IMMUNE RESPOSE

PART II

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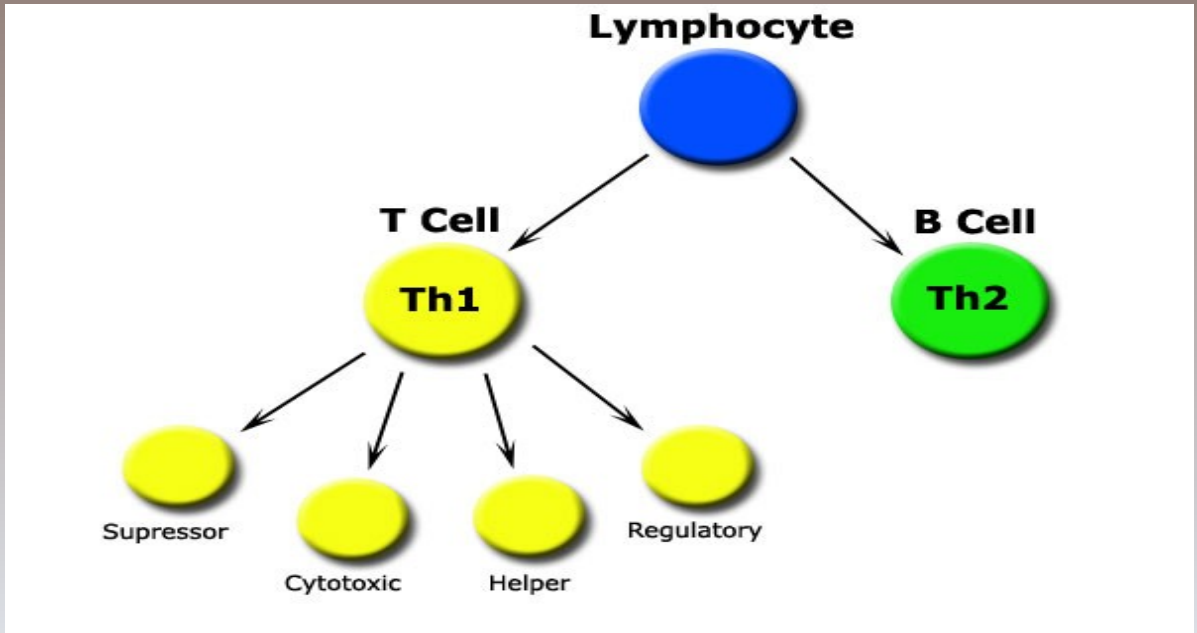
Lecture 3.

21/4/2019

Cell Mediated Immune Response

T Lymphocytes



Word/Terms List

- Development
- Activation
- Differentiation
- Double negative cells
- Double positive cells
- Effector cells
- Maturation
- Negative selection
- Positive selection

T lymphocytes (T cells)

- **Is a type of lymphocyte (a subtype of WBC) that plays a central role in cell-mediated immunity.**

- **T cells can be distinguished from other lymphocytes, such as B cell and natural killer cells , by the presence of a T-cell receptor on the cell surface.**
- **They are called T cells because they mature in the thymus from thymocytes . OR**

- **T lymphocytes (T cells) derive their letter designation from their site of maturation in the thymus gland.**

T lymphocytes (T cells)

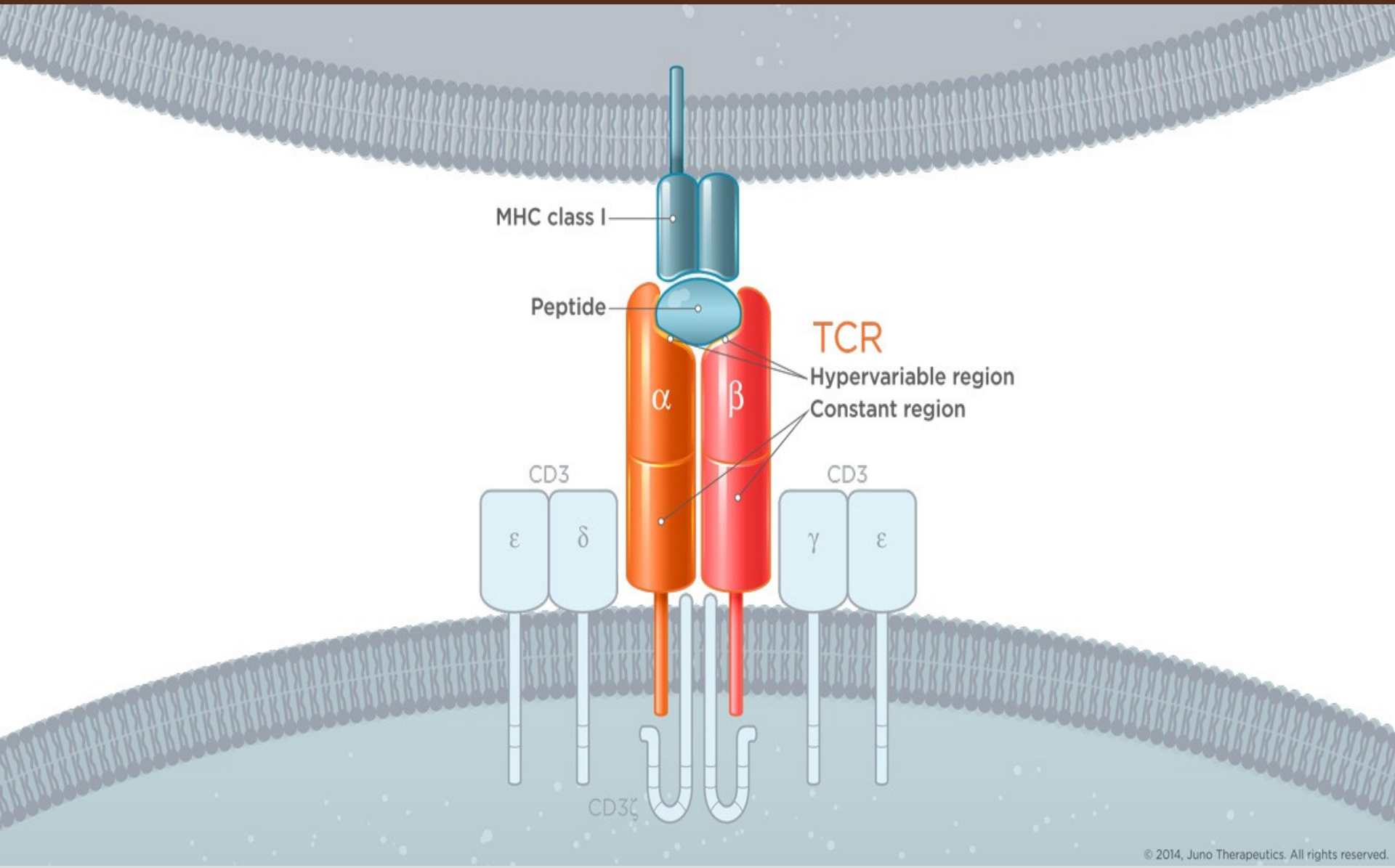
- Antigens that stimulate cellular response are mainly **intracellular.**
- Requires constant presence of antigen to remain effective.
- Unlike humoral immunity, cell mediated immunity is not transferred to the fetus.
- In addition to direct cytotoxicity, T cells produce **cytokines** that activate macrophages.

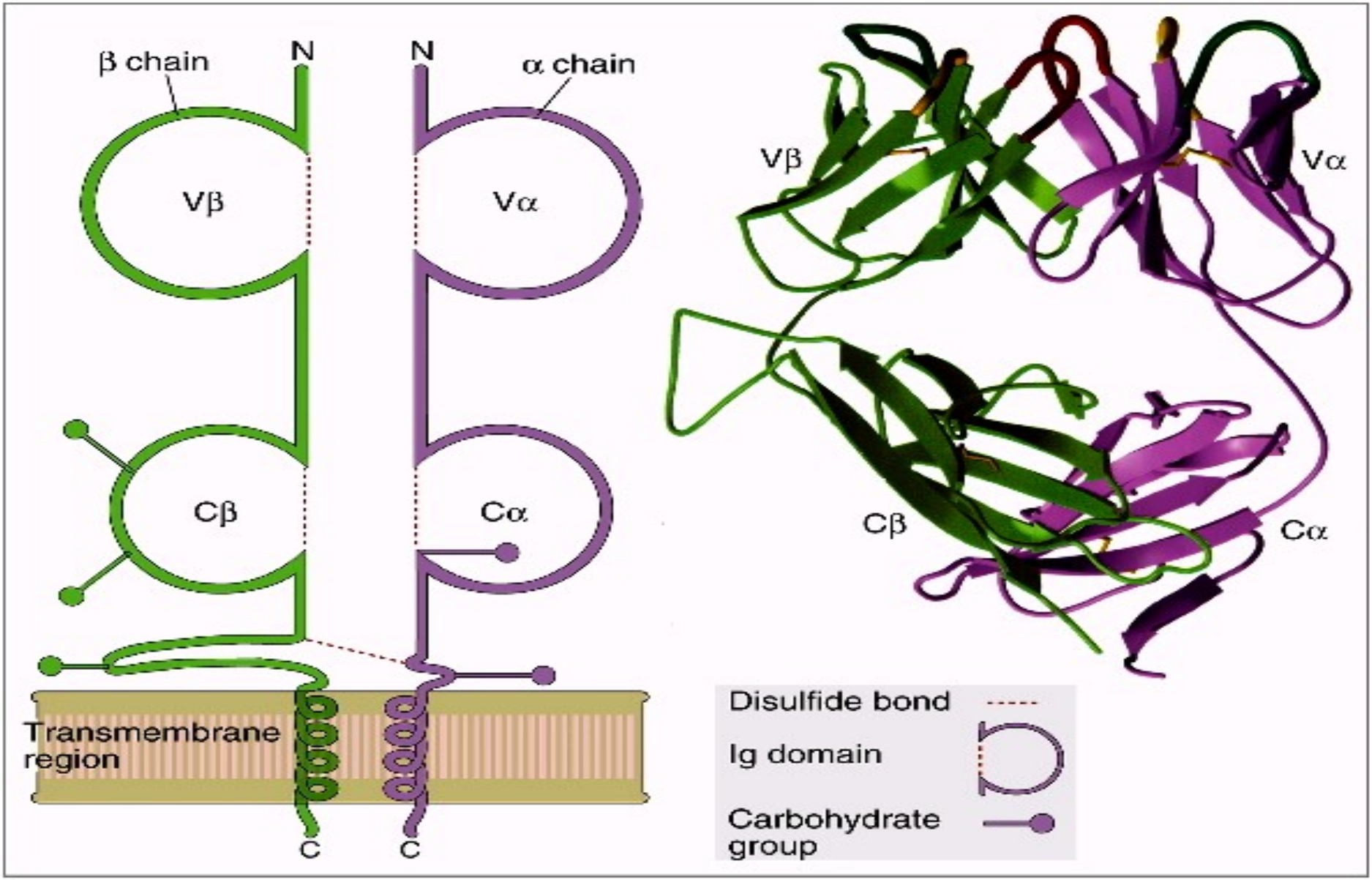
Cytokines:

- Chemical messengers of immune cells.
- Over 100 have been identified.
- Stimulate and/or regulate immune responses.
  - **Interleukins:** Communication between WBCs.
  - **Interferons:** Protect against viral infections.
  - **Chemokines:** Attract WBCs to infected areas.

T Cell Receptor (TCR)

- TCR is a heterodimer composed of two transmembrane polypeptide chains, either:
  - α and β chains or
  - of γ and δ chains.
- The αβ receptors account for 90% of T-cell helper function and cytotoxic activity.
- The γδ T cells receptors, its physiologic role is still unclear.
- The biochemical signals that are triggered in T cells by antigen recognition are transduced not by the T cell receptor itself but by the invariant proteins called CD3
- CD3 are noncovalenlty linked to the antigen receptor to form the TCR complex.

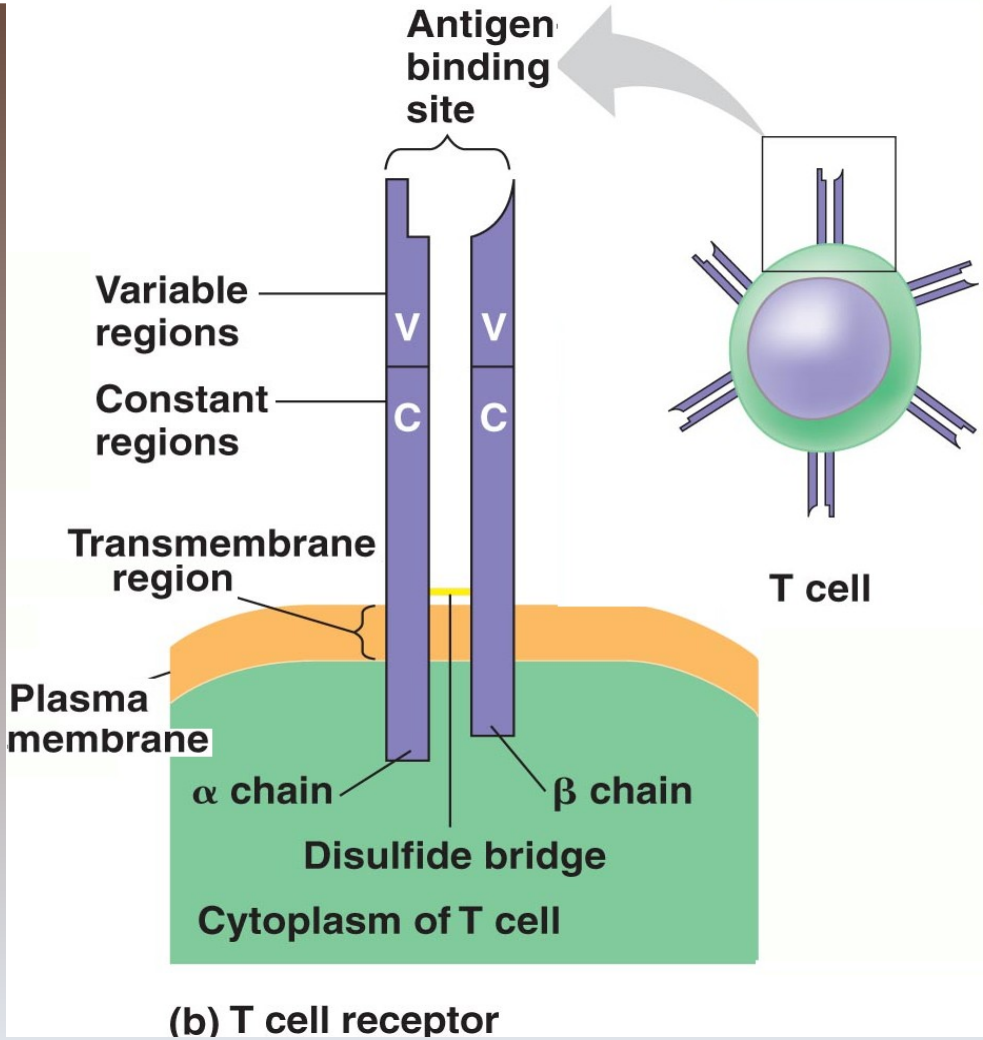



β chain
N
N
α chain
Vβ
Vα
Cβ
Cα
Transmembrane region
C
C
Vβ
Vα
Cβ
Cα
Disulfide bond
Ig domain
Carbohydrate group

TCR

T Cell Receptor

- T cells have T cell receptor (TCR) sites that can attach to an antigen that is presented by another cell such as a macrophage or dendritic cell.



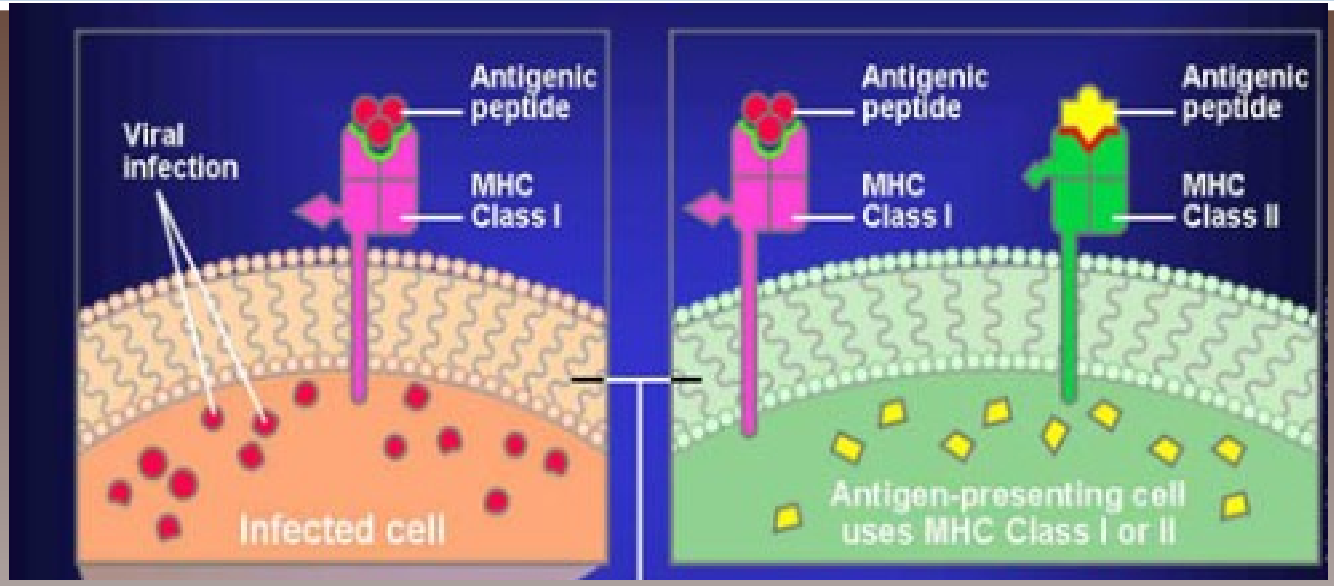
- Like the B cell, the T cell expresses a unique antigen-binding receptor called the T-cell receptor(TCR)are heterodimers consisting of either an αβ or γδ chain pair .
- However, unlike membrane-bound antibodies on B cells, which can recognize soluble or particulate antigen, T-cell receptors only recognize processed **pieces of antigen (typically peptides) bound to cell membrane protein**s called **Major Histocompatibility complex (MHC) molecules**
- **Also called the human leukocyte antigen (HLA) is segment of chromosome 6 contains several gene that are critical for immune function**.
- MHC molecules are genetically diverse glycoprotein's found on cell membranes .
- The ability of MHC molecules to form complexes with antigen allows cells to decorate their surfaces with internal (foreign and self) proteins, exposing them to browsing T cells.

Major Histocompatibility Complex (MHC)

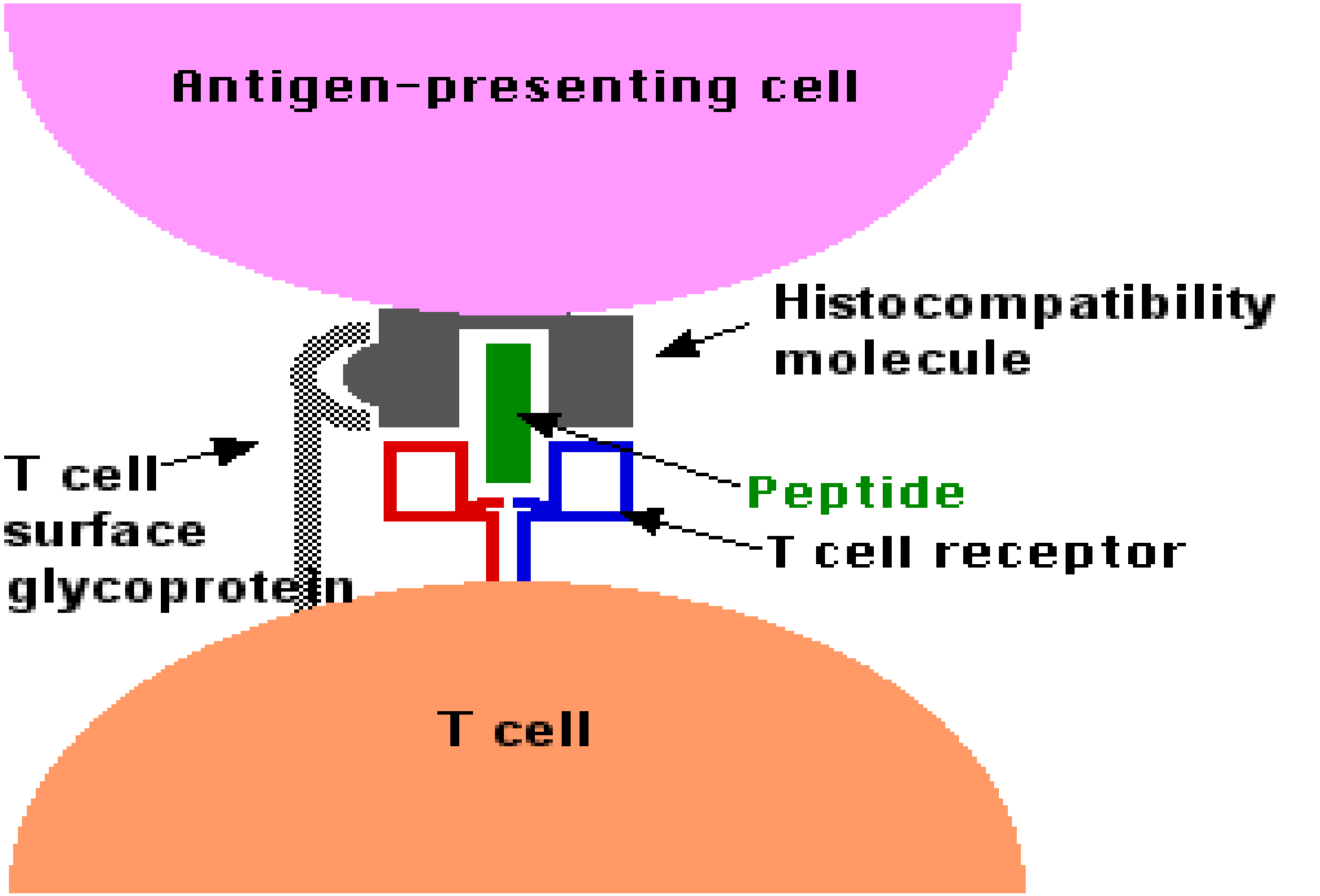
MHC comes in two classes:

- **Class I MHC molecules**, which are expressed by nearly all nucleated cells of vertebrate species.
- **Class II MHC molecules**, which are expressed by professional antigen-presenting cells and a few other cell types during inflammation .
- **Class III MHC molecules.**

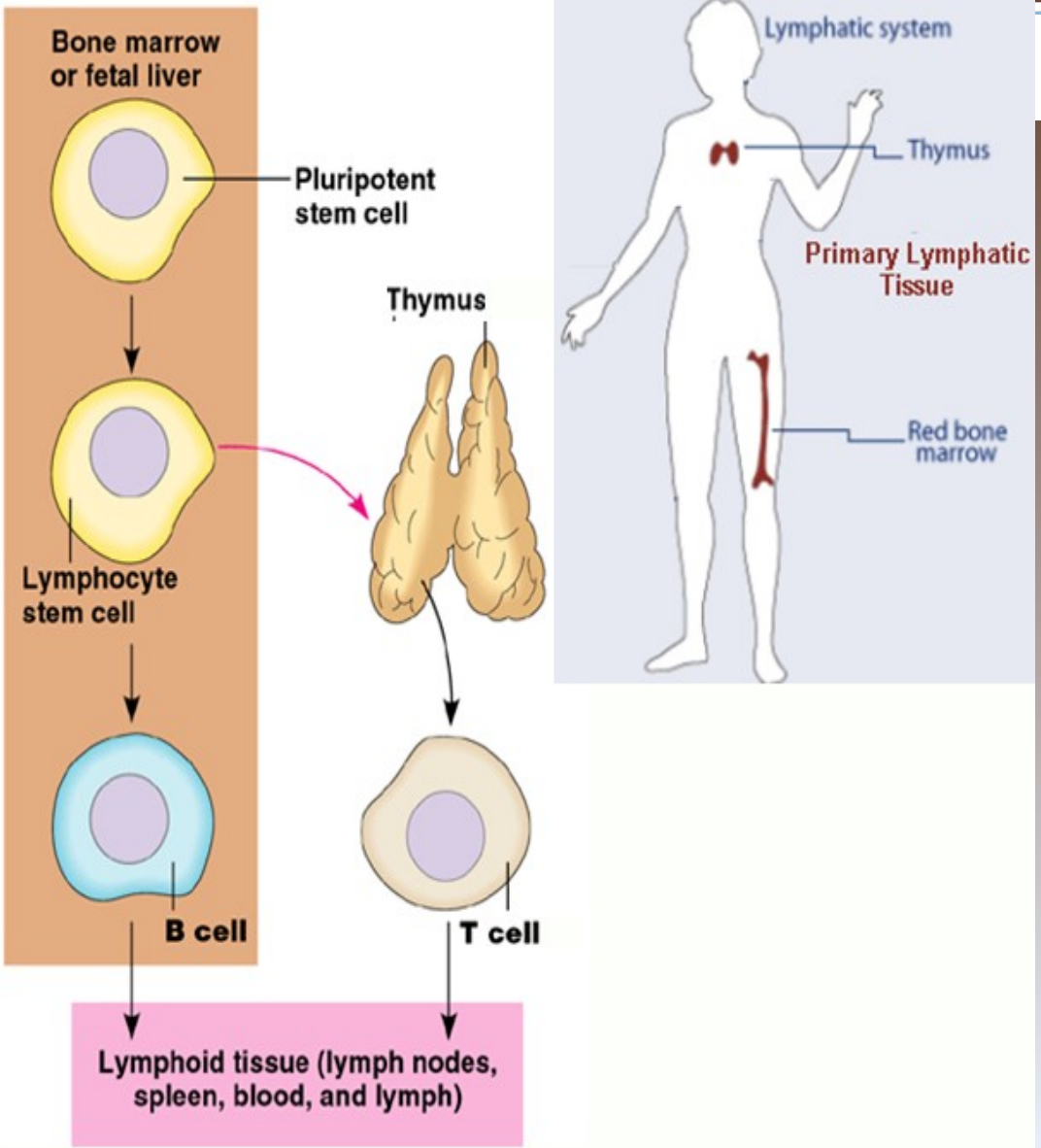
Major Histocompatibility Complex (MHC)



- **MHC I and II proteins have the ability to attach to foreign material (small polypeptides) and transport the foreign polypeptides to the surface of the infected cell.**
- **Antigen presenting cells (APC) are mostly phagocytes. As APC are in the process of cleaning up an infection, bits and pieces of the pathogens are displayed on the MHC proteins.**


Antigen-presenting cell
Histocompatibility molecule
T cell surface glycoprotein
Peptide
T cell receptor
T cell

Adaptive Immunity and Primary Lymphatic Tissue

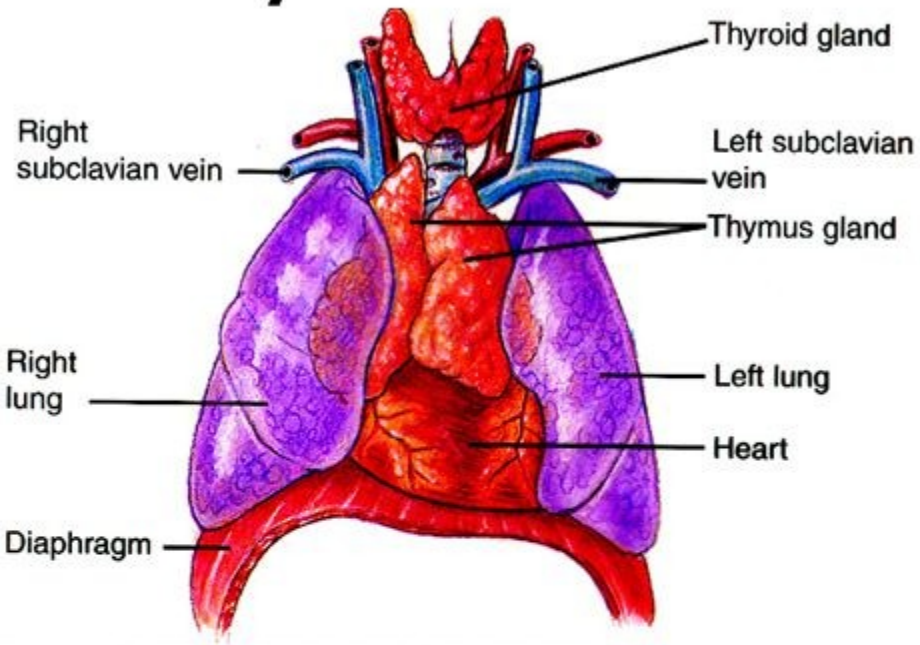


Primary lymphatic tissue

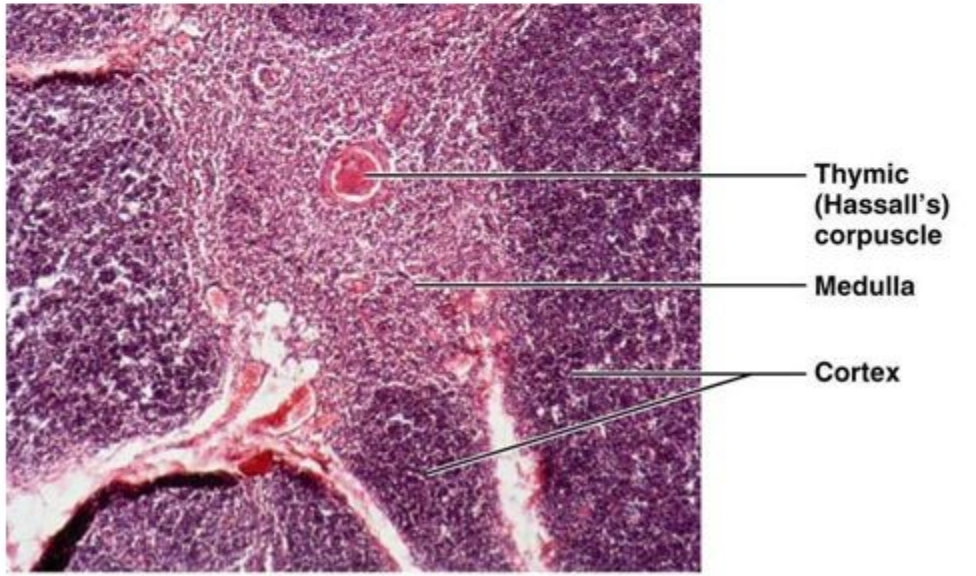
- All lymphocytes originate in the red bone marrow.
- T cells then migrate to, and mature in the thymus.
- B cells remain in the marrow to mature.

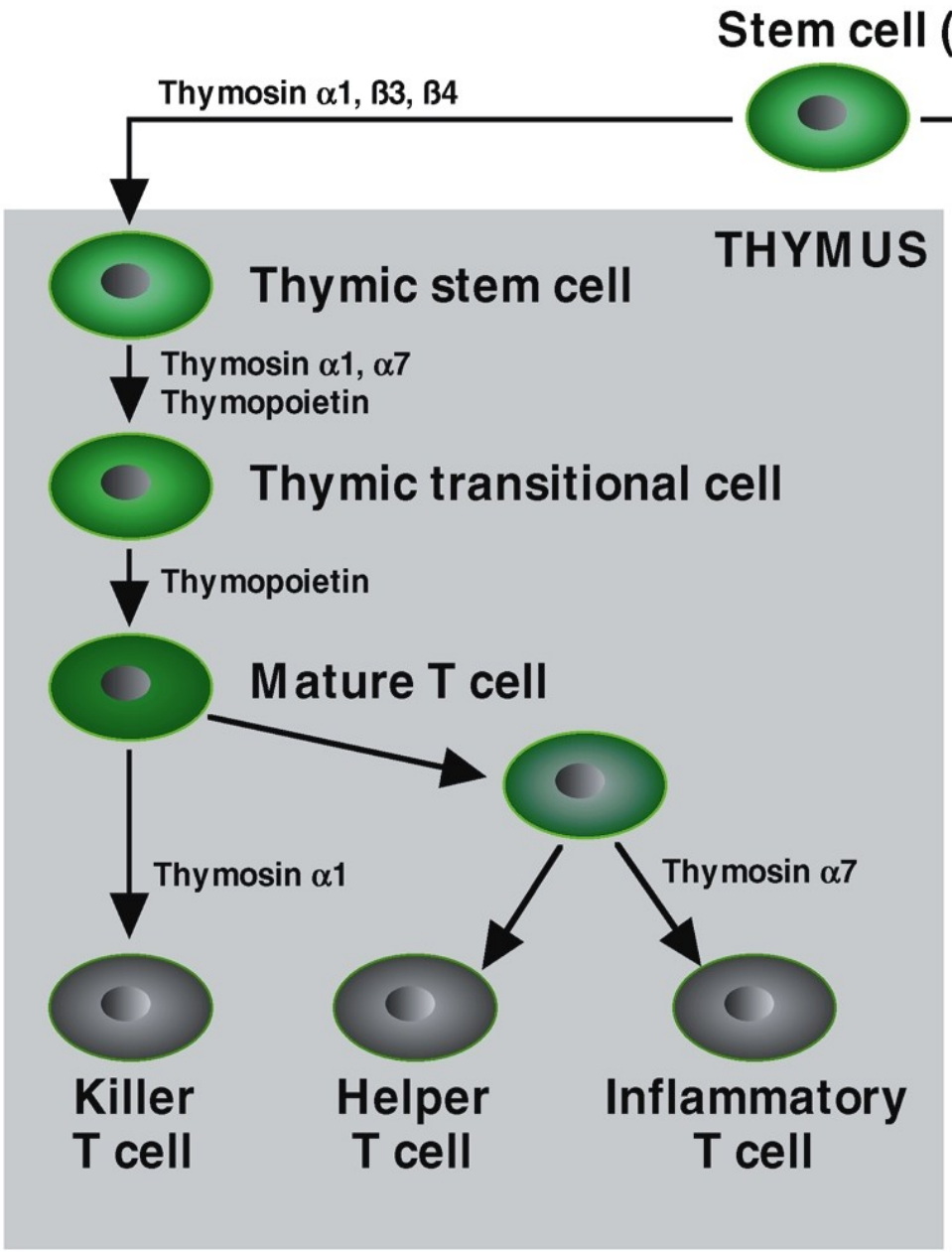
Lymphatic Organs – Thymus Gland

- Thymus Gland
  - Two lobes between the sternum and the heart
  - Thymocytes produce hormones
  - Atrophies with age (starting ~20)



- Structure/Function
  - Outer cortex – immature T cells
    - screened for functional capacity
    - stimulated to proliferation
    - stimulated to maturation
  - Inner medulla
    - defective T cells degenerate
    - mature T cells move into blood





The maturation and the maintenance of T cell require thymic factors

T Cell development & Maturation

- **Hematopoietic stem cells(HSC)**
- **Lymphoid stem cell (progenitor)**
- **Circulating lymphoid stem cells:** T cells develop from bone-marrow precursors called **prothymocytes**
- **Thymocytes:** These precursors travel from the bone marrow through the bloodstream and enter the thymus through venules at the cortico-medullary junction
- The most immature thymocytes are found in the sub capsular region of the cortex.
- These cells are rapidly dividing and give rise to large numbers of thymocytes.

The differentiation of thymocytes can be followed by examining the expression of TcR and certain CD molecules on the developing thymocytes

·The most immature thymocytes that are found under thymic capsule express CD2 but not CD4 or CD8 and are therefore called CD4–CD8– thymocytes, or double-negative thymocytes.

·At the end of the double-negative stage of differentiation the thymocytes rearrange their TcRβ genes. Those that successfully rearrange one of their TcR β genes and pass the checkpoint .

·rearrange their TcR α genes and, if this is successful, the cells express low levels of the TcR on their cell surface.

·These small resting thymocytes also express both CD4 and CD8 on their surface and are called double-positive thymocytes; they represent about 85% of all thymocytes and undergo positive and negative selection.

Finally, when the thymocytes cells arrive at the cortico-medullary junction they stop expressing either CD4 or CD8 and become mature single positive thymocytes expressing either CD4 or CD8, which either go to the medulla or leave the thymus.

T Cell Maturation

- Young thymocyte (T cell precursor)
- Double negative thymocytes
- Double negative with early TCR expression
- Double positive with TCR expression
- Naïve CD4 and CD8 T cells

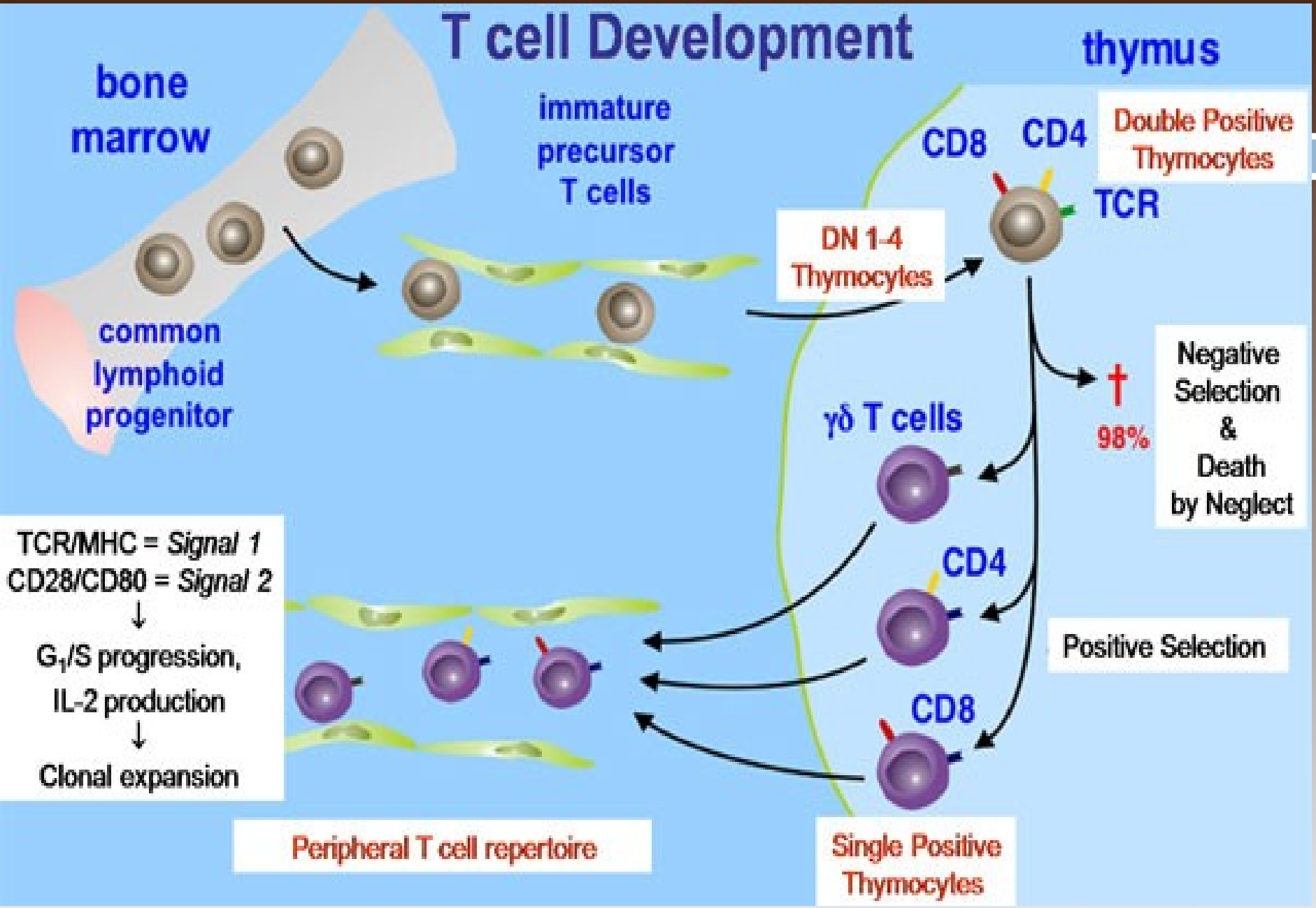
T cell development

- As the developing thymocytes carry on with the maturation process they stop dividing and move deeper into the cortex.

- Once they have finished their development T cells either leave the thymus via venules or lymphatic vessels located at the cortico-medullary junction, or migrate to the medulla eventually leaving by the same routes.

Naïve CD4 and CD8 T cells

- **A/ Naïve CD8+T cells** :browse the surfaces of antigen presenting cells with their T-cell receptors. If and when they bind to an MHC-peptide complex, they become activated, proliferate, and differentiate into an effector cell called a **cytotoxic T lymphocyte (CTL)**.
- The CTL has a vital function in monitoring the cells of the body and eliminating any cells that display foreign antigen complexed with class I MHC, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft . To proliferate and differentiate optimally, naïve CD8+ T cells also need help from mature CD4+ T cells**.**
- **B/ Naïve CD4+ T cells** also browse the surfaces of antigen presenting cells with their T-cell receptors. If and when they recognize an MHC-peptide complex, they can become activated and proliferate and differentiate into one of a variety of effector T cell subsets .


T cell Development
thymus
bone marrow
immature precursor T cells
common lymphoid progenitor
CD8
CD4
Double Positive Thymocytes
TCR
DN 1-4 Thymocytes
†
98%
Negative Selection & Death by Neglect
γδ T cells
CD4
Positive Selection
CD8
TCR/MHC = Signal 1
CD28/CD80 = Signal 2
↓
G1/S progression,
IL-2 production
↓
Clonal expansion
Peripheral T cell repertoire
Single Positive Thymocytes

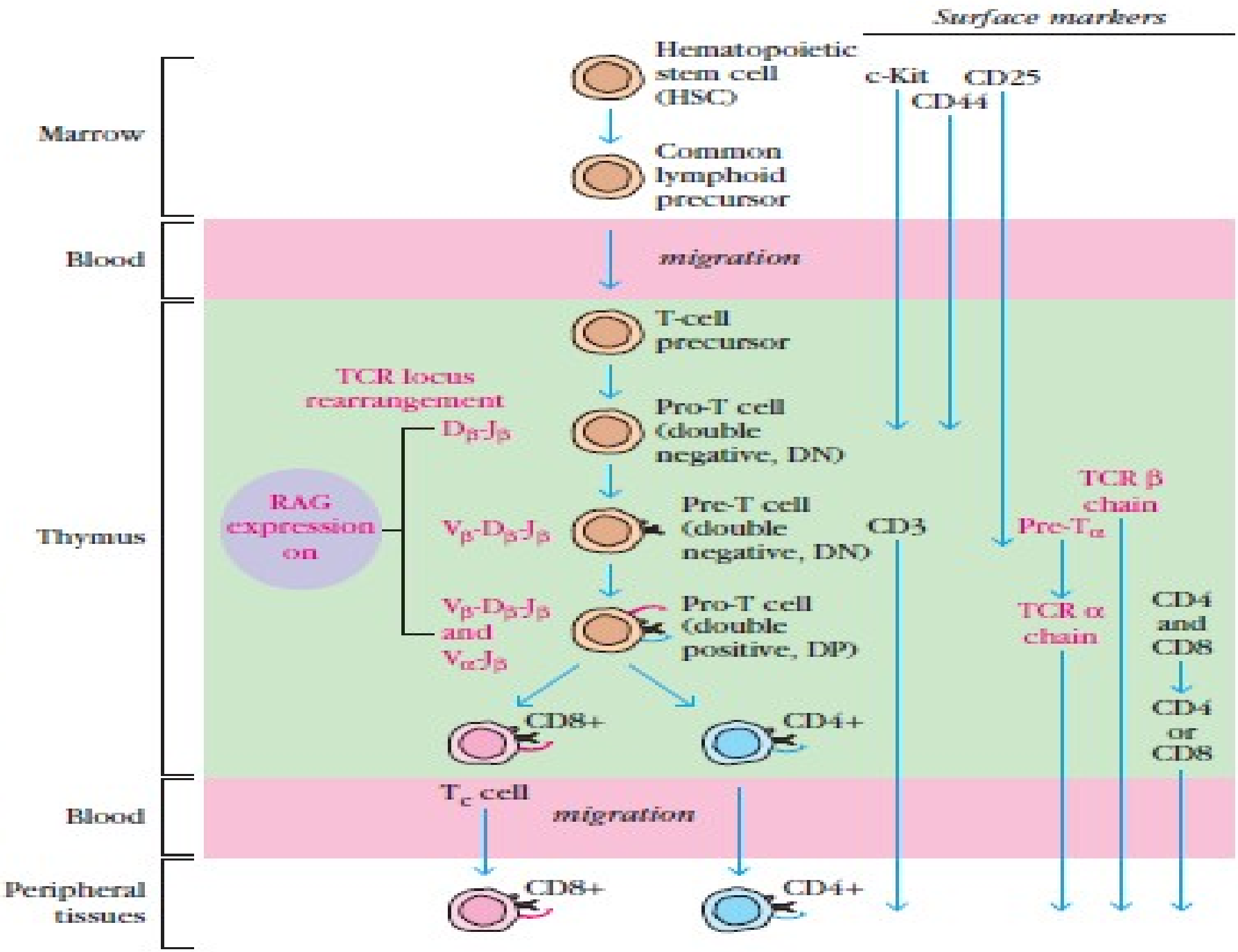
Thymocyte Changes

- **Double negative cells**
  - No expression of CD4 or CD8
  - Rearrangement of TCR *beta* genes (V,D,J)
  - Loss of stem cell markers (c-Kit, CD 44)

  - Expression of Pre TCR (*Beta* chain plus pre *alpha* chain)
  - Suppression of further *beta* chain changes
  - Signal to initiate *alpha* chain

Thymocyte Changes

- Double negative to double positive cells
  - Expression of CD3? (Associated with TCR)
  - Expression of CD4 and CD8
  - Proliferation of double negatives
  - Contributes to diversity of *alpha* chains and ultimately T cells
  - Population of T cells with defined TCRs and single CD4 or CD8 expression


Surface markers
Marrow
Blood
Thymus
Blood
Peripheral tissues
Hematopoietic stem cell (HSC)
Common lymphoid precursor
migration
T-cell precursor
TCR locus rearrangement
Pro-T cell (double negative, DN)
RAG expression on
Pre-T cell (double negative, DN)
Pro-T cell (double positive, DP)
CD8+
CD4+
Tc cell
migration
CD8+
CD4+
c-Kit
CD25
CD44
CD3
TCR β chain
Pre-Tα
TCR α chain
CD4 and CD8
CD4 or CD8

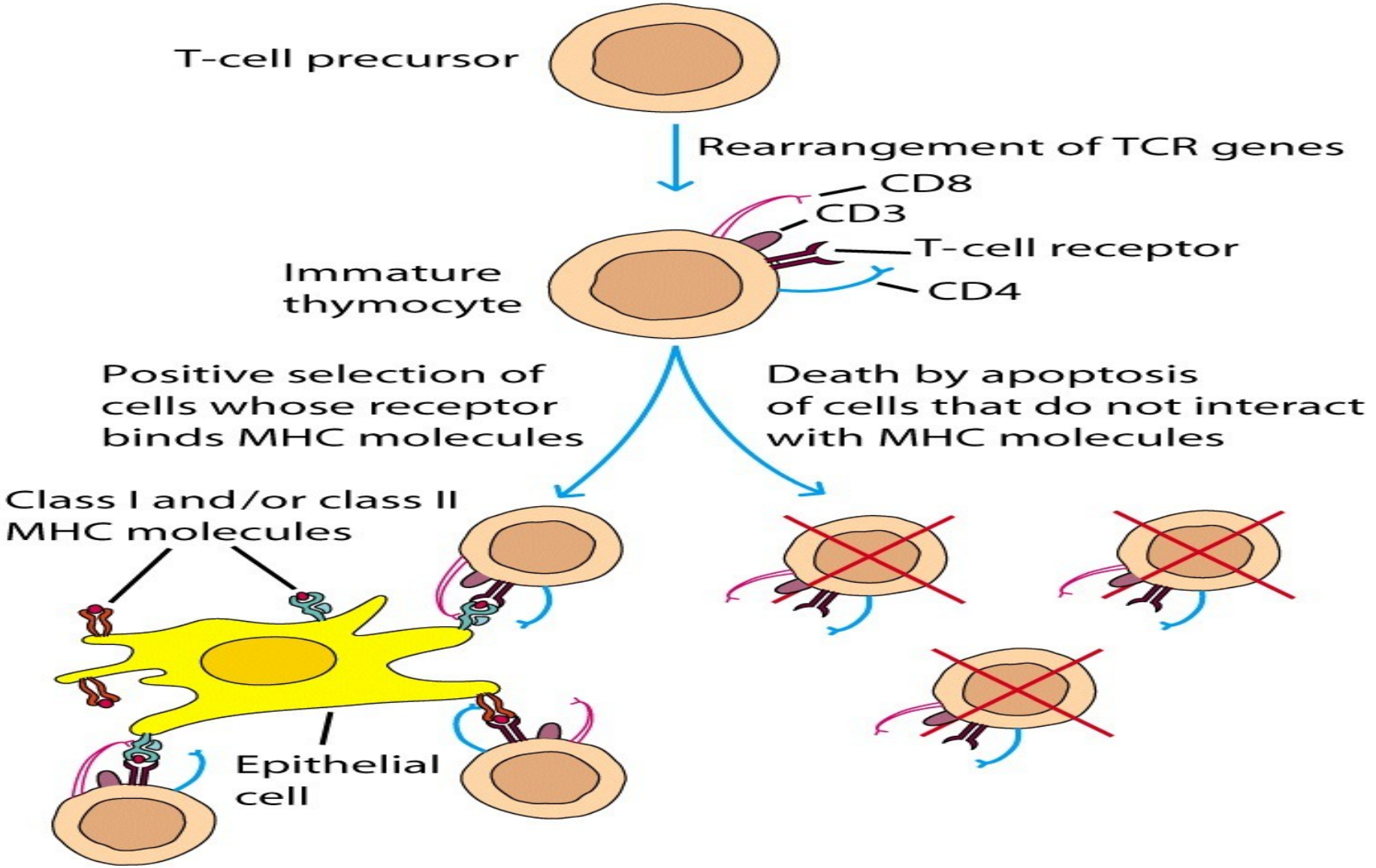
Two-step Selection Process of Thymocytes

I/ **Positive Selection**: permits the survival of only those T cells whose TCRs recognize self-MHC molecules. ⇒ generation of a self-*MHC-restricted* repertoire of T cells

II/ **Negative Selection**: eliminates T cells that too strongly with self-MHC or with self-MHC plus self-peptides. ⇒ generation of a T-cell repertoire that is *self-tolerant* Thymic stromal cells, which express high levels of class I and class II MHC molecules, play a role in this process

Thymic Positive Selection

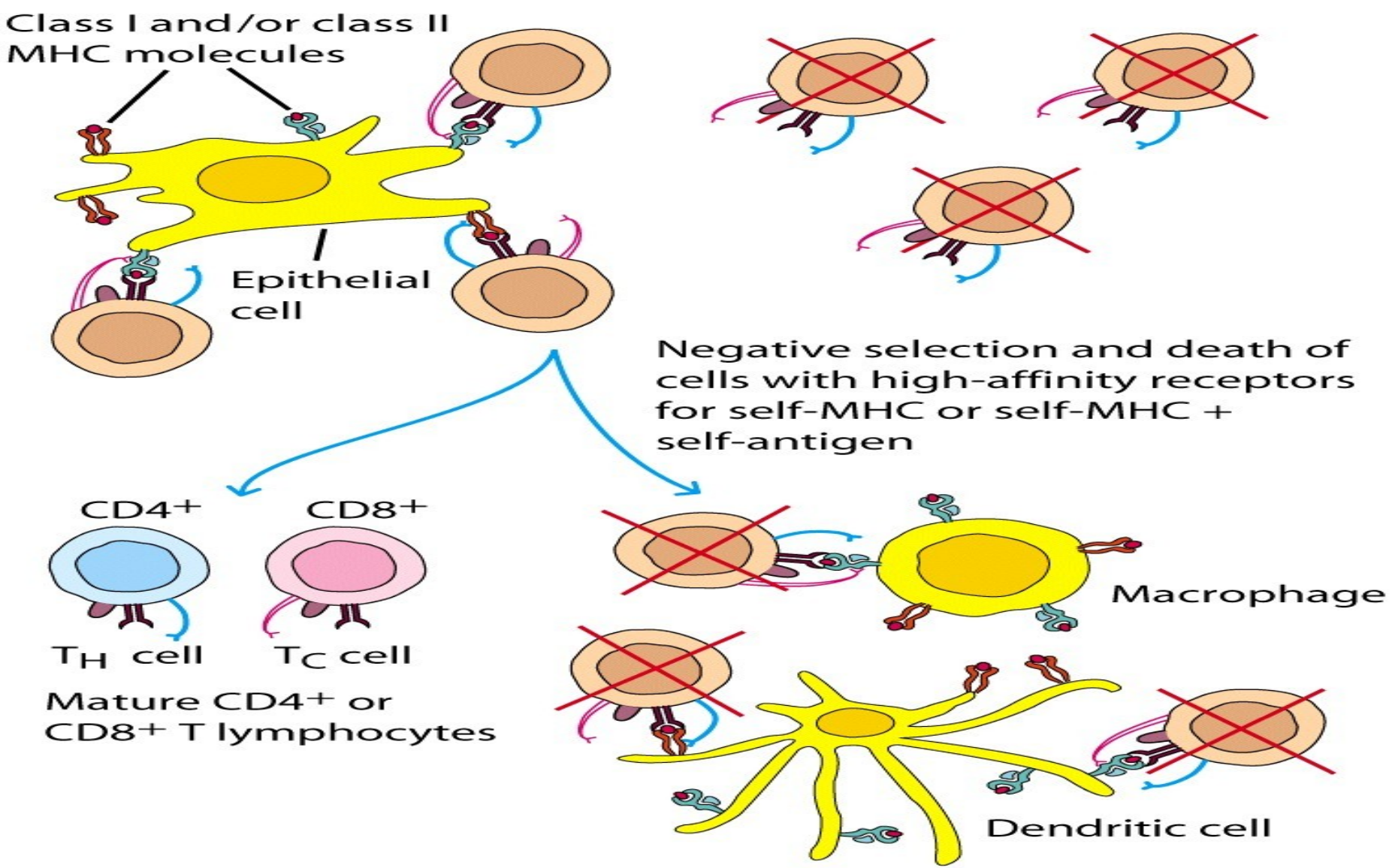
- Positive selection
  - Double positives bind MHC molecules
  - Non binders die
  - Possible that binding counters programmed apoptosis
  - Binders become single positives



Positive Selection

Thymic Negative Selection

- Negative selection
  - CD4 or CD8 cells that survive positive selection may react or bind to self MHC alone with high affinity or with Self MHC-self Ag complexes
  - These cells are programmed to die
  - Non binders survive



Negative Selection

T Cell Activation

- Initiation
  - TCR-CD3/MHC peptide complex interact
  - Involvement of coreceptor
    - CD4 to MHC II
    - CD8 to MHC I
  - Co-stimulatory signal
    - CD 28 to B7 (T_H Cells/APCs)
  - Inhibitory role of CTLA-4

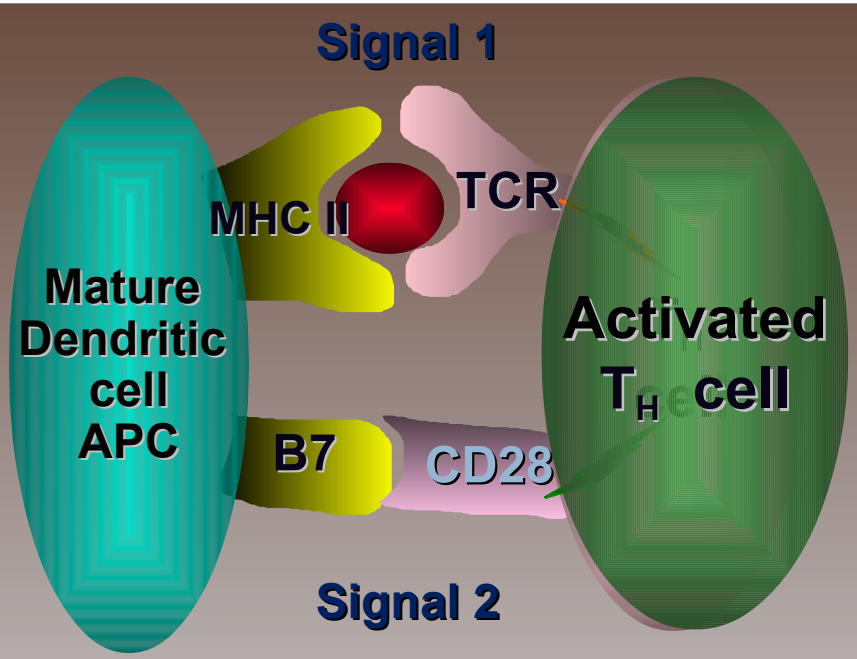
What are the Co-stimulatory Signals Are Required ????for Full T-cell Activation

Naïve T cells require 2 distinct signals for activation and proliferation into effector cells:

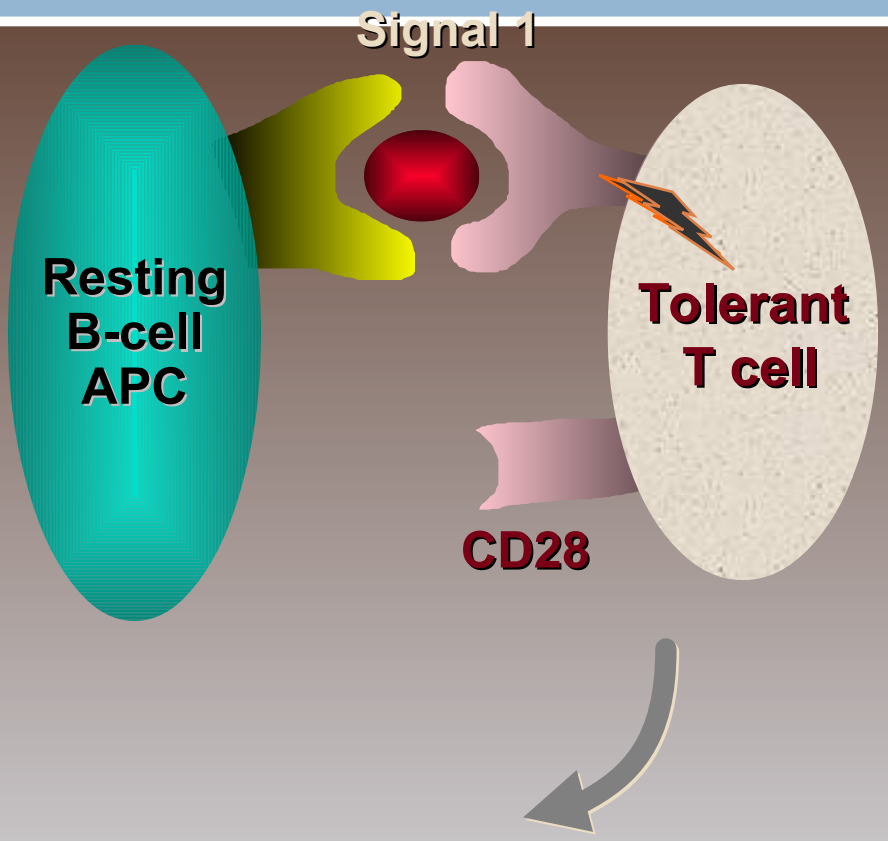
I/ Signal 1 : the initial signal, is generated by interaction of an antigen with the TCR-CD3 bound to /MHC peptide interact complex.

II/ Signal 2 : a subsequent Ag-nonspecific co- stimulatory signal, is provided by interactions between CD28 on the Th cell and members of the B7 family on the APC.

The Two Signal Hypothesis for T-cell Activation



Hypothetical mechanism of tolerance in mature T cells



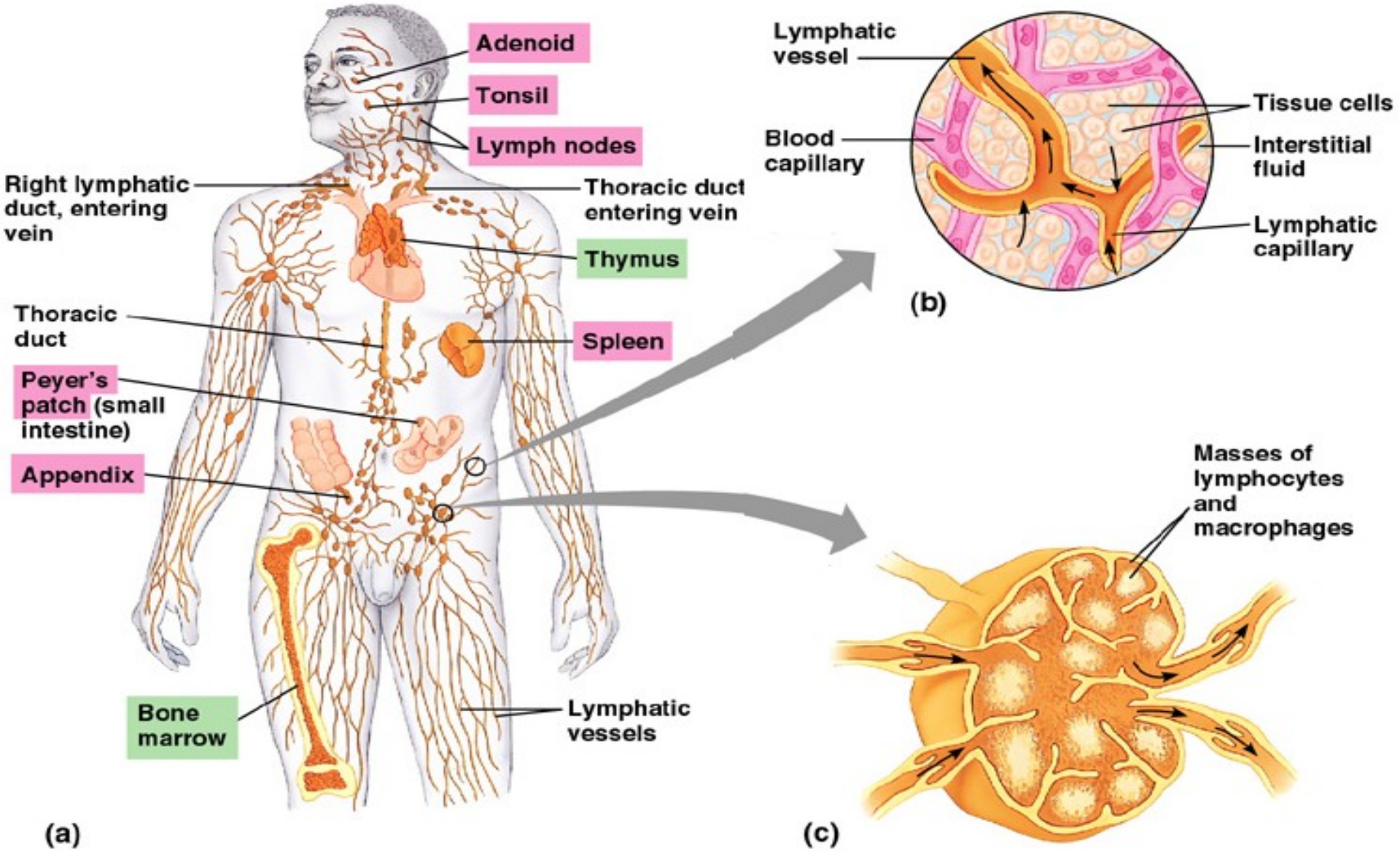
Tolerance (anergy or apoptosis)
from lack of signal 2

Results of Signaling Pathways

- Gene expression changes
- Functional changes
- Differentiation

Differentiation

- Occurs in secondary lymphoid tissue
- Activated cell becomes a blast cell
- IL-2 levels are increased 100 times
- Binds to IL-2 receptor on producing cell
- Takes several days to occur
- Effector cells and memory cells are produced



Secondary Lymphatic Tissue Where Lymphocytes are Activated

Differentiation

- **Functions of effectors**
  - B cell helper
  - Cytotoxicity
- Characteristics of memory cells
  - Last months to years vs. effector cells that last days to weeks
  - Memory cells more easily activated by all APCs then naïve T cells

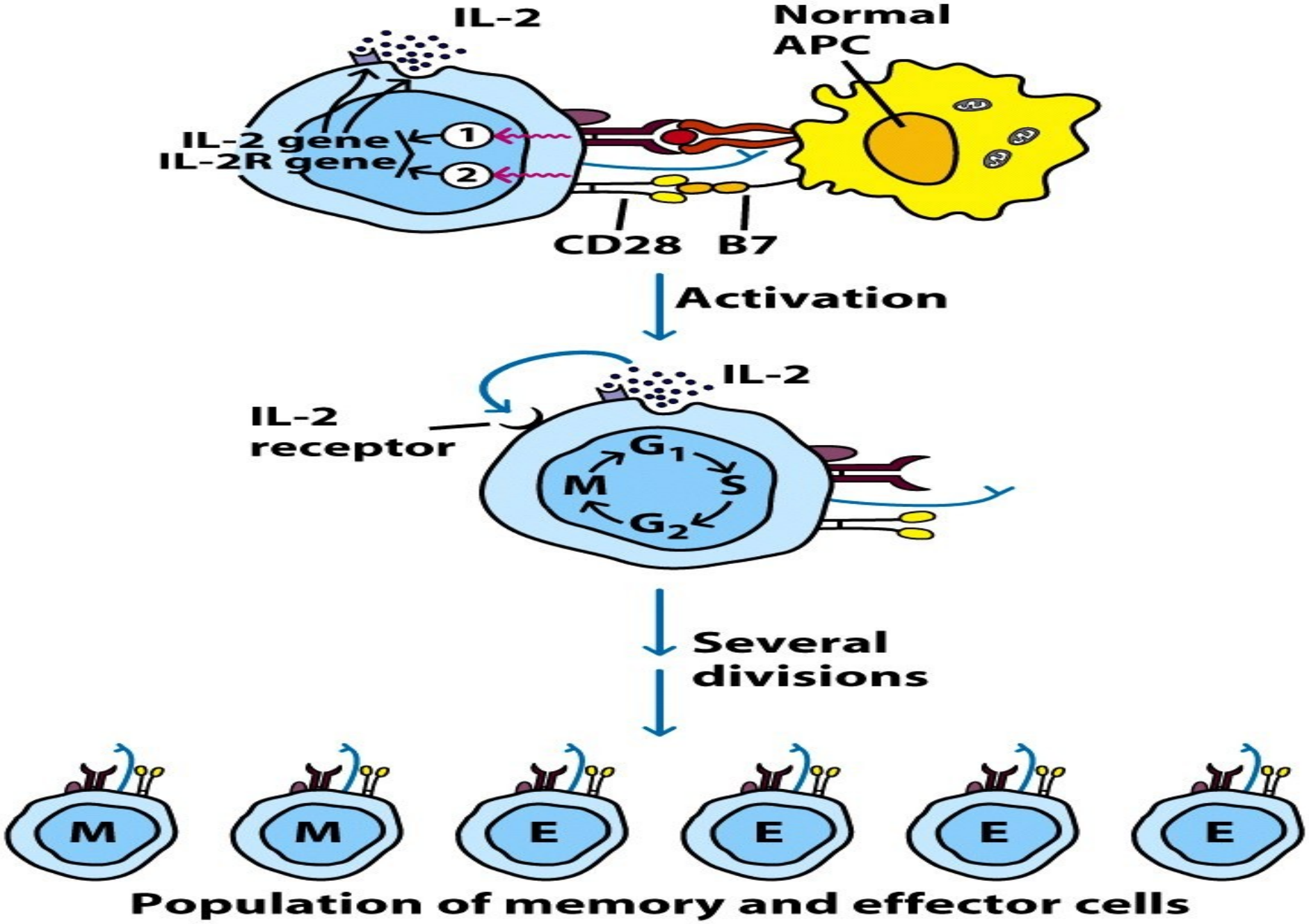
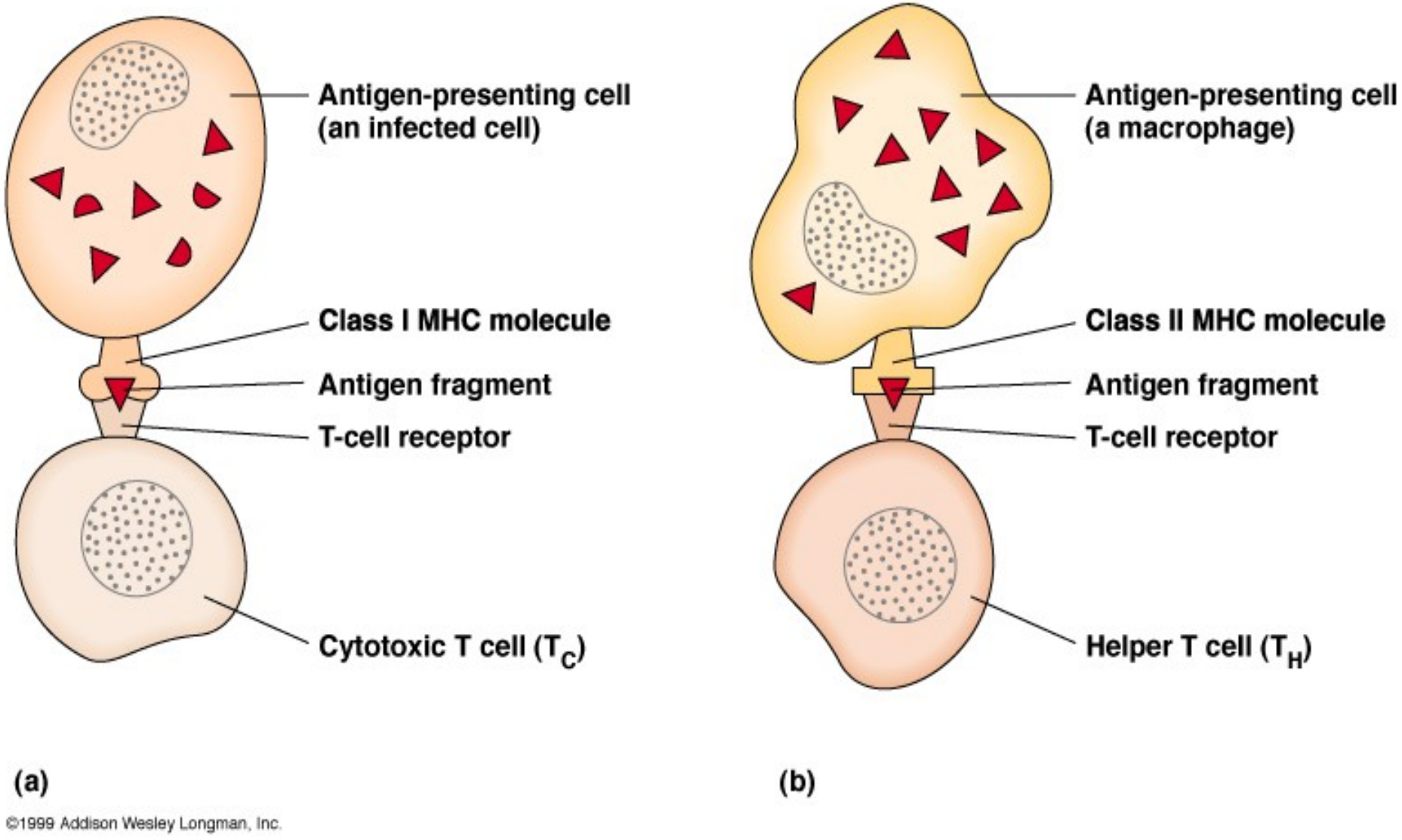


Figure 10-17
Kuby IMMUNOLOGY, Sixth Edition



T Cells Only Recognize Antigen Associated with MHC Molecules on Cell Surfaces

Types of T cells

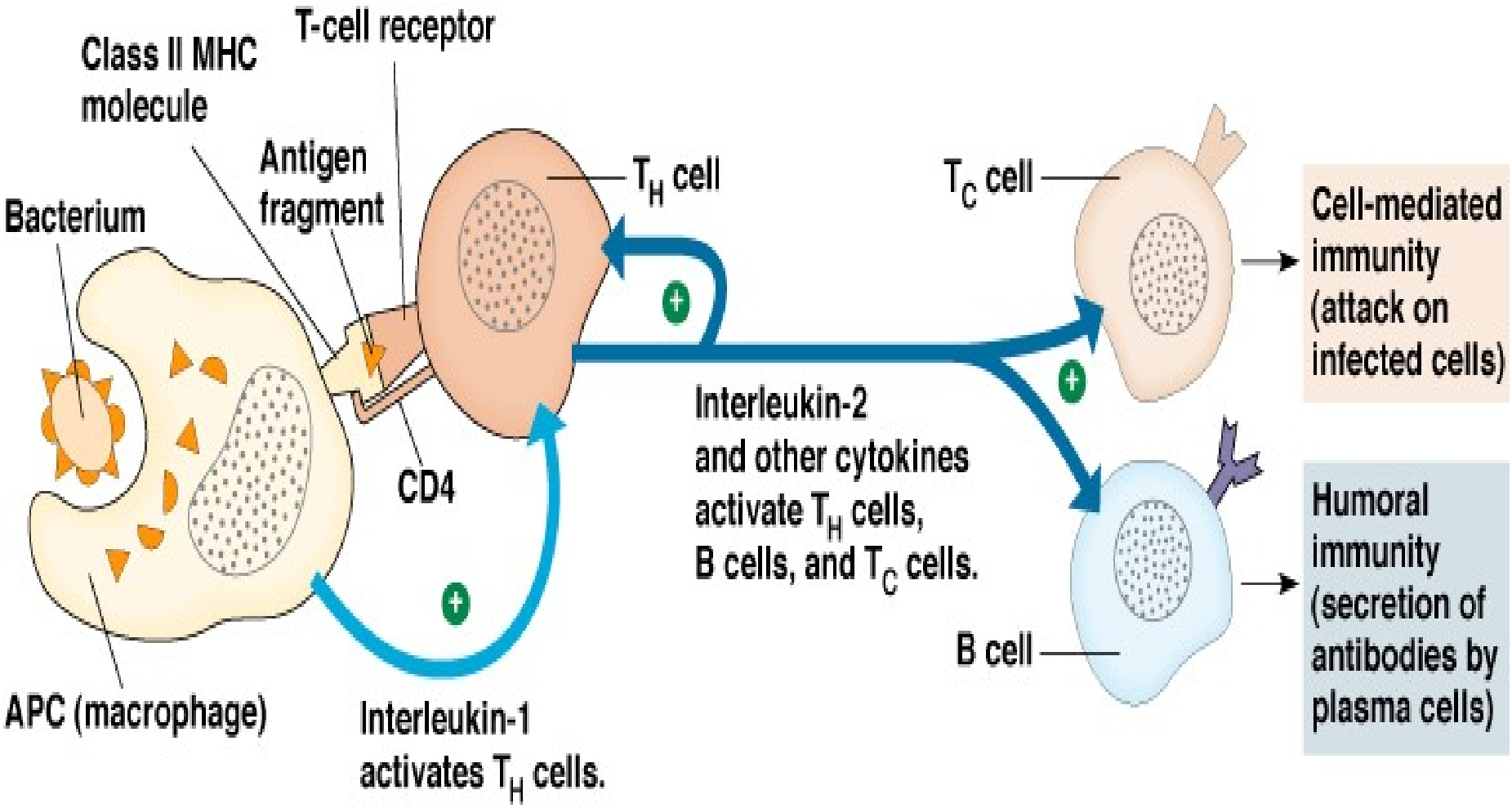
1. **T Helper (T_H) Cells:**

- Central role in immune response.
- There are three subpopulations of Th cells:

1. Th0 ***(naïve)***
2. Th1 ***(imflammatory)***
3. Th2 cells ***(helper)*.**

- Most are $CD4^+$
- Recognize antigen on the surface of antigen presenting cells e.g.: macrophage (MHC class II)
- Activate macrophages
- Induce formation of cytotoxic T cells
- Stimulate B cells to produce antibodies.*(helper)*

(inflammatory)



Central Role of Helper T Cells

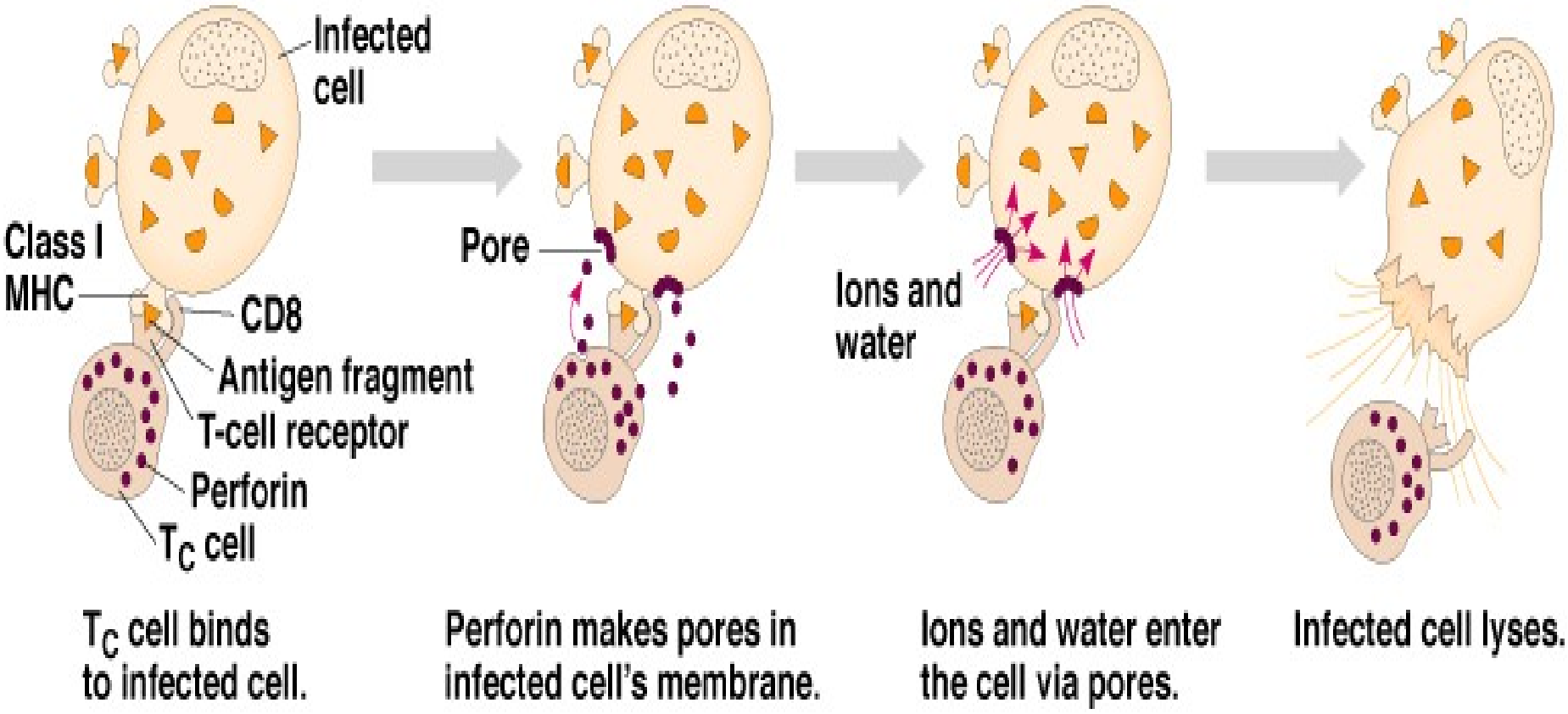
Types of T cells (Continued)

2. Cytotoxic T (Tc) Cells:

- Destroy target cells.
- $CD8^+$ ($CD4^-$).
- Recognize (MHC class I) antigens on the surface of all cells:
  - Kill host cells that are infected with viruses or bacteria.
  - Recognize and kill cancer cells.
  - Recognize and destroy transplanted tissue.
- Release two types proteins:

1) Perforin which forms pores in target cells, causing lysis of infected cells.
2) Granzymes (serine proteases)

- Undergo apoptosis when stimulating antigen is gone.



Cytotoxic T Cells Lyse Infected Cells

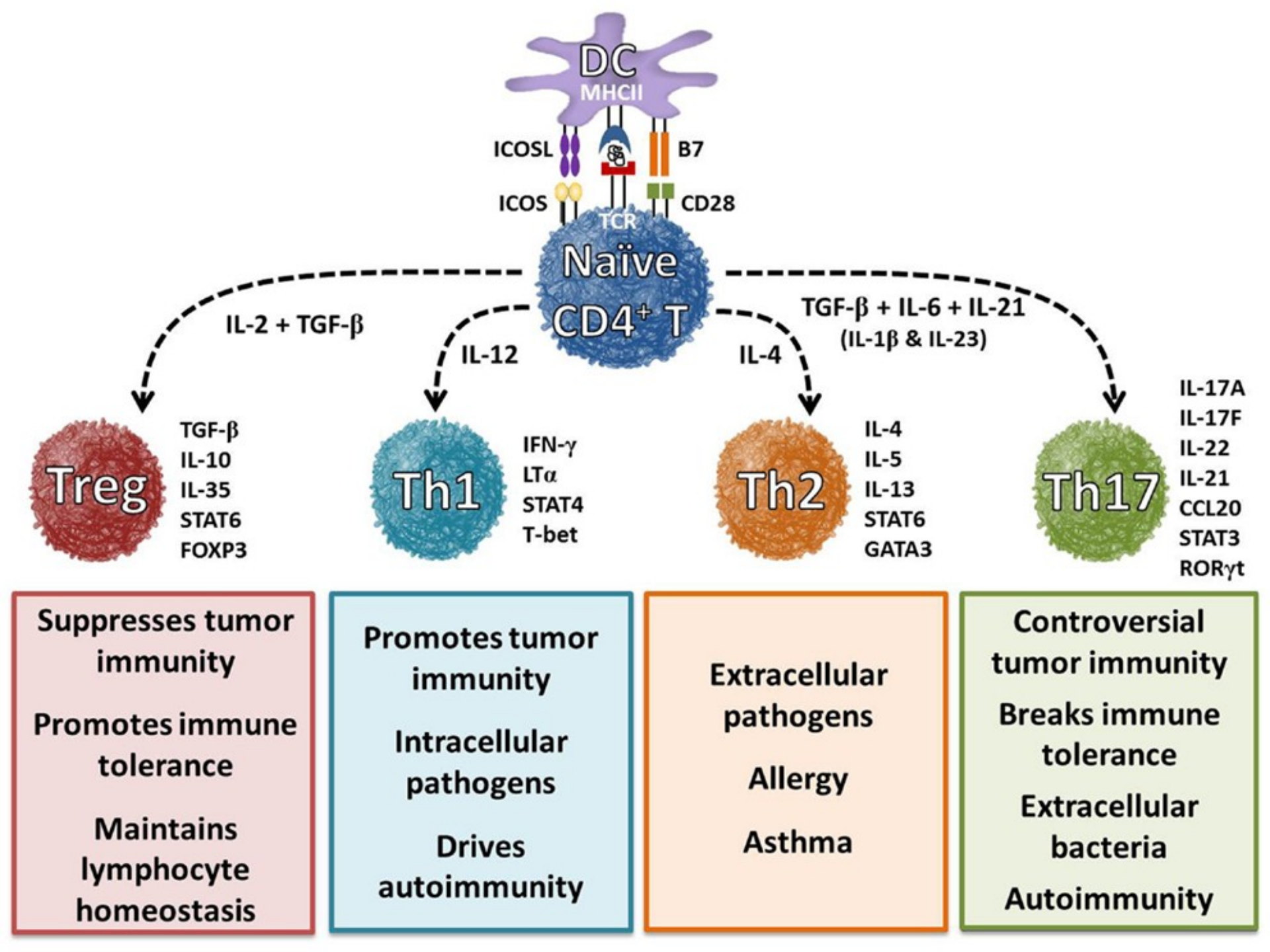
Types of T cells (Continued)

3.Delayed Hypersensitivity T (T_D) Cells:

Mostly T helper and a few cytotoxic T cells that are involved in some allergic reactions and rejection of transplanted tissue.

4.T Suppressor (Ts) Cells:

- **may shut down immune response.**
- **are a specialized subpopulation of T cells that act to suppress activation of the immune system and thereby maintain:**
- **immune system homeostasis and**
- **tolerance to self-antigens.**


DC
MHCII
ICOSL
B7
ICOS
CD28
TCR
Naïve
CD4+ T
IL-2 + TGF-β
IL-12
IL-4
TGF-β + IL-6 + IL-21
(IL-1β & IL-23)
Treg
TGF-β
IL-10
IL-35
STAT6
FOXP3
Th1
IFN-γ
LTα
STAT4
T-bet
Th2
IL-4
IL-5
IL-13
STAT6
GATA3
Th17
IL-17A
IL-17F
IL-22
IL-21
CCL20
STAT3
RORγt
Suppresses tumor immunity
Promotes immune tolerance
Maintains lymphocyte homeostasis
Promotes tumor immunity
Intracellular pathogens
Drives autoimmunity
Extracellular pathogens
Allergy
Asthma
Controversial tumor immunity
Breaks immune tolerance
Extracellular bacteria
Autoimmunity

Explain the Relationship Between Cell-Mediated and Humoral Immunity

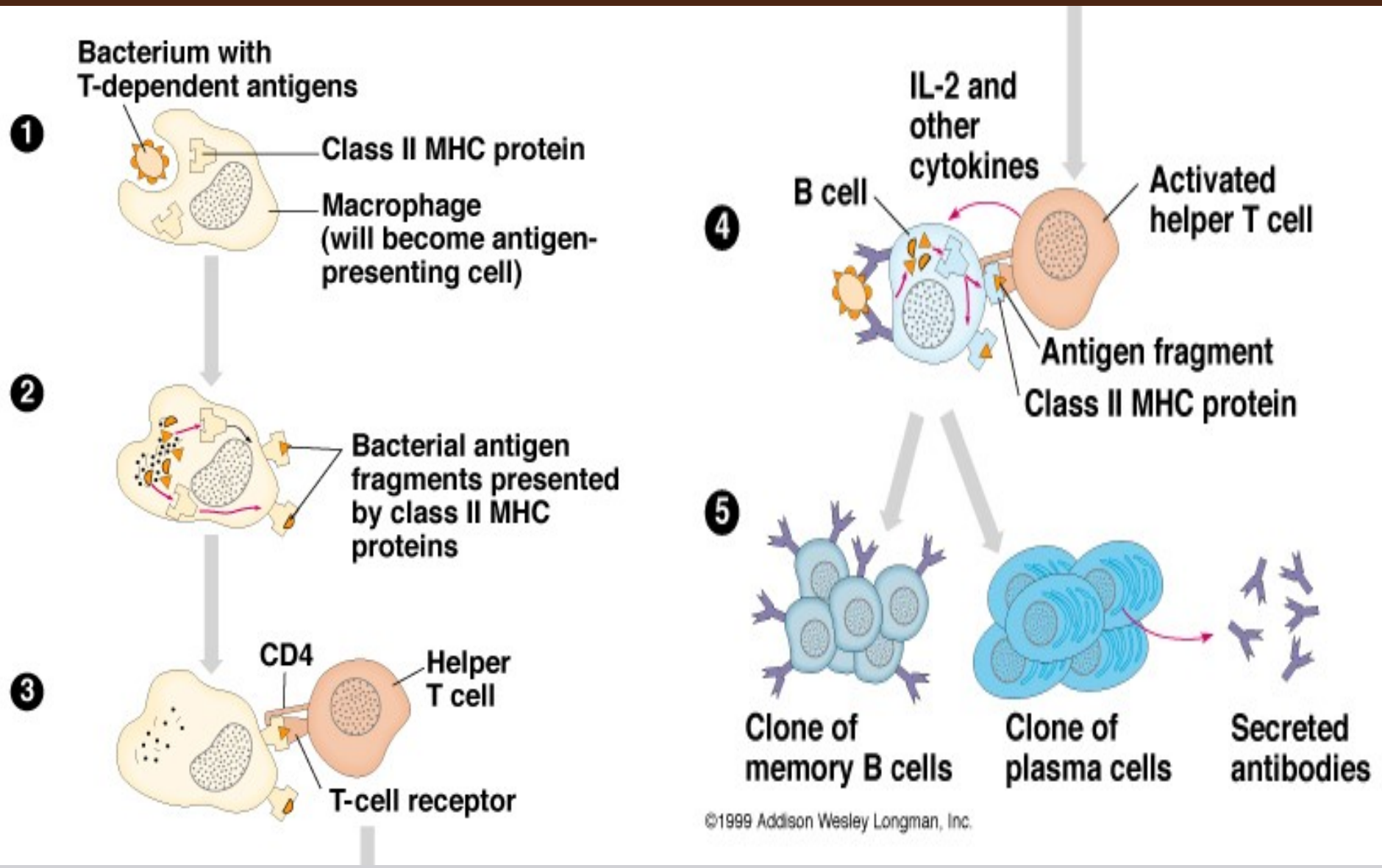
1. Antibody Production

T-Dependent Antigens:

- Antibody production requires assistance from T helper cells.
- Macrophages ingest antigens and present them to T_H cell.
- T_H cells stimulate B cells specific for that antigen to become plasma cells.
- Antigens are mainly proteins on viruses, bacteria, foreign red blood cells, and hapten-carrier molecules.

T-Independent Antigens:

- Antibody production does not require assistance from T cells.
- Antigens are mainly polysaccharides or lipopolysaccharides with repeating subunits (bacterial capsules).
- Weaker immune response than for T-dependent antigens.



Humoral Response to T Dependent Antigens

What are the similarities/differences between T-cell receptors and B-cell receptors?

Similarities:

1. Both bind antigen
2. Both have their variabilities located in one part of the molecule that bind antigen (V-region)
3. Three dimensional structures are remarkably similar

Differences:

1. Antibodies can be both soluble and membrane bound, TCR only membrane Bound
2. TCR has one binding site, Ab has two
3. TCR is shorter and wider than Fab portion of Ab.
4. B-cells/antibodies recognize circulating antibodies. T-cells require antigen to be presented by MHC-molecules
5. All energy of antigen-antibody focus on foreign antigens whereas a substantial fraction of the energy of the TCR-peptide-MHC is directed against self.
6. Antibodies have higher affinity than TCRs

What are the differences between?

1.**Effector T_H cells**: short-lived

T_H1 subset: - secretes IL-2, IFN-g, and TNF-b

- responsible for cell-mediated functions, such as delayed-type hypersensitivity and the activation of CTL

T_H2 subset: - secretes IL-4, IL-5, IL-6, and IL-10

- helper for B-cell activation

2.**Memory T_H cells:** long-lived

- Less stringent requirements for activation due to the expression of high levels of numerous adhesion molecules

Regulatory T cells (T_{reg}): $CD4^+CD25^+$ cells that inhibit the proliferation of other T-cell populations in vitro

The situation with T cells is more complex than with B cells , why?

- For two reasons:
- All B cells produced in the bone marrow are the same except for the specificity of their surface IgM and IgD. By contrast three types of T cell are produced in the thymus from the same type of precursor cell . Two of these cell types, the CD4 and CD8 T cells, express an α/β TcR, and the third type bears a different receptor for antigen,the γ/δ TcR. The rest of this section will cover the production of α/β TcR bearing T cells; the production of γ/δ T cells is covered . All of these cell types are produced in the thymus.
- The second reason why T cell development is more complicated is that T cells recognise antigen in association with MHC. T cells must be selected in each individual to recognize antigen in association with that individual's own MHC, a process known as thymic education.

THANK YOU