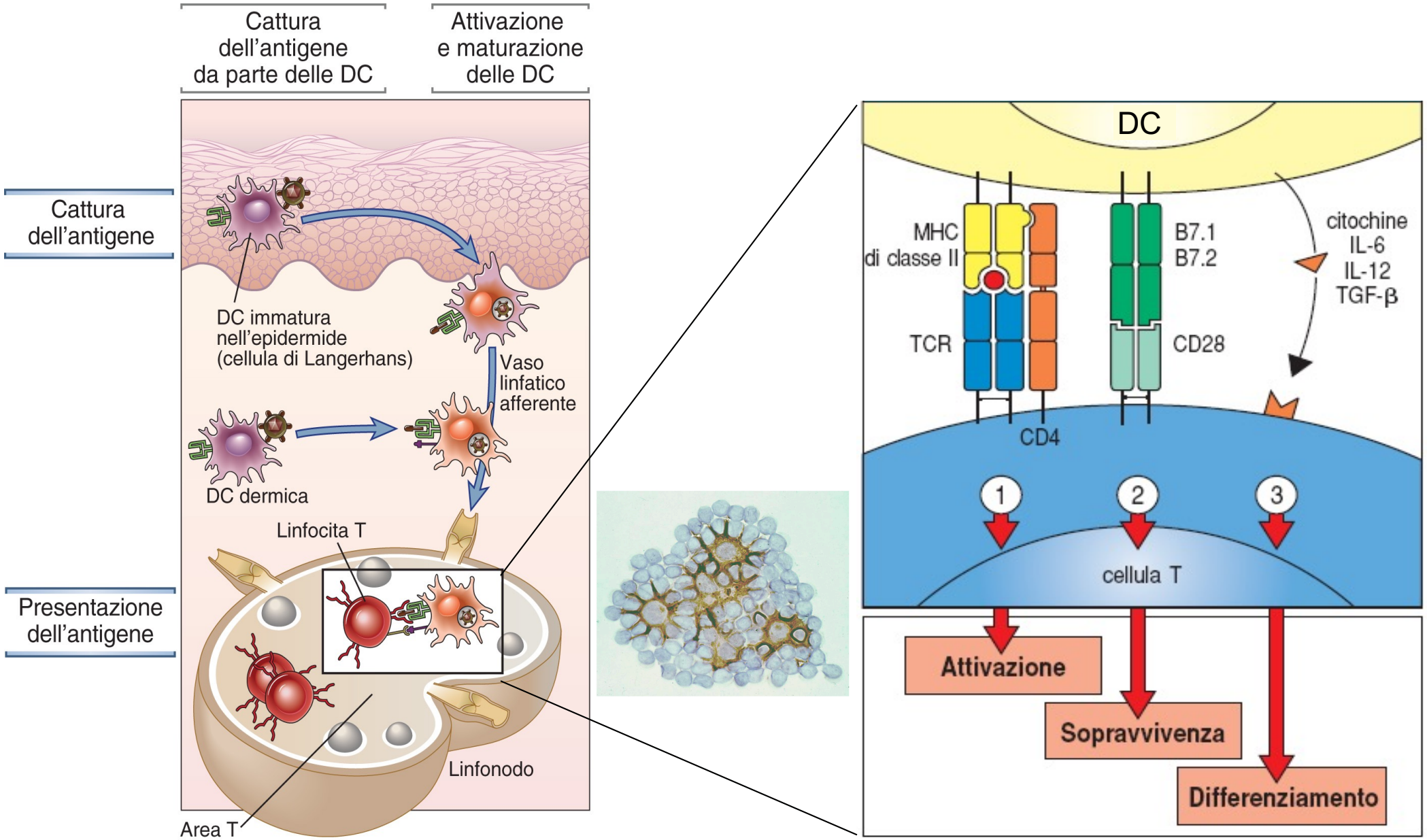
Corso di Immunologia - III anno
Prof. Paolini

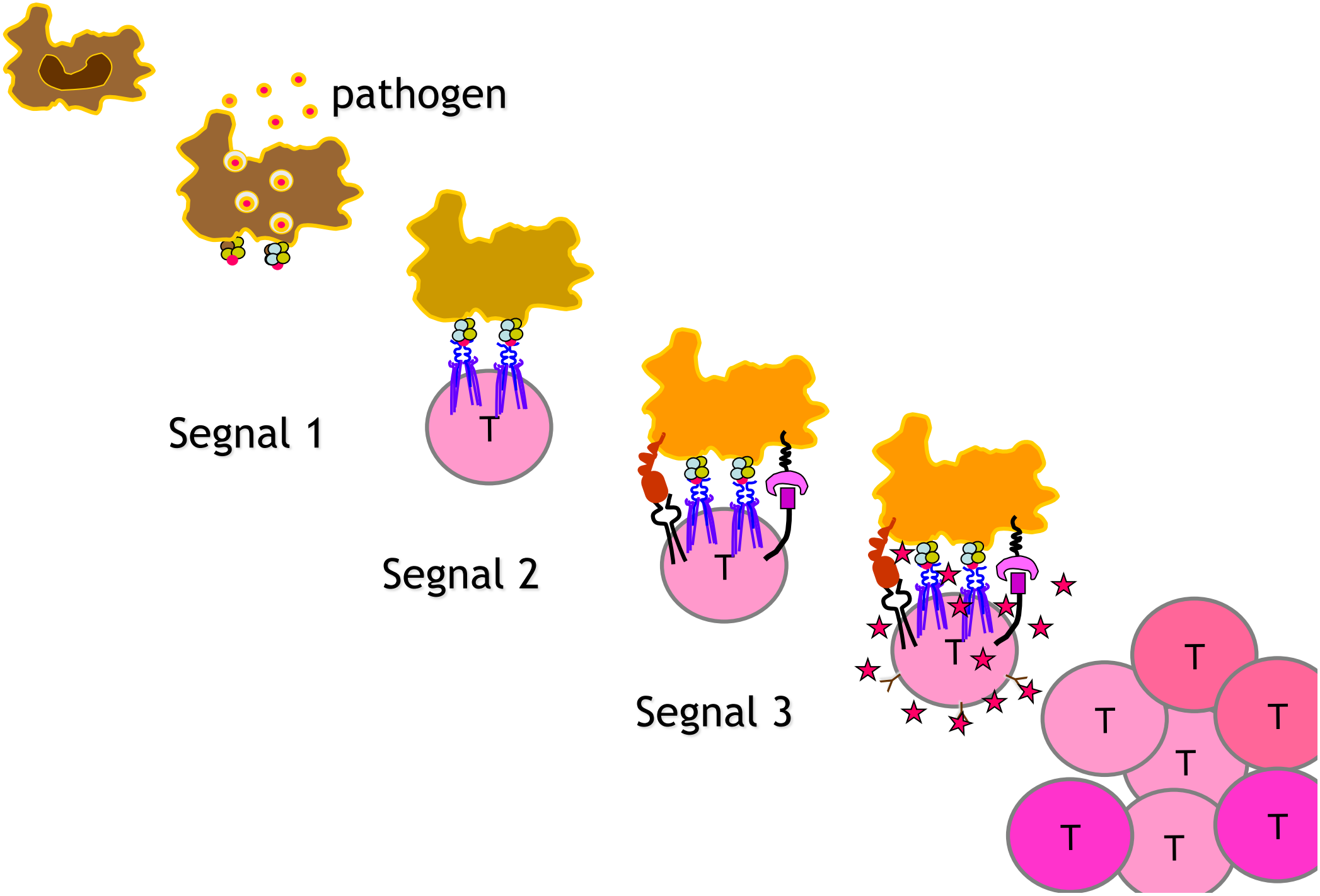
Lezione 24/10/2025

"L'attivazione dei linfociti T"

Il materiale presente in questo documento viene distribuito esclusivamente ad uso interno e per scopi didattici.

Mature DCs provide naive T cells with all the signals they need to be activated



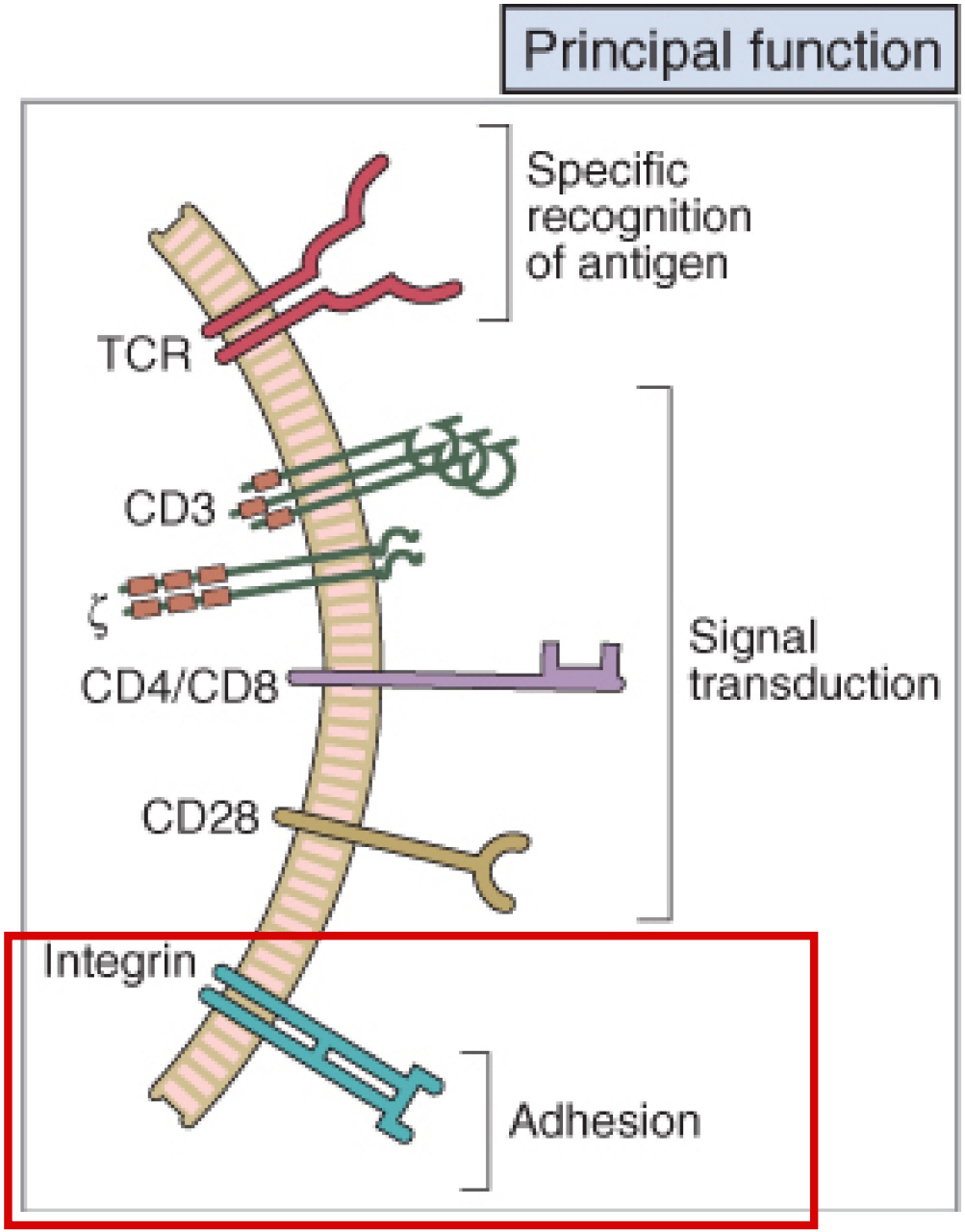

pathogen
Segnal 1
Segnal 2
Segnal 3
T
T
T
T
T
T
T
T
T

How to communicate? Starting by touching each other

Intercellular Adhesion Molecules (ICAMs) of the integrin-binding immunoglobulin superfamily

The molecules involved in signal propagation are located in the contact area between the APC and the T lymphocyte

LFA-1 integrin receptor



- Belongs to the β2 family of integrins
- Its ligands are ICAM-1, 2, 3, expressed on APCs,and endothelium
- It is responsible for cell-cell adhesion between:

  T cell/APC

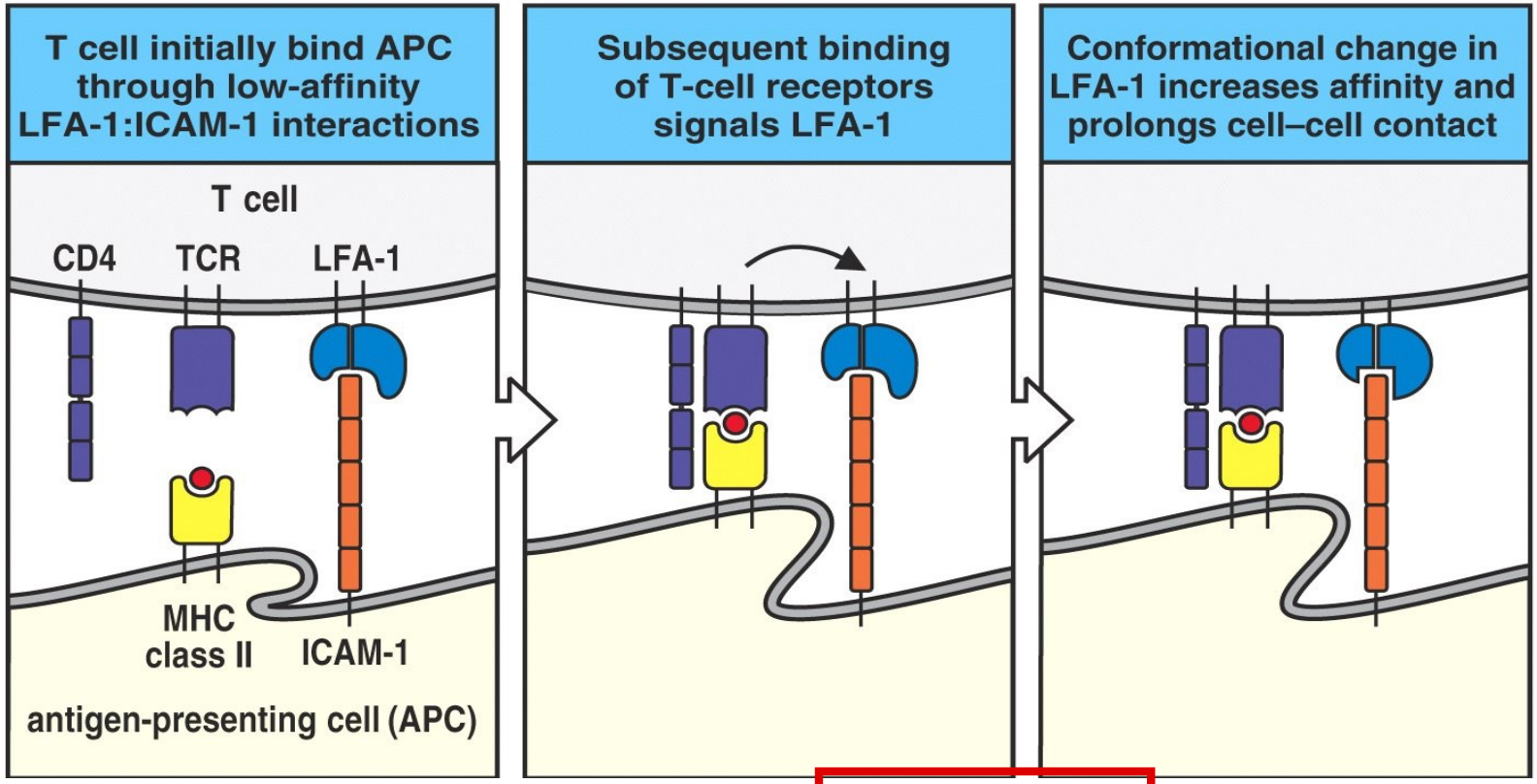
  CTL/target cell

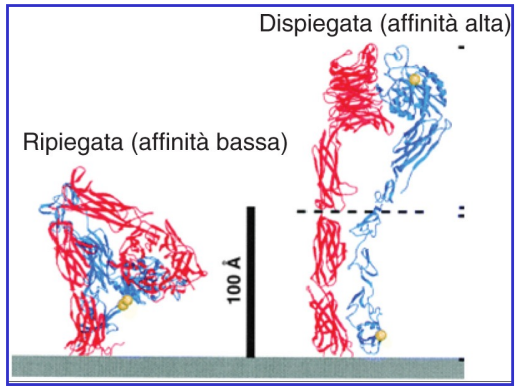
  Leukocyte/endothelium

- LFA-1 affinity & avidity for ligands are regulated

Low → Ag recognition → High

Adhesion molecules participate to T cell/APC interaction



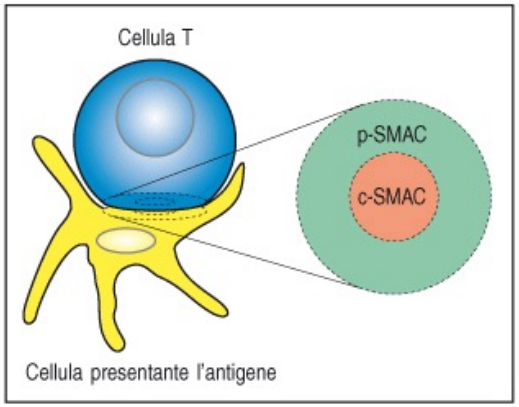


How to communicate? Starting by touching each other

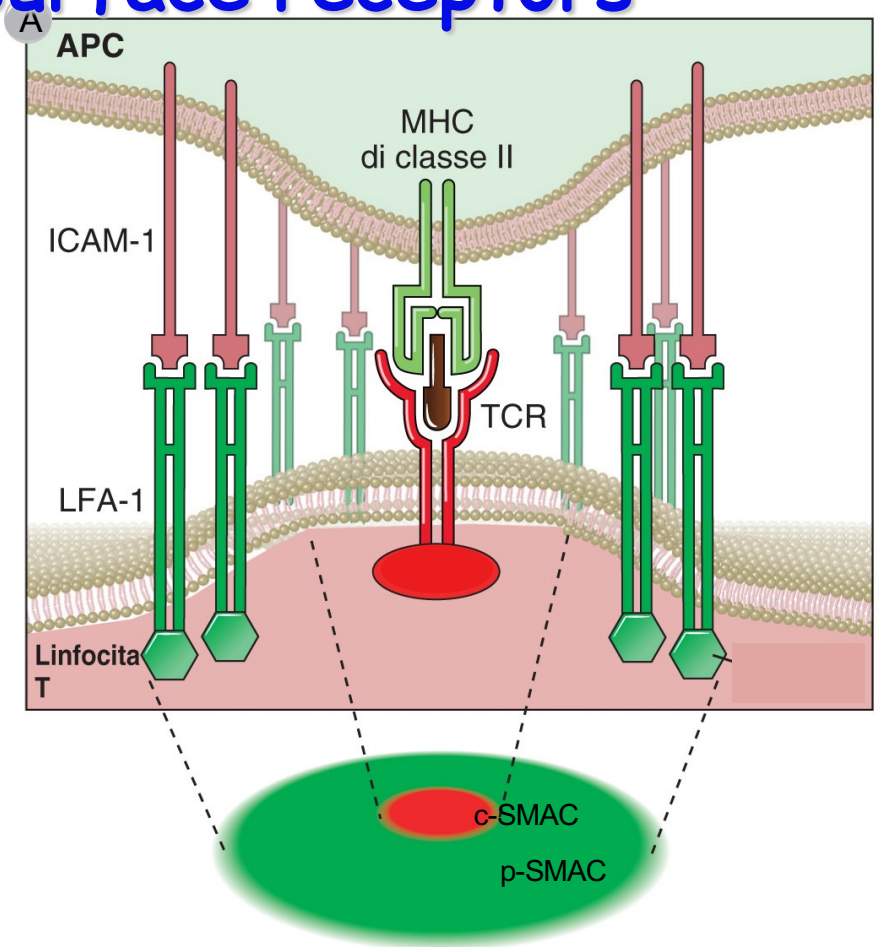
Intercellular Adhesion Molecules (ICAMs) of the integrin-binding immunoglobulin superfamily

The molecules involved in signal propagation are located in the contact area between the APC and the T lymphocyte

Antigen recognition induces a re-organization of T cell surface receptors



The region where the T cell contacts the APC is called the immunological synapse.
In the synapse, all the interacting proteins form a structure known as the SupraMolecular Adhesion Complex.
SMAC = SupraMolecular Activation Cluster



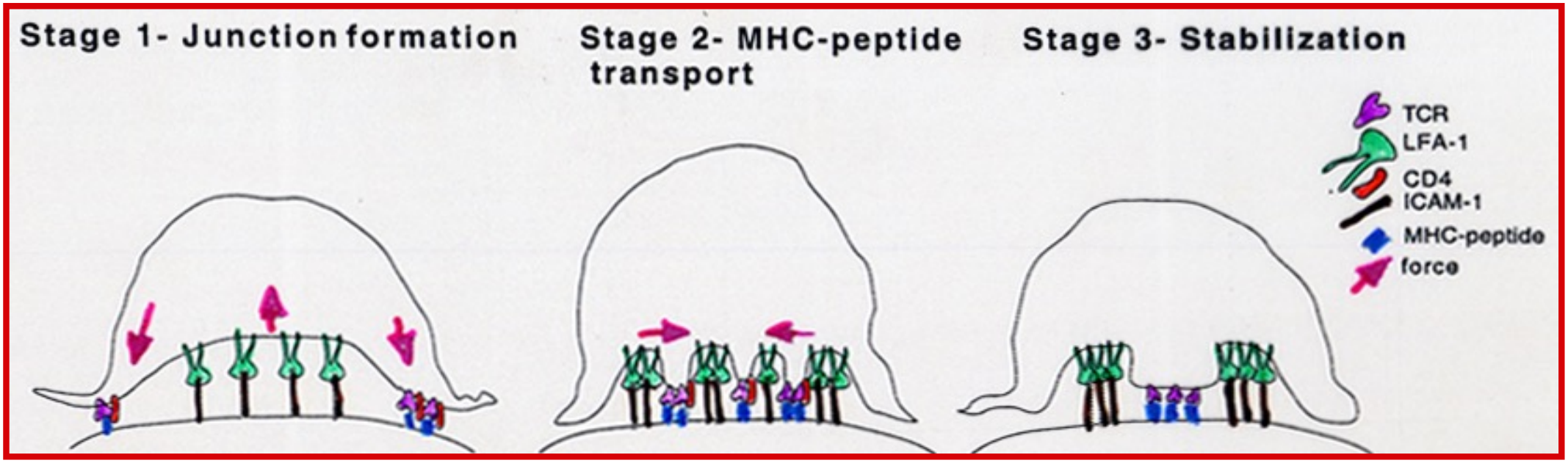
LFA-1 TCR

The immunological synapse

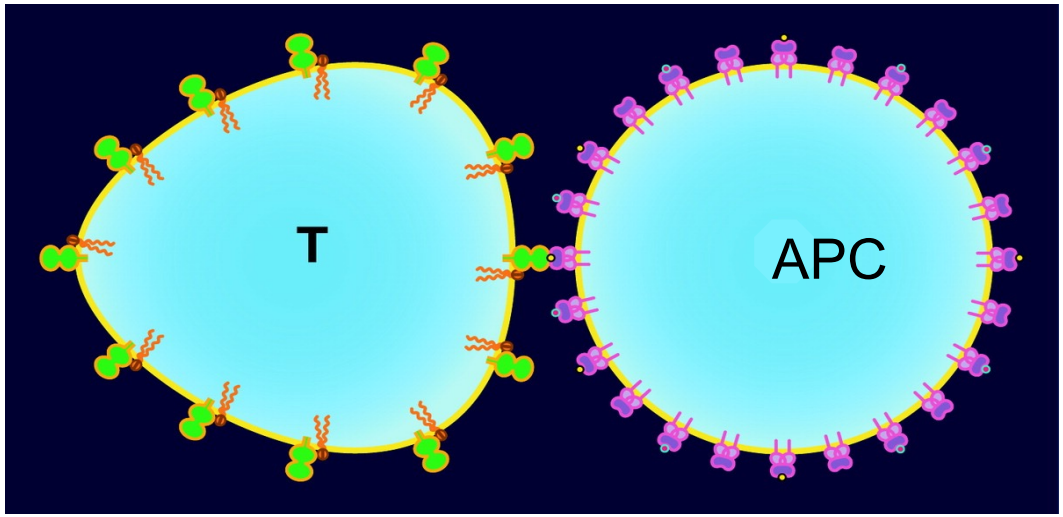
An organized membrane structure which facilitates, stabilizes and prolongs TCR/MHC/peptide interactions by:

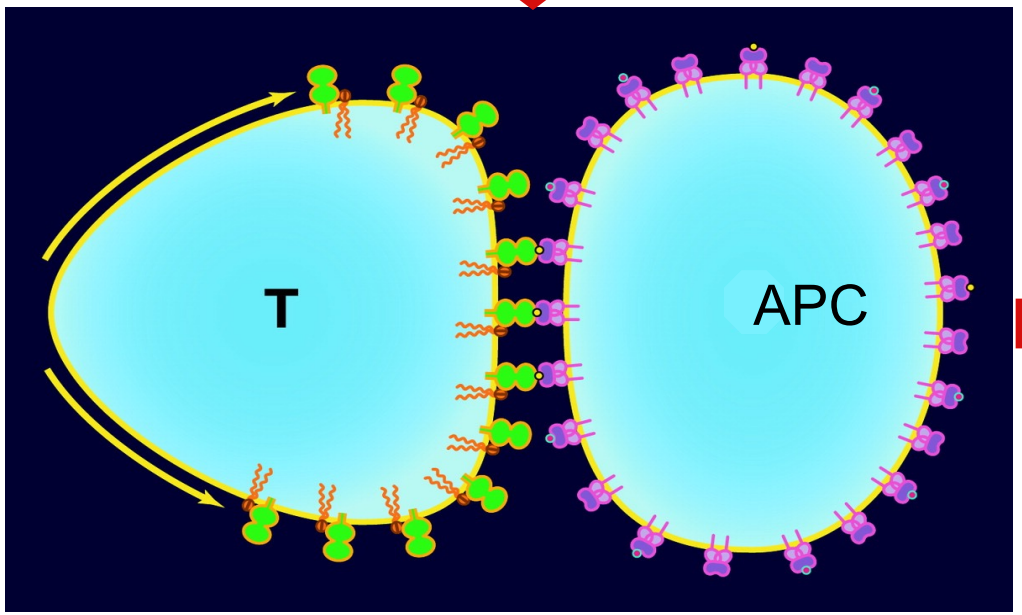
1. Excluding long receptors and inhibitory receptors from the interaction area
2. Facilitates the aggregation and the accumulation of TCR and MHC molecules (higher local ligand concentration)
3. Promotes cytoskeleton rearrangement

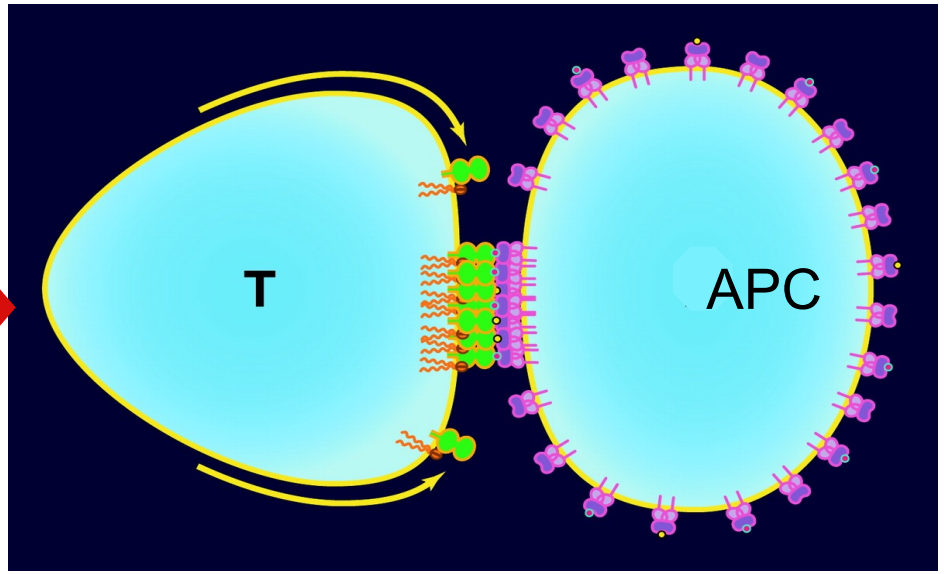
Cytoskeletal rearrangement is involved in the formation and the stabilization of the immunological synapse



TCR aggregation upon antigen recognition

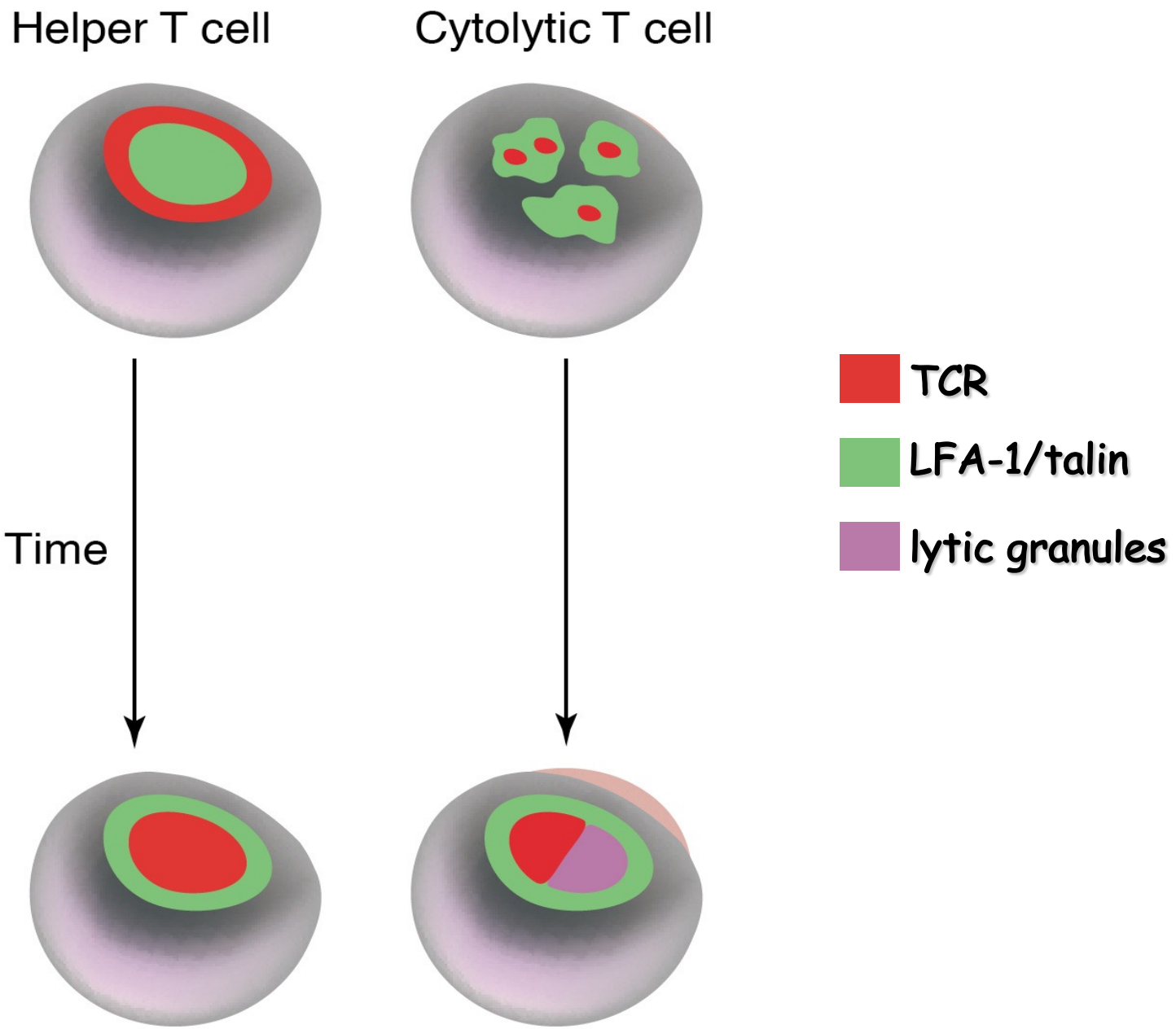




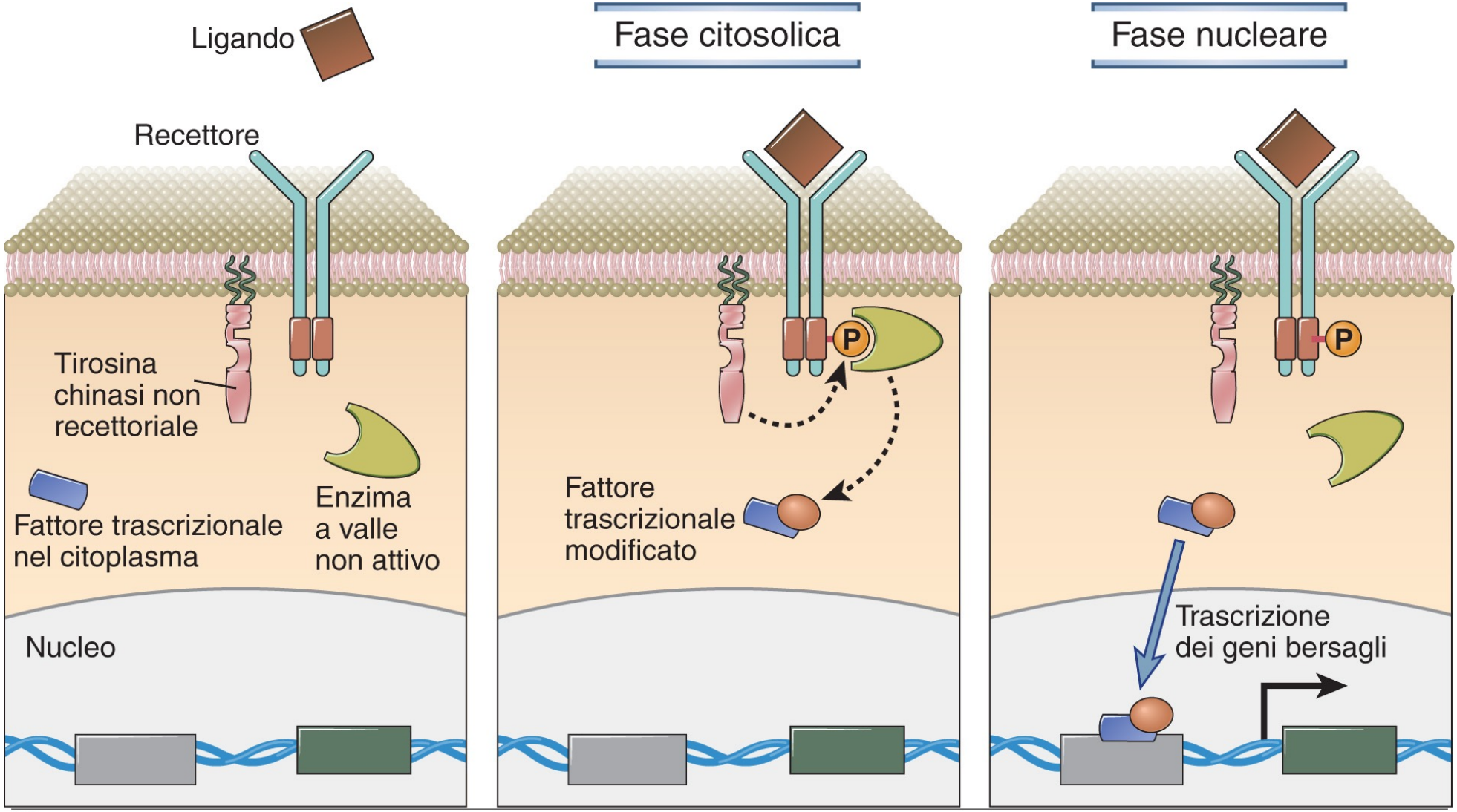


After interacting with the MHC-peptide complex, the TCR translocates to a microdomain of the membrane (LIPID RAFT) rich in cholesterol, unsaturated fatty acids, sphingomyelin and glycosphin

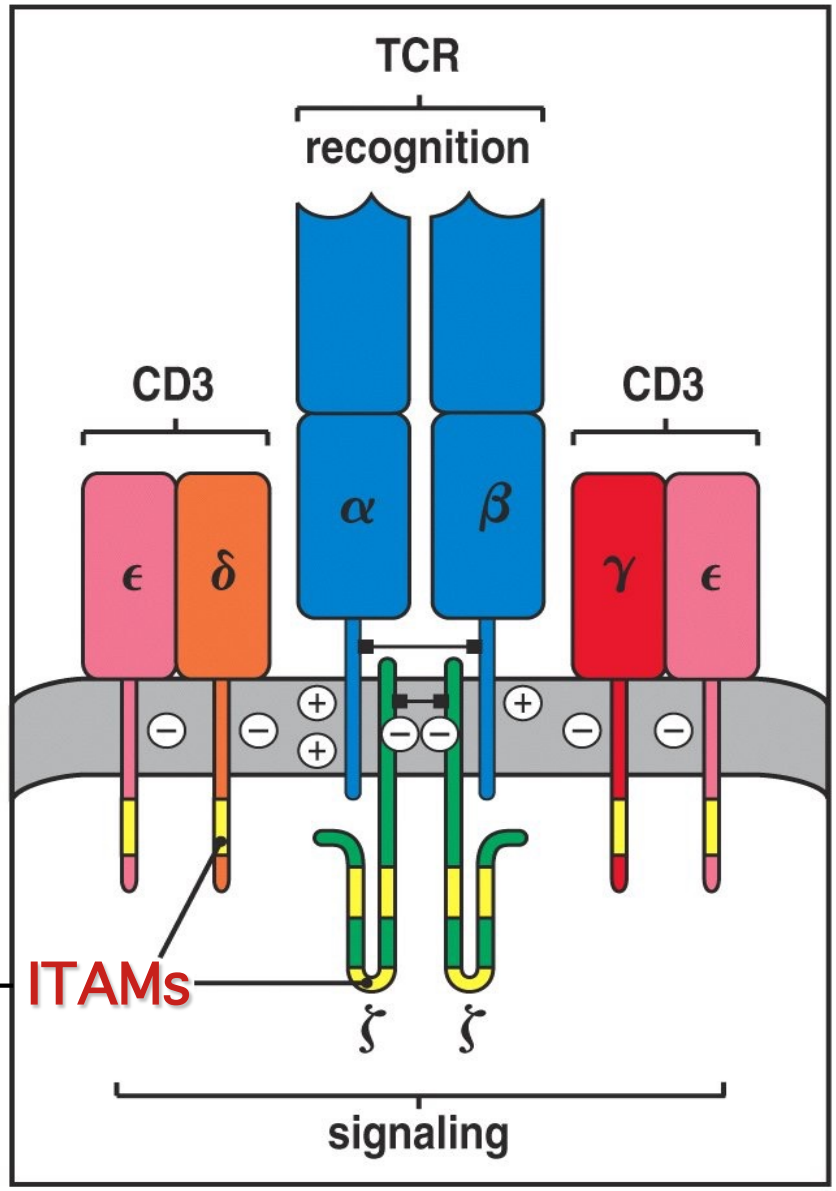
The immunological synapse in different types of T cell interactions



La trasduzione del segnale da parte di recettori di membrana prevede una fase citosolica e una nucleare



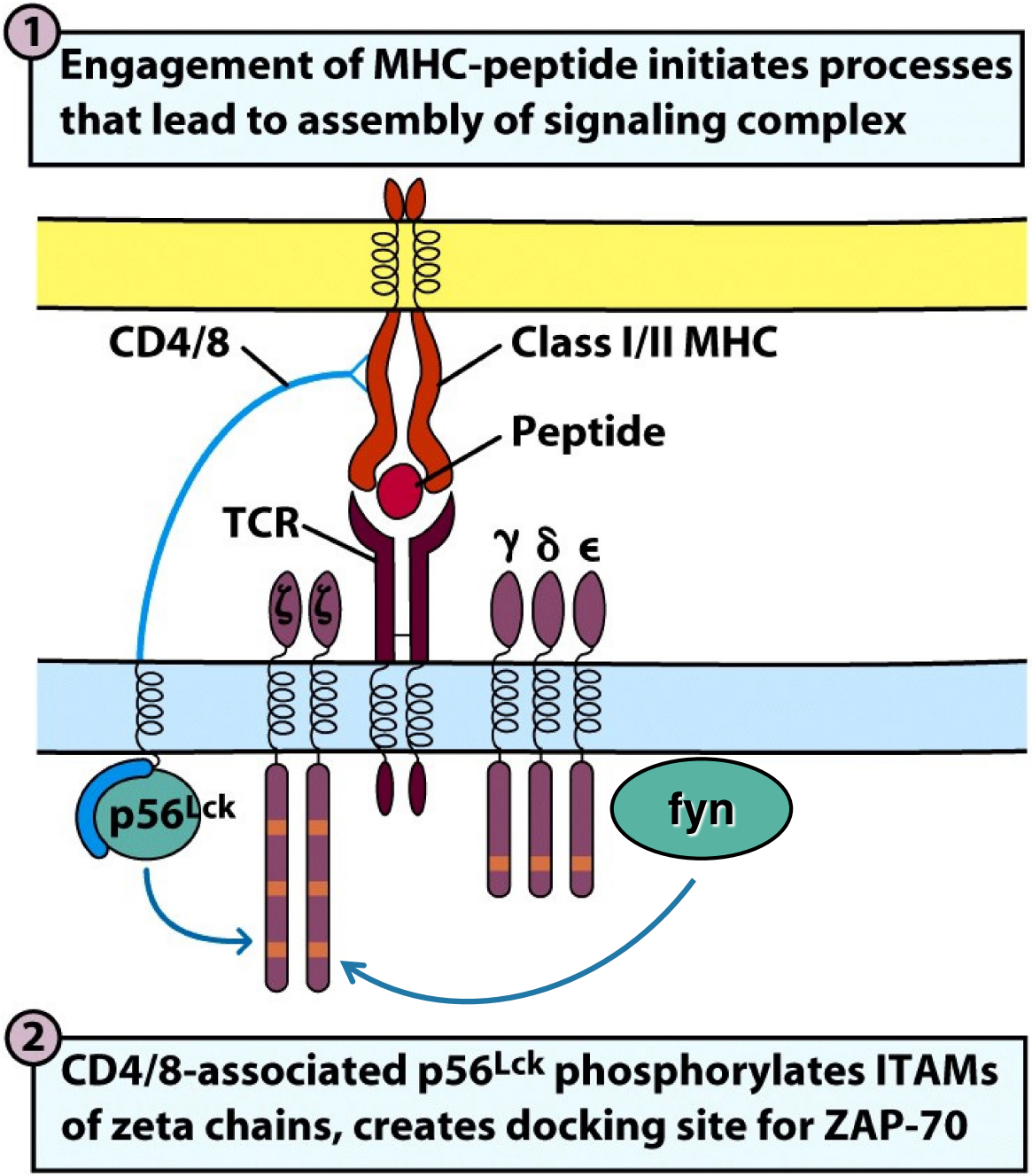
CD3 complex associates with TcR and initiates signal transduction



ITAM motif:
YxxL/Ixxxxxx YxxL/I

Immunoreceptor Tyrosine-based Activation Motif

Src family tyrosine kinases initiate TCR/CD3 signal transduction

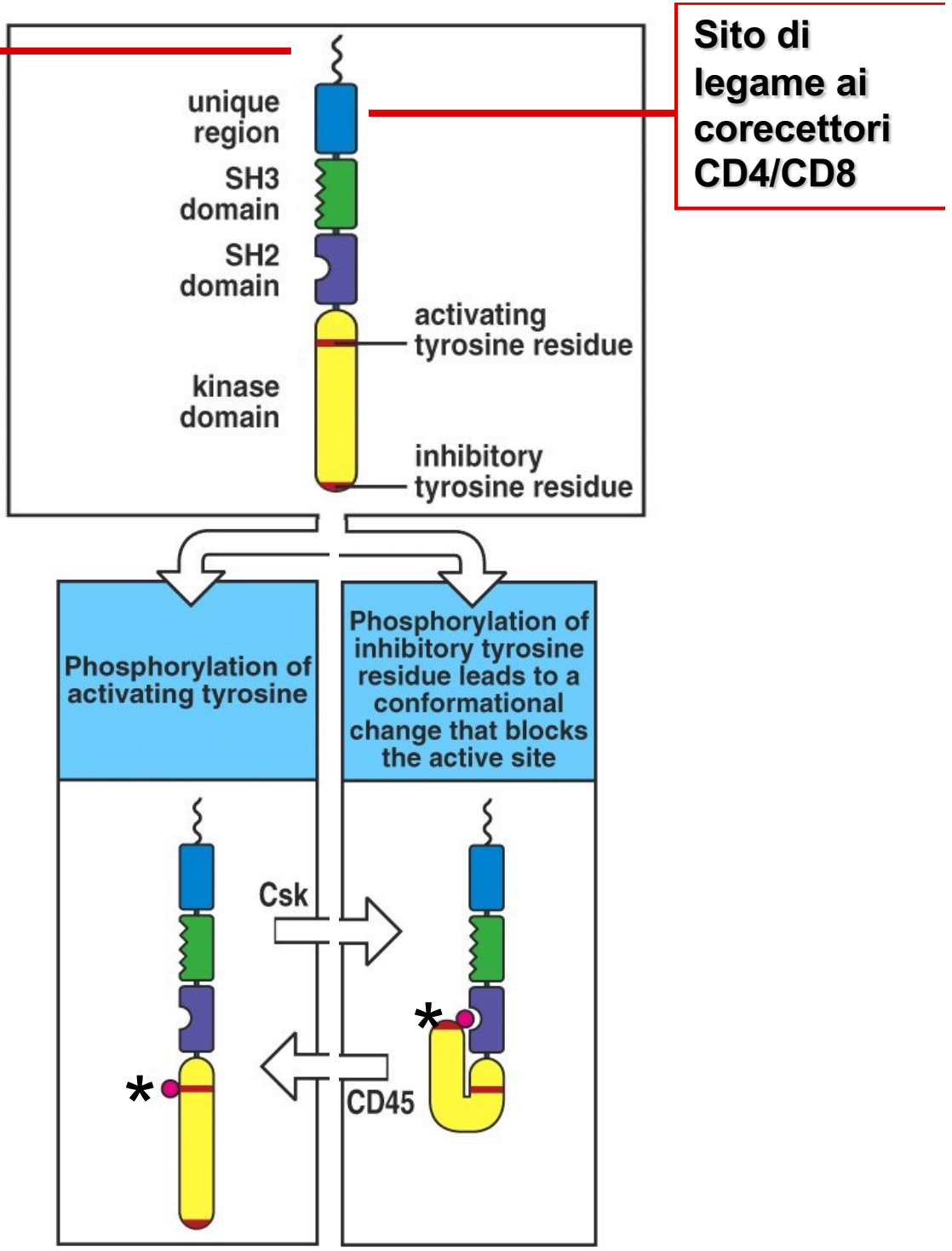


Src family tyrosine kinases (fyn and lck) initiate signal transduction in T cells

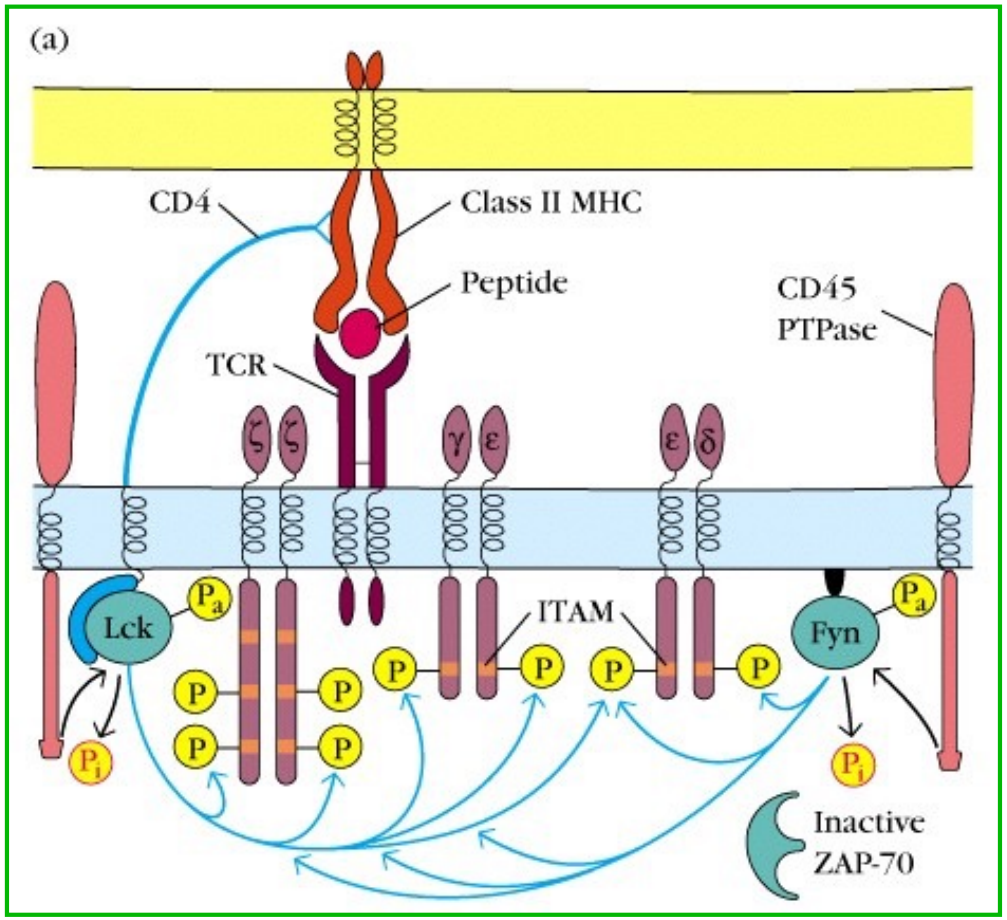
Their activity is regulated by inhibitory and activating tyrosine residues

Csk= tyrosine kinase

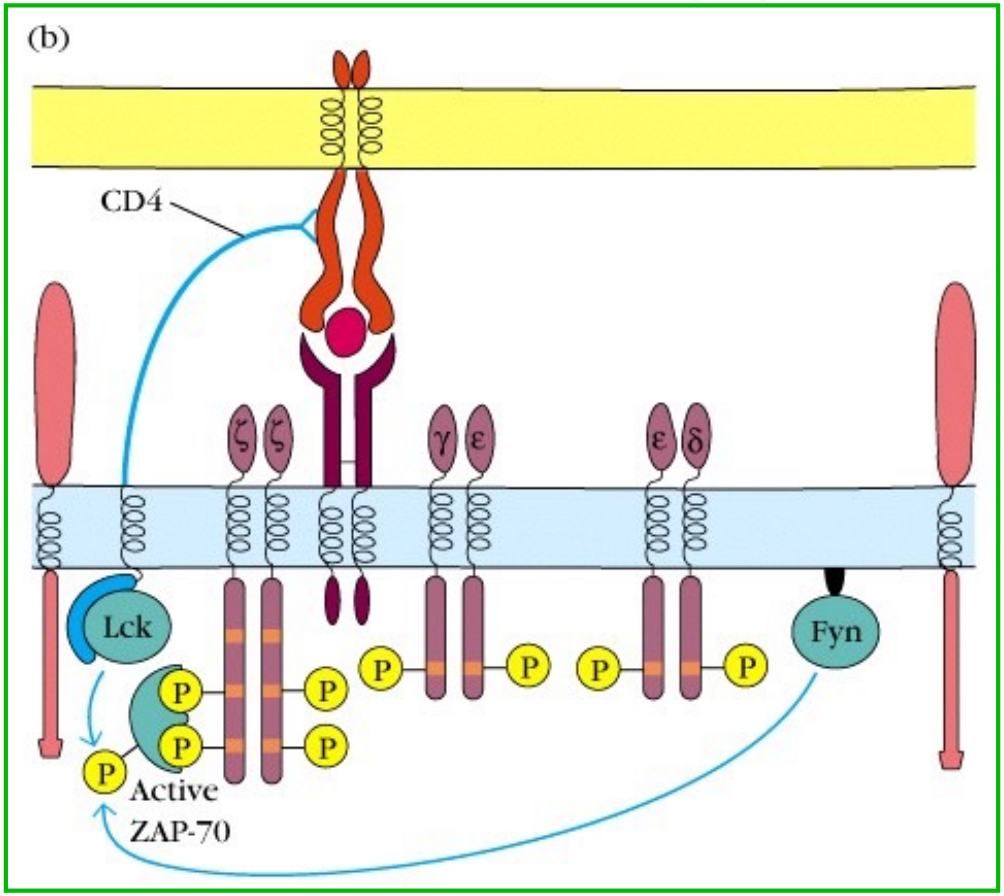
CD45= tyrosine phosphatase



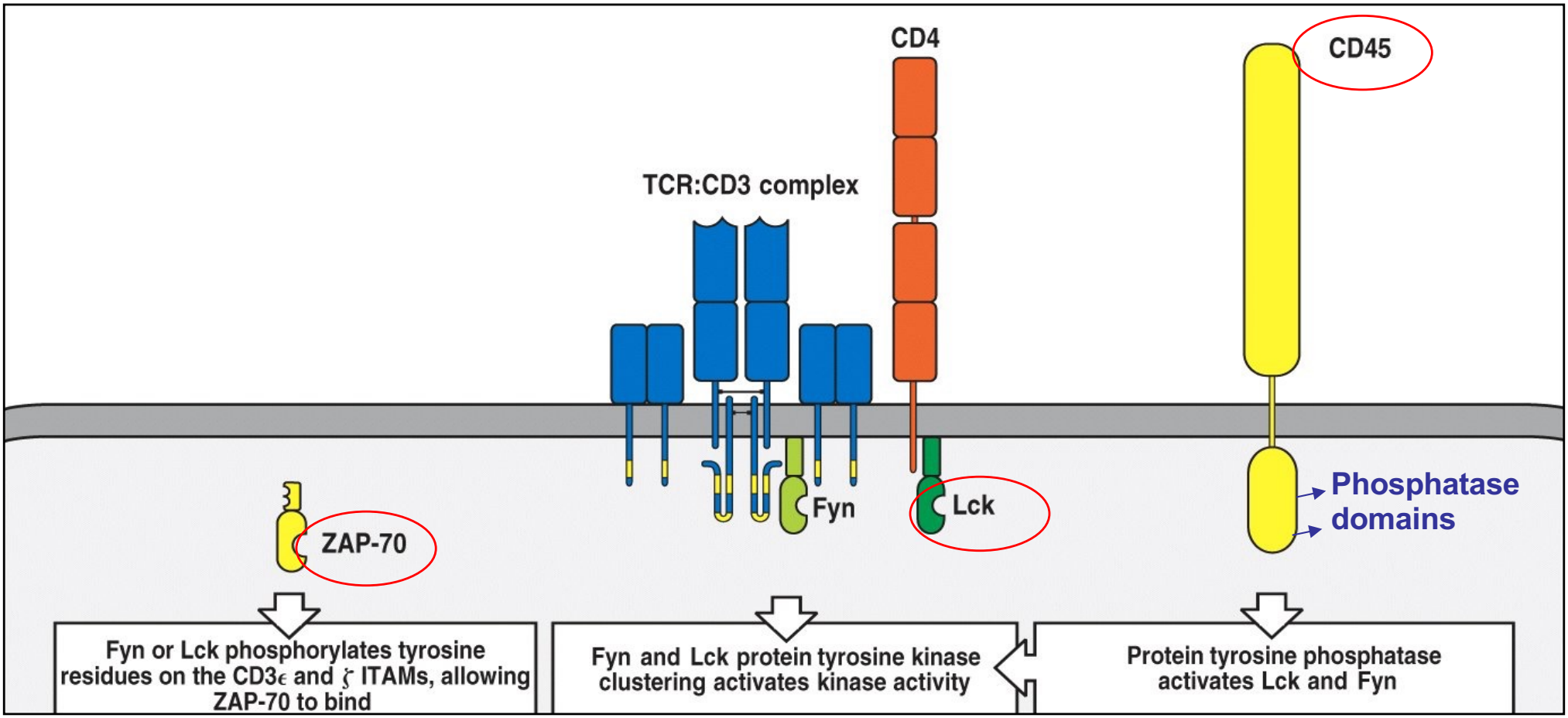
1. lck and fyn phosphorylate CD3 ITAMs



2. ZAP70 tyrosine kinase is recruited and activated at the cell membrane

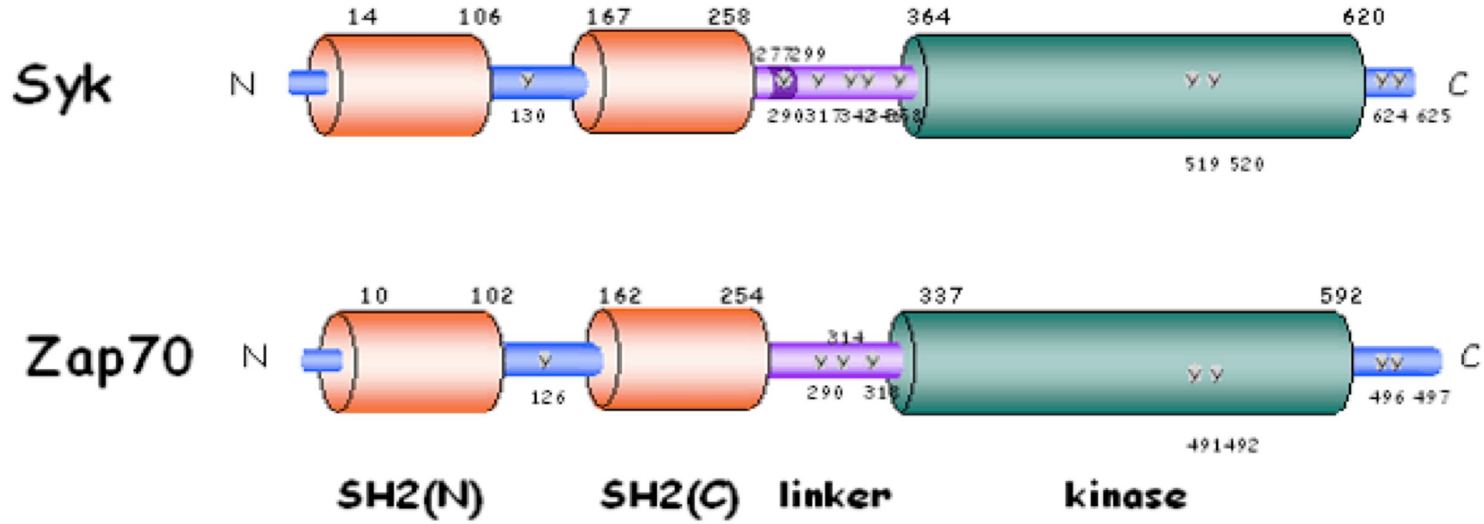


Principali enzimi coinvolti nell'attivazione dei linfociti T



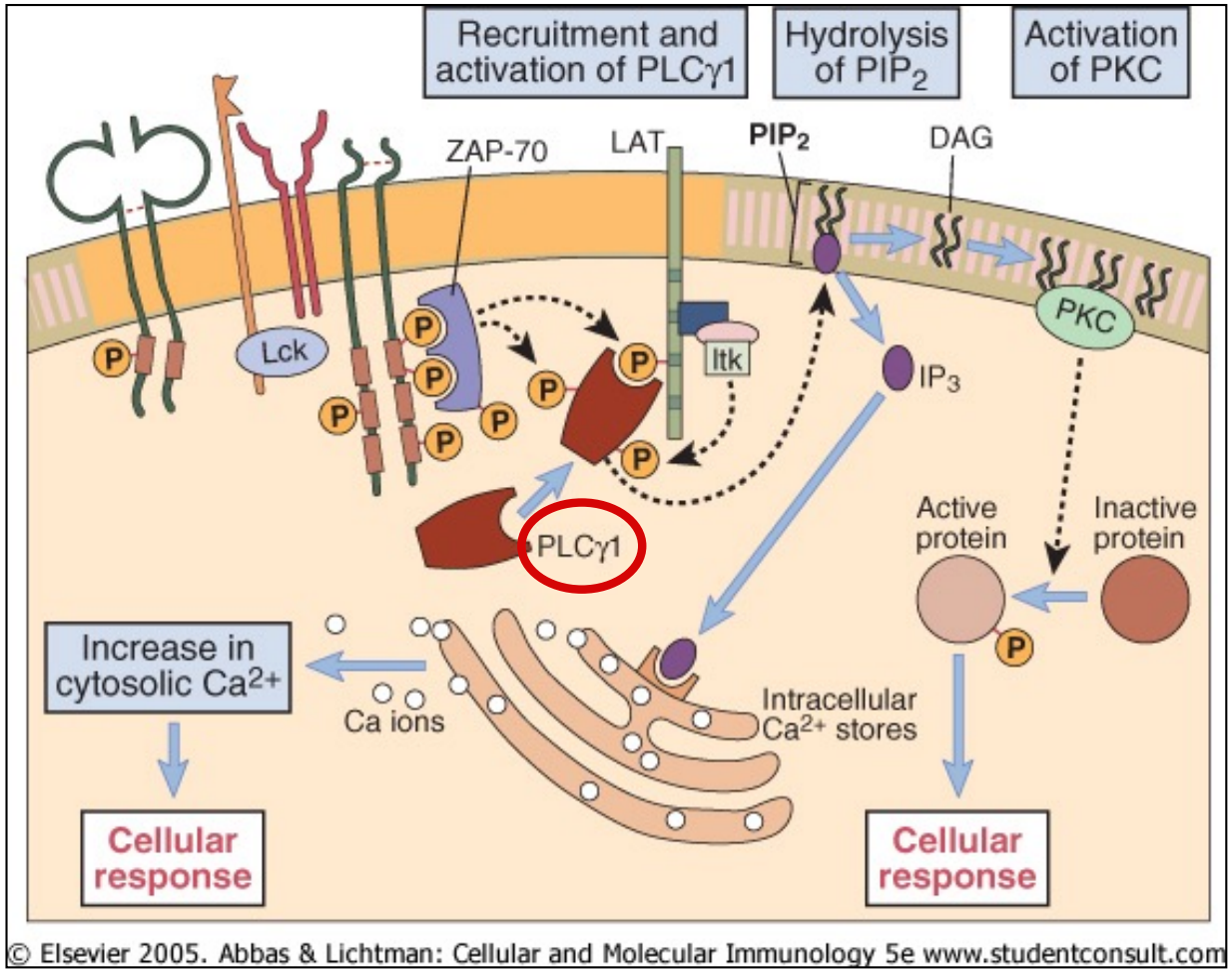
Structure of the related Syk and Zap-70 tyrosine kinases

B cells and mast cells

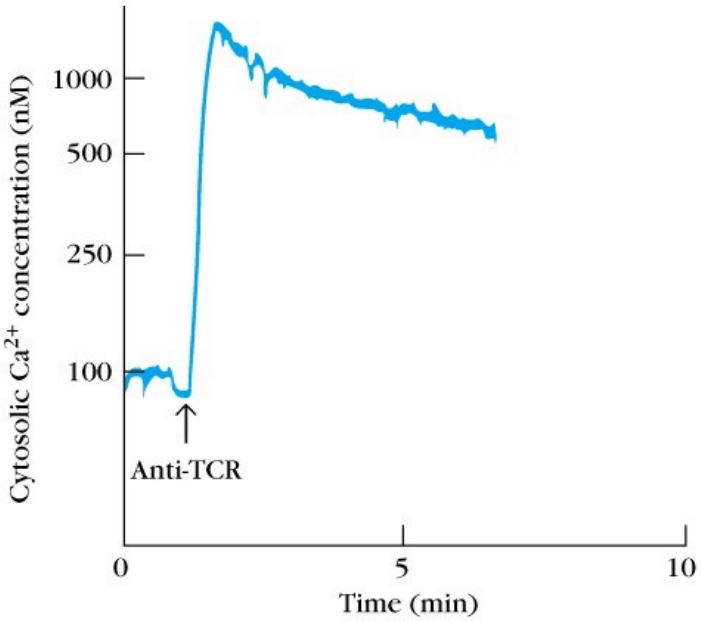


T cells

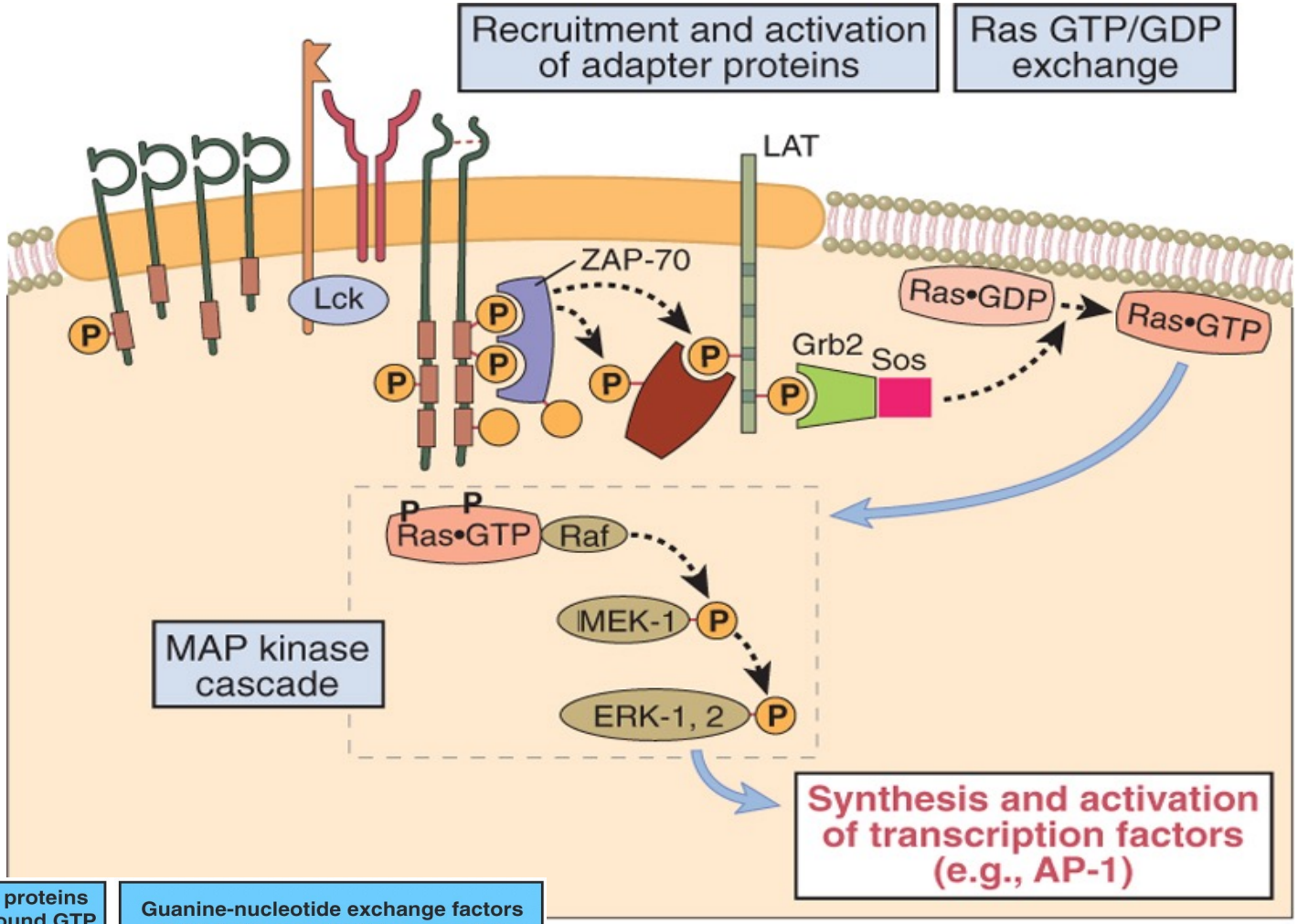
ZAP70 activates many intracellular pathways.
1. adaptors and PLCγ



A rapid augmentation of cytosolic Ca^{2+} concentration is one of the earliest activation events upon antigen recognition



RAS pathway in T cell activation



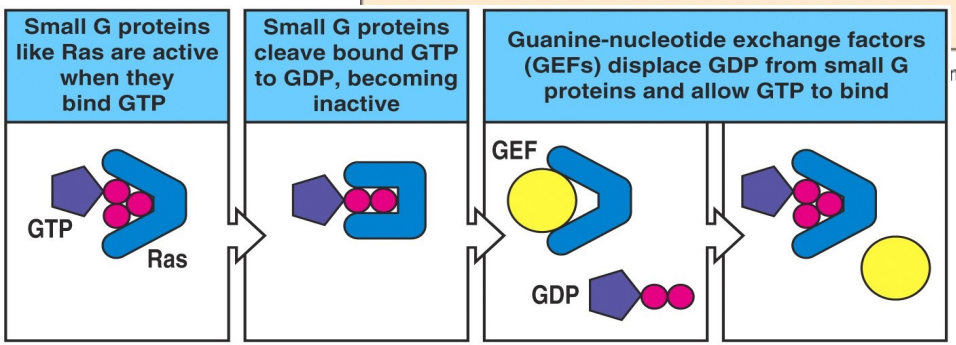


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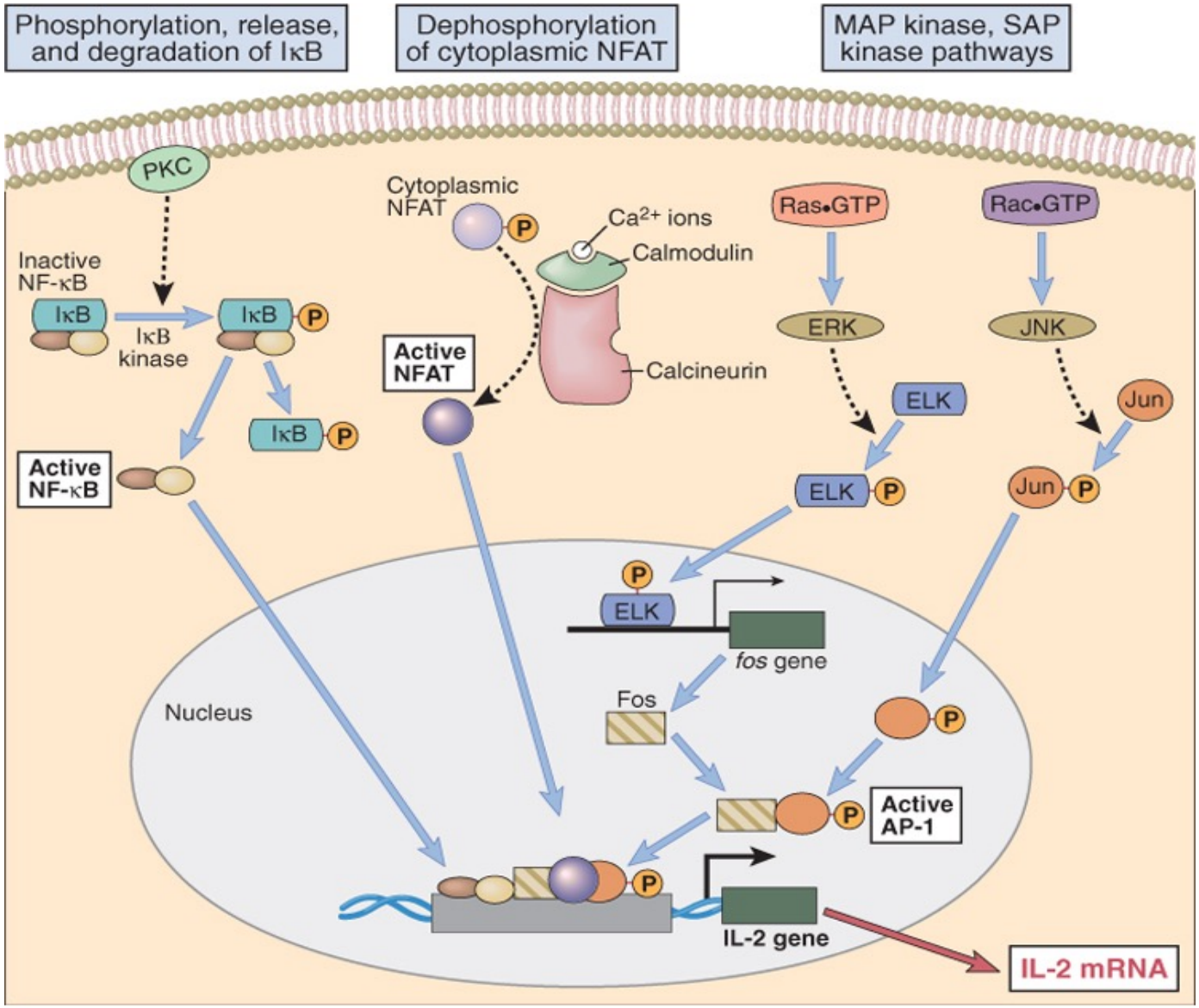
Figure 6-7 Immunobiology, 6/e. (© Garland Science 2005)

TCR signal transduction leads to the activation of multiple transcription factors



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T lymphocytes need 2 signals for activation

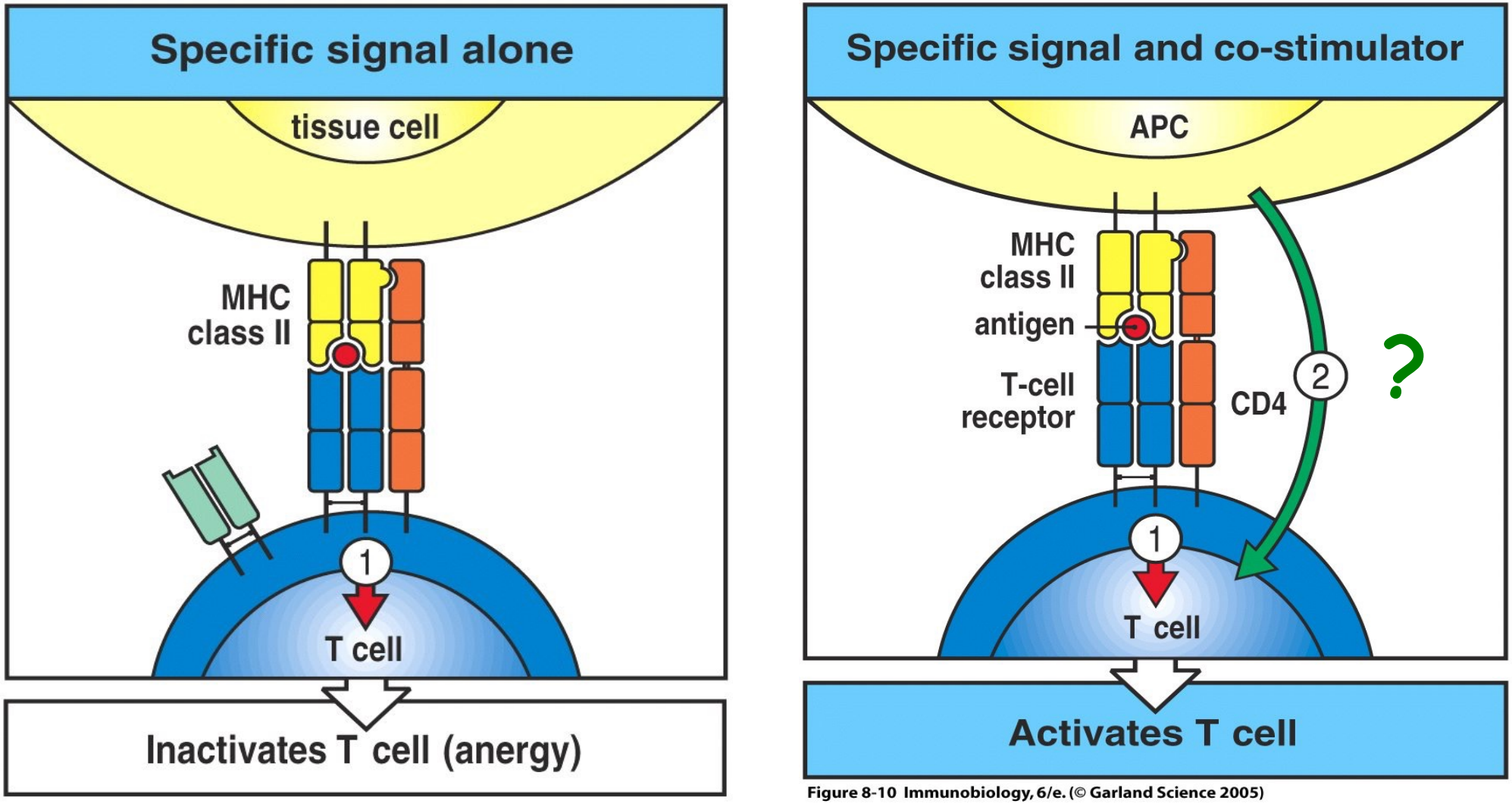
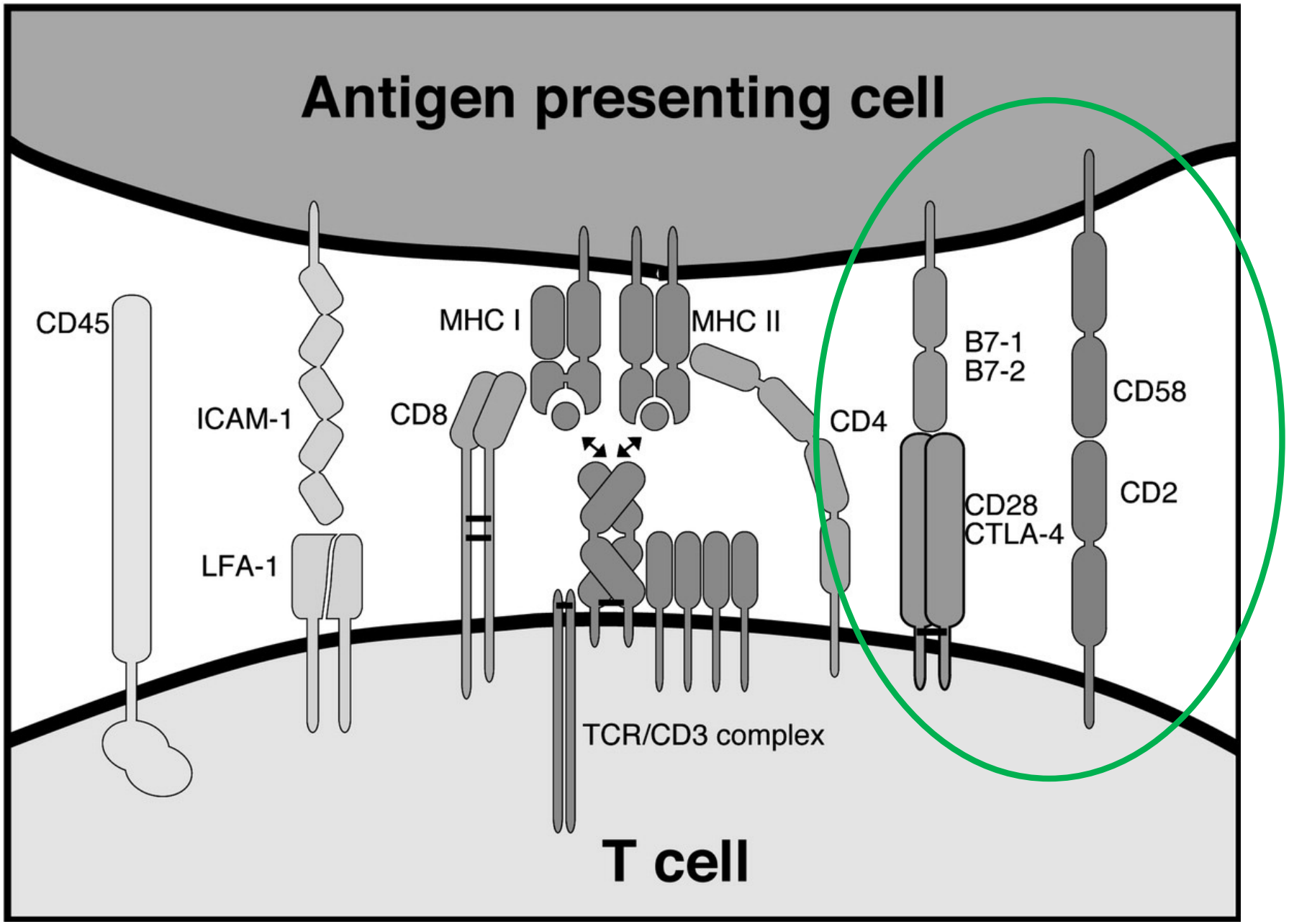


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

Cell surface molecules involved in T cell activation



What is the second signal?

CYTOKINE — produced by APC

MEMBRANE INTERACTION — receptor (T cell) / ligand (APC)

The expression of the costimulatory signal can be:

CONSTITUTIVE

or

INDUCIBLE (inflammation, infection, tissue injury)

CD28 costimulatory molecule

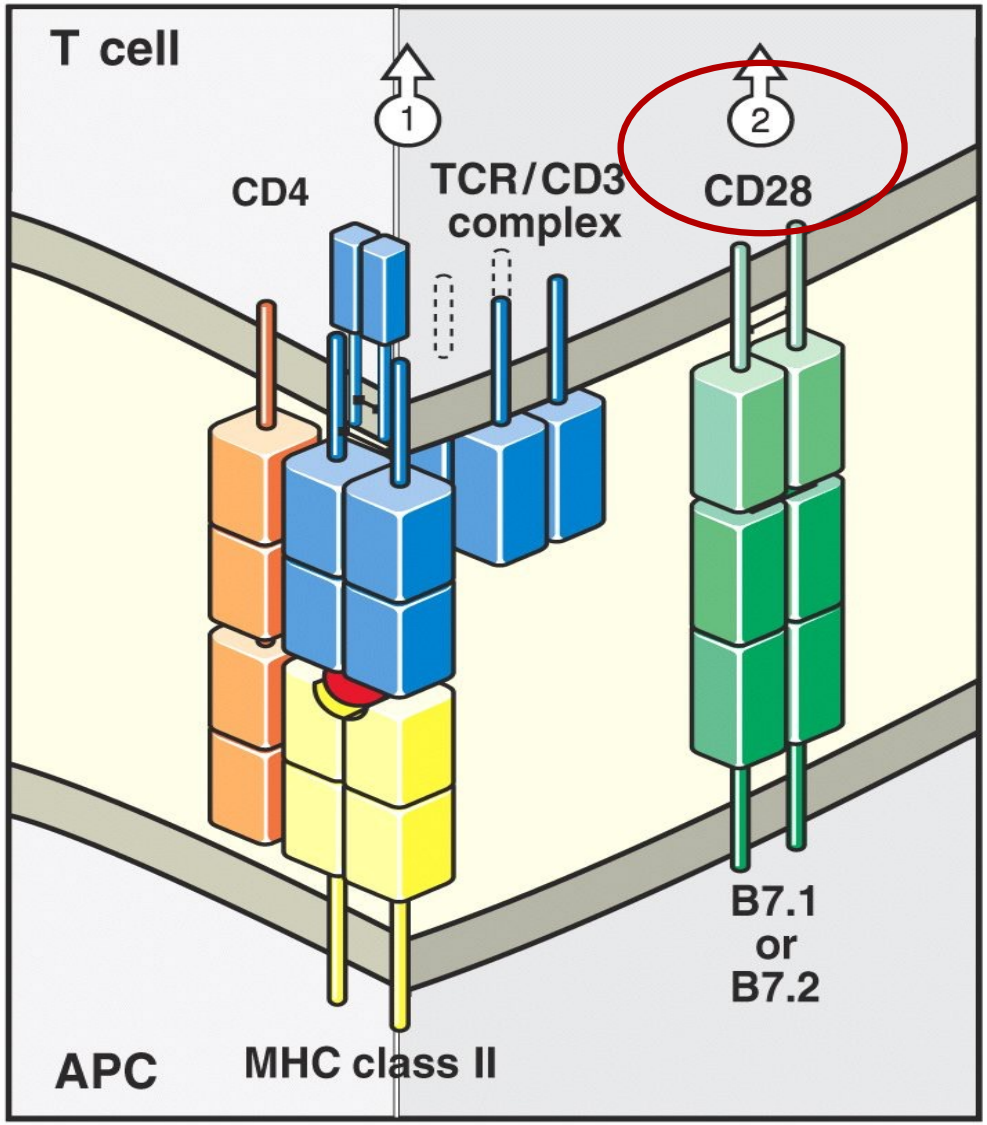
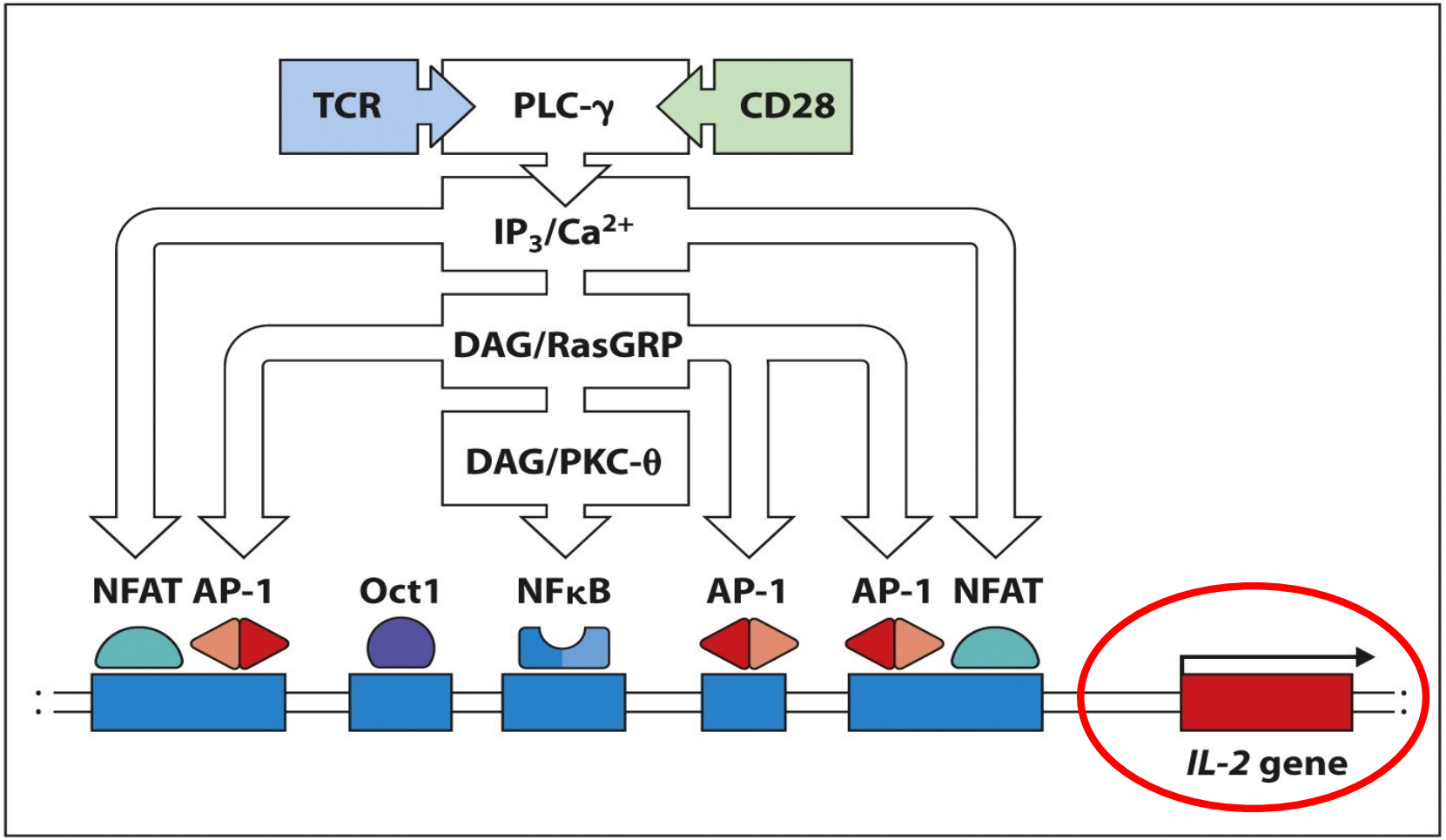


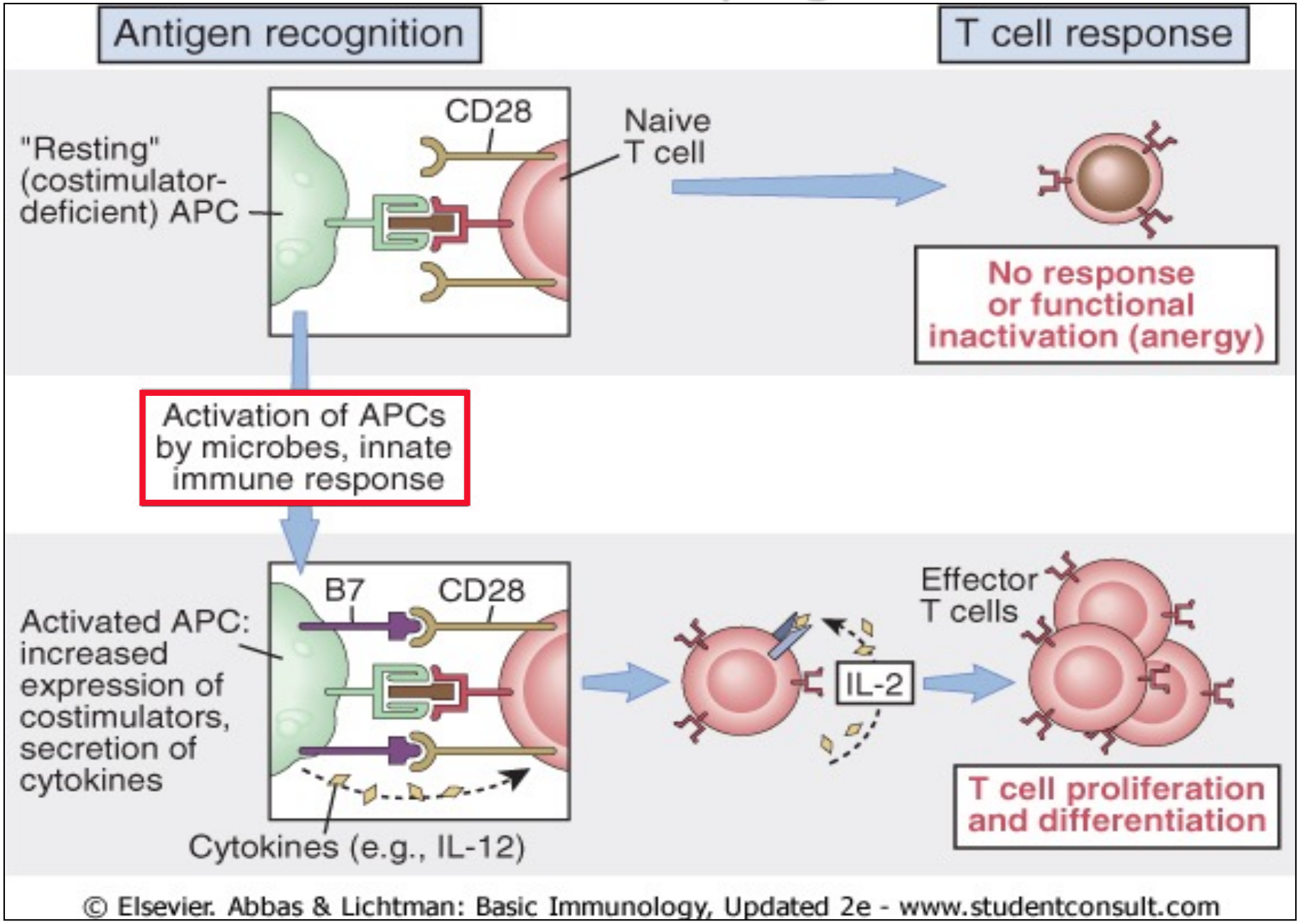
Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

- Expressed on almost all CD4+ 50% CD8+
- Binds to CD80 and CD86 (B7.1 and B7.2), expressed on mature DC, activated B cells and macrophages
- Integrates signals of TCR/CD3 to gene activation

The signal transduced by CD28 amplifies the first signal by increasing the transcription levels of the IL-2 gene



Only "mature", "activated" APCs can provide the costimulatory signal



Why T cells need TWO signal for activation? (1)

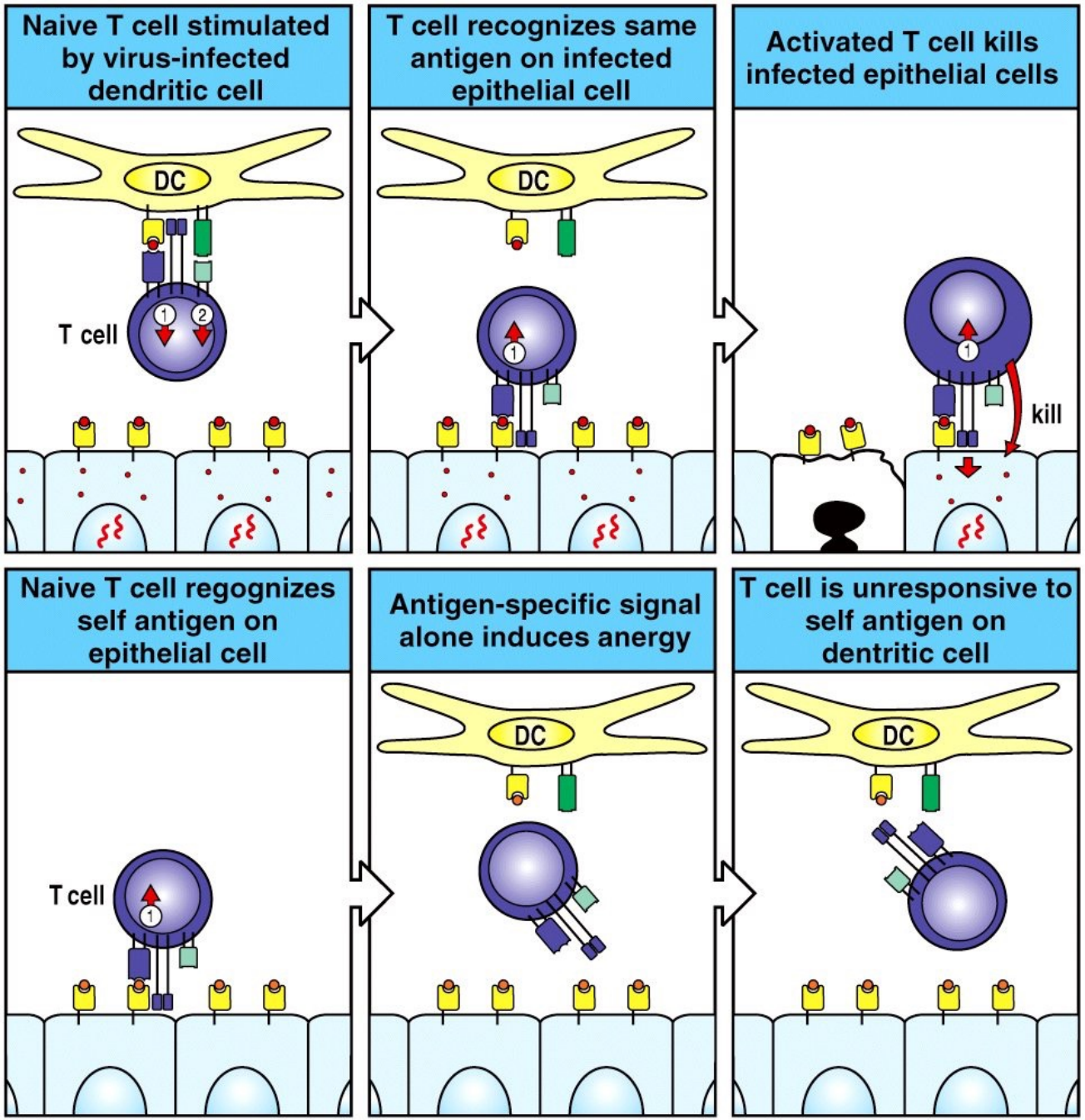


Figure 8-13 Immunobiology, 6/e. (© Garland Science 2005)

Usually, only professional APC can give costimulatory signal

This limits the possibility of self-antigen recognition on tissue cells…

..and represents a mechanism of peripheral TOLERANCE

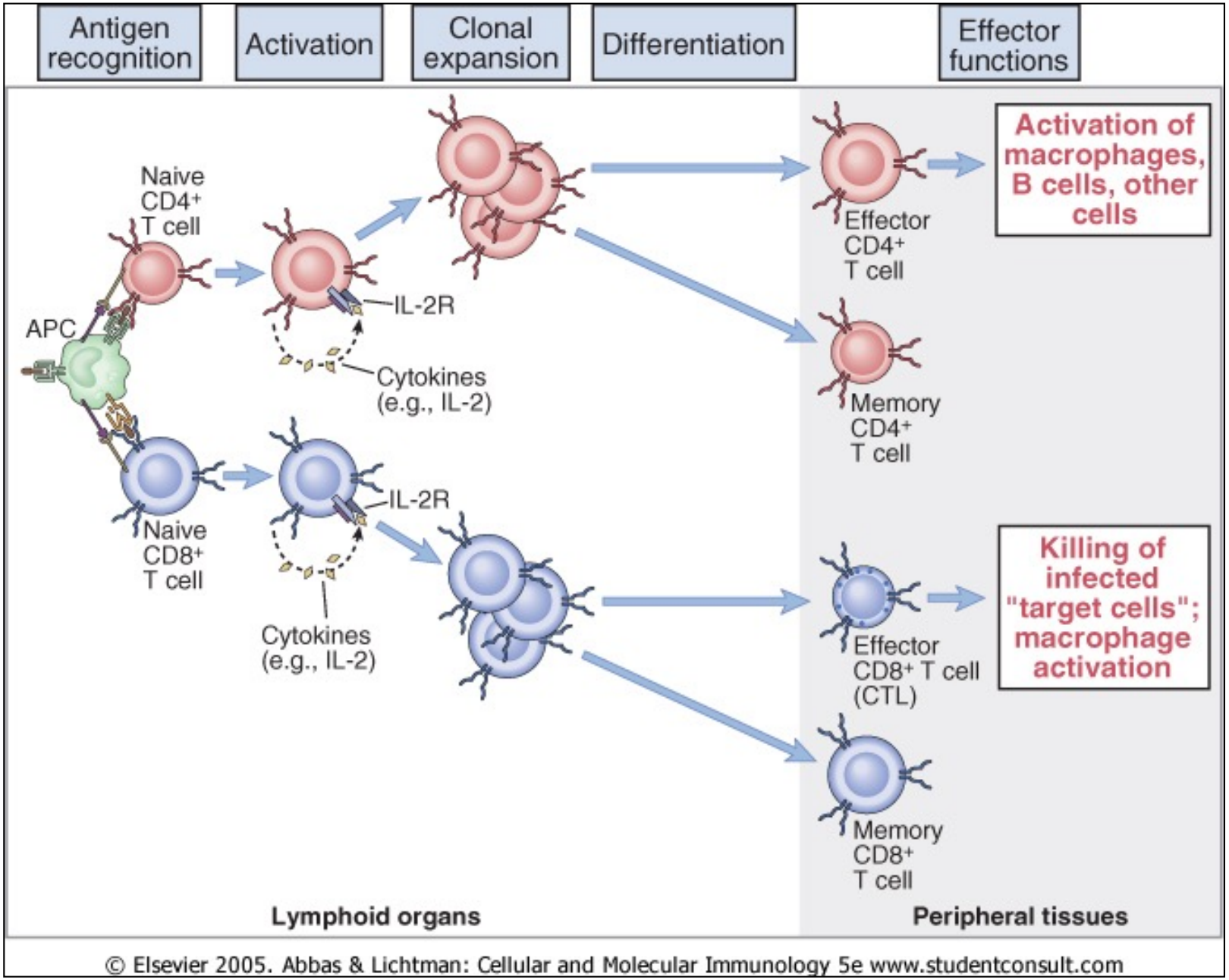
Why T cells need TWO signal for activation? (2)

Costimulatory signals are induced by pathogens, inflammation, tissue injury

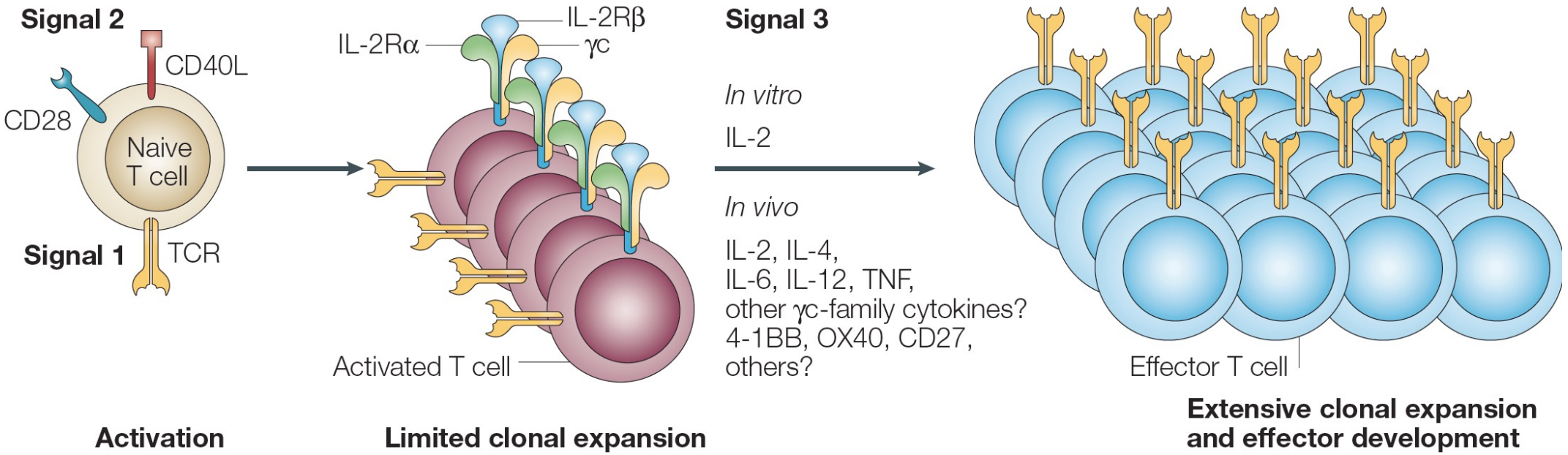
They carry information about DANGEROUSNESS…..

…and focus T cell responses against AGGRESSIVE NON SELF

Antigen-specific T cells proliferate before becoming EFFECTORS (= clonal expansion)

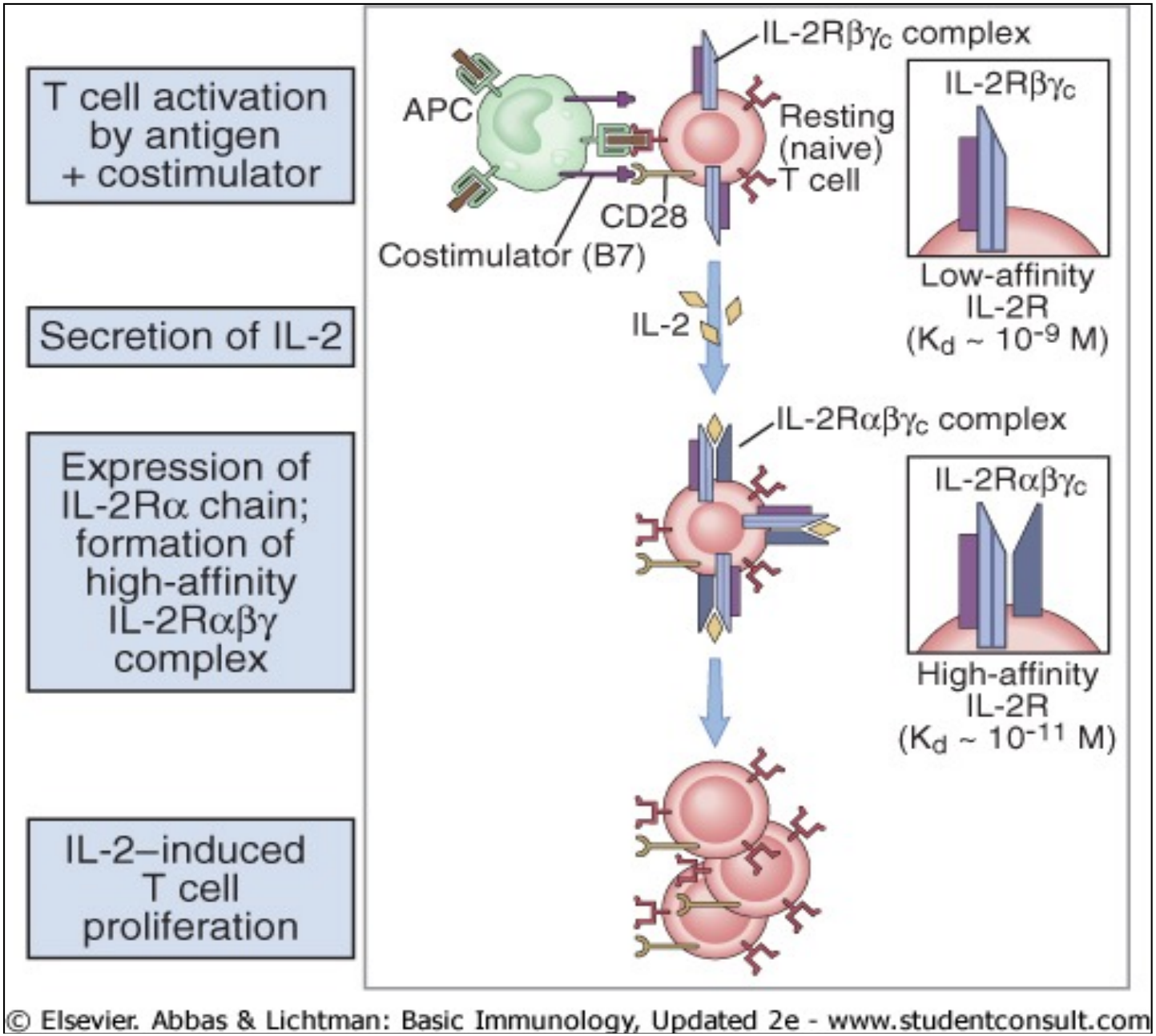


Generation of effector T lymphocytes



Nature Reviews Immunology, 2004

Only antigen specific T cells proliferate!



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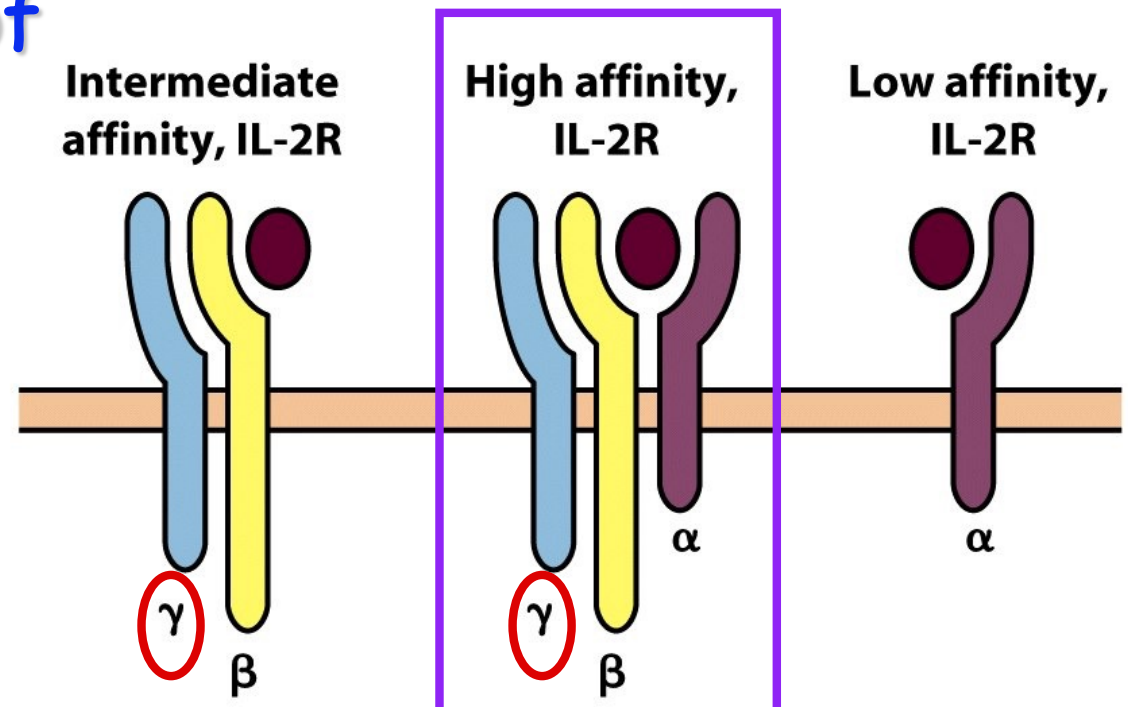
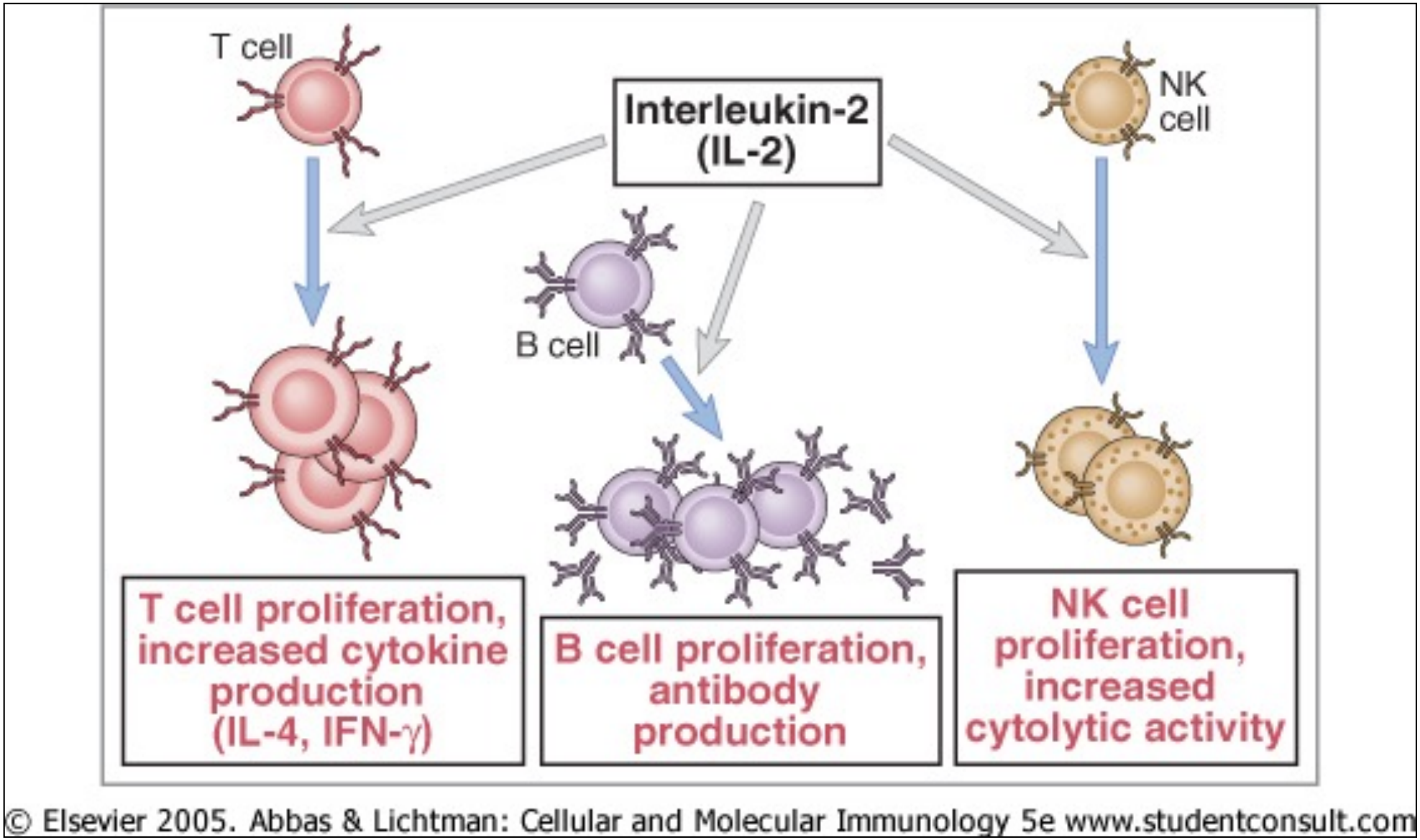
The expression of the high affinity IL-2 receptor (αβγ) is tightly regulated

Molecular composition of the IL-2 receptor



	Intermediate affinity, IL-2R	High affinity, IL-2R	Low affinity, IL-2R
Subunit composition:	IL-2Rβ IL-2Rγ	IL-2Rα IL-2Rβ IL-2Rγ	IL-2Rα
Dissociation constant (K_d):	10^{-9} M	10^{-11} M	10^{-8} M
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated CD4+ and CD8+ T cells Activated B cells (low numbers)	

IL-2: a growth factor for innate and adaptive lymphocytes



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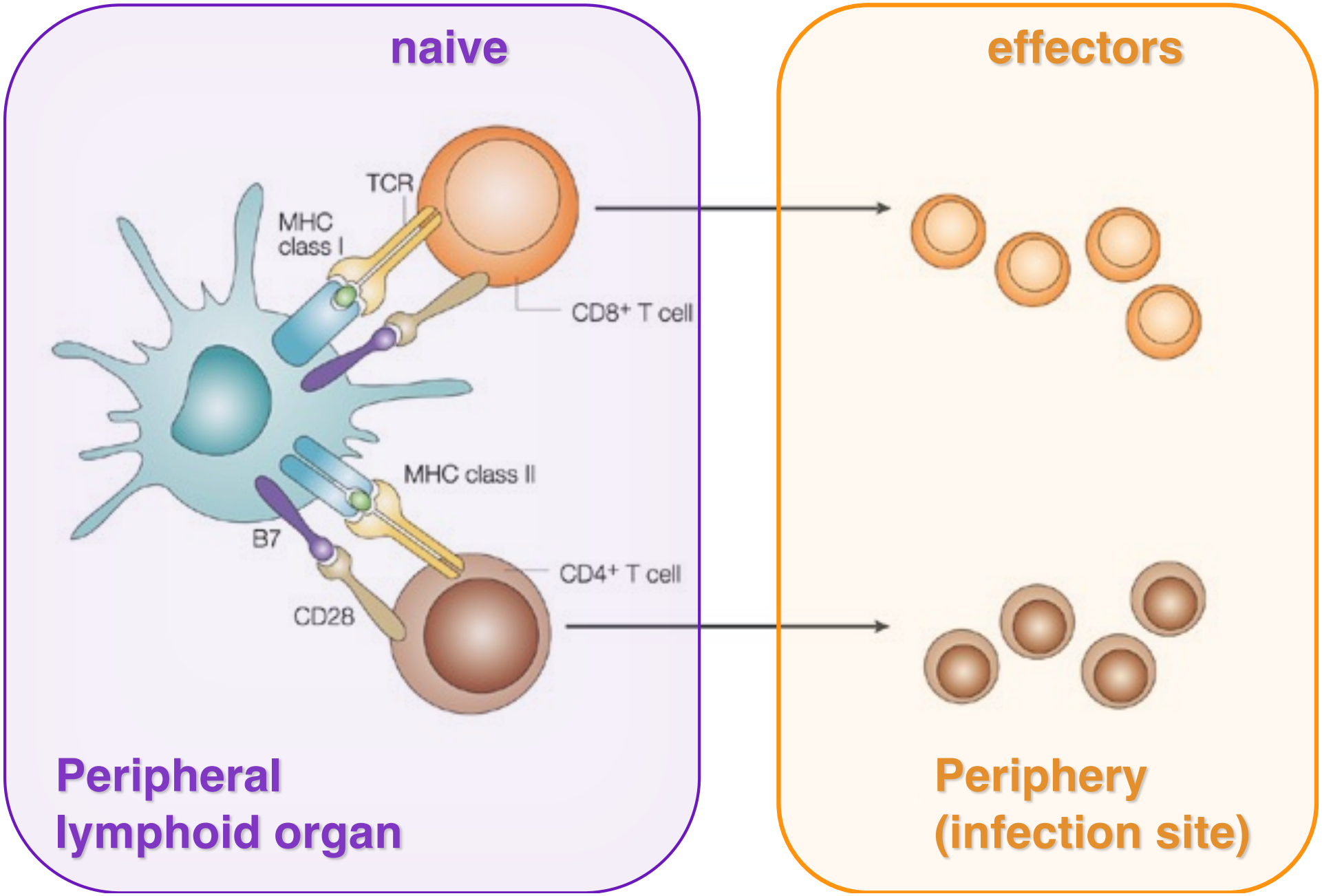
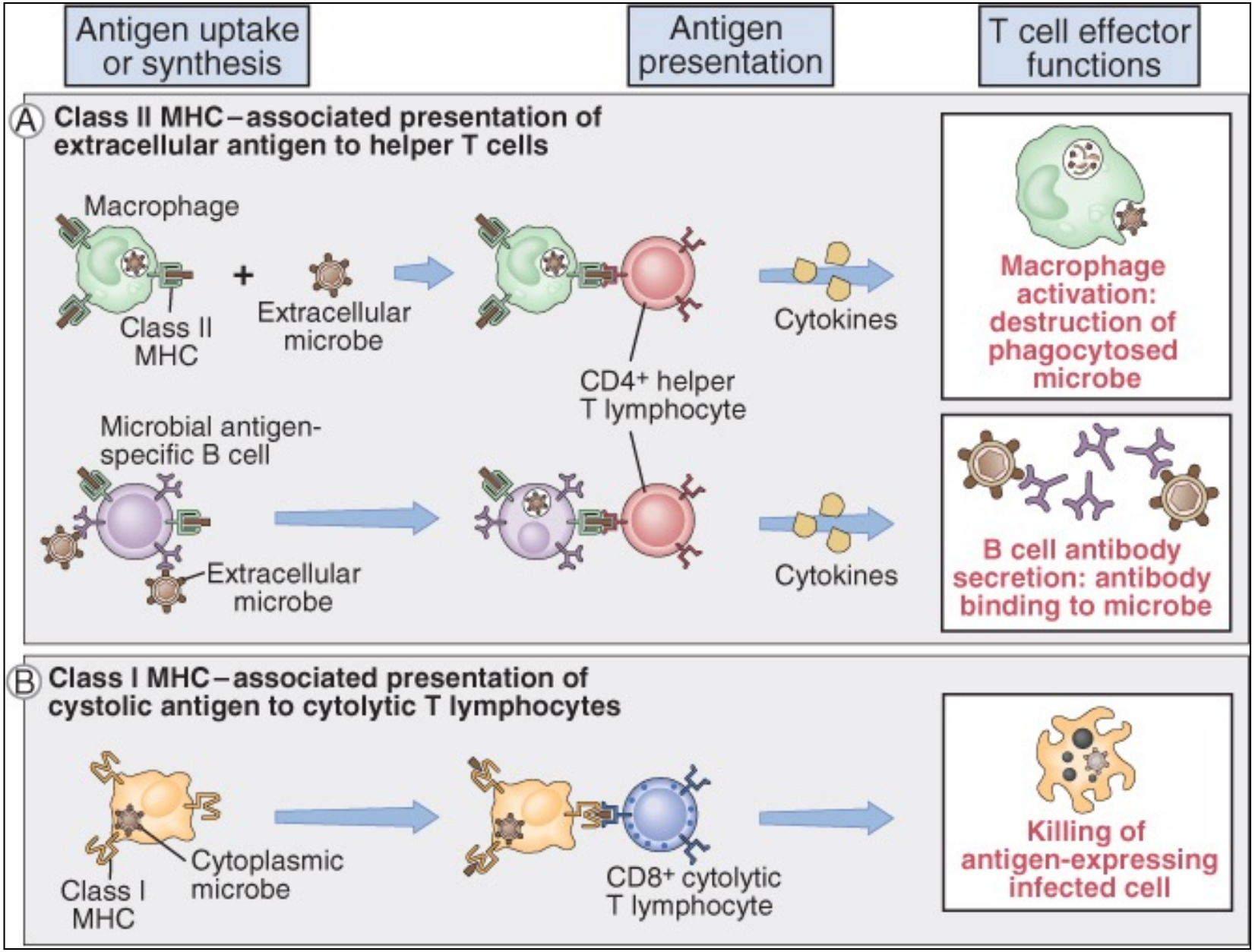
Effector T cells migrate to the infection site to perform their function



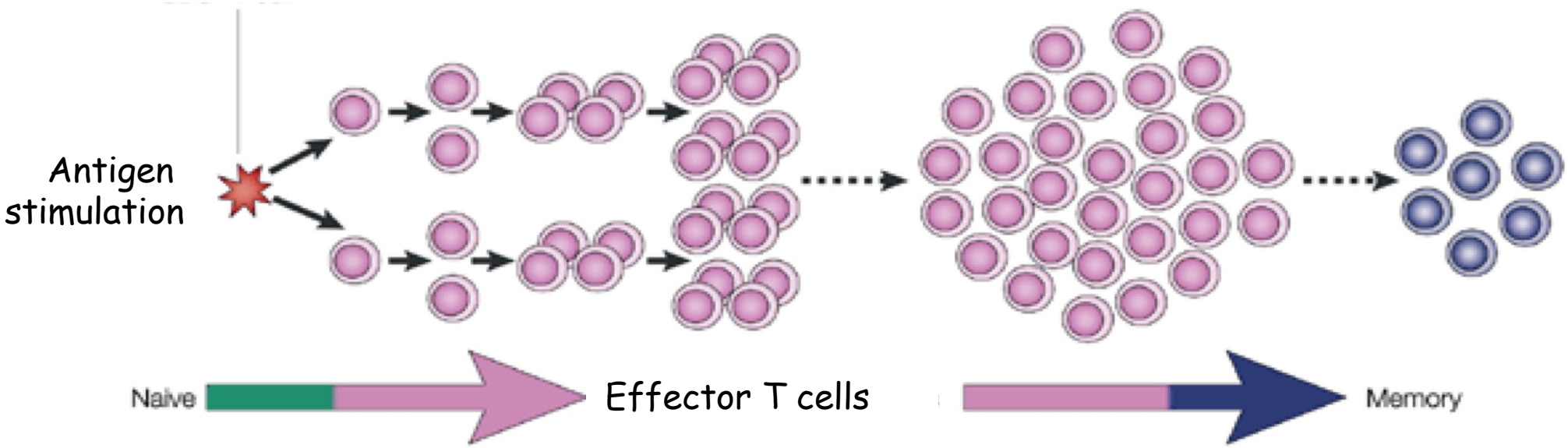
Naive and effector lymphocytes differ phenotypically and functionally

Property	Naive T cells	Effector T cells
Cell adhesion molecules (CD2 and LFA-1)	Low	High
Trafficking patterns	HEVs* in secondary lymphoid tissue	Tertiary lymphoid tissues; inflam-matory sites
Costimulatory signal (CD28-B7 interaction)	Required for activation	Not required for activation

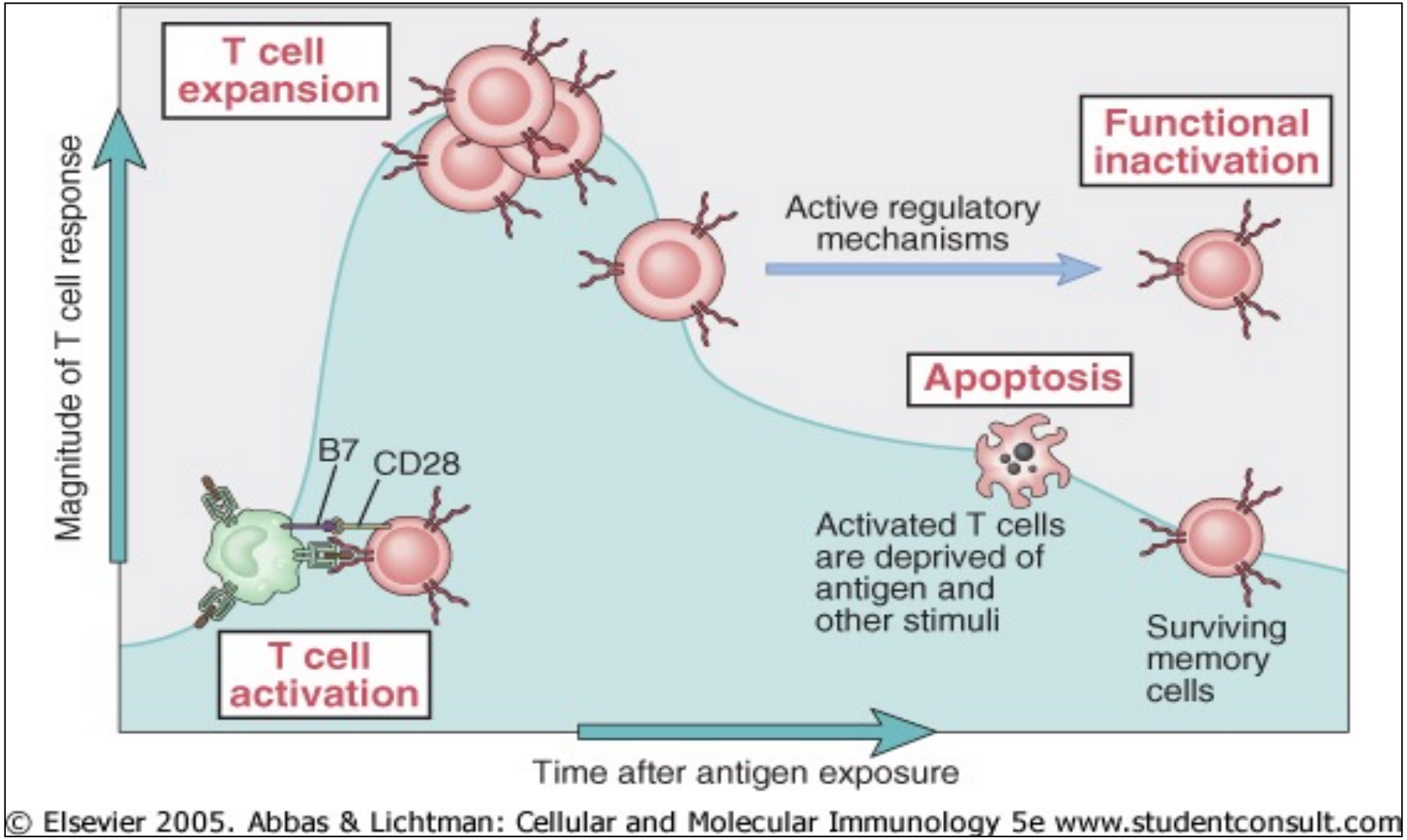
Effector T lymphocytes recognize the antigen again: eradication of the infection



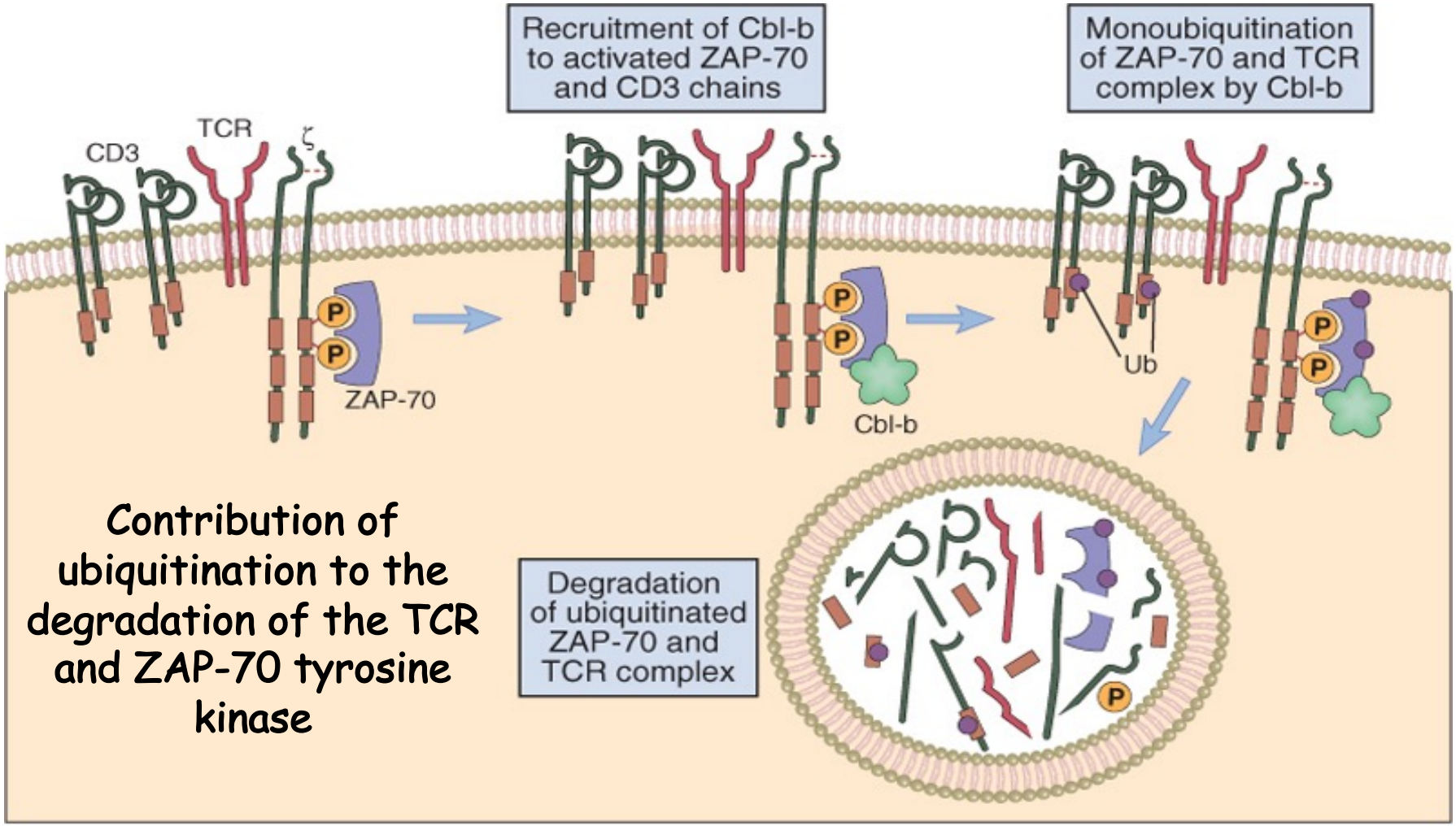
Development of effector and memory T cells



NEGATIVE SIGNALS INACTIVATE OR KILL EFFECTOR T LYMPHOCYTES

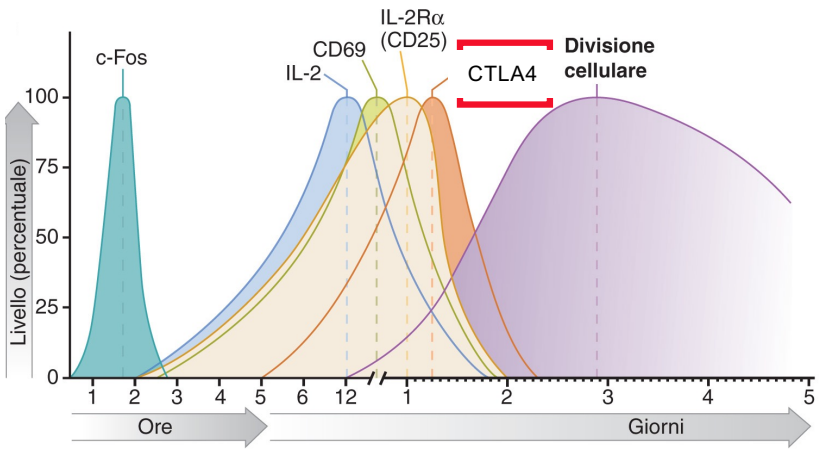


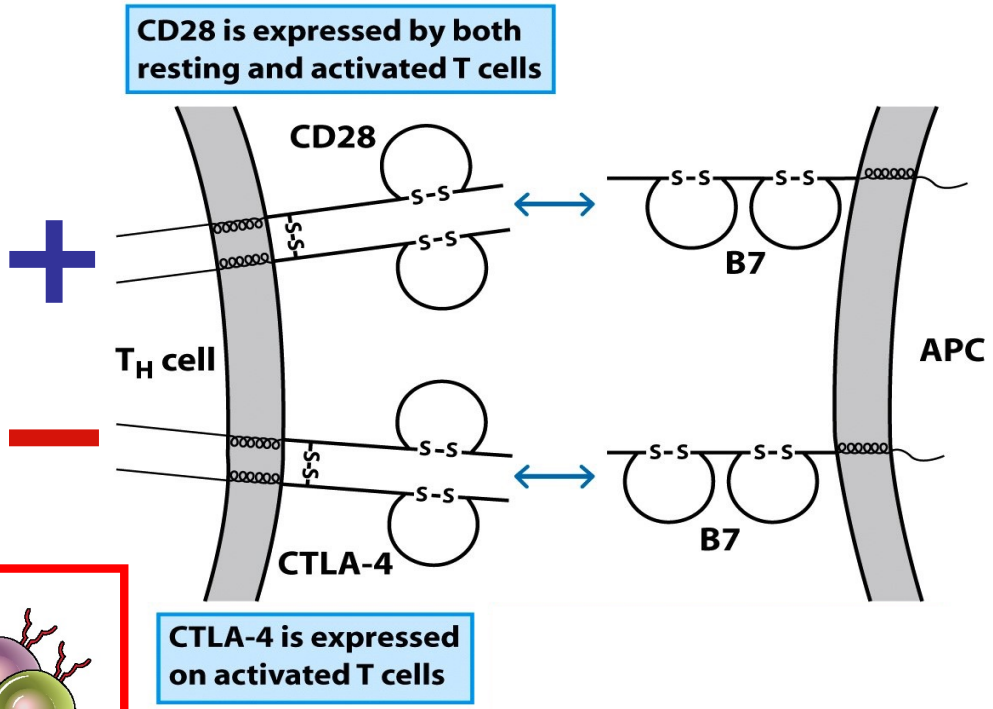
Switching off T-specific signaling: The role of Cbl ubiquitin ligase and ubiquitination

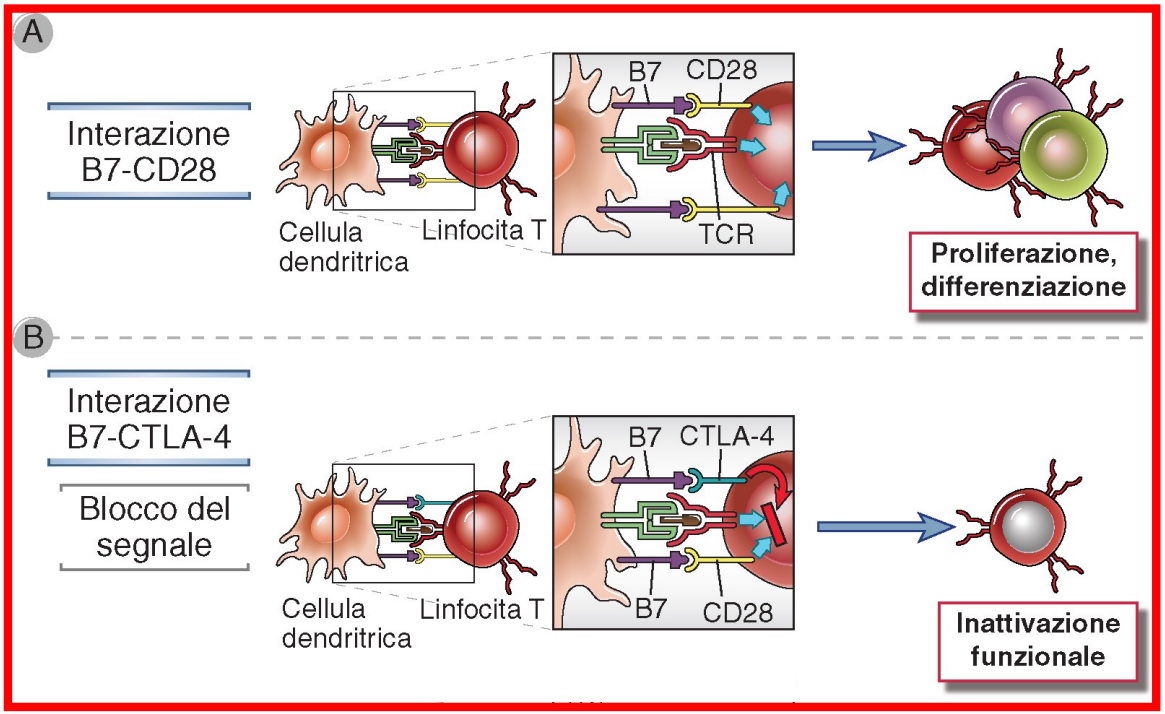


Contribution of ubiquitination to the degradation of the TCR and ZAP-70 tyrosine kinase

Activation of naive T lymphocytes induces the expression of the inhibitory receptor CTLA4

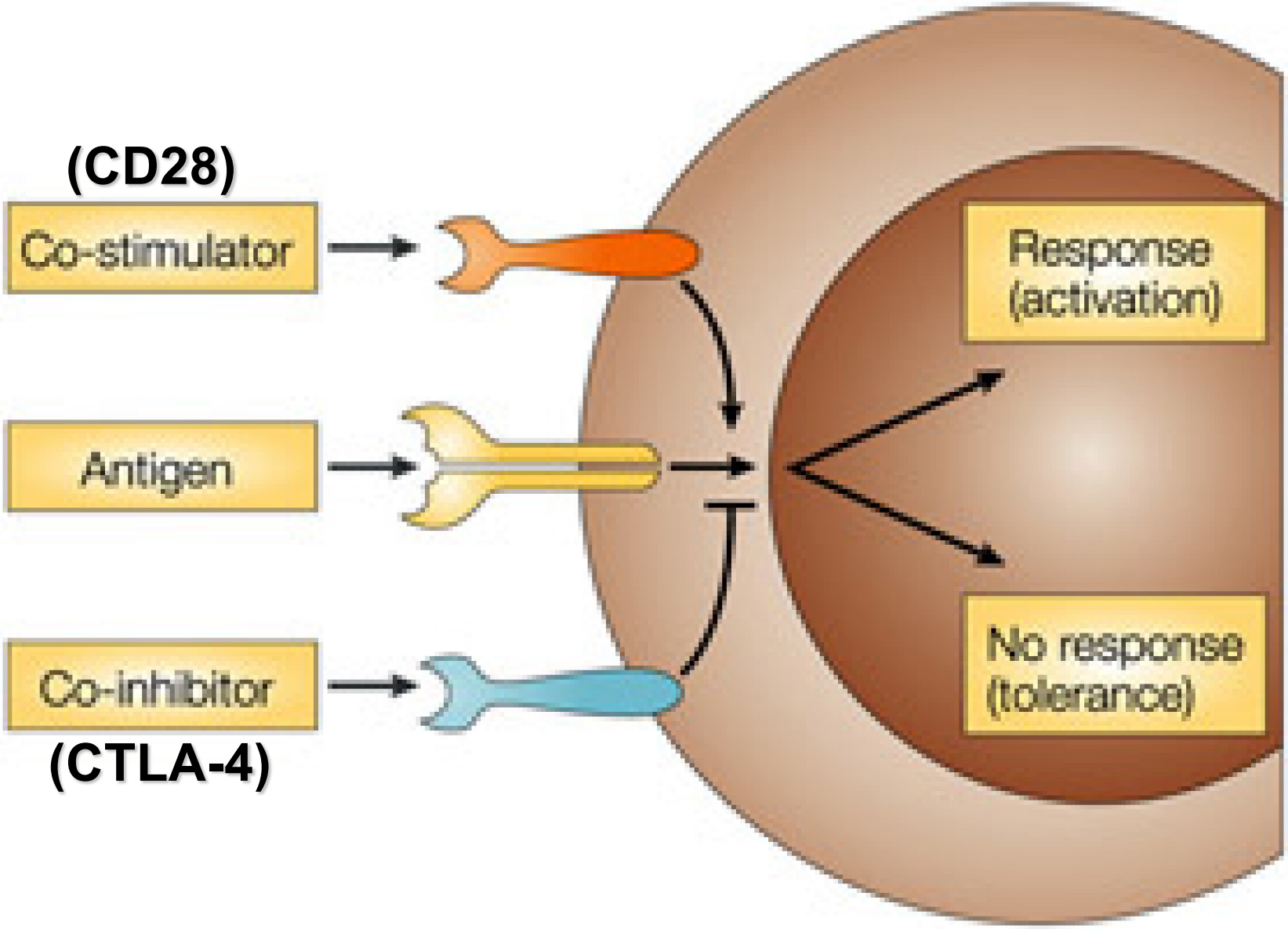






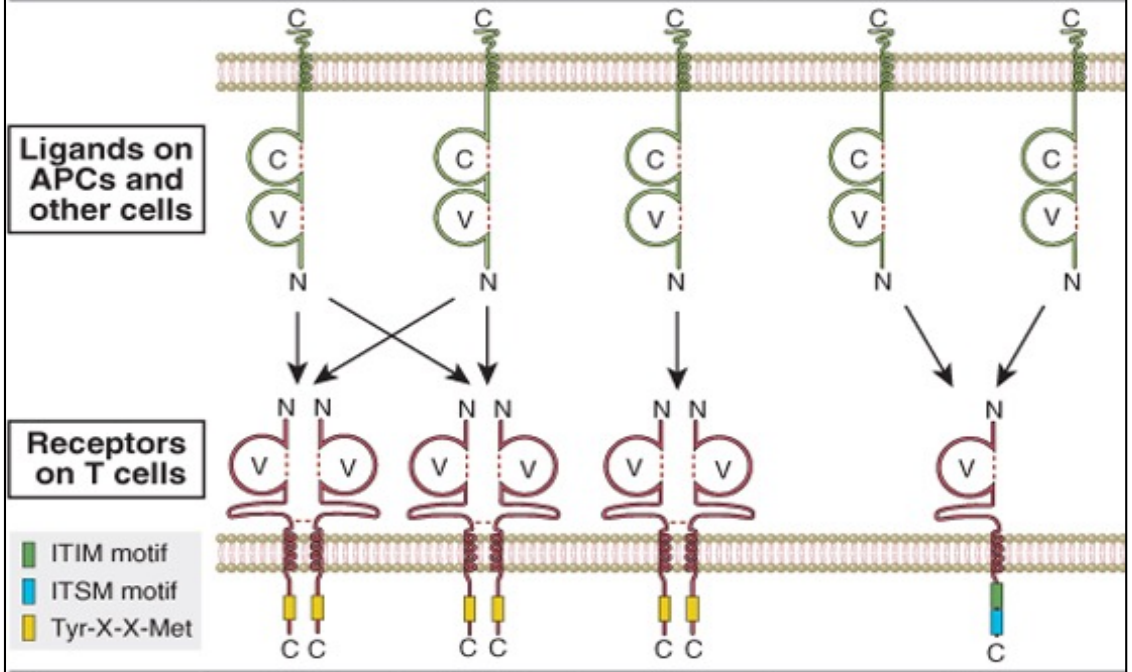
- CTLA4 binds the same ligands as CD28, but with a 20-fold higher affinity.
- It transduces inhibitory signals responsible for the functional inactivation of T lymphocytes.

Co-stimulatory and co-inhibitory molecules set the threshold for T cell activation



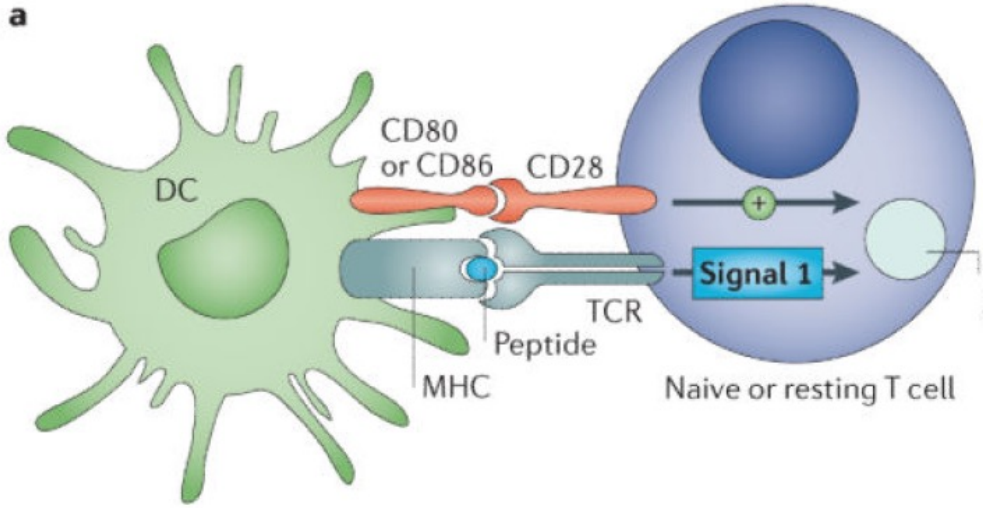
Principal members of B7-family proteins

Expression	DCs, macrophages, B cells	DCs, macrophages, B cells	DCs, macrophages, B cells, other cells	DCs, macrophages, B cells, other cells	
Name	**B7-1 (CD80)**	**B7-2 (CD86)**	**ICOS-L**	**PD-L1 (B7-H1)**	**PD-L2 (B7-DC)**



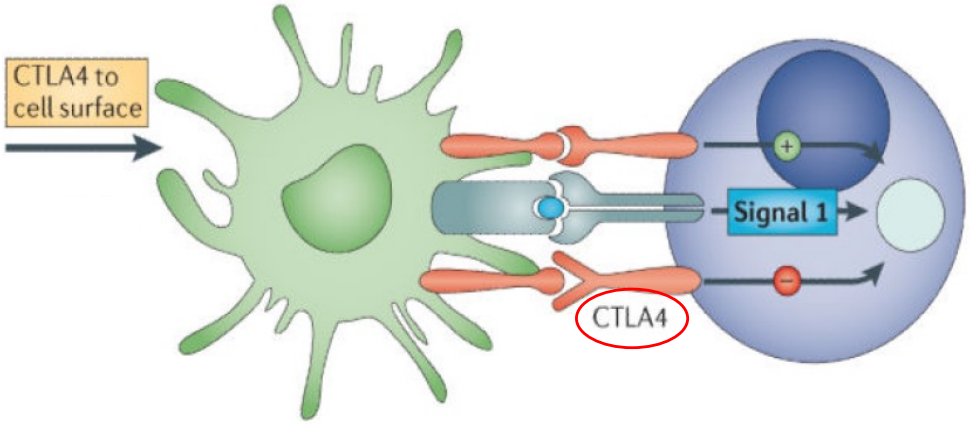
Name	**CD28**	**CTLA-4**	**ICOS**	**PD-1**
Expression	T cells; constitutive	T cells; inducible	T cells; inducible	T cells, B cells, Myleoid cells; inducible
Major function	Costimulation of naive T cells; generation of regulatory T cells	Negative regulation of immune responses; self-tolerance	Costimulation of effector T cells	Negative regulation of T cells

Major functions of selected B7-CD28 family members

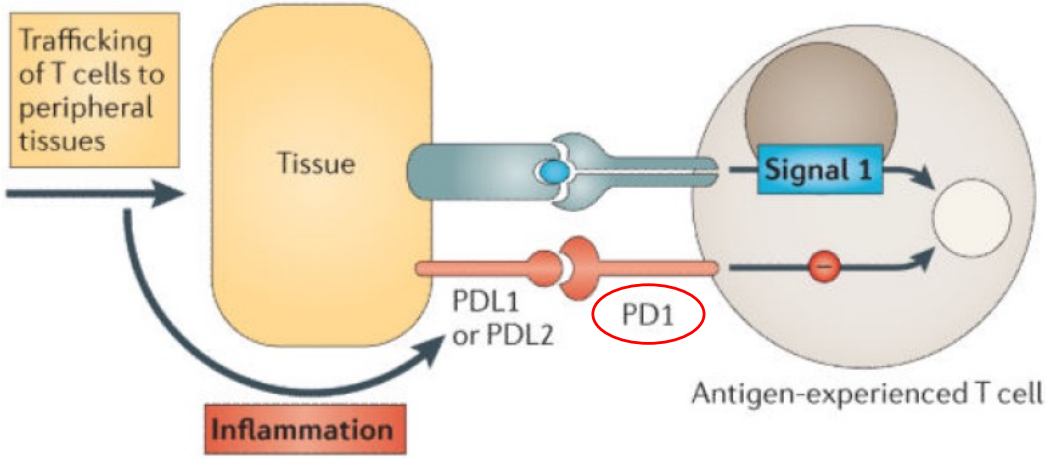


CD28-B7: initiation of immune responses

CTLA-4-B7: inhibits early T cell responses in lymphoid organs



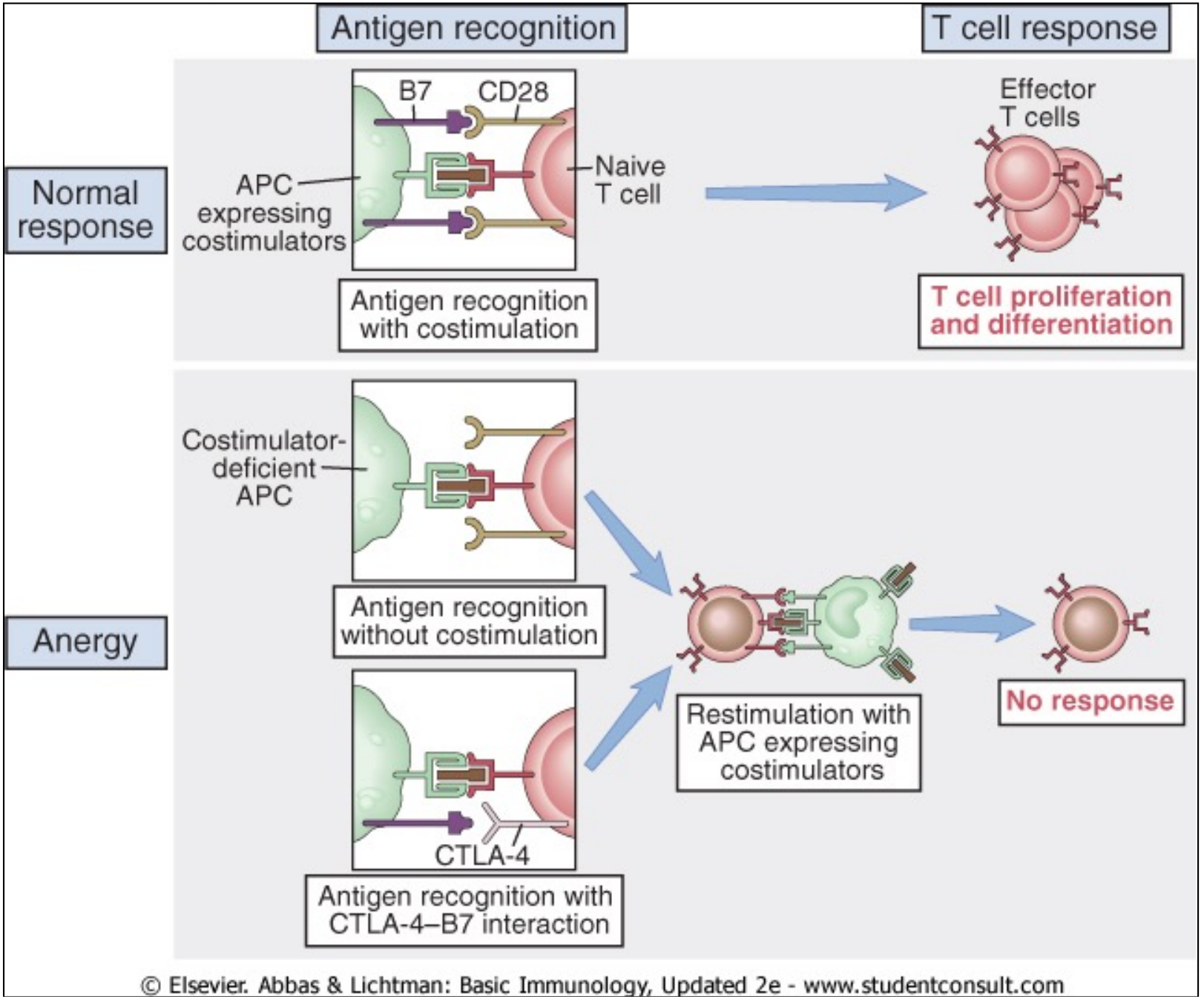
PD-1:PD-L1,2: inhibits effector T cell responses in peripheral tissues



Inhibitory functions of CTLA-4 e PD-1

	CTLA-4	PD-1
Action site	Lymphoid organs	Peripheral tissues
Inhibition phase	Upon initial activation	During effector phase
Inhibited signals	CD28 co-stimulation	Chronic stimulation
Inhibited lymphocyte subsets	CD4+ and CD8+	CD8+ > CD4+

TWO different mechanisms for peripheral TOLERANCE of T cells!



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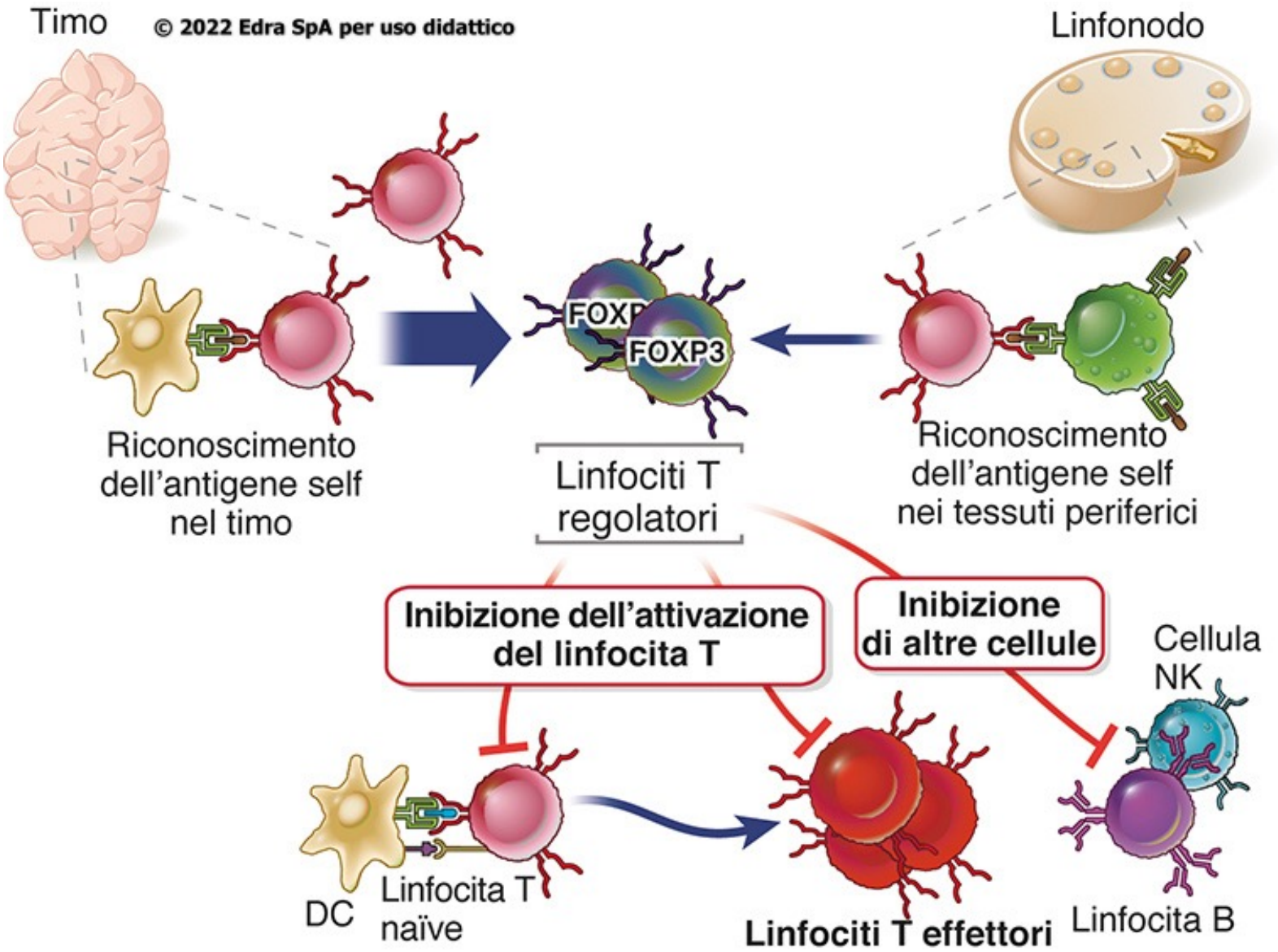
Turning off T-cell specific signaling: The role of regulatory lymphocytes (Tregs)