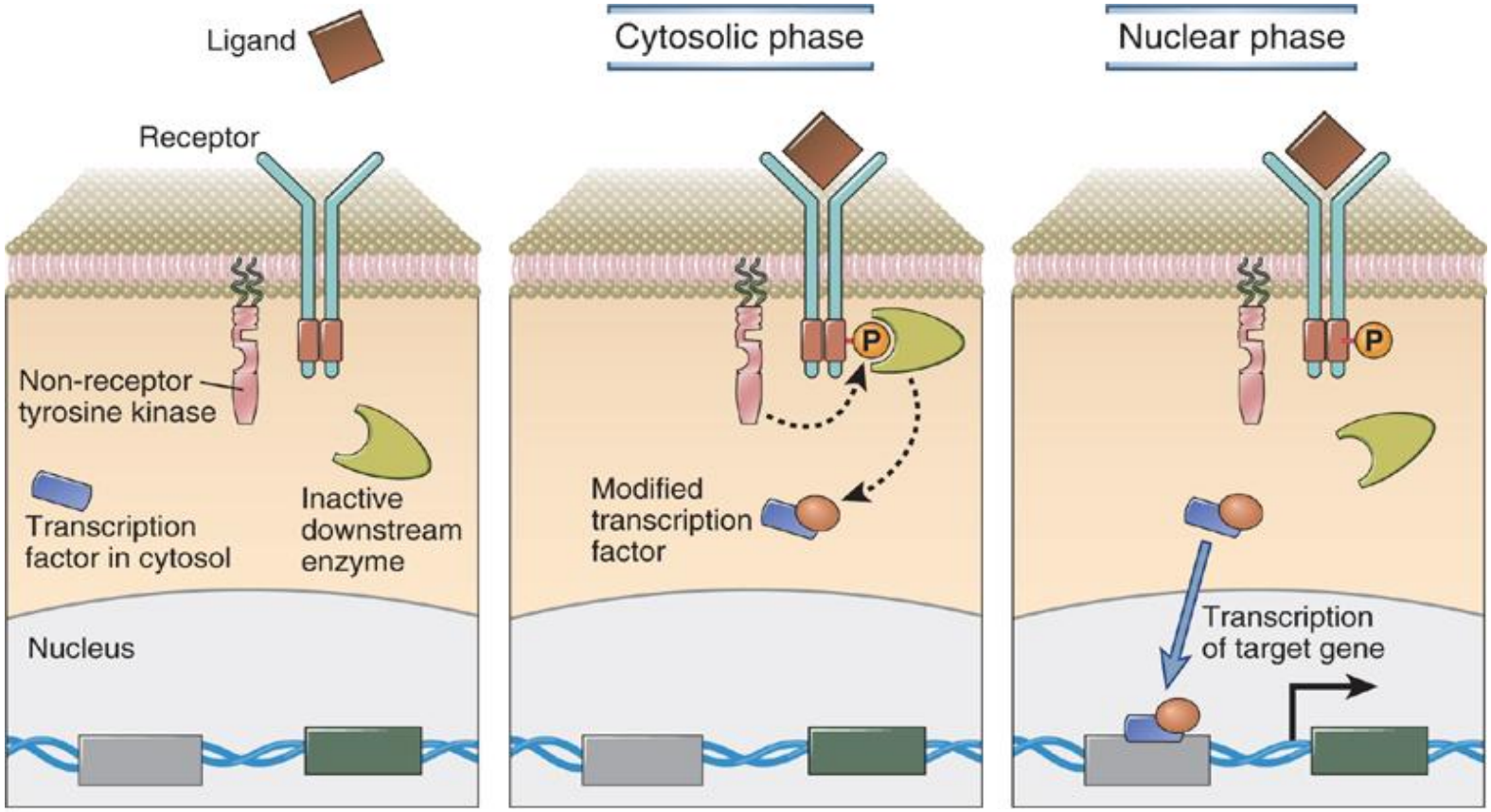
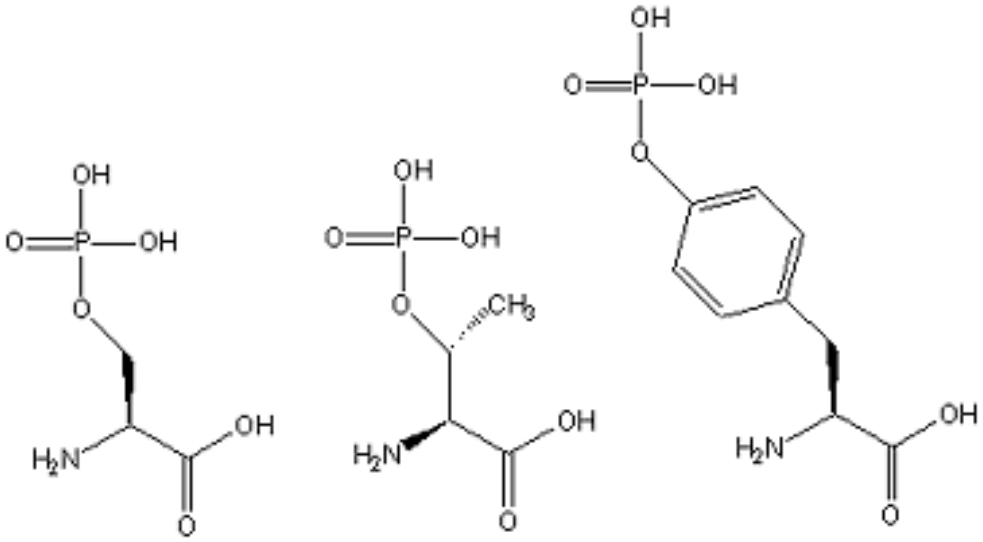
Signalling from the cell surface involves cytosolic and nuclear phases (Abbas Chapter 7)



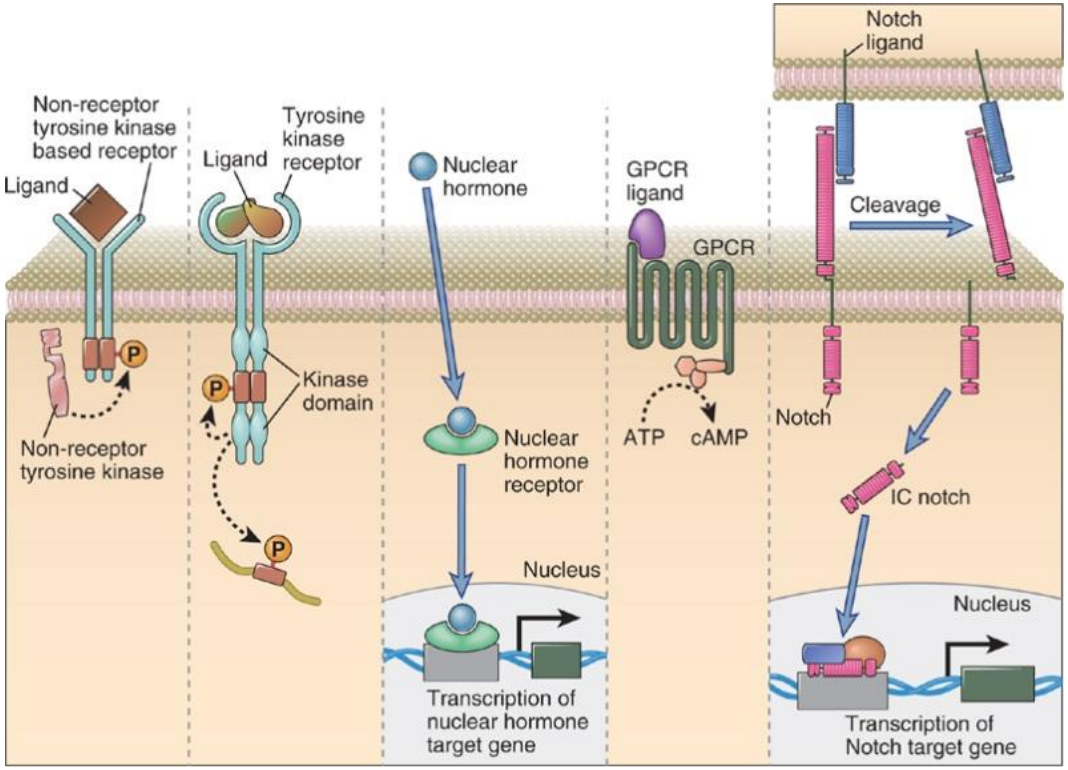
Phosphorylation

Phosphate from ATP to AA



Phospho Serine, Threonine and Tyrosine amino acids

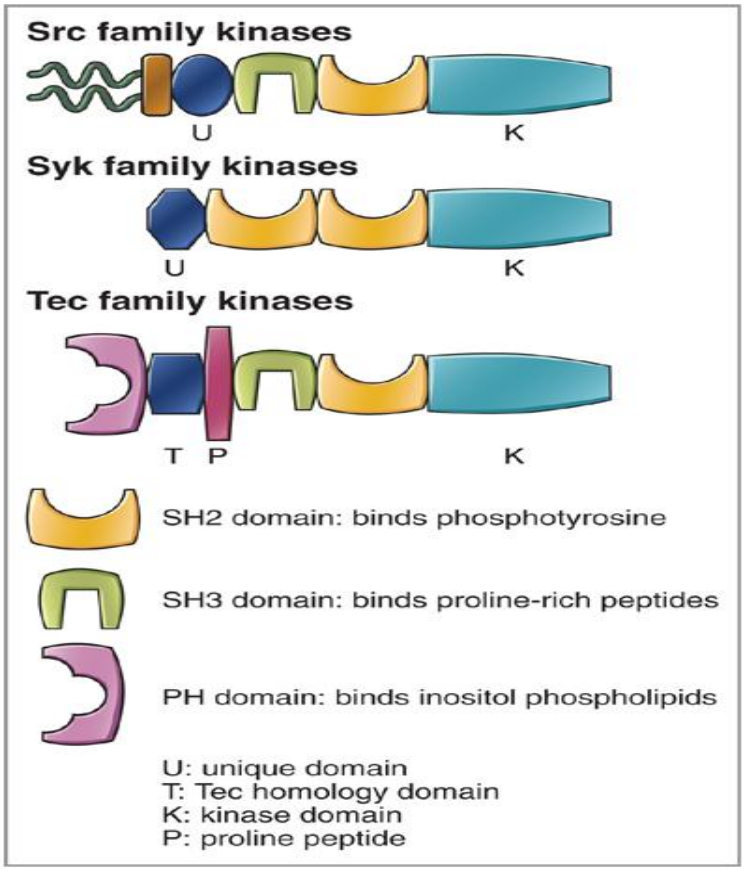
Major categories of signaling receptors (Abbas Chapter 7)



GPCR = G Protein-coupled receptors

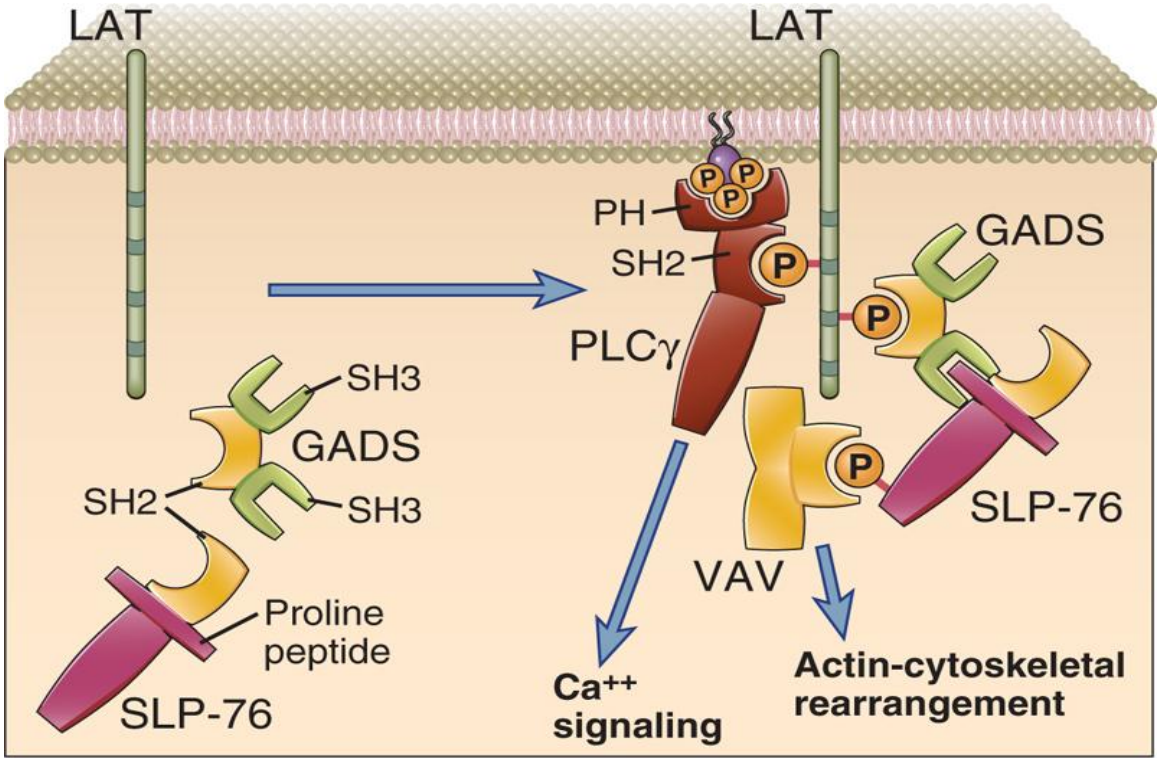
- **Non-receptor tyrosine kinases (NRTKs) - Src, Jaks, Abl in immune receptors**
- **Receptor tyrosine kinases (RTKs) - insulin receptor, EGF receptor**
- **Nucelar receptors - hormon receptors (vitamin D receptor, RAR)**
- **Seven-transmembrane receptors - GPCRs, histamine, complement receptors**
- **Notch receptors - embryonic development, lymphocyte development**

Modular structure of tyrosine kinases (Abbas Chapter 7)



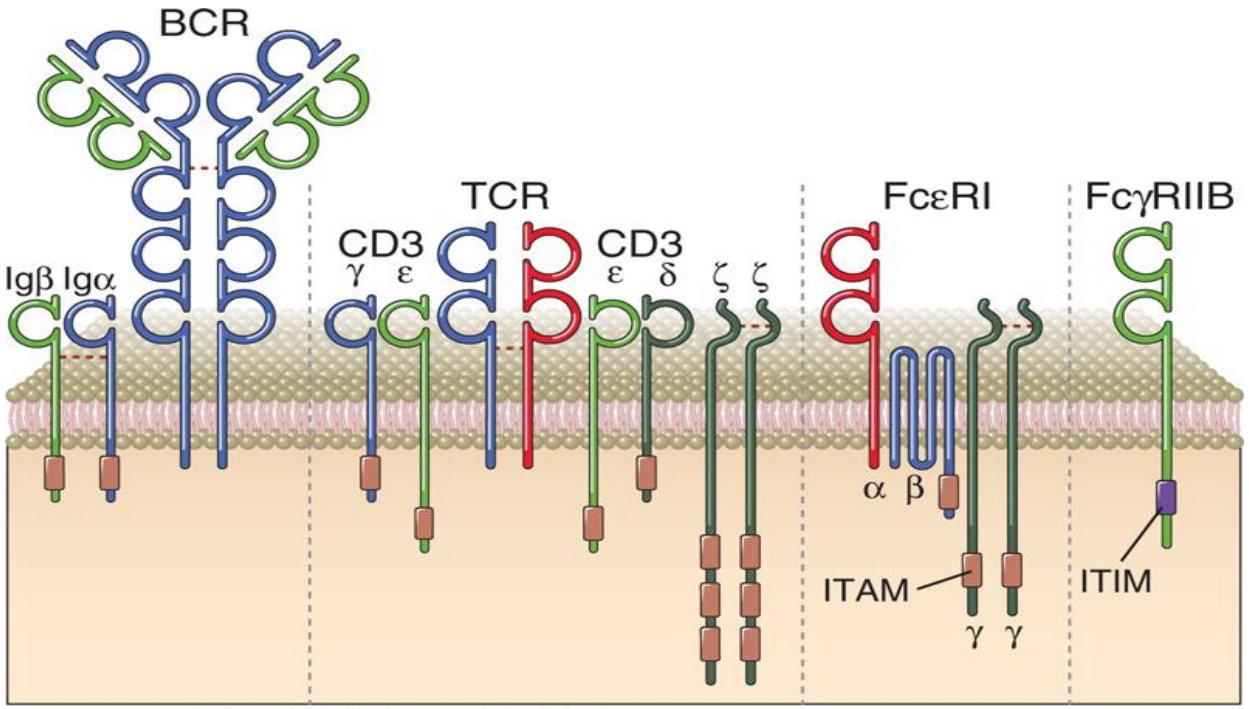
SH domain = src (sarcomy) Homology domain
PH domain = pleckstrin Homology domain

Adaptors involved in lymphocyte activation (Abbas Chapter 7)



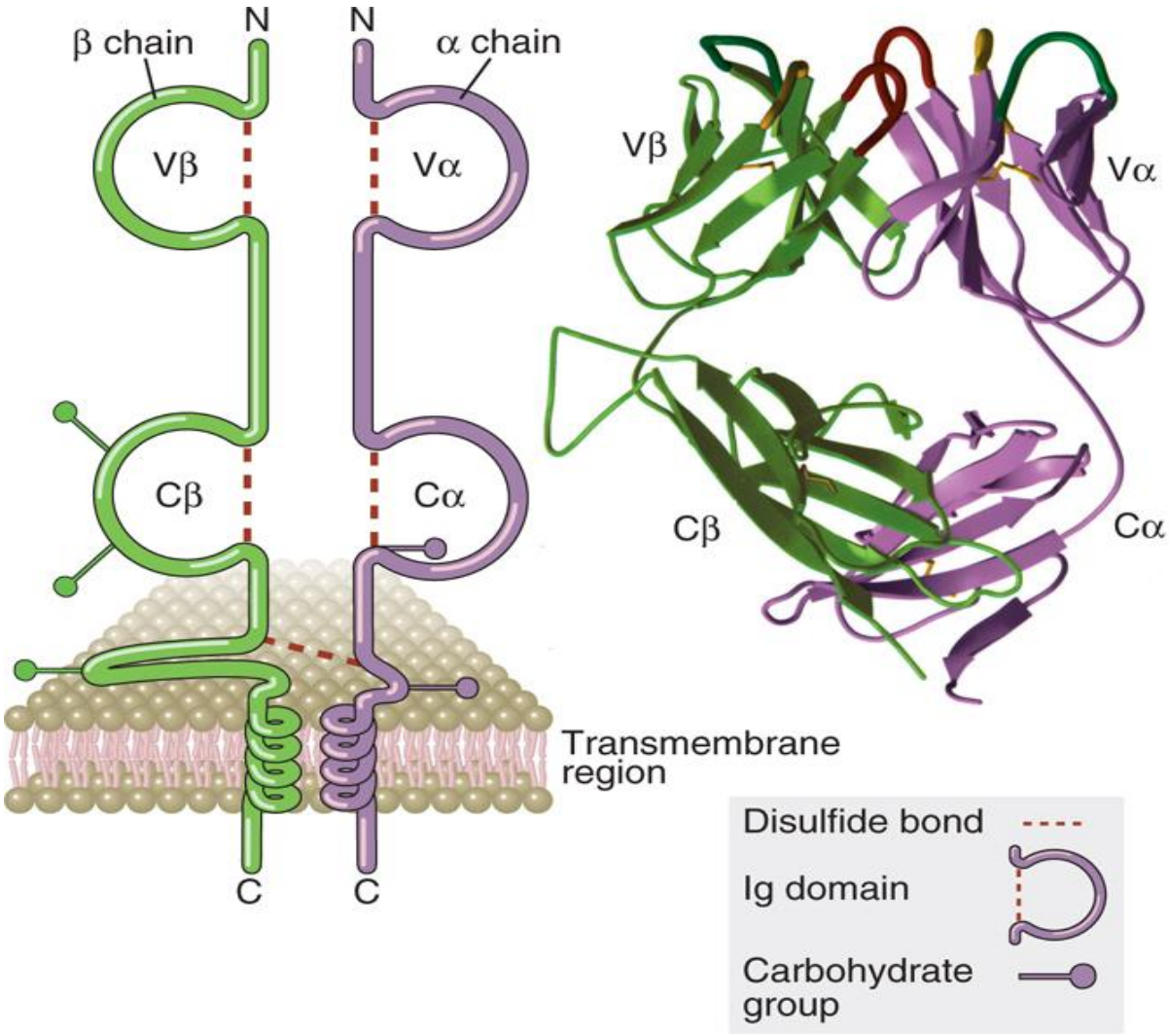
LAT = linker for the activation of T cells
SLP-76 = SH2 domain–containing linker protein of 76 kD

Members of the immune receptor family (Abbas Chapter 7)

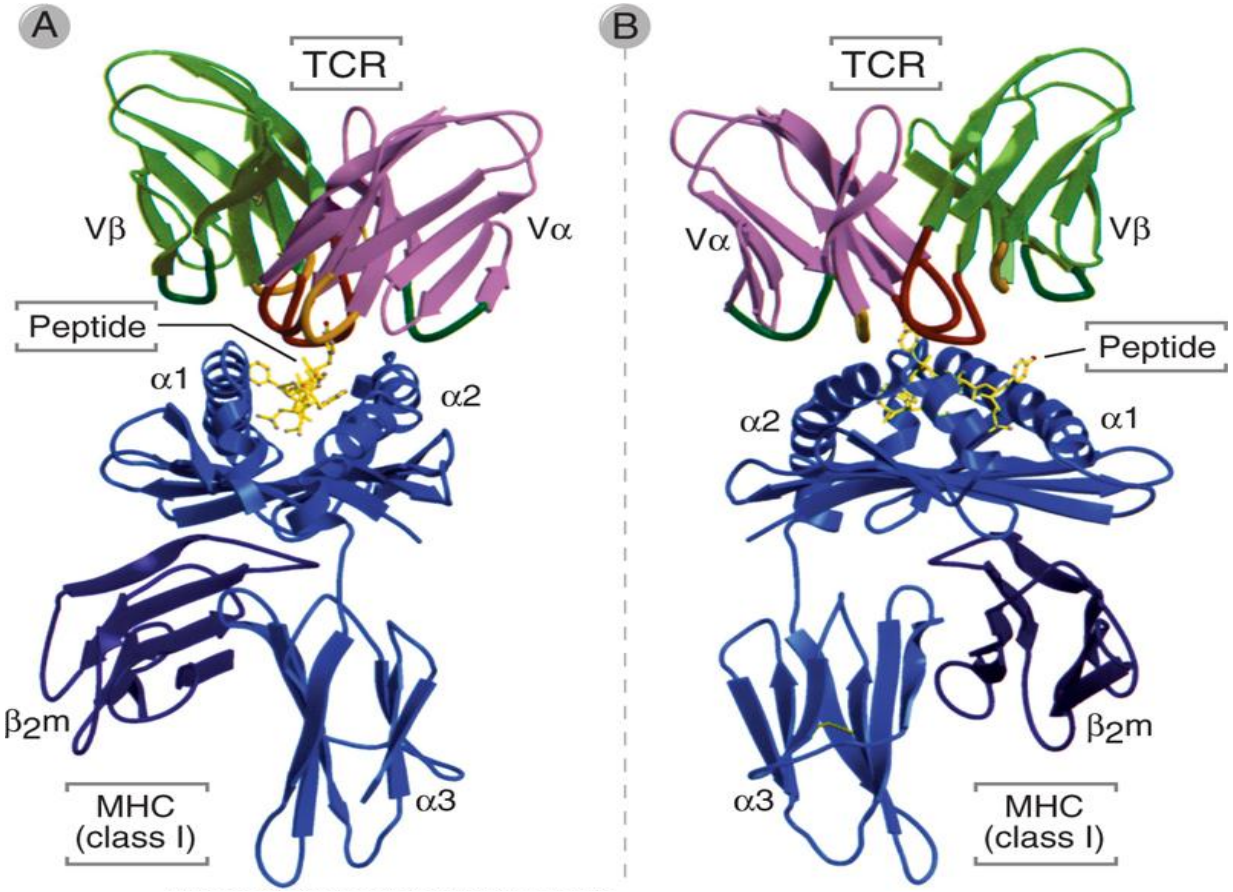


ITAM = immunoreceptor tyrosine-based activating motif
ITIM = immunoreceptor tyrosine-based inhibitory motif

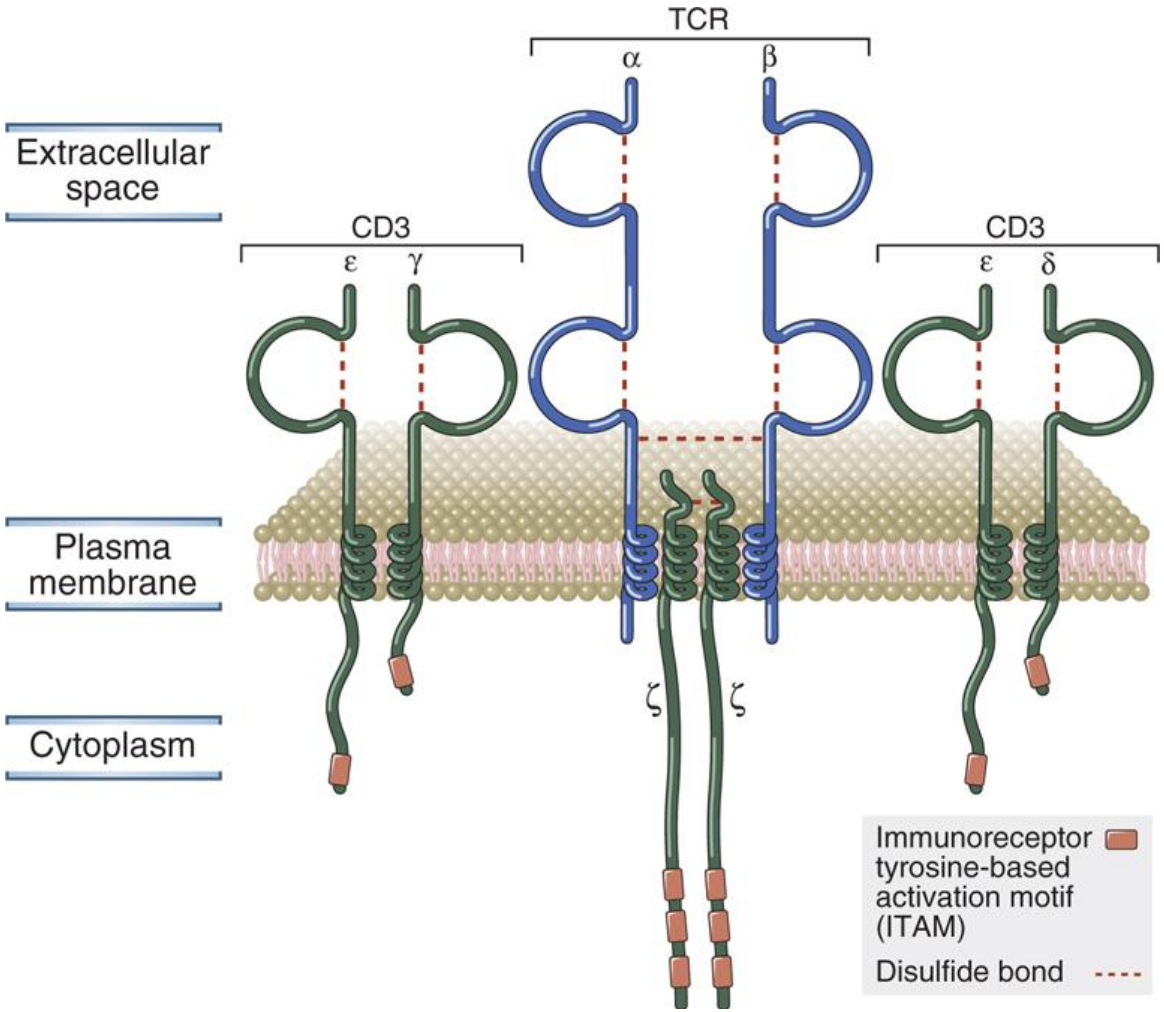
Structure of the T cells receptor – TcR (Abbas Chapter 7)



TcR-MHC interaction (Abbas Chapter 7)

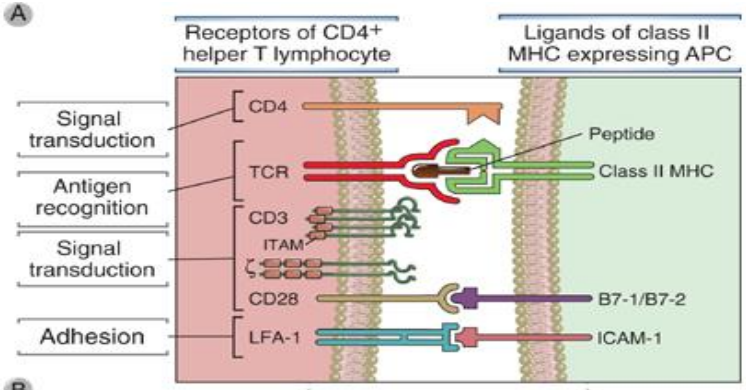


Components of the TcR complex (Abbas Chapter 7)



Ligand receptor pairs in T cell stimulation (Abbas Chapter 7)

A

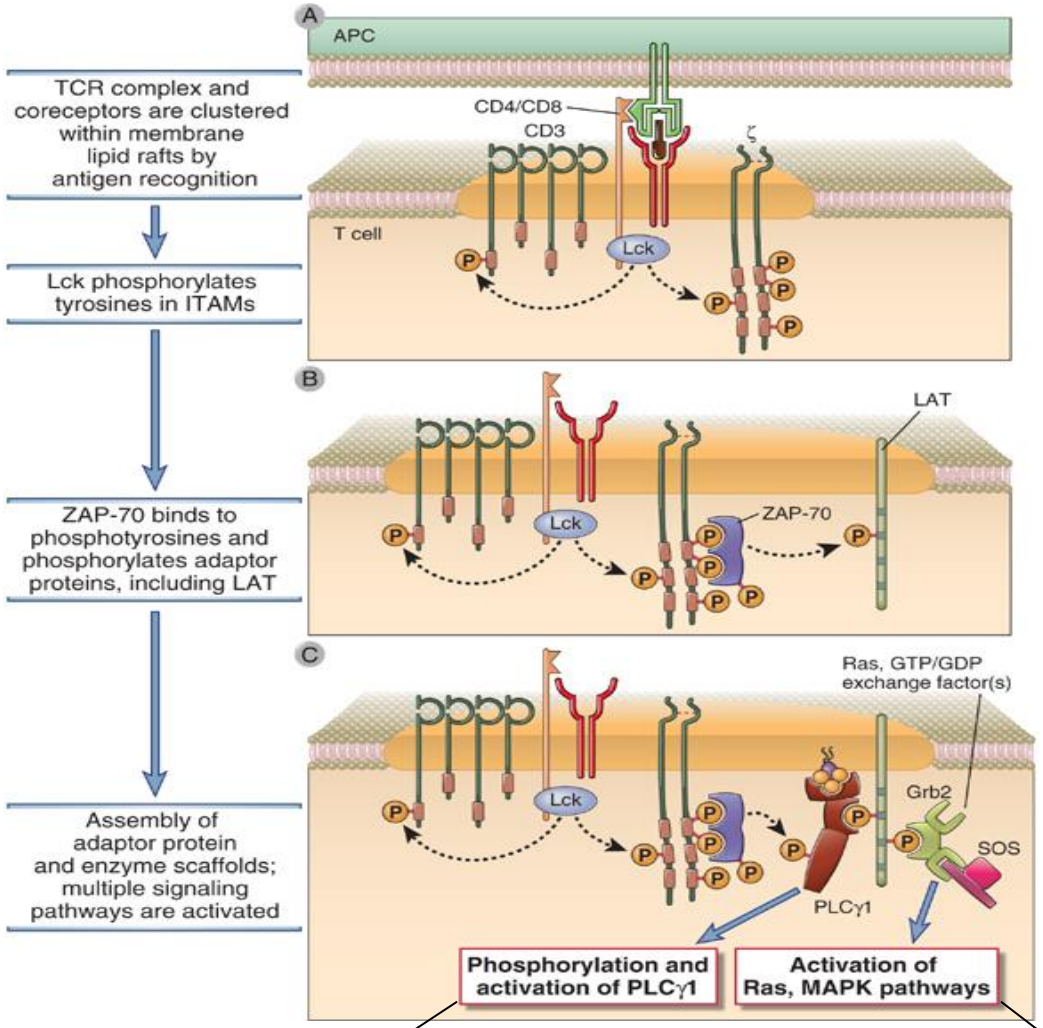


B

T cell accessory molecule	Function	Ligand	
		Name	Expressed on
CD3	Signal transduction by TCR complex	None	
ζ	Signal transduction by TCR complex	None	
CD4	Signal transduction	Class II MHC	Antigen presenting cells
CD8	Signal transduction	Class I MHC	Antigen presenting cells, CTL target cells
CD28	Signal transduction (costimulation)	B7-1/B7-2	Antigen presenting cells
CTLA-4	Signal transduction (negative regulation)	B7-1/B7-2	Antigen presenting cells
LFA-1	Adhesion	ICAM-1	Antigen presenting cells, endothelium
VLA-4	Adhesion	VCAM-1	Endothelium

Tyrosine phosphorylation (Abbas Chapter 7)

Early events in T cell activation



Lck = lymphocyte-specific protein tyrosine kinase

ZAP70 = Zeta-chain-associated protein kinase 70

LAT = linker for the activation of T cells

PLCg1 =Phospho-lipase C γ 1

Ras = rat sarcoma (G protein)

MAPK = mitogen-activated protein kinase

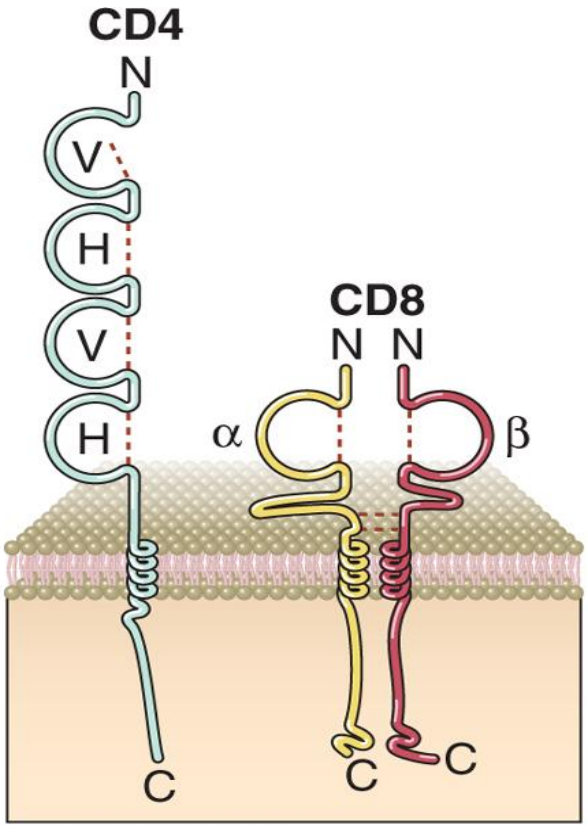
will be continued

will be continued

Structure of the CD4 and CD8 coreceptors

V resembles IgV domains

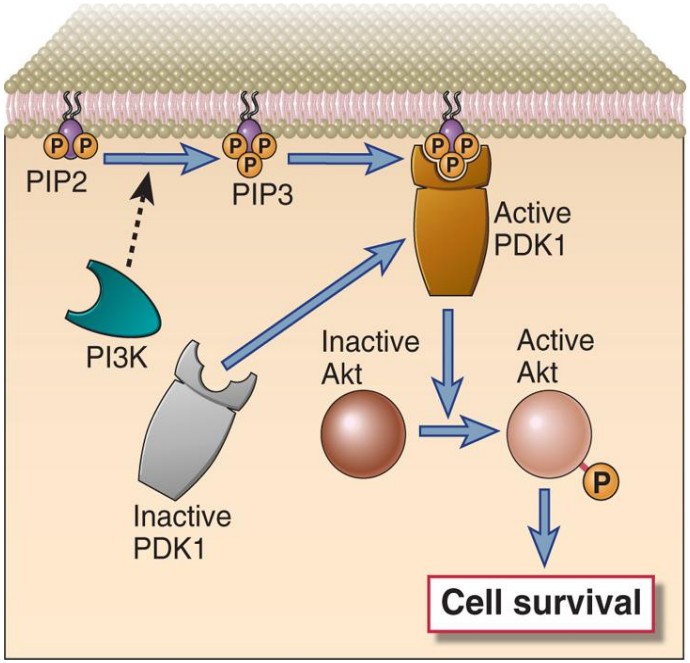
H resembles IgC domains



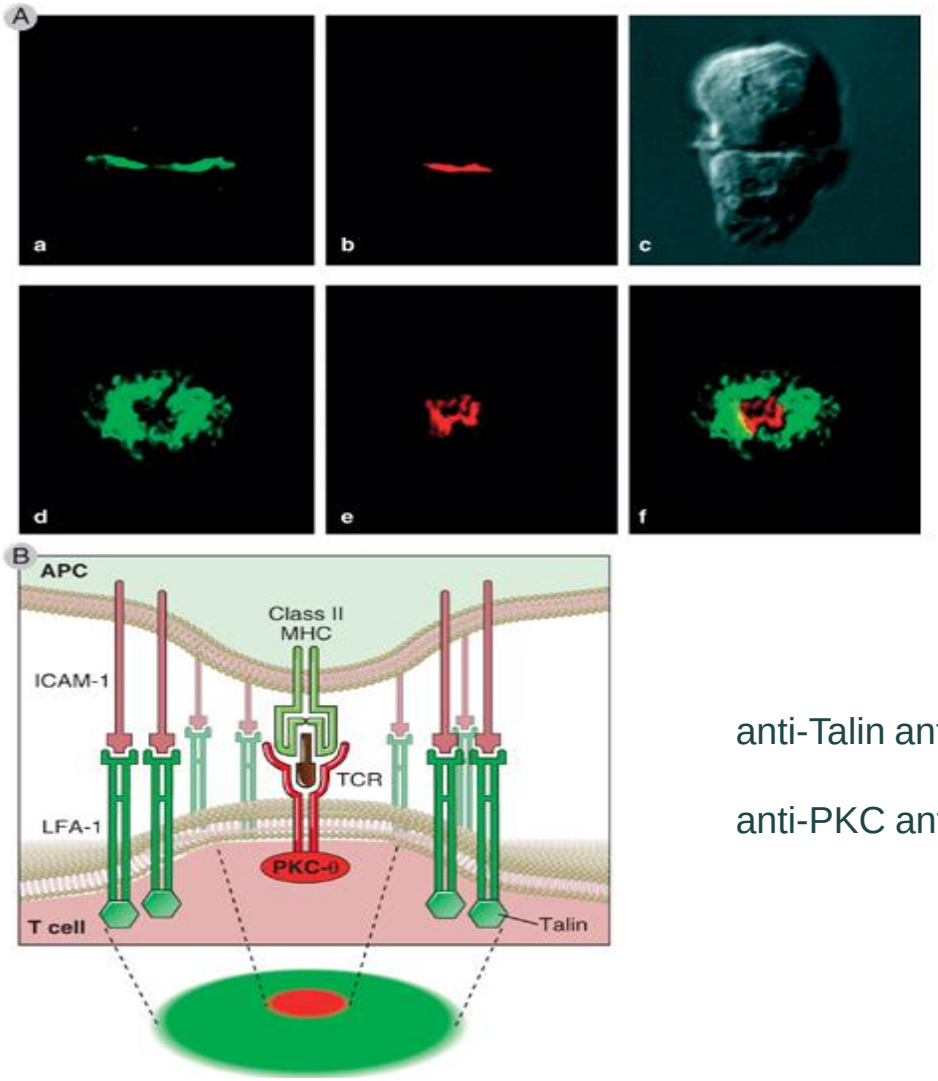
The role of PI3 kinase (Abbas Chapter 7)

Another signaling pathway in T cells involves the activation of PI3-kinase, which hosphorylates a specific membrane-associated inositol lipid (Fig. 7-12). This enzyme is recruited to the TCR complex and associated adaptor proteins and generates phosphatidylinositol trisphosphate (PIP3) from membrane phosphatidylinositol bisphosphate (PIP2) on the inner leaflet of the plasma membrane. Certain signaling proteins in the cytosol have specialized PH domains that have an affinity for PIP3, and as a result, PH domain–containing proteins can bind to the inside of the cell membrane only when PIP3 is generated. Examples of PH domain–containing proteins include kinases such as Itk in T cells and Btk in B cells. Another important PIP3-dependent kinase is PDK1, which is required for the phosphorylation and activation of an important downstream kinase called Akt. Activated Akt phosphorylates crucial targets and contributes to cell survival in a number of ways. Phosphorylation by Akt leads to the inactivation of two proapoptotic members of the Bcl-2 family, BAD and BAX.

optional



The immunological synapse (Abbas Chapter 7)



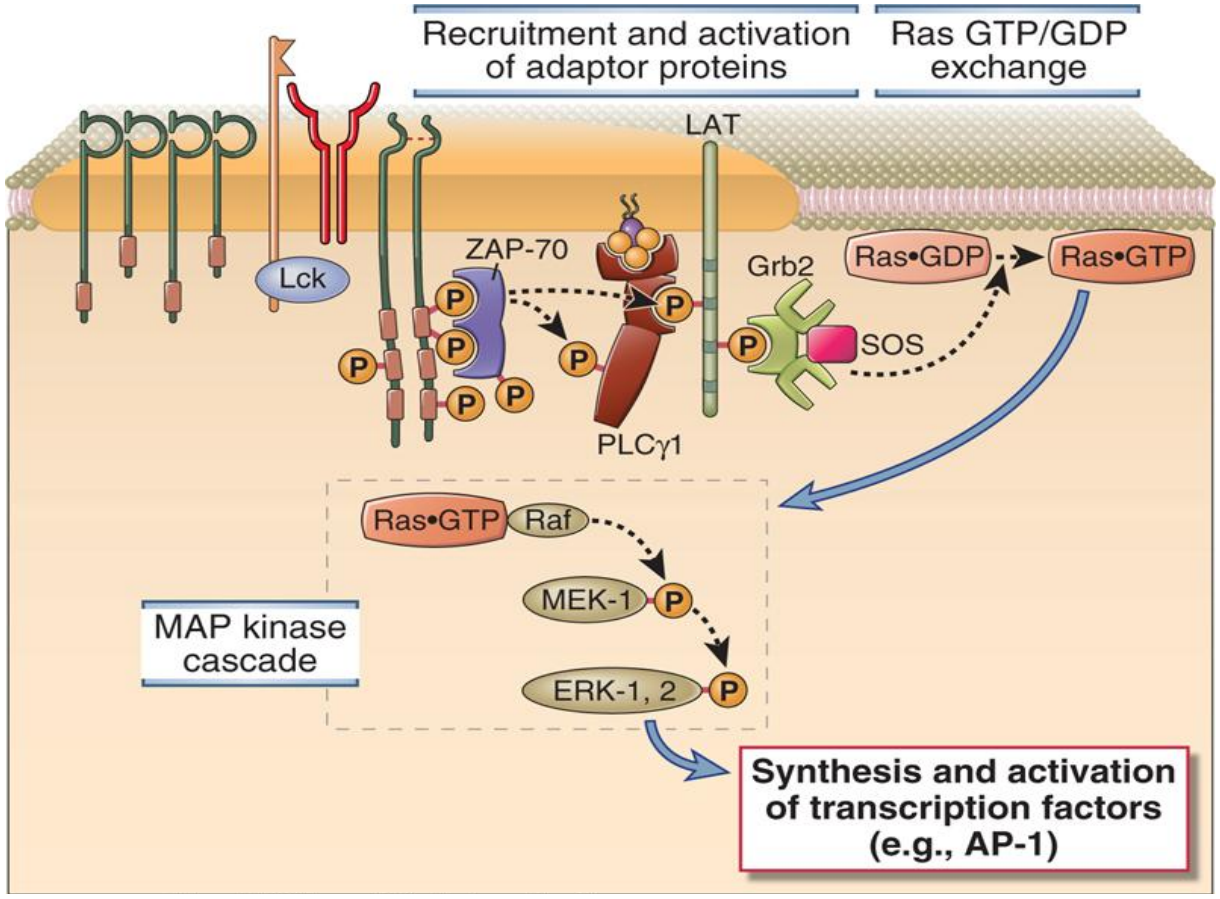
anti-Talin antibody = green fluorescence

anti-PKC antibody = red fluorescence

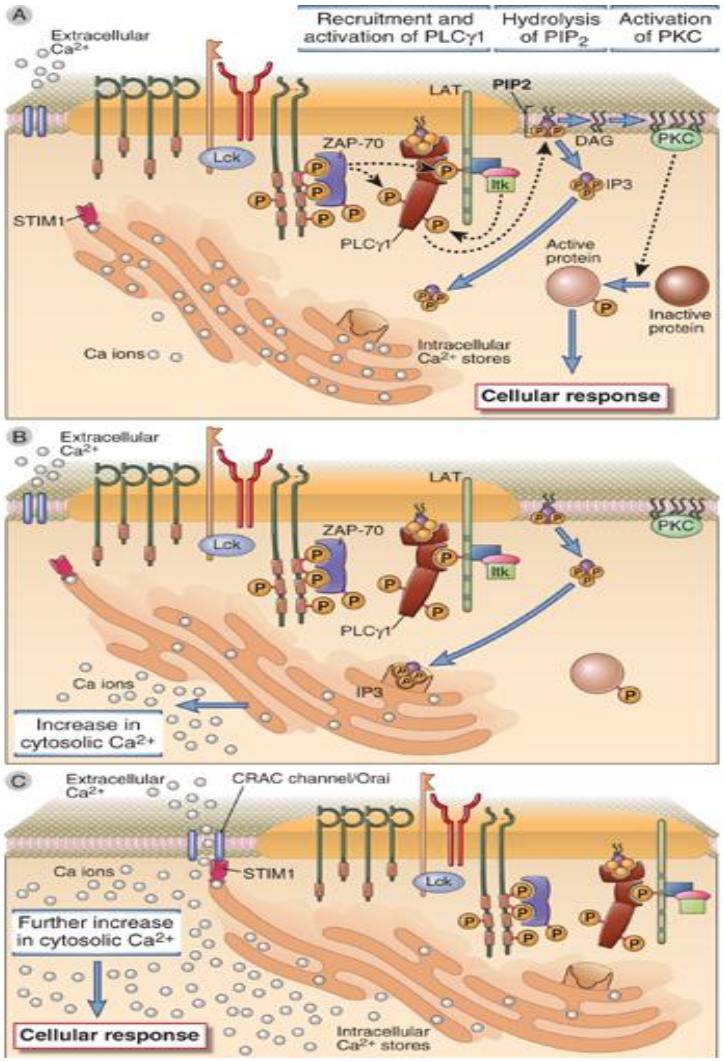
The Ras-Map kinase pathway (Abbas Chapter 7)

Optional

continued from Fig. 7-10



Downstream events of PLCγ1 (Abbas Chapter 7)



Optional

continued from Fig. 7-10

Activation of transcription factors in T cells (Abbas Chapter 7)

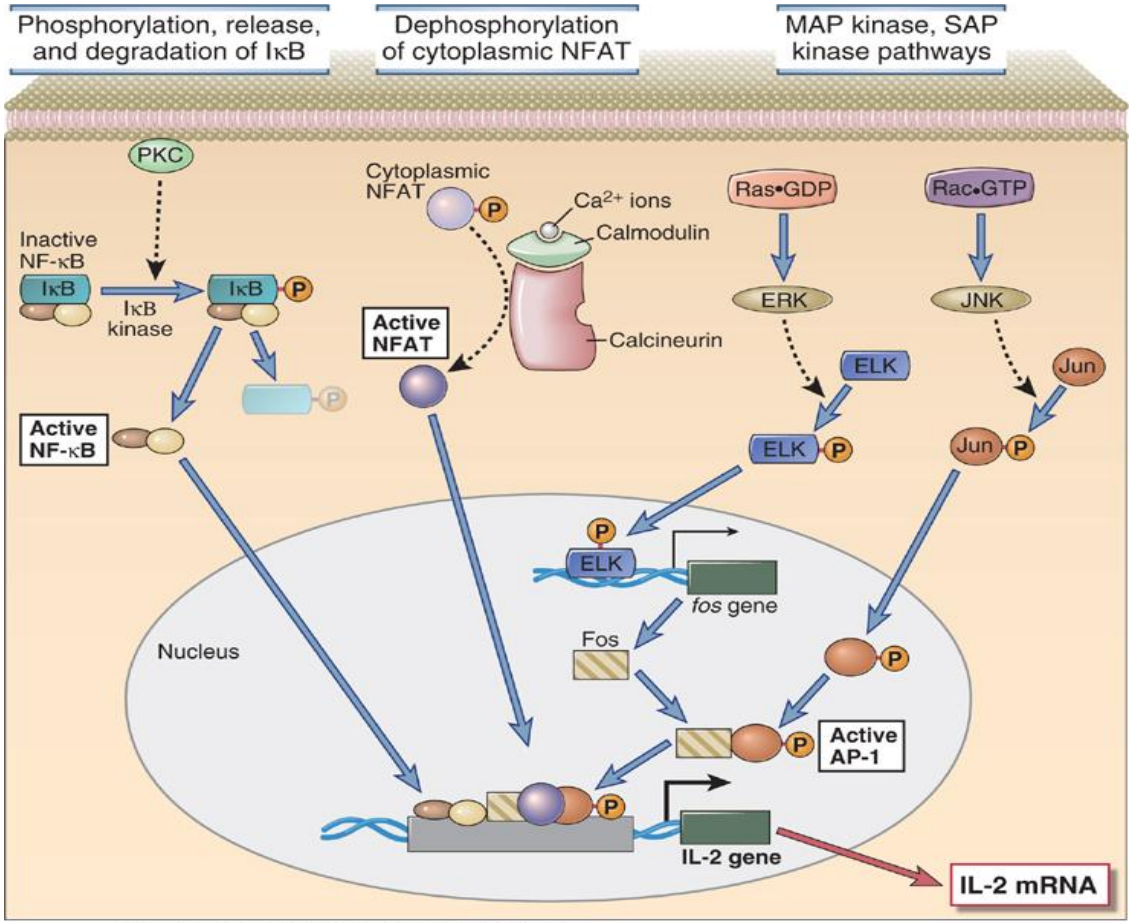
Enzymes generated by TCR signaling activate transcription factors that bind to regulatory regions of numerous genes in T cells and thereby enhance transcription of these genes

NFAT (nuclear factor of activated T-cells) is a transcription factor required for the expression of IL-2, IL-4, TNF, and other cytokine genes. NFAT is present in an inactive, serine-phosphory-lated form in the cytoplasm of resting T lymphocytes. It is activated by calcineurin via dephosphorylation, thereby uncovering a nuclear localization signal that permits NFAT to translocate into the nucleus. Once it is in the nucleus, NFAT binds to the regulatory regions of IL-2, IL-4, and other cytokine genes, usually in association with other transcription factors, such as AP-1

AP-1 (activator protein 1) is a transcription factor found in many cell types; it is specifically activated in T lymphocytes by TCR-mediated signals. AP-1 is actually the name for a family of DNA-binding factors composed of dimers of two proteins that bind to one another through a shared structural motif called a leucine zipper. The best characterized AP-1 factor is composed of the proteins Fos and Jun. TCR-induced signals lead to the appearance of active AP-1 in the nucleus of T cells

NF-κB (nuclear factor 'kappa-light-chain-enhancer' of activated B-cells) is a transcription factor that is activated in response to TCR signals and is essential for cytokine synthesis. NF-κB proteins are homodimers or heterodimers of proteins that are homologous to the product of a cellular proto-oncogene called c-*rel* and are important in the transcription of many genes in diverse cell types, particularly in innate immune cells

Activation of transcription factors in T cells (Abbas Chapter 7)

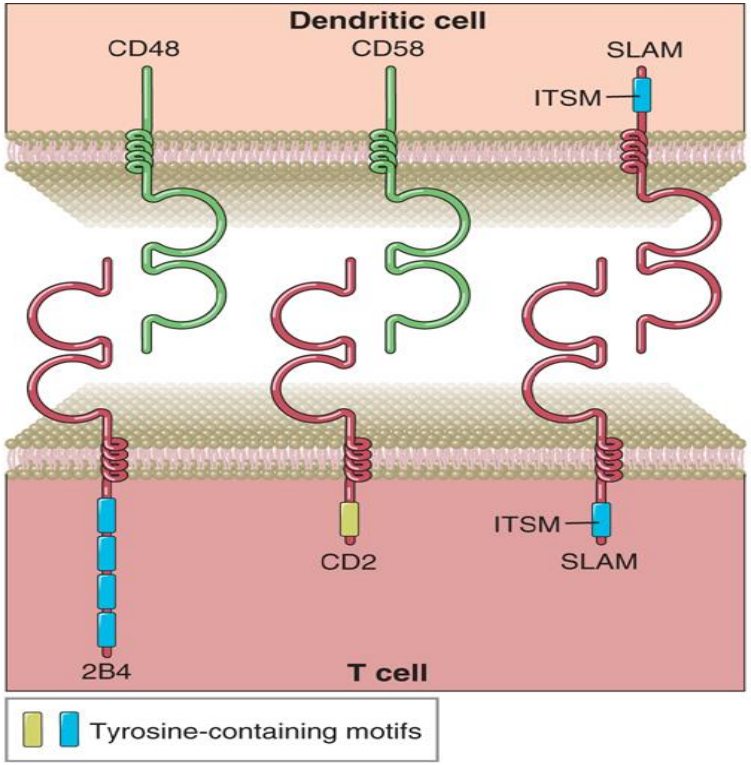


Multiple signaling pathways converge in antigen-stimulated T cells to generate transcription factors that stimulate expression of various genes (in this case, the IL-2 gene). The calcium-calmodulin pathway activates NFAT, and the Ras and Rac pathways generate the two components of AP-1. Less is known about the link between TCR signals and NF-κB activation. (NF-κB is shown as a complex of two subunits, which in T cells are typically the p50 and p65 proteins, named for their molecular sizes in kilodaltons.) PKC is important in T cell activation, and the PKC-θ isoform is particularly important in activating NF-κB. These transcription factors function coordinately to regulate gene expression. Note also that the various signaling pathways are shown as activating unique transcription factors, but there may be considerable overlap, and each pathway may play a role in the activation of multiple transcription factors.

Costimulatory receptors of the CD2 family (Abbas Chapter 7)

The best defined costimulators for T lymphocytes are a pair of related proteins, called B7-1 (CD80) and B7-2 (CD86), which are expressed on activated dendritic cells, macrophages, and B lymphocytes

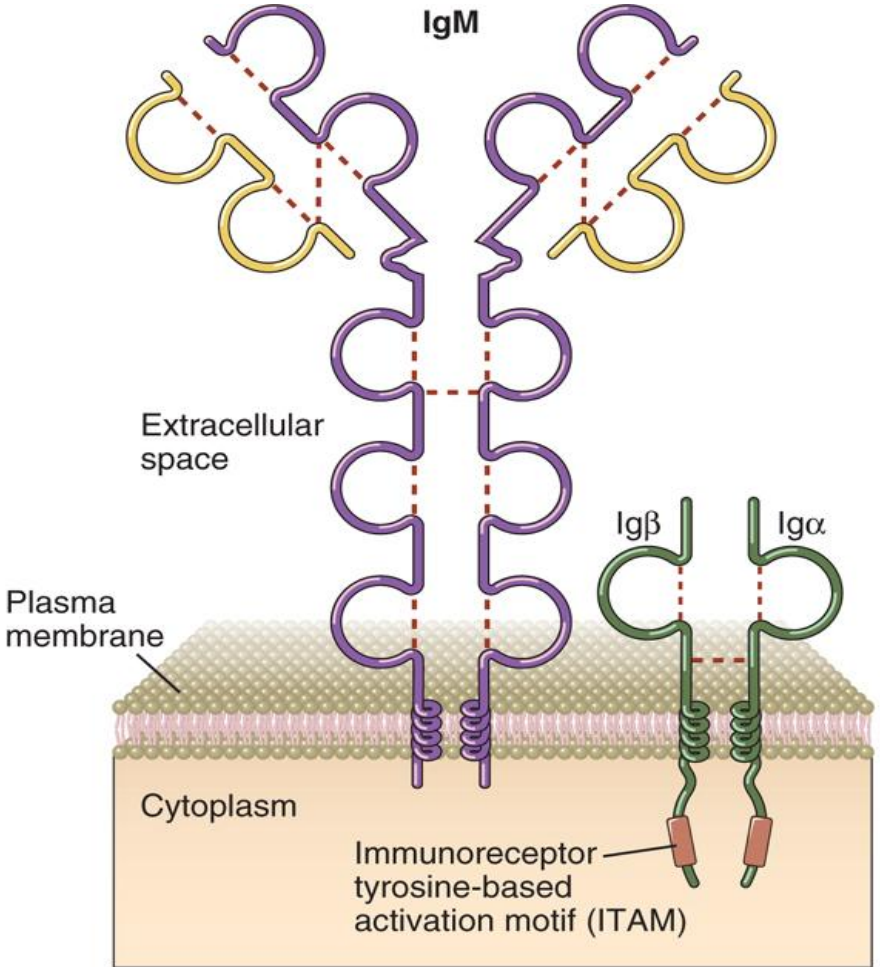
The CD2/SLAM Family of Costimulatory Receptors



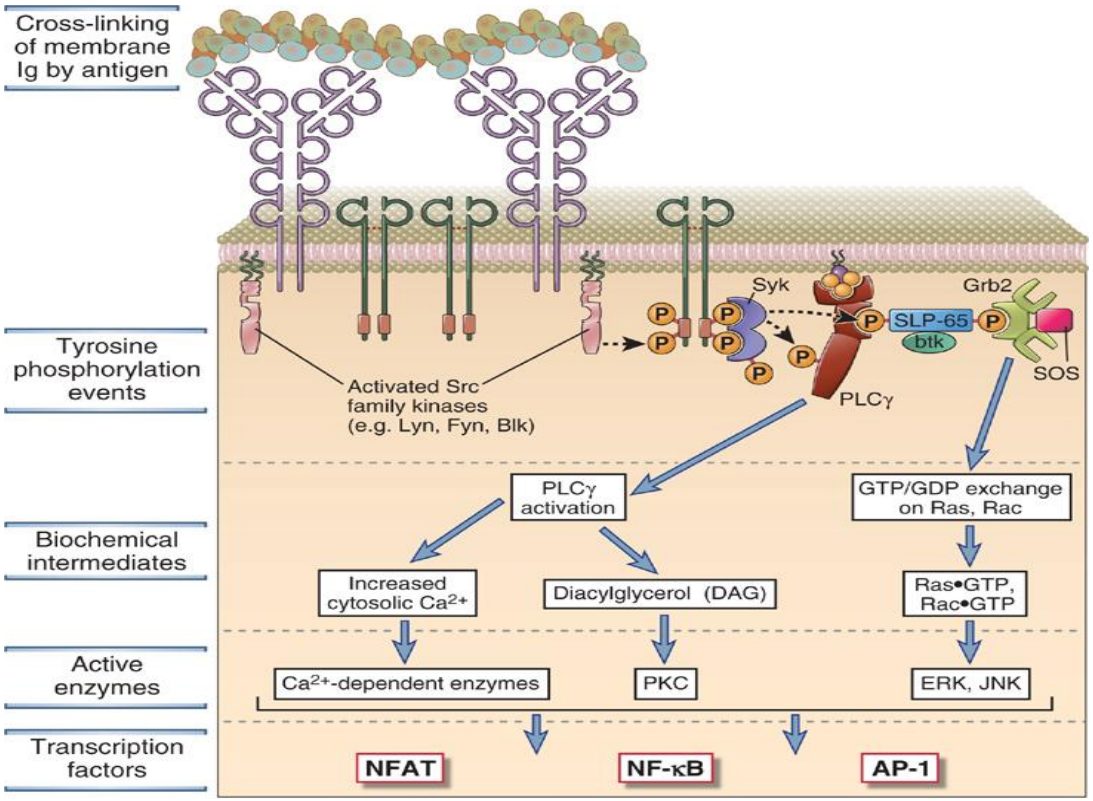
CD58 = LFA-3

SLAMs contain Tyrosins with ITSM (immunoreceptor tyrosine-based switch motifs)
ITSM can switch from an inhibitory to an activating function

B cell antigen receptor (BCR) complex (Abbas Chapter 7)

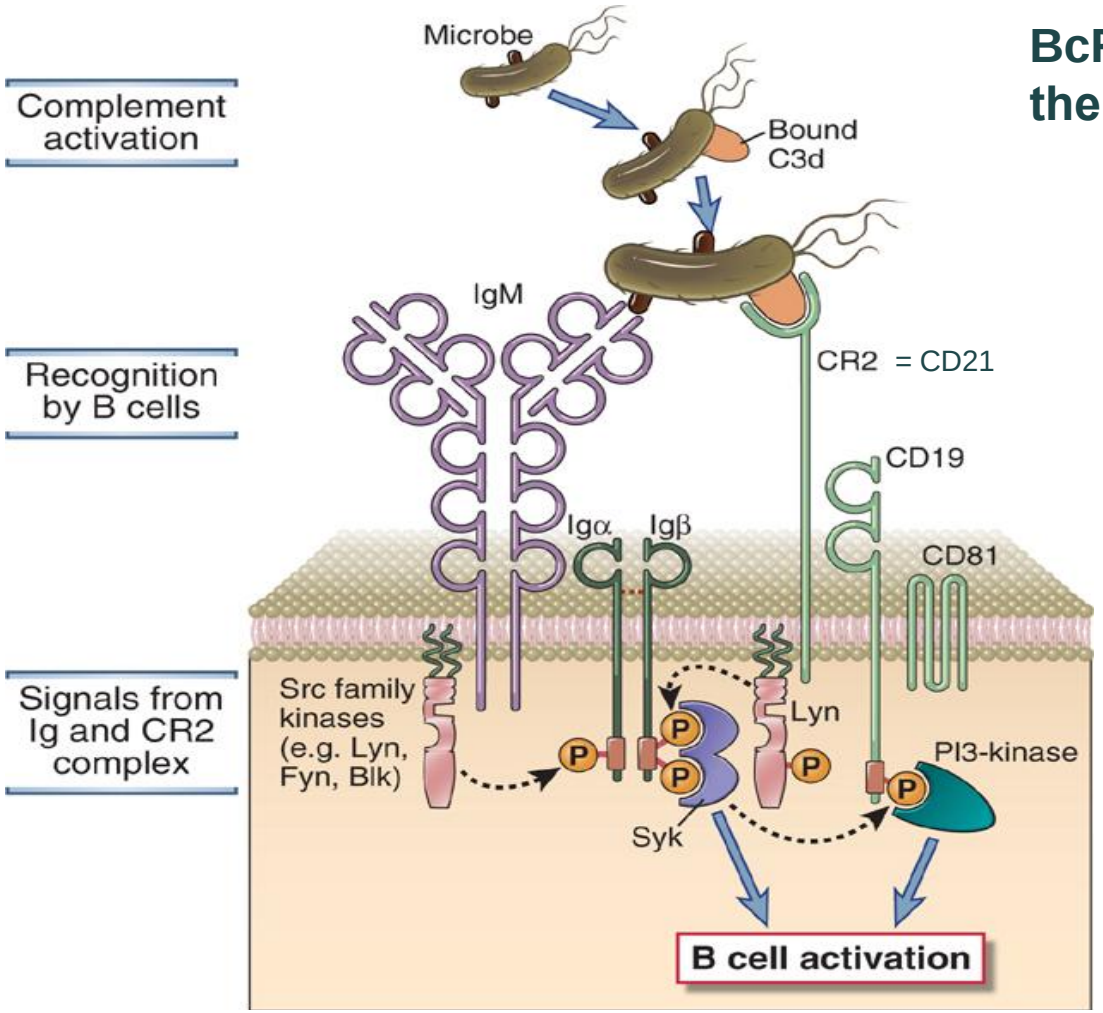


Signal transduction of the BCR complex (Abbas Chapter 7)



Antigen-induced cross-linking of membrane Ig on B cells leads to clustering and activation of Src family tyrosine kinases and tyrosine phosphorylation of the ITAMs in the cytoplasmic tails of the Igα and Igβ molecules. This leads to docking of Syk and subsequent tyrosine phosphorylation events as depicted. Several signaling cascades follow these events, as shown, leading to the activation of several transcription factors. These signal transduction pathways are similar to those described in T cells

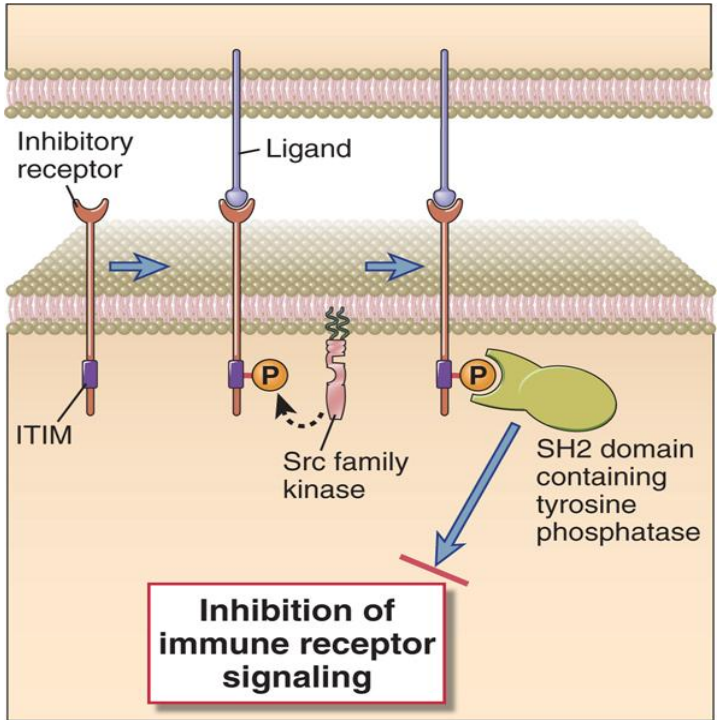
Role of complement in B cell activation (Abbas Chapter 7)



BcR+CD19/21/81 = the „real“ BcR complex

Attenuation of immune receptor signaling

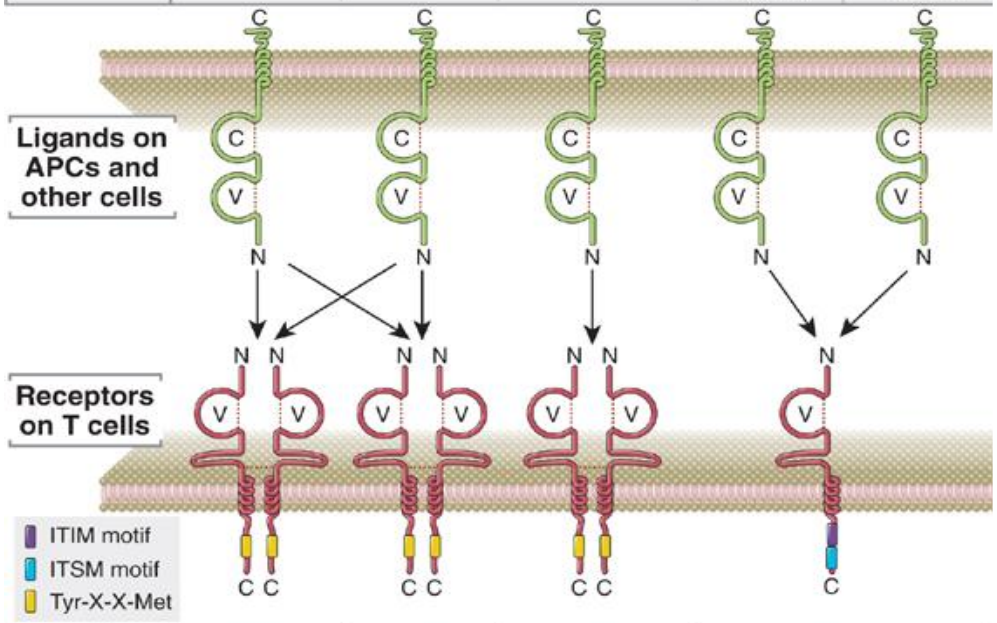
by inhibitory receptors



A schematic depiction is provided of an inhibitory receptor with an extracellular ligand-binding domain and a cytosolic ITIM motif. Ligand binding results in phosphorylation of the ITIM tyrosine by a Src family kinase, followed by recruitment of an SH2 domain–containing tyrosine phosphatase that can attenuate immune receptor signaling

Inhibition by CTLA4 and PD-1

Expression	DCs; macrophages, B cells	DCs; macrophages, B cells	DCs; macrophages, B cells, other cells	DCs; macrophages, B cells, other cells	
Name	B7-1 (CD80)	B7-2 (CD86)	ICOS-L (CD275)	PD-L1 (B7-H1, CD274)	PD-L2 (B7-DC, CD273)

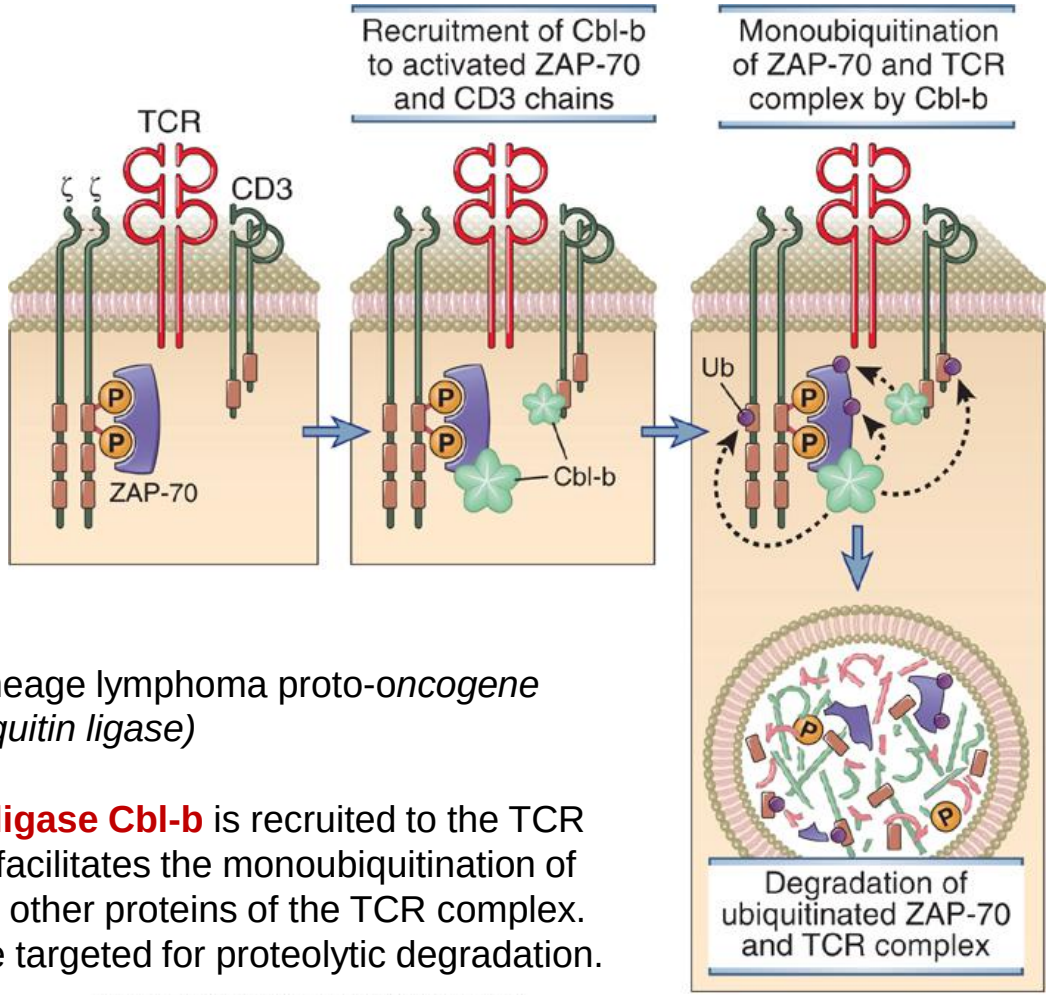


Name	CD28	CTLA-4 (CD152)	ICOS (CD278)	PD-1 (CD279)
Expression	T cells; constitutive	T cells; inducible	T cells; inducible	T cells, B cells, myeloid cells; inducible
Major function	Costimulation of naive T cells; generation of regulatory T cells	Negative regulation of immune responses; self-tolerance	Costimulation of effector and regulatory T cells; generation of follicular helper T cells	Negative regulation of T cells

CTLA4 = Cytotoxic T-Lymphocyte Antigen 4

PD-1 = Programmed cell death Protein 1

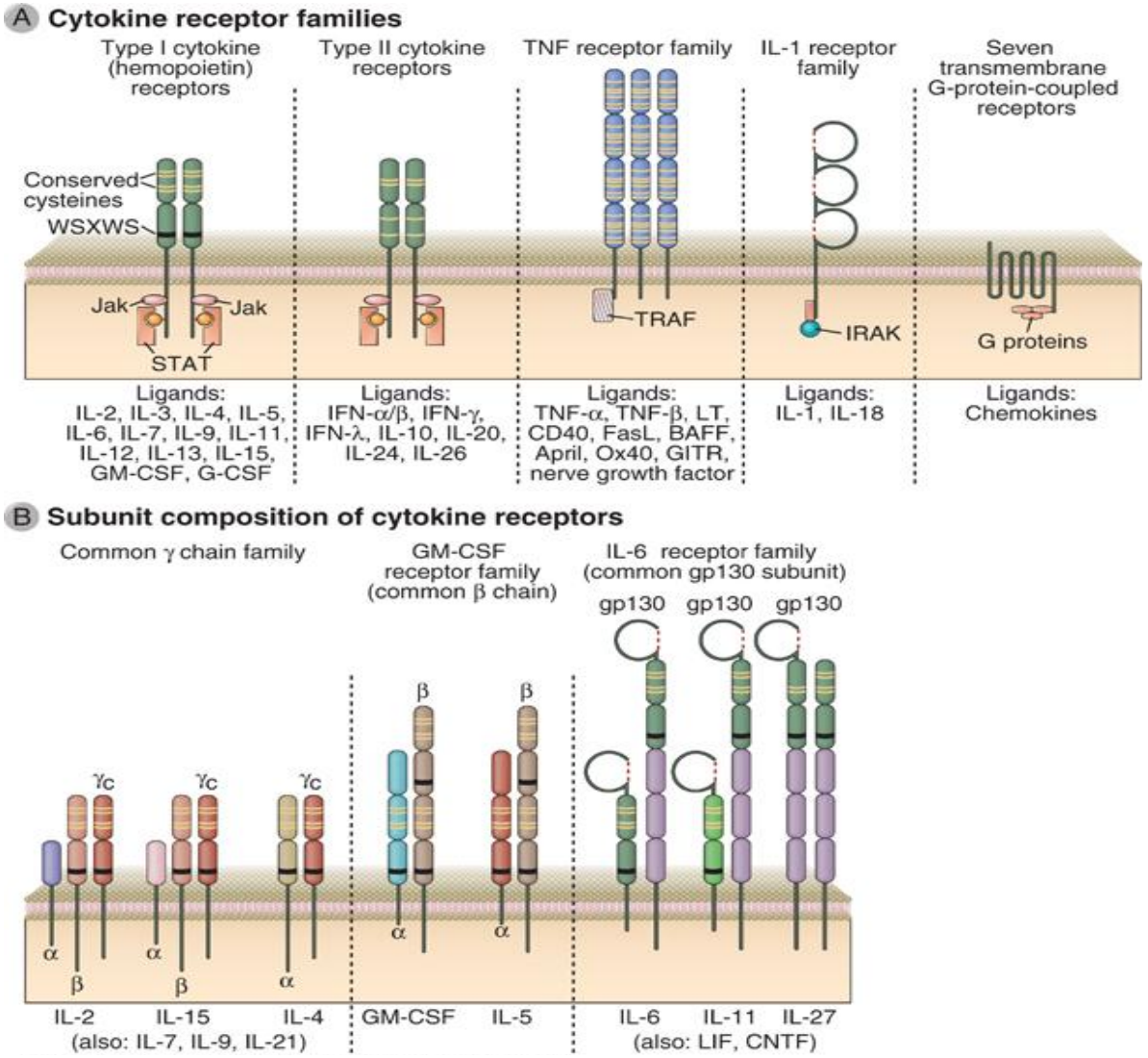
Termination of T cell responses by Cbl-b



Cbl = Casitas B-lineage lymphoma proto-o*ncogene (coding for E3 ubiquitin ligase)*

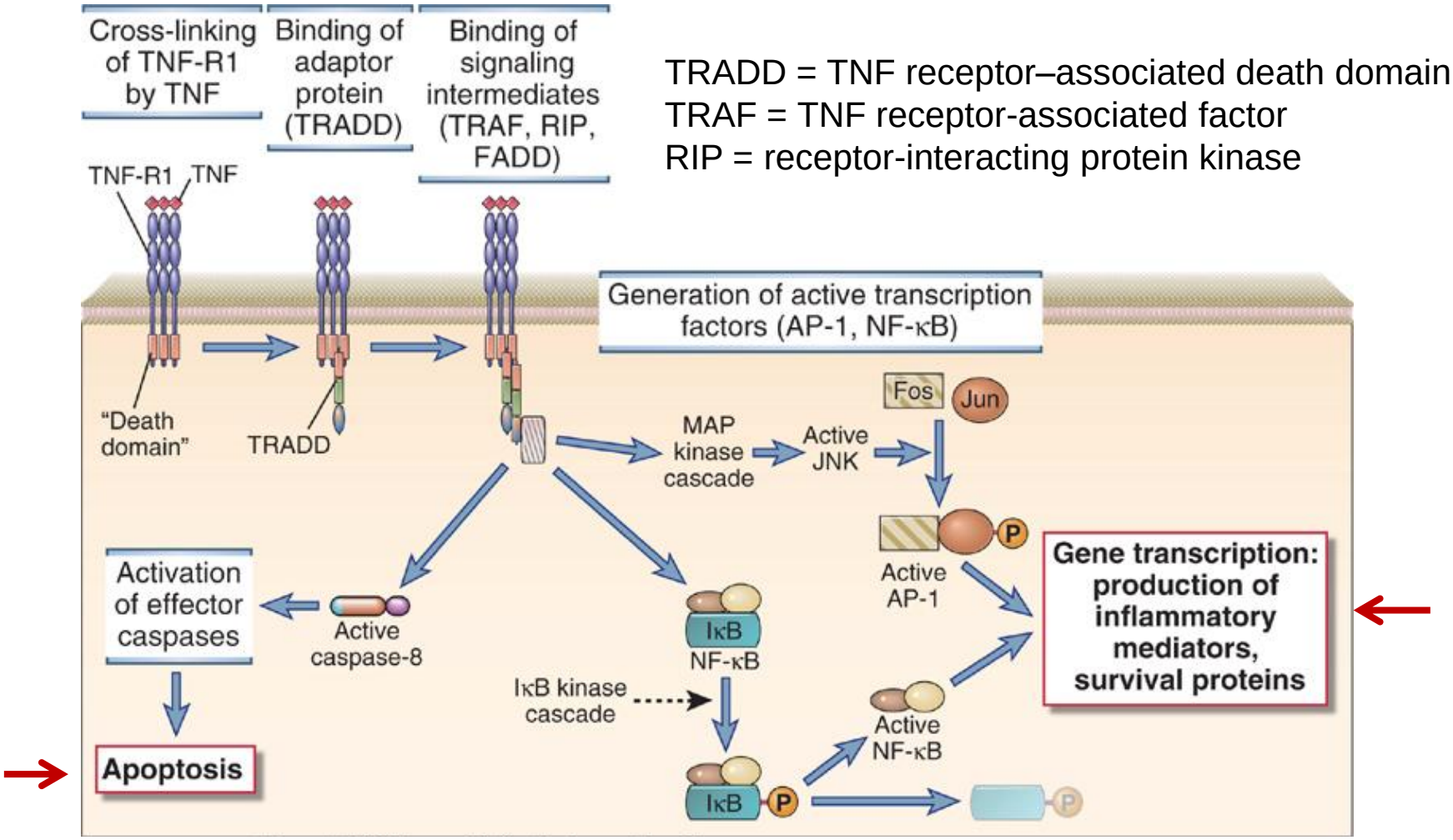
The **E3 ubiquitin ligase Cbl-b** is recruited to the TCR complex, where it facilitates the monoubiquitination of CD3, ZAP-70, and other proteins of the TCR complex. These proteins are targeted for proteolytic degradation.

Cytokine receptors and signaling (Abbas Chapter 7)



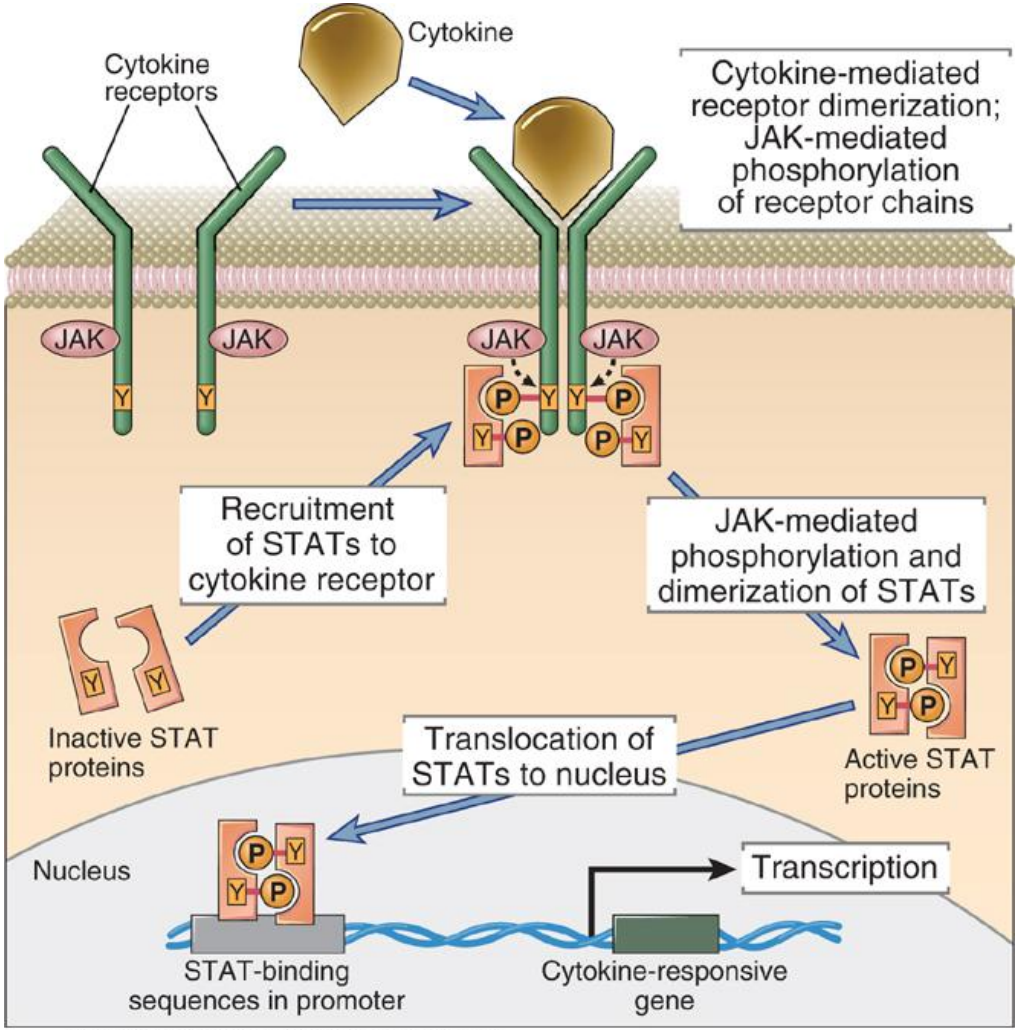
Signaling through TNF receptor (Abbas Chapter 7)

TRADD = TNF receptor–associated death domain
TRAF = TNF receptor-associated factor
RIP = receptor-interacting protein kinase



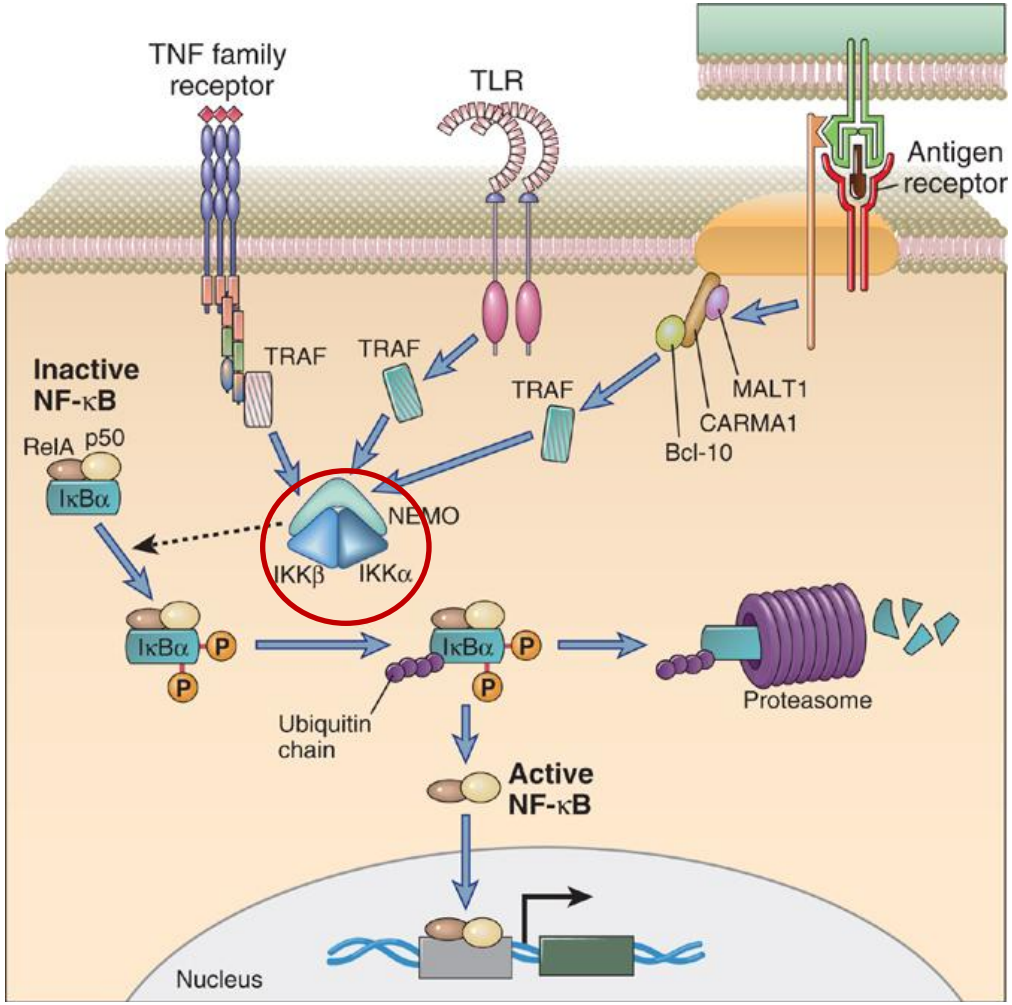
Ligation of the type I TNF receptor results in the recruitment of an adaptor protein called TRADD, which in turn can activate TRAF molecules (E3 ubiquitin ligase) and the RIP1 kinase. Downstream consequences include the activation of the NF-κB pathway and the JNK MAP kinase pathway or the induction of poptotic death

JAK-STAT signaling (Abbas Chapter 7)



Cytokine receptors of the type I and type II receptor families engage signal transduction pathways that involve non-receptor tyrosine kinases called Janus kinases (JAKs) and transcription factors called signal transducers and activators of transcription (STATs)

The canonical NF-kappaB pathway (Abbas Chapter 7)



IKK = IkB kinase

IkB = inhibitor of kappa B (inhibiert Nf-kB)

NF-kB = nuclear factor kappa-light-chain-enhancer of activated B-cells


SCENE
TAKE
2
DAY