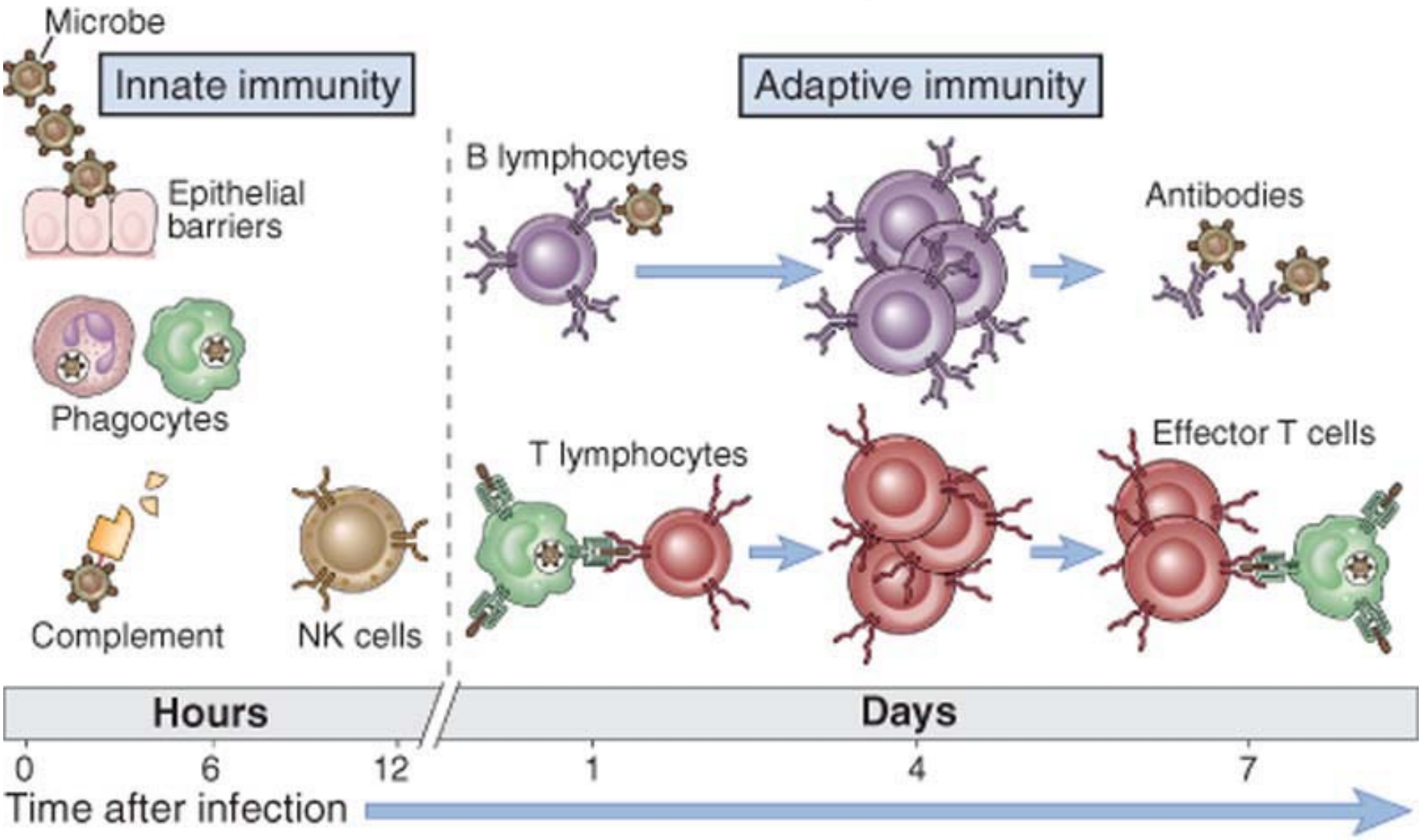
Immune response



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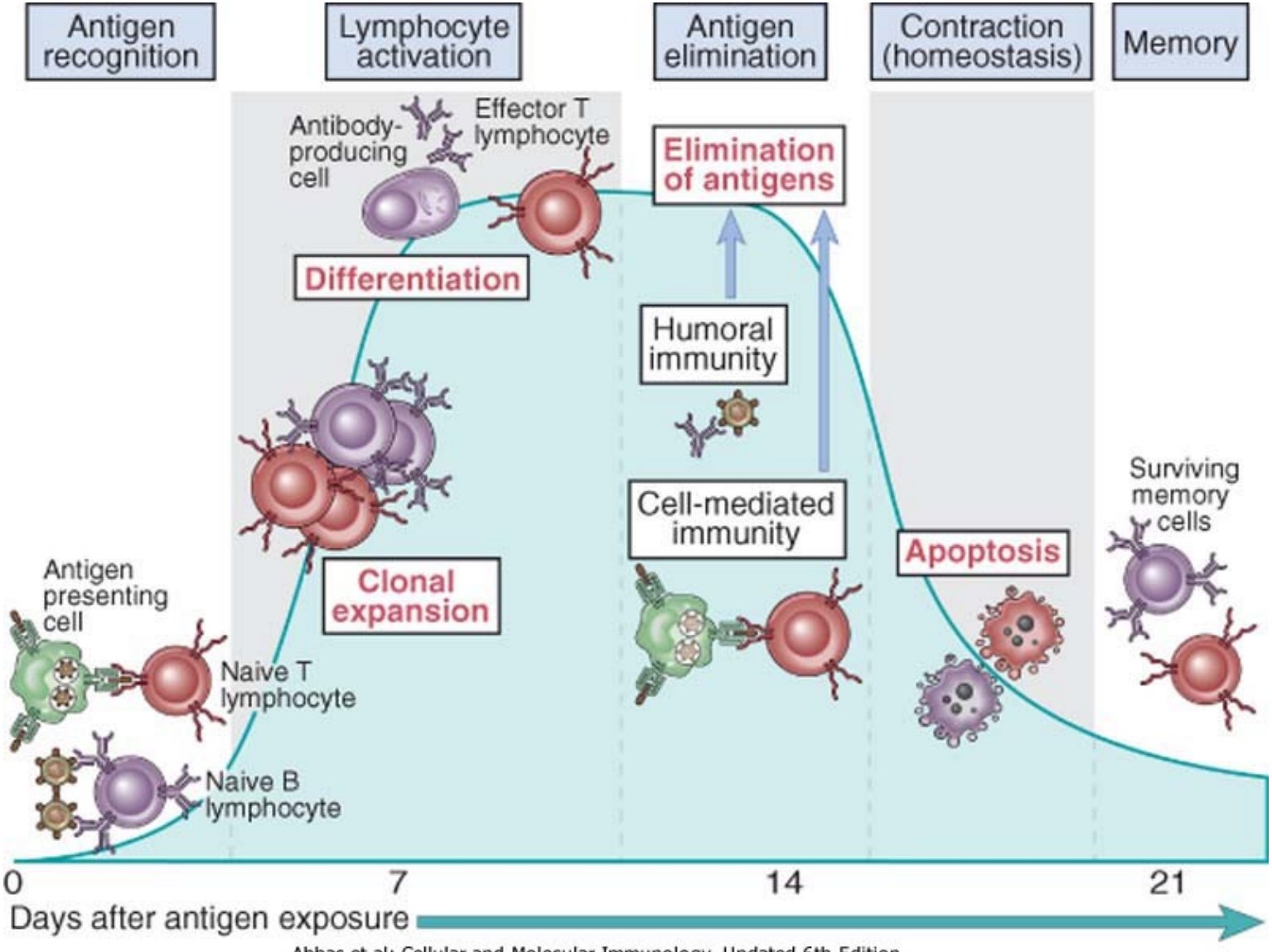
Phases of adaptive immune response



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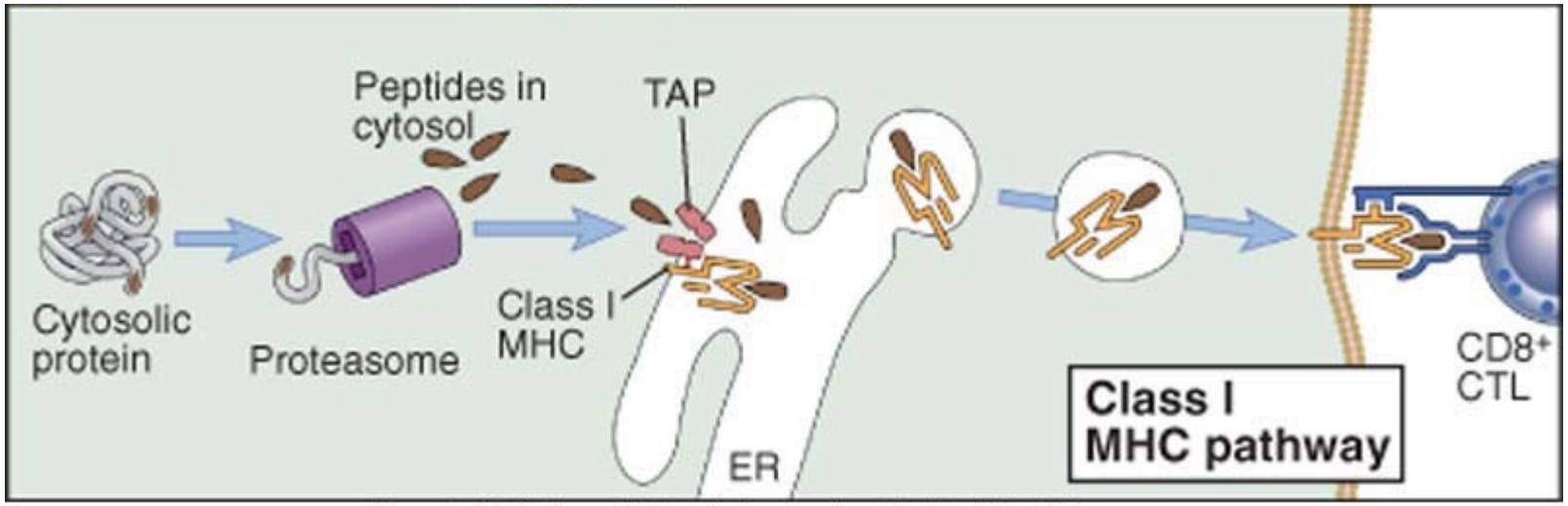
Antigen uptake	Antigen processing	MHC biosynthesis	Peptide-MHC association



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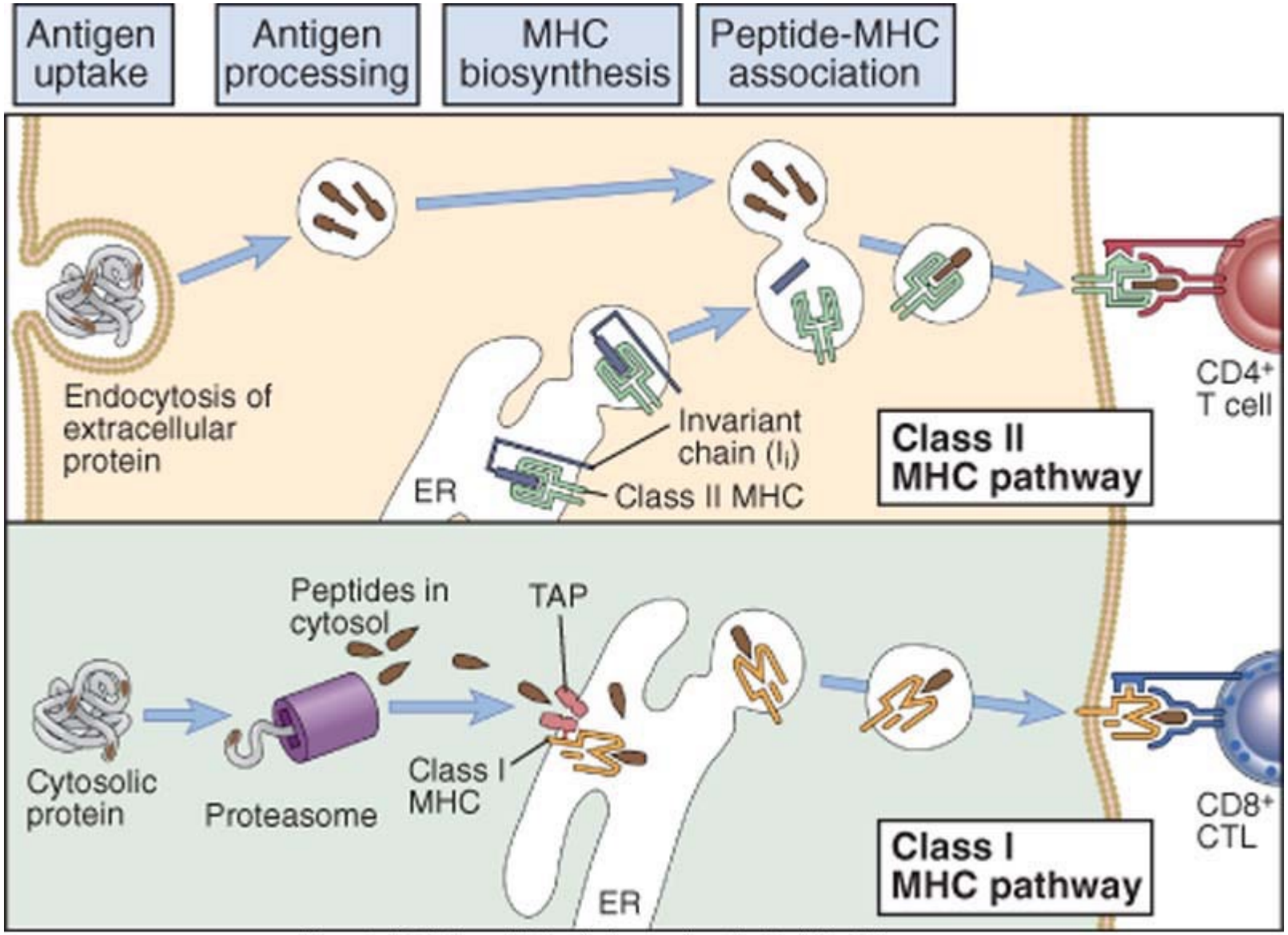

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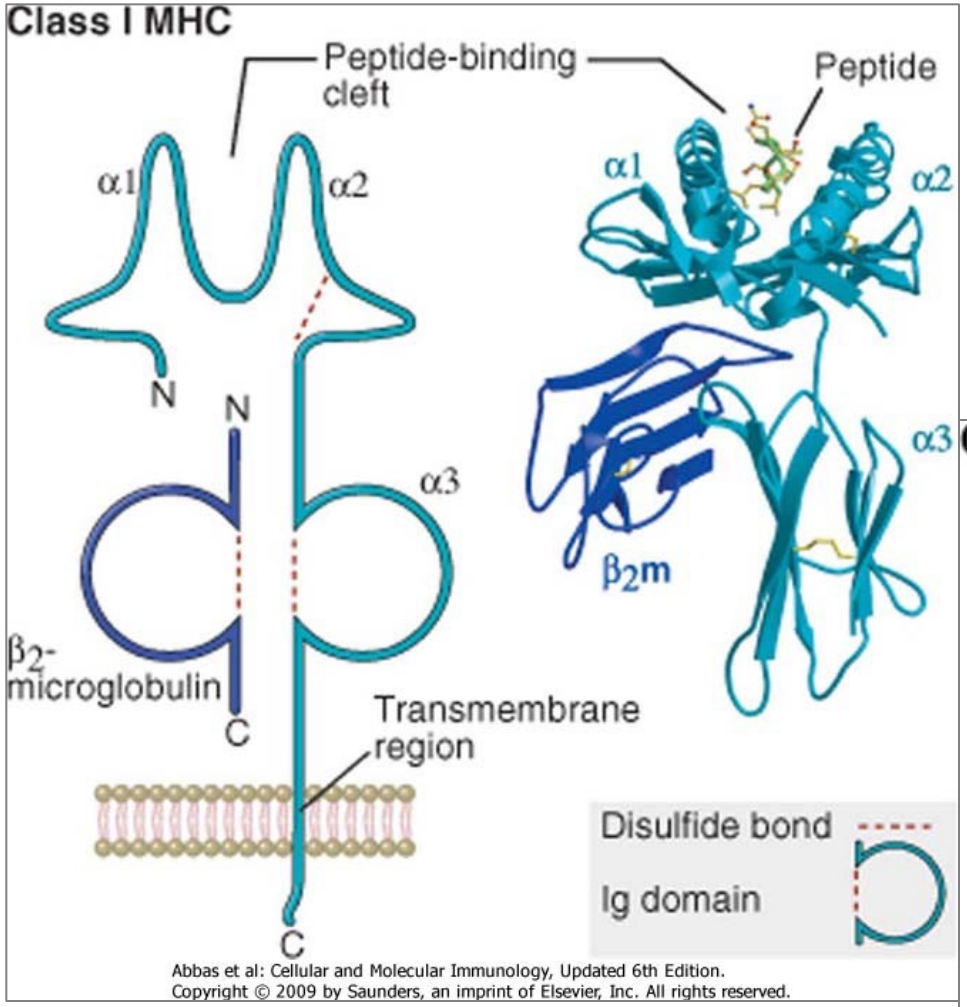

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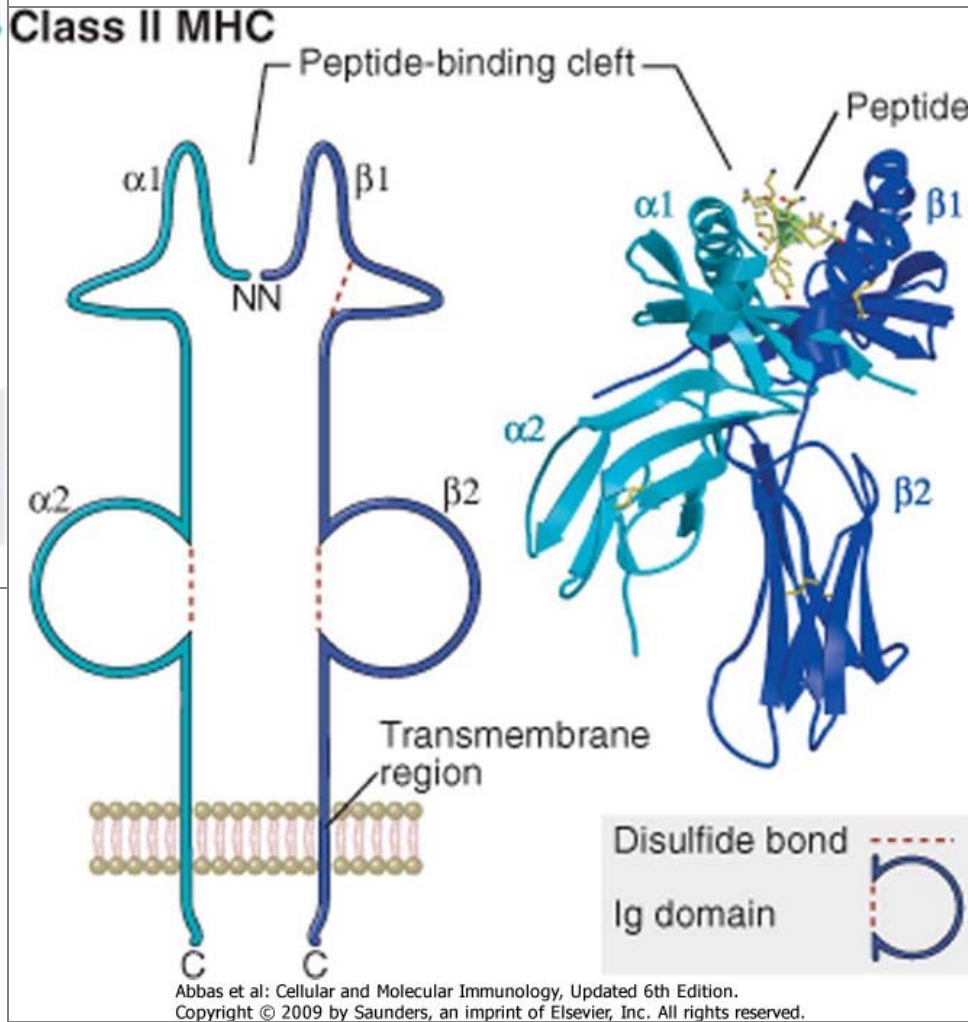

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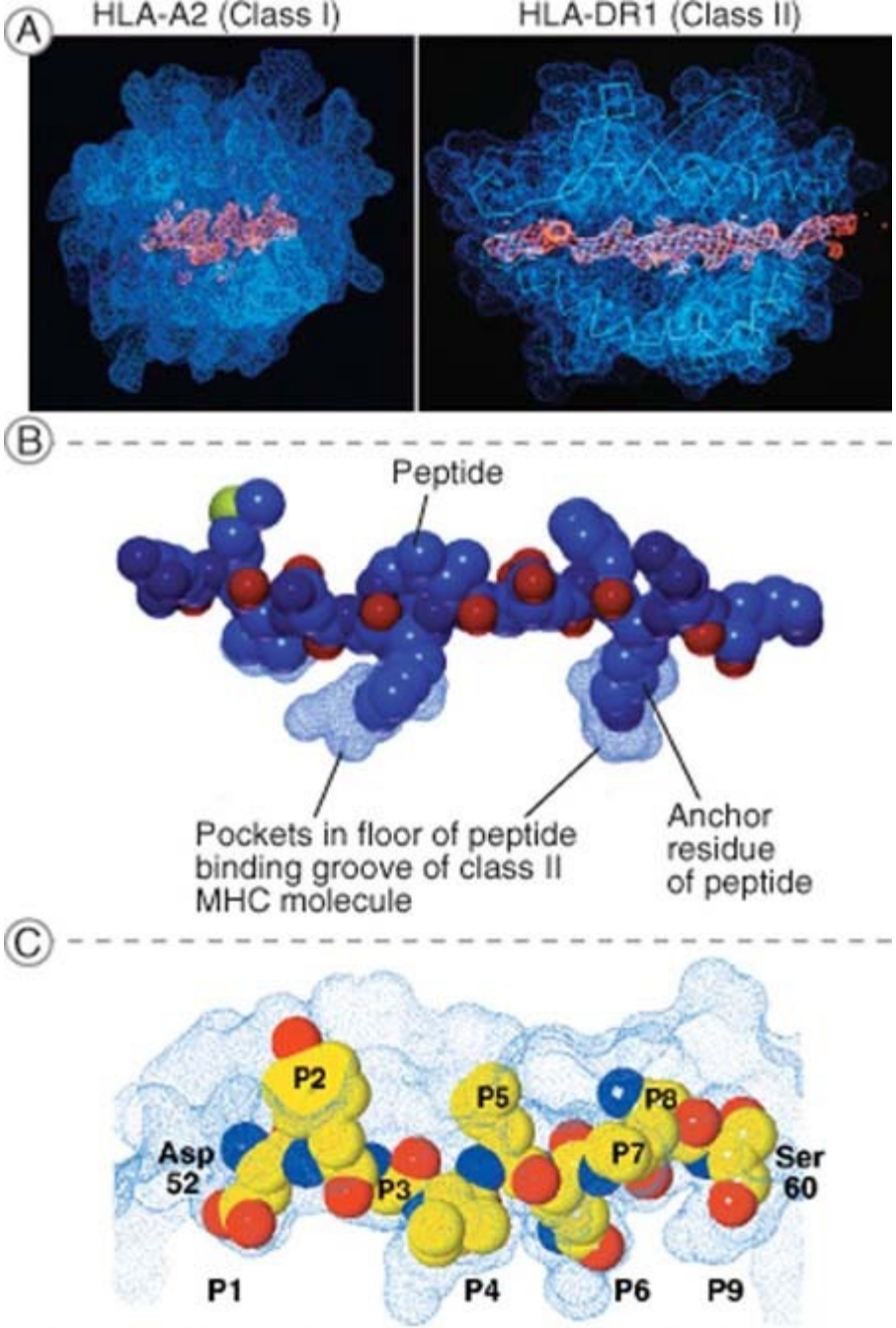

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Antigen Presenting Cells

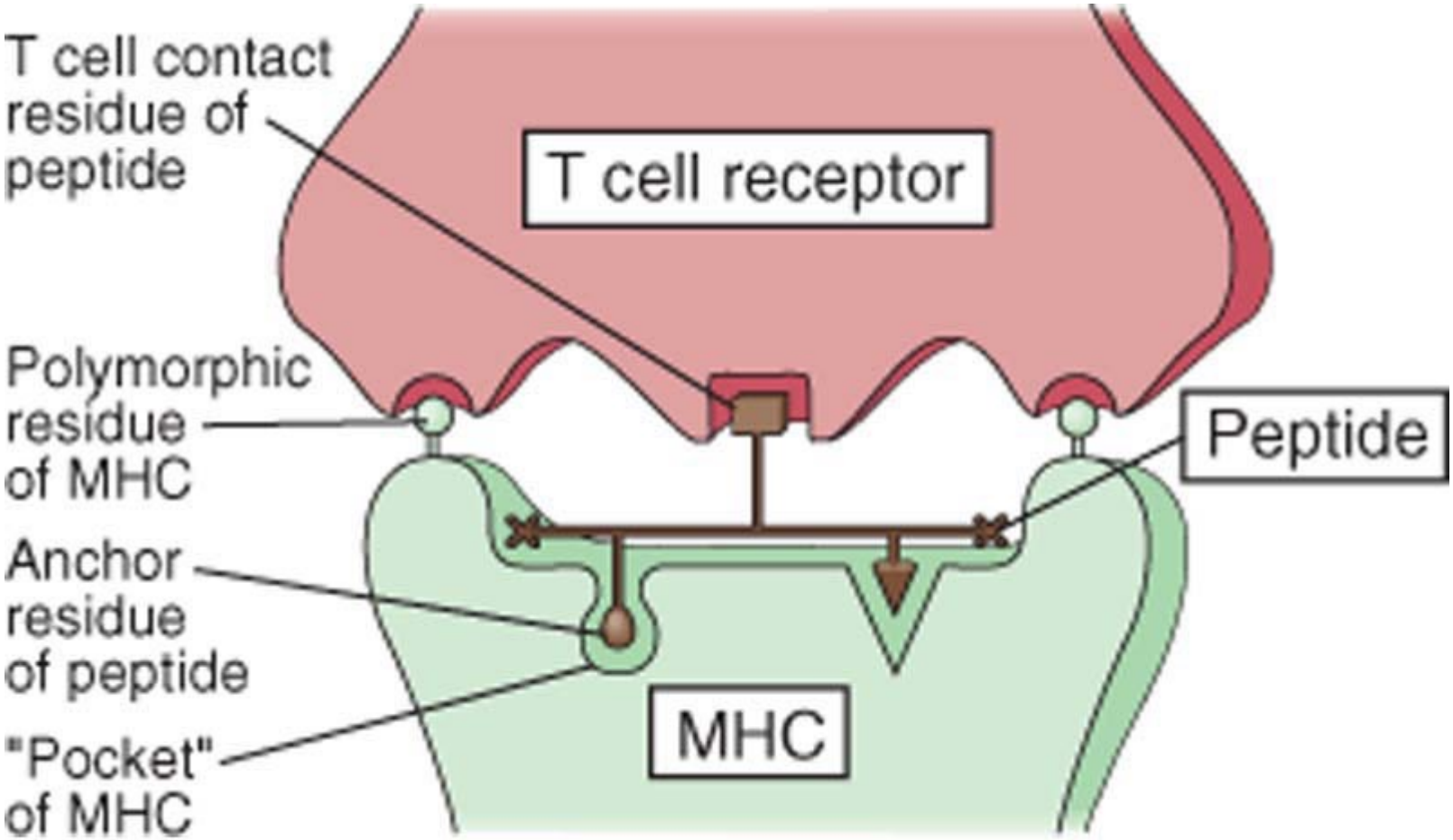
Dendritic cells:
- costitutive MHC II; Increase with INFg
- Co-stimulatory molecoles are constitutively expressed and inducible

Macrophages:
- costitutive MHC II; Increase with INFg
- co-stimulatory molecoles are inducible by LPS

B Lymphocytes:
- costitutive MHC II; Increase with IL4
- co-stimulatory molecoles are inducible by T lymphocytes interaction (CD40-CD40L)

Vascular endothelial cells:
- costitutive MHC II; Increase with INFg
- Co-stimulatory molecoles are constitutively expressed

Epithelial and mesenchymal cells:
- costitutive MHC II; Increase with INFg
- Co-stimulatory molecules seem not to be expressed



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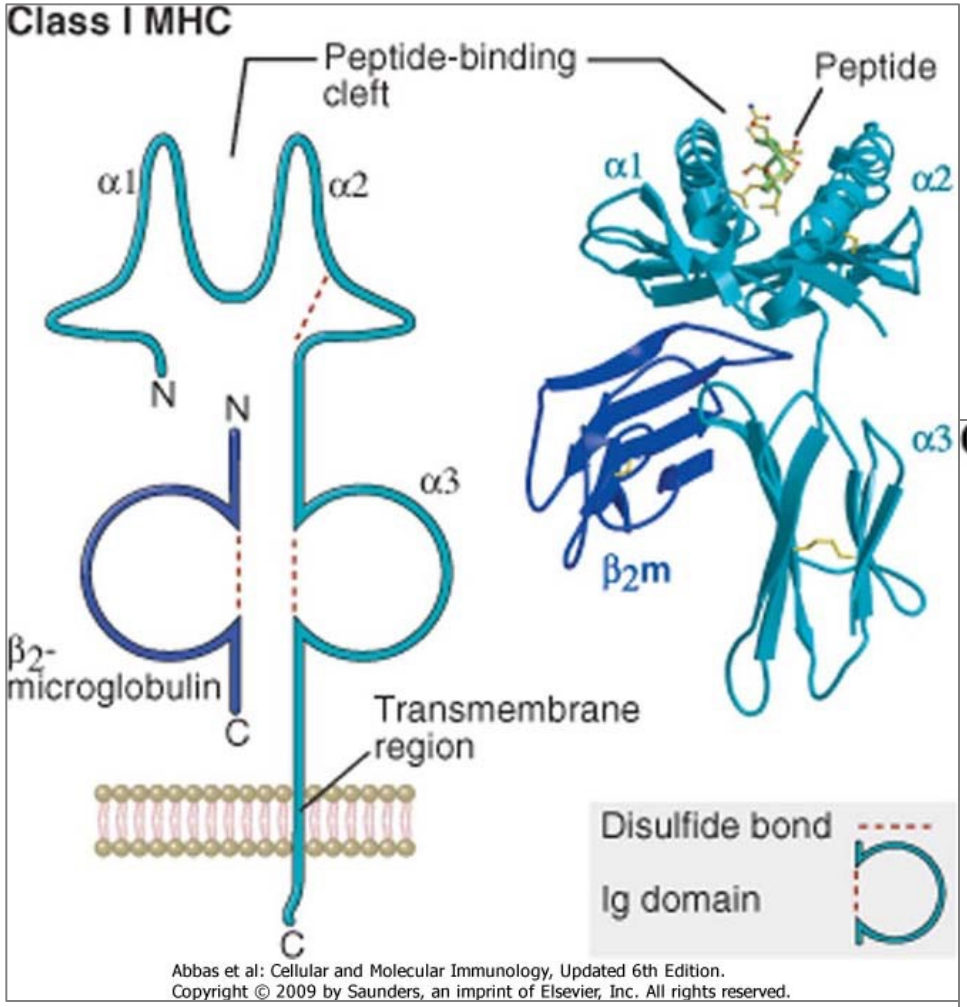

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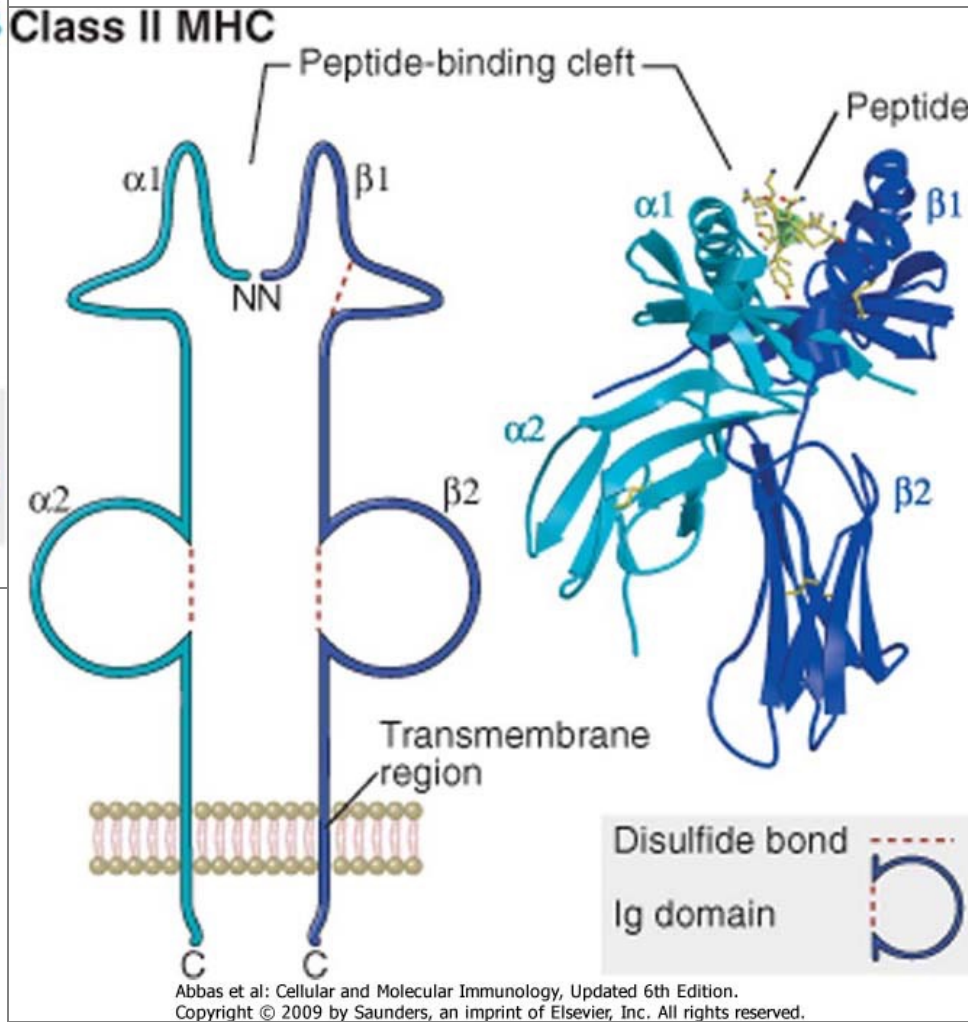

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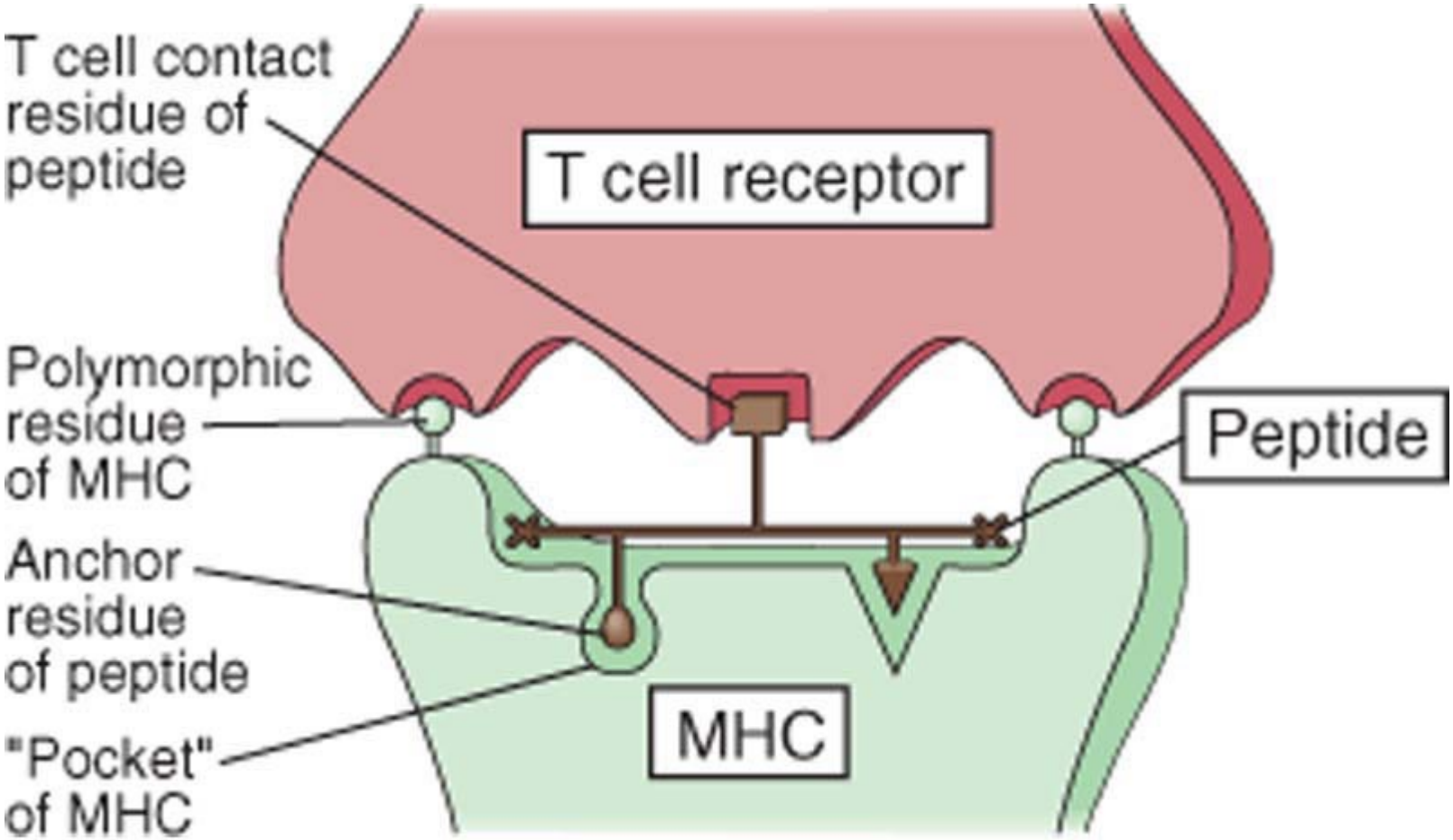

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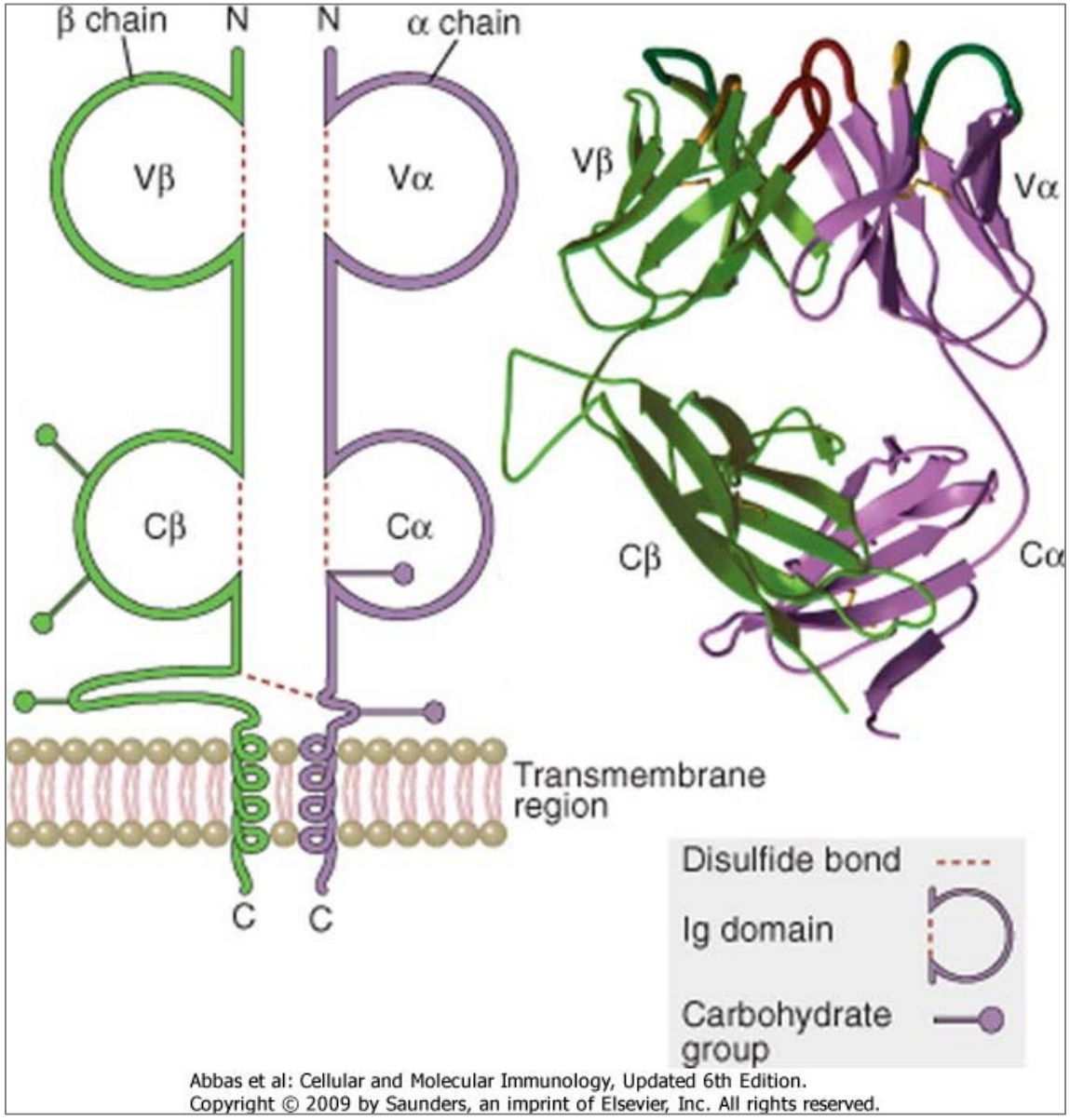
T-cell Receptor



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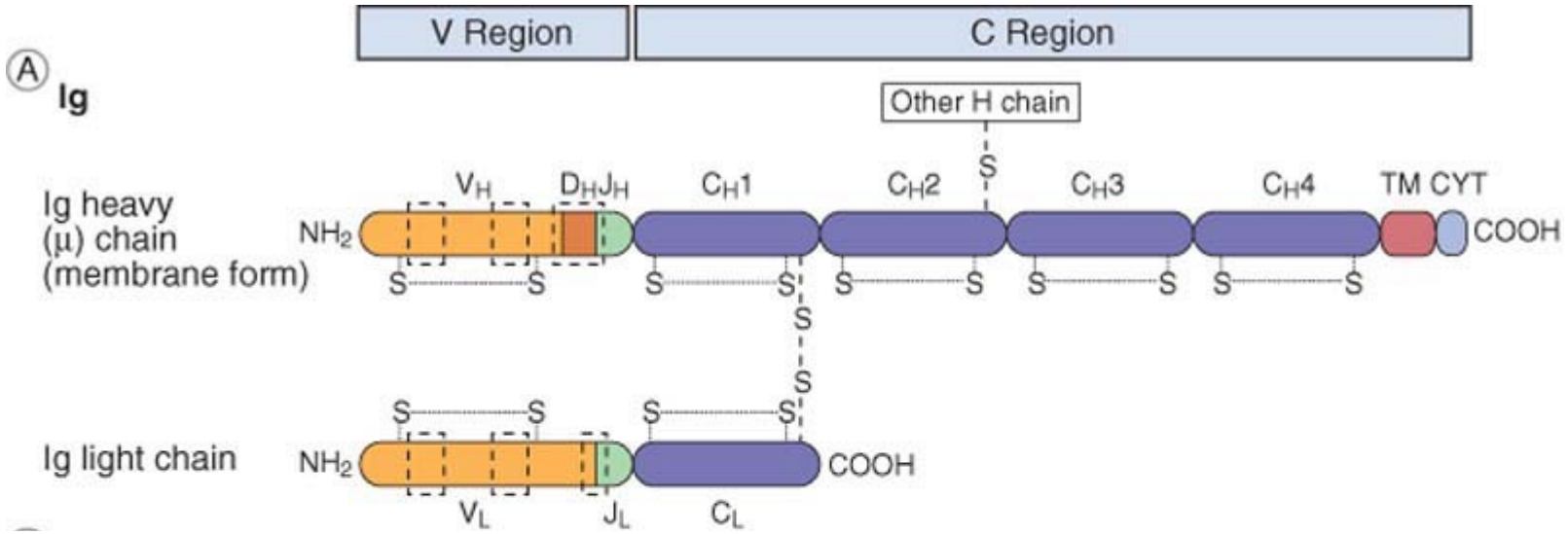
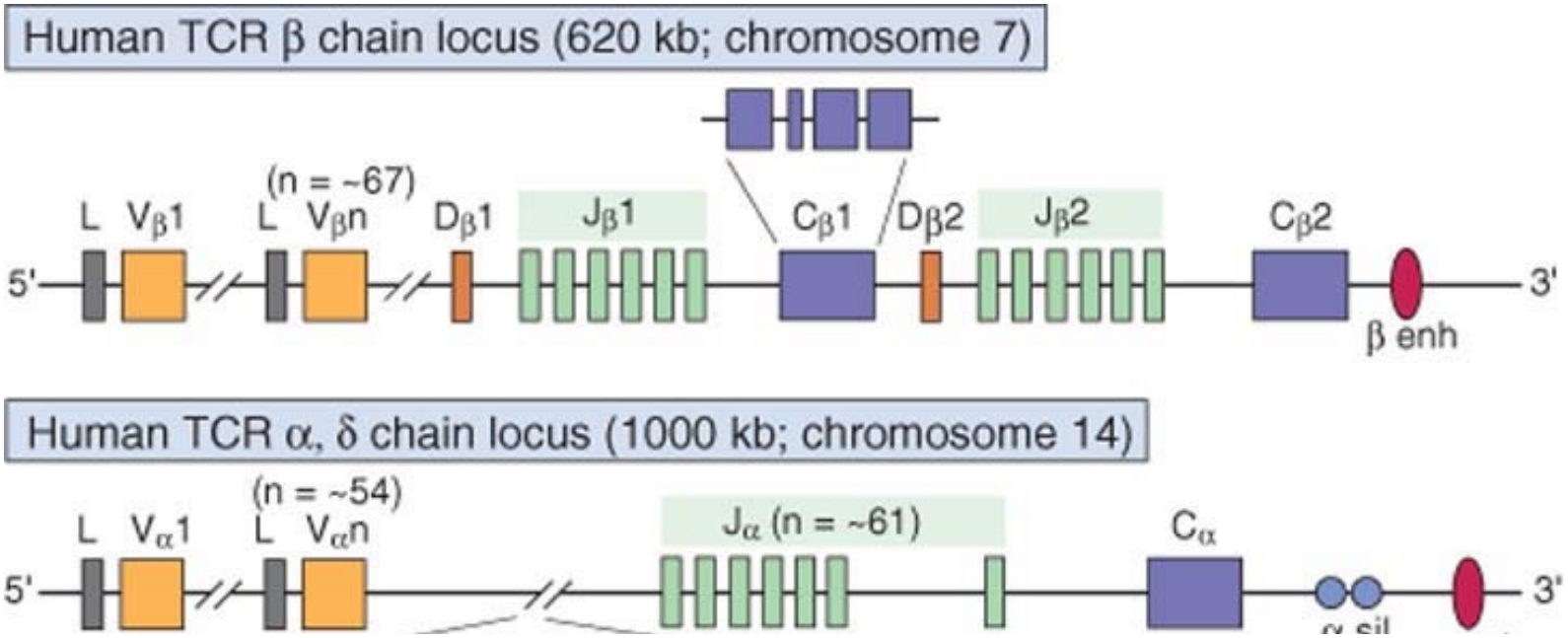
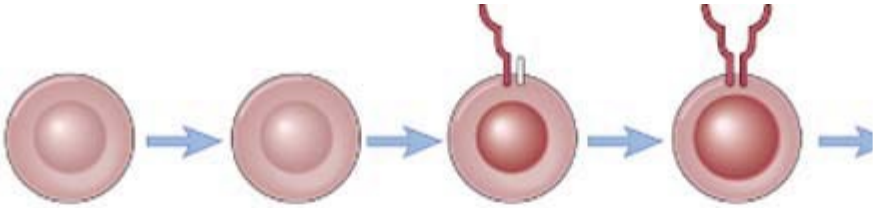

A
Ig
V Region
C Region
Other H chain
Ig heavy
(μ) chain
(membrane form)
NH2
VH
DHJH
CH1
CH2
CH3
CH4
TM CYT
COOH
S
Ig light chain
NH2
COOH
VL
JL
CL


Human TCR β chain locus (620 kb; chromosome 7)
(n = ~67)
L Vβ1
L Vβn
Dβ1
Jβ1
Cβ1
Dβ2
Jβ2
Cβ2
5'
3'
β enh
Human TCR α, δ chain locus (1000 kb; chromosome 14)
(n = ~54)
L Vα1
L Vαn
Jα (n = ~61)
Cα
5'
3'

Feature	αβ T cells	γδ T cells
CD4 and CD8 phenotype	Major subsetting based on CD4 or CD8 expression	Predominantly $CD4^{-}CD8^{-}$ (double-negative); murine intestinal IELs may be $CD8\alpha\alpha^{+}$
Antigen type and presentation	Peptide antigen in the grooves of MHC-I or -II; primary responses require antigen-presenting cell	Identification of TCR ligands incomplete; β_2 microglobulin independent; some subsets recognize MHC-Ib molecules
T helper functions	Predominantly $CD4^{+}$; T helper 1 and 2 cytokine profiles	T helper 1 and 2 cytokine profiles
T cytotoxic functions	Predominantly $CD8^{+}$; e.g., perforin/granzyme production, Fas ligand-mediated, NKG2D-mediated	Various subsets using the same mechanisms
T regulatory functions	Various T regulatory subsets including $CD4^{+}CD25^{+}$ cells	Attributable to various subsets, including murine $V\gamma5^{+}$ DETCs and human $V\gamma1^{+}$ peripheral cells
TCR junctional diversity	Relatively vast	Relatively limited; especially limited for IEL populations

Abbreviations: DETC, dendritic epidermal T cell; IEL, intraepithelial lymphocyte; MHC, major histocompatibility complex.

T-cell maturation



Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive
Proliferation				
Rag expression				
TdT expression				
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^-$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}
Anatomic site	Bone marrow	Thymus		
Response to antigen	None	None	None	Positive and negative selection

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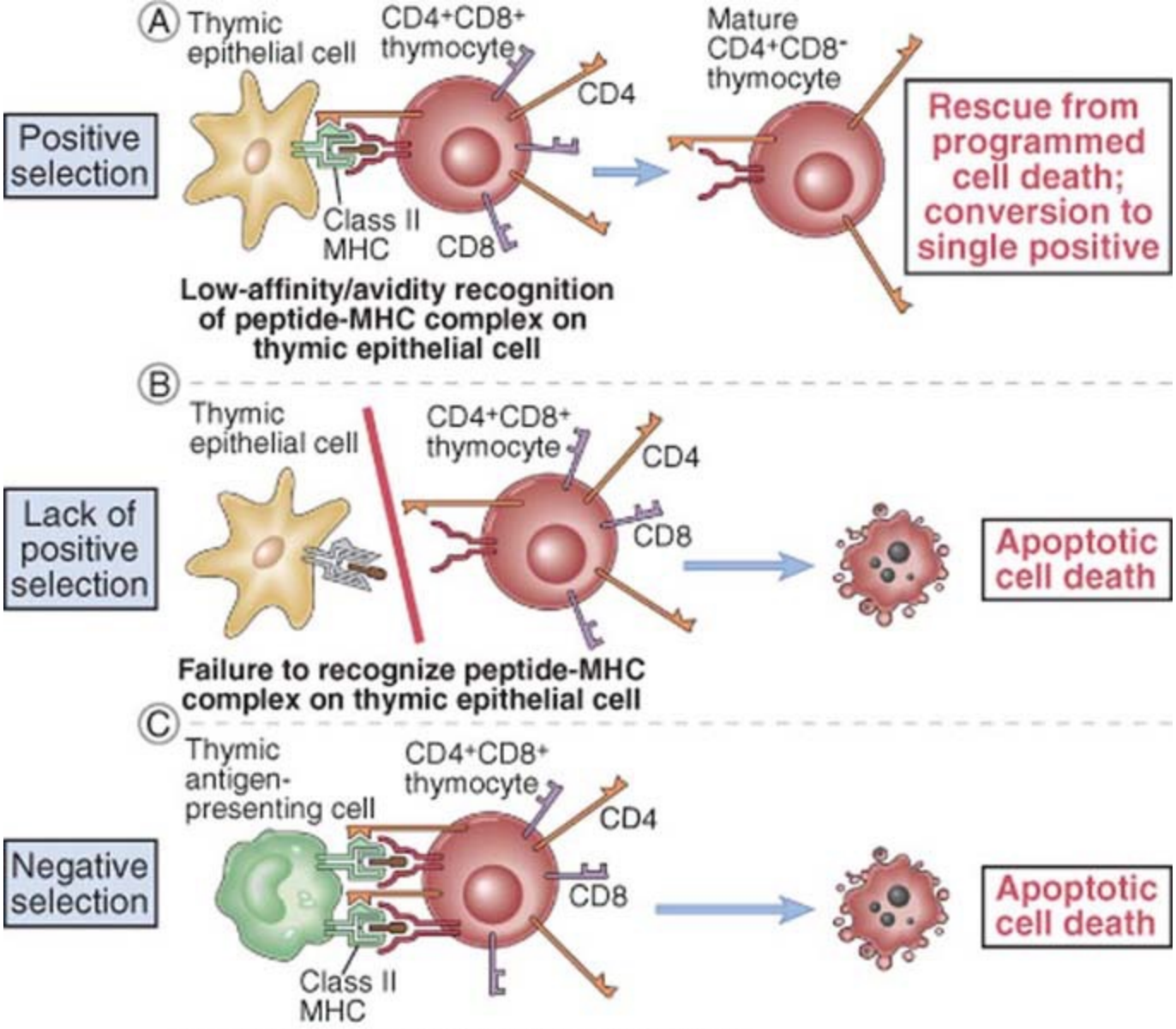

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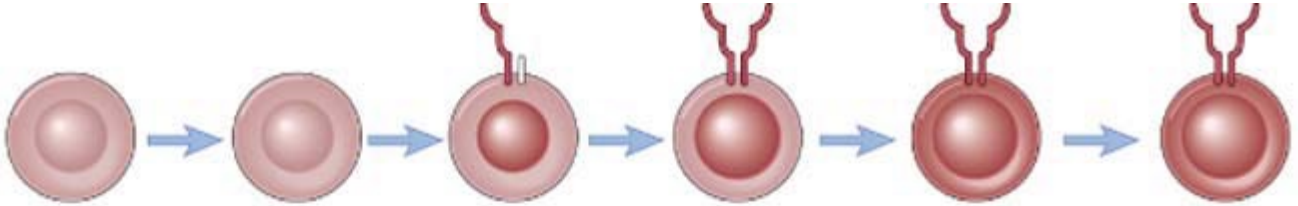

Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
Rag expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^-$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection		Activation (proliferation and differentiation)

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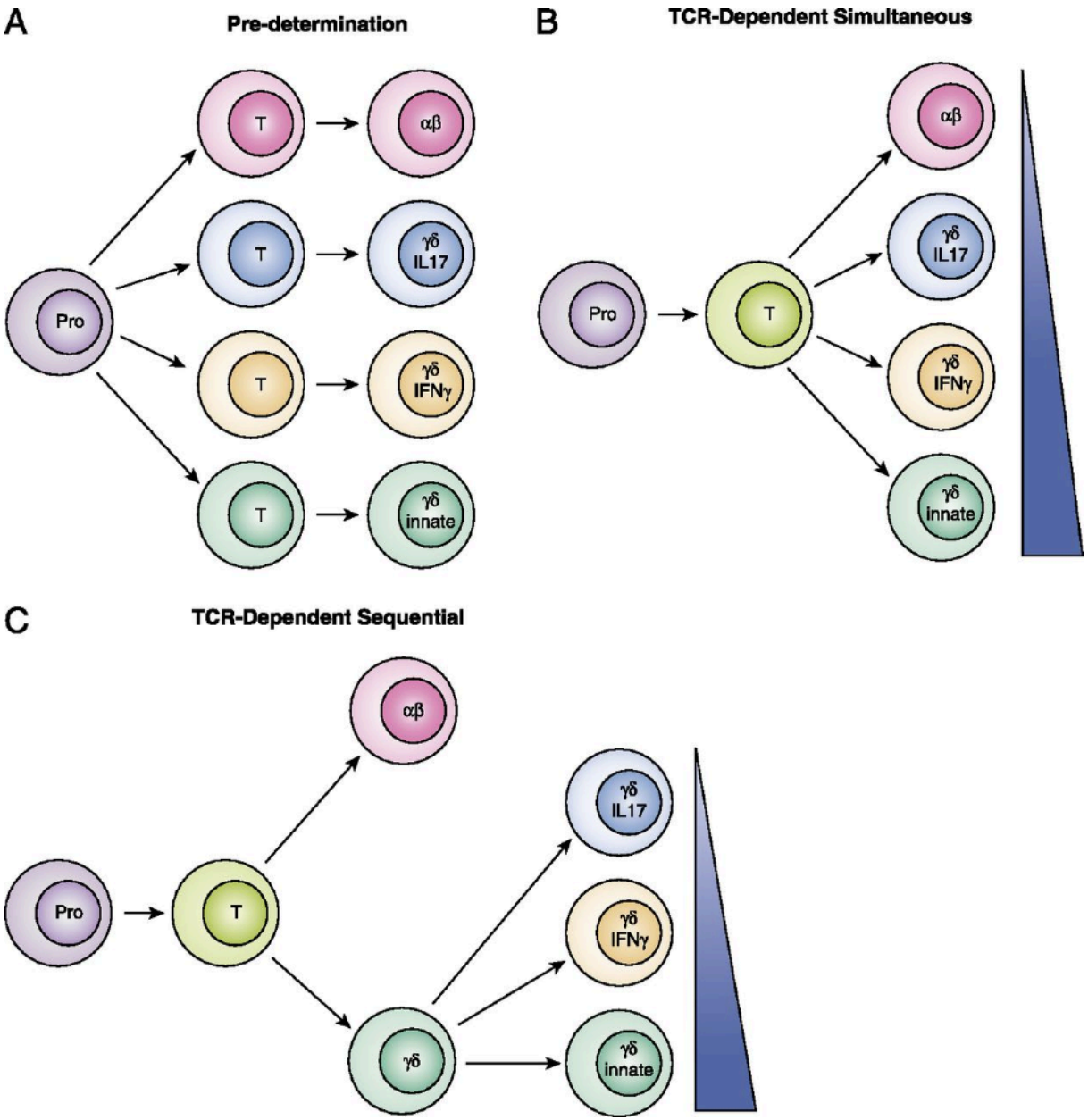
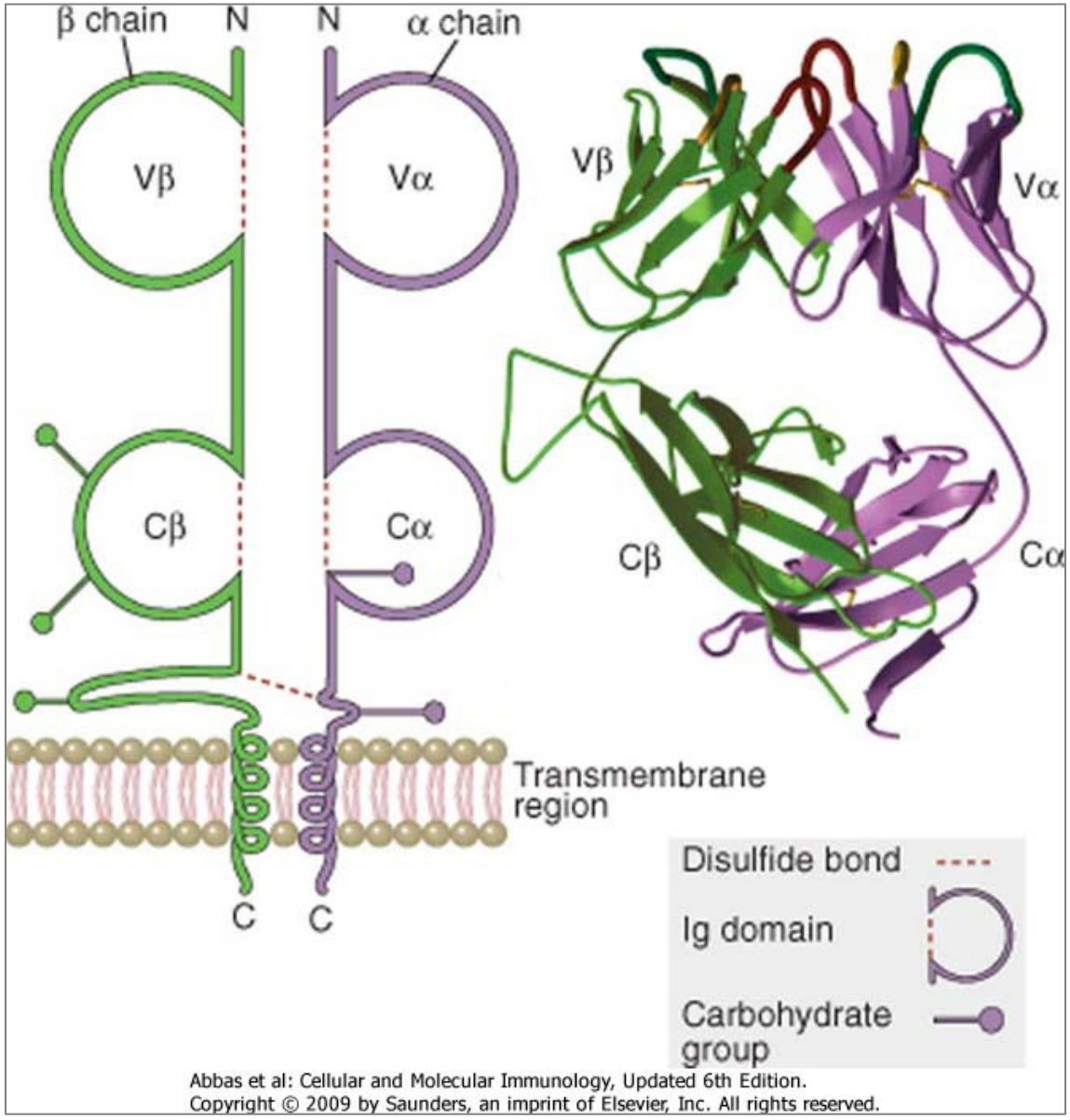
Hypothesis of T-cell maturation



T-cell Receptor



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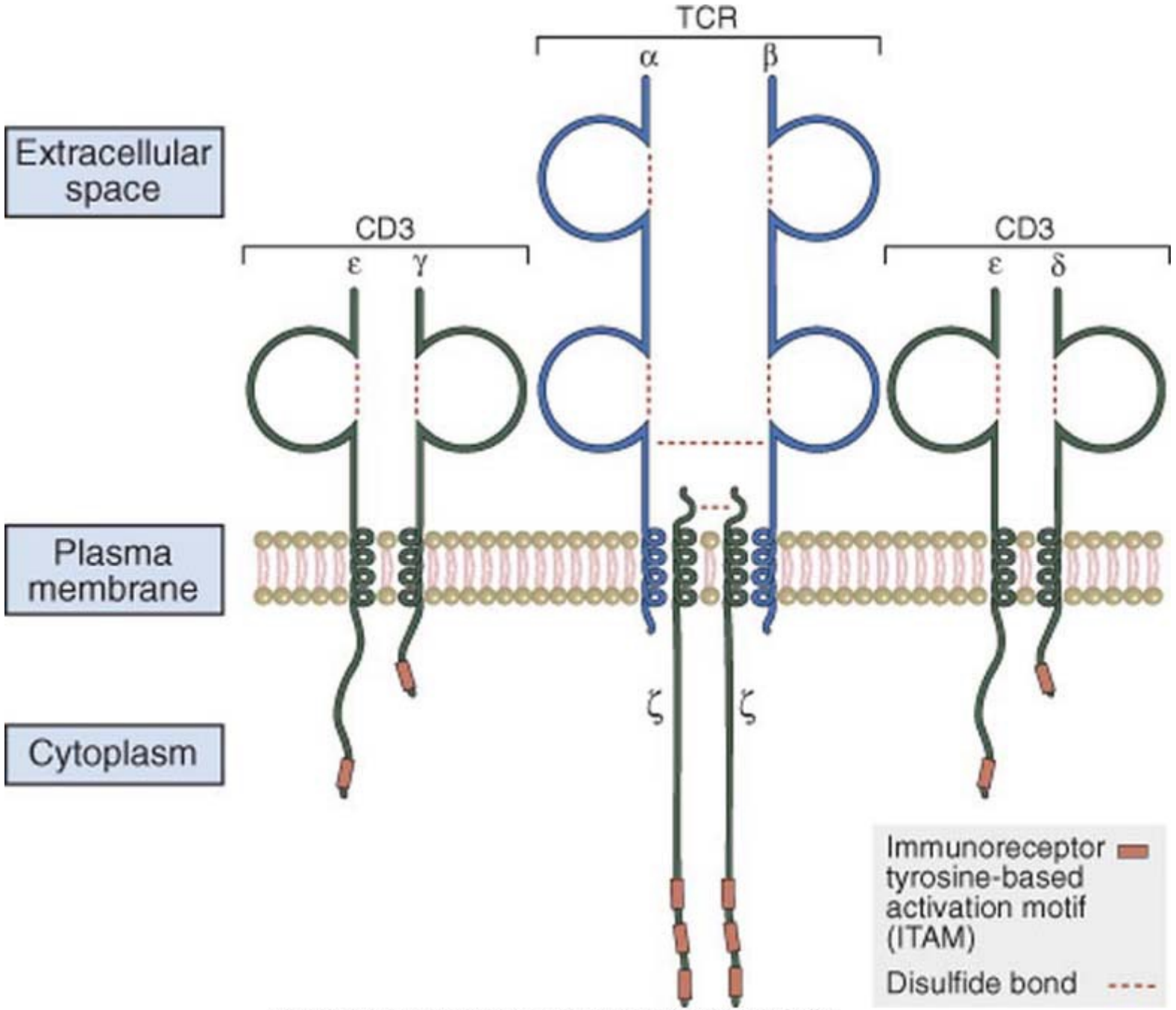

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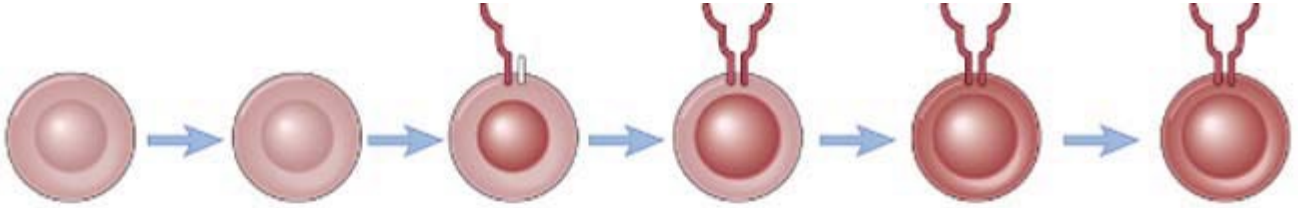

Stage of maturation	Stem cell	Pro-T	Pre-T	Double positive	Single positive (immature T cell)	Naive mature T cell
Proliferation						
Rag expression						
TdT expression						
TCR DNA, RNA	Unrecombined (germline) DNA	Unrecombined (germline) DNA	Recombined β chain gene [V(D)J-C]; β chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA	Recombined β, α chain genes [V(D)J-C]; β and α chain mRNA
TCR expression	None	None	Pre-T receptor (β chain/pre-T α)	Membrane αβ TCR	Membrane αβ TCR	Membrane αβ TCR
Surface markers	c-*kit*$^+$ CD44$^+$ CD25$^-$	c-*kit*$^+$ CD44$^+$ CD25$^+$	c-*kit*$^+$ CD44$^-$ CD25$^+$	CD4$^+$CD8$^+$ TCR/CD3^{lo}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}	CD4$^+$CD8$^-$ or CD4$^-$CD8$^+$ TCR/CD3^{hi}
Anatomic site	Bone marrow	Thymus				Periphery
Response to antigen	None	None	None	Positive and negative selection		Activation (proliferation and differentiation)

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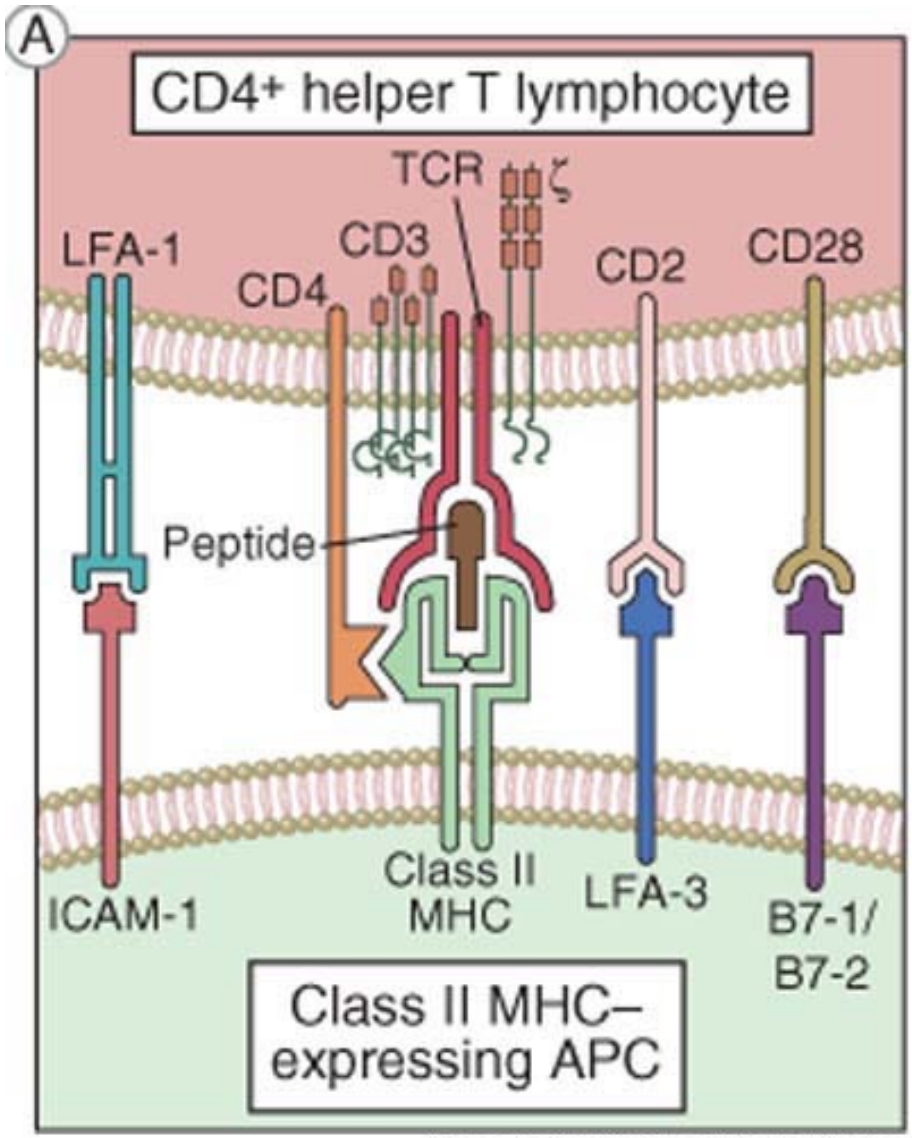

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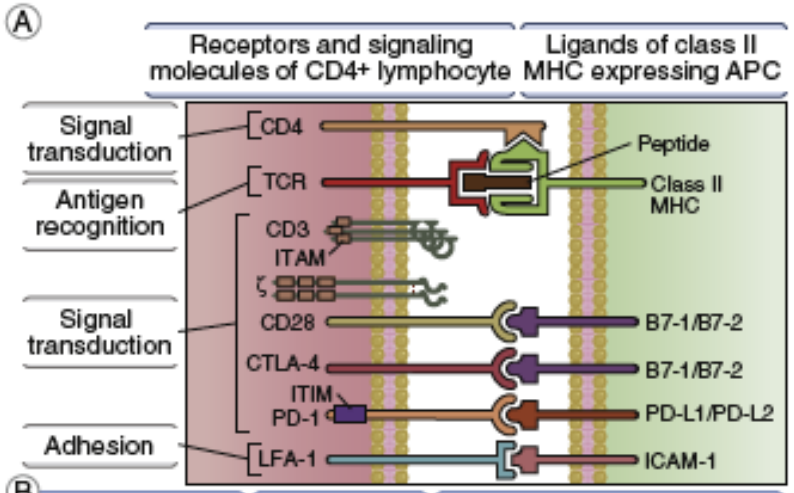
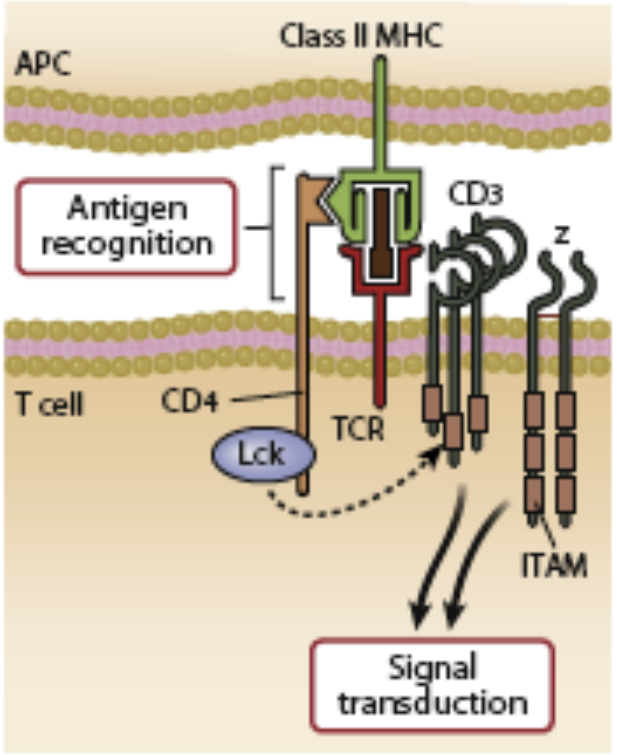
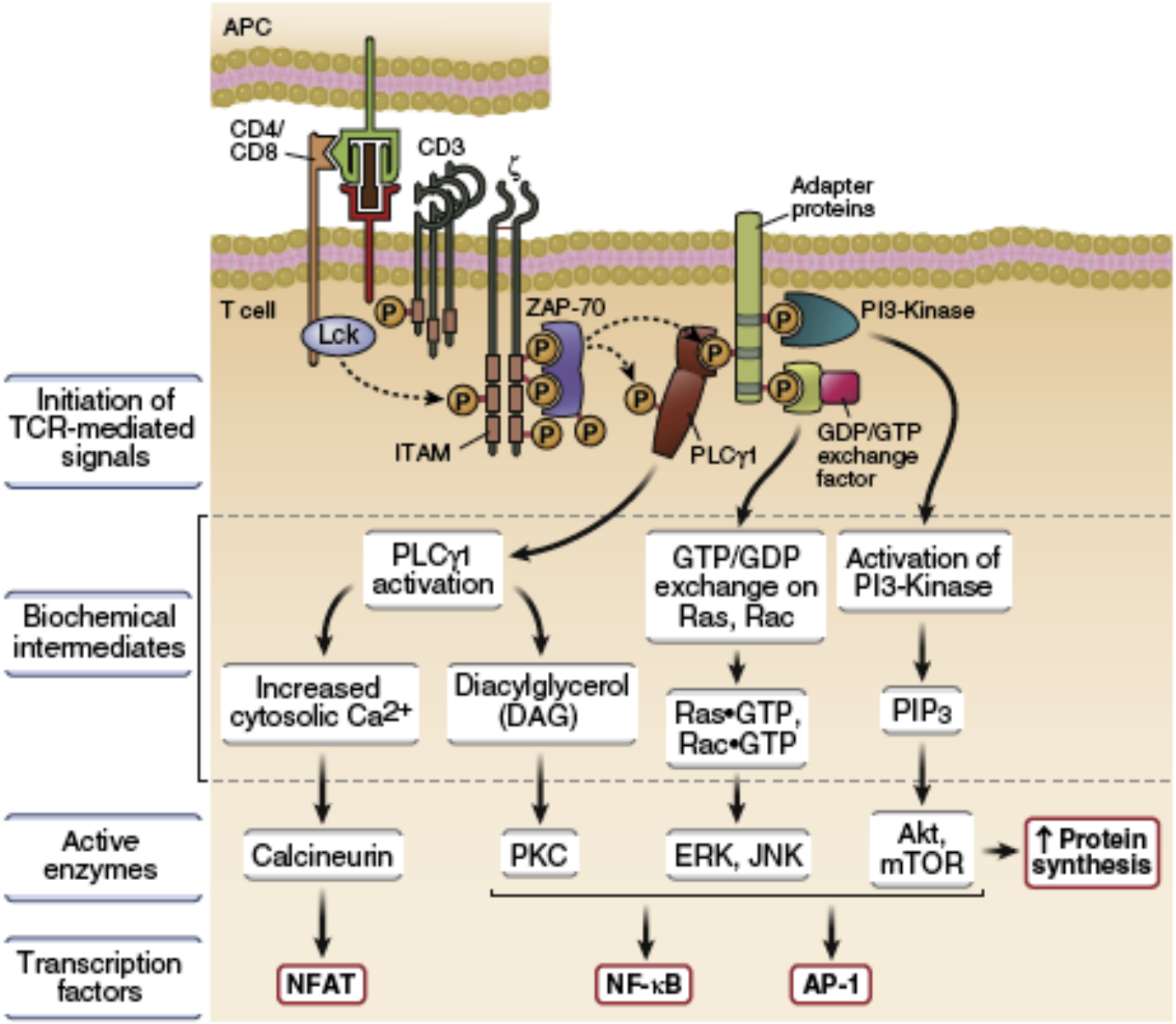
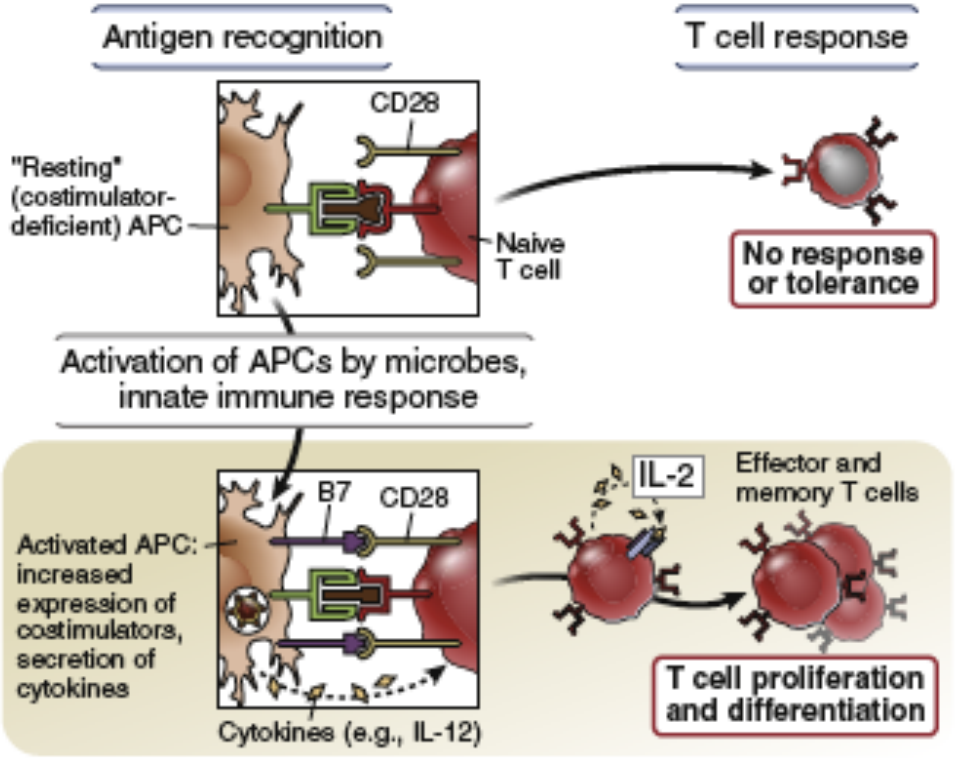


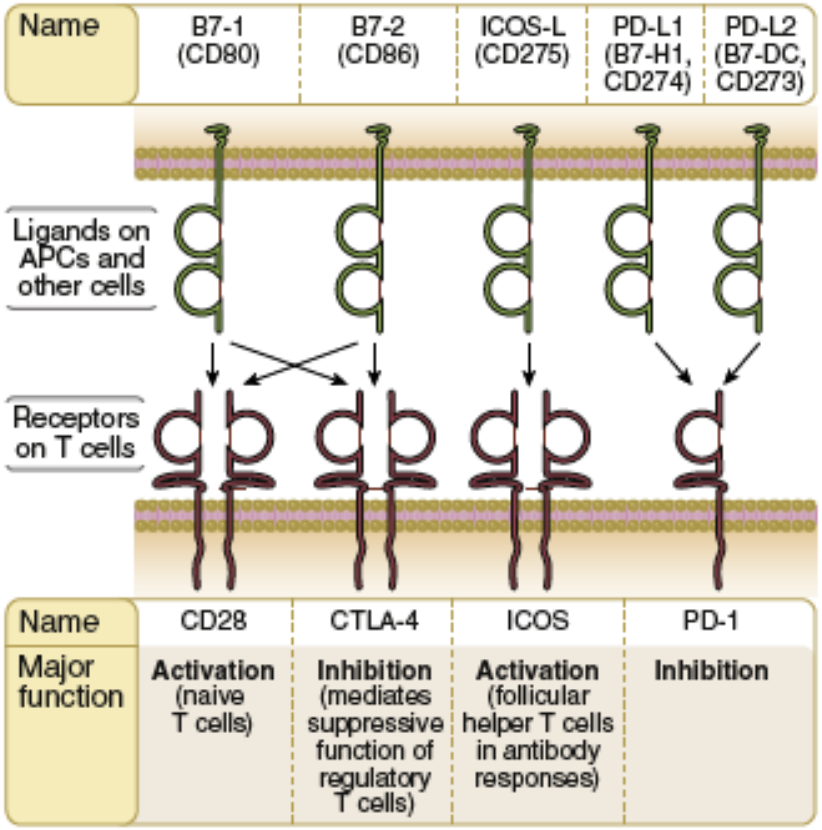
B

Surface molecules of T lymphocytes	Function	Ligand	
		Name	Expressed on
CD3	Signal transduction by TCR complex	None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen presenting cells
CD8	Signal transduction	Class I MHC	All nucleated cells
CD28	Signal transduction (costimulation)	B7-1/B7-2	Antigen presenting cells
CTLA-4	Inhibition	B7-1/B7-2	Antigen presenting cells
PD-1	Inhibition	PD-L1/PD-L2	Antigen presenting cells, tissue cells, tumor cells
LFA-1	Adhesion, signal transduction	ICAM-1	Antigen presenting cells, endothelium

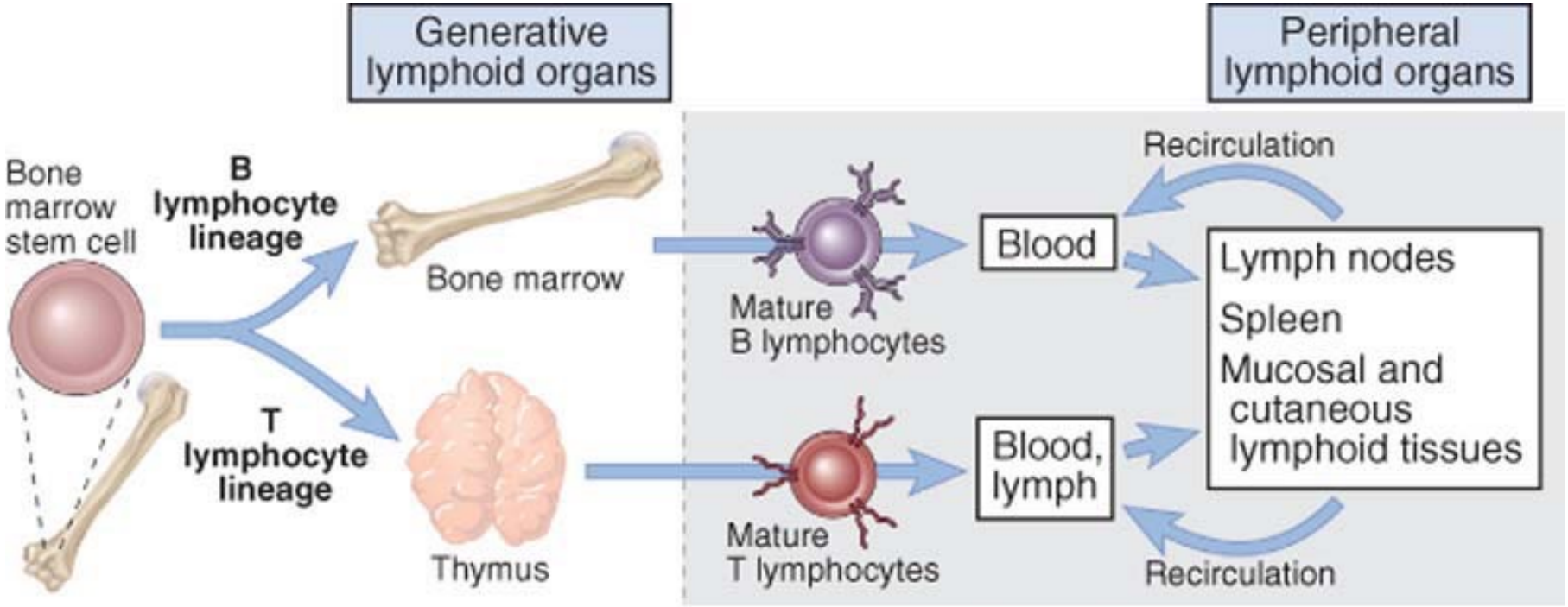



APC
CD4/
CD8
CD3
ζ
Adapter
proteins
T cell
Lck
ZAP-70
PI3-Kinase
ITAM
PLCγ1
GDP/GTP
exchange
factor
Initiation of
TCR-mediated
signals
Biochemical
intermediates
PLCγ1
activation
GTP/GDP
exchange on
Ras, Rac
Activation of
PI3-Kinase
Increased
cytosolic Ca2+
Diacylglycerol
(DAG)
Ras•GTP,
Rac•GTP
PIP3
Active
enzymes
Calcineurin
PKC
ERK, JNK
Akt,
mTOR
↑ Protein
synthesis
Transcription
factors
NFAT
NF-κB
AP-1


Antigen recognition
T cell response
CD28
"Resting" (costimulator-deficient) APC
Naive T cell
No response or tolerance
Activation of APCs by microbes, innate immune response
B7
CD28
IL-2
Effector and memory T cells
Activated APC: increased expression of costimulators, secretion of cytokines
T cell proliferation and differentiation
Cytokines (e.g., IL-12)


Name
B7-1 (CD80)
B7-2 (CD86)
ICOS-L (CD275)
PD-L1 (B7-H1, CD274)
PD-L2 (B7-DC, CD273)
Ligands on APCs and other cells
Receptors on T cells
Name
CD28
CTLA-4
ICOS
PD-1
Major function
Activation (naive T cells)
Inhibition (mediates suppressive function of regulatory T cells)
Activation (follicular helper T cells in antibody responses)
Inhibition

Lymphocytes maturation



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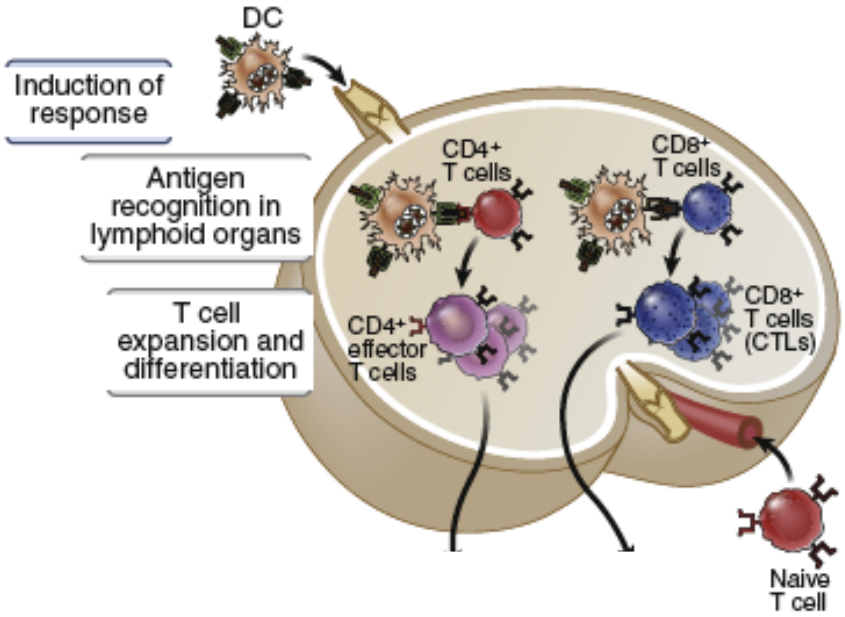
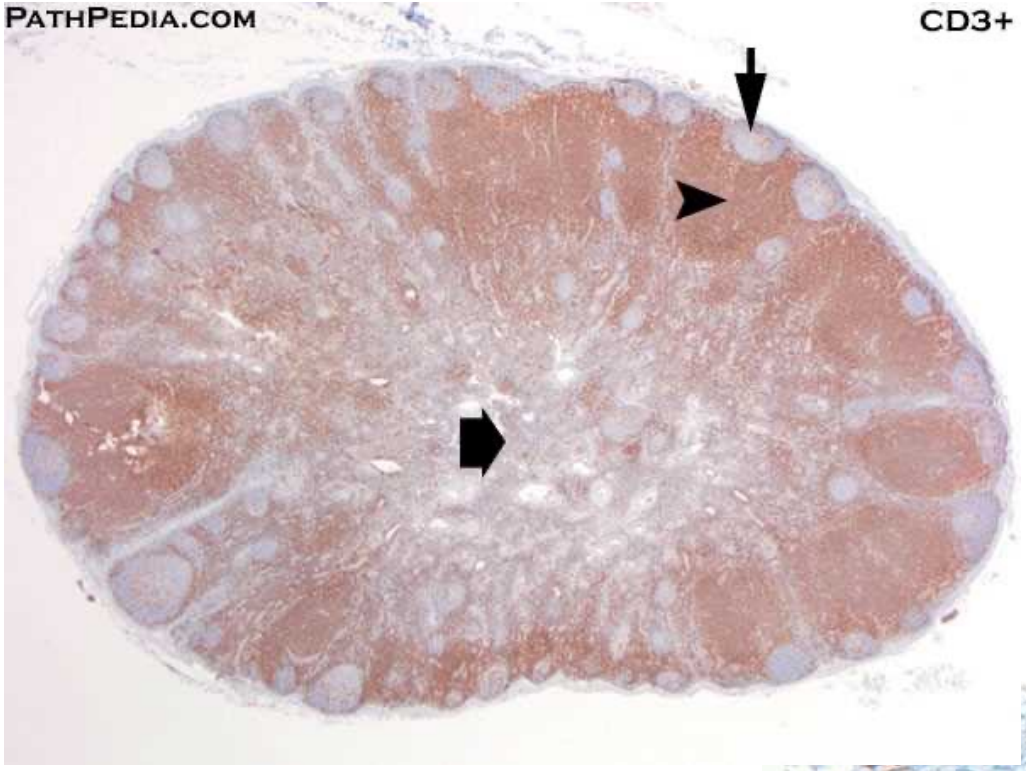
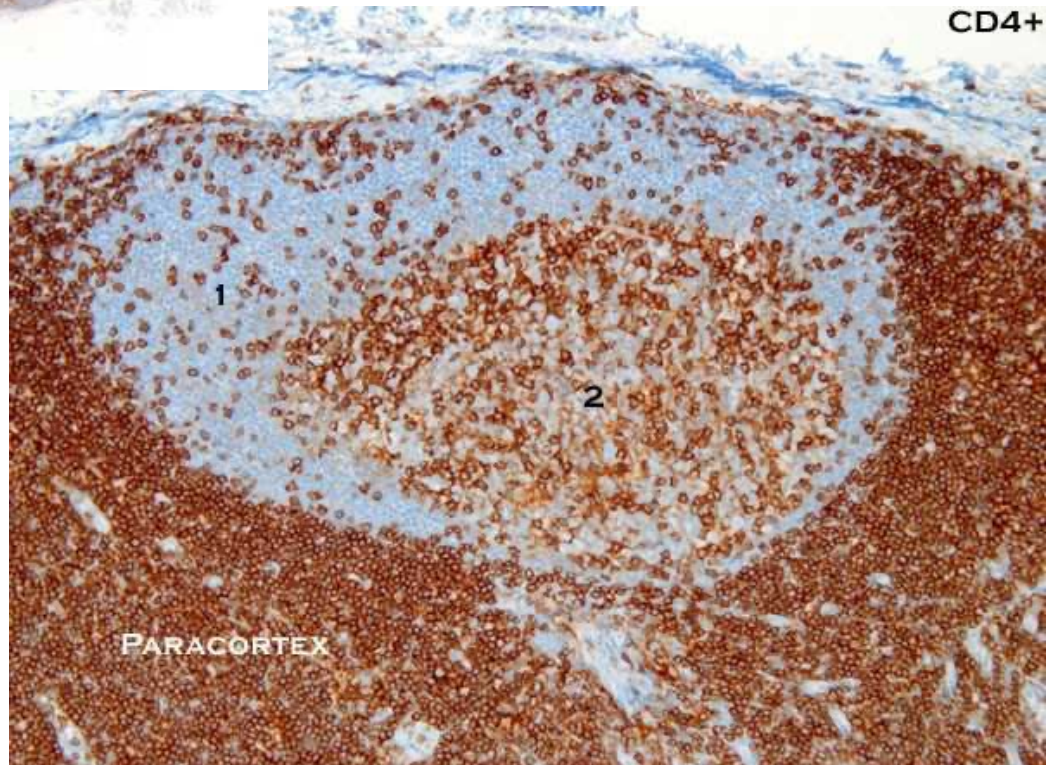
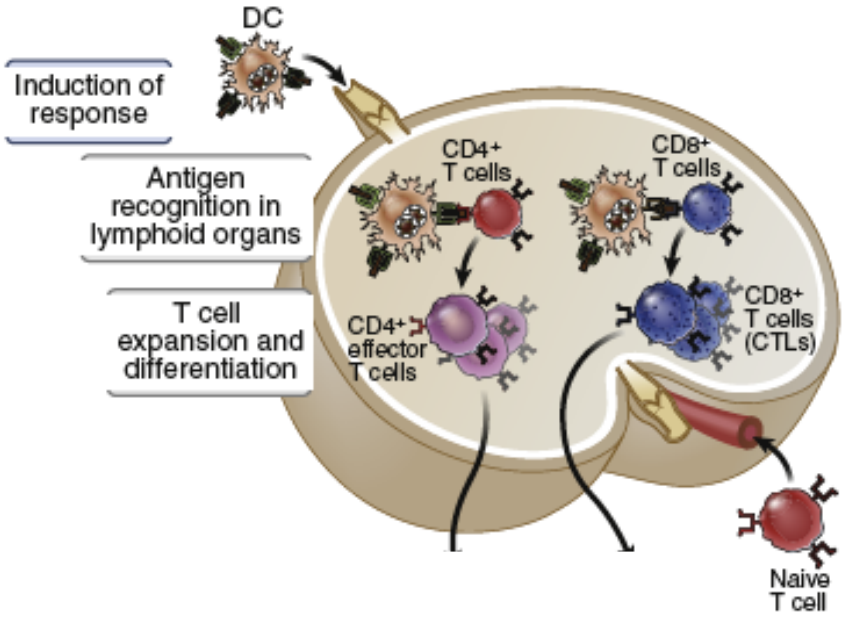

DC
Induction of response
Antigen recognition in lymphoid organs
T cell expansion and differentiation
CD4+ T cells
CD8+ T cells
CD4+ effector T cells
CD8+ T cells (CTLs)
Naive T cell


PATHPEDIA.COM
CD3+


CD4+
1
2
PARACORTEX


DC
Induction of response
Antigen recognition in lymphoid organs
T cell expansion and differentiation
CD4+ T cells
CD8+ T cells
CD4+ effector T cells
CD8+ T cells (CTLs)
Naive T cell

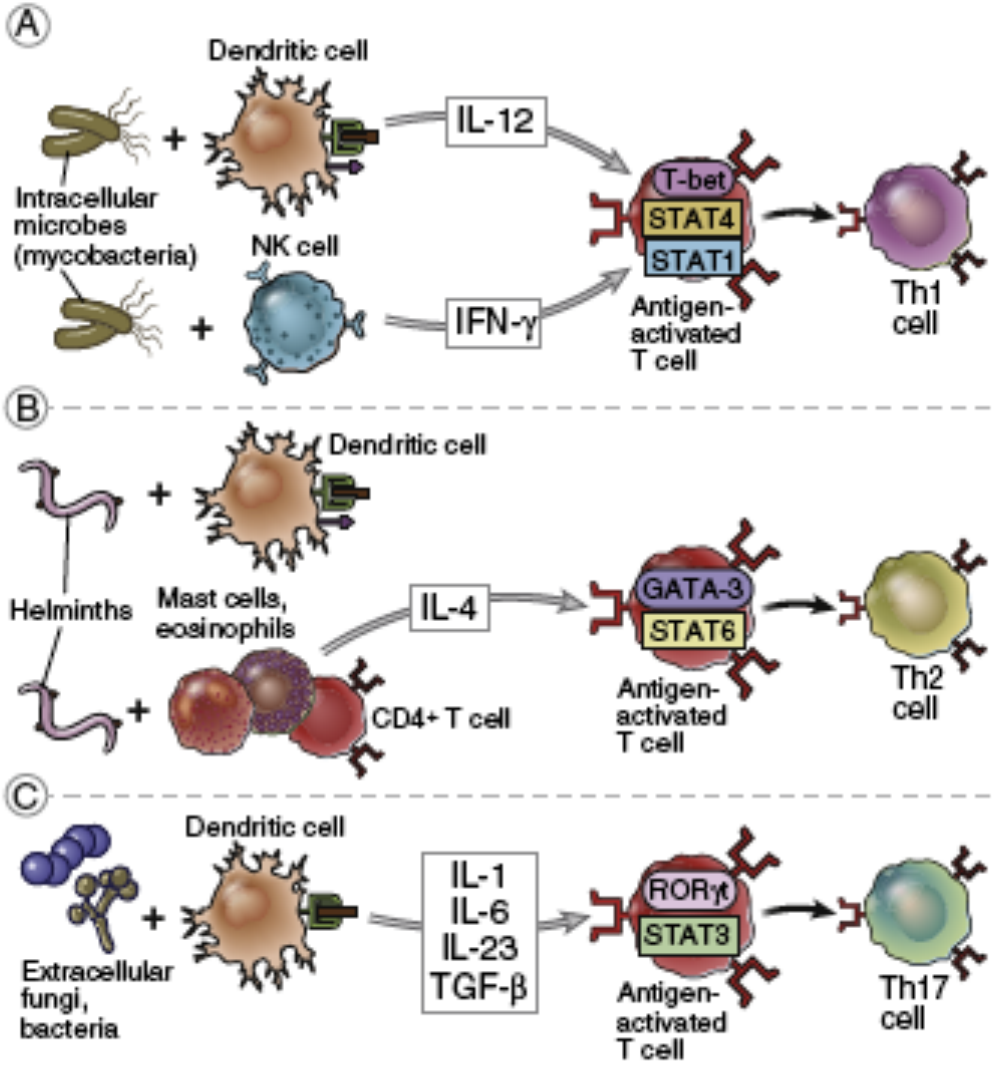
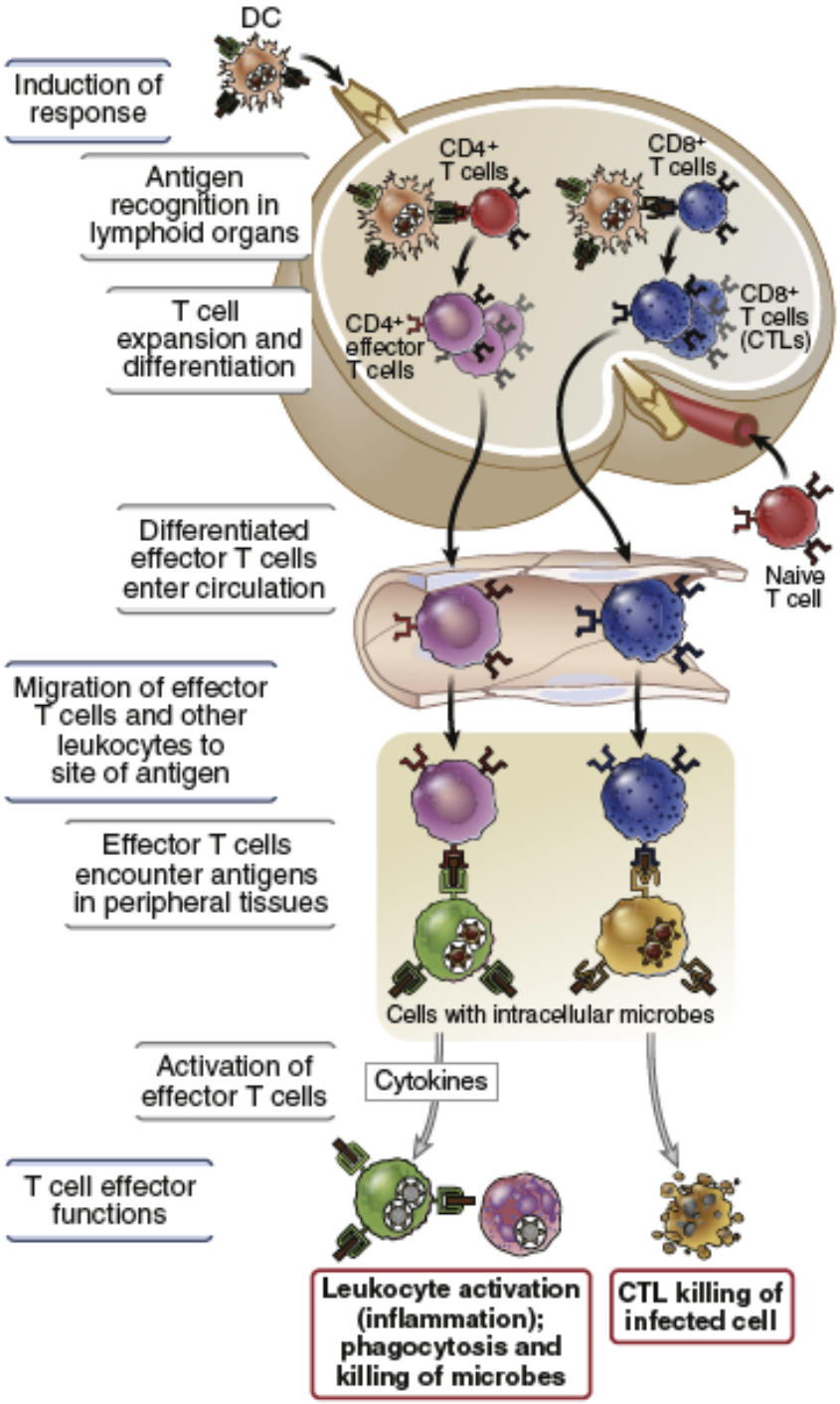


FIGURE 6-7 Development of Th1, Th2, and Th17 effector cells. Dendritic cells and other immune cells that respond to different types of microbes secrete cytokines that induce the development of antigen-activated CD4+ T cells into Th1 (**A**), Th2 (**B**), and Th17 (**C**) subsets. The transcription factors that are involved in T cell differentiation are indicated in boxes in the antigen-activated T cells.


DC
Induction of response
Antigen recognition in lymphoid organs
CD4+ T cells
CD8+ T cells
T cell expansion and differentiation
CD4+ effector T cells
CD8+ T cells (CTLs)
Differentiated effector T cells enter circulation
Naive T cell
Migration of effector T cells and other leukocytes to site of antigen
Effector T cells encounter antigens in peripheral tissues
Cells with intracellular microbes
Activation of effector T cells
Cytokines
T cell effector functions
Leukocyte activation (inflammation); phagocytosis and killing of microbes
CTL killing of infected cell

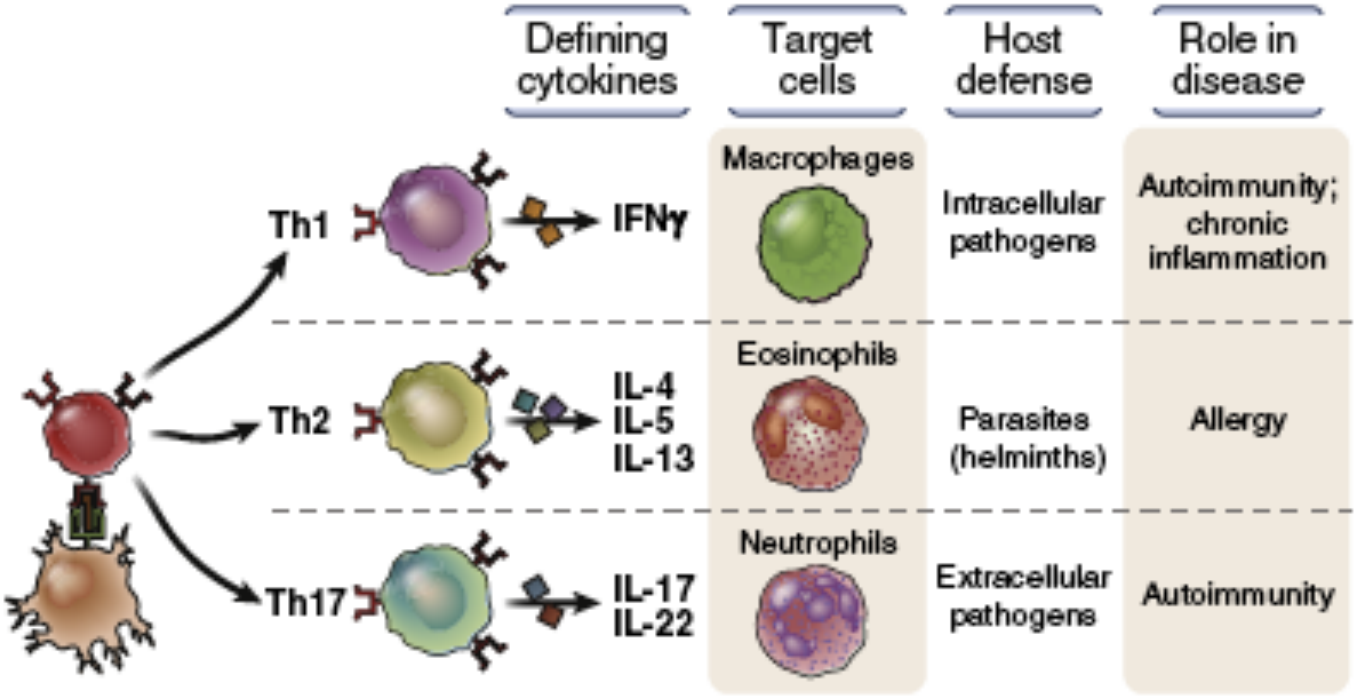
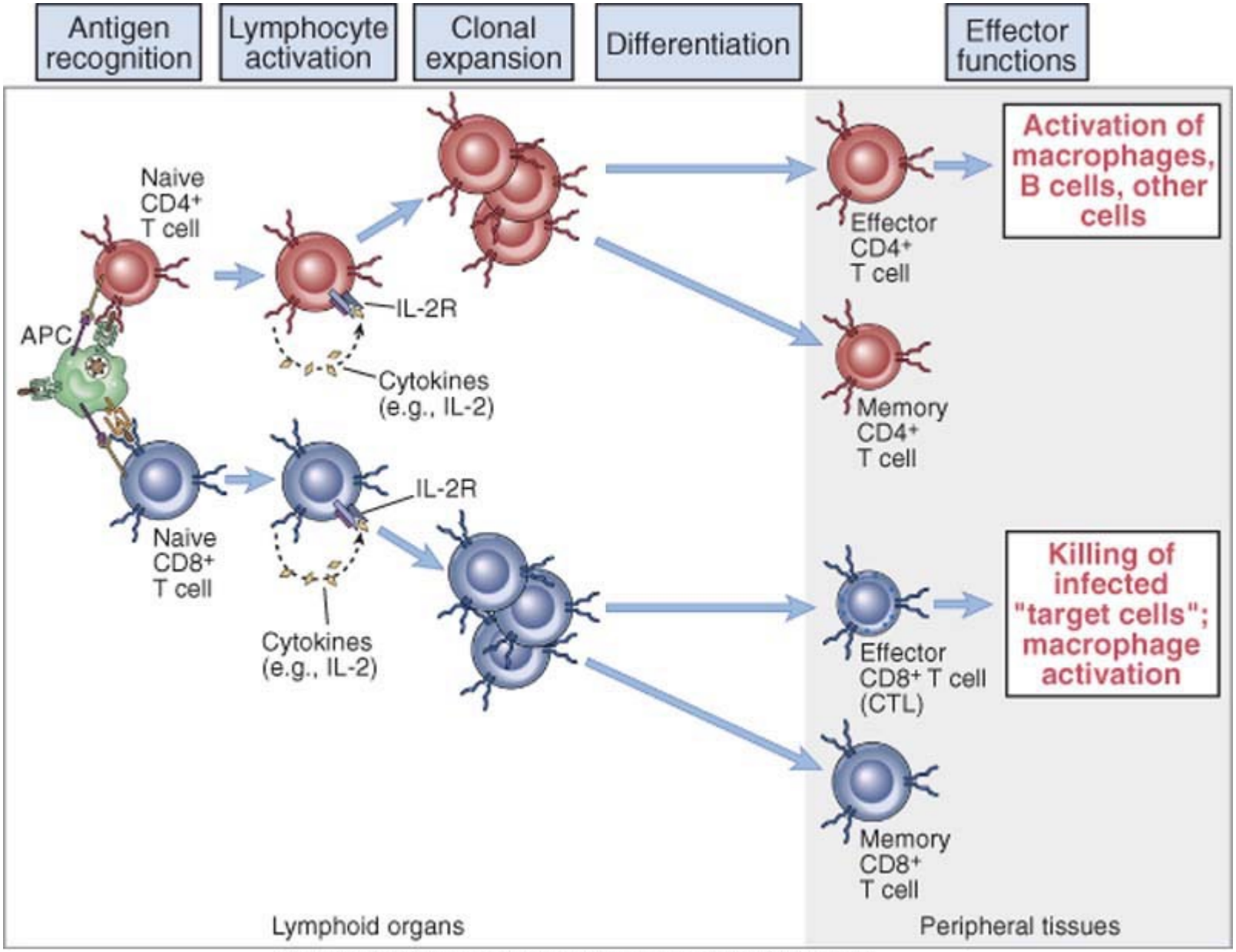


FIGURE 6-3 Characteristics of subsets of CD4+ helper T lymphocytes. A naive CD4+ T cell may differentiate into subsets that produce different cytokines that recruit and activate different cell types (referred to as *target cells*) and combat different types of infections in host defense. These subsets also are involved in various kinds of inflammatory diseases. The table summarizes the major differences among Th1, Th2, and Th17 subsets of helper T cells. *IFN*, Interferon; *IL*, interleukin.



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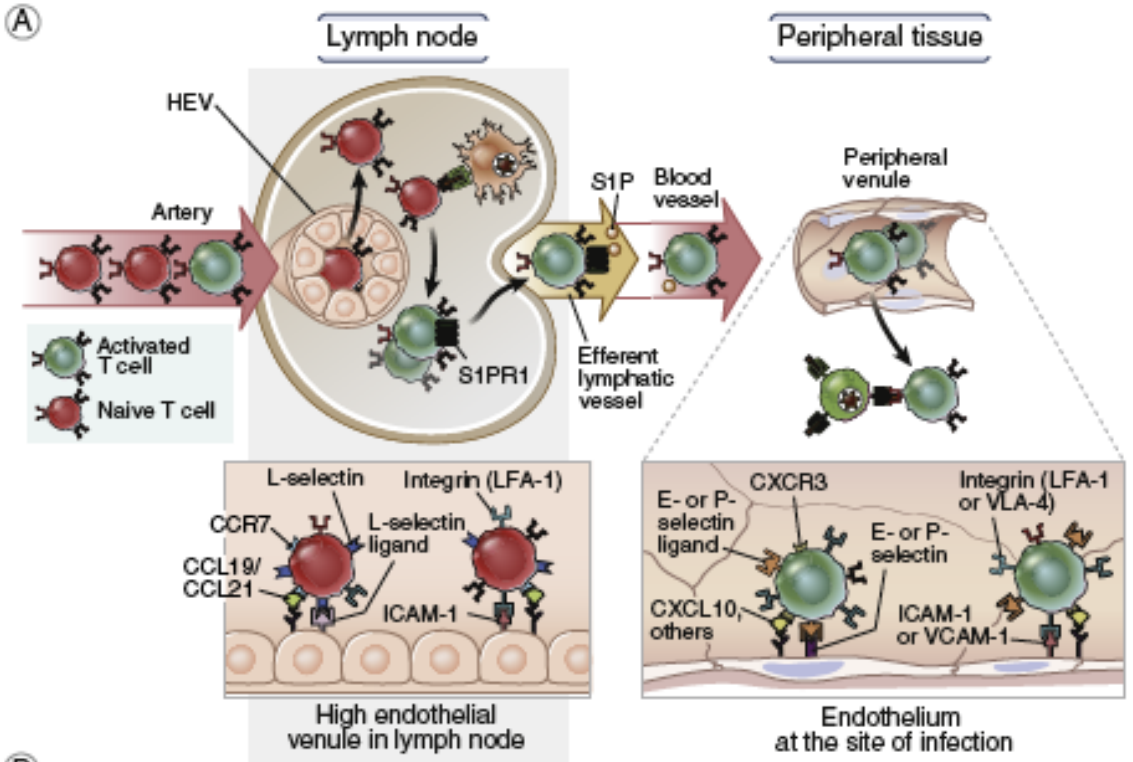
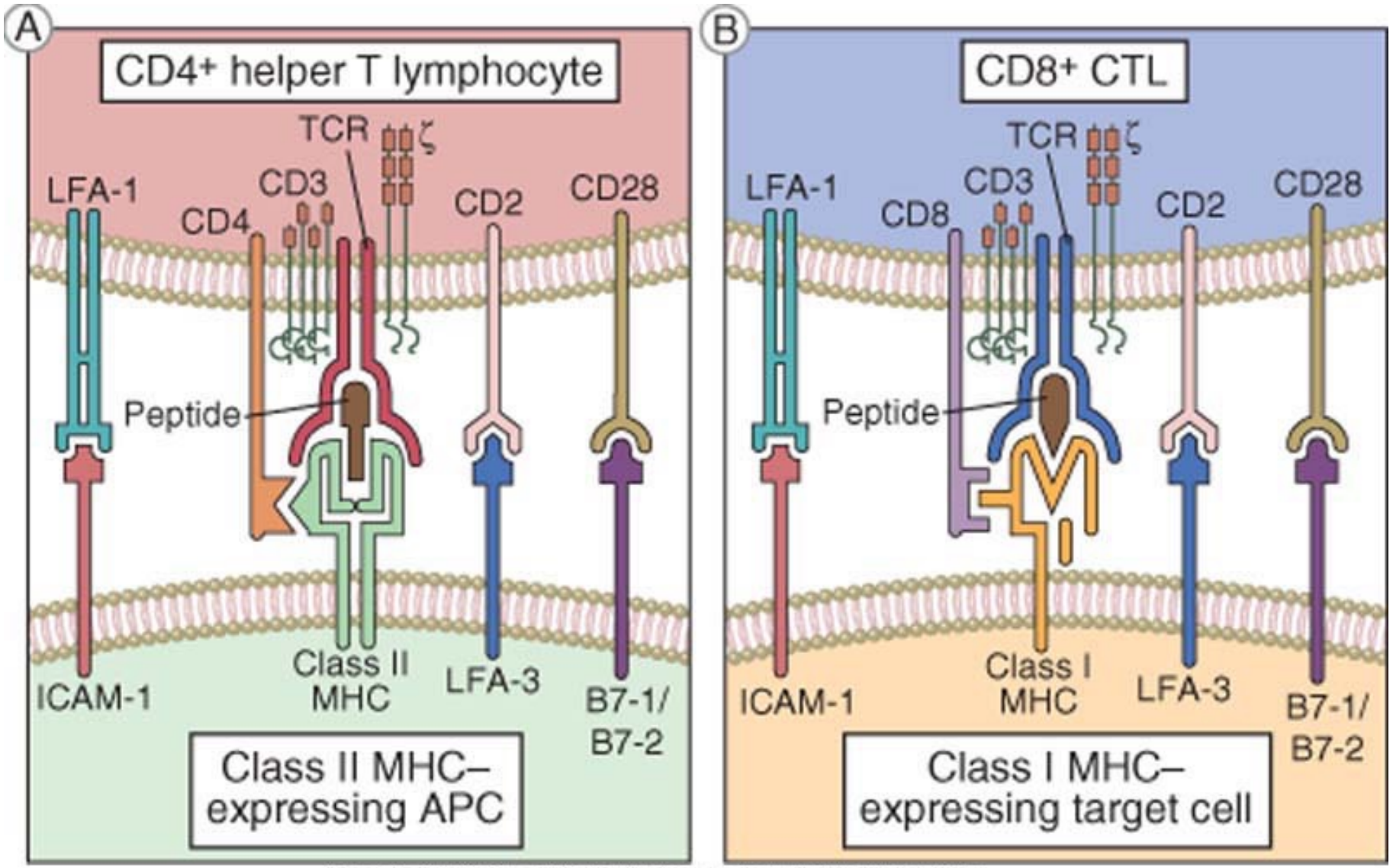


B

T cell homing receptor	Ligand on endothelial cell	Function of receptor: ligand pair
Naive T cells		
L-selectin	L-selectin ligand	Initial weak adhesion of naive T cells to high endothelial venule (HEV) in lymph node
LFA-1 (β_2-integrin)	ICAM-1	Stable arrest on HEV
CCR7	CCL19 or CCL21	Activation of integrins and chemotaxis
Activated (effector and memory) T cells		
E- and P-selectin ligand	E- or P-selectin	Initial weak adhesion of effector and memory T cells to cytokine-activated endothelium at peripheral site of infection
LFA-1 (β_2-integrin) or VLA-4 (β_1 integrin)	ICAM-1 or VCAM-1	Stable arrest on cytokine-activated endothelium at peripheral site of infection
CXCR3, others	CXCL10, others	Activation of integrins and chemotaxis



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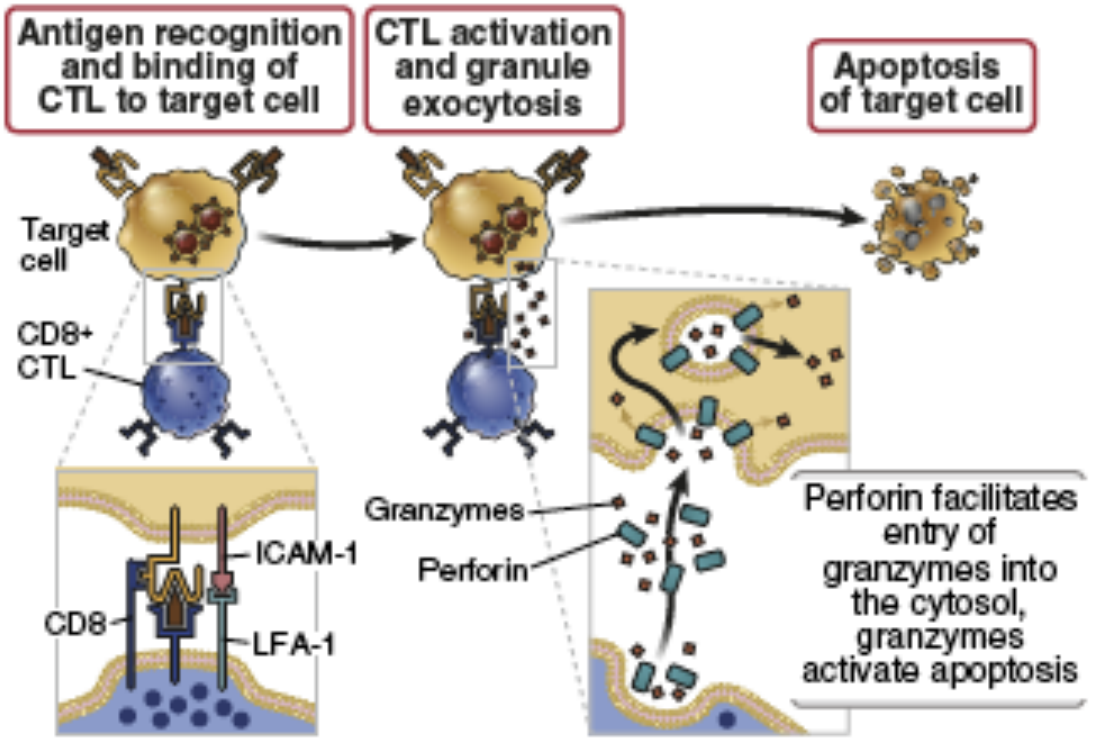
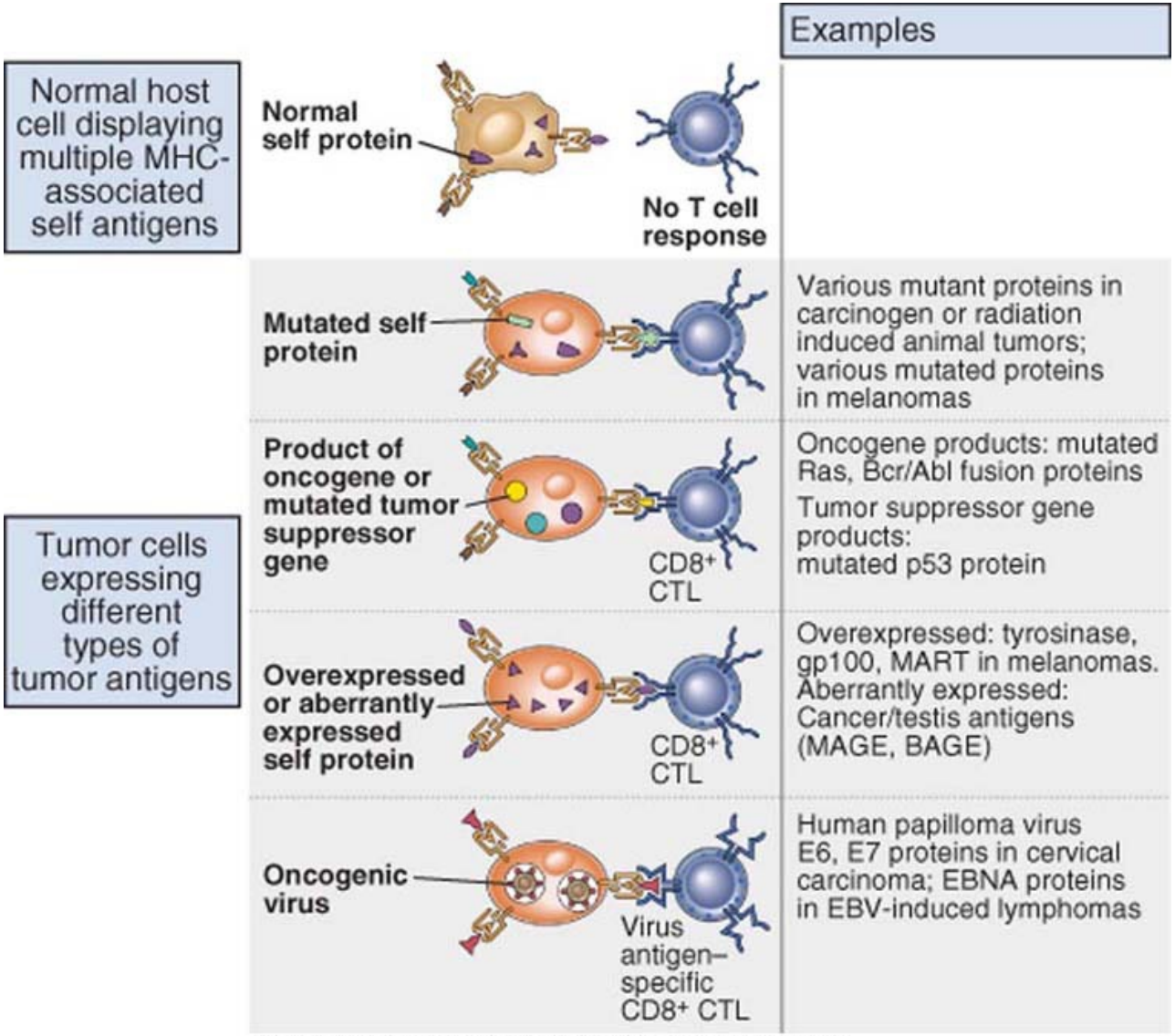


FIGURE 6-12 Mechanisms of killing of infected cells by CD8+ cytotoxic T lymphocytes (CTLs). CTLs recognize class I MHC–associated peptides of cytoplasmic microbes in infected cells and form tight adhesions (conjugates) with these cells. Adhesion molecules such as integrins stabilize the binding of the CTLs to infected cells (not shown). The CTLs are activated to release (exocytose) their granule contents (perforin and granzymes) toward the infected cell, referred to as the target cell. Granzymes are delivered to the cytosol of the target cell by a perforin-dependent mechanism. Granzymes then induce apoptosis. *ICAM-1*, Intercellular adhesion molecule 1; *LFA-1*, leukocyte function–associated antigen 1.

How APC present tumor Ags???

Tumor antigens recognized by CTL



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Escape of immune response by cancer cells (tumor escape)

“Several data showed that tumors developed in immunodeficient mice were easily rejected with respect to tumors from WT mice, studying transplantation in WT mice.
It indicates that tumors developed in immune-sufficient mice generate less immunogenic tumor variants”

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Escape of immune response by cancer cells (tumor escape) (1)

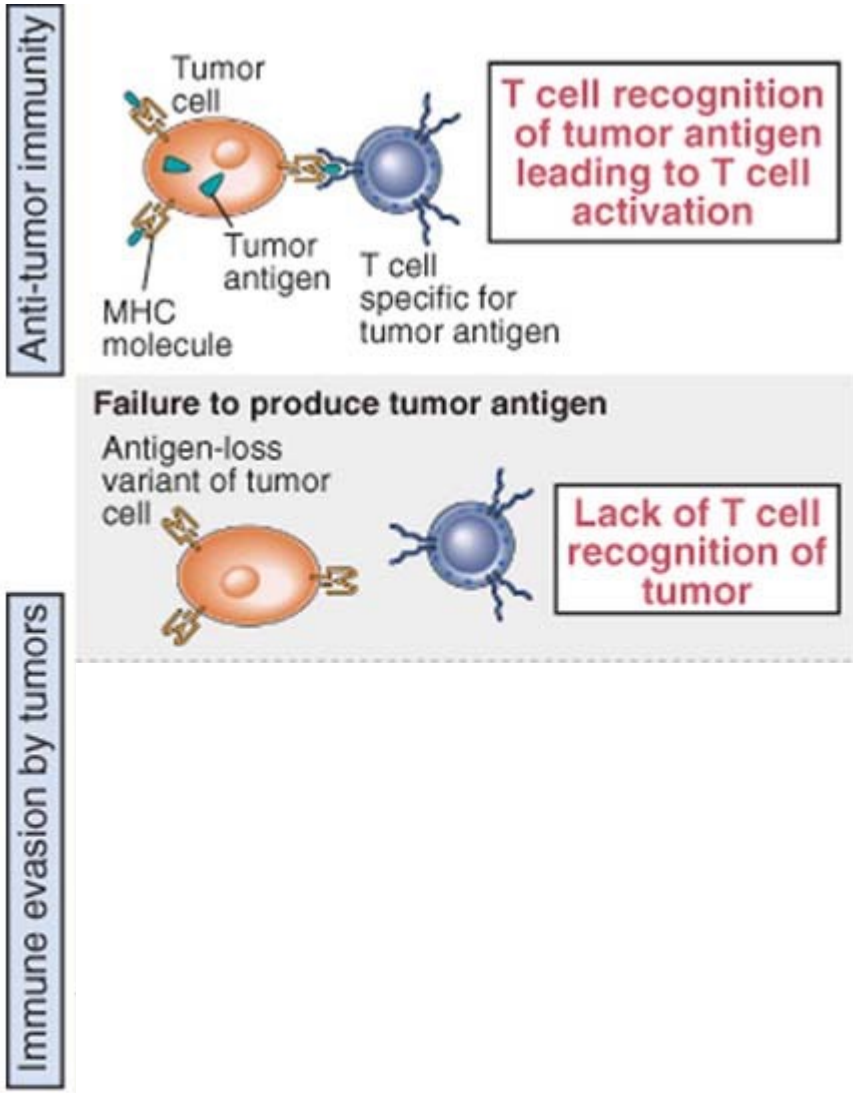
- **Tumor Ags may induce specific immune tollerance**

(in particular viral Ags)

Tumor escape (2)

- **Tumor cells reduce the expression of tumor Ags**

(particularly evident in tumor with very fast growth in which mut/del can be included in the sequence of TAA)



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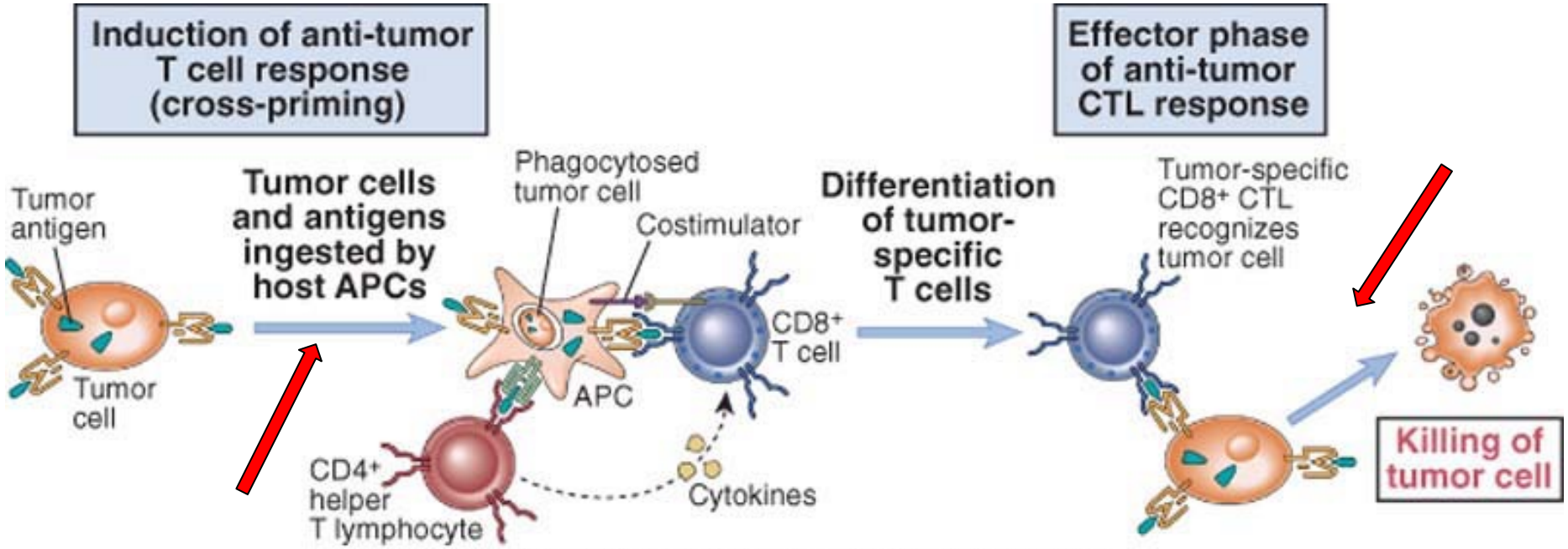
Induction of a T-response against tumor



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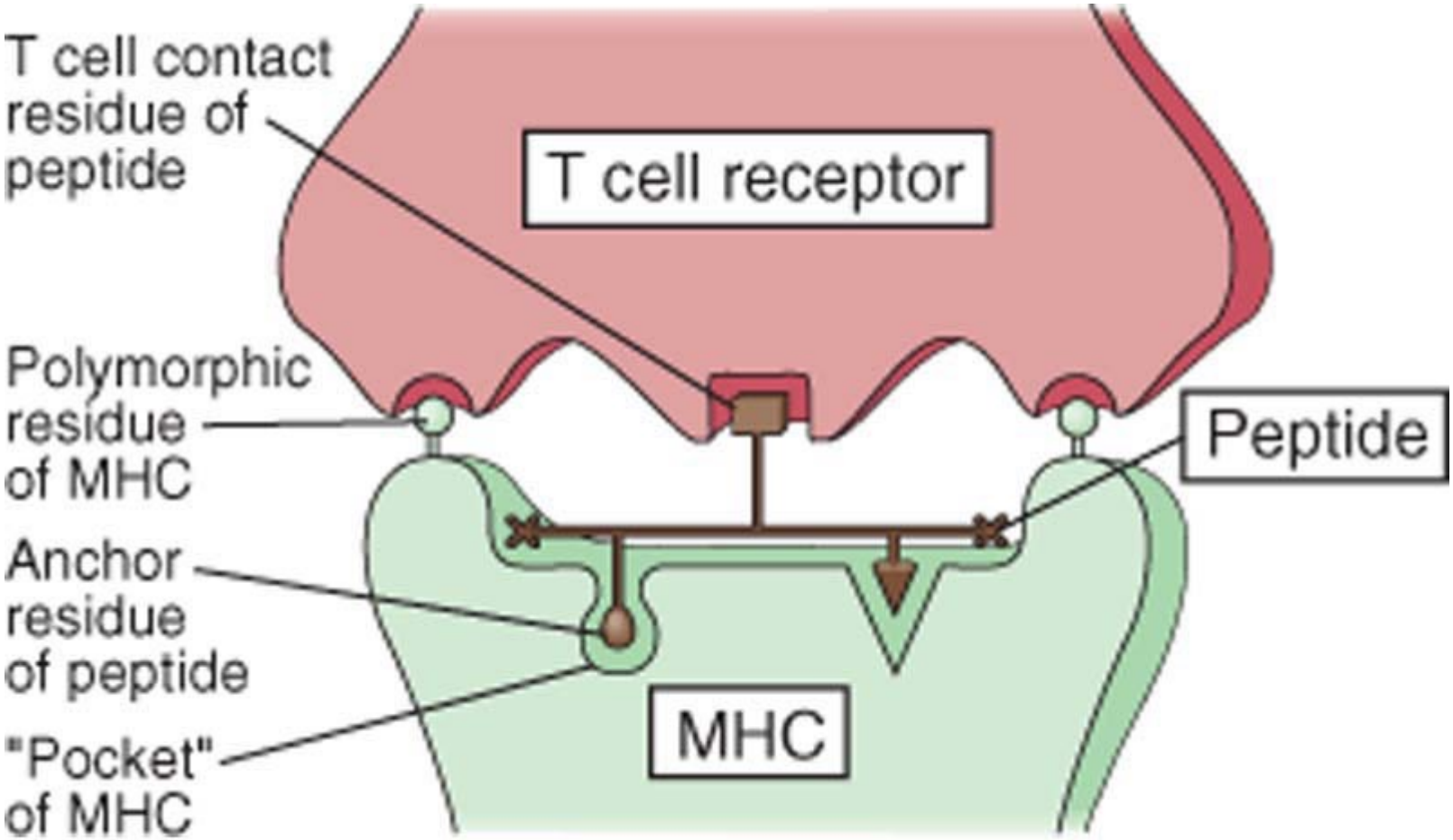

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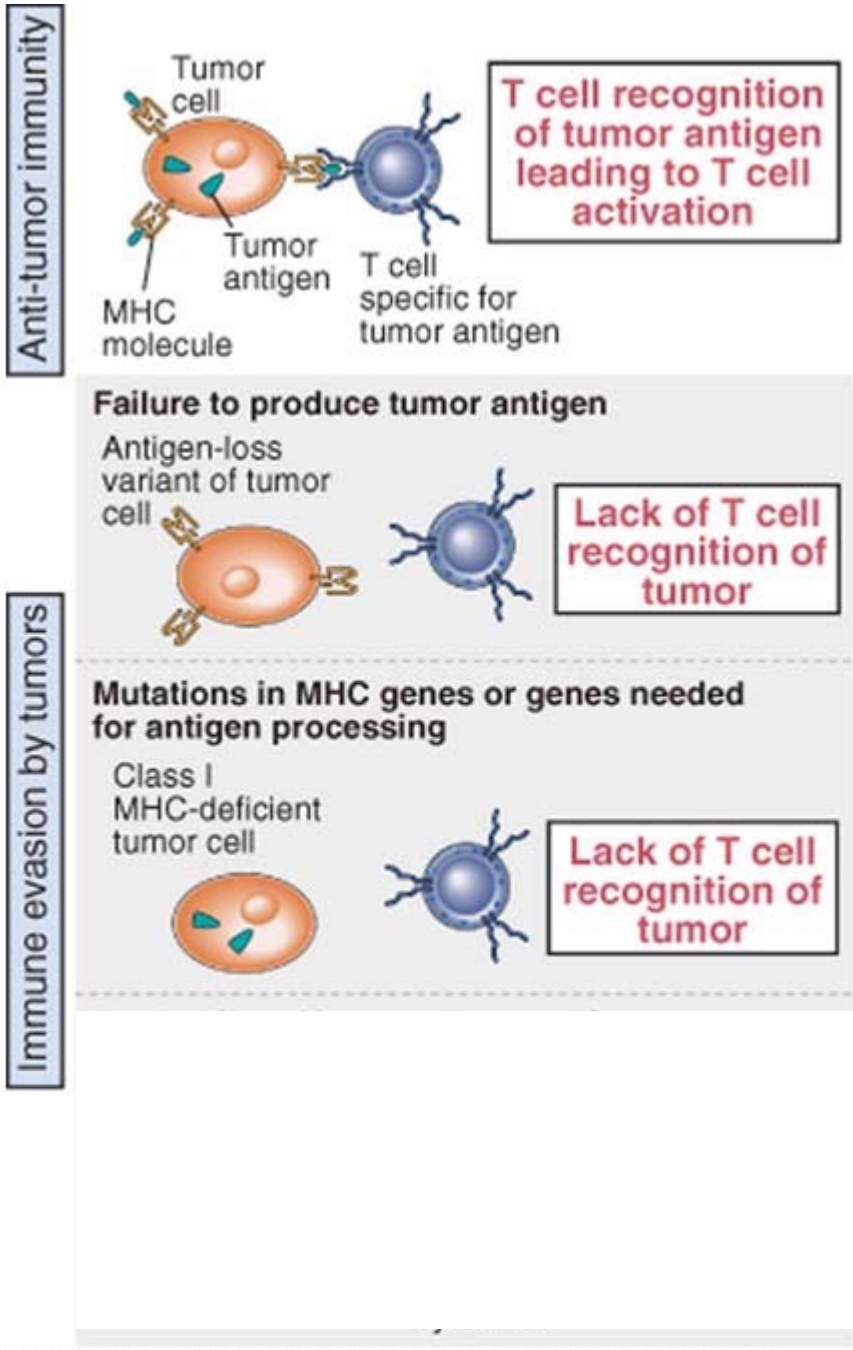
Tumor escape (3)

- **Some tumor cells reduce the expression of MHC I**



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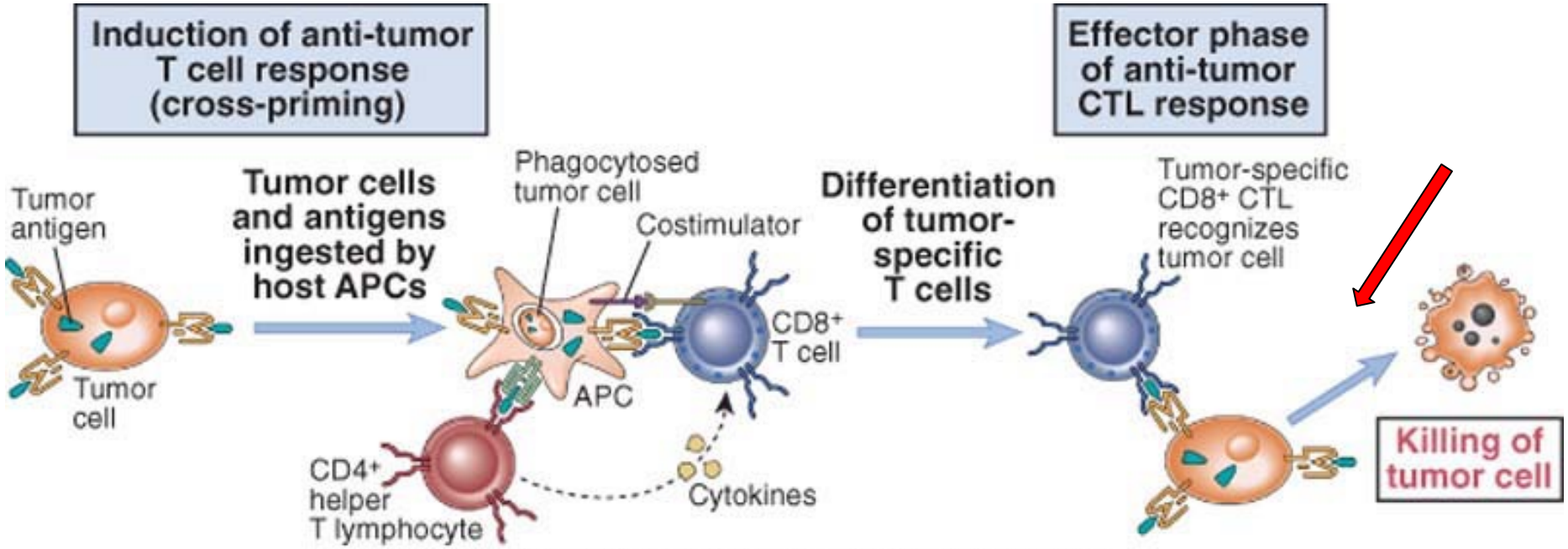
Induction of a T-response against tumor



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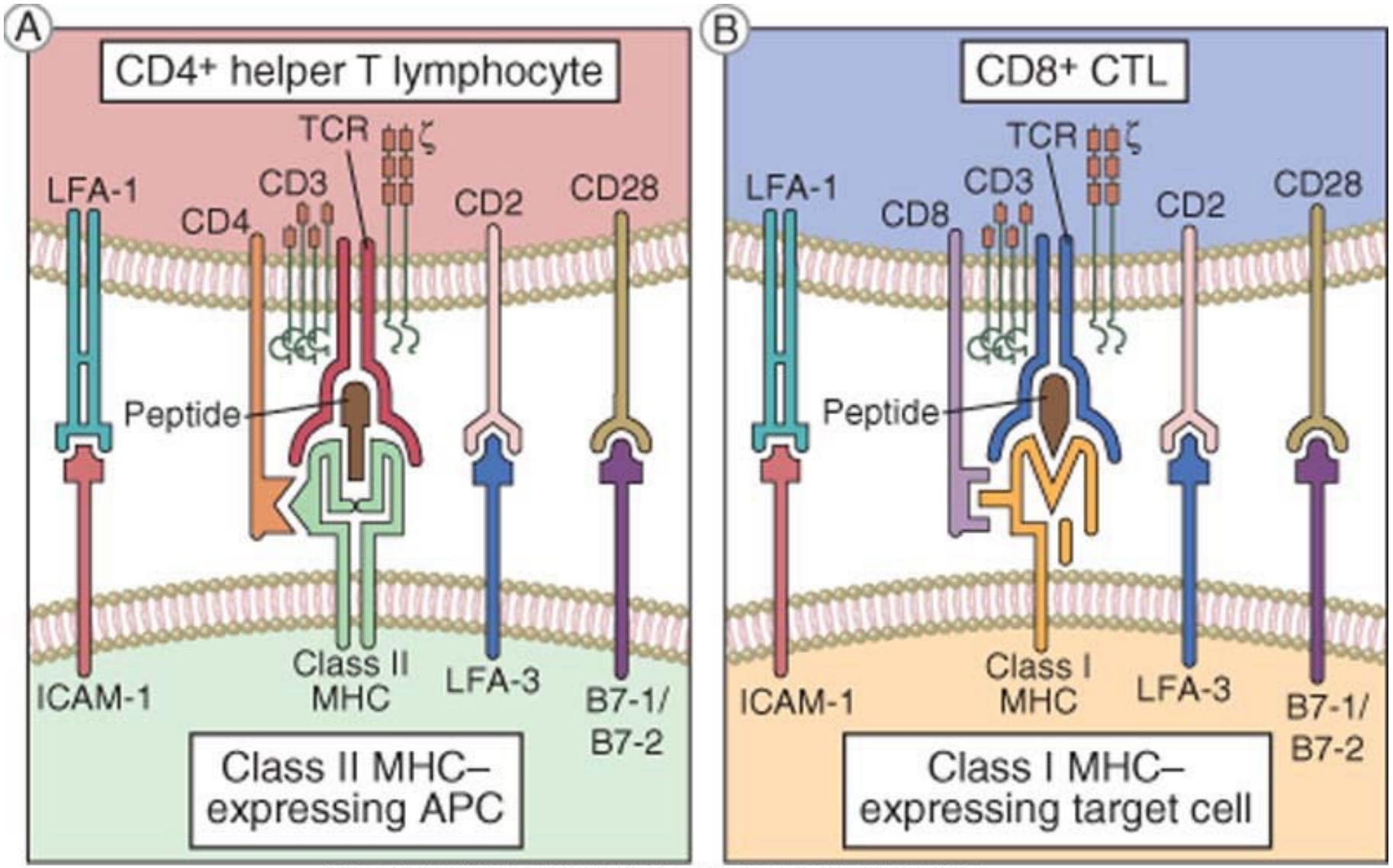
Tumor escape (4)

- **Several tumor cells do not express the ideal co-stimulatory molecules, avoiding a correct response of CTL**

(moreover, tumor cells over-expressing CD80 or CD86 induce a strong cell-mediated immune response)



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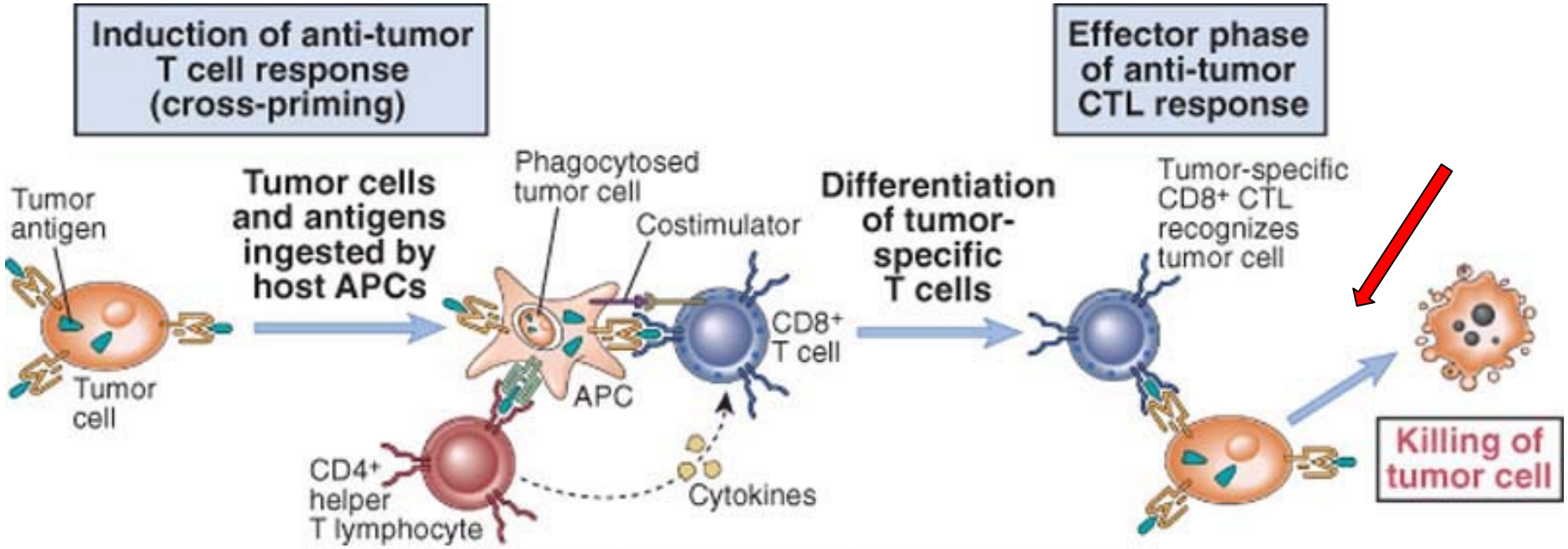
Induction of a T-response against tumor



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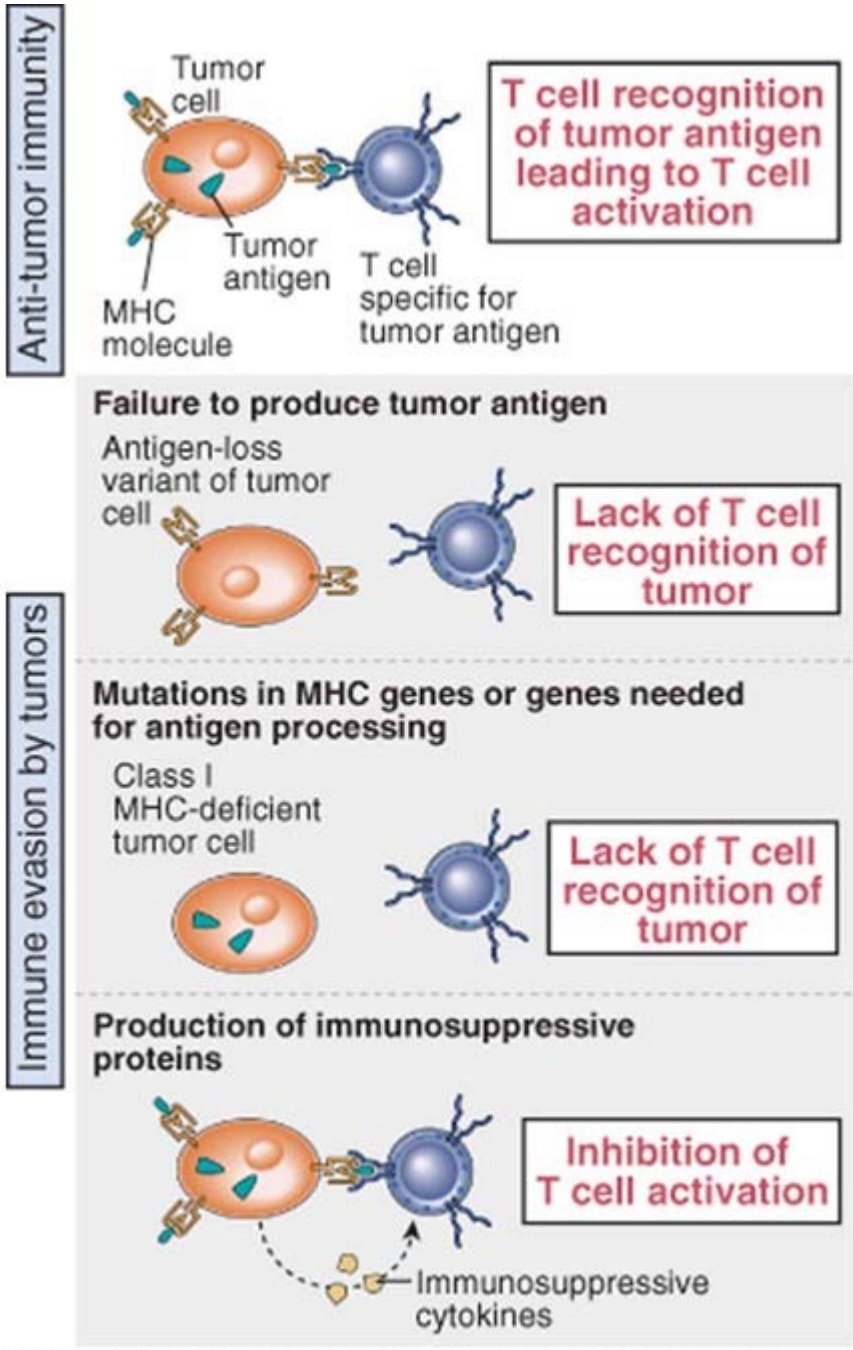
Tumor escape (5)

- **products secreted by tumor cells can inhibit effector T-cell response**

(es. TGF-B secreted by tumor cells inhibit proliferation and functional activation of CD8+ T-lymphocytes)



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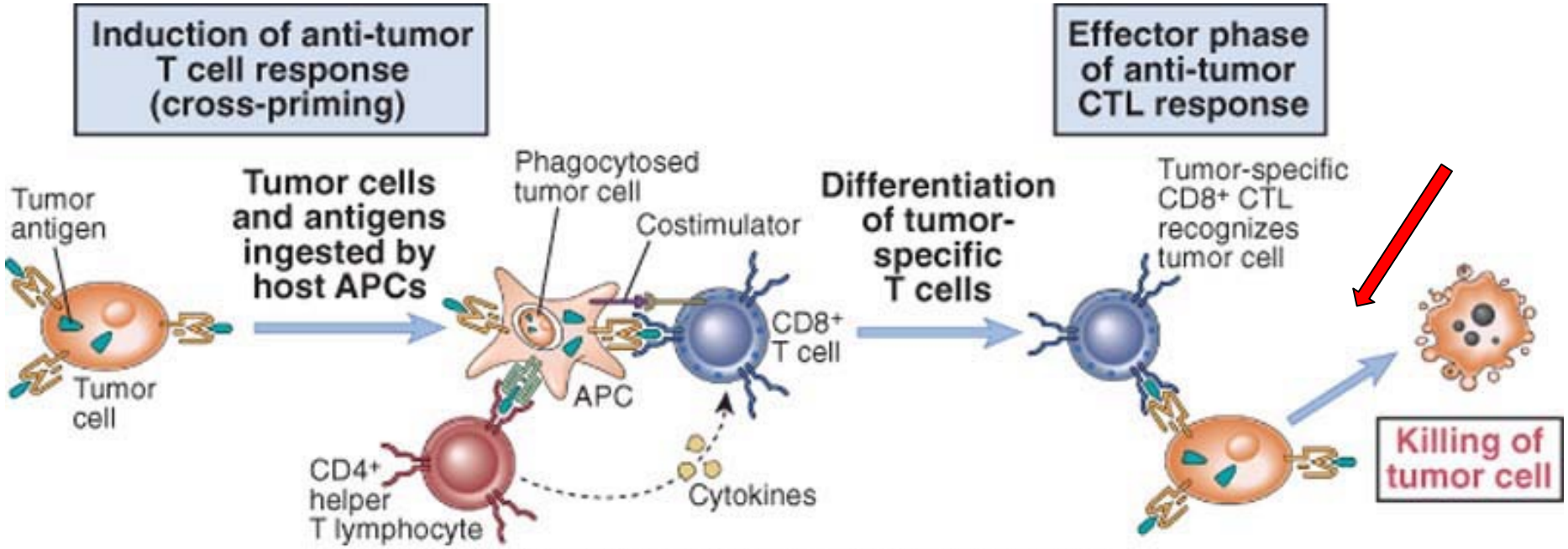
Induction of a T-response against tumor



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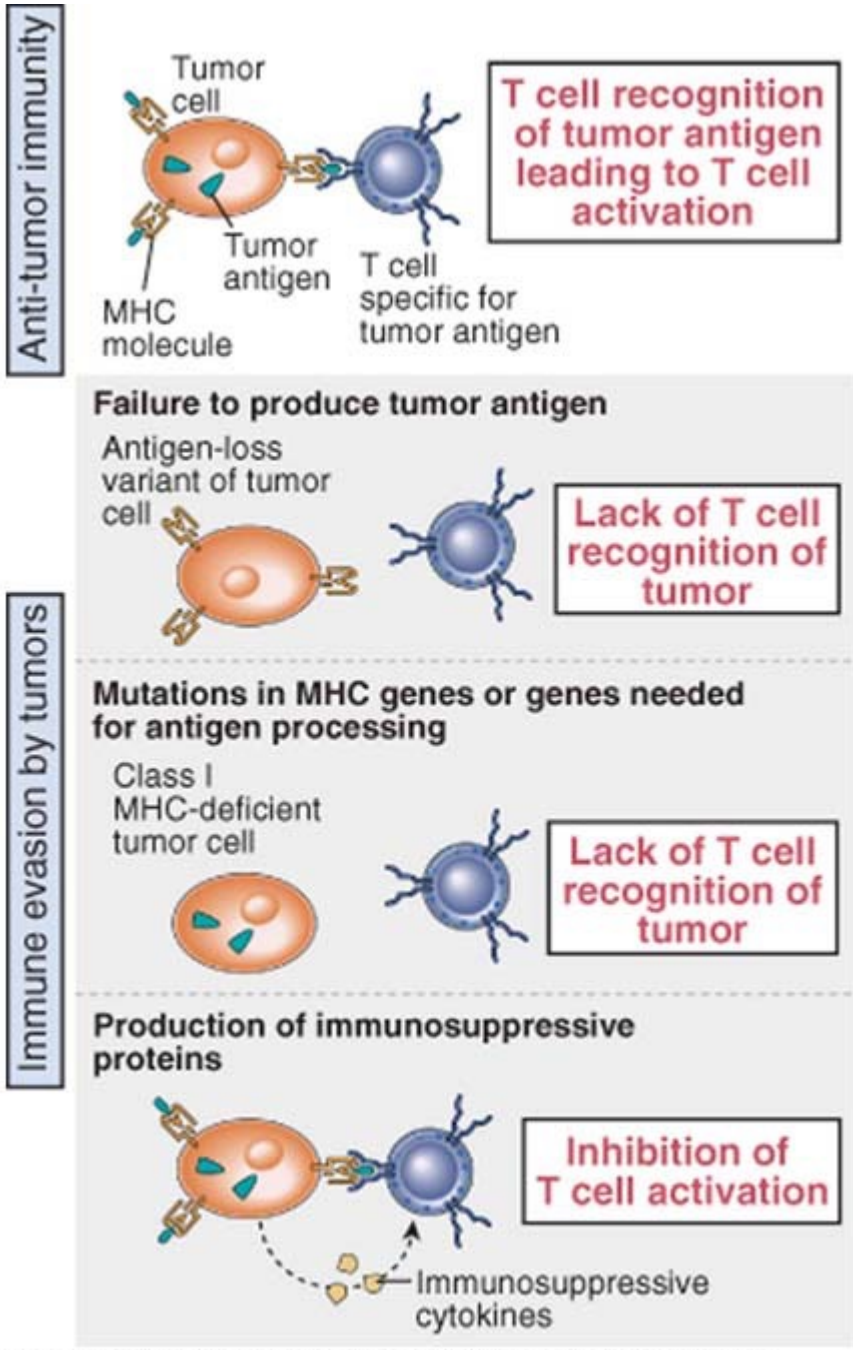
Tumor escape (5)

- **products secreted by tumor cells can inhibit effector T-cell response**

(es. TGF-B secreted by tumor cells inhibit proliferation and functional activation of CD8+ T-lymphocytes)

… but also of macrophages (APC but also part of the innate immunity)



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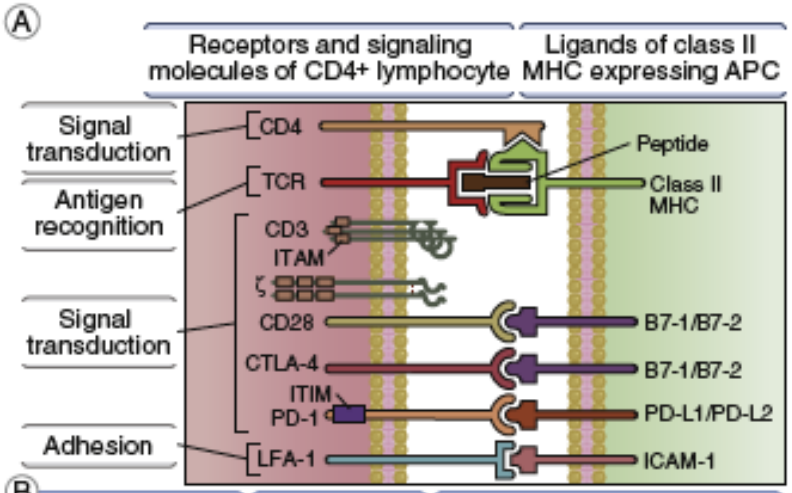


B

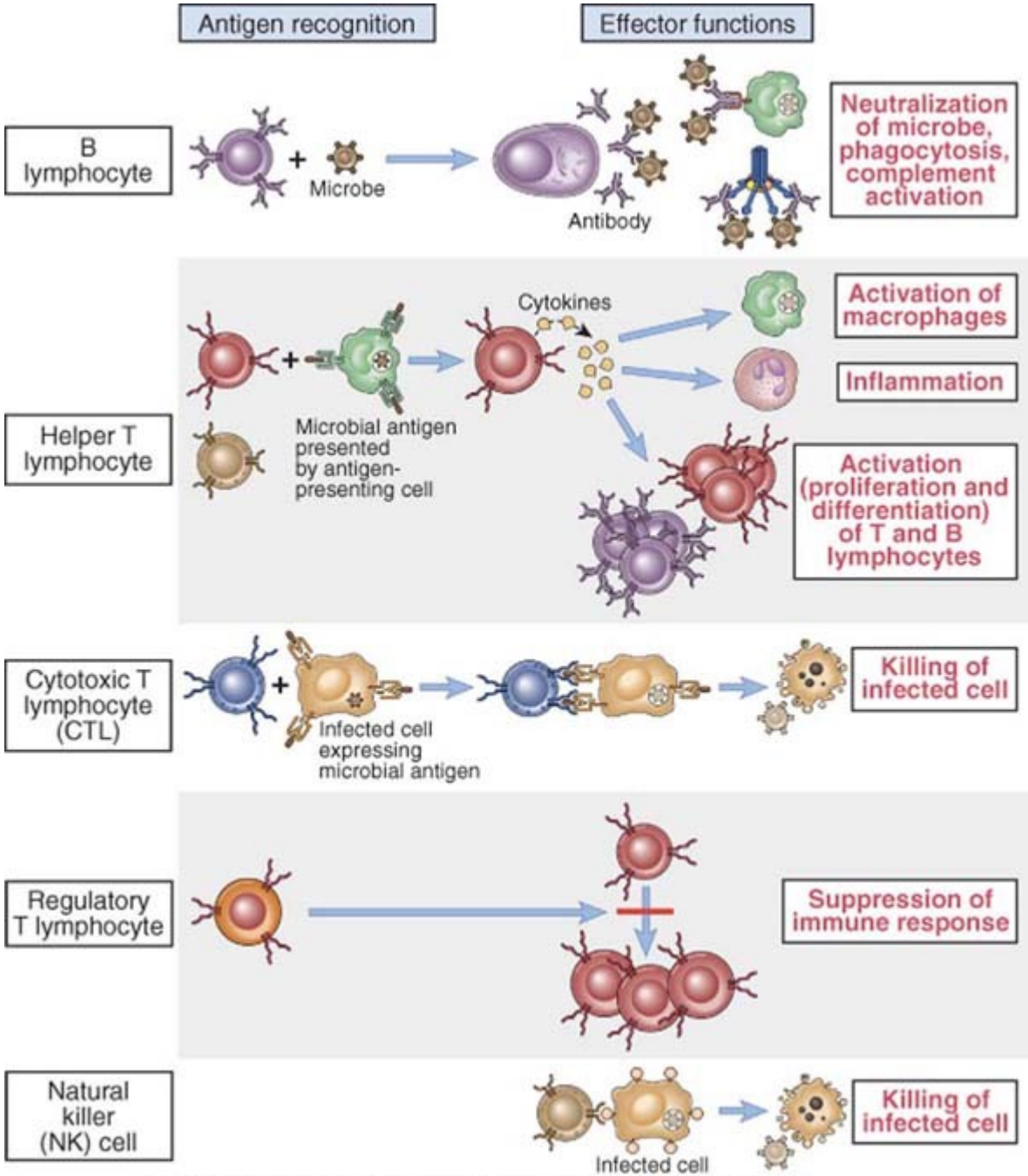
Surface molecules of T lymphocytes	Function	Ligand	
		Name	Expressed on
CD3	Signal transduction by TCR complex	None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen presenting cells
CD8	Signal transduction	Class I MHC	All nucleated cells
CD28	Signal transduction (costimulation)	B7-1/B7-2	Antigen presenting cells
CTLA-4	Inhibition	B7-1/B7-2	Antigen presenting cells
PD-1	Inhibition	PD-L1/PD-L2	Antigen presenting cells, tissue cells, tumor cells
LFA-1	Adhesion, signal transduction	ICAM-1	Antigen presenting cells, endothelium

Escape of immune response by cancer cells (tumor escape) (6)

- **Regulatory T lymphocytes inhibit T-cell response against cancer cells**

(Studies in animal models or in patient' samples evidenced and incresce number of Treg and their preferential localization in tumor microenvironment)

Classes of lymphocytes



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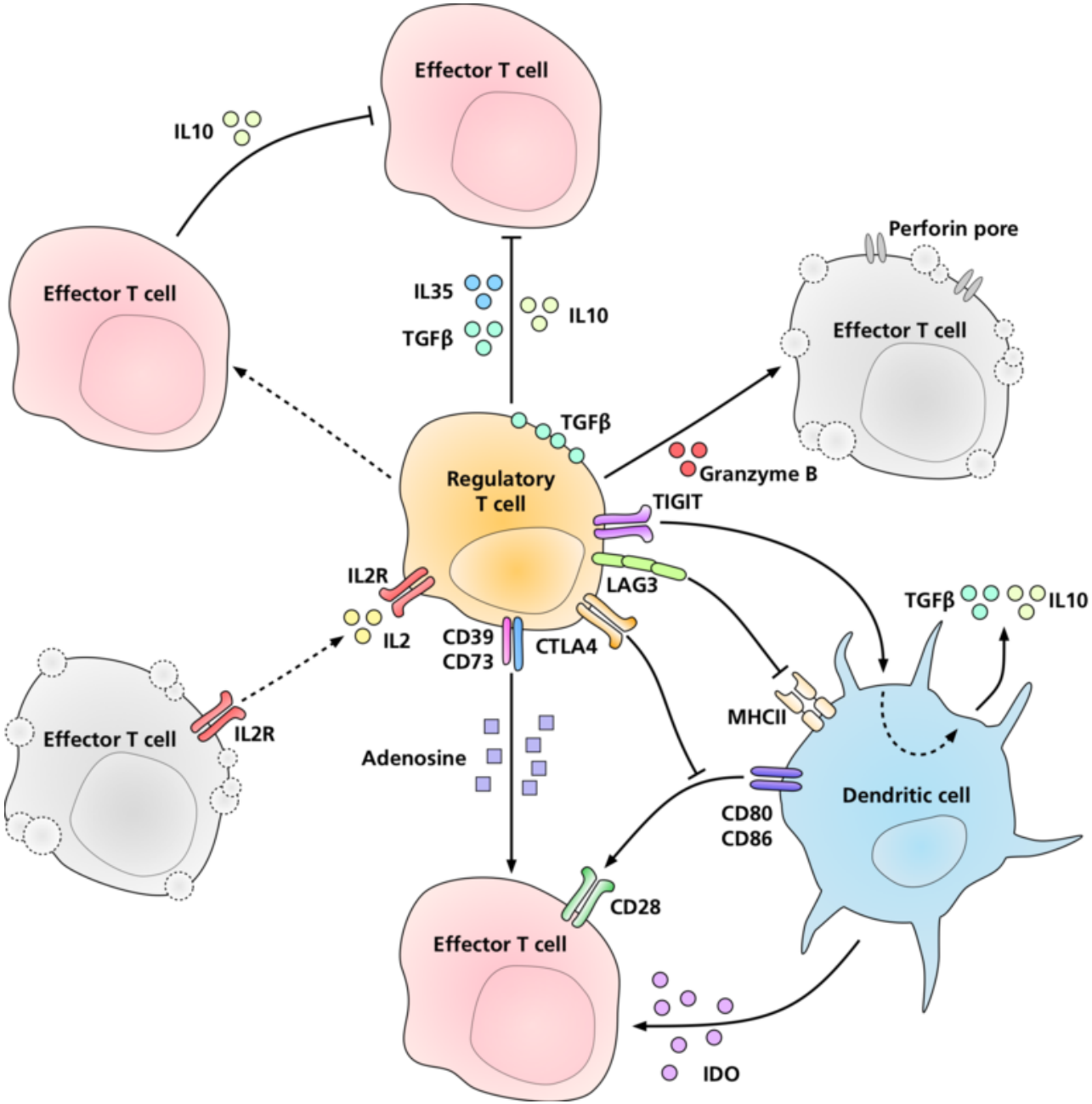
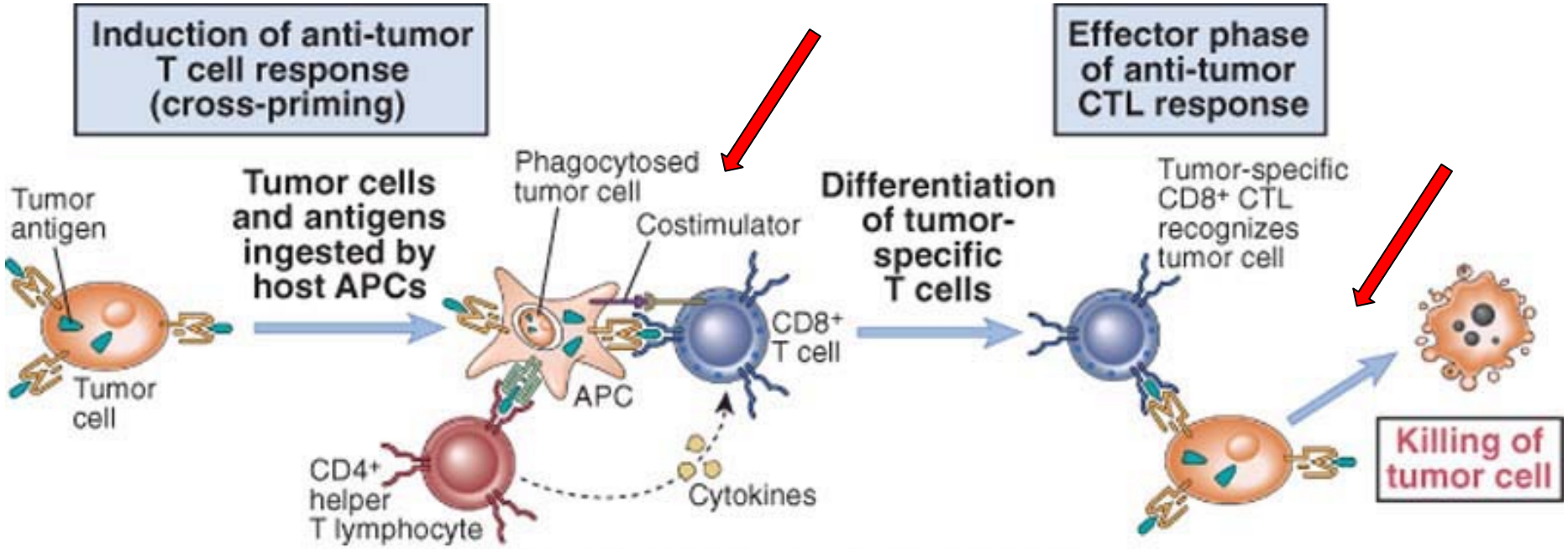

Effector T cell
IL10
Effector T cell
IL35
TGFβ
IL10
Perforin pore
Effector T cell
TGFβ
Granzyme B
Regulatory
T cell
TIGIT
LAG3
IL2R
IL2
CD39
CD73
CTLA4
TGFβ
IL10
MHCII
Effector T cell
IL2R
Adenosine
Dendritic cell
CD80
CD86
CD28
Effector T cell
IDO

Induction of a T-response against tumor



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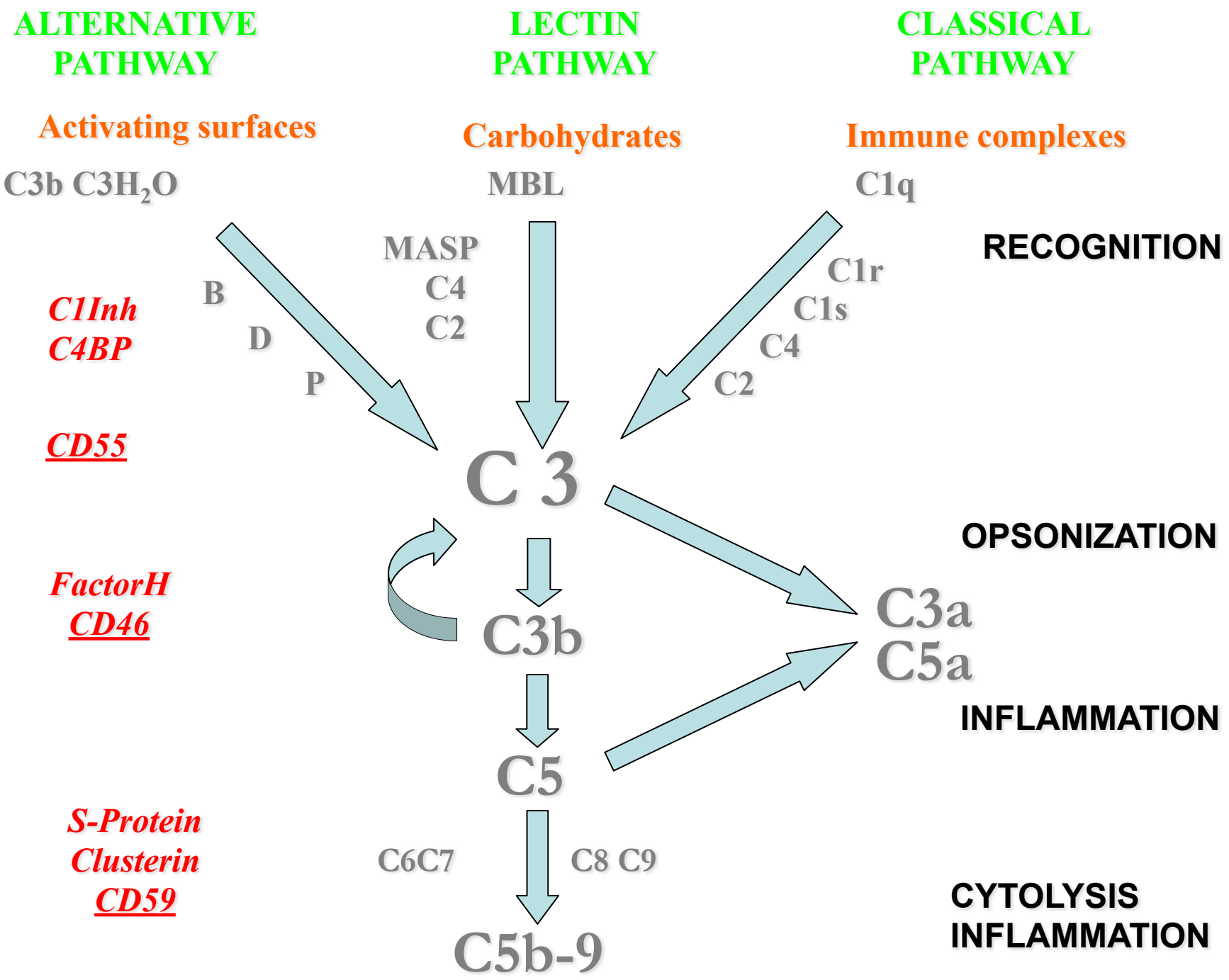
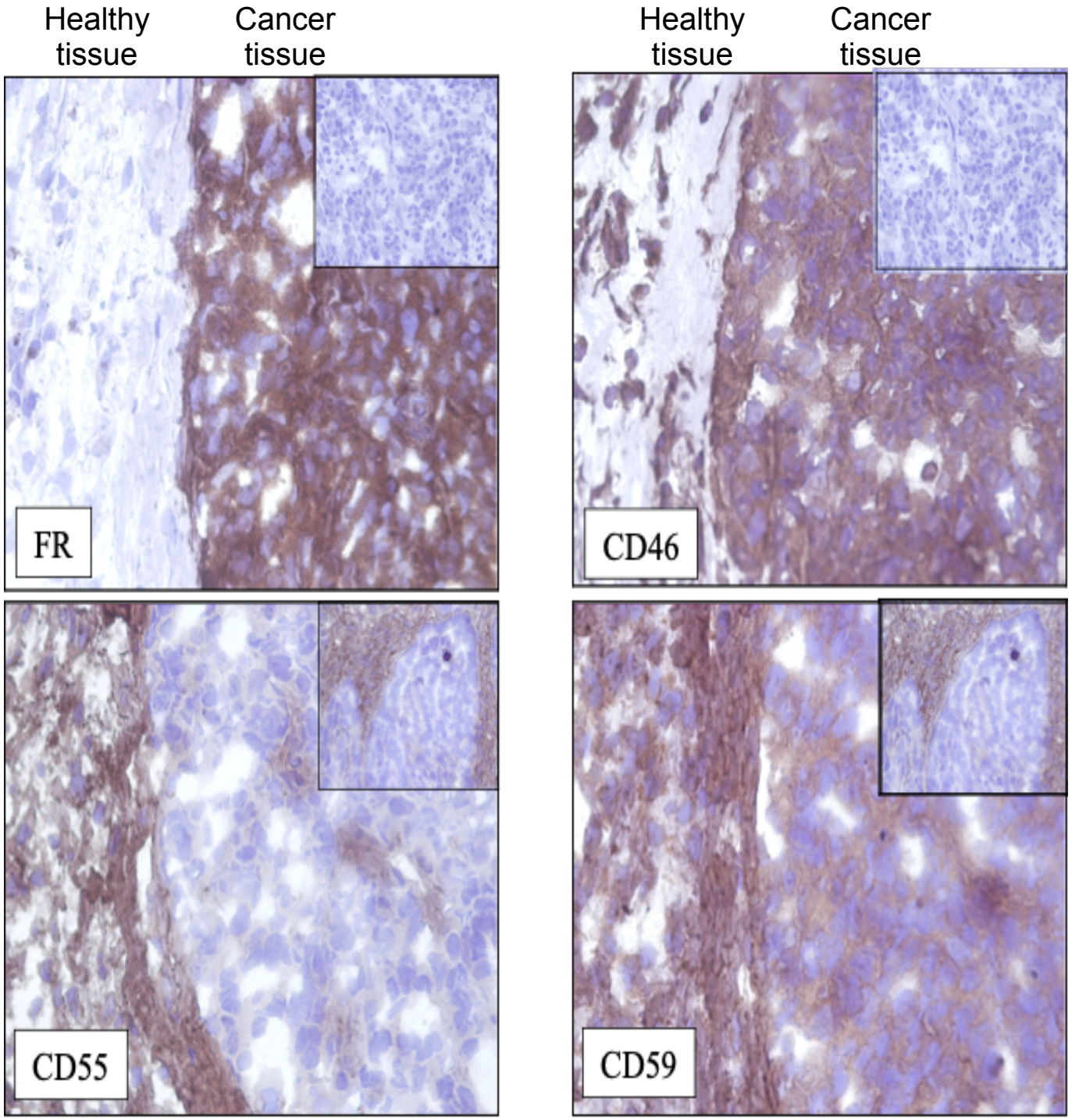
Tumor escape (7)

- **increased expression of membrane complement inhibitors on tumor cells**

(iper-espression of CD46, CD55 e CD59 neutralized the lytic activity of the complement system)


ALTERNATIVE PATHWAY
LECTIN PATHWAY
CLASSICAL PATHWAY
Activating surfaces
Carbohydrates
Immune complexes
C3b C3H2O
MBL
C1q
RECOGNITION
B
D
P
MASP
C4
C2
C1r
C1s
C4
C2
C1Inh
C4BP
CD55
C 3
OPSONIZATION
FactorH
CD46
C3b
C3a
C5a
INFLAMMATION
C5
S-Protein
Clusterin
CD59
C6C7
C8 C9
CYTOLYSIS
INFLAMMATION
C5b-9

Ovarian carcinoma



Question:

Is it possible enhance immune response against tumor cells and avoid tumor escape?

Answer:

Cancer Immunotherapy