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Commentary

G Protein-Coupled Receptors: The Molecular Switches of Cellular Signaling

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DESCRIPTION

G Protein-Coupled Receptors (GPCRs) are an integral transmembrane protein family with seven transmembrane domains that are connected to a heterotrimeric G protein. This is the biggest family of membrane proteins and receptors in mammals, with about 800 members. When all animal species are counted, the total number exceeds 5000. Mammalian GPCRs are divided into five broad families: rhodopsin-like, secretin-like, metabotropic glutamate, adhesion, and frizzled/smoothened, with a few GPCR groups, such as vomeronasal receptors, being difficult to define due to poor sequence similarity. Additional eukaryotic classes include Dictyostelium cyclic AMP receptors and fungal mating pheromone receptors.

Signal transduction by a GPCR begins with an inactive G protein that is linked to the receptor; the G protein is a heterotrimer composed of G, G, and G subunits When a ligand is recognized by the GPCR, the receptor's conformation changes to activate the G protein, prompting G to bind a molecule of GTP and dissociate from the other two G-protein subunits. The dissociation exposes subunits' interactions with other molecules. Activated G protein subunits separates from the receptor and trigger the signaling from a variety of downstream effector proteins including phospholipases and ion channels, the latter of which allows the release of second messenger molecules.

The lifetimes of the ligand-receptor complex and receptor-effector protein complex, as well as the deactivation time of the activated receptor and effectors *via* intrinsic enzymatic activity, such as protein kinase phosphorylation or b-arrestin-dependent internalization, determine the total strength of signal amplification by a GPCR. A point mutation was introduced into the gene encoding the chemokine receptor CXCR2; mutant cells experienced malignant transformation due to CXCR2 expression in an active conformation despite the absence of chemokine-binding.

This implied that chemokine receptors might play a role in cancer formation.

The AC family of enzymes produces cyclic AMP (cAMP) from ATP. Gs subunits activate ACs, whereas Gi/o subunits block most isoforms. G dimers have the ability to either adversely or favorably control AC isoforms. cAMP stimulates protein kinase A (PKA), which not only phosphorylates transcription factors such as CREB and AP1 family members, but also affects the activity of other signaling pathways. GPCR activity activates the AC/cAMP and PLC/PKC second messenger pathways. cAMP stimulates RAP-1/B-Raf/ERK pathways directly or via PKA, and may decrease Raf-1 activated ERK activity.

The signal transduction pathways activates by mitogenic GPCR agonists in the early G1 phase of the cell cycle, as outlined in the preceding sections, eventually converge on the control of the levels and activities of the proteins responsible for cell cycle progression. The Rb pocket proteins (pRb, p107, and p130) play an important role in G1/S progression, at least in part, by binding to and inactivating factors that stimulate transcription of genes essential for DNA replication (e.g., E2F). When active (underphosphorylated) pRb is hyperphosphorylated (in mid-late G1) by cyclin/cdk4,6 complexes, it is inactivated and driven to release transcription factors. The cyclin/cdk complexes are then negatively controlled by two families of inhibitors: the p21 family (p21Cip1/Waf1, p27Kip1, and p57Kip2), which interacts with all cyclin/cdks, and the p16 family (INK4), which inhibits the cdk4,6-mediated phosphorylation of pRb. Although it is beyond the scope of this chapter to discuss the literature linking early signal transduction pathways with late events in the cell cycle, it is worth noting that GPCR agonists such as angiotensin II, bombesin, bradykinin, gastrin, PGE2, and TSH induce cyclin expression, p27Kip1 downregulation, and Rb hyperphosphorylation in a variety of cell types.

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