

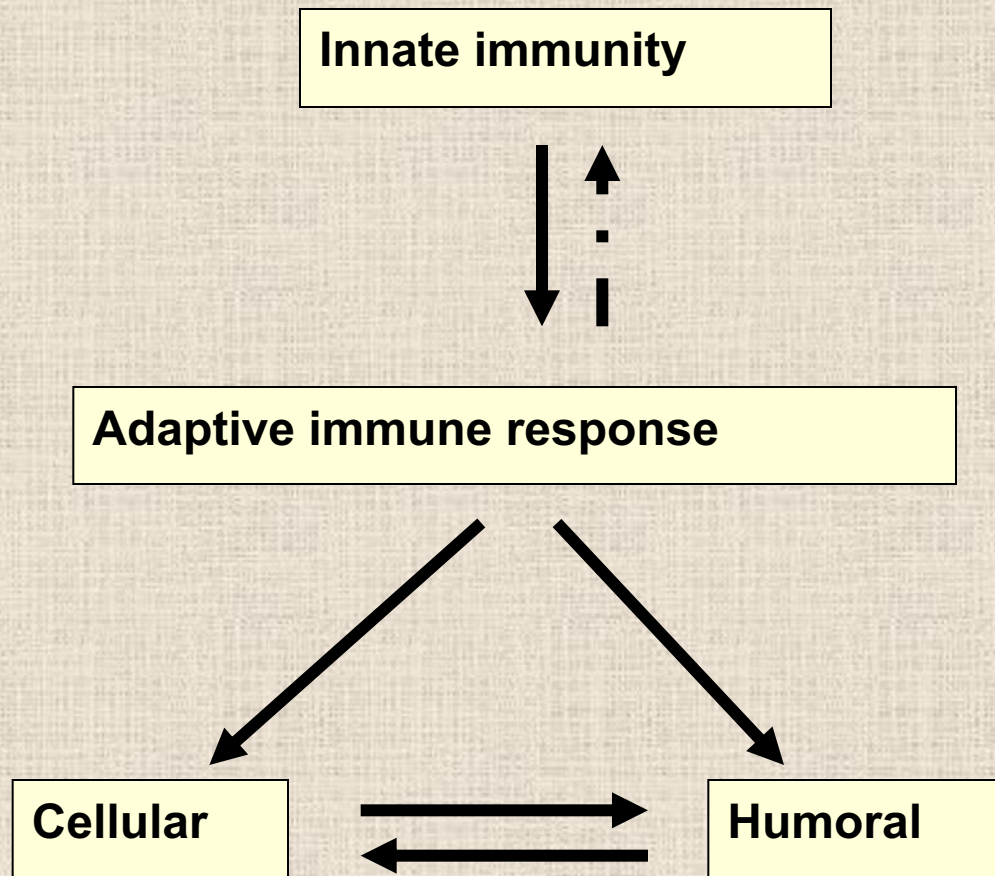
Basic Immunology

(Dentistry)

Lectures 11.-12.

Humoral immune response

Ferenc Boldizsár



Main stages of the adaptive immune response

Antigen recognition



Activation, differentiation



Effector functions

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

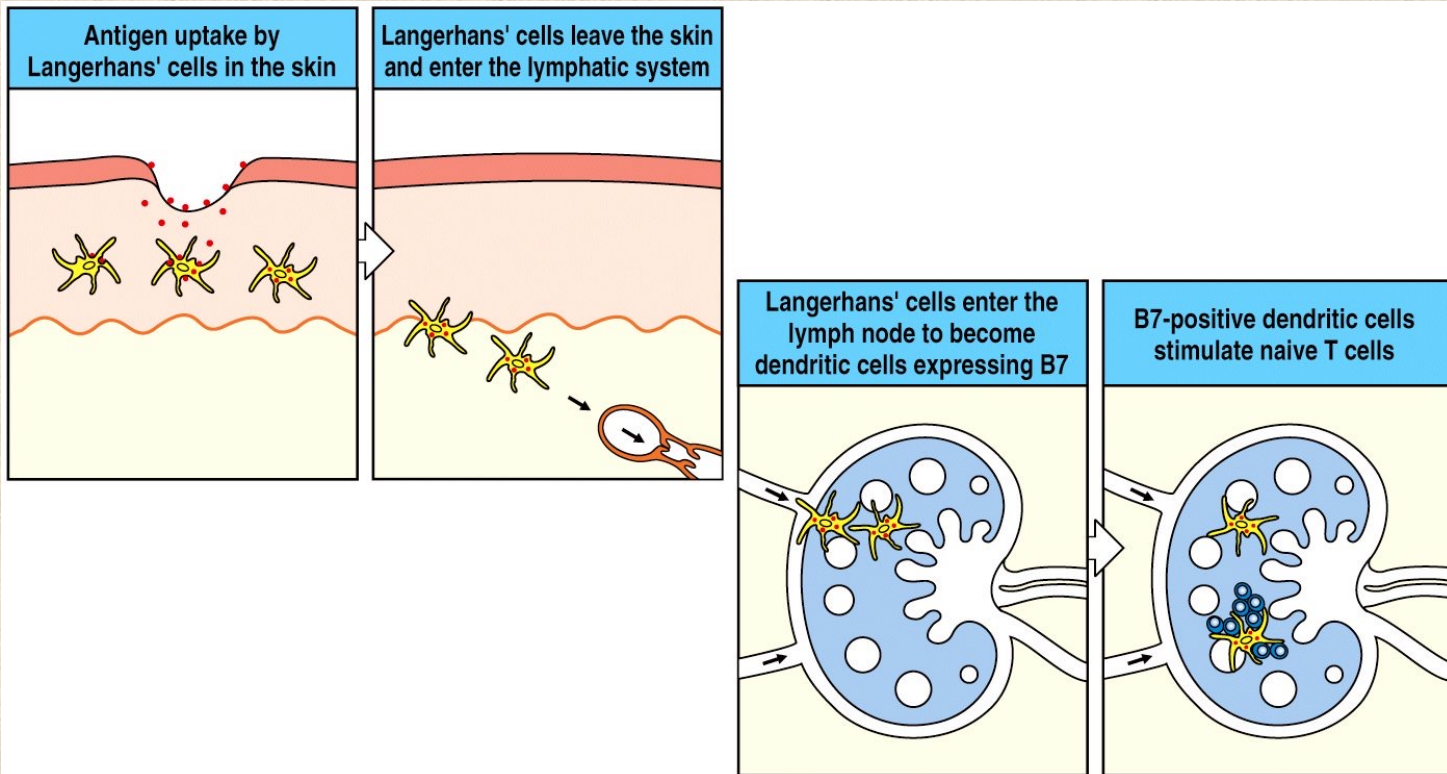
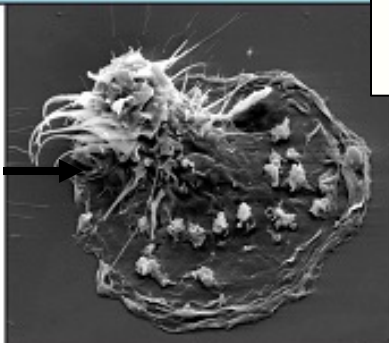
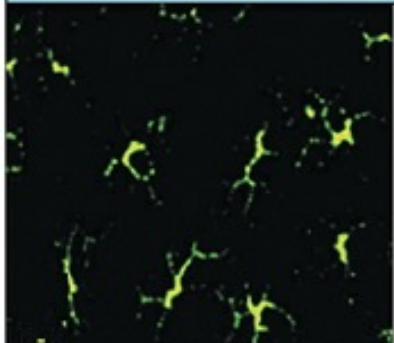


Figure 8-15 Immunobiology, 6/e. (© Garland Science 2005)

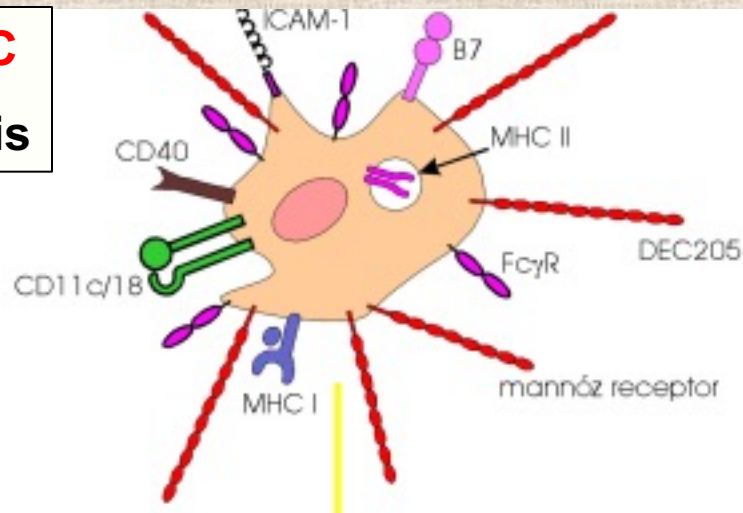
Fluorescence microscopy

Scanning electron microscopy

Dendritic cells in peripheral tissues



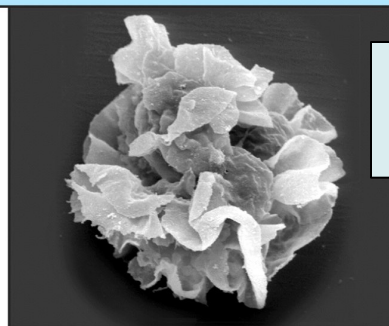
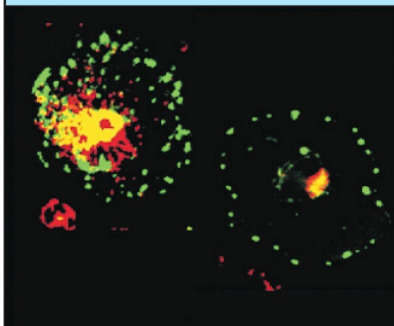
Immature DC
Phagocytosis



Fluorescence microscopy

Scanning electron microscopy

Dendritic cells in the lymphatic circulation



Phagocytosis stops

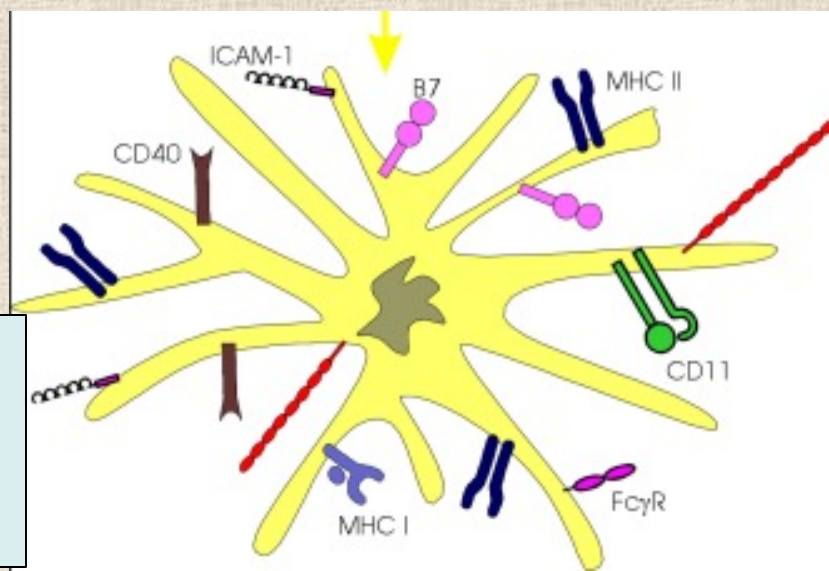
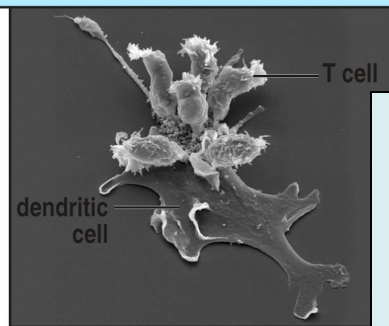
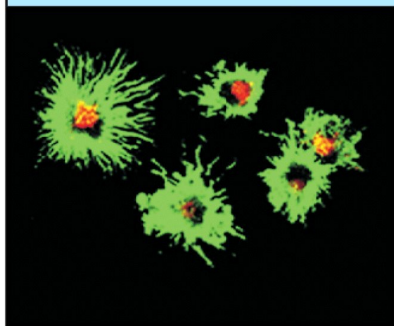


Figure 8-2 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

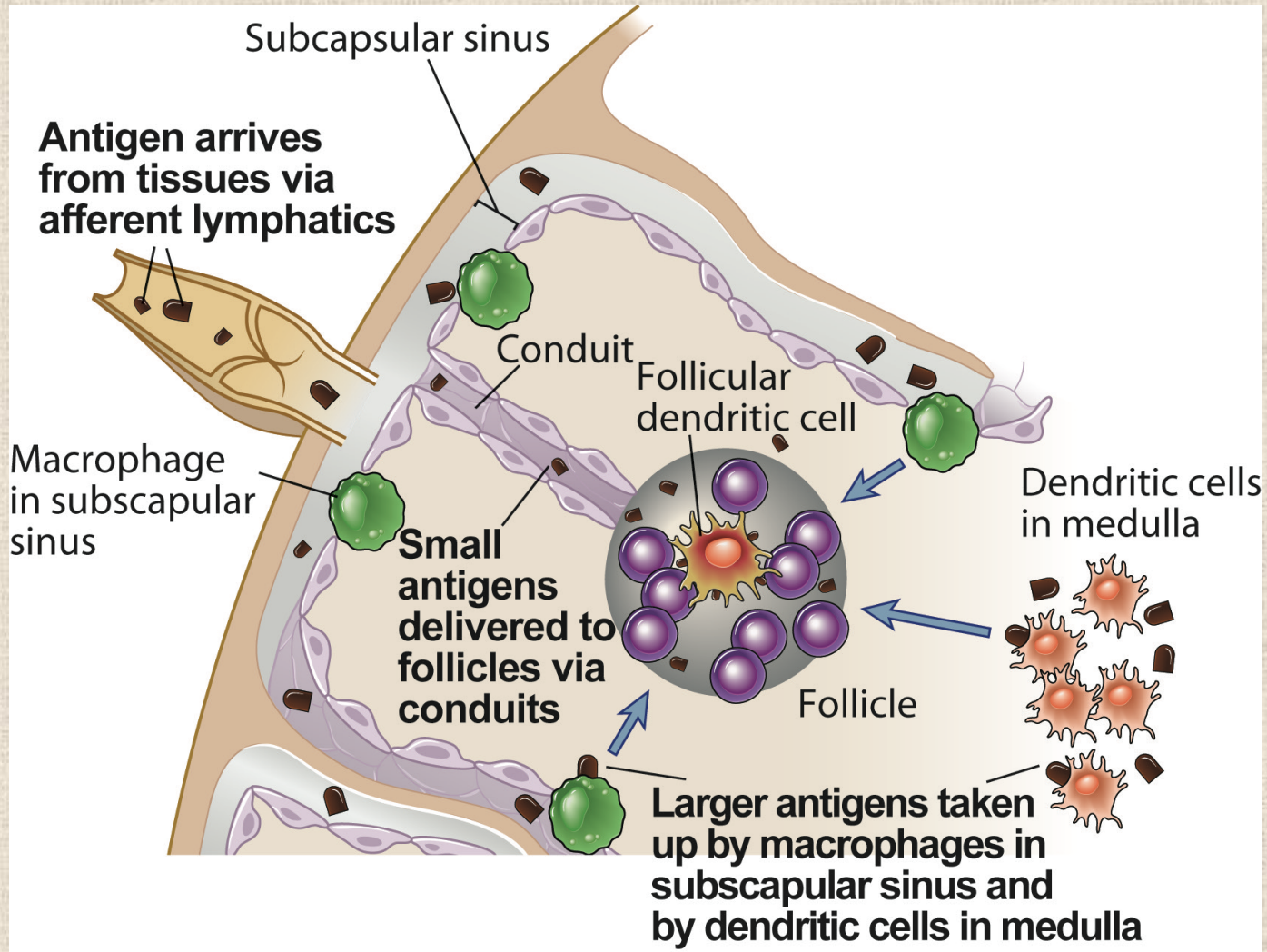
Dendritic cells in lymphoid tissues



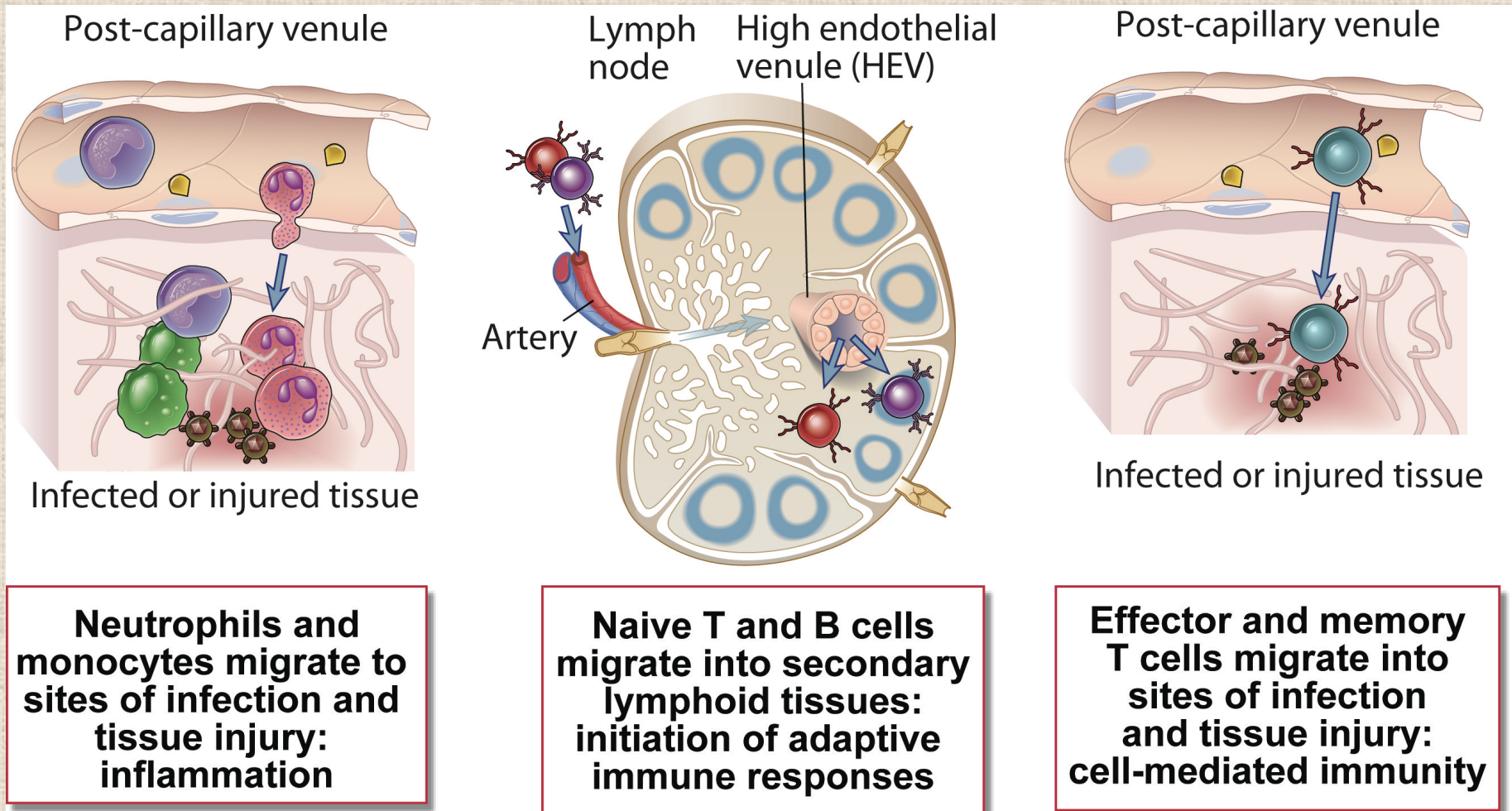
Mature DC
T cell activation (B7)

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

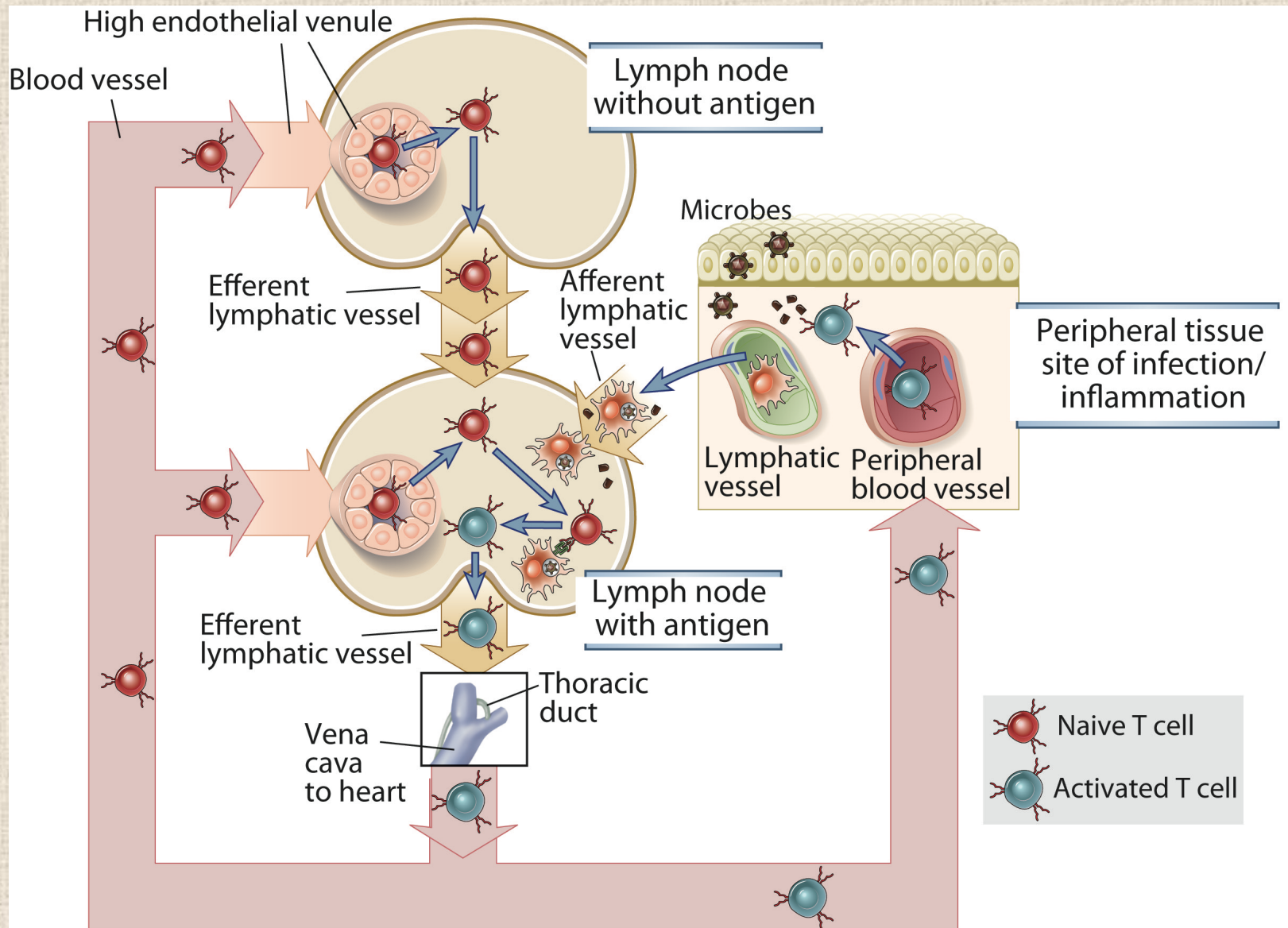
Antigen Delivery to Follicular B cells



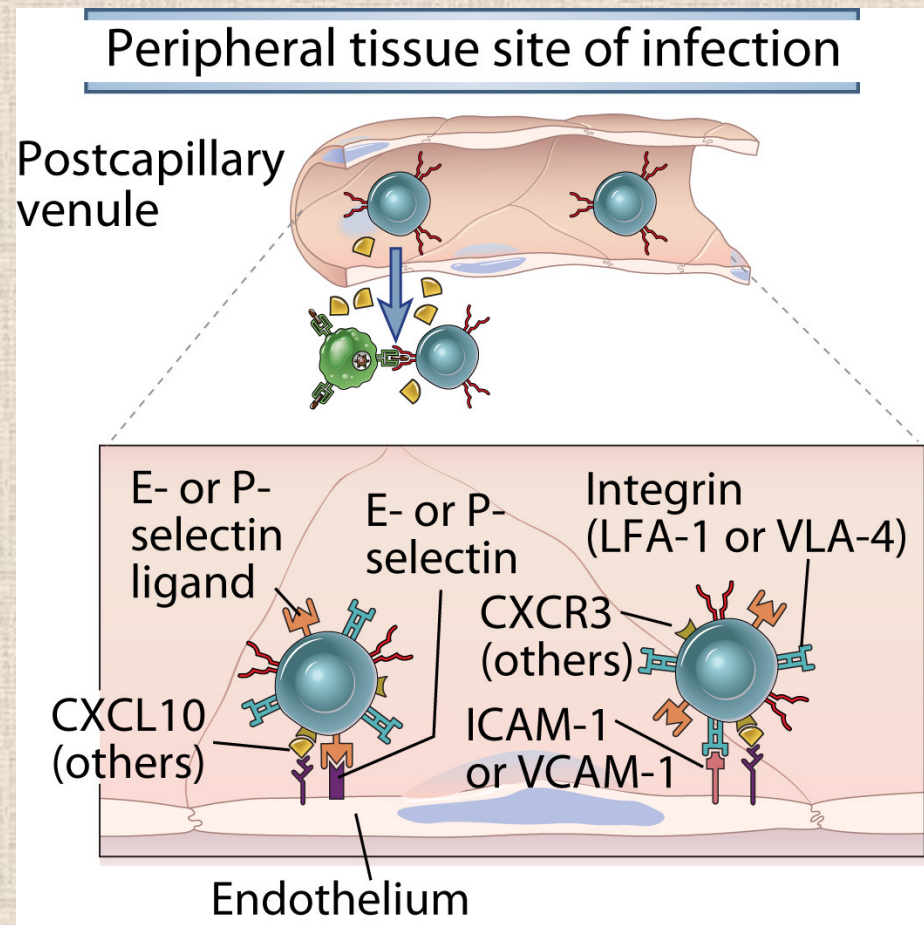
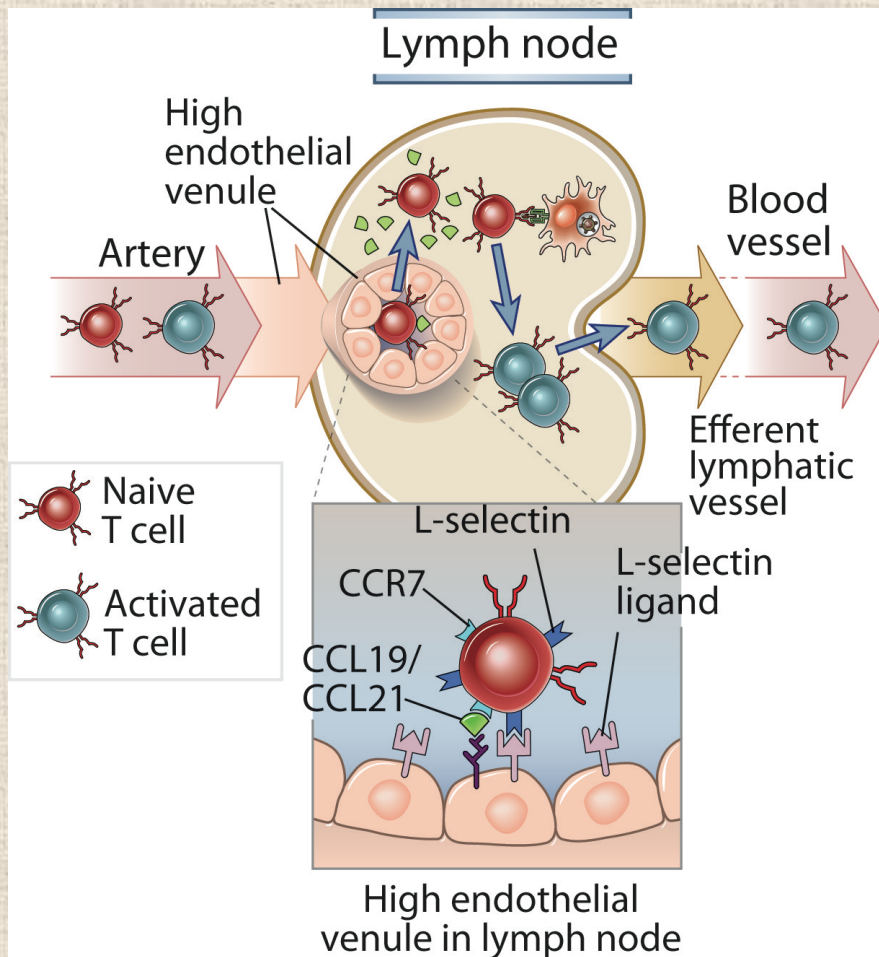
Lymphocyte recirculation



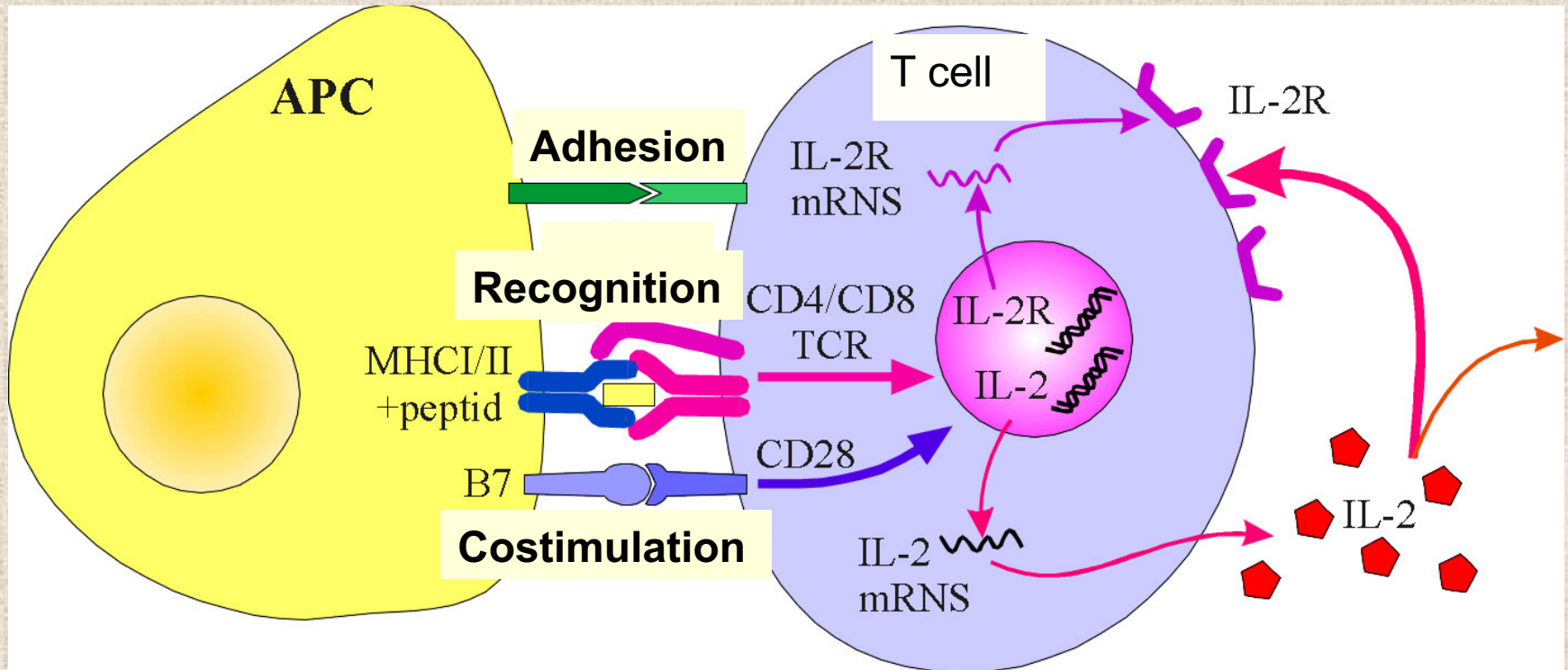
T cell recirculation



Regulation of T cell recirculation

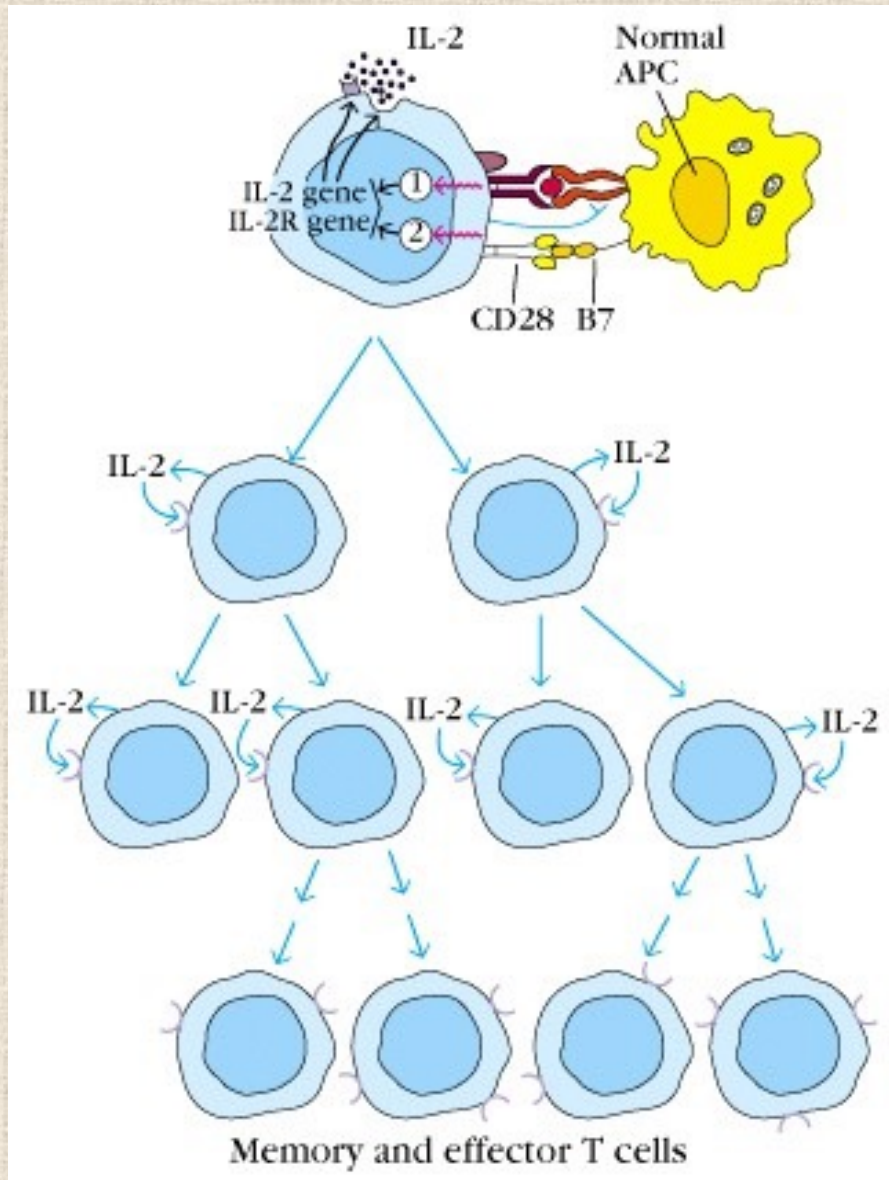


T cell activation



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

2 signals are necessary for T cell activation

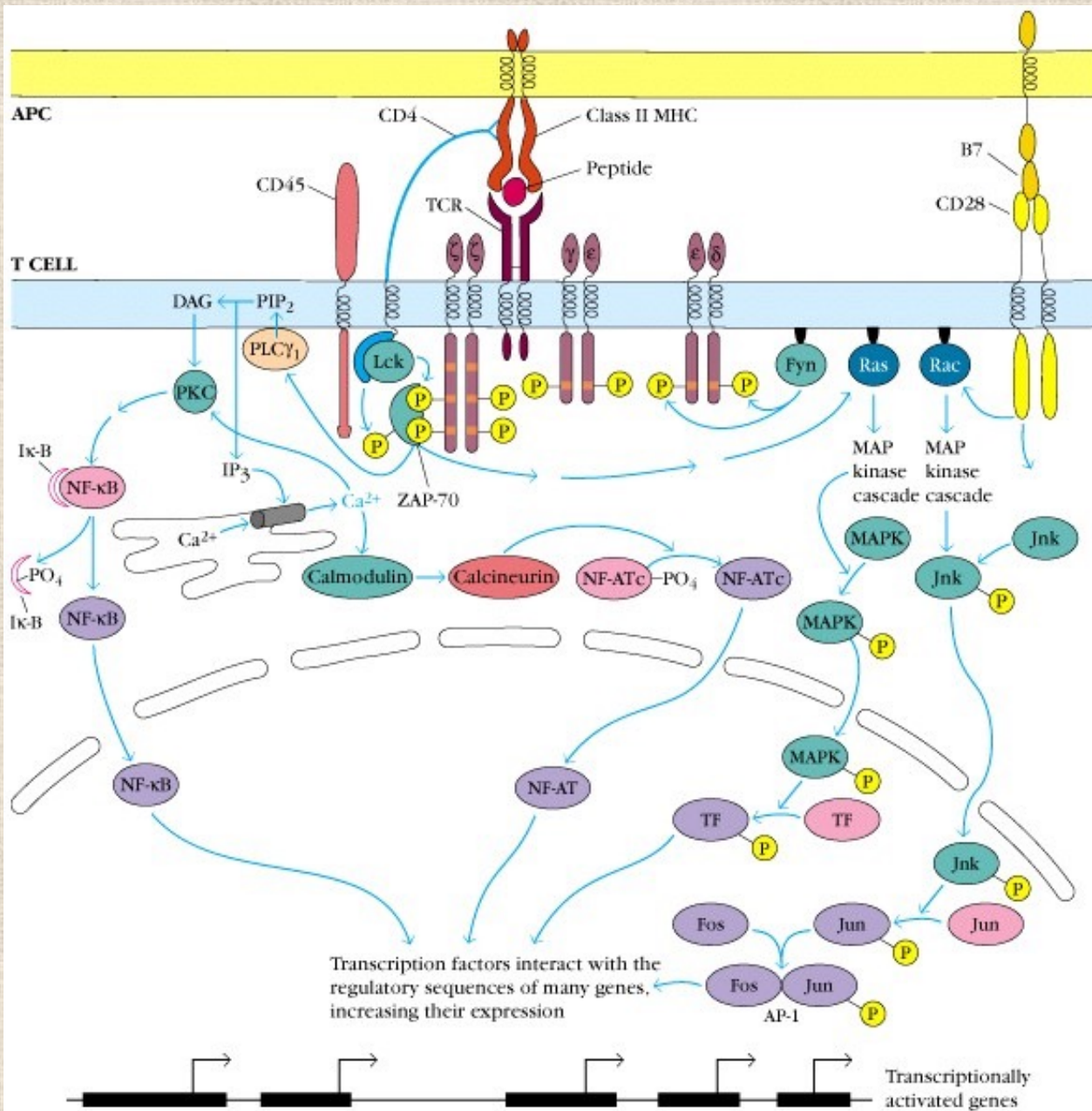


1. signal: TCR-CD3 complex
Antigen-specific

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

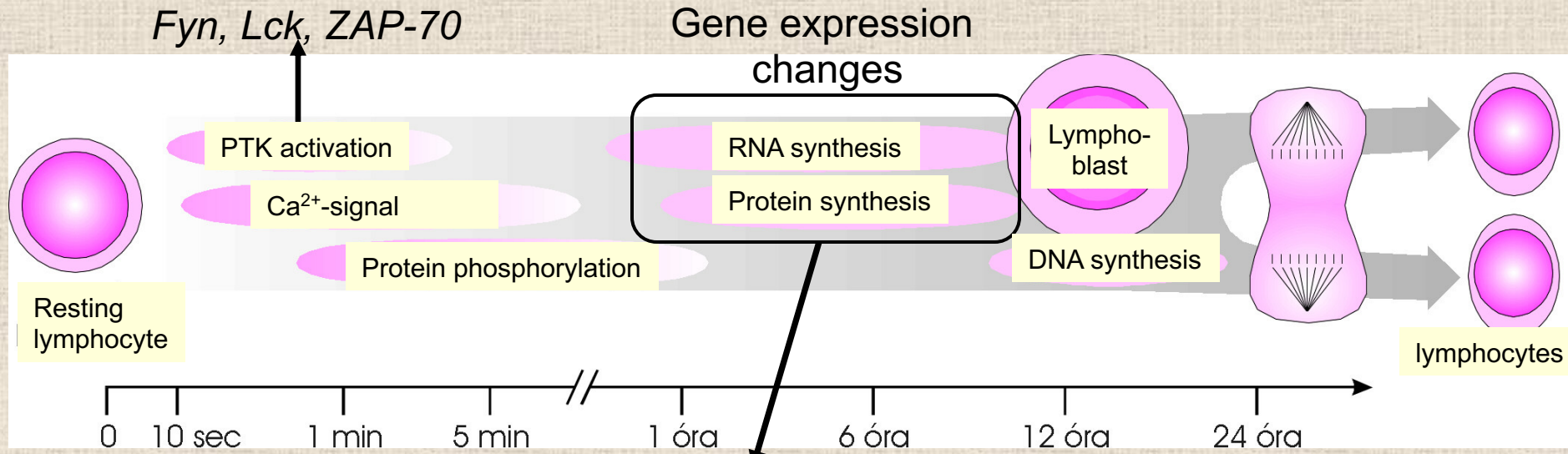
T cell differentiation
and proliferation

Effector and memory
T cells

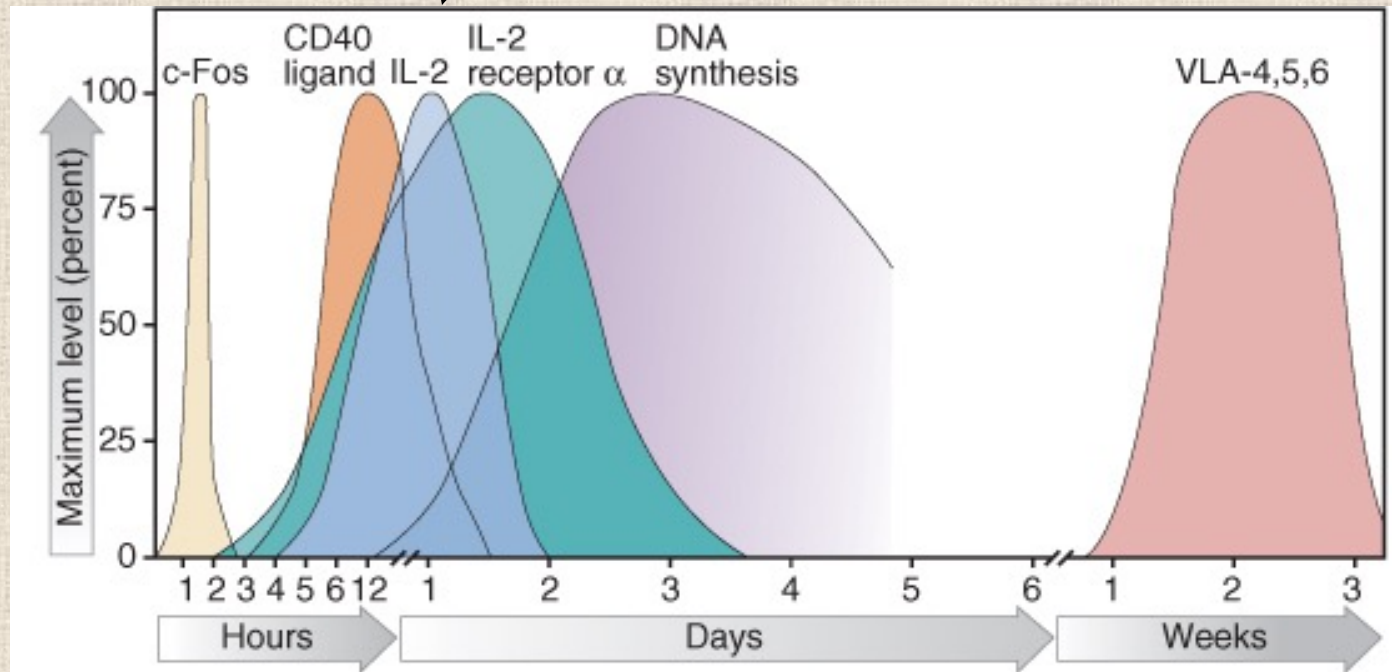


1. Antigen recognition
2. PTK activation
3. Ca²⁺ signal
4. Protein phosphorylation
5. Translocation of transcription factors
6. Gene activation

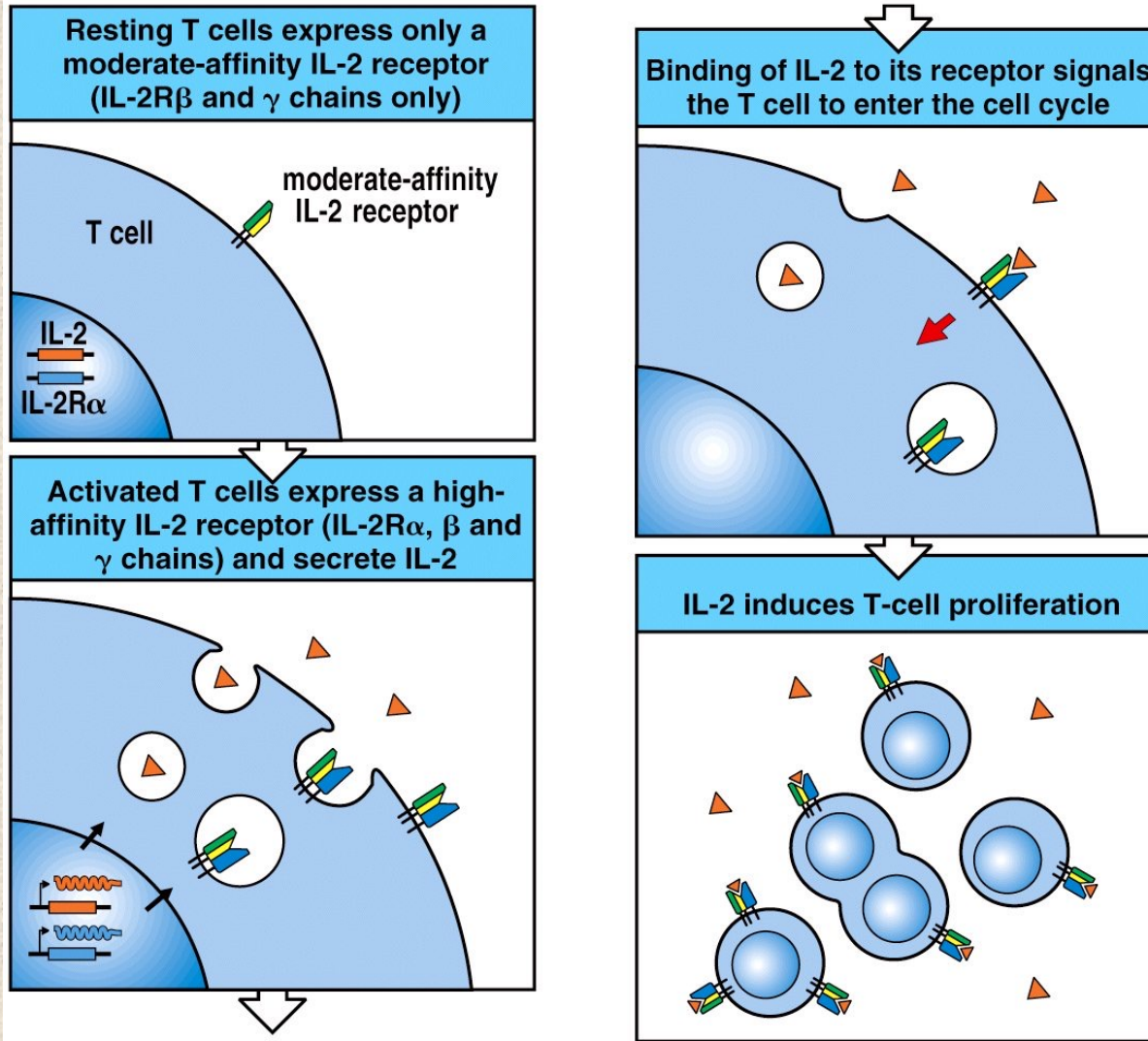
Kinetics of T cell activation



Activation



Autocrine IL-2 effect - CD25 (IL-2R α chain)



IL-2 receptor chains:

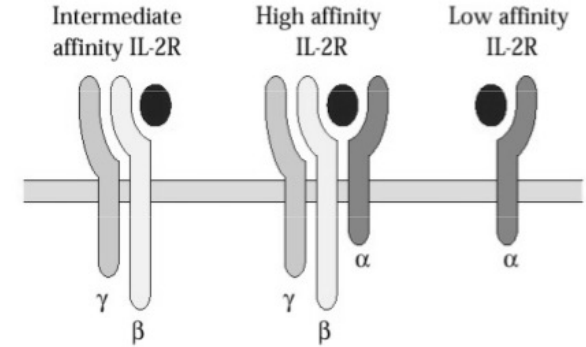
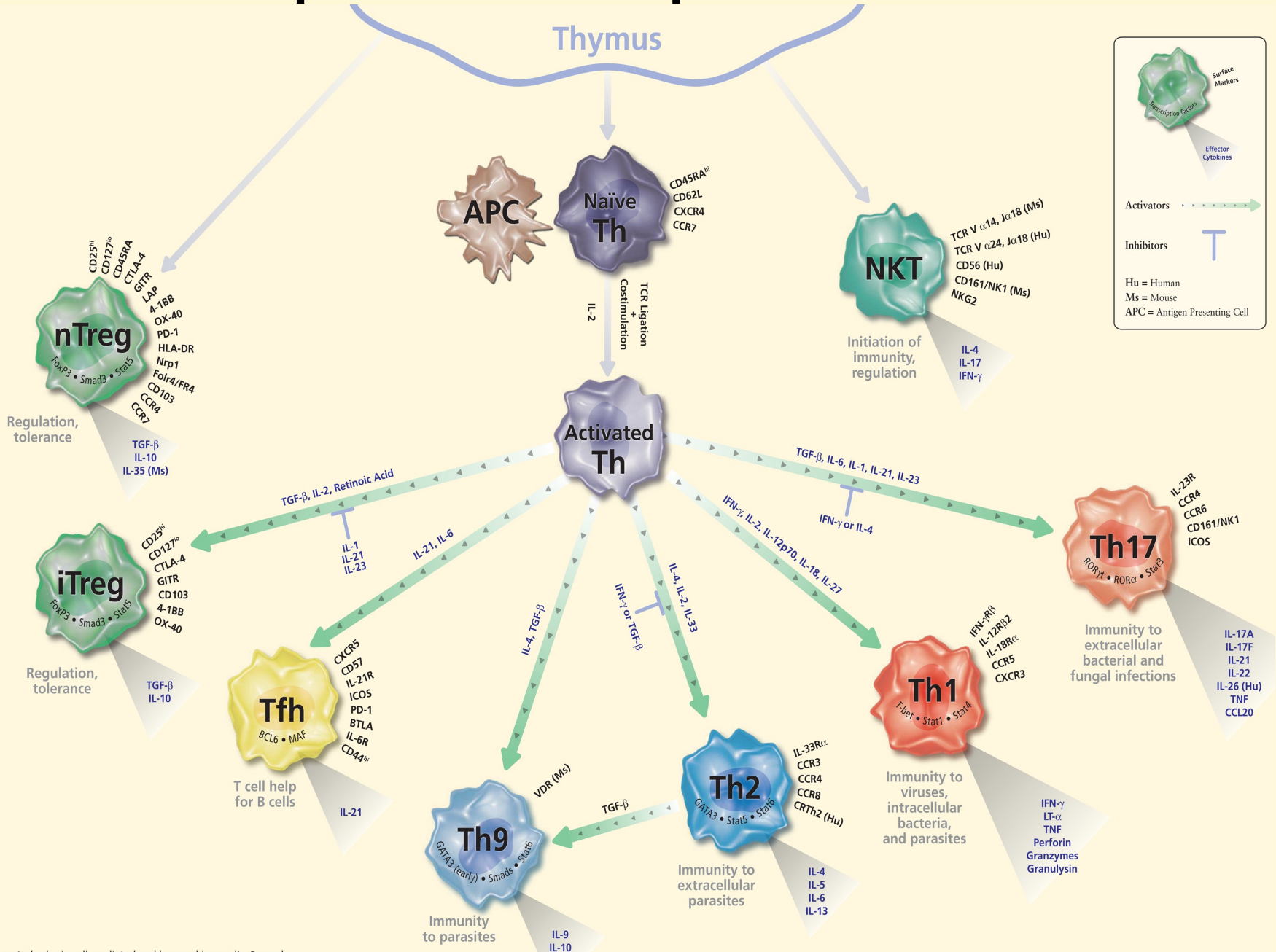


Figure 8-20 Immunobiology, 6/e. (© Garland Science 2005)

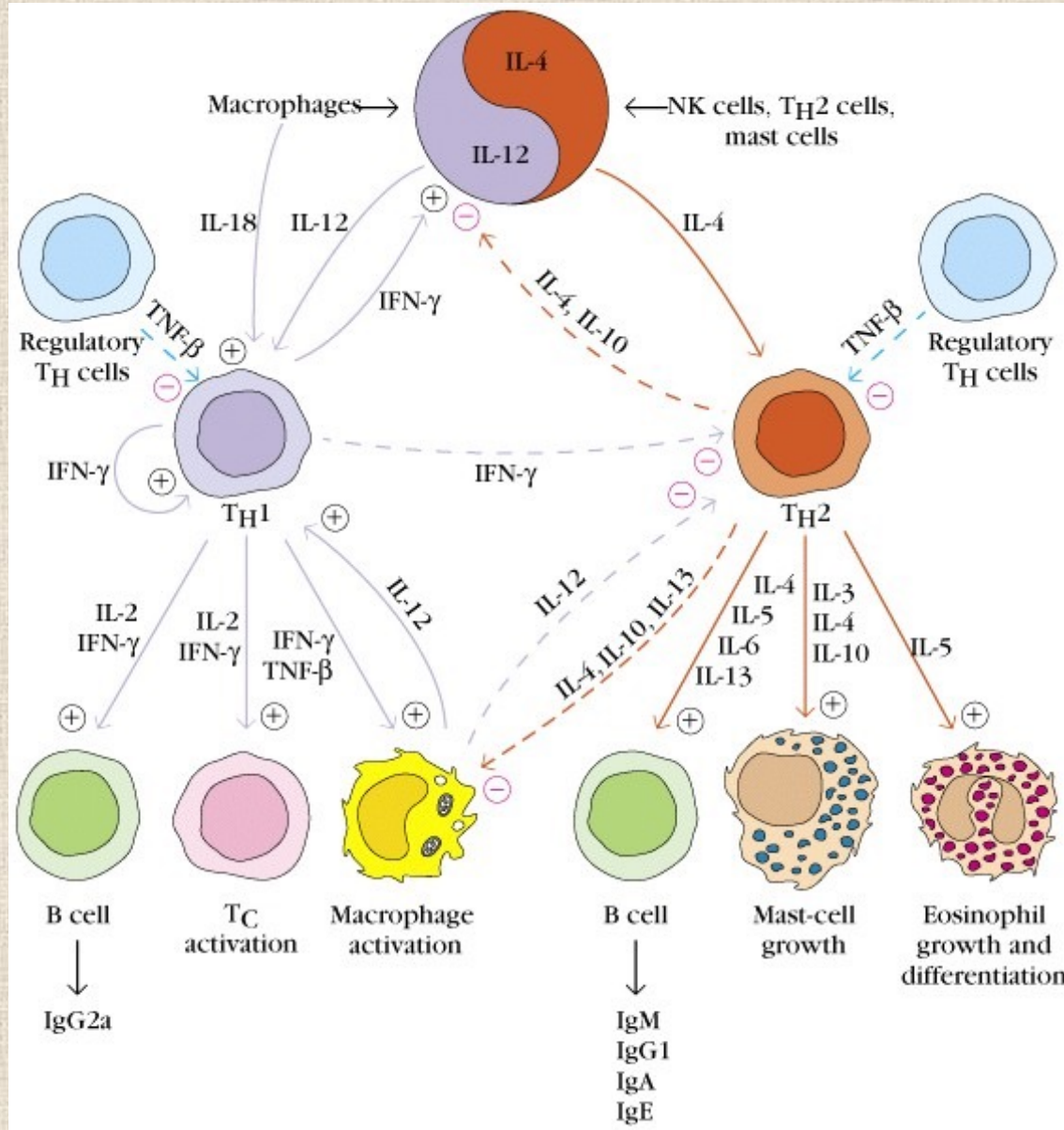
Helper T cell polarization



Peripheral helper T cell differentiation

Lineage	Inducer	TF	Cytokines
Th1	IL-12 (Stat-4)	T-bet	IL-2, TNF, IFN γ
Th2	IL-4 (Stat-6)	GATA-3	IL-4,5,6,13
Th17	TGF β , IL-6,-21,-23	ROR γ t	IL-17
Treg	TGF β , IL-2	FoxP3	IL-10, TGF β

Peripheral helper T cell differentiation



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

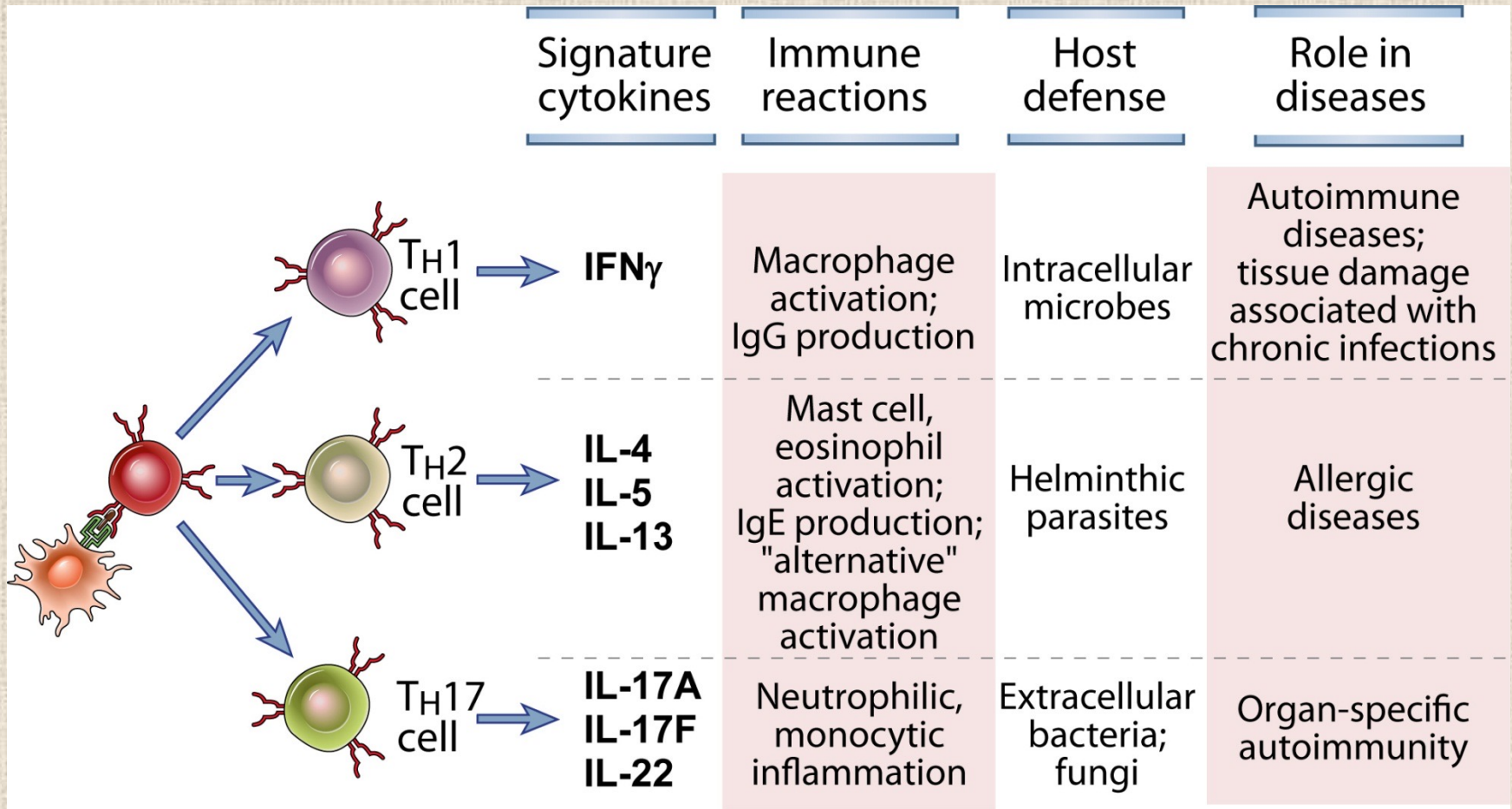
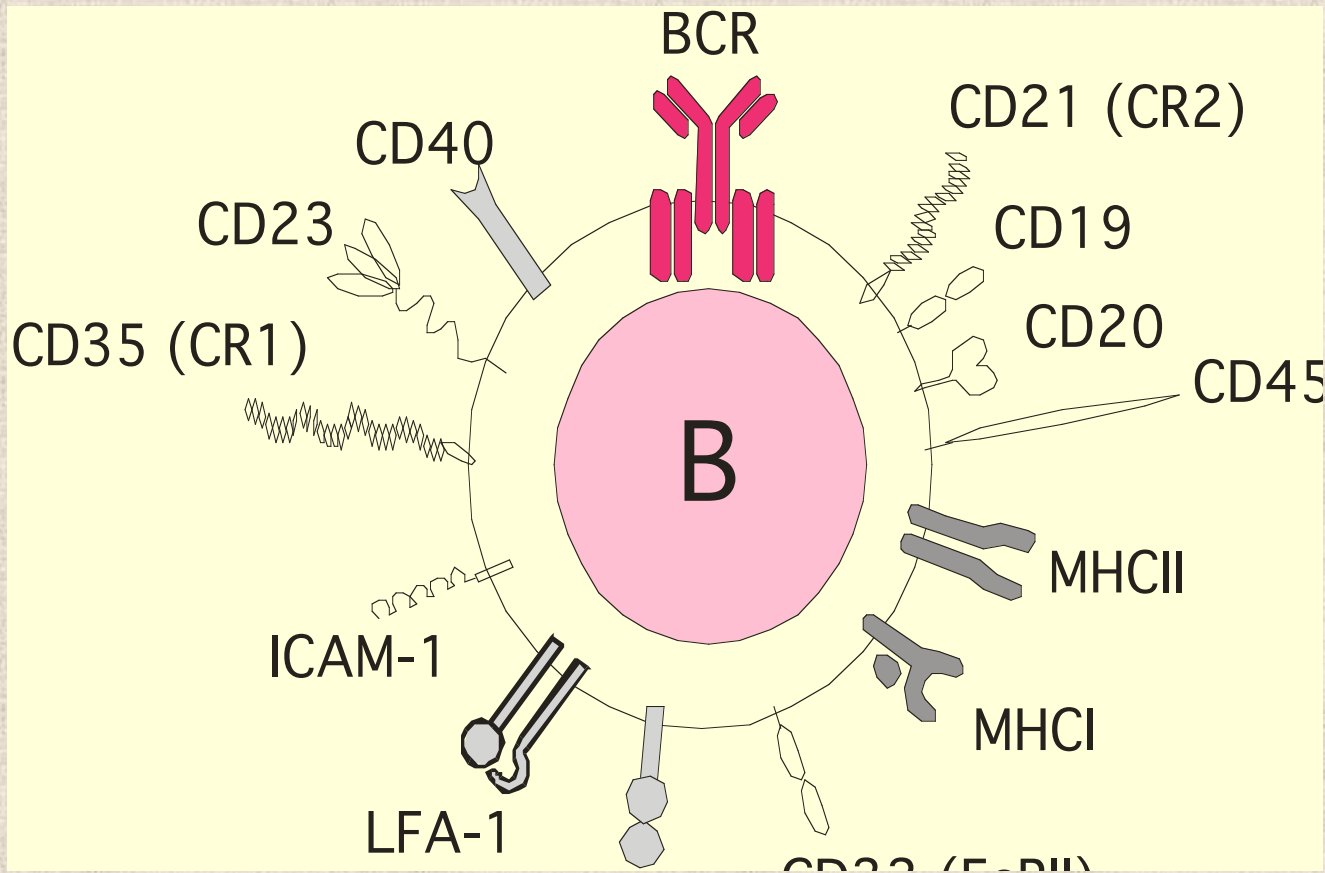


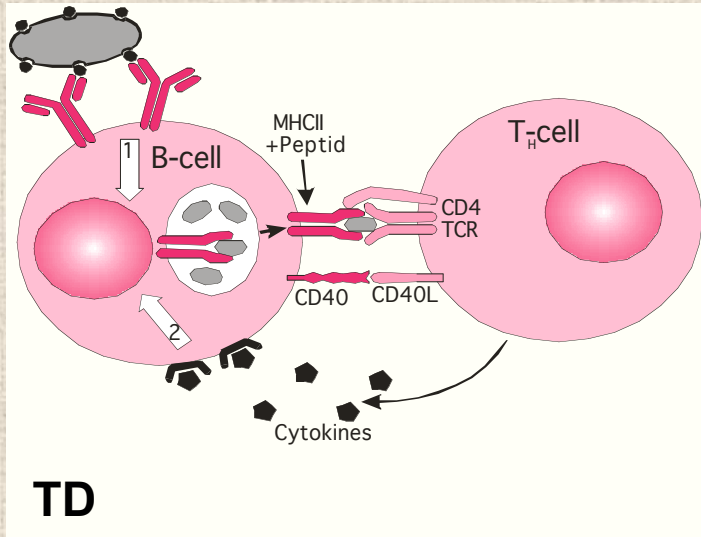
Fig. 9-

B cell activation

Important cell surface molecules on B cells

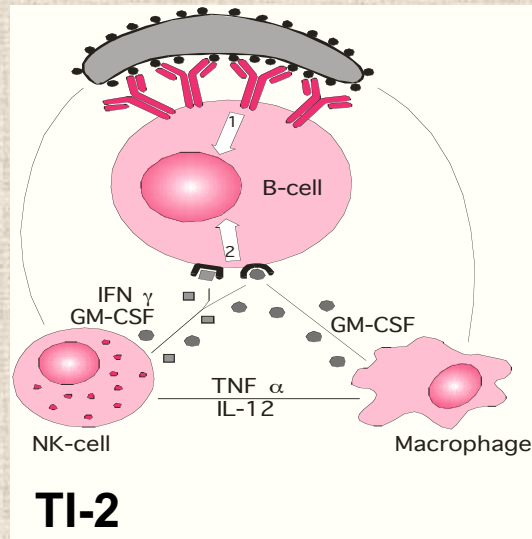
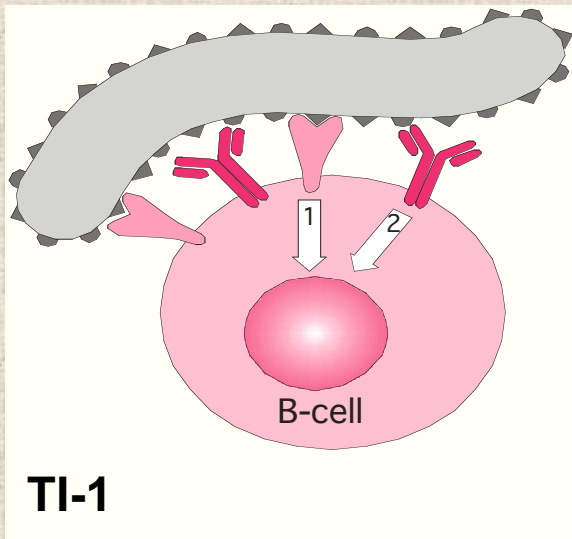


T-dependent and -independent antigens



T-dependent (TD):

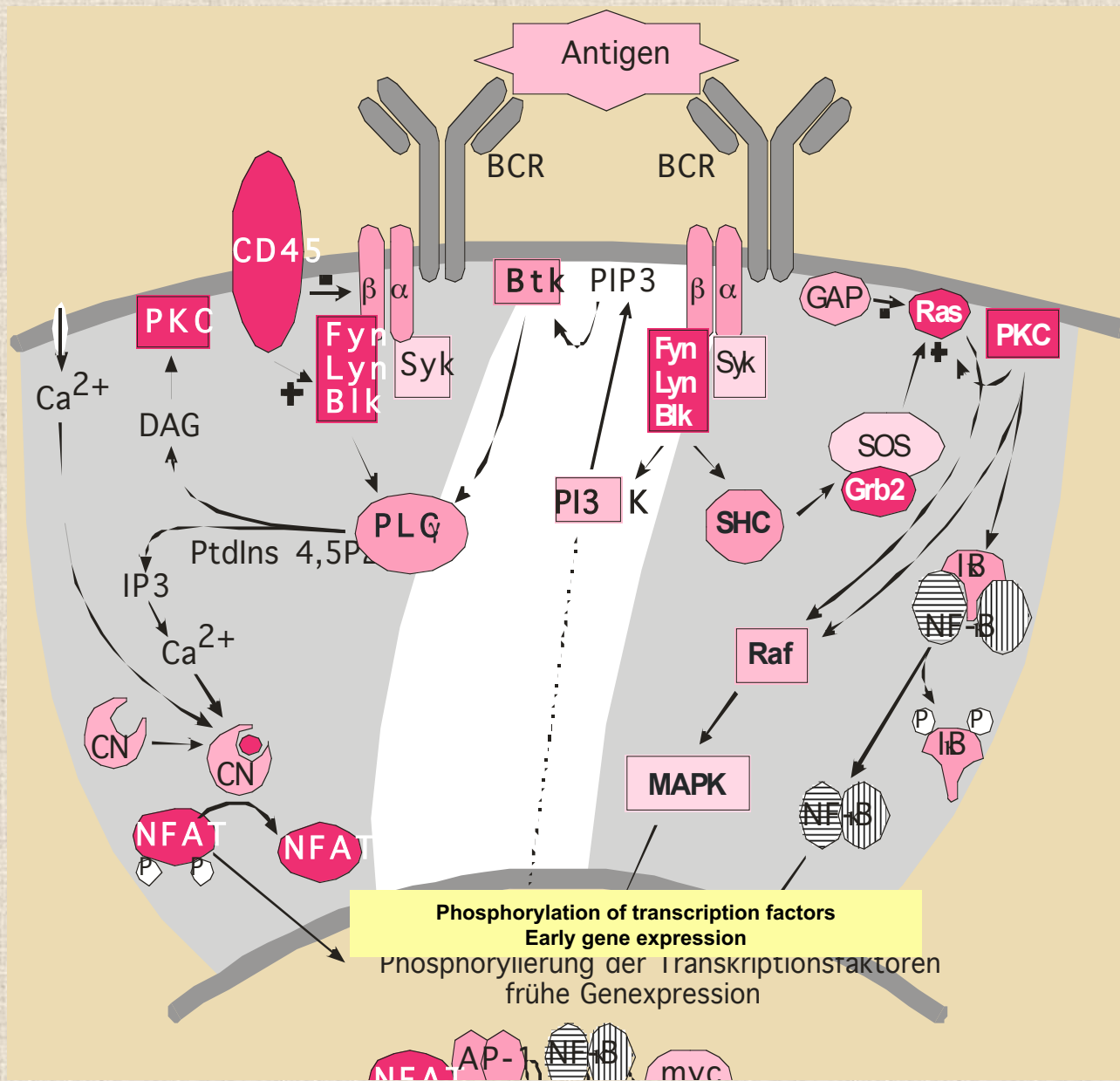
- Protein antigens
- Response without T cells ✗
- Affinity maturation ✓
- Isotype switch ✓
- Memory cell formation ✓



T-independent (TI):

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

B cell receptor signaling



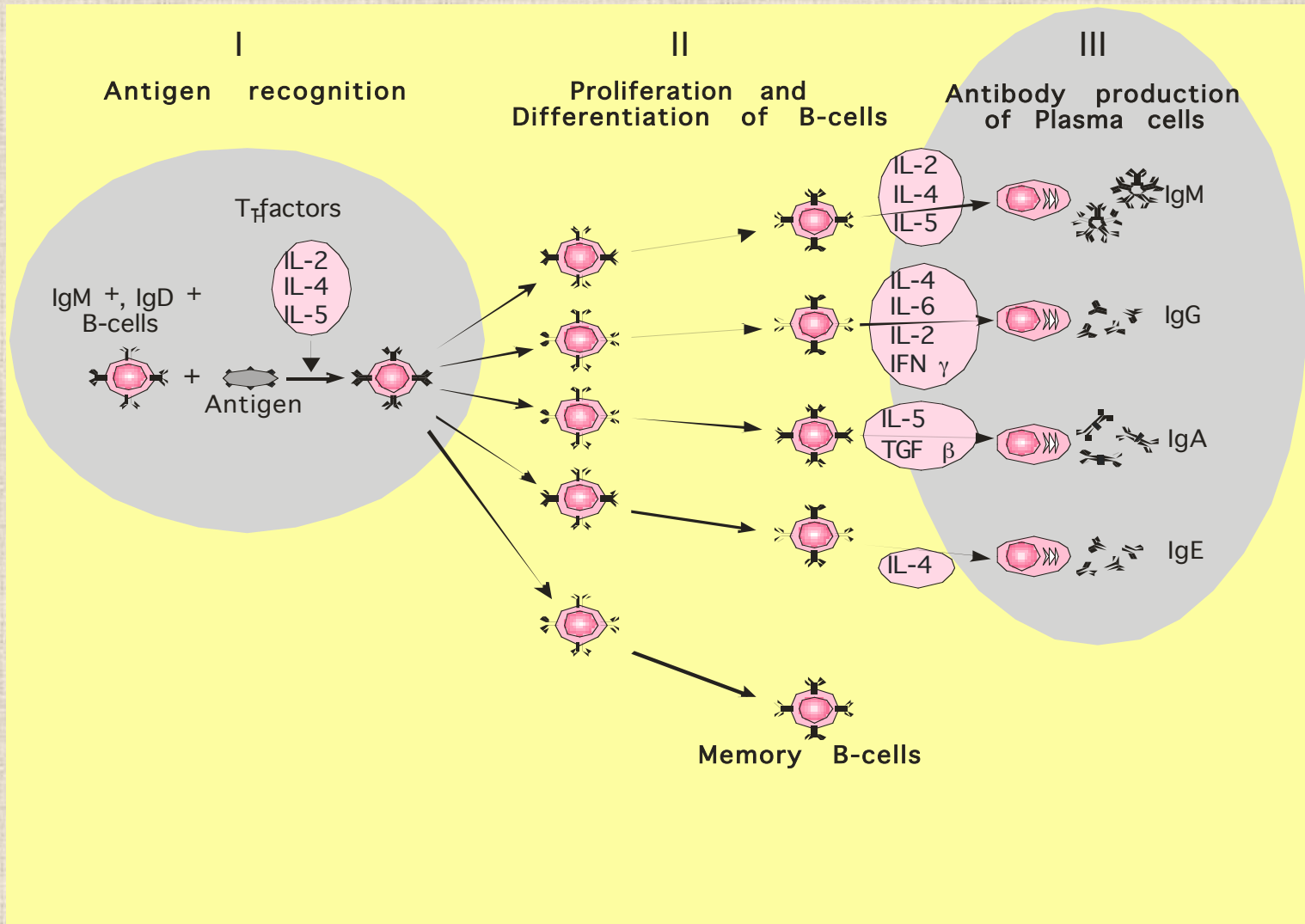
1. PTK activation

2. Ca²⁺ signal

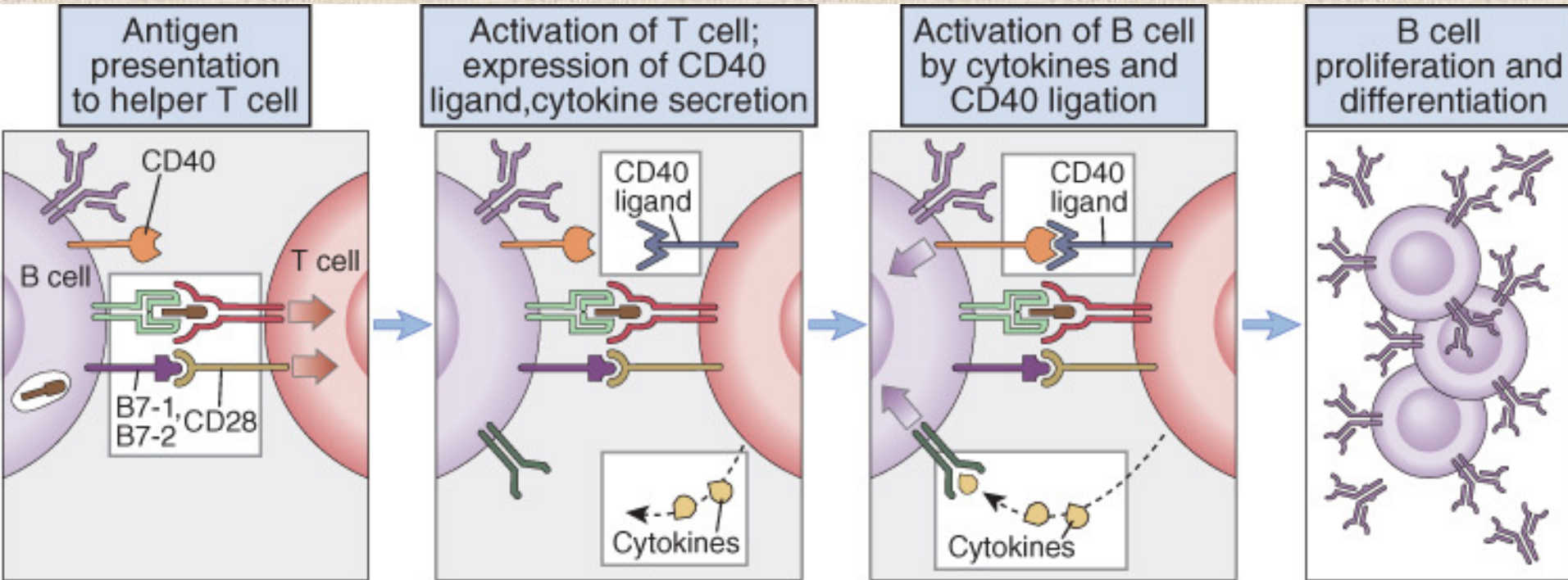
3. Activation of transcription factors

4. Gene expression

Steps of B cell activation



T-helper cell-dependent B-cell activation



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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

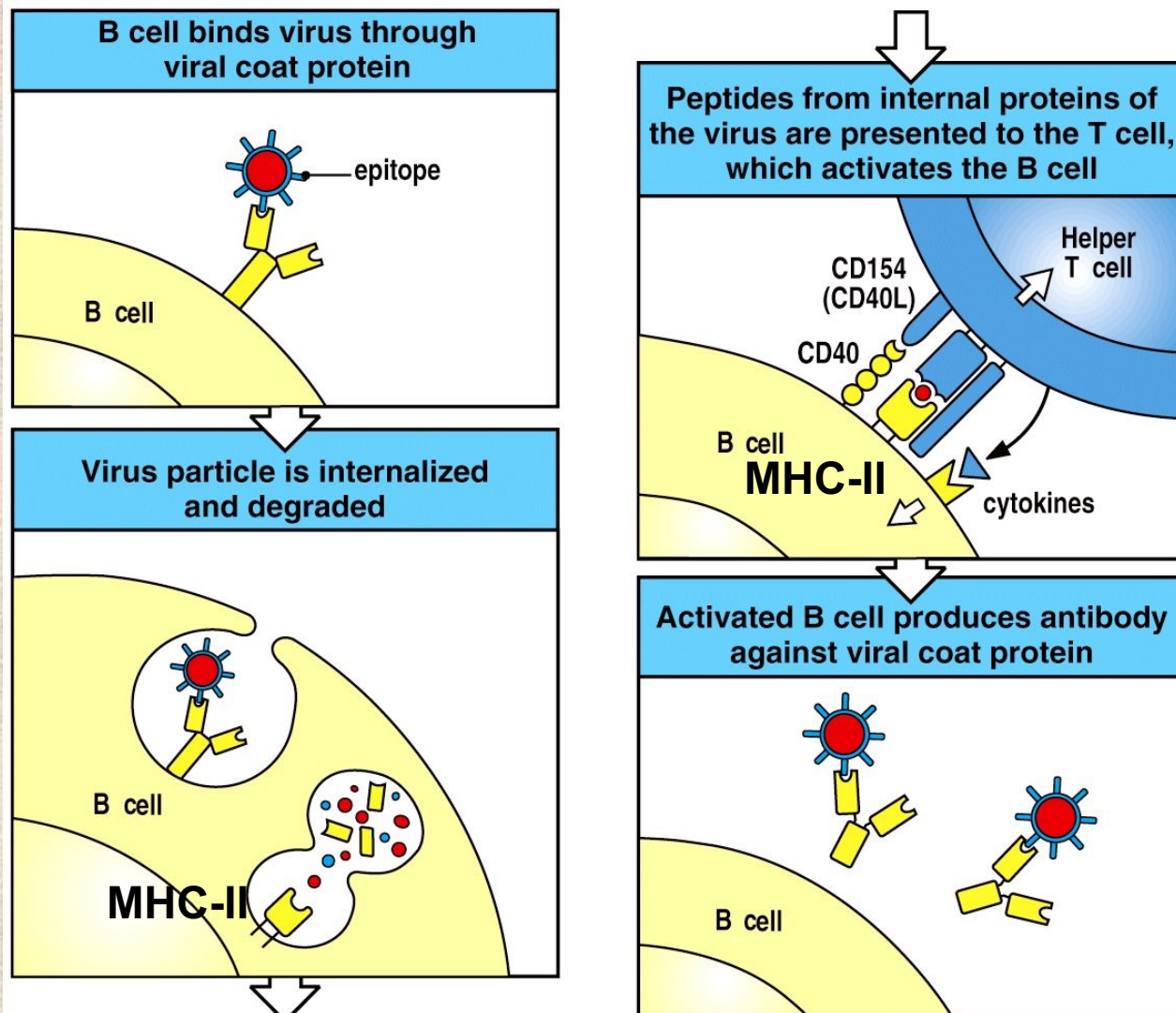
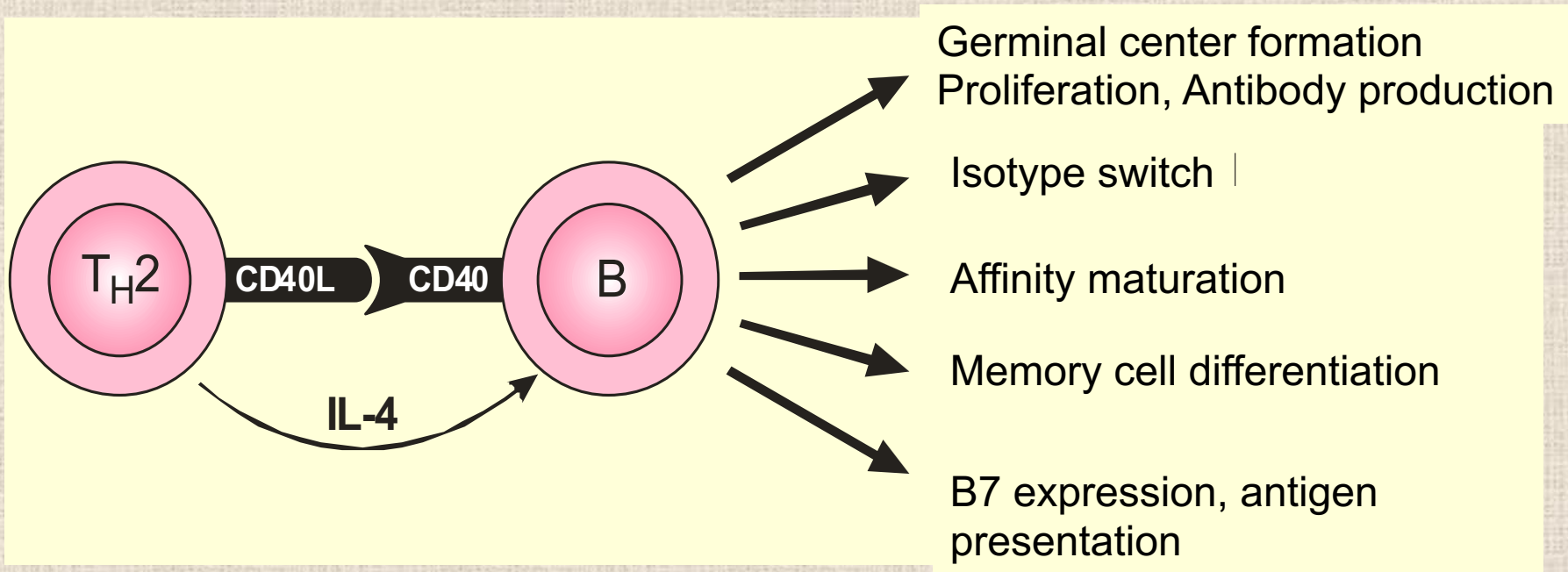


Figure 9-3 Immunobiology, 6/e. (© Garland Science 2005)

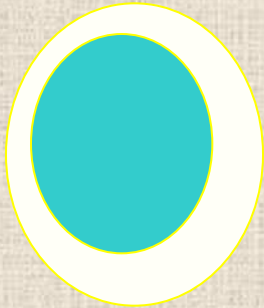
Functional consequences of CD40-CD40L interaction



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

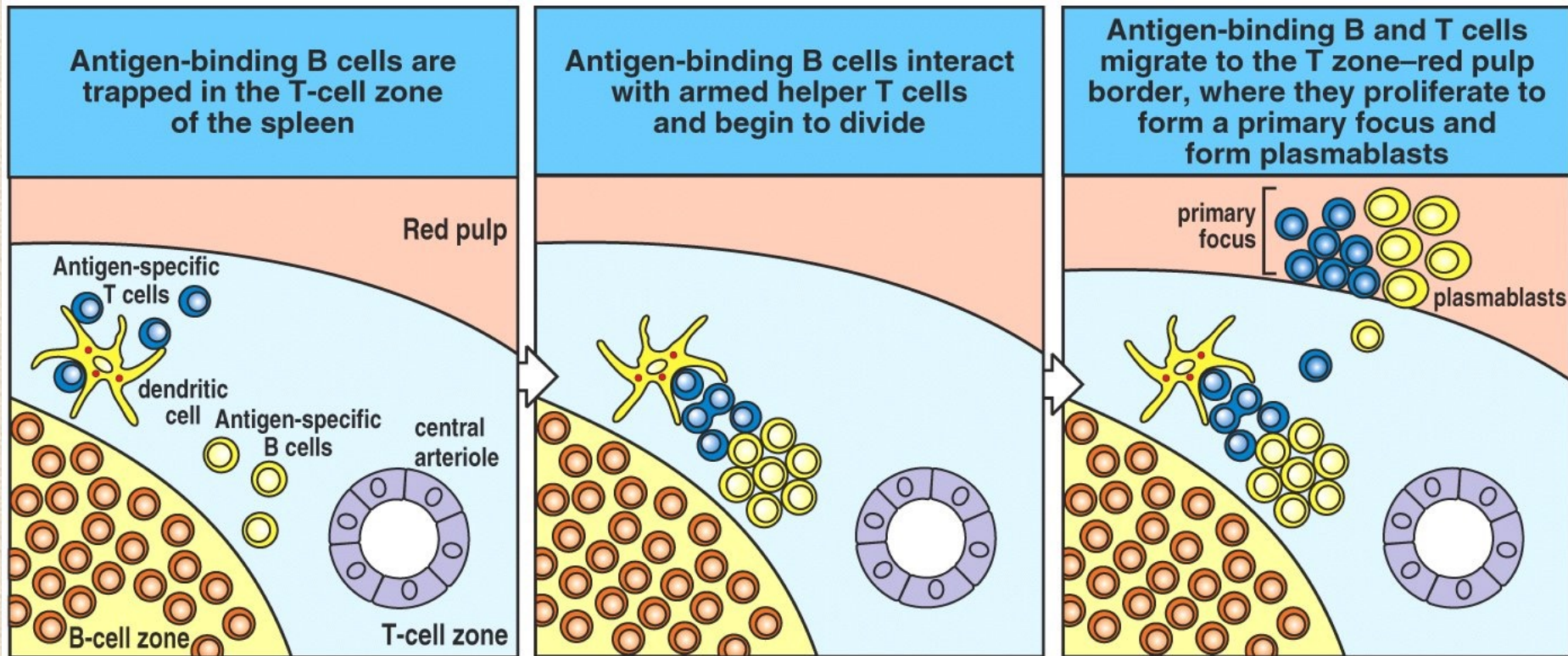


Figure 9-9 Immunobiology, 6/e. (© Garland Science 2005)

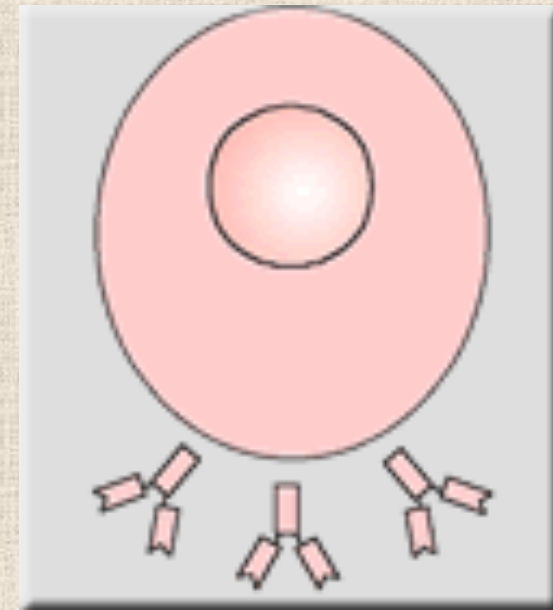
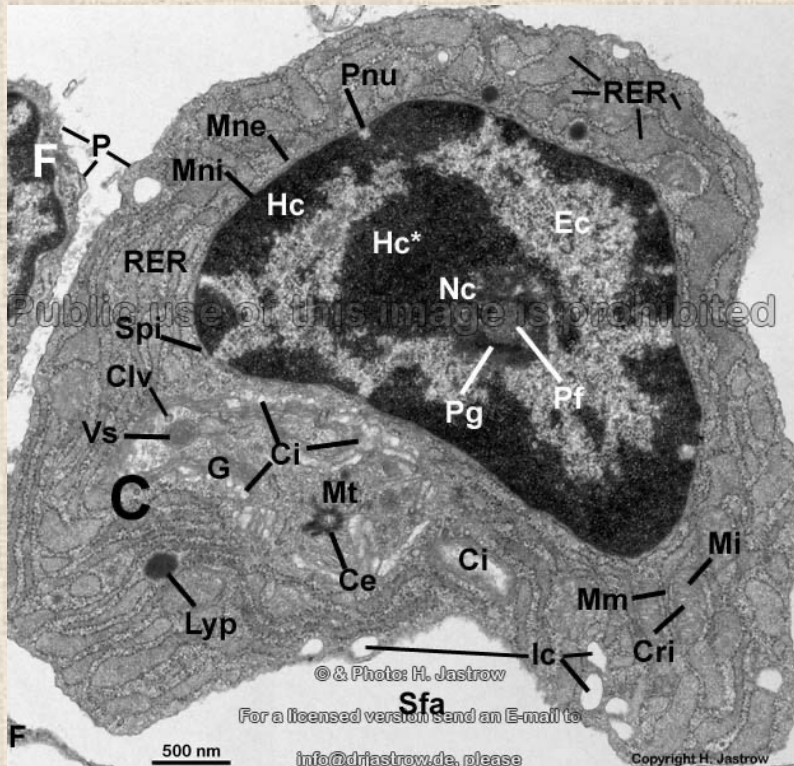
Spleen – marginal Zone binding channels =
T cell-zone/red pulp border

Lymphnodes – parafollicular regions

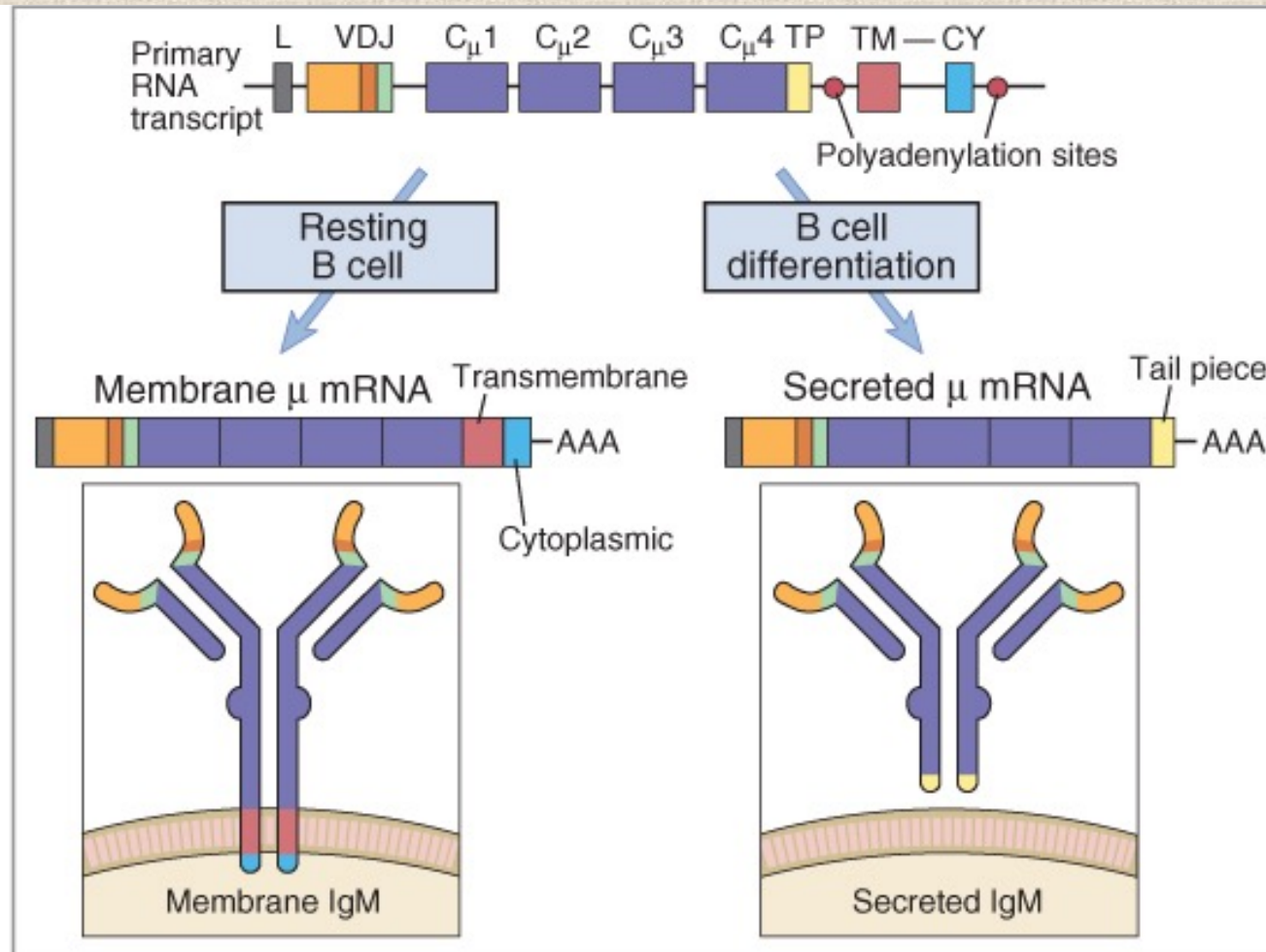
→ **short-lived IgM-secreting plasmacells**

→ **first defense against the antigen**

Plasma cells are the final differentiation forms of the B cells



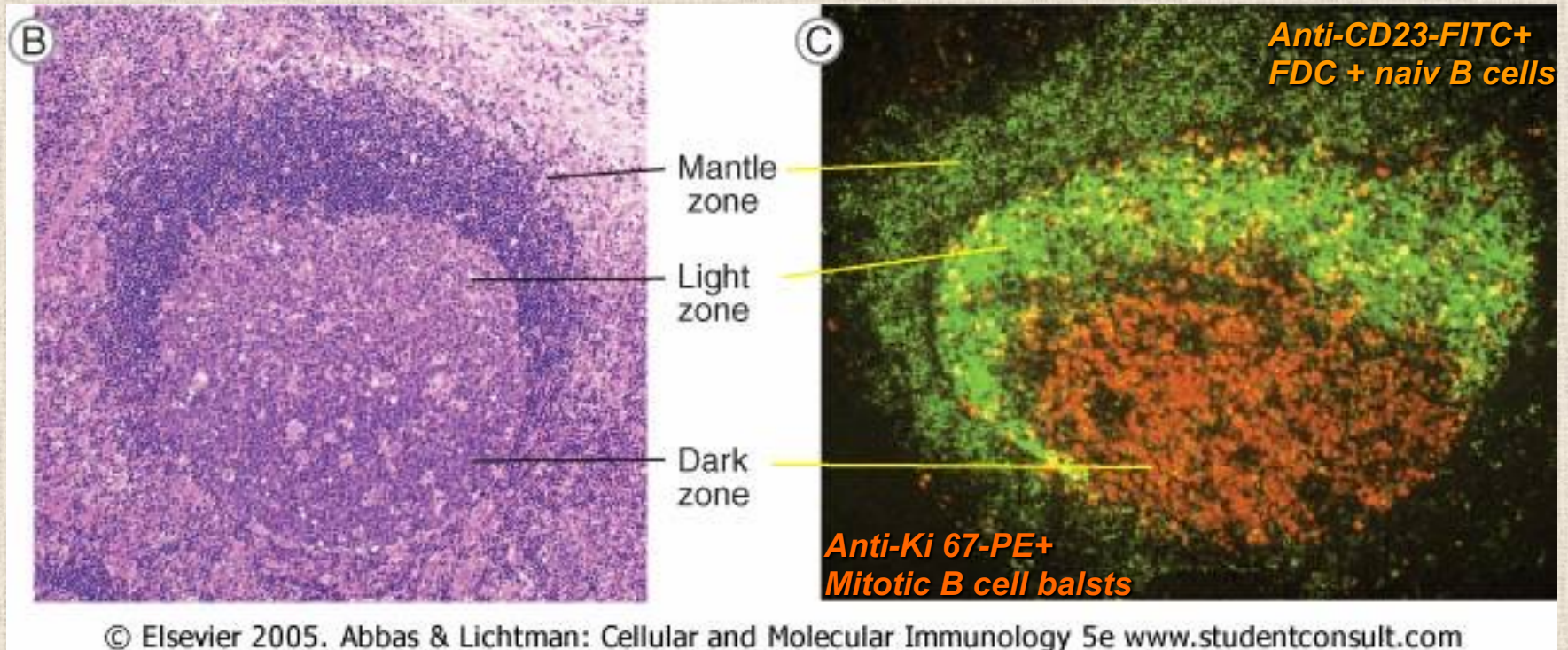
Plasma cells secrete Ig



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**

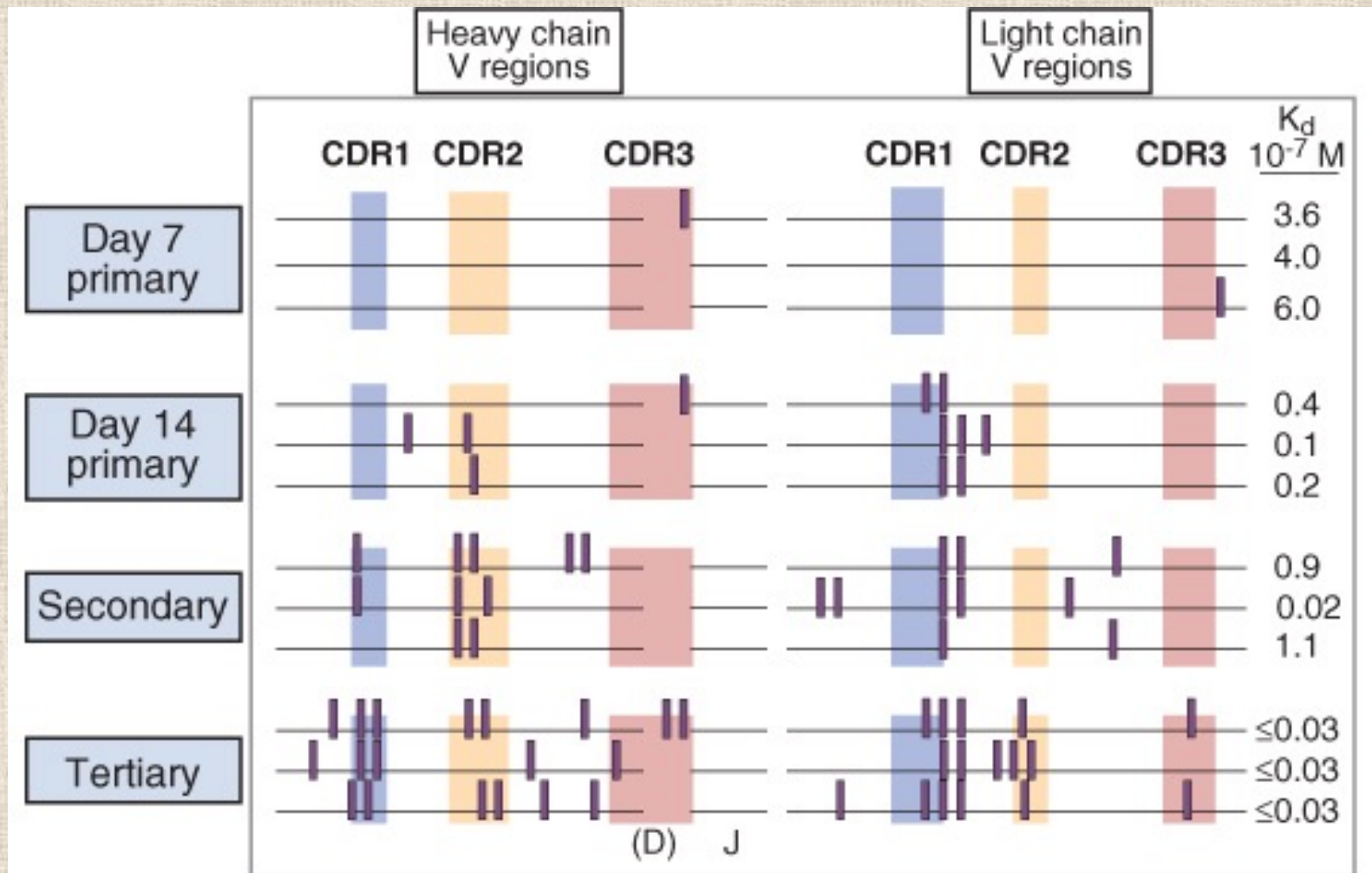
Light zone: centrocytes → decreased proliferation – **affinity maturation**

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.

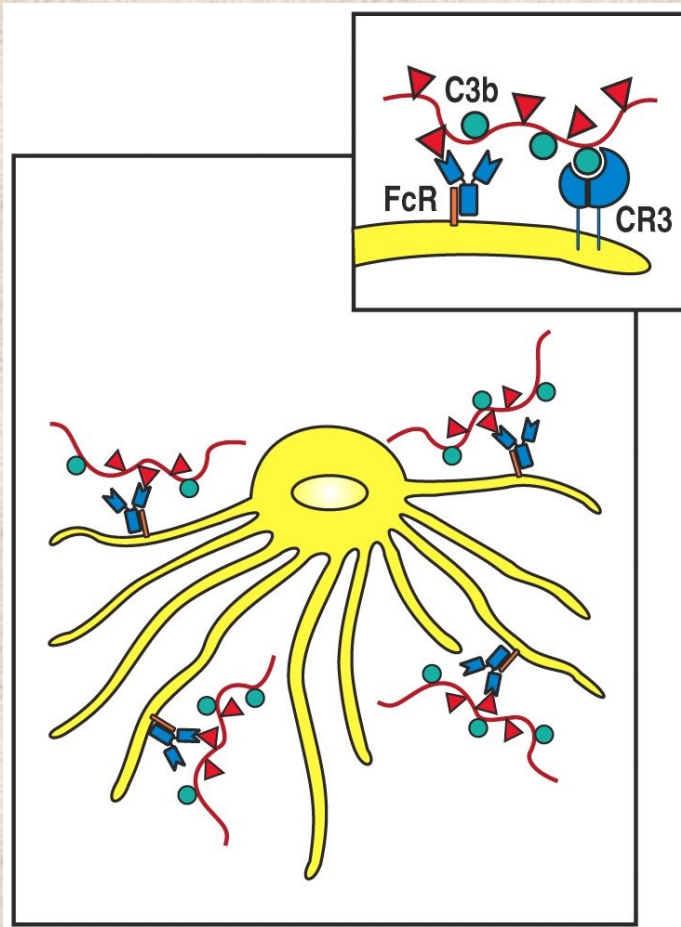
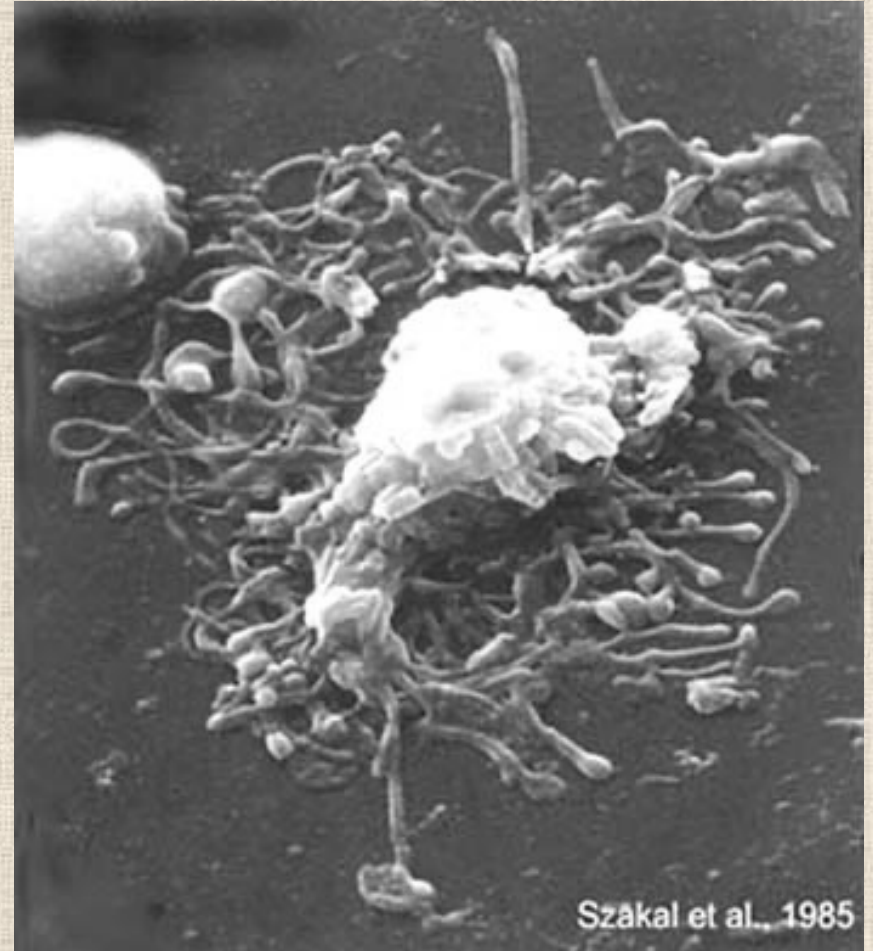


Figure 9-14 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)



Szakal et al., 1985

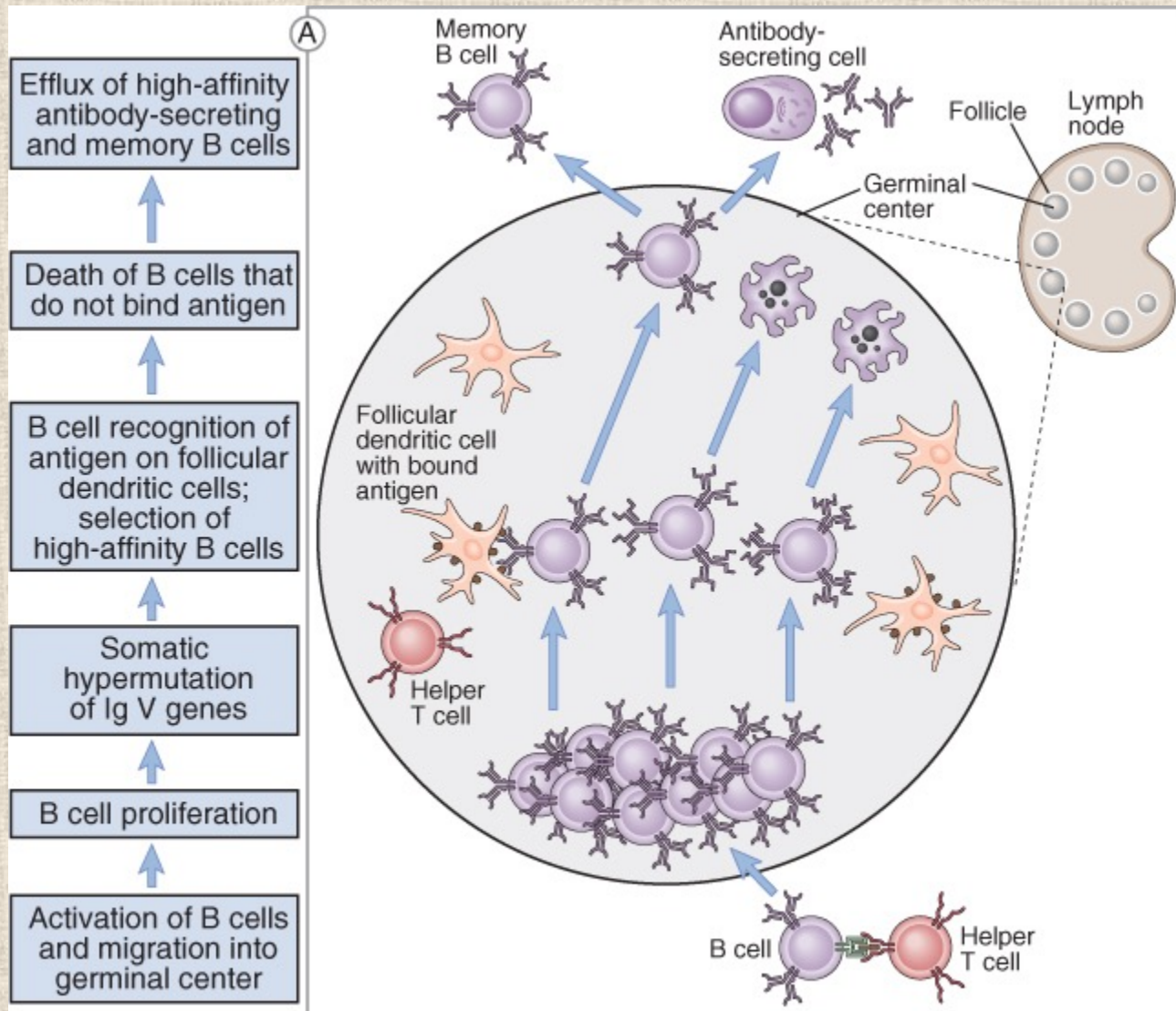
Follicular dendritic cells 2.

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

Function:

- long term storage of antigens in the form of immunocomplexes (*Antibody/Complement*) – ICCOSOME – Centrocytes
- 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

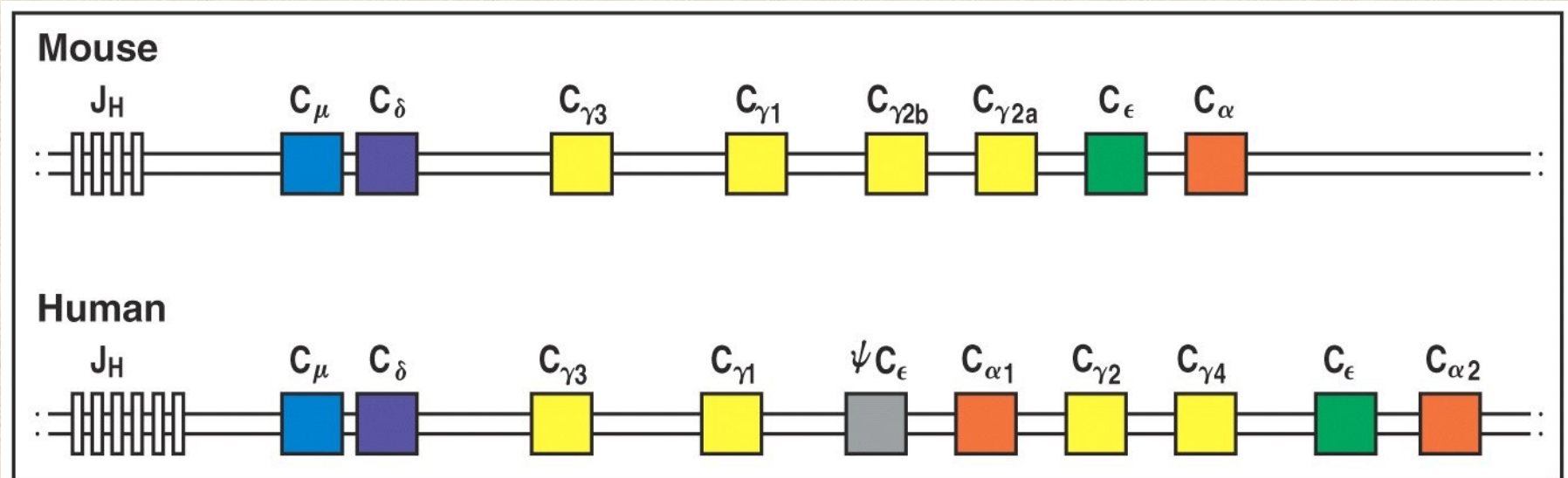
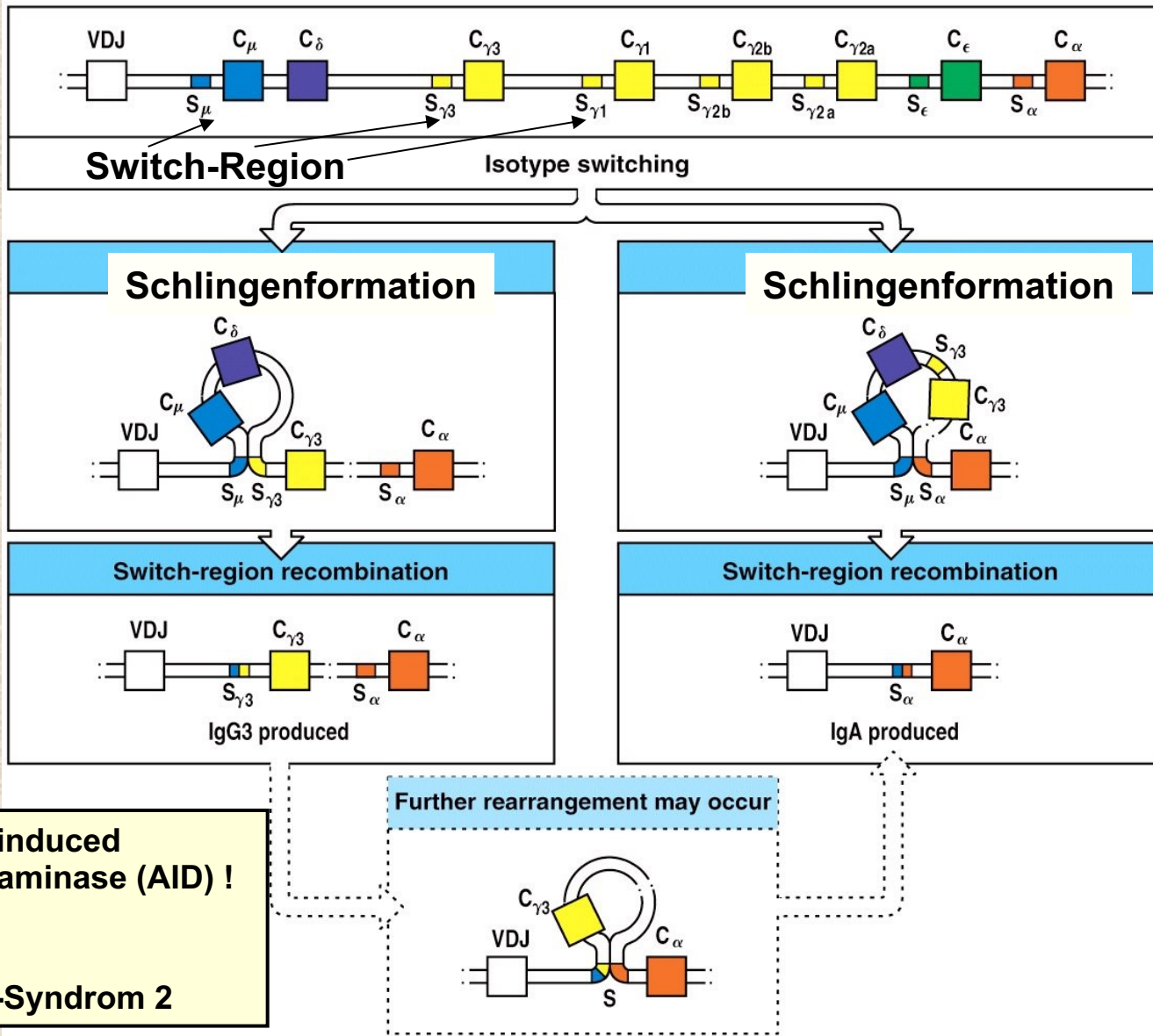


Figure 4-19 Immunobiology, 6/e. (© Garland Science 2005)

Class switch recombination



**activation-induced
Cytidin-Deaminase (AID) !**

Hyper-IgM-Syndrom 2

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

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

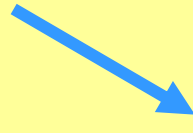


Mature, naive B cell



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:

Lymph nodes –
Blood - Spleen