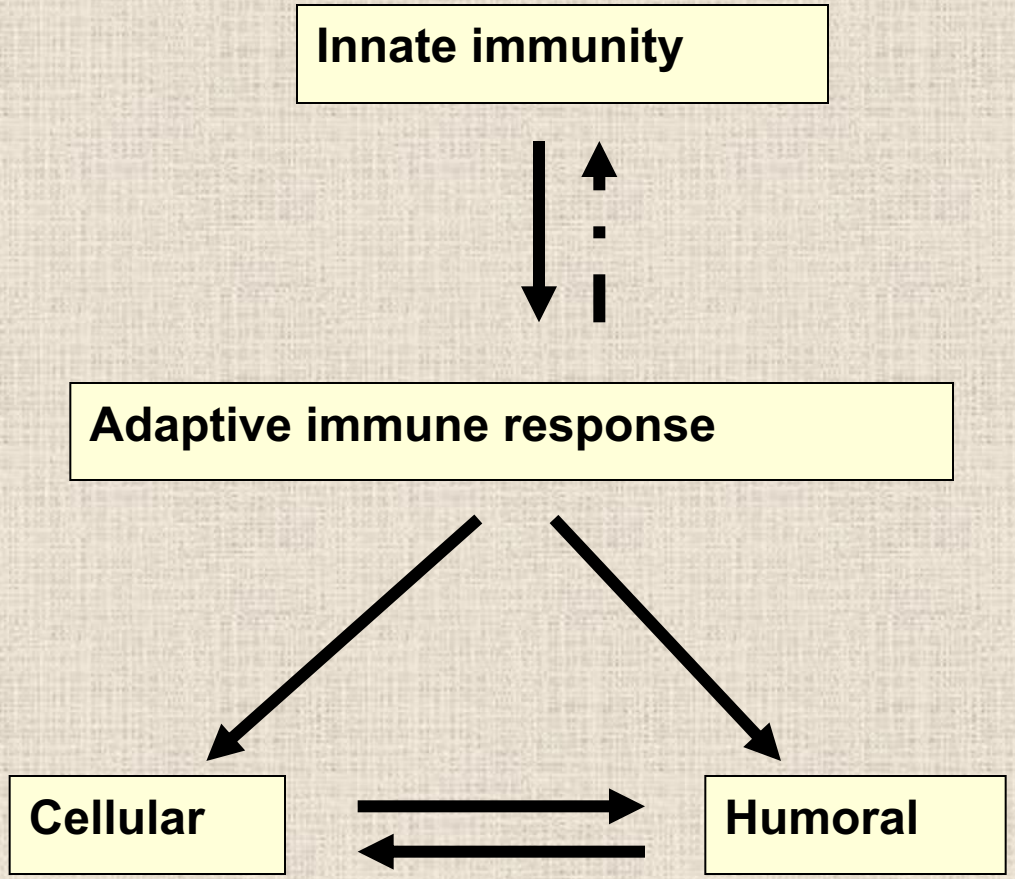
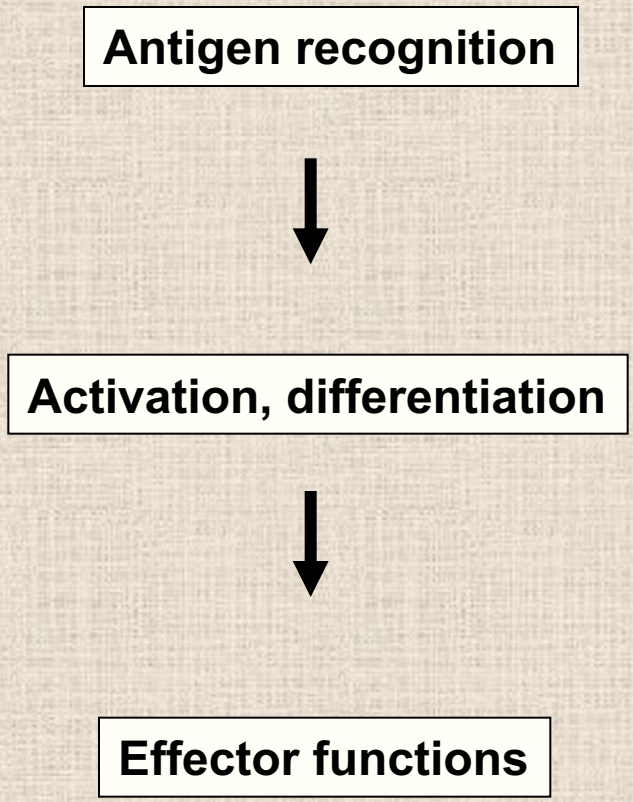
Basic Immunology

Initial phase of the immune response:
T cell activation, CD3 complex and signaling.
Costimulation. Peripheral T cell differentiation.

Ferenc Boldizsar


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

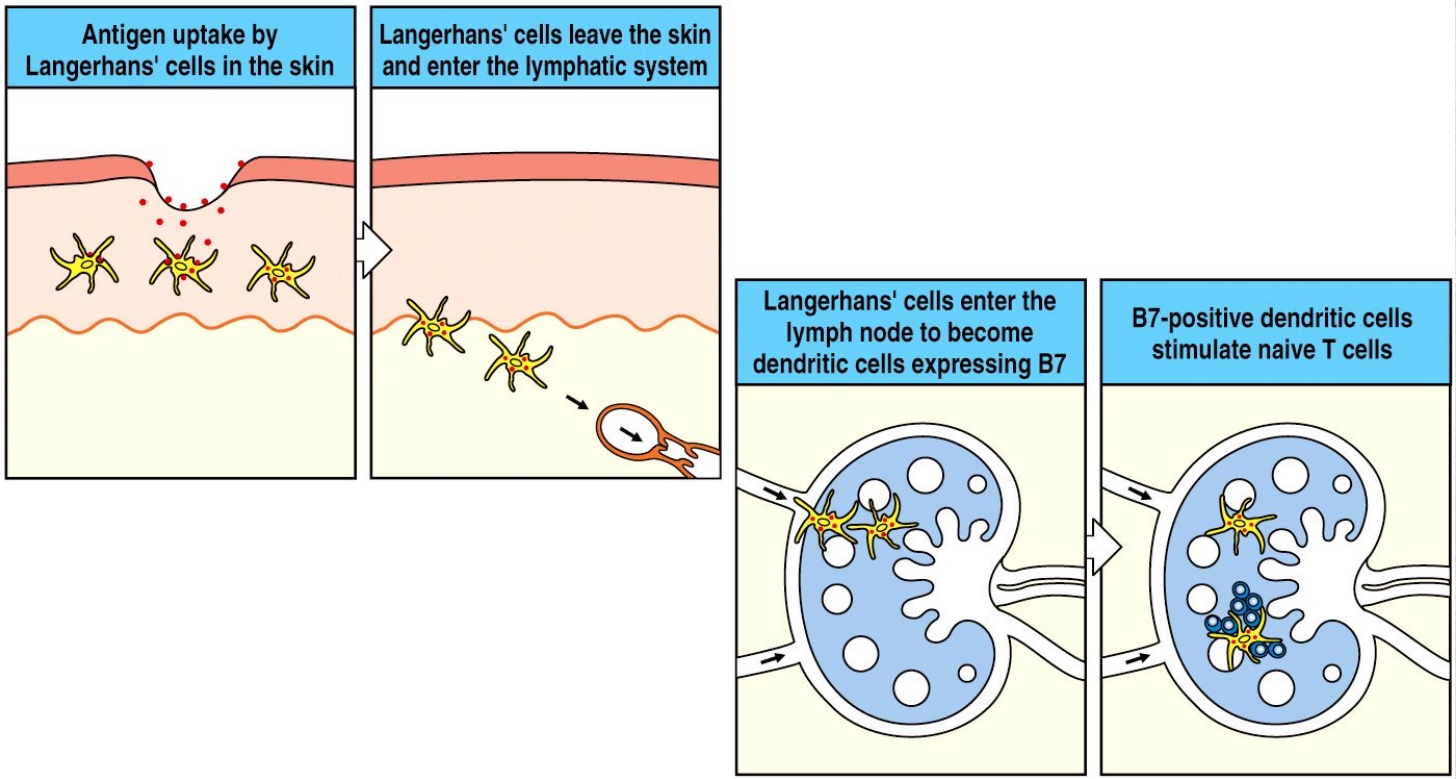


Figure 8-15 Immunobiology, 6/e. (© Garland Science 2005)

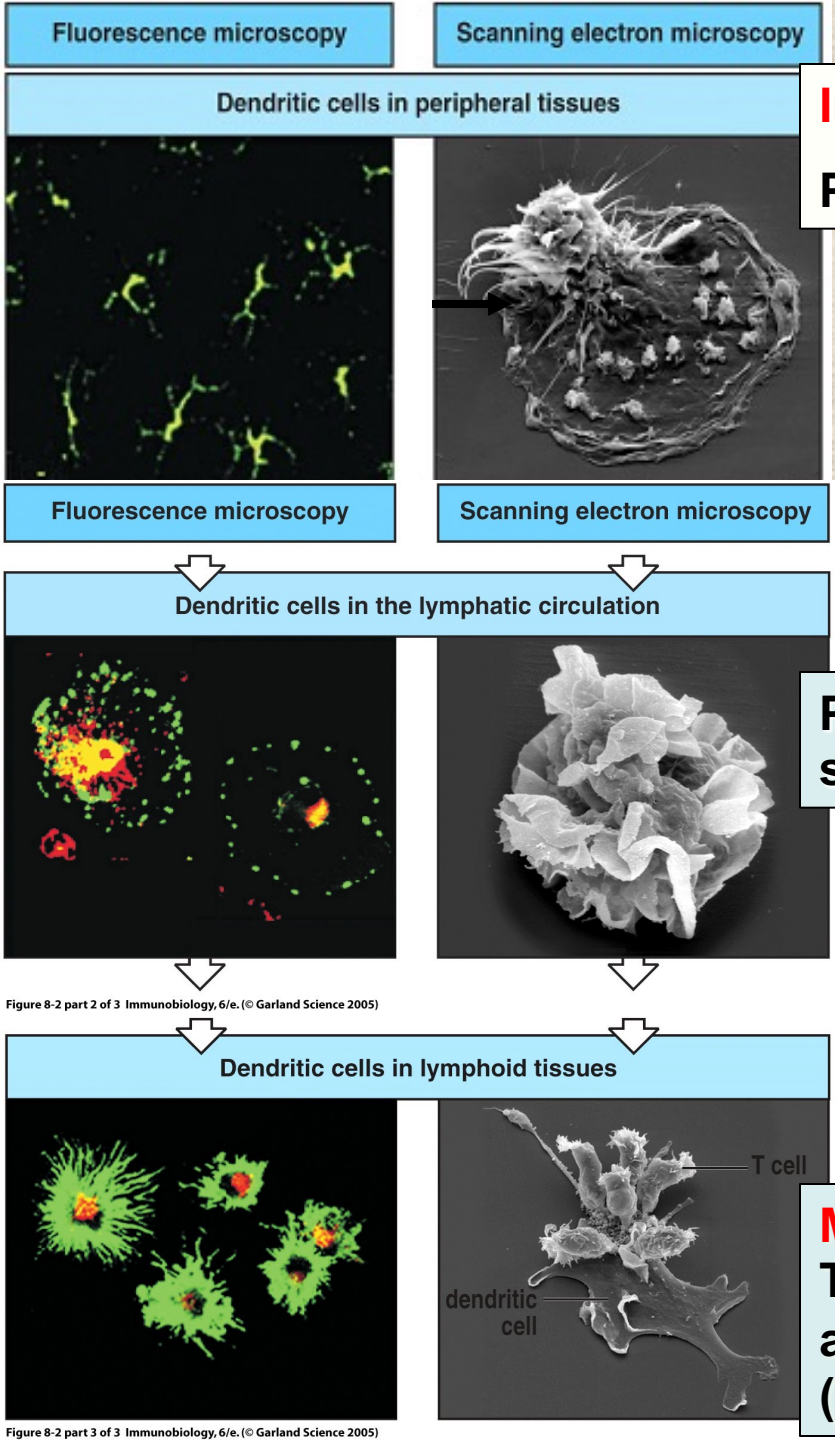
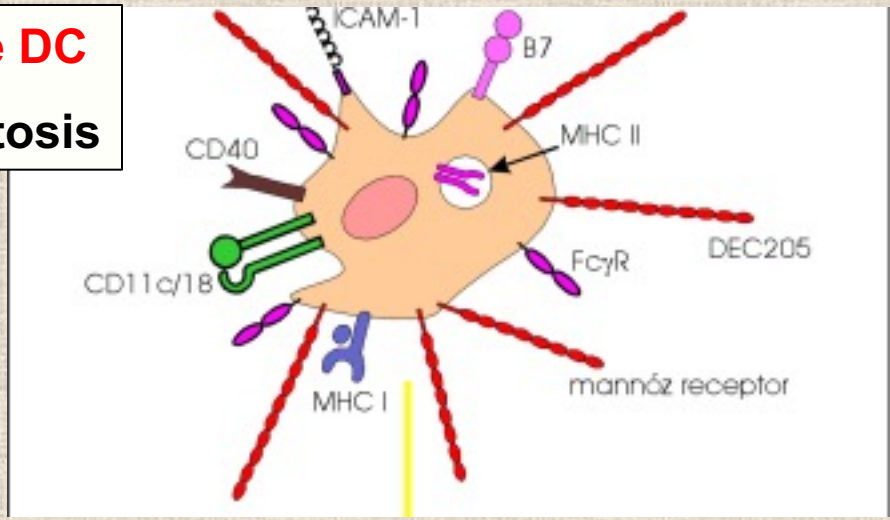


Figure 8-2 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

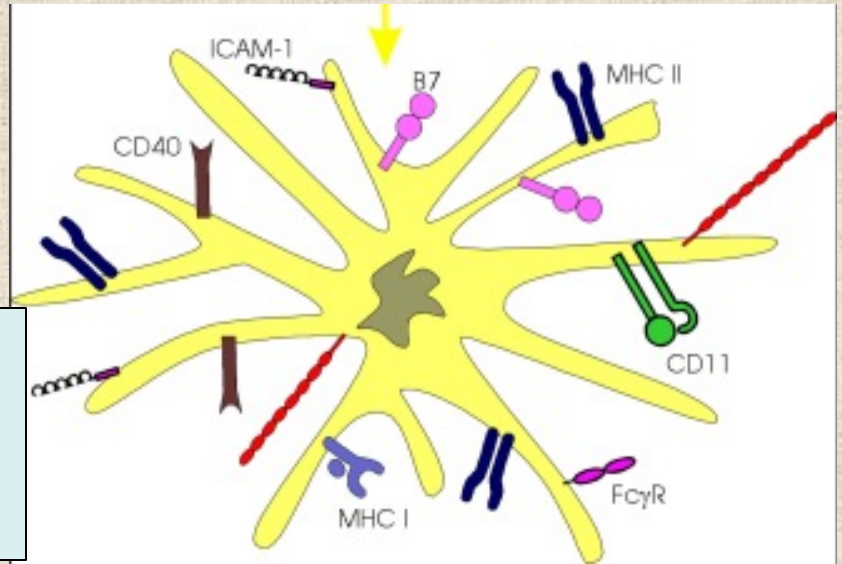
Figure 8-2 part 3 of 3 Immunobiology, 6/e. (© Garland Science 2005)

Immature DC

Phagocytosis



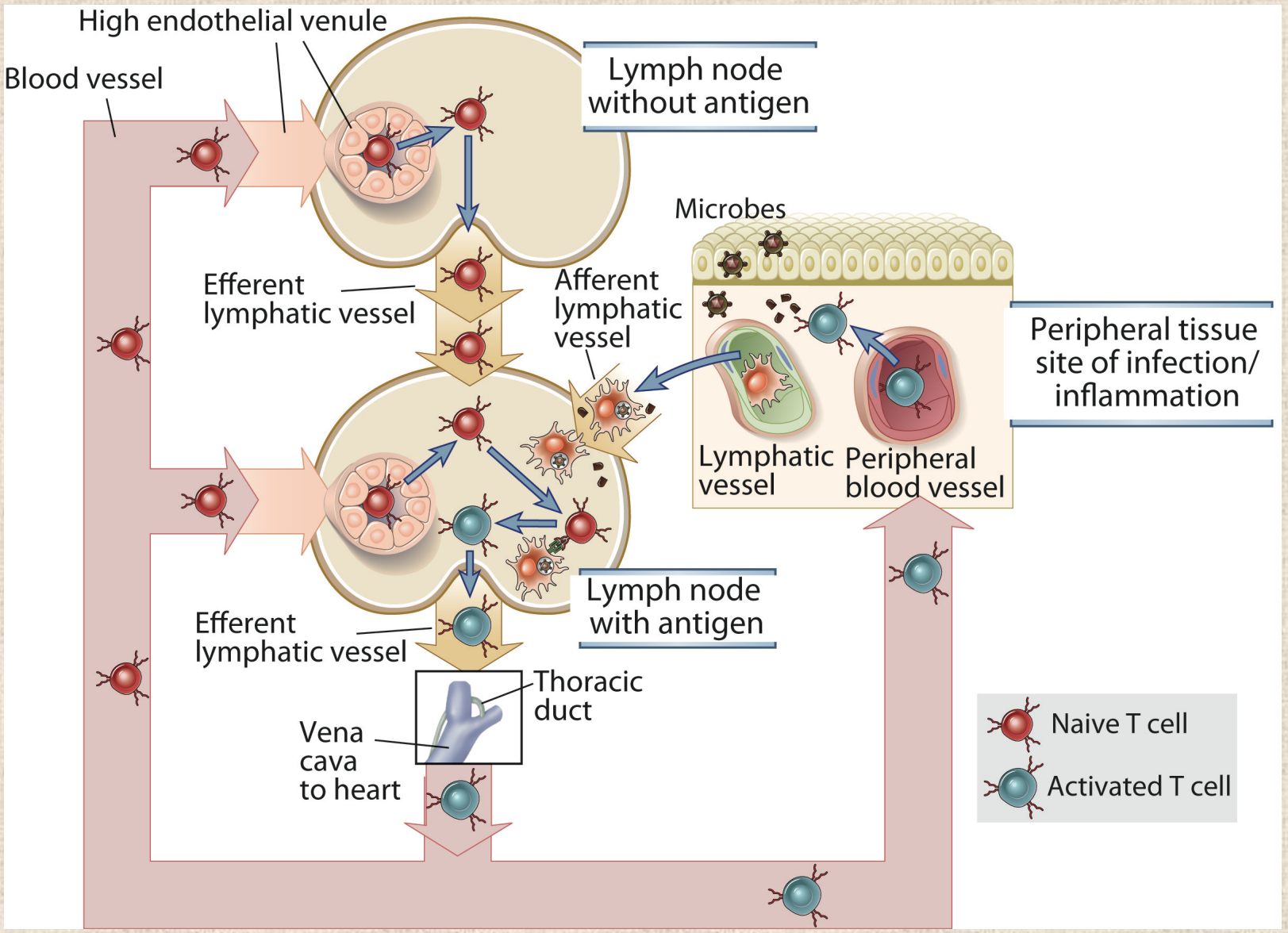
Phagocytosis stops



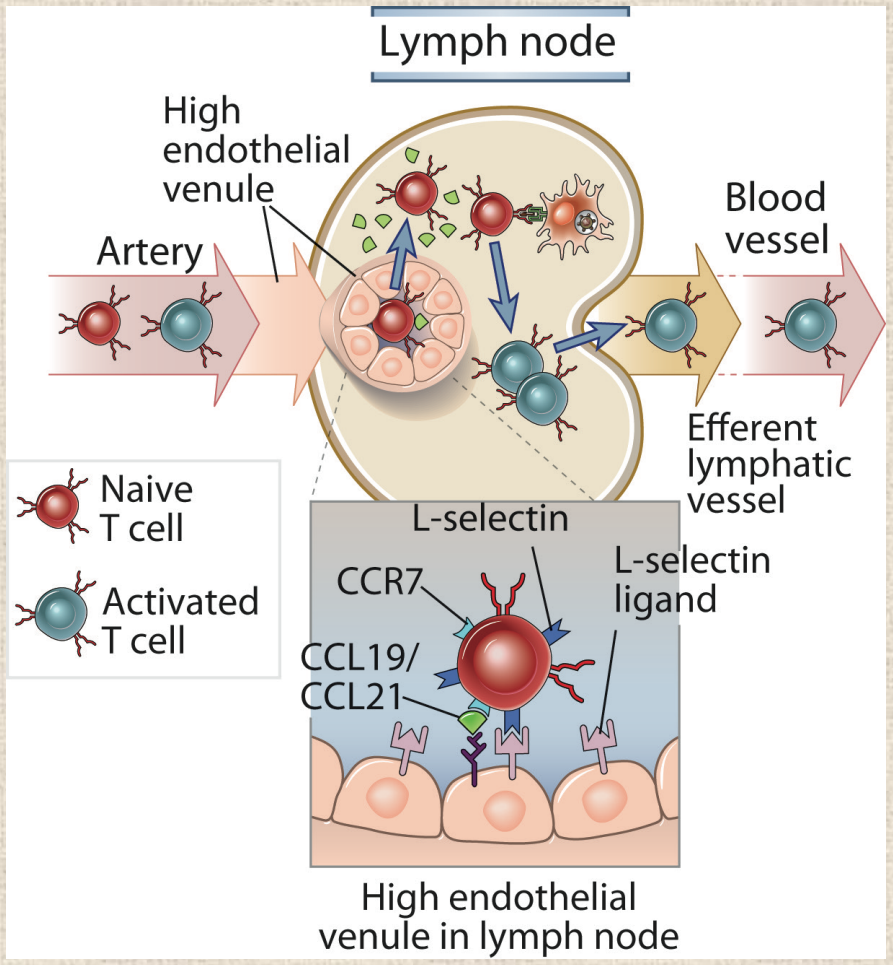
Mature DC

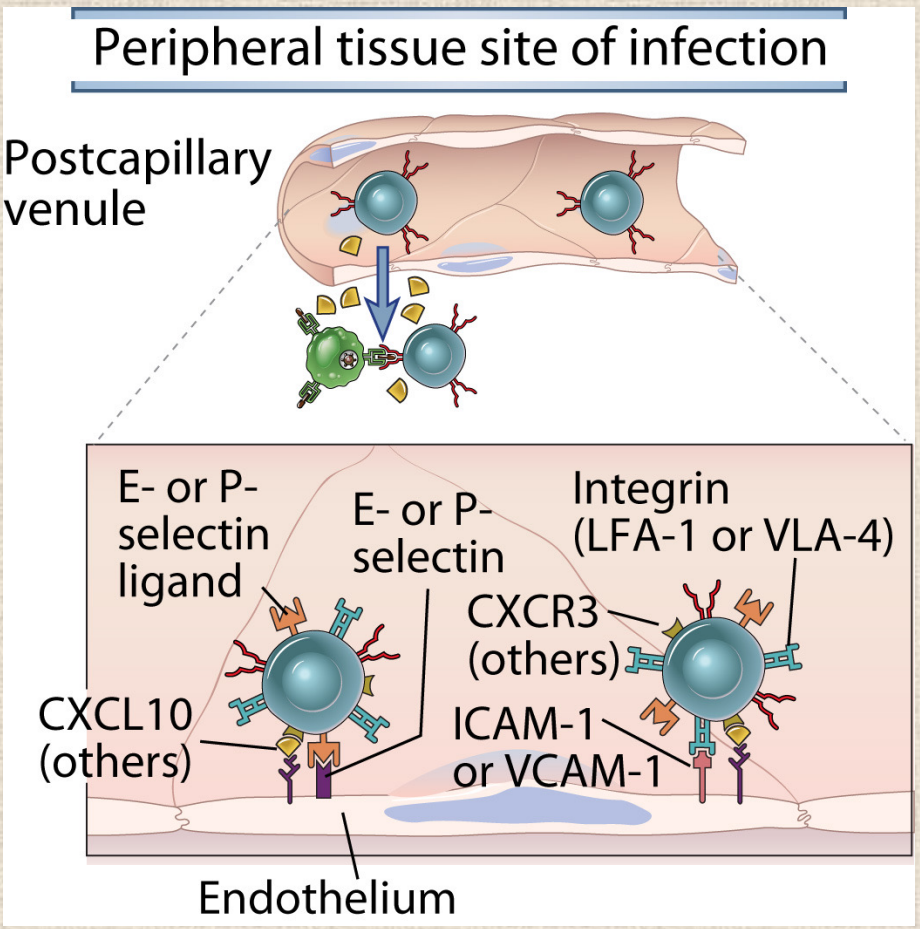
T cell activation (B7)

T cell recirculation

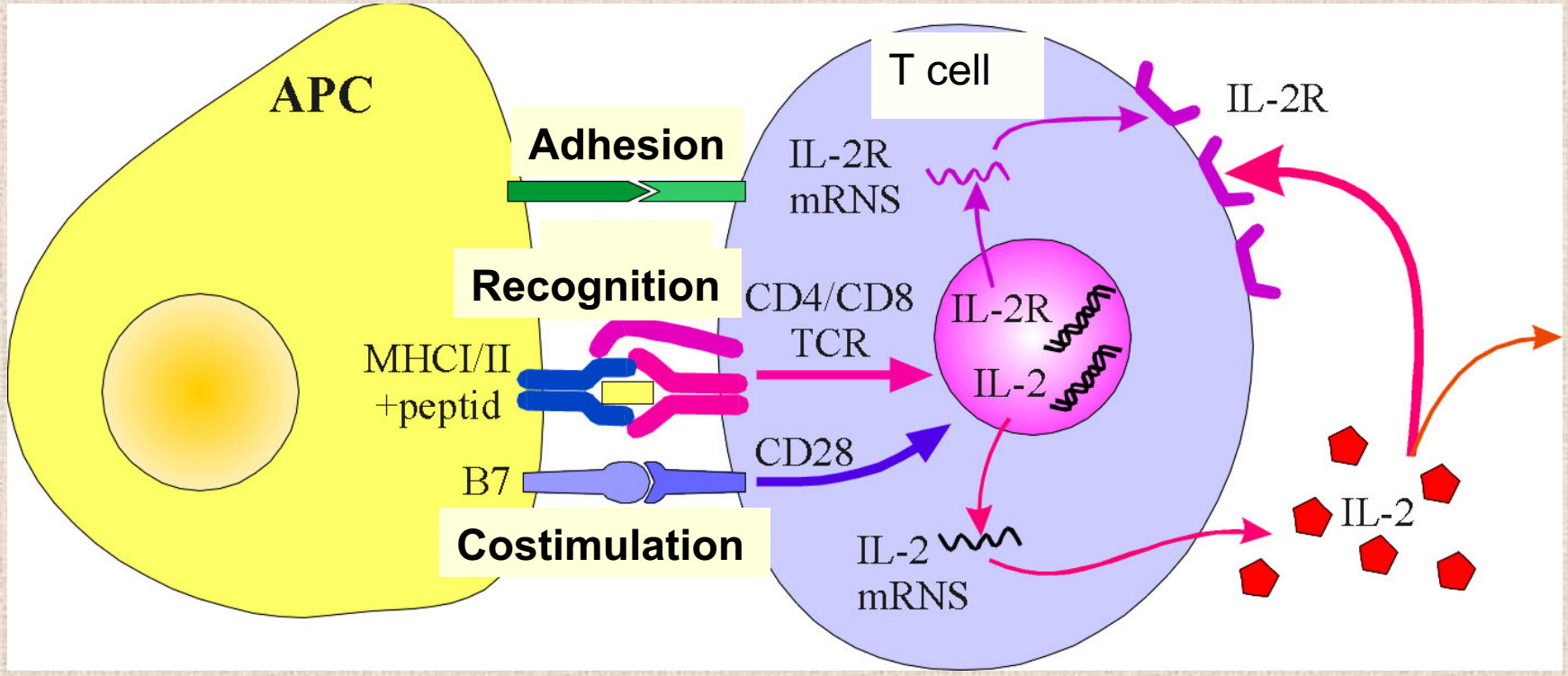


Regulation of T cell recirculation



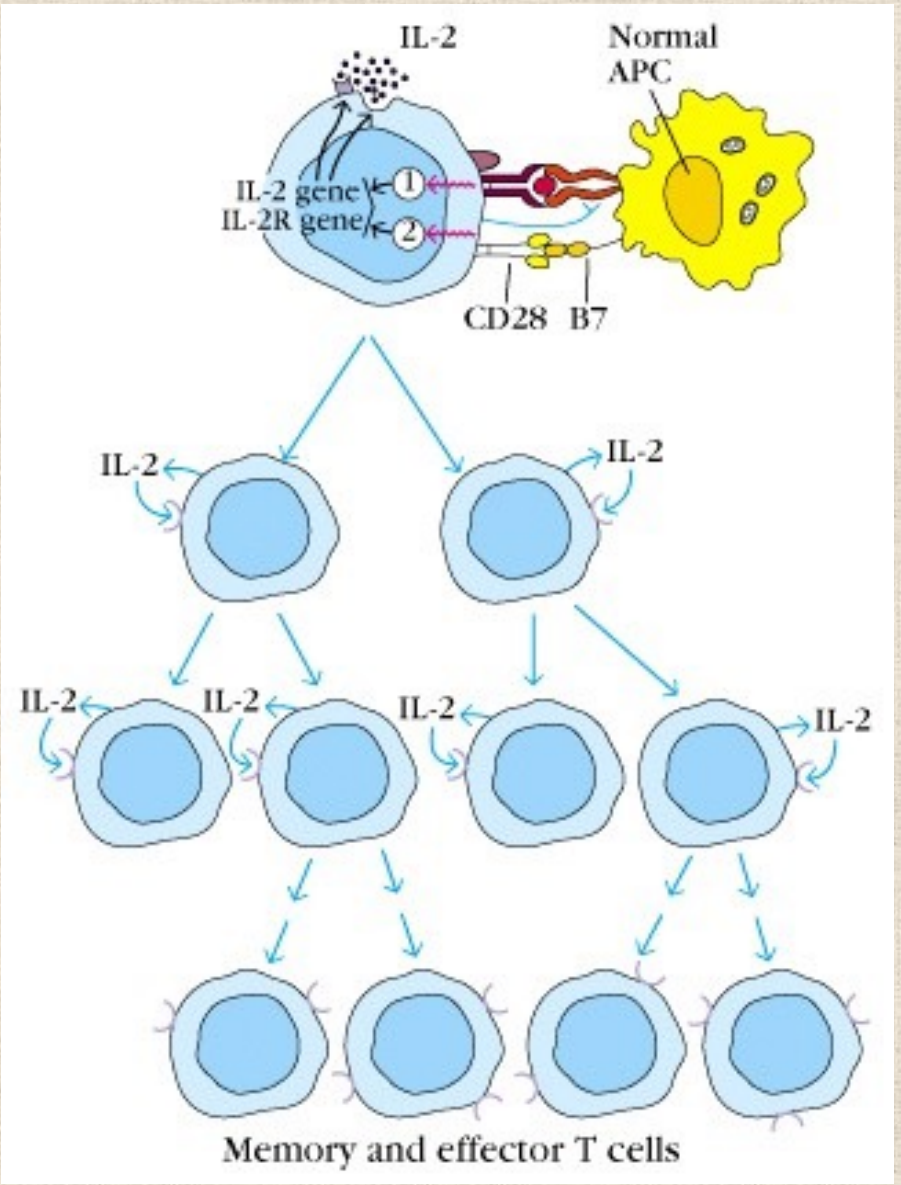


T cell activation



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

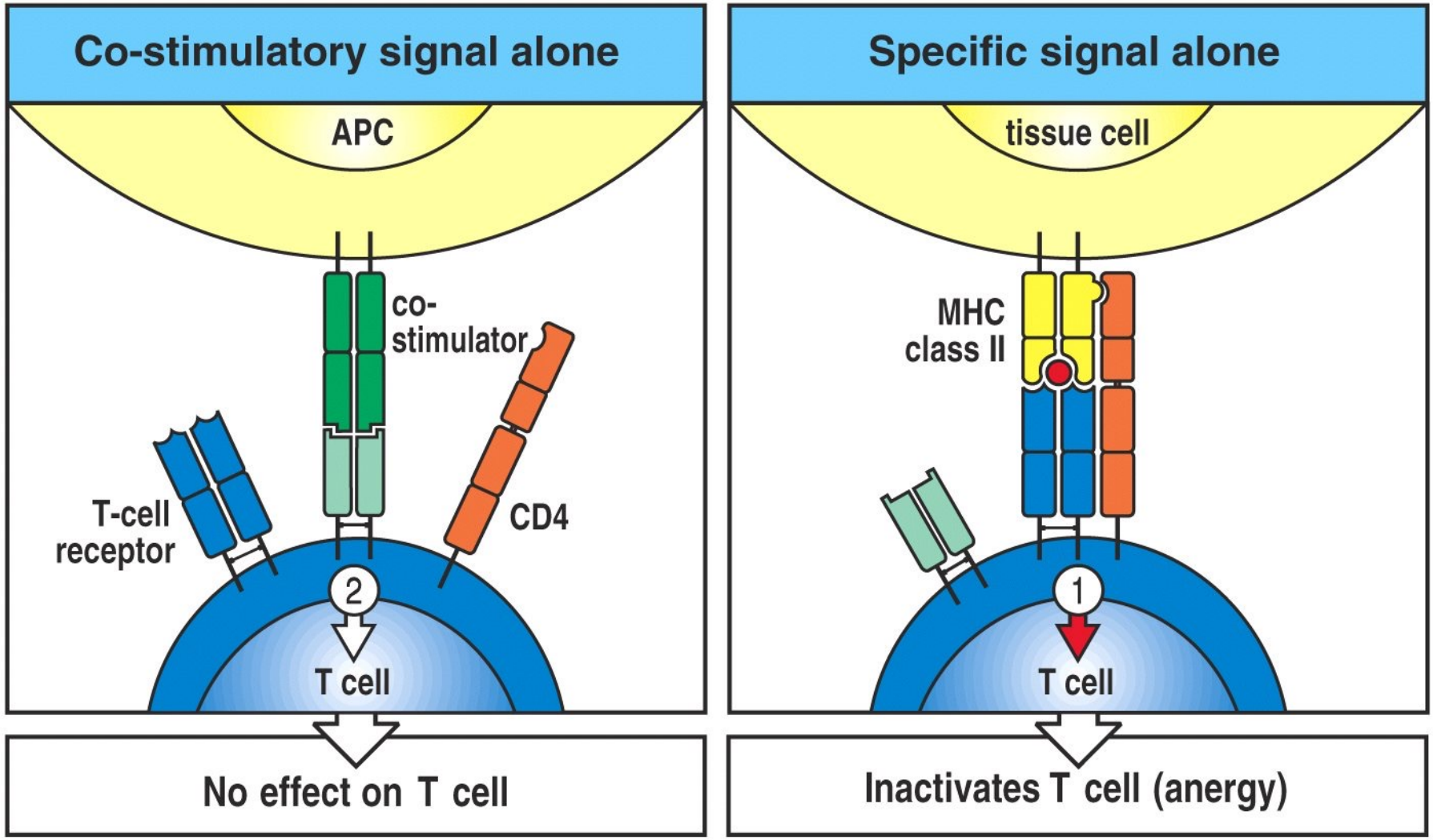
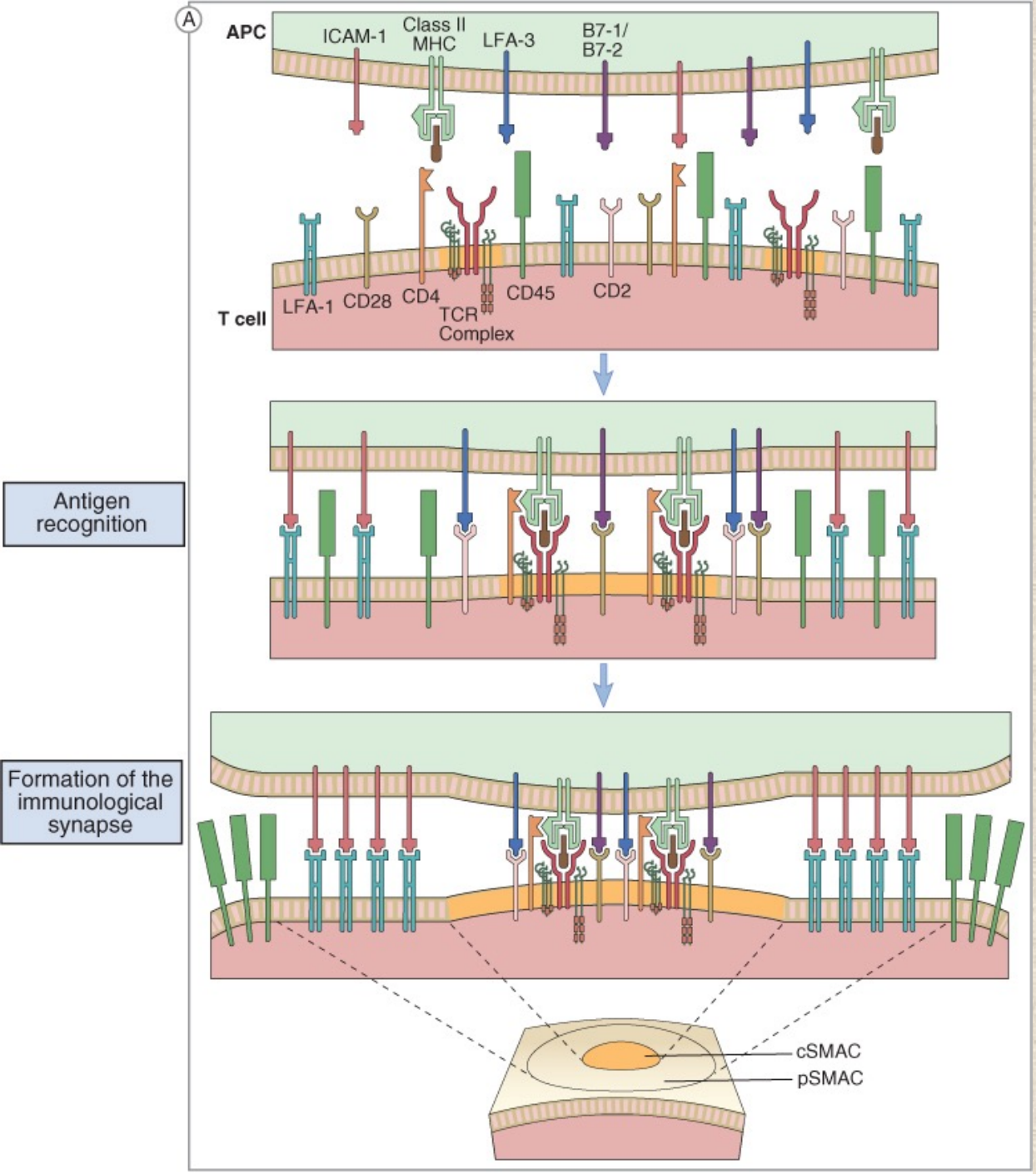


Figure 8-21 Immunobiology, 6/e. (© Garland Science 2005)



The immunological synapse

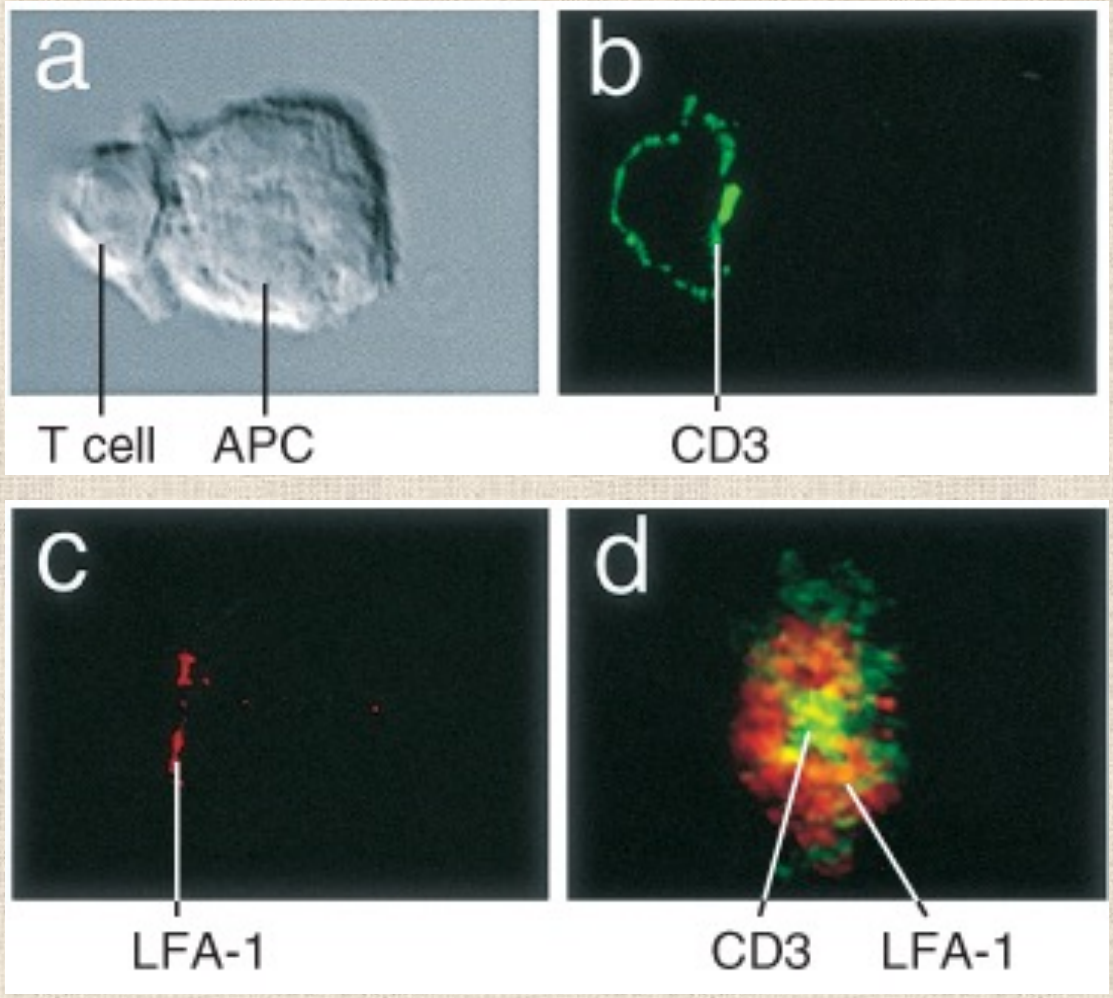
(A. Kupfer, M. Dustin)

=activation interface between the T cell and APC

SMAC=supramolecular activation complex

- **Central (c)** - TcR complex, CD4, CD28
- **Peripheral (p)** - adhesion molecules eg. LFA-1
- **CD45 exclusion**

The immunological synapse



Outer ring (red) pSMAC	Inner circle (green) cSMAC
LFA-1:ICAM-1	TCR, CD4, CD28 MHC:peptide

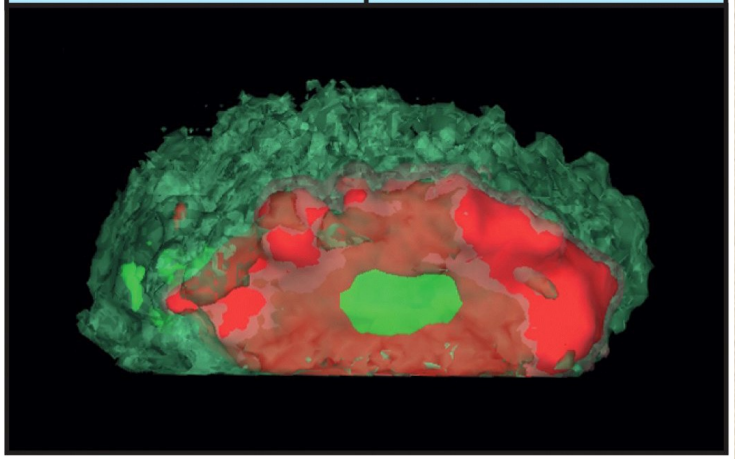
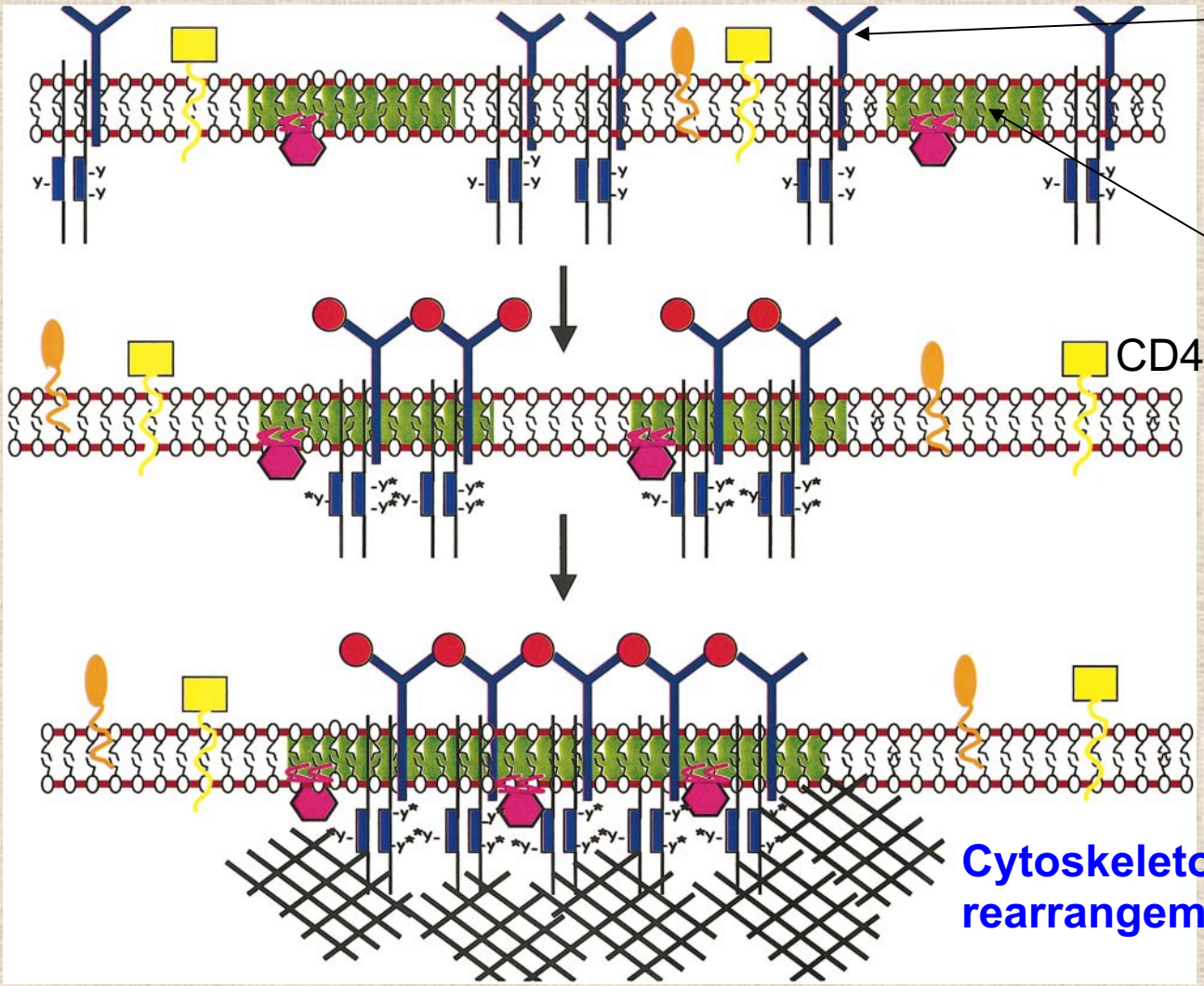


Figure 8-30 Immunobiology, 6/e. (© Garland Science 2005)

1. Resting cell - antigen recognition receptors outside of rafts

2.Antigen binding→ receptor oligomerization →raft association

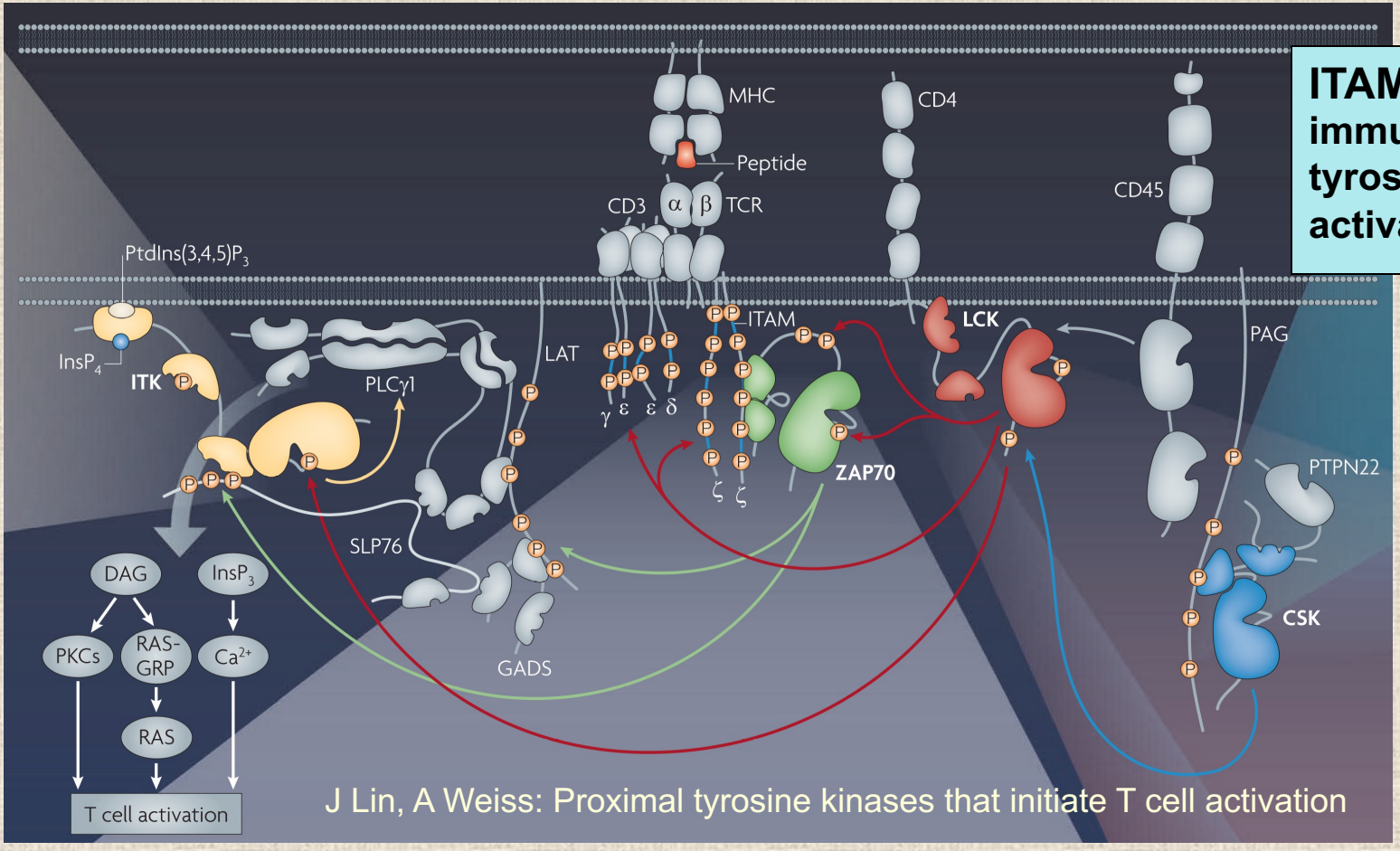
3.Raft clustering - development of the immunological synapse



M. Dykstra, A. Cherukuri, S.K. Pierce: Rafts and synapses in the spatial organization of immune cell signaling receptors J. Leukoc. Biol. 70: 699–707; 2001.

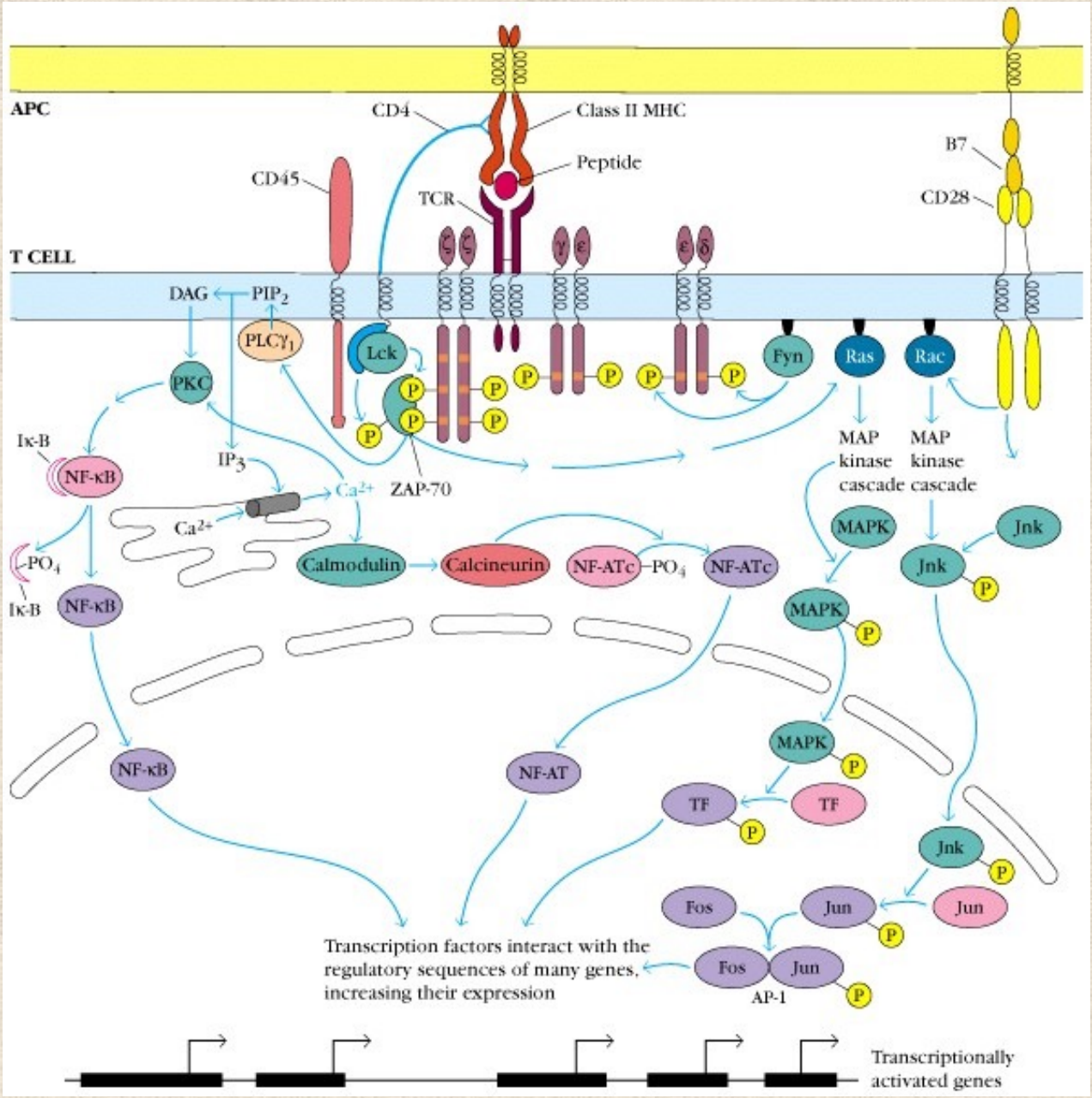
Lipid rafts=cholesterol&sfingolipid containing membrane microdomains - more “rigid”, than other membrane regions → provide optimal platform for the immunoreceptor signaling molecules (10-200nm)

TcR signaling - early steps



ITAM= immunoreceptor tyrosine-based activation motif

1. After TcR cross linking coreceptors (CD4, CD3, CD45) associate to TcR
2. Protein tirosine kinase (PTK) Lck and Fyn activation: CD45 phosphatase removes an inhibitory phosphate
3. Fyn and Lck phosphorylates ITAMs of the CD3 complex
4. ZAP-70 PTK “docks” to the phosphorylated ITAMS of the ζ-chain and phosphorylates



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

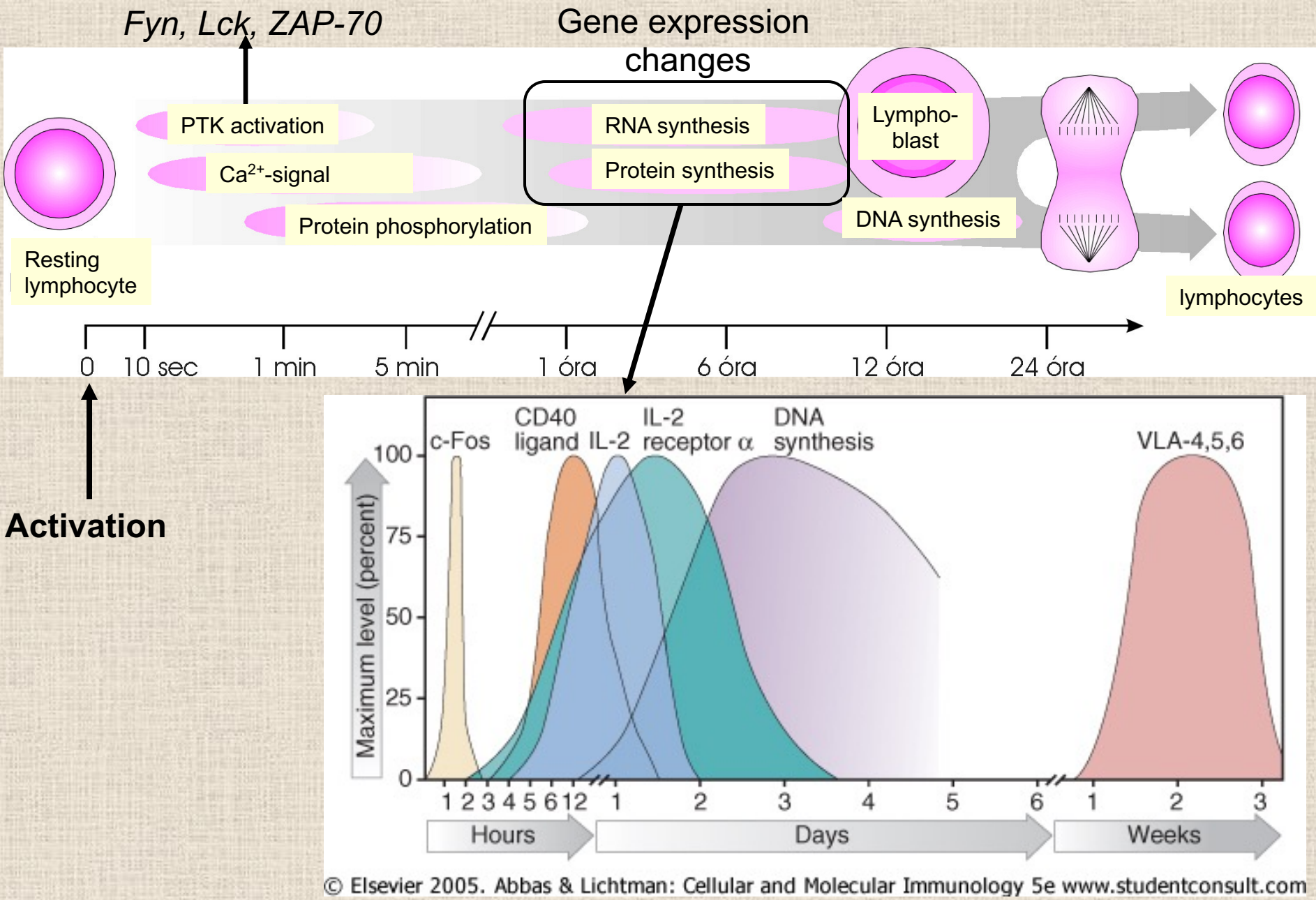


TABLE 10-3 TIME COURSE OF GENE EXPRESSION BY T_H CELLS FOLLOWING INTERACTION WITH ANTIGEN

Gene product	Function	Time mRNA expression begins	Location	Ratio of activated to nonactivated cells
		Immediate		
c-Fos	Protooncogene; nuclear-binding protein	15 min	Nucleus	> 100
c-Jun	Cellular oncogene; transcription factor	15–20 min	Nucleus	?
NF-AT	Transcription factor	20 min	Nucleus	50
c-Myc	Cellular oncogene	30 min	Nucleus	20
NF-κB	Transcription factor	30 min	Nucleus	> 10
		Early		
IFN-γ	Cytokine	30 min	Secreted	> 100
IL-2	Cytokine	45 min	Secreted	> 1000
Insulin receptor	Hormone receptor	1 h	Cell membrane	3
IL-3	Cytokine	1–2 h	Secreted	> 100
TGF-β	Cytokine	<2 h	Secreted	> 10
IL-2 receptor (p55)	Cytokine receptor	2 h	Cell membrane	> 50
TNF-β	Cytokine	1–3 h	Secreted	> 100
Cyclin	Cell-cycle protein	4–6 h	Cytoplasmic	> 10
IL-4	Cytokine	<6 h	Secreted	> 100
IL-5	Cytokine	<6 h	Secreted	> 100
IL-6	Cytokine	<6 h	Secreted	> 100
c-Myb	Protooncogene	16 h	Nucleus	100
GM-CSF	Cytokine	20 h	Secreted	?
		Late		
HLA-DR	Class II MHC molecule	3–5 days	Cell membrane	10
VLA-4	Adhesion molecule	4 days	Cell membrane	> 100
VLA-1, VLA-2, VLA-3, VLA-5	Adhesion molecules	7–14 days	Cell membrane	> 100, ?, ?, ?

SOURCE: Adapted from G Crabtree, *Science* **243**:357.

Main consequences of T cell activation

1. ***Clonal proliferation (expansion)*** – IL-2-mediated autocrine signaling; CD25

2. Peripheral T helper cell differentiation/polarization – different functional subgroups based on cytokine production ➔regulation of the immune response

3. CTLA-4 expression – stopping of the activation

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

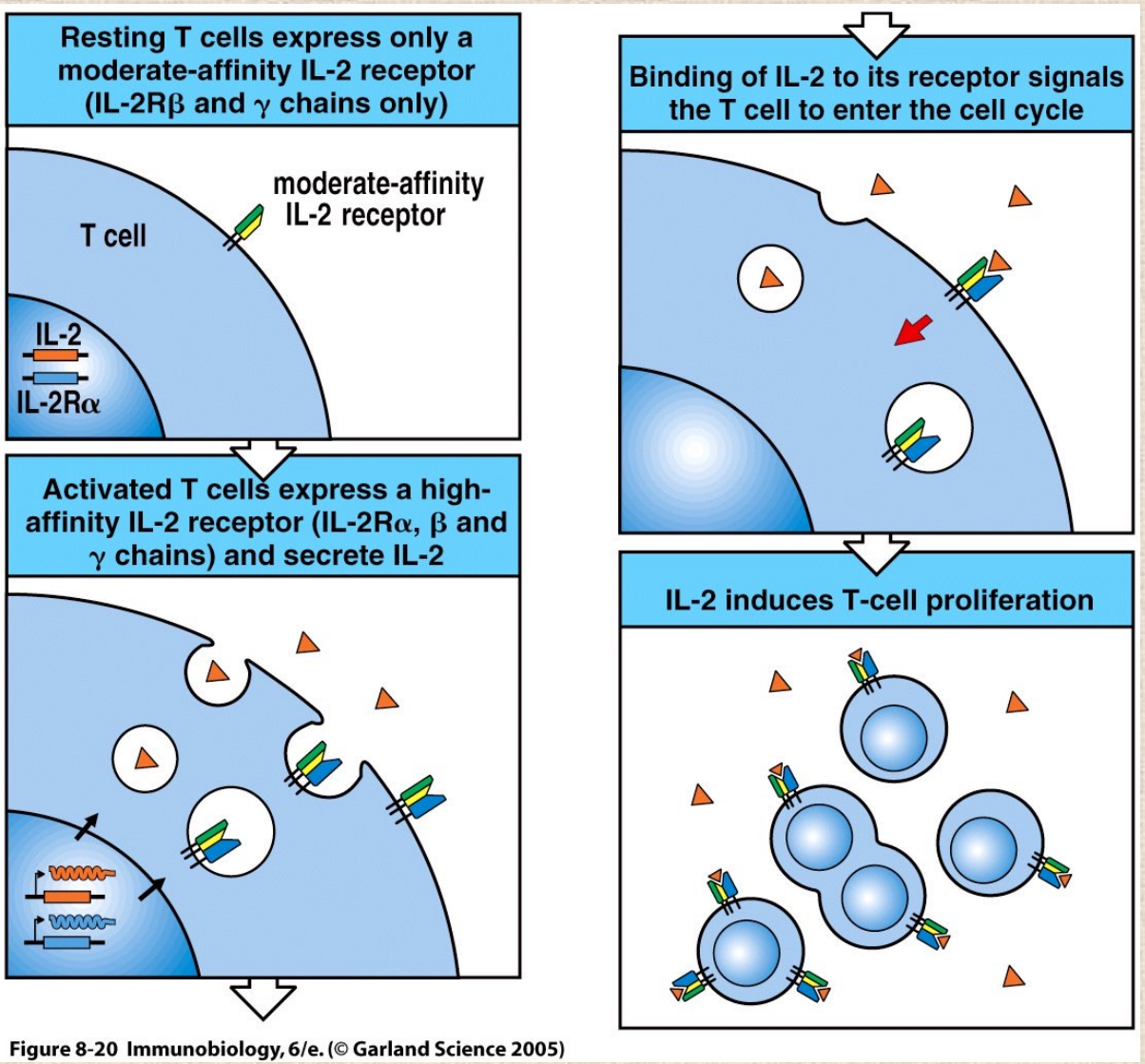
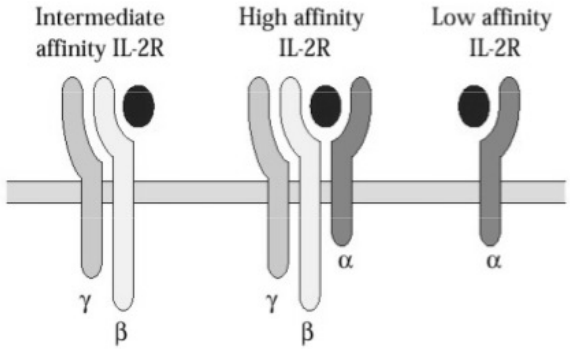
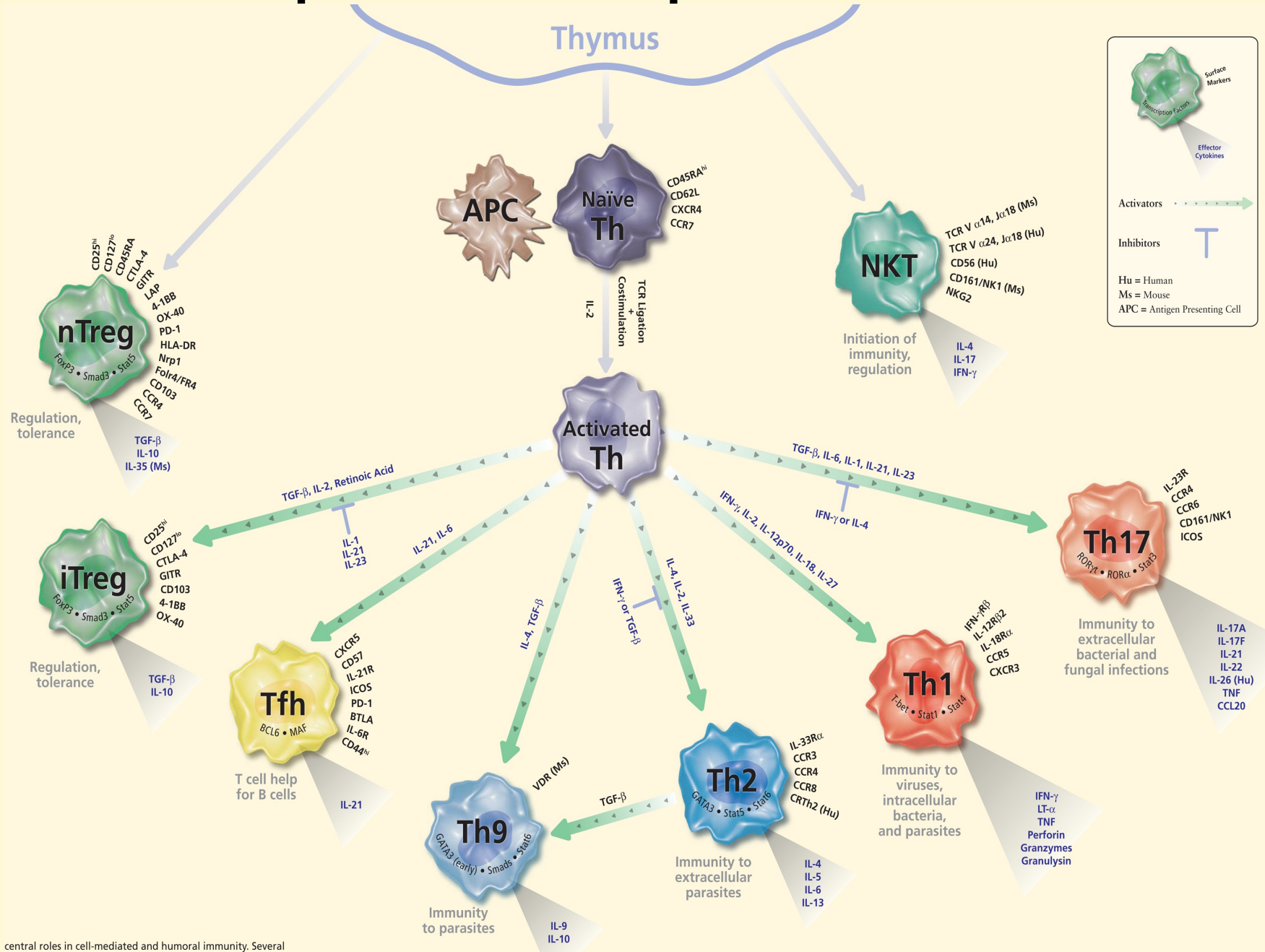


Figure 8-20 Immunobiology, 6/e. (© Garland Science 2005)

IL-2 receptor chains:



Helper T cell polarization



central roles in cell-mediated and humoral immunity. Several

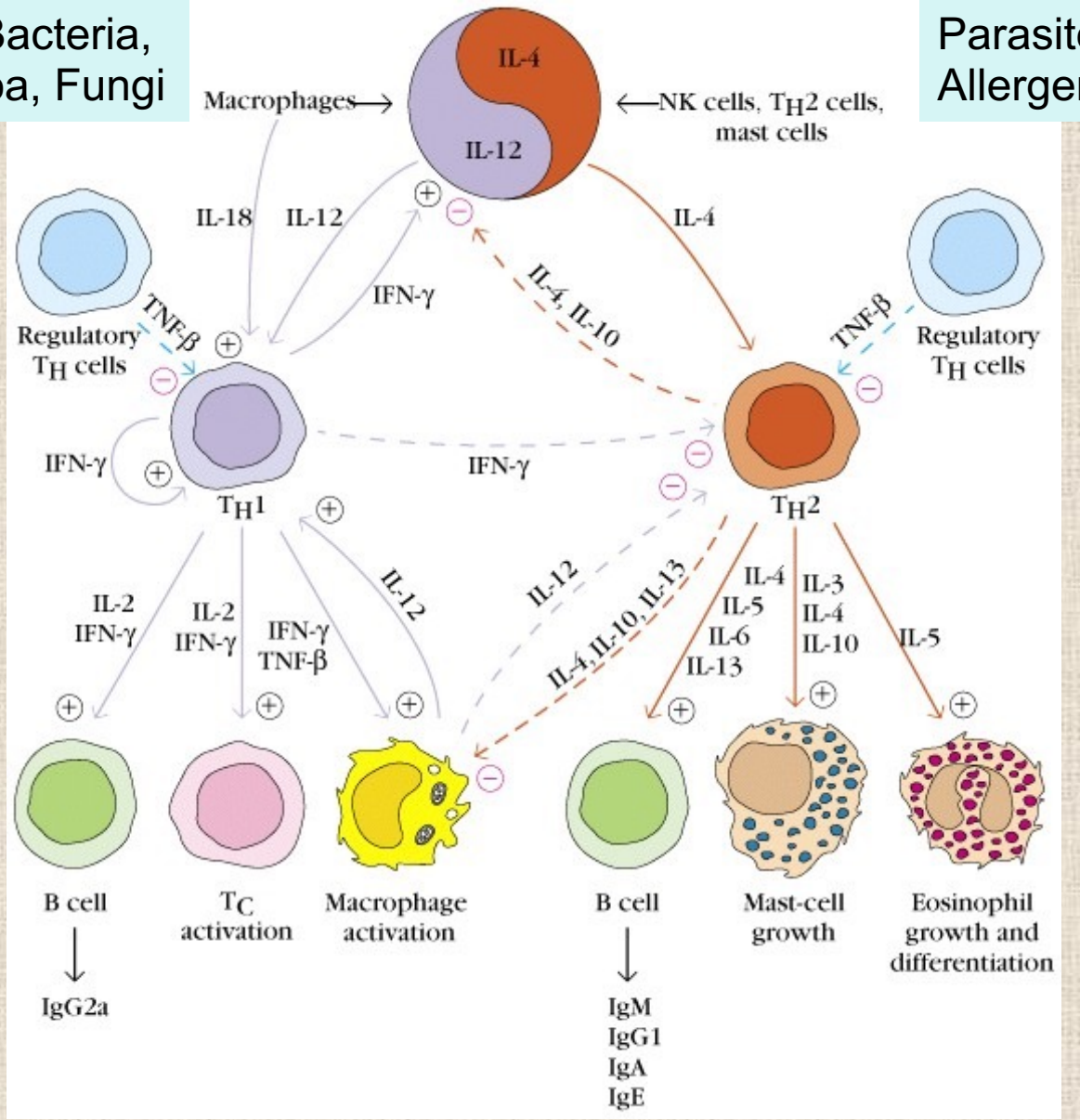
Peripheral helper T cell differentiation

Lineage:	Inducer →	Transcription Factor →	Cytokine production
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

Virus, Bacteria, Protozoa, Fungi

Parasites, Allergenes



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

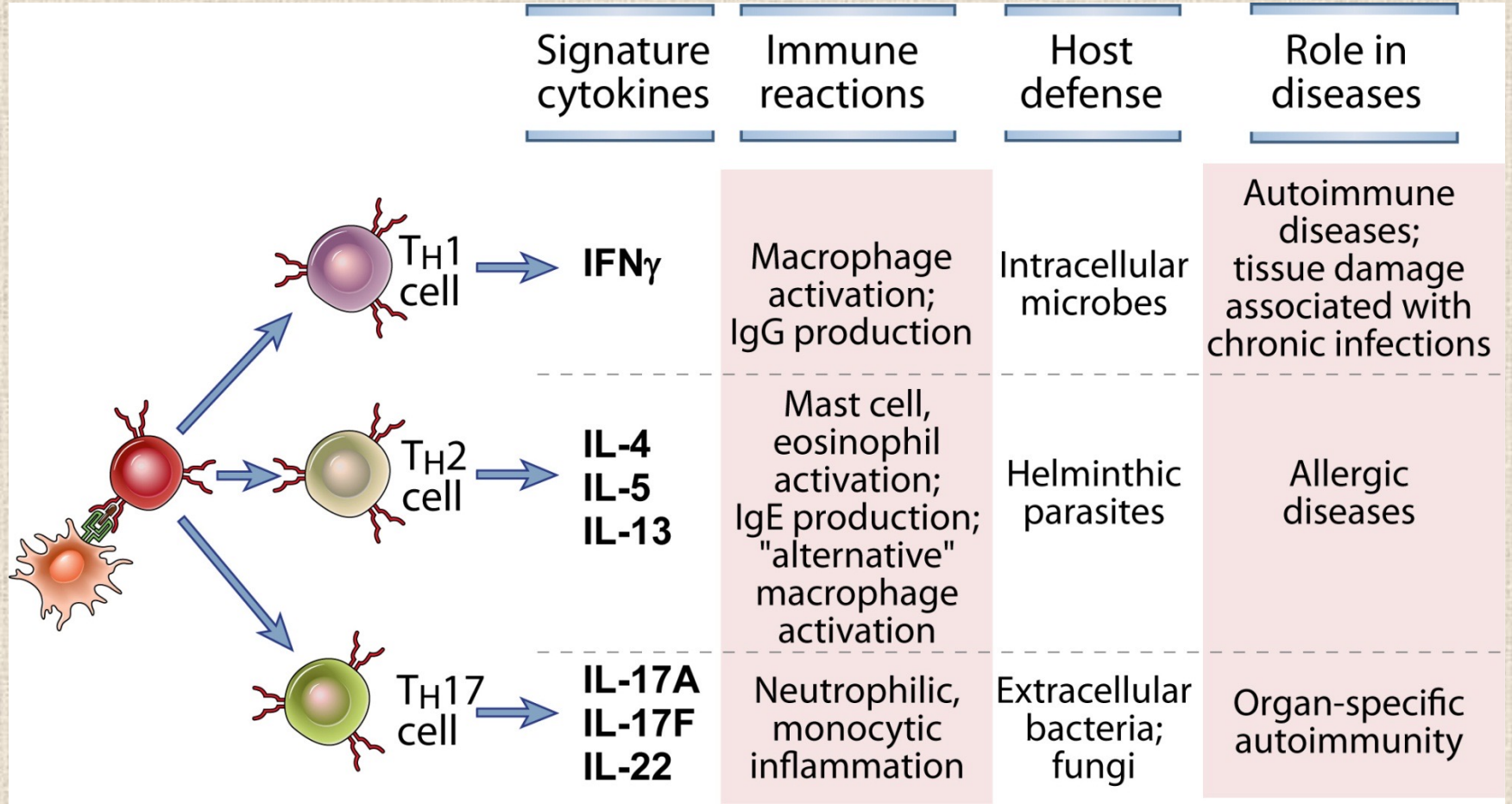


Fig. 9-13

Role of CD28 and CTLA-4 molecules in T cell activation

CD28 (naive T cell) - Activation **CTLA-4 (activated T cell) - Inhibition**

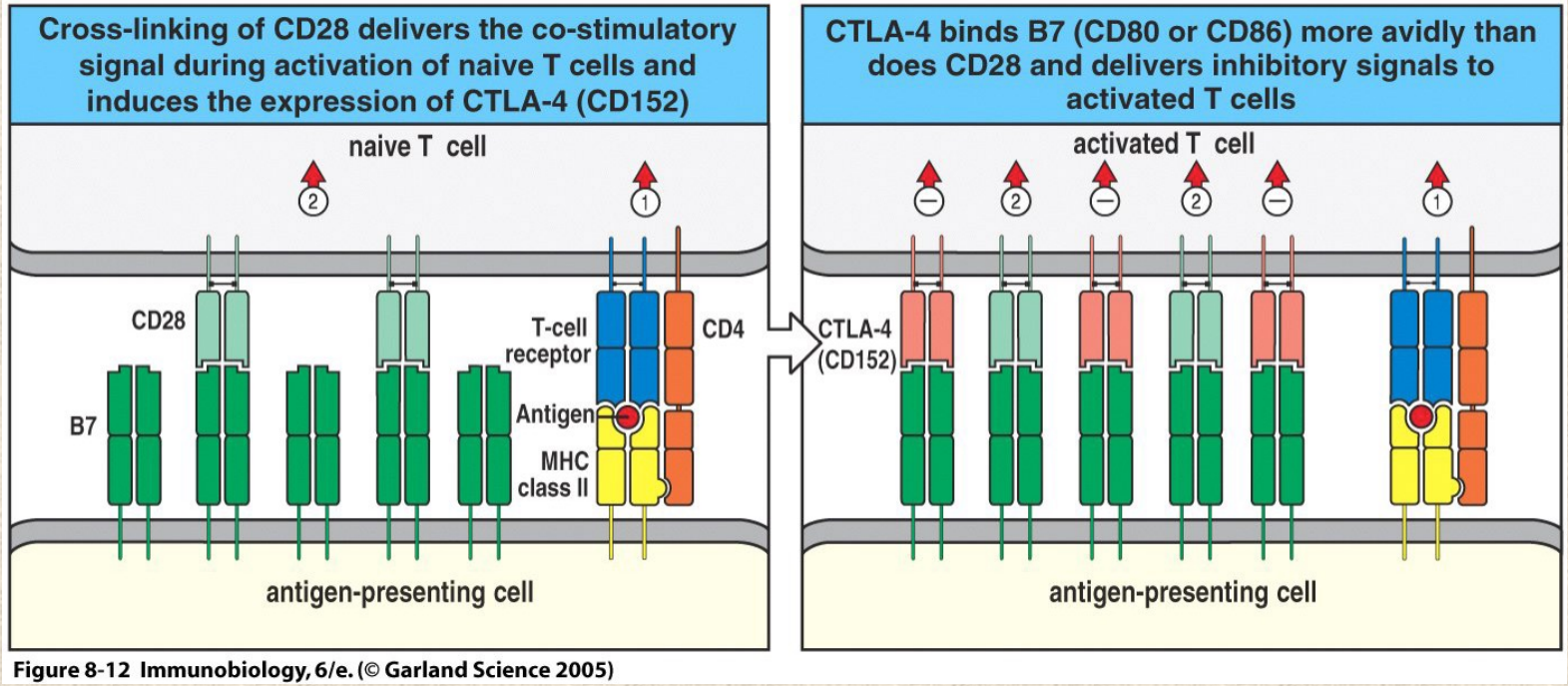
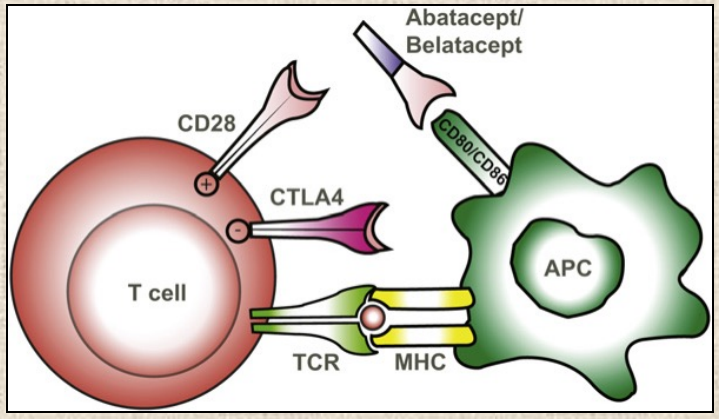


Figure 8-12 Immunobiology, 6/e. (© Garland Science 2005)

CTLA-4 binds B7 with higher affinity than CD28.

Therapeutic possibility:
Inhibition of abnormal T cell activation in autoimmune diseases



CTLA-4-Ig
(Abatacept)
Rheumatoid Arthritis (RA) therapy

T cell signaling as “target”

Name	Target	Effect	Application
Anti-CD3 (OKT3)	CD3	T cell depletion	transplantation
Anti-CD25 (Daclizumab)	CD25	T cell suppression	transplantation
Cyclosporin A	calcineurin	T cell suppression	transplantation
Tacrolimus	calcineurin	T cell suppression	transplantation
CTLA-4-Ig (Abatacept)	B7	T cell suppression	RA
Anti-CTLA-4* (Ipilimumab)	CTLA-4	blocking T cell suppression	cancer immunotherapy
Anti-PD-1* (Nivolumab)	PD-1	blocking T cell suppression	cancer immunotherapy
Anti-PD-L1* (Atezolimumab)	PD-L1	blocking T cell suppression	cancer immunotherapy

*checkpoint inhibitors