T Cell Mediated Immunity:
Selected Features Relevant to Cancer Immunotherapy

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Lecture Outline

- Overview of T cell functions
- T cell antigen recognition/ MHC restriction
- Antigen receptor signaling
- Costimulation
- Effector T cell subsets (Th subsets and CTLs)
- Molecules that inhibit T cells (CTLA-4, PD-1, others)
- Cells that inhibit T cells (Treg)

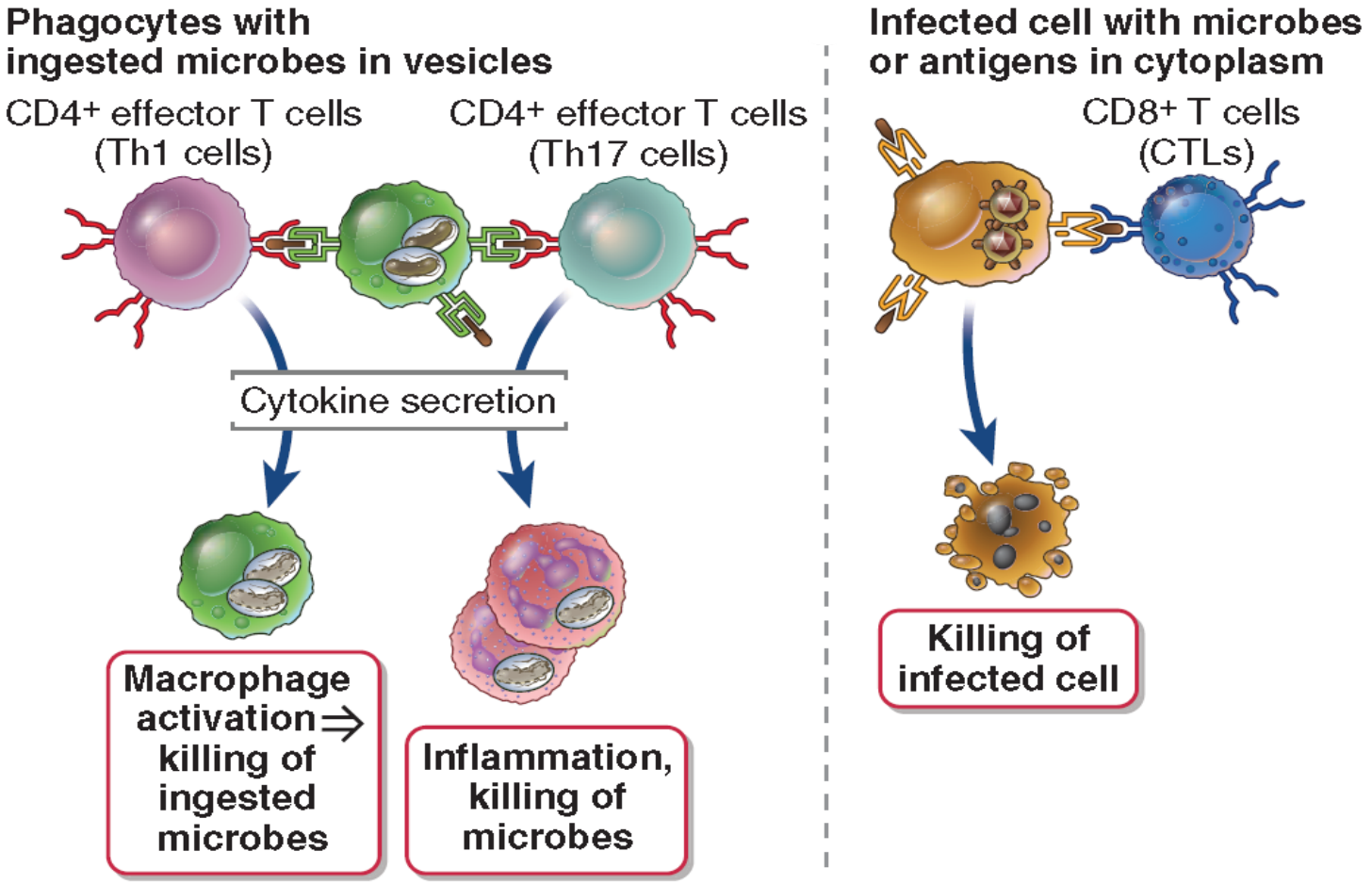
Types of T Cell–Mediated Immune Reactions

CD4+ helper T cells (Th)

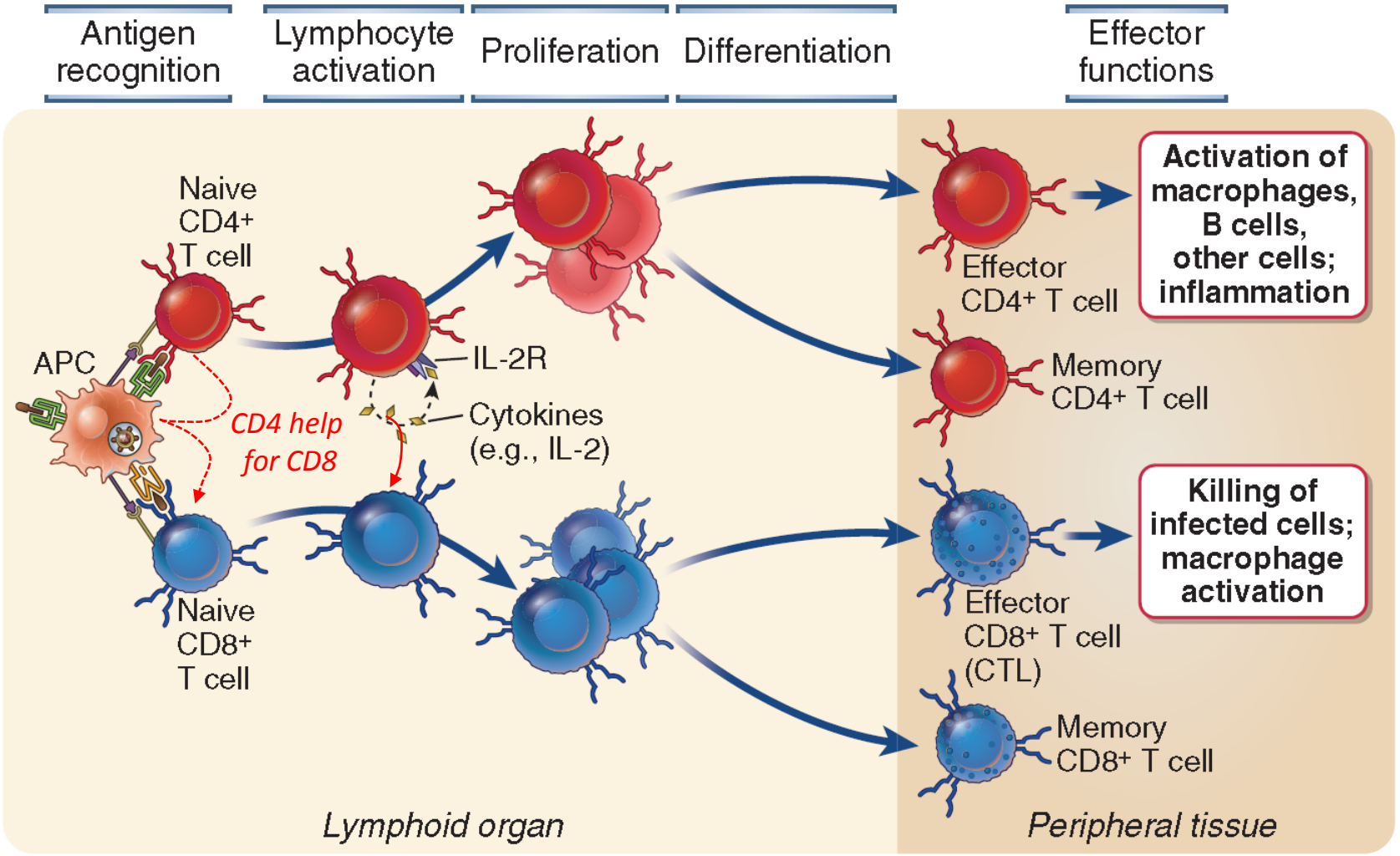
Microbes that live inside phagocytes
Microbes that are readily killed by phagocytes

CD8+ Cytotoxic T lymphocytes (CTL)

Microbes that live inside
tissue cells

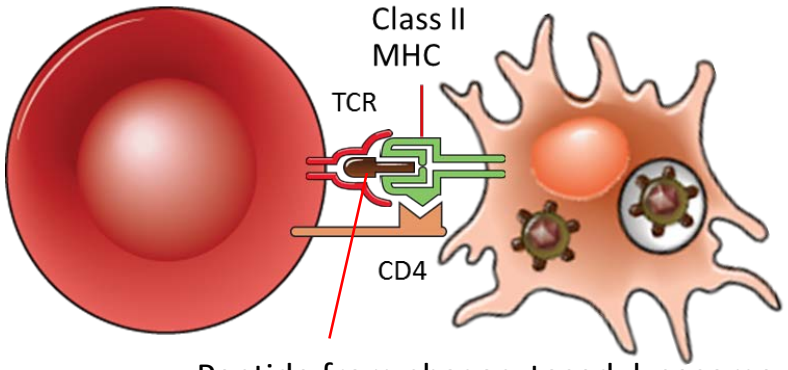


Sequence of events in T cell responses



CD4+ and CD8+ T cells
Antigen recognition/ MHC Class Restriction

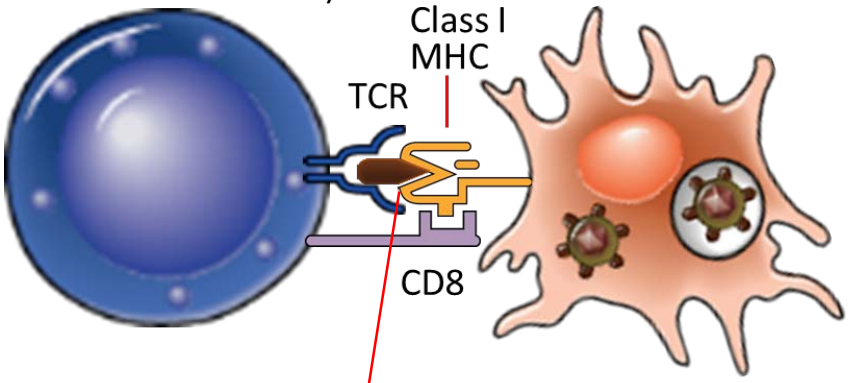
CD4+ T cells (helper T cells)



Peptide from phagocytosed, lysosome-processed protein (microbial, tumor, normal self)

CD4+ T cell recognition is class II MHC restricted

CD8+ T cells (cytotoxic T lymphocytes)



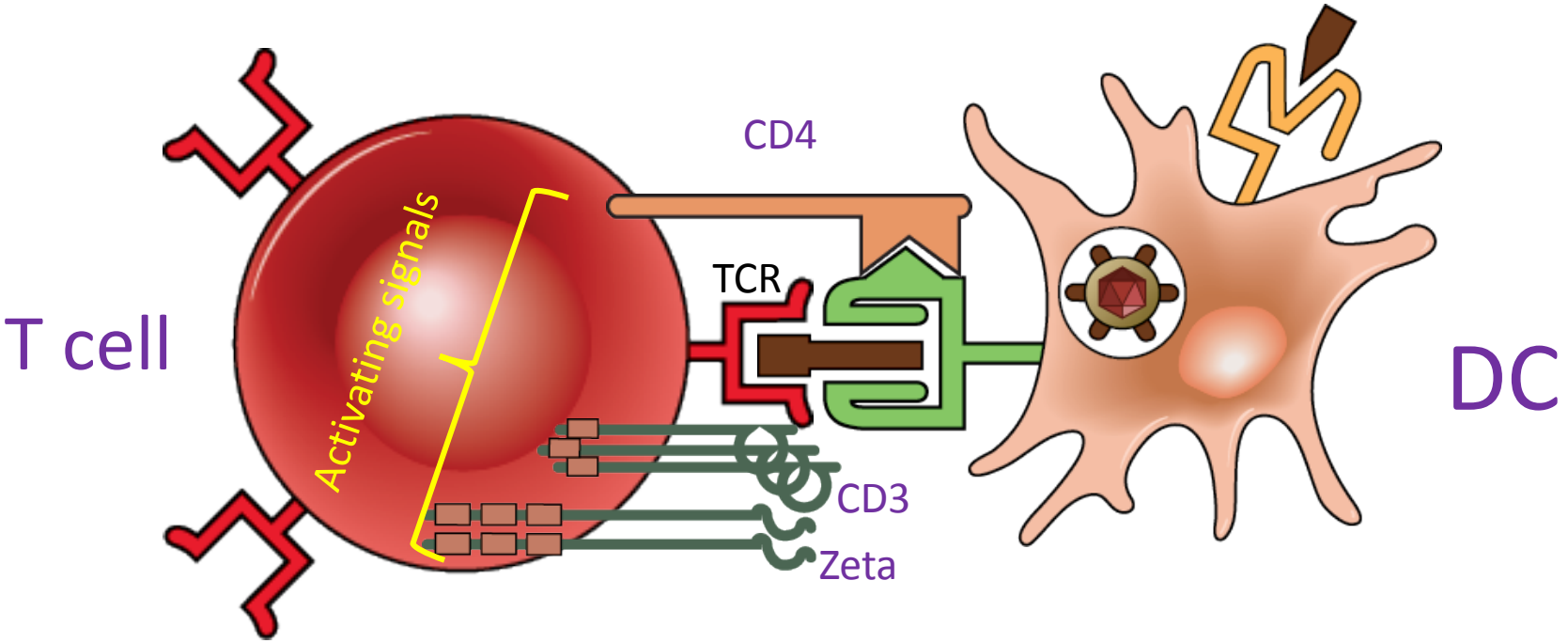
Peptide from cytosolic, proteasome-processed protein (microbial, tumor, normal self)

CD8+ T cell recognition is class I MHC restricted

Signaling Events in T Cell Activation

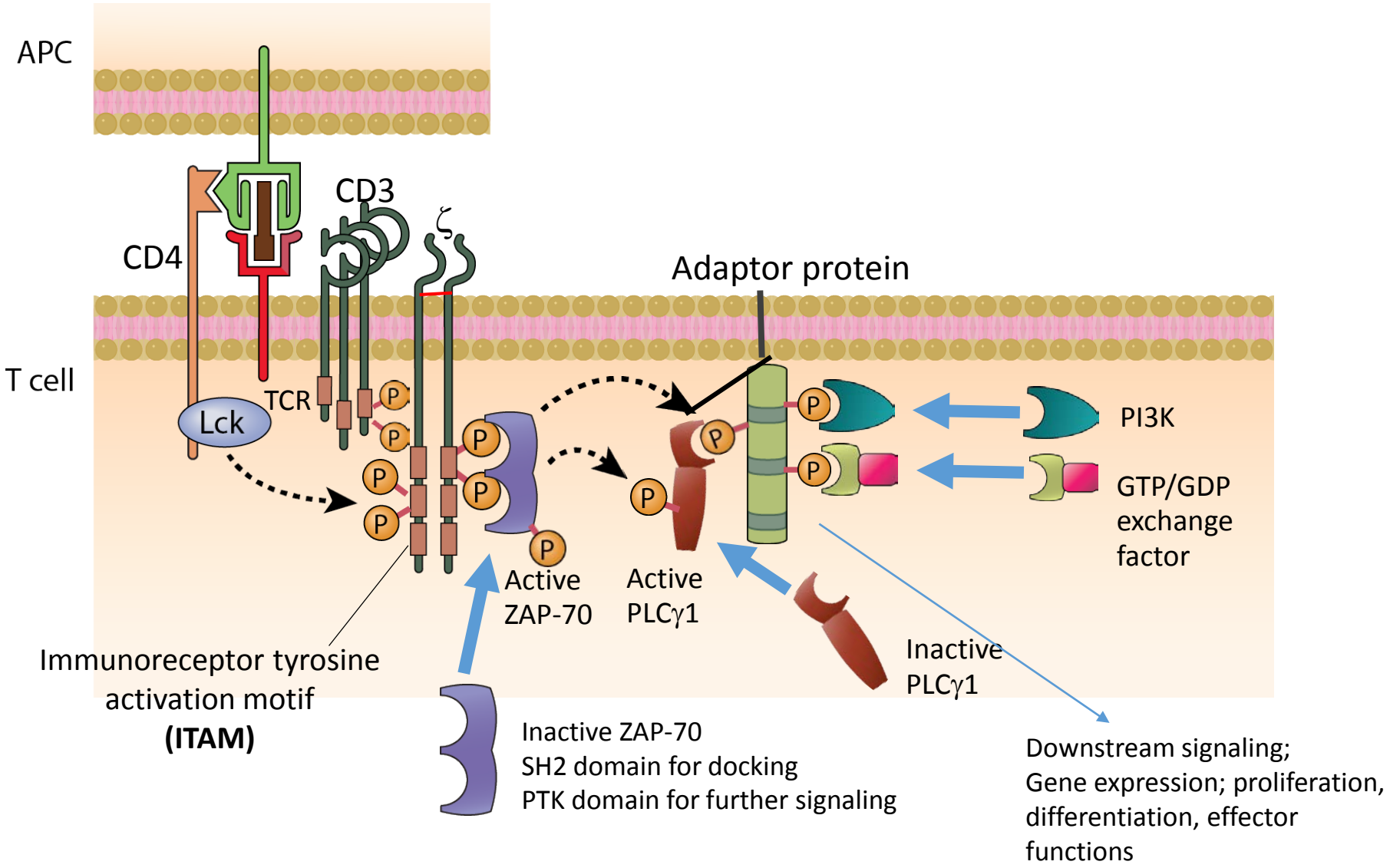
The signals generated by antigen recognition require the participation of cytoplasmic tails of:

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



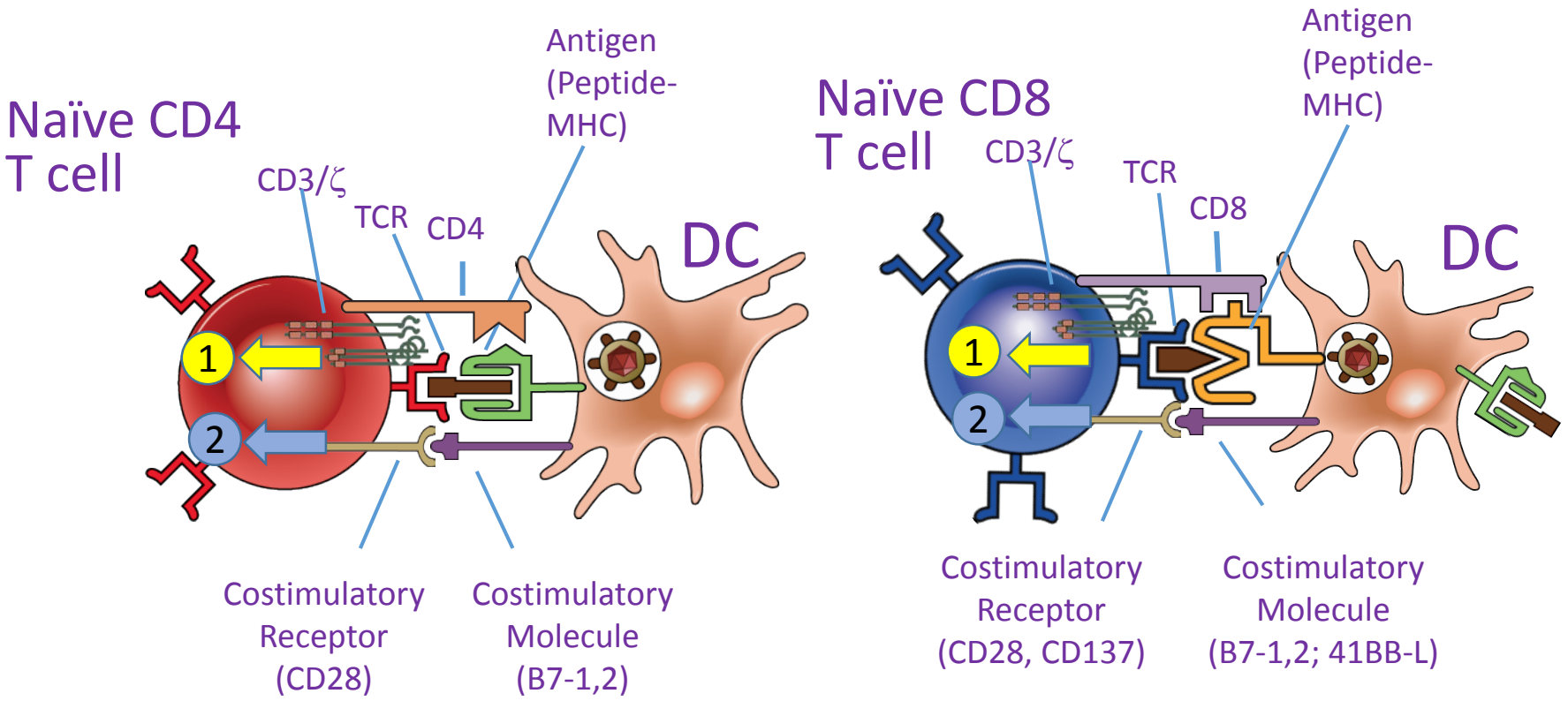
Relevant to activation of naive T cells (initiation) and activation of effector T cell

TCR signaling: Protein tyrosine kinase (PTK)-mediated ITAM phosphorylation, recruitment and activation of other enzymes

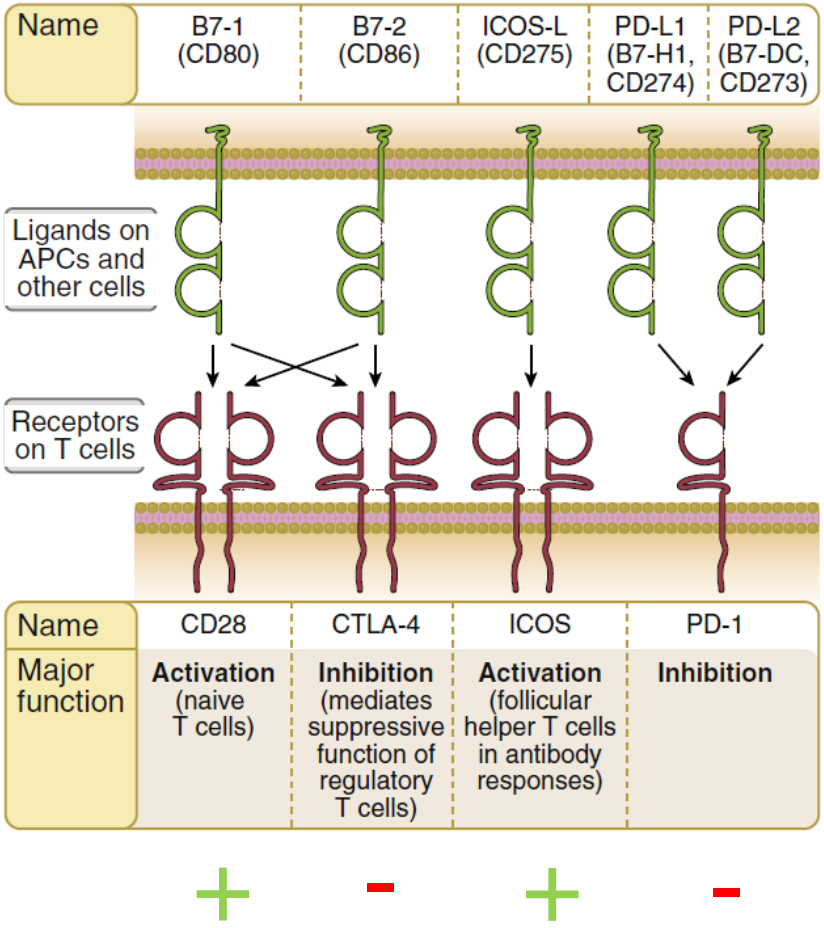


Antigen recognition-Signal 1: Costimulation-Signal 2

- TCR binding to pMHC antigen to MHC is necessary to generate intracellular signals that activate the naïve T cell, ….***but*** is not sufficient. (“***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. (“***costimulatory signals***” or “***Signal 2***”)
- Signal 1 without signal 2 leads to anergy, death or Treg differentiation: peripheral tolerance

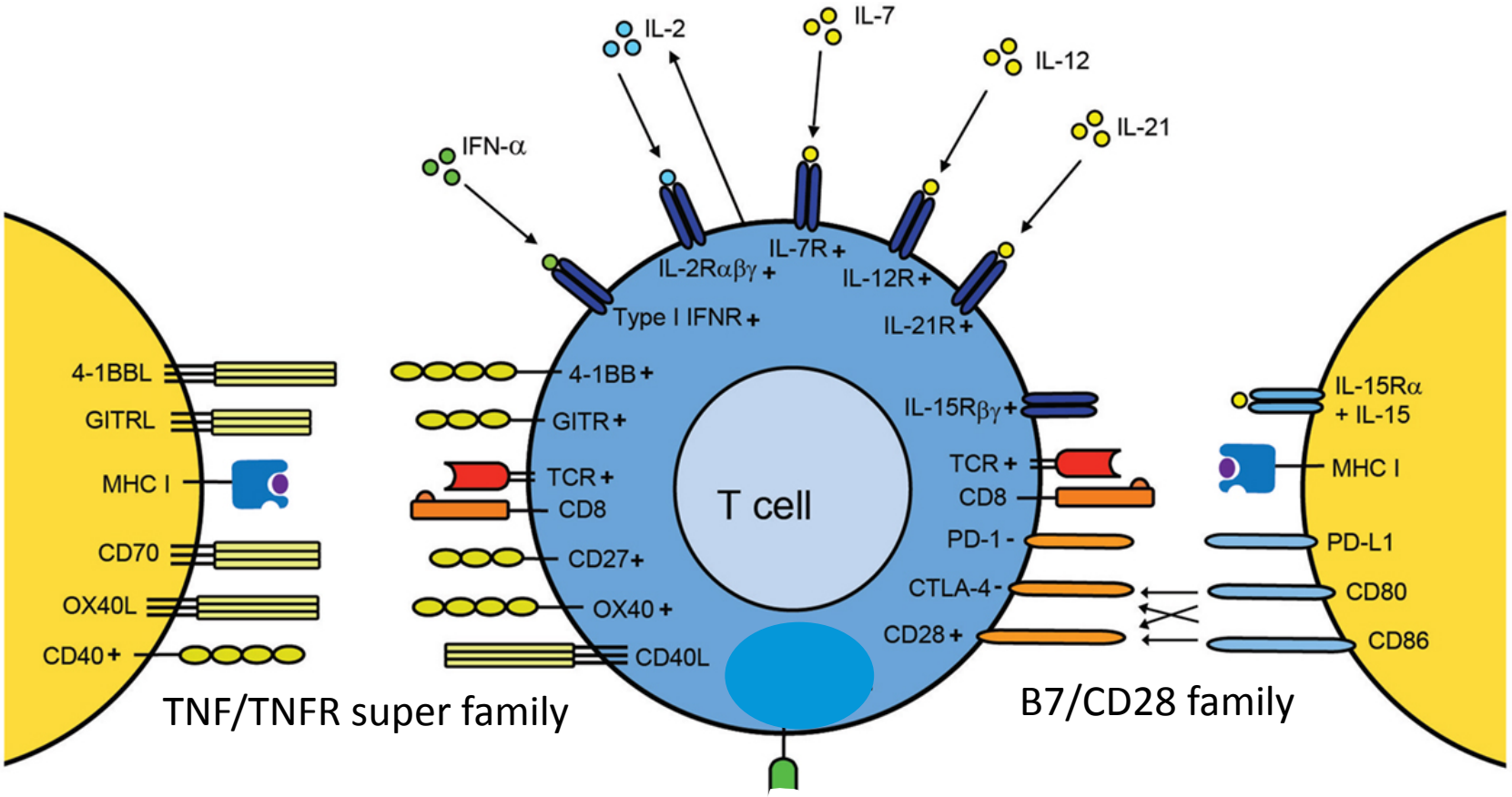


Proteins of the B7 and CD28 families: Costimulatory and inhibitory functions



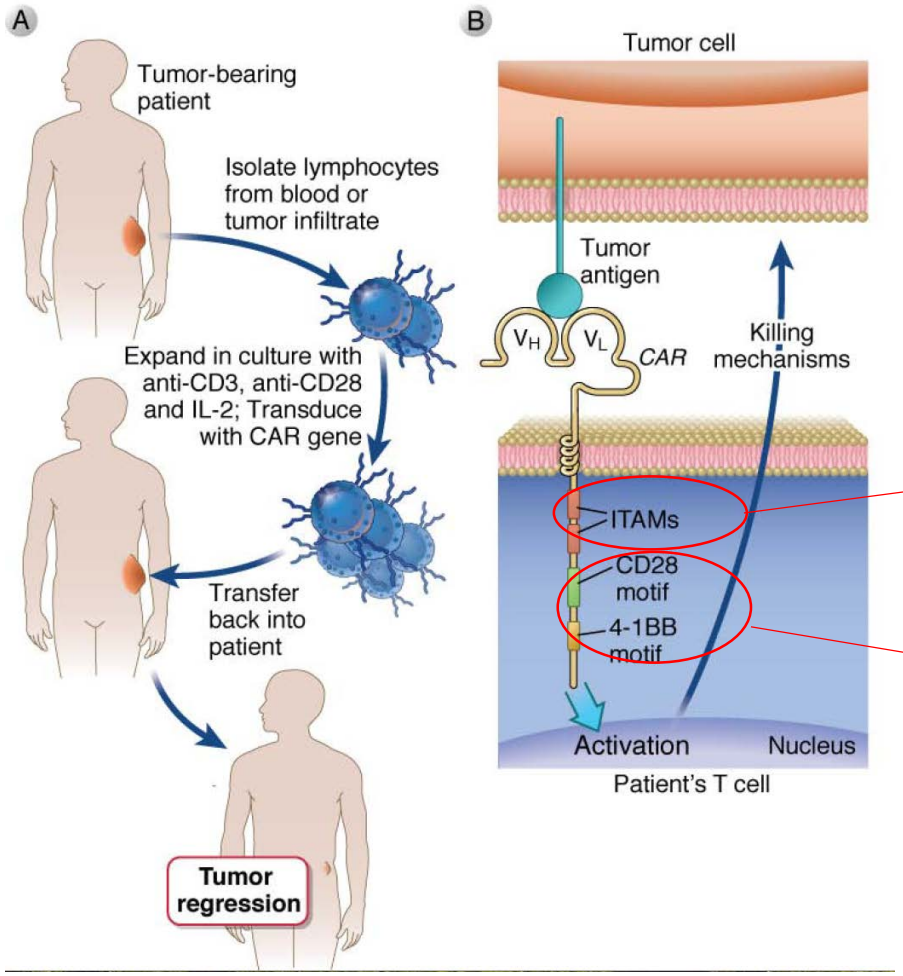
- All are members of Ig superfamily
- B7-1, B7-2 and ICOS-L are costimulators
- CD28 and ICOS are costimulatory receptors
- B7-1 (CD80) and B7-2 (CD86) are the best characterized and probably most important costimulators for naïve T cells
  - B7-1 and B7-2 are highly homologous, with similar functions.
  - 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

Other T Cell Costimulatory Molecules

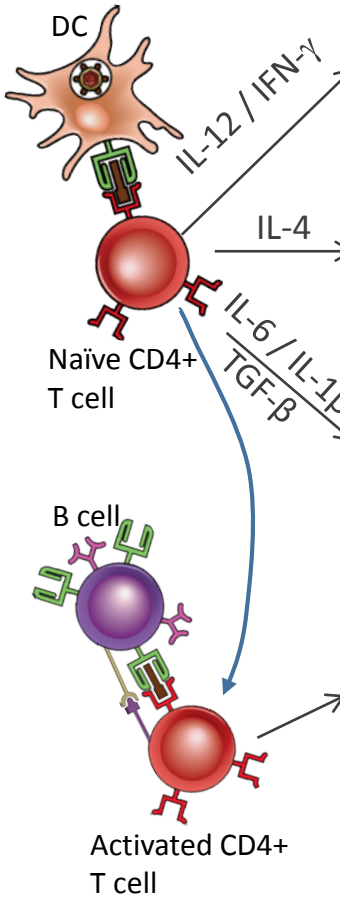


Relevance of TCR and costimulatory signaling to immunotherapy

- 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

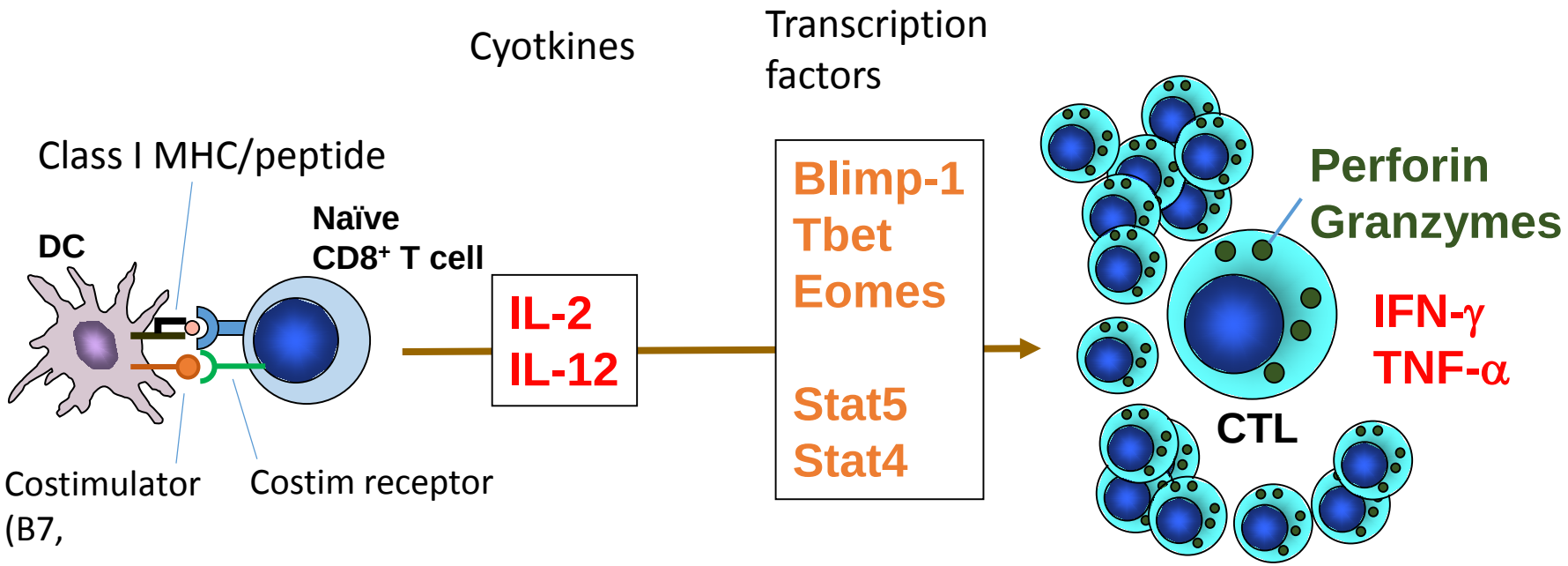


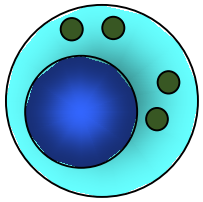
Properties of the major subsets of CD4 + helper T cells



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 (Blocks tumor growth)
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths	Allergy (Promotes tumor growth)
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)

Differentiation and function of CD8+ T cells

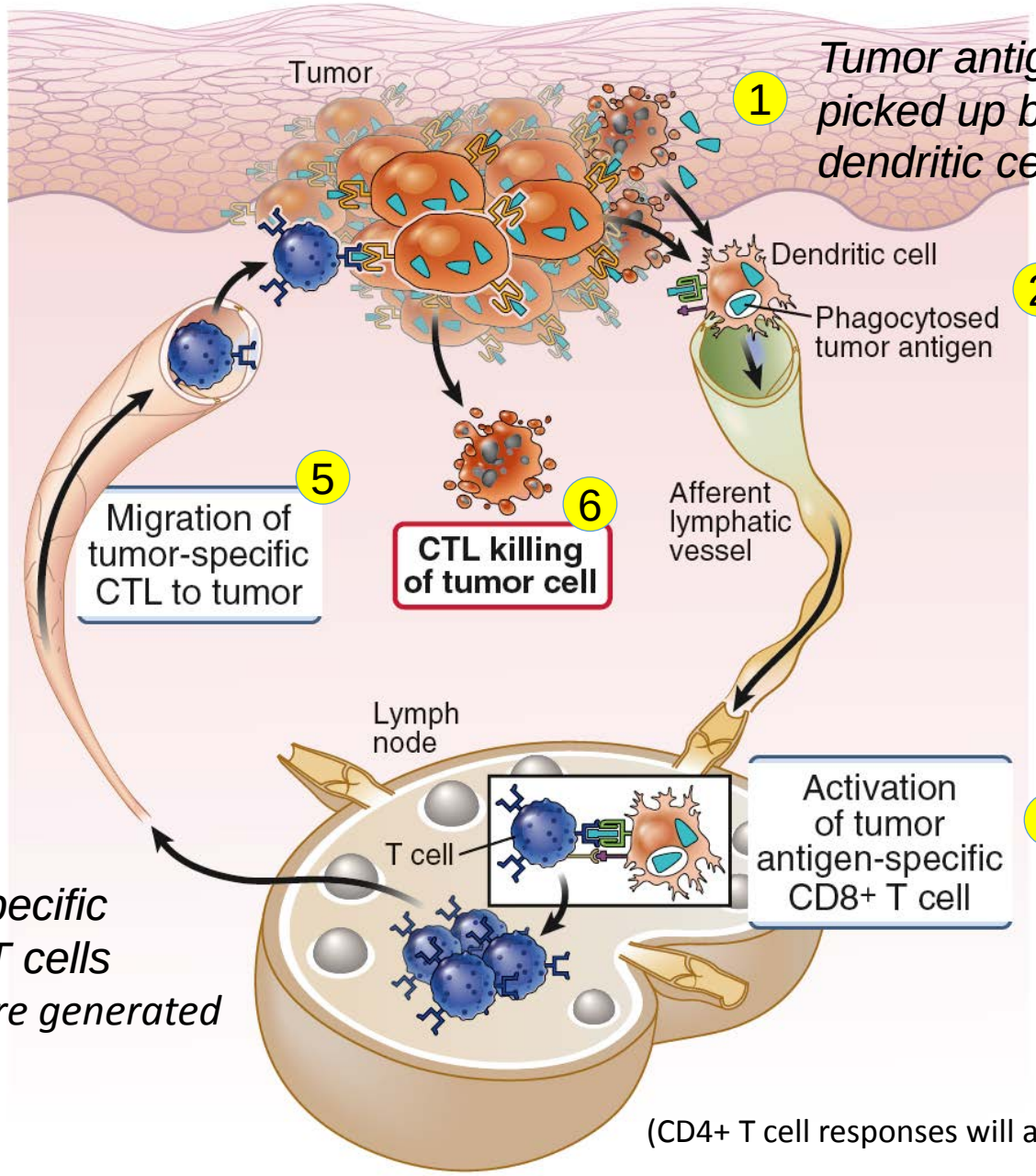




Two main functions:

1. Direct killing of target cells
2. Secretion of inflammatory cytokines: IFNγ and TNF

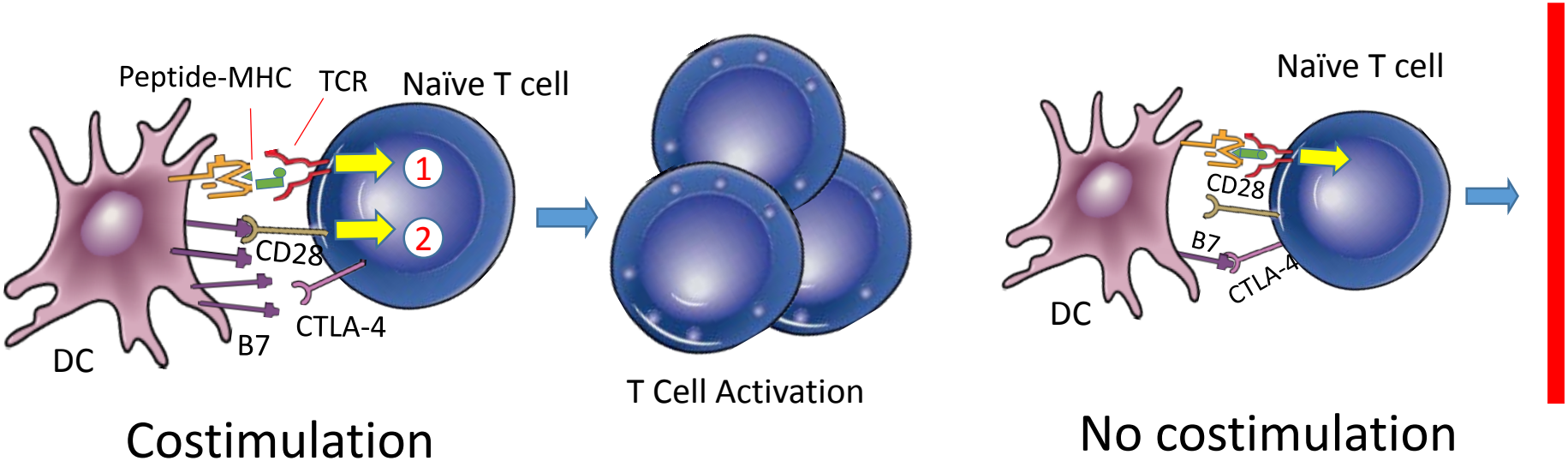
Putting it all together: CD8+ T cell response to tumor



Cell injury/death at tumor site will generate DAMPs that activate DCs

(CD4+ T cell responses will also occur)

CTLA-4 Inhibits T cell Activation: Competitive Blockade of CD28 –B7 Costimulation

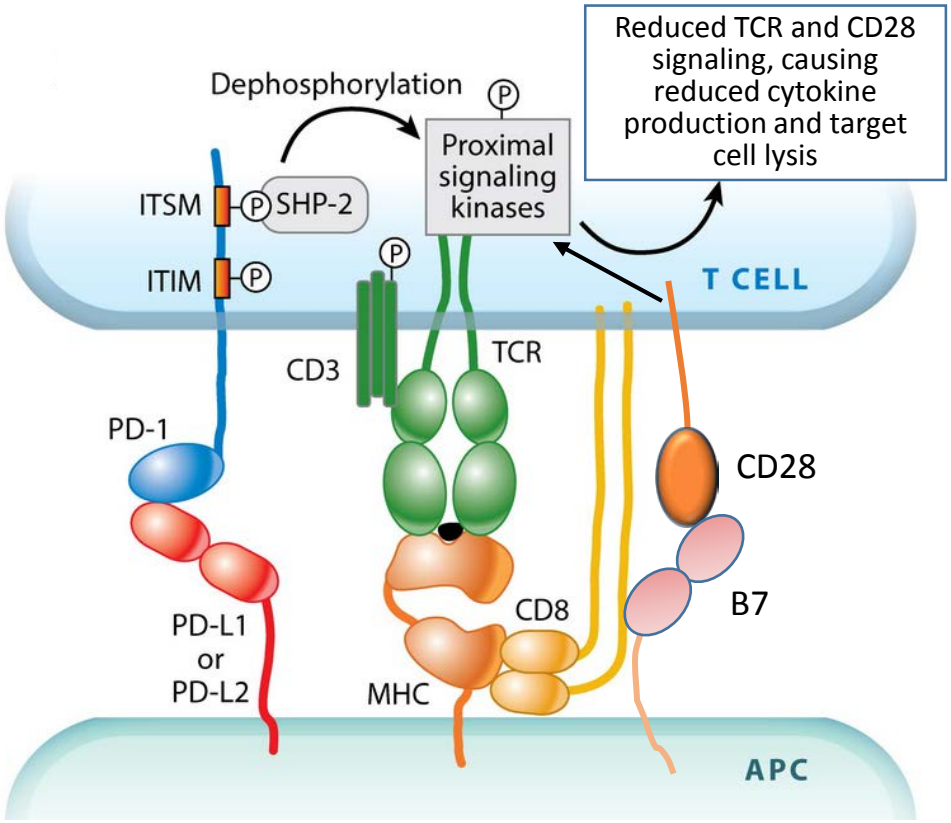


Costimulation

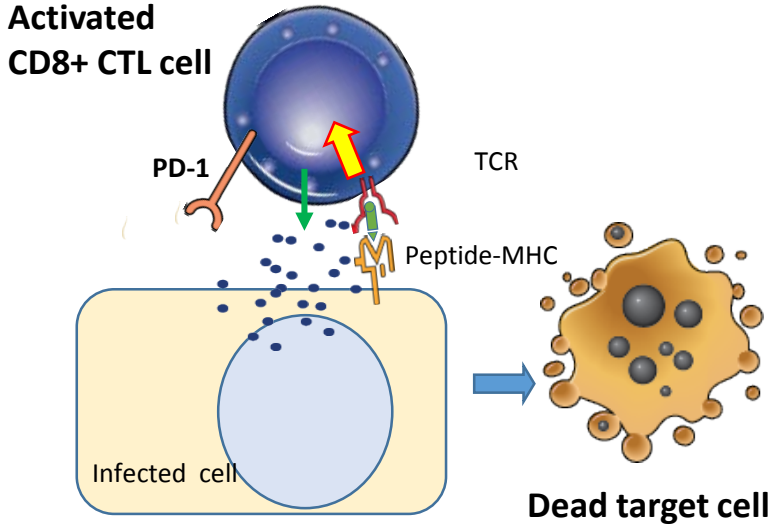
No costimulation

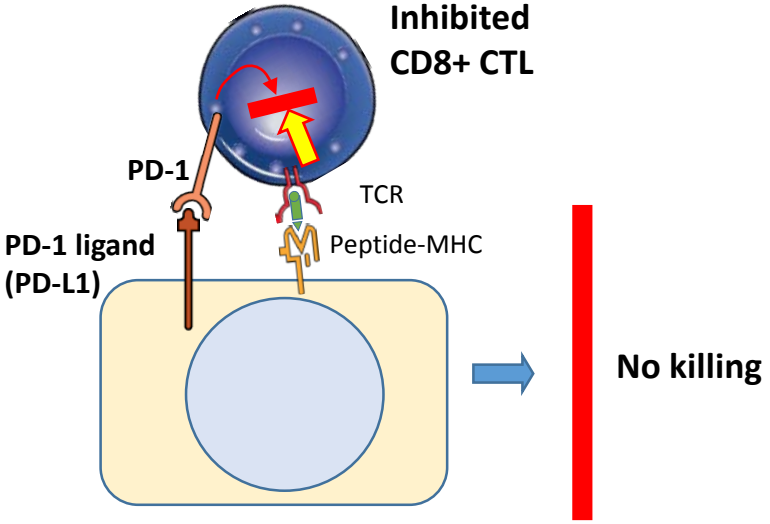
- CTLA-4 binds B7's with higher affinity than CD28; acts as a competitive inhibitor of CD28 costimulation
- CTLA-4 is most effective when B7 expression is low
- CTLA4 may also delver inhibitory signals into the T cells it is expressed on

PD-1 Inhibits T cell Activation: Inhibitory Signals Block Effector T Cell Activation

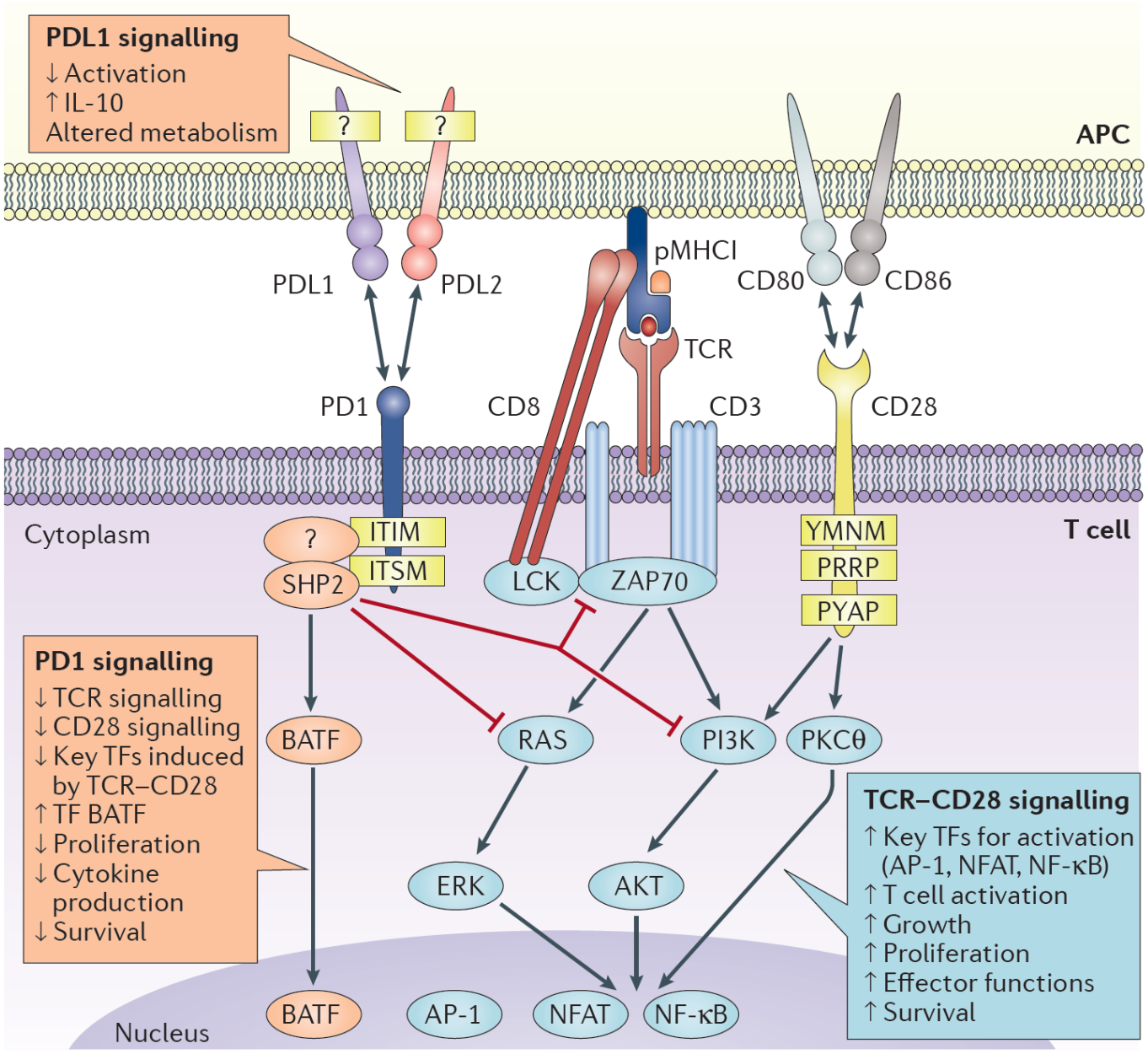


Baumeister SH, et al. 2016.
Annu. Rev. Immunol. 34:539–73



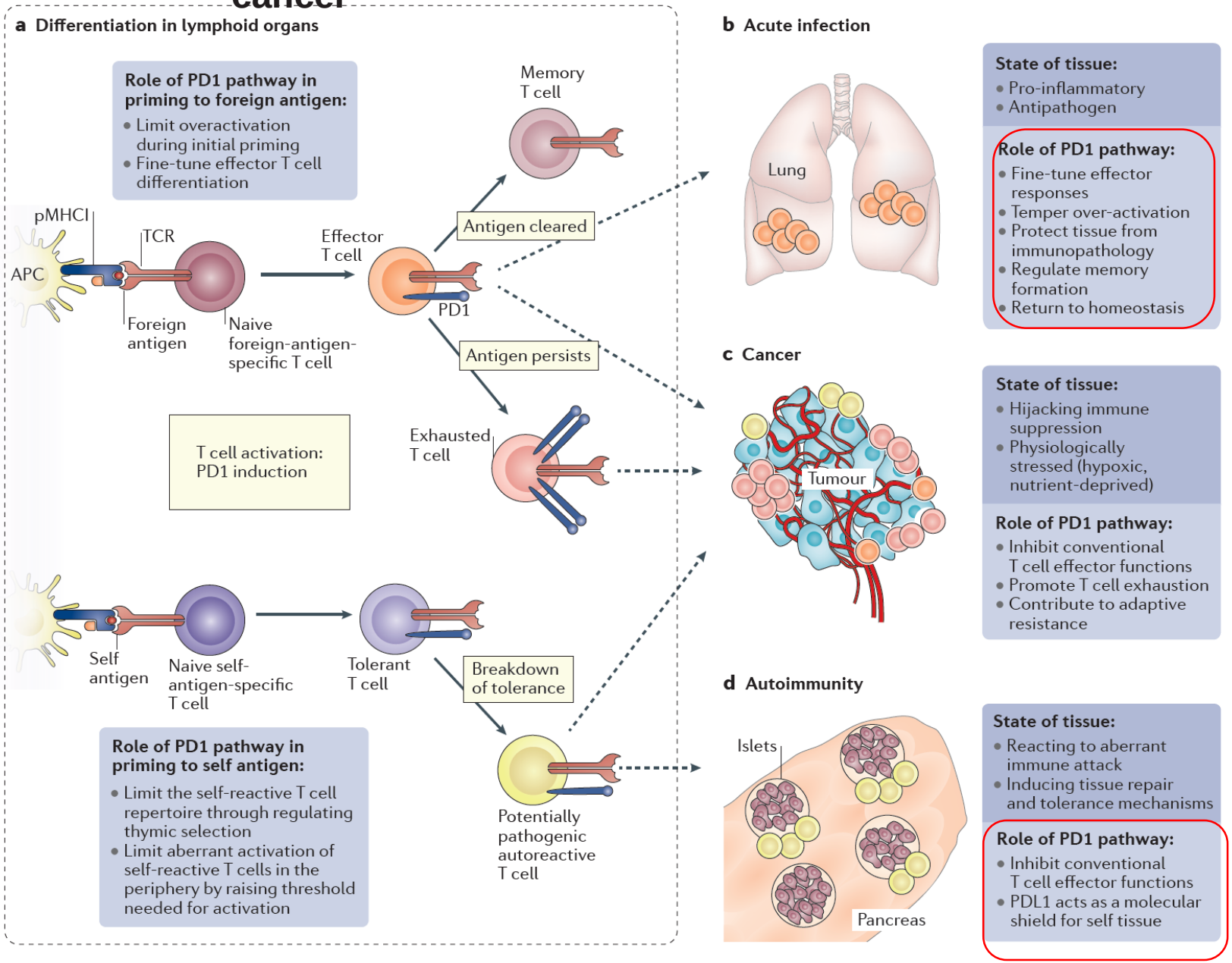


PD-1 Inhibits Both TCR and CD28 Signaling



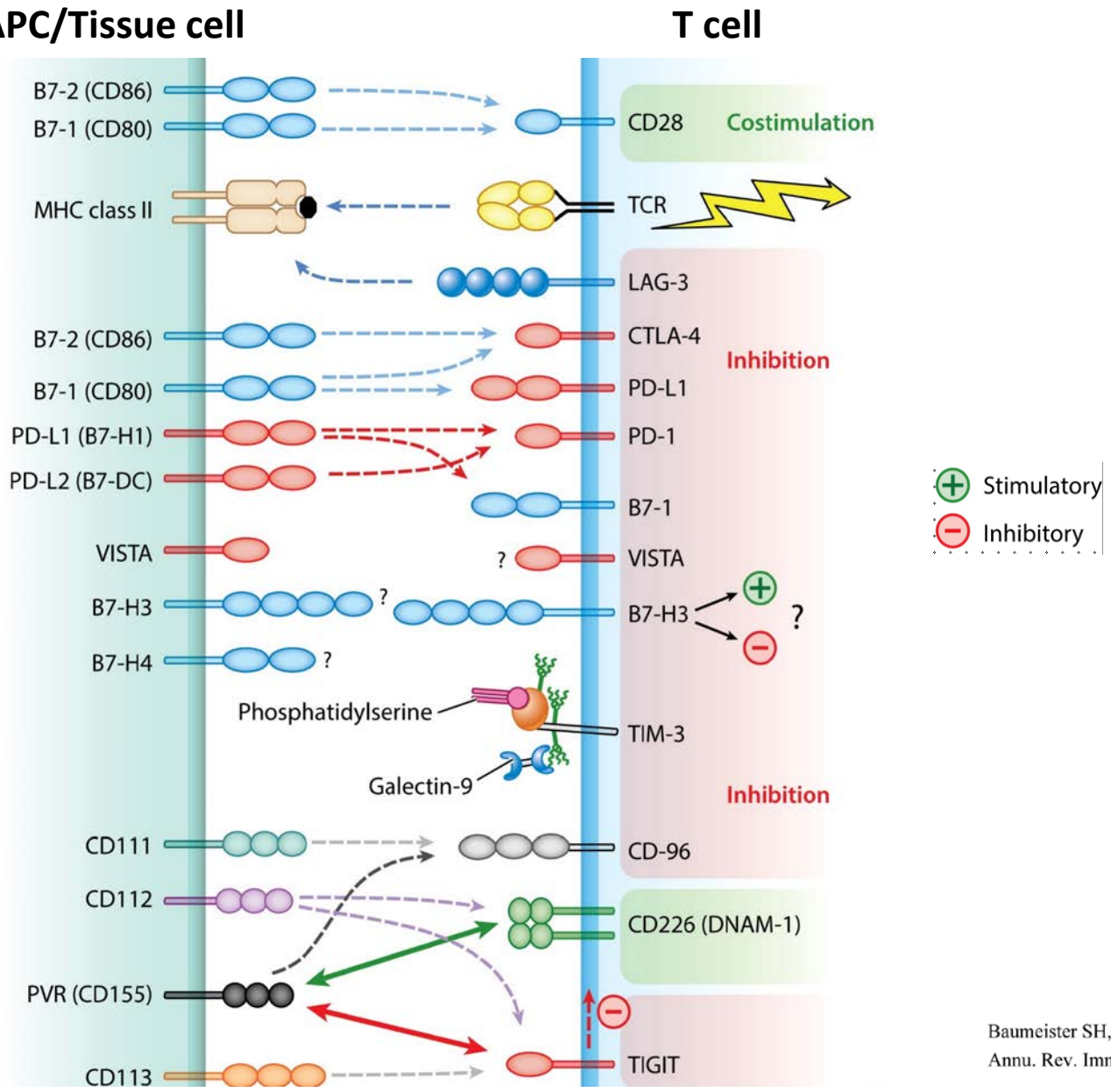
Sharpe A and Pauken K. Nature Rev Immunol 2017

Roles of PD1 in acute infection, tolerance and cancer



Sharpe A and Pauken K. Nature Rev Immunol 2017

Many T cell inhibitory/regulatory molecules



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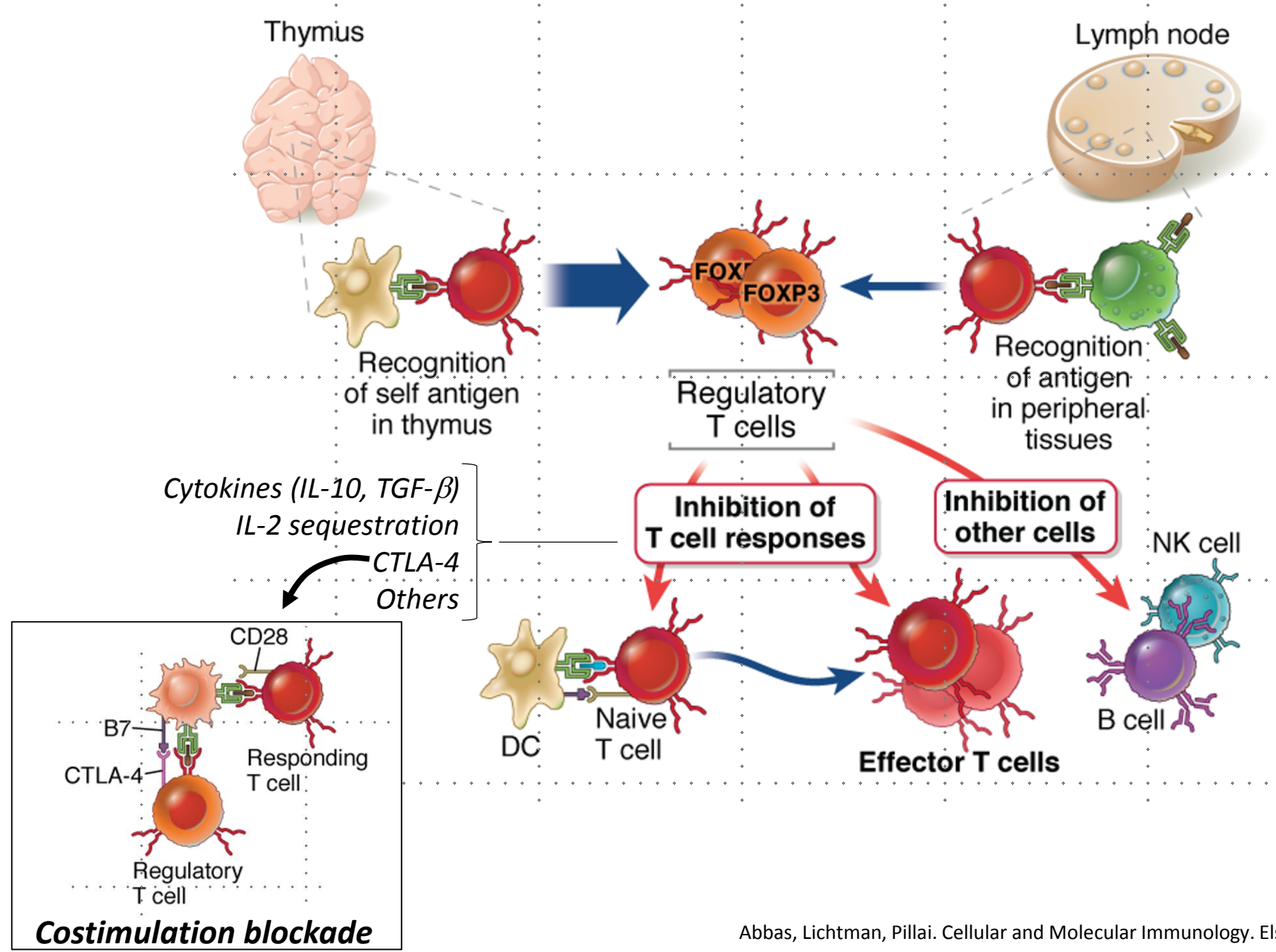
Regulatory T Cells



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