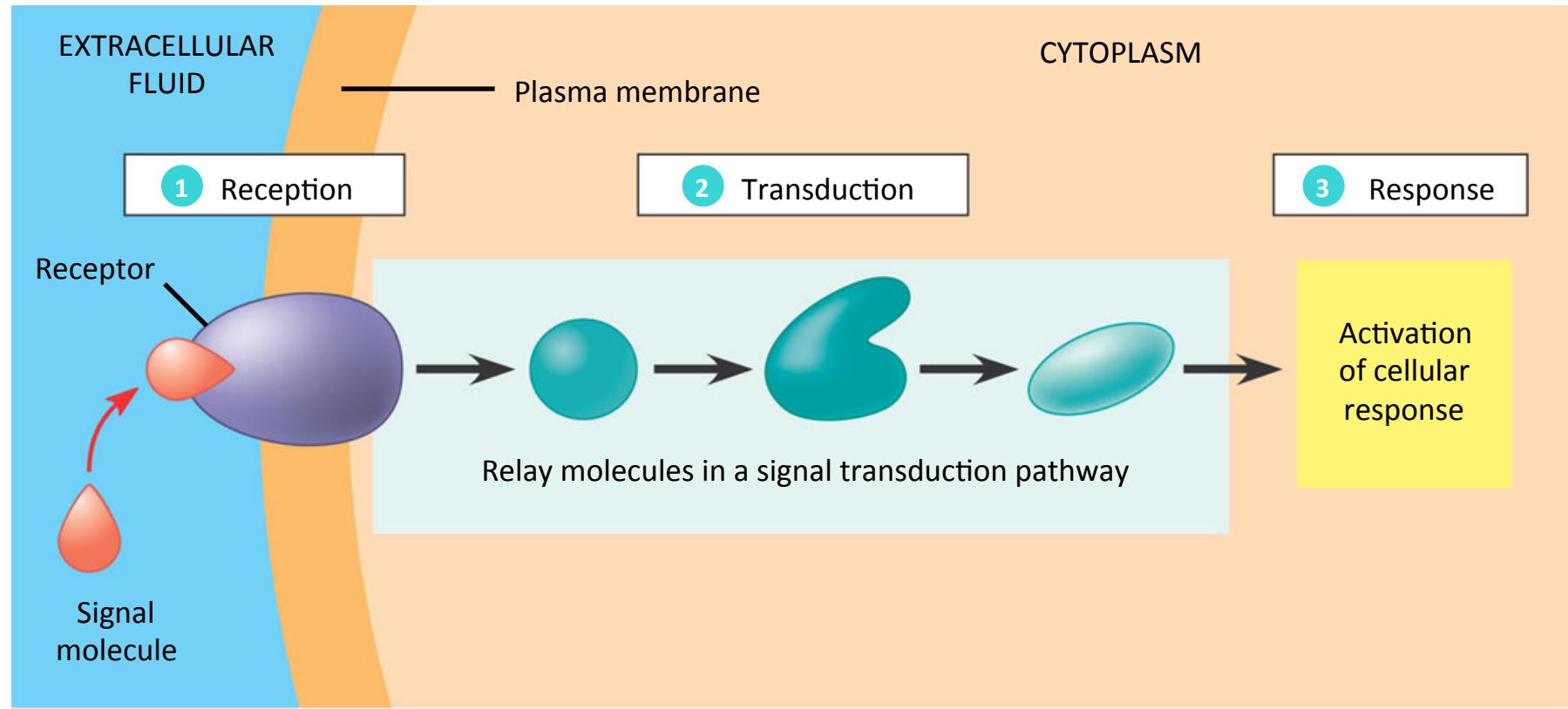


Growth Factors, Signal Transduction and Transcription Factors

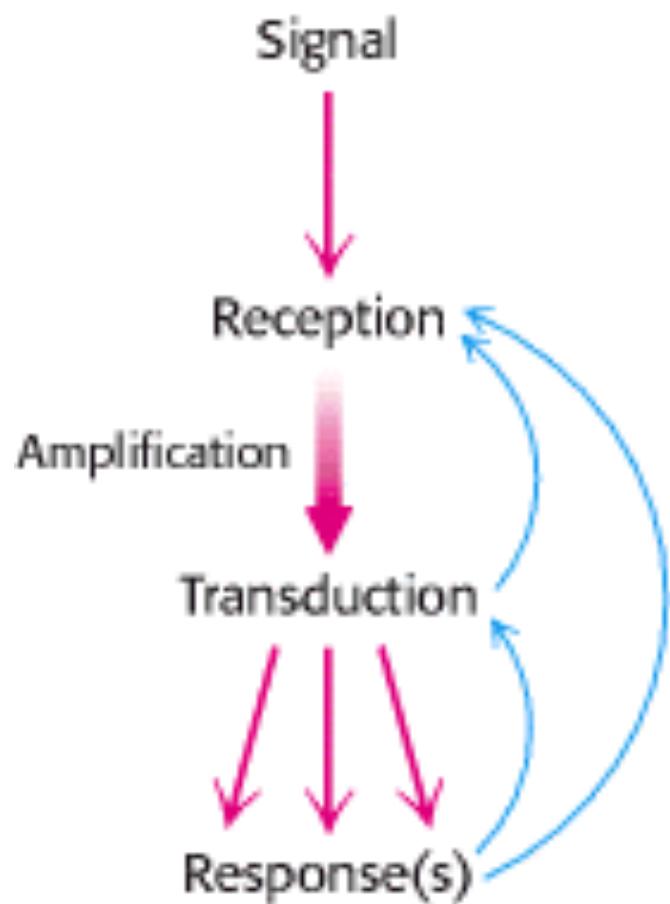


D. KARUNAGARAN
IIT MADRAS

OVERVIEW OF CELL SIGNALING



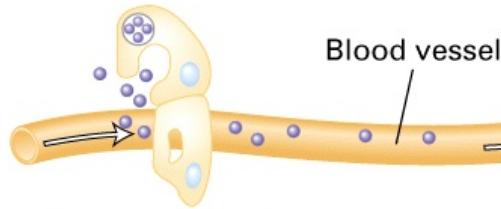
Main steps of a Signaling Process



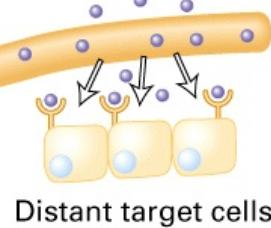
- **Generation of signal**
Ligands
- **Recognition of signal**
Receptor
- **Transduction**
Change of external signal
into intracellular message
- **Effect**
Modification of cell
behavior
- **Termination of signal**
Receptor endocytosis,
Dephosphorylation

Signaling Molecules Operate Over Various Distances

(a) Endocrine signaling

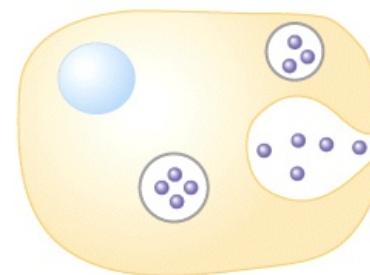


Hormone secretion
into blood by endocrine gland

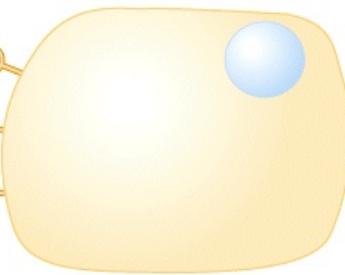


Distant target cells

(b) Paracrine signaling

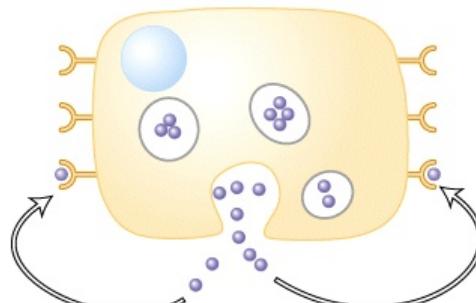


Secretory cell



Adjacent target cell

(c) Autocrine signaling



Target sites on same cell

Key:

- Extracellular signal
- ▲ Receptor
- Membrane-attached signal

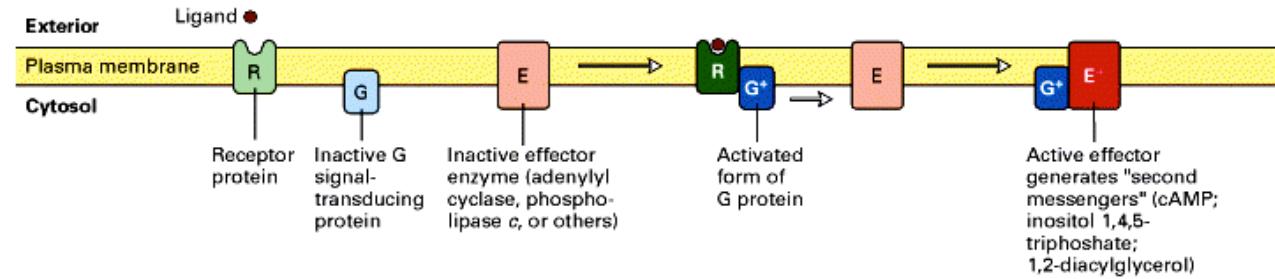
RECEPTORS: Molecules specialized in recognizing signals

- Has to have an endogenous ligand
- Has to bind its Ligand with high affinity (strength)
- Ligand will produce response only in cells that have receptors for this particular ligand
- Specific for a signal (they will recognize only a signal that they are made for)
- Has to recognize the specific biologically active ligand from other similar molecules (specificity)
- Energy from the signal (stimulus) or ligand binding alters the structure of the receptor
- Has to produce the biological response

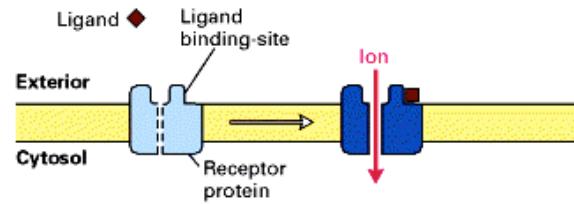
All the conditions have to be met!!!

Cell-Surface Receptors Belong to Four Major Classes

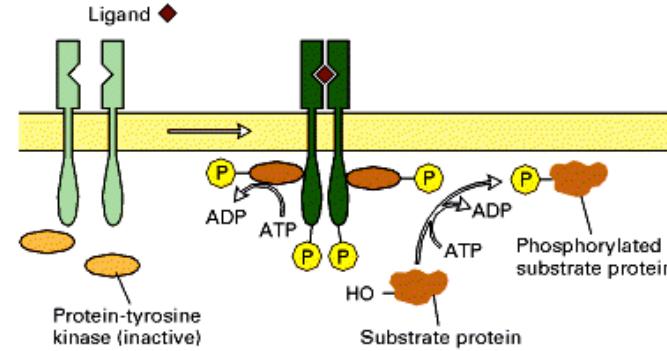
(a) G protein-coupled receptors (epinephrine, glucagon, serotonin) (Smell and vision)



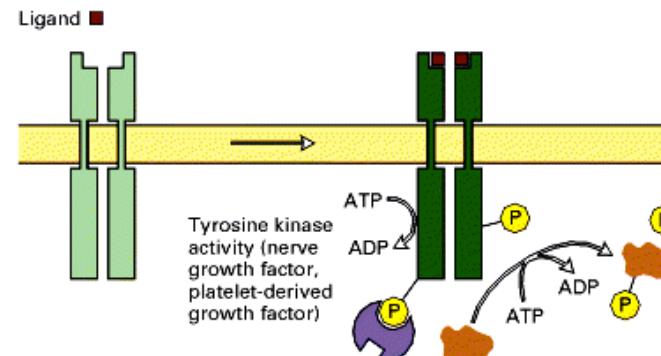
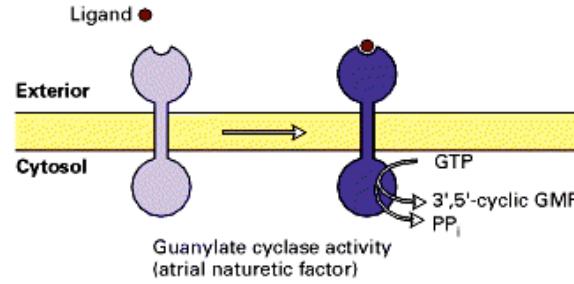
(b) Ion-channel receptors (acetylcholine)



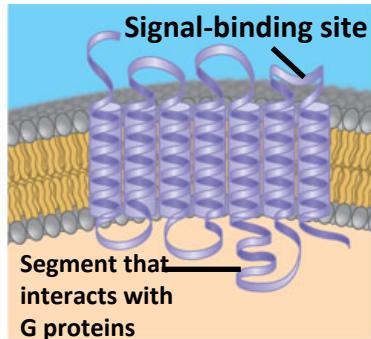
(c) Tyrosine kinase-linked receptors (erythropoietin, interferons)



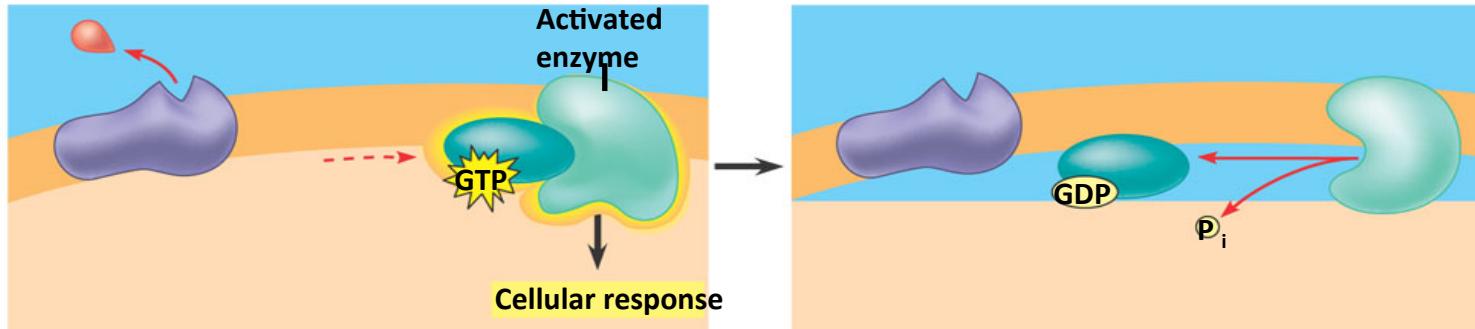
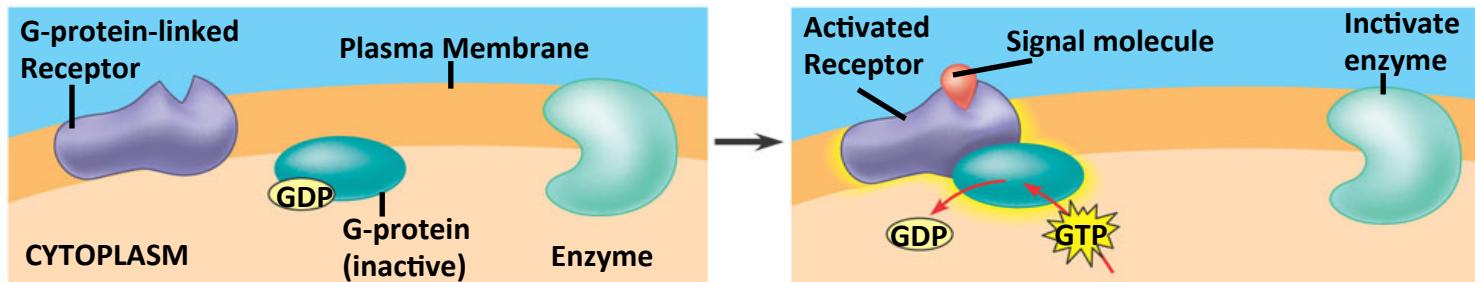
(d) Receptors with intrinsic enzymatic activity



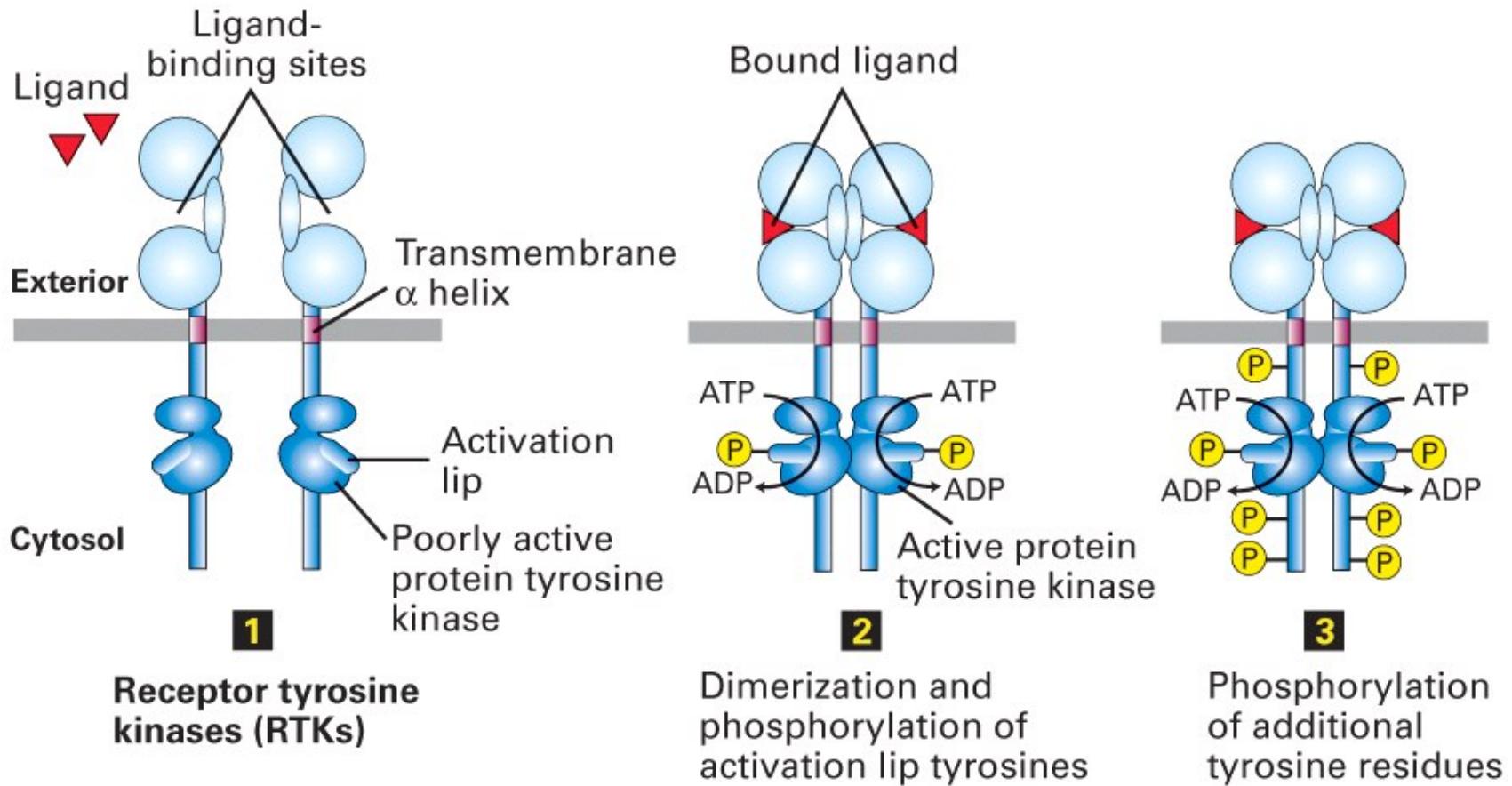
G-protein-linked receptors



GPCRs include receptors for several hormones, Neurotransmitters, Light activated receptors in the eye, Odorant receptors in the nose



Receptor tyrosine kinases (RTKs) auto-phosphorylate when activated

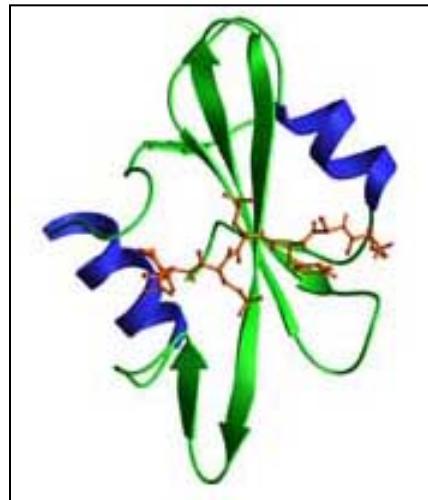


“Cellular signaling circuits are composed from a modular toolkit of components including **kinases, phosphatases, GTPases** and **interaction domains.**”

Src-homology 2 (SH2) domains

Src-homology 2 (SH2) domains are modules of ~100 amino acids that bind to specific phospho (pY)-containing peptide motifs.

Phosphopeptides of optimal sequence bind to SH2 domains with dissociation constants of ~50-500 nM.



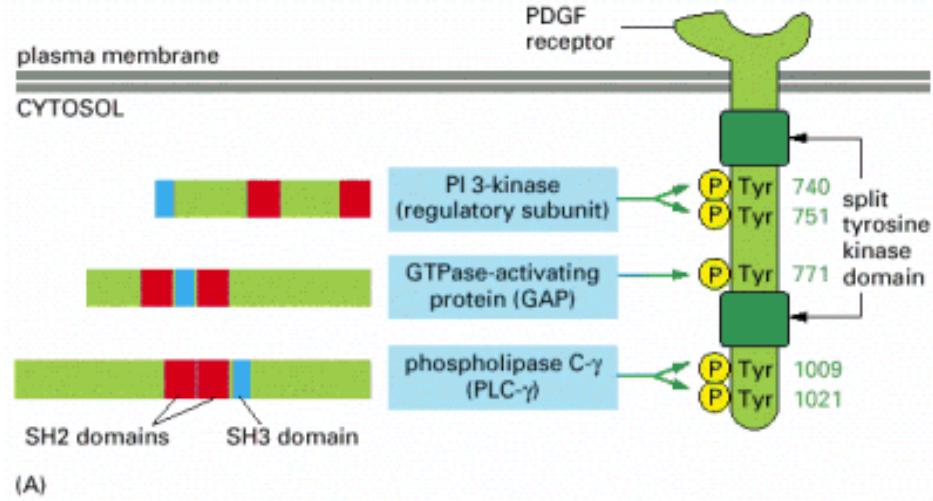
The figure shows the SH2 domain of v-src bound to a pYEEI peptide ligand.

SH2 domains contain a central anti-parallel β -sheet surrounded by two α -helices.

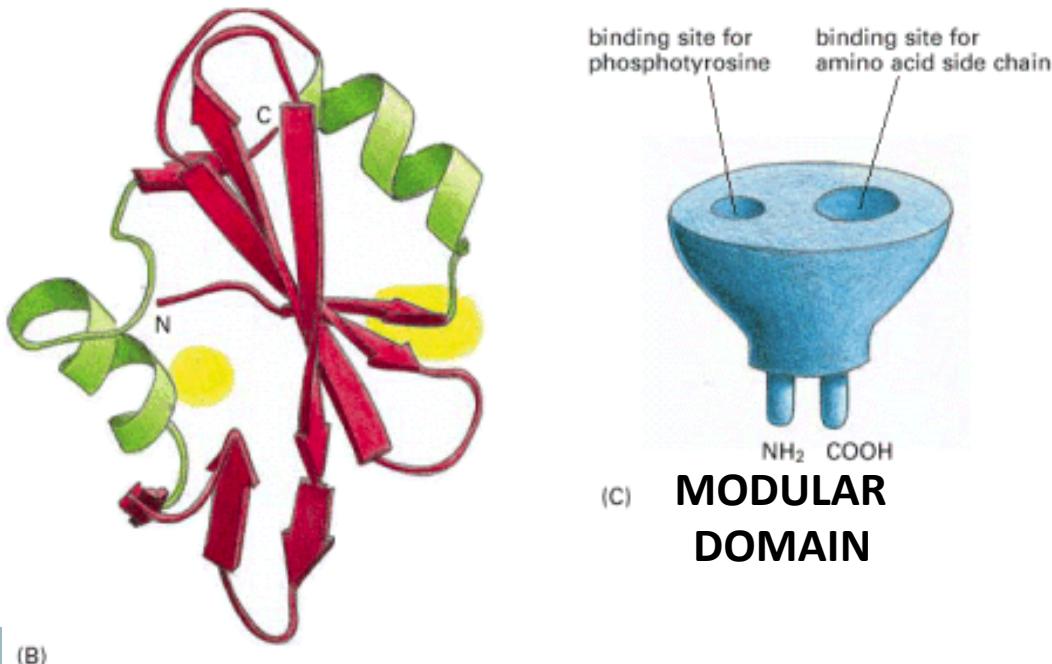
The phosphopeptide generally binds as an extended β -strand that lies at right angles to the SH2 β -sheet.

An invariant Arg residue in the SH2 domain coordinates the phosphate oxygens of pY and is essential for high affinity phosphopeptide binding.

SH2 domains bind P-Tyr



(A)



PTB Domain: Phospho-Tyr binding

Phosphotyrosine binding (PTB) domains are 100-150 residue modules that commonly bind Asn-Pro-X-Tyr motifs.

The PTB domains of the docking proteins Shc and IRS-1 require ligand phosphorylation on the tyrosine residue (NPXpY) for binding.

The PTB domains of proteins such as X11, Dab, Fe65 and Numb apparently recognize NPXY or related peptide motifs, but are not dependent on ligand phosphorylation.

Src-homology 3 (SH3) domains

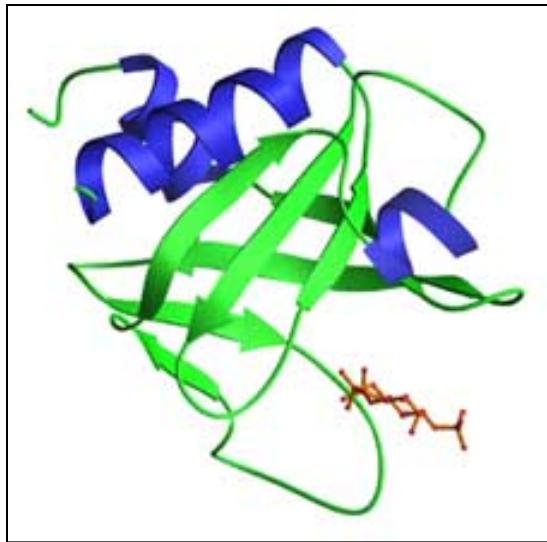
Src-homology 3 (SH3) domains generally bind to Pro-rich peptides with the minimal consensus Pro-X-X-Pro.

Each Pro is usually preceded by an aliphatic residue. Each of these aliphatic-Pro pairs binds to a hydrophobic pocket on the SH3 domain.

The ligand-binding site consists of a hydrophobic patch that contains a cluster of conserved aromatic residues and is surrounded by two charged and variable loops.

The binding affinity and specificity can be markedly increased by tertiary interactions involving loops on the SH3 domain.

Pleckstrin-homology (PH) domains



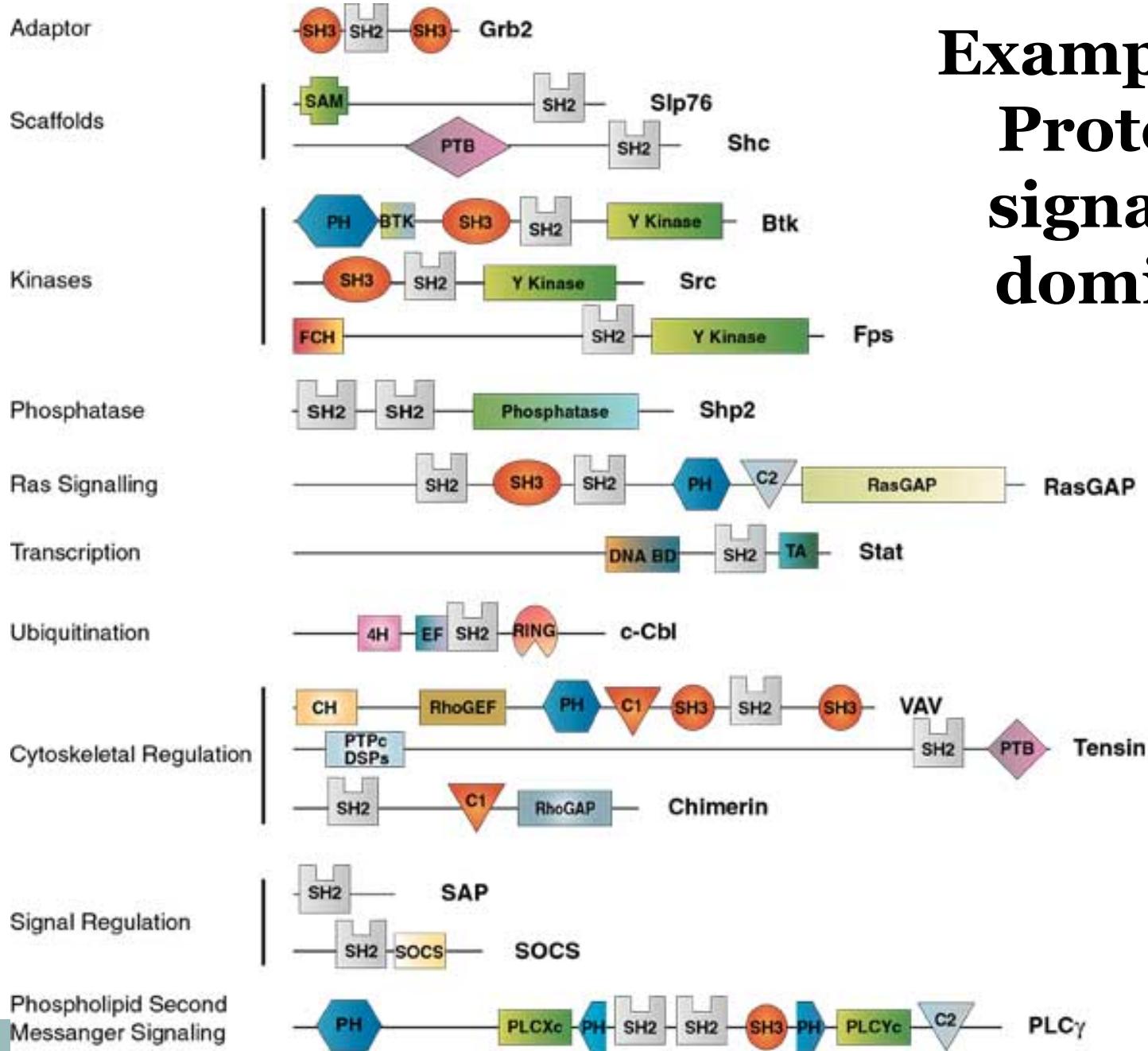
The figure shows the complex between the PH domain of Phospholipase C-d and inositol-(1,4,5)-trisphosphate (red).

Pleckstrin-homology (PH) domains are protein modules of approximately 120 amino acids.

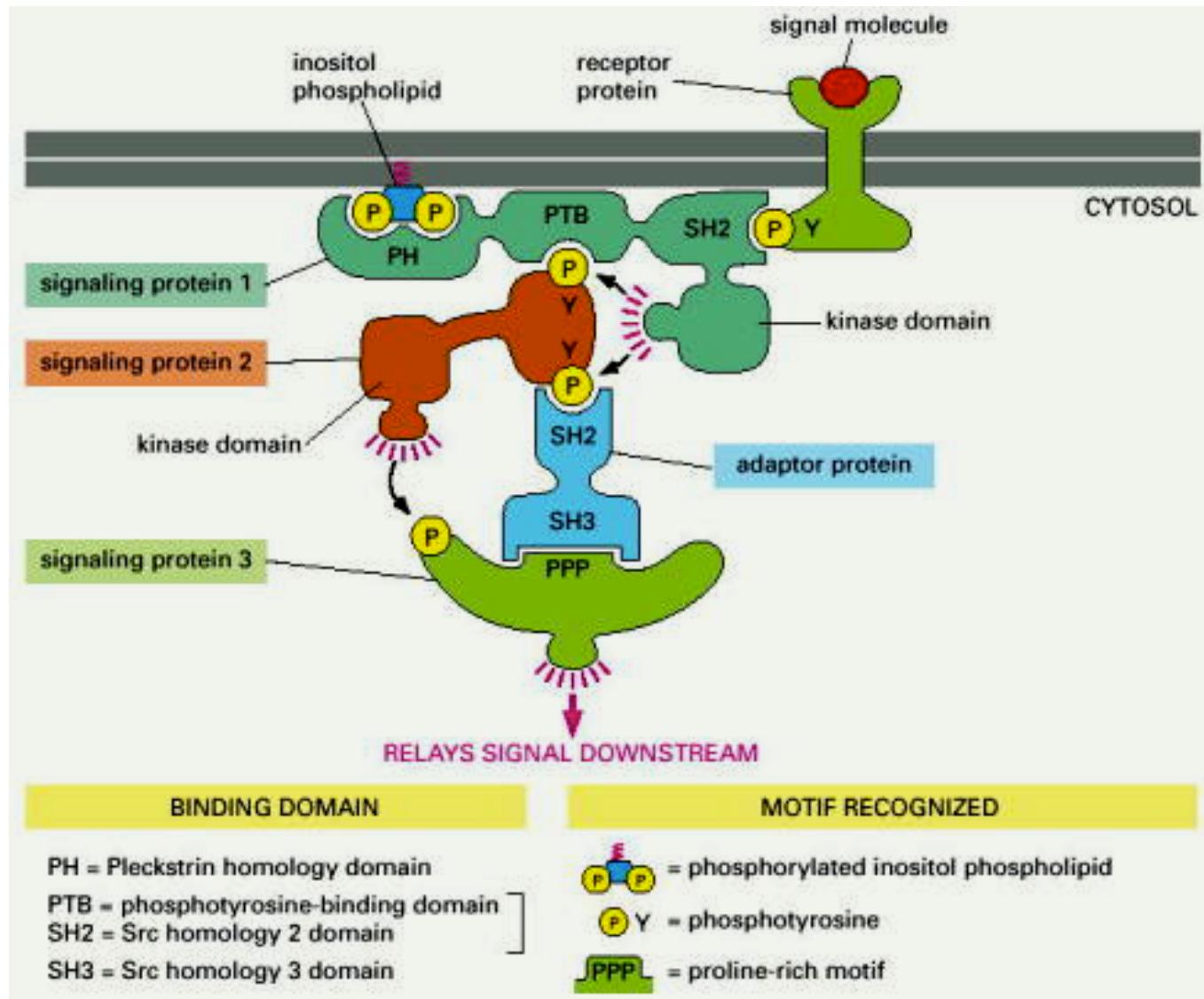
PH domains bind with high affinity (low mM or nM K_d) to specific phosphoinositides such as phosphatidyl-inositol (PI) -4,5-bisphosphate, PI-3,4-P₂ or PI-3,4,5-P₃.

Binding to phosphoinositides may allow PH proteins to respond to lipid messengers for example by relocation to membranes.

Examples of Proteins signaling domains

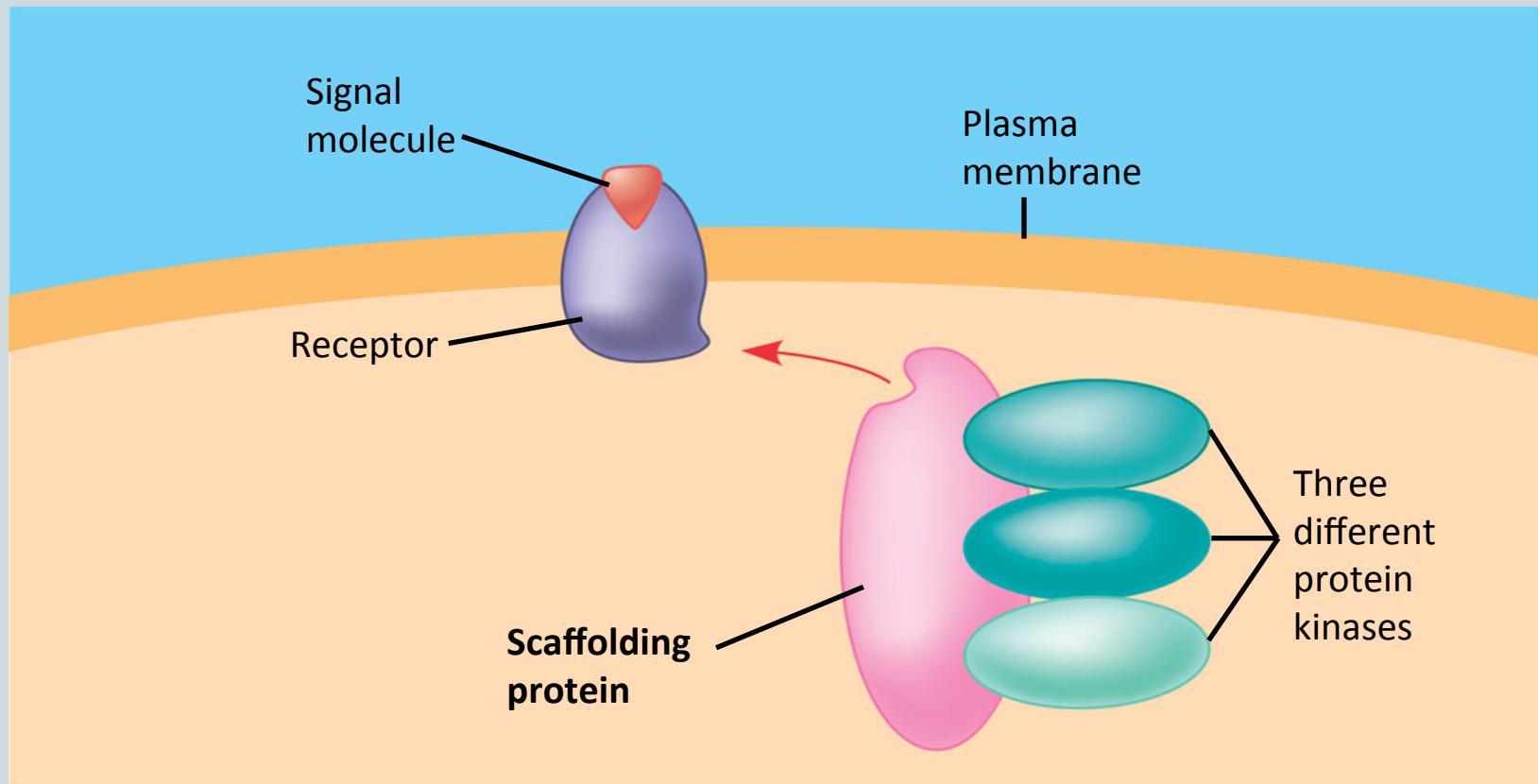


Interactions Between Intracellular Signaling Proteins Are Mediated by Modular Binding Domains



Signaling Efficiency: Scaffolding Proteins and Signaling Complexes

- Scaffolding proteins
 - Can increase the signal transduction efficiency



A Phosphorylation Cascade

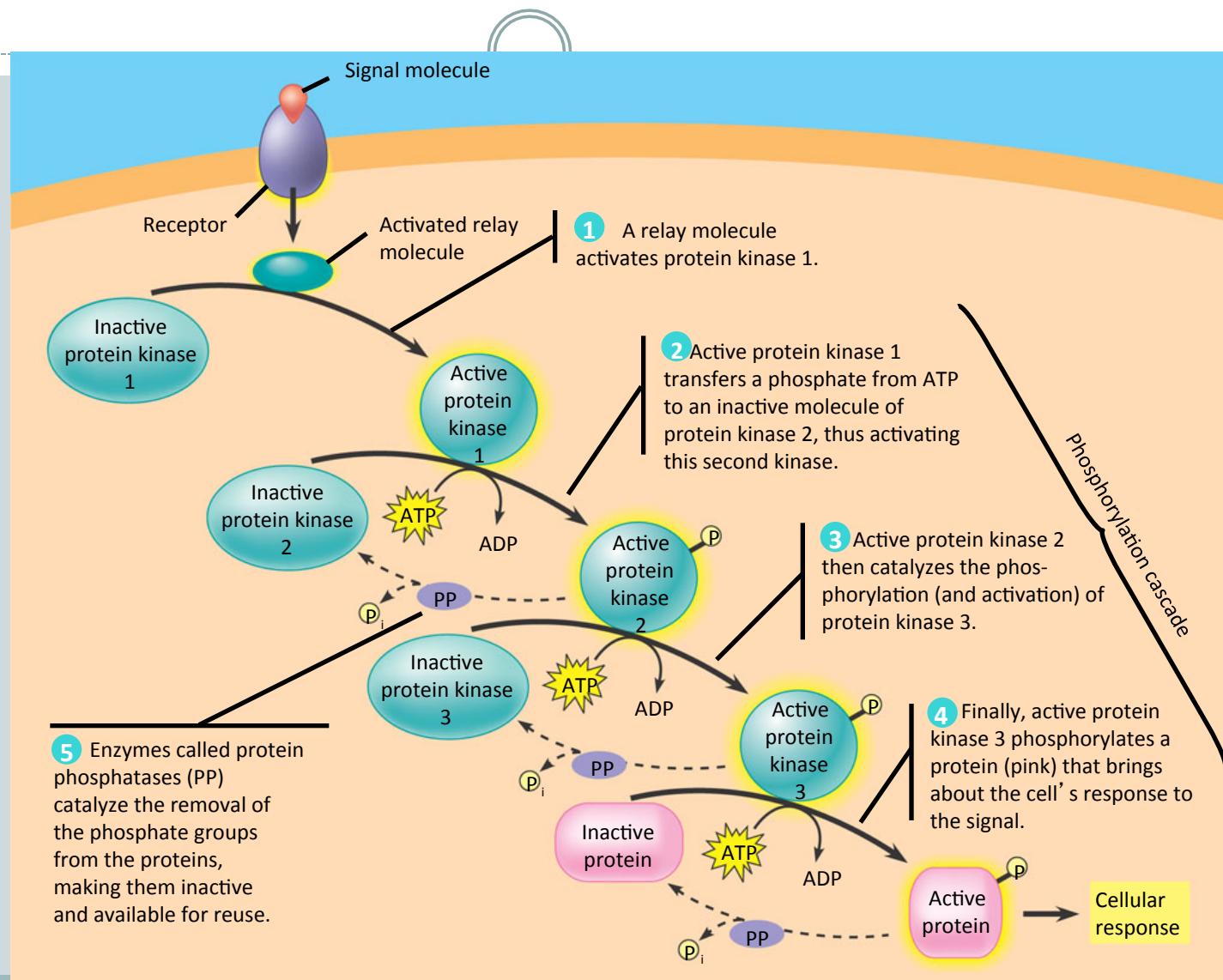


Figure 11.8

Further Reading



- Molecular Biology of the Cell; Bruce Alberts