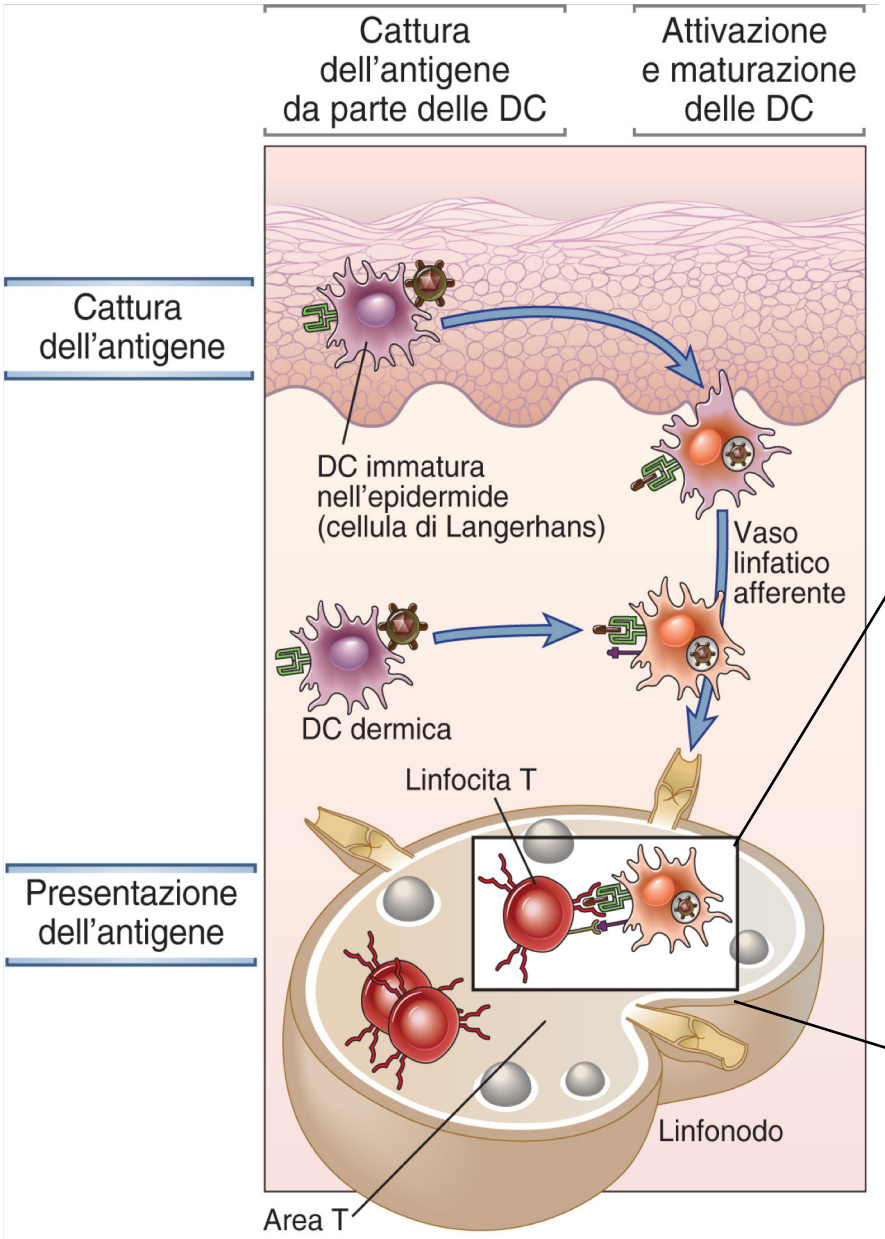
Corso di Immunologia - III anno
Prof. Paolini

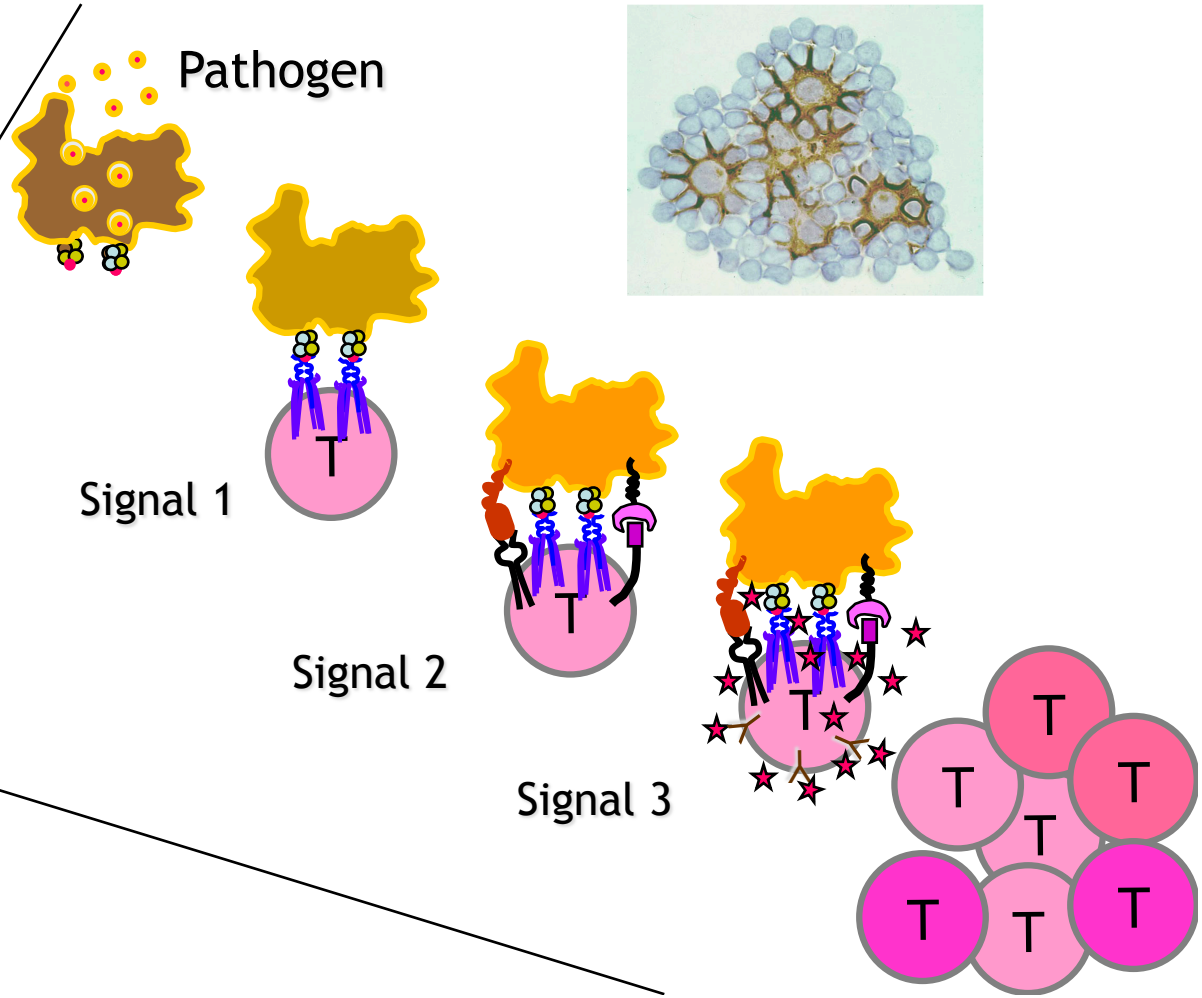
Lezione 06/11/2026

"L'attivazione dei linfociti T"

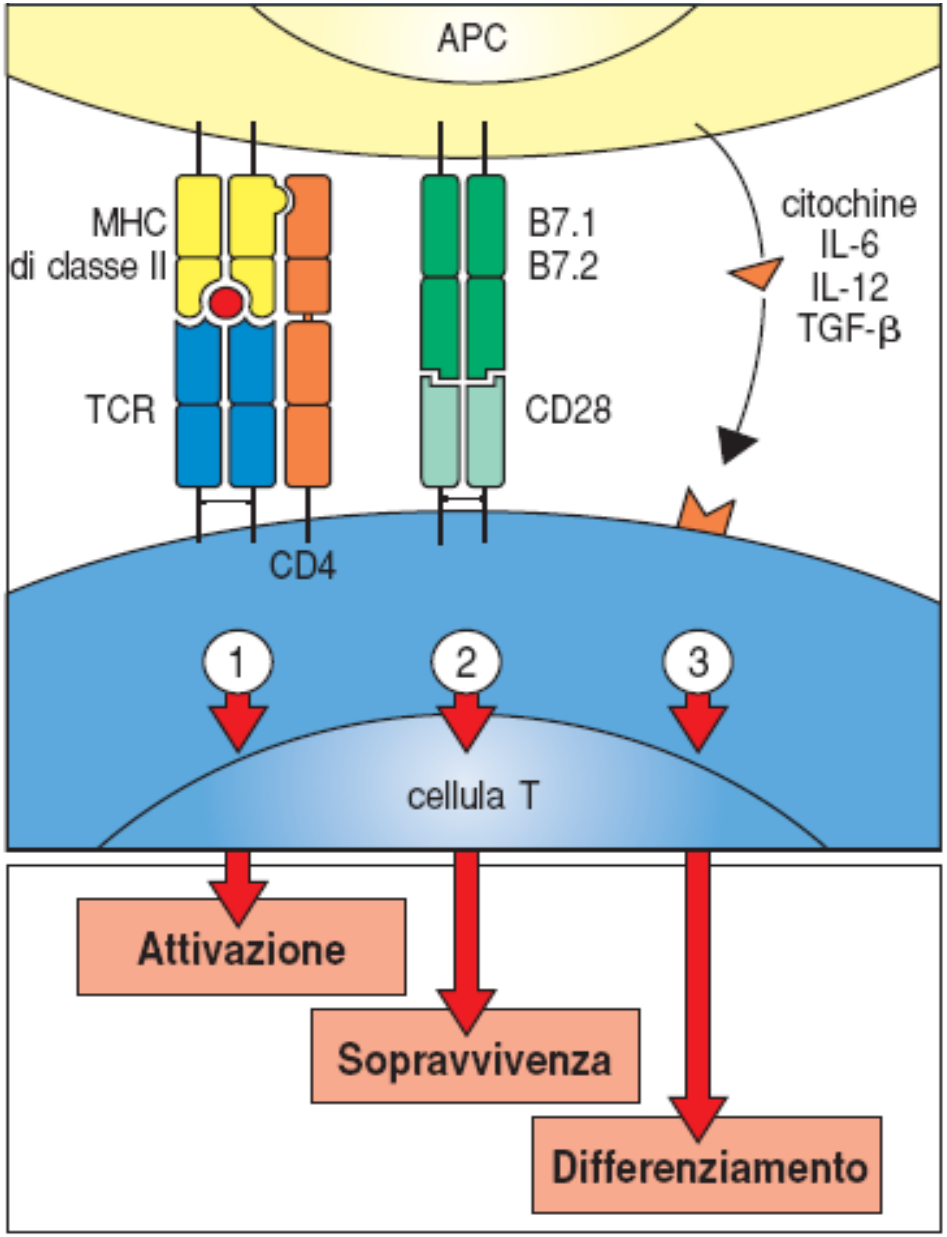
Il materiale presente in questo documento viene distribuito esclusivamente ad uso interno e per scopi didattici.

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





Mature DCs provide naive T cells with the 3 signals they need to be activated

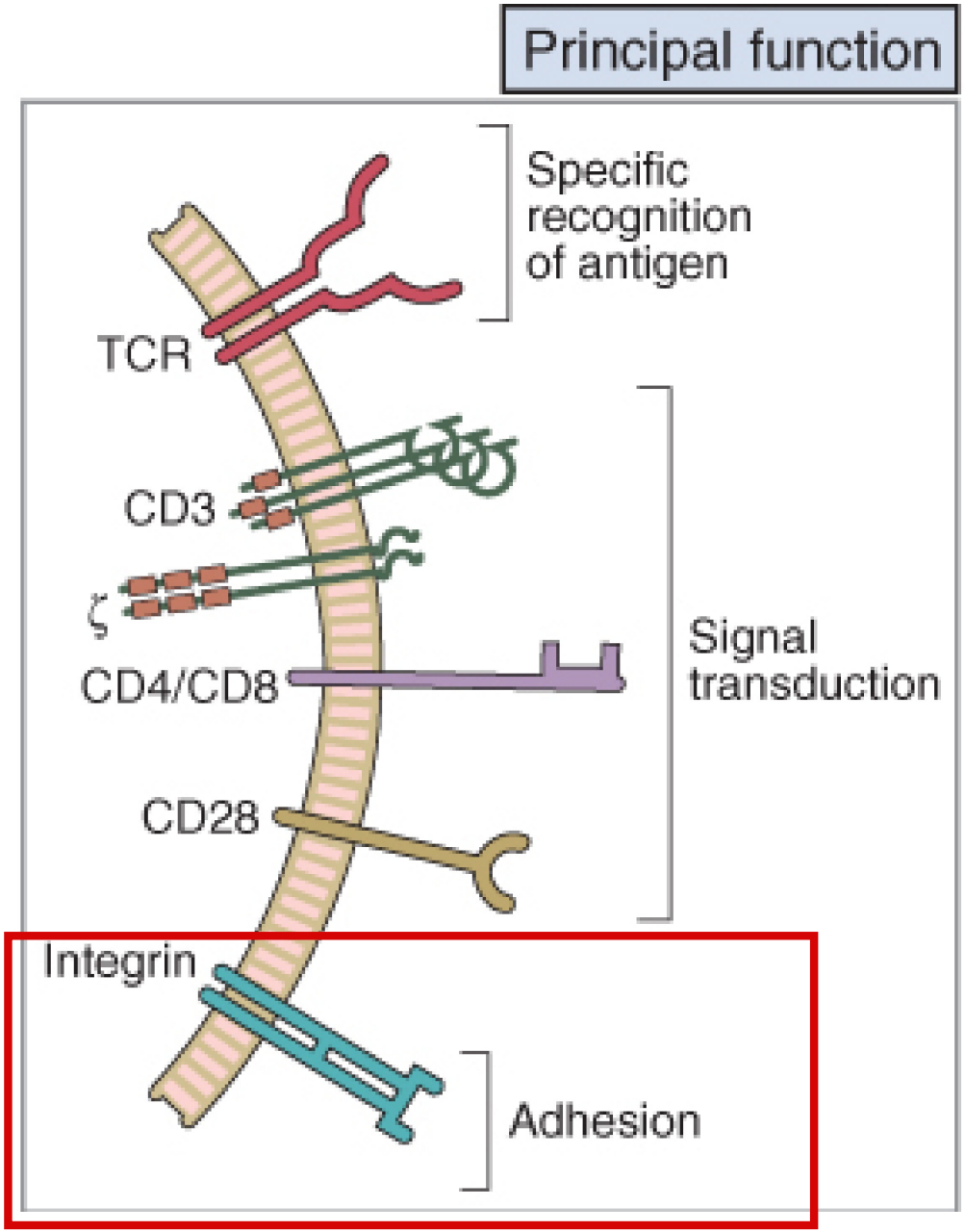


How to communicate? **Starting by touching each other**

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

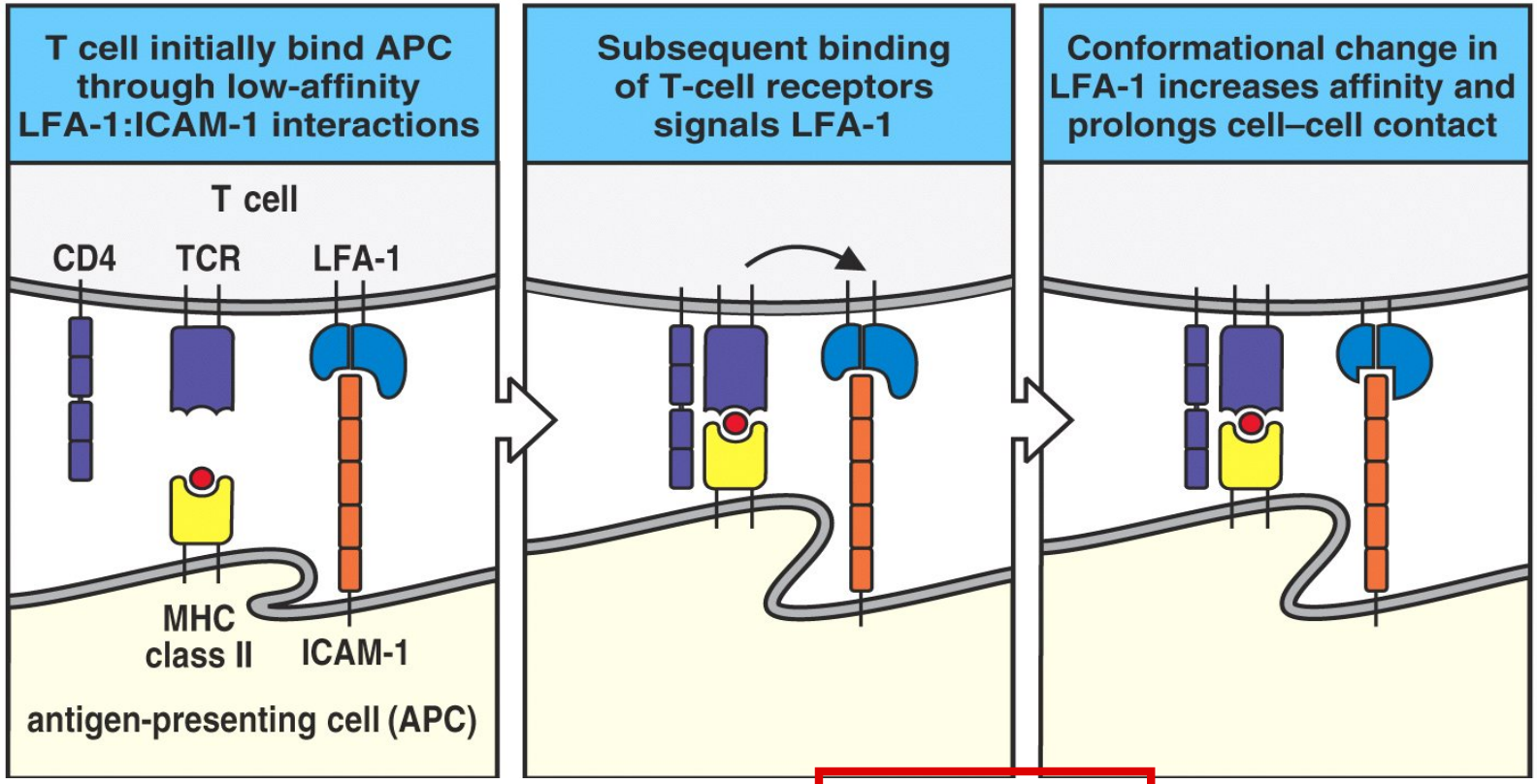


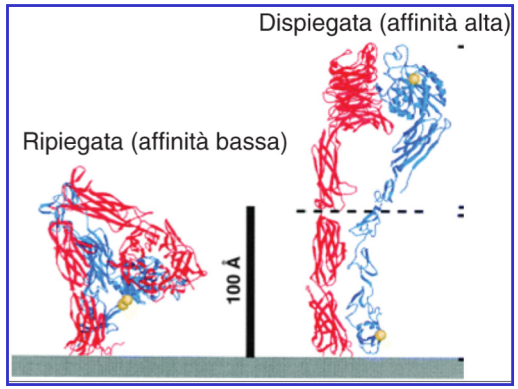
- Belongs to the β2 family of integrins
- Its ligands are ICAM-1, 2, 3, expressed on APCs, and endothelium
- It is responsible for cell-cell adhesion between:
  - T cell/APC
  - CTL/target cell
  - Leukocyte/endothelium

- LFA-1 affinity & avidity for ligands are regulated

Low → Ag recognition → High

Adhesion molecules participate to T cell/APC interaction



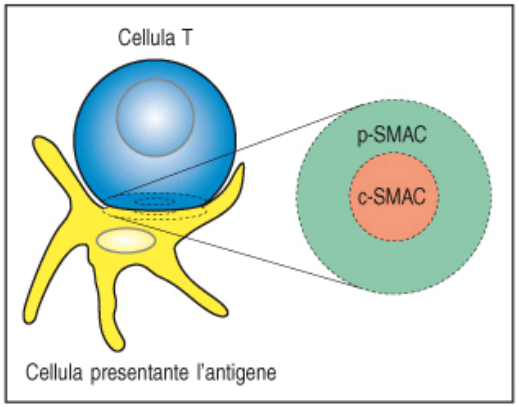


How to communicate? Starting by touching each other

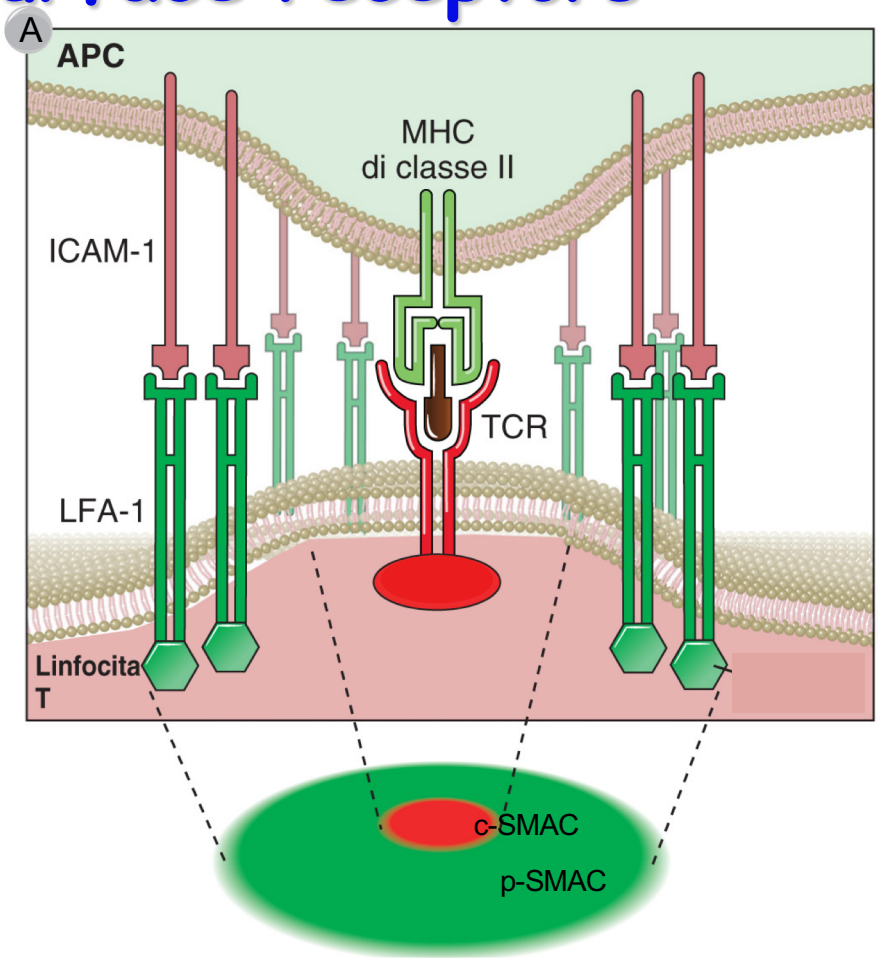
Intercellular Adhesion Molecules (ICAMs) of the integrin-binding immunoglobulin superfamily

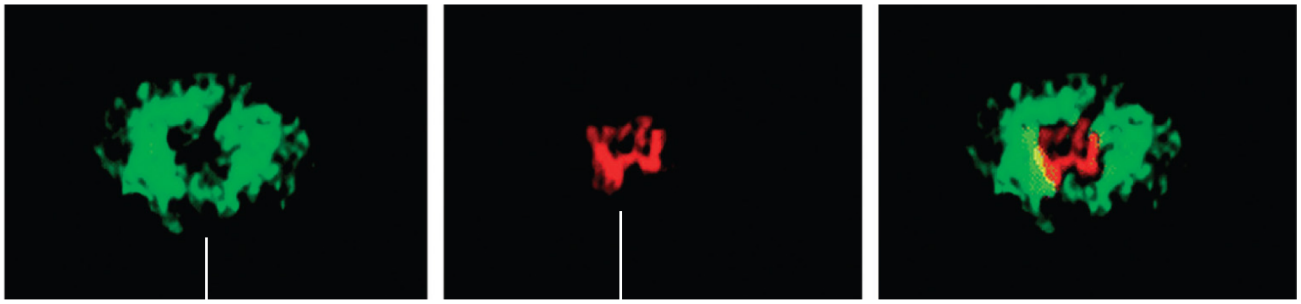
The molecules involved in signal propagation are located in the contact area between the APC and the T lymphocyte

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



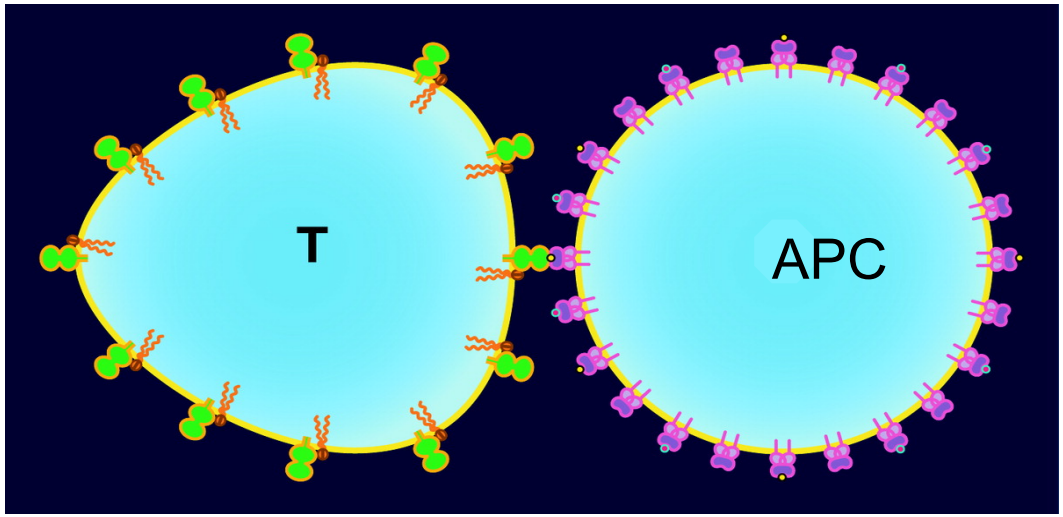
The region where the T cell contacts the APC is called the **immunological synapse**.
In the synapse, all the interacting proteins form a structure known as the SupraMolecular Adhesion Complex.
SMAC = SupraMolecular Activation Cluster



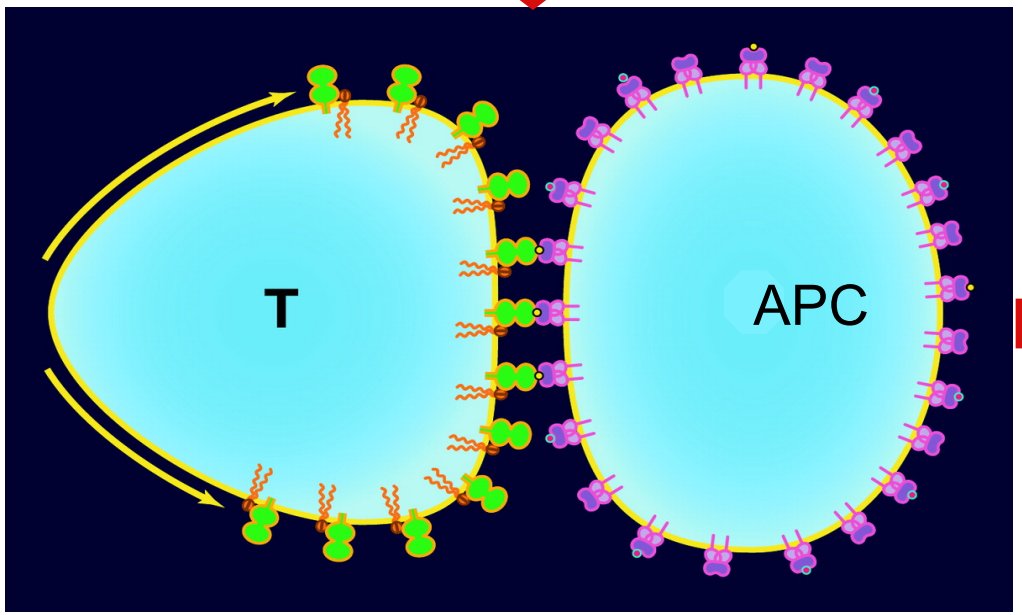


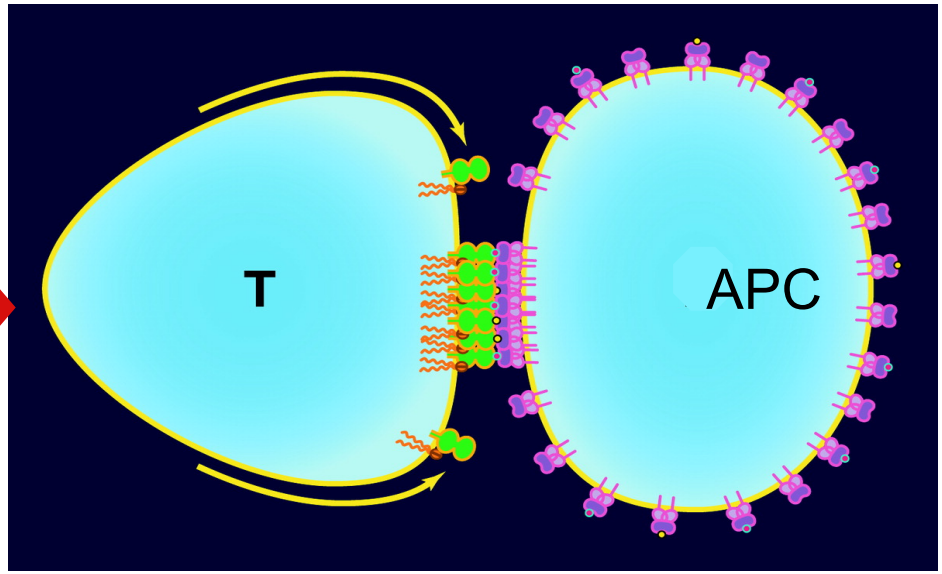
LFA-1 TCR

TCR aggregation occurs upon antigen recognition



After antigen recognition, the TCR translocates to a microdomain of the membrane (LIPID RAFT) rich in cholesterol, unsaturated fatty acids, sphingomyelin and glycosphingolipids



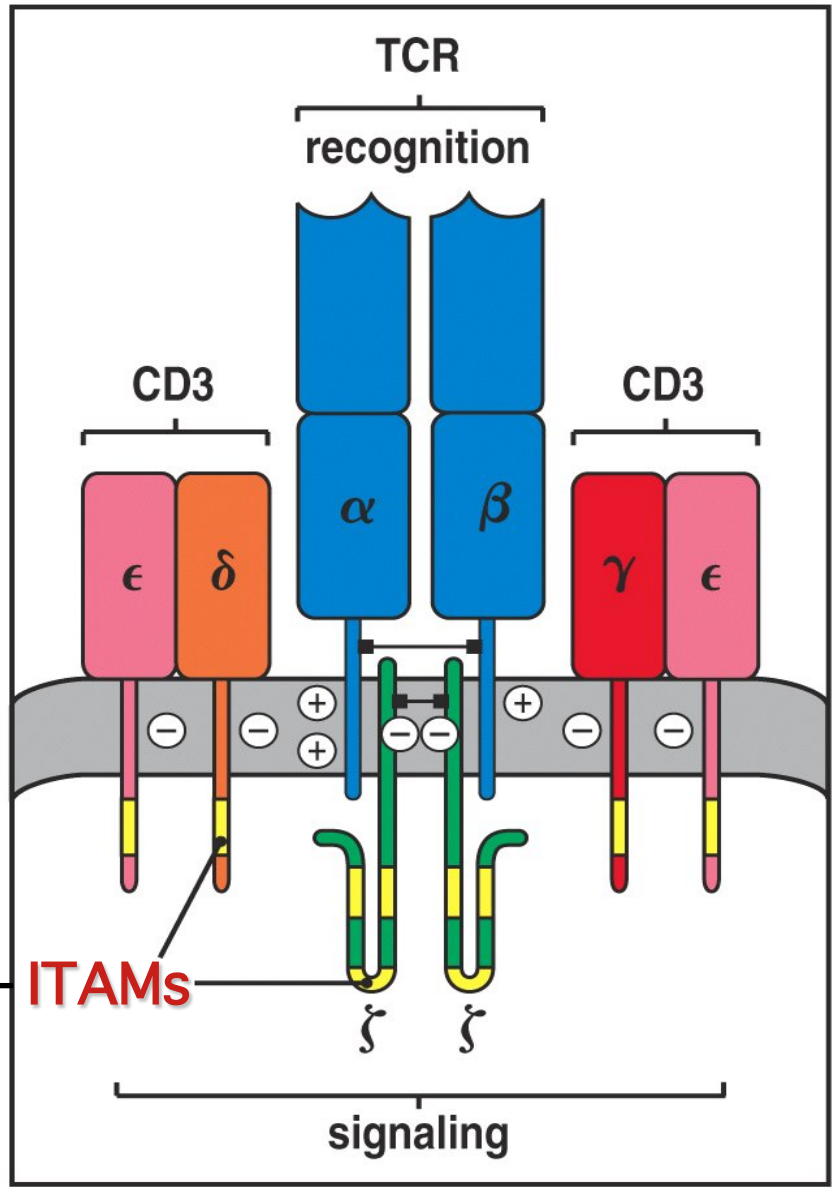


The immunological synapse

An organized membrane structure that facilitates, stabilizes, and prolongs TCR–MHC–peptide interactions by:

1. Excluding inhibitory receptors from the interaction area, thereby reducing inhibitory signaling.
2. Promoting the clustering and accumulation of TCRs and MHC–peptide complexes, increasing their local concentration and facilitating receptor engagement.
3. Promoting cytoskeletal rearrangement, which helps organize and stabilize the immunological synapse.

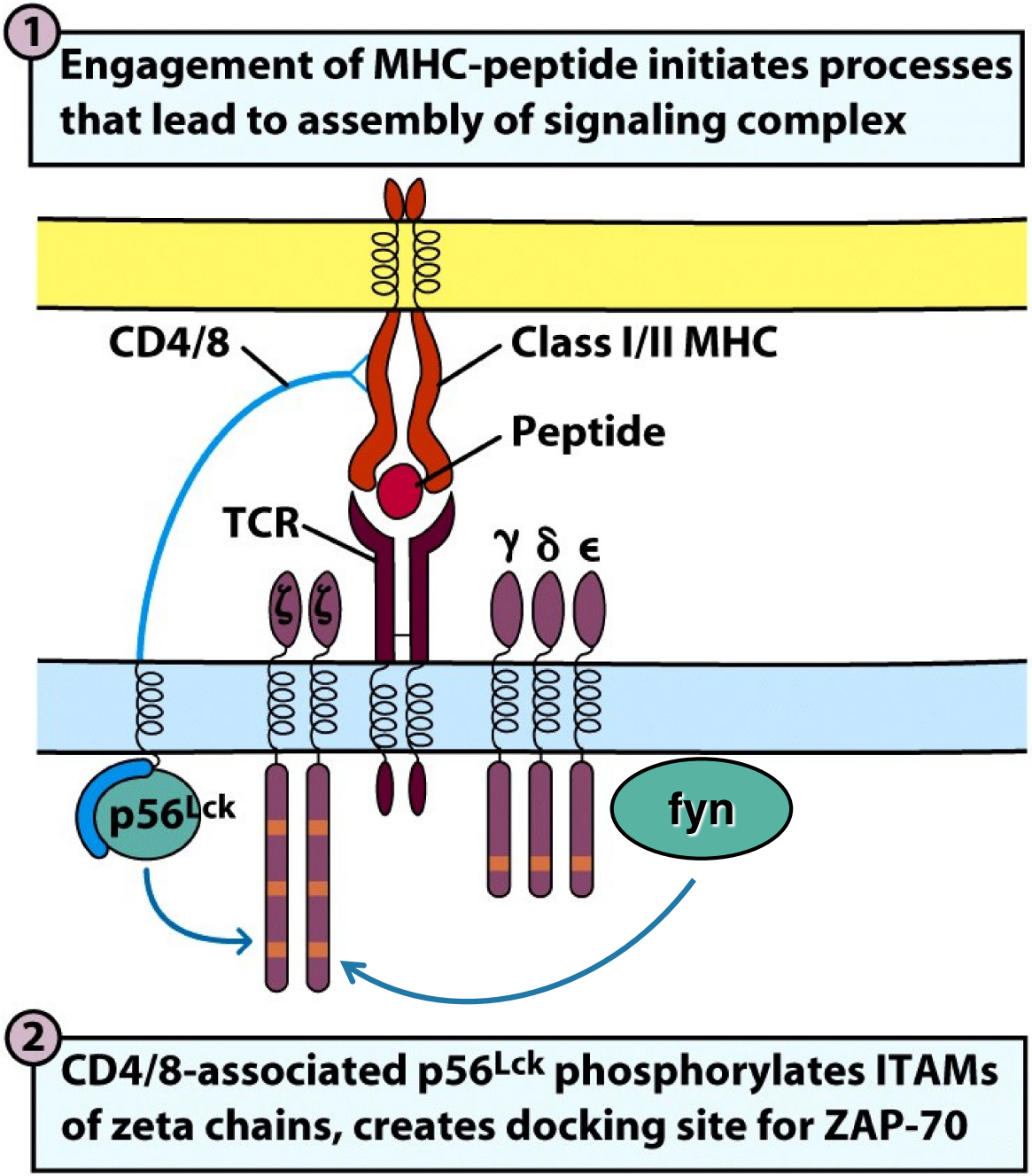
I° signal: CD3 complex initiates signal transduction



ITAM motif:
YxxL/Ixxxxxx YxxL/I

Immunoreceptor Tyrosine-based Activation Motif

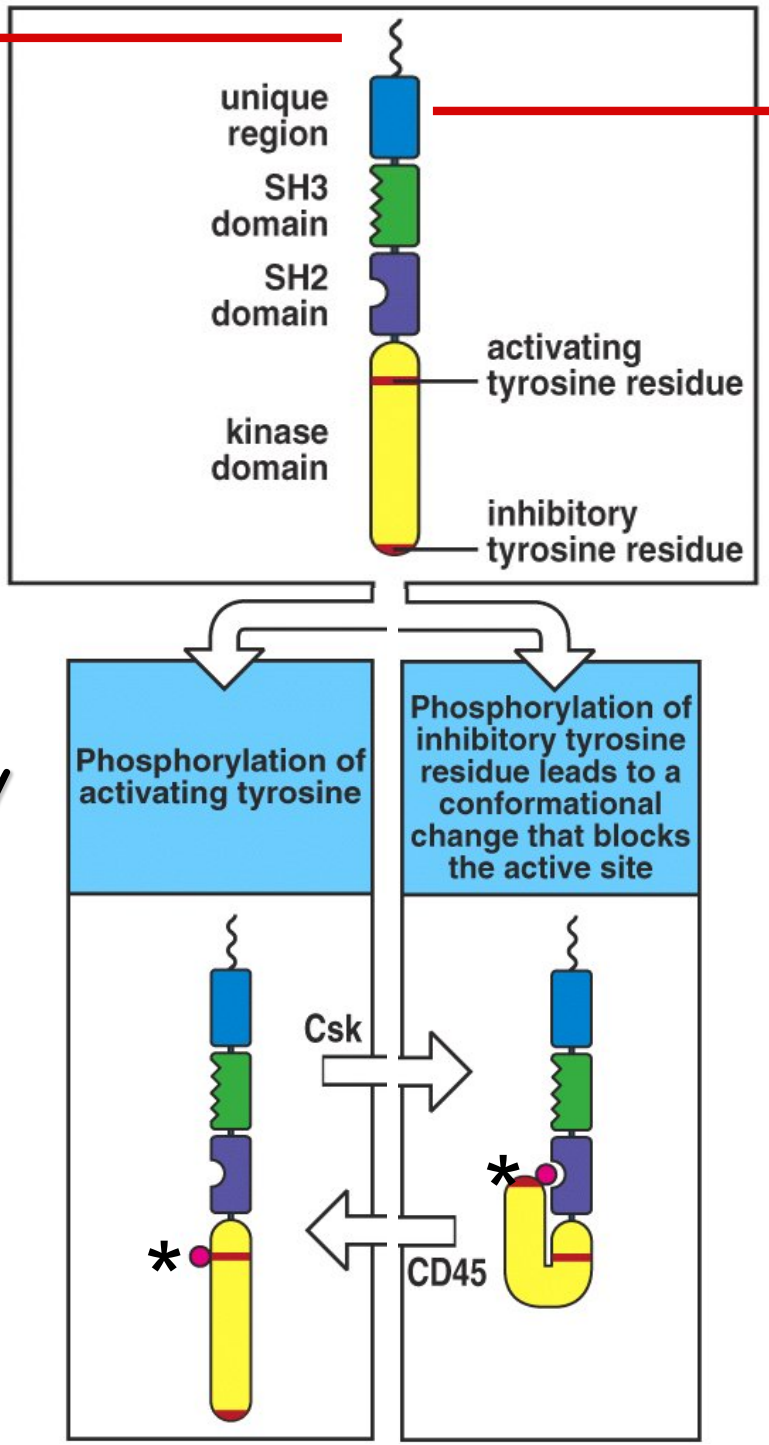
Src family tyrosine kinases are activated and phosphorylate CD3/ζζ ITAMs



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

Sito di legame alla membrana

Sito di legame ai corecettori CD4/CD8

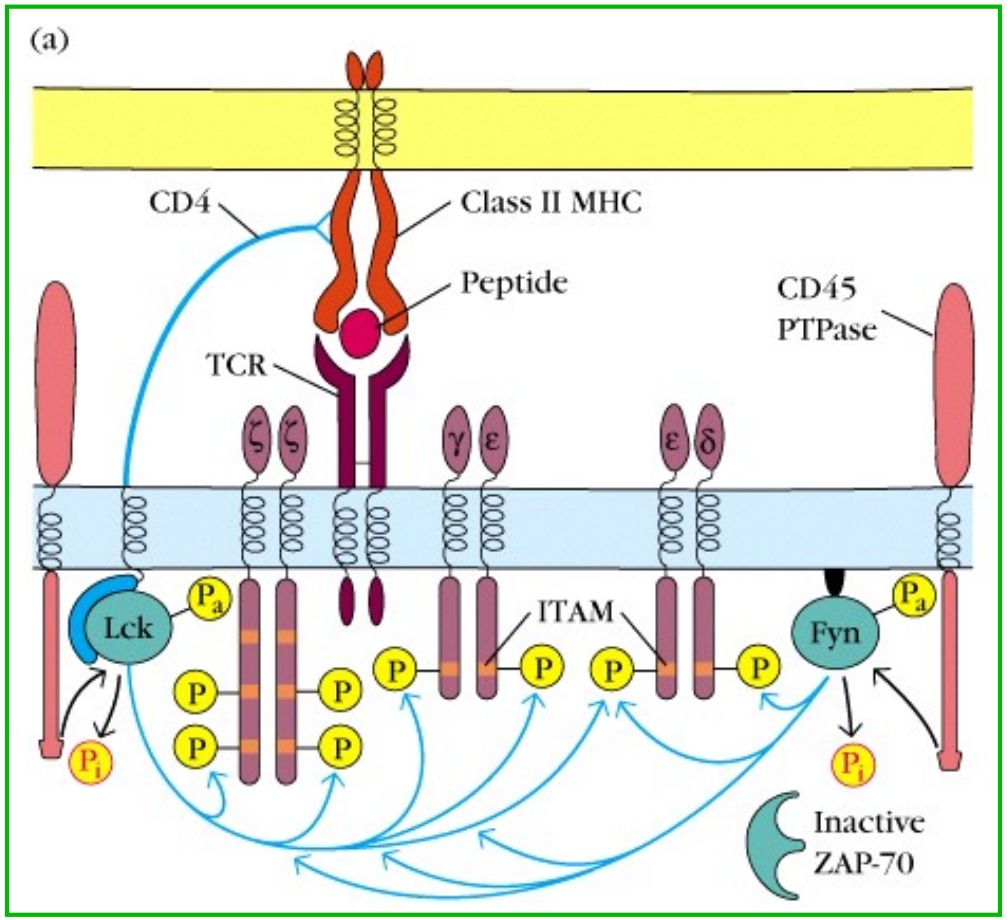


Their activity is regulated by inhibitory and activating tyrosine residues

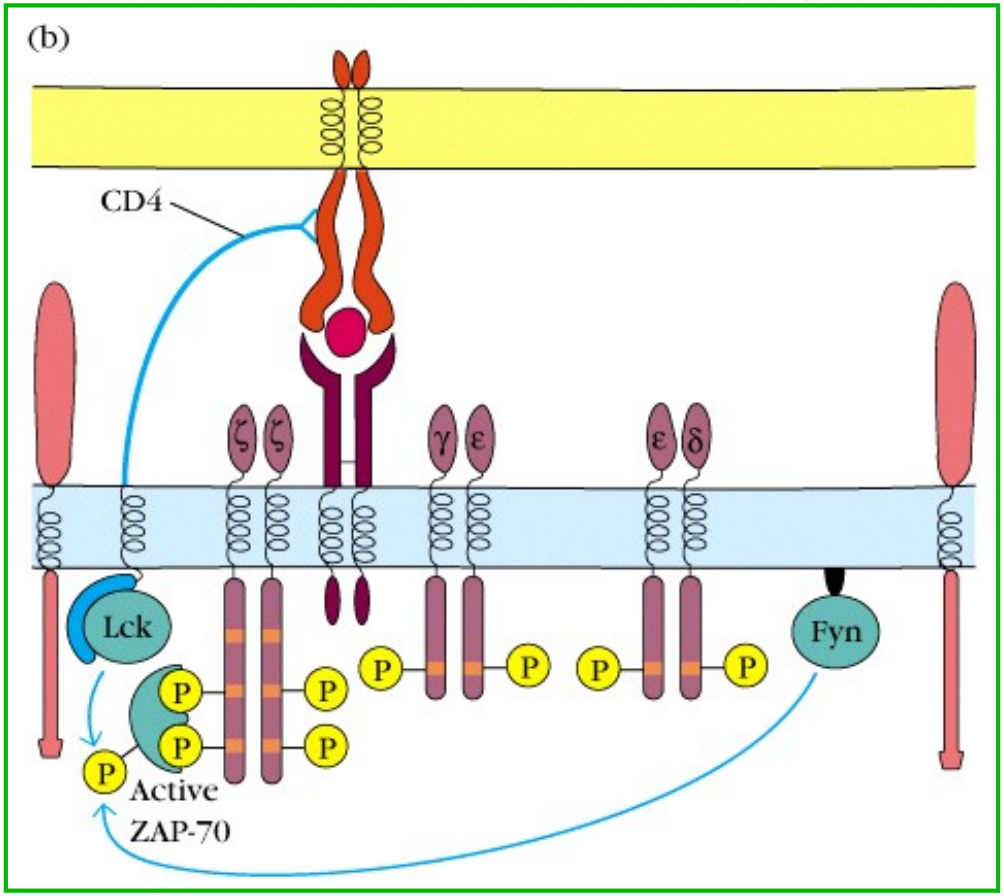
Csk= tyrosine kinase

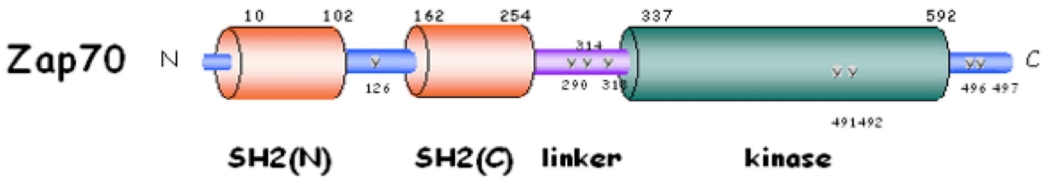
CD45= tyrosine phosphatase

1. lck and fyn phosphorylate CD3 ITAMs

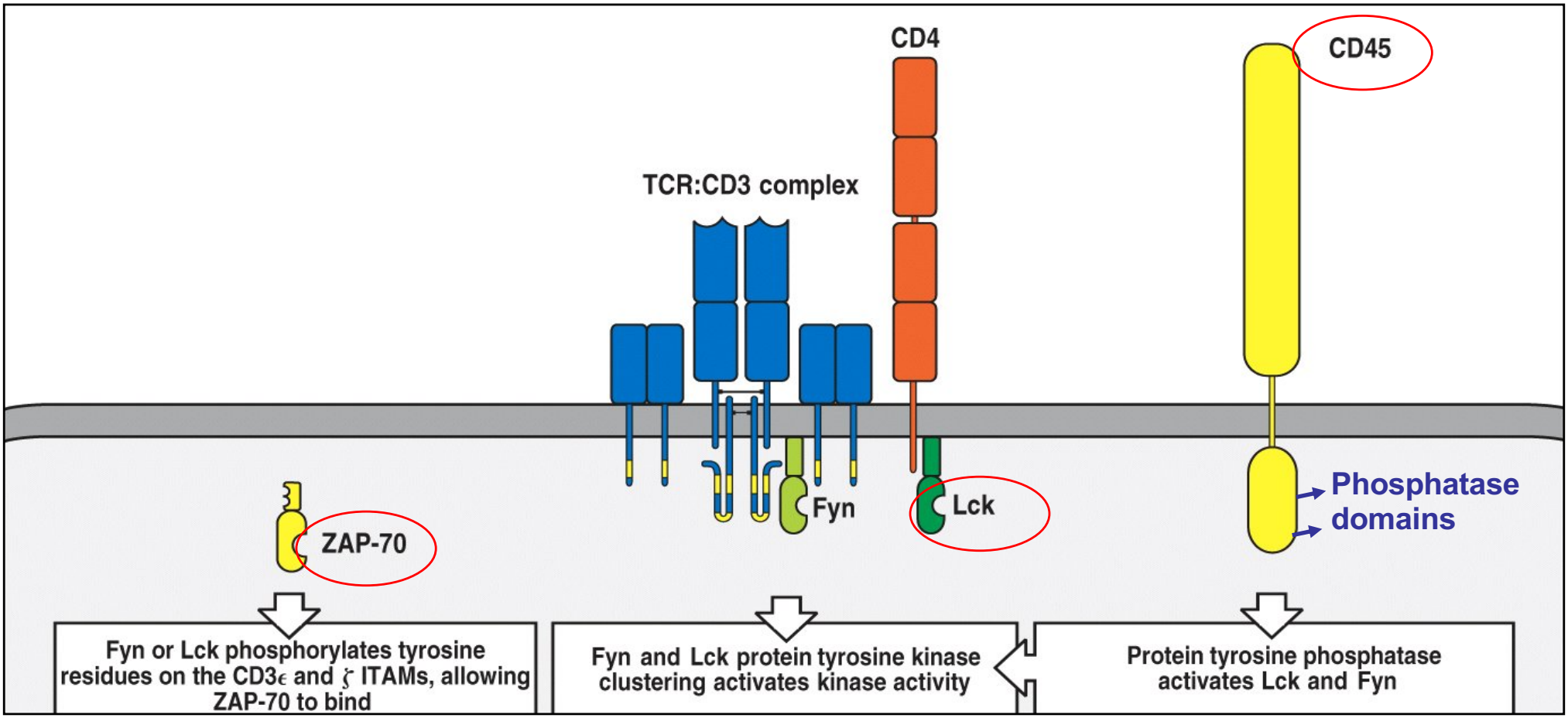


2. ZAP70 tyrosine kinase is recruited and activated at the cell membrane

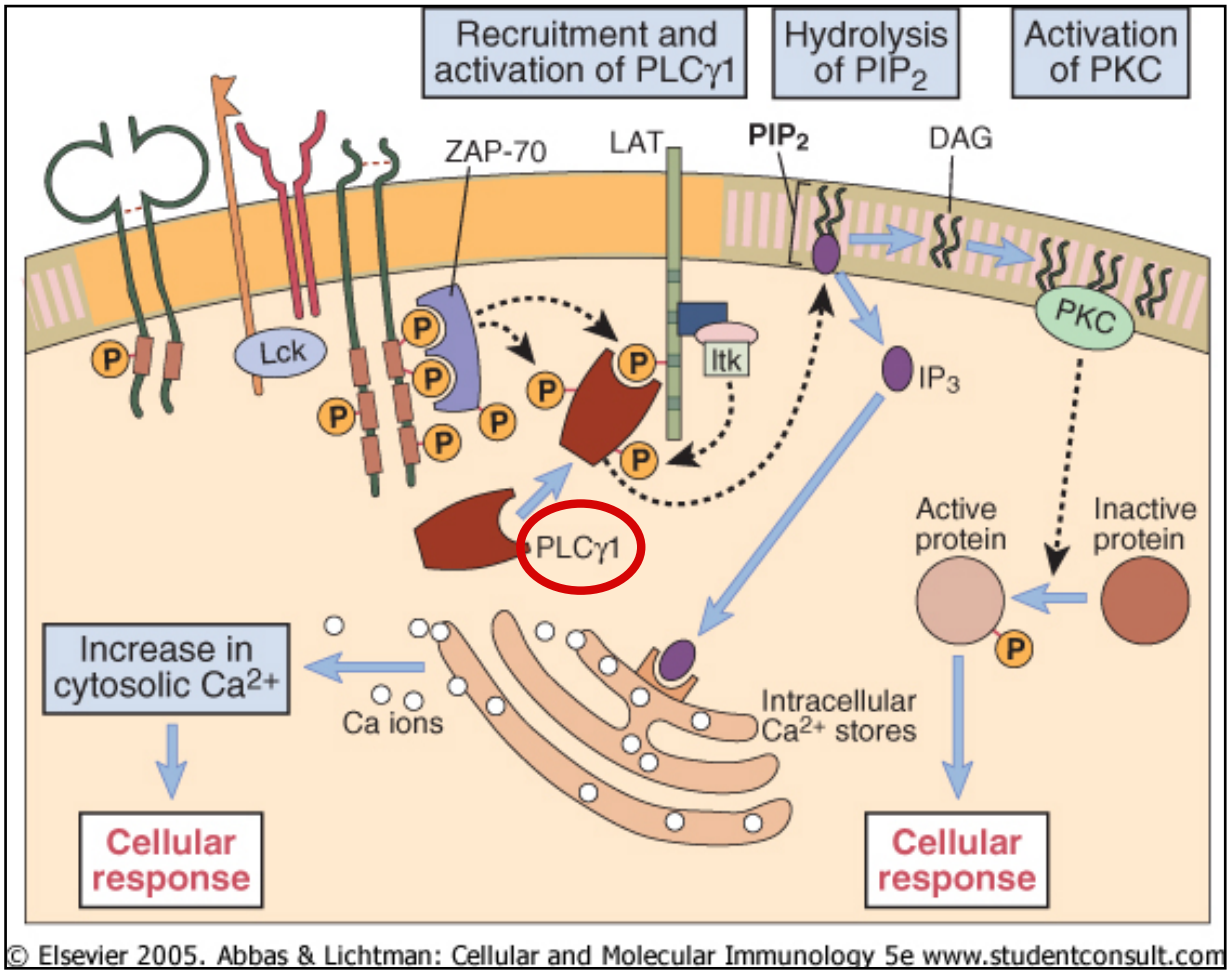




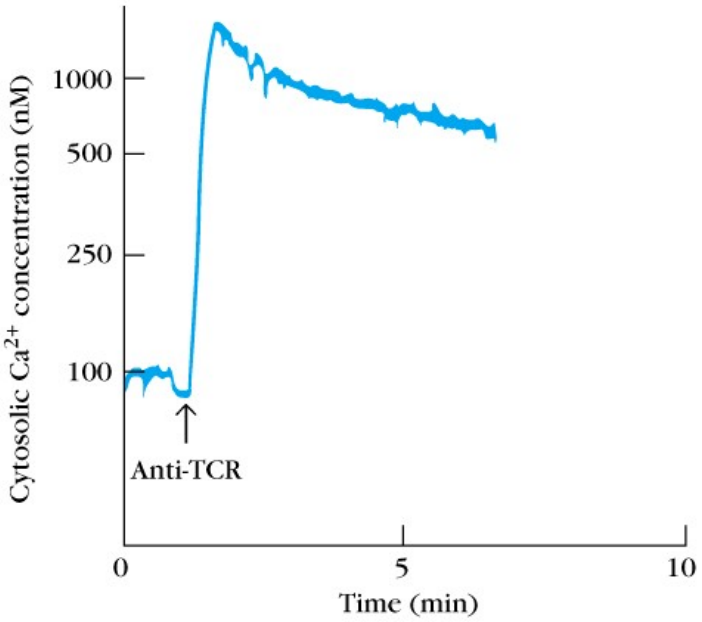
The main enzymes involved in T cell activation



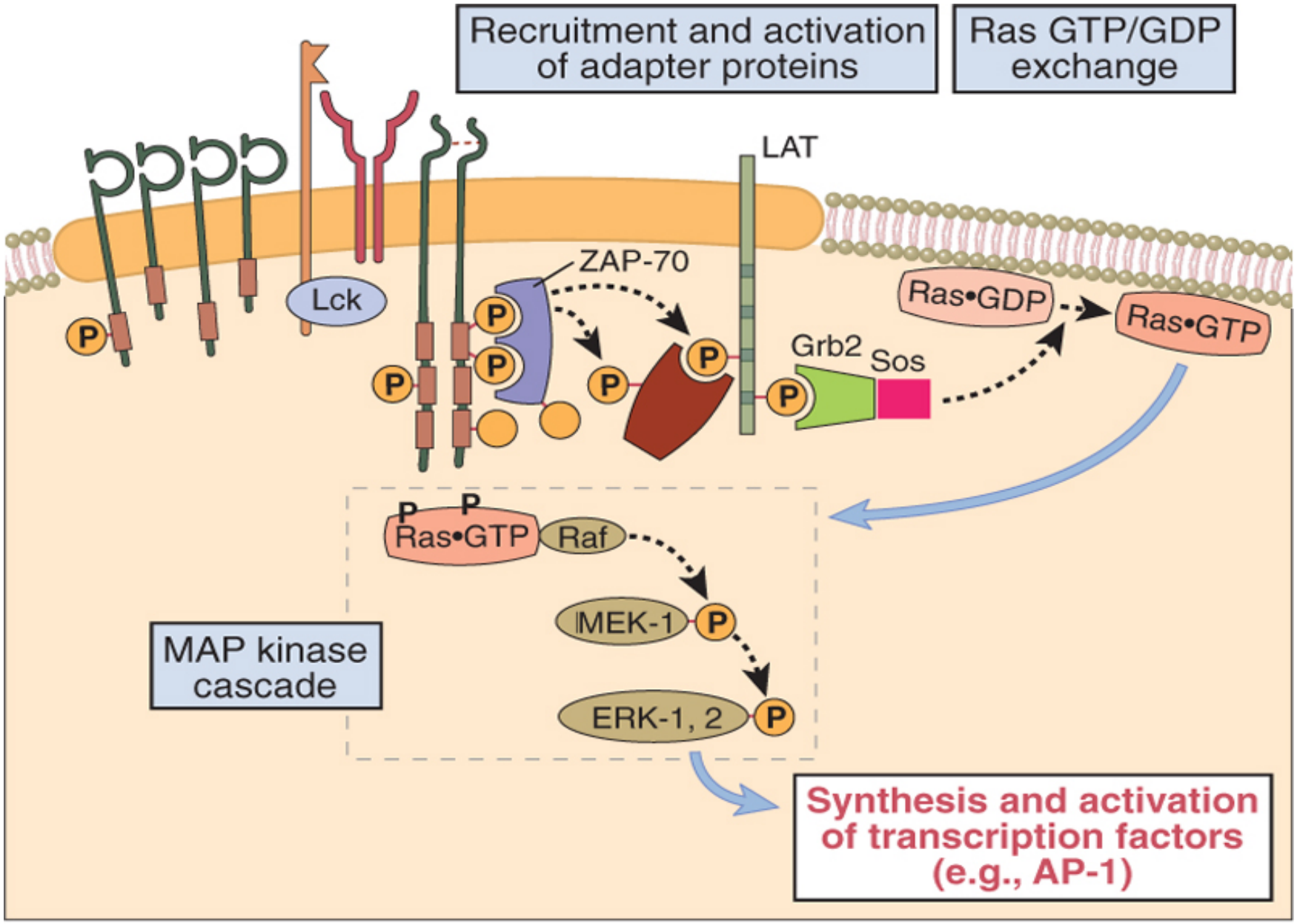
ZAP-70 activates many intracellular pathways
1. PLCγ activation and phospholipid hydrolysis



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

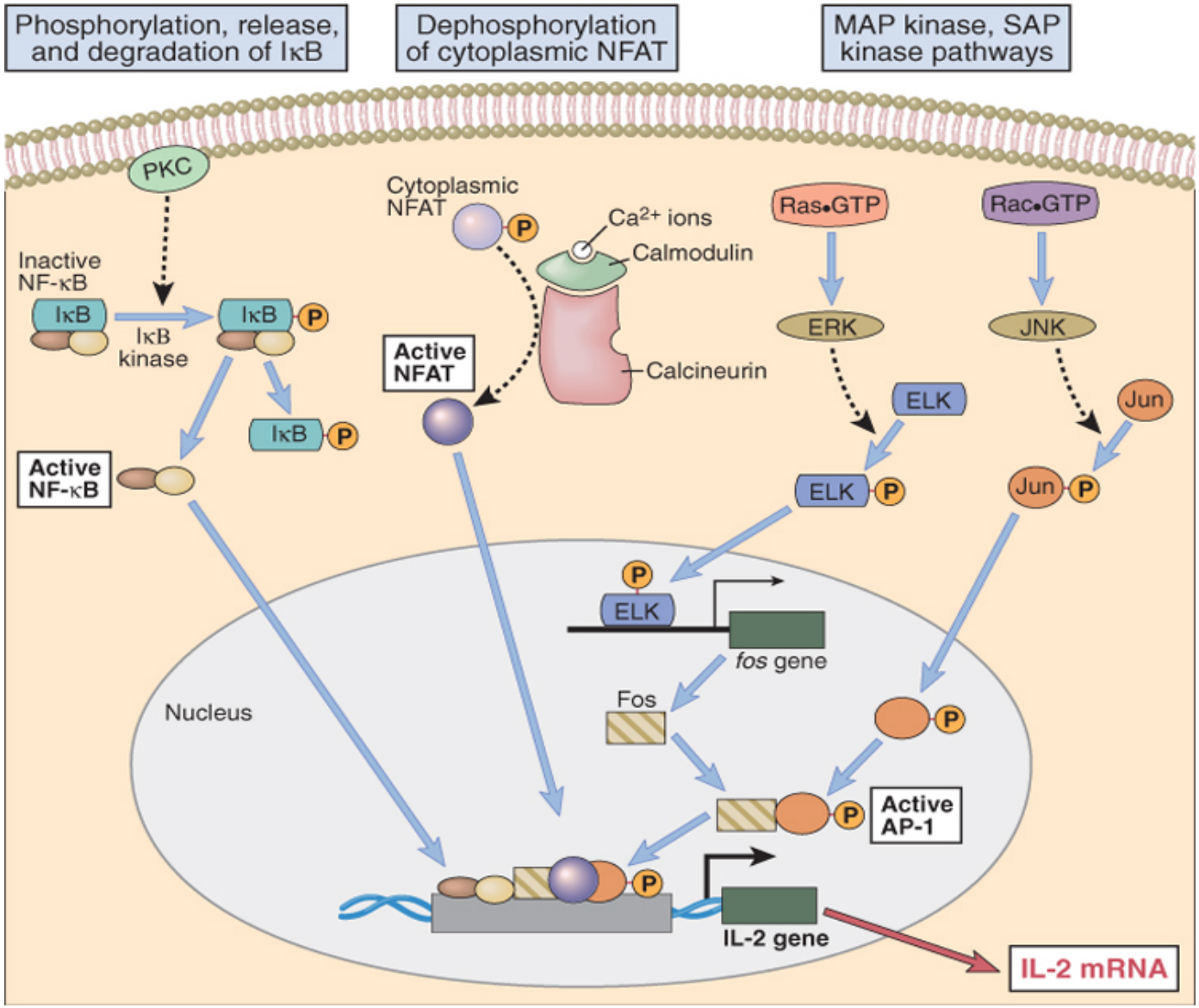


2. Ras/Rac pathways



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TCR signal transduction leads to the activation of multiple transcription factors



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T lymphocytes need 2 signals for activation

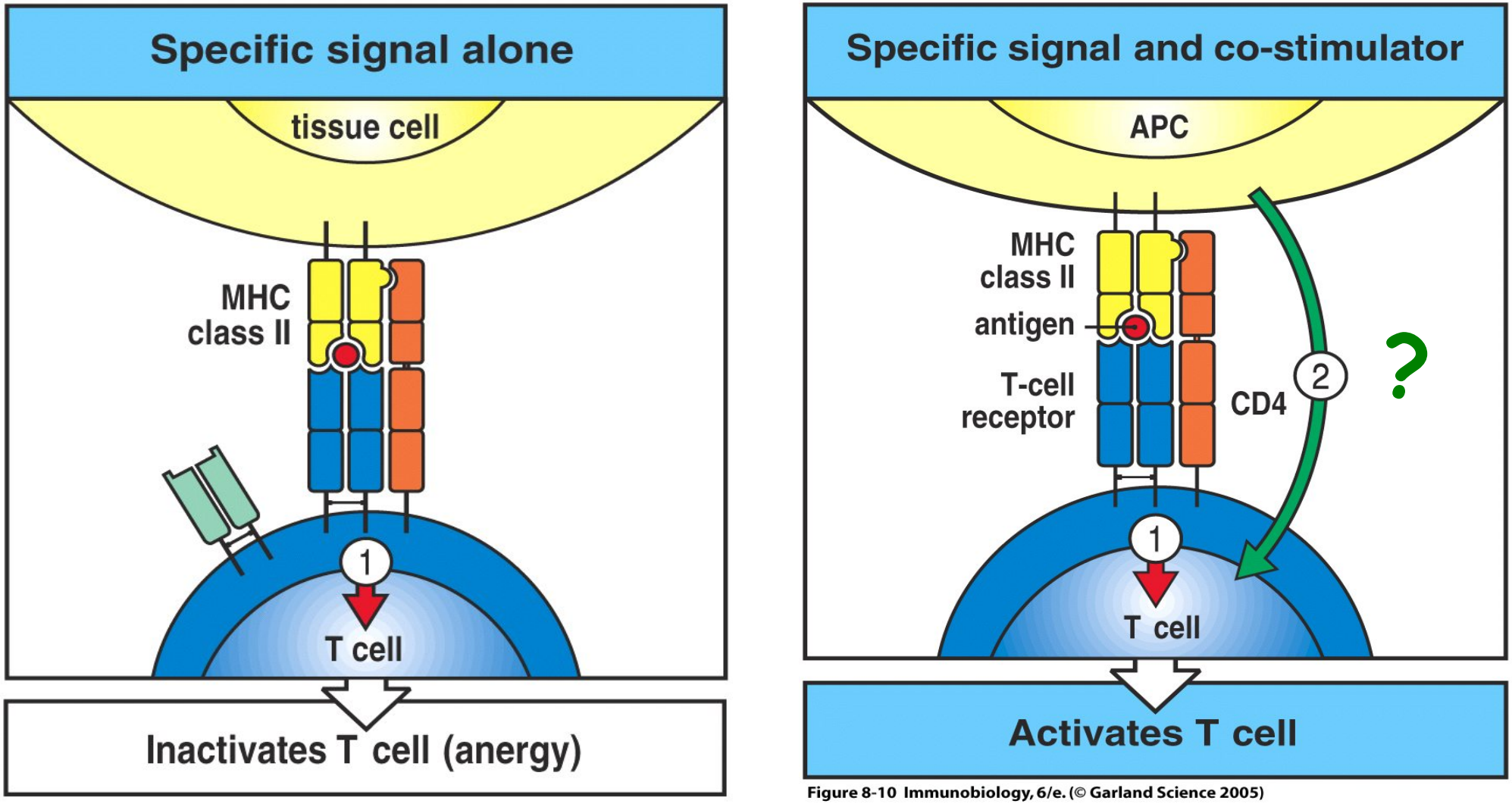


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

What is the second signal?

CD28 costimulatory molecule

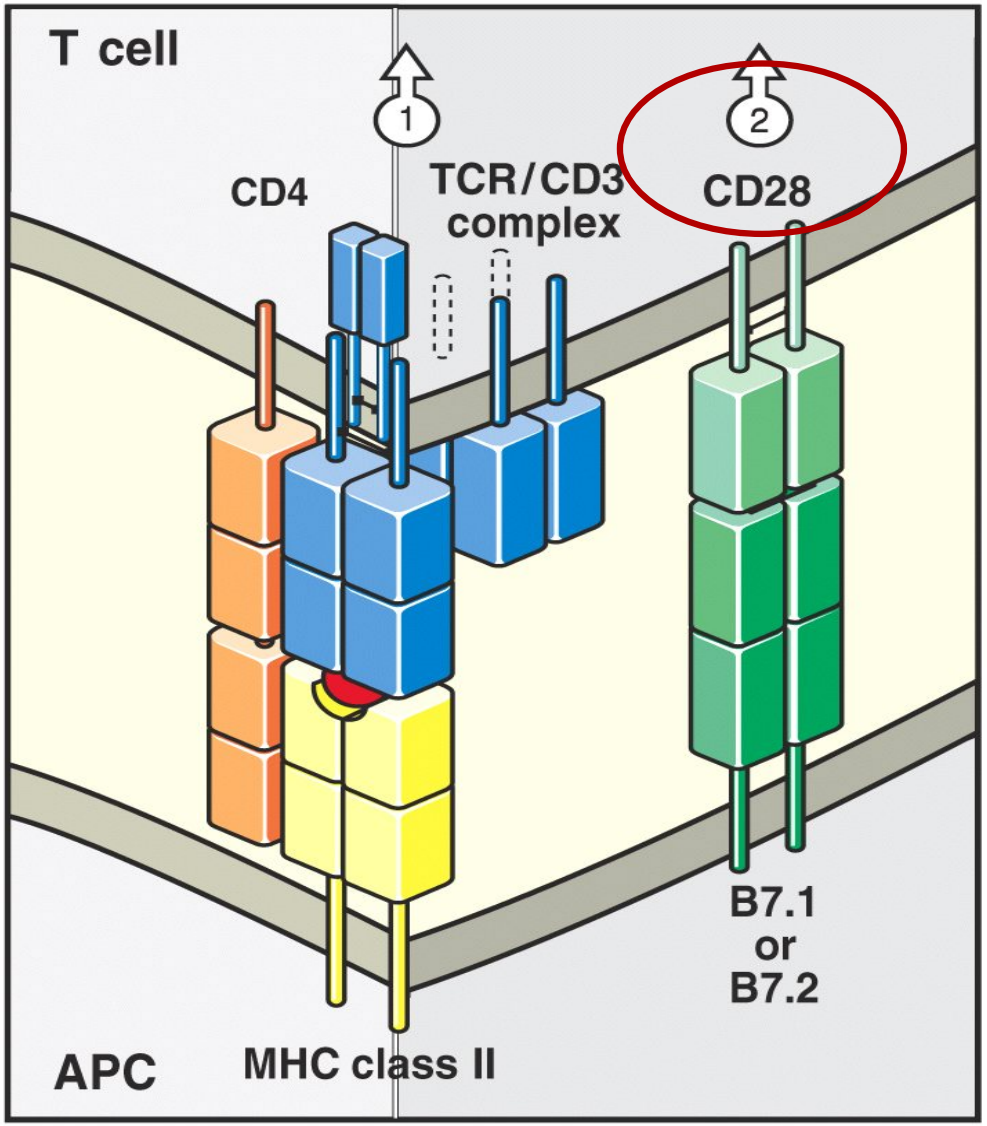
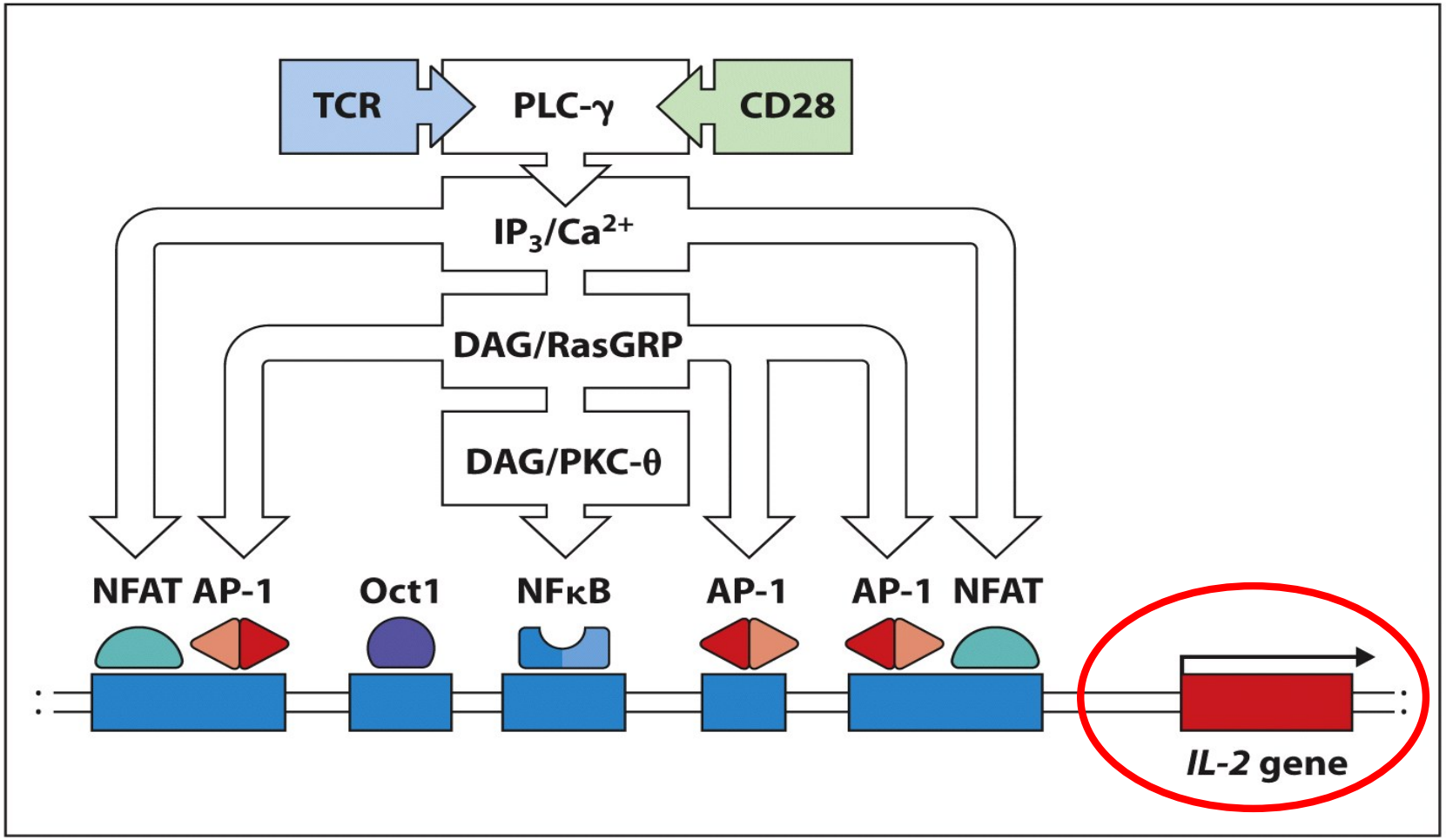


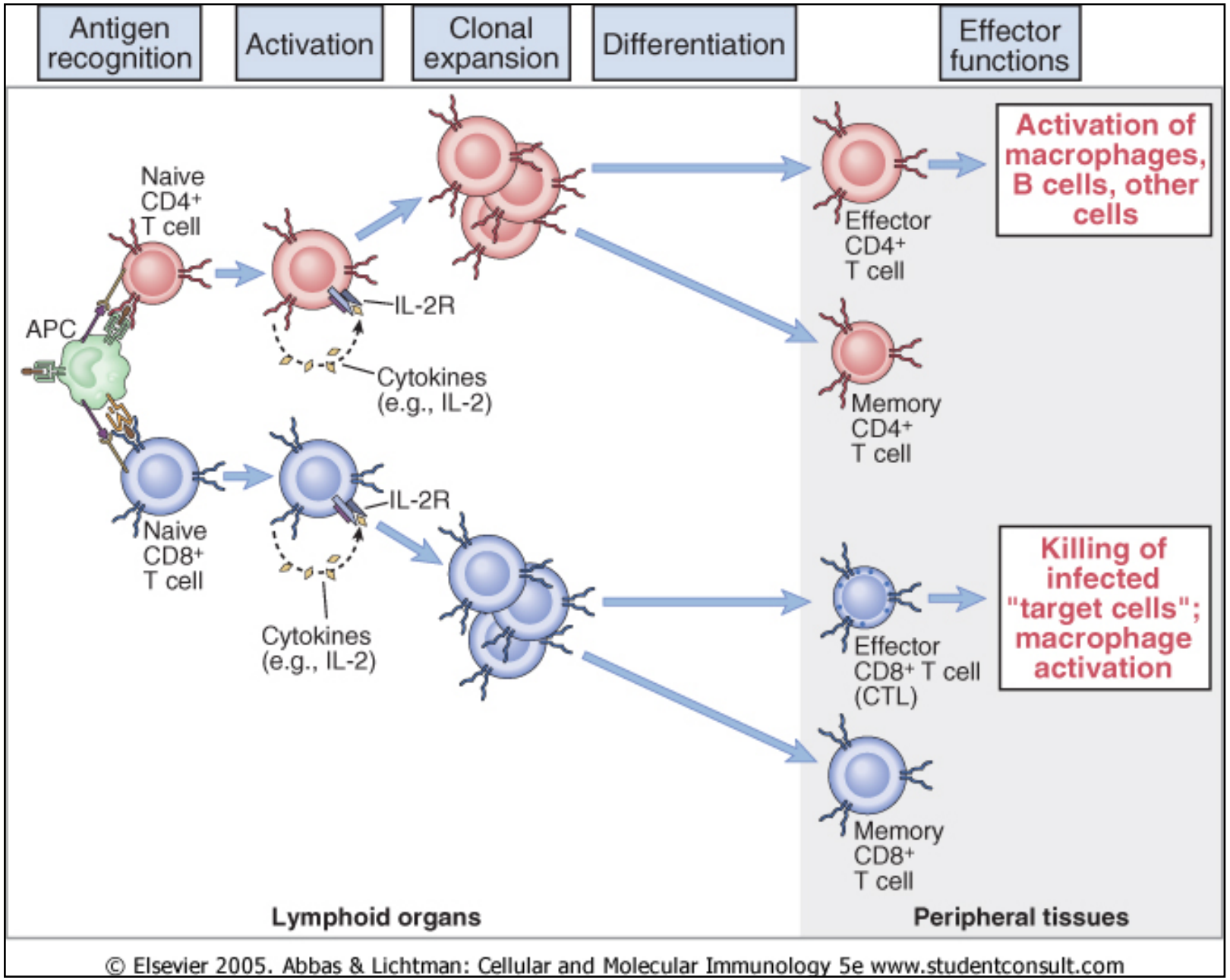
Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

- 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

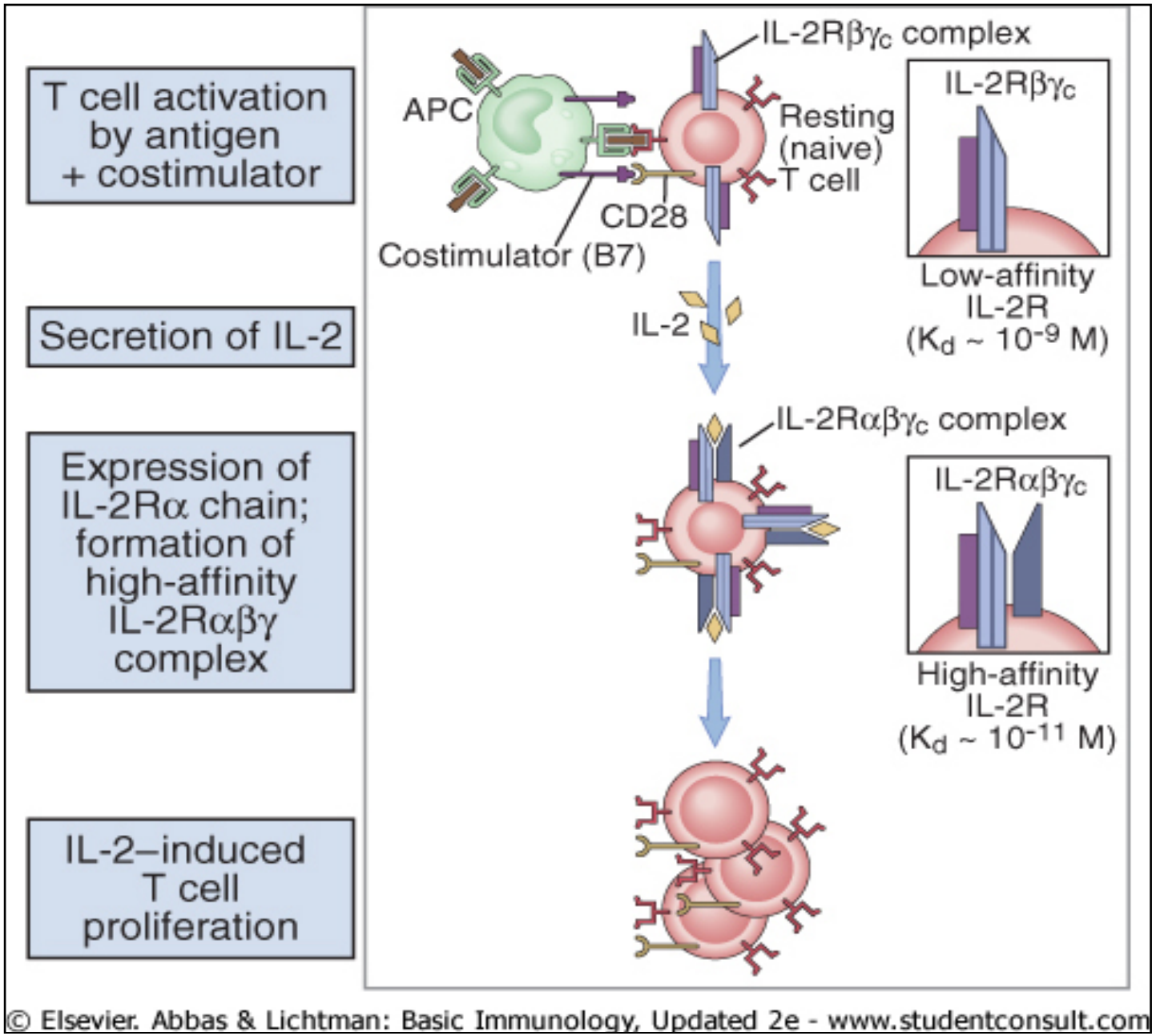
The signal transduced by CD28 amplifies the first signal by increasing the transcription levels of the IL-2 gene



IL-2 induces proliferation of antigen-specific T cells (= clonal expansion)



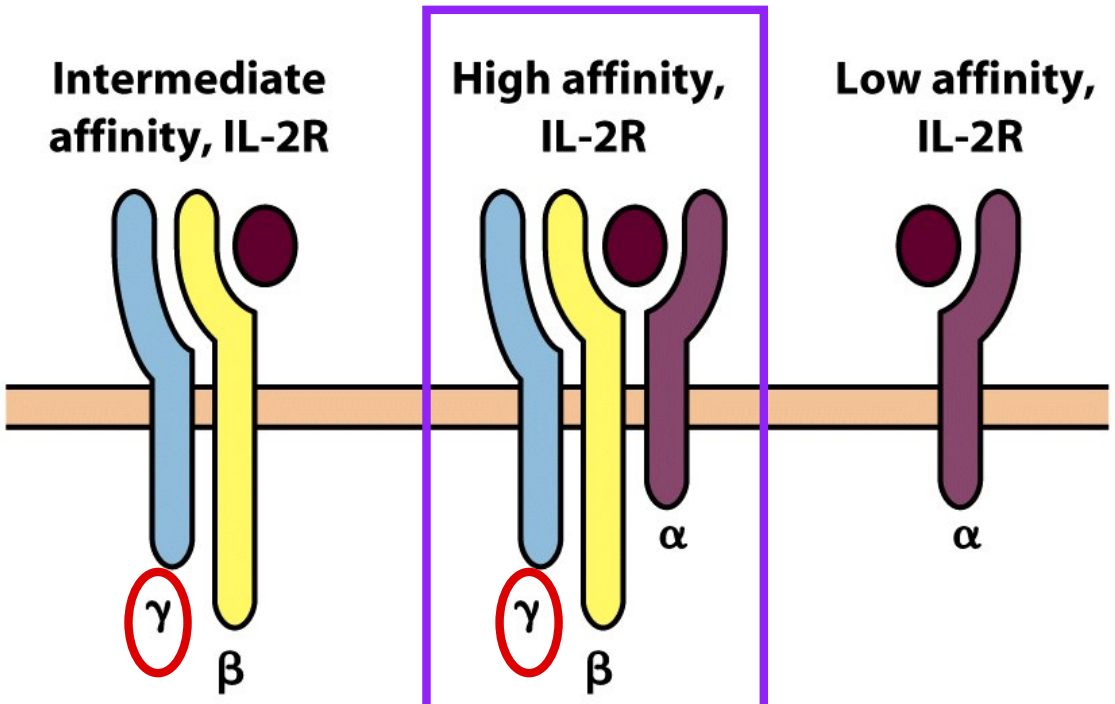
Only antigen specific T cells proliferate!



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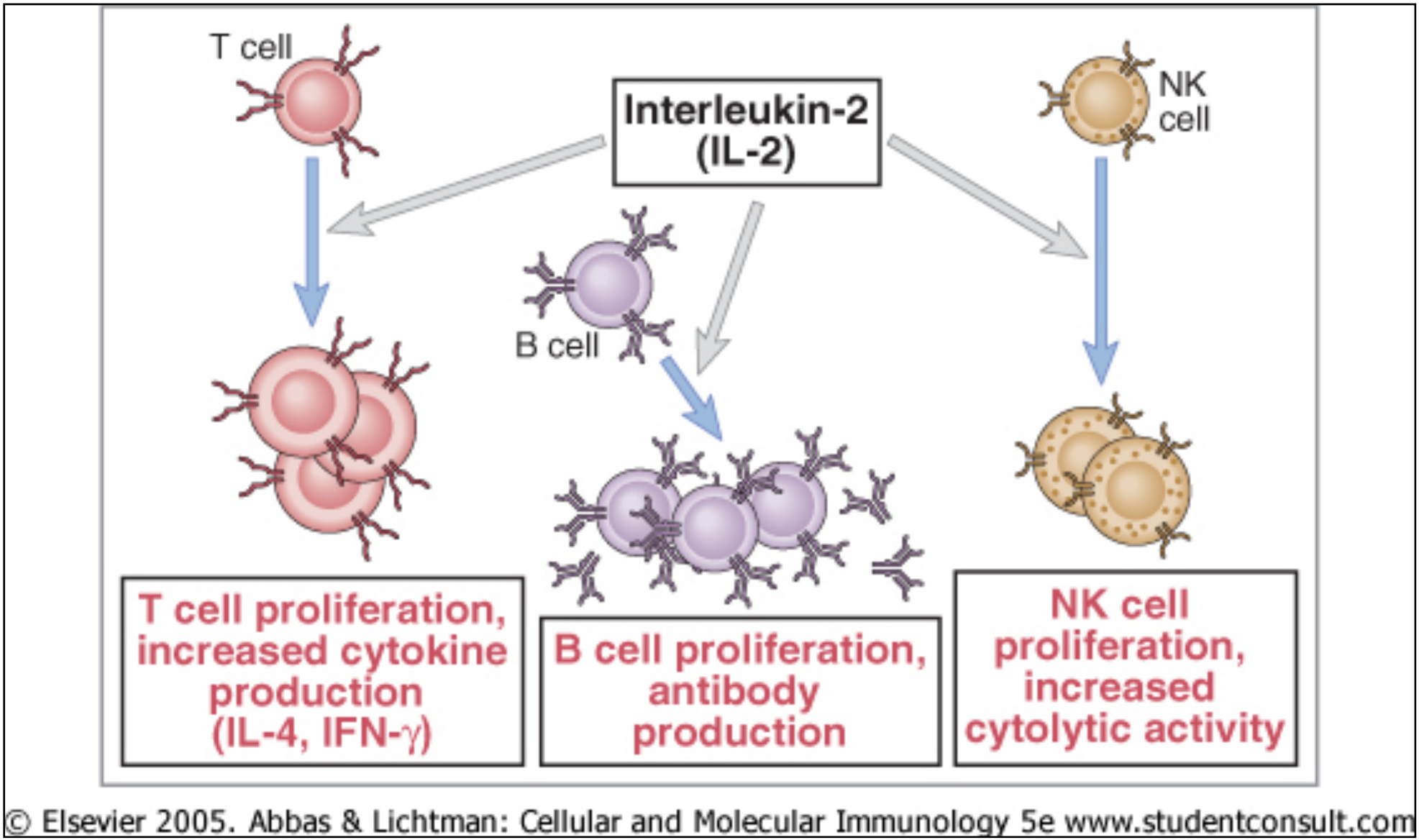
The expression of the high affinity IL-2 receptor (αβγ) is tightly regulated

Molecular composition of the IL-2 receptor



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

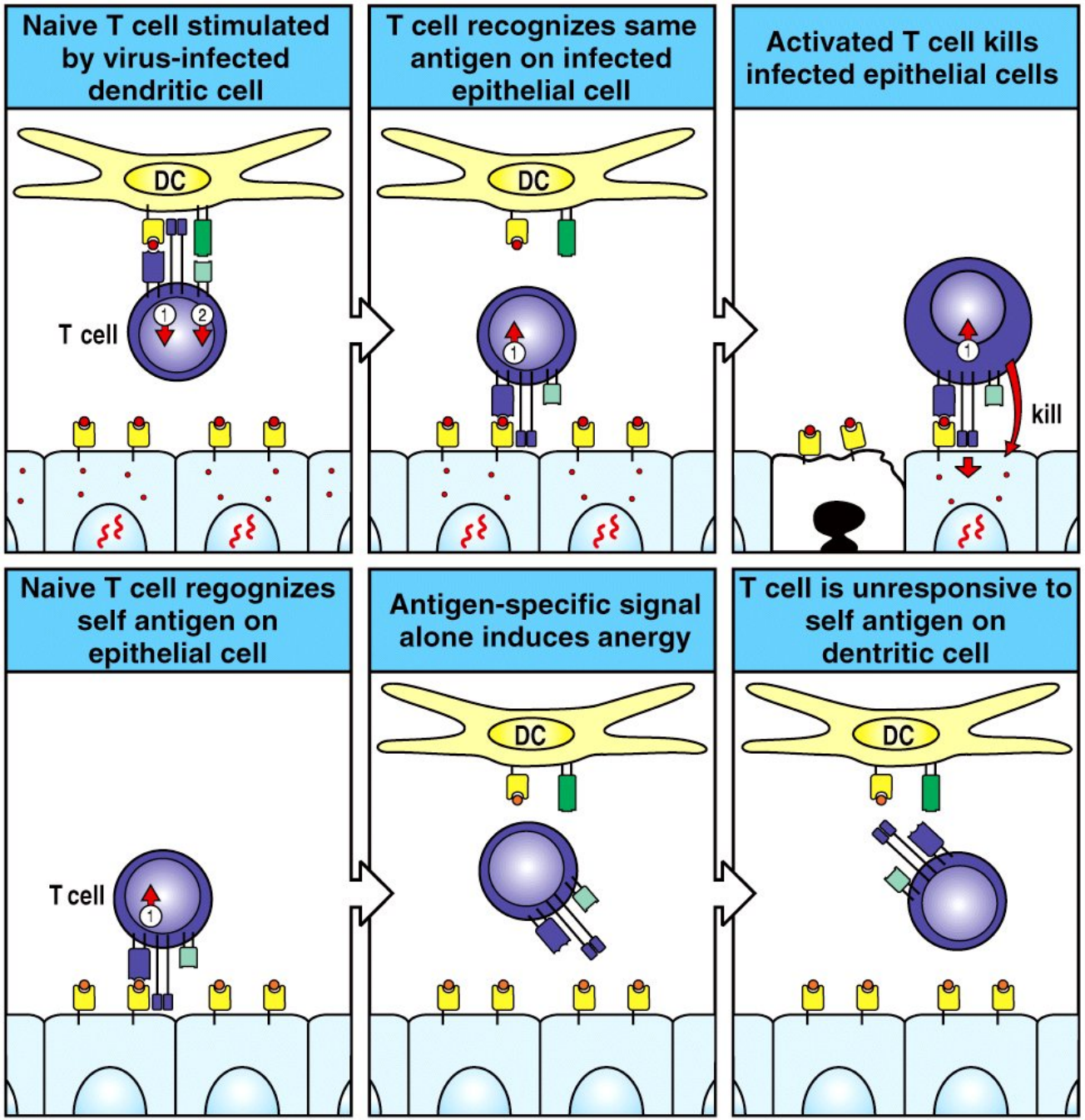


Figure 8-13 Immunobiology, 6/e. (© Garland Science 2005)

Usually, only professional APC can give costimulatory signal

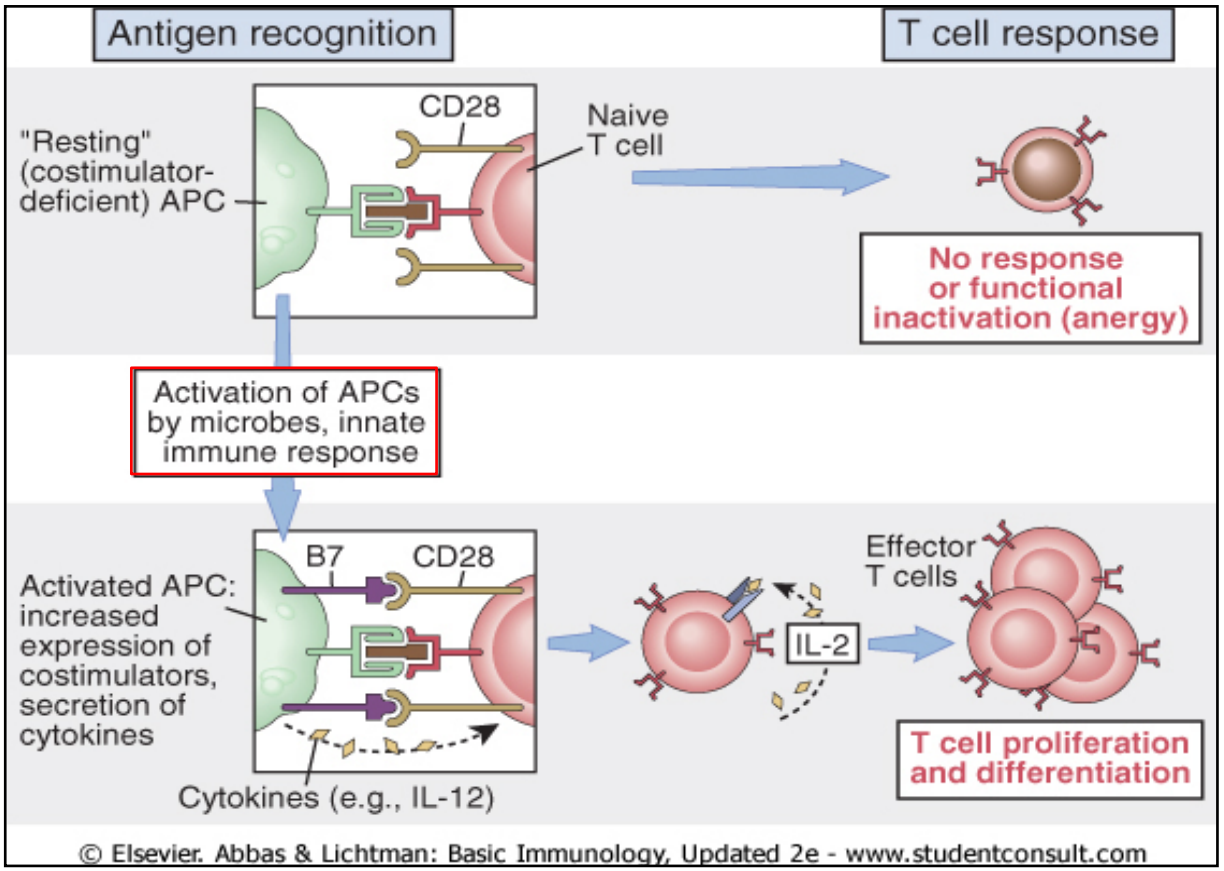
This limits the possibility of self-antigen recognition on tissue cells…

..and represents a mechanism of peripheral TOLERANCE

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

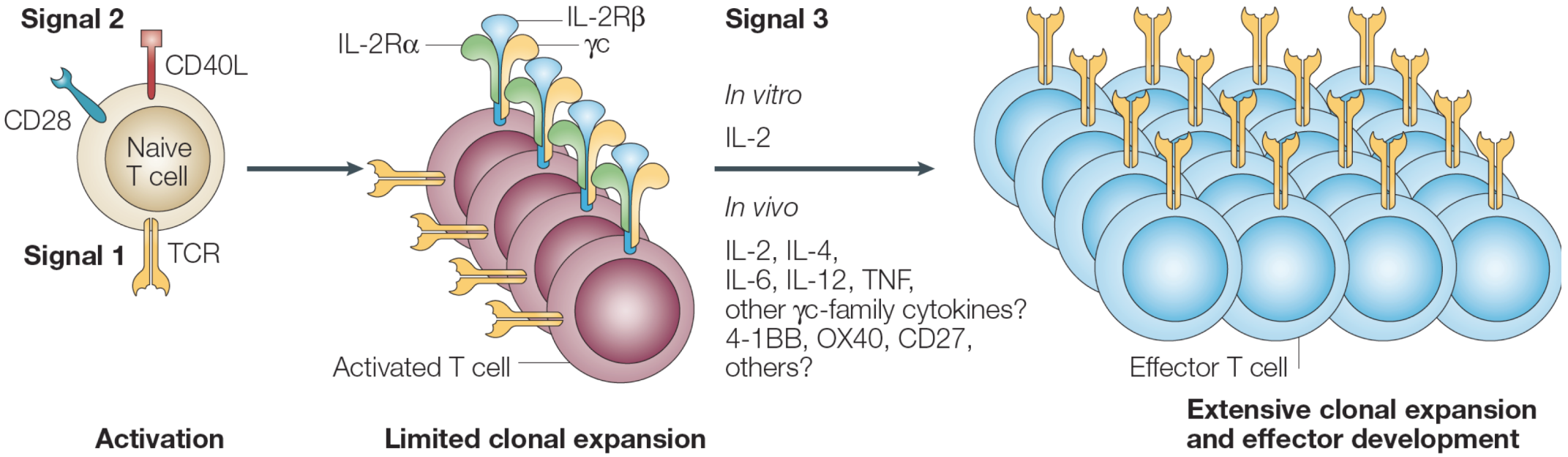
Costimulatory signals are induced by pathogens, inflammation, tissue injury

They carry information about DANGEROUSNESS…..



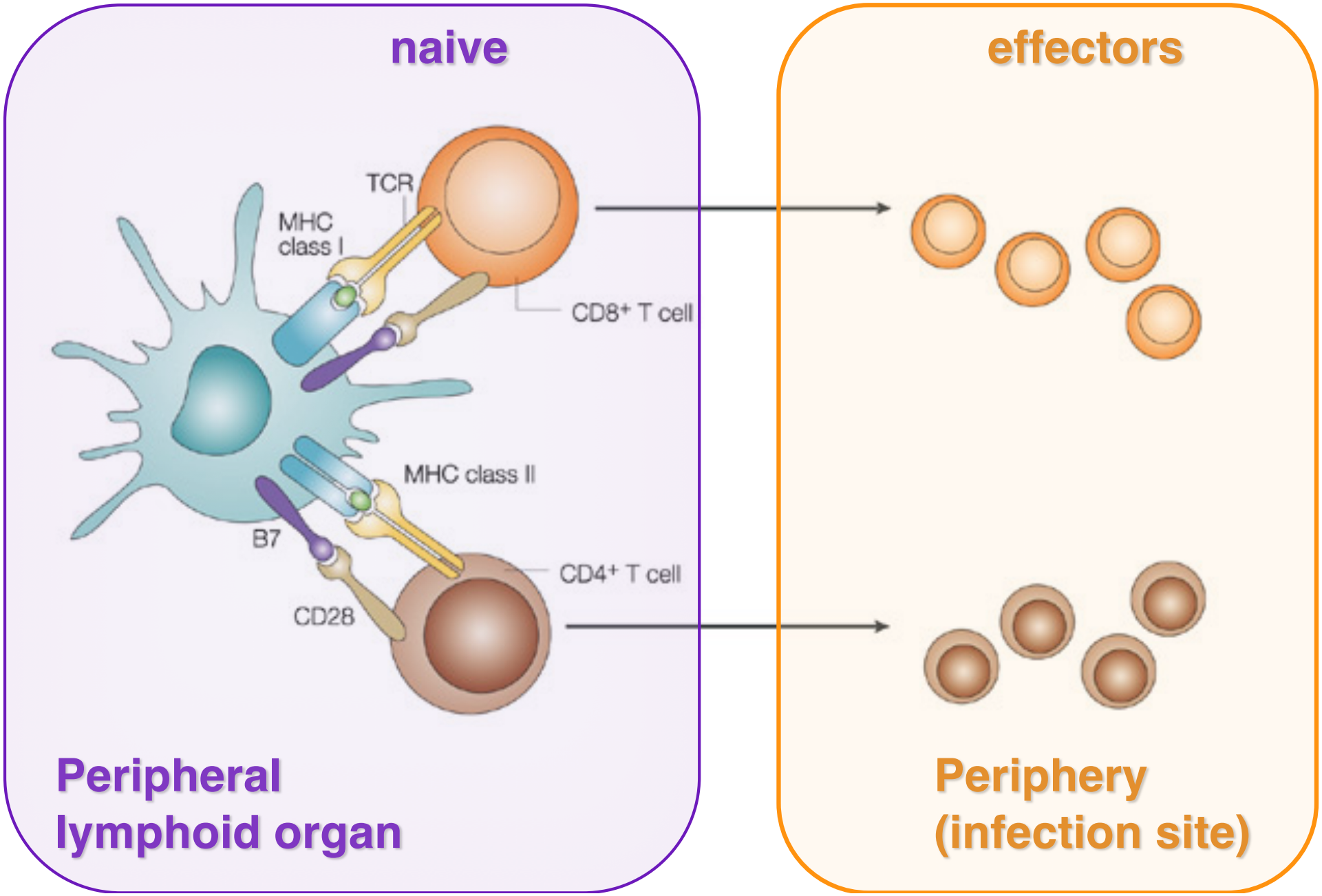
…and focus T cell responses against AGGRESSIVE NON SELF

Generation of effector T lymphocytes

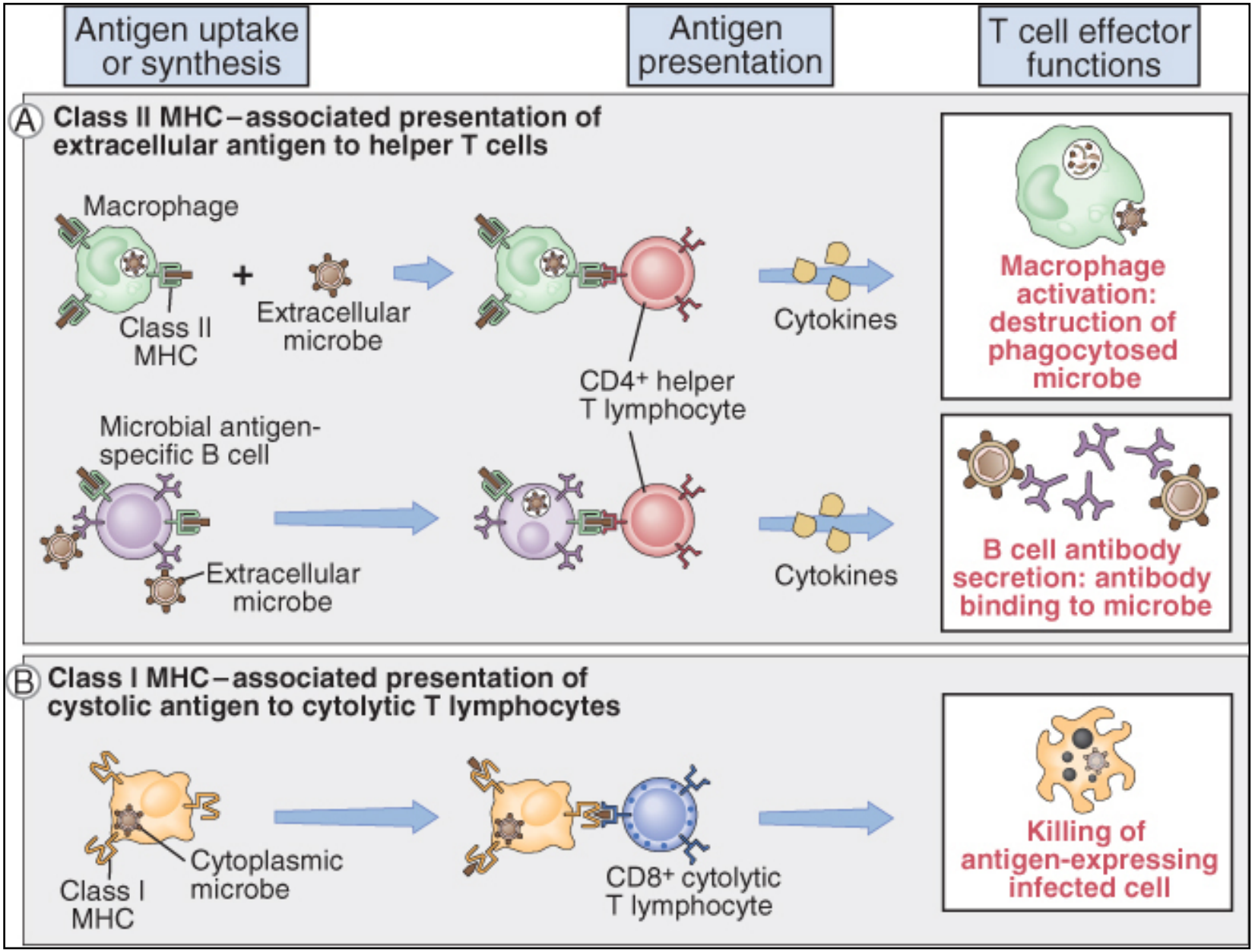


Nature Reviews Immunology, 2004

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



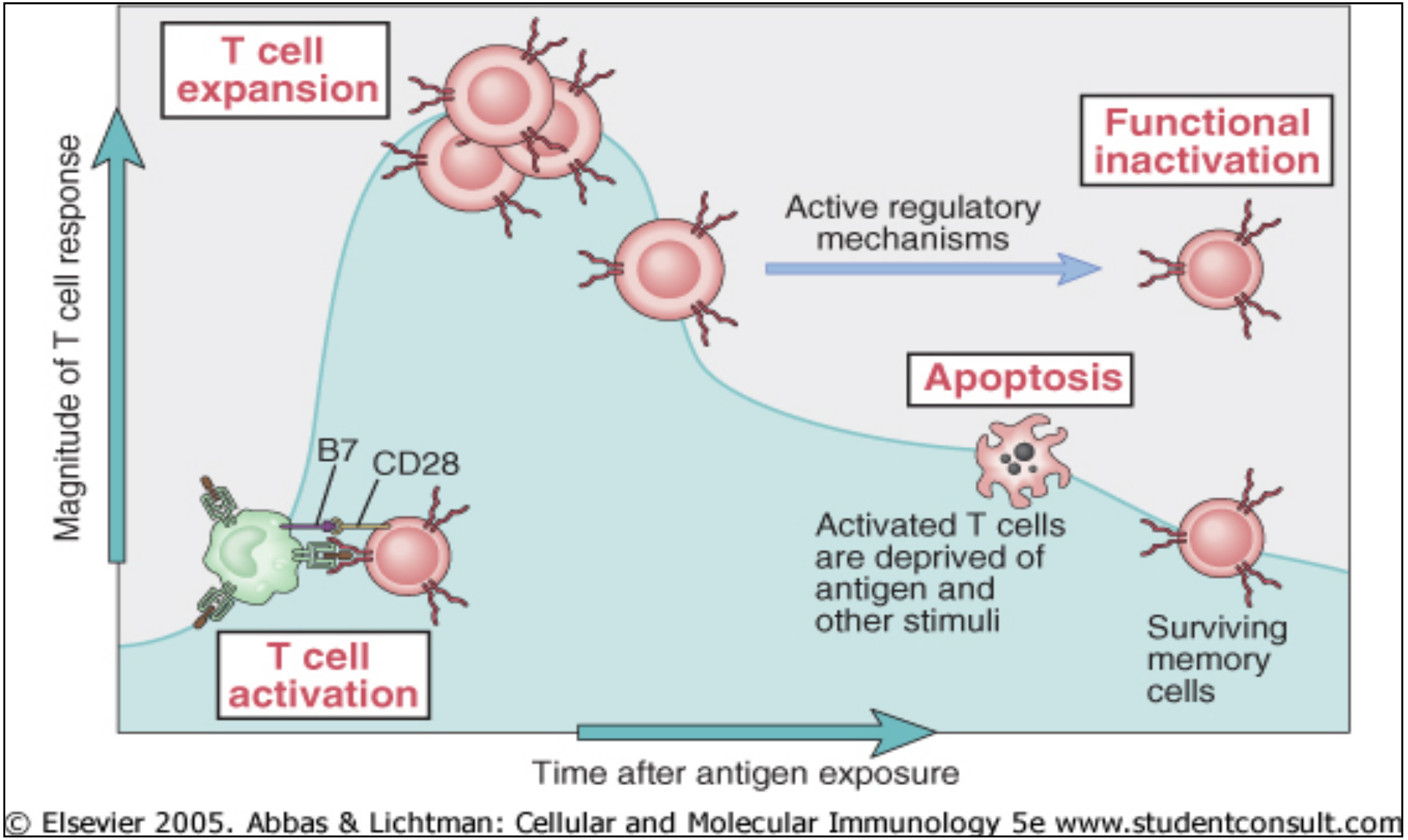
Effector T lymphocytes recognize the antigen again: eradication of the infection



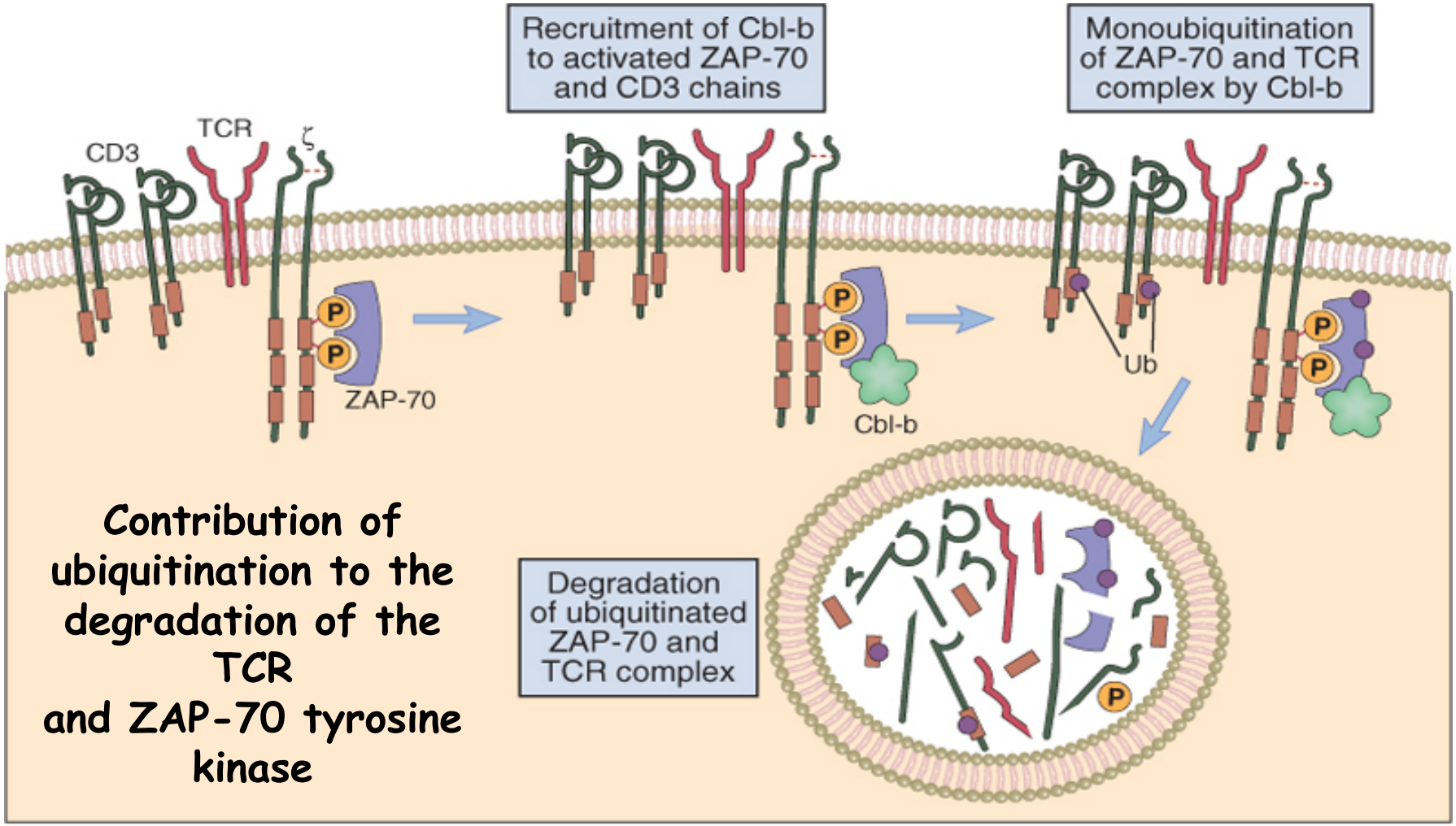
Naive and effector lymphocytes differ phenotypically and functionally

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

NEGATIVE SIGNALS INACTIVATE OR KILL EFFECTOR T LYMPHOCYTES

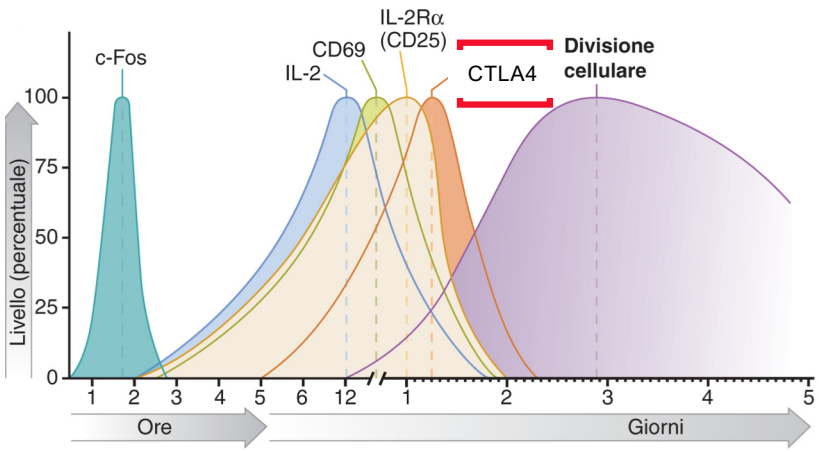


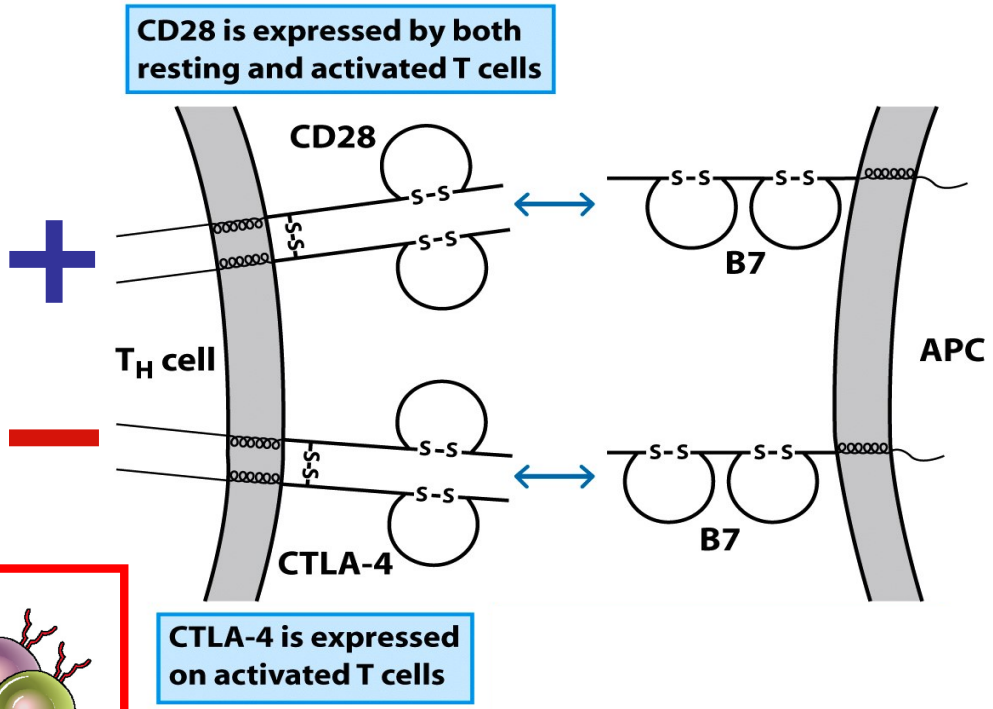
Switching off T-specific signaling: The role of Cbl ubiquitin ligase and ubiquitination

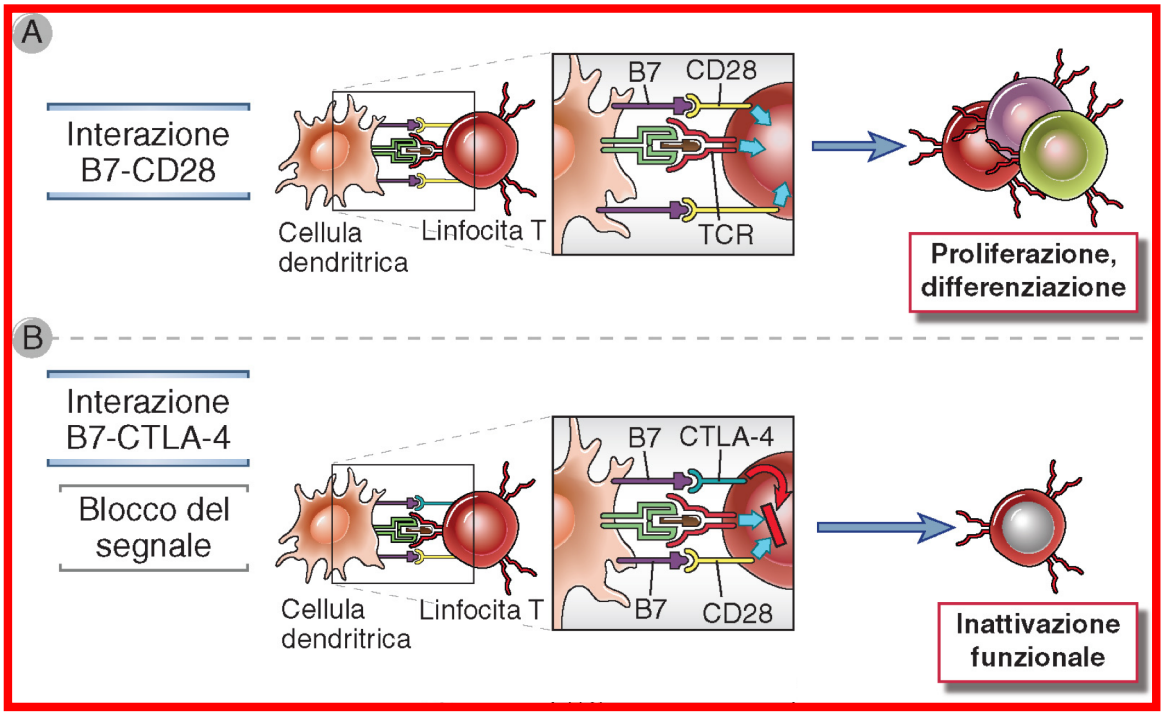


Contribution of ubiquitination to the degradation of the TCR and ZAP-70 tyrosine kinase

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

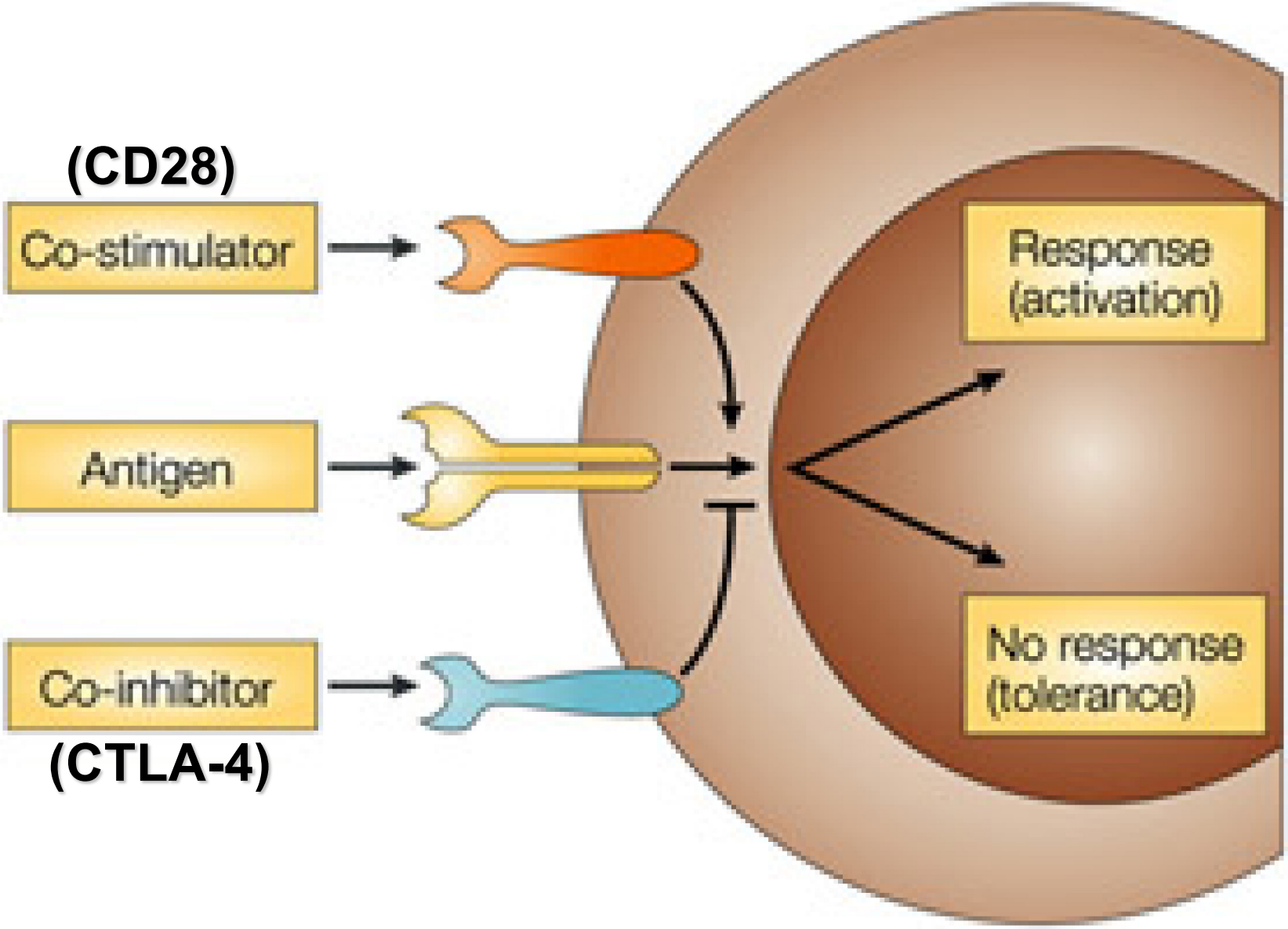






- **CTLA4** binds the same ligands as CD28, but with a 20-fold higher affinity.
- It transduces inhibitory signals responsible for the functional inactivation of T lymphocytes.

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



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

