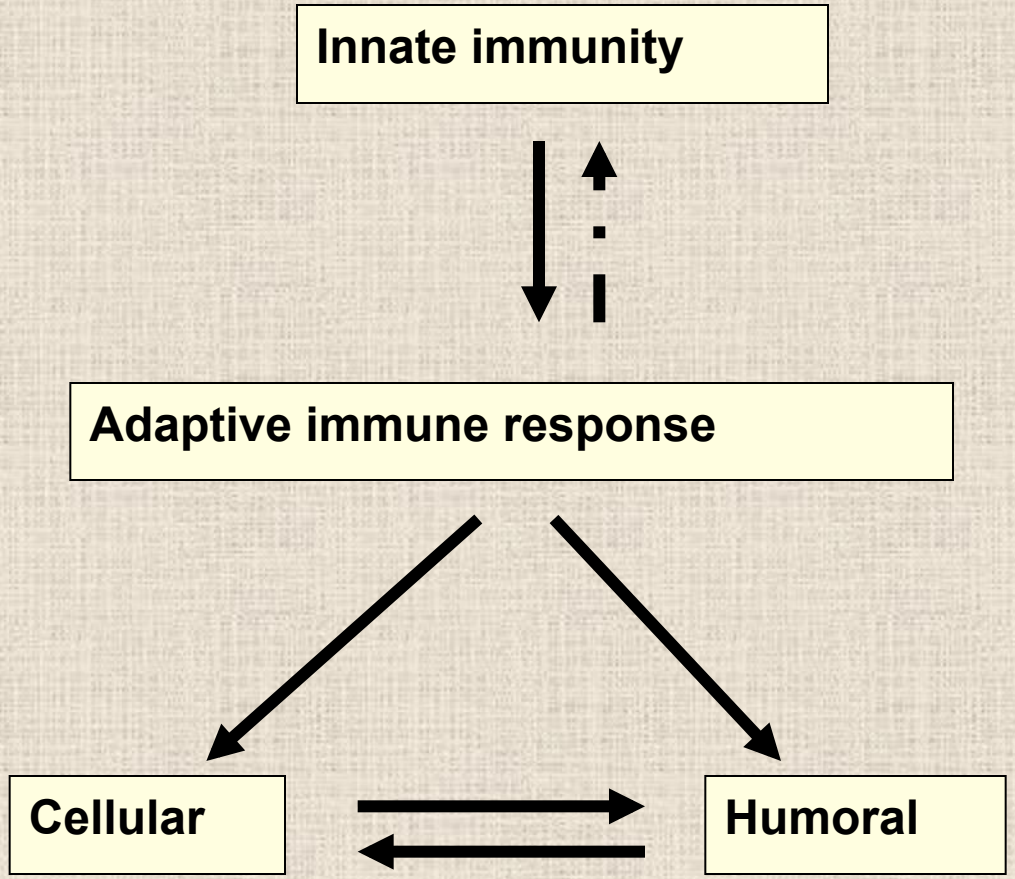
Basic Immunology
(Dentistry)

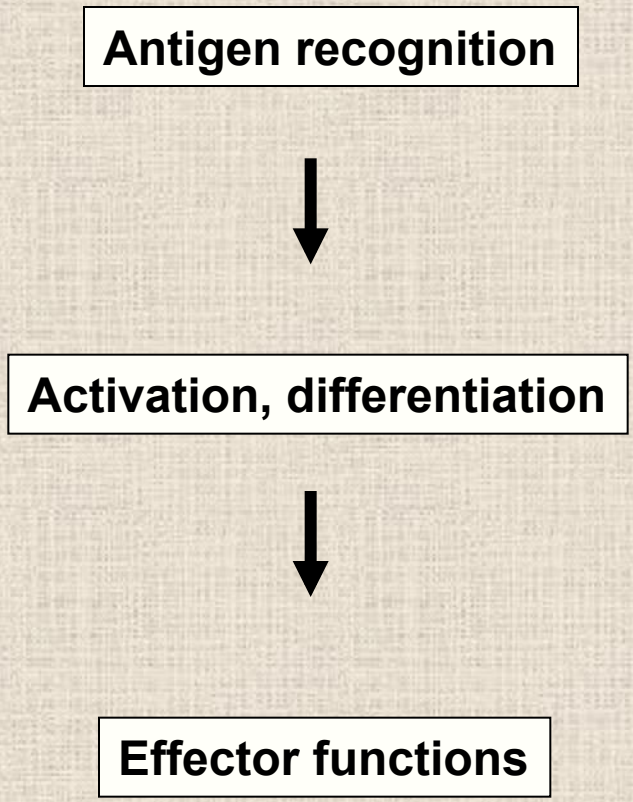
Lectures 11.-12.

Humoral immune response

Ferenc Boldizsár


Innate immunity
Adaptive immune response
Cellular
Humoral

Main stages of the adaptive immune response

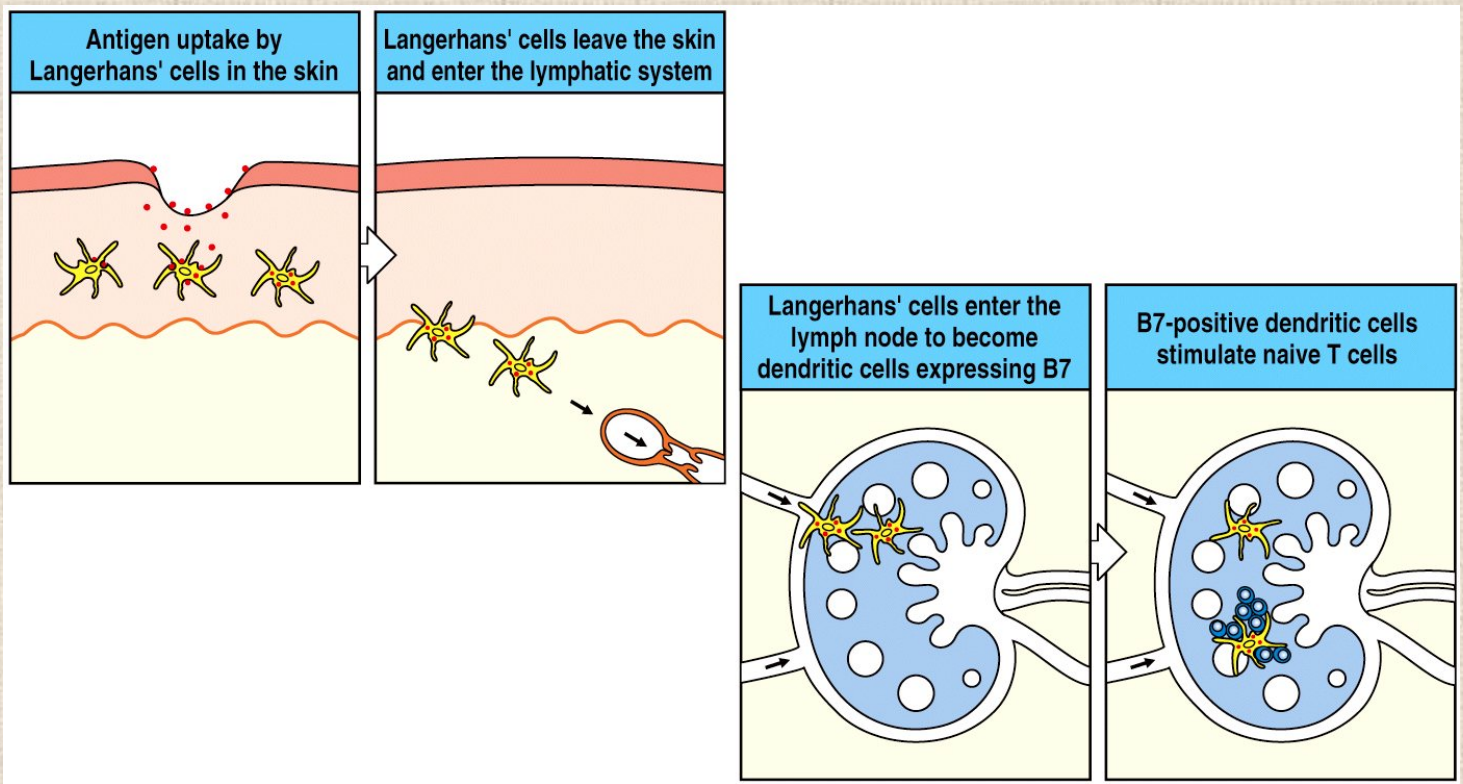


Antigen transport to the secondary lymphoid organs

DCs – 1. periphery, ag take-up, processing

2. migration to T-dependent areas of secondary lymphoid organs (through afferent lymphatics)
3. ag presented on MHC-II to T cells in secondary lymphoid organs (lymph nodes, spleen)

Native ag – lymph drainage to local lymph node or blood



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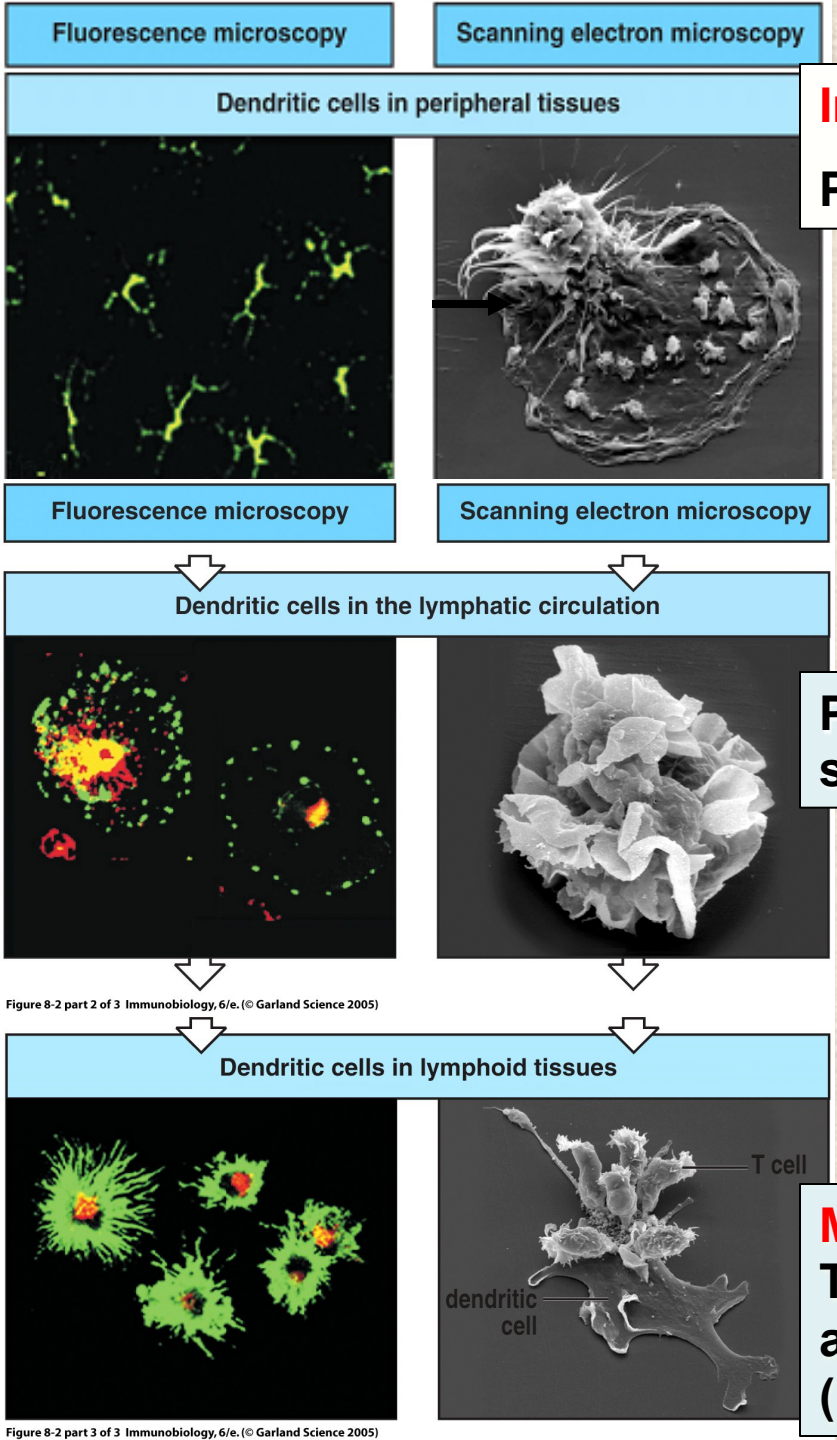
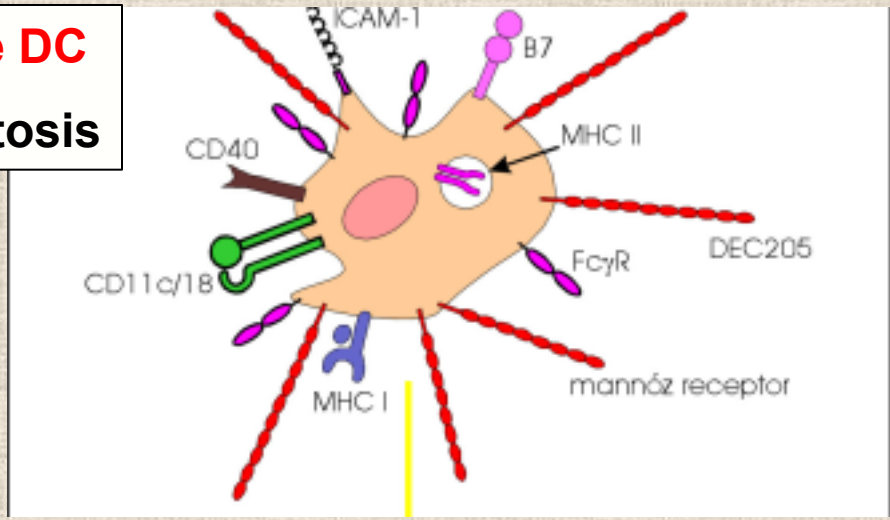


Figure 8-2 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

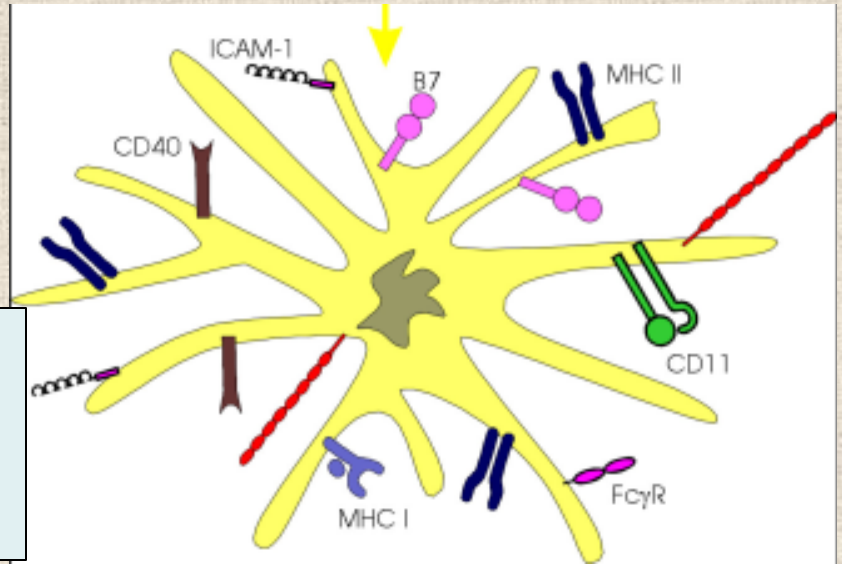
Figure 8-2 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Immature DC

Phagocytosis



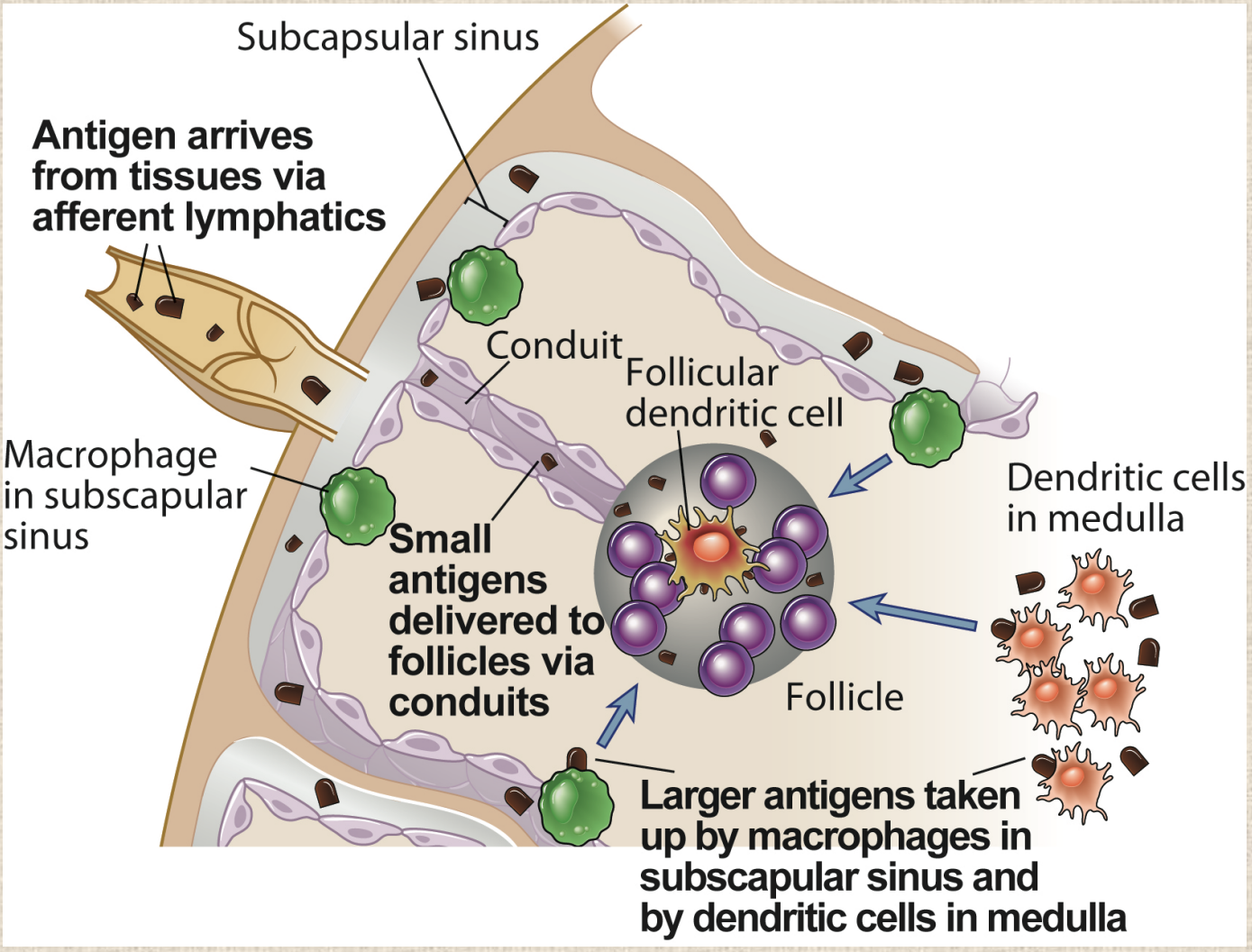
Phagocytosis stops



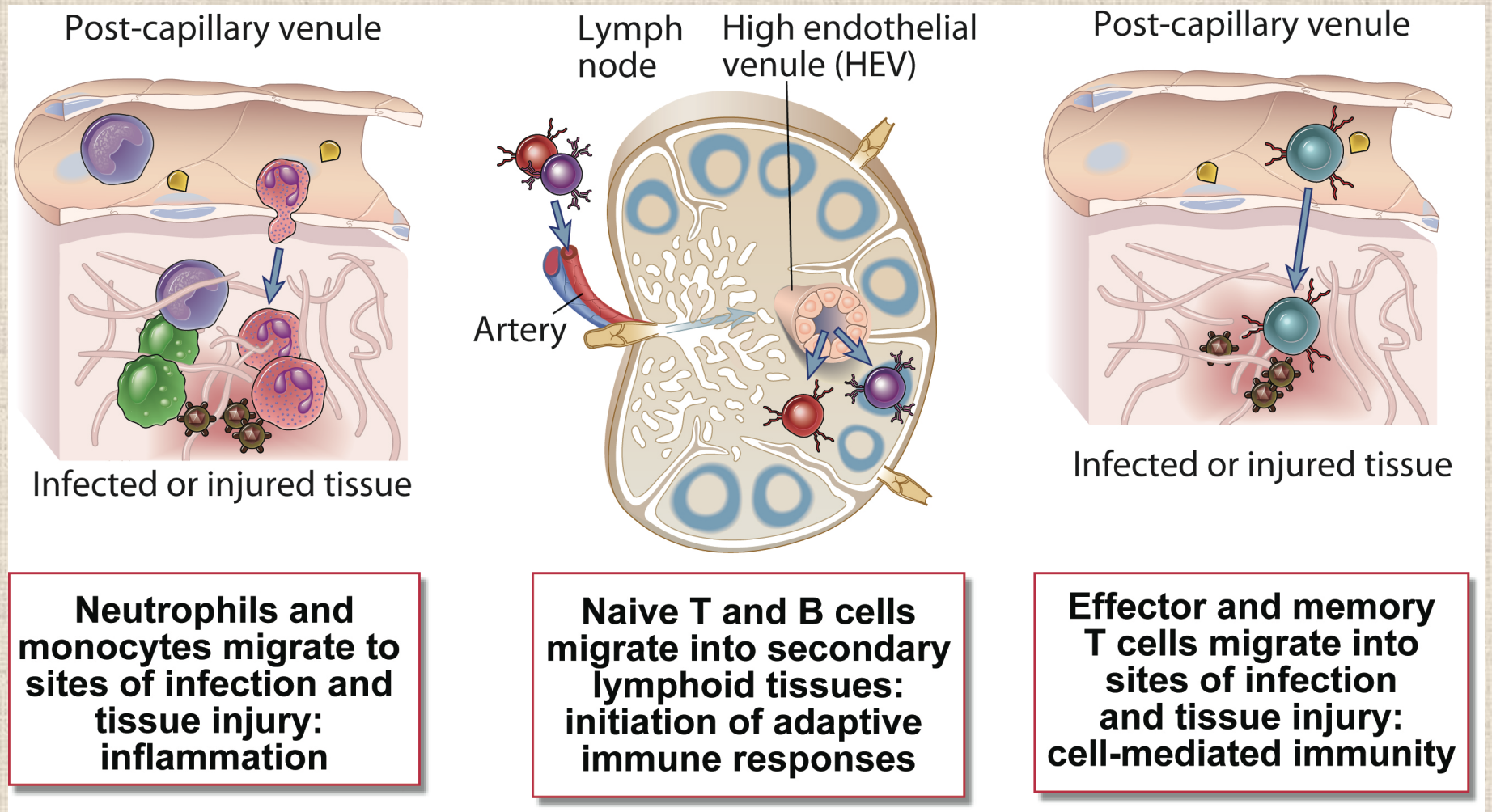
Mature DC

T cell activation (B7)

Antigen Delivery to Follicular B cells



Lymphocyte recirculation

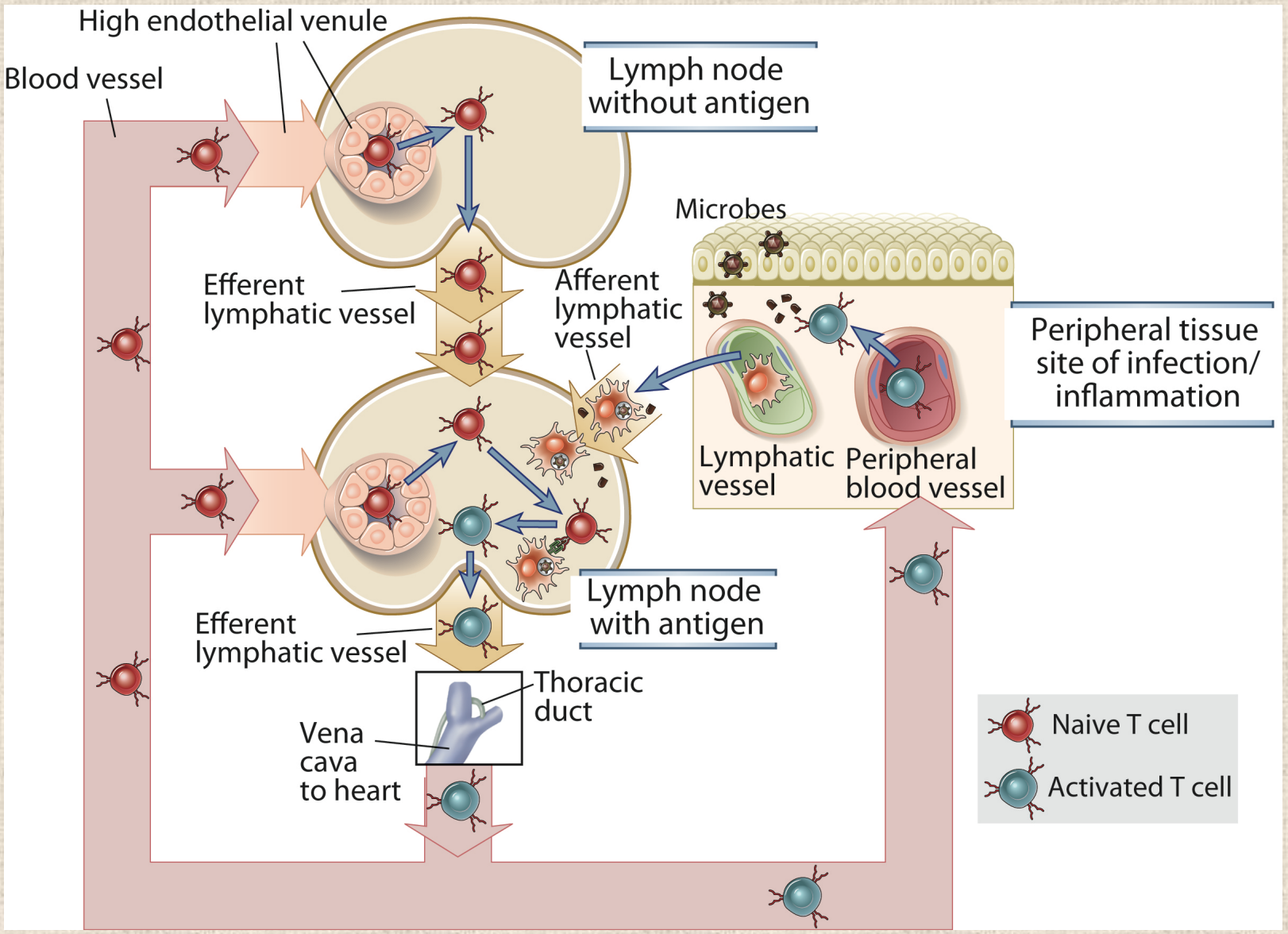


Neutrophils and monocytes migrate to sites of infection and tissue injury: inflammation

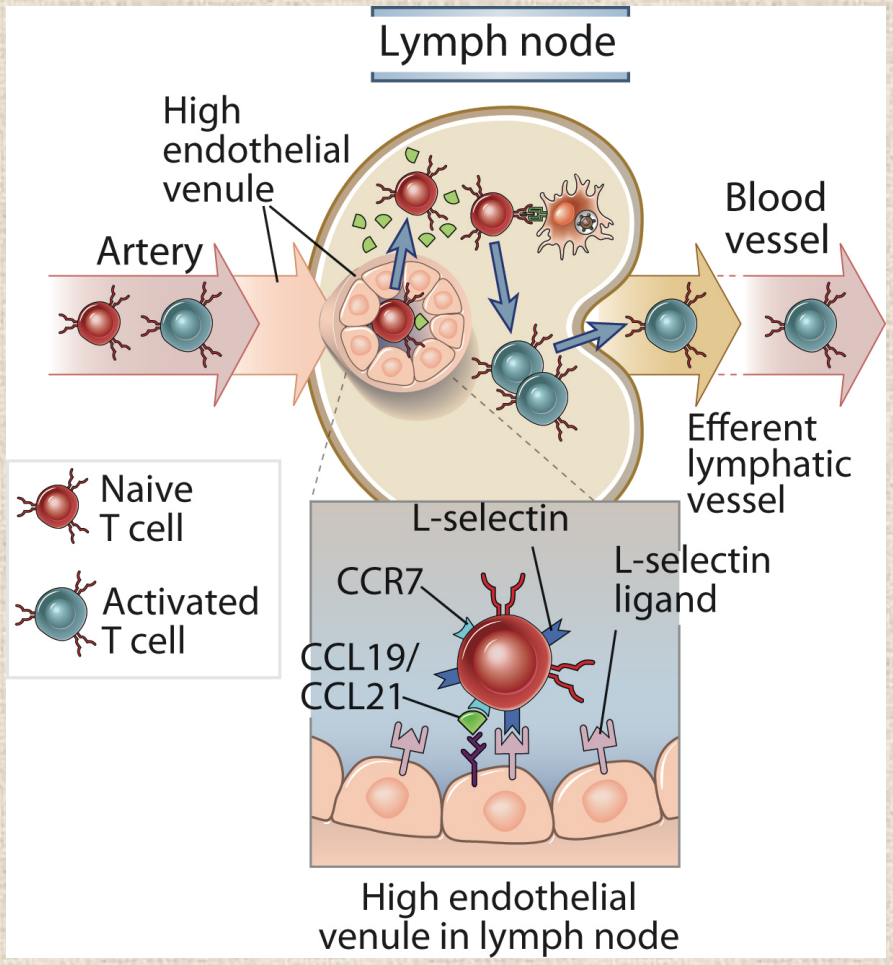
Naive T and B cells migrate into secondary lymphoid tissues: initiation of adaptive immune responses

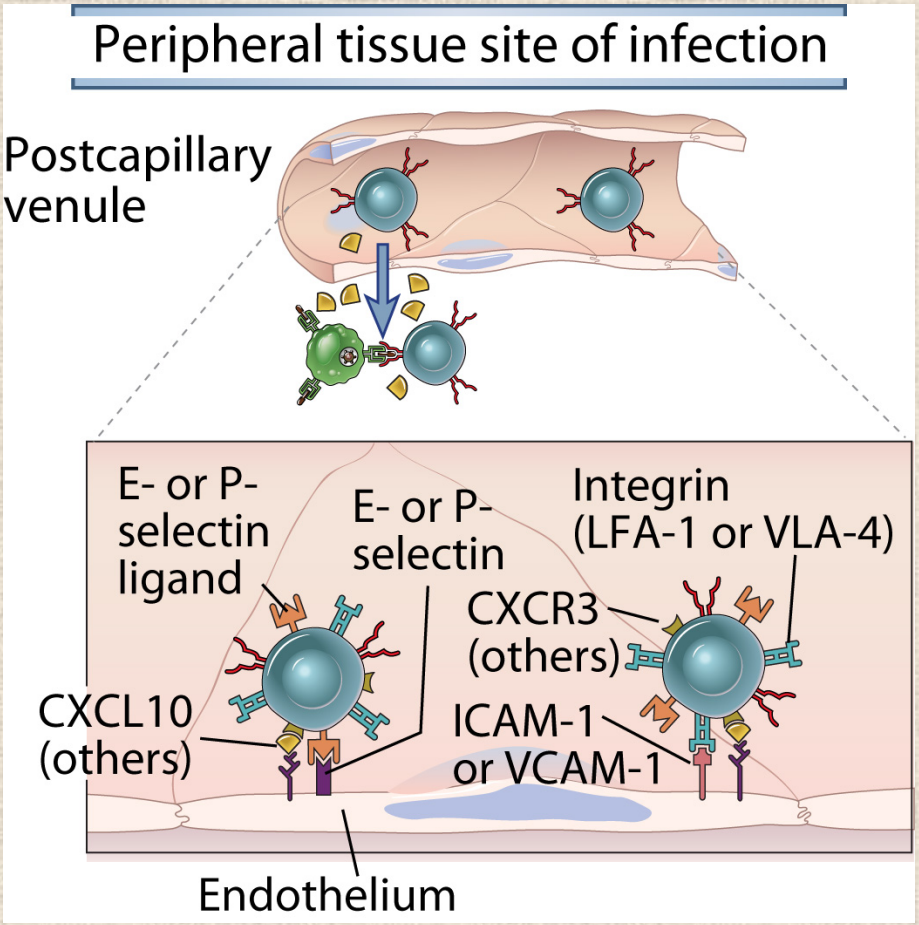
Effector and memory T cells migrate into sites of infection and tissue injury: cell-mediated immunity

T cell recirculation

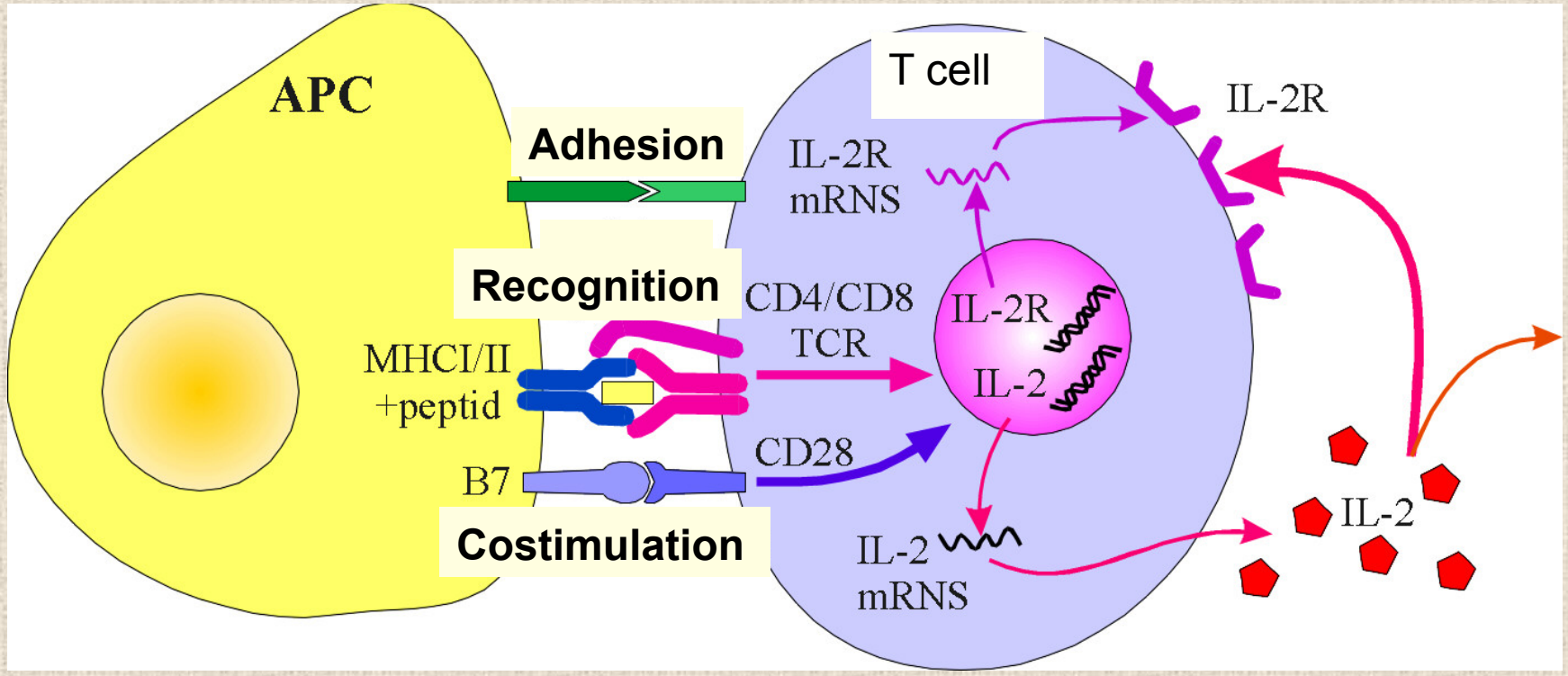


Regulation of T cell recirculation



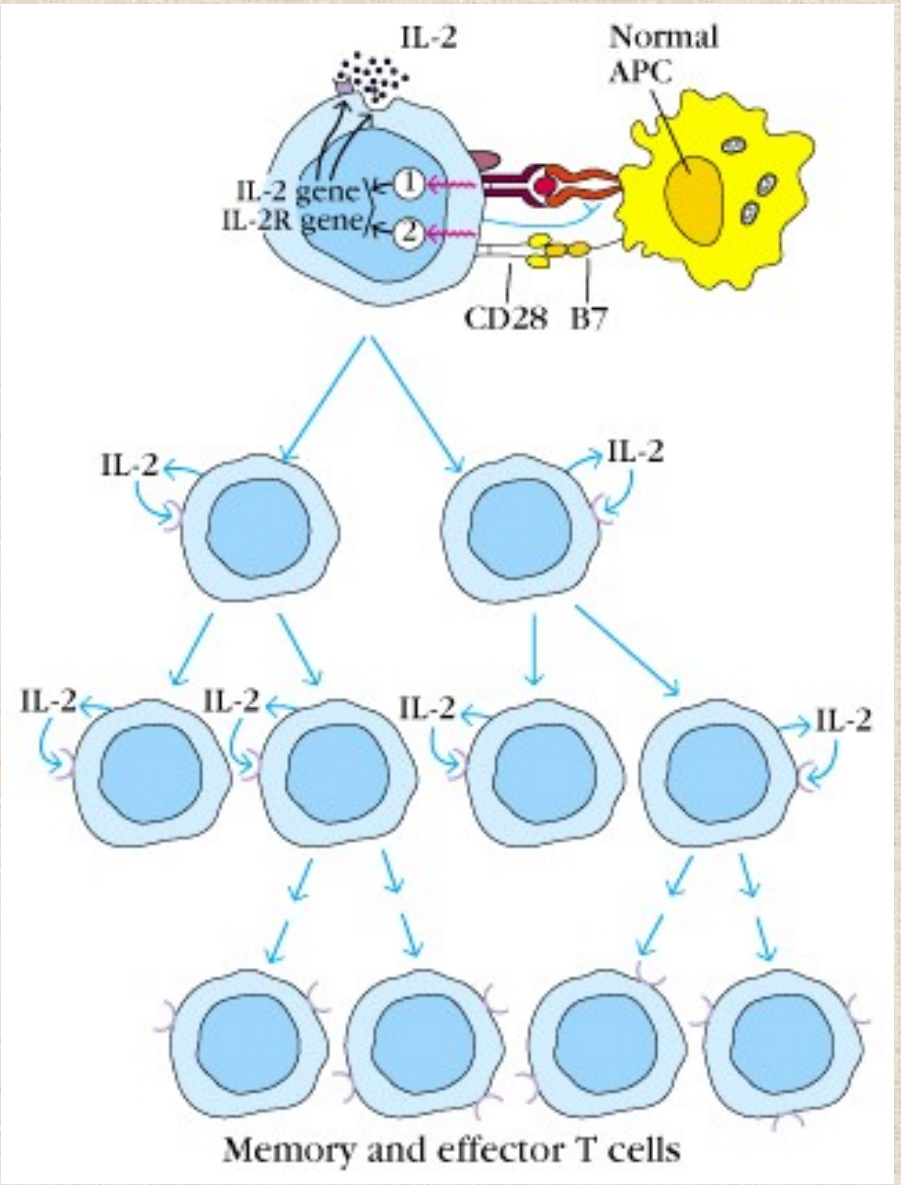


T cell activation



The first antigen recognition encounter of naïve T cells with the APC is called „***priming***”.

2 signals are necessary for T cell activation



1. signal: TCR-CD3 complex
Antigen-specific

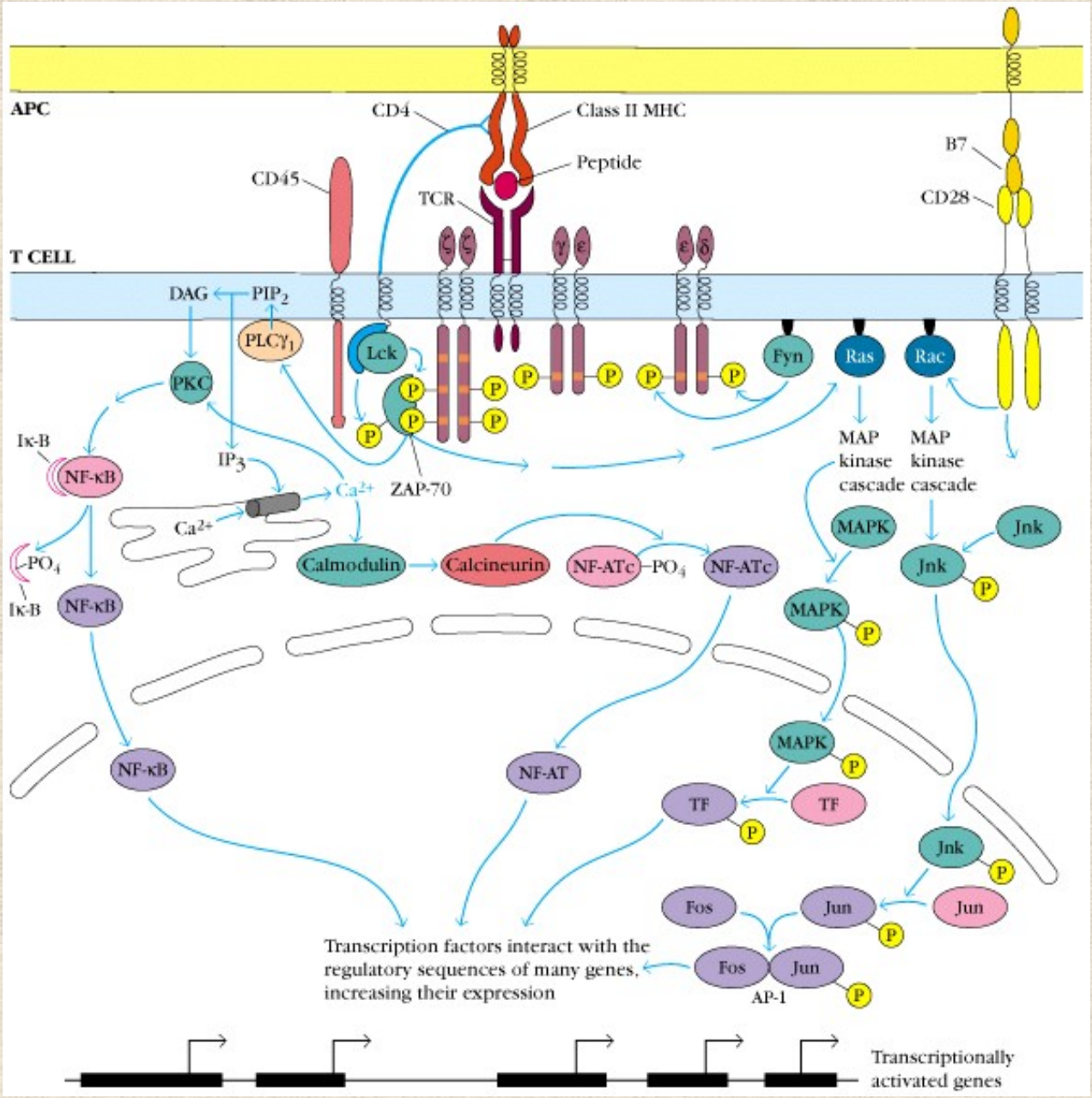
2. signal: costimulatory signal
CD28 - B7 interaction
Not antigen specific

↓

T cell differentiation and proliferation

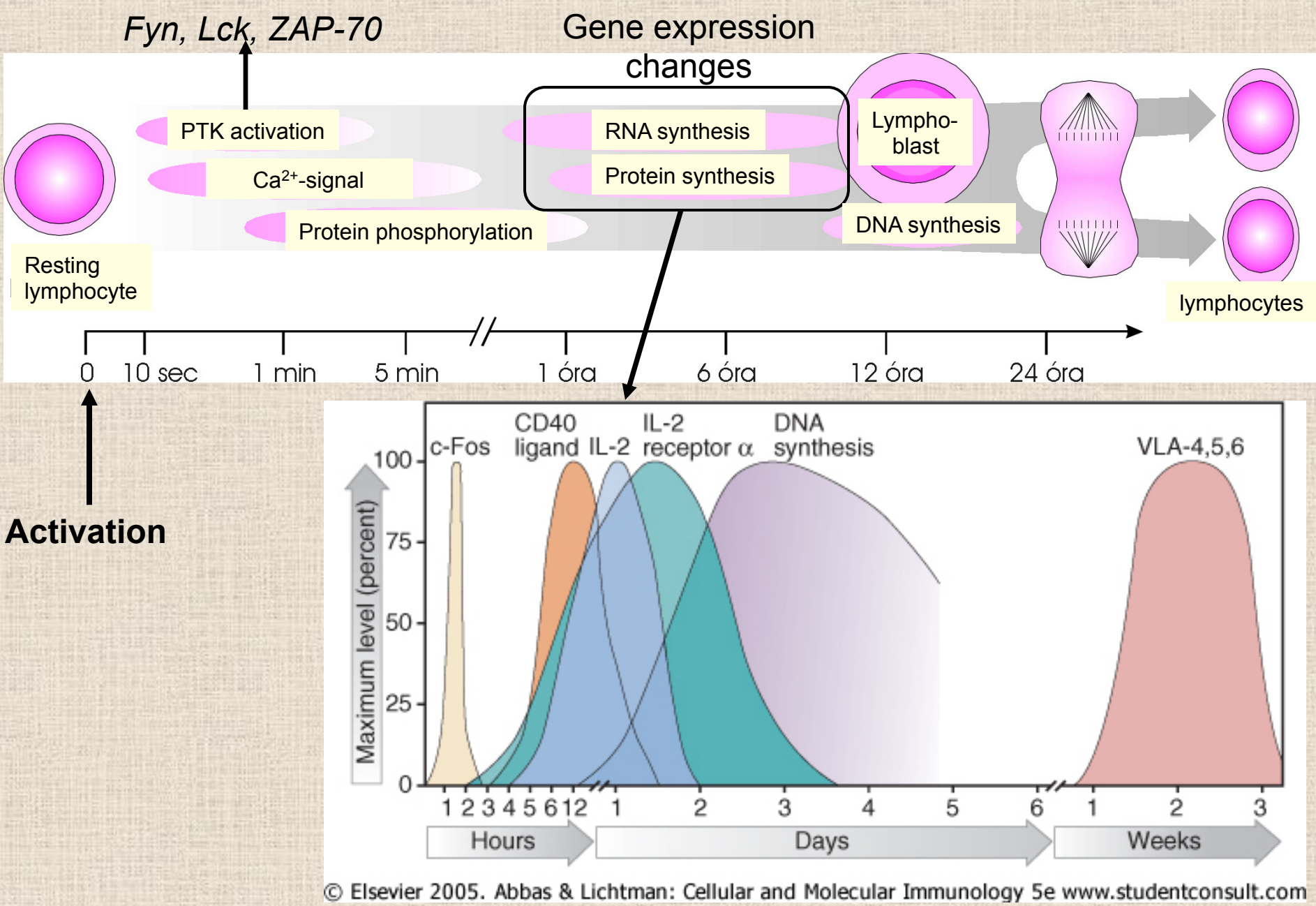
↓

Effector and memory T cells

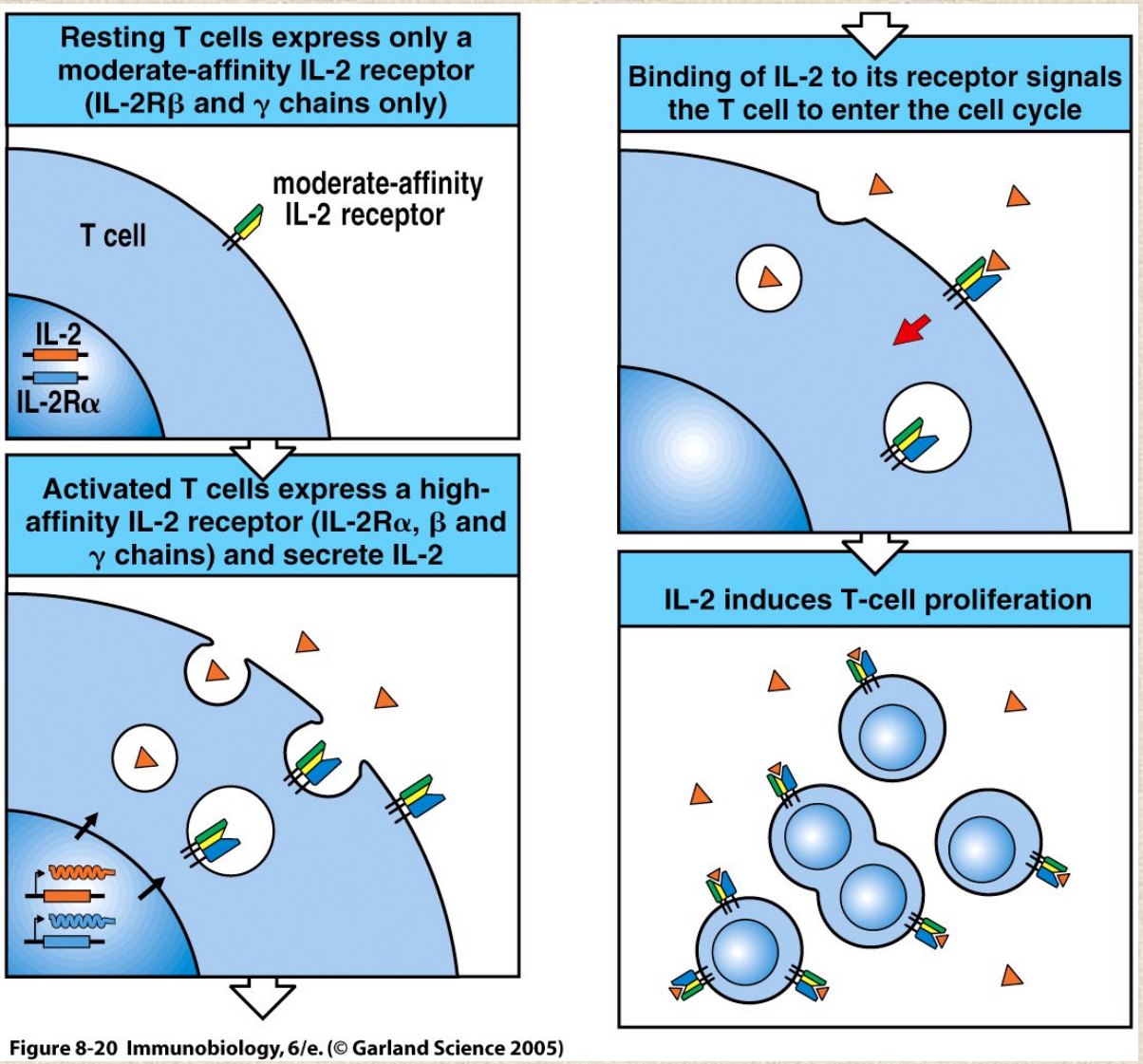


1. Antigen recognition
2. PTK activation
3. Ca^{2+} signal
4. Protein phosphorylation
5. Translocation of transcription factors
6. Gene activation

Kinetics of T cell activation



Autocrine IL-2 effect - CD25 (IL-2Rα chain)



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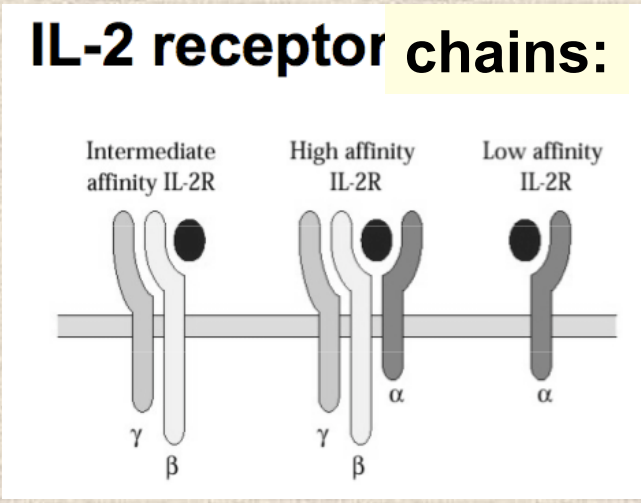
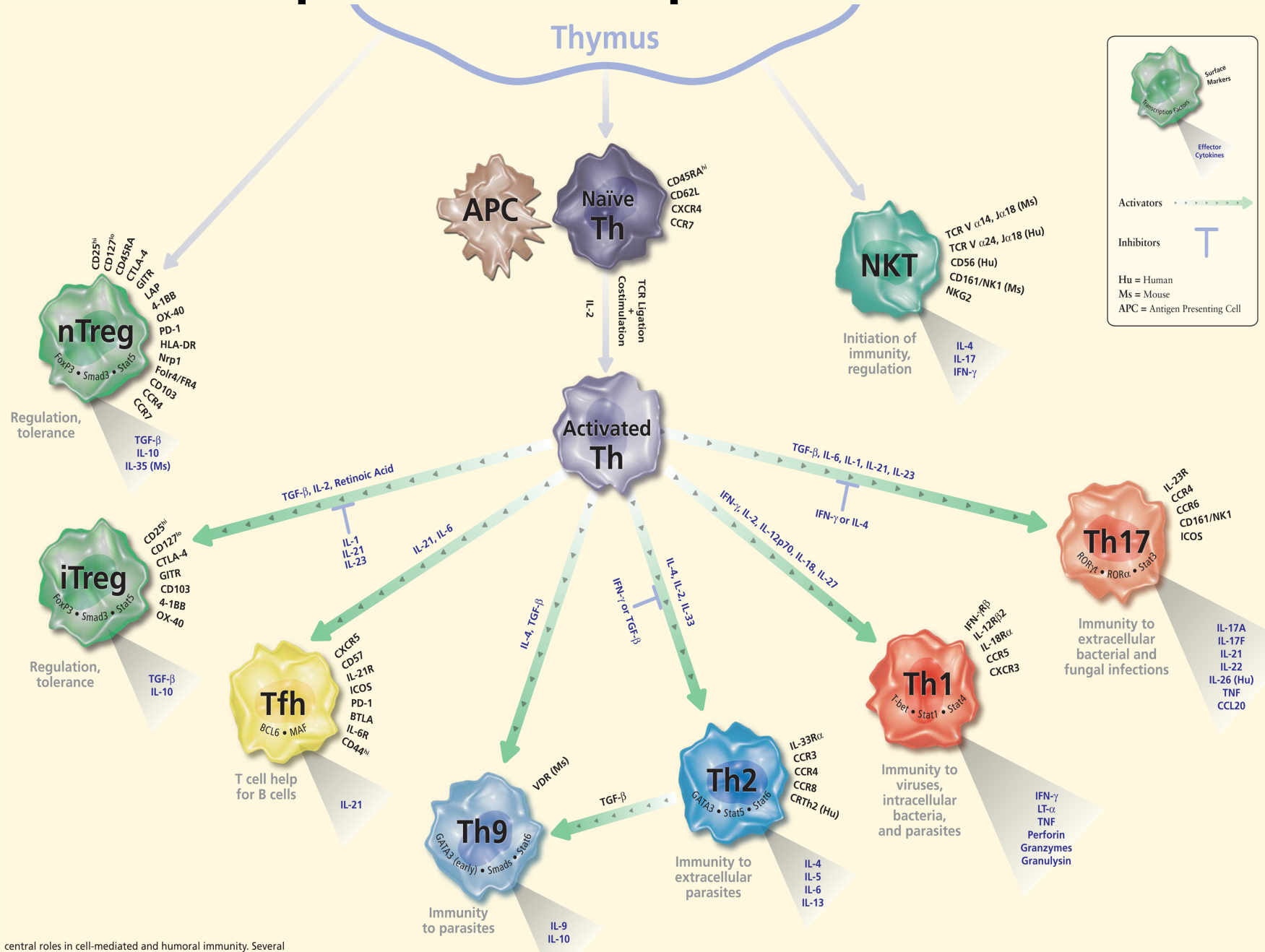


Helper T cell polarization

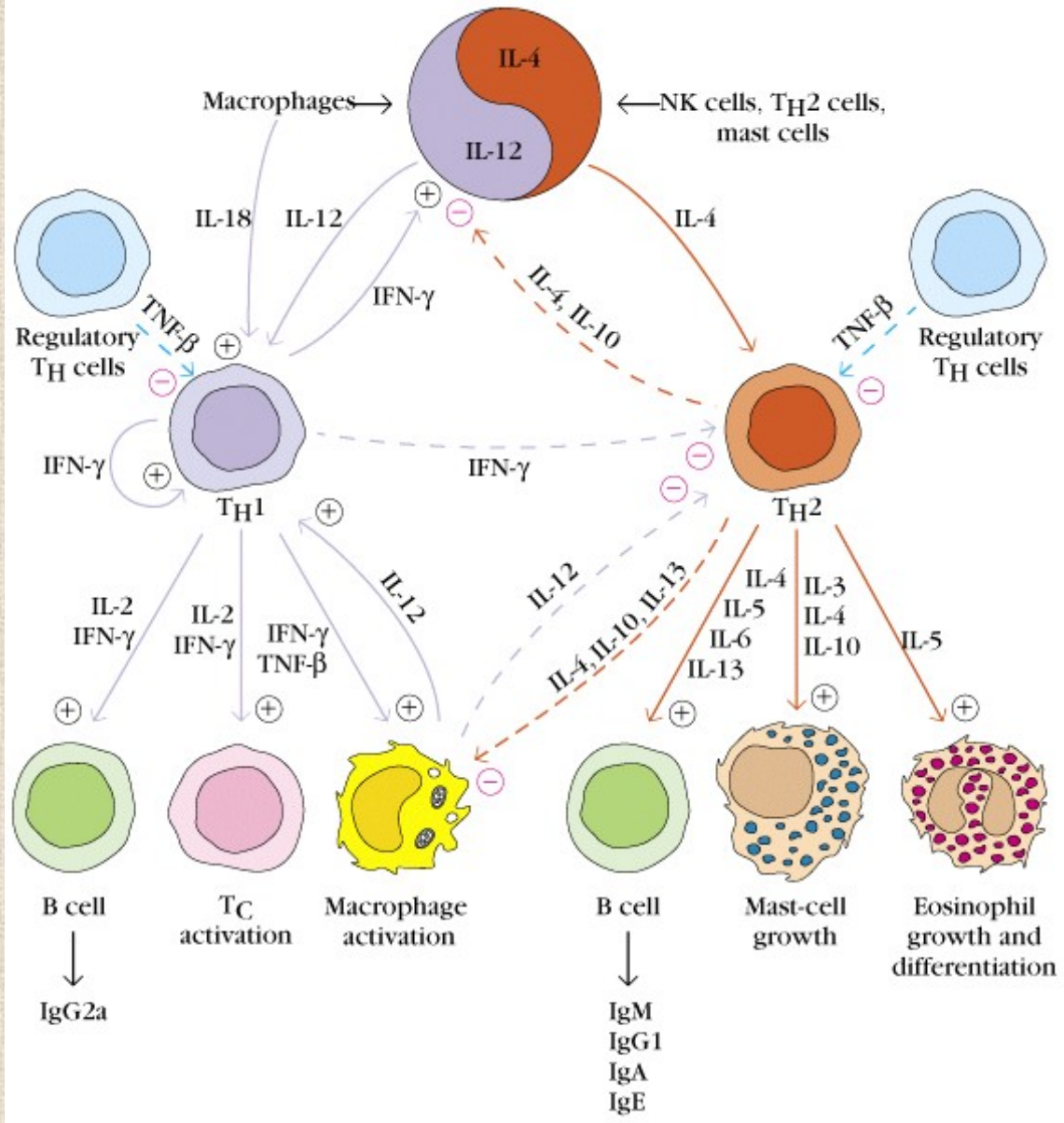


central roles in cell-mediated and humoral immunity. Several

Peripheral helper T cell differentiation

Lineage	Inducer	TF	Cytokines
Th1	IL-12 (Stat-4)	T-bet	IL-2, TNF, IFNγ
Th2	IL-4 (Stat-6)	GATA-3	IL-4,5,6,13
Th17	TGFβ, IL-6,-21,-23	RORγt	IL-17
Treg	TGFβ, IL-2	FoxP3	IL-10, TGFβ

Peripheral helper T cell differentiation



T_H1, T_H2, and T_H17 Subsets of $CD4^+$ T Cells

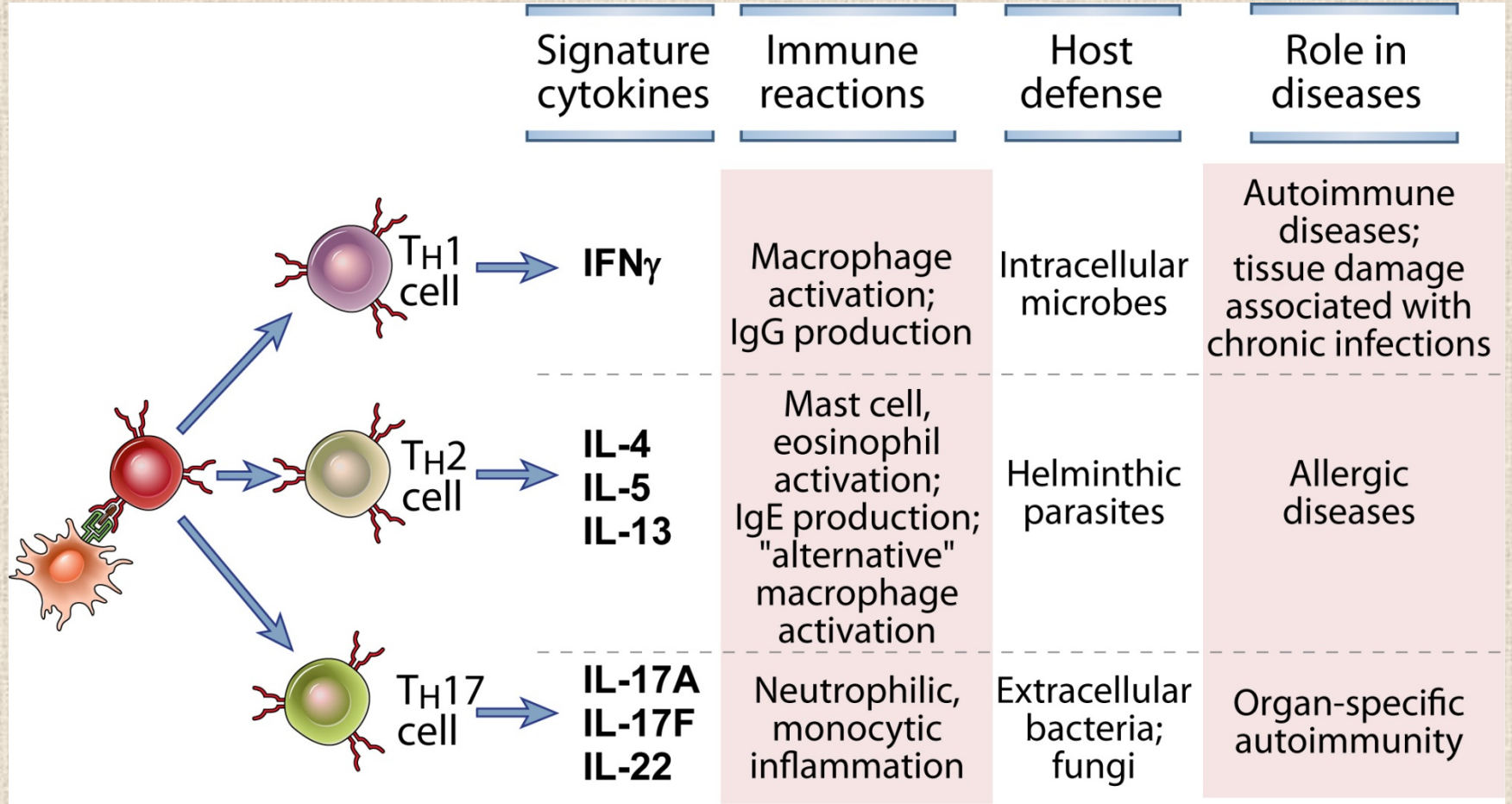
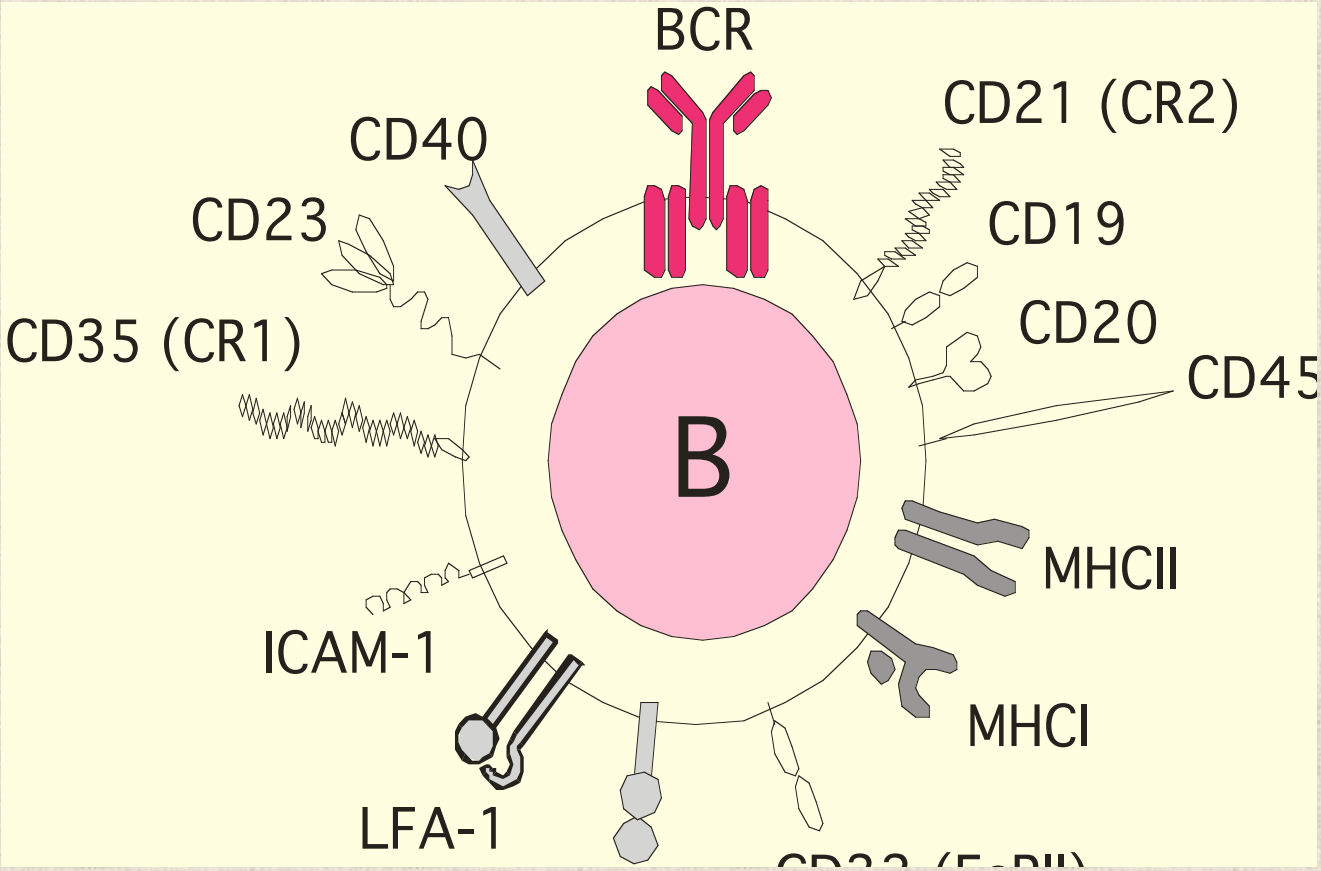


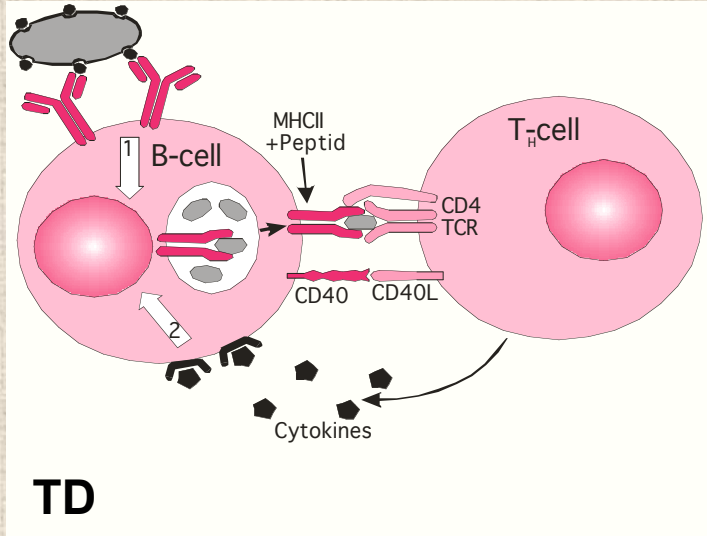
Fig. 9-13

B cell activation

Important cell surface molecules on B cells



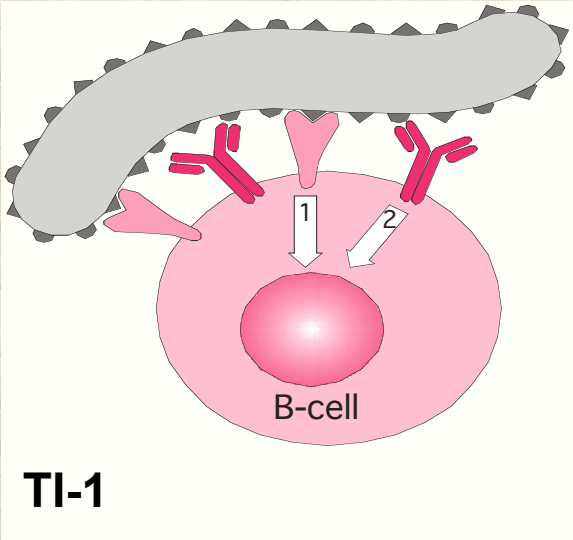
T-dependent and -independent antigens



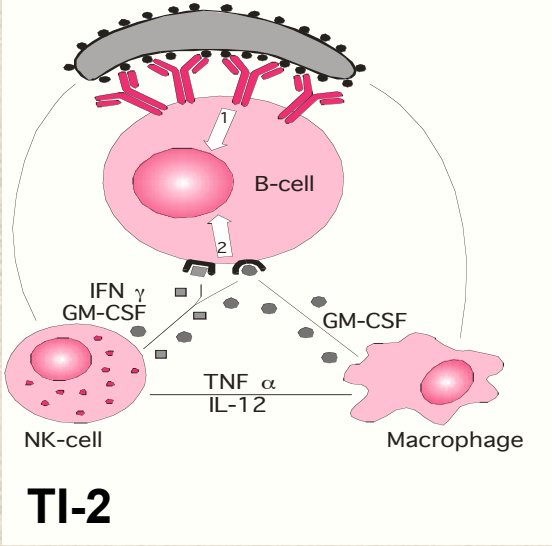
TD

T-dependent (TD):

- Protein antigens
- Response without T cells ✖
- Affinity maturation ✔
- Isotype switch ✔
- Memory cell formation ✔



TI-1

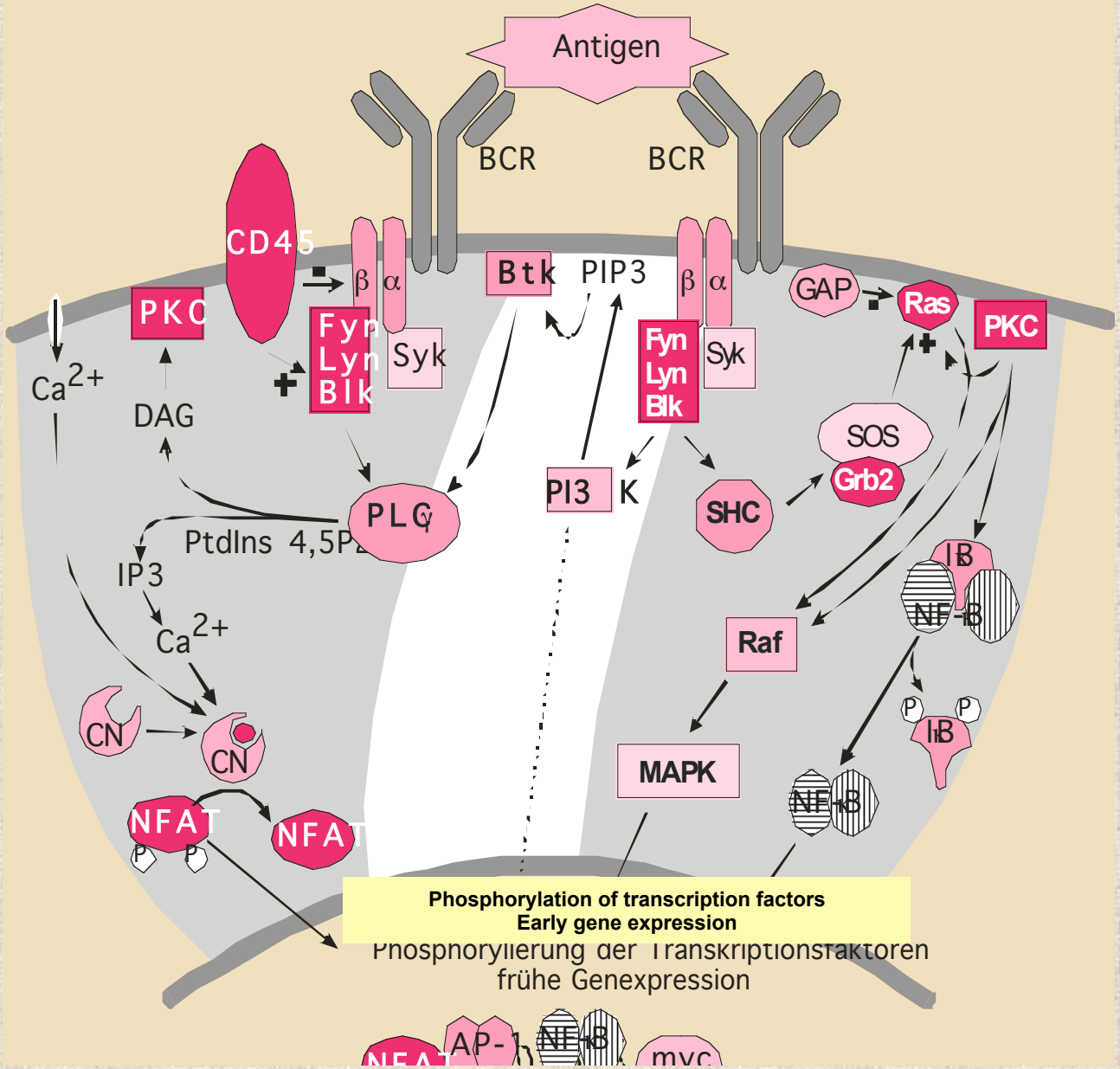


TI-2

T-independent (TI):

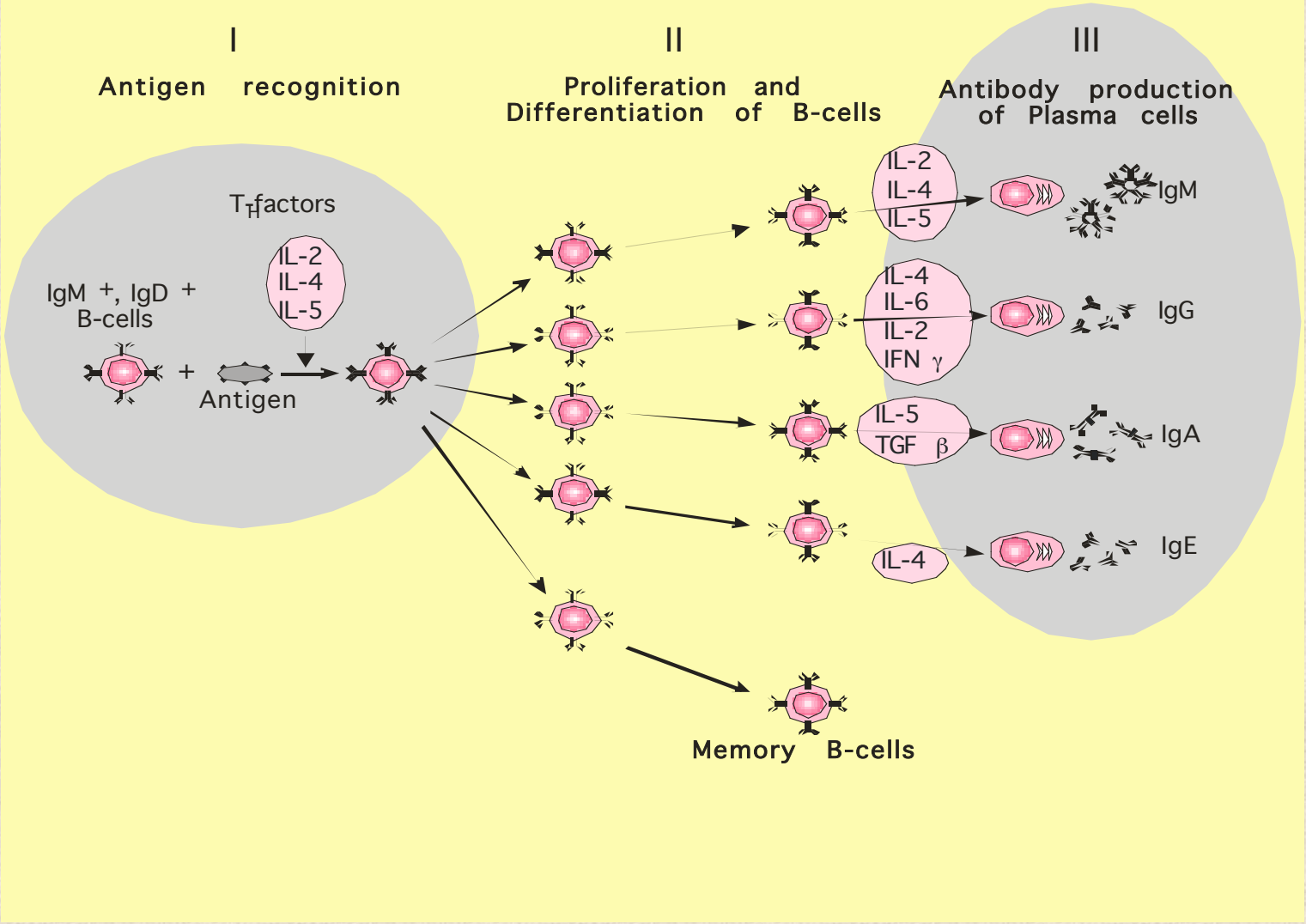
- Polimer structure
  (eg. polisacharides, lipids, nucleic acids)
- Spleen marginal zone
- Response without T cells ✔
- Affinity maturation ✖
- Isotype switch ✖
- Memory cell formation ✖

B cell receptor signaling

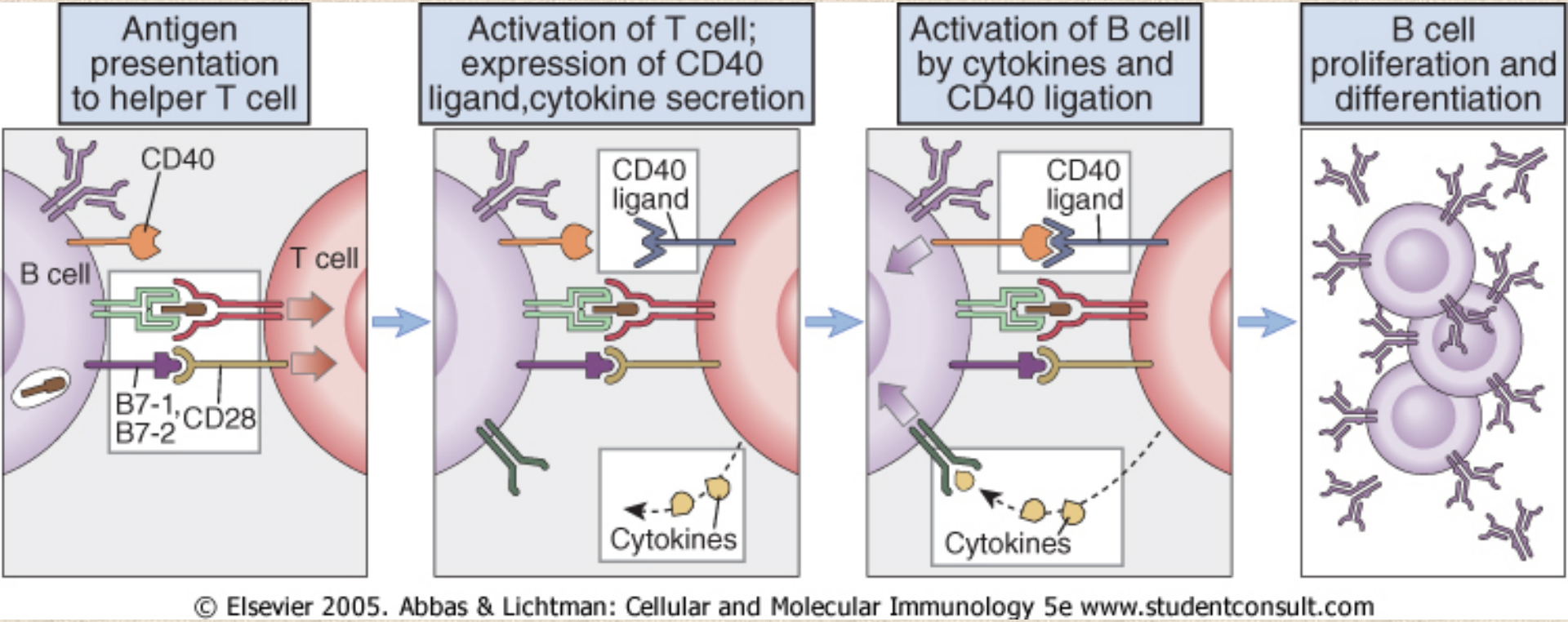


1. PTK activation
2. Ca^{2+} signal
3. Activation of transcription factors
4. Gene expression

Steps of B cell activation



T-helper cell-dependent B-cell activation



1. Activation:

- **Signal 1: BcR**
- **Signal 2: co-receptors**

2. Contact-dependent signals:

(B*) B7 – CD28 (T)
CD40 – CD40L (T*)

Cytokine receptor expression on B-cells

3. Signals derived from Th-dependent cytokines:

IL-2, IL-4, IL-5

Proliferation and differentiation

Internalization of the antigen-BcR-signal-complexes B-cells = APC

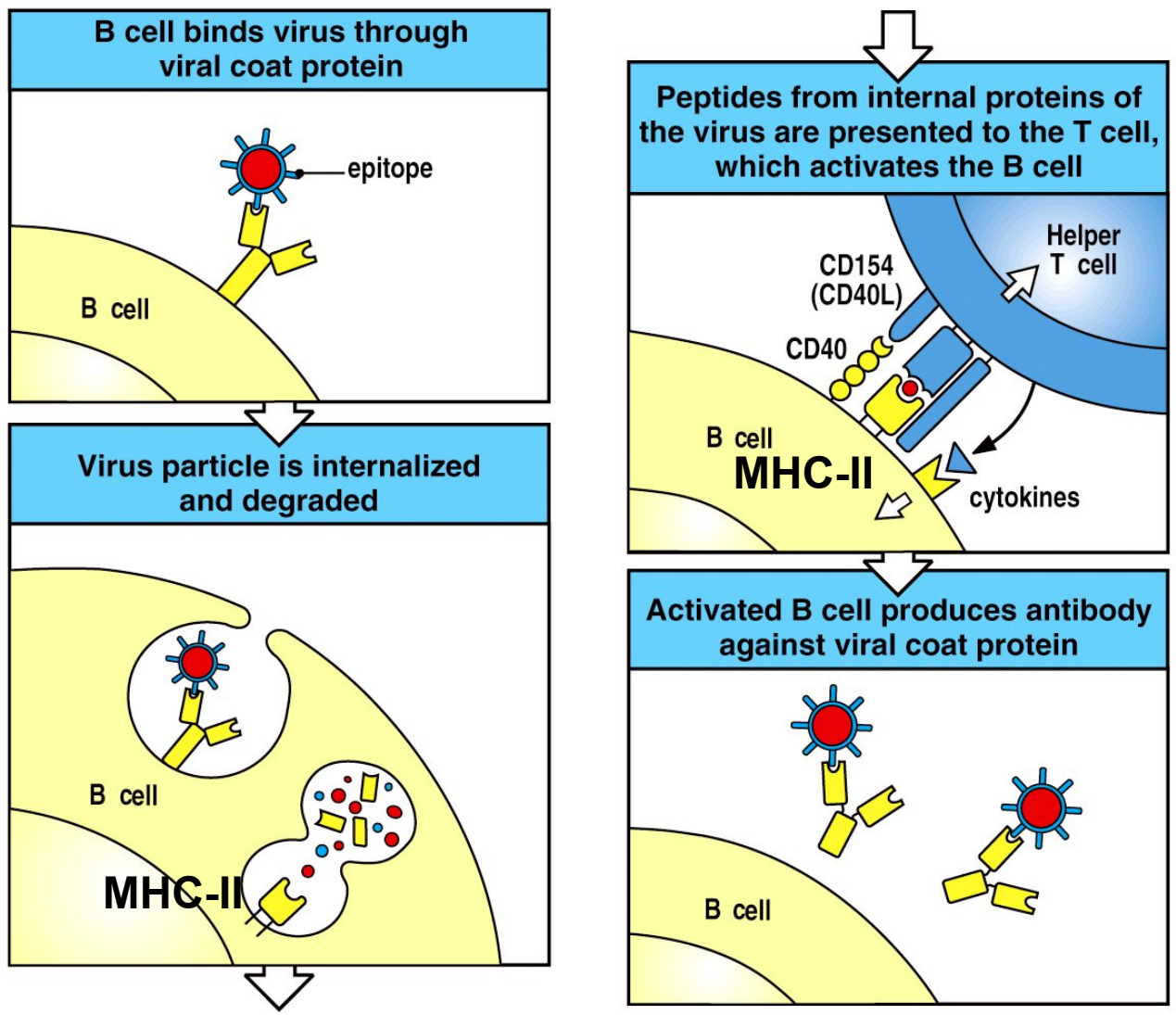
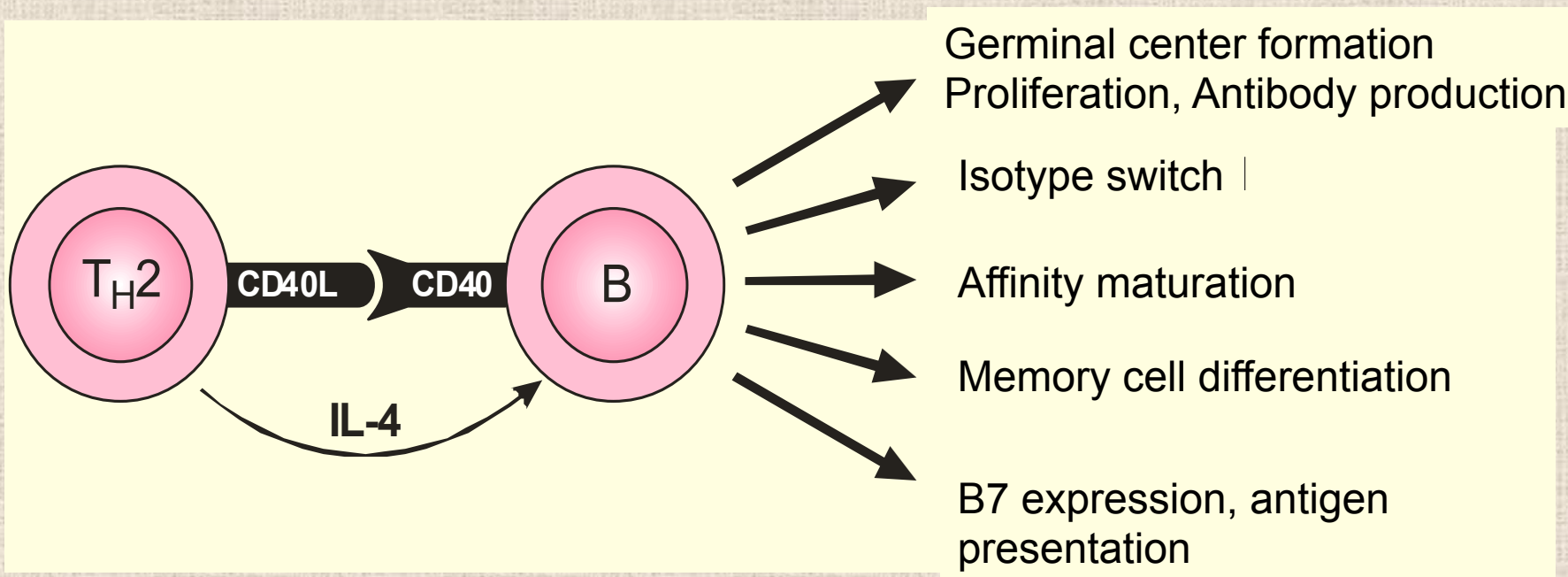


Figure 9-3 Immunobiology, 6/e. (© Garland Science 2005)

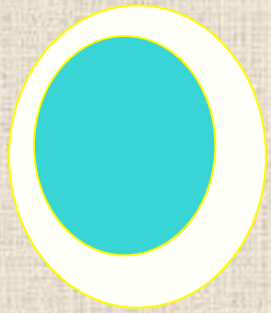
Functional consequences of CD40-CD40L interaction



Defect in CD40-CD40L interaction leads to **Hyper-IgM syndrome**

Follicular or extrafollicular differentiation:
Bcl-6 / Blimp-1 ratio

border of T/B zone



activated B cell

Follicular:
(Germinal center reaction)

Bcl-6 ↑ : Blimp-1 inhibition

PAX-5: XBP-1 inhibition

Result: Centroblast

Extrafollicular:
(Primary focus formation)

Blimp-1 ↑: PAX-5 inhibition

Result: Plasmoblast

Primary focus= Extrafollicular-reaction

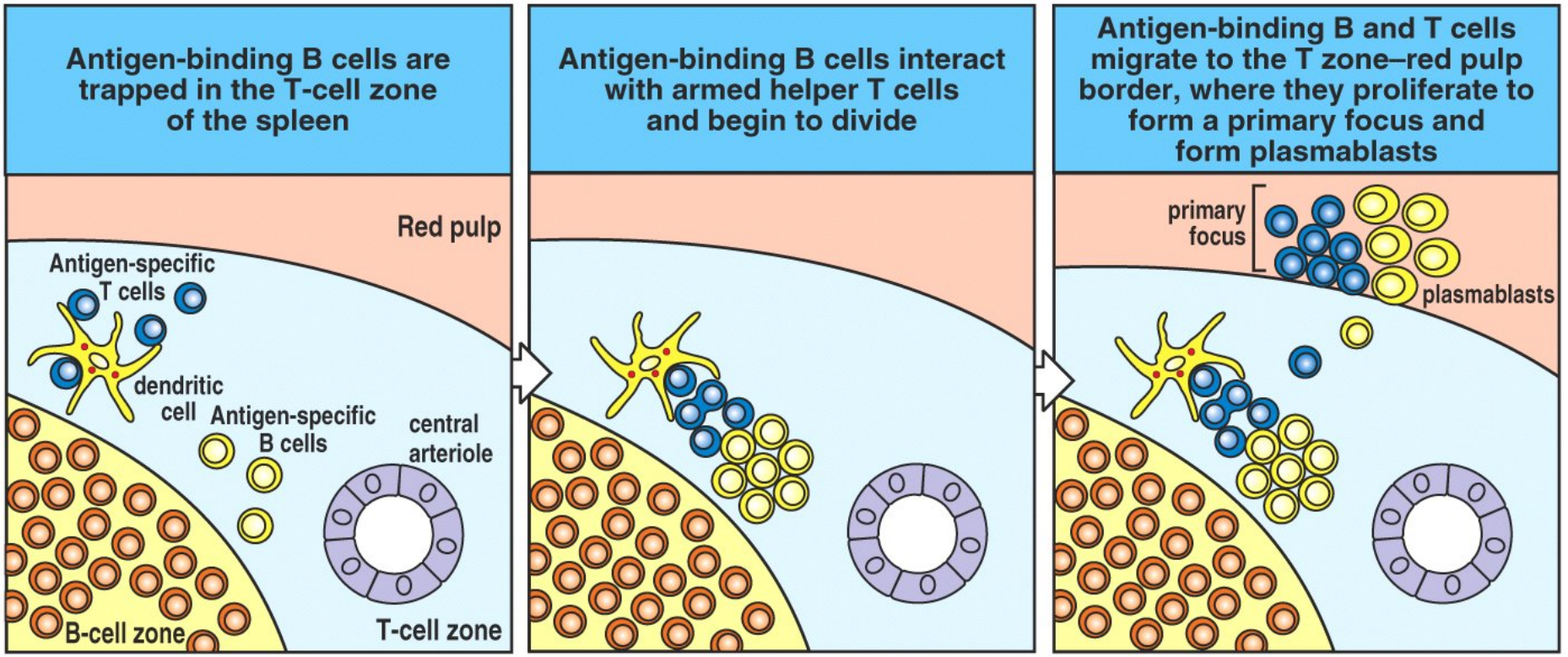
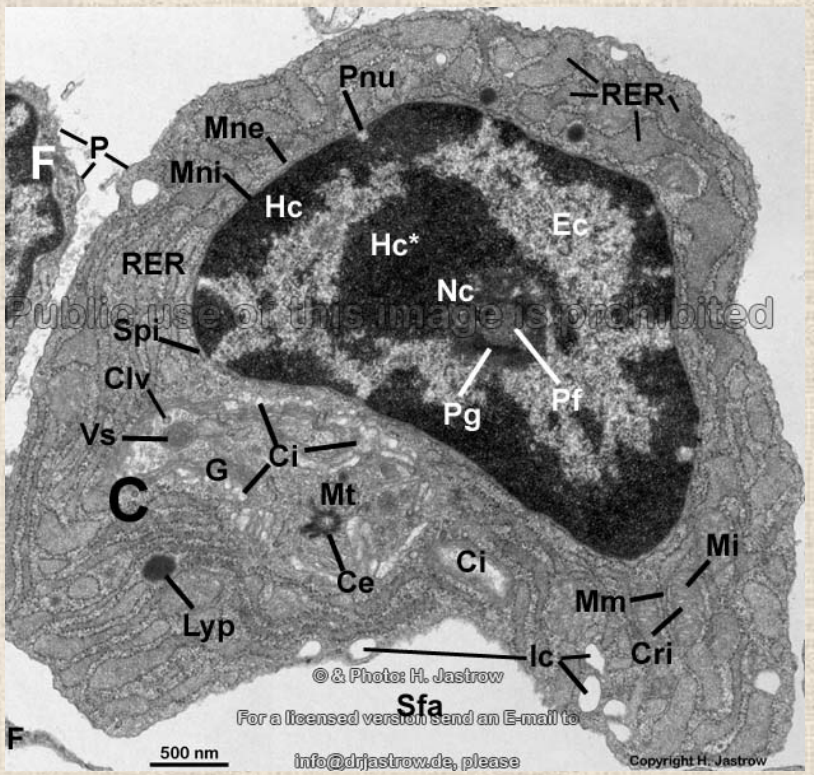


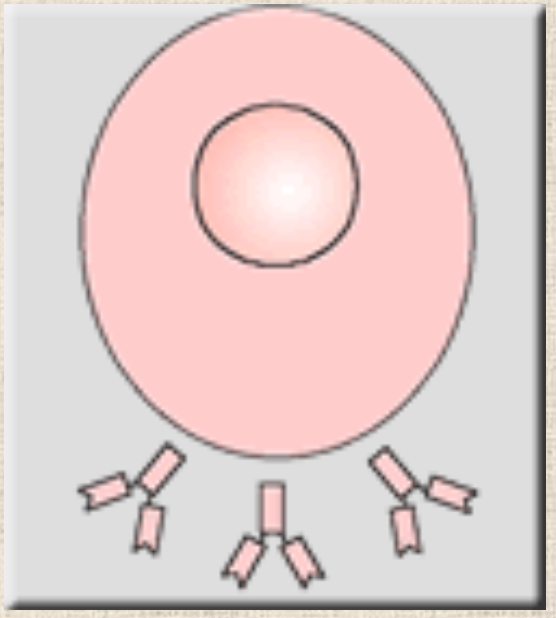
Figure 9-9 Immunobiology, 6/e. (© Garland Science 2005)

Spleen – marginal Zone binding channels =
T cell-zone/red pulp border

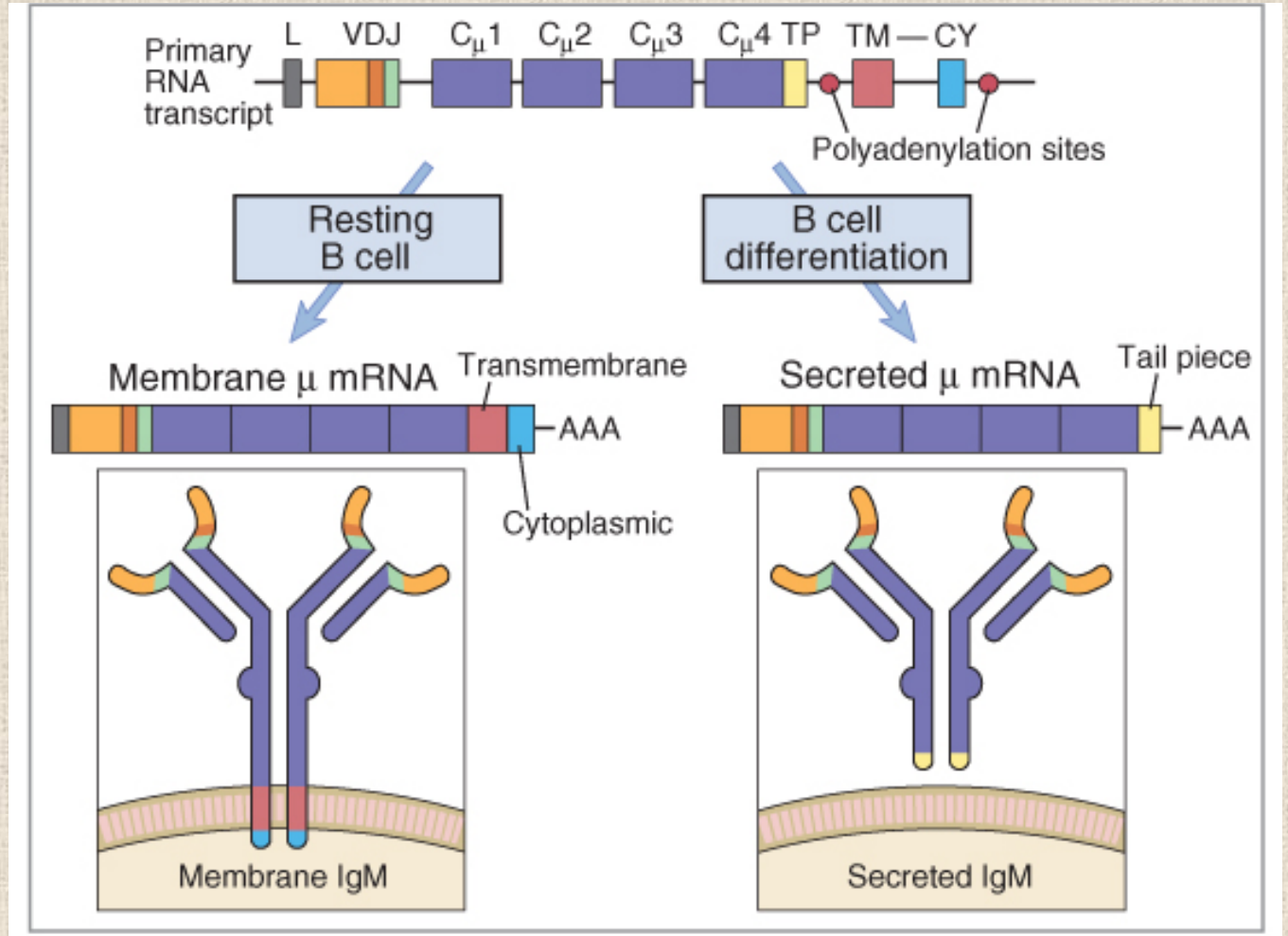
Lymphnodes – parafollicular regions
→ **short-lived IgM-secreting plasmacells**
→ **first defense against the antigen**

Plasma cells are the final differentiation forms of the B cells





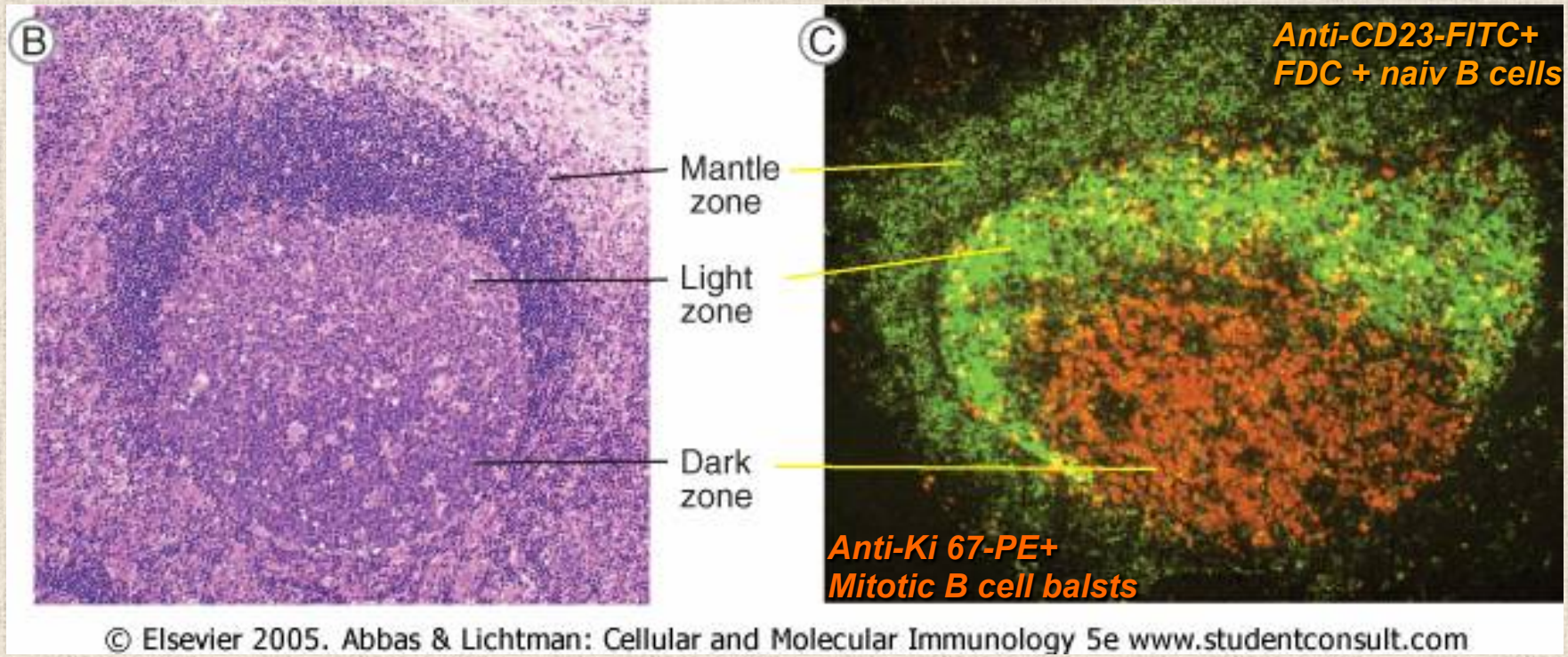
Plasma cells secrete Ig



Germinal center (GC) reaction

- proliferating B cells (centroblasts, centrocytes), ~10 % T cells, follicular dendritic cells (FDC)
- Proliferation
- Affinity maturation − somatic hypermutation – V-Genes
- Isotype switch – H C-Gene

Secondary follicle with GC



Dark zone: centroblasts → intensive proliferation – **somatic hypermutation**

Light zone: centrocytes → decreased proliferation – **affinity maturation**

Germinal center 1.

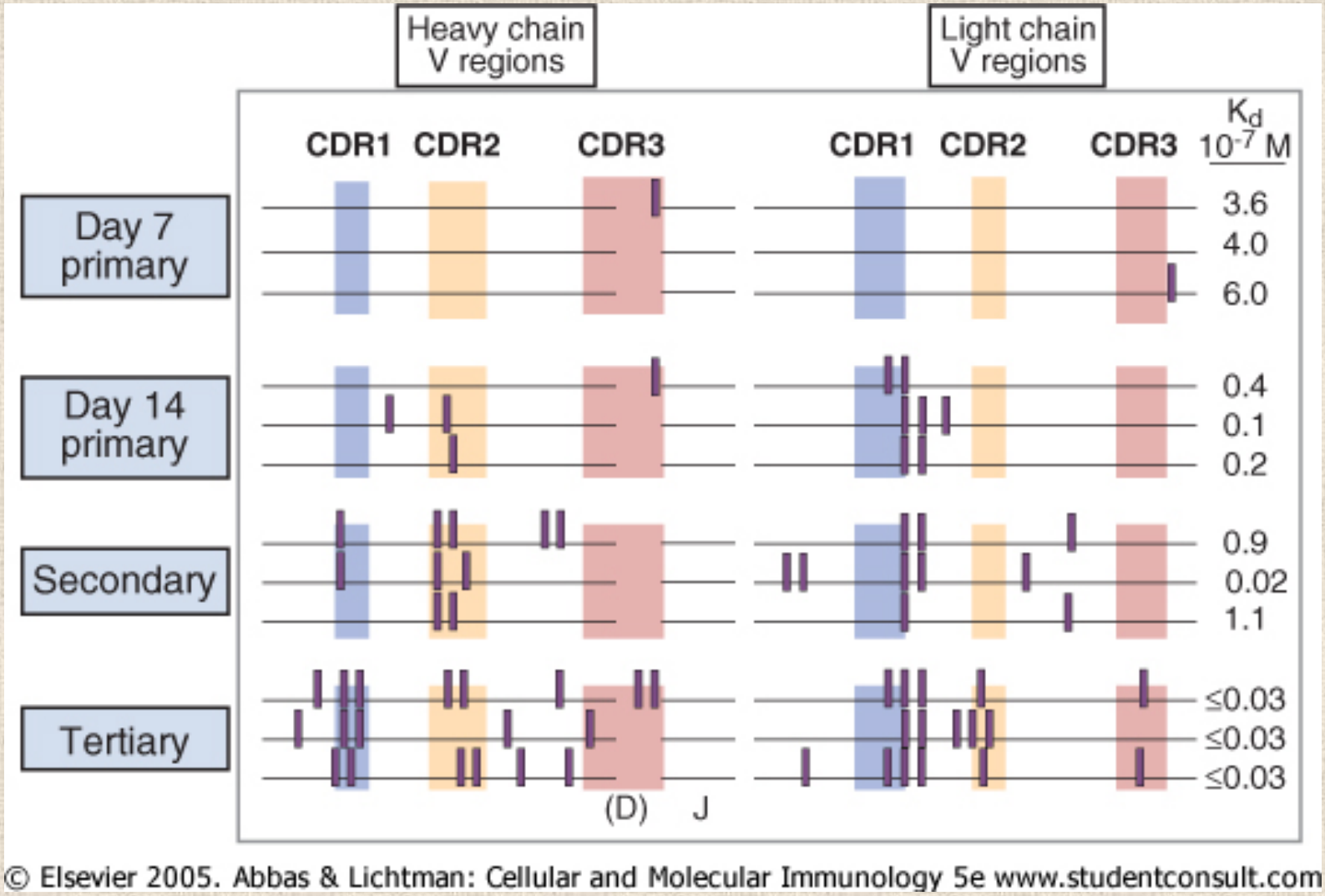
Dark zone: centroblasts

- Intensive proliferation (6-8 hours)
- cell surface-Ig ↓
- somatic hypermutation – V-region gene pointmutations - 1/1000 base / division

  ⟶ changes in some amino acids in the hypervariable region

  ⟶ changes in BcR affinity

Point mutations in the V region of the Ig-gene = somatic hypermutation



Germinal center 2.
Affinity maturation

Light zone: centrocytes

- **Division ↓**
- **cell surface-Ig ↑**
- **FDC, Th**
- **Affinity maturation: Selection of the centrocytes based on their BcR affinity (Ag on FDC)**

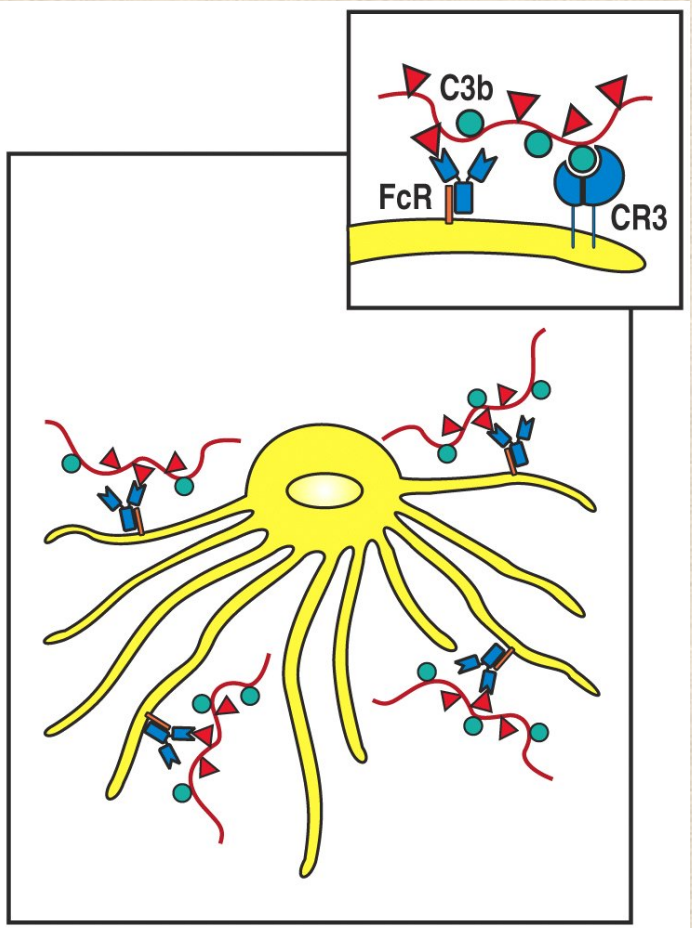
  high affinity – survival

  low affinity – apoptosis

Result:

The average affinity of the BcR increases on the surviving centrocytes.

Follicular dendritic cells 1.



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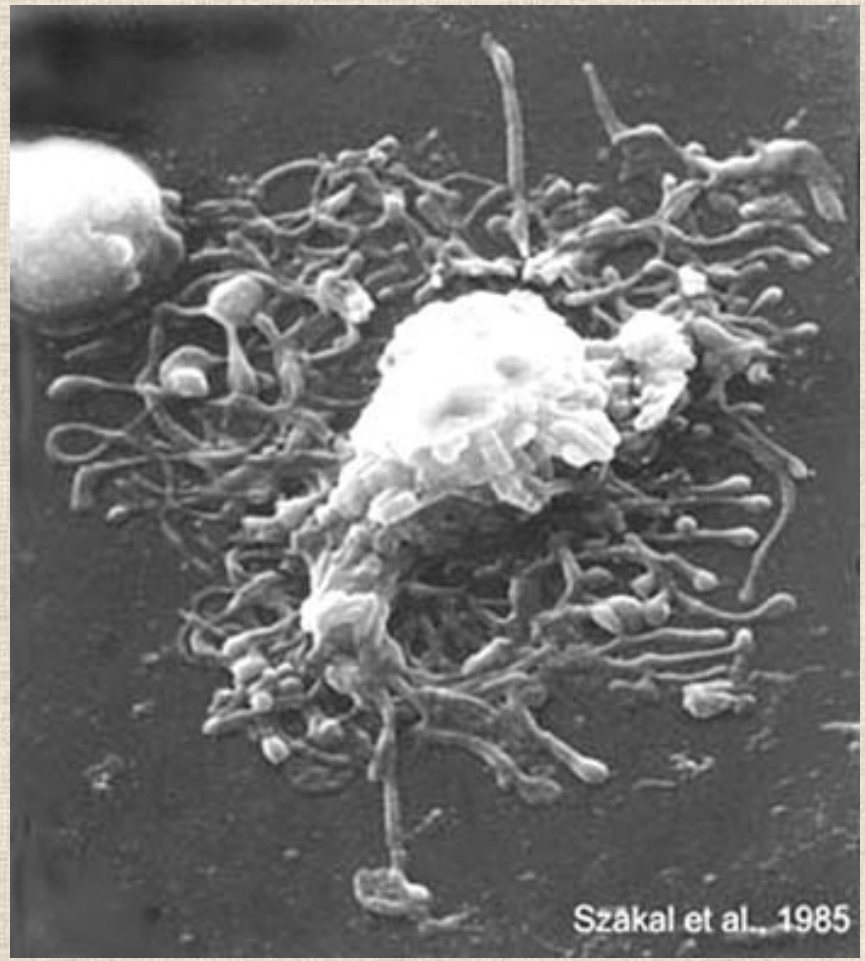


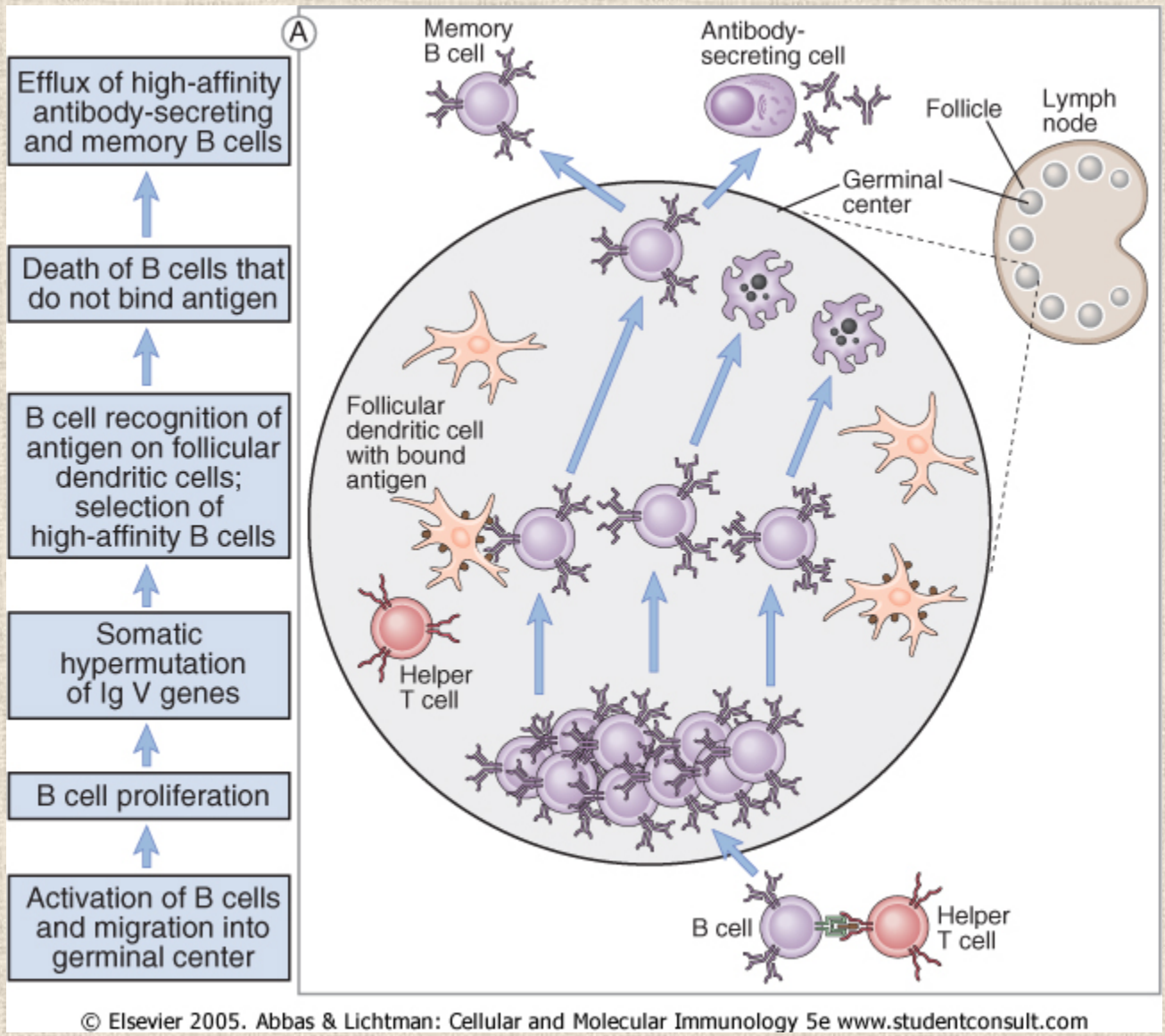
Follicular dendritic cells 2.

- Uncertain origin *(hematopoetic or mesenchymal)*
- not-phagocytic, not-adherent
- Phenotype markers: CD21/35, FcγR, inducible VCAM-1
- CXCL13 production → B cell attraction

Function:

- long term storage of antigens in the form of immuncomplexes *(Antibody/Complement) – ICCOSOME – C*entrocytes
- cellular mediator of B cell-selection in the germinal center
- immunological memory

B cell selection in the germinal center



Isotype switch

= C-Gene of the heavy chain changes

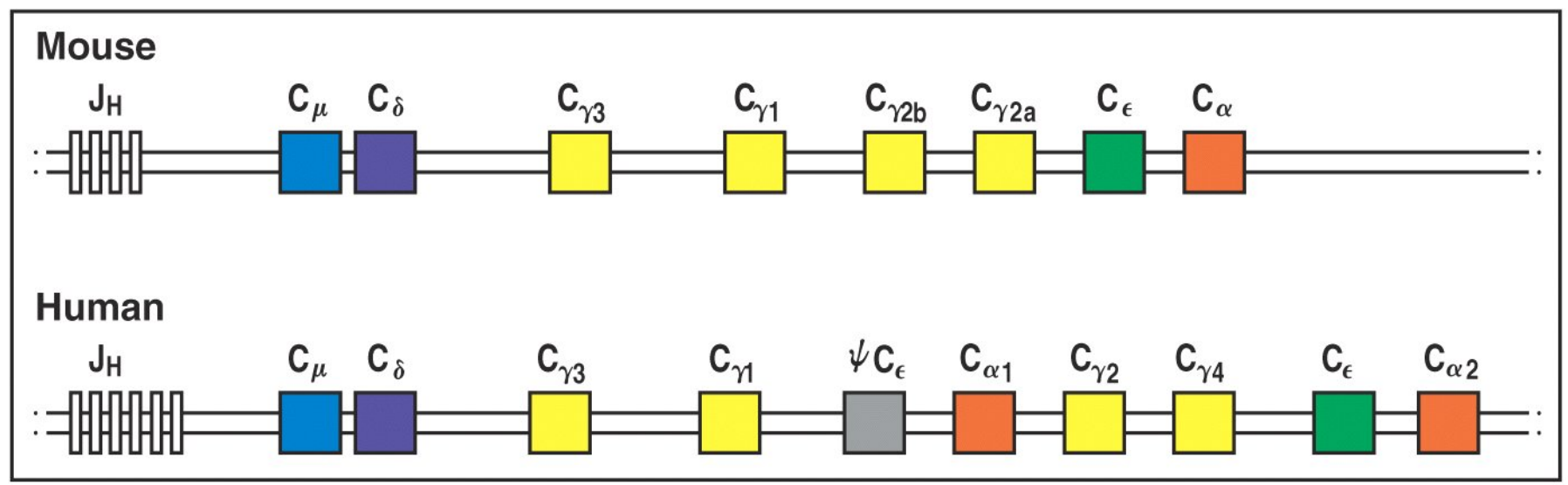


Figure 4-19 Immunobiology, 6/e. (© Garland Science 2005)

Class switch recombination

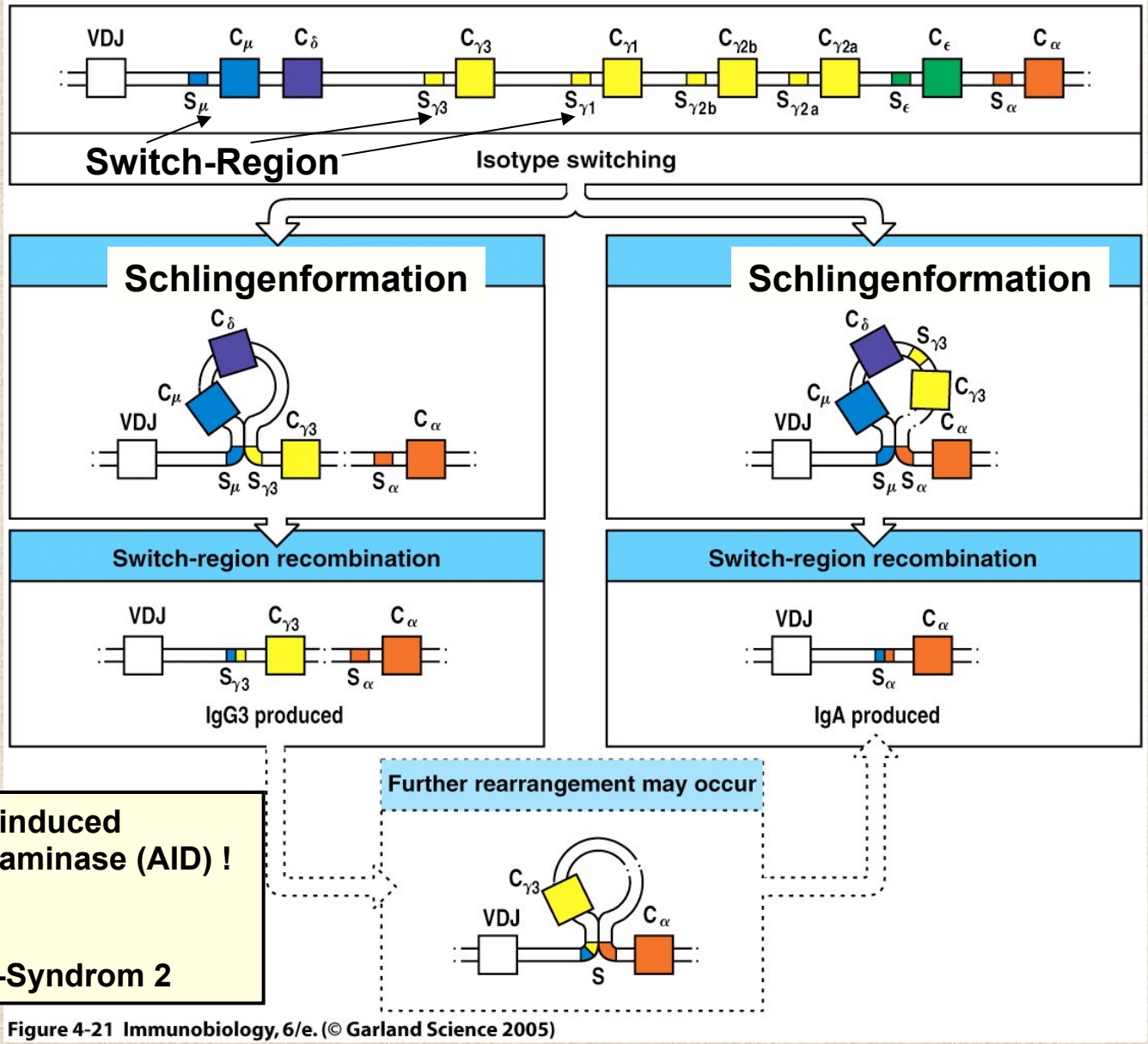
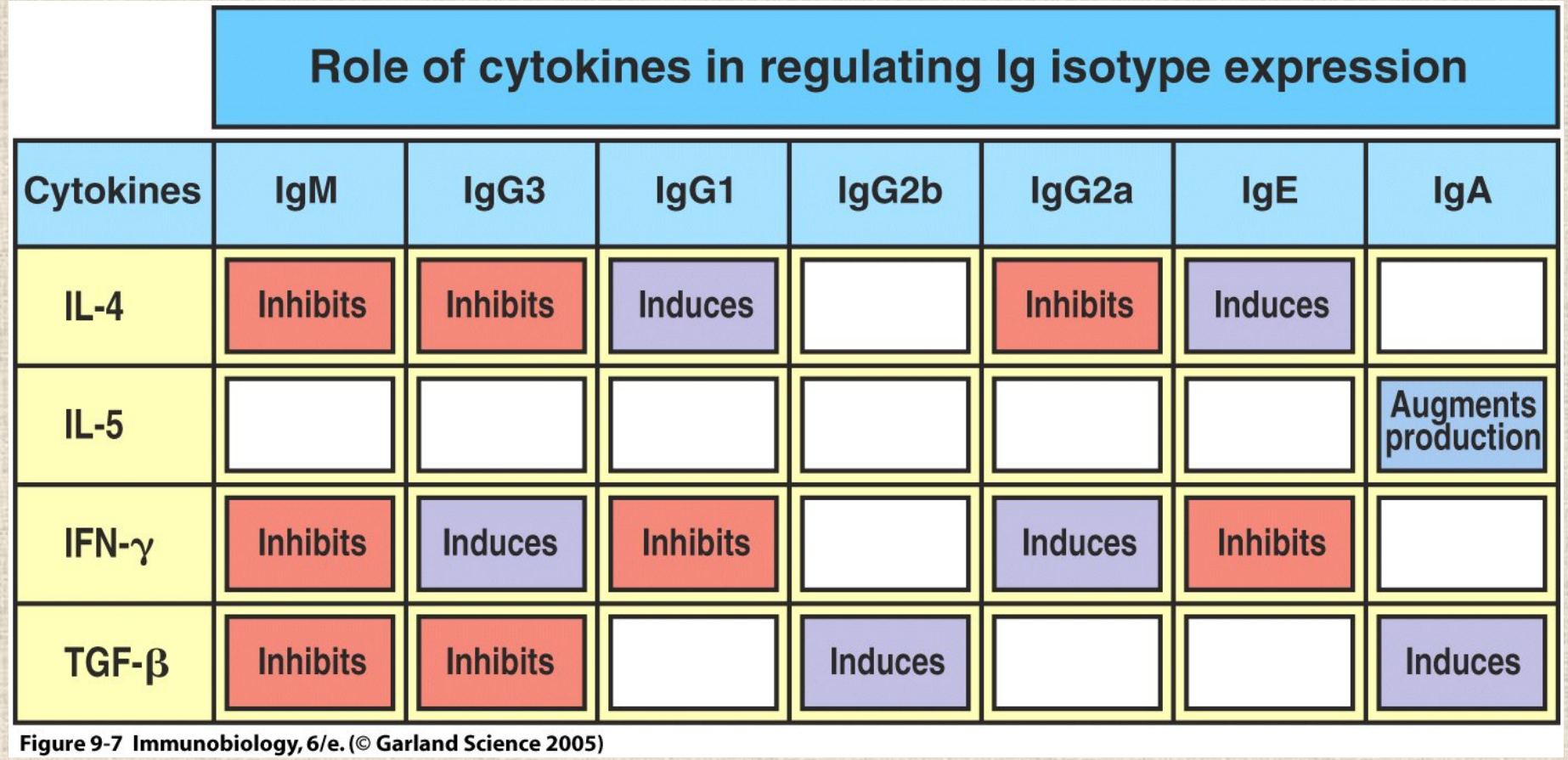


Figure 4-21 Immunobiology, 6/e. (© Garland Science 2005)

activation-induced Cytidin-Deaminase (AID) !

Hyper-IgM-Syndrom 2

Regulation of isotype switching



Role of cytokines in regulating Ig isotype expression

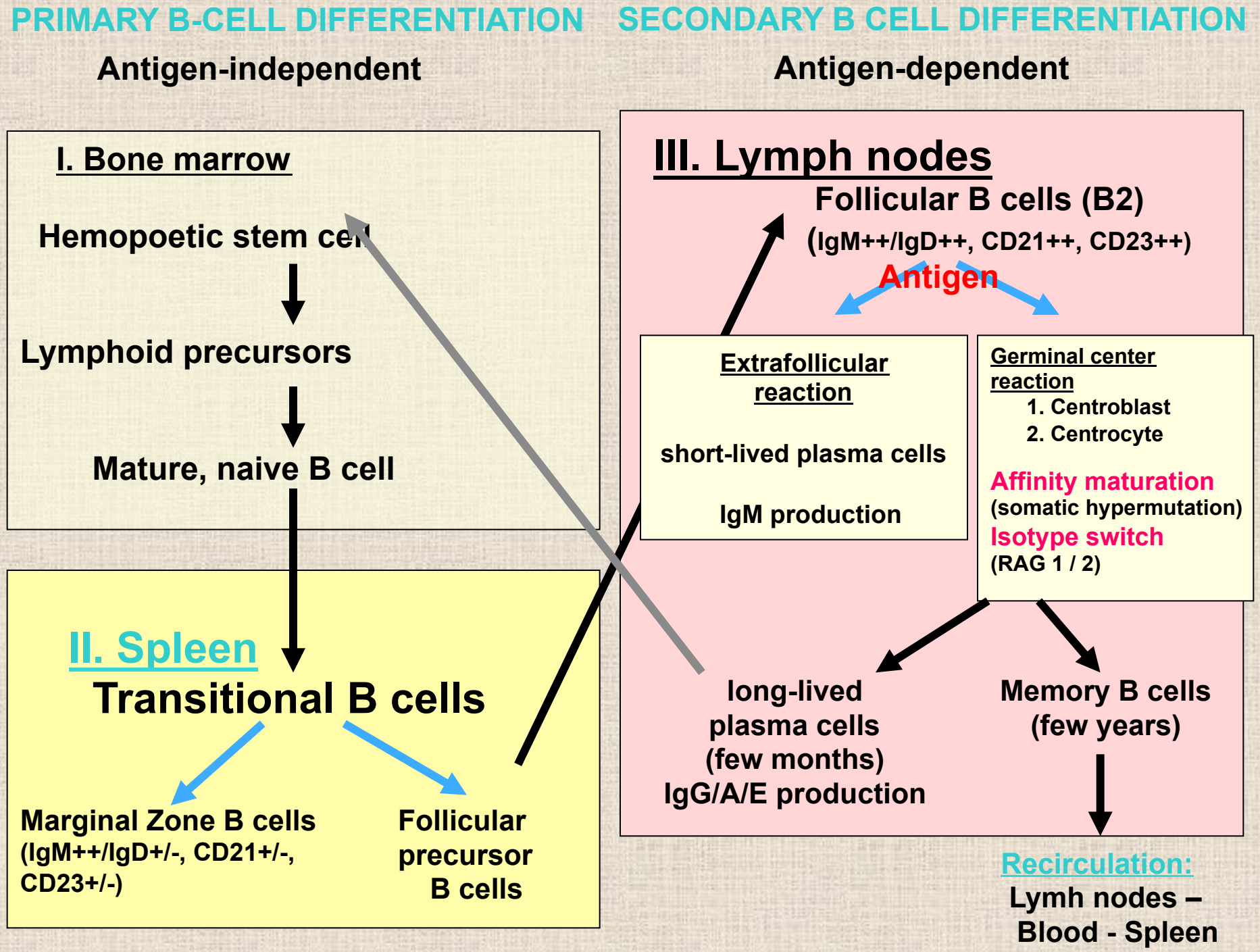
Cytokines	IgM	IgG3	IgG1	IgG2b	IgG2a	IgE	IgA
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces

Figure 9-7 Immunobiology, 6/e. (© Garland Science 2005)

3 Signals:
- Antigen
- Cytokines
- CD40

Summary

	T-dependent	T-independent
Affinity-maturation	+	-
Isotype-switch	+	limited
Memory	+	-


PRIMARY B-CELL DIFFERENTIATION
SECONDARY B CELL DIFFERENTIATION
Antigen-independent
Antigen-dependent
I. Bone marrow
Hemopoetic stem cell
Lymphoid precursors
Mature, naive B cell
II. Spleen
Transitional B cells
Marginal Zone B cells
(IgM++/IgD+/-, CD21+/-, CD23+/-)
Follicular precursor B cells
III. Lymph nodes
Follicular B cells (B2)
(IgM++/IgD++, CD21++, CD23++)
Antigen
Extrafollicular reaction
short-lived plasma cells
IgM production
Germinal center reaction
1. Centroblast
2. Centrocyte
Affinity maturation
(somatic hypermutation)
Isotype switch
(RAG 1 / 2)
long-lived plasma cells
(few months)
IgG/A/E production
Memory B cells
(few years)
Recirculation:
Lymh nodes –
Blood - Spleen