1、What are the 3 major pathways mediated by receptors on the cell surface?

**1) Ion-Channel-Coupled Receptor Pathway**

Ion-channel-coupled receptors belong to a large family of multi-pass transmembrane proteins, primarily involving voltage-gated ion channel receptors and ligand-gated ion channel receptors. This pathway is involved in synaptic signaling between neurons (or neurons and other electrically excitable target cells). Below is a detailed process of synaptic signaling.

An electrical signal passes to the presynaptic nerve terminal, leading to the depolarization of the presynaptic cell. Simultaneously, voltage-gated Ca2+ channels are activated, causing an increase in intracellular Ca2+ concentration. This, in turn, induces the rapid release of neurotransmitters with the assistance of the SNARE complex. Once neurotransmitters are released into the synaptic cleft, they bind to the ligand-gated ion channel receptors on the postsynaptic cell, causing a change in membrane potential and thus relaying the signal.

**2) G Protein-Coupled Receptor (GPCR) Pathway**

GPCRs are the largest family of cell surface receptors that transmit signals from the extracellular environment to the inside of the cell. Most GPCRs have a uniform structure, consisting of a single peptide chain that crosses the membrane seven times. At the C-terminal of the GPCR, there are abundant Ser and Thr residues, which serve as phosphorylation sites allowing for GPCR desensitization. GPCRs can be categorized into two types: stimulating GPCRs and inhibiting GPCRs.

When a ligand binds to the GPCR, it induces a conformational change in the receptor, activating an associated G protein. The activated G protein then initiates a cascade of intracellular events, often leading to the activation of enzymes and ultimately resulting in a cellular response. Various classes of G protein α subunits are involved in different GPCR pathways.

**3) Receptor Tyrosine Kinase (RTK) Pathway**

RTKs constitute the second major type of cell surface receptors, primarily involved in the regulation of cell growth and differentiation. Ligands for RTKs can be classified into seven groups, primarily consisting of growth factors.

RTKs possess a tyrosine kinase domain, conferring intrinsic kinase activity. Upon binding of most ligands to these receptors, they induce the formation of receptor dimers, leading to cross-autophosphorylation on tyrosine residues. The phosphorylated tyrosine residues then function as docking sites for various intracellular signaling proteins, initiating a series of phosphorylation events.

2、How Gq activates the Twin signals (Double messenger system)?

Gq is a subtype of G protein that initiates the IP3-Ca2+ and DAG-PKC pathway, commonly known as the 'double messenger system.' Many GPCRs, including the histamine receptor H1 (HRH1) and acetylcholine receptor, activate the plasma membrane-bound enzyme phospholipase C-β (PLCβ) through Gq.

The process begins with the binding of a signal molecule (ligand) to the GPCR, inducing a conformational change that enables interaction with and activation of the Gq protein. The activated Gq protein subsequently activates PLCβ, which is located on the membrane. Upon activation, PLCβ catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into two second messengers: free inositol trisphosphate (IP3) and membrane-associated diacylglycerol (DAG).

Free IP3 binds to the IP3-gated Ca2+ release channel, located on the surface of the endoplasmic reticulum (ER), leading to the release of Ca2+ in the ER lumen and an elevation in cytosolic Ca2+. The released cytosolic calcium binds to calcium-binding proteins (Calmodulin, CaM), influencing other proteins. Simultaneously, membrane-associated DAG activates protein kinase C (PKC), working in conjunction with calcium released from the ER lumen, resulting in the phosphorylation of Ser and Thr on target proteins.

In summary, Gq activates the twin signals (IP3 and DAG) by activating PLCβ.

3、How a receptor tyrosine kinase is activated and steps in the activation of Ras by RTKs?

**1) Activation of RTKs**

The activity of most RTKs is stimulated by cross-autophosphorylation. Inactive RTKs often separate from each other. Upon binding of a signal protein (ligand) to the RTK, the receptors are induced to form a dimer and undergo cross-autophosphorylation at the tyrosine kinase domain, generating binding sites for signaling proteins. These signaling proteins then relay signals downstream.

An exception is the activation of the EGF receptor. It is not activated by cross-autophosphorylation. EGF binding induces the two inactive receptor monomers to form an asymmetric dimer. This activates the receiver receptor, and the receiver subsequently phosphorylates tyrosine residues in both the receiver and activator receptors to create docking sites.

**2) Steps in the activation of Ras by RTKs**

After RTK activation, a specific adaptor protein with an SH2 domain, called GRB2, binds to the docking sites provided by phosphorylated tyrosine residues. The SH3 domain of GRB2 then recruits the Sos protein (Ras-GEF), a GTP/GDP exchange factor for Ras. A GDP molecule binds to Ras, inhibiting its activity. Thus, when the Sos protein binds to Ras, the GDP is replaced by GTP, activating Ras. The activation of Ras initiates downstream signaling cascades crucial for cell growth and differentiation.

4、What’s difference between PLCβ and PLCγ?

Below is a summary of the differences between PLCβ and PLCγ mentioned in class.

| **Feature** | **PLCβ** | **PLCγ** |
| --- | --- | --- |
| **Cellular Localization** | Mainly on the plasma membrane | Mainly in the cytoplasm |
| **Function** | Mainly involved in GPCR signaling | Mainly involved in RTK signaling |
| **Activation** | Mainly activated by the Gq | Mainly activated by the RTK |

5、Which GPCR responds to light in a rod photoreceptor cell?

Rhodopsin (a photosensitive GPCR) responds to light in a rod photoreceptor cell. A rod photoreceptor cell is a highly specialized cell with four main parts: outer segment, inner segment, cell body, and synaptic region. The outer segment is primarily composed of around 1000 discs, each containing numerous rhodopsins. The phototransduction cascade, triggered by the absorption of light by rhodopsin and the subsequent conversion to metarhodopsin, initiates a series of events resulting in changes in membrane potential and signal transmission within the rod photoreceptor cell.