

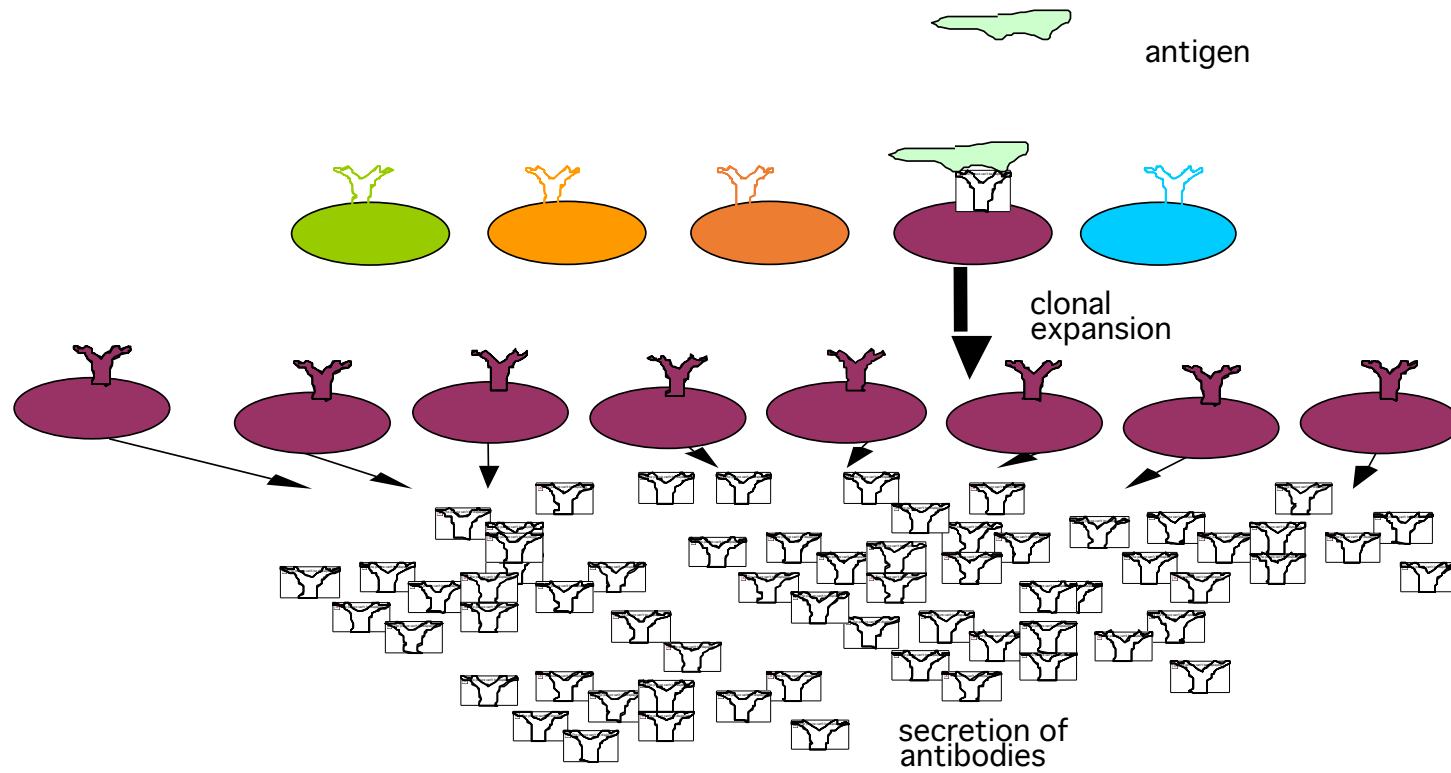
Antigen Presentation and T Cell Activation
FOCIS Basic Course 2023



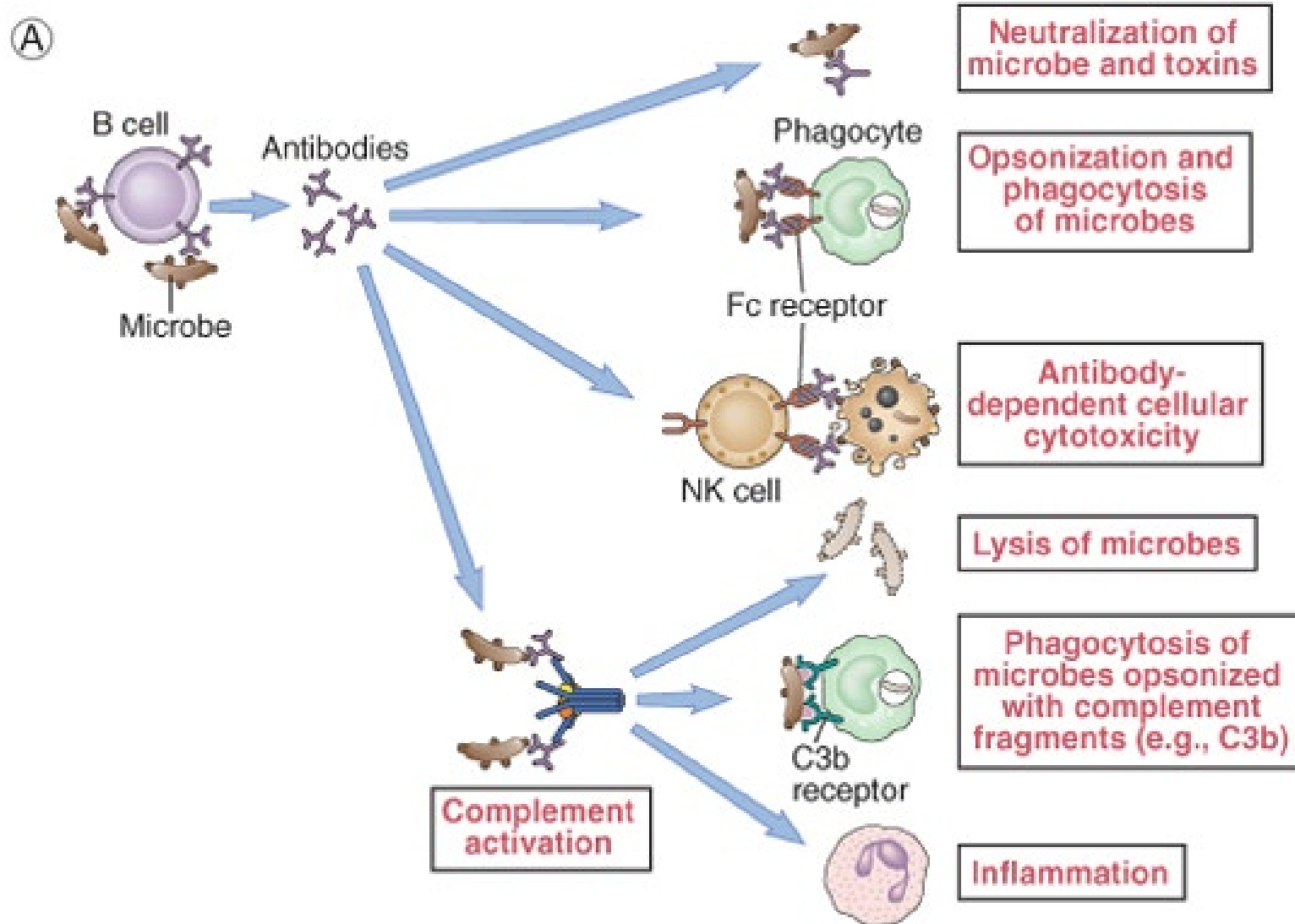
Shiv Pillai MD, PhD
Massachusetts General Hospital
Harvard Medical School

Lecture Outline

- Adaptive Immunity and why we need T cells
- The T cell receptor and what it sees
- TCR signaling: Signal 1
- Costimulation: Signal 2
- MHC structures
- Antigen presentation pathways
- “Lord of the Rings”

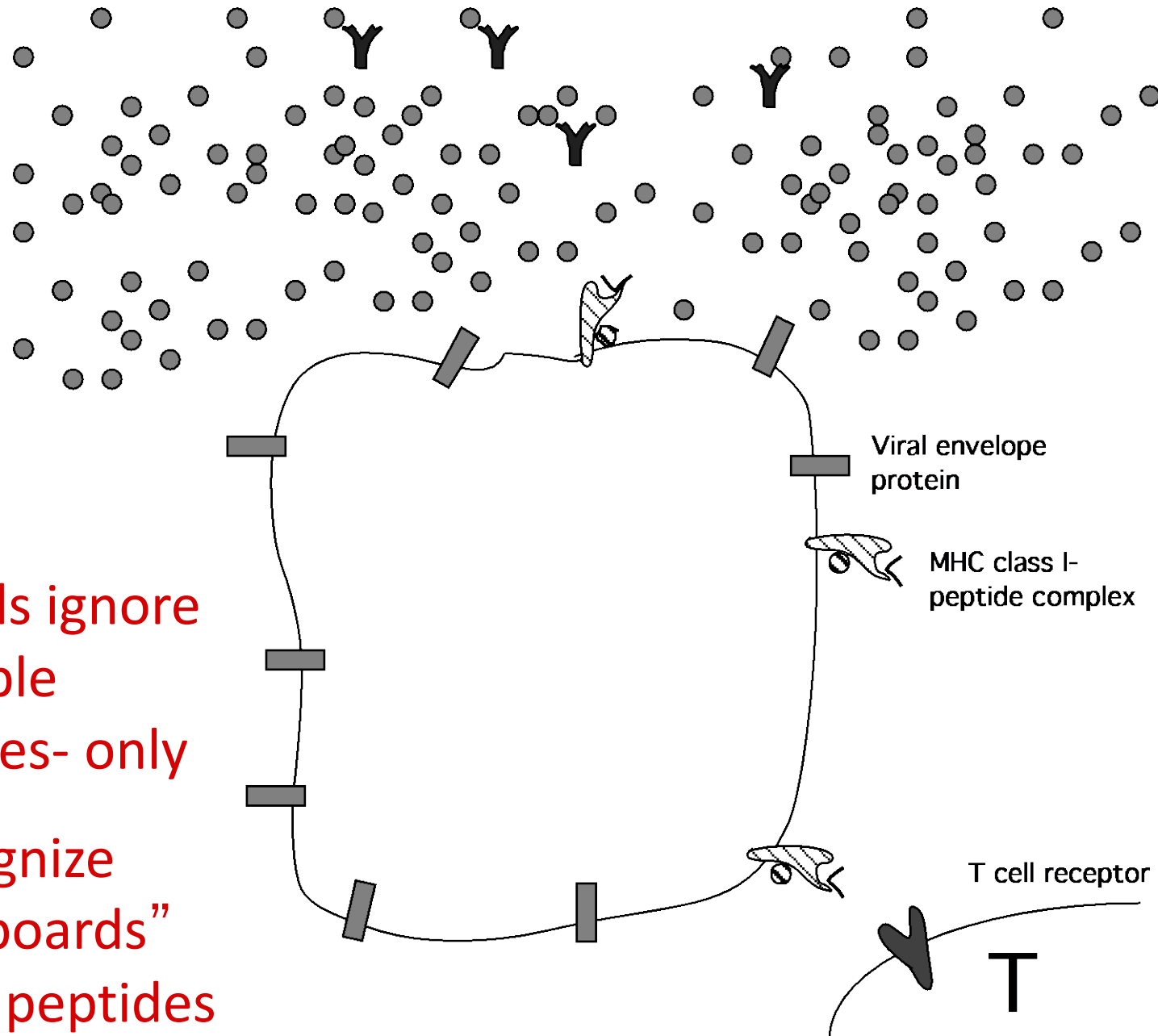


The effector functions of antibodies

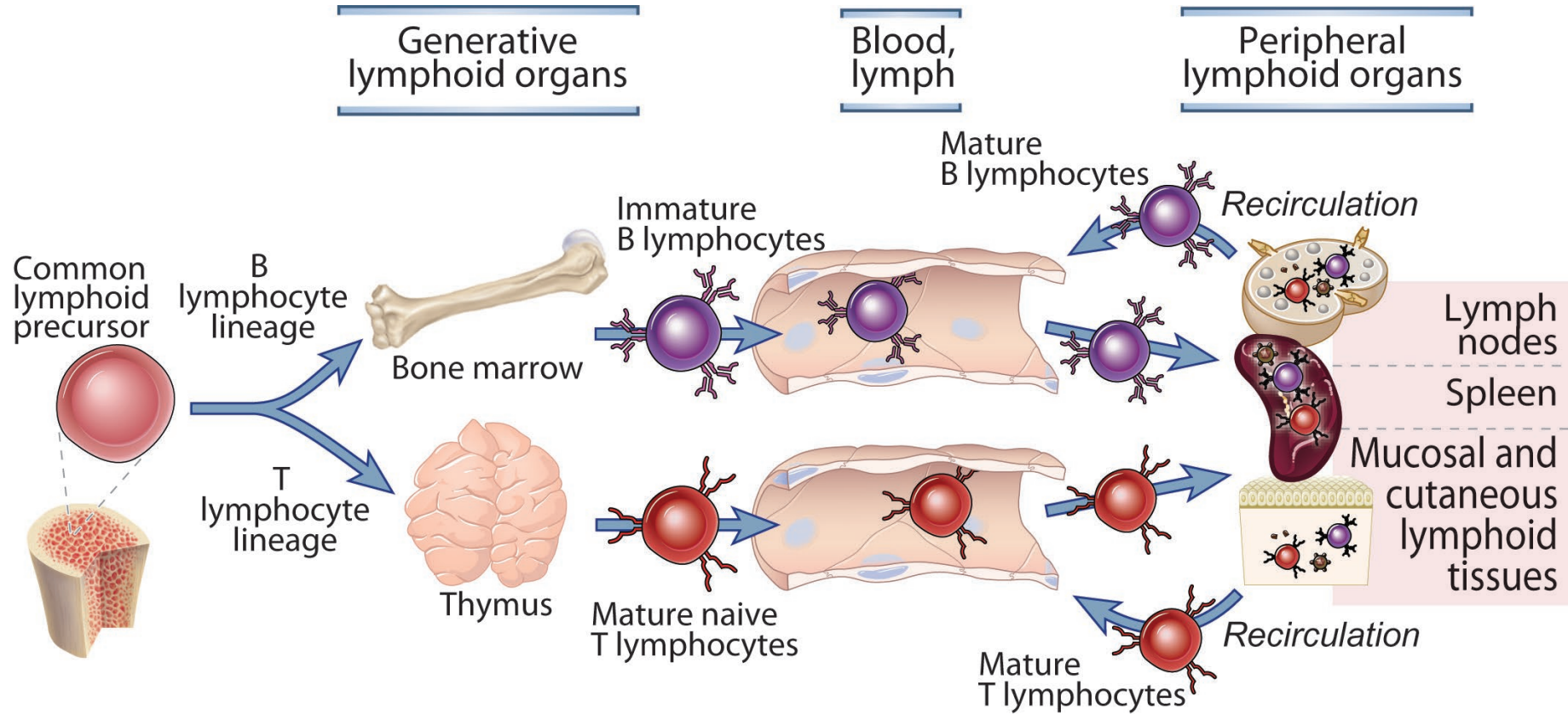


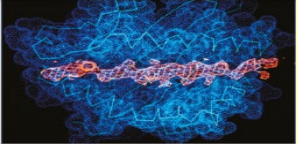
Why do we need T cells?

T cells ignore
soluble
shapes- only
recognize
“billboards”
with peptides

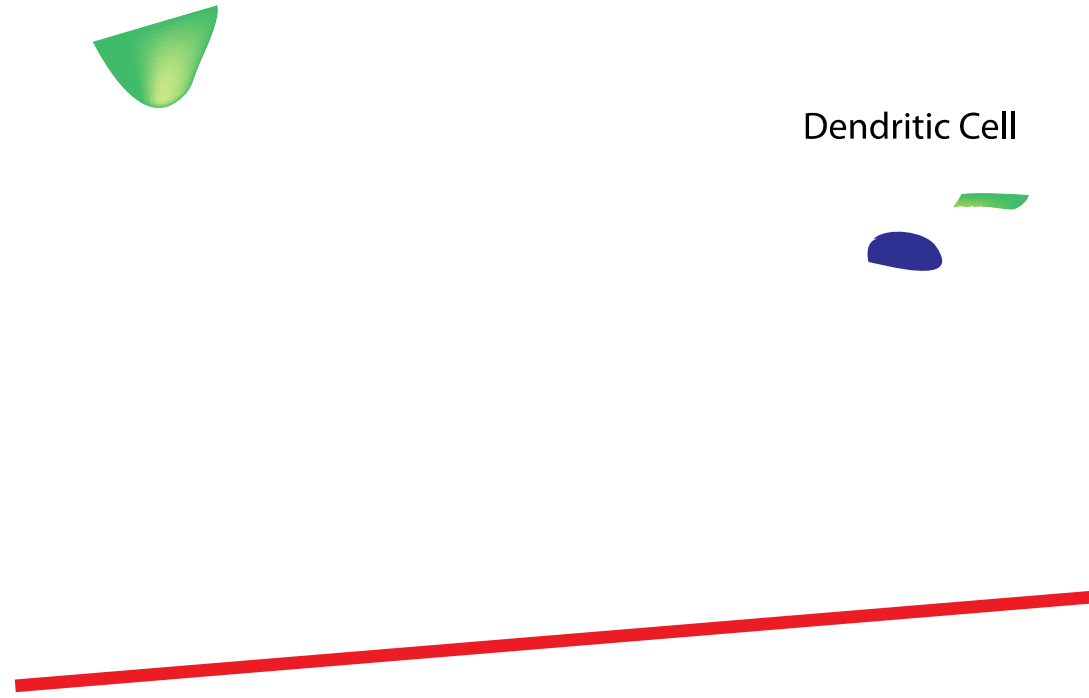


Maturation of Lymphocytes

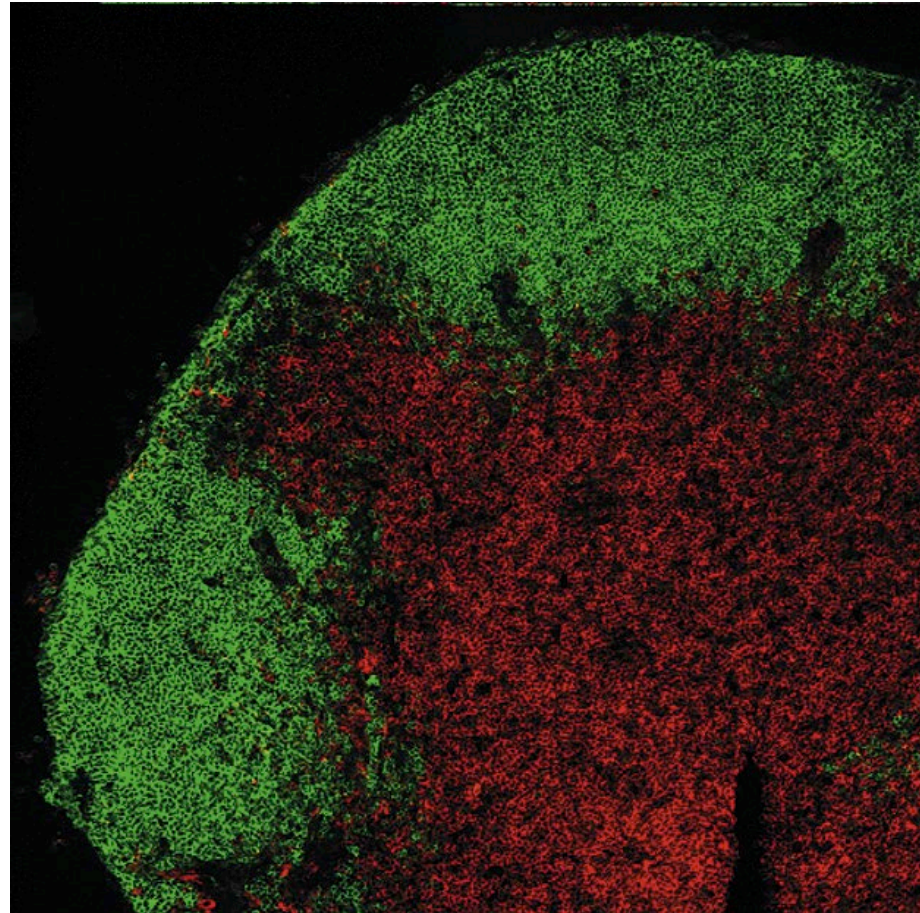
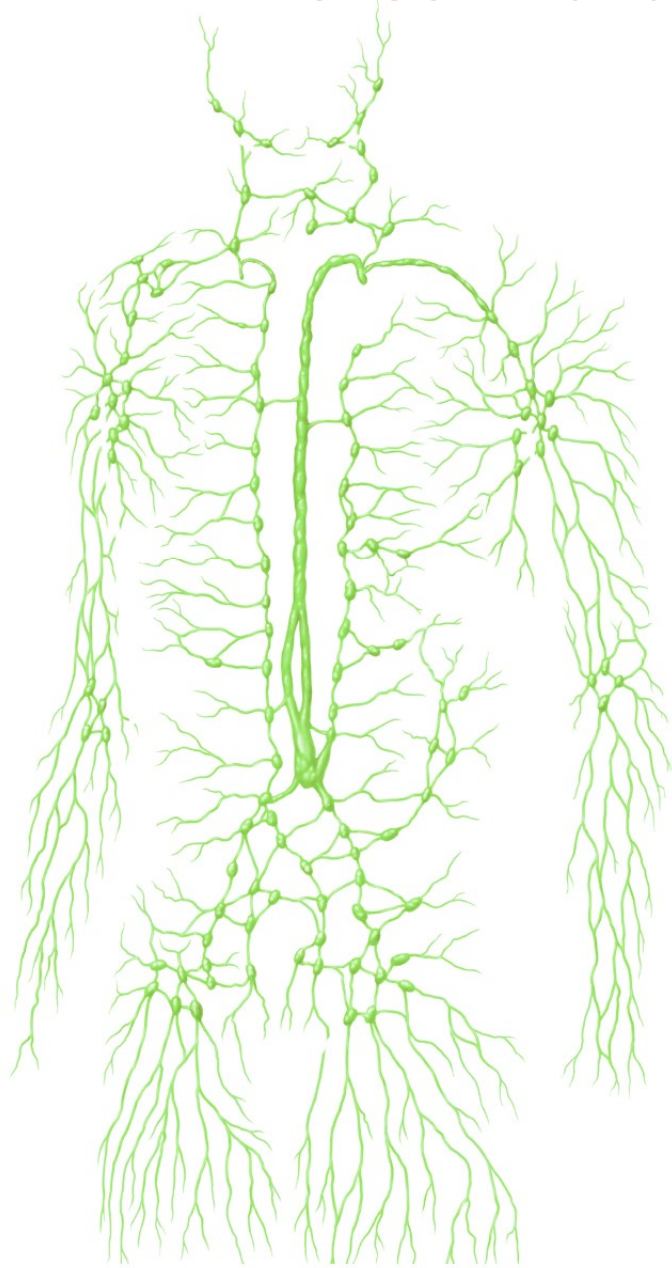




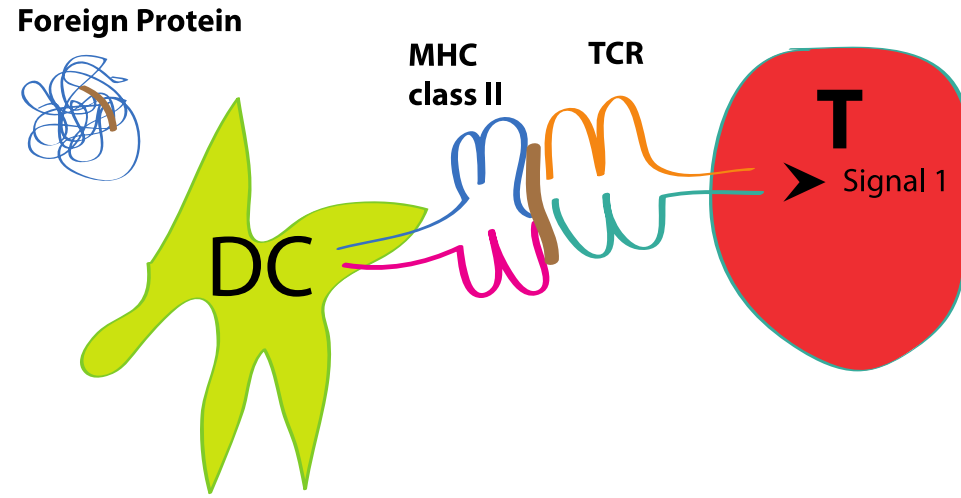
A Third Type of Sentinel Cell Initiates Adaptive Immunity



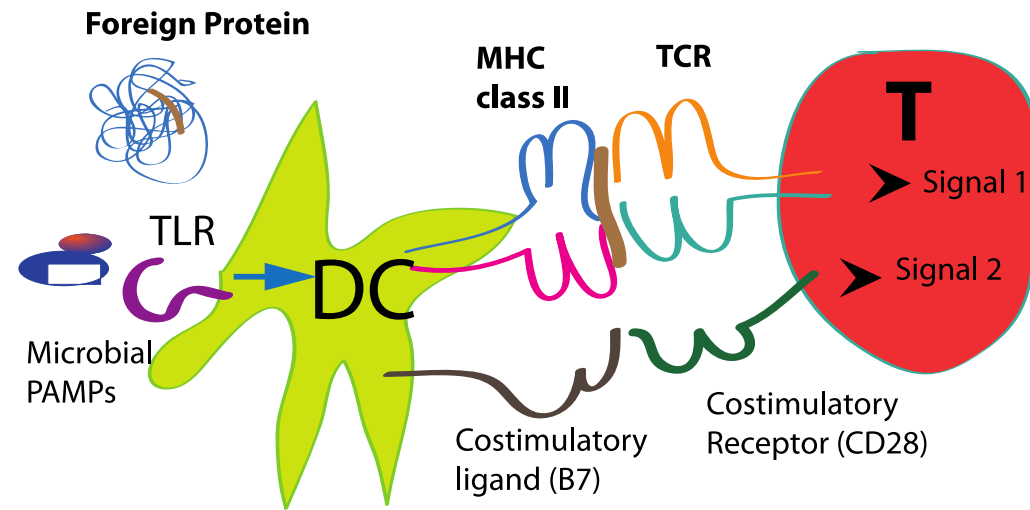
SLOs - T and B cell zones

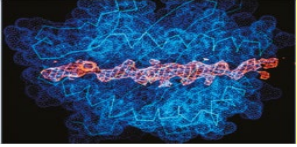


Foreign Protein but no "Danger"

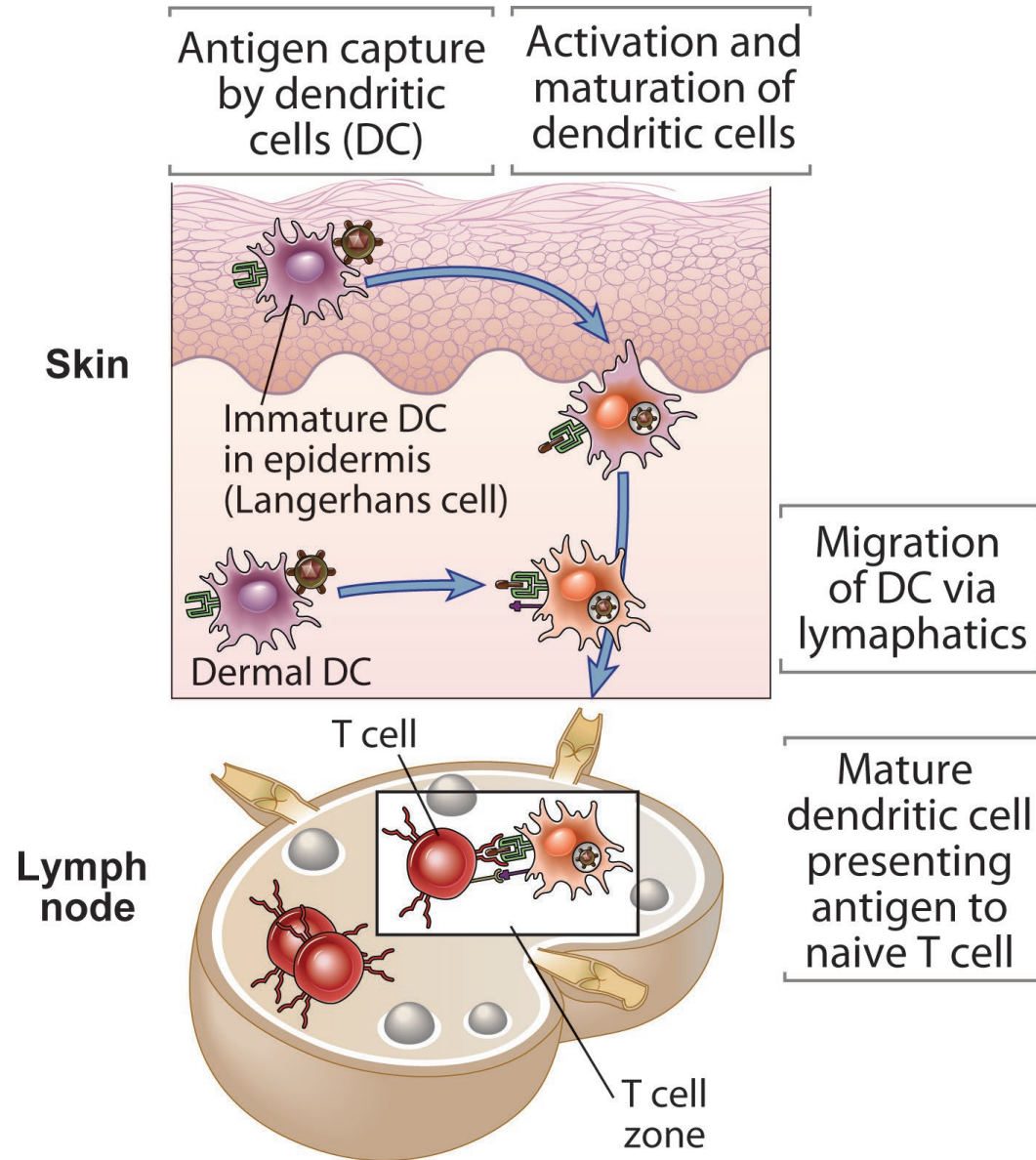


Foreign protein but also "Danger"!

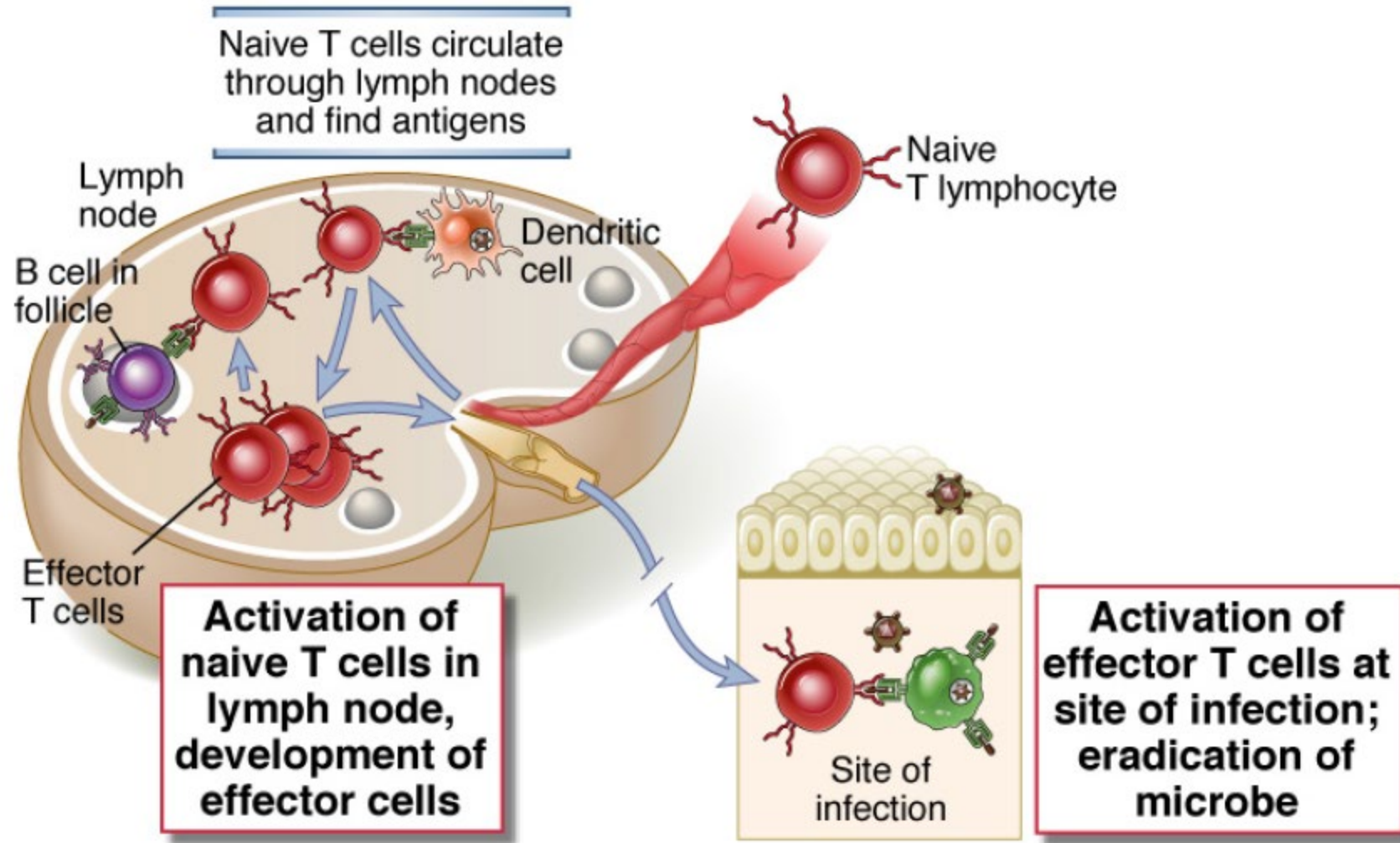




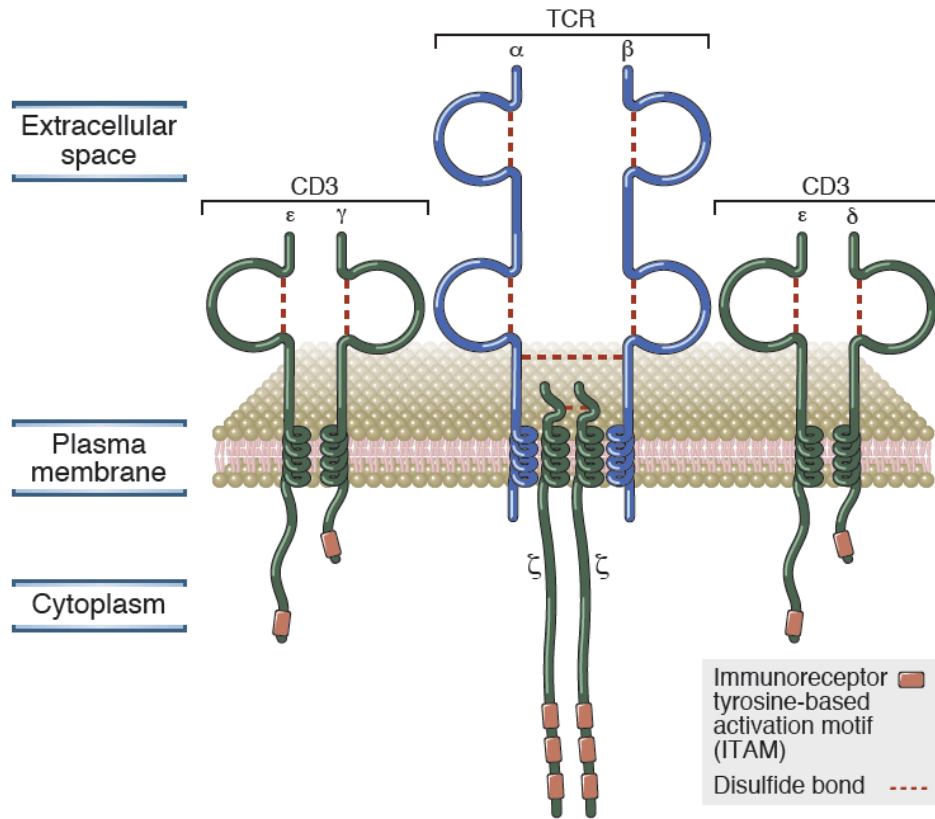
DC Antigen Capture and Presentation



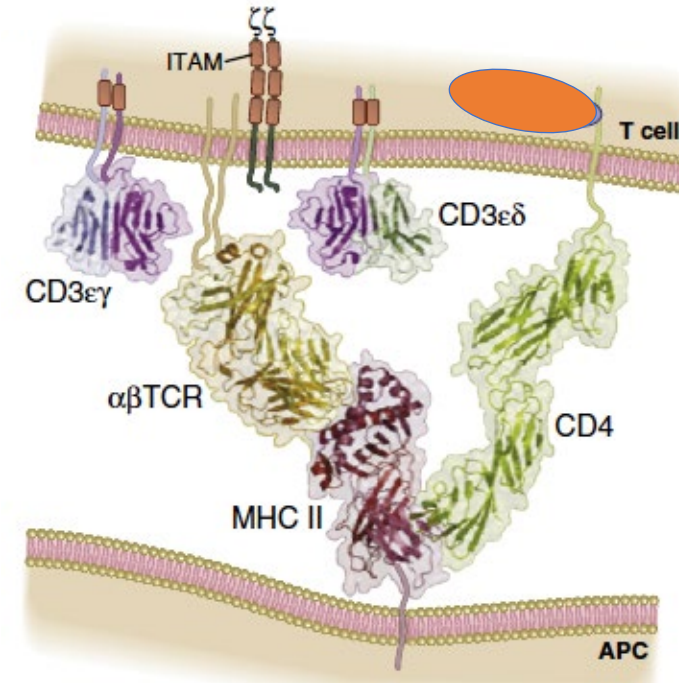
DCs and antigen find specific Naïve T cells in SLOs in the T cell zone: activated Effector T cells return to the site of infection



The T cell receptor complex: associated proteins have cytoplasmic tyrosine-based motifs called ITAMs



LCK binds tightly to CD4 but poorly to CD8

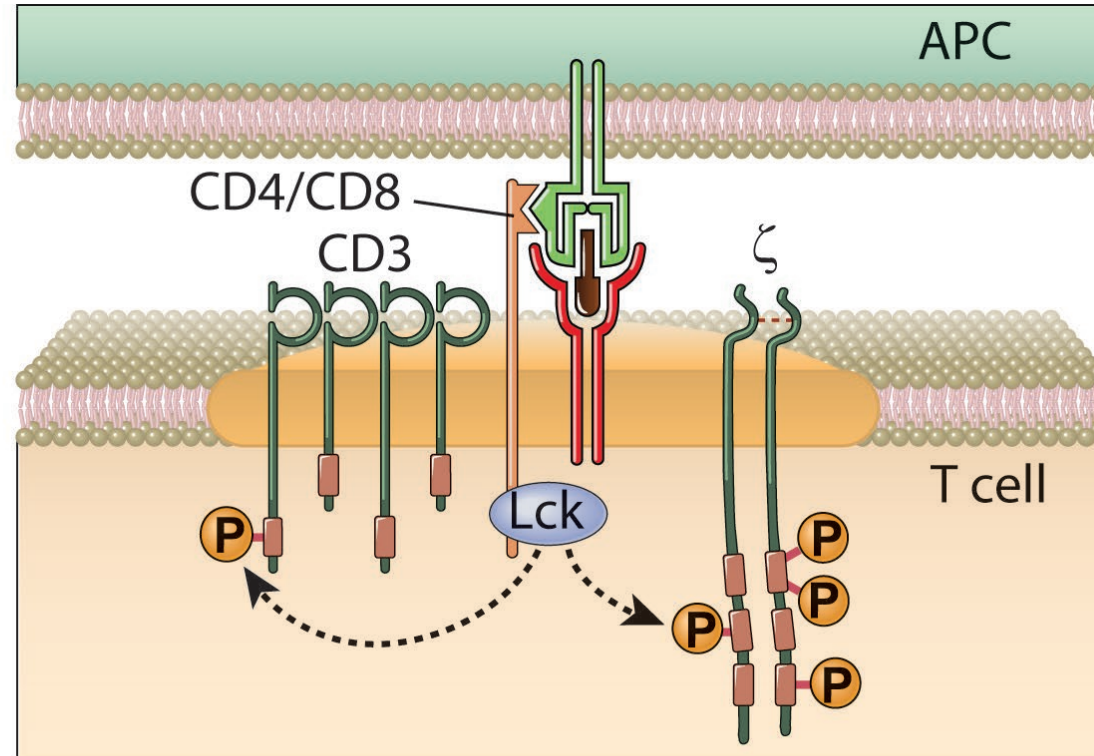


Early Signaling Events in T cell Activation (1)

TCR complex and coreceptors cluster within membrane lipid rafts upon antigen recognition



Lck phosphorylates tyrosines in ITAMs

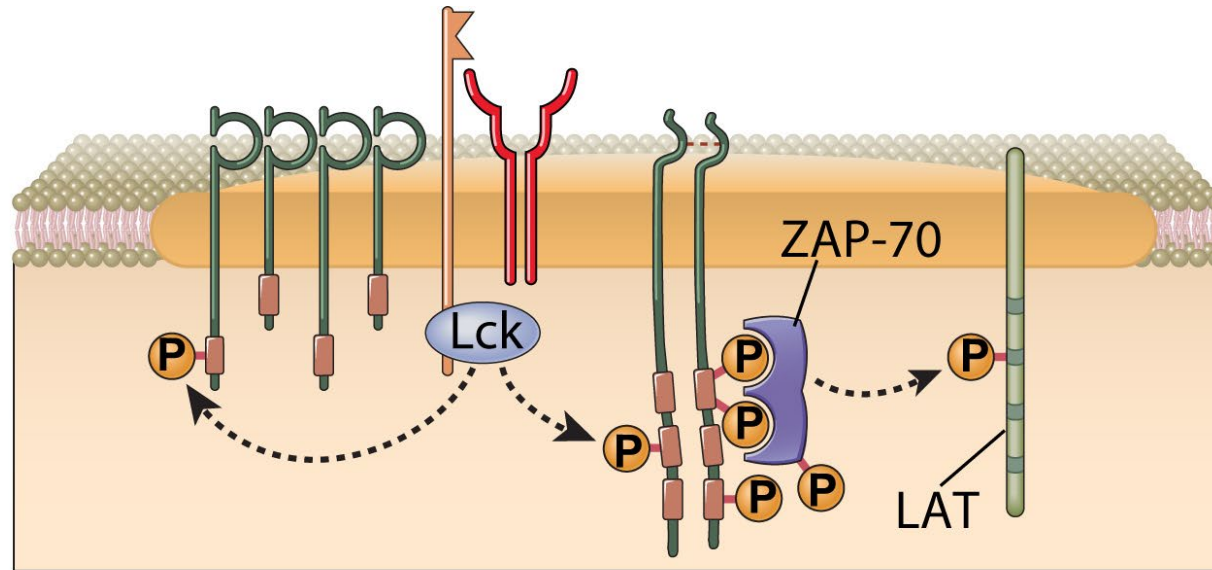


Early Signaling Events in T cell Activation (2)

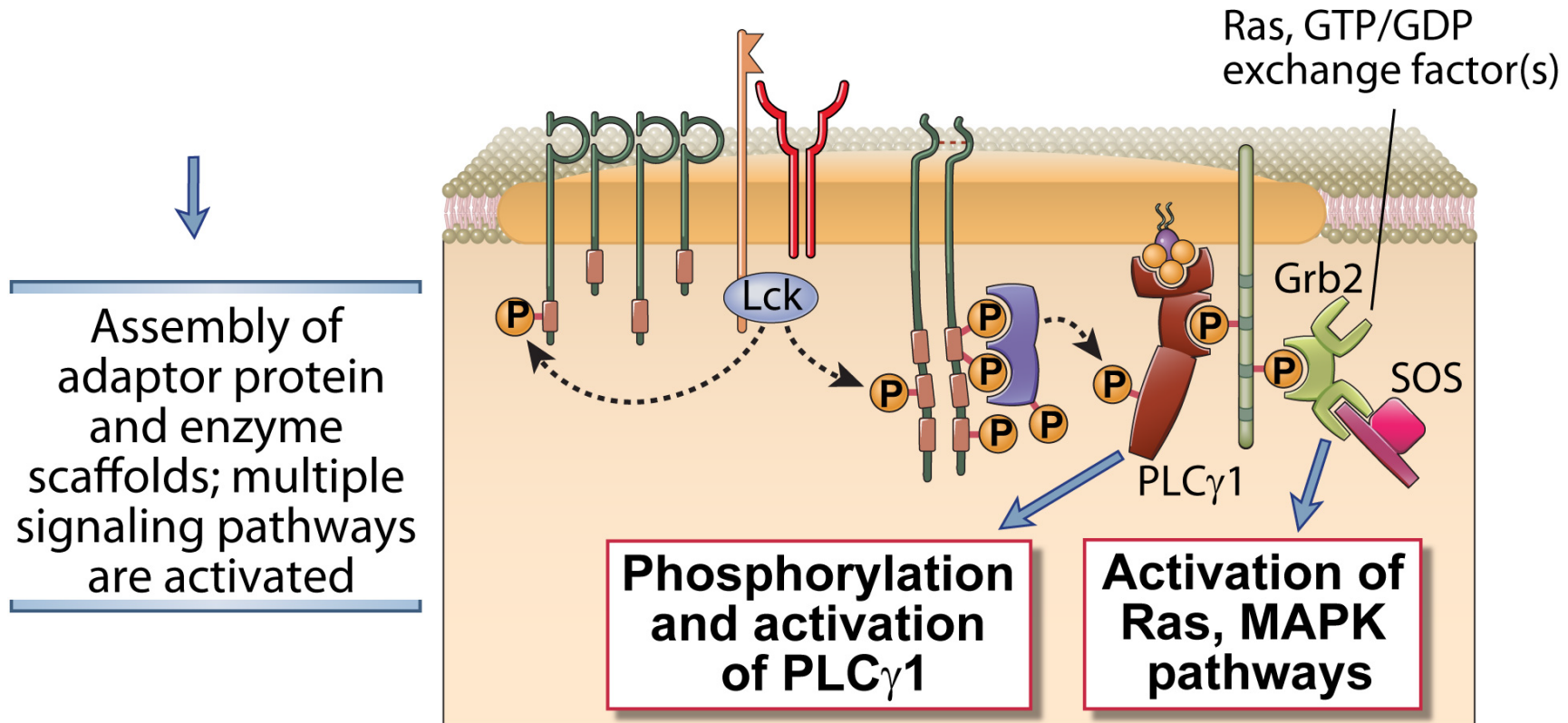
↓

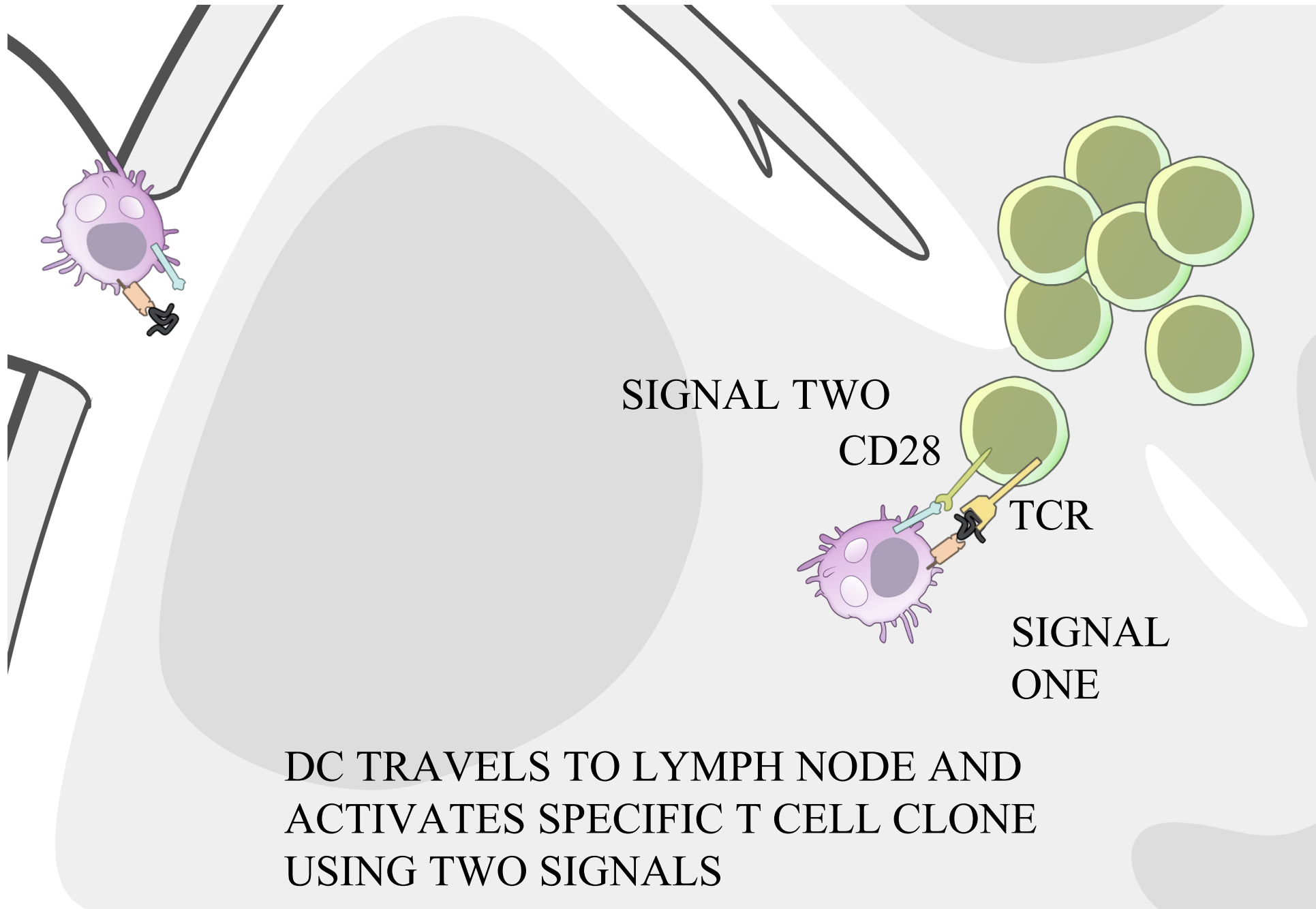
ZAP-70 binds to phosphotyrosines and phosphorylates adaptor proteins, including LAT

↓



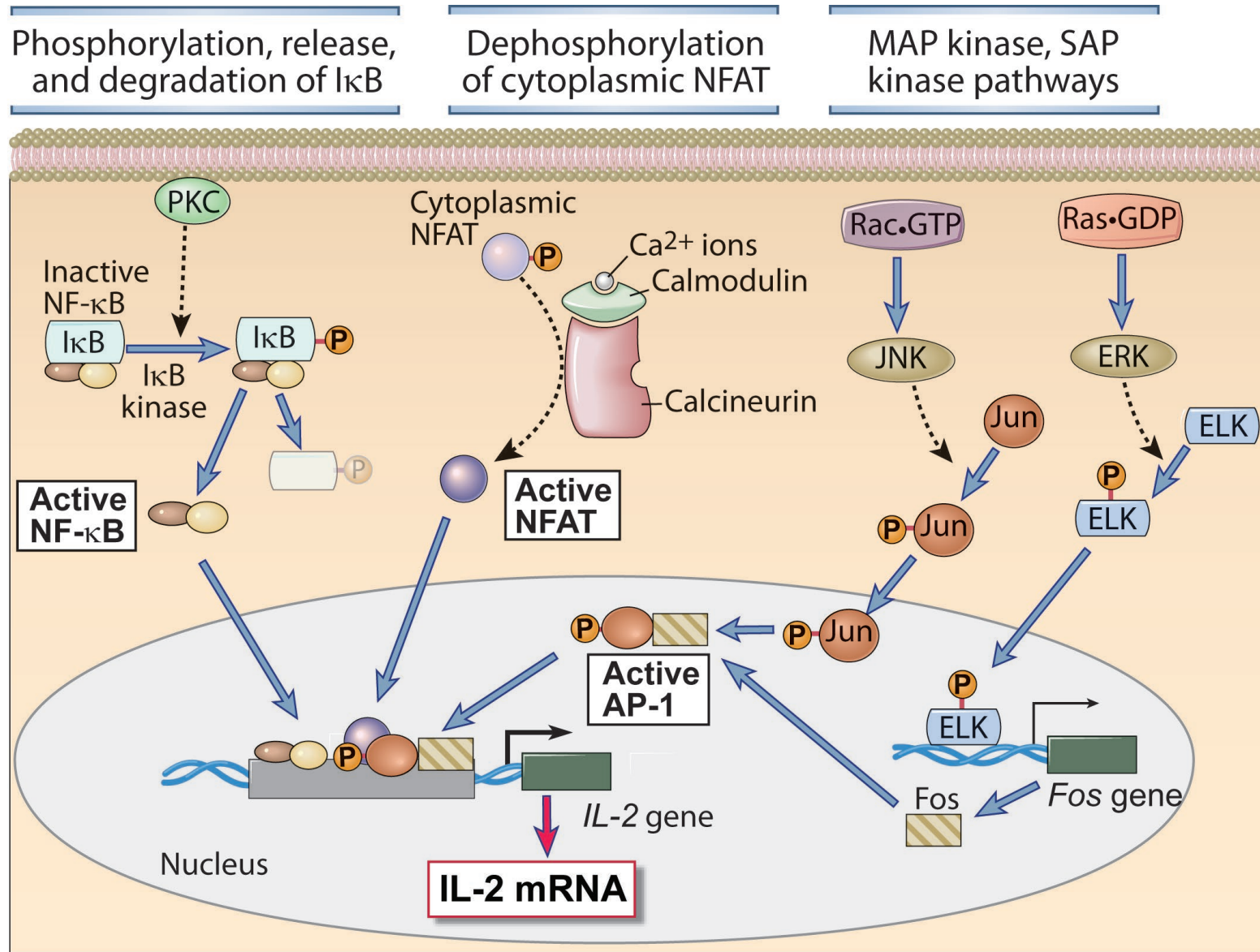
Early Signaling Events in T cell Activation (3)

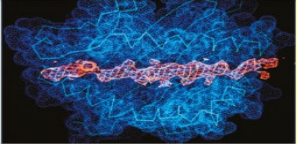




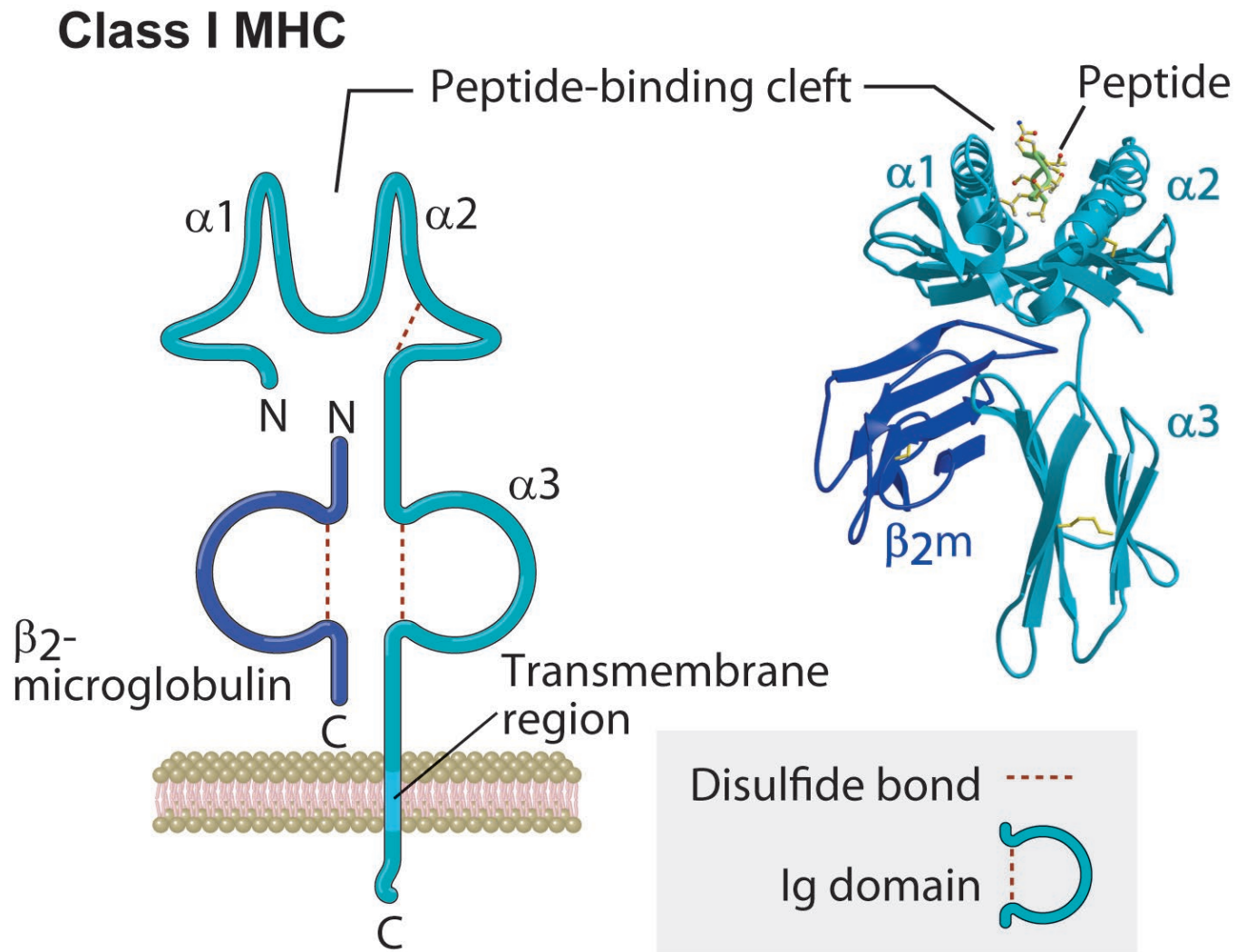
DC TRAVELS TO LYMPH NODE AND
ACTIVATES SPECIFIC T CELL CLONE
USING TWO SIGNALS

Activation of Transcription Factors in T Cells

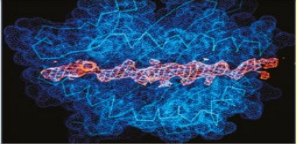




Structure of a Class I MHC Molecule

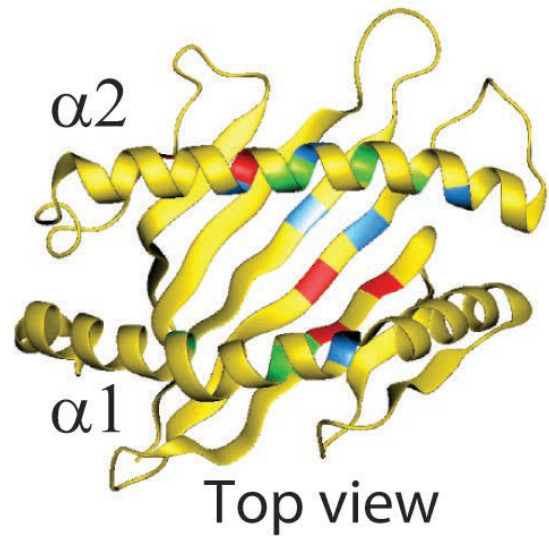


**EXPRESSED ON
ALL NUCLEATED
CELLS IN
VERTEBRATES**

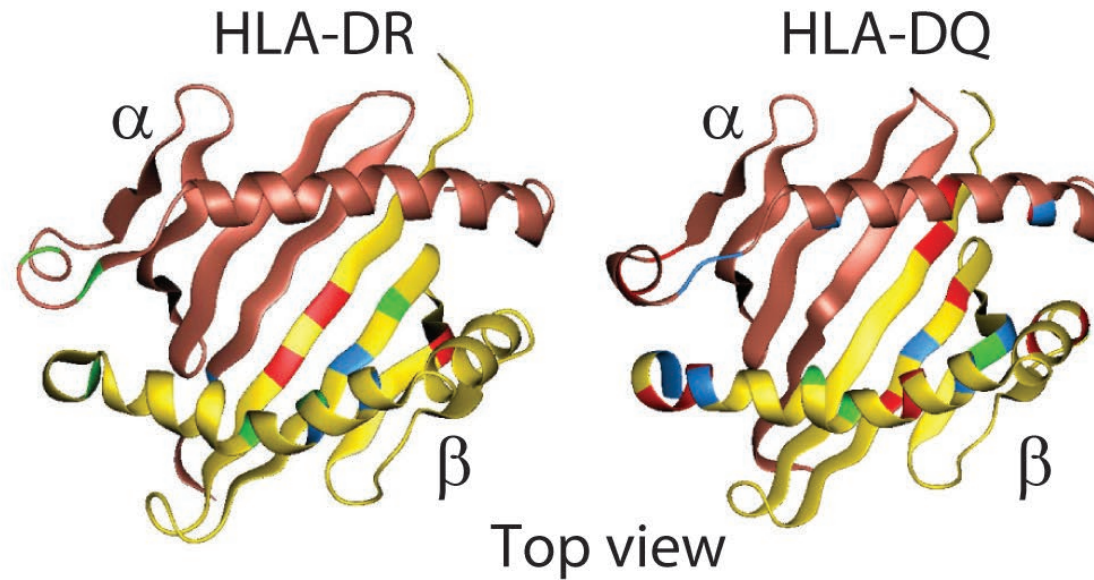


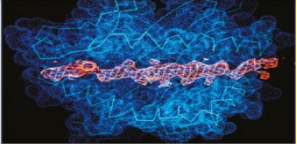
Polymorphic Residues of MHC Molecules

HLA class I



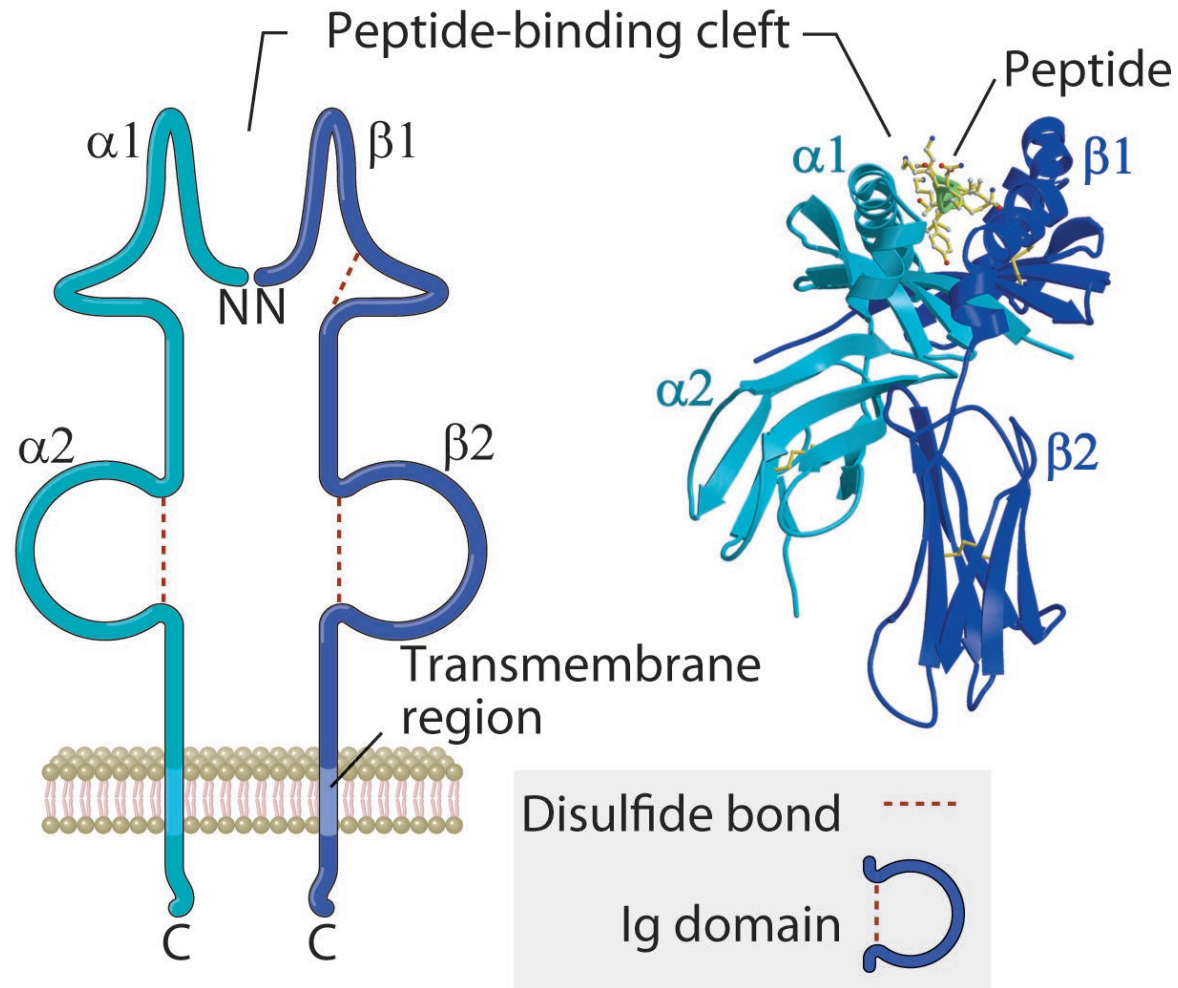
HLA class II



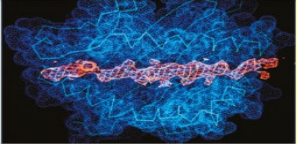


Structure of a Class II MHC Molecule

Class II MHC

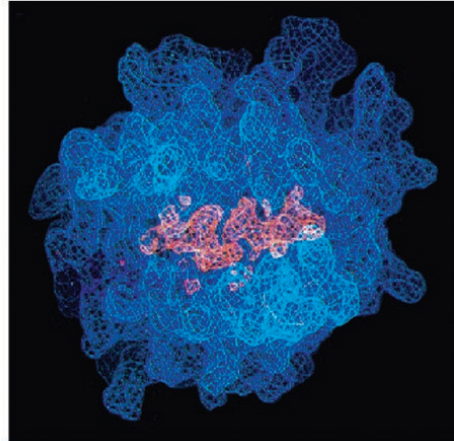


**EXPRESSED
PRIMARILY ON
"PROFESSIONAL"
APCS = DCS, B
CELLS,
MACROPHAGES**

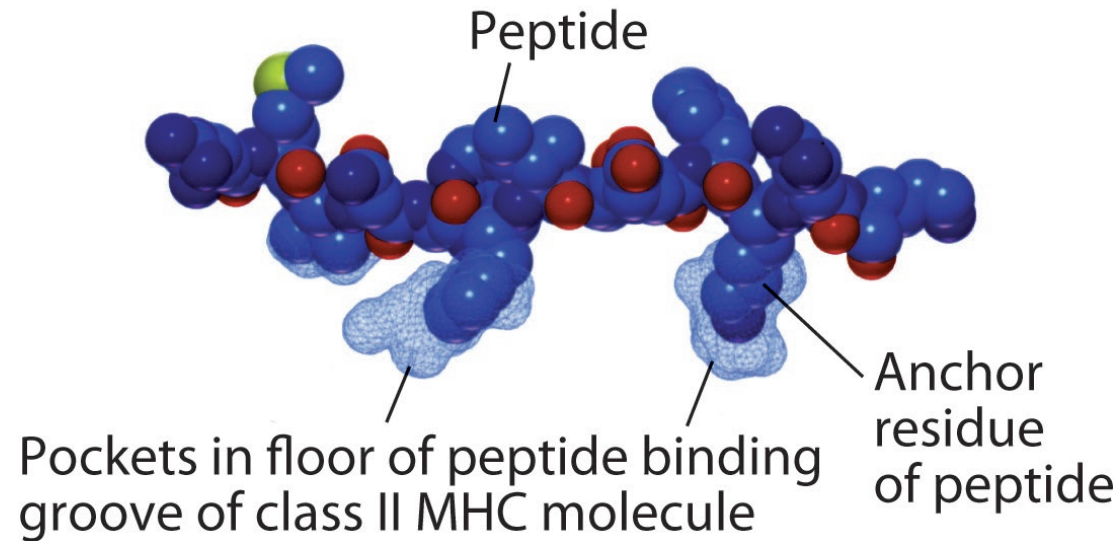
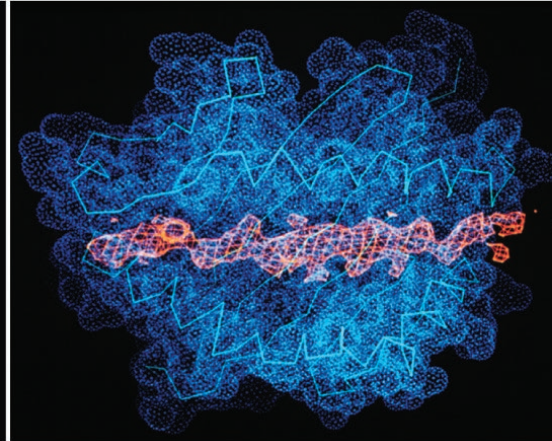


Peptide Binding to MHC Molecules

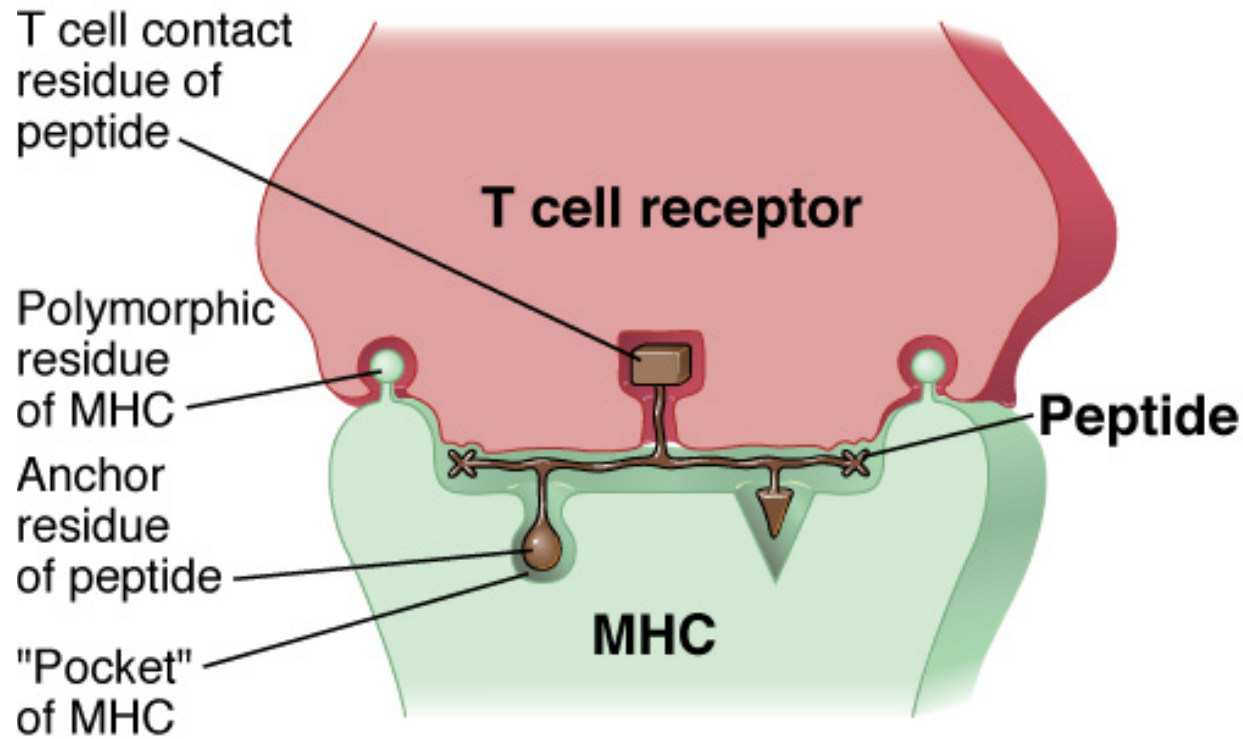
HLA-A2 (Class I)



HLA-DR1 (Class II)



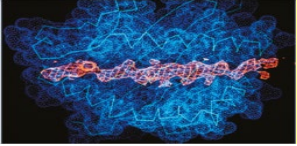
A model of T cell recognition of peptide displayed by an MHC molecule



Human MHC = HLA

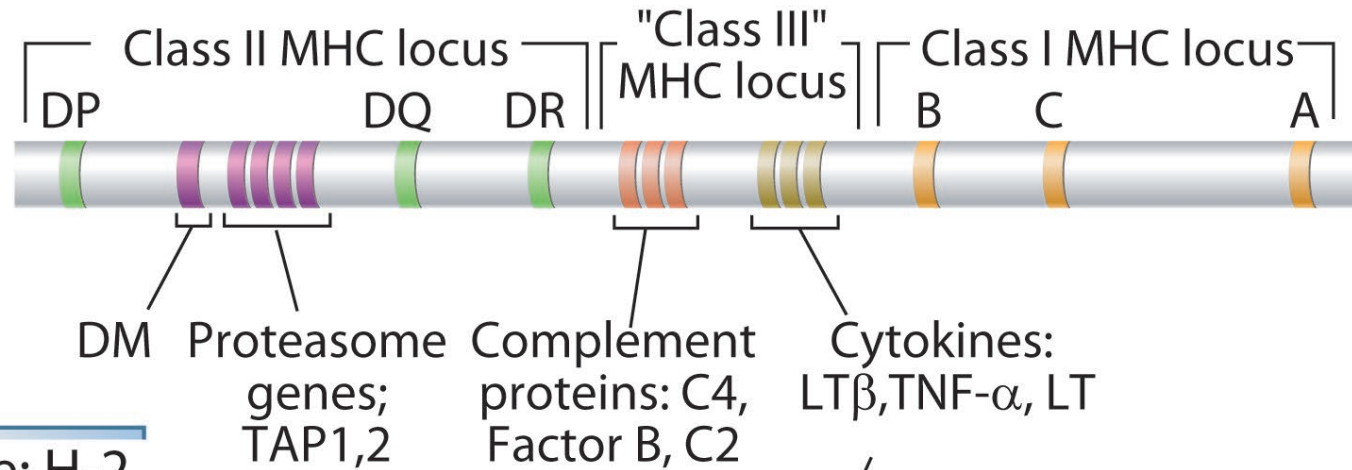
Because MHC molecules are on cells and can display only peptides, T lymphocytes can recognize only cell-associated protein antigens

Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology*, 7th edition, 2011 © Elsevier

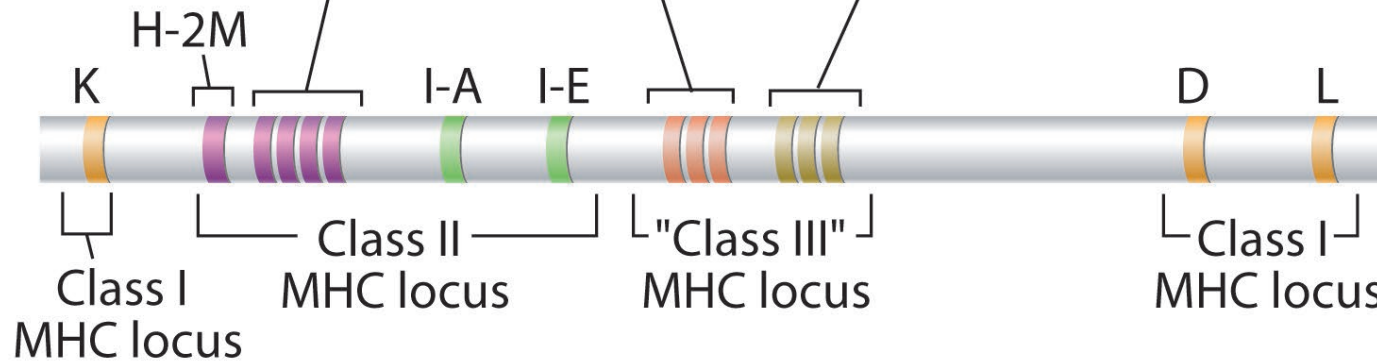


Human and Mouse MHC

Human: HLA

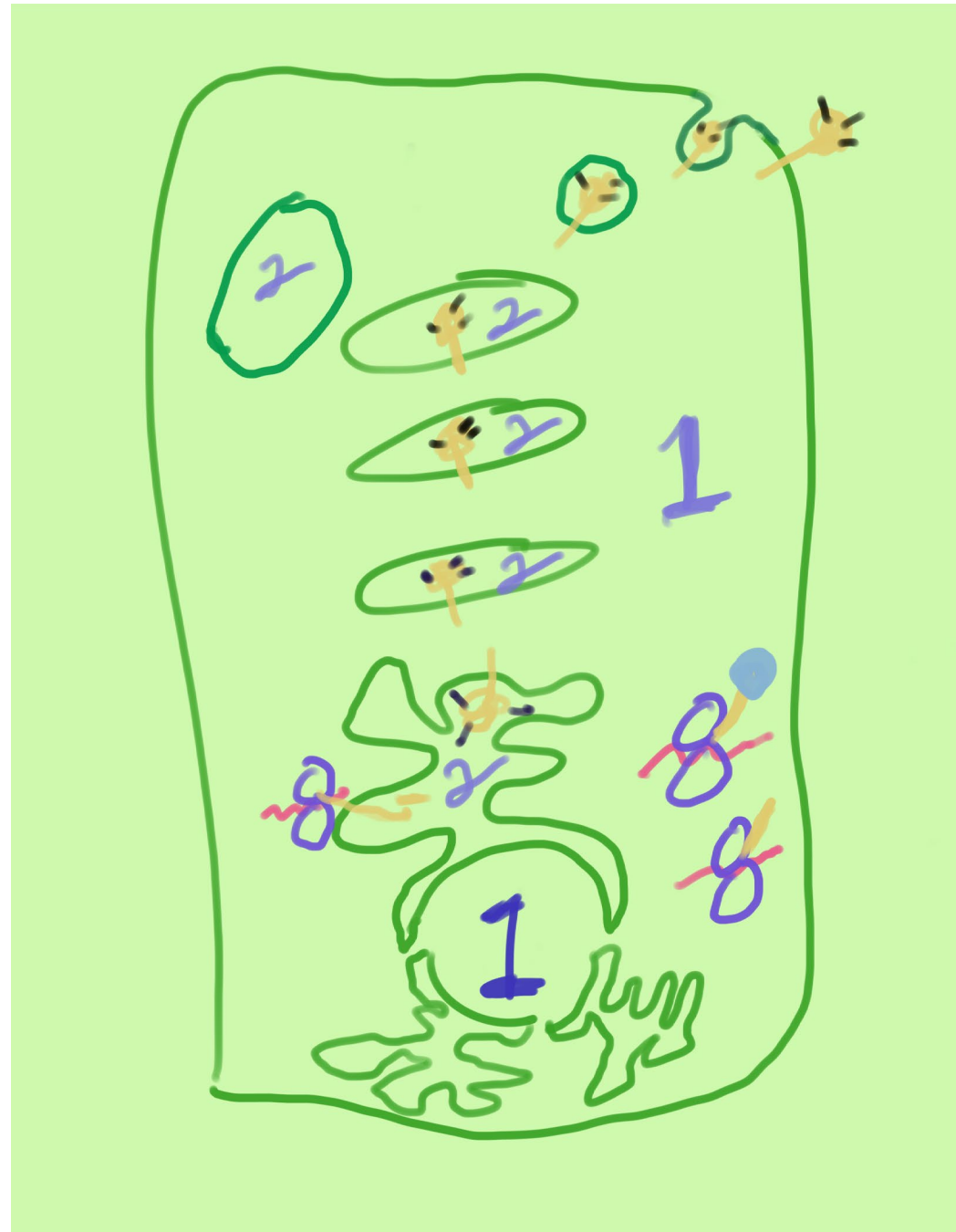


Mouse: H-2

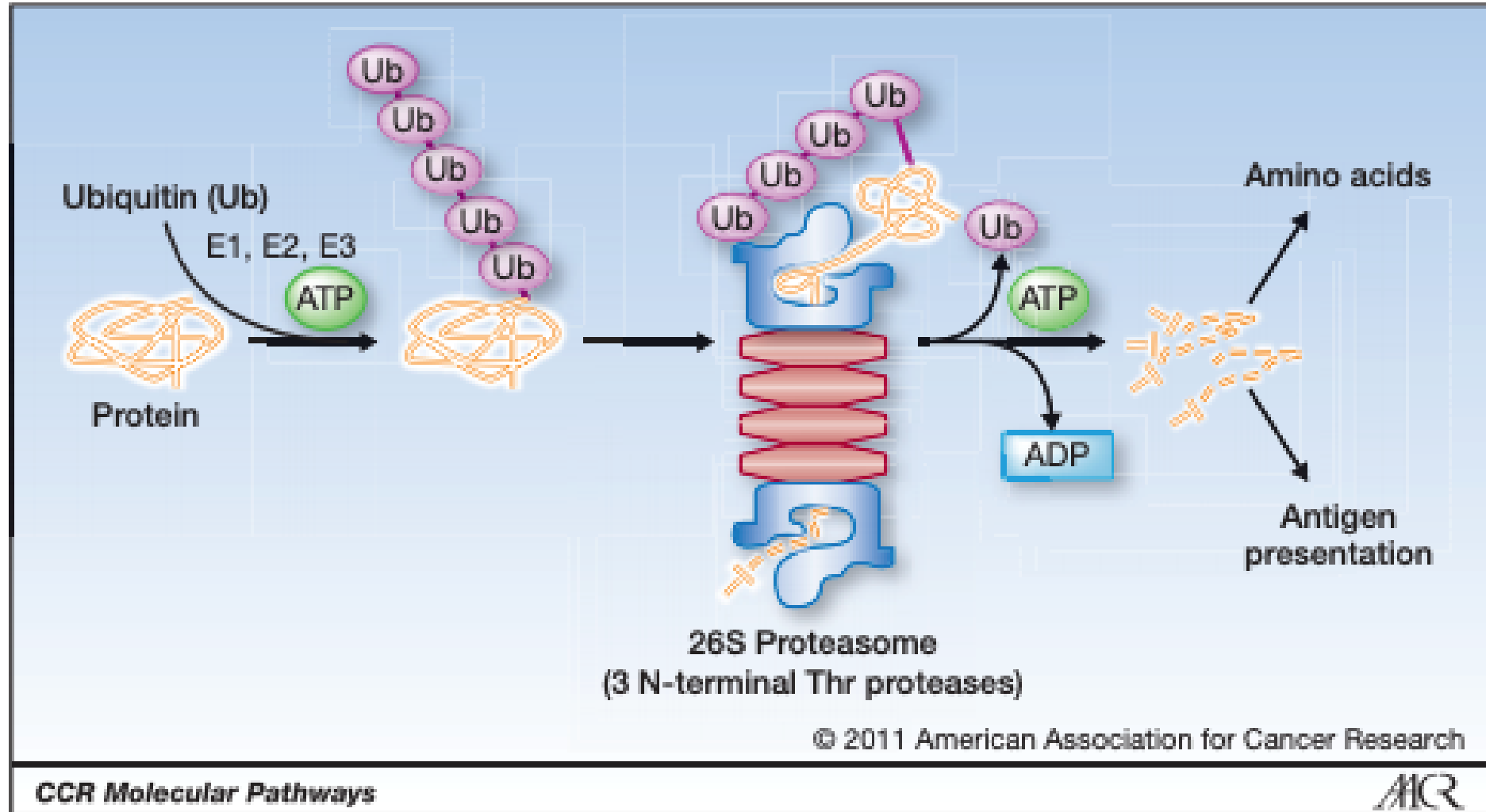


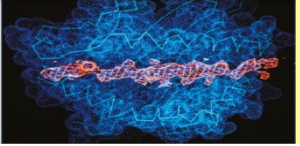
TWO CELLULAR COMPARTMENTS; INSIDE AND OUTSIDE MEMBRANES

- 2 DISTINCT COMPARTMENTS
- 2 DIFFERENT SITES FOR DEGRADATION
- 2 DIFFERENT MHC MOLECULES TO LOAD
- 2 TYPES OF T CELLS TO ENGAGE



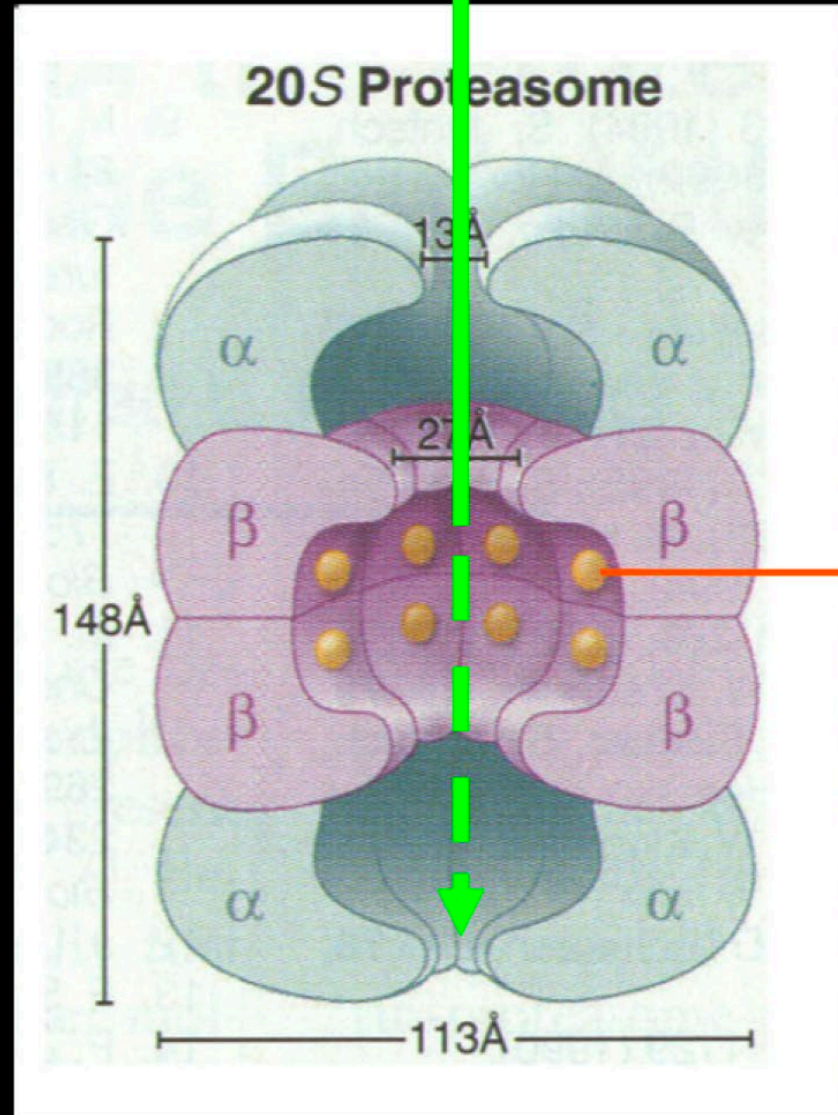
PROTEASOMES





Proteolysis by Proteasomes

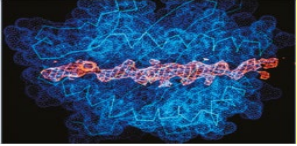
Protein



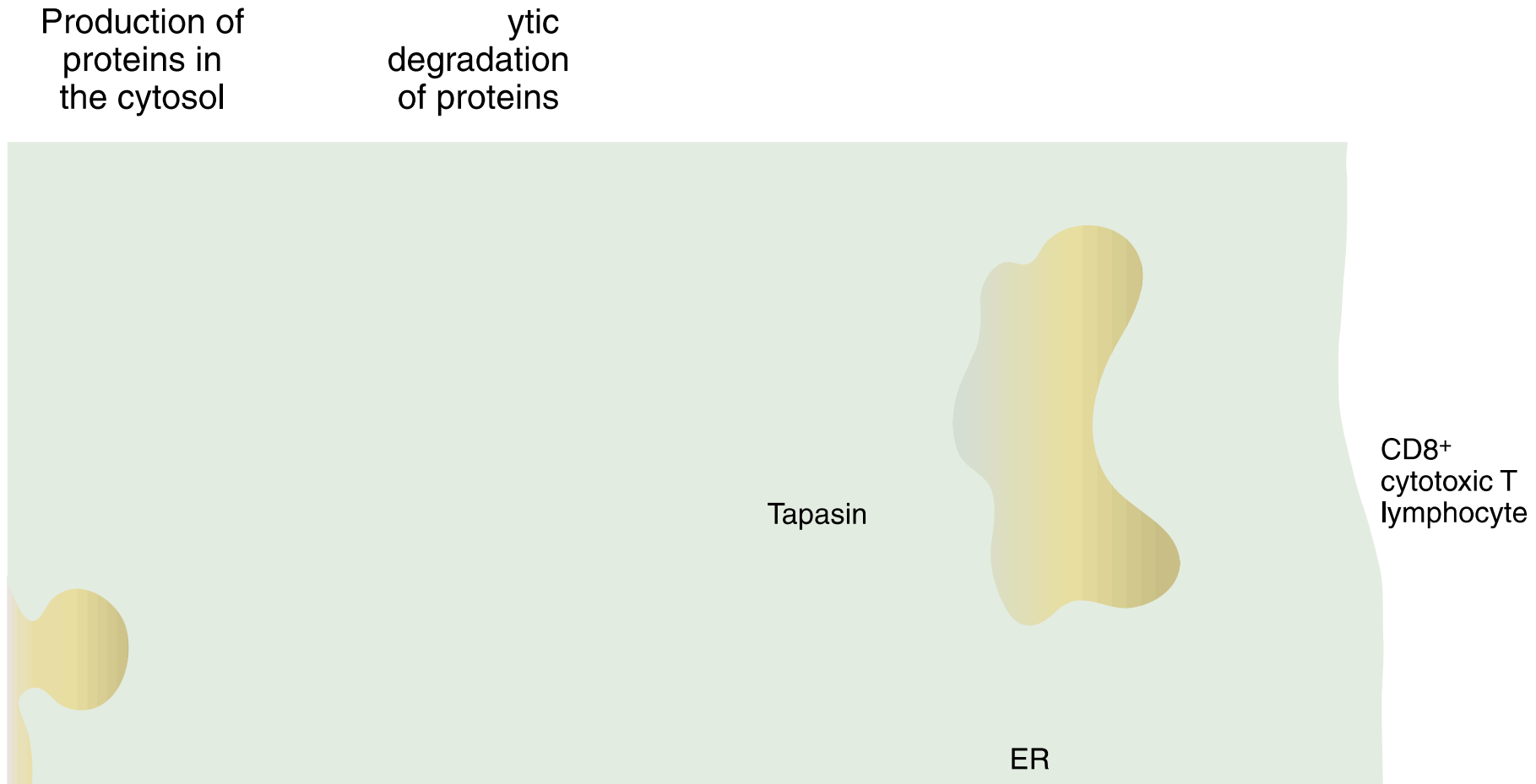
Active sites

IMMUNO-
PROTEASOMES

iβ1
iβ2
iβ5



Class I MHC Pathway of Antigen Presentation



“PEPTIDE EDITING” IN THE PEPTIDE LOADING COMPLEX IN THE ER

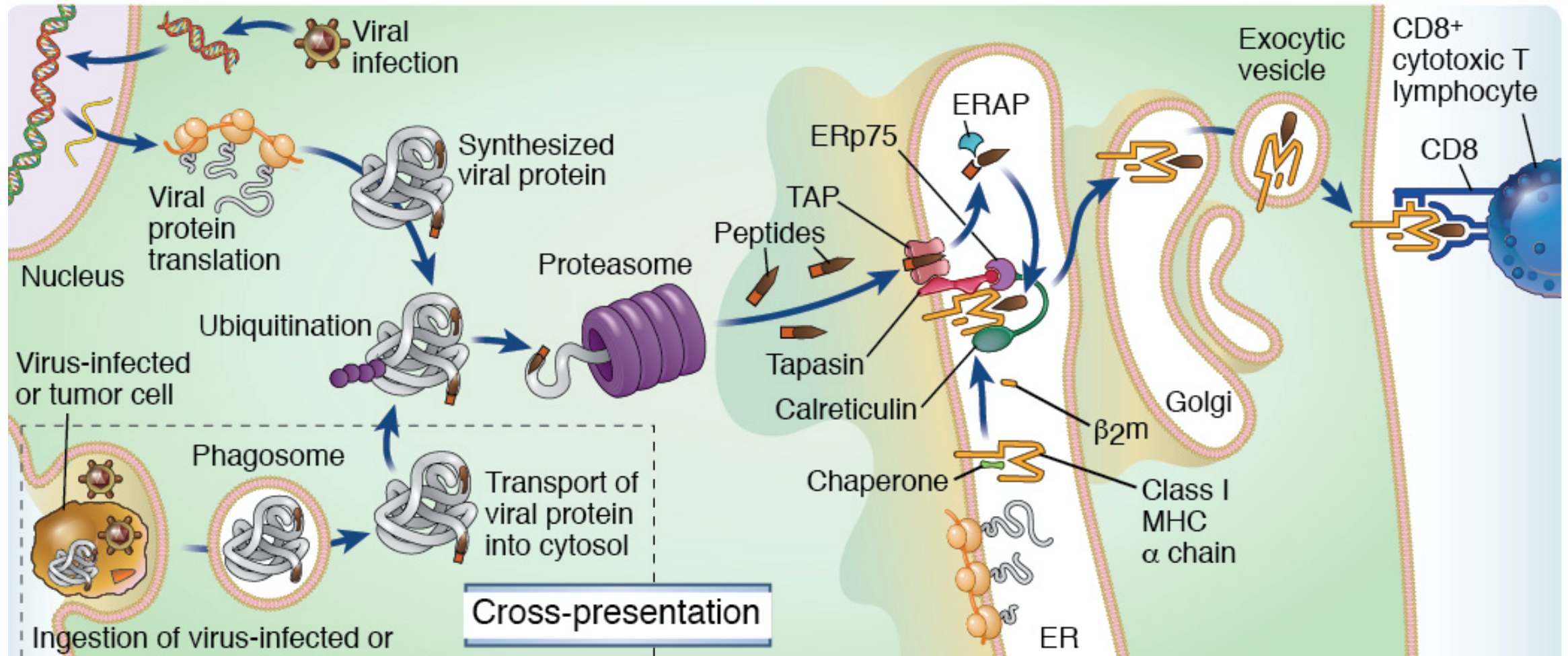
Production of proteins in or delivery to the cytosol

Proteolytic degradation of proteins

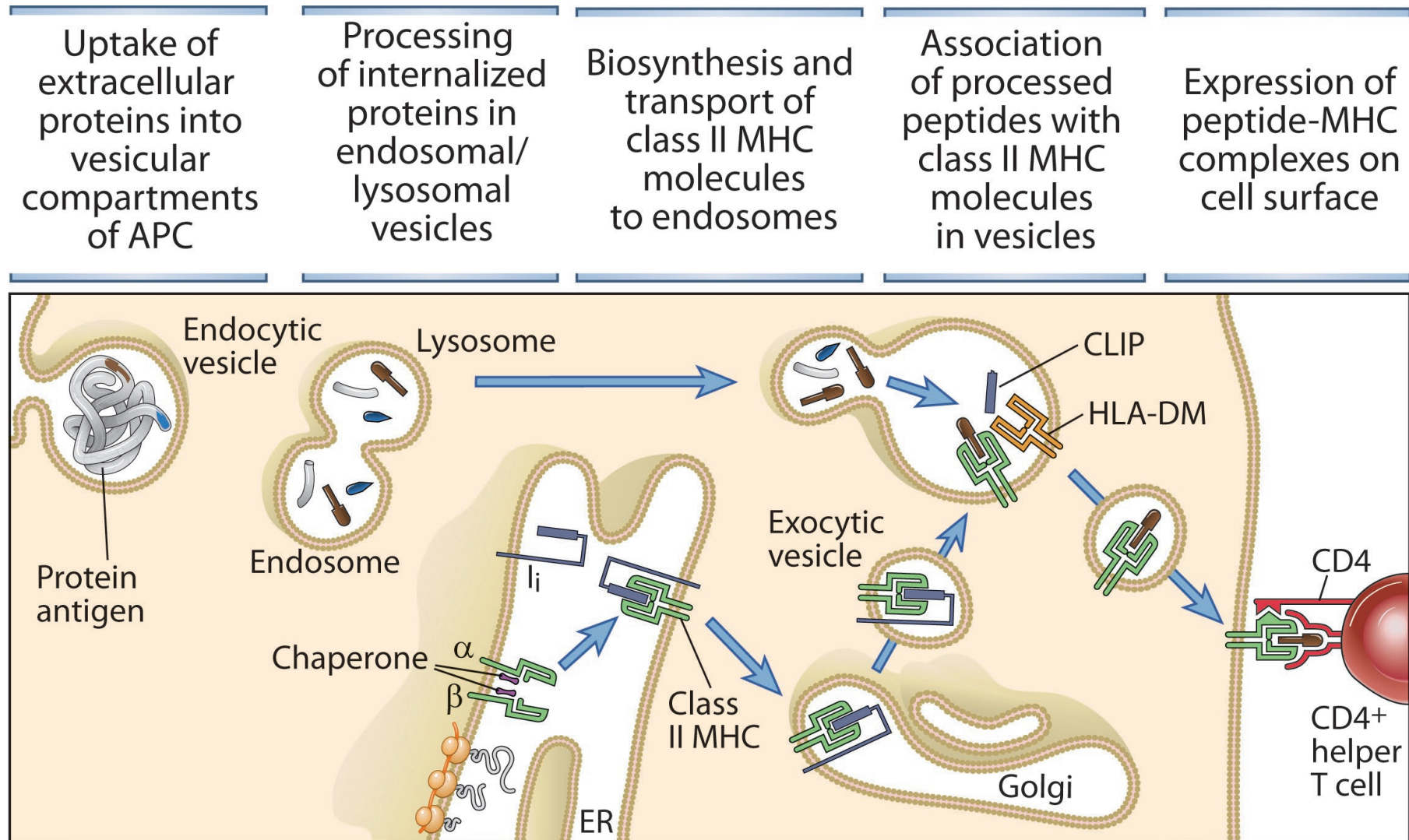
Peptide transport from cytosol to ER

Assembly of peptide-class I complexes in ER

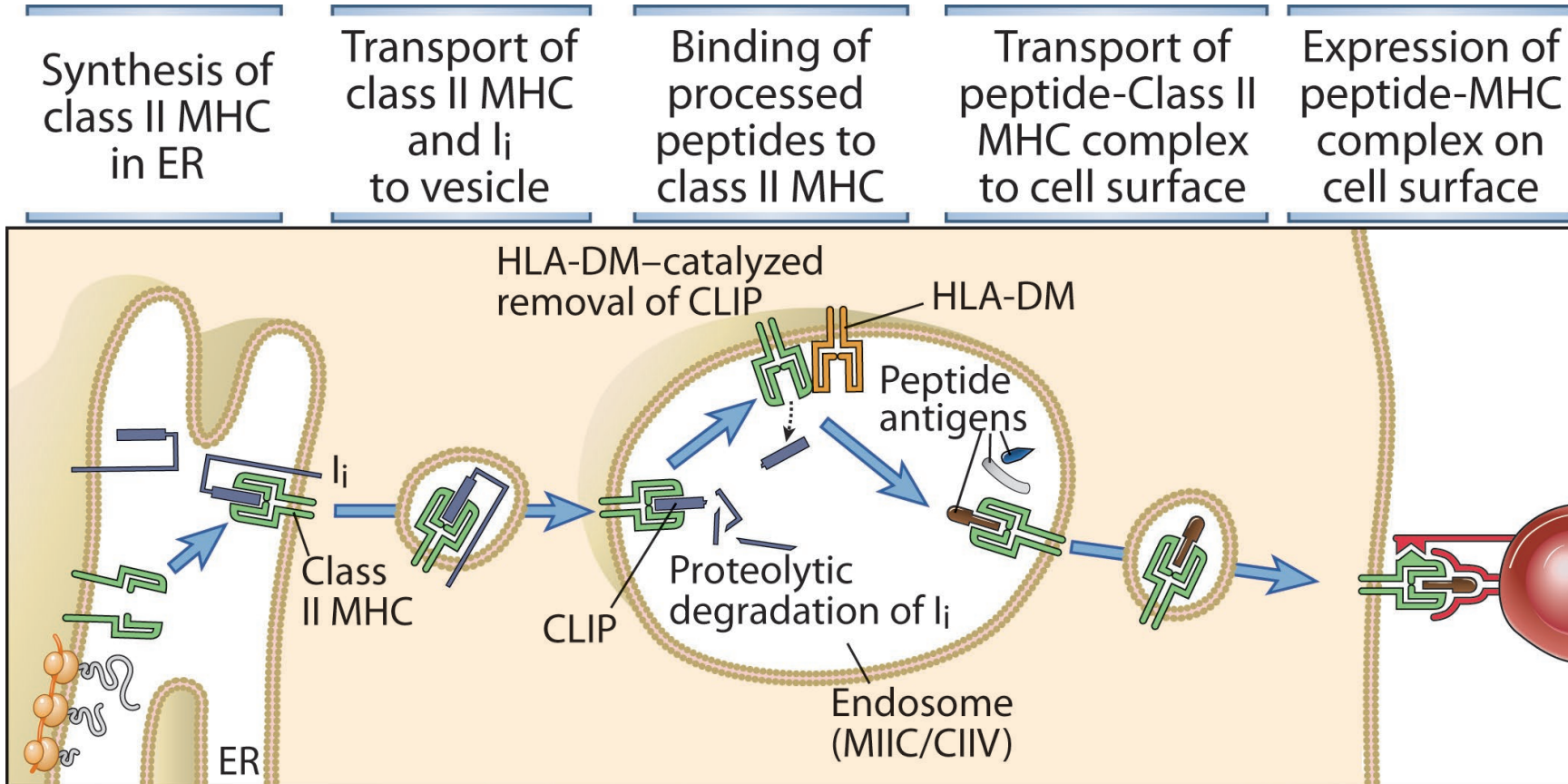
Surface expression of peptide-class I complexes



Class II Pathway of Antigen Presentation



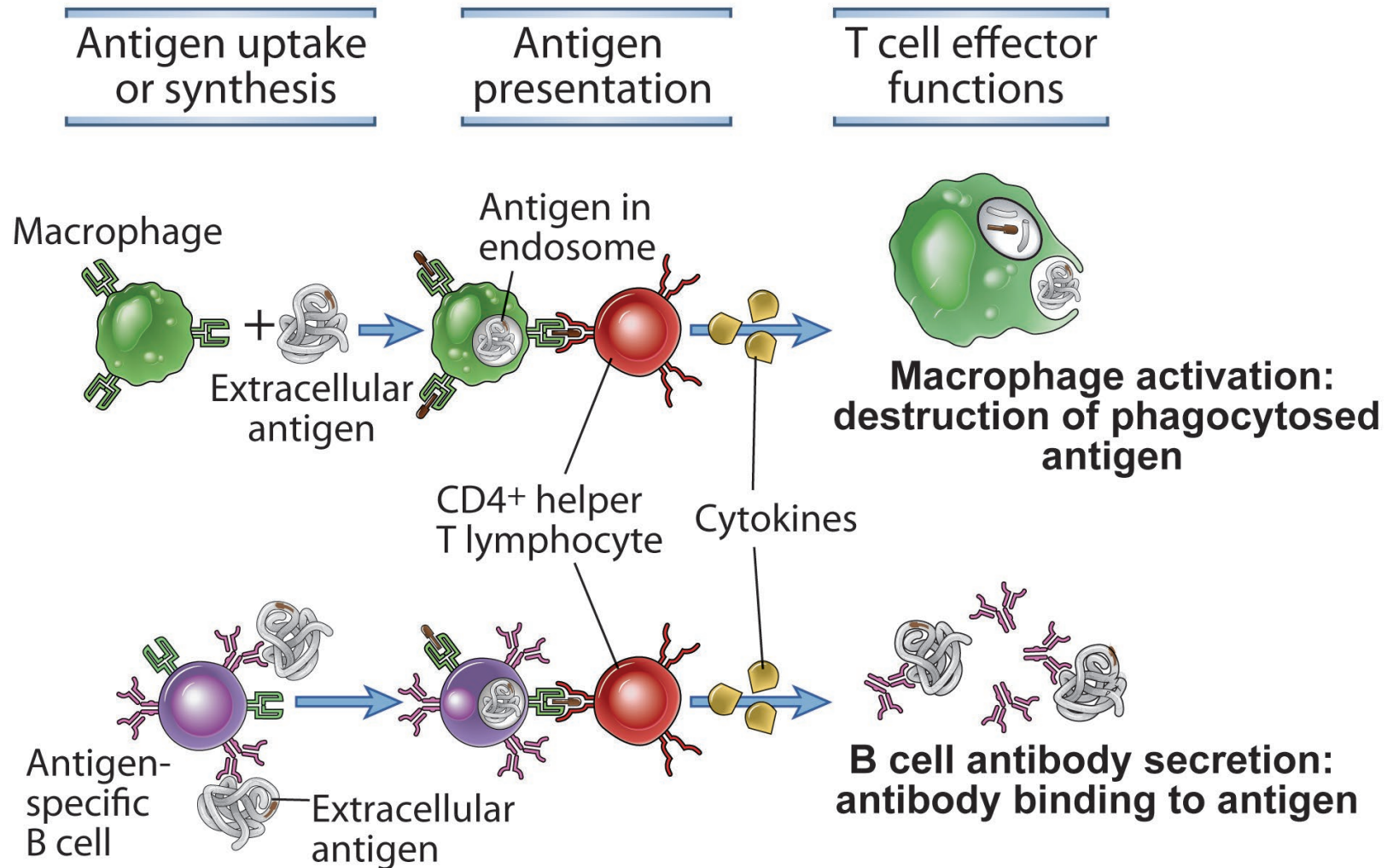
Functions of Invariant Chain and HLA-DM



**HLA-DM HELPS WITH
PEPTIDE EDITING**

Lysosomal Peptides Presented to CD4⁺ T Cells

Class II MHC–associated presentation of extracellular antigen to helper T cells



Lord of the Rings