



T Cell-Mediated Immunity: Activation of T Lymphocytes

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After today's lecture, you should know:

- How are T cells stimulated?
- How do few naïve T cells become many effector T cells?
- How do T cells communicate with other cells?

Why should we care?

- T cells are everywhere in the body
- T cells can see inside other cells
- T cells can see the future

Of 14 Nobel Prizes given to immunology research, 5 were related to T cells
(tolerance, histocompatibility, cellular immunity, antigen presentation, checkpoint inhibition)

Why should we care?

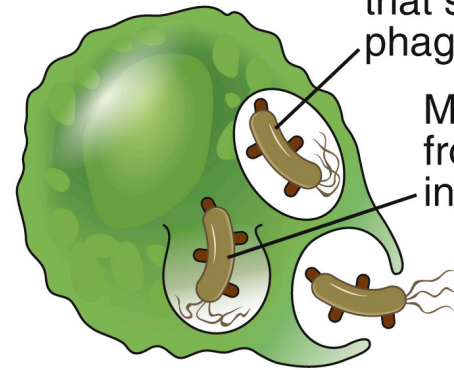
- People born without functional T cells (“T-cell immunodeficiency, congenital alopecia, and nail dystrophy”, FOXP1 mutations) develop repeated and persistent infections and die during infancy without treatment
- People that lose their CD4⁺ T cells (“Acquired immunodeficiency syndrome” – AIDS) develop persistent infections and cancers and die 8-10 years following infection without treatment
- T cells can be modified to treat tumors using chimeric antigen receptors (CARs). CAR T cell therapies can lead to up in 93% remission in patients that did not respond to other treatments. But CAR T cells also have fatal side effects more often (5% vs. 0.3-1%)

What do T cells see?

Intracellular microbes

Examples

A Phagocyte



Phagocytosed microbes that survive within phagolysosomes

Microbes that escape from phagolysosomes into cytoplasm

Intracellular bacteria:

Mycobacteria

Listeria monocytogenes

Legionella pneumophila

Fungi:

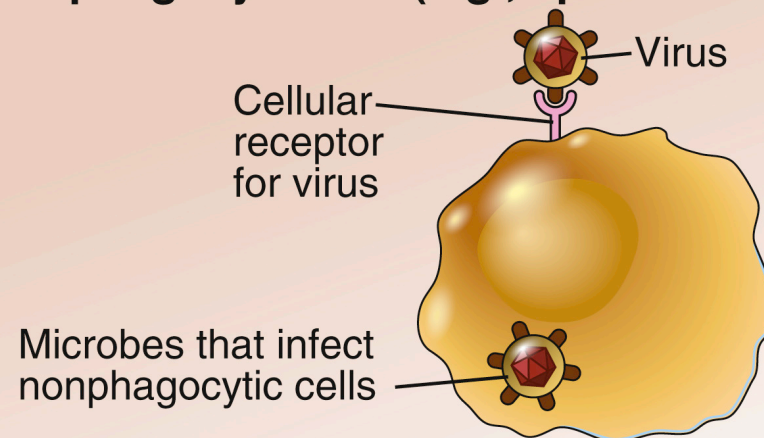
Cryptococcus neoformans

Protozoa:

Leishmania

Trypanosoma cruzi

B Nonphagocytic cell (e.g., epithelial cell)



Virus

Cellular receptor for virus

Microbes that infect nonphagocytic cells

Viruses:

All

Rickettsiae:

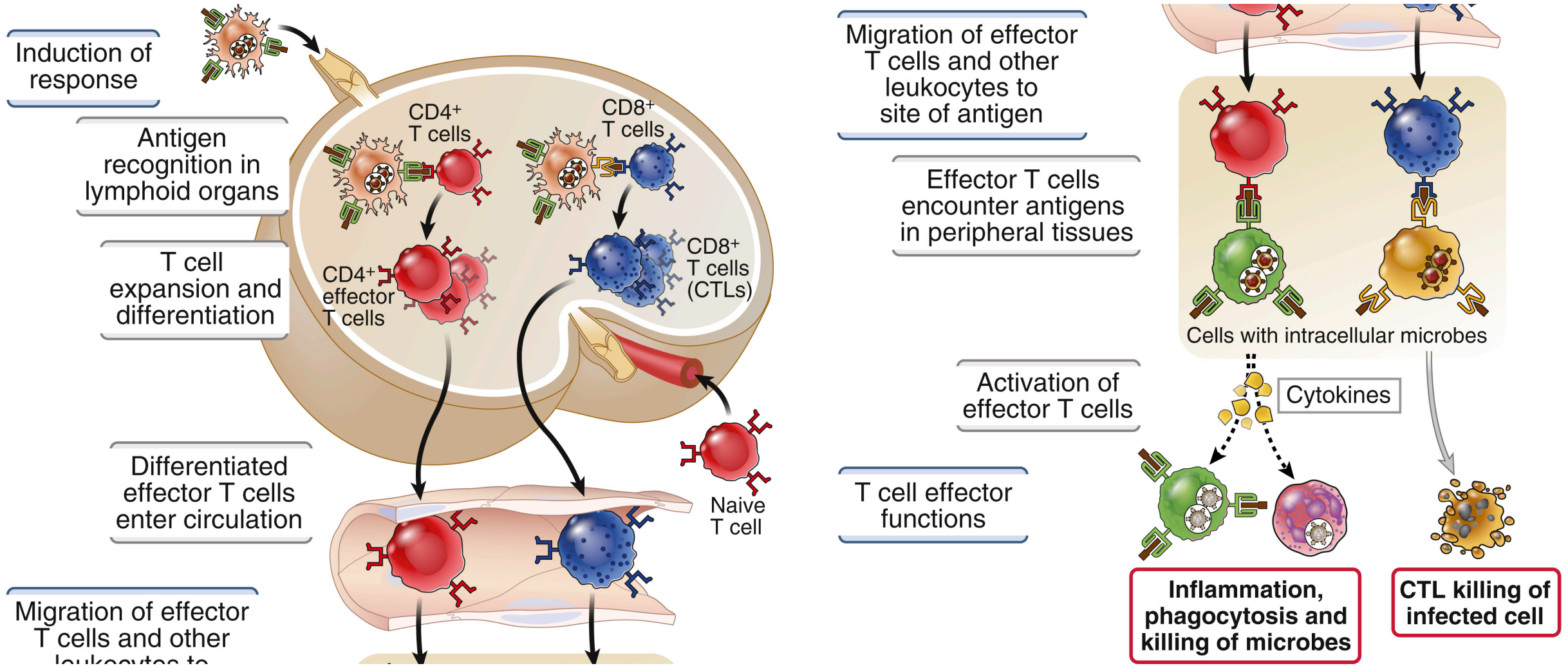
All

Protozoa:

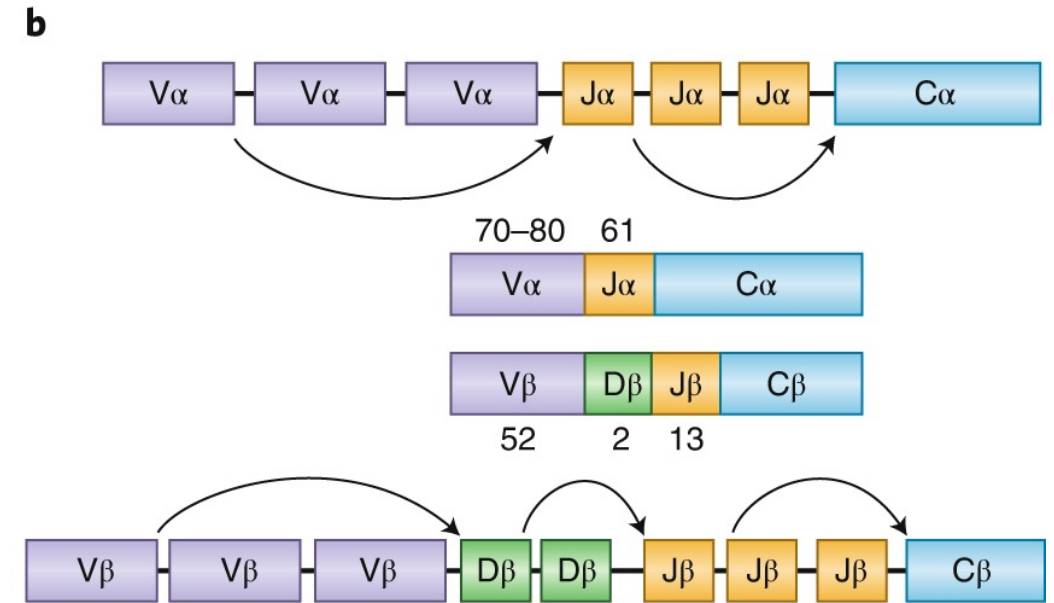
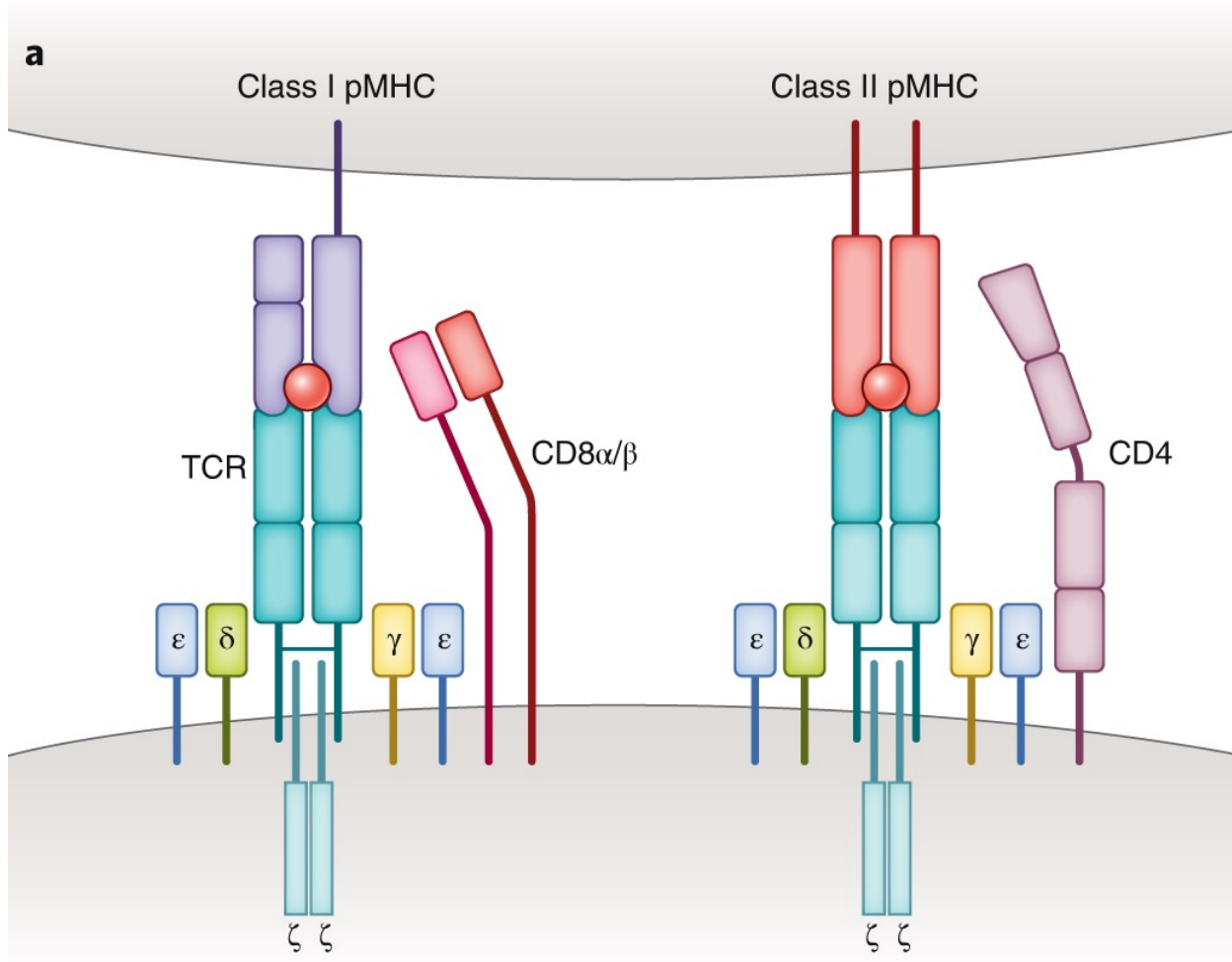
Plasmodium falciparum

Cryptosporidium parvum

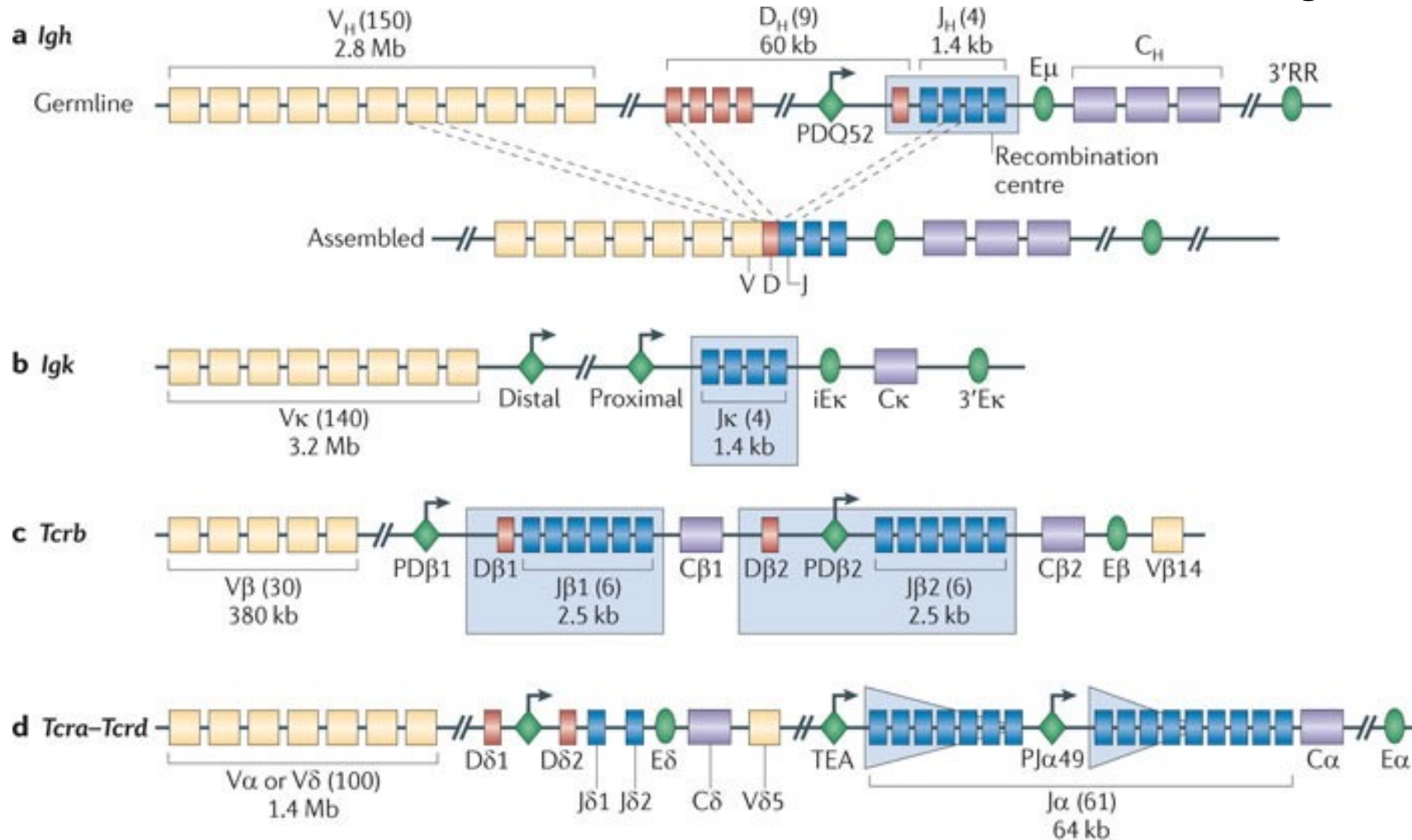
Naïve T cells see antigens in lymphoid organs, become activated, and execute their function in tissues upon seeing the same antigens



How do T cells see?

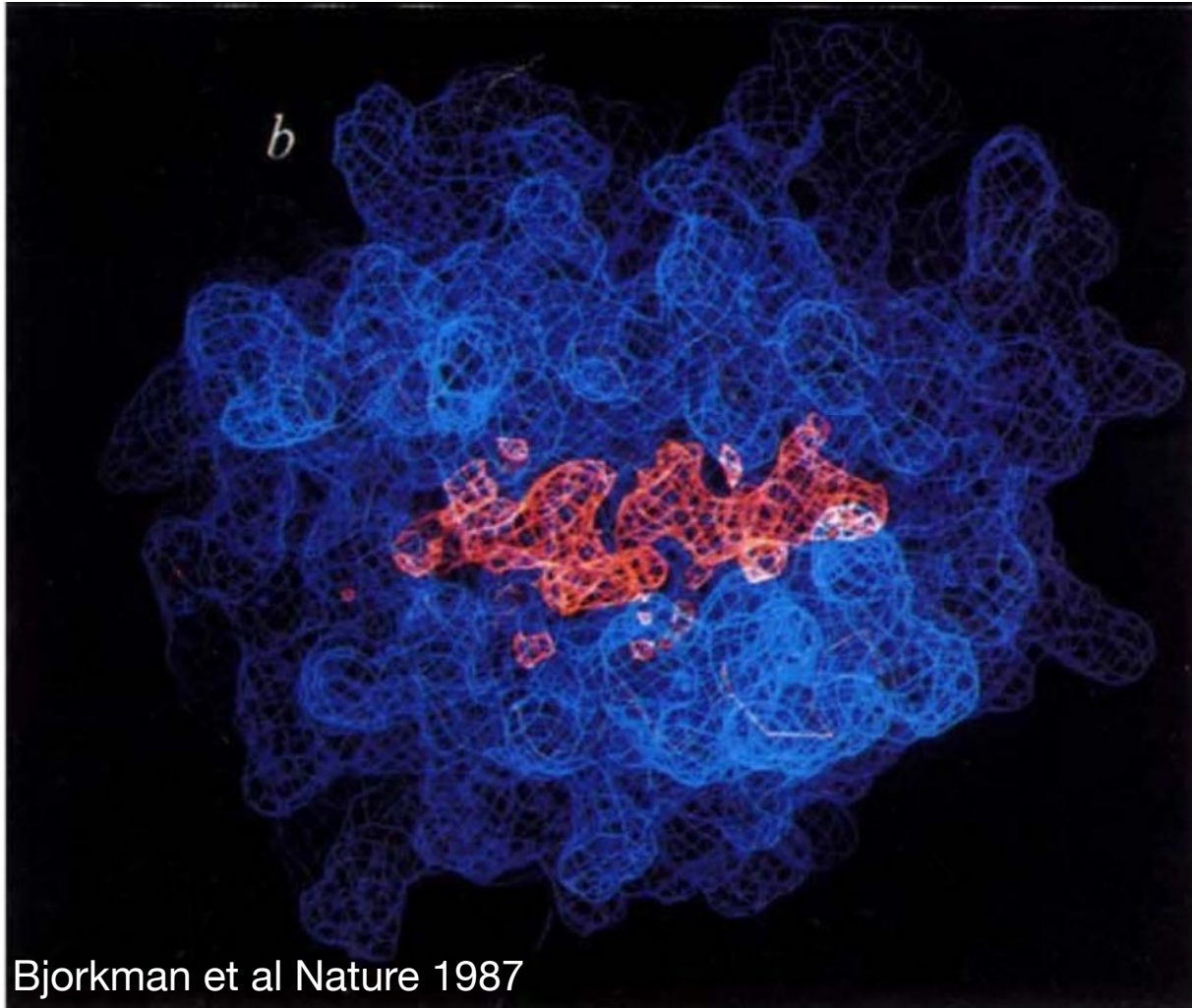


GOD – Generator of Diversity

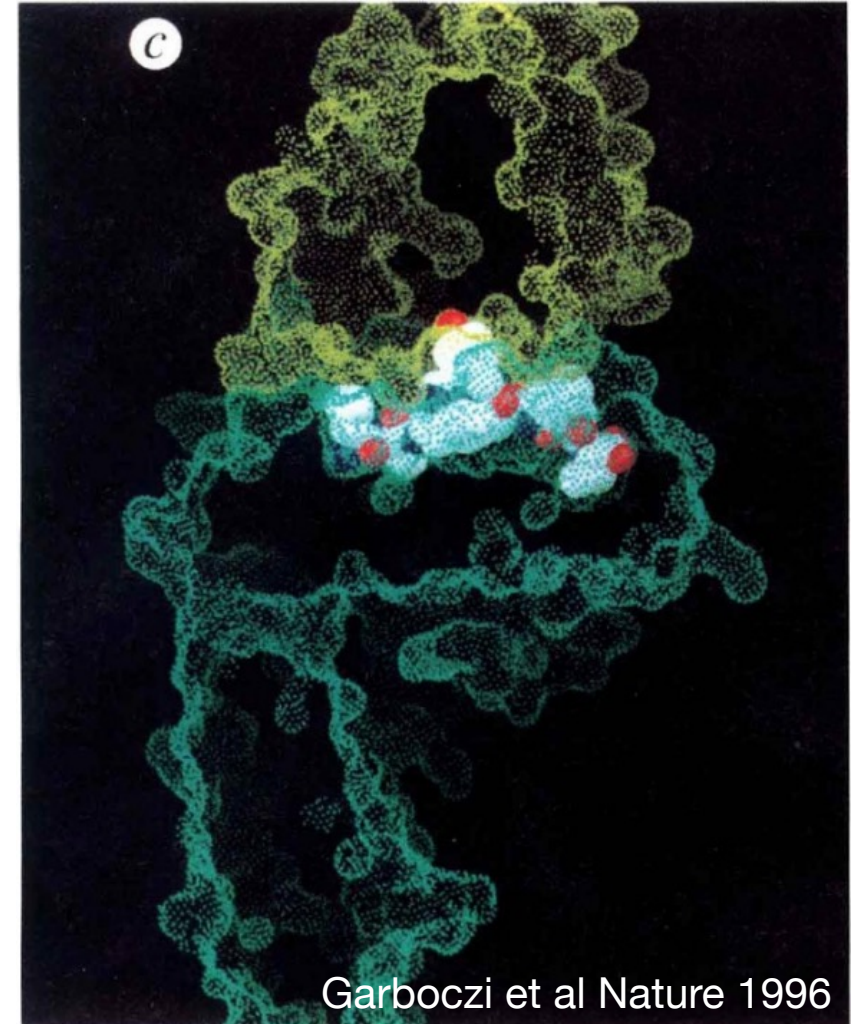


The immune synapse

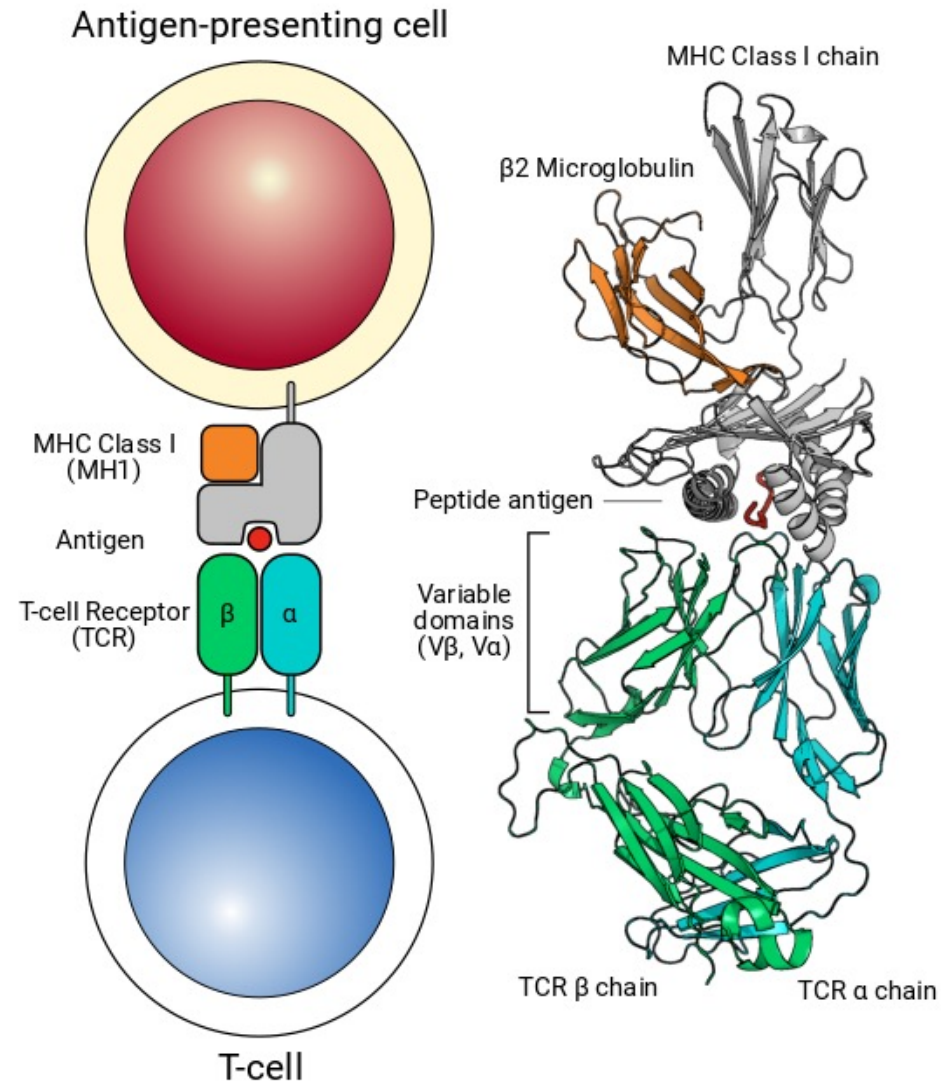
HLA-A2 peptide binding groove



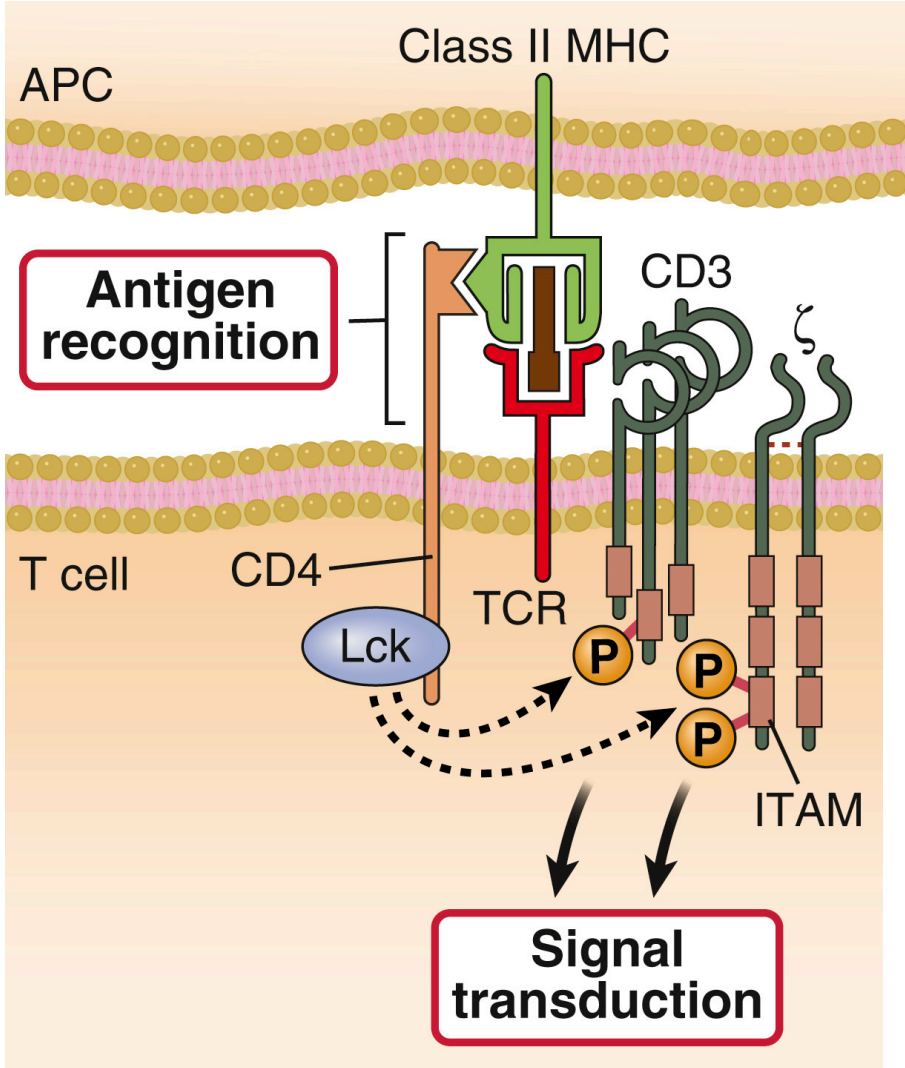
TCR-peptide-HLA-A2 complex



The immune synapse



T cell signal 1: TCR activation

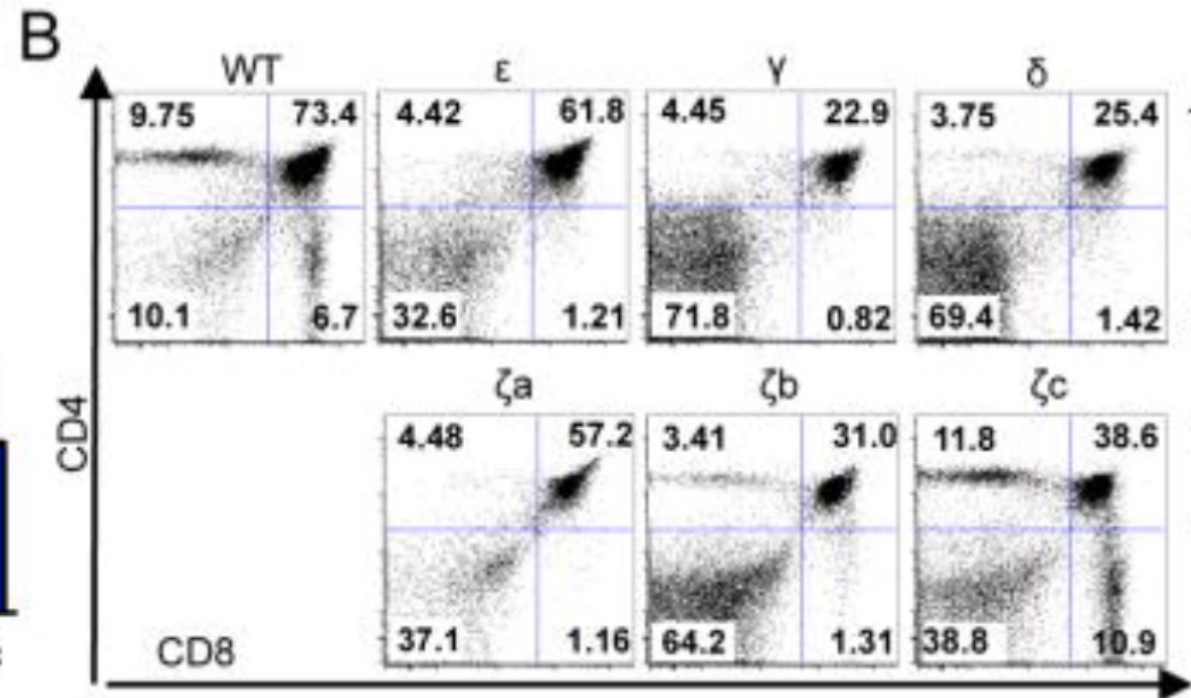
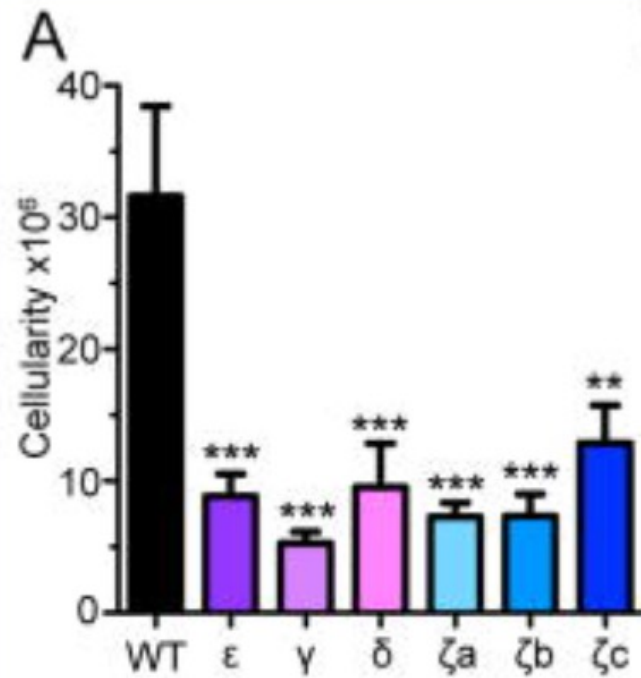
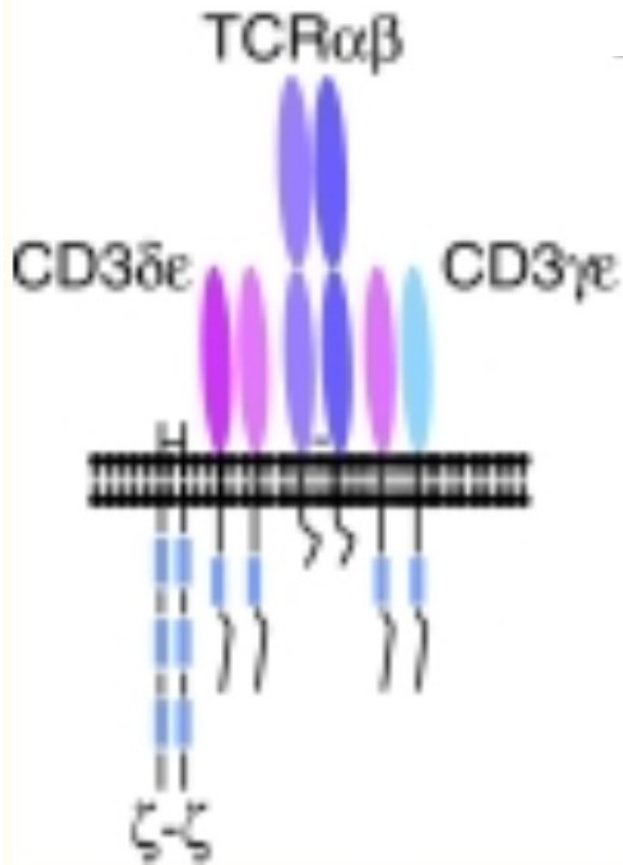


APC
antigen-presenting cell

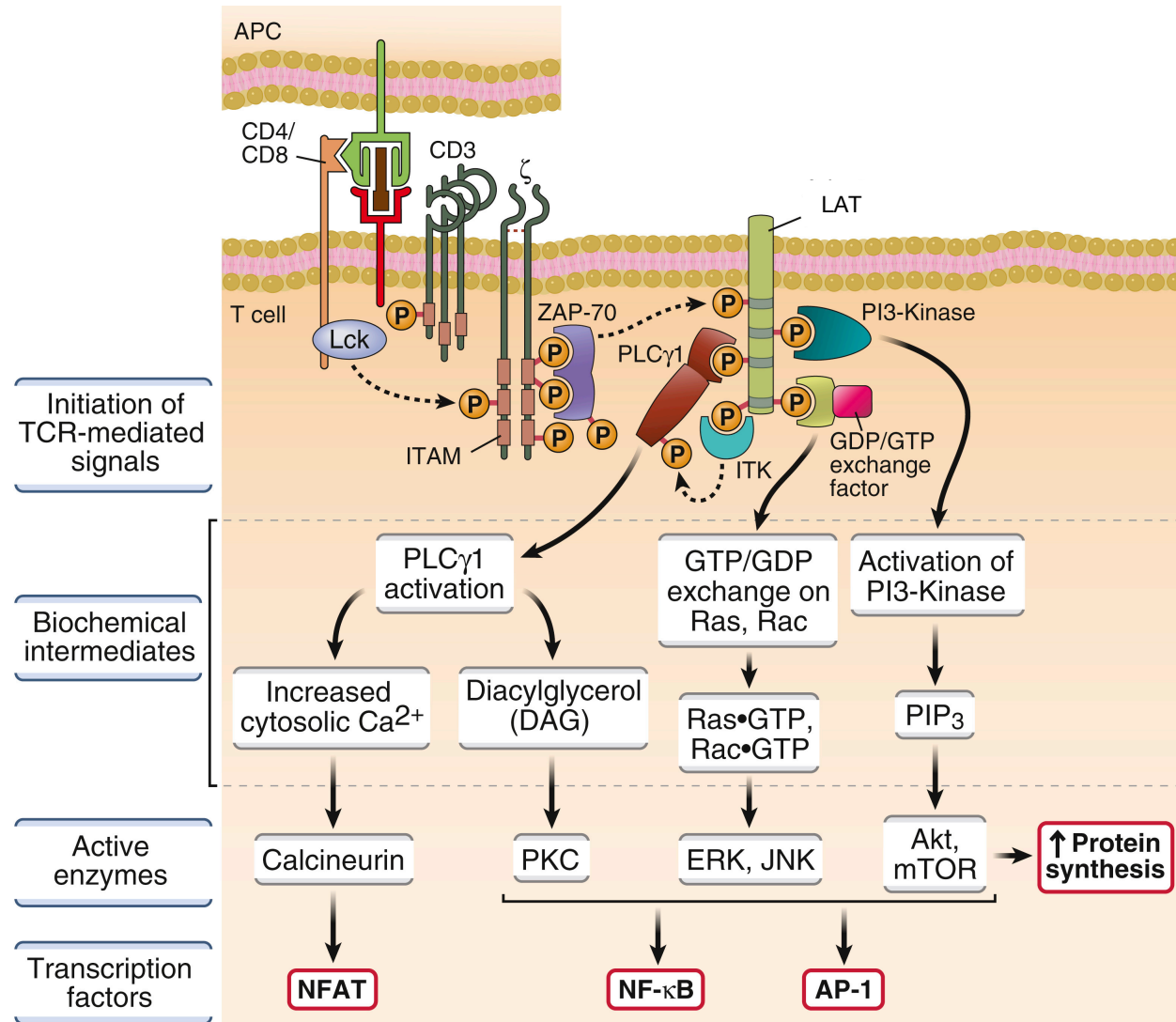
Lck
lymphocyte-specific
protein tyrosine kinase

ITAM
immunoreceptor tyrosine-based
activation motif

CD3 ITAM diversity is required for T cell signaling and development



T cell signal 1: signal transduction



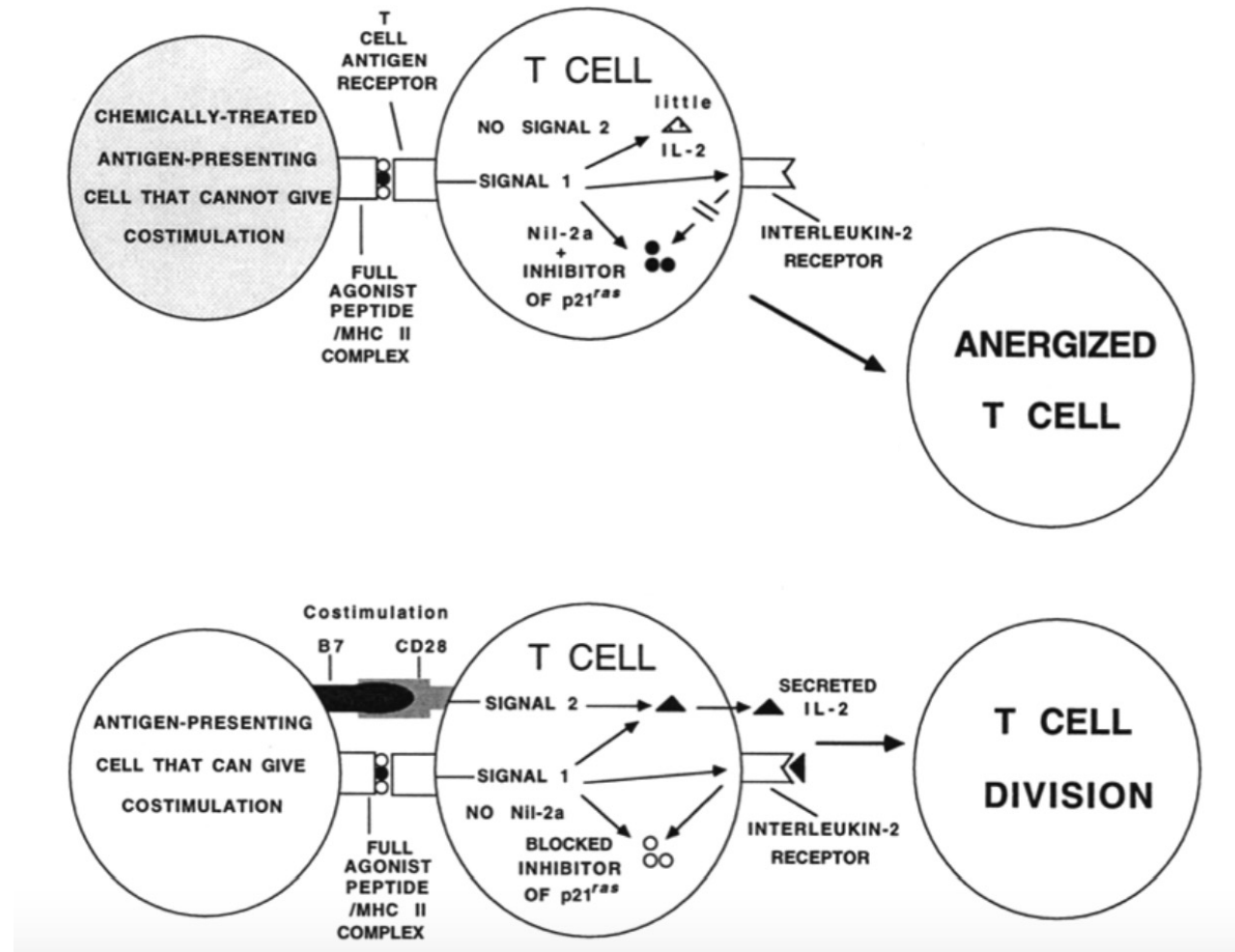
ZAP-70
zeta chain-associated
protein of 70 kDa

LAT
linker for activation of T cells

ITK
interleukin-2-inducible
T-cell kinase

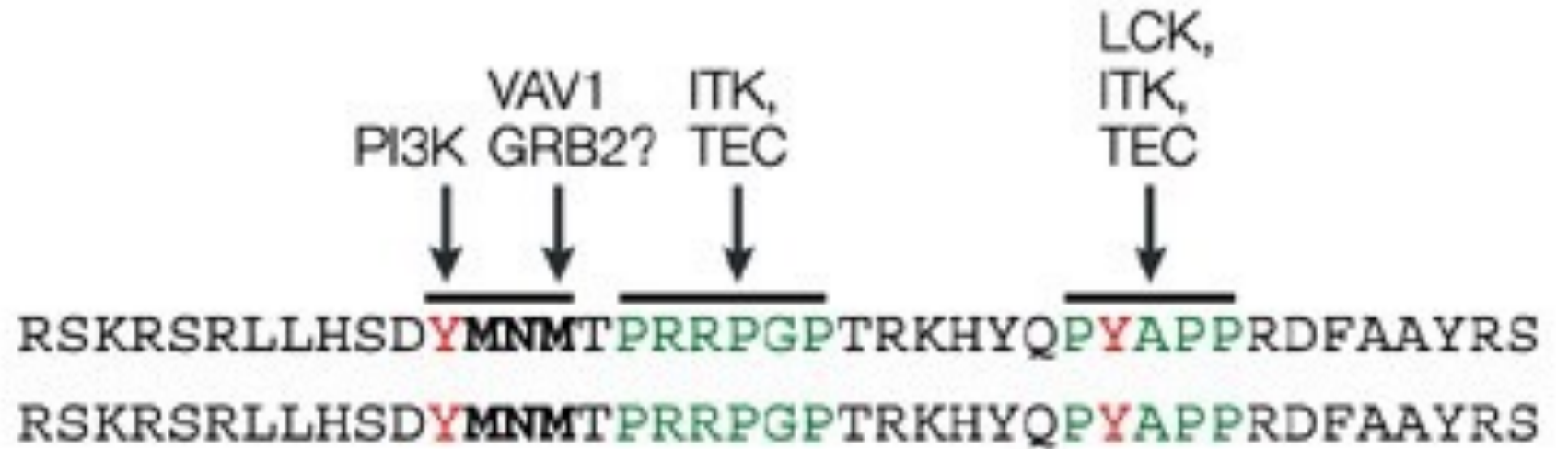
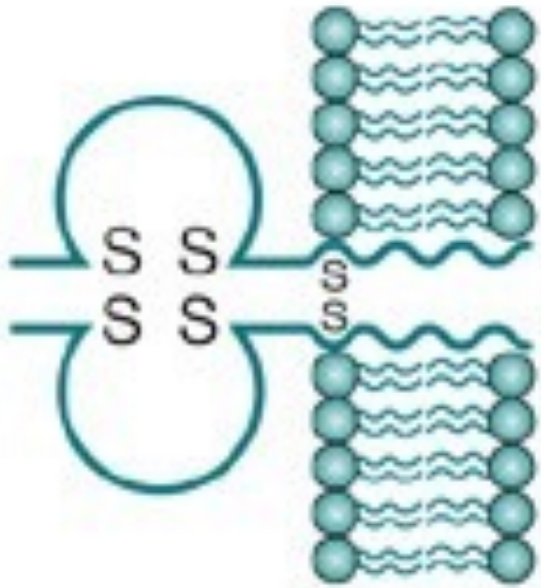
NFAT
Nuclear factor of activated
T cells

Signal 1 is not enough

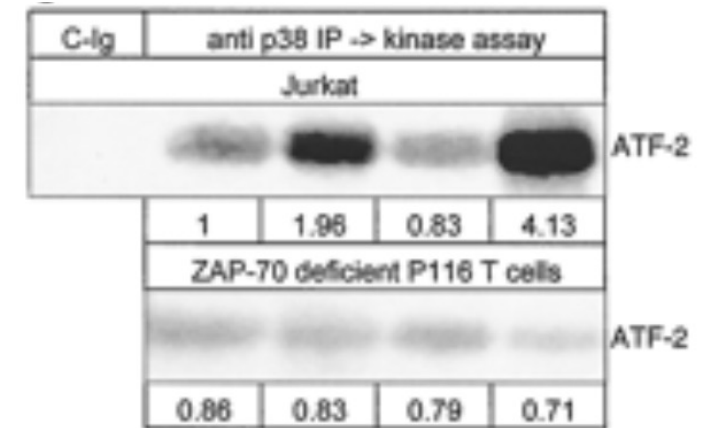
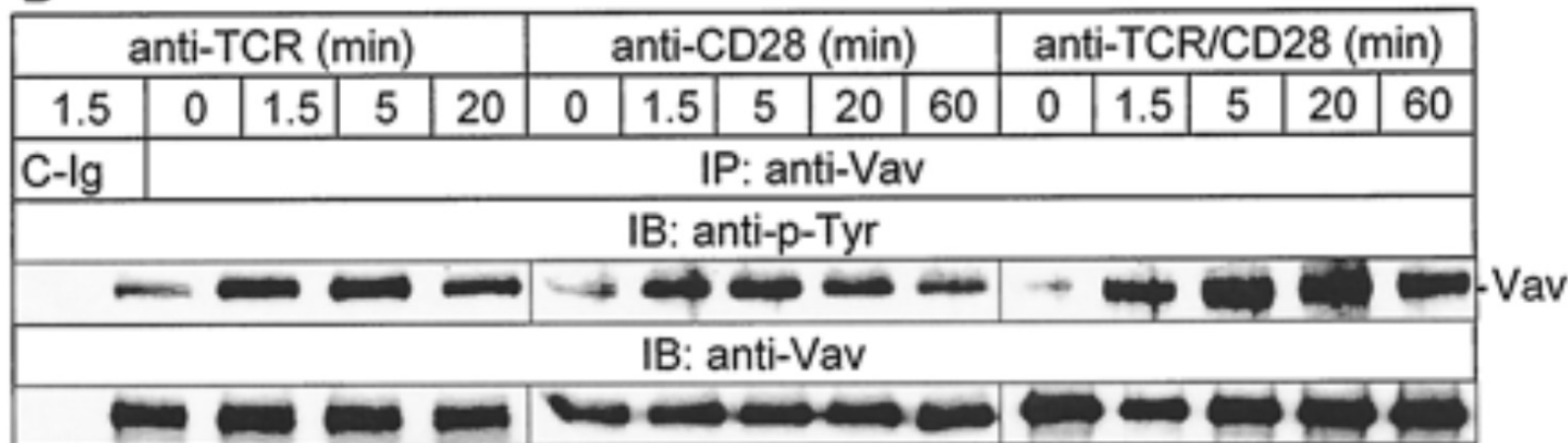
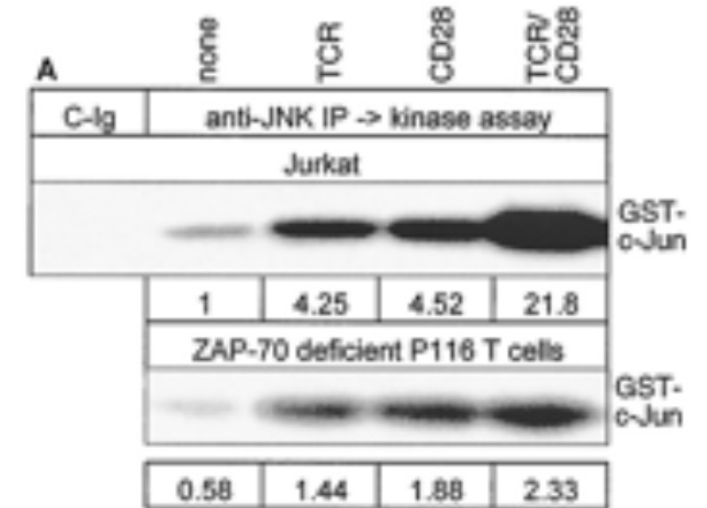
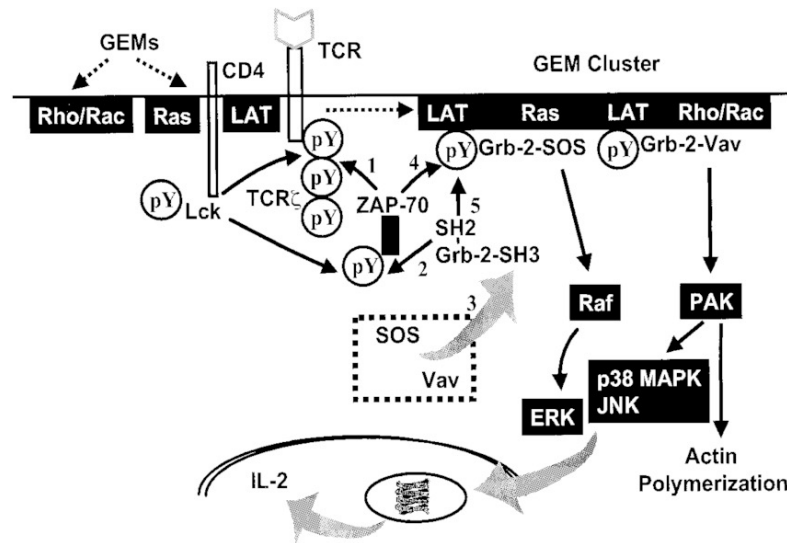


CD28 co-stimulation

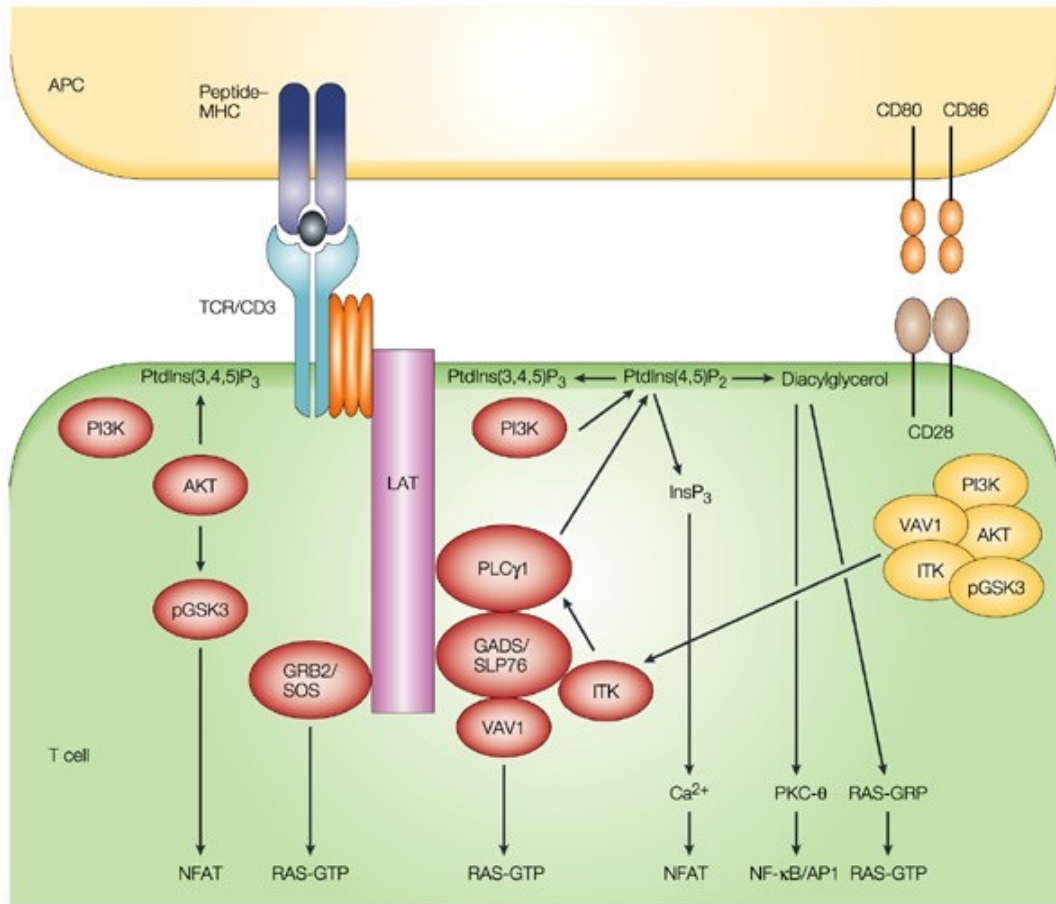
CD28



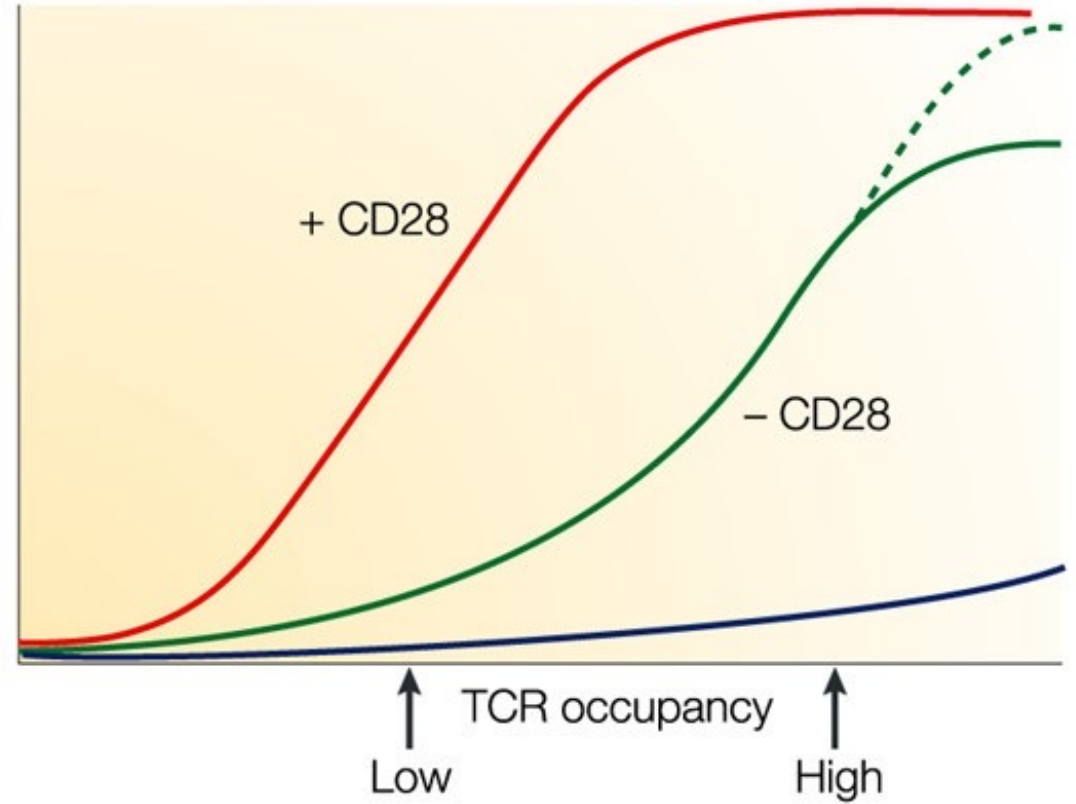
CD28: a signal 2 to amplify signal 1?



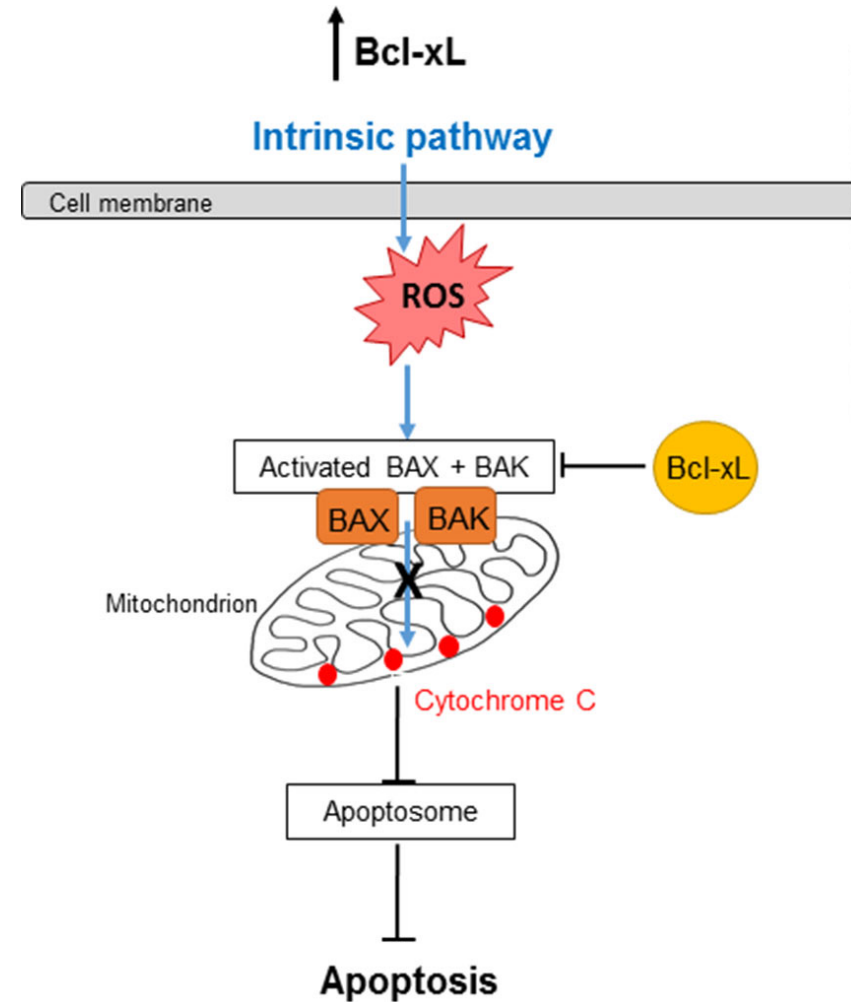
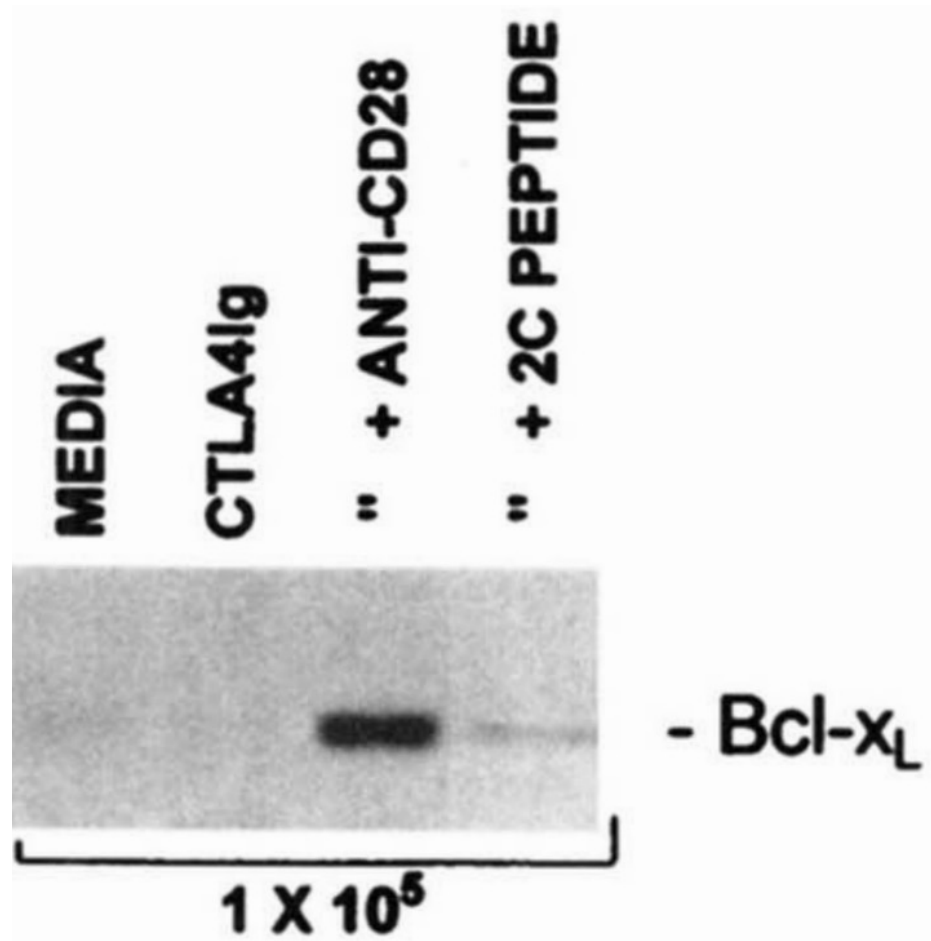
CD28 amplifies TCR signaling



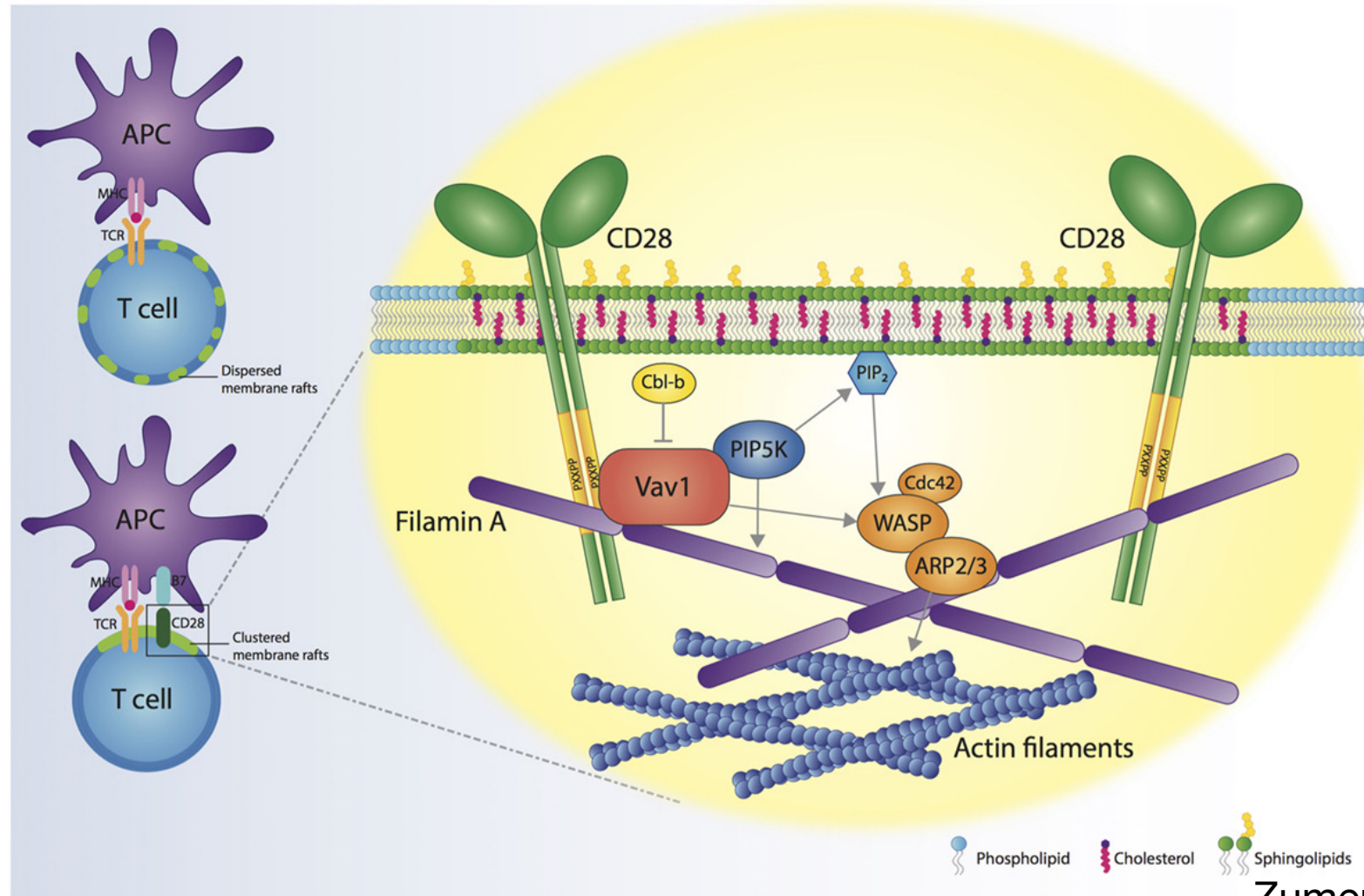
Intracellular Ca²⁺ concentration, proliferation and IL-2 production



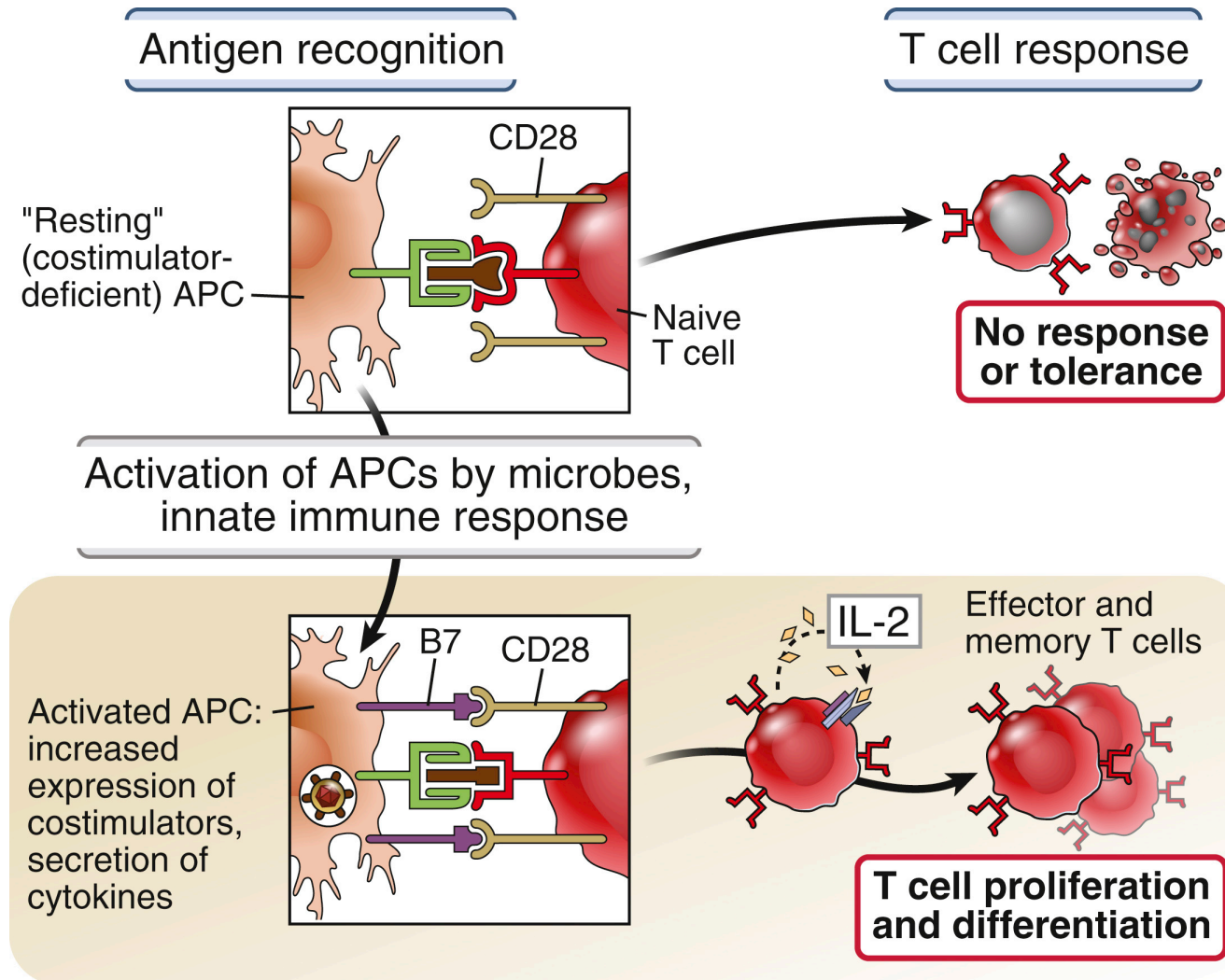
CD28 induces a unique survival signal



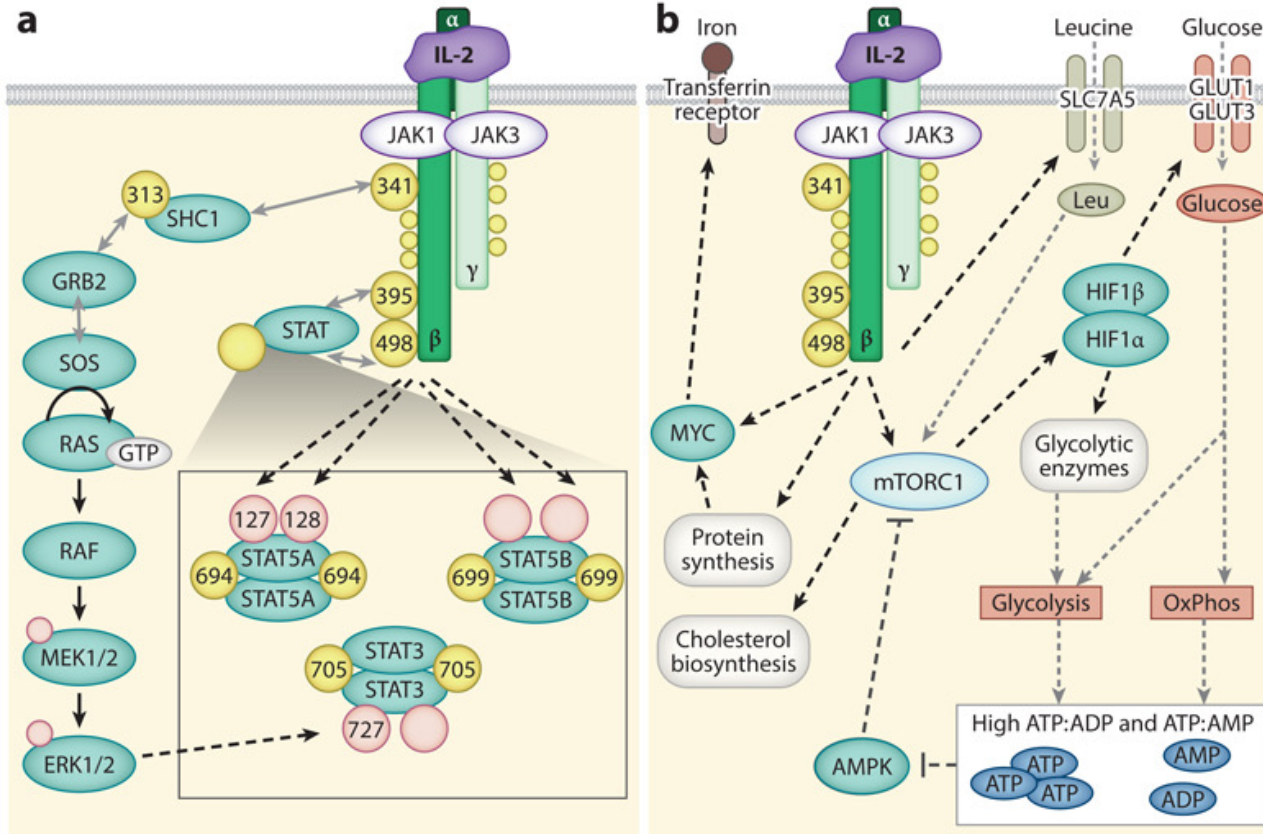
CD28 orchestrates membrane raft trapping and cytoskeletal reorganization



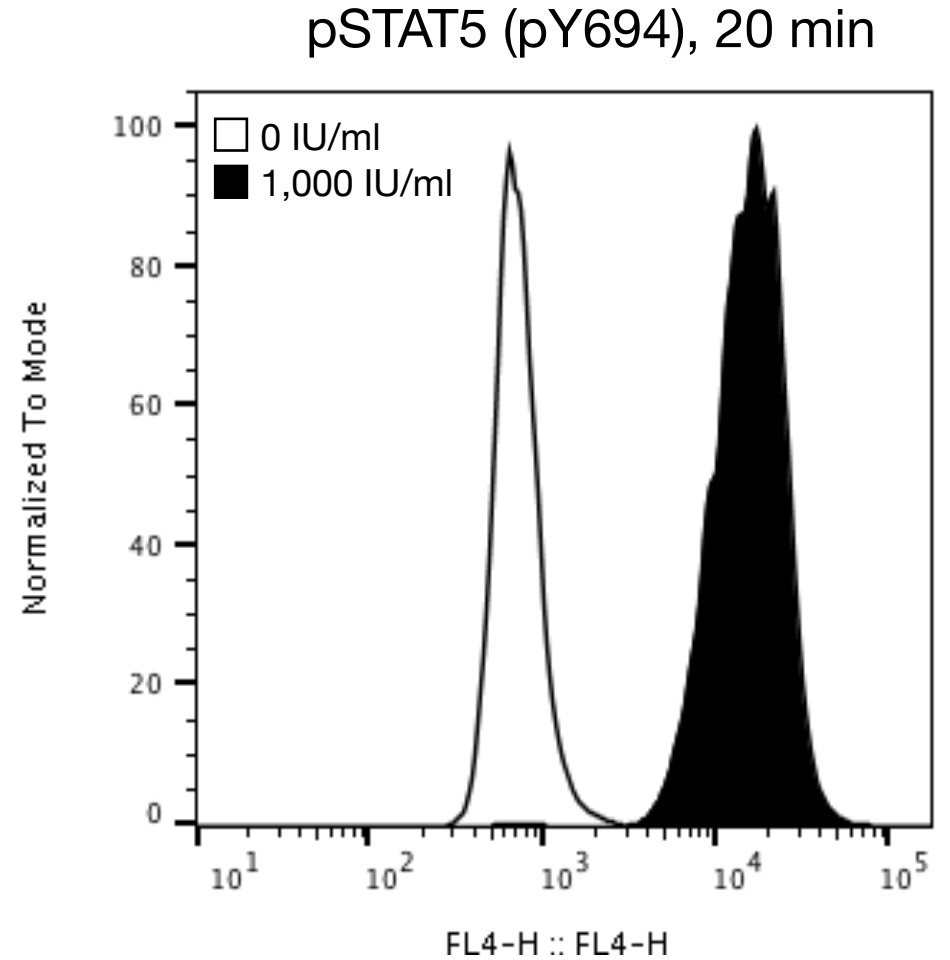
T cell activation requires costimulation



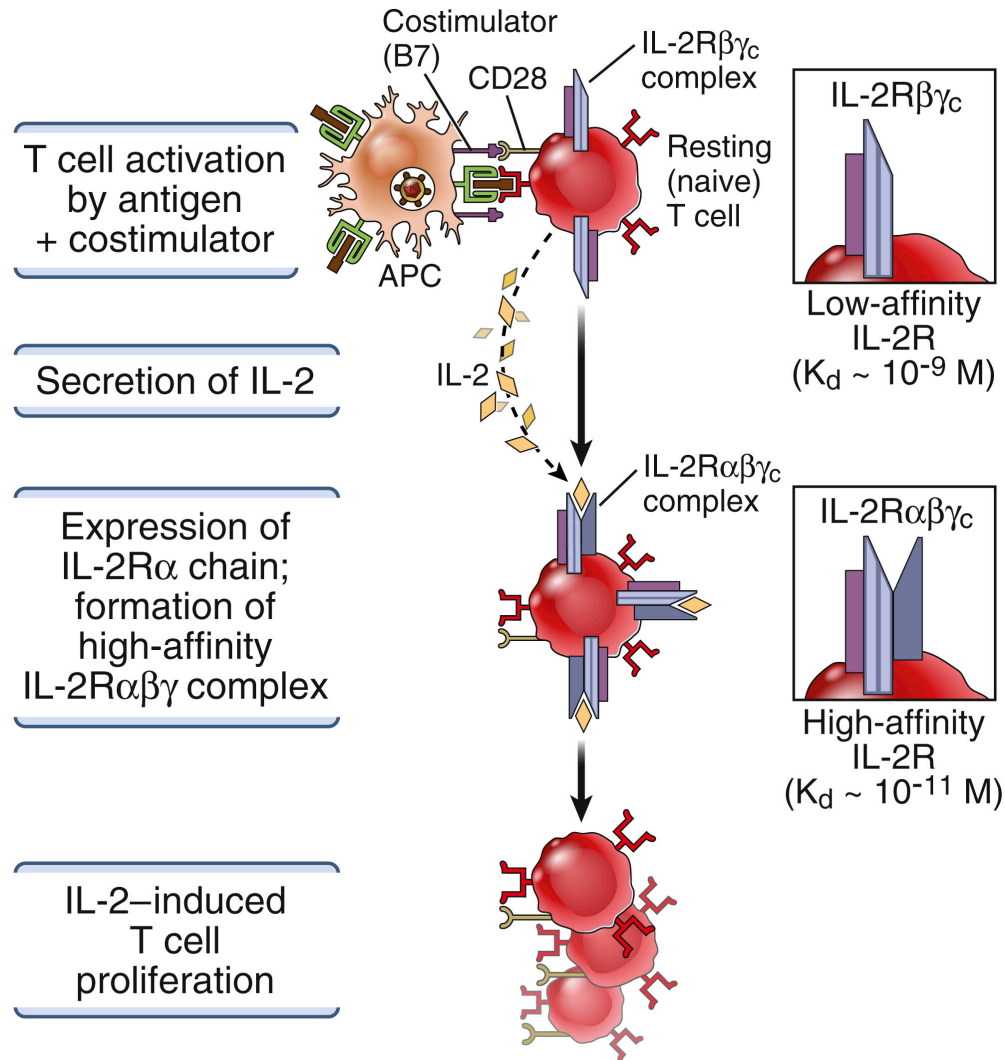
T-cell growth factor a.k.a. interleukin-2



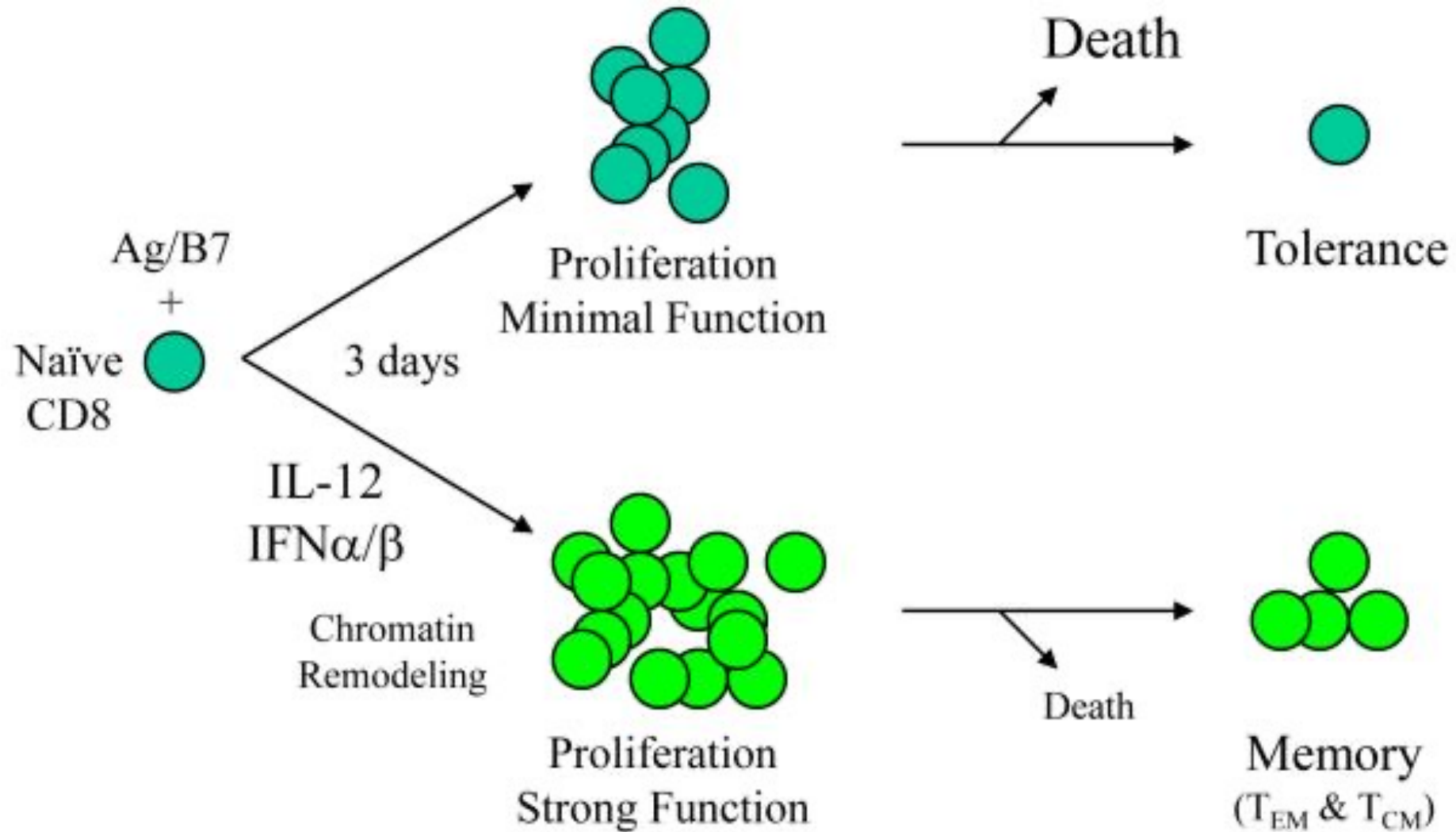
- Direct signaling steps
- - Regulation is dependent but may involve intermediate steps
- - Pathways influenced by nutrients/metabolism (involving multiple steps)
- ↔ Molecular interaction
- ↻ GDP to GTP exchange
- Ser/Thr phosphorylations
- Tyr phosphorylations



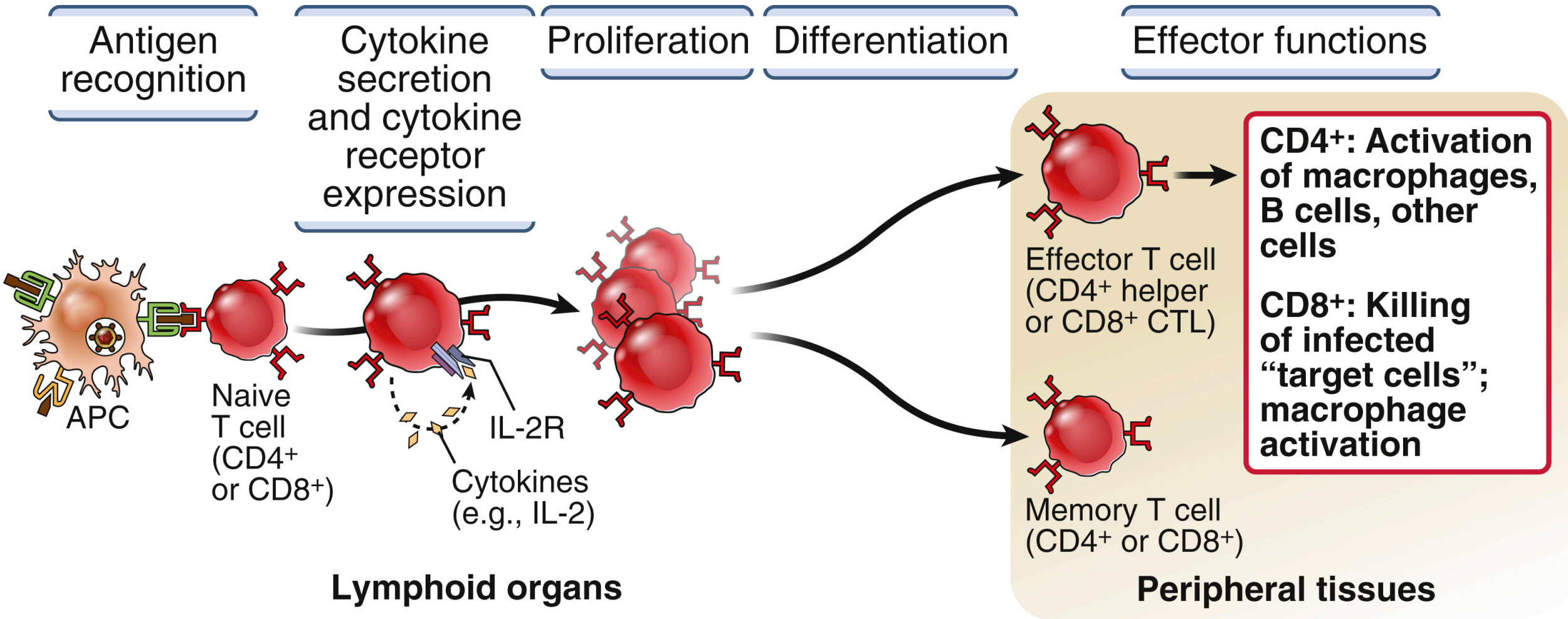
IL-2 drives T-cell proliferation



T cell signal 3: cytokines

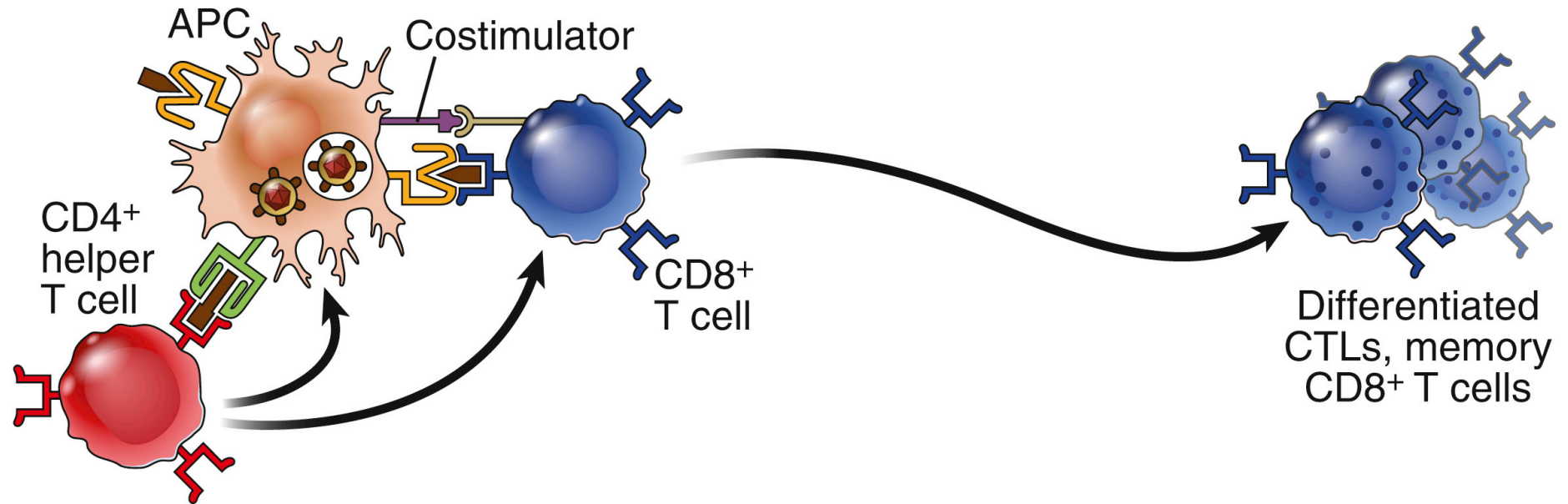


T cell activation



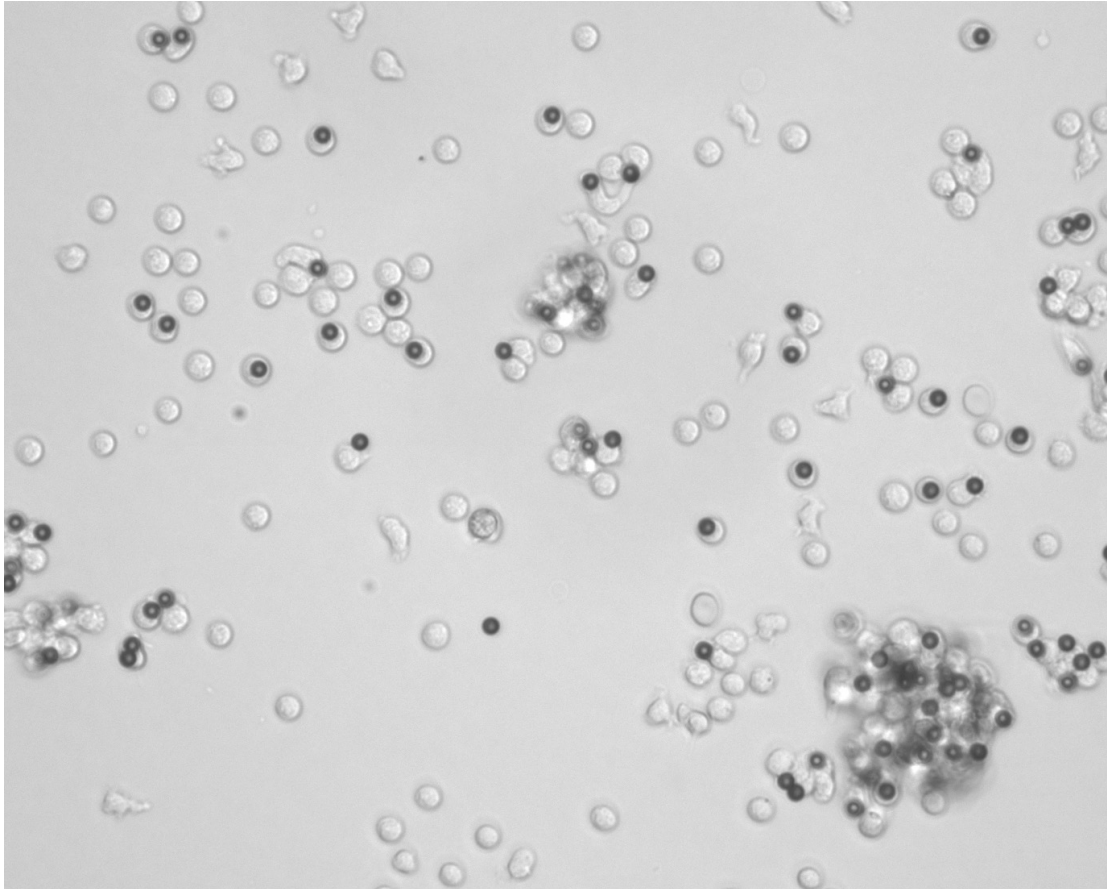
CD8⁺ T cell activation requires CD4⁺ T cell help

CD4⁺ helper T cells produce molecules that stimulate CTL differentiation

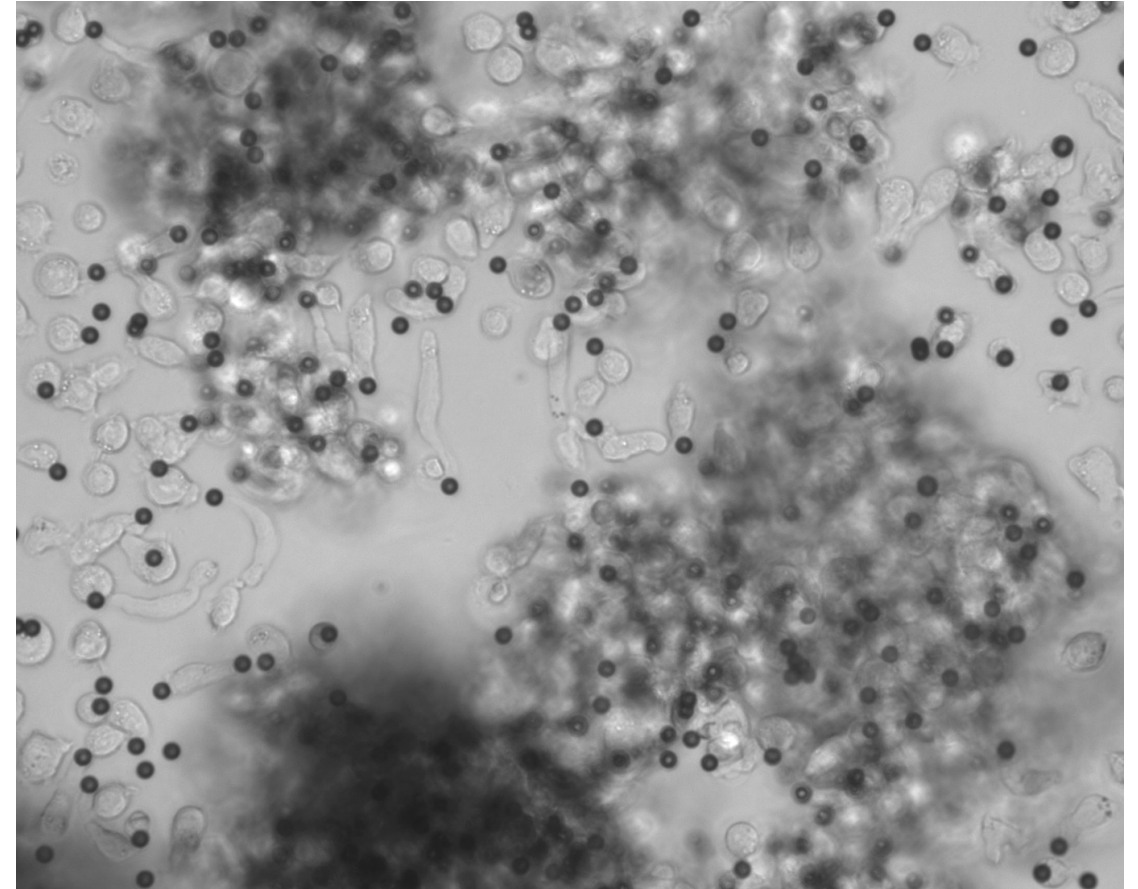


T cell activation: seeing is believing

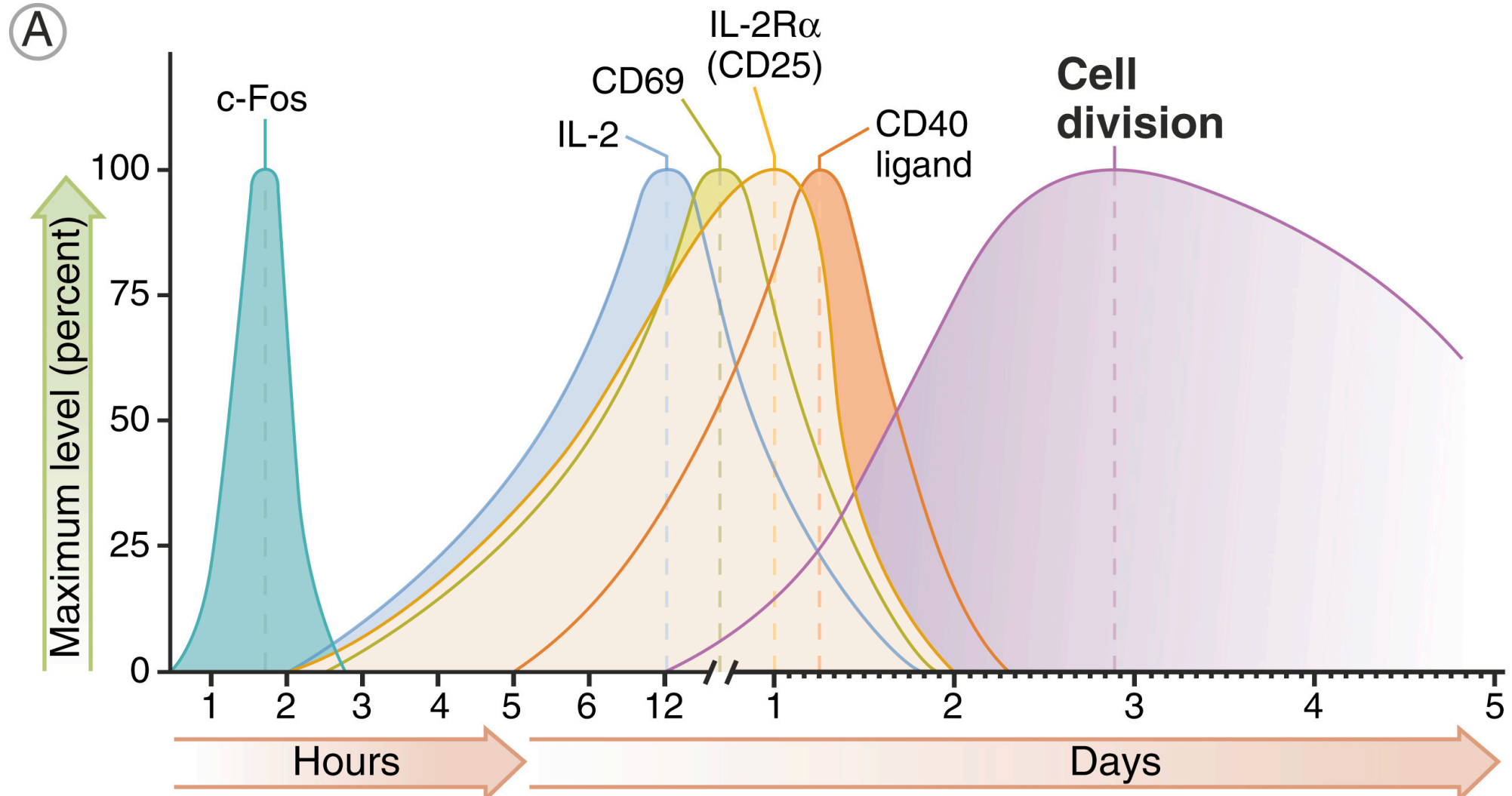
Resting



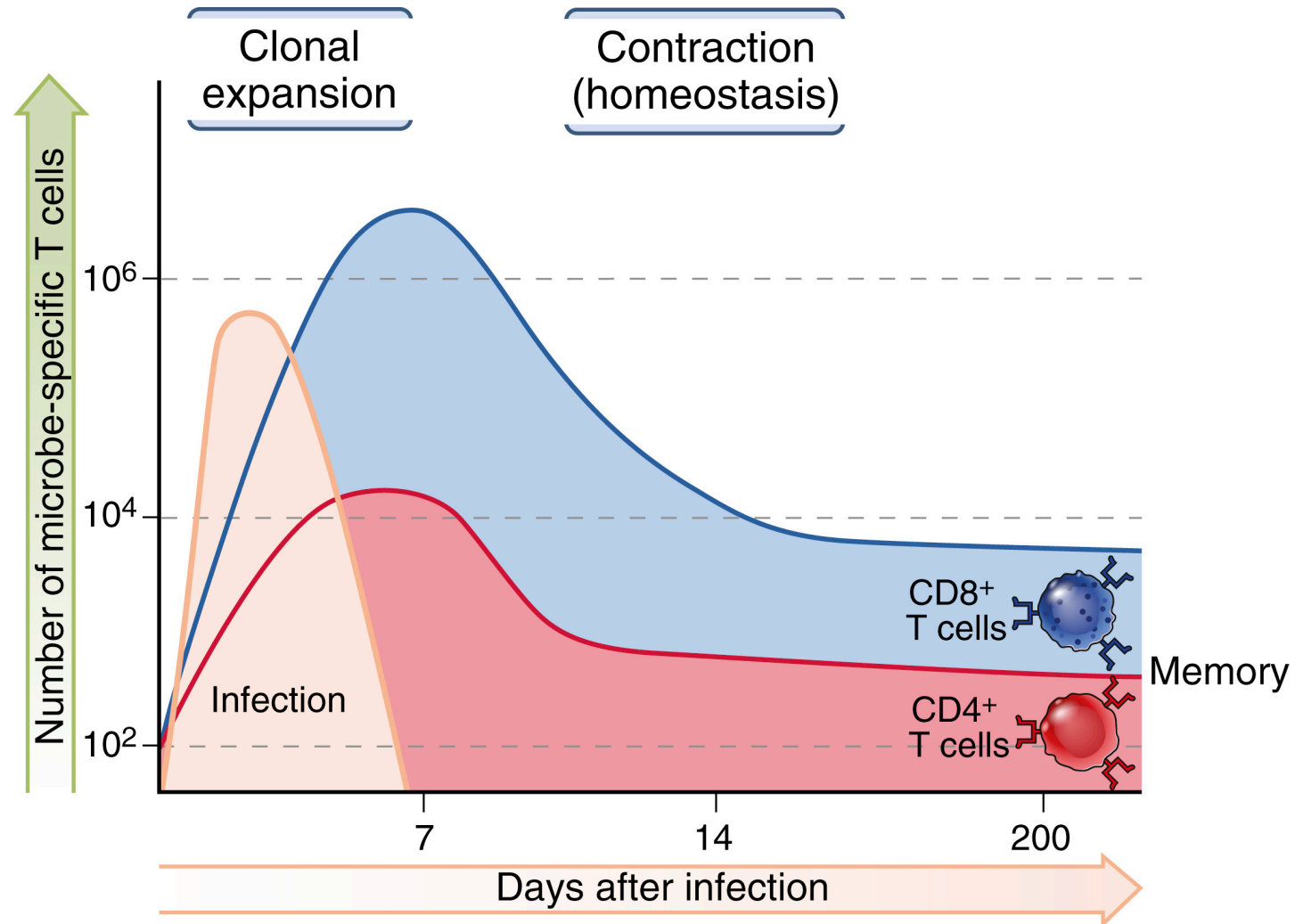
Activated



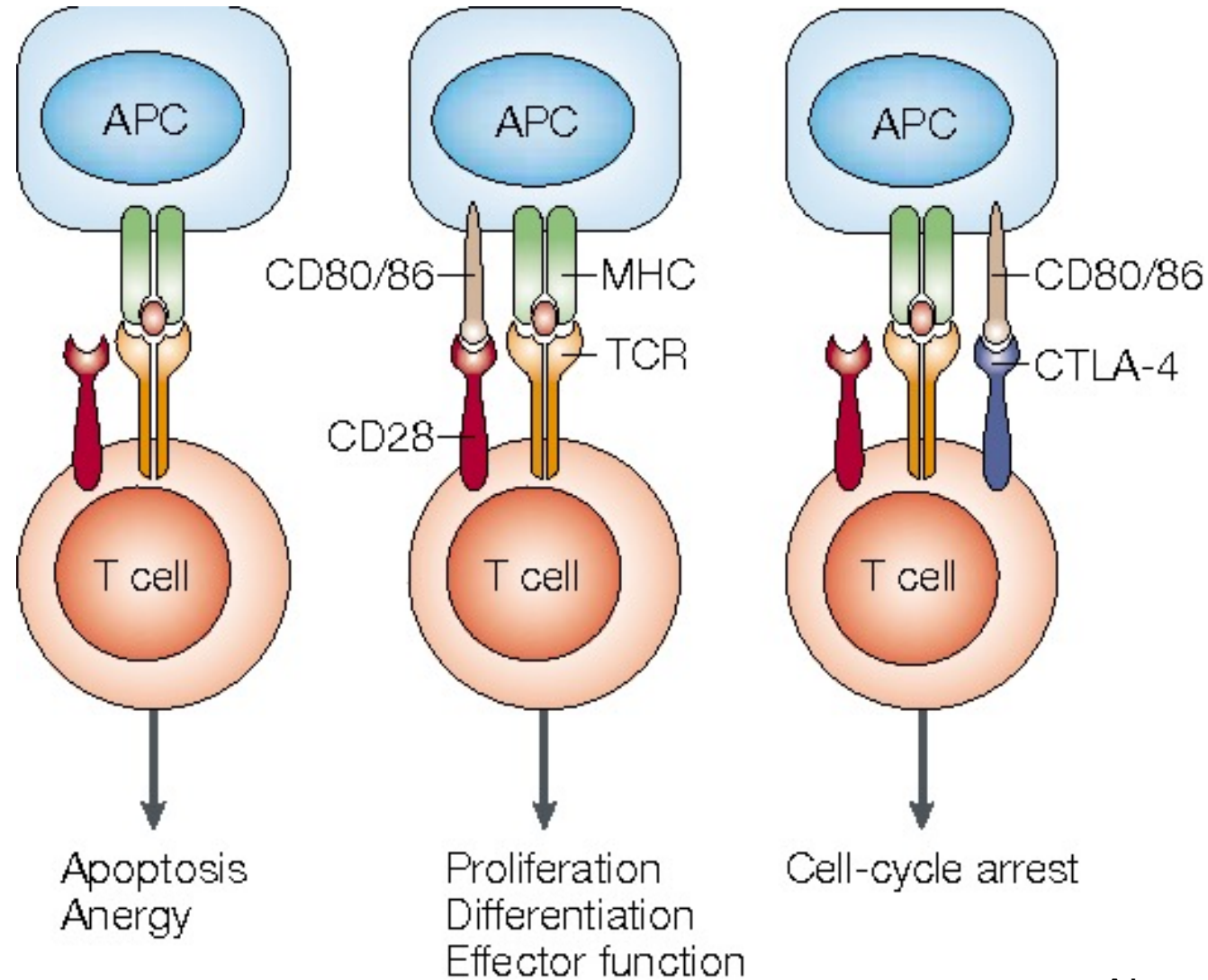
Time course of T cell activation



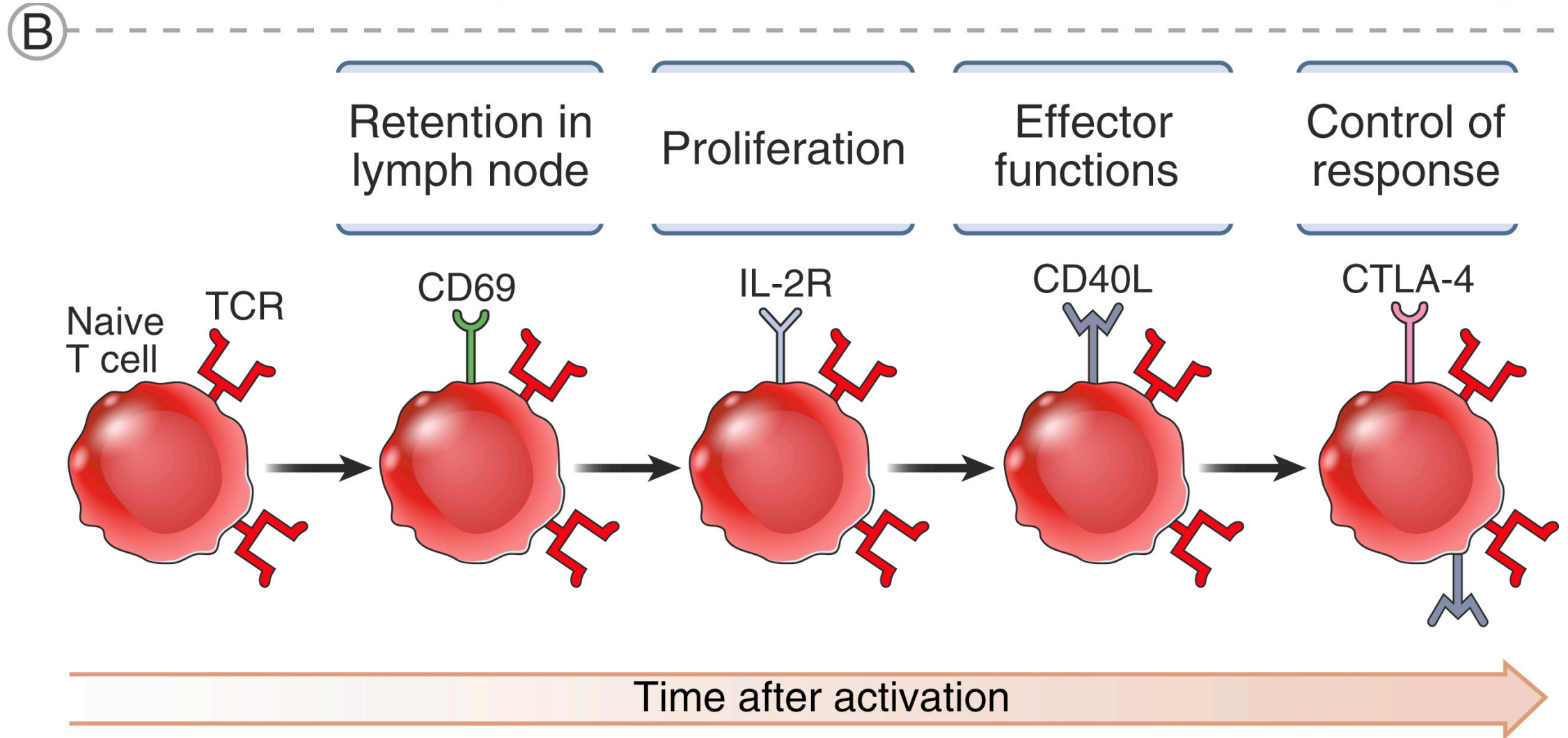
Wax and wane of the T cell response



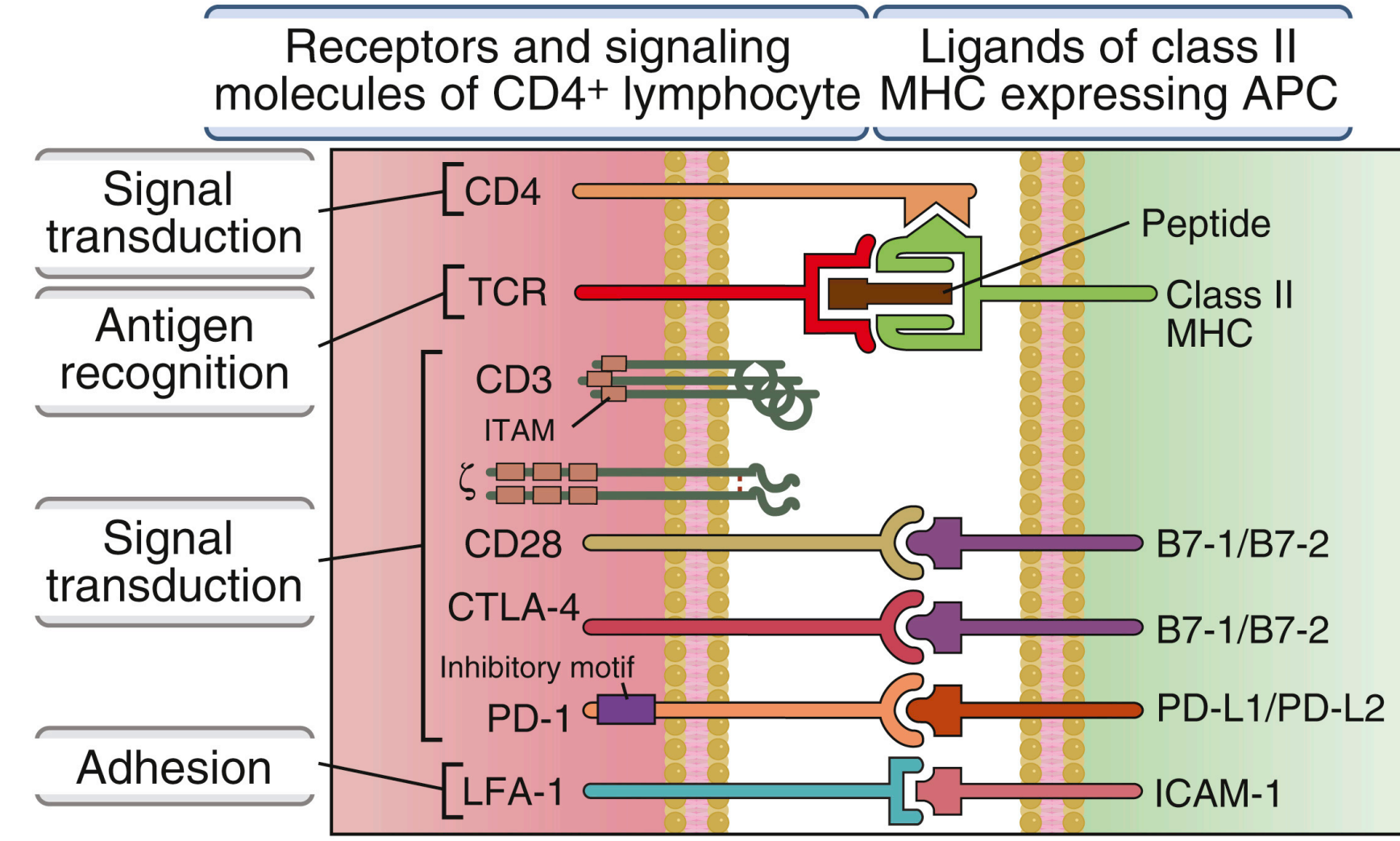
The T cell brakes: CTLA-4



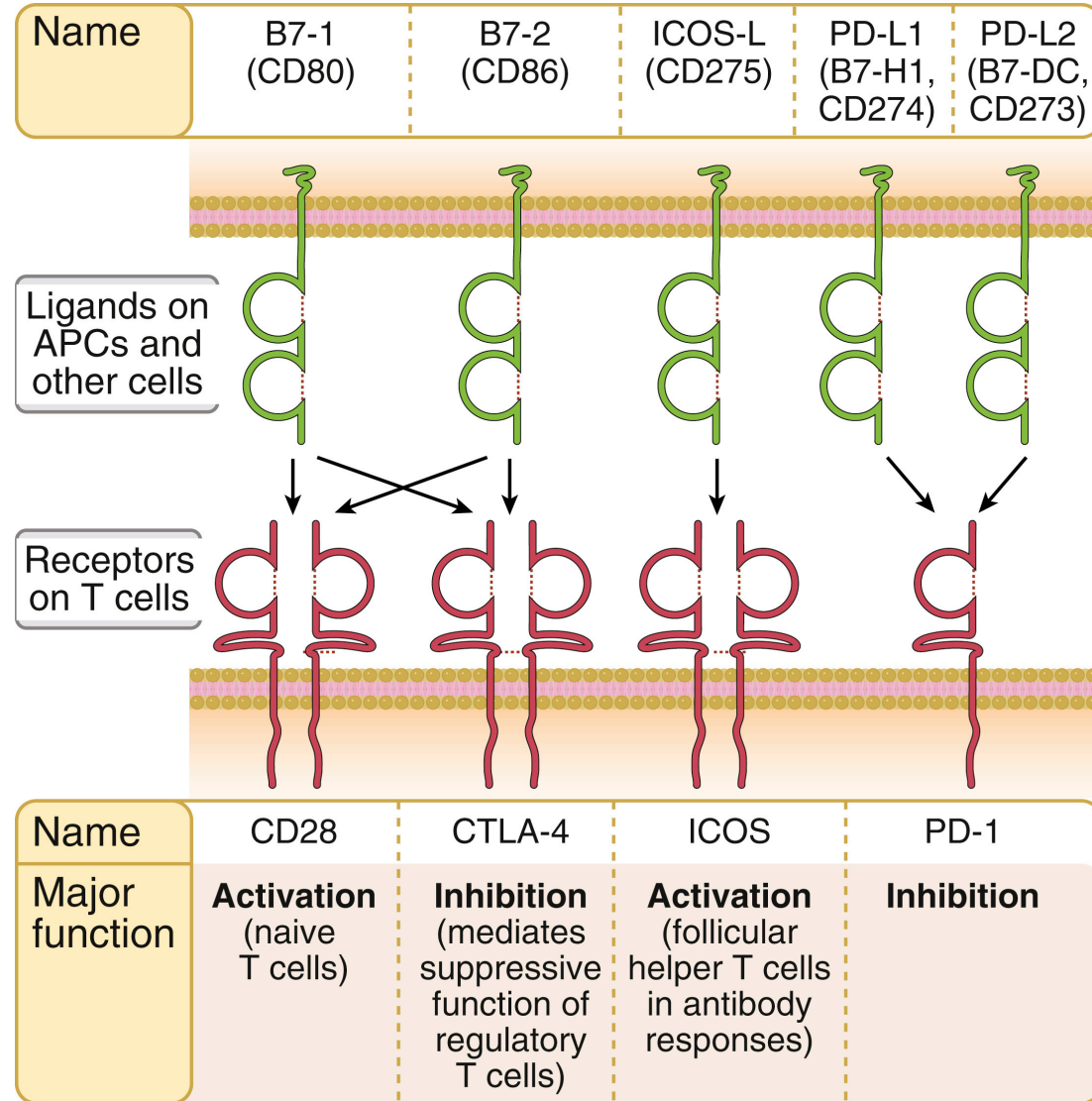
Time course of T cell activation



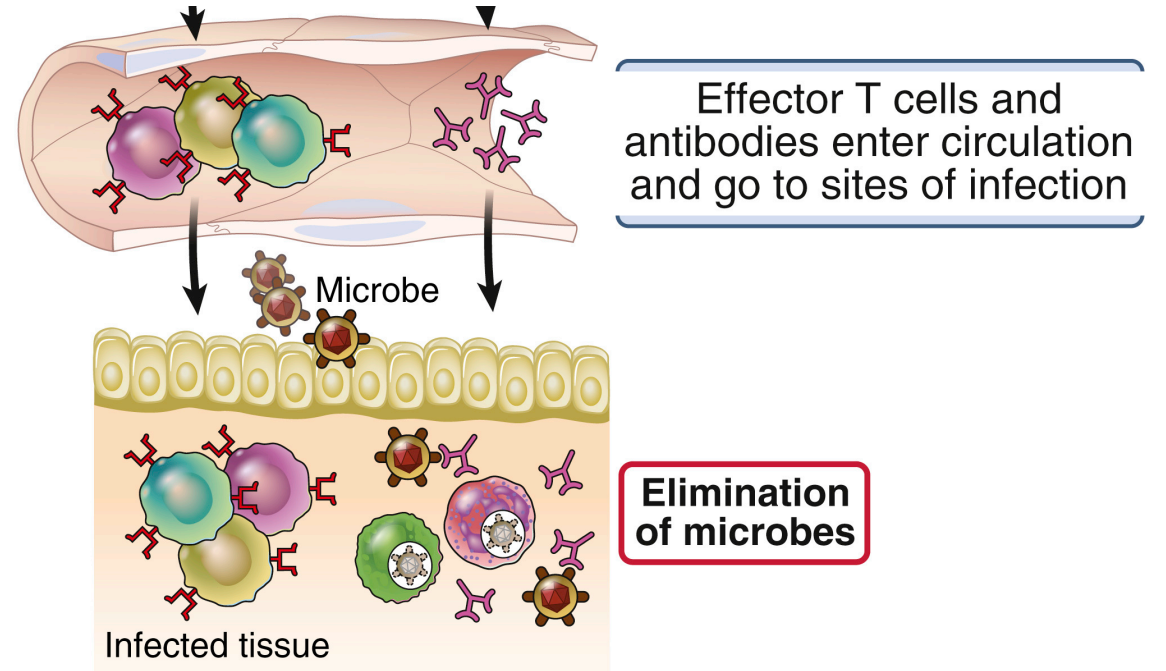
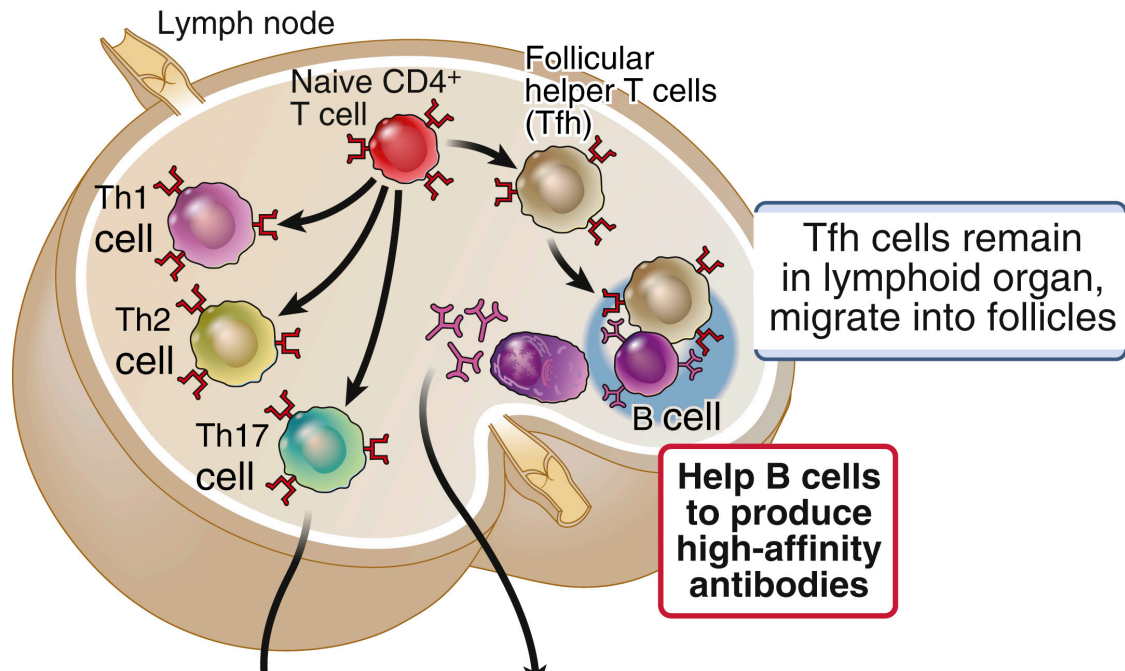
Receptors on the surface of T cells



The CD28 and B7 protein families

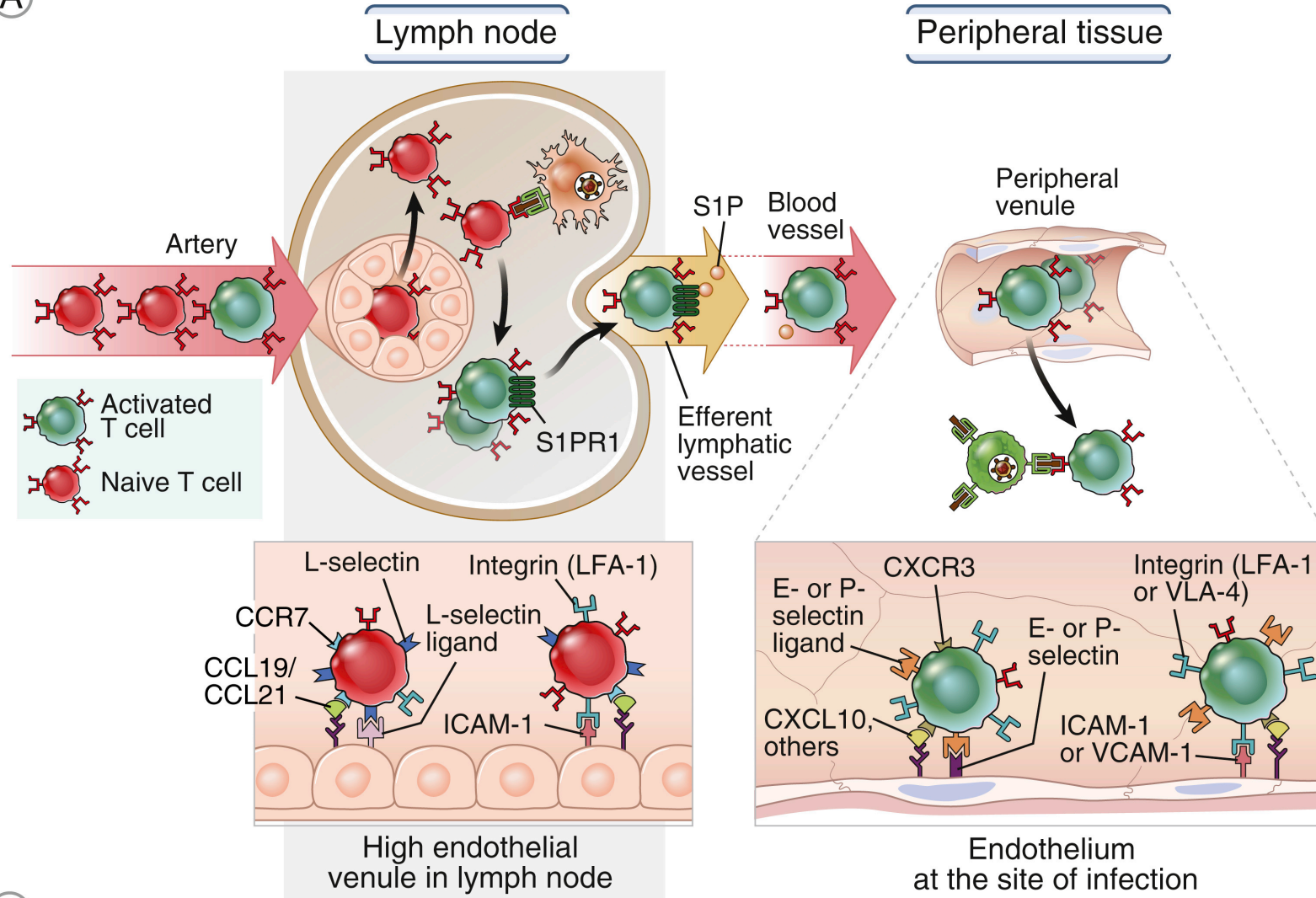


CD4⁺ T cell differentiation















T cell migration

A

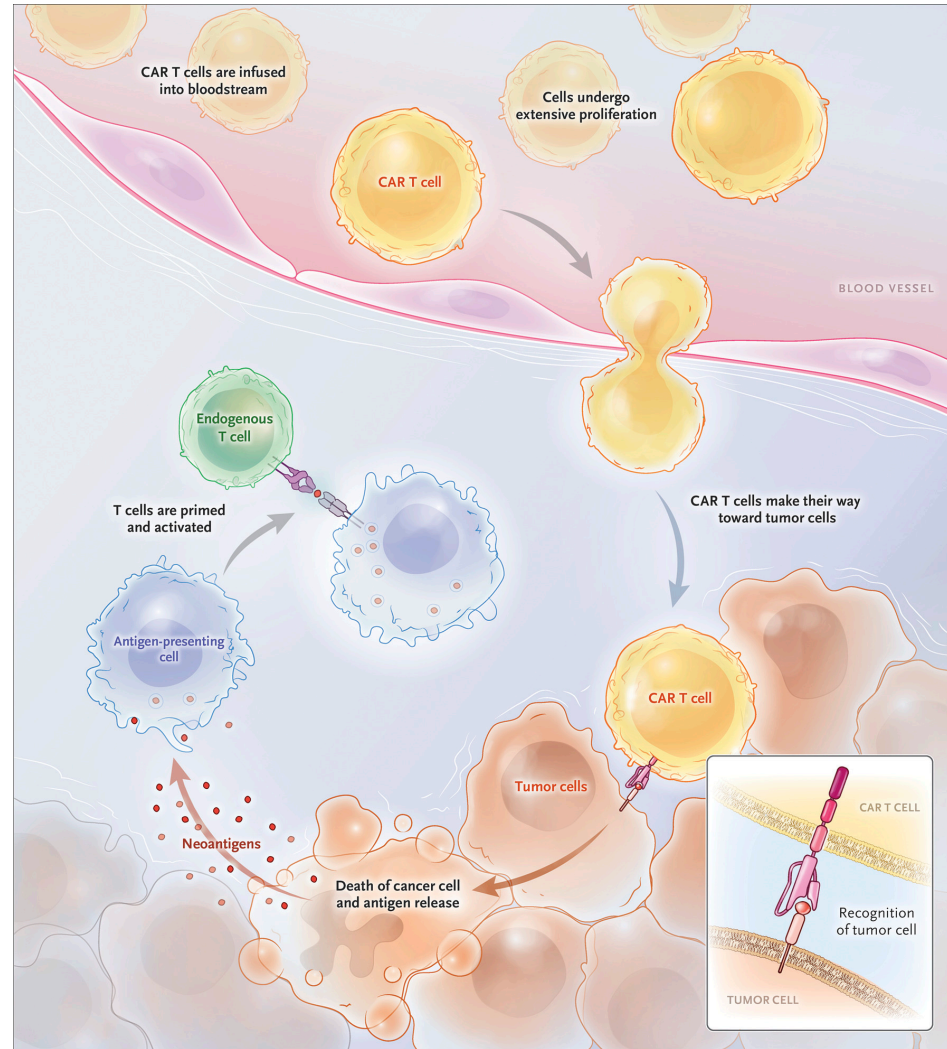


B

T cell migration molecule cheat sheet

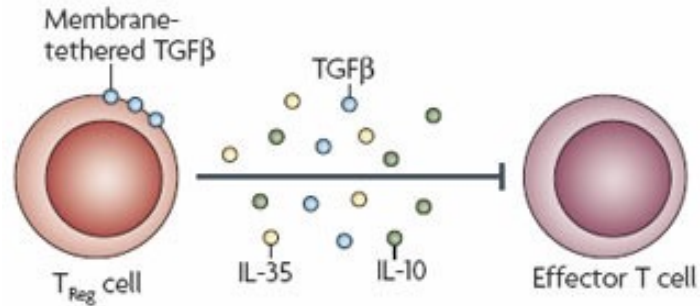
| B T cell homing receptor | Ligand on endothelial cell | Function of receptor: ligand pair |
|---|---|--|
| Naive T cells  L-selectin |  L-selectin ligand | Adhesion of naive T cells to high endothelial venule (HEV) in lymph node |
|  LFA-1 (β_2 -integrin) |  ICAM-1 | Stable arrest on HEV |
|  CCR7 |  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 |

Chimeric antigen receptor T cells

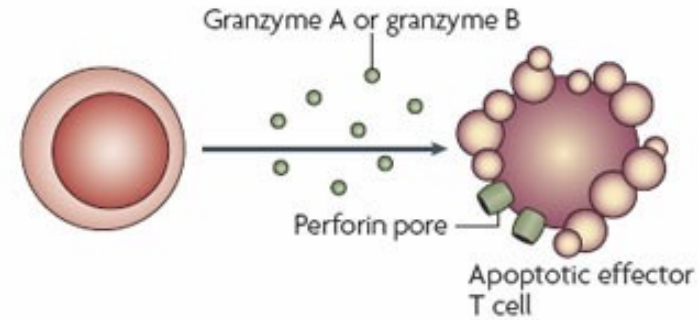


Regulatory T cells

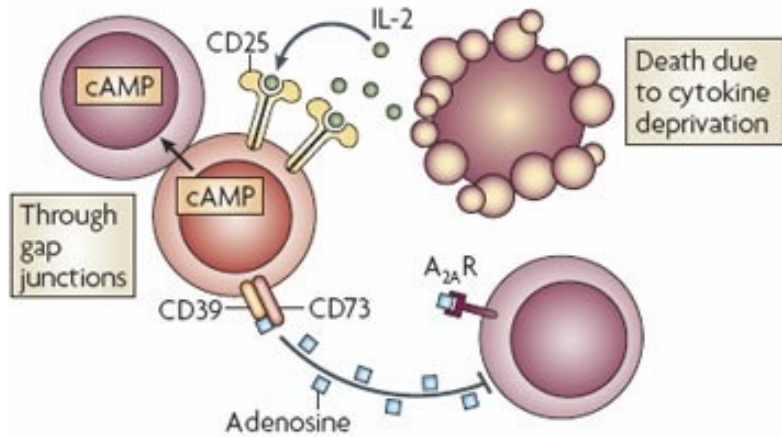
a Inhibitory cytokines



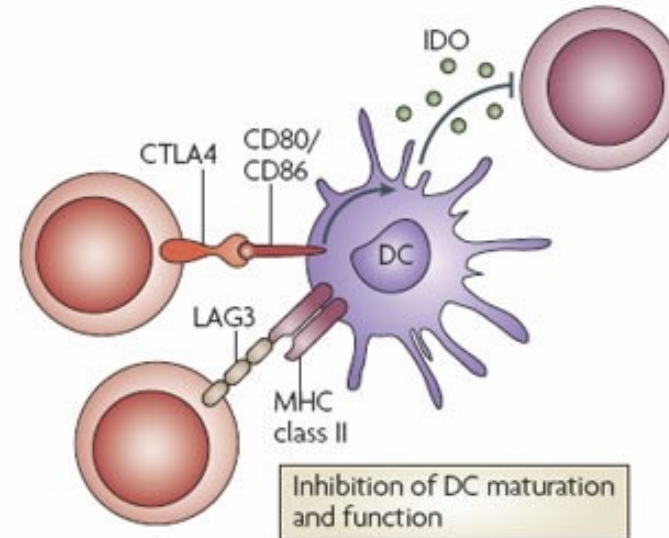
b Cytolysis



c Metabolic disruption



d Targeting dendritic cells



What are the components of the TCR complex? Which of these components are responsible for antigen recognition and which for signal transduction?

What are some of the molecules in addition to the TCR that T cells use to initiate their responses to antigens, and what are the functions of these molecules?

What is the principal growth factor for T cells? Why do antigen-specific T cells expand more than other (bystander) T cells on exposure to an antigen?

What are the mechanisms by which CD4⁺ effector T cells activate other leukocytes?

Why do naive T cells migrate preferentially to lymphoid organs and differentiated effector T cells (which have been activated by antigen) migrate preferentially to tissues that are sites of infection?