

Biology 151 Lec 9

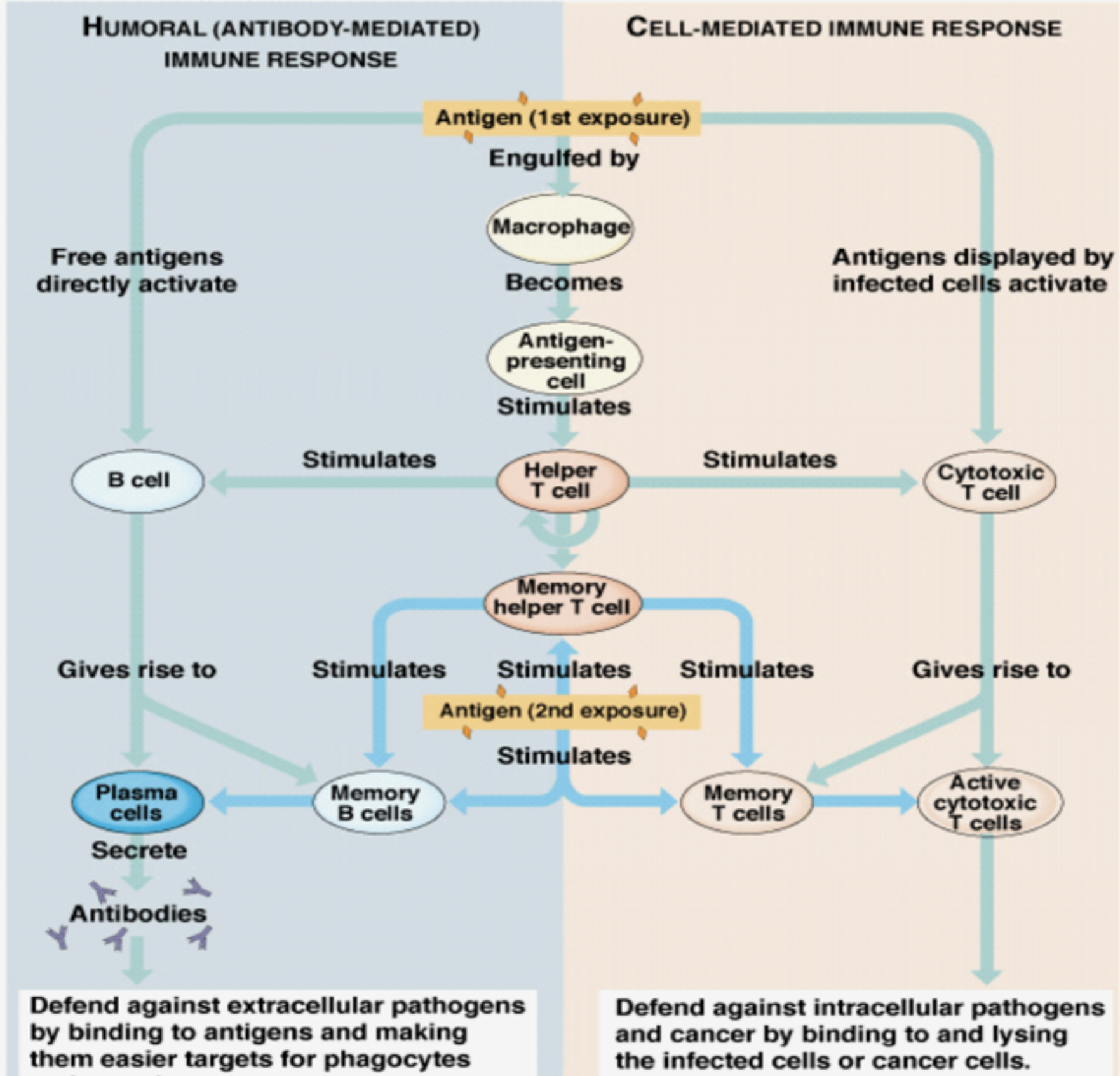
T-cells and B-cells

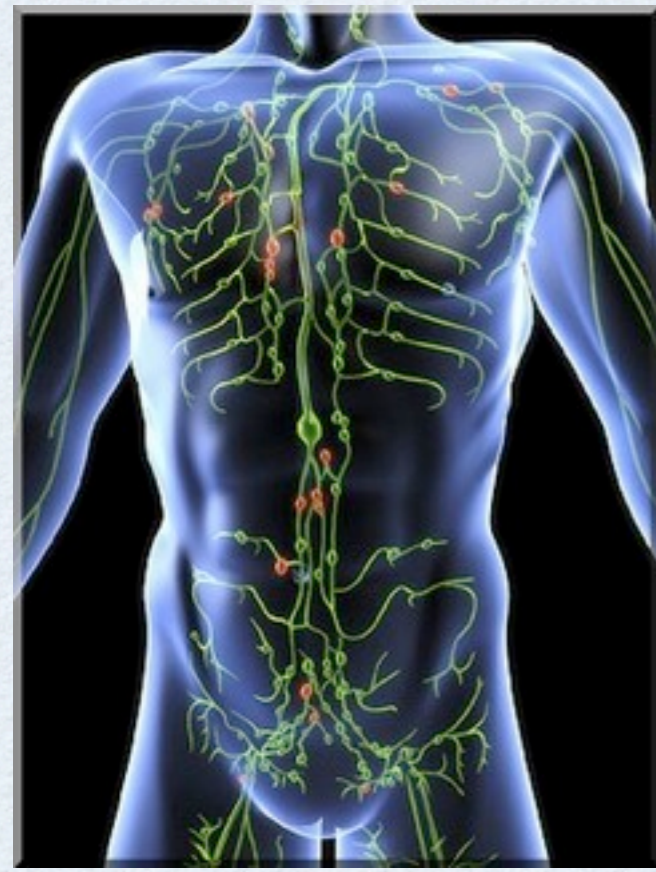
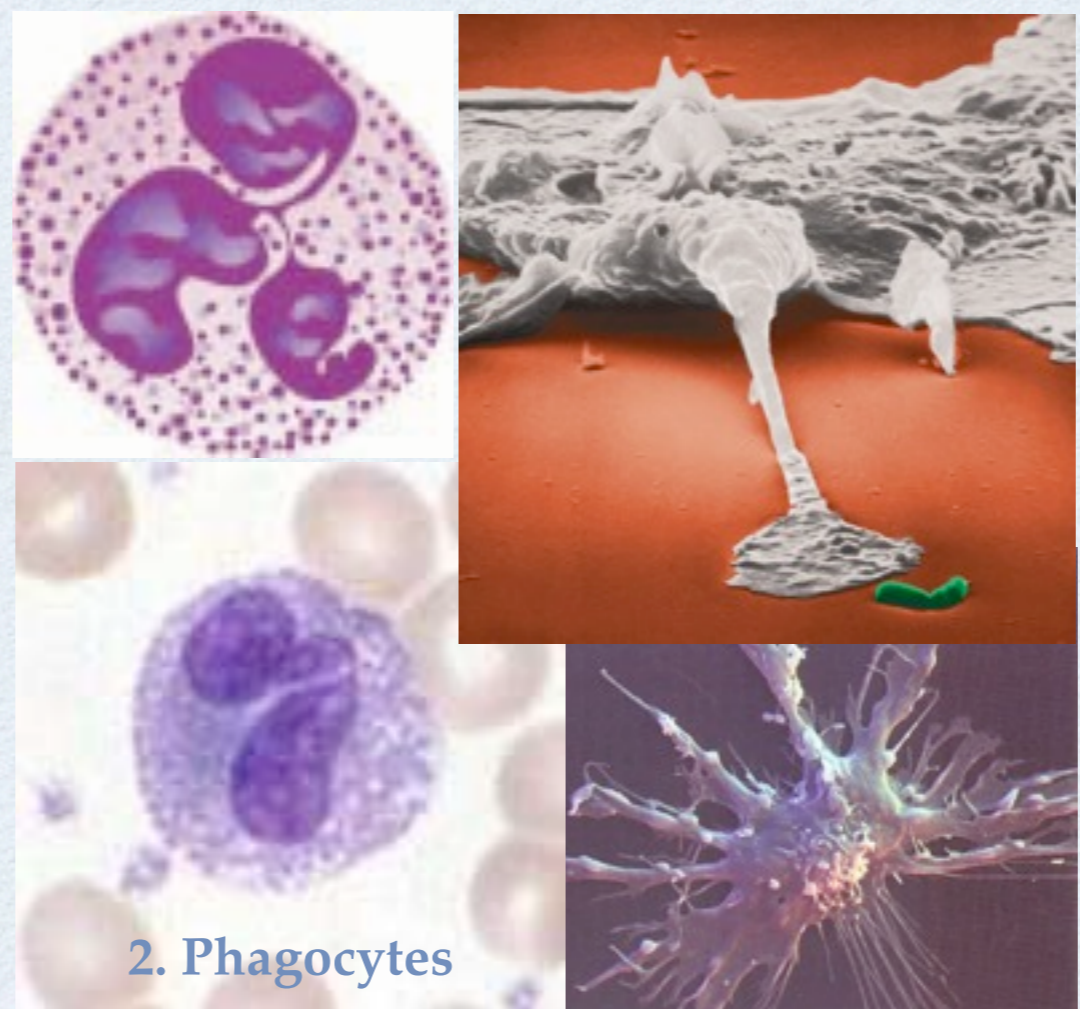
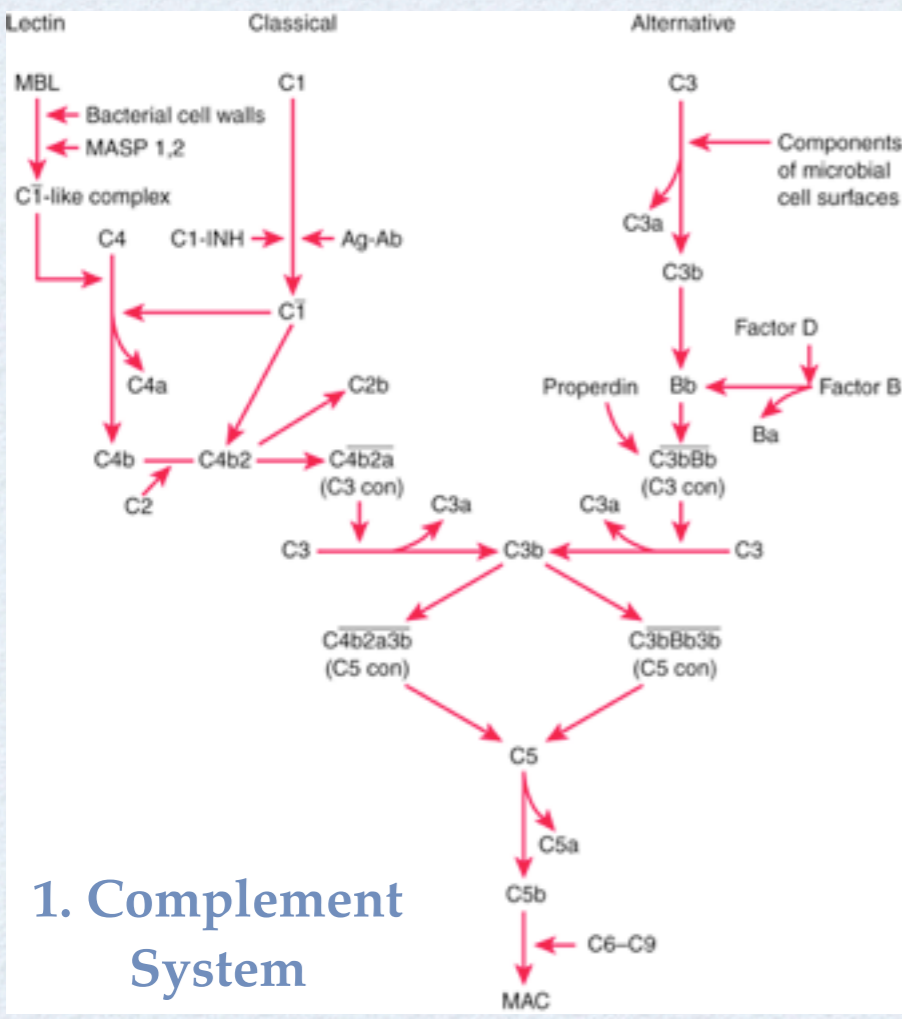
WHAT YOU NEED TO KNOW

- Recall: Immune Response
- T- Cell Maturation, Activation and Differentiation
- B-Cell Generation, Activation and Differentiation

RECALL:
IMMUNE RESPONSE
(ADAPTIVE IMMUNITY)

Overview of the Immune





3. Lymphocytes: T and B Cells

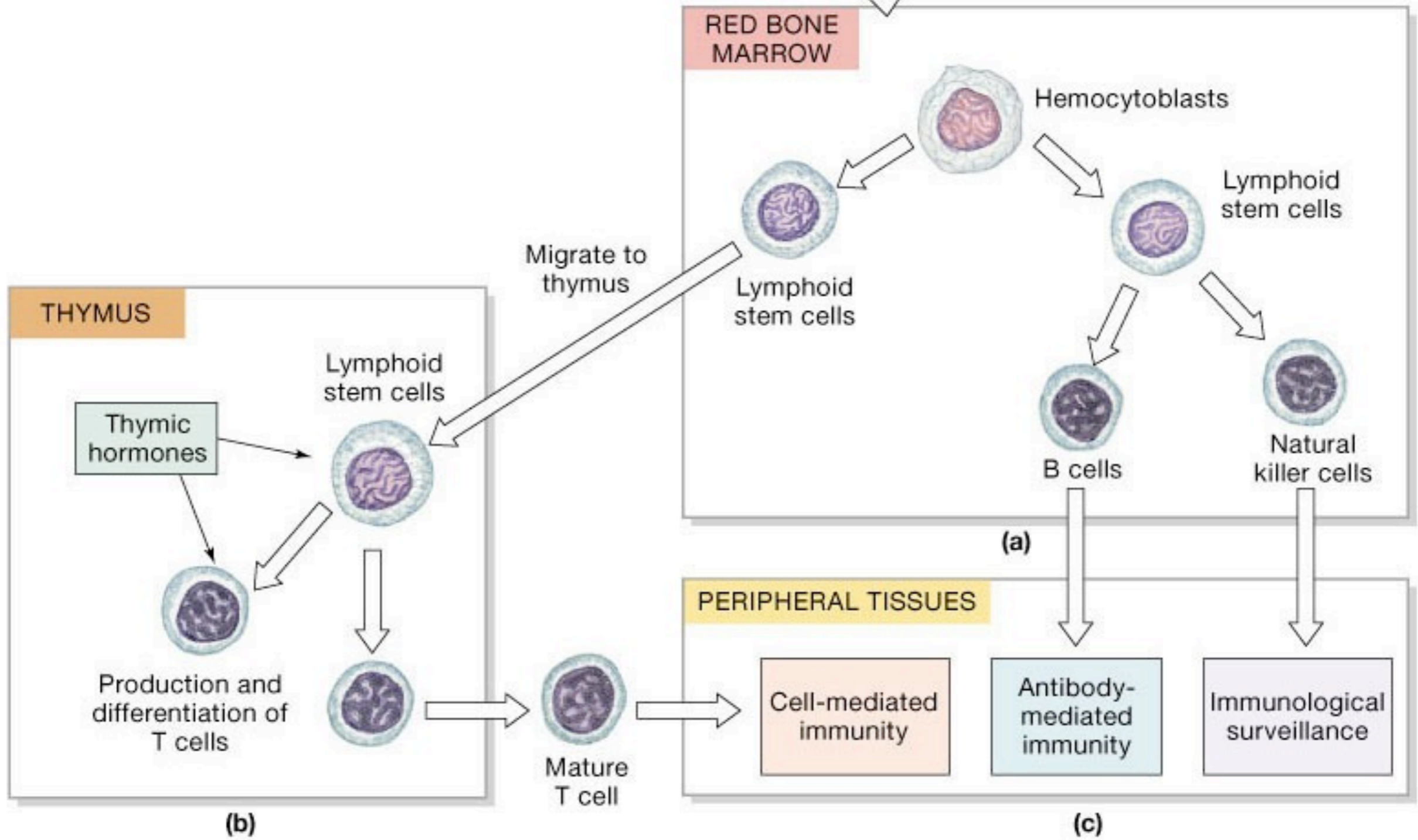
(a) B cell
Antigen-binding receptor (antibody)

(b) T_H cell
TCR, CD4

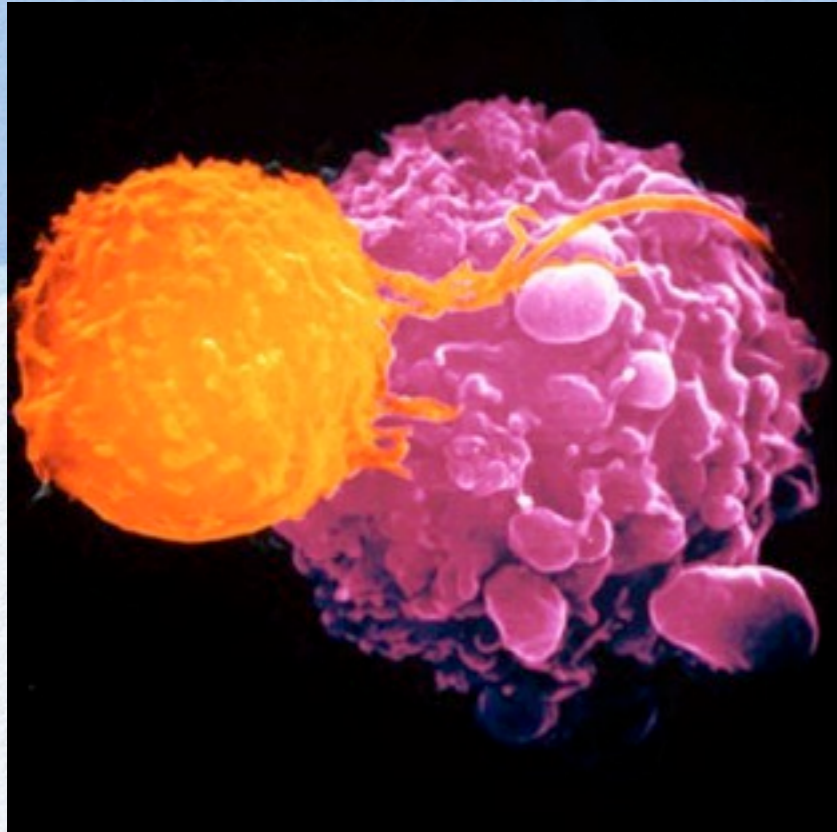
(c) T_C cell
TCR, CD8

“T suppressor cells: prevent overreaction of the system = Inhibit B-lymphocyte production”

FIGURE 1-5 Distinctive membrane molecules on lymphocytes. (a) B cells have about 10⁵ molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell have the same antigenic specificity and can interact directly with antigen. (b) T cells bearing CD4 (CD4⁺ cells) recognize only antigen bound to class II MHC molecules. (c) T cells bearing CD8 (CD8⁺ cells) recognize only antigen associated with class I MHC molecules. In general, CD4⁺ cells act as helper cells and CD8⁺ cells act as cytotoxic cells. Both types of T cells express about 10⁵ identical molecules of the antigen-binding T-cell receptor (TCR) per cell, all with the same antigenic specificity.



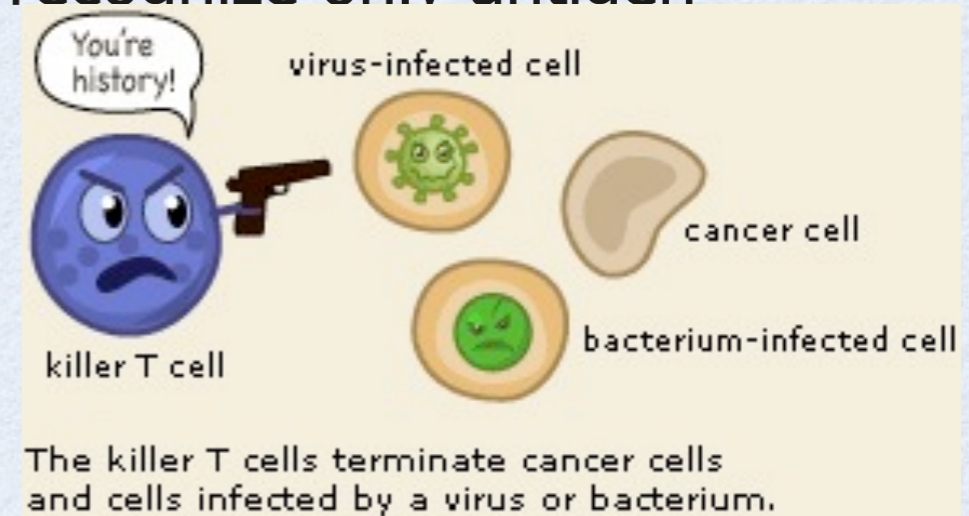
THE LYMPHOCYTES : T-CELLS



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T CELLS

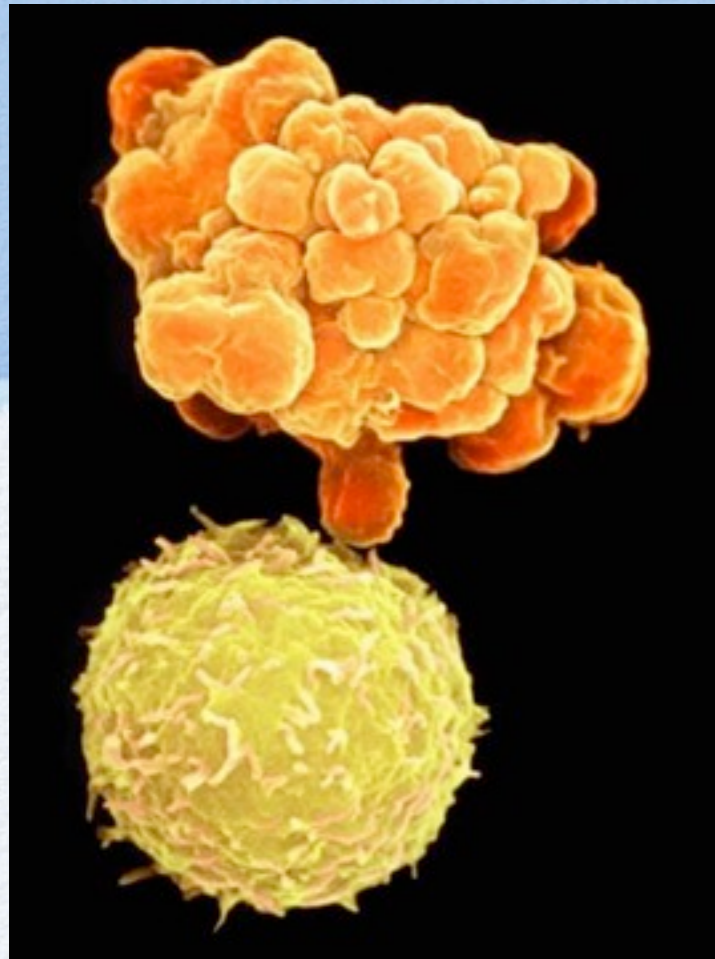
- arise in the bone marrow **BUT** migrate to the thymus gland to mature
- cannot recognize antigen alone, T-cell receptors can recognize only antigen bound to cell-membrane proteins (MHC molecules)
 - CD4-TH; CD8-TC
- TYPES:
 - Helper T cells, Cytotoxic T cells, Suppressor T cells
- CRUCIAL STEPS:
 - a naive T cell encounters antigen combined with a MHC molecule on a cell
 - T cell proliferates
 - differentiates into memory T cells and various effector T cells



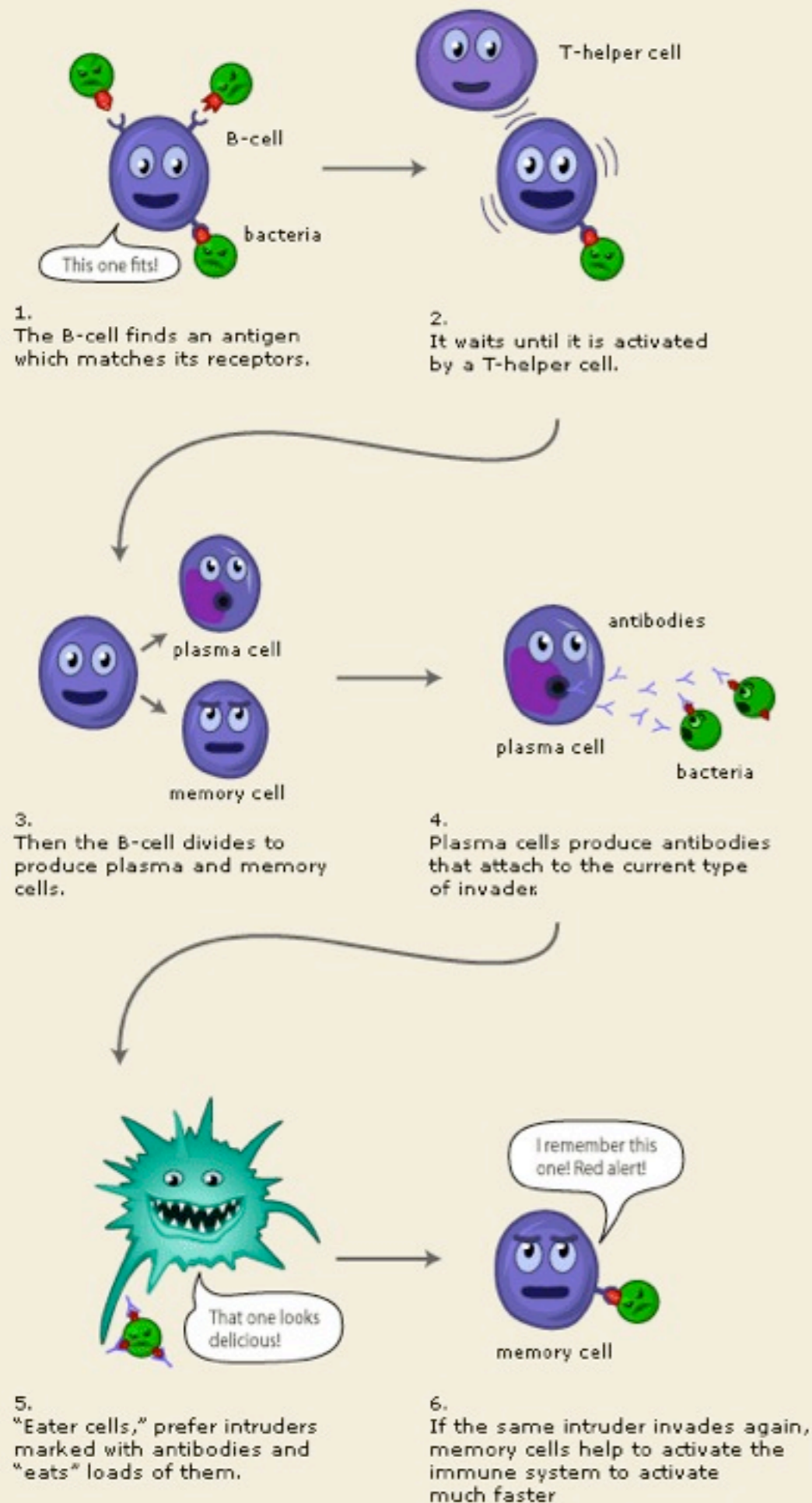
NOTE:

THE ATTRIBUTE THAT DISTINGUISH
ANTIGEN RECOGNITION BY MOST
T-CELLS FROM RECOGNITION BY
B-CELLS IS MHC RESTRICTION!

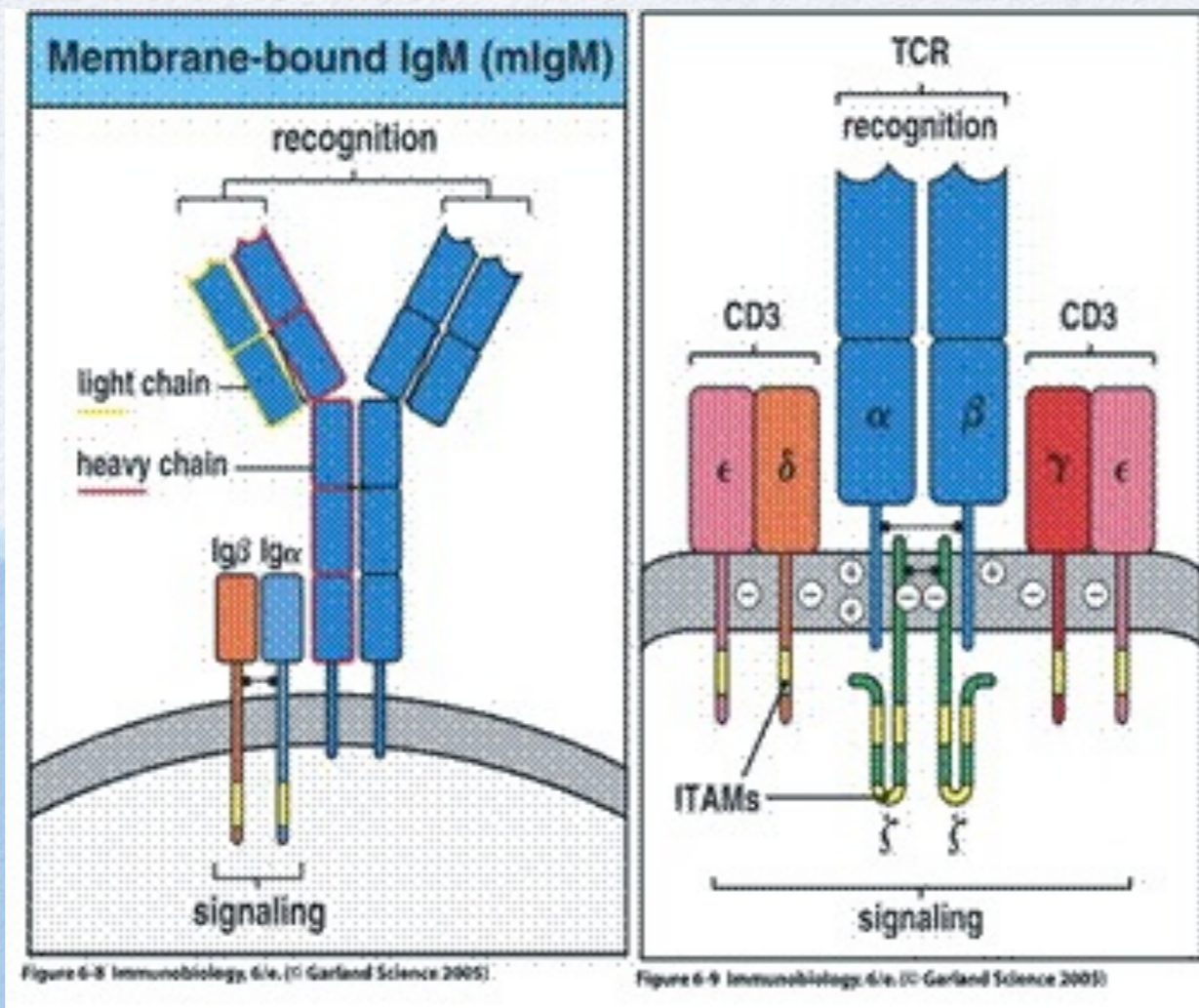
THE LYMPHOCYTES: B-CELLS



THE B CELLS



- B lymphocytes mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane
- Plasma cells live for only a few days, they secrete enormous amounts of antibody (2000/sec)



RECEPTORS

T-cell receptors (TCRs) and B-cell receptors (BCRs) have different structures thus they bind to different molecular structures and have different genetic codes

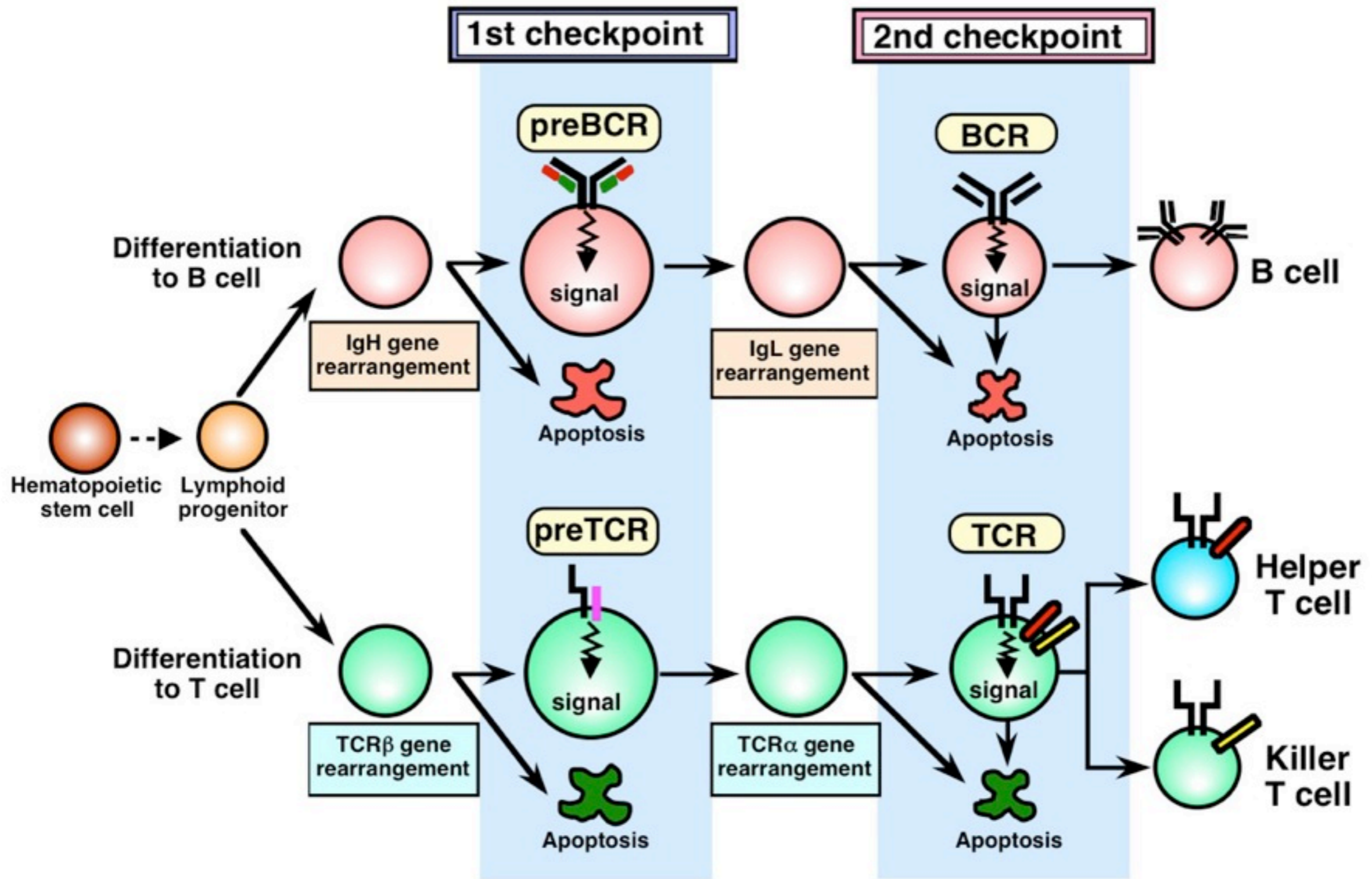
COMPARING NOTES...

- T-cell receptors (**TCRs**) enable the cell to bind to and, if additional signals are present, to be activated by and respond to an epitope presented by **APCs**
- There are two types of T cells and thus two types of TCRs: CD8 and CD4
 - CD8 T cells destroy the cells they bind to, such as virus cells.
 - CD4 T cells group together to cause inflammation, which isolates an infected area so it can heal = helps build immunities
- B-cell receptors (**BCRs**) enable the cell to bind to and, if additional signals are present, to be activated by and respond to an epitope on molecules of a **soluble antigen**
 - B cells bind to these toxins and digest them into smaller pieces
 - the response ends with descendants of the B cell secreting **antibodies** (via the plasma cells)

DEVELOPMENT & MATURATION

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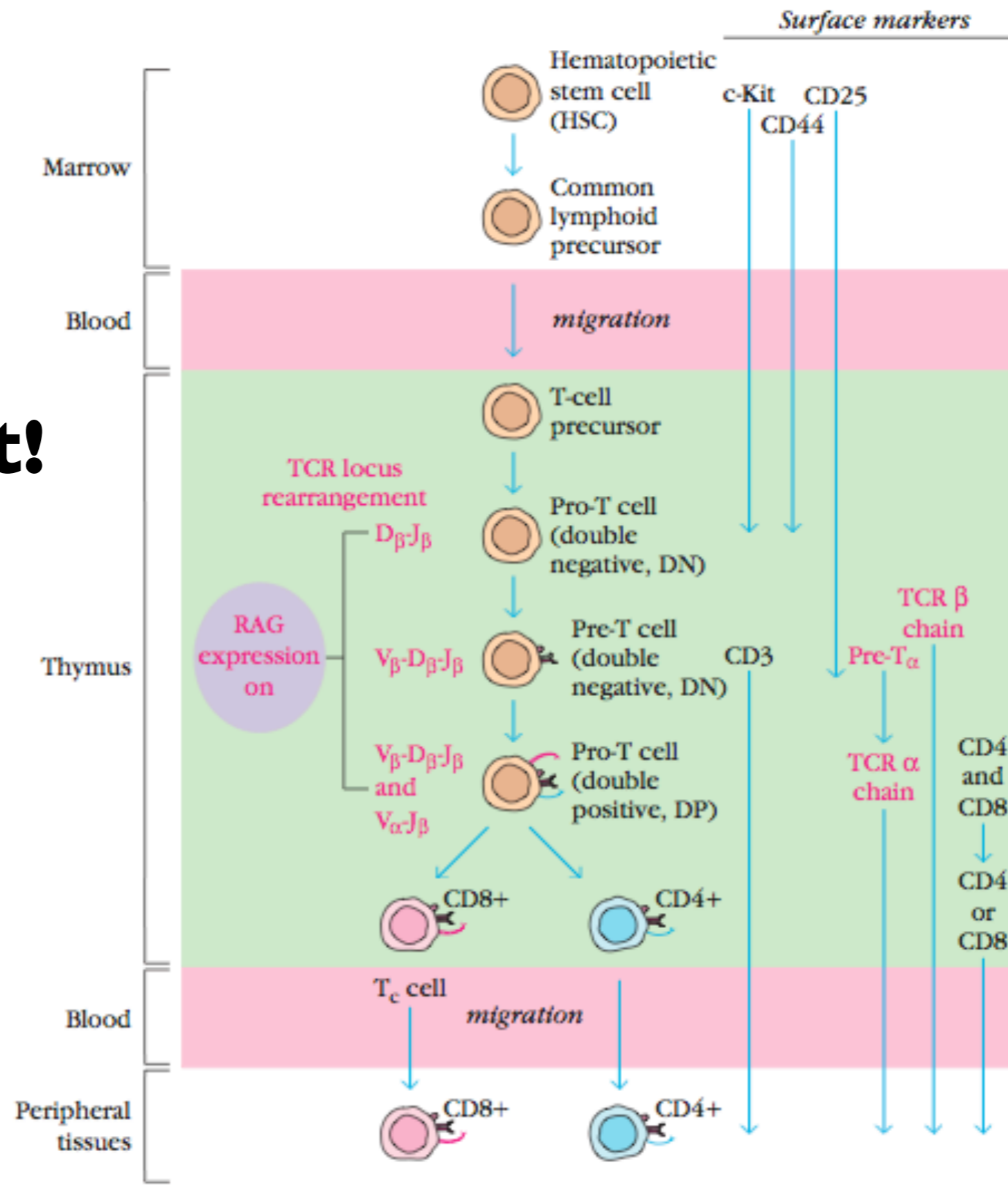
T cells versus B cells





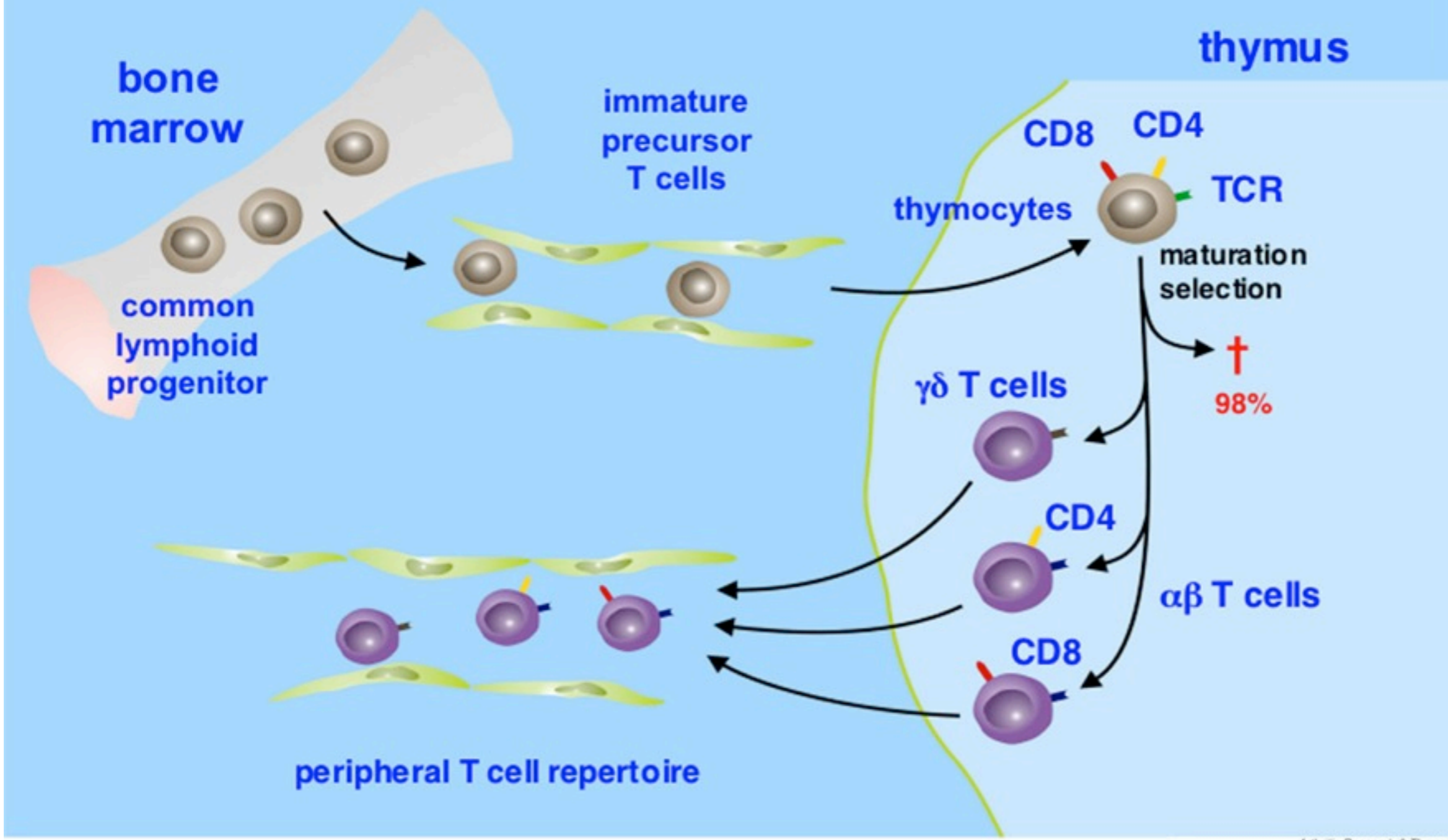
Experiment!

FIGURE 10-1 Development of $\alpha\beta$ T cells in the mouse. T-cell precursors arrive at the thymus from bone marrow via the bloodstream, undergo development to mature T cells, and are exported to the periphery where they can undergo antigen-induced activation and differentiation into effector cells and memory cells. Each stage of development is characterized by stage-specific intracellular events and the display of distinctive cell-surface markers.



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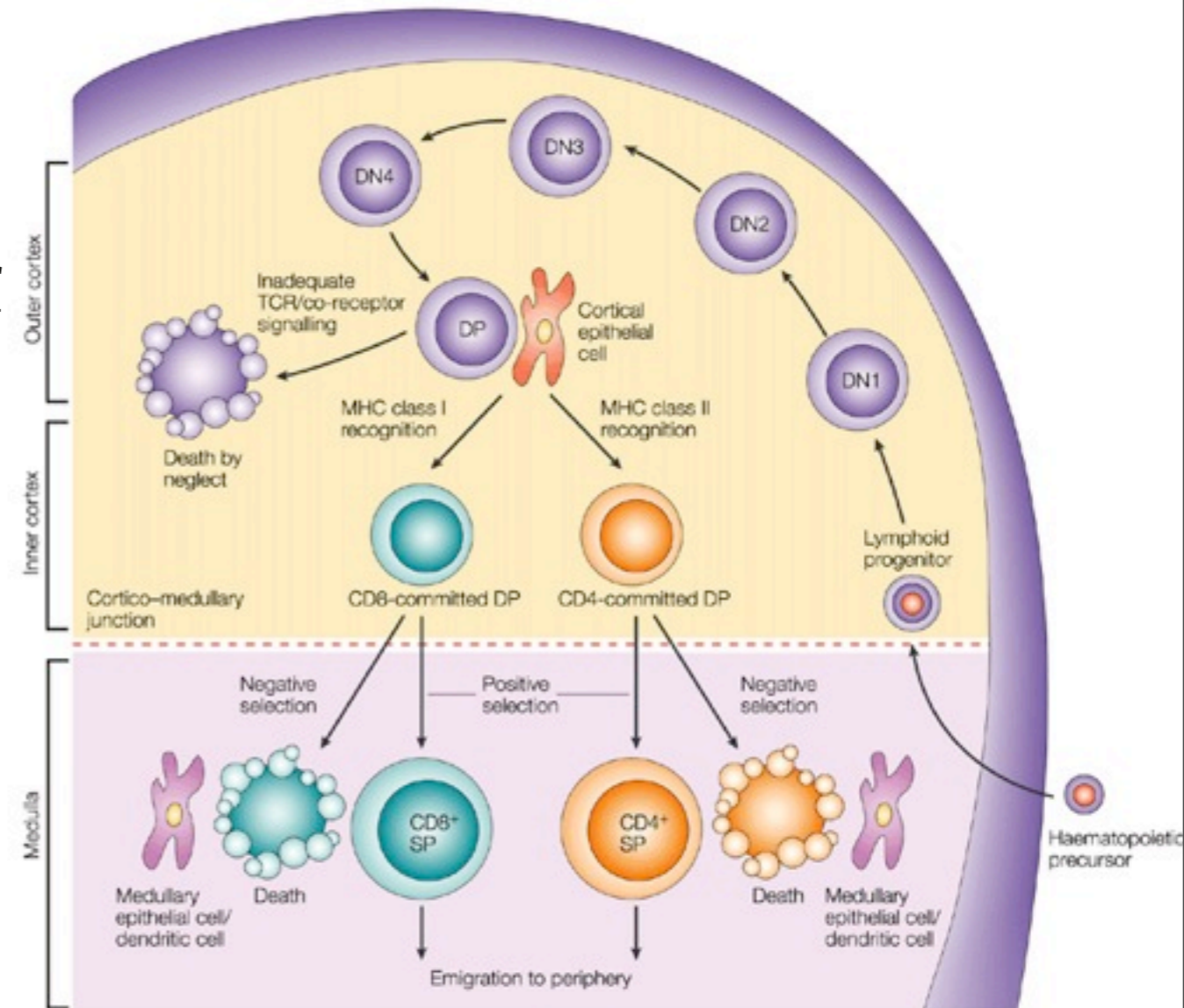
Arthritis Research & Therapy

- In the thymus, developing T cells, known as thymocytes, proliferate and differentiate along developmental pathways that generate functionally distinct subpopulations of mature T cells
- Aside from being the main source of all T cells, it is where T cells diversify and then are shaped into an effective primary T-cell repertoire by an extraordinary pair of selection processes (+ and - SELECTION)

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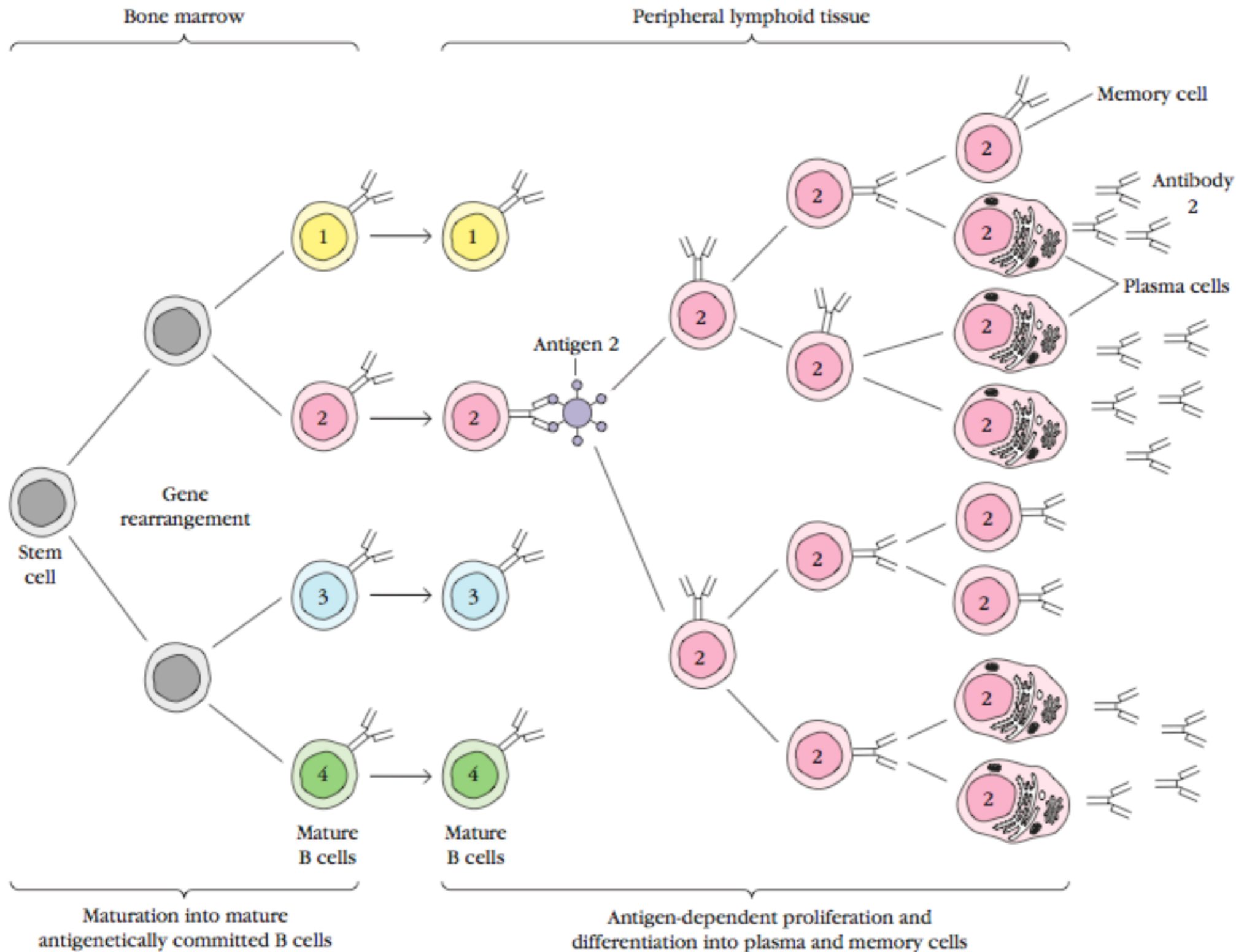
POSITIVE AND NEGATIVE SELECTION

- **positive selection**, permits the survival of only those T cells whose TCRs are capable of recognizing self-MHC molecules
- It is thus responsible for the **creation of a self-MHC-restricted repertoire of T cells**
 - Cells that fail positive selection are eliminated within the thymus by apoptosis
- **negative selection**, eliminates T cells that react too strongly with self-MHC or with self-MHC plus self-peptides
- bearing high-affinity receptors for self-MHC molecules alone or self-antigen presented by self-MHC, which results in self-tolerance
- It is an extremely important factor in **generating a primary T-cell repertoire that is self-tolerant**



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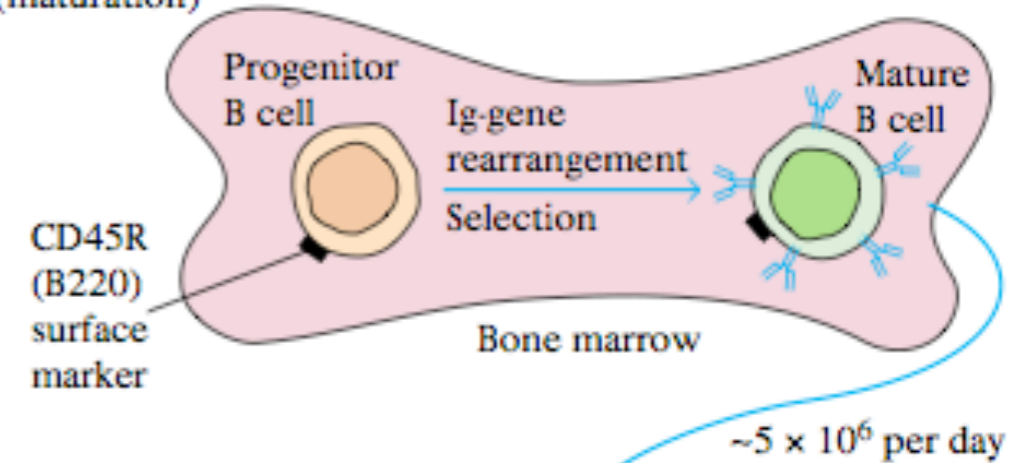
B - CELLS

- B cells develop in bone marrow and undergo antigen-induced activation and differentiation in the periphery
- Activated B cells can give rise to antibody-secreting plasma cells or memory B cells

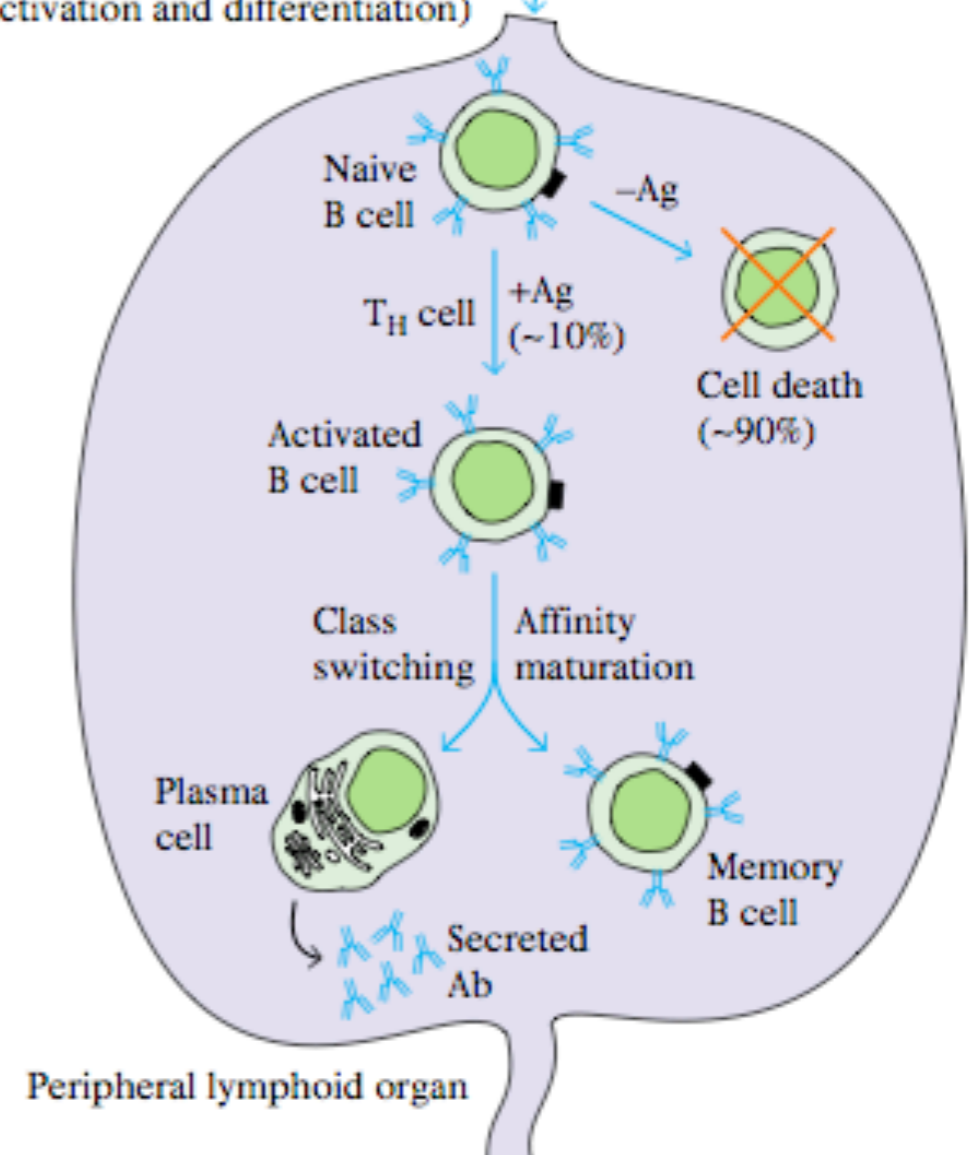
B CELL MATURATION AND DEVELOPMENT

- During B-cell development, sequential Ig-gene rearrangements transform a pro-B cell into an immature B cell expressing mIgM with a single antigenic specificity
- Further development yields mature naive B cells expressing both mIgM and mIgD

ANTIGEN-INDEPENDENT PHASE (maturation)



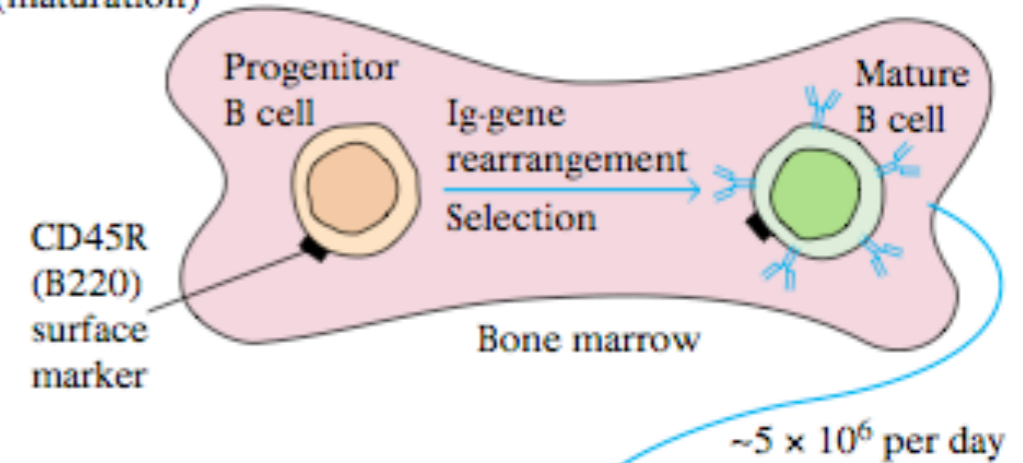
ANTIGEN-DEPENDENT PHASE (activation and differentiation)



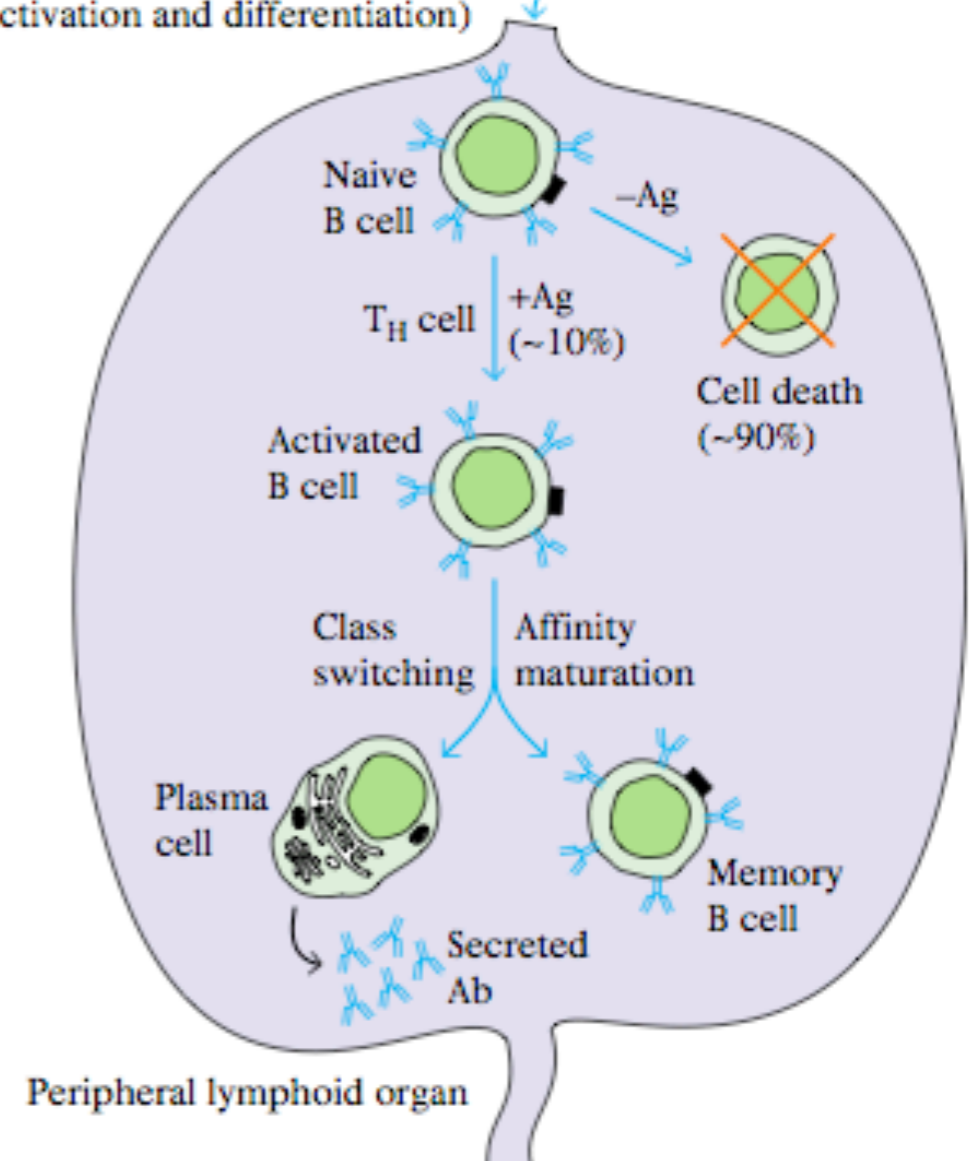
B CELL MATURATION AND DEVELOPMENT

- When a self-reactive BCR is expressed in the bone marrow, negative selection of the self-reactive immature B cells occurs
- The selected cells are deleted by apoptosis or undergo receptor editing to produce non-self-reactive mIg
- B cells reactive with self-antigens encountered in the periphery are rendered **anergic**

ANTIGEN-INDEPENDENT PHASE (maturation)



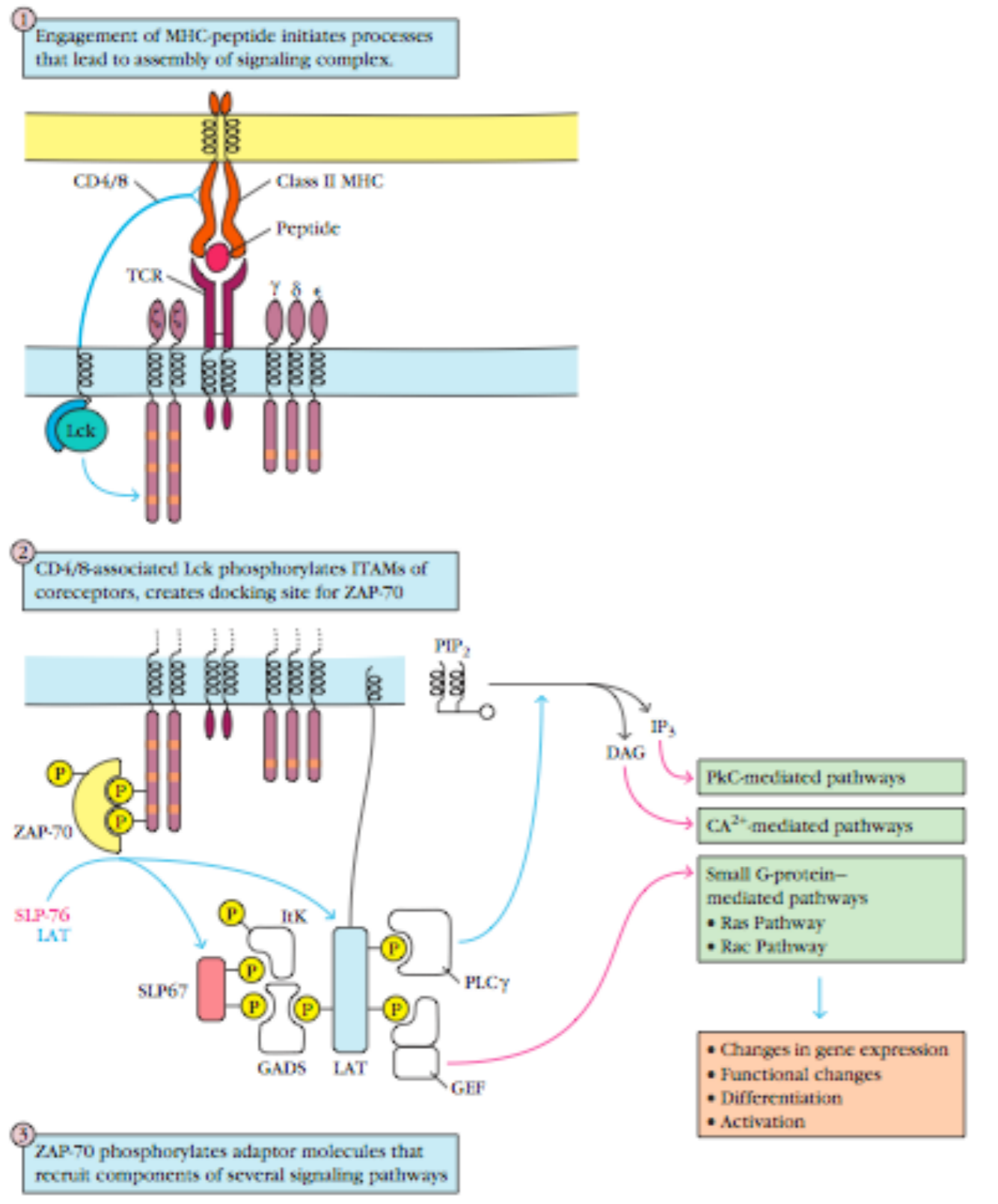
ANTIGEN-DEPENDENT PHASE (activation and differentiation)



ACTIVATION & DIFFERENTIATION

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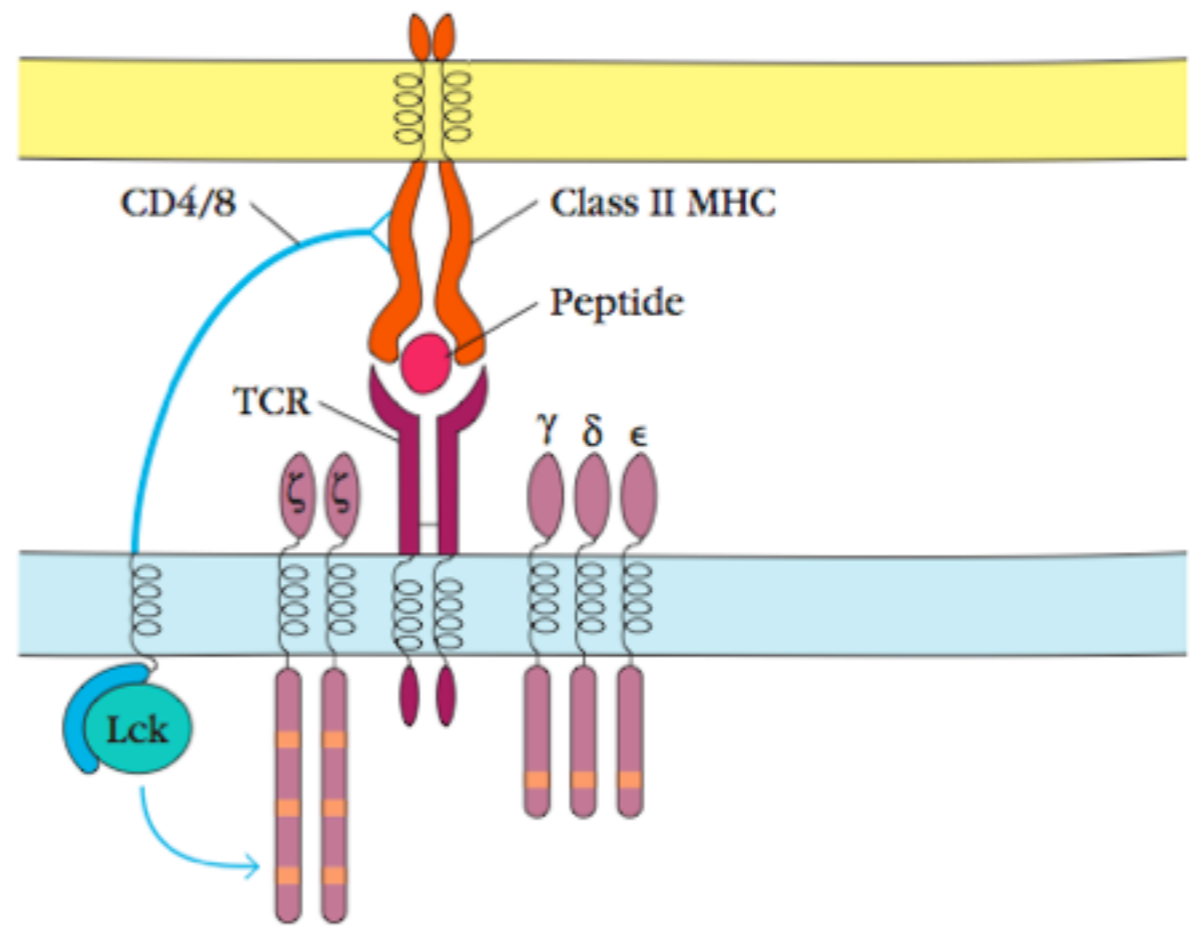
T CELL ACTIVATION



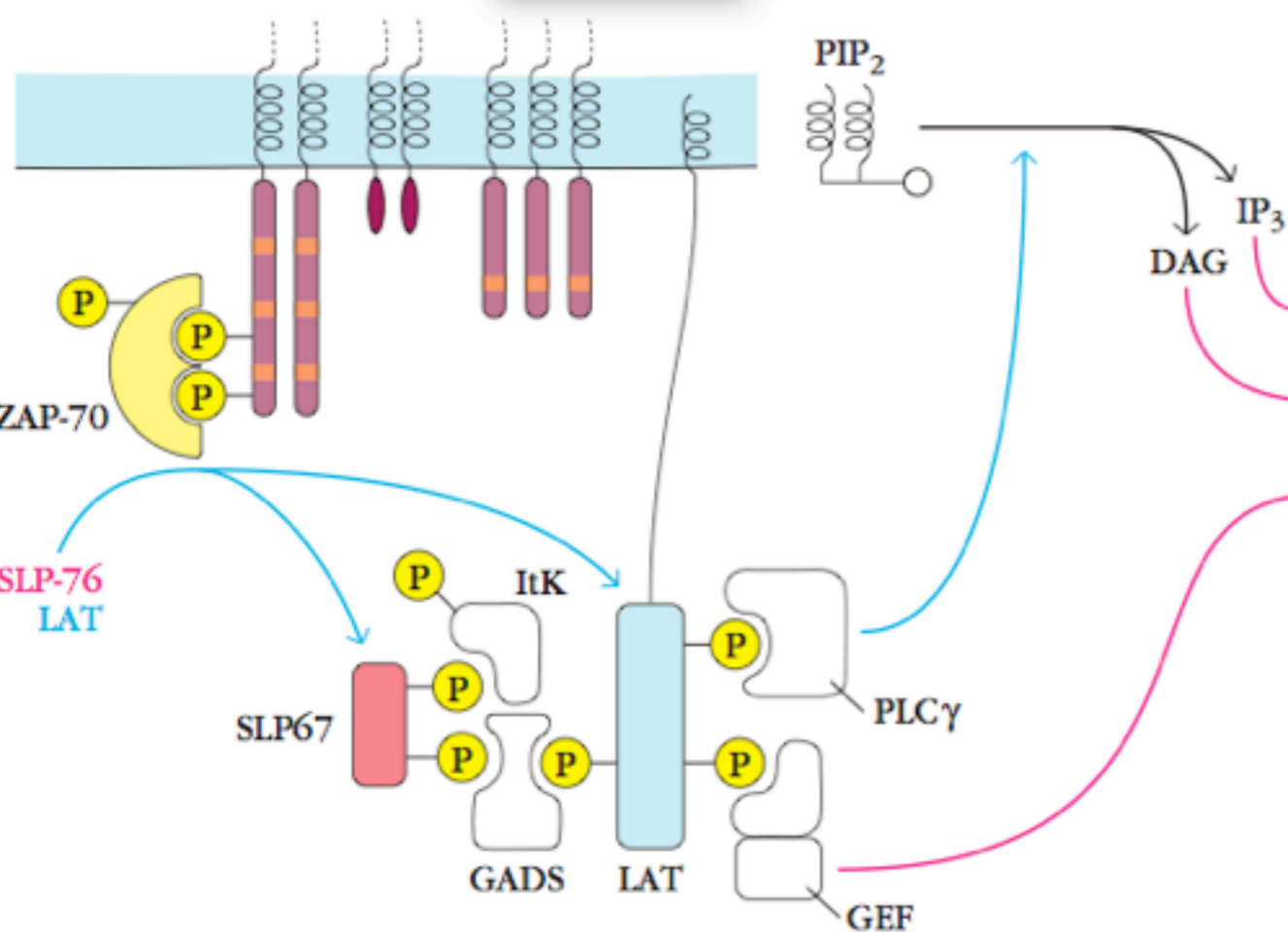
- TH-cell activation is initiated by interaction of the TCR- CD3 complex with a peptide-MHC complex on an antigen-presenting cell
- Activation also requires the activity of accessory molecules, including the coreceptors CD4 and CD8
- Many different intracellular signal-transduction pathways are activated by the engagement of the TCR

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1 Engagement of MHC-peptide initiates processes that lead to assembly of signaling complex.



2 CD4/8-associated Lck phosphorylates ITAMs of coreceptors, creates docking sites for ZAP-70



- PkC-mediated pathways
- CA²⁺-mediated pathways
- Small G-protein-mediated pathways
 - Ras Pathway
 - Rac Pathway
- Changes in gene expression
- Functional changes
- Differentiation
- Activation

3 ZAP-70 phosphorylates adaptor molecules that recruit components of several signaling pathways

SIGNALS FOR ACTIVATION

- In addition to the signals mediated by the T-cell receptor and its associated accessory molecules (signal 1), activation of the TH cell requires a co-stimulatory signal (signal 2) provided by the antigen-presenting cell
- The co-stimulatory signal is commonly induced by interaction between molecules of the B7 family on the membrane of the APC with CD28 on the TH cell
- Engagement of CTLA-4, a close relative of CD28, by B7 inhibits T-cell activation

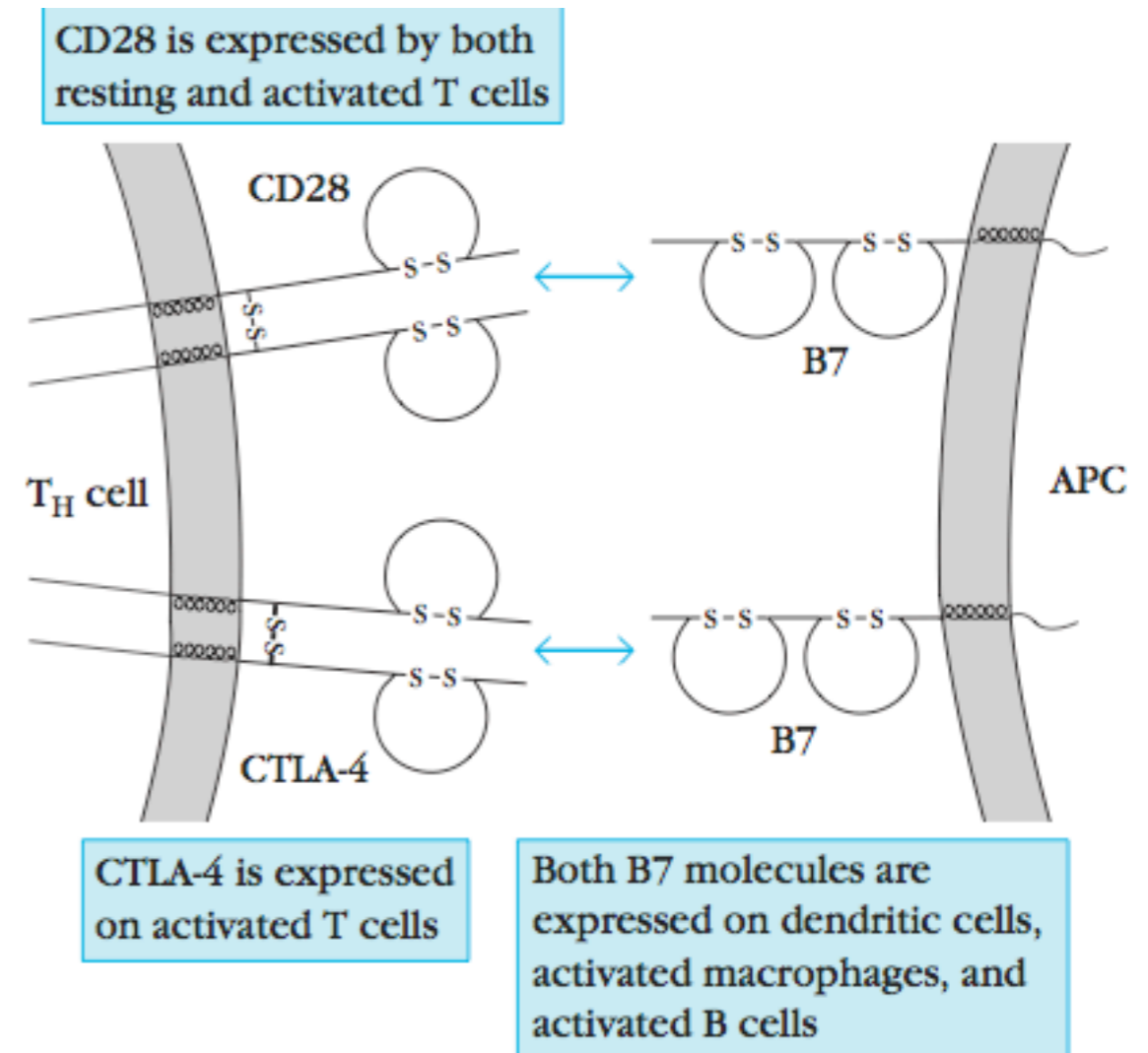
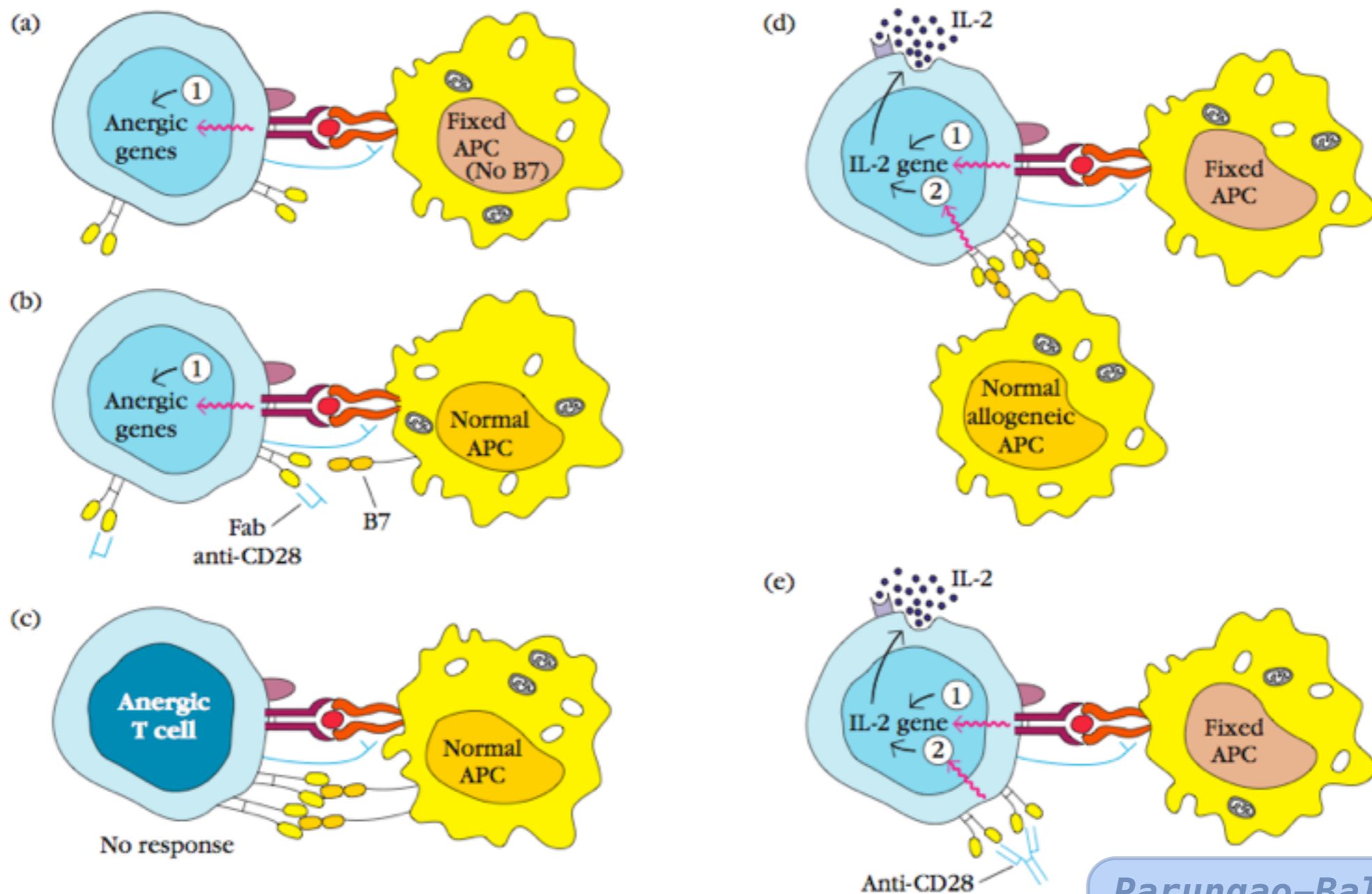


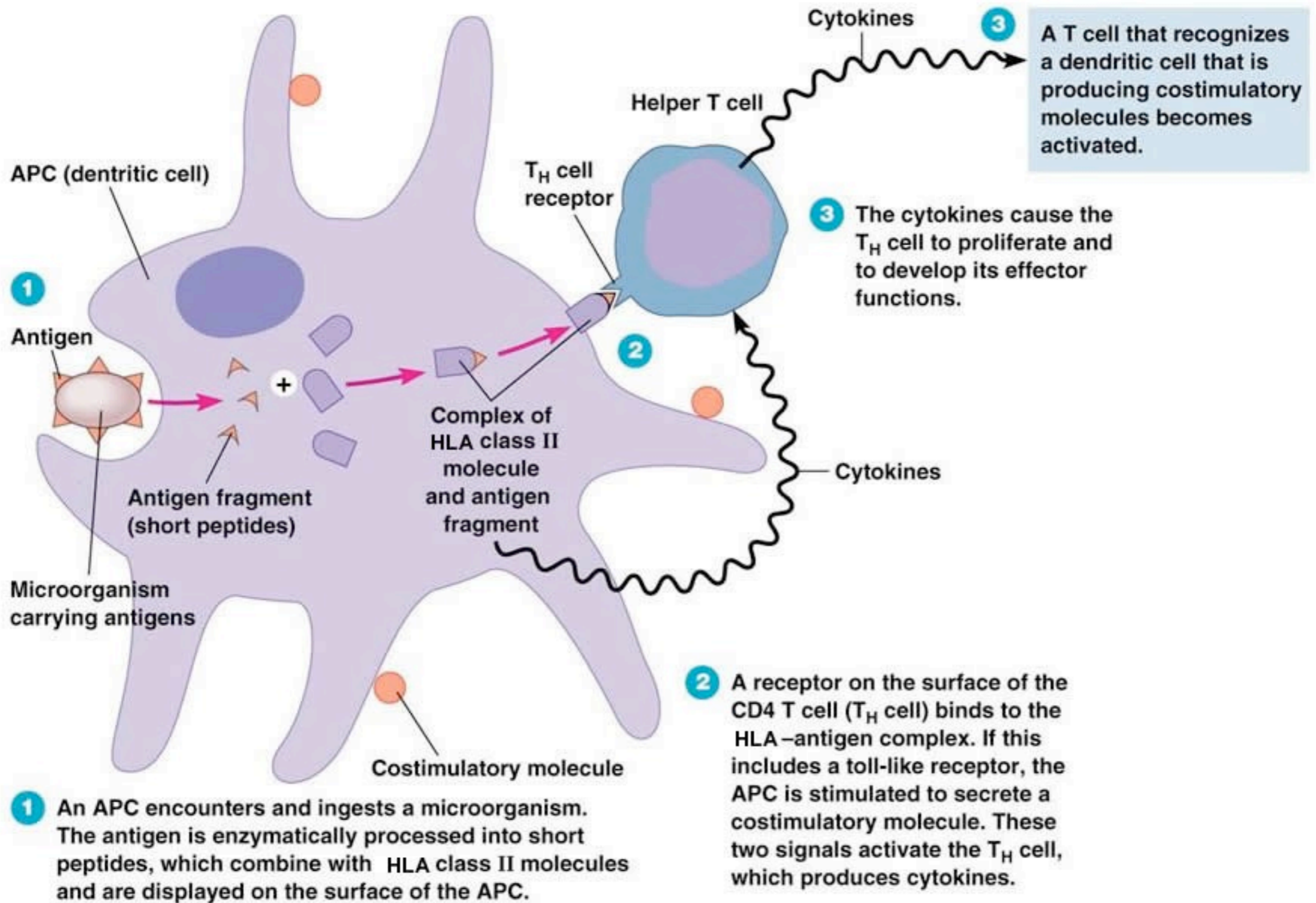
FIGURE 10-13 T_H-cell activation requires a co-stimulatory signal provided by antigen-presenting cells (APCs). Interaction of B7 family members on APCs with CD28 delivers the co-stimulatory signal. Engagement of the closely related CTLA-4 molecule with B7 produces an inhibitory signal. All of these molecules contain at least one immunoglobulin-like domain and thus belong to the immunoglobulin superfamily. [Adapted from P. S. Linsley and J. A. Ledbetter, 1993,

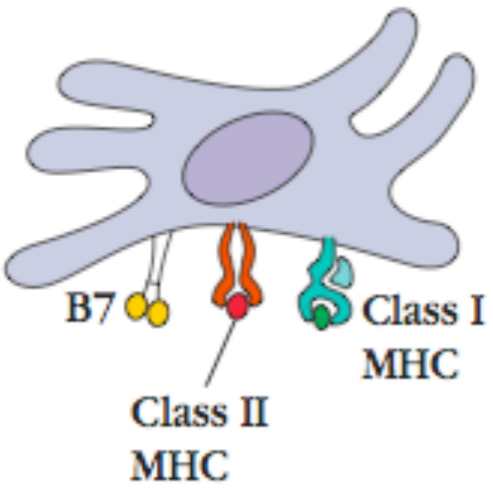

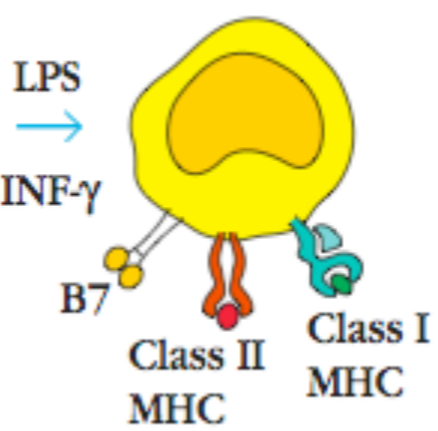
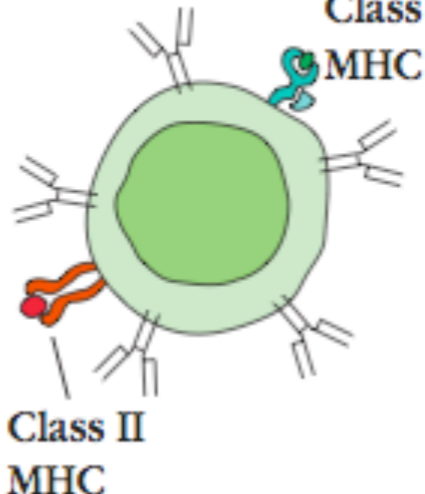
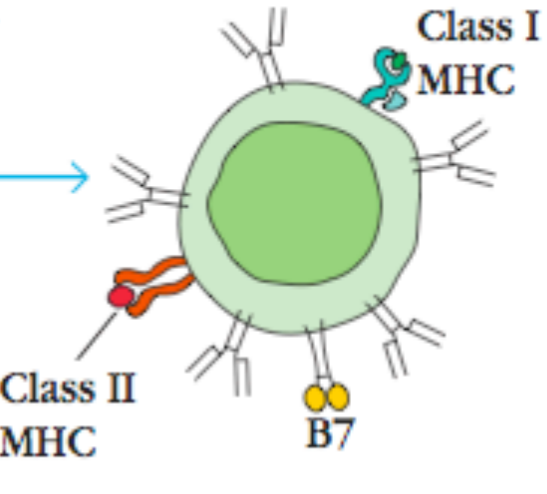
SIGNALS FOR ACTIVATION

- TCR engagement with antigenic peptide-MHC may induce activation or clonal anergy
- The presence or absence of the co-stimulatory signal (signal 2) determines whether activation results in clonal expansion or clonal anergy



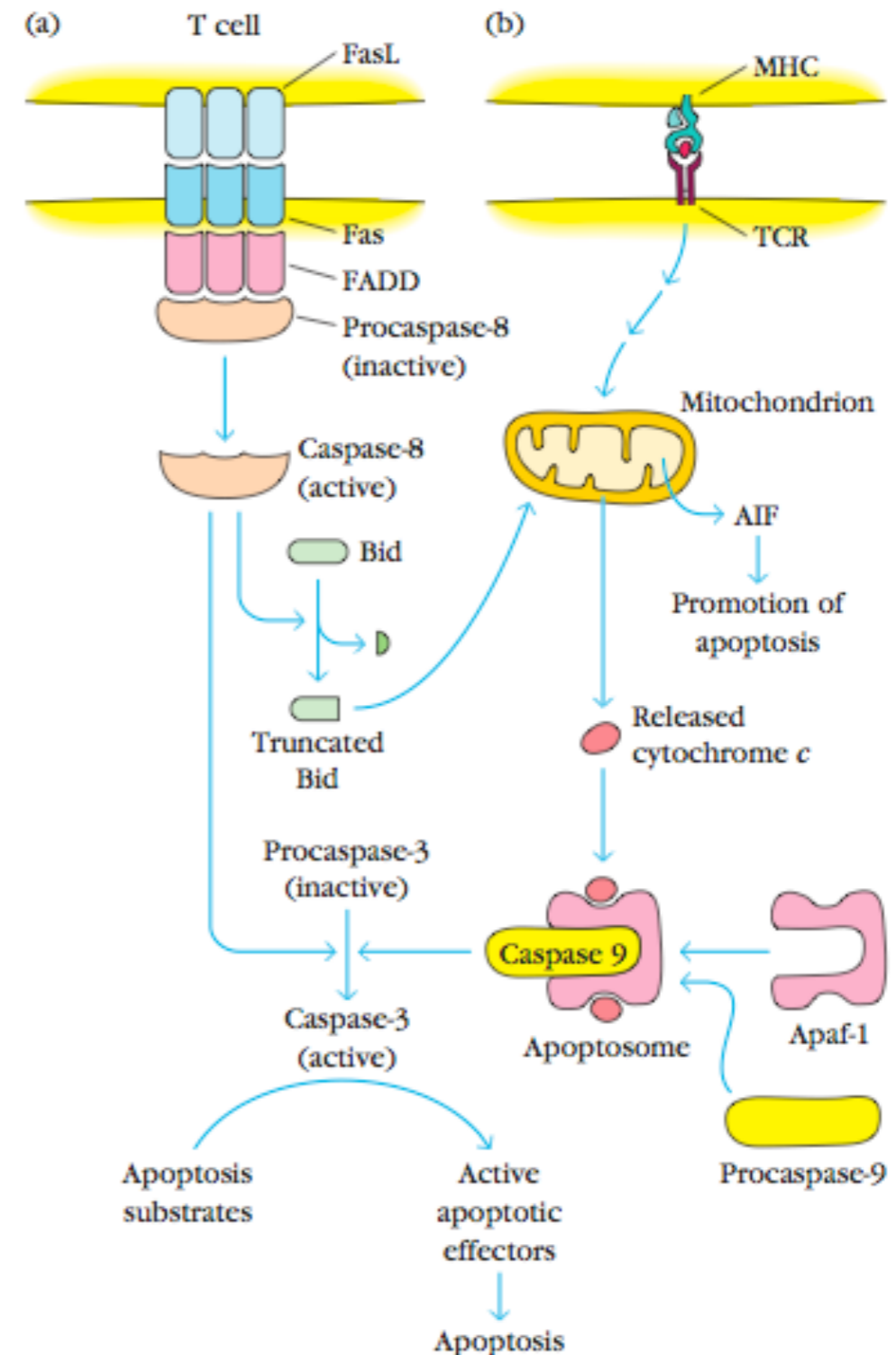
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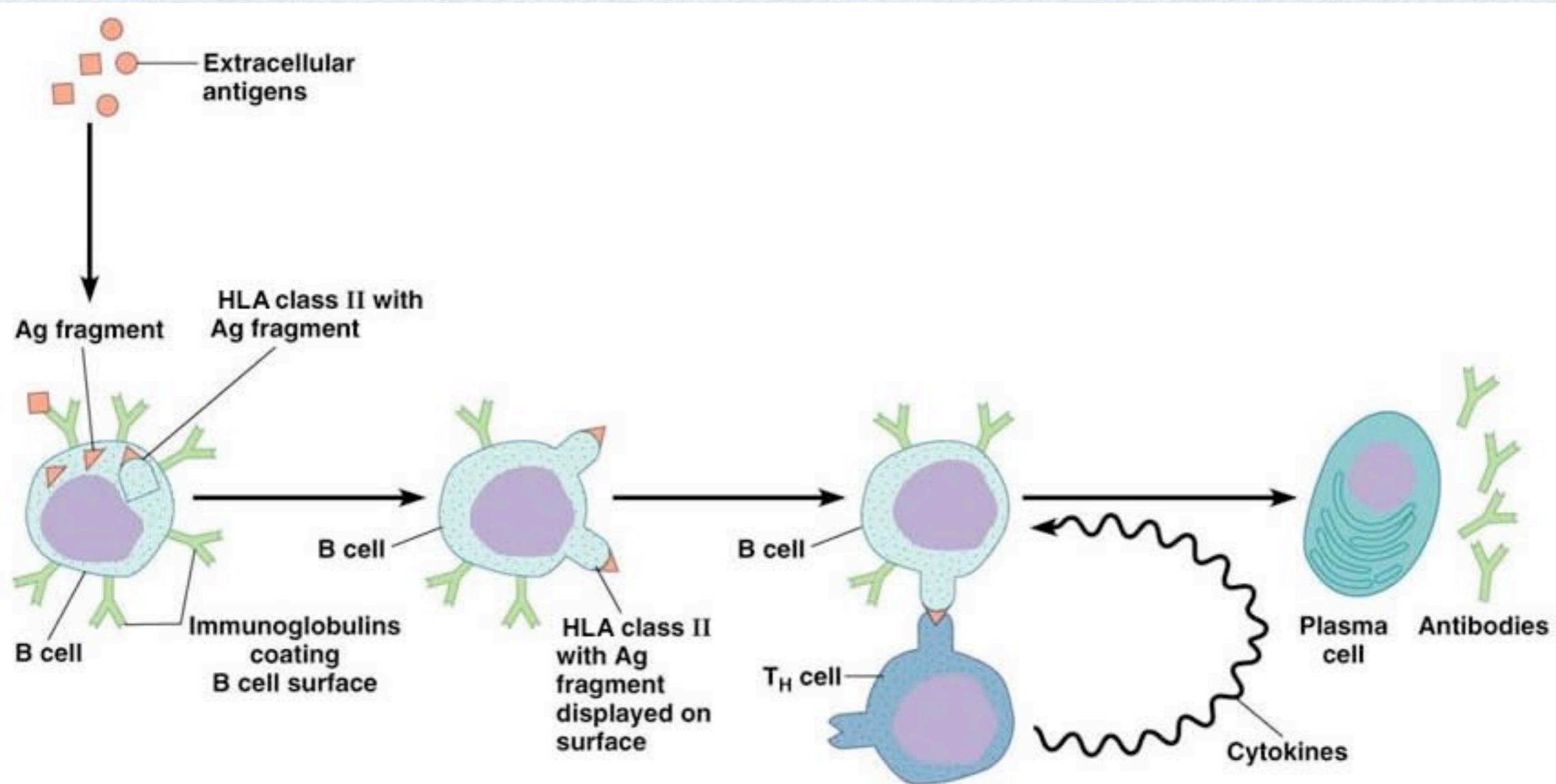
	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (-)	Inducible (++)	Constitutive (++)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (-)	Inducible B7 (++)	Inducible B7 (-)	Inducible B7 (++)
T-cell activation	Naive T cells Effector T cells Memory T cells	(-)	Effector T cells Memory T cells	Effector T cells Memory T cells	Naive T cells Effector T cells Memory T cells

DIFFERENTIATION IN T-CELLS

- Naive T cells are resting cells (G0) that have not encountered antigen. Activation of naive cells leads to the generation of effector and memory T cells
- Memory T cells, which are more easily activated than naive cells, are responsible for secondary responses
- Effector cells are short lived and perform helper, cytotoxic, or delayed-type hypersensitivity functions.
- The T-cell repertoire is shaped by apoptosis in the thymus and periphery
- gamma delta T cells are not MHC restricted



B CELL ACTIVATION



1 Immunoglobulins on B cell surface recognize and attach to antigen, which is then internalized and processed. Within the B cell a fragment of the antigen combines with HLA class II.

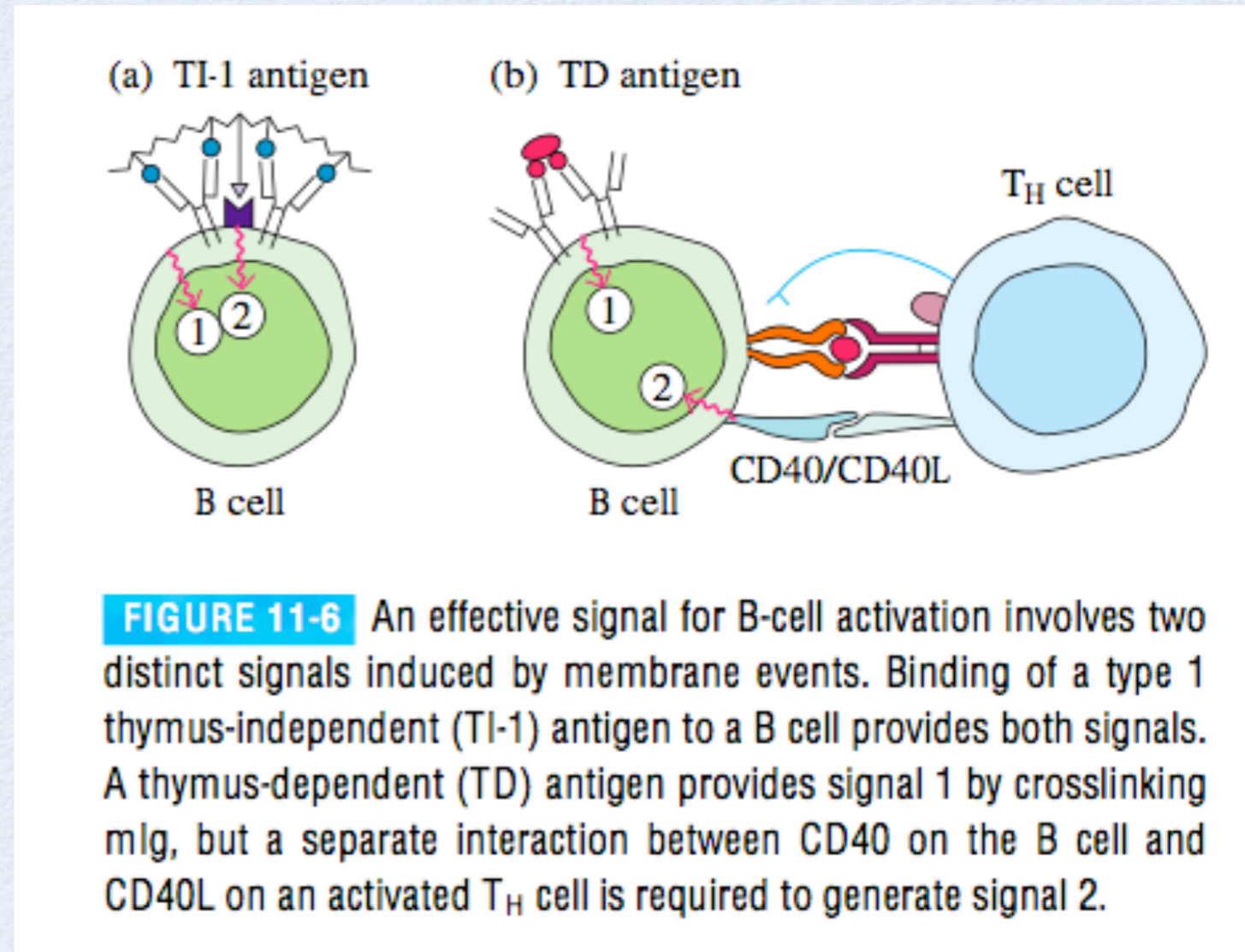
2 HLA class II-antigen-fragment complex is displayed on B cell surface.

3 Receptor on the helper T cell (T_H) recognizes complex of HLA class II and antigen fragment and is activated—producing cytokines, which activate the B cell.

4 B cell is activated by cytokines and begins clonal expansion. Some of the progeny become antibody-producing plasma cells.

B CELL ACTIVATION

- B-cells are activated when antigen binds to receptors on the B-cell surface, followed by a co-stimulatory signal, usually provided by a helper T-cell.
- Antigens that require co-stimulation by a T-cell to activate a B-cell are T-dependent antigens and are usually proteins
- In order for the helper T-cell to stimulate the B-cell both must be activated - this usually requires that the B-cell internalize the antigen, process it, and then present it on the cell surface bound to a class II HLA molecule
- The HLA-antigen complex is recognized by a receptor on the surface of the T-cell (the T-cell receptor, or TCR)



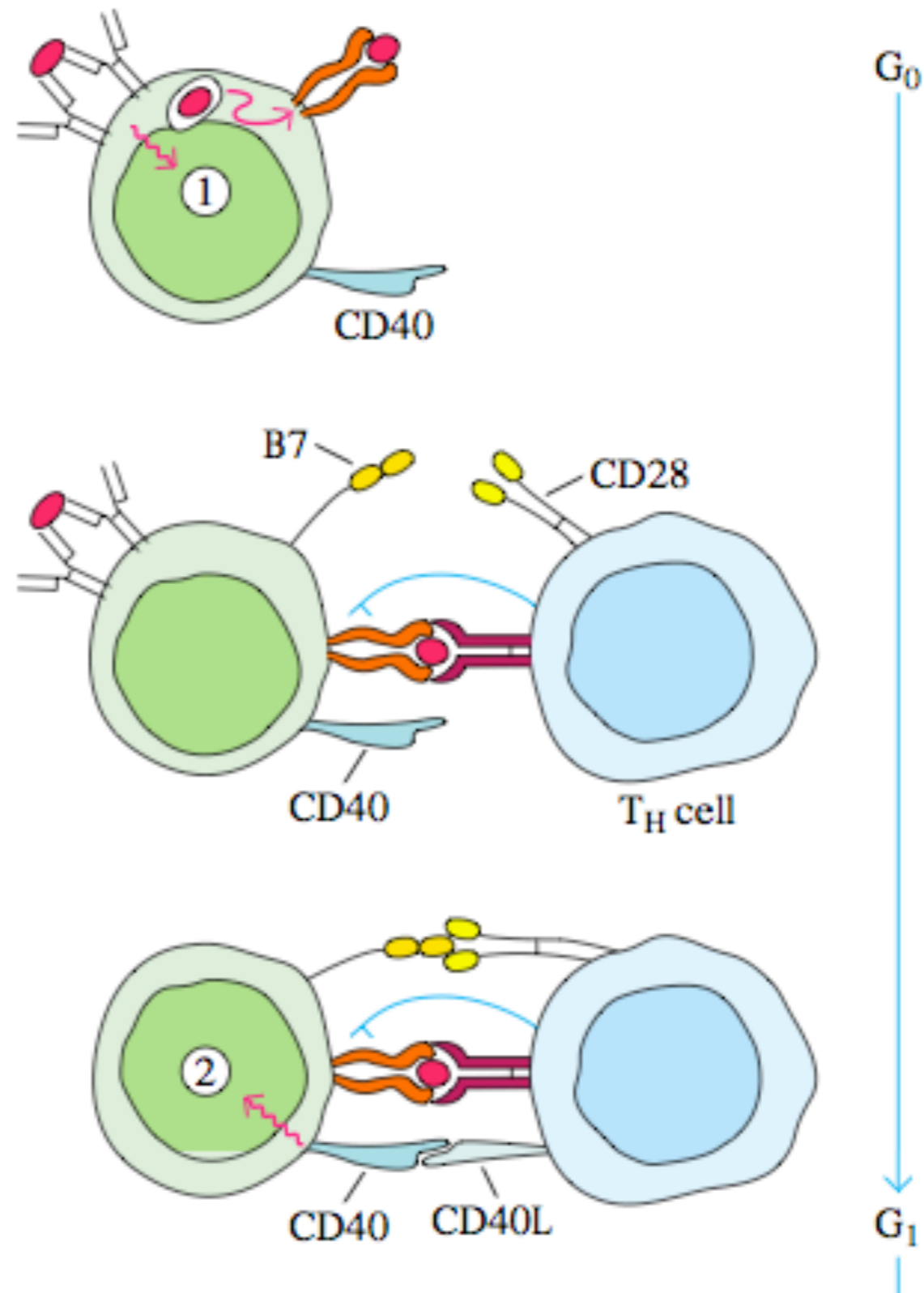
B CELL ACTIVATION

- The B-cell expresses an activation receptor on its surface (CD40) that binds to a complementary ligand (CD154) on the surface of the helper T-cell
- This interaction will co-stimulate the B-cell, activating it to clonally proliferate
- In addition, the helper T-cell will secrete interleukins that will promote growth and antibody production by the activated B-cell
- The helper T-cell would normally have been activated by interaction with a macrophage or dendritic cell but the B-cell can act as an antigen presenting cell as well
- The B-cell can express B7 proteins on its surface which will bind to CD28 on the surface of the helper T-cell
- The combination of TCR-HLA/antigen binding and B7-CD28 binding will activate the T-cell

(a) Antigen crosslinks mIg, generating signal ①, which leads to increased expression of class II MHC and co-stimulatory B7. Antigen-antibody complexes are internalized by receptor-mediated endocytosis and degraded to peptides, some of which are bound by class II MHC and presented on the membrane as peptide-MHC complexes.

(b) T_H cell recognizes antigen-class II MHC on B-cell membrane. This plus co-stimulatory signal activates T_H cell.

(c) 1. T_H cell begins to express CD40L.
2. Interaction of CD40 and CD40L provides signal ②.
3. B7-CD28 interactions provide co-stimulation to the T_H cell.



- (d) 1. B cell begins to express receptors for various cytokines.
2. Binding of cytokines released from T_H cell in a directed fashion sends signals that support the progression of the B cell to DNA synthesis and to differentiation.

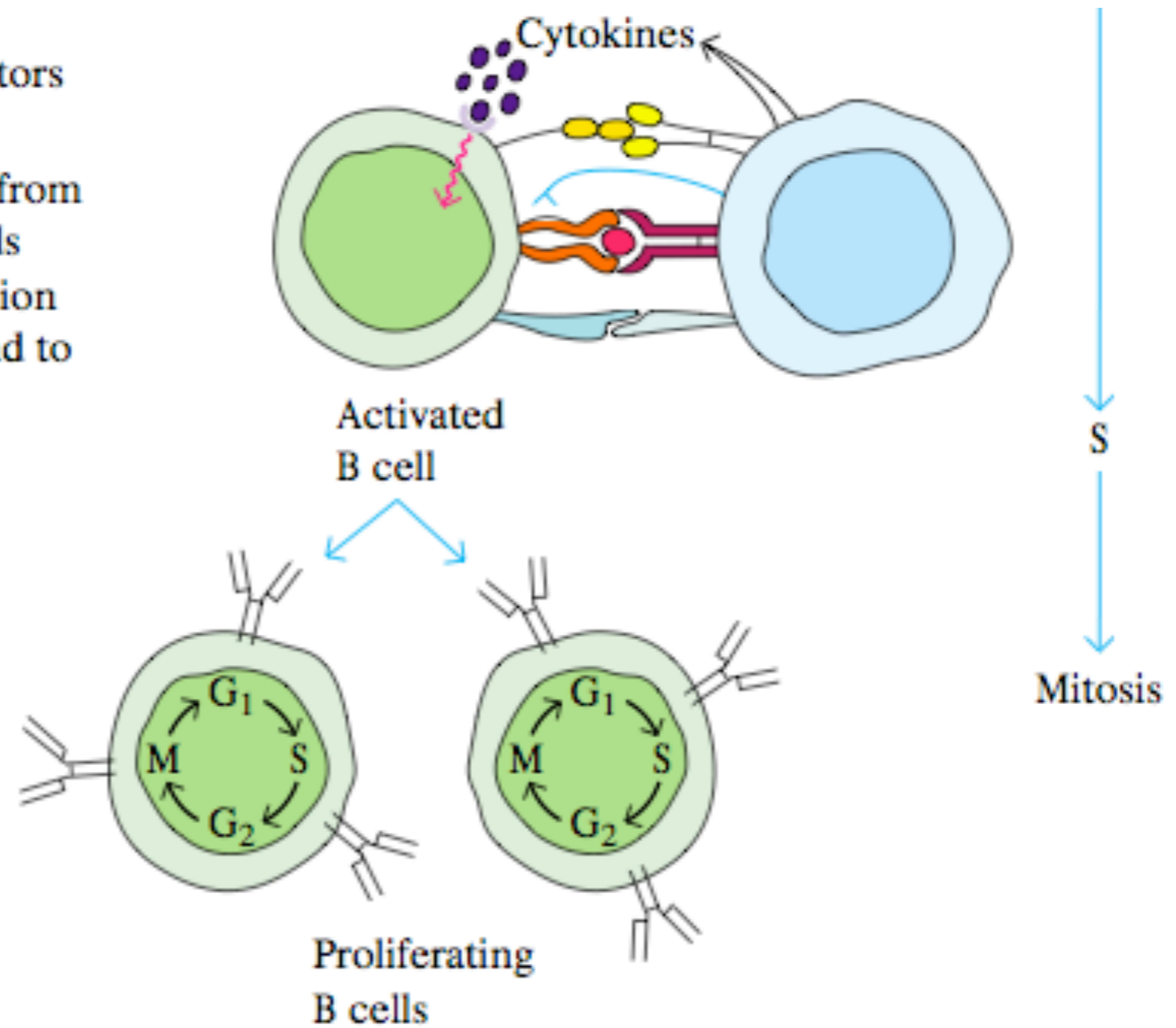
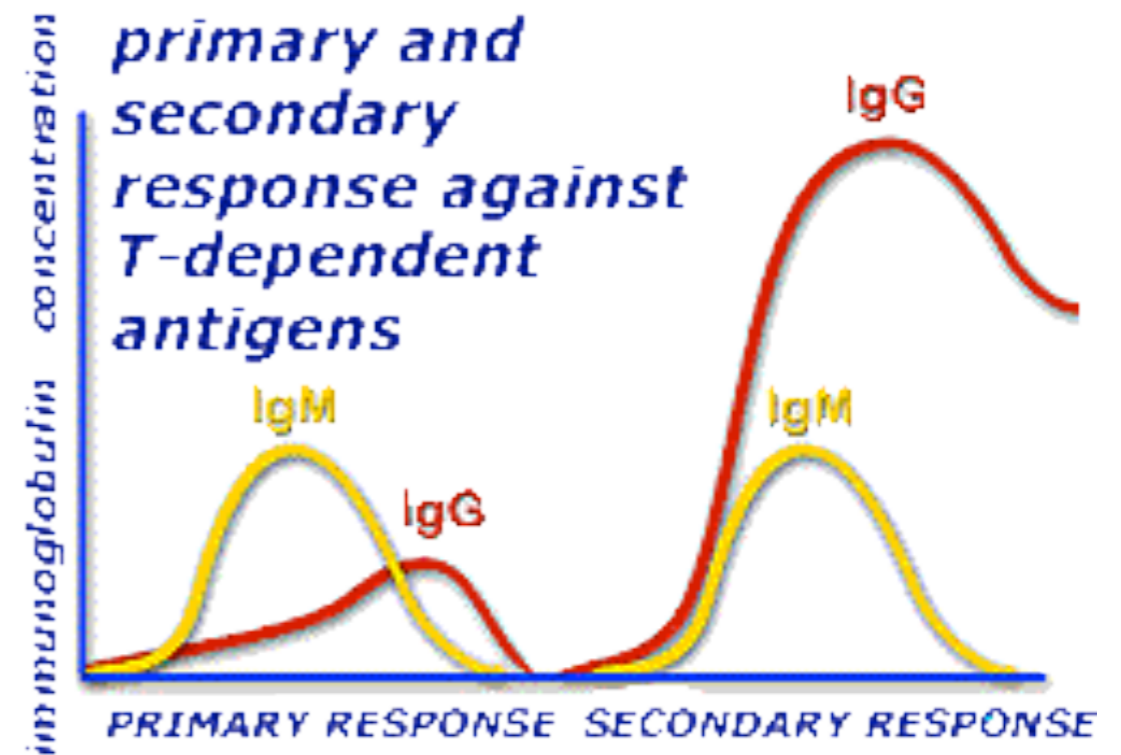
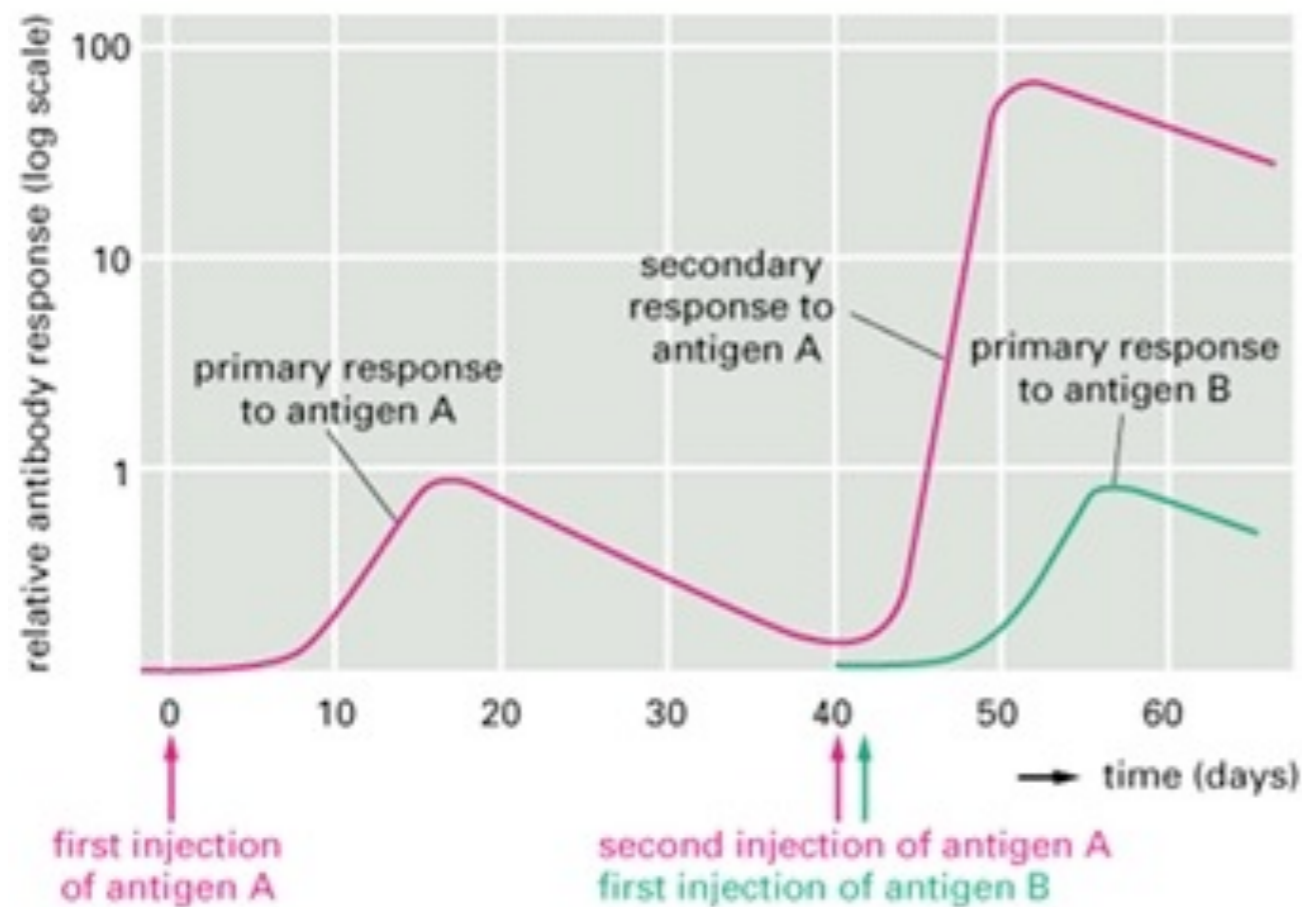


TABLE 11-4**Comparison of primary and secondary antibody responses**

Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher than primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher



END OF FIRST EXAM
COVERAGE