

Lymphocyte Activation
FOCIS Advanced Course 2024



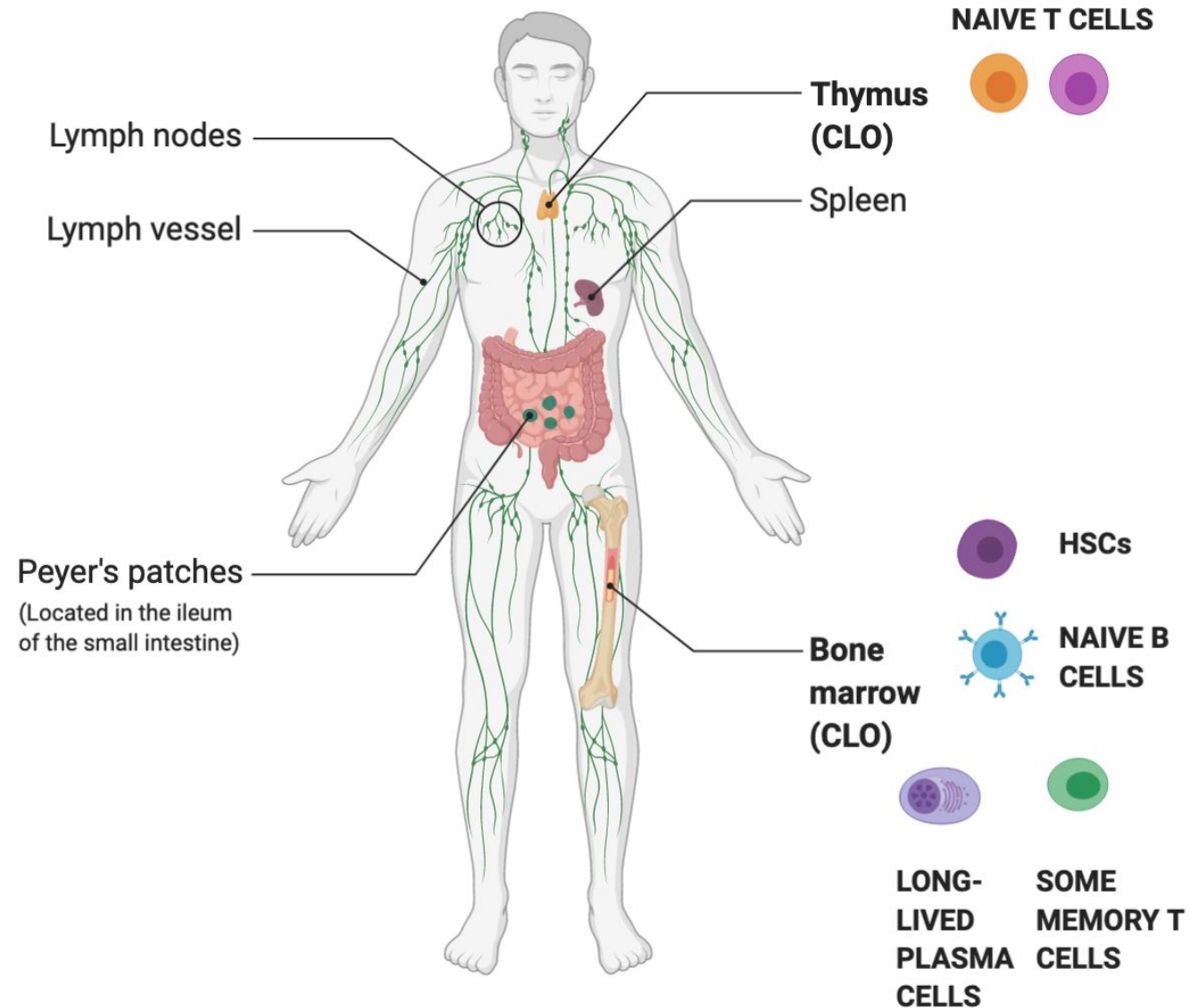
Shiv Pillai MD, PhD
Ragon Institute, Massachusetts General Hospital
Harvard Medical School

Lecture Outline

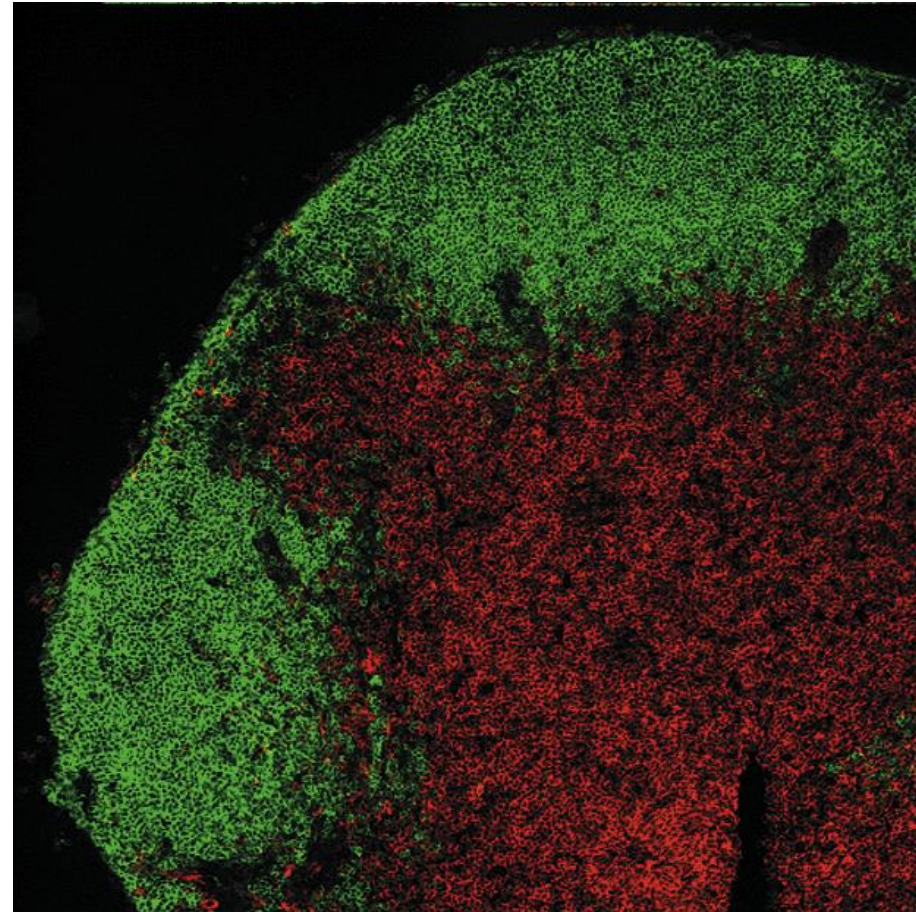
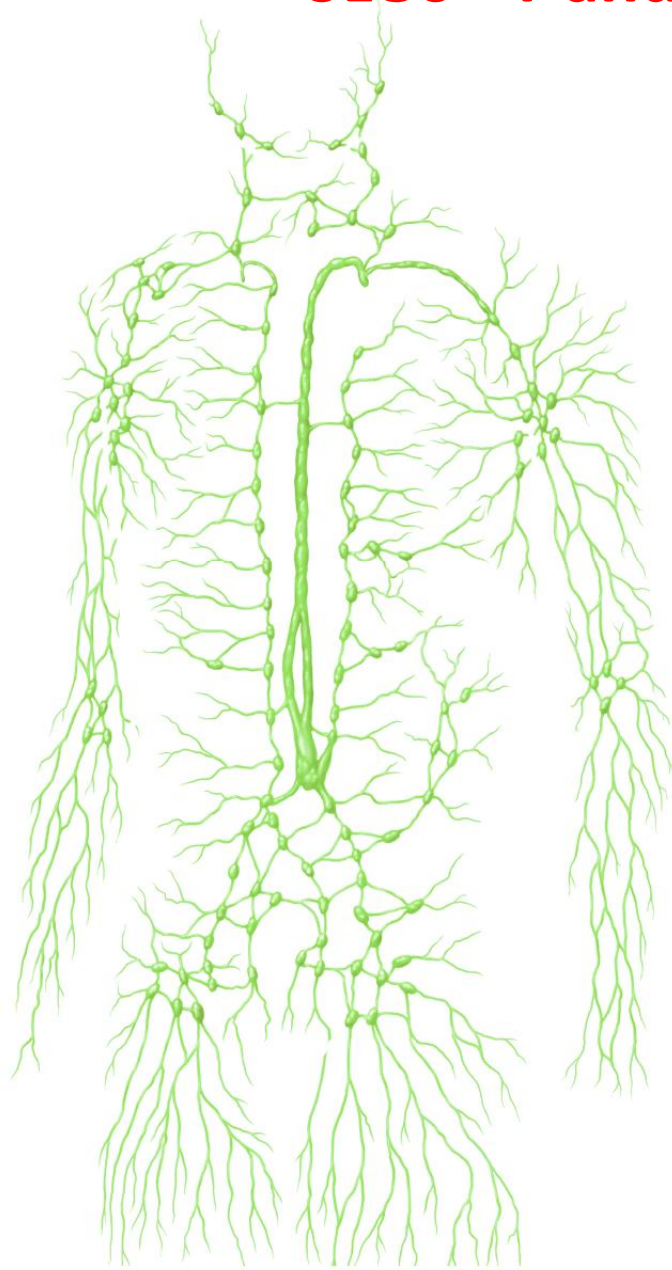
- T and B cell signaling: Coreceptors v Costimulators
- Antigen receptor signaling: Signal 1
- Costimulation: Signal 2
- Inhibitory receptors
- Cytokine signaling
- “Lord of the Rings”

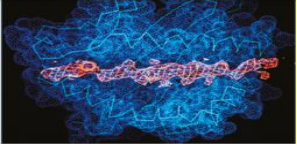
ALL ACTIVATION OF NAÏVE LYMPHOCYTES
OCCURS IN SECONDARY LYMPHOID ORGANS

CENTRAL AND PERIPHERAL LYMPHOID ORGANS

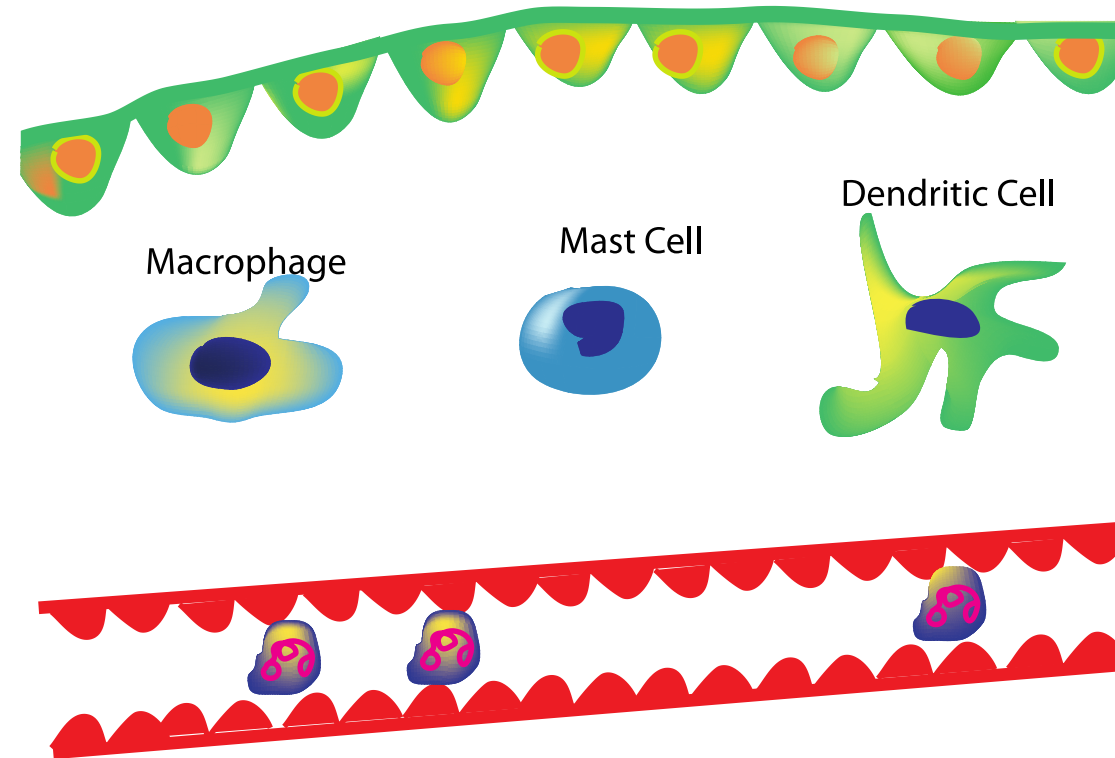


SLOs - T and B cell zones

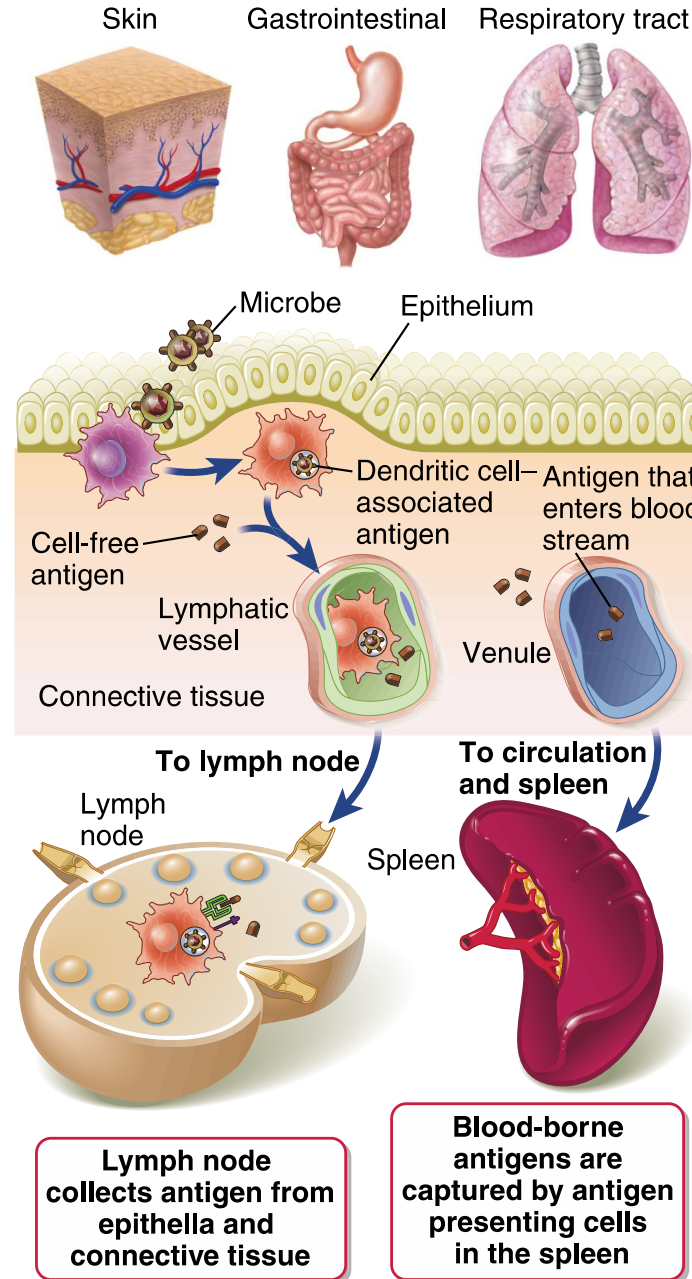




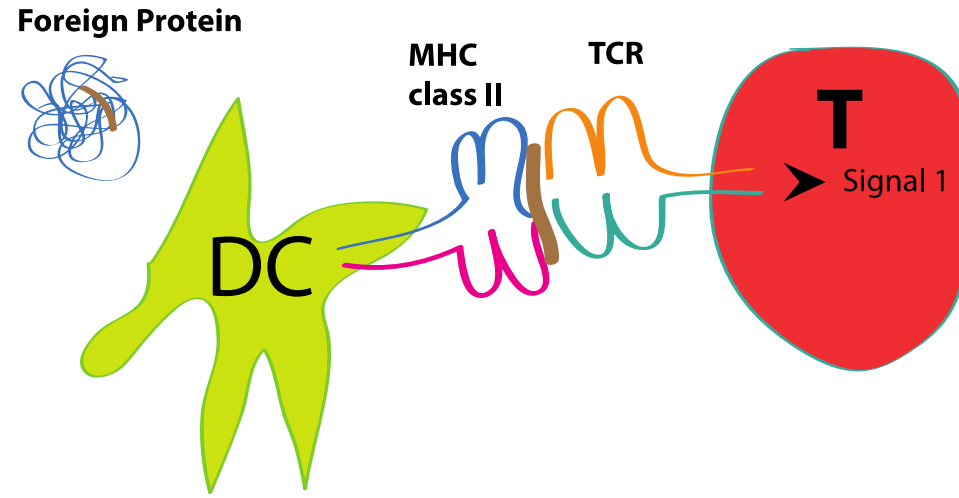
A Third Type of Sentinel Cell Initiates Adaptive Immunity



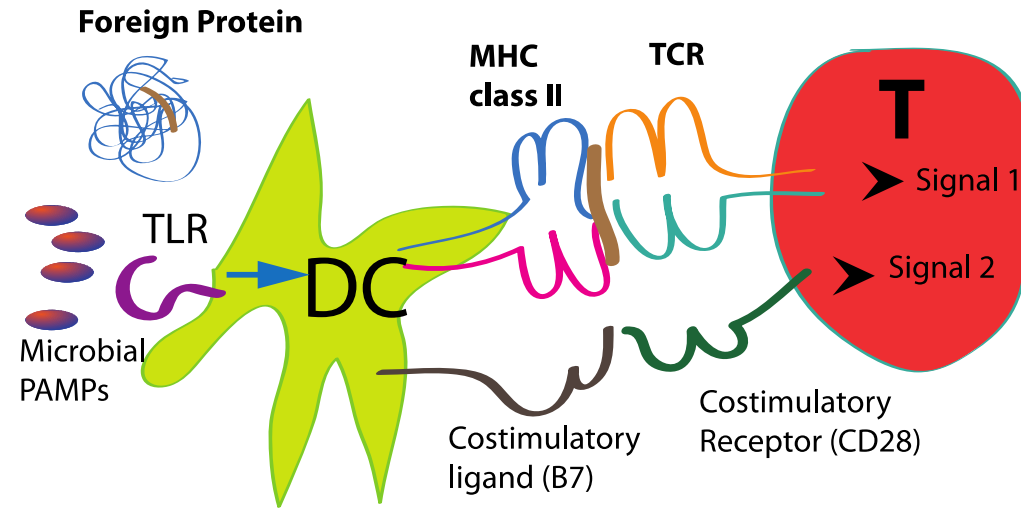
MULTIPLE ROUTES OF ANTIGEN ENTRY



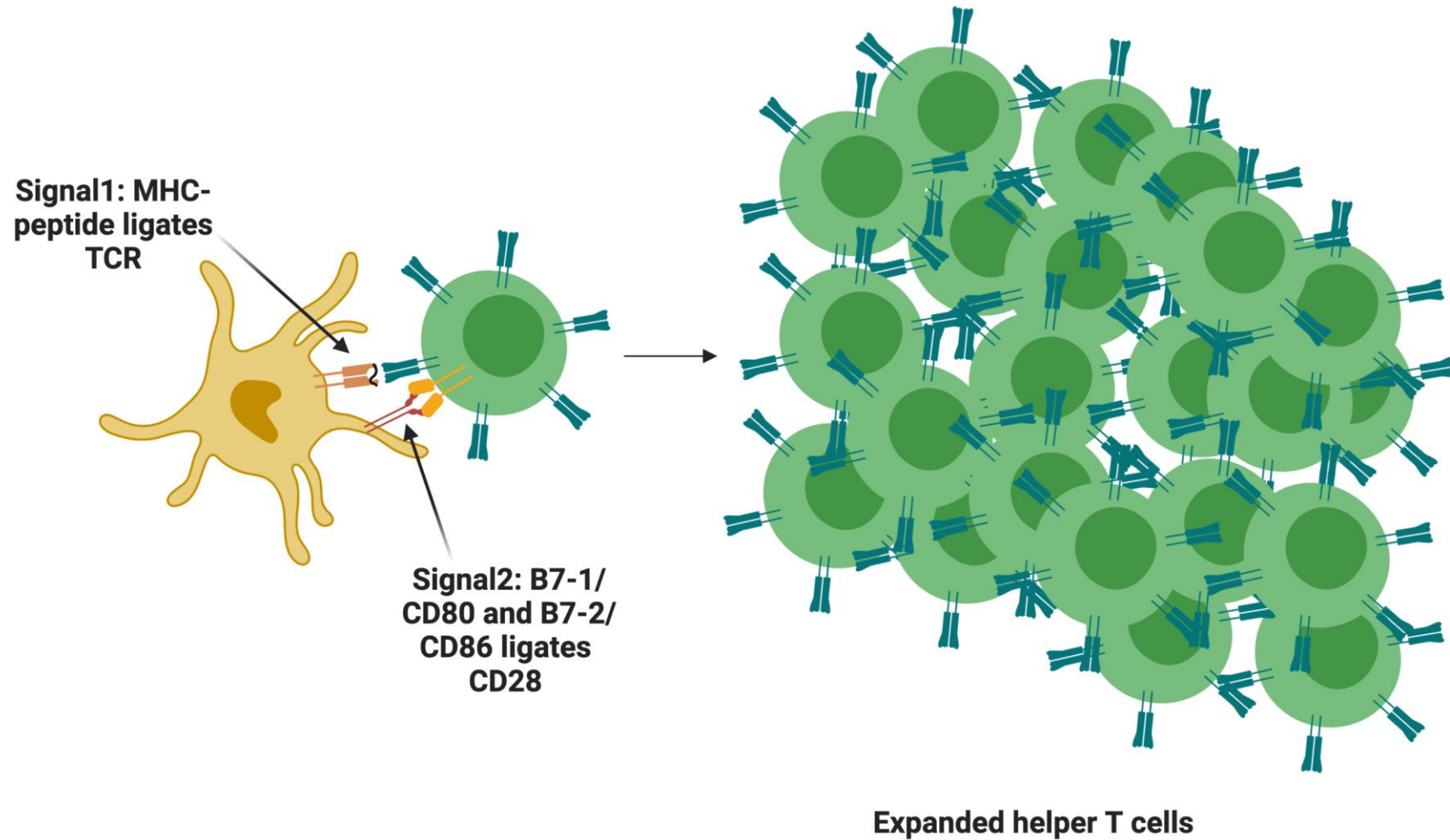
Foreign Protein but no "Danger"

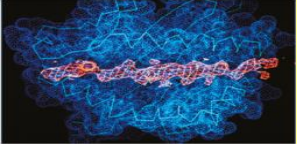


Foreign protein but also "Danger"!

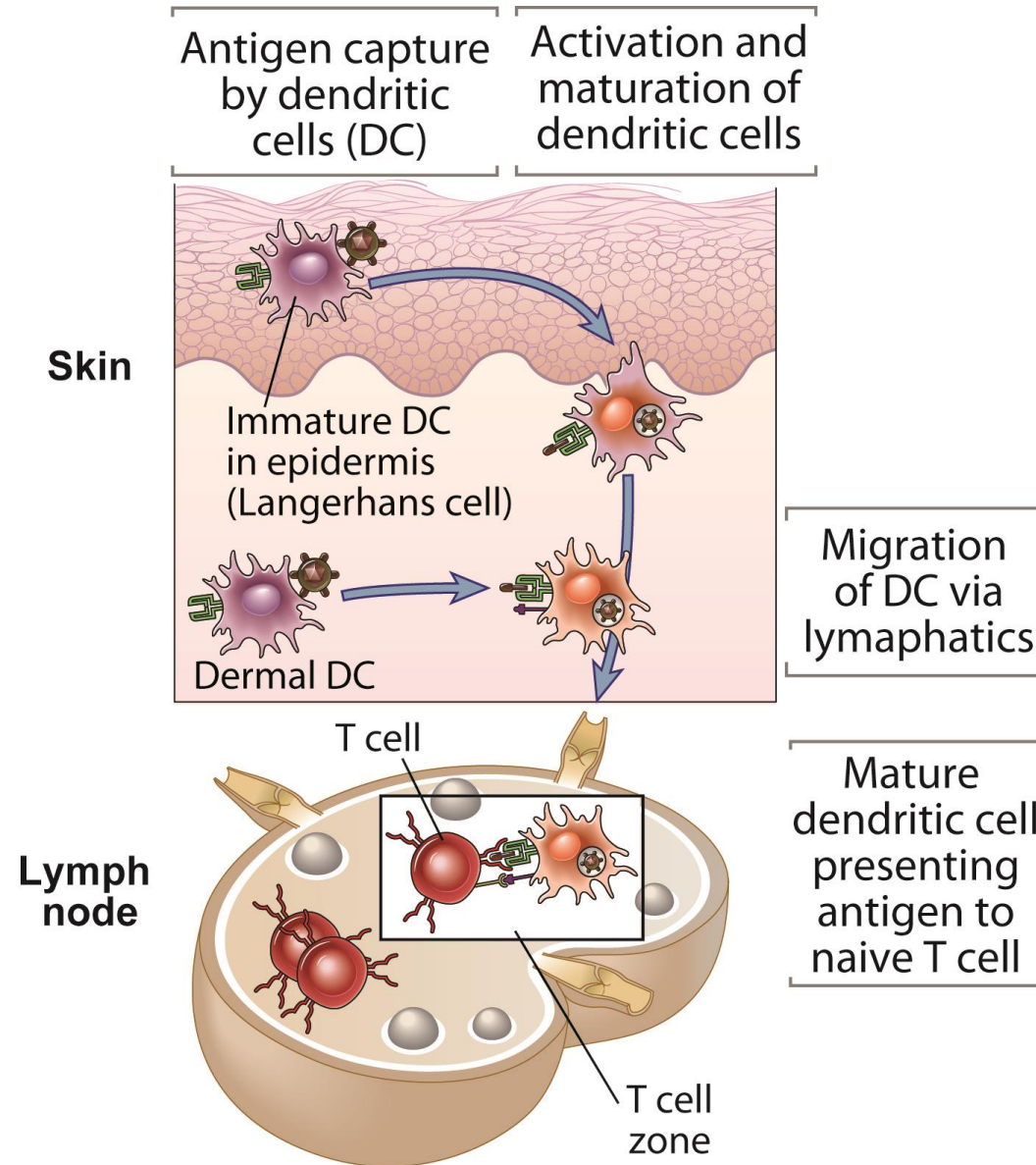


SIGNAL ONE AND SIGNAL TWO ARE REQUIRED FOR NAÏVE T CELL ACTIVATION AND PROLIFERATION

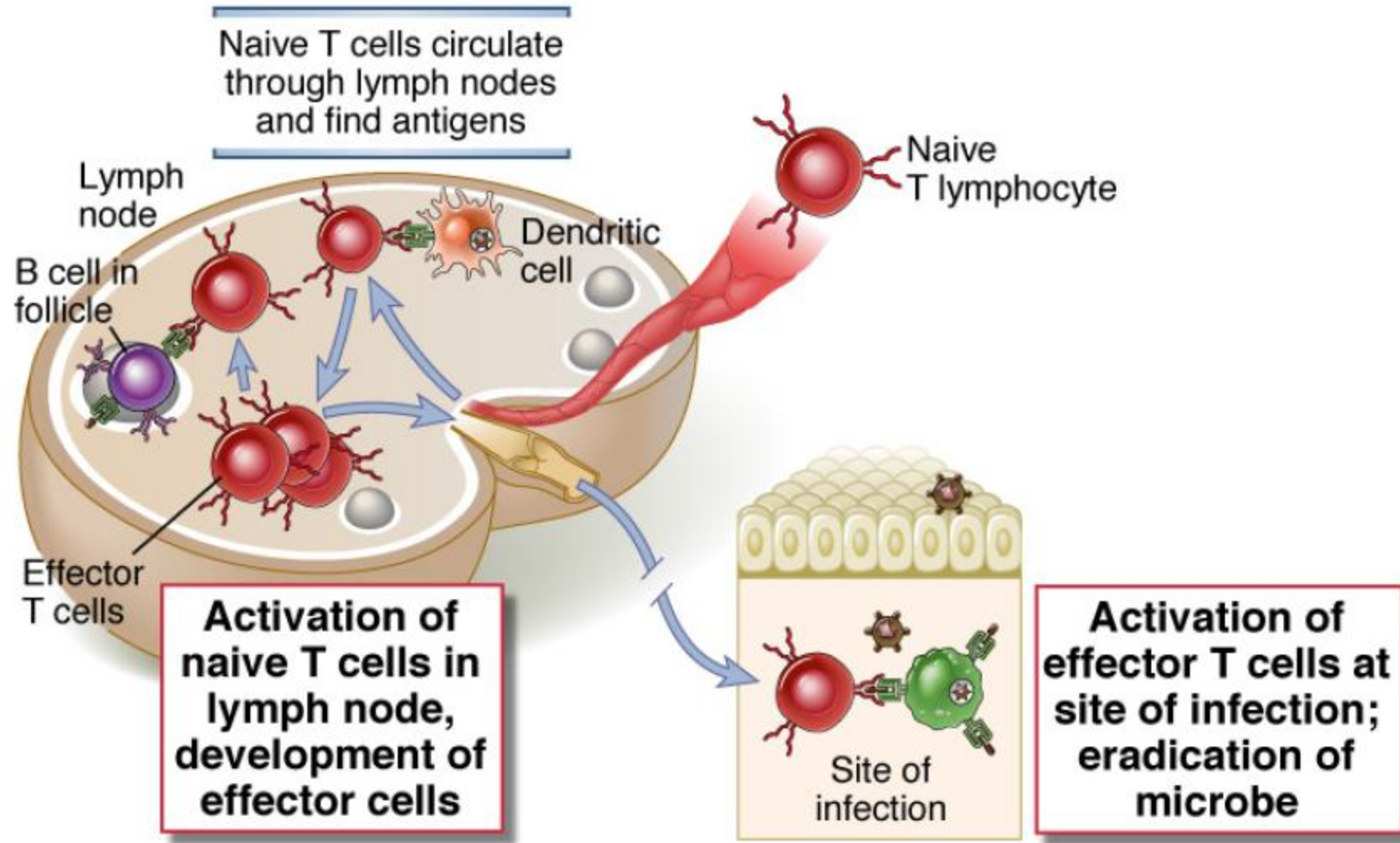




DC Antigen Capture and Presentation



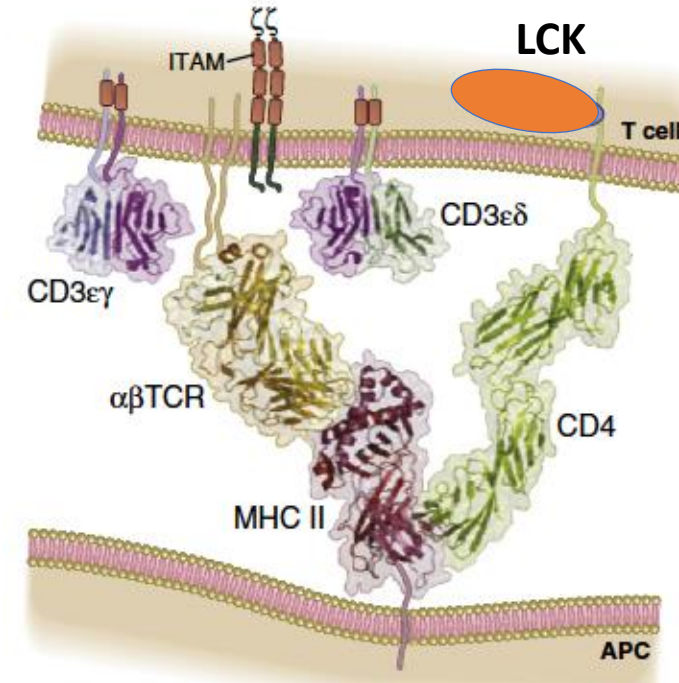
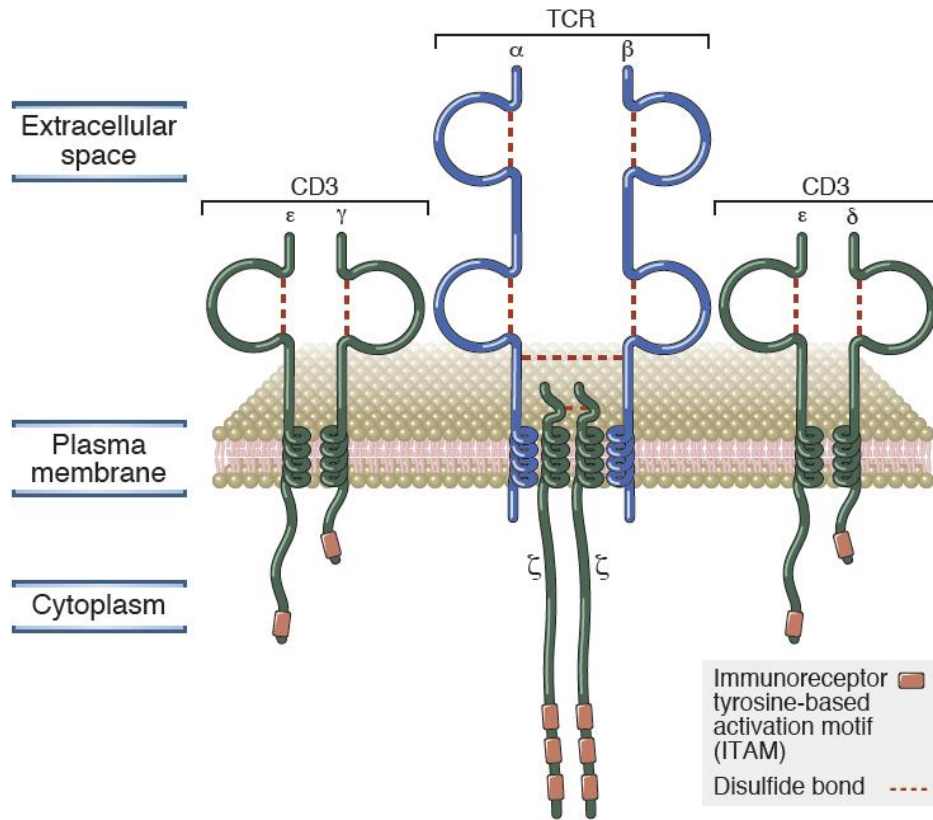
DCs and antigen find specific Naïve T cells in SLOs in the
T cell zone: activated Effector T cells return to the site of infection

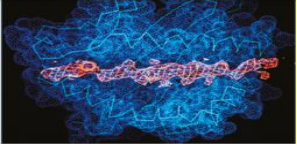


CORECEPTORS ARE PART OF SIGNAL ONE

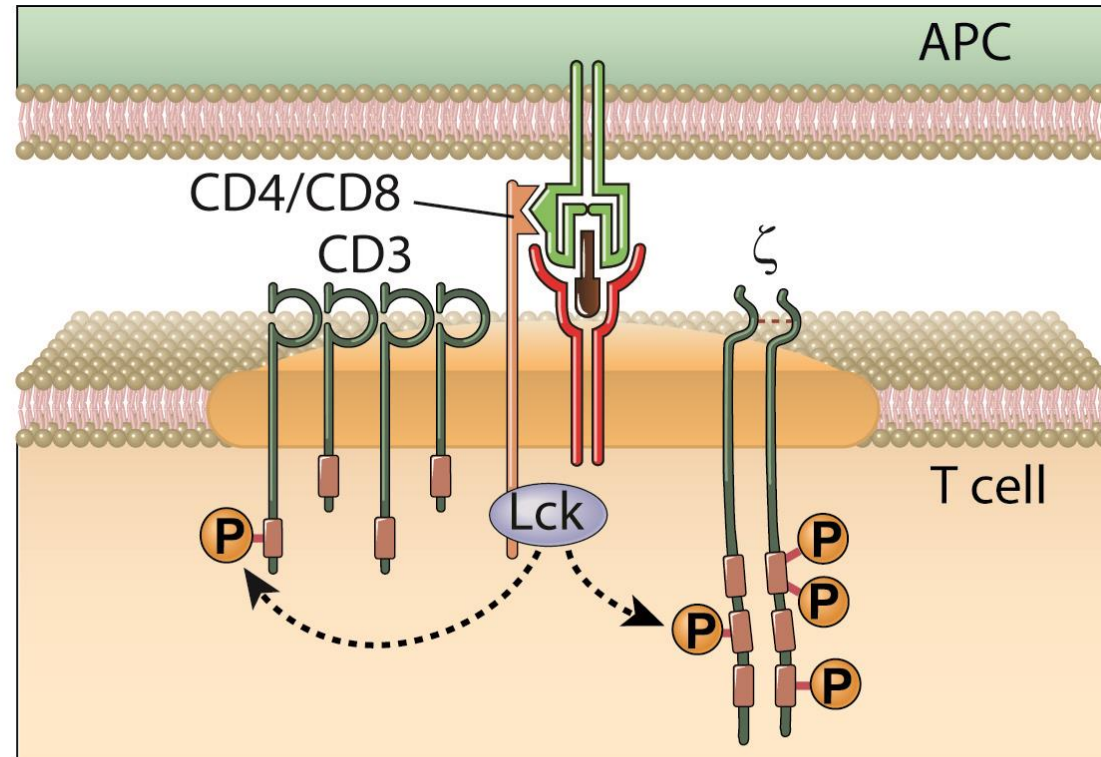
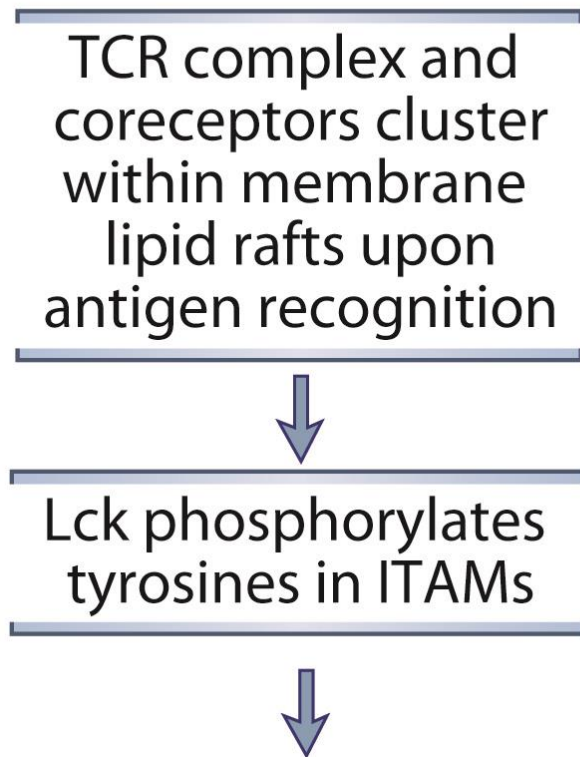
- A CO-RECEPTOR BINDS TO THE SAME ANTIGEN OR ANTIGEN COMPLEX AS THE ANTIGEN RECEPTOR
- ITS CYTOPLASMIC TAIL IS ASSOCIATED WITH SIGNALING ENZYME/S AND IT FACILITATES ANTIGEN RECEPTOR SIGNALING aka SIGNAL ONE

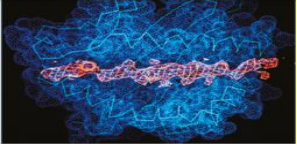
The T cell receptor complex: associated proteins have cytoplasmic tyrosine-based motifs called ITAMs





Early Signaling Events in T cell Activation (1)



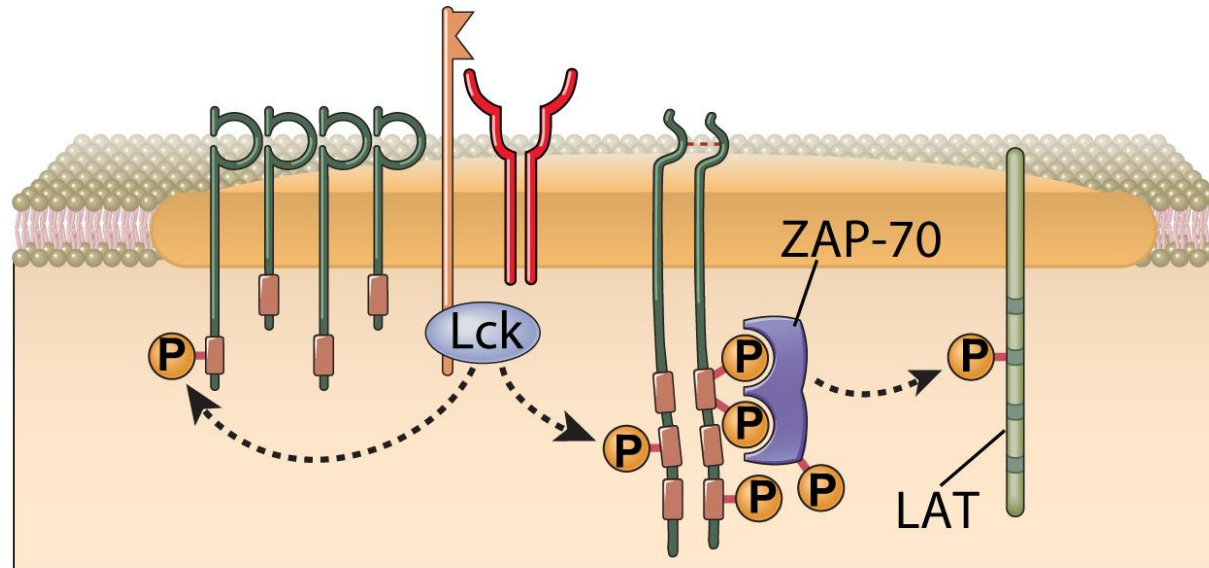


Early Signaling Events in T cell Activation (2)

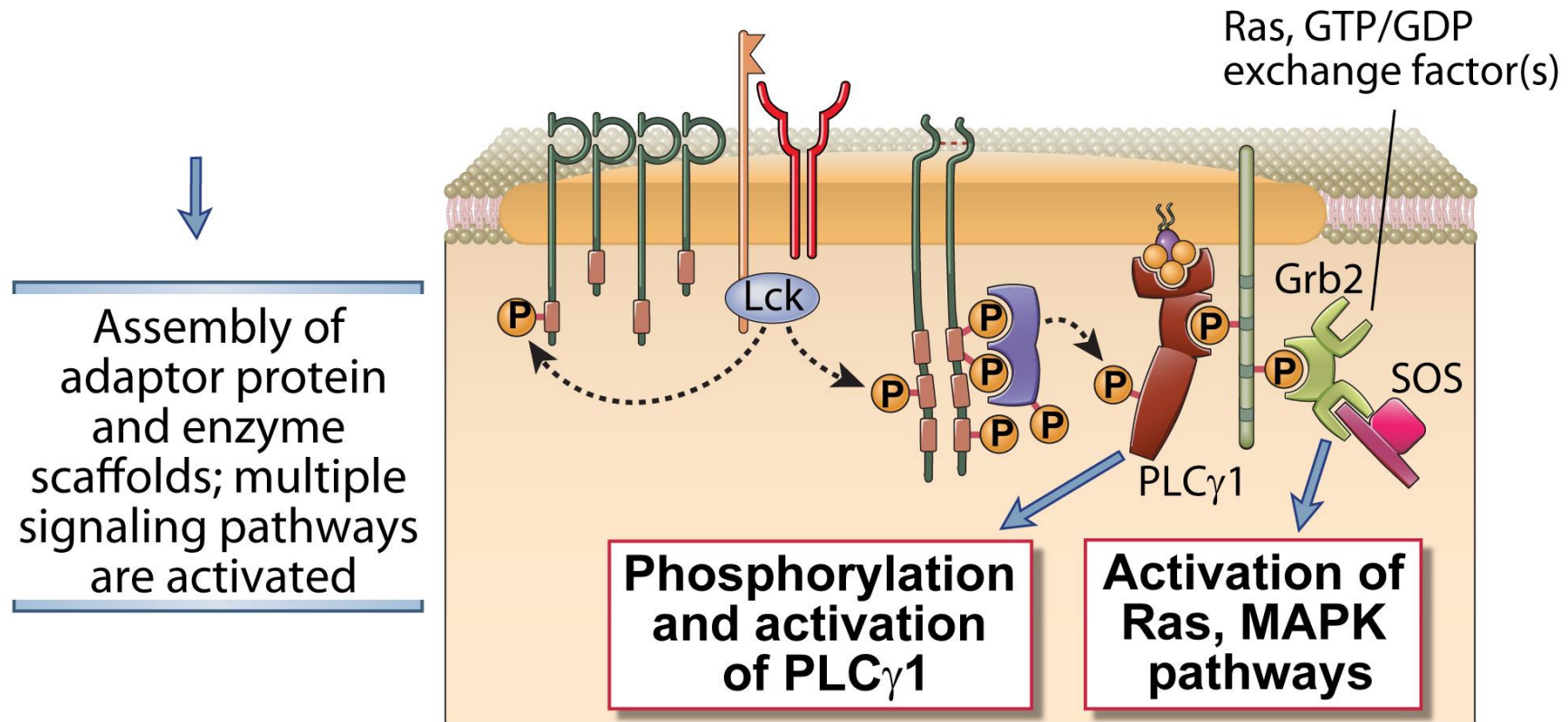
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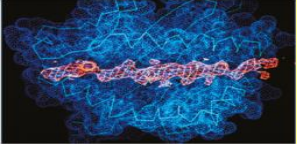
ZAP-70 binds to phospho-tyrosines and phosphorylates adaptor proteins, including LAT

↓

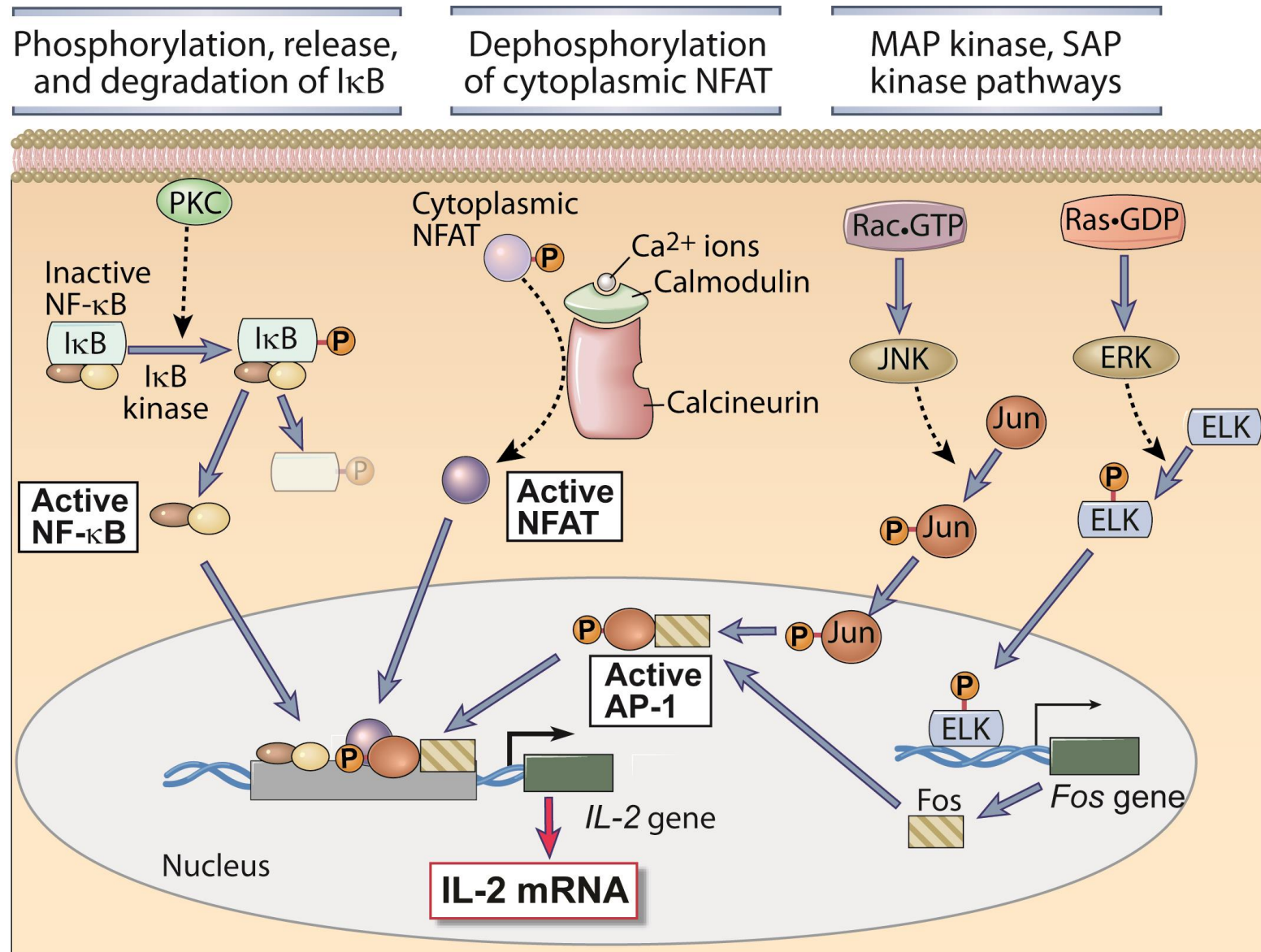


Early Signaling Events in T cell Activation (3)

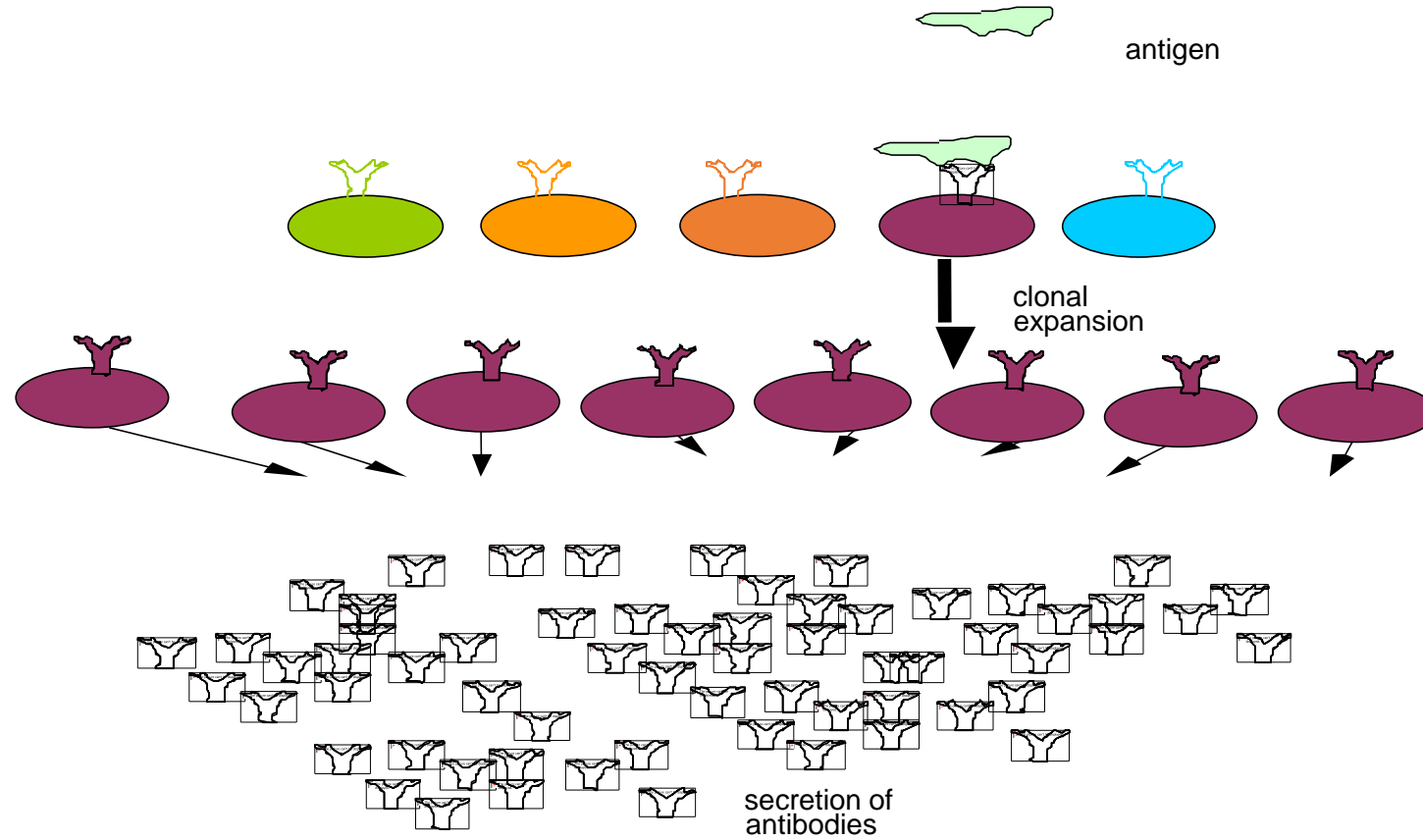




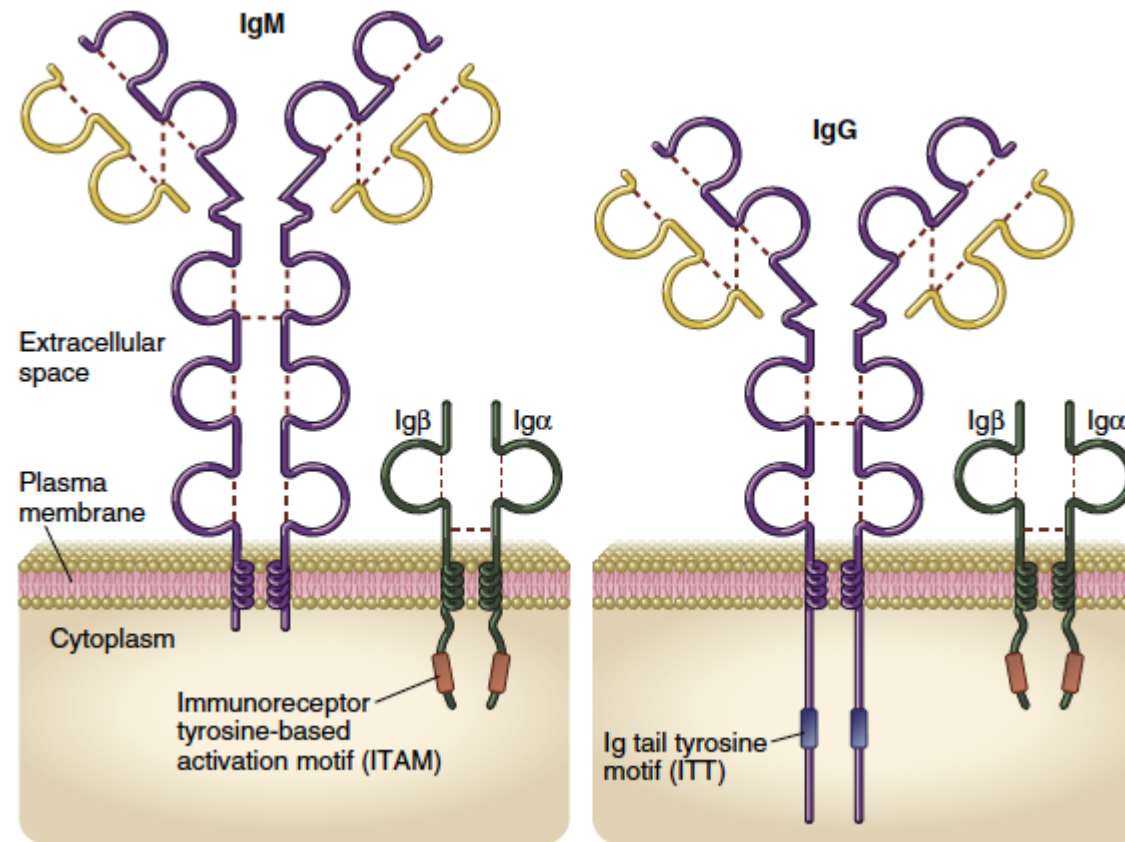
Activation of Transcription Factors in T Cells



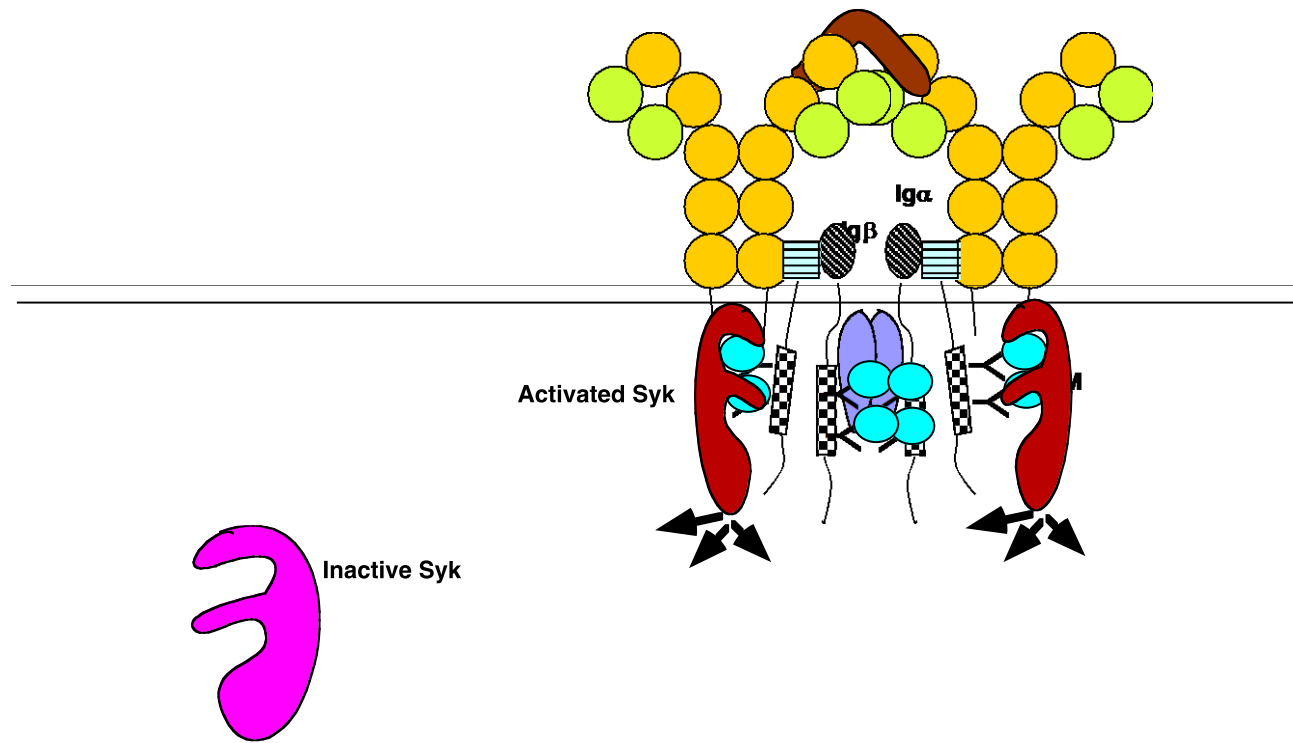
WHAT ABOUT B LYMPHOCYTES?



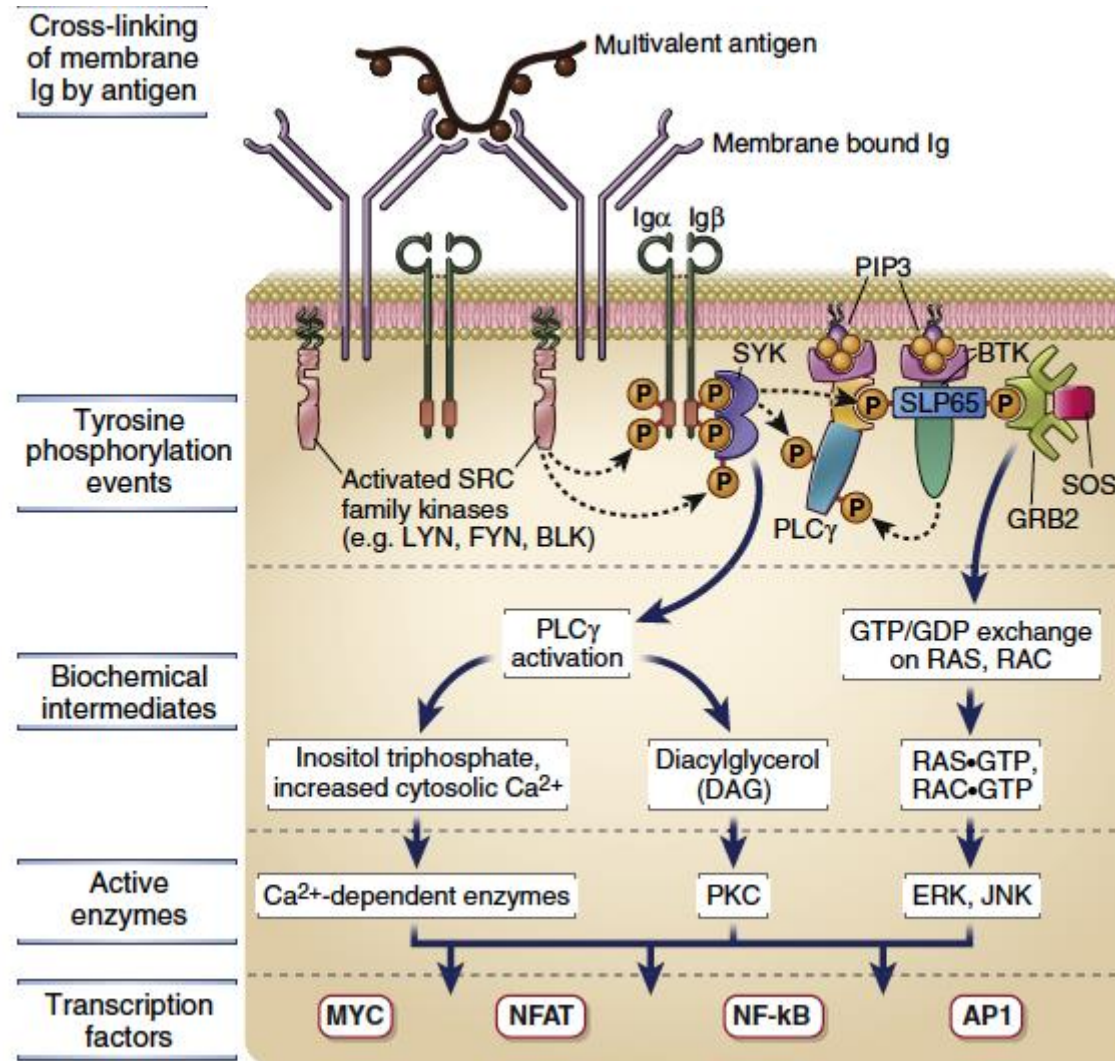
The B cell receptor

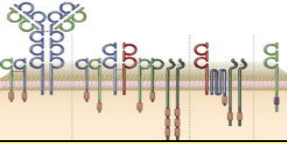


B cell Activation

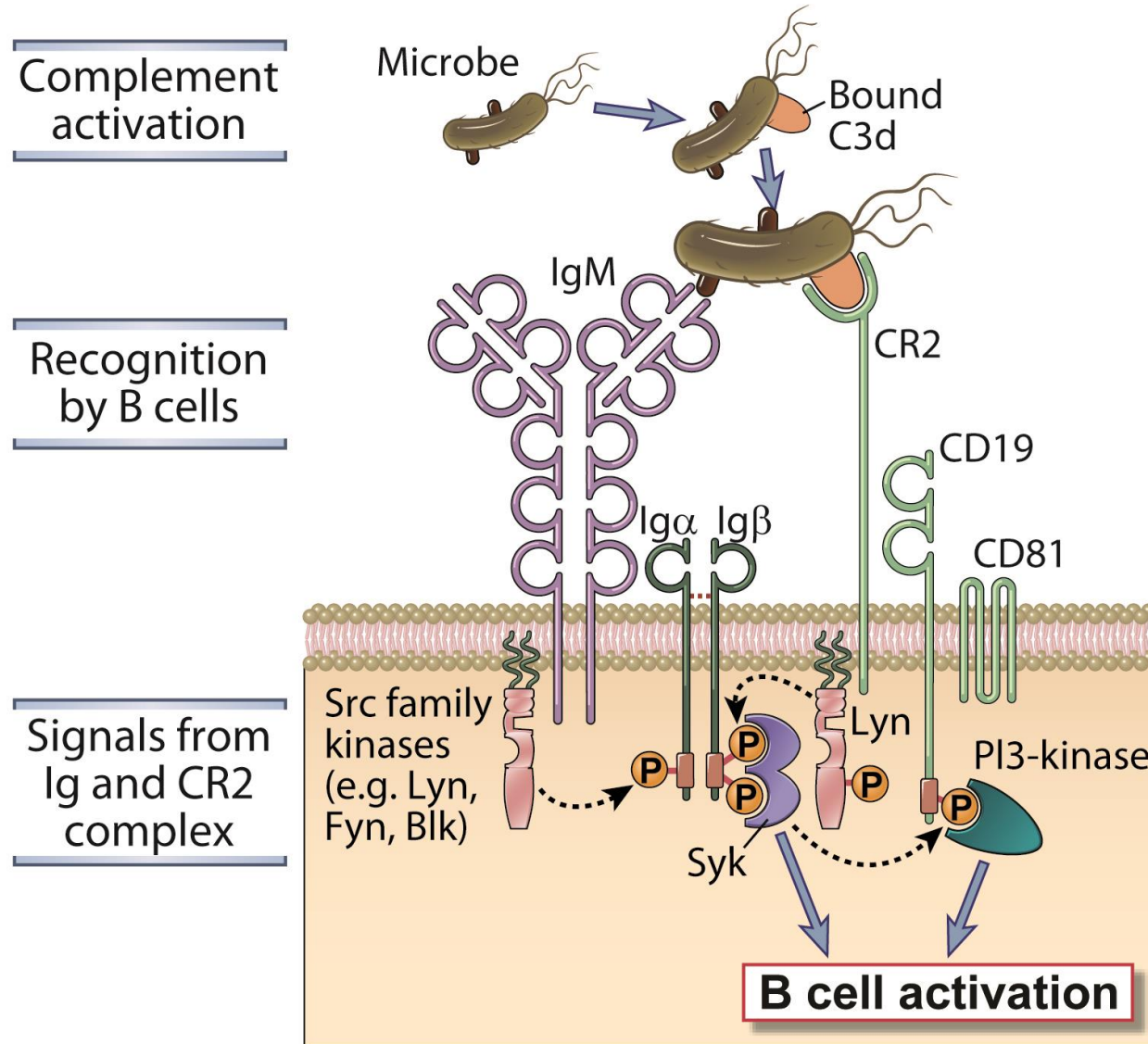


B cell receptor signaling

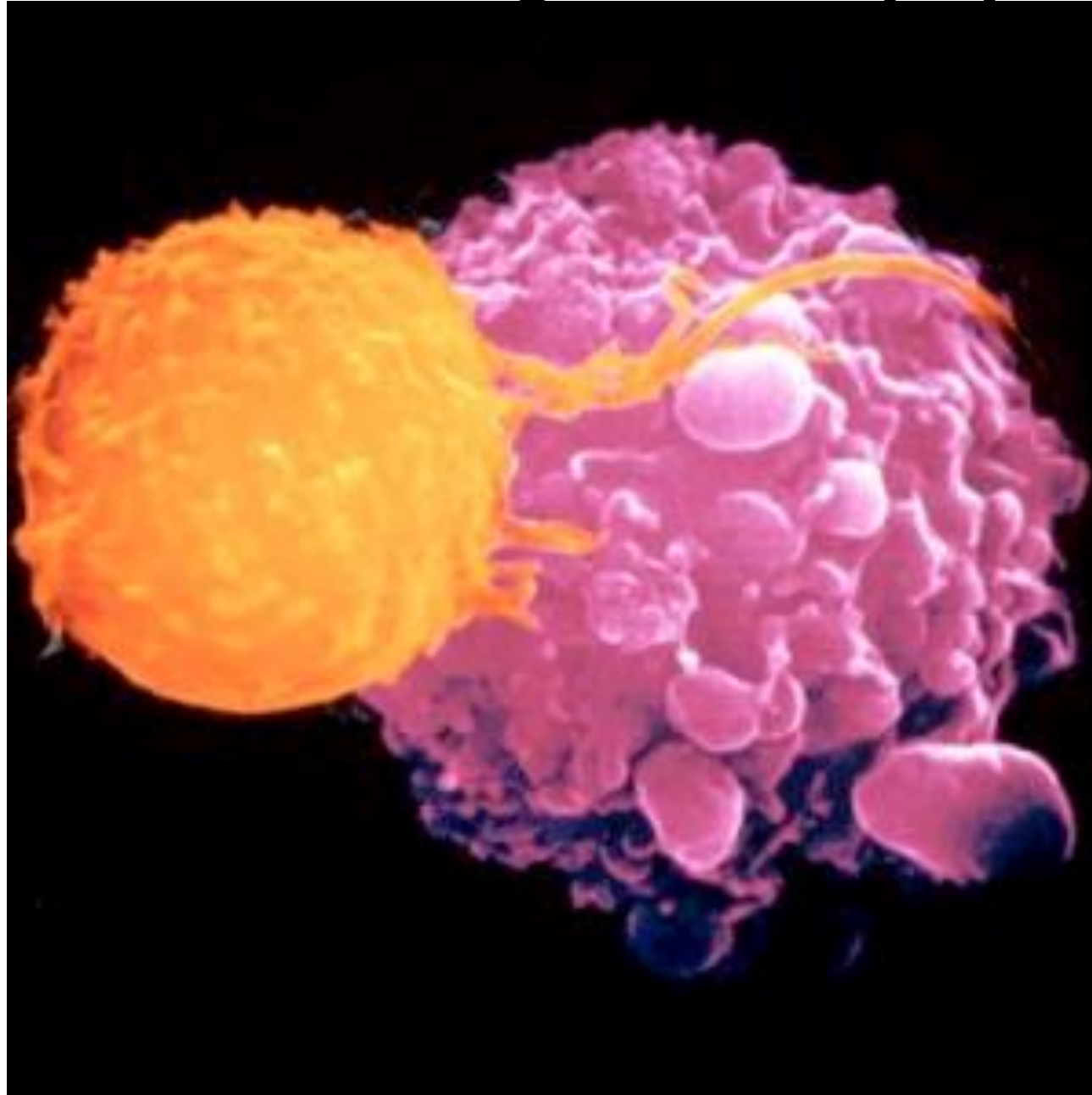




Role of Complement in B cell Activation - CD21 is a Coreceptor



CTL inducing tumor apoptosis

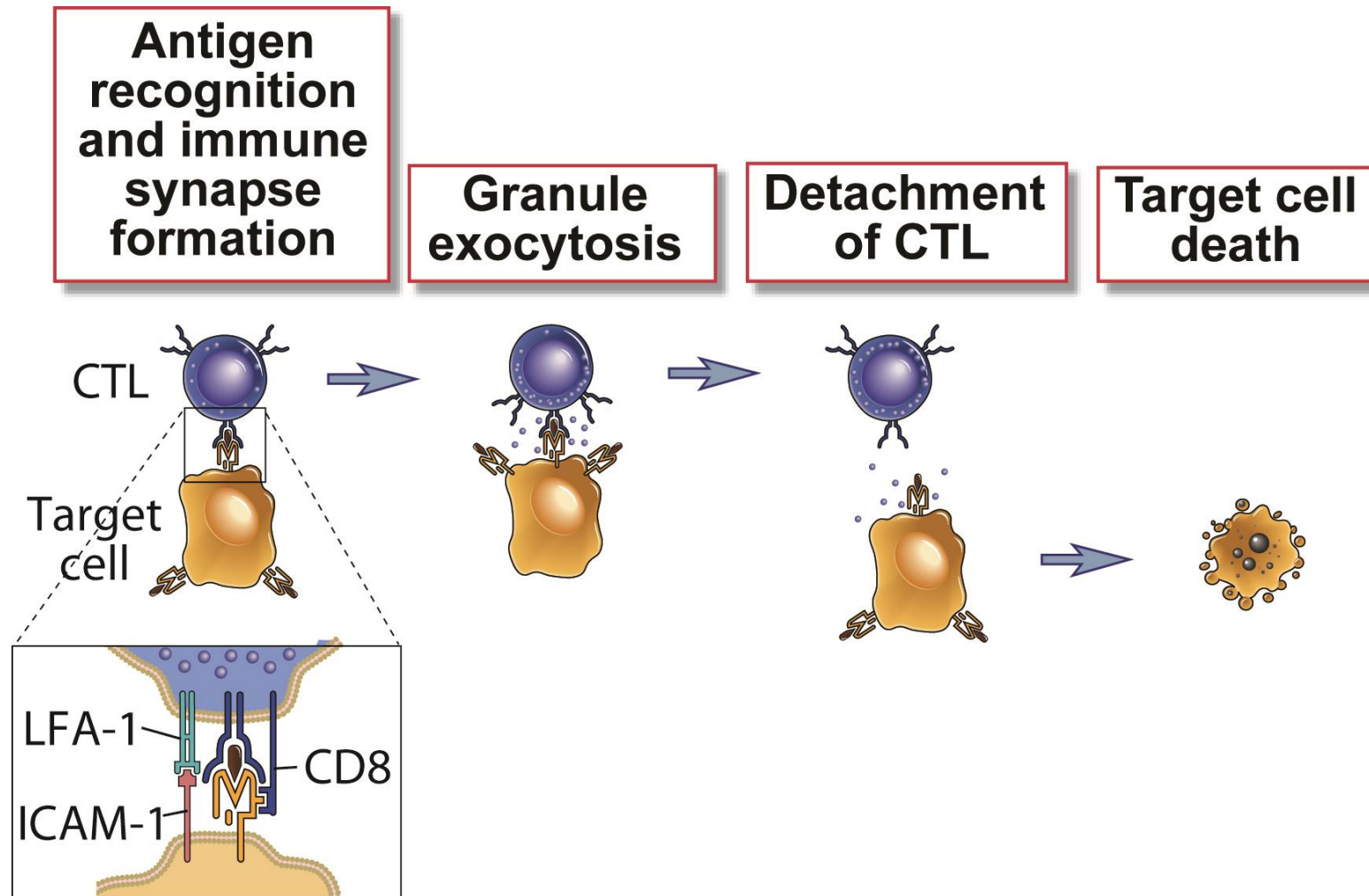


Major Roles of CD8⁺ CTLs in Defense and Disease

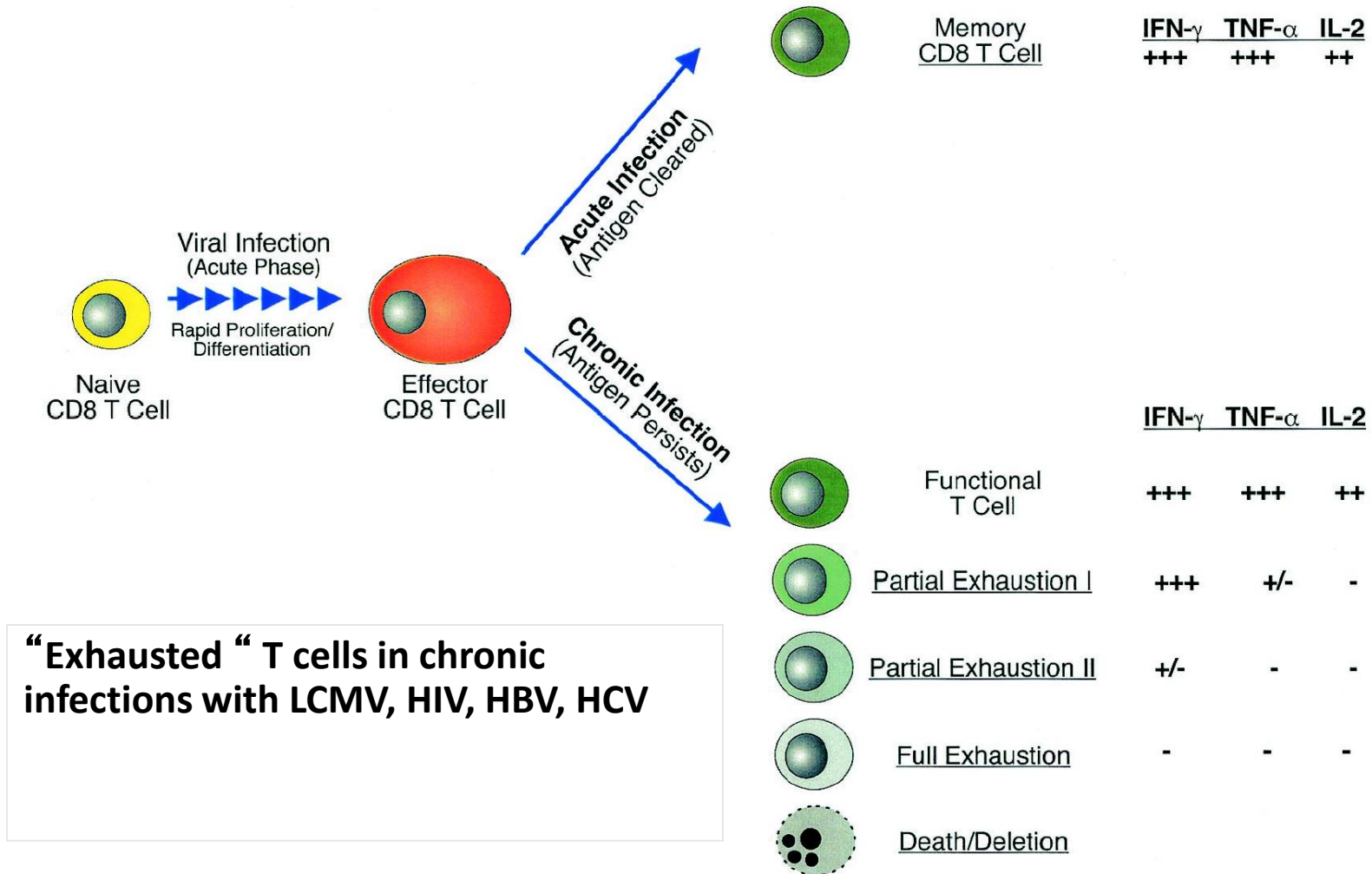
- Defense against viral infections
- Defense against bacteria and fungi that resist phagosomal destruction
- Immune surveillance of tumors
- Autoimmune attack on self tissues
- Allograft rejection

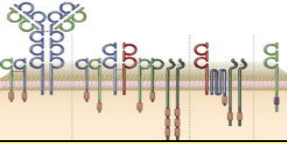
How do antigens from tissue-tropic viruses and tumors target naïve CD8+ T cells for activation?
???

Steps in CTL-Mediated Lysis of Target Cells

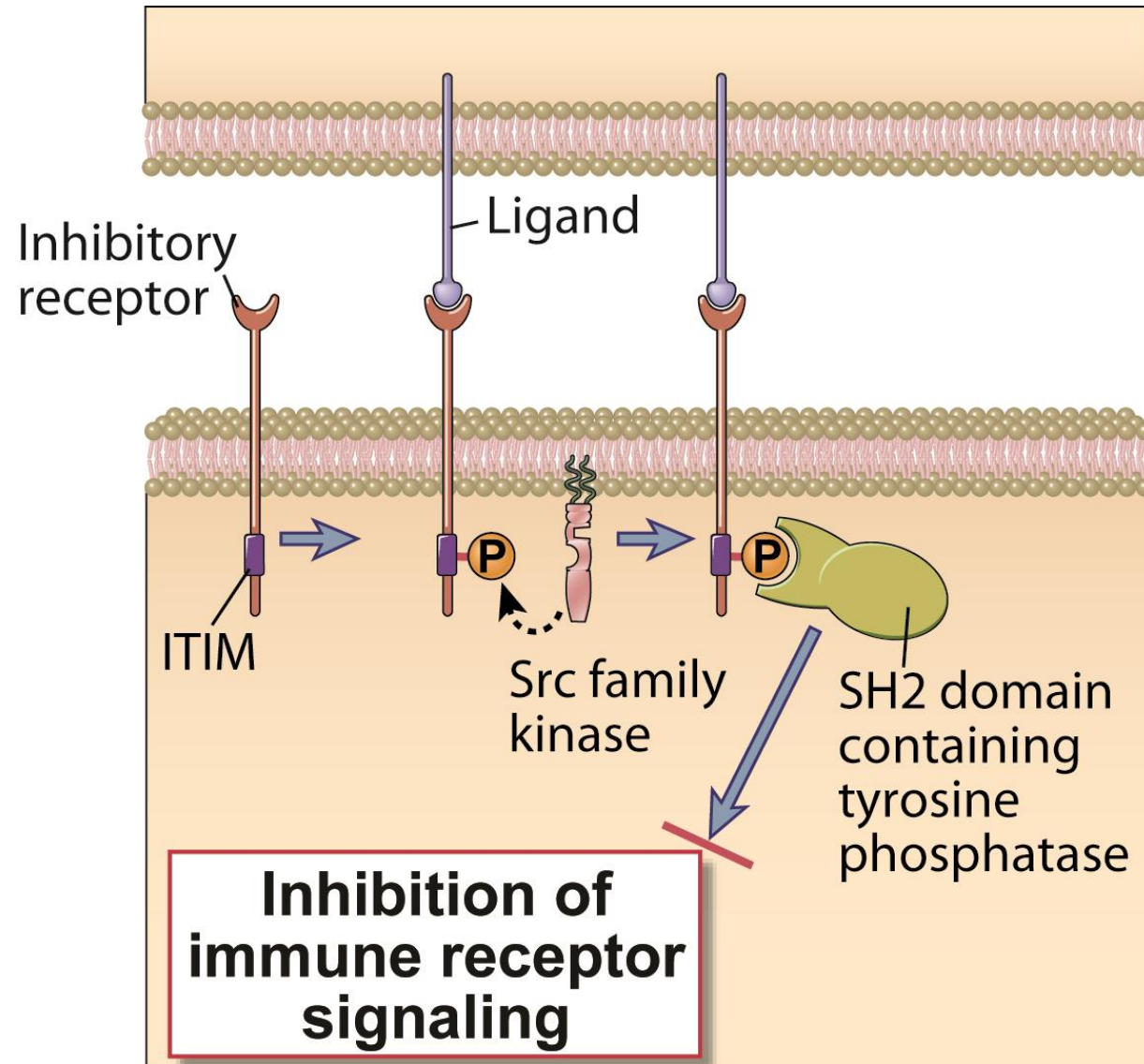


CD8 T cells become Exhausted During Chronic Viral Infection





Inhibitory Signaling in Lymphocytes

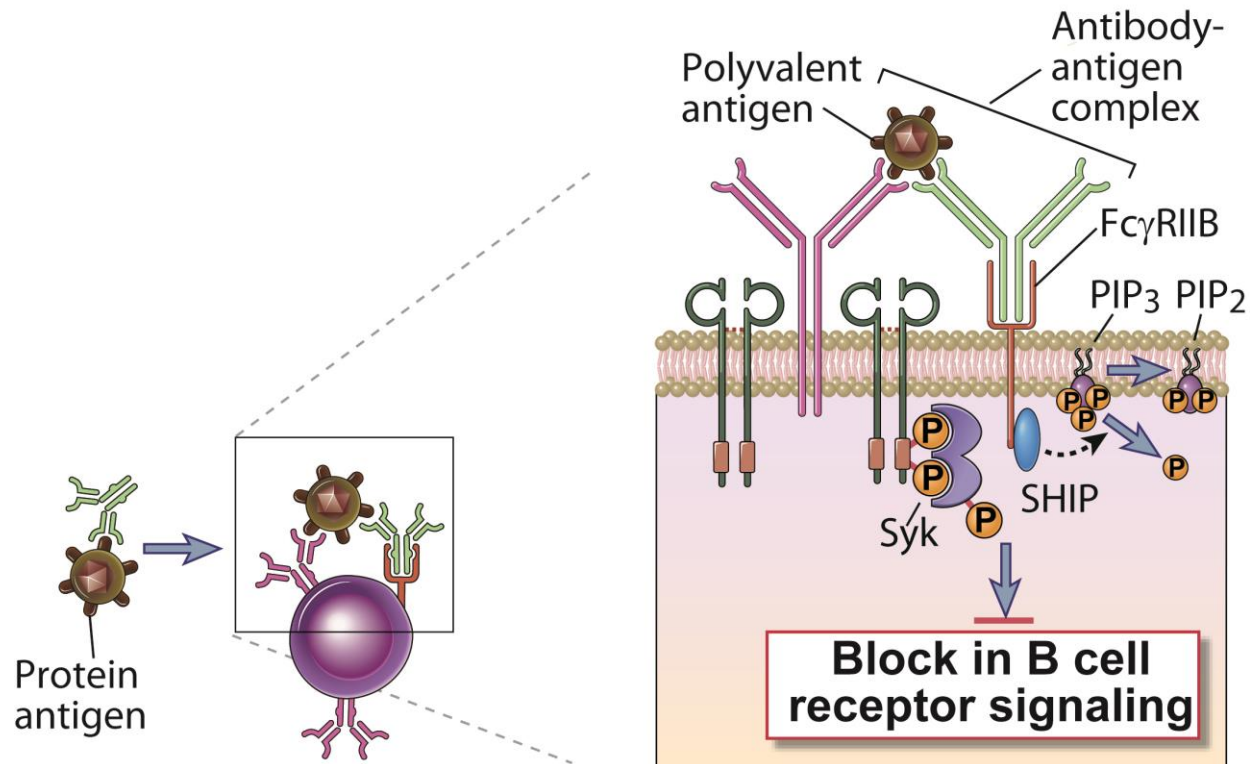


Regulation of B Cell Activation by Fc γ RIIB

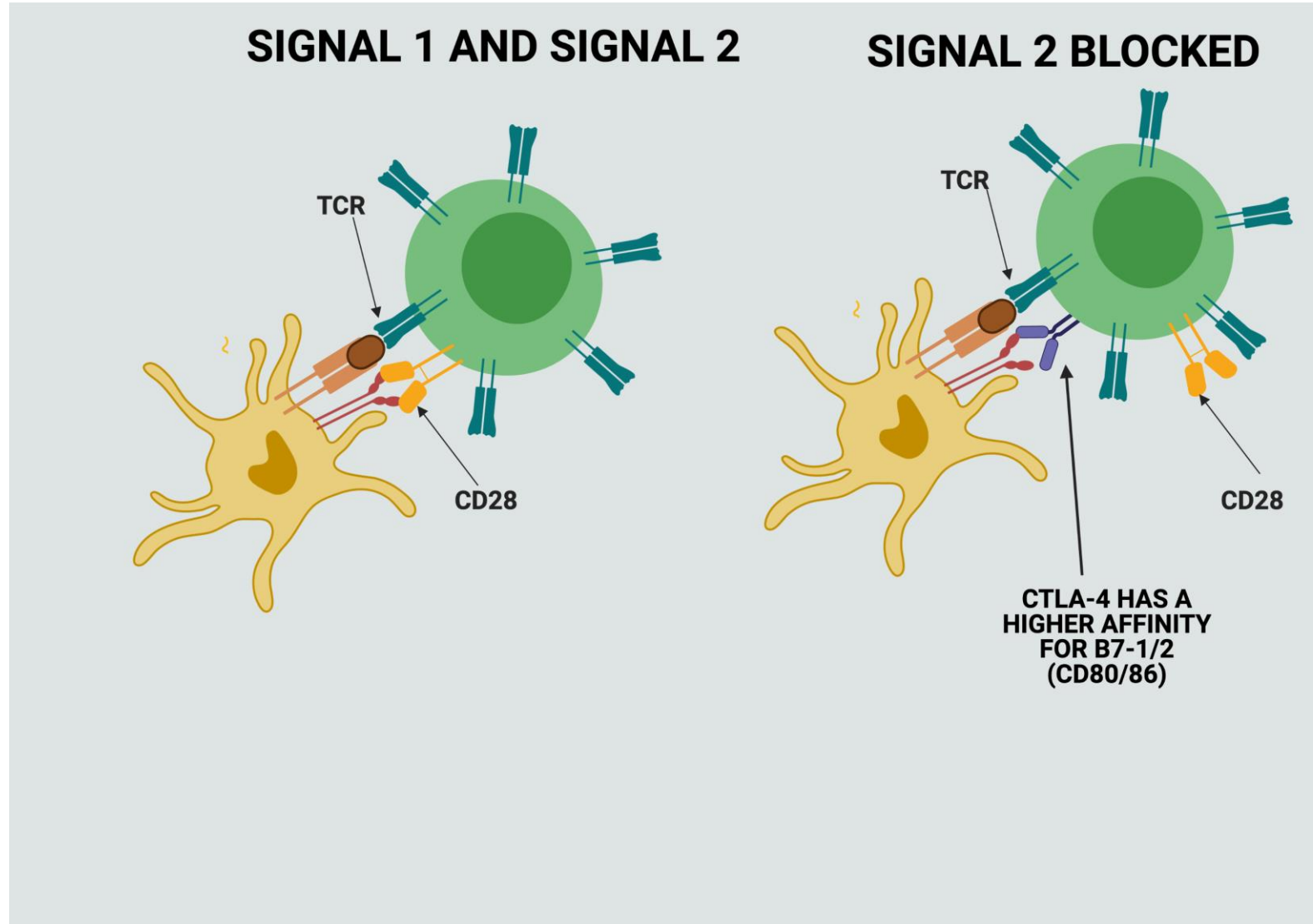
Secreted antibody
forms complex
with antigen

Antigen-antibody
complex binds to
B cell Ig and
Fc receptor

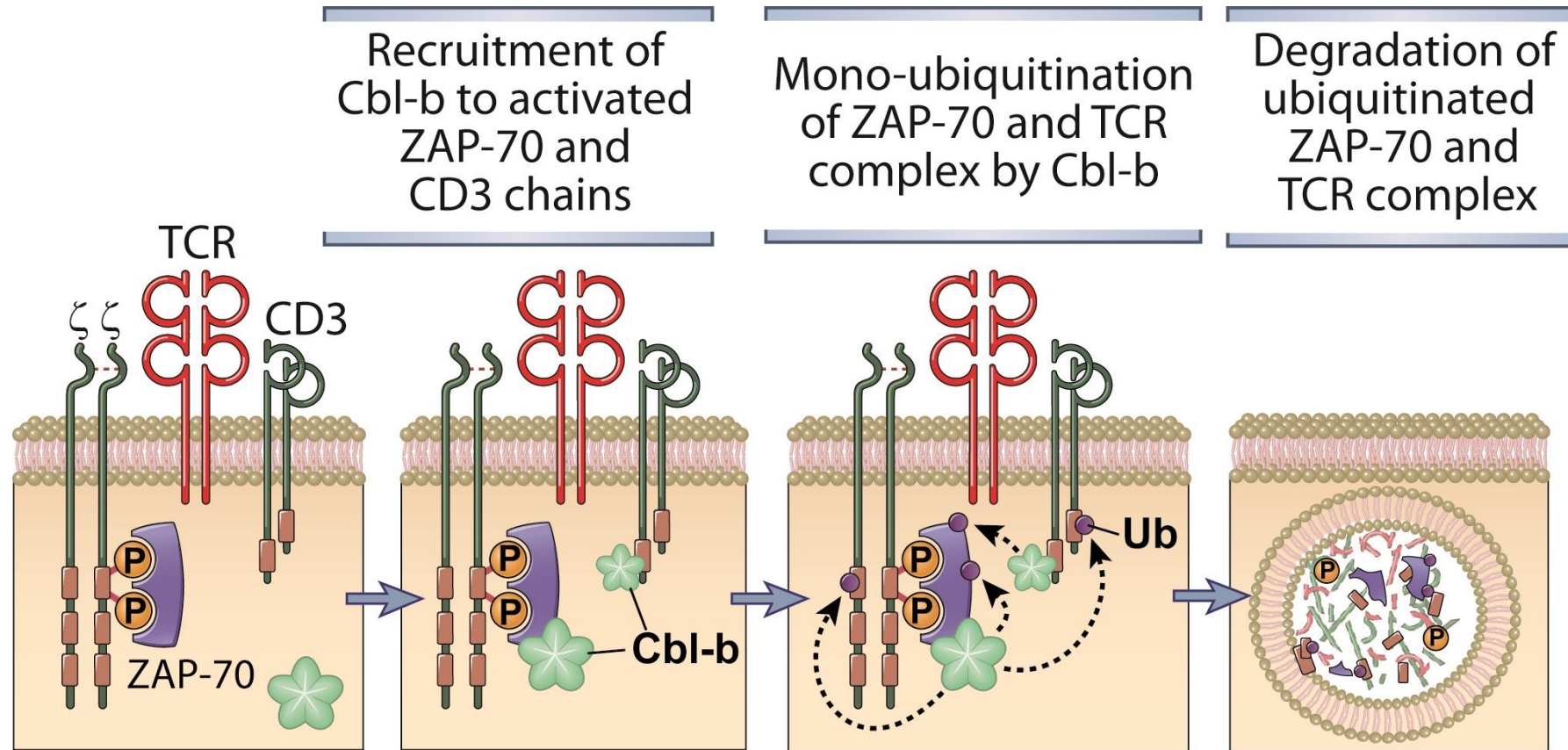
Fc receptor-
associated
phosphatase, SHIP,
converts PIP₃ to PIP₂

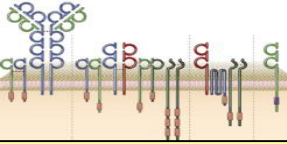


CTLA-4 IS A “DIFFERENT” KIND OF INHIBITORY RECEPTOR

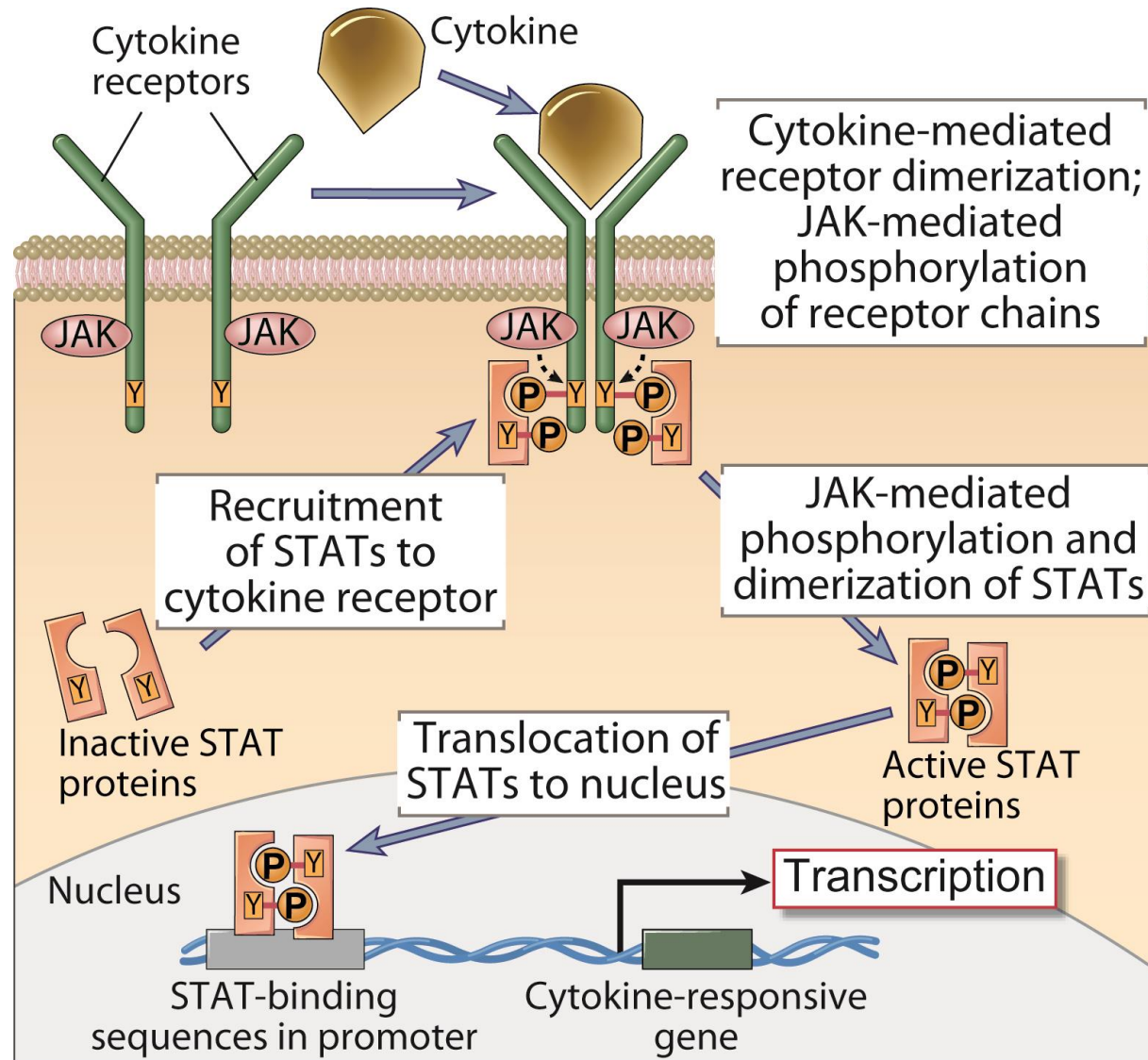


Role of Cbl-b in Terminating T cell Responses





Cytokine Induction of JAK-STAT Signaling



Lord of the Rings....