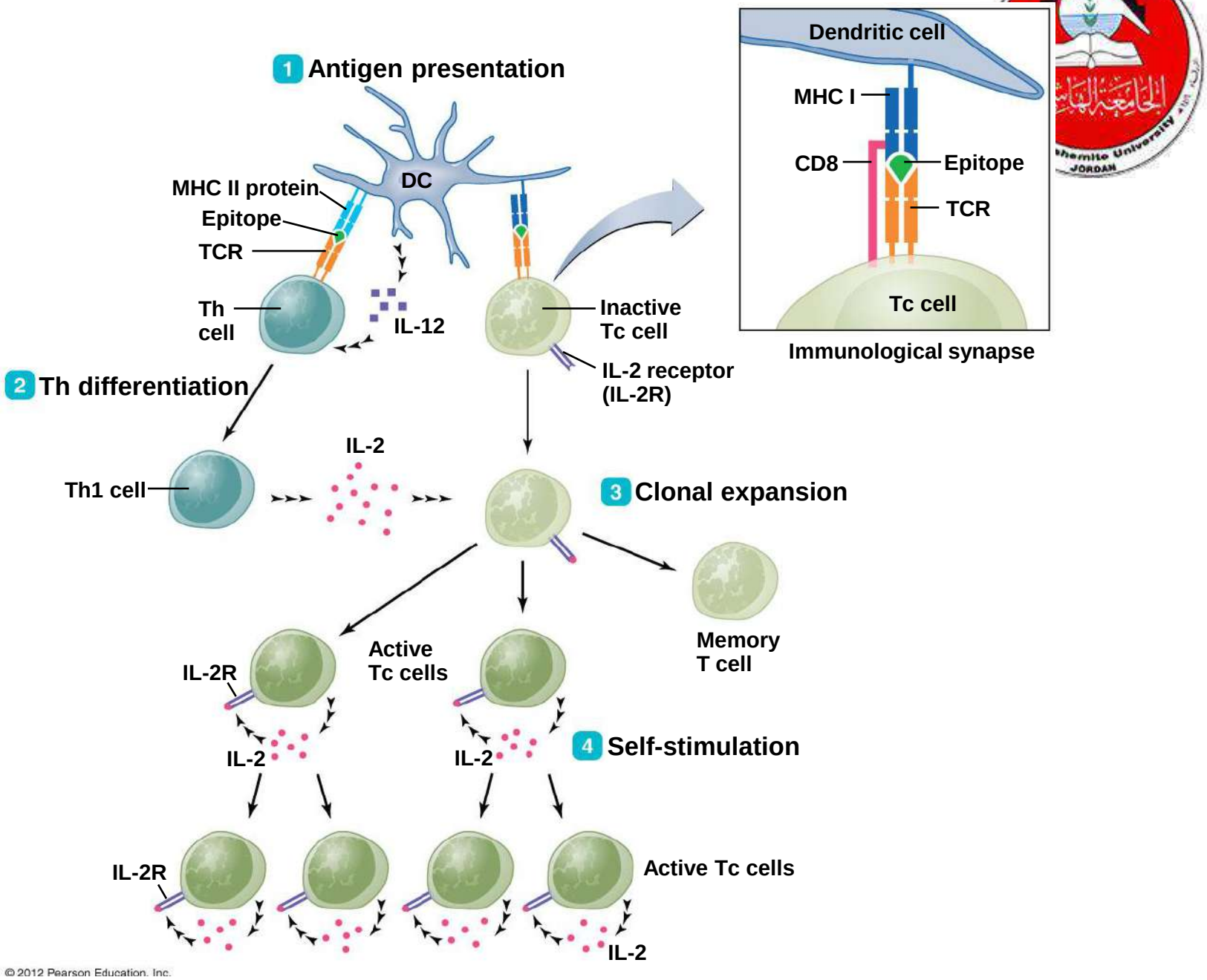


T cell Activation

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

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)
- 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)
2 Th differentiation
Th1 cell
IL-2
3 Clonal expansion
Memory T cell
Active Tc cells
IL-2R
IL-2
IL-2
4 Self-stimulation
IL-2R
Active Tc cells
IL-2
Dendritic cell
MHC I
CD8
Epitope
TCR
Tc cell
Immunological synapse
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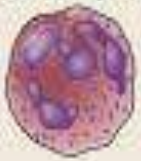
5. Effector Mechanisms

- 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 cells
3. Activation of B cells and humoral response

T Helper Cells

- **$CD4^+$ or T_H cells**
  - T_H cells produce cytokines and differentiate into
    - T_H1
    - T_H2
    - T_H17
    - 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

Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1 	IFN-γ	Macrophages 	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2 	IL-4 IL-5 IL-13	Eosinophils 	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17 	IL-17 IL-22	Neutrophils 	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh 	IL-21 (and IFN-γ or IL-4)	B cells 	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

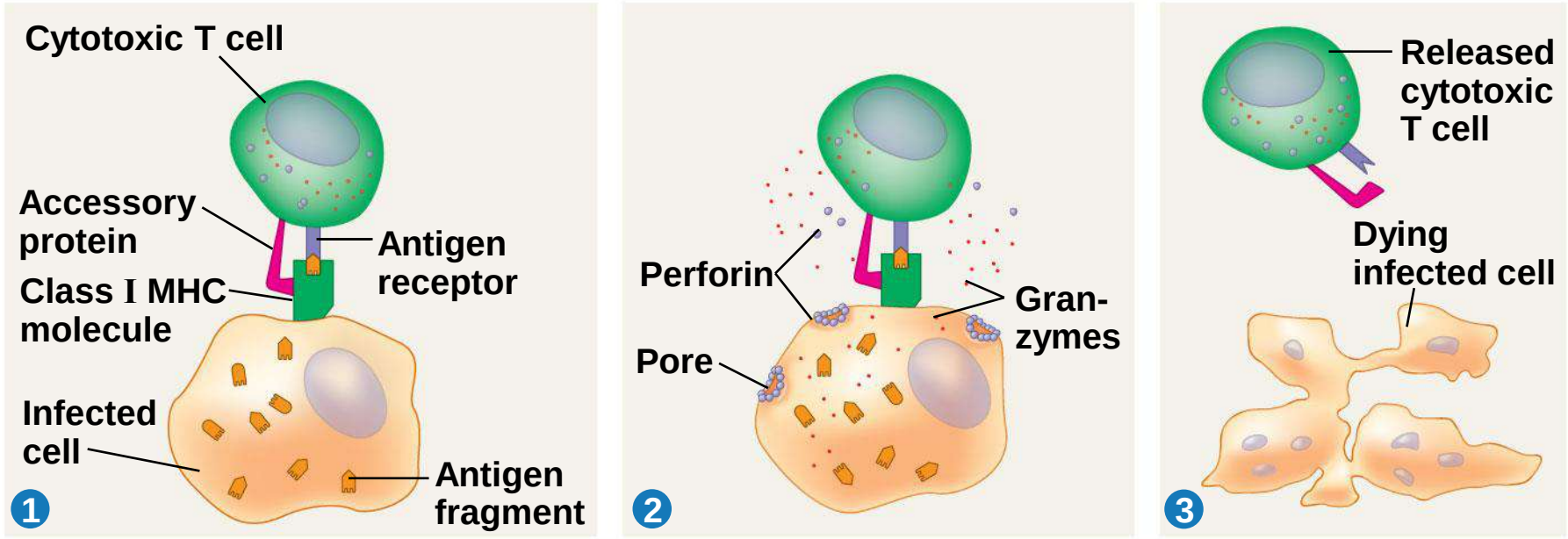
B

Biologic actions of selected T cell cytokines

Cytokine	Principal action	Cellular source(s)
IL-2	T cell proliferation; regulatory T cell survival	Activated T cells
Interferon-γ (IFN-γ)	Activation of macrophages (classical pathway)	$CD4^+$ Th1 and $CD8^+$ T cells, natural killer (NK) cells
IL-4	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells
IL-5	Activation of eosinophils	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-13	B cell switching to IgE; alternative macrophage activation	$CD4^+$ Th2 T cells, mast cells, innate lymphoid cells
IL-17	Stimulation of acute inflammation	$CD4^+$ Th17 T cells, other cells
IL-21	B cell activation; Tfh differentiation	$CD4^+$ Tfh T cells
IL-22	Maintenance of epithelial barrier function	$CD4^+$ Th17 T cells, NK cells, innate lymphoid cells

T Cytotoxic Cells

- **$CD8^+$** 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



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

- 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