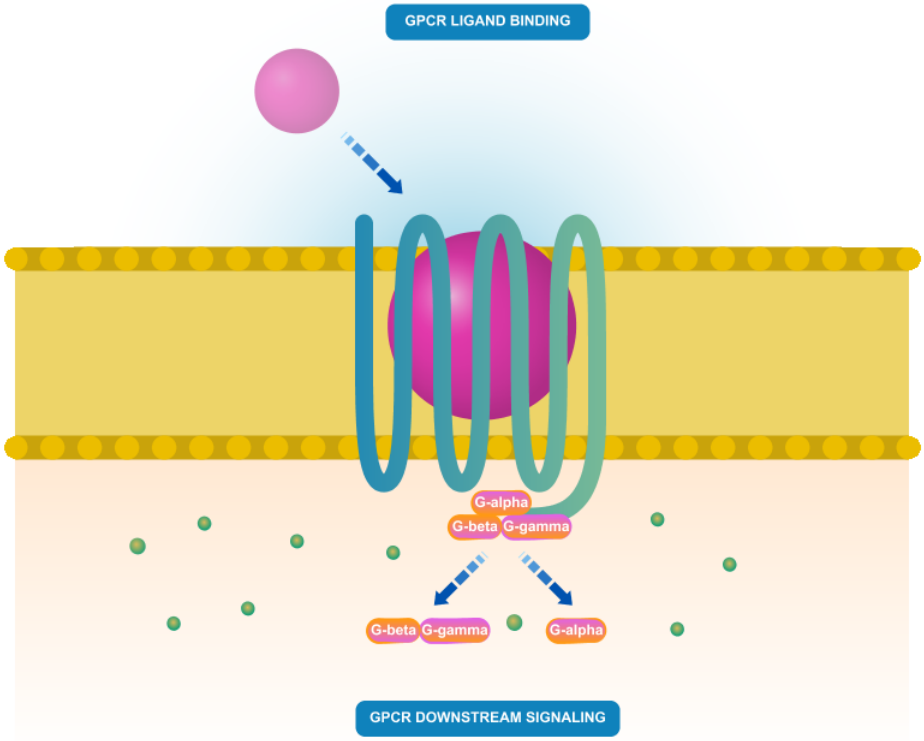
Signaling by GPCR



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

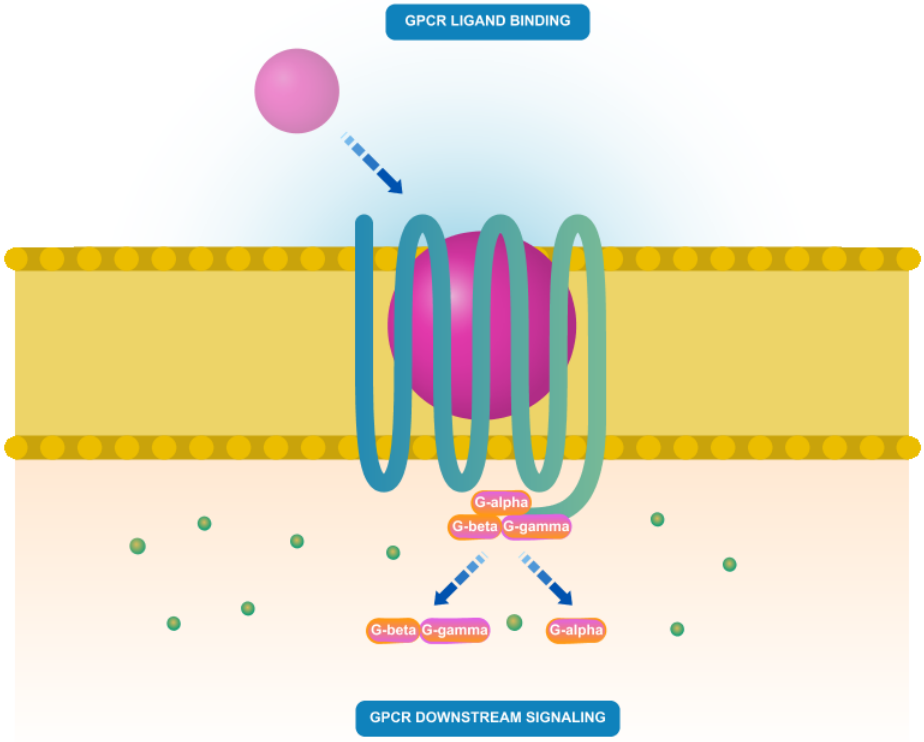
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by GPCR ↗

Stable identifier: R-HSA-372790



G protein-coupled receptors (GPCRs; 7TM receptors; seven transmembrane domain receptors; heptahelical receptors; G protein-linked receptors [GPLR]) are the largest family of transmembrane receptors in humans, accounting for more than 1% of the protein-coding capacity of the human genome. All known GPCRs share a common architecture of seven membrane-spanning helices connected by intra- and extracellular loops. The extracellular loops contain two highly-conserved cysteine residues that form disulphide bonds to stabilize the structure of the receptor. They recognize diverse messengers such as light, odorants, small molecules, hormones and neurotransmitters. Most GPCRs act as guanine nucleotide exchange factors; activated by ligand binding, they promote GDP-GTP exchange on associated heterotrimeric guanine nucleotide-binding (G) proteins. There are two models for GPCR-G Protein interactions: 1) ligand-GPCR binding first, then binding to G Proteins; 2) "Pre-coupling" of GPCRs and G Proteins before ligand binding (review Oldham WM and Hamm HE, 2008). These in turn activate effector enzymes or ion channels. GPCRs are involved in a range of physiological roles which include the visual sense, smell, behavioural regulation, functions of the autonomic nervous system and regulation of the immune system and inflammation.

GPCRs are divided into classes based on sequence homology and functional similarity. The main mammalian classes, in order of size, are the Rhodopsin-like family A, the Secretin receptor family B, and the Metabotropic glutamate/pheromone receptor family C.

Literature references

Oldham, WM., Hamm, HE. (2008). Heterotrimeric G protein activation by G-protein-coupled receptors. *Nat Rev Mol Cell Biol, 9*, 60-71. ↗

Jacoby, E., Bouhelal, R., Gerspacher, M., Seuwen, K. (2006). The 7 TM G-protein-coupled receptor target family. *ChemMedChem, 1*, 761-82. ↗

Bockaert, J., Pin, JP. (1999). Molecular tinkering of G protein-coupled receptors: an evolutionary success. *EMBO J, 18* , 1723-9. ↗

Editions

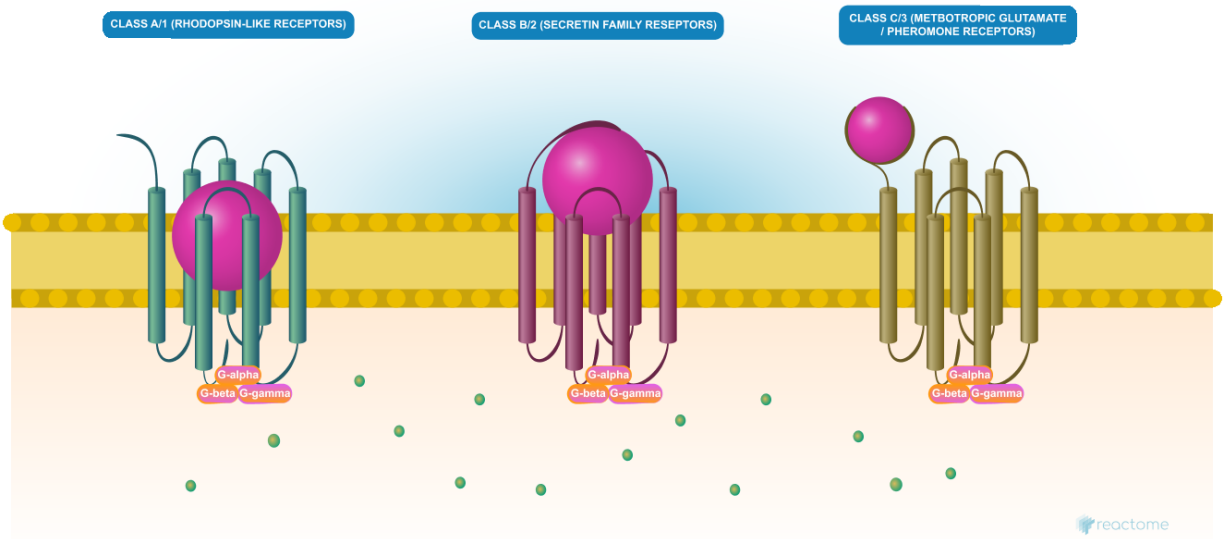
2008-07-02	Authored	Jassal, B.
2008-09-01	Reviewed	Bockaert, J.
2008-09-01	Edited	D'Eustachio, P.

GPCR ligand binding ↗

Location: Signaling by GPCR

Stable identifier: R-HSA-500792

Compartments: plasma membrane



There are more than 800 G-protein coupled receptor (GPCRs) in the human genome, making it the largest receptor superfamily. GPCRs are also the largest class of drug targets, involved in virtually all physiological processes (Frederiksson 2003). GPCRs are receptors for a diverse range of ligands from large proteins to photons (Kristiansen et al. 2004) and have an equal diversity of ligand-binding mechanisms (Gether et al. 2002). Classical GPCR signaling involves signal transduction via heterotrimeric G-proteins, though G-protein independent mechanisms have been reported.

Rhodopsin-like receptors (class A/1) are by far the largest group of GPCRs and the best studied, though a large proportion of the functional and structural studies have focused on a very few members; many remain functionally uncharacterized. This large family can be subdivided into at least 19 subfamilies (Subfamily A1-19) based on phylogenetic analysis (Joost & Methner 2002). Family A includes receptors for a wide variety of ligands including hormones, light and neurotransmitters, encompassing a wide range of functions including many autocrine, paracrine and endocrine processes.

The secretin-like family B/2 GPCRs includes receptors for many hormone-like peptides, such as secretin, calcitonin, parathyroid hormone/parathyroid hormone-related peptides and vasoactive intestinal peptide, which activate adenylyl cyclase and the phosphatidyl-inositol-calcium pathway (Harmar 2001).

The class C/3 GPCRs include the metabotropic glutamate receptors and taste receptors (Brauner-Osborne et al. 2007). All have a large extracellular N-terminus that structurally resembles a clamshell and has an important role in ligand binding.

Literature references

Kristiansen, K. (2004). Molecular mechanisms of ligand binding, signaling, and regulation within the superfamily of G-protein-coupled receptors: molecular modeling and mutagenesis approaches to receptor structure and function. *Pharmacol Ther, 103*, 21-80. ↗

Editions

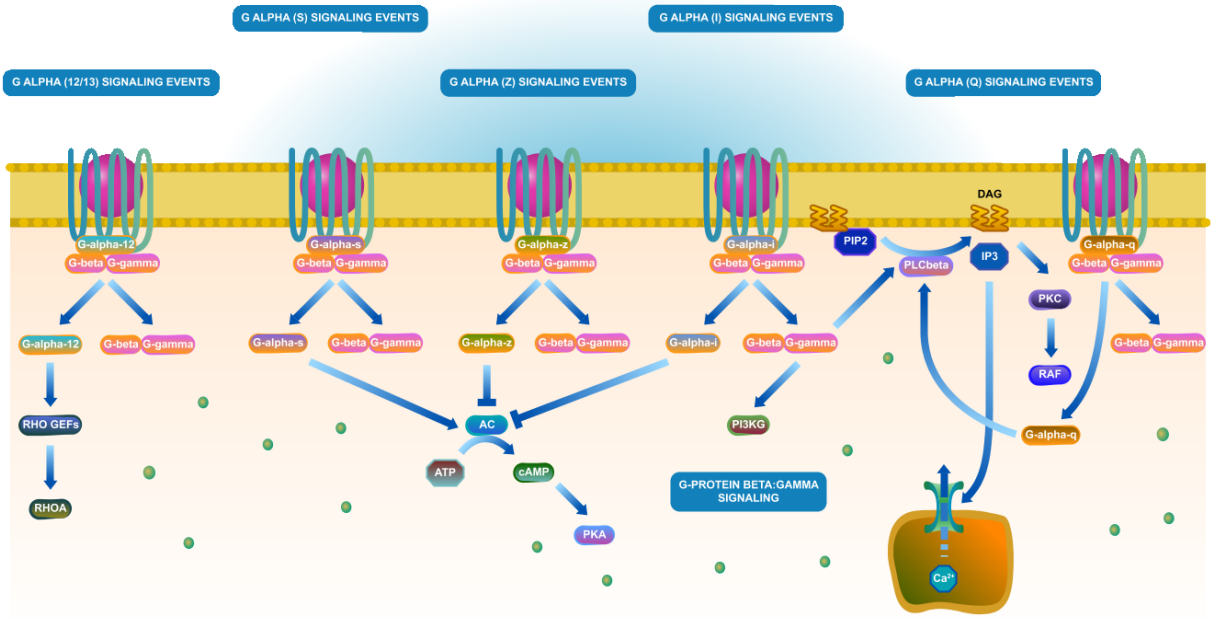
2009-12-11	Reviewed	D'Eustachio, P.
2010-02-05	Authored	Jassal, B.
2010-02-10	Edited	Jupe, S.

GPCR downstream signalling ↗

Location: Signaling by GPCR

Stable identifier: R-HSA-388396

Compartments: plasma membrane



G protein-coupled receptors (GPCRs) are classically defined as the receptor, G-protein and downstream effectors, the alpha subunit of the G-protein being the primary signaling molecule. However, it has become clear that this greatly oversimplifies the complexities of GPCR signaling (Gurevich & Gurevich 2008). The beta:gamma G-protein dimer is also involved in downstream signaling (Smrcka 2008) and some receptors form metastable complexes with accessory proteins such as the arrestins.

GPCRs are involved in many diverse signaling events (Kristiansen 2004), using a variety of pathways that include modulation of adenylyl cyclase, phospholipase C, the mitogen activated protein kinases (MAPKs), extracellular signal regulated kinase (ERK) c-Jun-NH2-terminal kinase (JNK) and p38 MAPK. Regulator of G-protein Signalling (RGS) proteins can directly inhibit the activity of the G-alpha subunit (Soundararajan et al. 2008).

The general function of the G alpha-s subunit (Gs) is to activate adenylate cyclase (Tesmer et al. 1997), which in turn produces cyclic-AMP (cAMP), leading to the activation of cAMP-dependent protein kinases (often referred to collectively as Protein Kinase A). The signal from the ligand-stimulated GPCR is amplified because the receptor can activate several Gs heterotrimers before it is inactivated.

The classical signalling mechanism for G alpha-i (Gi) is inhibition of the cAMP dependent pathway through inhibition of adenylate cyclase (Dessauer et al. 2002). Decreased production of cAMP results in decreased activity of cAMP-dependent protein kinases.

G alpha-z (Gz) is a member of the Gi family. Unlike other Gi family members it is pertussis toxin-insensitive. Gz interacts with Rap1 GTPase activating protein (RAP1GAP) to attenuate Rap1 signaling.

The classic signalling route for G alpha-q (Gq) is activation of phospholipase C beta, leading to phosphoinositide hydrolysis, calcium mobilization and protein kinase C activation. This provides a path to calcium-regulated kinases and phosphatases, GEFs, MAP kinases and many other proteins.

The G-alpha-12/13 (G12/13) family is probably the least well characterized, at least in part because G12/13 coupling is more difficult to determine than for other subtypes, G12/13 is best known for involvement in the processes of cell proliferation and morphology, such as stress fiber and focal adhesion formation. Interactions with Rho guanine nucleotide exchange factors (RhoGEFs) are thought to mediate many of these processes. (Buhl et al.1995, Sugimoto et al. 2003). Activation of Rho or the regulation of events through Rho is often taken as evidence of G12/13 signaling. Receptors that are coupled with G12/13 invariably couple with one or more other G protein subtypes, usually Gq.

Literature references

Neves, SR., Ram, PT., Iyengar, R. (2002). G protein pathways. *Science, 296*, 1636-9. ↗

Editions

2009-03-26	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
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