

Signalling strategies by B- & T-cell receptors

Receptors and signalling:

- Binding of Ligand (antigenic determinant) to receptors (T/B cell)
- Binding results in signal transduction pathways.
- Signal transduction pathways are set of biochemical changes that occurs in the cell upon binding of ligand to its receptors.
- Cytokines & chemokines are examples of signalling molecules
- Often the signal transduction results in activation of Transcription factors that in turn codes for specific genes resulting in biochemical reactions by the gene product.

Common strategies used in signalling pathways -

When ligand binds to the receptors, it results in clustering of several associated molecules. ^{specialized places on the} The clustering occurs in ~~the~~ plasma membrane of the ~~cell~~ target cell rich in cholesterol & sphingolipids called Lipid rafts.

Tyrosine Kinases are commonly found in the lipid rafts. ~~they~~ They phosphorylate ~~the~~ tyrosine residues present in ITAM domains of the accessory molecules.

NOTE: ITAM domains are present in $Ig\alpha$, $Ig\beta$ accessory molecules and cytoplasmic tail of TCR.

LAT ← Adaptor molecules. Adaptor molecules connects the receptor with the downstream molecules. The Adaptor molecules will dock ~~at~~ at the ITAM domain sites. PLC- γ (phospholipase for T-cells)

Glycerol

C2, C3 → Fatty acid
C1 → Inositol

DATE: / /

type of
GLYCERO-phospholipid

↳ 2x Phosphate

Signalling molecules

CV) gets activated by the Adaptor molecule. PLC- γ converts PIP_2 (to Phosphatidyl inositol bisphosphate) to DAG (Diacylglycerol) & IP_3 (Inositol ^{1,4,5} triphosphate) by breaking the phospho-ester bond. IP_3 will bind to receptors present on ER. The ER will then release calcium ions. These calcium ions bind to proteins such as Calmodulin and Calcineurin. These molecules will dephosphorylate a transcription factor called NFAT (Nuclear Factor of Activated T-cells).

NOTE:

Phosphorylated NFAT present in the cytoplasm is inactive. The activated Calmodulin & Calcineurin will activate the NFAT that gets translocated to the nucleus for gene activation. They act as transcription factors.

DAG can activate another enzyme called PKC (Protein Kinase C). PKC phosphorylates an inhibitory protein called I- κ B (Inhibitory κ B). I- κ B remains associated with NF- κ B (Nuclear Factor κ B). NF- κ B remains inactive in the cytoplasm due to association of I- κ B. PKC phosphorylates I- κ B that directs it for Protein degradation (Ubiquitination). The released free NF- κ B is an active Transcription factor that gets translocated to nucleus.

There is another transcription factor called AP-1 (Activator Protein-1). AP-1 gets activated by RAS which is in turn activated by PKC. AP-1 activates the MAP Kinase Pathway.

Recap-

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Ligand binds to receptor → Conformational changes → Cluster formation
some receptors require ← forms Lipid raft ← (in the plasma membrane)
receptor-associated molecules
eg: ITAM in B/T cell receptors → cell → Signal for cell Activation



Example for co-receptors:

CD21 also interacts with antigen via a complement factor known as C3D. This interaction helps antigen receptor with sufficient time to interact with the antigen/APC.

NOTE: All co-receptors help in increasing the binding affinity of the BCR/TCR with the antigen or APC by extending its binding time.

- LYN \rightarrow Tyrosine Kinase Present in B-cells' receptor Lipid rafts
- LCK \rightarrow Tyrosine Kinase Present in T-cells' Lipid rafts

tyrosine residues in the
Phosphorylation of \wedge ITAM domain is crucial for most of the signalling pathways.

Phosphorylation of serine & threonine residues are also observed. They are often seen during downstream signalling processes.

Frequently encountered signalling pathways —

- * Activation of PLC- γ and subsequent activation of NR-NFAT.

TCR-Signalling

IL-2 \rightarrow signals B & T-cells to produce more clones.

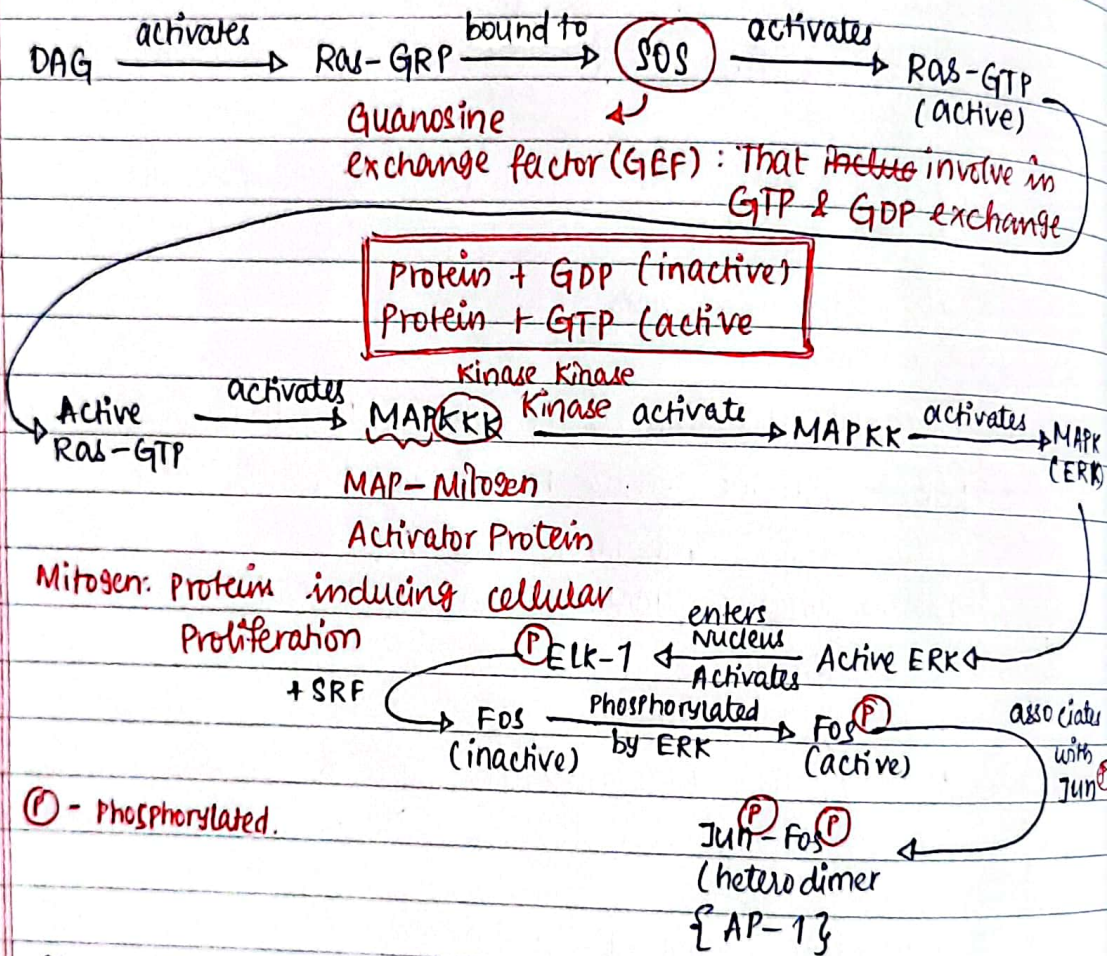
- * Activation of NF- κ B through DAG

ub \rightarrow ubiquitin & ubiquitination

A small protein which when tagged to another protein is destined to protein degradation.

\downarrow
A type of protein degradation

* Activation of AP-1 transcription through Ras/Map Kinase Cascade

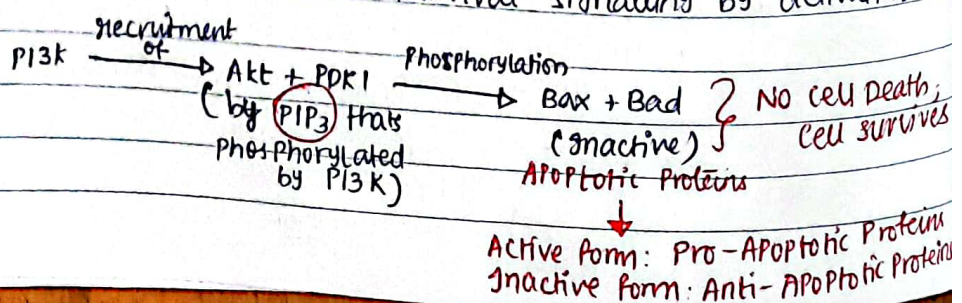


Signal transduction in B- & T-cells -

in B-cells:

BLNK \Rightarrow Adaptor molecule that docks near Phosphorylated ITAM domain sites

CD21 remain associated with CD19. They also have ITAM sites. They are involved in cell survival signalling by activating -



in T-cells:

ZAP-70 \rightarrow Phosphorylation of ITAM sites results in docking of
 \downarrow another tyrosine kinase called ZAP-70.

Present
only in T-cells

LAT \Rightarrow Adaptor molecule that docks near phosphorylated ITAM
to domain sites.

PKC θ \rightarrow PKC called in T-cells.

NOTE: B & T-cells ~~at have the same~~ share the same basic scheme
of signal transduction (except for few terms & ^{few} additional
molecules in T-cells).