Immunology Basics Relevant to Cancer Immunotherapy:

T Cell Activation, Costimulation, and Effector T Cells

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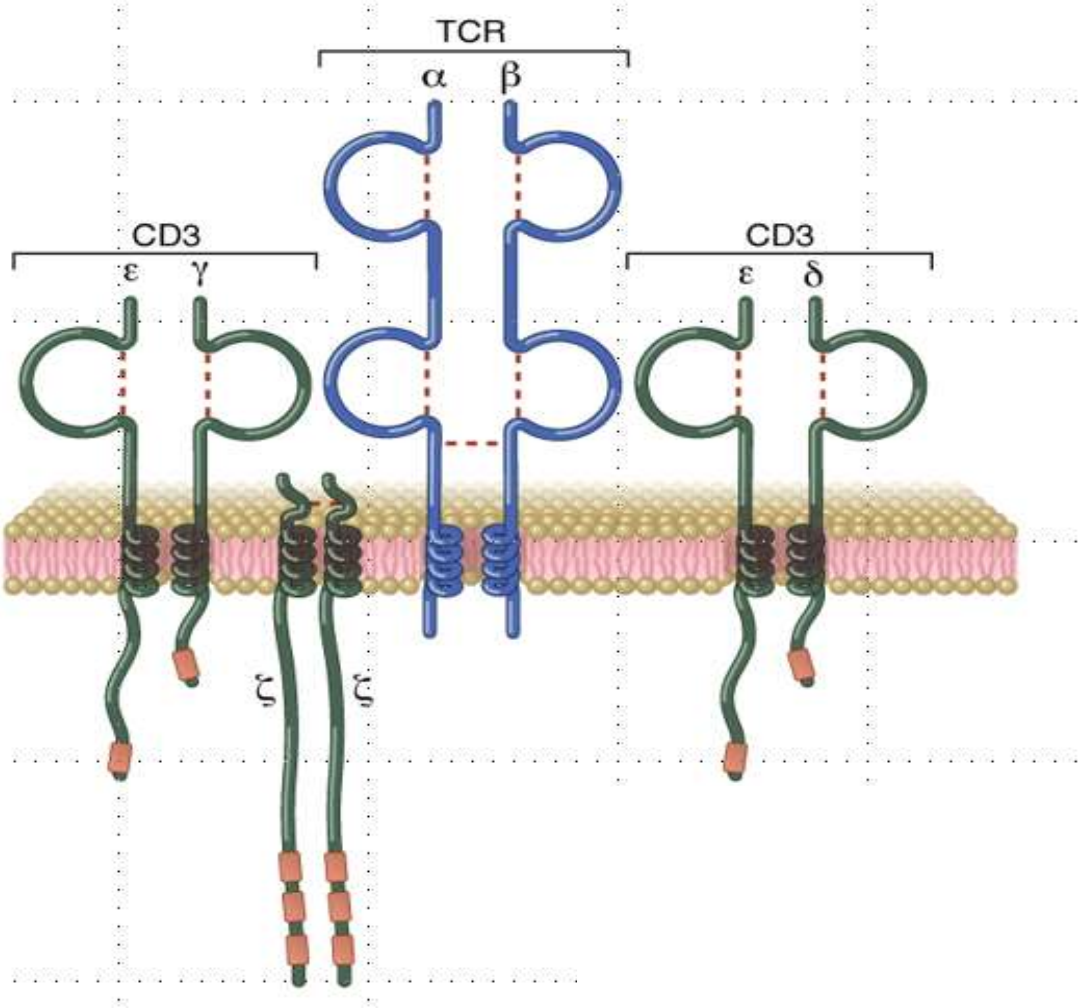
Lecture Outline

- TCR-complex structure
- TCR-complex signaling
- Costimulation
- Effector T Cell Differentiation
- CD4+ Helper T cells
- CD8+ Cytotoxic T lymphocytes

The TCR Complex

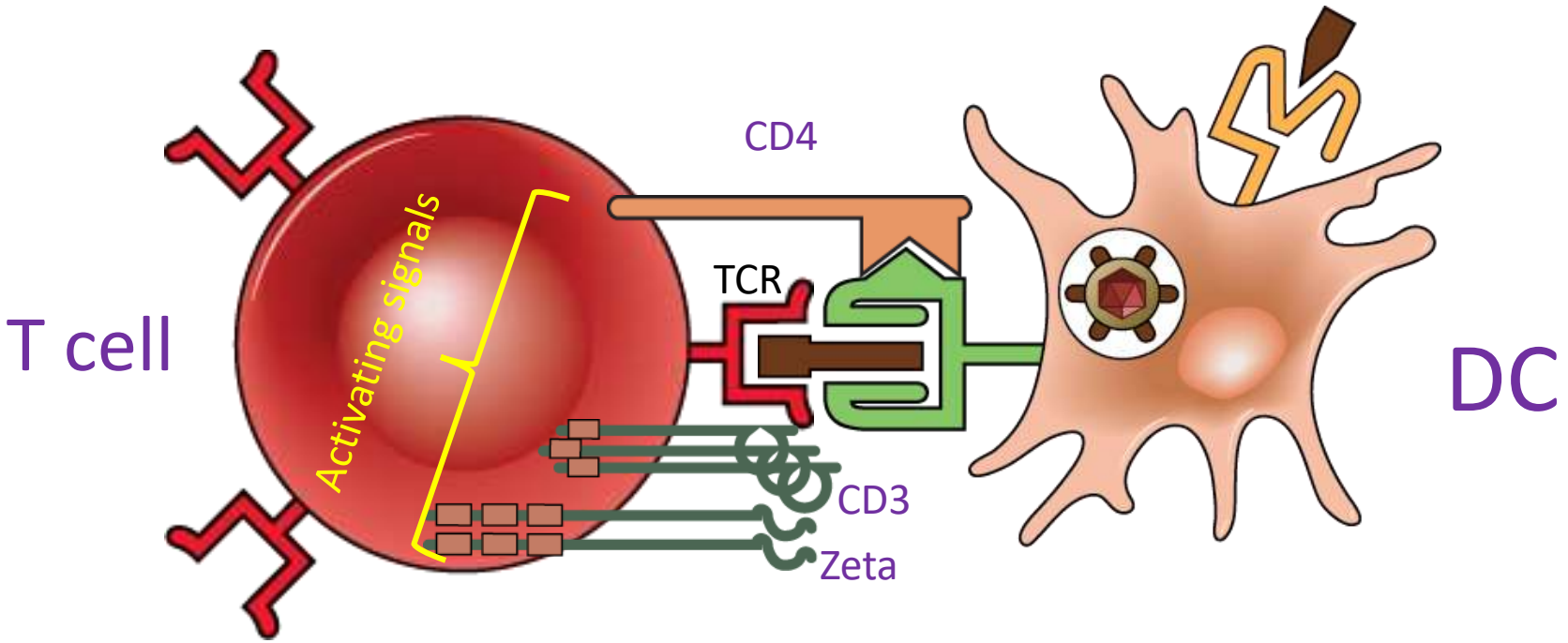


- **The TCR antigen binding αβ TCR heterodimer, which binds antigen (pMHC)**
- **Associated signaling molecules CD3 and ζ proteins, which transduce activating signals**

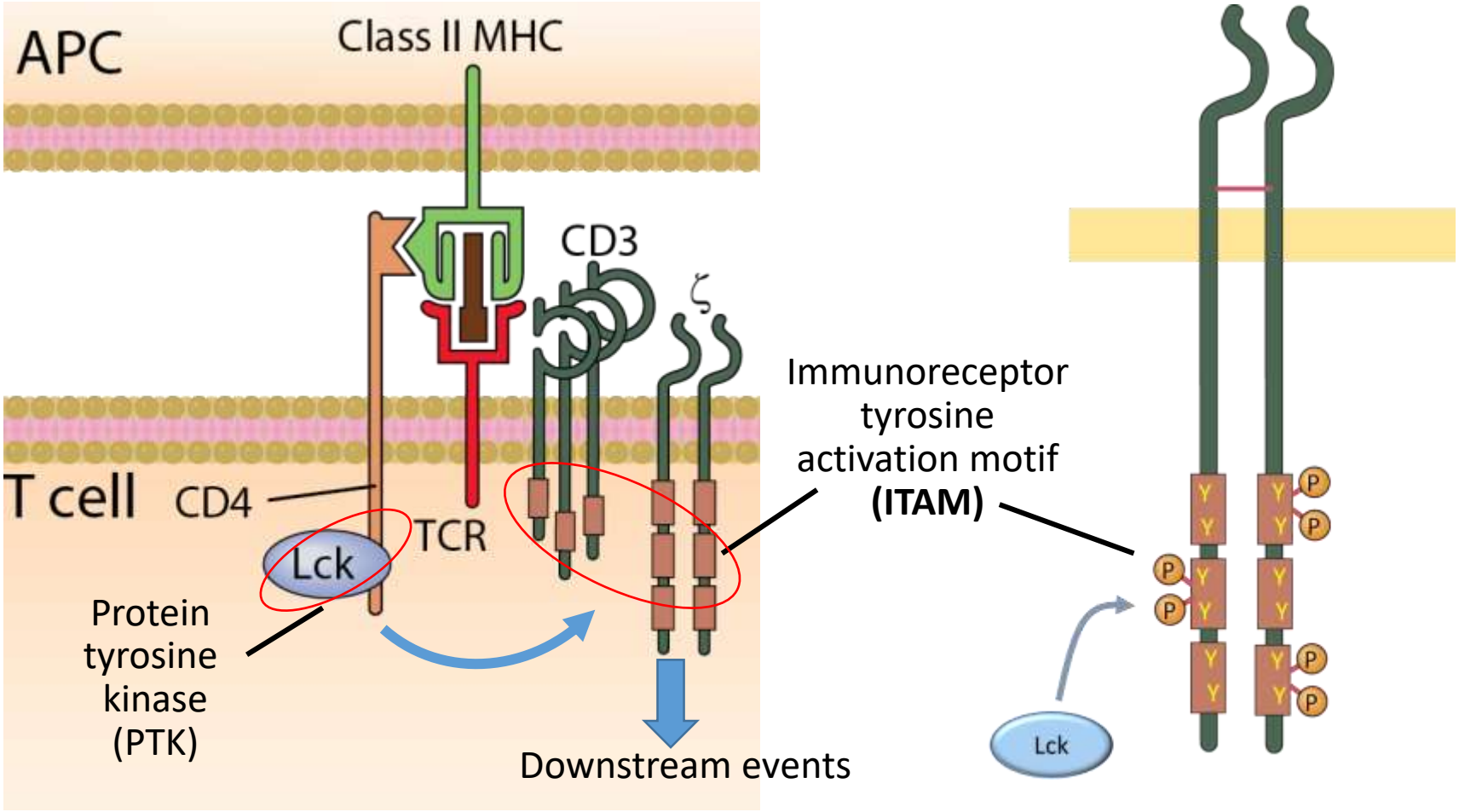
Signaling Events in T Cell Activation

The signals generated by antigen recognition require the participation of cytoplasmic tails of:

- The co-receptor (CD4 or CD8)
- Signaling proteins associated with the TCR (CD3 and zeta)

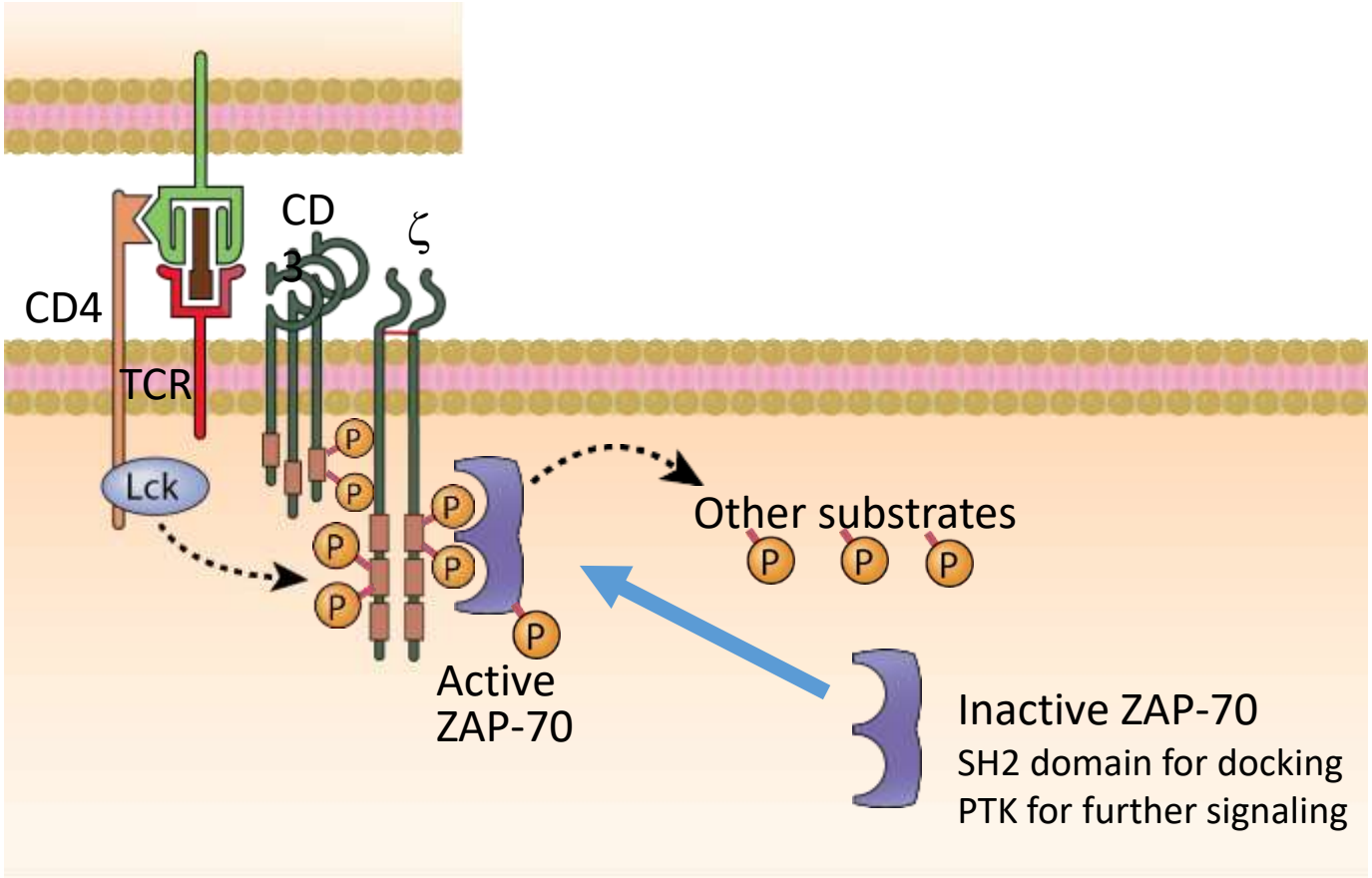


TCR signaling: ITAM phosphorylation

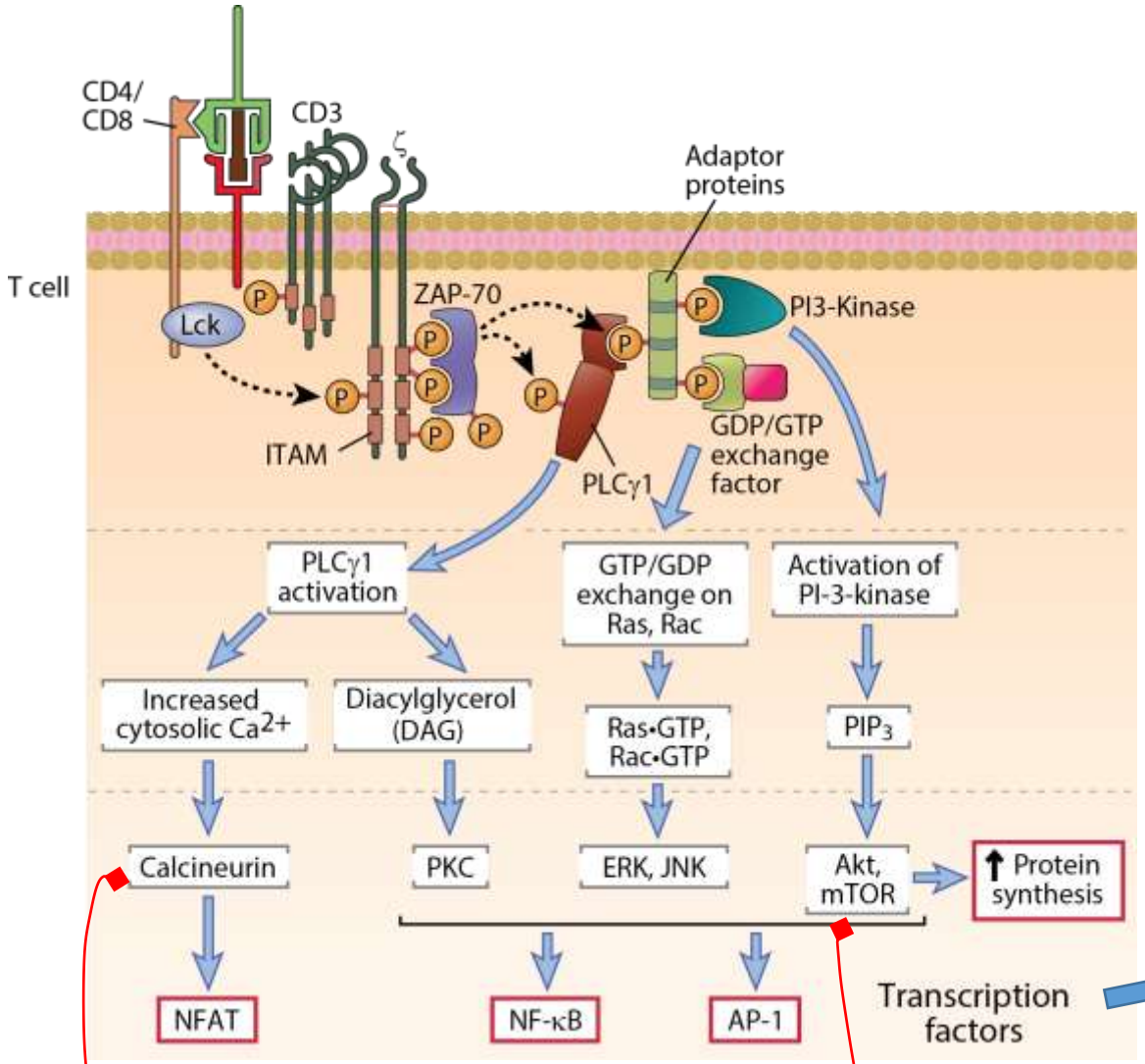


-TCR recognition of the peptide-MHC brings the CD3/ζ ITAMs to the neighborhood
-CD4 or CD8 binding to the same MHC brings the Lck PTK near the ITAMs

TCR signaling: Recruitment of ZAP-70 (a Protein Tyrosine Kinase)



TCR signaling: downstream pathways



- Cytokine growth factor IL-2
- IL-2 receptor
- Other transcription factors required for effector differentiation
- Effector proteins (cytokines, CD40-ligand, perforin, granzymes, …)

Cyclosporin, Tacrolimus

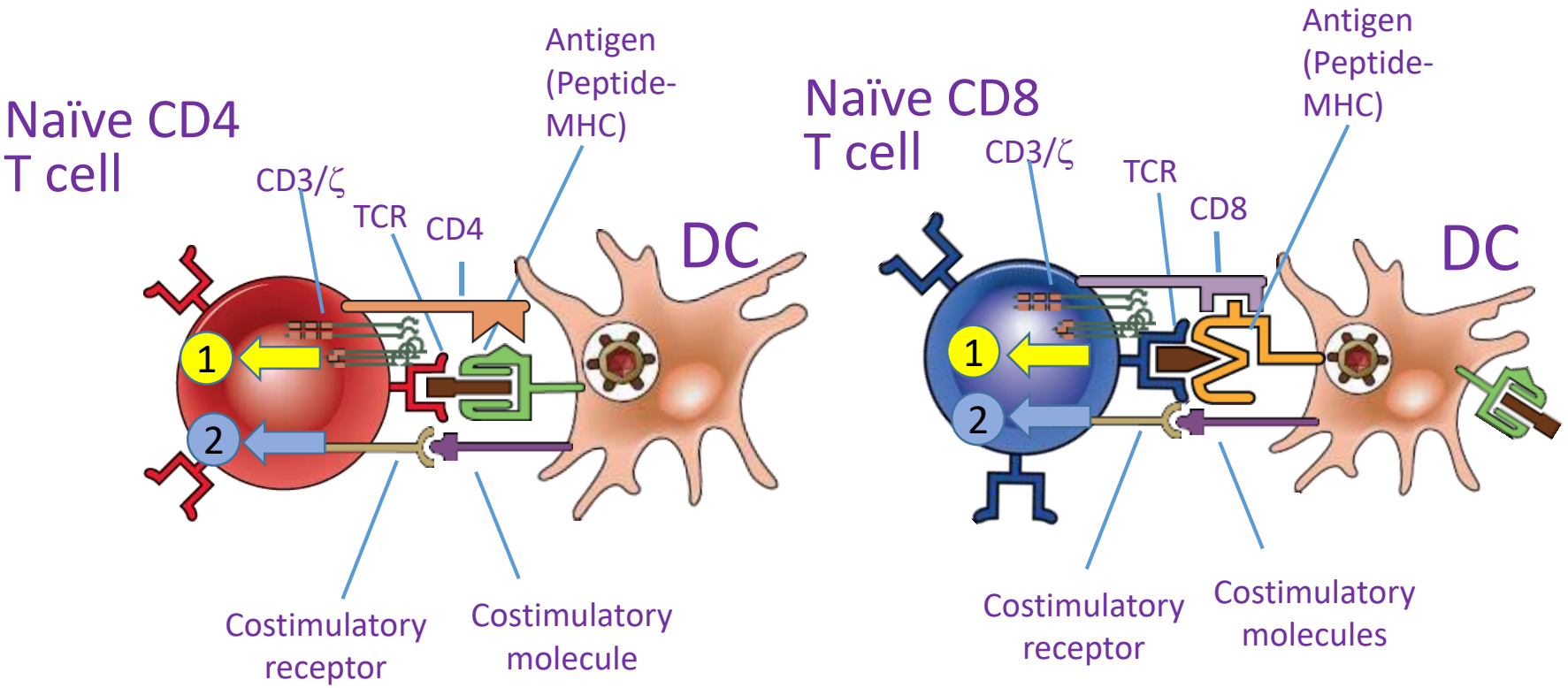
Rapamycin (Sirolimus)

Antigen Recognition is Not Enough to Start a T Cell Response

- TCR binding to peptide-MHC antigen, plus co-receptor (CD4 or CD8) binding to MHC is necessary to generate intracellular signals that activate the naïve T cell, ….***but*** is not sufficient.
  These signals are called "***antigen recognition***" signals or "***Signal 1***"

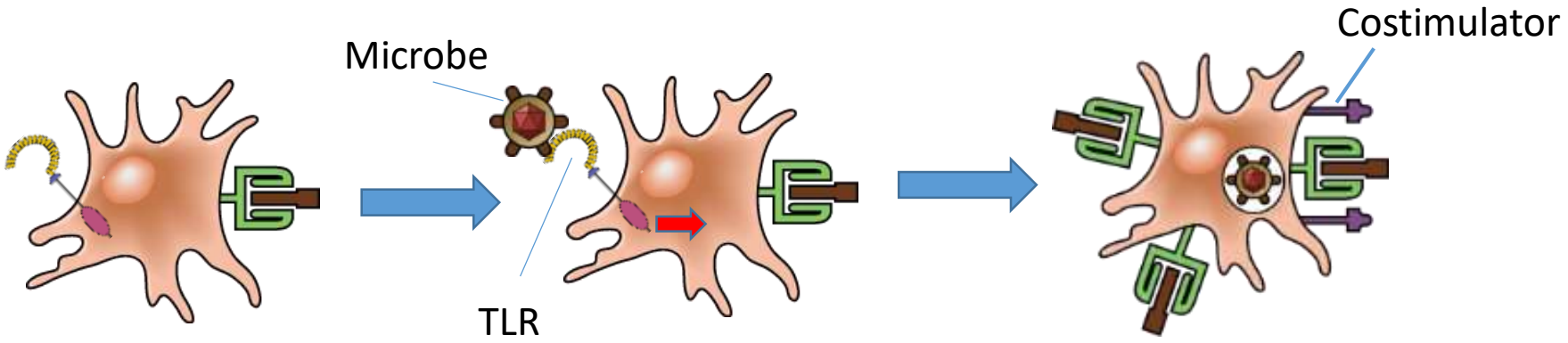
- Additional signals generated by the binding of molecules called costimulators on the APC to costimulatory receptors on the naïve T cell are also necessary for naïve T cell activation. These signals are called "***costimulatory signals***" or "***Signal 2***"

Antigen recognition-Signal 1
Costimulation-Signal 2



Costimulators are “danger signals”

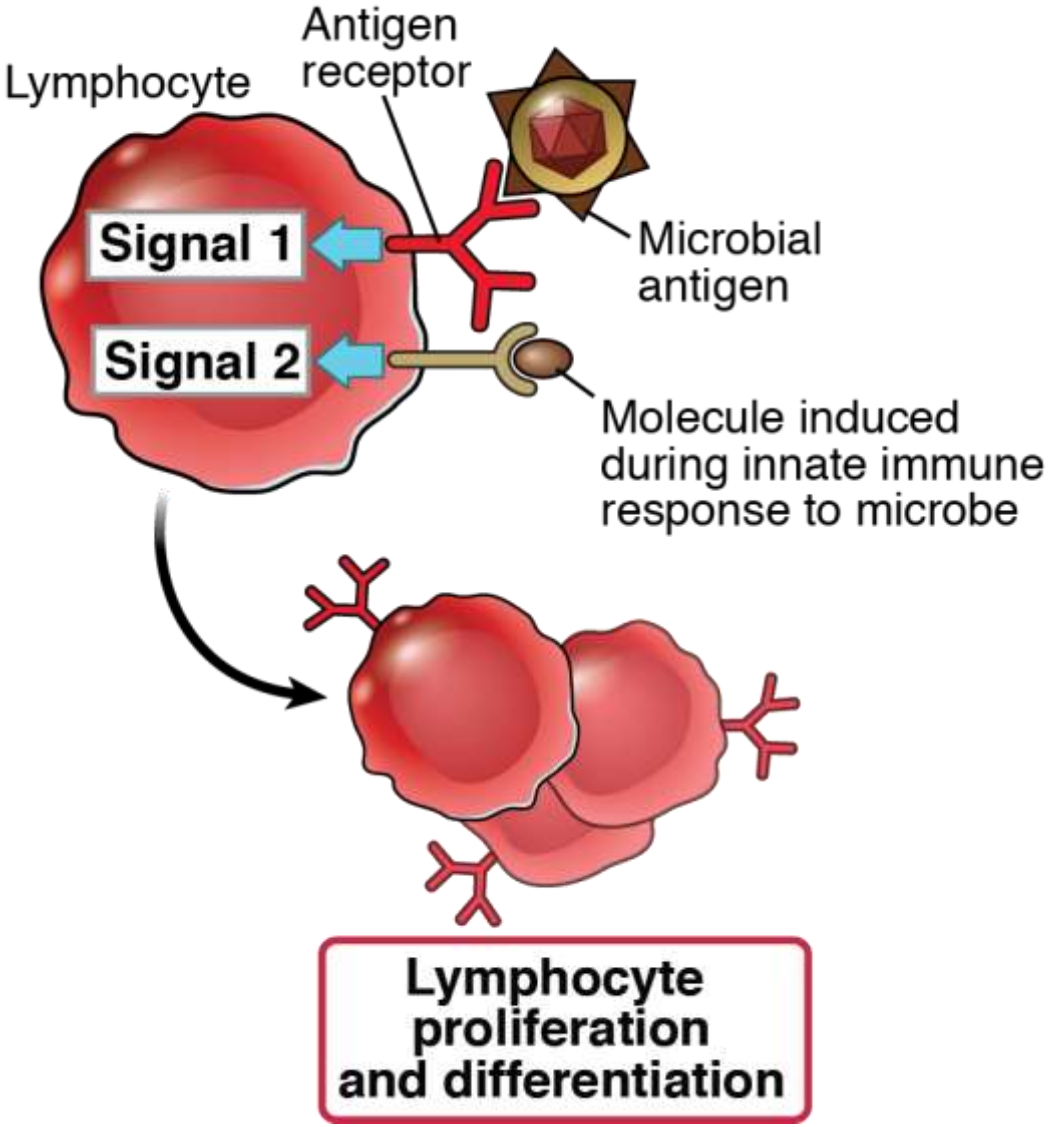
Their expression is up-regulated by innate signals (PAMPs) from microbes



In immune responses to tumors, costimulator expression is up-regulated by innate signals from injured or dead cells (DAMPs)

And also
More MHC
More antigen processing molecules
CCR7
Cytokines

The two-signal requirement for lymphocyte activation

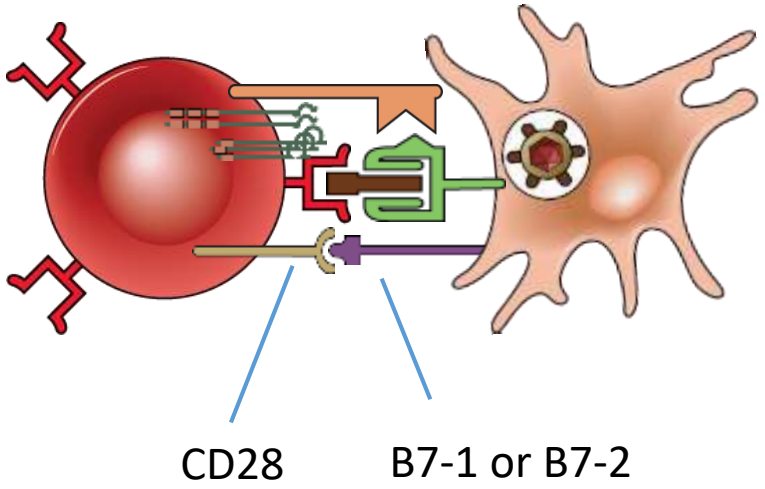


Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

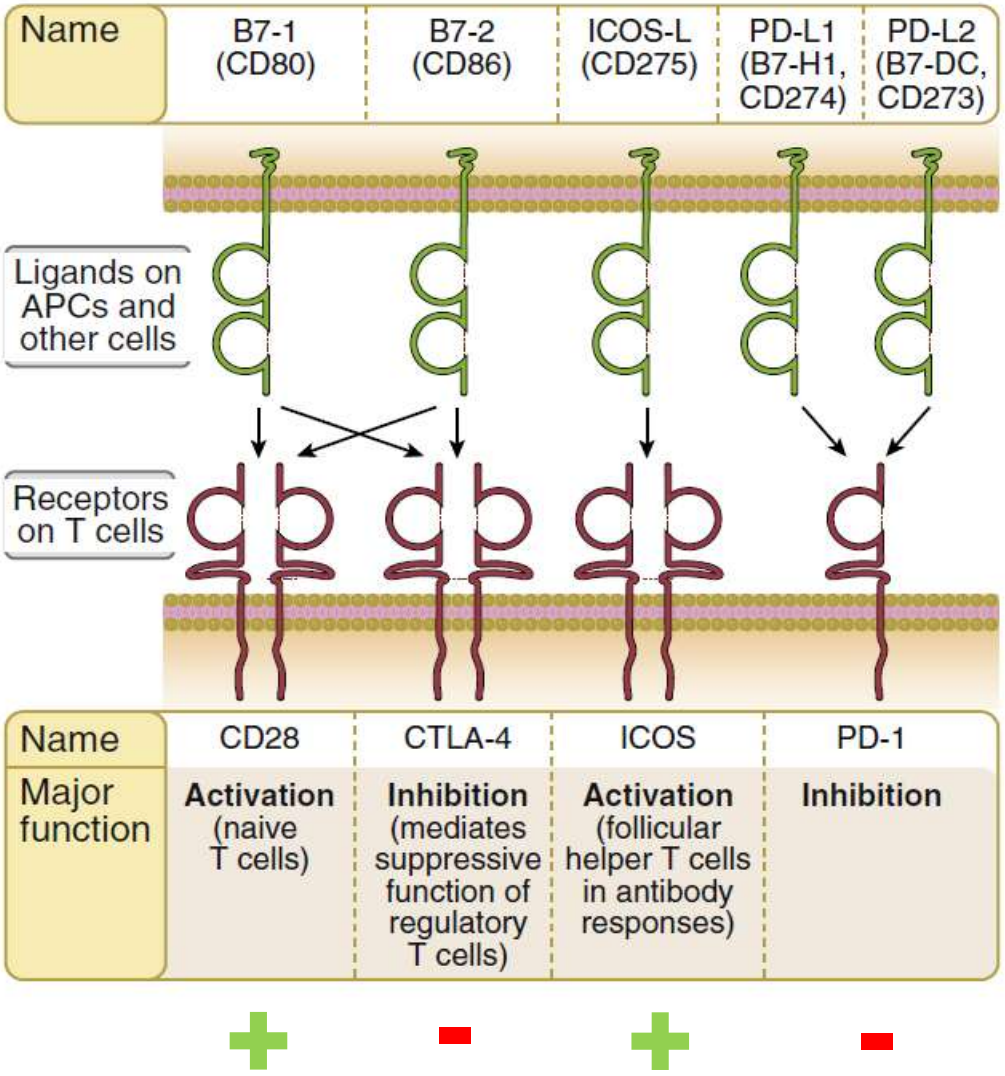
Second signals for B cells: products of complement activation recognized by B cell complement receptors

Costimulators: B7-1, B7-2

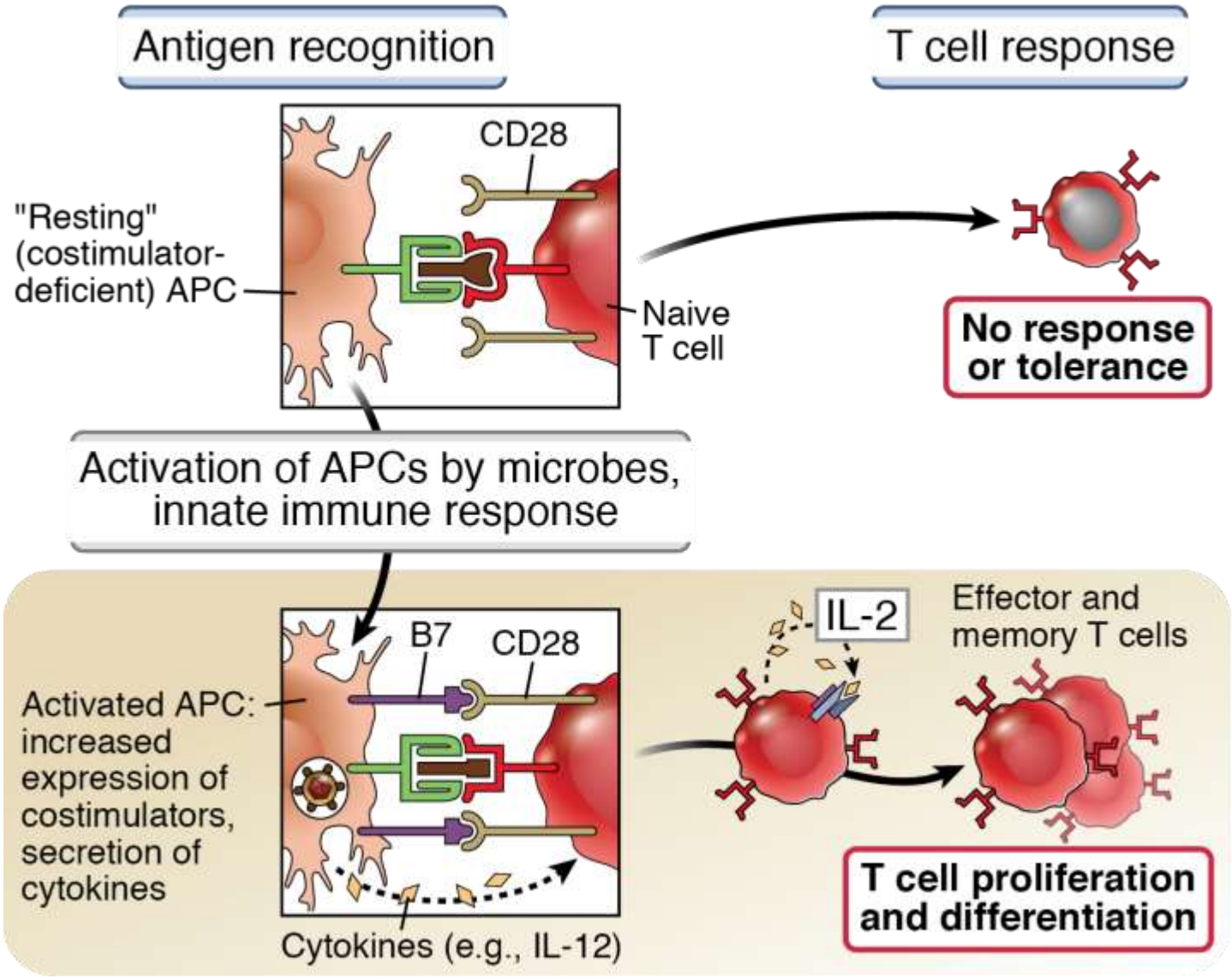
- The best characterized and probably most important costimulators for naïve T cells are B7-1 (CD80) and B7-2 (CD86)
- B7-1 and B7-2 are highly homologous, with similar functions.
- B7-1 and B7-2 are highly expressed on activated DCs
- B7-1 and B7-2 bind to the same receptor on T cells, called CD28
- CD28 is expressed on most T cells



Proteins of the B7 and CD28 families: Costimulatory (and Inhibitory) functions

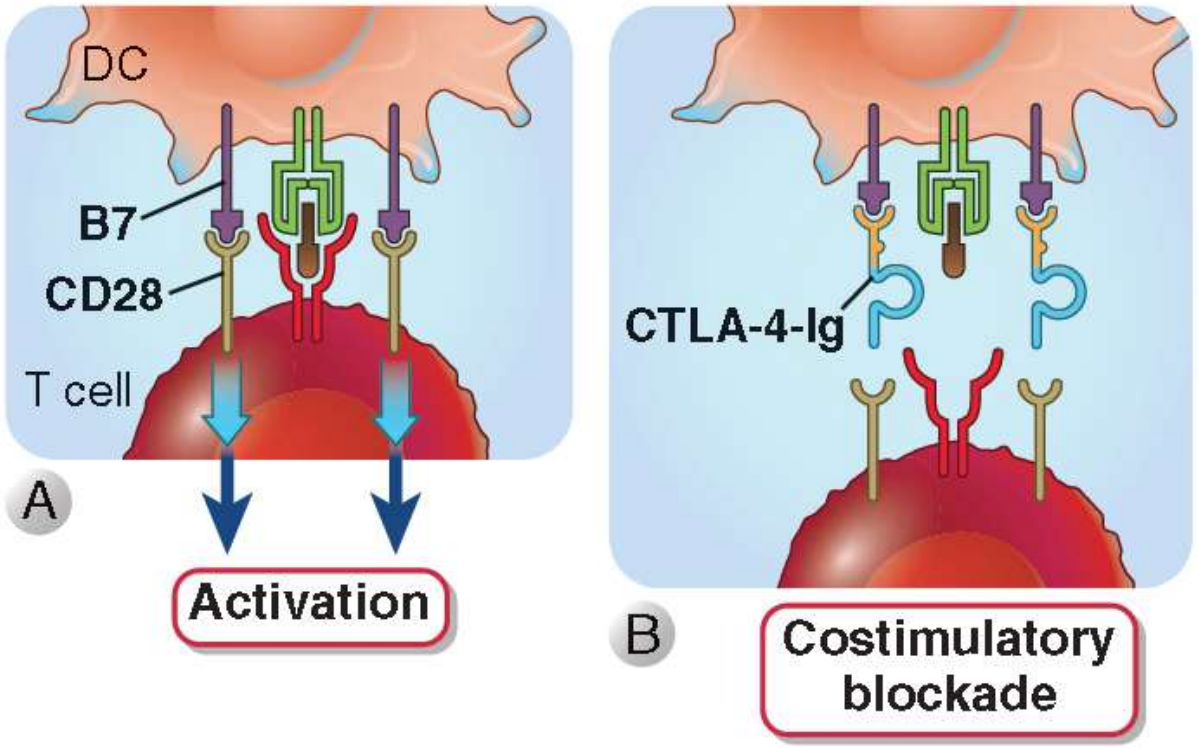


Role of Costimulation in T Cell Activation



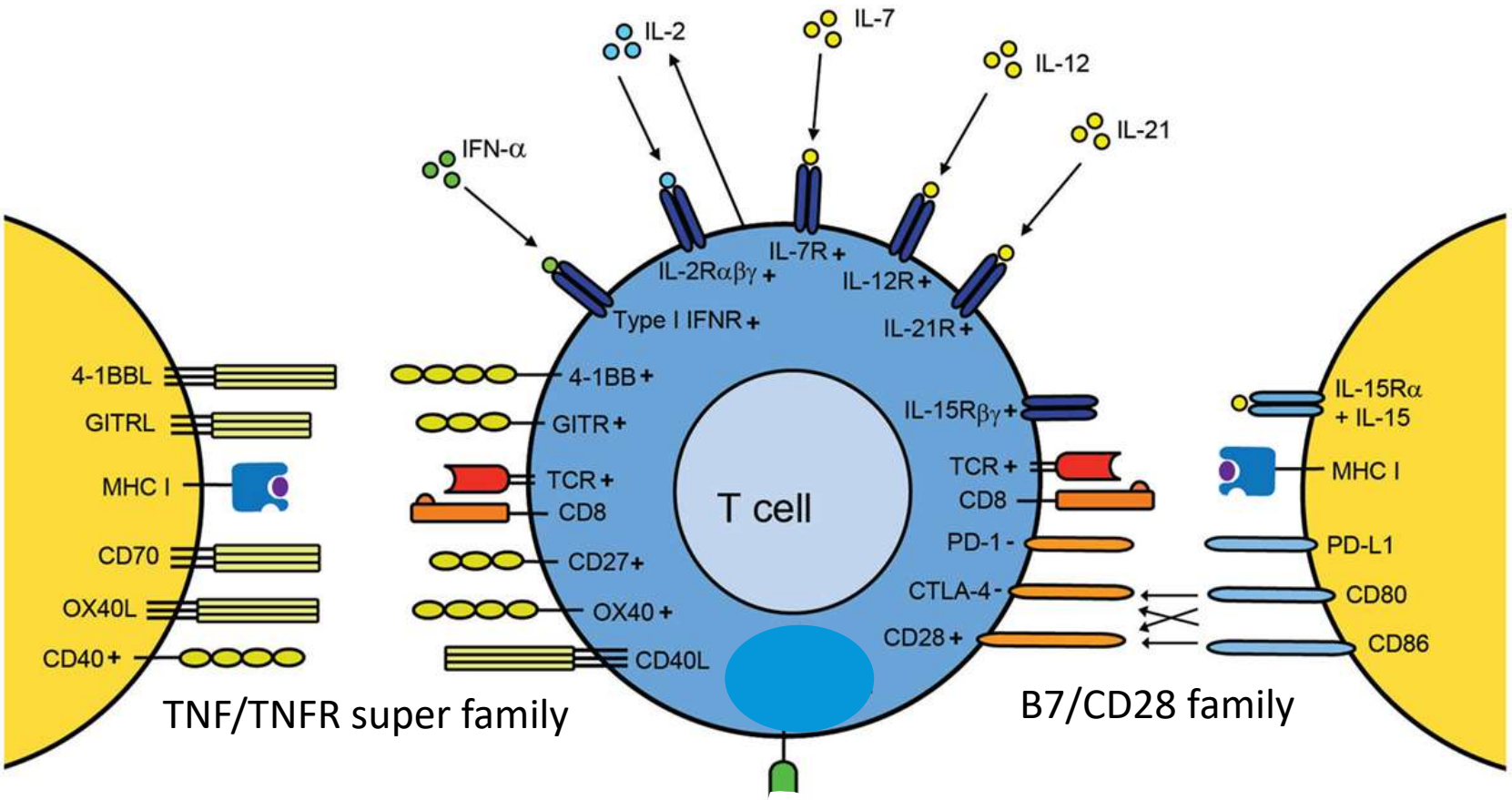
Therapeutics Targeting the B7:CD28 family

Costimulatory blockade



- **CTLA-4-Ig inhibits T cell activation and is used in diseases caused by T cell responses (autoimmunity, graft rejection)**
- **CTLA-4-Ig is a soluble form of CTLA-4, with an IgG-Fc tail for good pharmacokinetics.**
- **CTLA-4 Ig *IS NOT* anti-CTLA-4**

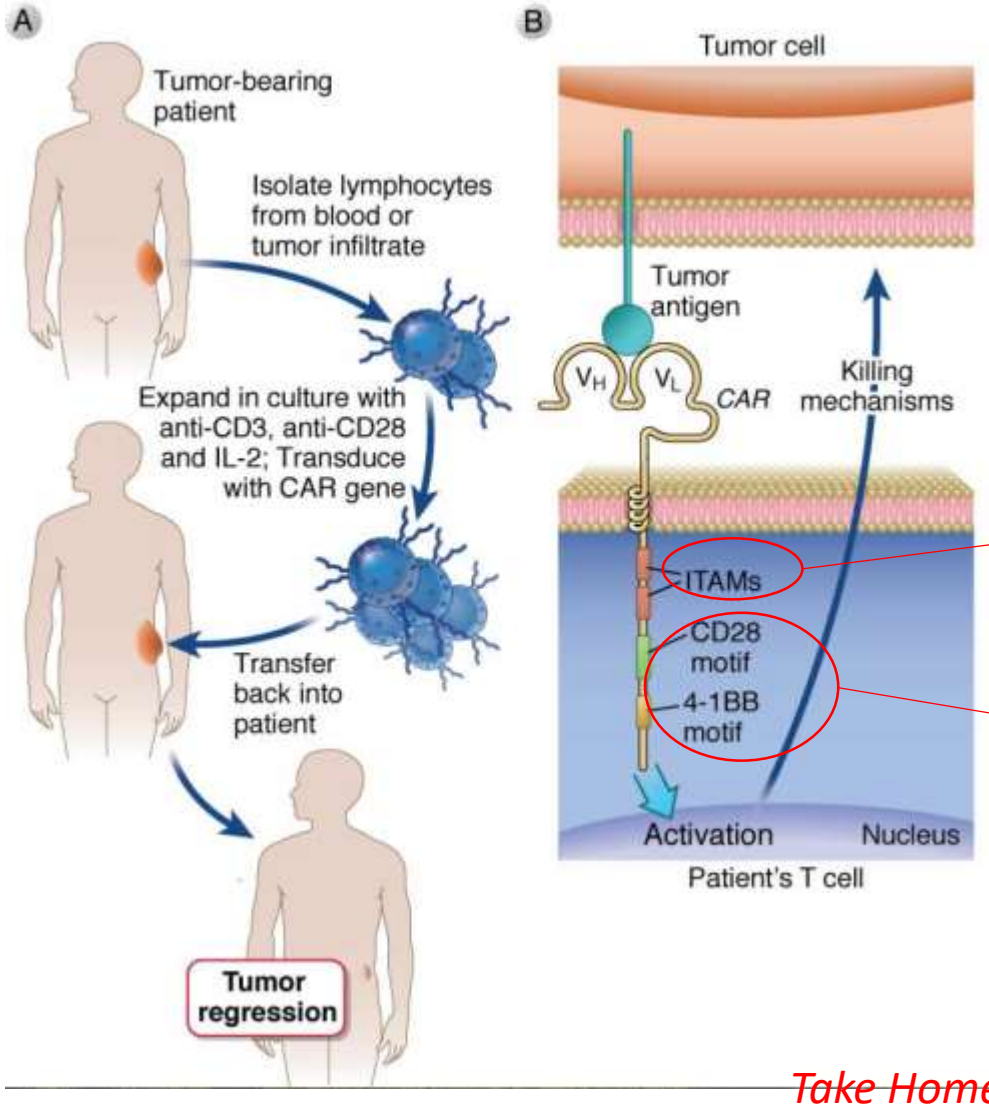
Other T Cell Costimulatory Molecules



Some costimulatory molecules and receptors are not needed for naive T cell activation but rather for maximal effector T cell activation: e.g. 4-1BBL/4-1BB for CTL activation

Relevance of TCR and costimulatory signaling to immunotherpary

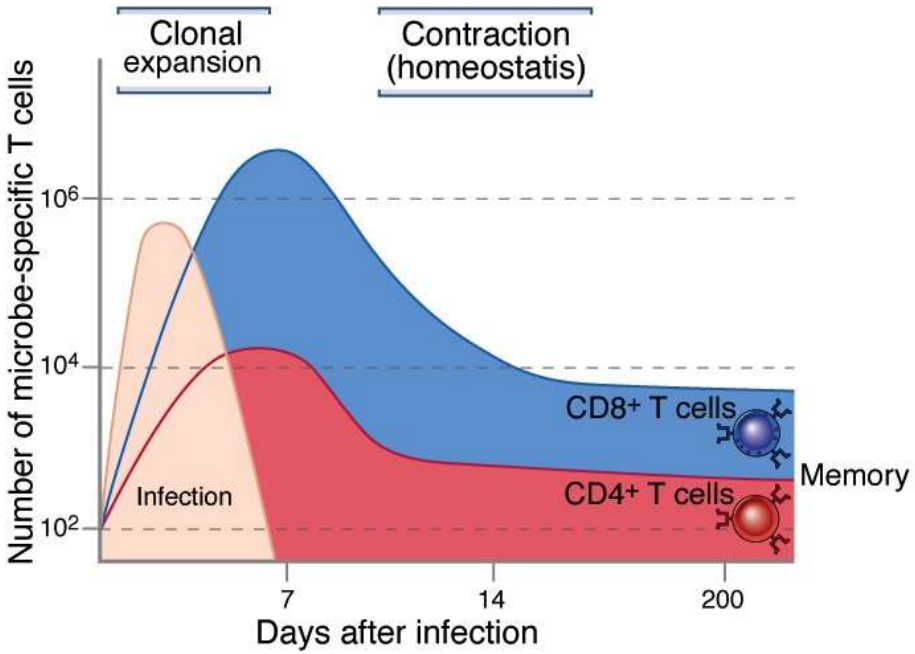
- Chimeric antigen receptors (CARs) make any T cell specific for a tumor antigen
- CARs use TCR-complex and costimulatory signaling motifs to activate the T cells



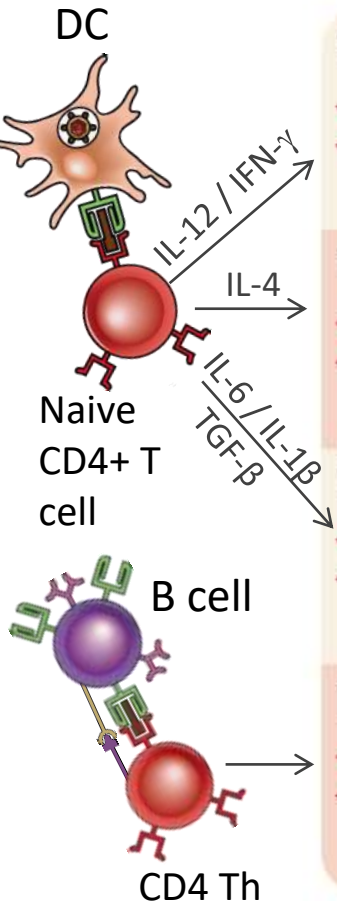
Take Home Points

Clonal Expansion of T cells

- **Stimulated mainly by autocrine IL-2**
  - **Antigen recognition → secretion of IL-2 and expression of high-affinity IL-2 receptors → preferential expansion of antigen-specific cells**
- **CD8+ T cells may expand >50,000-fold within a week after an acute viral infection**
  - **Up to 10% of all CD8+ T cells in the blood may be specific for a pathogen**
  - **Minimal expansion of "bystander" cells (not specific for the virus)**
  - **CD8+ cells expand much more than do CD4+ cells**

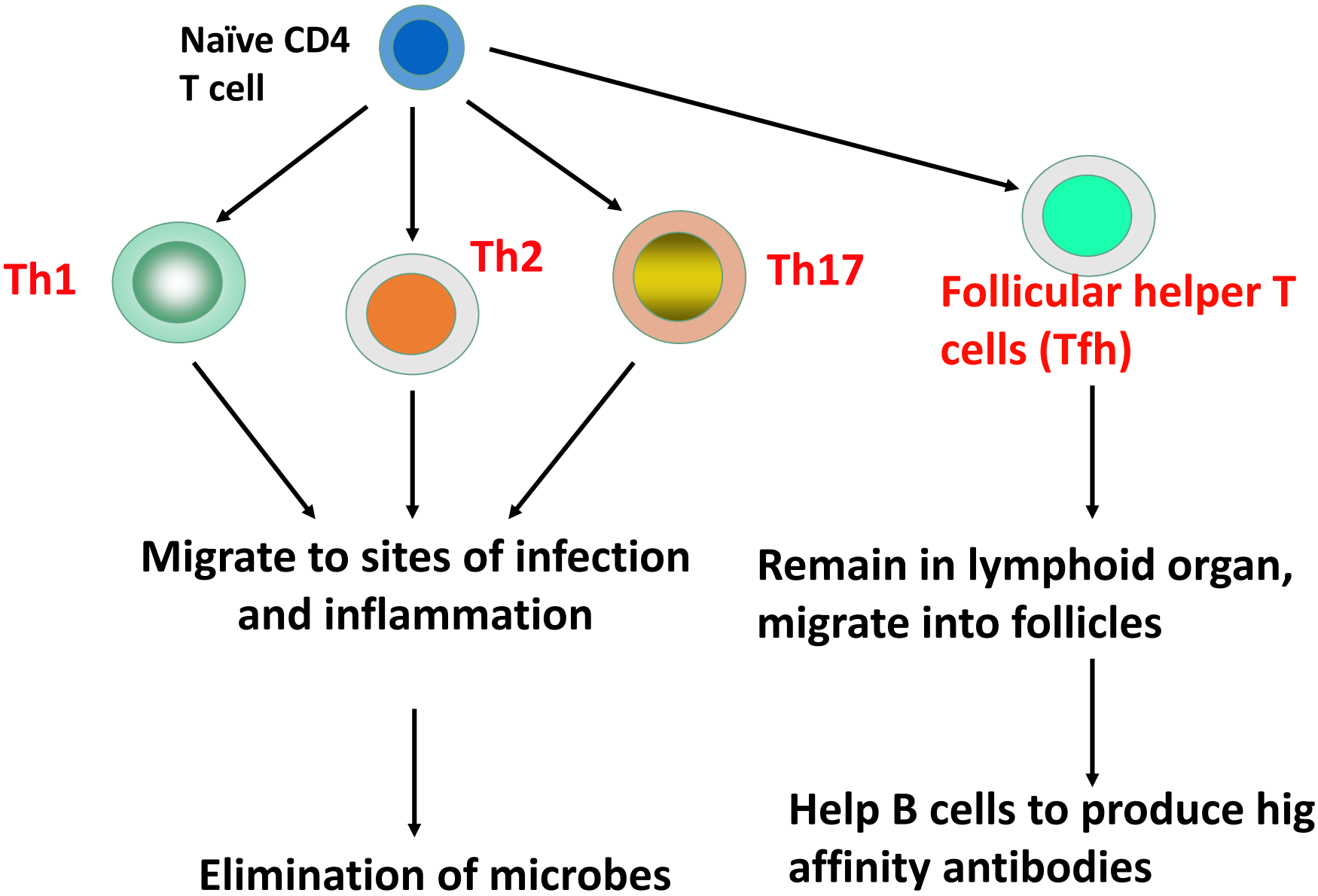


CD4+ Helper T Cell (Th) Subsets

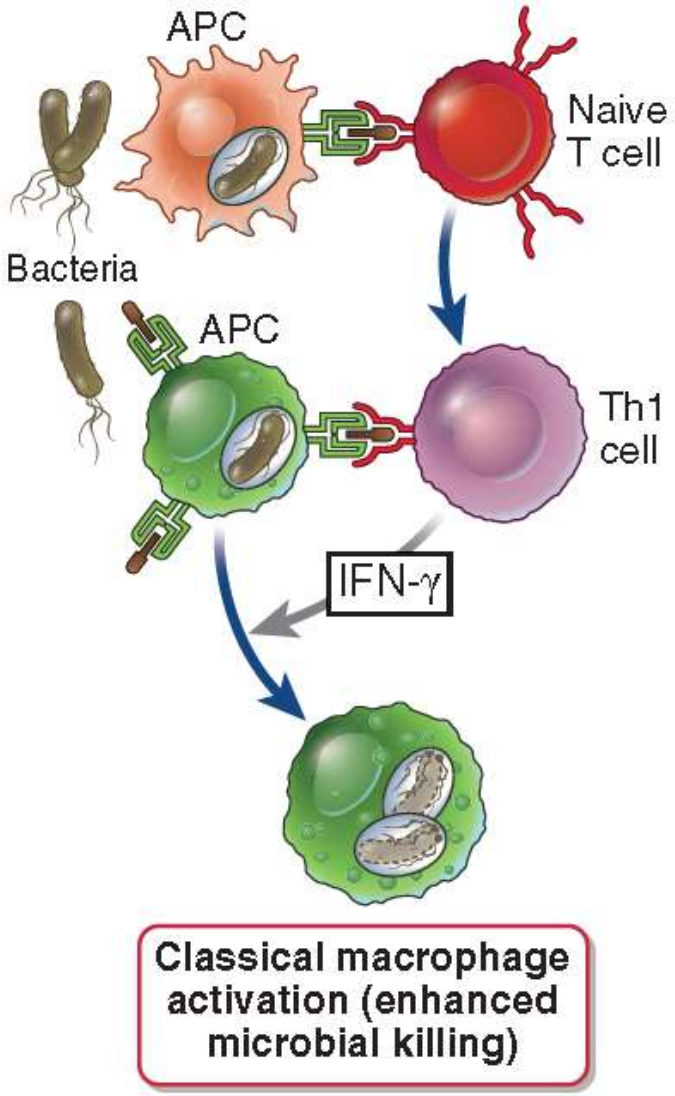


Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense	Role in disease
Th1	IFN-γ	Macrophages	Macrophage activation	Intracellular pathogens	Autoimmunity; chronic inflammation
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy
Th17	IL-17 IL-22	Neutrophils	Neutrophil recruitment and activation	Extracellular bacteria and fungi	Autoimmunity; inflammation
Tfh	IL-21 (and IFN-γ or IL-4)	B cells	Antibody production	Extracellular pathogens	Autoimmunity (autoantibodies)

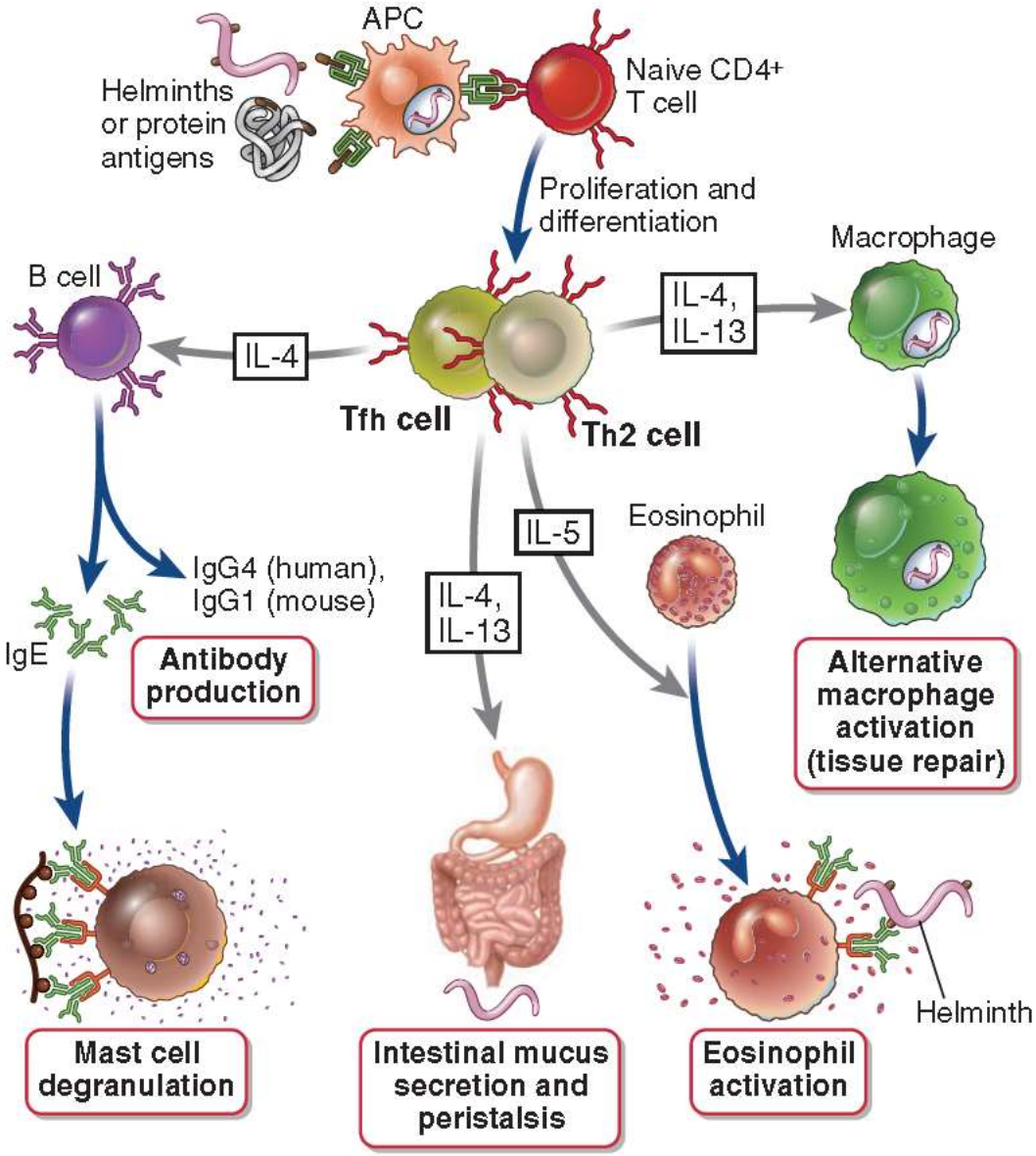
CD4 Effector T Cell Subsets



Effector functions of TH1 Cells: Phagocyte-Mediated Host Defense

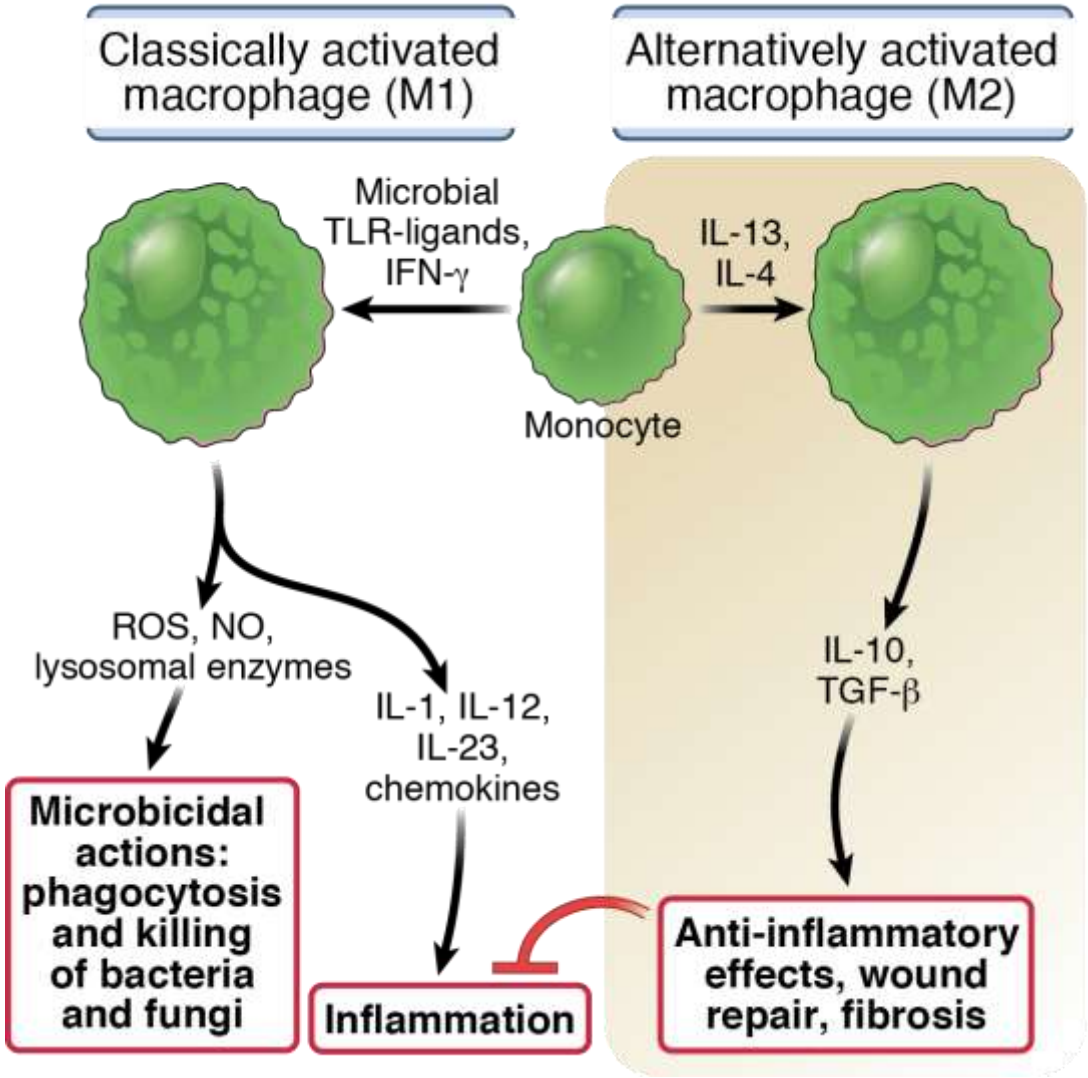


Effector Functions of Th2 Cells



Most relevant for tumor immunity: Good for tumors, bad for immunotherapy

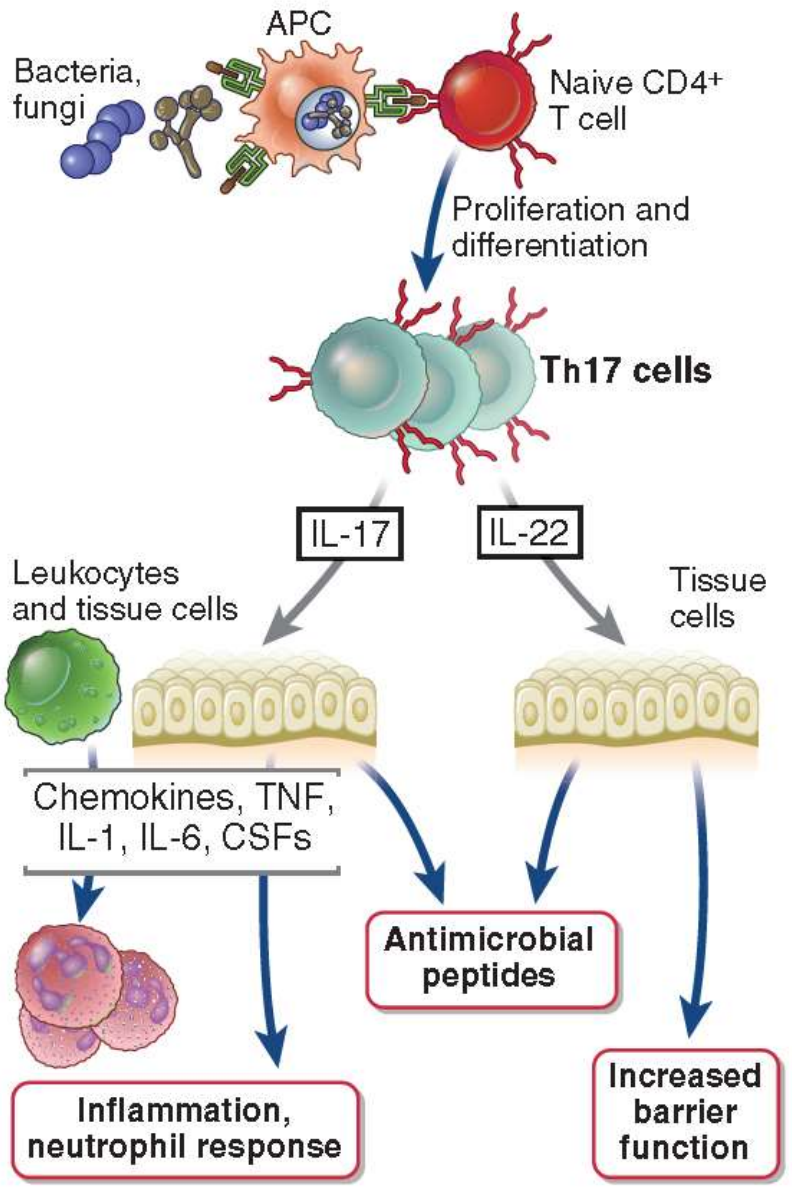
Classical and Alternative Macrophage Activation



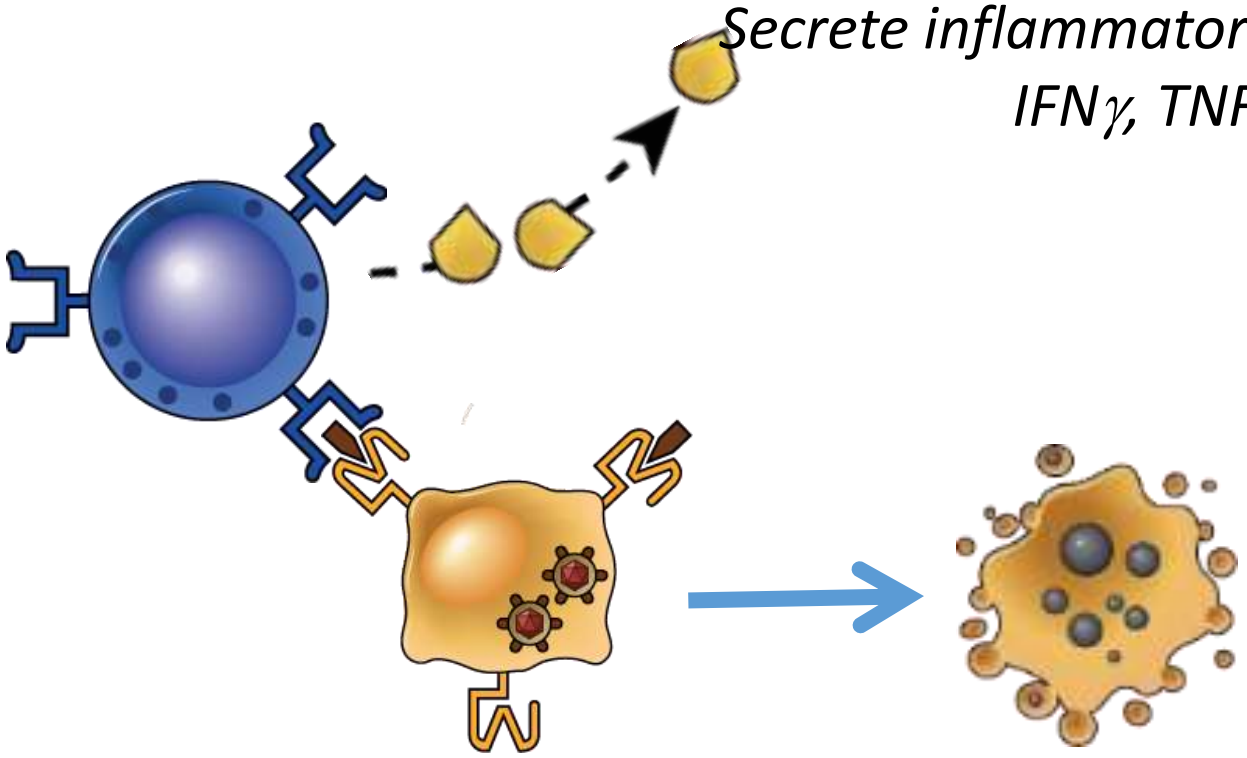
Chronic inflammation
Tumor destruction

Fibrosing disorders
Tumor promotion

Effector functions of Th17 Cells



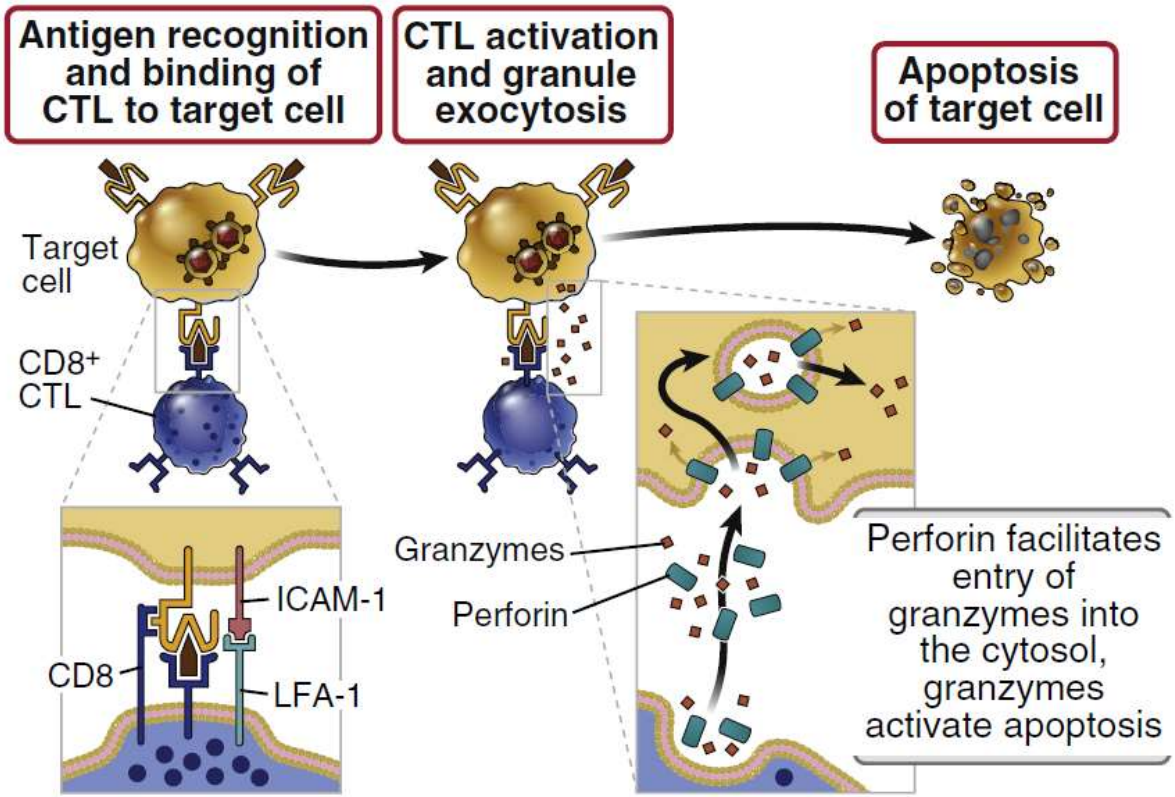
Two Main Effector Functions of CTLs



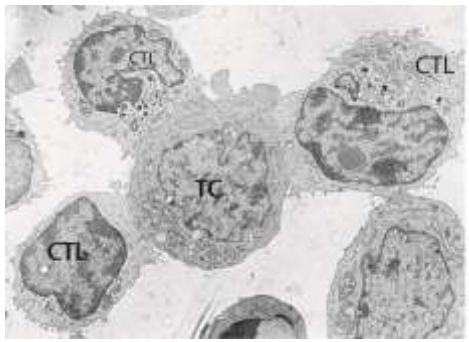
Secrete inflammatory cytokines:
IFNγ, TNF

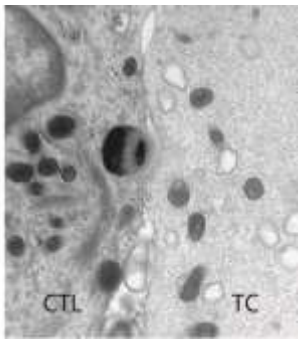
Directly kill infected cells, tumor cells

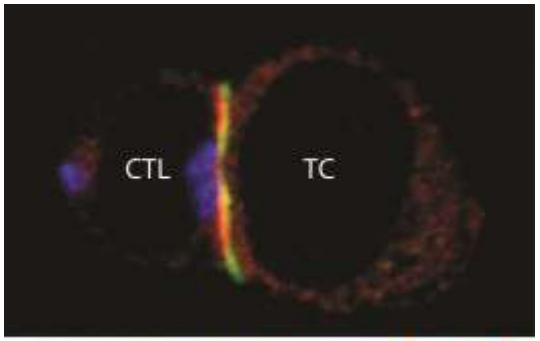
Mechanisms of CTL killing of infected cells



Note:
NK cells use same Perforin/Granzyme mechanisms to kill cells. But NK cells don't have TCRs, and are activated by different mechanisms.







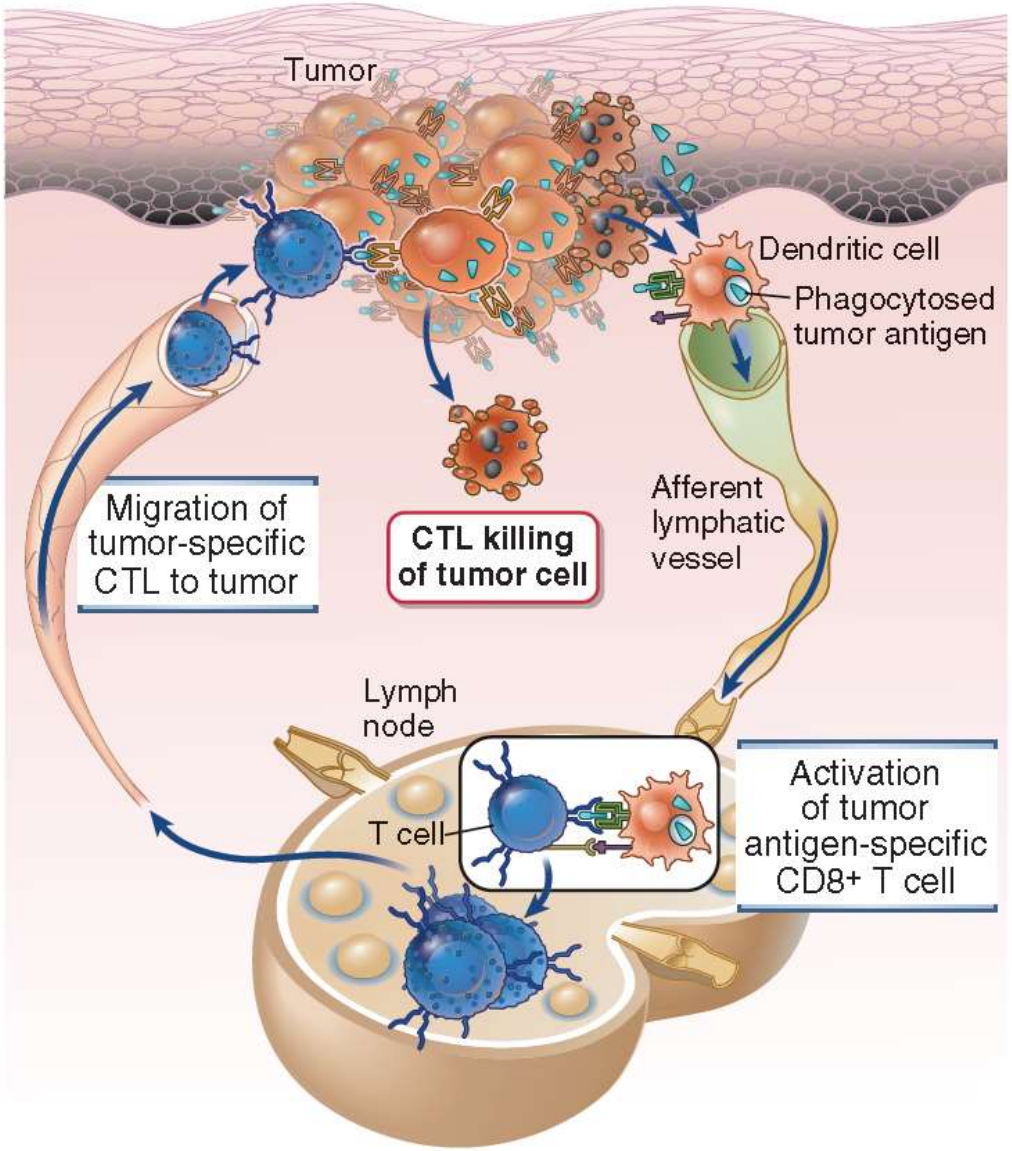
Cathepsins (blue), LFA-1 (green), Talin (red)

Immune synapse

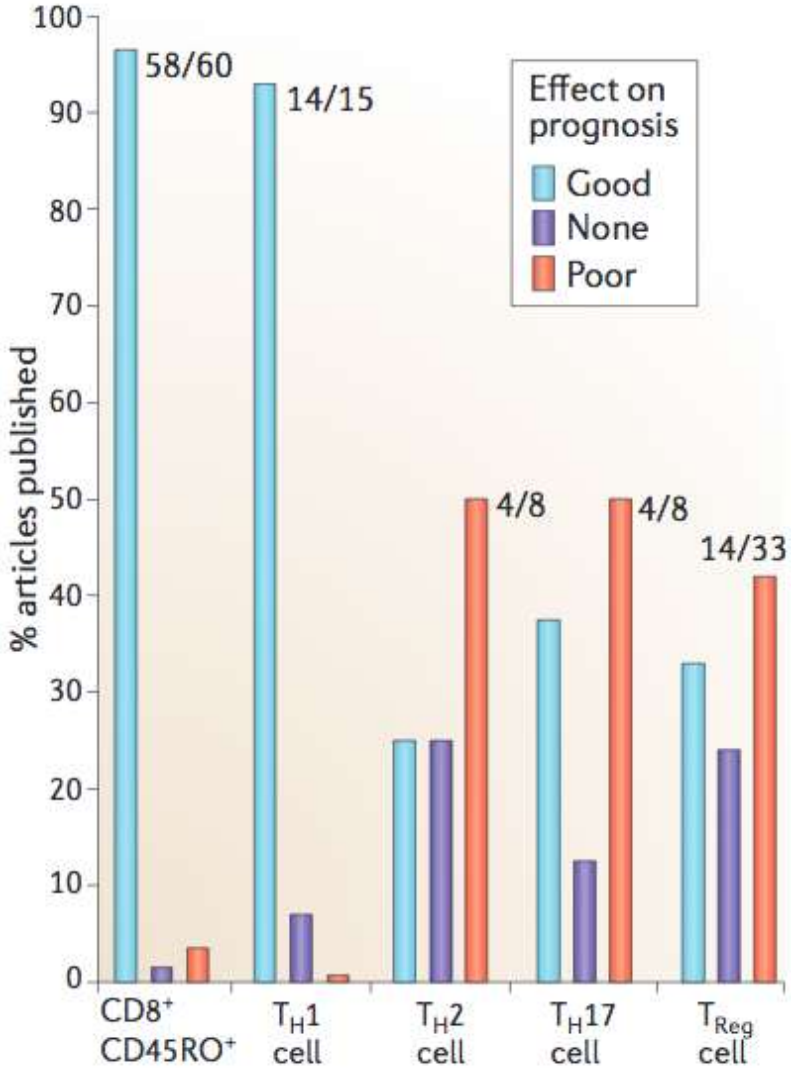
CTL Serial Killing and Self Protection

- CTLs are serial killers. One CTL cell can sequentially kill several target cells and survive
- The CTL may protect itself by cathepsins that degrade released perforin that binds to the CTL membrane
- Perforin molecules that diffuse away are inhibited by plasma lipids
- The formation of an immune synapse between a CTL and its target cell limits bystander cell damage.
- Bystander cells (e.g. antigen presenting cells) may be protected from death by expressing specific and irreversible granzyme inhibitors (serpins).

Putting it all together: CTL response against tumors



T Cell Effector Subsets in Cancers That Predict Better Survival



Analysis of 124 published articles on correlation of T cell subsets and prognosis of 20 cancer types

Fridman et al. Nat Rev Cancer 12:298, 2012