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M.Sc. Zoology (Semester IV)
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Unit: 3.6

Cell surface receptors of signaling molecules

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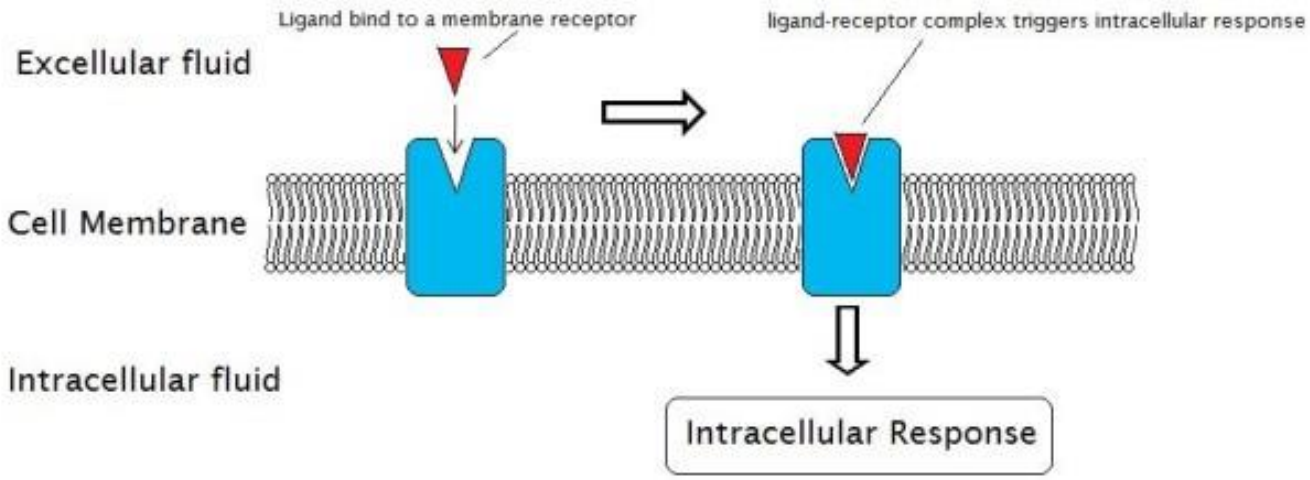
A receptor is a molecule that receives signals (chemical or hormonal) from outside the cell and is usually located on the cell surface.

Receptors are proteins that undergo a conformational change upon attachment of their corresponding signaling molecule, which in turn induces a chain reaction (also known as signal transduction) within the cell leading to various cellular responses.

The signaling molecule that binds to the receptor (also known as a ligand) can be a peptide, a hormone, neurotransmitter, drug, toxin, etc.

Generally, each receptor possesses 2 functional domains: the recognition domain which binds ligands and the coupling domain which is involved in signal transduction.



Cell surface receptors

Cell surface receptors are located on the cell surface and are integral membrane proteins that translate extracellular information into intracellular signaling events that leads into physiological cell response. The cascade of events or process is called transmembrane signal transduction.

When the ligands bind to their corresponding receptor, a conformational change is triggered which initiates an intracellular signaling pathway. Note that each ligand has its own specific cell surface receptor.

Cell surface receptors have the following components/domains:

- Extracellular domain which binds ligands and is exposed to the outer surface of the cell; also known as the recognition domain
- Membrane-spanning region made up of hydrophobic protein molecules
- Intracellular domain which is in contact with the cytoplasm; also known as the coupling domain

Cell surface receptors can be classified structurally into single-pass trans-membrane receptors (with one extracellular, one trans-membrane and one intracellular region) and multi-pass trans-membrane receptors. However, in terms of their signal transduction characteristics, it is easier to distinguish four groups of receptors

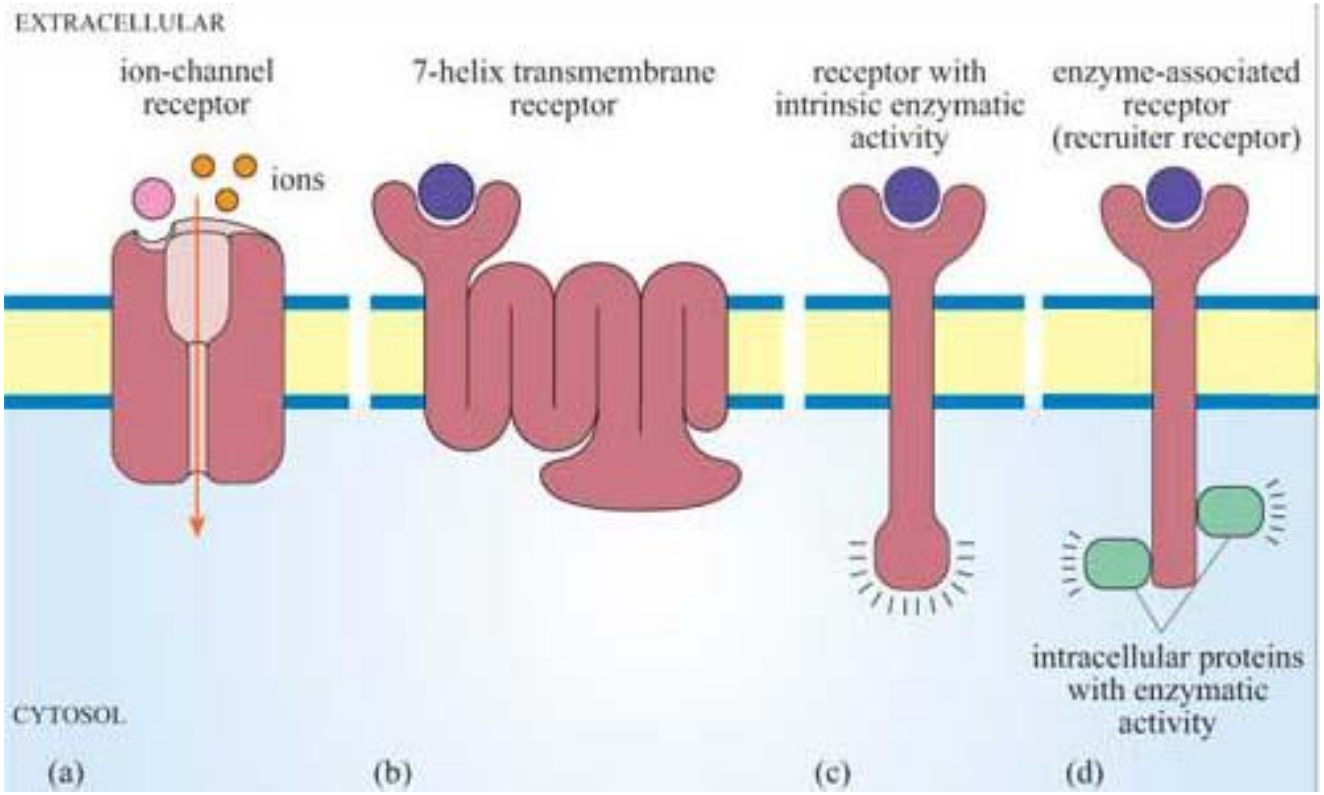


Figure 1: The four major classes of cell surface receptors: (a) ion-channel receptors; (b) 7-helix transmembrane receptors (7TM receptors); (c) receptors with intrinsic enzymatic activity (d) enzyme-associated receptors .

Four major classes of cell surface receptors

1. Receptors that also serve as the effector For example, one type of acetylcholine receptor is also an ion channel, and belongs to a family of receptors called **ion-channel receptors**. In response to acetylcholine, these receptors allow the passage of specific ions, thereby effecting changes in the membrane potential of a cell.

2. Seven-helix transmembrane receptors 7TM receptors possess seven membrane-spanning regions, an N-terminal extracellular region and a C-terminal intracellular tail. The famous example of this type is **G protein-coupled receptors (GPCRs)**.

3. Receptors whose intracellular tail contains an enzymatic domain, which are known as **receptors with intrinsic enzymatic activity.** This group includes the receptor tyrosine kinases, involved in the response to many growth factors.

4. Receptors that require association with cytosolic or membrane-bound proteins with enzymatic activity for signalling. These receptors do not have intrinsic enzymatic activity, and have been referred to as **enzyme-associated receptors.**

Next section we will discuss in more details:

1. G protein-coupled receptors
2. Receptor protein tyrosine kinases
3. Enzyme- associated receptors

1. G protein-coupled receptors

G protein coupled receptors (GPCRs) are integral membrane proteins that are used by cells to convert extracellular signals into intracellular responses, including responses to hormones, neurotransmitters, as well as responses to vision, olfaction and taste signals.

Approximately 2% of all genes in the human genome encode G-protein-coupled receptors (GPCRs), which represent the largest family of cell-surface molecules involved in signal transmission.

They are so called because their signals are transduced by heterotrimeric G proteins.

The GPCR family regulate a wide range of key physiological functions, including neurotransmission, blood pressure, cardiac activity, vascular integrity, hemostasis after tissue injury, glucose and lipid metabolism, sensory perception, regulation of endocrine and exocrine gland function, immune responses, multiple developmental processes, and stem cell function and maintenance

Structure of GPCRs

A GPCR is basically composed of three parts:

1. The extracellular region: contains N terminus and three extracellular loops (ECL1–ECL3)

2. The TM region: contains seven TM α-helices (TM1–TM7)

3. The intracellular region: contains three intracellular loops (ICL1–ICL3) and an intracellular amphipathic short α-helix (H8) lying perpendicular to the membrane plane, and the C terminus.

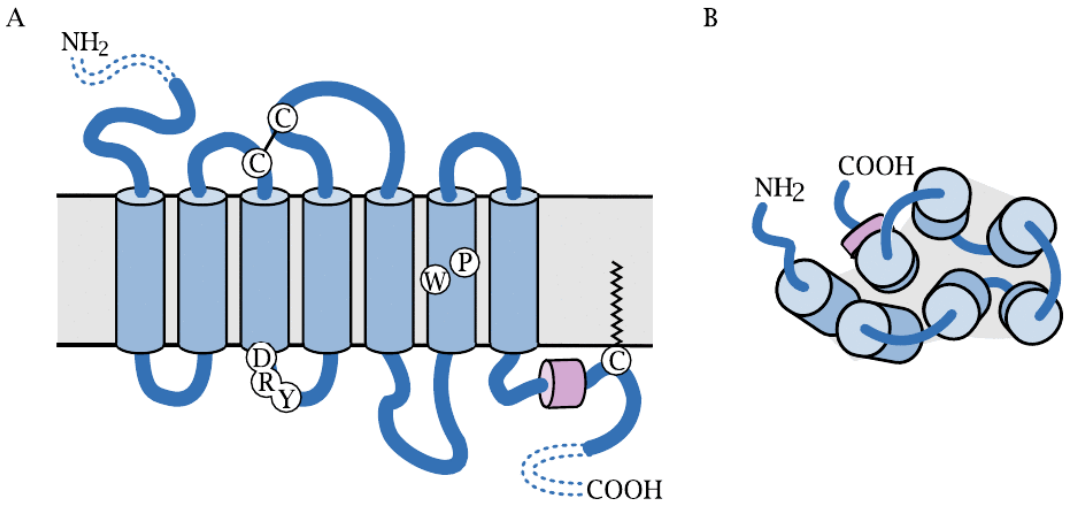


Figure 2: A) Schematic of GPCRs, B) View from the extracellular side

Structure of GPCRs

The inactive conformation of the GPCR is stabilized by noncovalent interactions between specific residues in the transmembrane α-helices.

Ligand binding disturbs these interactions, thereby causing the receptor to assume an active conformation.

This requires rotations and shifts of the transmembrane α-helices relative to each other.

Because they are attached to the cytoplasmic loops, rotation or movement of these transmembrane α-helices causes changes in the conformation of the cytoplasmic loops.

This in turn leads to an increase in the affinity of the receptor for a G protein that is present on the cytoplasmic surface of the plasma membrane .

Types of GPCRs

GPCRs are categorized into six classes based on sequence and function. All GPCR members share a common seven transmembrane (7TM) architecture linked by three extracellular (ECL) and three intracellular (ICL) loops.

1. Class A—rhodopsin-like receptors
2. Class B—secretin family
3. Class C—metabotropic glutamate receptors
4. Class D—fungal mating pheromone receptors
5. Class E—cAMP receptors
6. Class F—frizzled (FZD) and smoothened (SMO) receptors

Of these, classes D and E are not found in vertebrates. An alternative classification scheme "GRAFS" divides vertebrate GPCRs into five classes.

GRAFS stands for Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2, Secretin

‘GRAFS’ Classification

Glutamate family (class C), which includes metabotropic glutamate receptors, a calcium-sensing receptor and $GABA_B$ receptors, as well as three taste type 1 receptors and a family of pheromone receptors (V2 receptors).

Rhodopsin family (class A), which includes receptors for a wide variety of small molecules, neurotransmitters, peptides and hormones, together with olfactory receptors, visual pigments, taste type 2 receptors and five pheromone receptors (V1 receptors).

Adhesion family GPCRs are phylogenetically related to class B receptors, from which they differ by possessing large extracellular N-termini that are auto proteolytically cleaved from their 7TM domains at a conserved site.

Frizzled family consists of 10 Frizzled proteins (FZD(1-10)) and Smoothened (SMO). The FZDs are activated by secreted lipoglycoproteins of the WNT family, whereas SMO is indirectly activated by the Hedgehog (HH) family of proteins acting on the transmembrane protein Patched (PTCH).

Secretin family, ligands are polypeptide hormones.

The G proteins

The G proteins is a heterotrimeric complex that relay signals from GPCRs are associated with the underside of the plasma membrane and are composed of an α subunit and a βγ dimer.

Agonist-activated GPCRs act as GEFs that catalyze the exchange of GDP bound to the a subunit for GTP, causing release of Gβγ.

A single ligand-bound GPCR can activate several G proteins, providing the first layer of signal amplification.

The GTP-bound Gα subunits and Gβγ subunits can then promote the activation of a variety of downstream effectors, stimulating a network of signaling events that is highly dependent on the G-protein-coupling specificity of each receptor.

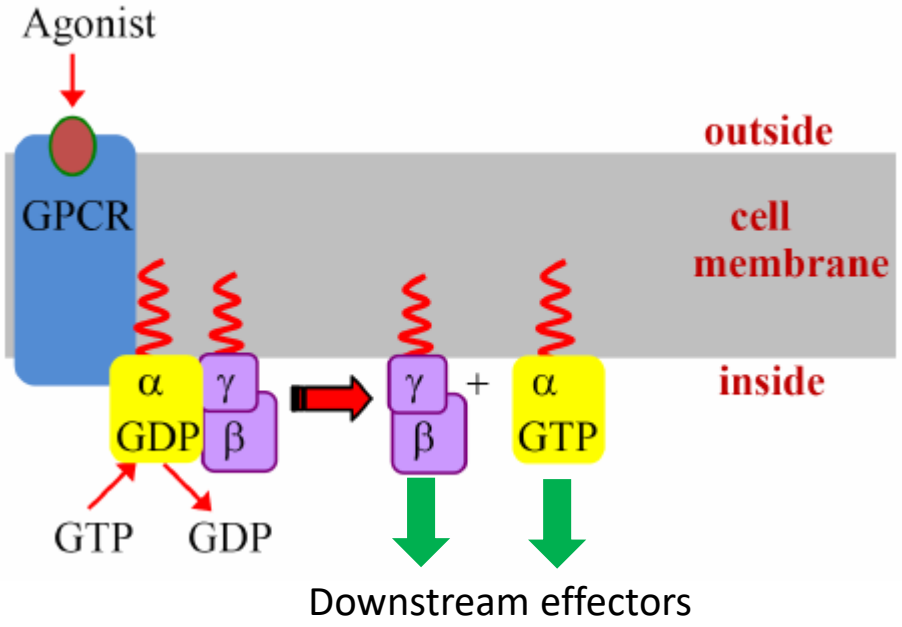


Figure 3: Schematic of G-protein activation

2. Receptor protein-tyrosine kinases

In contrast to the 7-TM receptors, the receptor protein tyrosine kinases (RPTK) pass through the membrane only once, and have a built-in enzyme domain - a protein tyrosine kinase.

Like the GPCRs, receptor tyrosine kinases bind a signal, then pass the message on through a series of intracellular molecules, the last of which acts on target proteins to change the state of the cell.

The signal binding domain of the RPTK is on the cell surface, while the tyrosine kinase enzymatic activity resides in the cytoplasmic part of the protein . A trans-membrane α-helix connects these two regions of receptor.

Binding of signal molecules to the extracellular domains of RPTK causes two receptor molecules to dimerize (come together and associate). This brings the cytoplasmic tails of the receptors close to each other and causes the tyrosine kinase activity of these tails to be turned on.

The activated tails then phosphorylate each other on several tyrosine residues and leads to activation of RPTK.

SH2 domains mediate binding/activation of downstream signaling molecules

Schematics of Receptor protein-tyrosine kinase activation

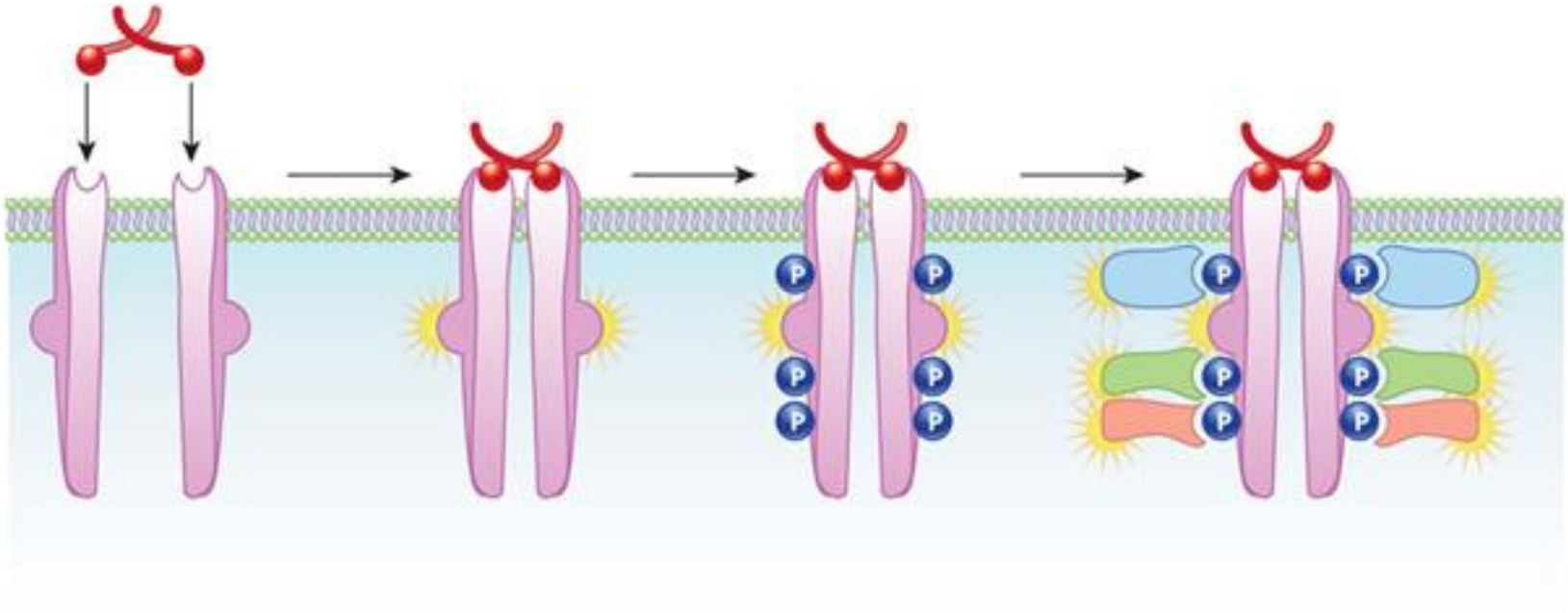


Figure 4: RTK activation involves the joining together and phosphorylation of proteins. On the left, an inactivated RTK receptor (pink) encounters a ligand (red). Upon binding, the receptor forms a complex of proteins that phosphorylate each other. In turn, this phosphorylation affects other proteins in the cell that relays the signal downstream.

Humans have at least 59 RPTK.

Signaling molecules of RPTK are EGF (epidermal growth factor), FGF (fibroblast growth factor), NGF (nerve growth factor) PDGF, and other growth factors as well as insulin.

Classification of RPTKs

There are seven subfamilies of receptor protein tyrosine kinases (RPTK) based on their structure and function.

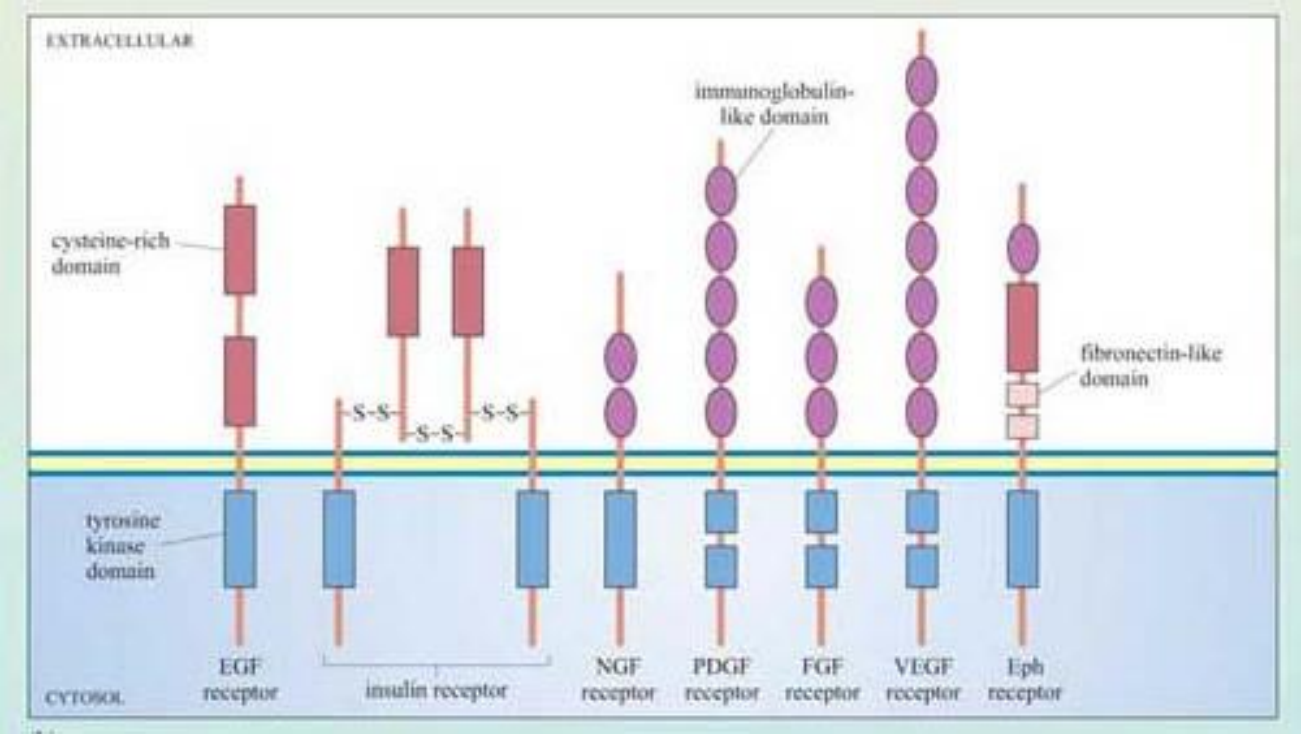


Figure 5: The subfamilies have cysteine-rich, immunoglubulin-like, and fibronectin-like extracellular domains. Note that the PDGF, FGF and VEGF receptors have a split tyrosine kinase domain. (EGF = epidermal growth factor; NGF = nerve growth factor; PDGF = platelet-derived growth factor; FGF = fibroblast growth factor; VEGF = vascular endothelial growth factor; Eph = ephrin.)

3. Enzyme associated Receptors

Similar to RPTK, but the cytosolic domains of enzyme associated receptors have no catalytic activity.

The signal from the receptor is received by an intracellular cytoplasmic proteins which can trigger intracellular signals derived from extracellular receptor.

Enzyme-associated or recruiter receptors also form dimers (or oligomers) on activation by their ligand, in a similar way to receptors with intrinsic enzymatic activity.

Dimerization facilitates an interaction between the cell surface receptor (which lacks a catalytic domain) and cytosolic proteins with enzymatic activity.

This family of receptors called the cytokine receptor superfamily includes the receptors for most cytokines and for some polypeptide hormones

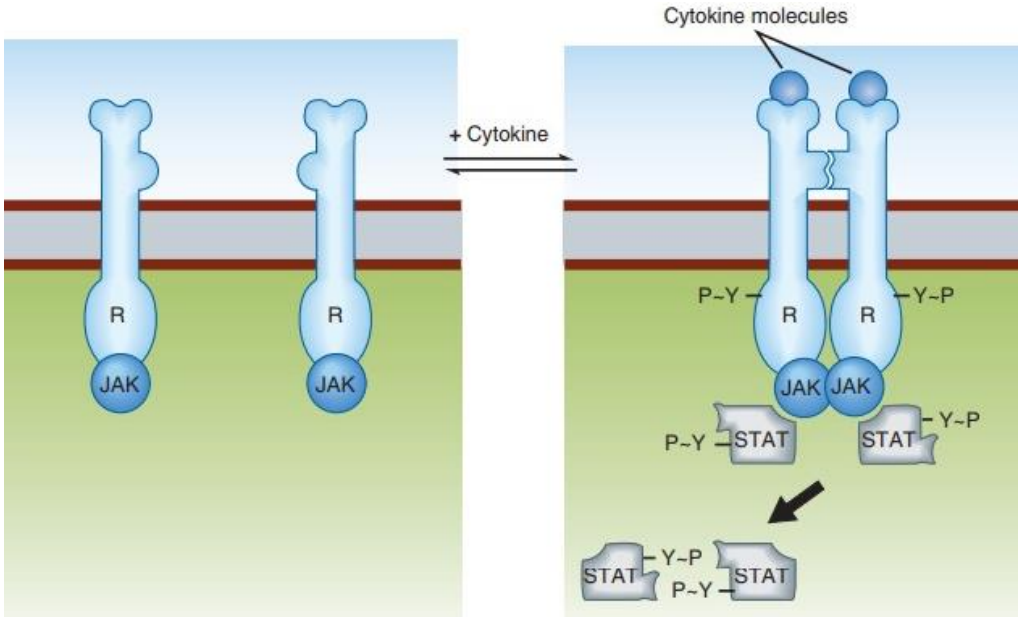
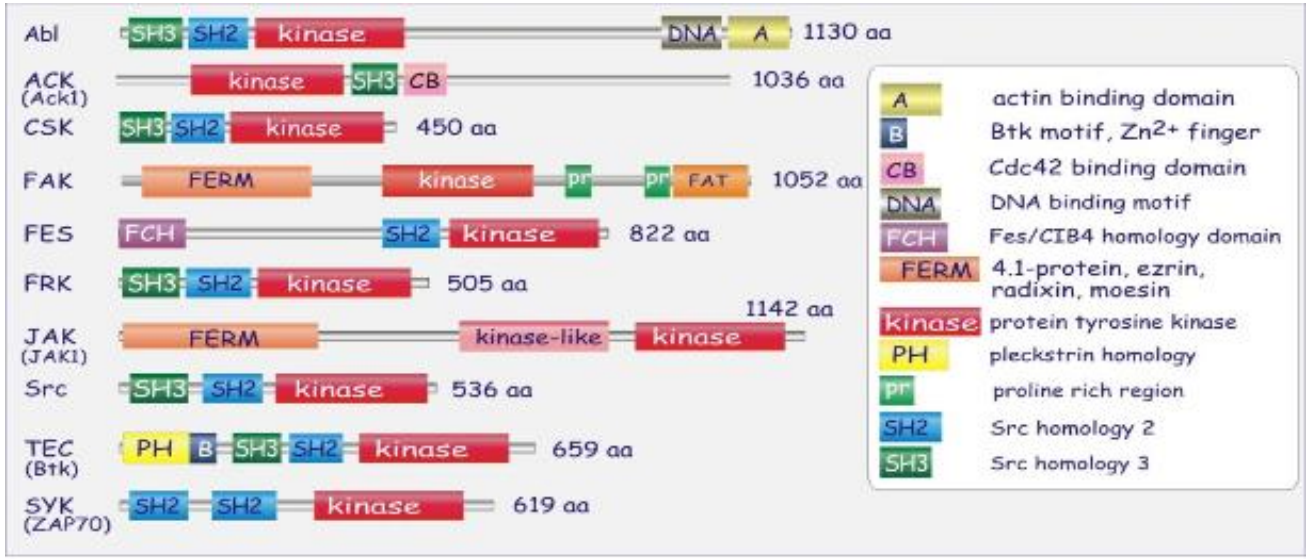


Figure 6: cytokine receptors are associated with kinases in the cytosolic side

Cytokine receptors functions in association with non-receptor protein tyrosine kinases, (NRTKs) which are activated as a result of ligand binding.

NRTKs can be classified into ten subfamilies according to sequence similarities, primarily within the kinase domains, including ABL, ACK, CSK, FAK, FES, FRK, JAK, SRC, TEC and SYK.



In addition to the kinase domain, NRTKs also have several signaling or protein-protein interaction domains, such as SH2 and PH domains.These include ABL, FES, JAK, ACK, SYK, TEC, FAK, SRC, and CSK family of kinases.

NRTKs contributes to various components of signaling pathways which regulate fundamental cellular functions such as cell differentiation, apoptosis, survival, and proliferation.

Receptors linked to other enzymatic activities

Although the vast majority of enzyme-associated receptors stimulate protein tyrosine phosphorylation, some receptors are associated with other enzymatic activities. These receptors includes protein tyrosine phosphatases, protein –serine /threonine kinases and guanyl cyclases.

Protein tyrosine phosphatase (PTP)

The PTP superfamily of enzymes functions in a coordinated manner with protein tyrosine kinases to control signalling pathways that underlie a broad spectrum of fundamental physiological processes.

The signature motif of PTP contains a catalytic cysteine that is paramount for the catalytic activity of the phosphatases, as it catalyzes the removal of phosphate moiety from the phosphotyrosine substrate.

The PTPs are sub-classified into two major sub-groups based on the enzymes' cellular location; into receptor-like and cytosolic PTPs.

The human genome encodes 21 such receptors-like PTPs.

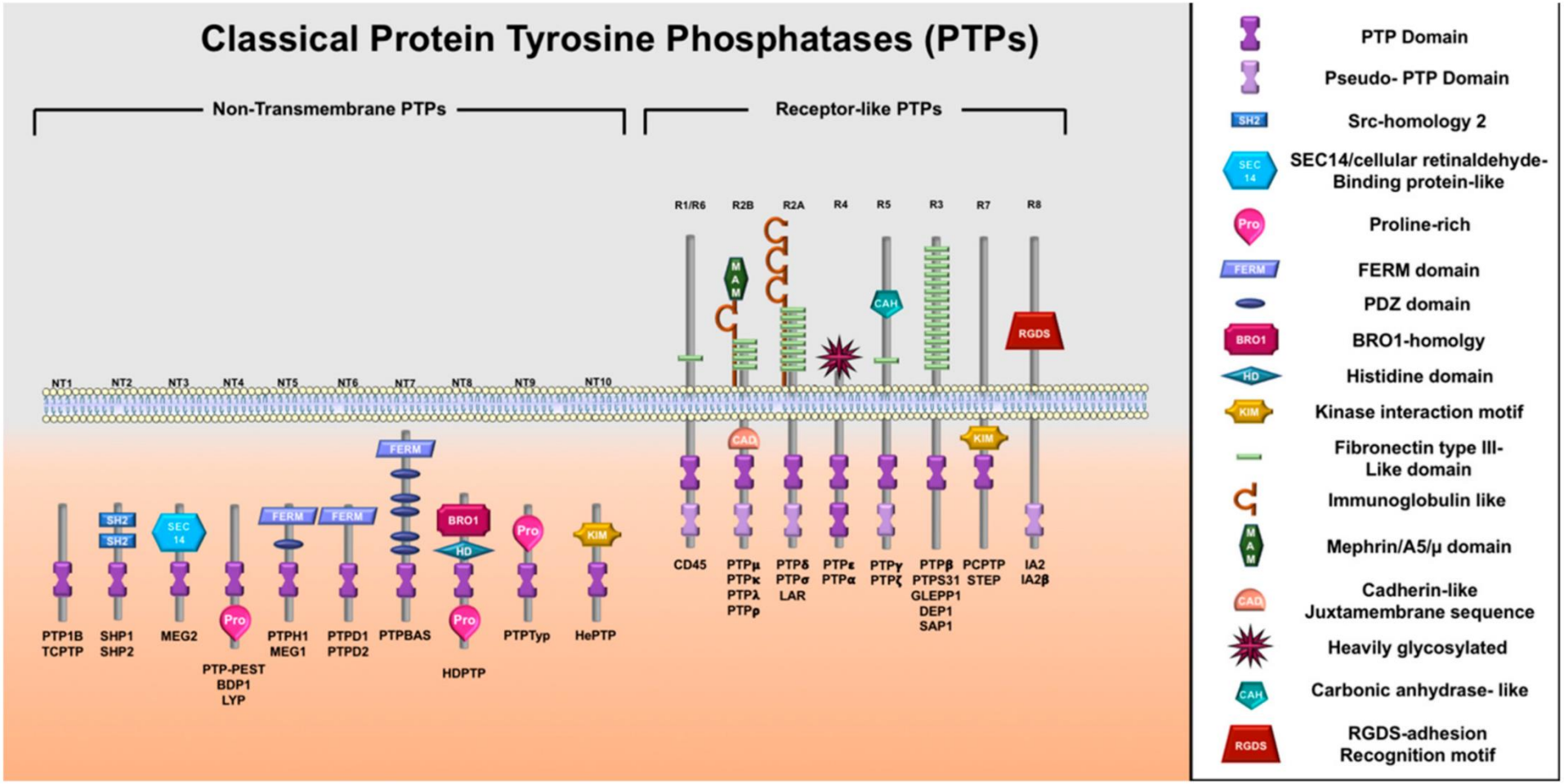


Figure 7: Classical PTPs. The classical PTPs are a large family of tyrosine phosphatases composed of 37 family members that are subdivided based on their cellular localization into 16 non-transmembrane (cytosolic) PTPs and 21 transmembrane receptor-like PTPs. The non-transmembrane phosphatases have one catalytic domain while receptor-like PTPs have either one or two catalytic domains, having the intrinsic catalytic cysteine residue.

Receptor threonine/serine kinases (RTSK)

The receptor threonine/serine kinase (RTSK) family, exemplified by TGF-β and BMP receptors, has intrinsic serine/threonine protein kinase activity in the heterodimeric functional unit.

The TGF-β is prototype of a family of polypeptide growth factors that controls proliferation and differentiation of various cell types.

The binding of ligand to these receptors result in association of two distinct type of polypeptide chains, which are encoded by two different members of TGF-β receptor family, to form heterodimers in which one of the receptor kinases phosphorylates the other.

The activated TGF-β receptors then phosphorylates Smads that continue the signaling downstream.

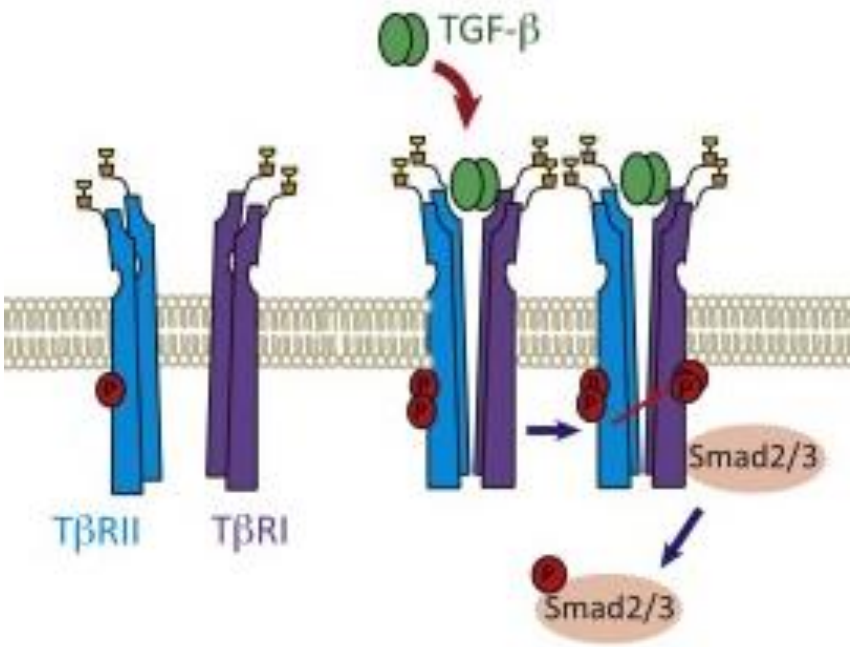


Figure 8: TGF-β family receptors

Receptor Guany cyclases

cGMP controls many cellular functions ranging from growth, viability, and differentiation to contractility, secretion, and ion transport.

The mammalian genome encodes seven guanylyl cyclases, GC-A to GC-G, that are homodimeric transmembrane receptors activated by a diverse range of endogenous ligands.

These enzymes convert guanosine-5'-triphosphate to the intracellular second messenger cyclic guanosine-3',5'-monophosphate (cyclic GMP).

The Nitric oxide and carbon monoxide also acts by stimulating guanyl cyclases but the target of these gases are intracellular enzymes rather than a transmembrane receptors.

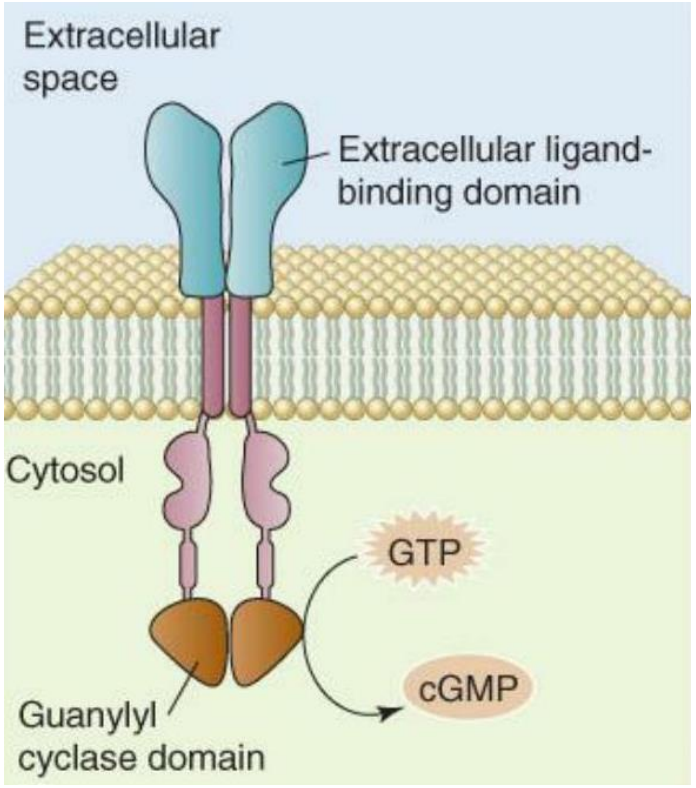
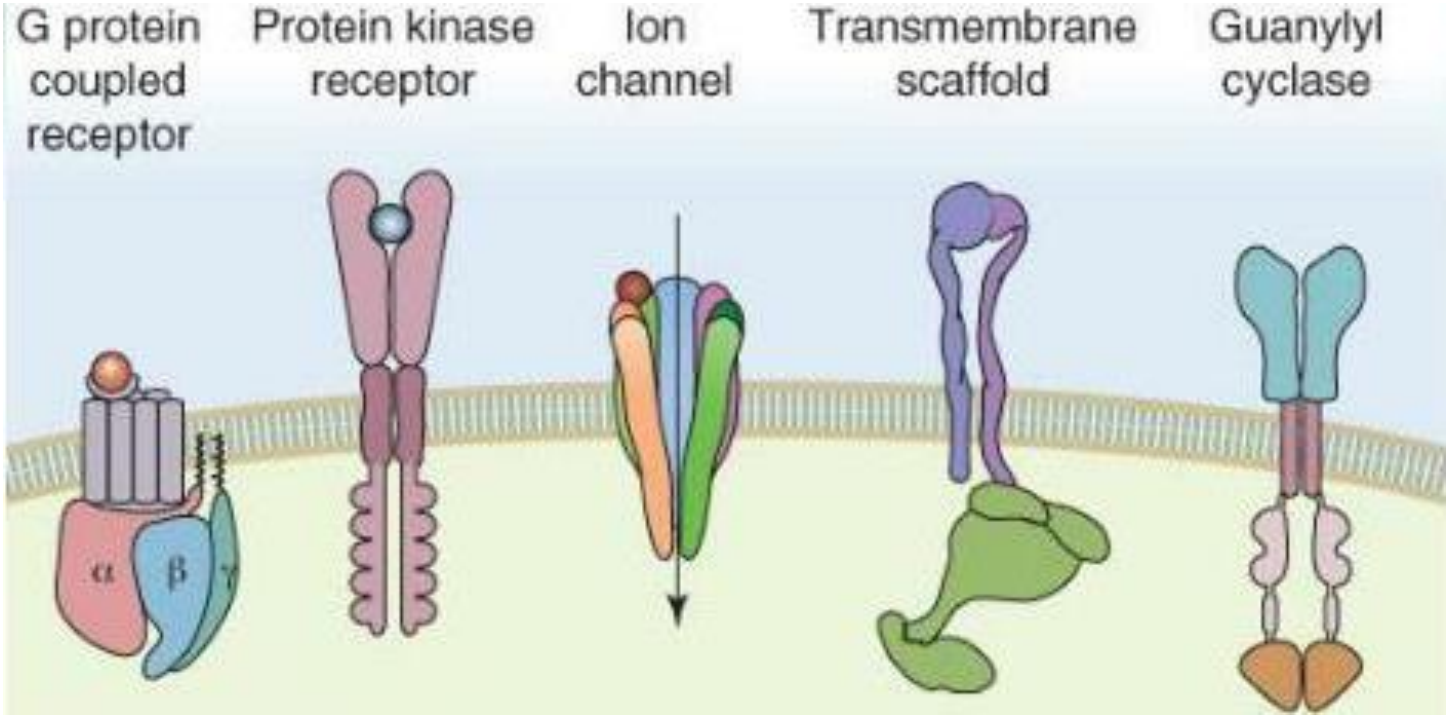


Figure: Receptor Guany cyclases

The receptor guanyl cyclases have an extracellular ligand binding domain, a single transmembrane α-helix, and a cytosolic domain with catalytic activity.

Summary: Various types of cell surface receptors



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