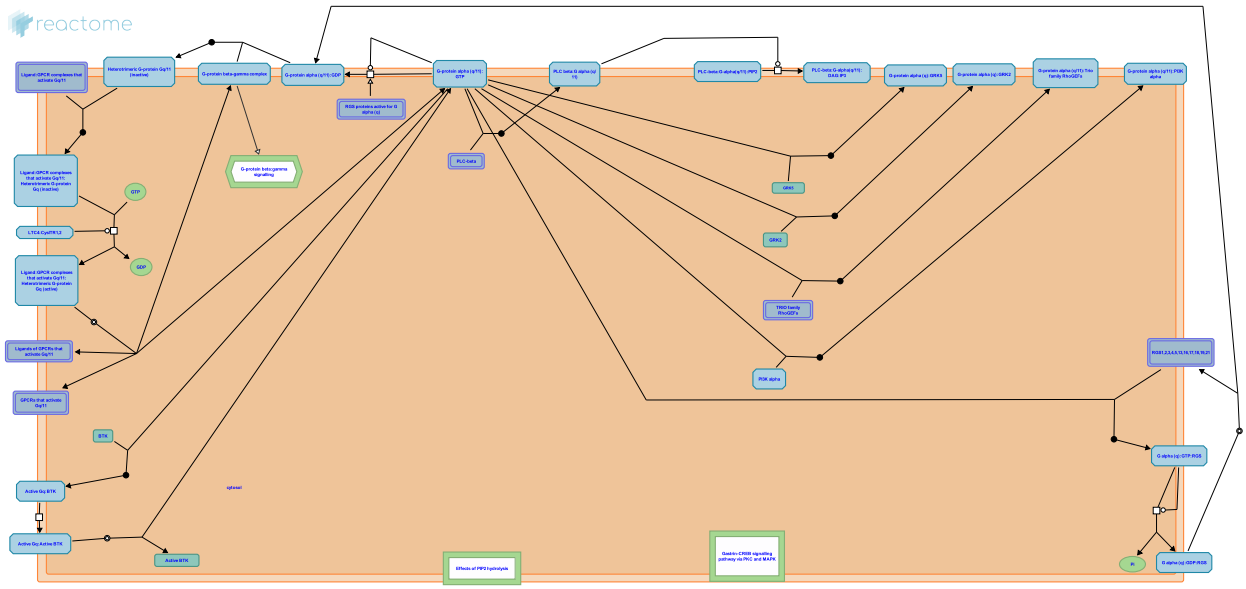
G alpha (q) signalling events



Akkerman, JW., D'Eustachio, P., Huang, X., Jassal, B., Jupe, S., Siderovski, D., Tripathi, S., Varusai, TM.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

20/01/2021

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

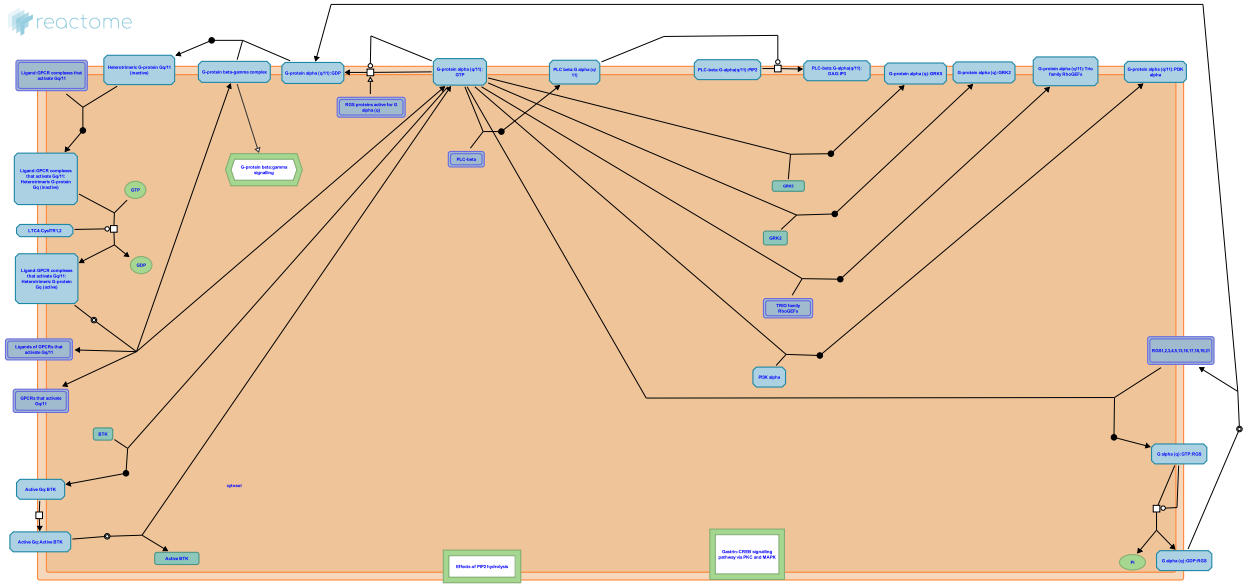
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

G alpha (q) signalling events ↗

Stable identifier: R-HSA-416476

Compartments: plasma membrane



The classic signalling route for G alpha (q) is activation of phospholipase C beta thereby triggering phosphoinositide hydrolysis, calcium mobilization and protein kinase C activation. This provides a path to calcium-regulated kinases and phosphatases, GEFs, MAP kinase cassettes and other proteins that mediate cellular responses ranging from granule secretion, integrin activation, and aggregation in platelets. Gq participates in many other signalling events including direct interaction with RhoGEFs that stimulate RhoA activity and inhibition of PI3K. Both in vitro and in vivo, the G-protein Gq seems to be the predominant mediator of the activation of platelets. Moreover, G alpha (q) can stimulate the activation of Burton tyrosine kinase (Ma Y C et al. 1998). Regulator of G-protein Signalling (RGS) proteins can regulate the activity of G alpha (z) (Soundararajan M et al. 2008).

Literature references

Mizuno, N., Itoh, H. (2009). Functions and regulatory mechanisms of Gq-signaling pathways. *Neurosignals, 17*, 42-54. ↗

Editions

2009-03-09	Authored, Edited	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2017-07-10	Revised	Varusai, TM.

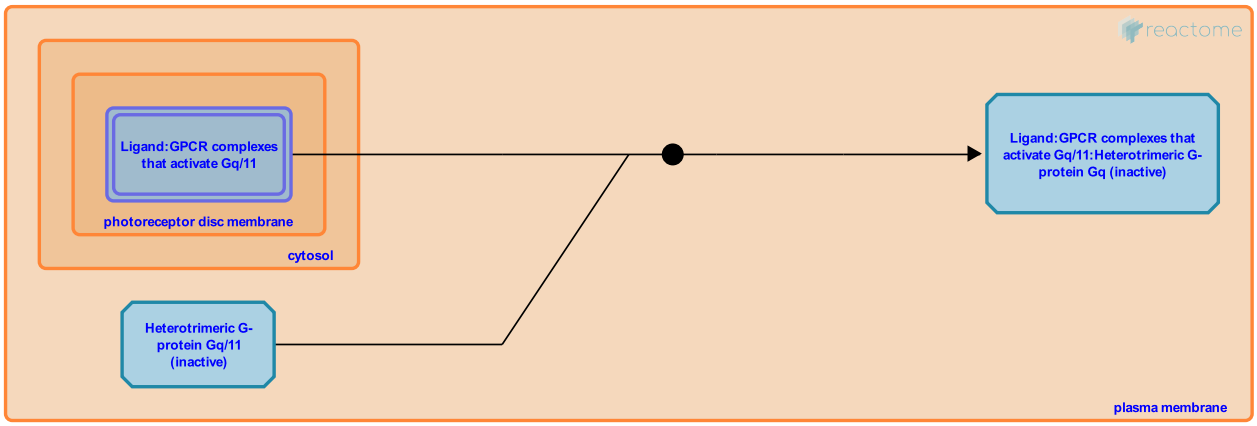
Liganded Gq-activating GPCRs bind inactive heterotrimeric Gq ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-749448

Type: binding

Compartments: plasma membrane



Numerous functionally unrelated GPCRs couple with the Gq G-protein subtype.

Followed by: Liganded Gq/11-activating GPCRs act as GEFs for Gq/11

Literature references

Dowal, L., Provitera, P., Scarlata, S. (2006). Stable association between G alpha(q) and phospholipase C beta 1 in living cells. *J Biol Chem, 281,* 23999-4014. ↗

Editions

2010-05-18	Authored	Jupe, S.
2010-05-22	Reviewed	D'Eustachio, P.
2010-05-26	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

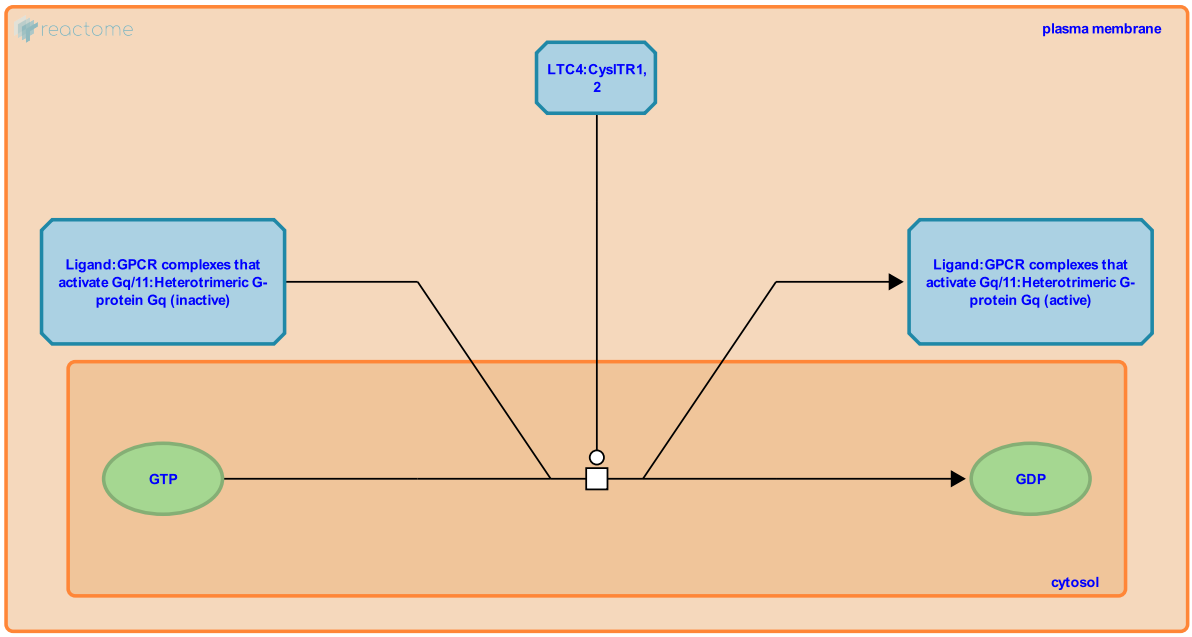
Liganded Gq/11-activating GPCRs act as GEFs for Gq/11 ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-379048

Type: transition

Compartments: cytosol, plasma membrane



G alpha q protein (or Gq/11) consists of four family members (G-alpha 11, -alpha 14, -alpha 15 and -alpha q). It activates phospholipase C (PLC) (Dowal L et al, 2006). PLC hydrolyzes phosphatidylinositol (PIP2) to diacyl glycerol (DAG) and inositol triphosphate (IP3). DAG acts as a second messenger that activates protein kinase C (PKC) and IP3 can bind to IP3 receptors, particular calcium channels in the endoplasmic reticulum (ER). Calcium flow causes the cytosolic concentration of calcium to increase, causing a cascade of intracellular changes and activity.

Preceded by: Liganded Gq-activating GPCRs bind inactive heterotrimeric Gq

Followed by: The Ligand:GPCR:Gq complex dissociates

Literature references

Ferguson, KM., Higashijima, T., Smigel, MD., Gilman, AG. (1986). The influence of bound GDP on the kinetics of guanine nucleotide binding to G proteins. *J Biol Chem, 261*, 7393-9. ↗

Dowal, L., Provitera, P., Scarlata, S. (2006). Stable association between G alpha(q) and phospholipase C beta 1 in living cells. *J Biol Chem, 281*, 23999-4014. ↗

Rubio, JP., Levy, ER., Dobson-Stone, C., Monaco, AP. (1999). Genomic organization of the human galpha14 and Galphaq genes and mutation analysis in chorea-acanthocytosis (CHAC). *Genomics, 57*, 84-93. ↗

Amatruda TT, 3rd., Steele, DA., Slepak, VZ., Simon, MI. (1991). G alpha 16, a G protein alpha subunit specifically expressed in hematopoietic cells. *Proc Natl Acad Sci U S A, 88*, 5587-91. ↗

Chen, B., Leverette, RD., Schwinn, DA., Kwatra, MM. (1996). Human G(alpha q): cDNA and tissue distribution. *Biochim Biophys Acta, 1281*, 125-8. ↗

Editions

2008-11-07	Authored	Jassal, B.
2008-11-29	Reviewed	D'Eustachio, P.
2010-05-26	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

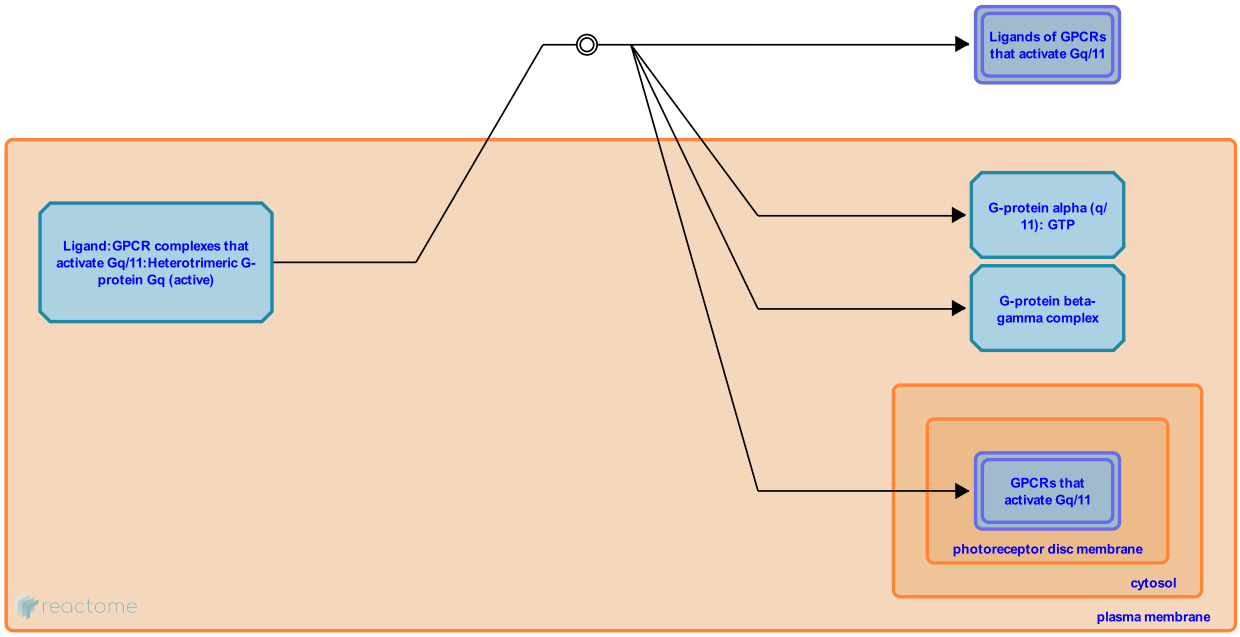
The Ligand:GPCR:Gq complex dissociates ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-749452

Type: dissociation

Compartments: extracellular region, plasma membrane



The classical view of G-protein signalling is that the G-protein alpha subunit dissociates from the beta:gamma dimer. Activated G alpha (q) and the beta:gamma dimer then participate in separate signaling cascades. Although G protein dissociation has been contested (e.g. Bassi et al. 1996), recent in vivo experiments have demonstrated that dissociation does occur, though possibly not to completion (Lambert 2008).

Preceded by: Liganded Gq/11-activating GPCRs act as GEFs for Gq/11

Followed by: Active Gq binds BTK, Active G alpha (q) binds RGS proteins, GRK5 sequesters activated Gq, G alpha (q) auto-inactivates by hydrolysing GTP to GDP, G alpha (q) binds to Trio family RhoGEFs, PLC beta is activated by G alpha (q), GRK2 sequesters activated Gq, G alpha (q) inhibits PI3K alpha

Literature references

Lambert, NA. (2008). Dissociation of heterotrimeric g proteins in cells. *Sci Signal, 1*, re5. ↗

Editions

2010-05-18	Authored	Jupe, S.
2010-05-22	Reviewed	D'Eustachio, P.
2010-05-26	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

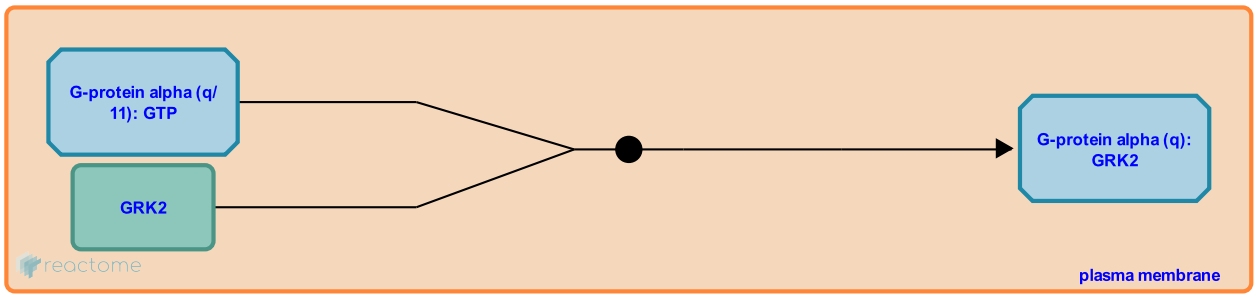
GRK2 sequesters activated Gq ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-416516

Type: binding

Compartments: plasma membrane



GRK2 can inhibit GPCR signaling via phosphorylation-independent sequestration of Gq/11/14 subunits utilising its RGS homology (RH) domain. GRK2 may be an effector of activated Gq, initiating signalling cascades other than the classical PLC beta signalling associated with Gq.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Literature references

Carman, CV., Parent, JL., Day, PW., Pronin, AN., Sternweis, PM., Wedegaertner, PB. et al. (1999). Selective regulation of Galpha(q/11) by an RGS domain in the G protein-coupled receptor kinase, GRK2. *J Biol Chem, 274*, 34483-92 . ↗

Tesmer, VM., Kawano, T., Shankaranarayanan, A., Kozasa, T., Tesmer, JJ. (2005). Snapshot of activated G proteins at the membrane: the Galphaq-GRK2-Gbetagamma complex. *Science, 310*, 1686-90. ↗

Sallese, M., Mariggiò, S., D'Urbano, E., Iacovelli, L., De Blasi, A. (2000). Selective regulation of Gq signaling by G protein-coupled receptor kinase 2: direct interaction of kinase N terminus with activated galphaq. *Mol. Pharmacol., 57*, 826-31. ↗

Editions

2009-03-27	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

GRK5 sequesters activated Gq ↗

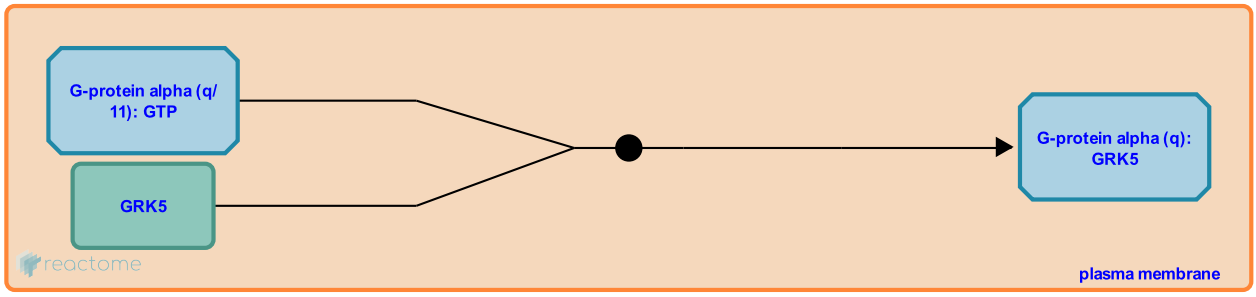
Location: G alpha (q) signalling events

Stable identifier: R-HSA-416510

Type: binding

Compartments: plasma membrane

Inferred from: GRK2 sequesters activated Gq (Homo sapiens)



GRKs are serine/threonine kinases that phosphorylate GPCRs leading to receptor desensitization. GRK5 appears to be the predominant regulator of PAR1 desensitization in endothelial cells.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Literature references

Tiruppathi, C., Yan, W., Sandoval, R., Naqvi, T., Pronin, AN., Benovic, JL. et al. (2000). G protein-coupled receptor kinase-5 regulates thrombin-activated signaling in endothelial cells. *Proc Natl Acad Sci U S A, 97*, 7440-5. ↗

Editions

2009-03-27	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

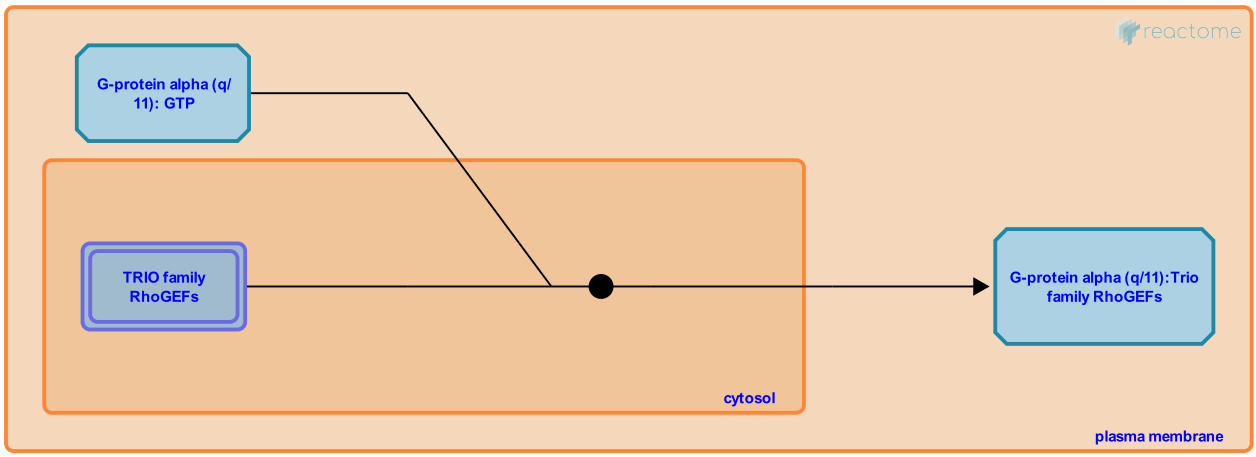
G alpha (q) binds to Trio family RhoGEFs ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-400586

Type: binding

Compartments: cytosol, plasma membrane



The Trio family of RhoA guanine nucleotide exchange factors (RhoGEFs) are directly activated by G alpha (q), possibly within a Gq:Trio:RhoA signalling complex, thereby linking Gq to RhoA-mediated processes such as cell migration, proliferation, and contraction. Like most other RhoGEFs, they have a tandem motif consisting of a Dbl homology (DH) and a pleckstrin homology (PH) domain. Trio and Duet have a number of other domains including an immunoglobin domains that may be involved in interacting with Rho, but the considerably smaller GEFT (p63RhoGEF) does not have any identifiable additional domains yet appears to be sufficient to mediate the activation of RhoA by G alpha (q). The structure represented by GEFT is proposed to represent the core of an ancient signal transduction pathway.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Literature references

Shankaranarayanan, A., Thal, DM., Tesmer, VM., Roman, DL., Neubig, RR., Kozasa, T. et al. (2008). Assembly of high order G alpha q-effector complexes with RGS proteins. *J Biol Chem, 283*, 34923-34. ↗

Editions

2009-03-24	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

PLC beta is activated by G alpha (q) ↗

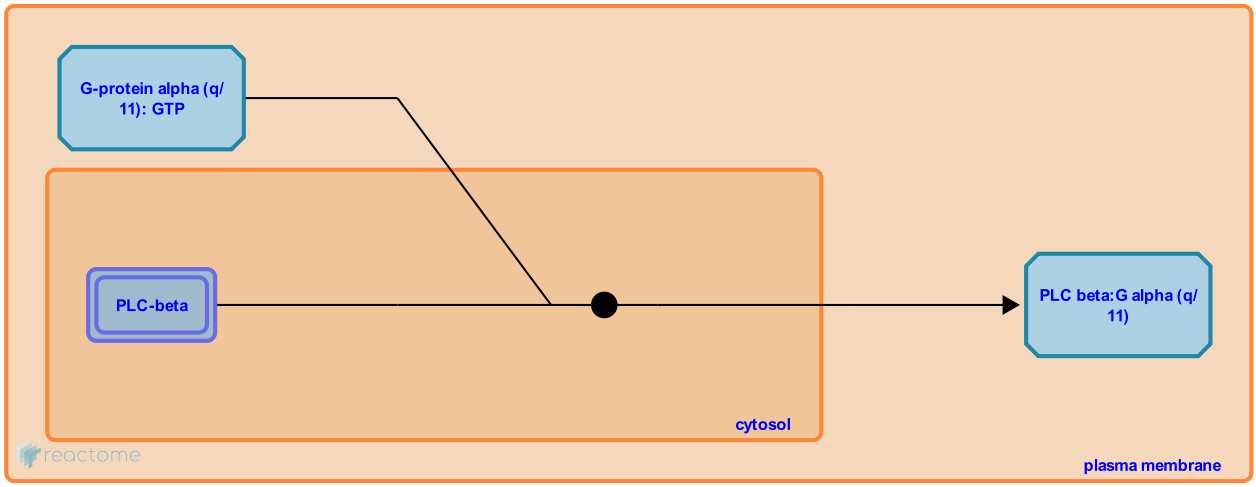
Location: G alpha (q) signalling events

Stable identifier: R-HSA-398188

Type: binding

Compartments: cytosol, plasma membrane

Inferred from: Activation of PLC beta-1 (Bos taurus)



The active form of G protein alpha subunit q (Gq-alpha) was found to activate phospholipase C beta-1 (PLC-beta1), in investigations using bovine membranes. Subsequently, all 4 human isoforms have been shown to be activated by Gq, though activation of PLCbeta-4 is limited. In recombinant assays, several activated rat G alpha q family members were found to stimulate human PLC-beta isoforms with the same rank order of decreasing potency. PLC-beta1 stimulation was slightly more than for PLC-beta3; PLC-beta3 stimulation was 10-fold greater than for beta-2. PLC-beta2 is expressed specifically in hematopoietic cells. PLC-beta acts directly on Gq to accelerate hydrolysis of bound GTP, thus PLC-betas are GTPase activating proteins (GAPs). The crystal structure of the C-terminal region from Turkey PLC-beta, revealed a novel fold composed almost entirely of three long helices forming a coiled-coil that dimerizes along its long axis in an antiparallel orientation. The extent of the dimer interface and gel exclusion chromatography data suggest that PLC-betas are functionally dimeric.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Literature references

Singer, AU., Waldo, GL., Harden, TK., Sondek, J. (2002). A unique fold of phospholipase C-beta mediates dimerization and interaction with G alpha q. *Nat Struct Biol, 9*, 32-6. ↗

Hubbard, KB., Hepler, JR. (2006). Cell signalling diversity of the Gqalpha family of heterotrimeric G proteins. *Cell Signal, 18*, 135-50. ↗

Editions

2009-06-03	Reviewed	Akkerman, JW.
2009-06-03	Authored	Jupe, S.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

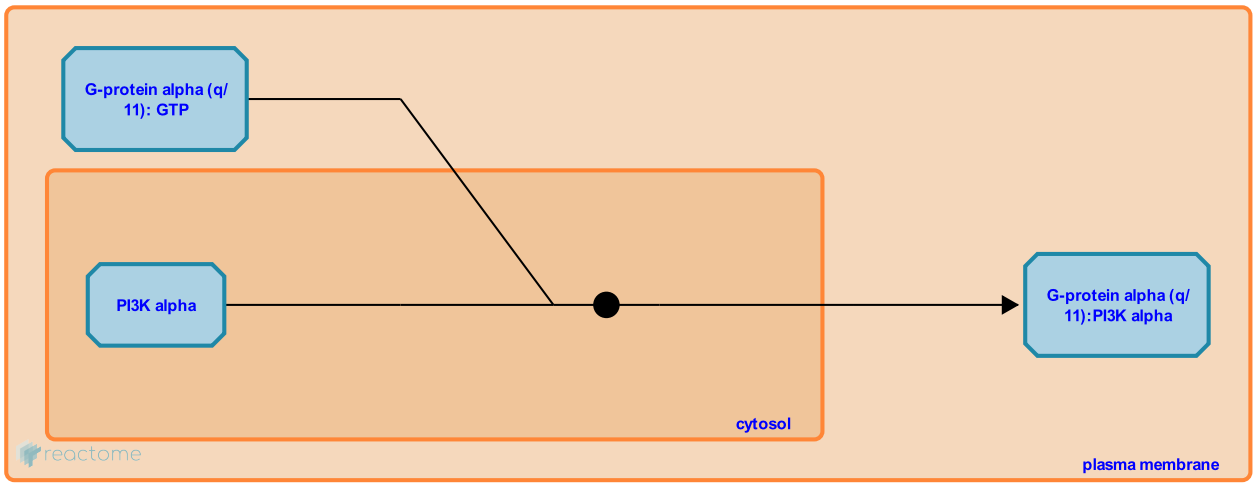
G alpha (q) inhibits PI3K alpha ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-416358

Type: binding

Compartments: cytosol, plasma membrane



Phospholipase C activation is the classical signalling route for G alpha (q) but an additional mechanism is an inhibitory interaction between G alpha (q) and phosphatidylinositol 3-kinase alpha (PI3K alpha). There are several PI3K subtypes but only the p85 alpha/p110 alpha subtype (PI3K alpha) is a G alpha (q) effector (PMID: 18515384). Activated G alpha (q) inhibits PI3K alpha directly, in a GTP-dependent manner. G alpha(q) binding of PI3K competes with Ras, a PI3K activator (PMID: 16268778).

Preceded by: The Ligand:GPCR:Gq complex dissociates

Literature references

Golebiewska, U., Scarlata, S. (2008). Galphaq binds two effectors separately in cells: evidence for predetermined signaling pathways. *Biophys J, 95*, 2575-82. ↗

Ballou, LM., Chattopadhyay, M., Li, Y., Scarlata, S., Lin, RZ. (2006). Galphaq binds to p110alpha/p85alpha phosphoinositide 3-kinase and displaces Ras. *Biochem J, 394*, 557-62. ↗

Editions

2009-03-26	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

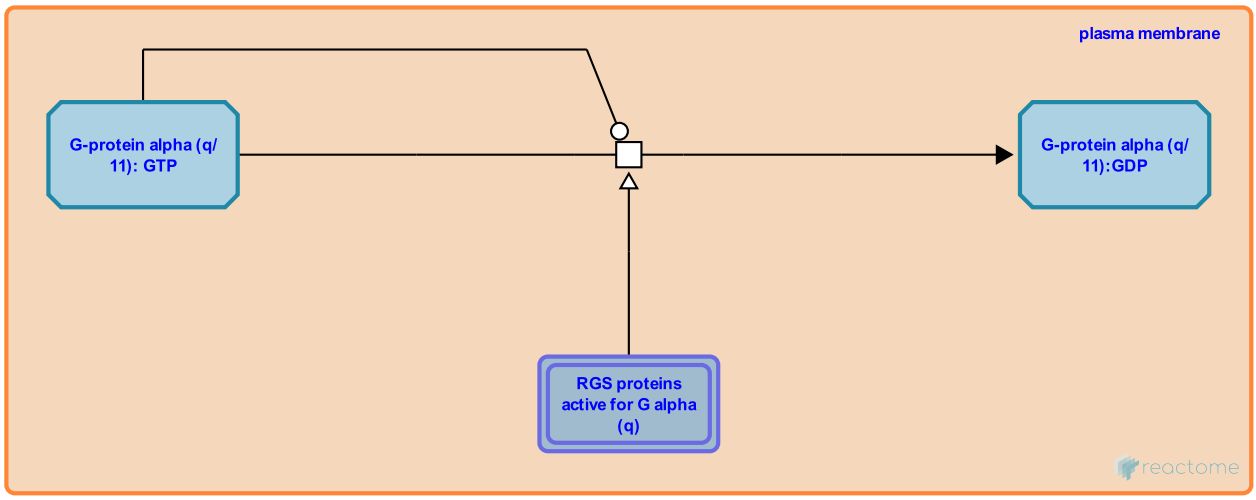
G alpha (q) auto-inactivates by hydrolysing GTP to GDP ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-418582

Type: transition

Compartments: plasma membrane



When a ligand activates a G protein-coupled receptor, it induces a conformational change in the receptor (a change in shape) that allows the receptor to function as a guanine nucleotide exchange factor (GEF), stimulating the exchange of GDP for GTP on the G alpha subunit. In the traditional view of heterotrimeric protein activation, this exchange triggers the dissociation of the now active G alpha subunit from the beta:gamma dimer, initiating downstream signalling events. The G alpha subunit has intrinsic GTPase activity and will eventually hydrolyze the attached GTP to GDP, allowing reassociation with G beta:gamma. Additional GTPase-activating proteins (GAPs) stimulate the GTPase activity of G alpha, leading to more rapid termination of the transduced signal. In some cases the downstream effector may have GAP activity, helping to deactivate the pathway. This is the case for phospholipase C beta, which possesses GAP activity within its C-terminal region (Kleuss et al. 1994).

Preceded by: The Ligand:GPCR:Gq complex dissociates

Followed by: Inactive G alpha (q) reassociates with G beta:gamma

Literature references

Kleuss, C., Raw, AS., Lee, E., Sprang, SR., Gilman, AG. (1994). Mechanism of GTP hydrolysis by G-protein alpha subunits. *Proc Natl Acad Sci U S A, 91*, 9828-31. ↗

Editions

2009-04-24	Authored	Jupe, S.
2009-06-03	Reviewed	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

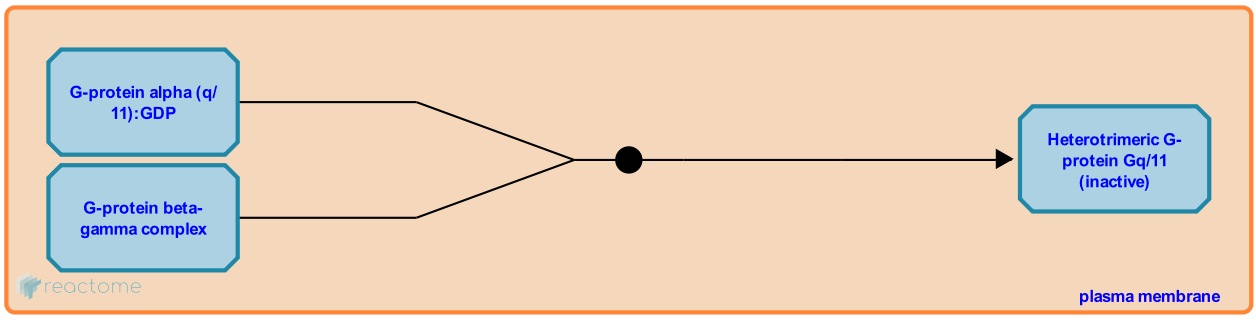
Inactive G alpha (q) reassociates with G beta:gamma ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-750993

Type: binding

Compartments: plasma membrane



The classical model of G-protein signaling suggests that the G-protein dissociates upon GPCR activation. The active G alpha (q) subunit then participates in signaling, until its intrinsic GTPase activity degrades the bound GTP to GDP. The inactive G alpha (q):GDP complex has much higher affinity for the G beta:gamma complex and consequently reassociates.

Preceded by: G alpha (q) auto-inactivates by hydrolysing GTP to GDP

Literature references

Oldham, WM., Hamm, HE. (2006). Structural basis of function in heterotrimeric G proteins. *Q Rev Biophys, 39*, 117-66 . ↗

Siderovski, DP., Willard, FS. (2005). The GAPs, GEFs, and GDIs of heterotrimeric G-protein alpha subunits. *Int J Biol Sci, 1*, 51-66. ↗

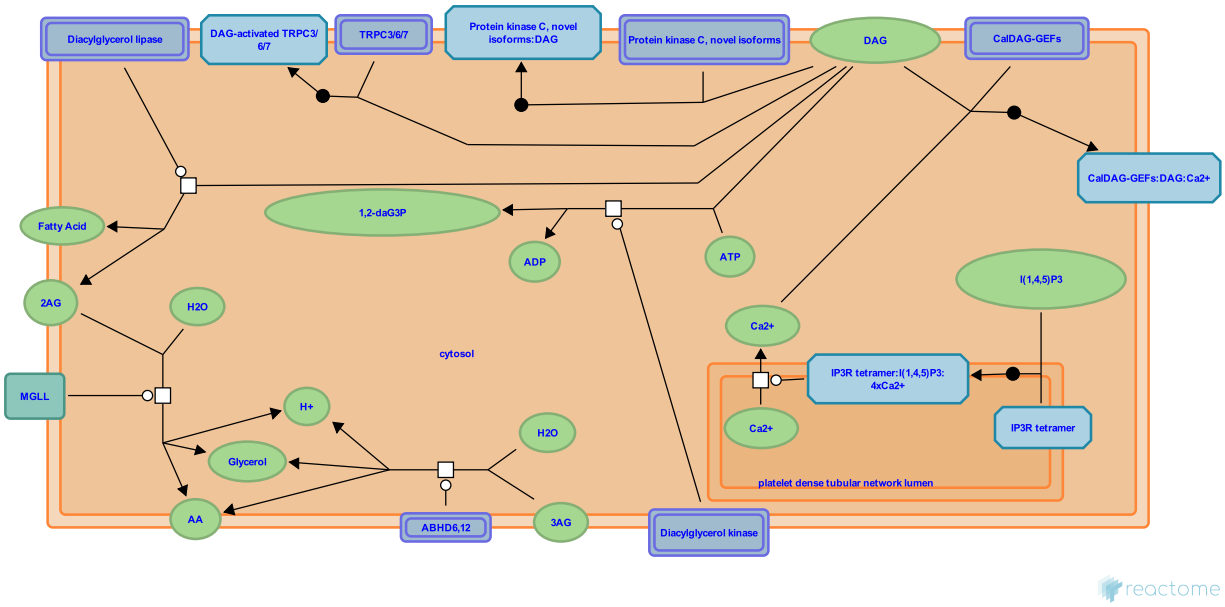
Editions

2010-05-18	Authored	Jupe, S.
2010-05-22	Reviewed	D'Eustachio, P.
2010-05-26	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

Effects of PIP2 hydrolysis ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-114508



Hydrolysis of phosphatidyl inositol-bisphosphate (PIP2) by phospholipase C (PLC) produces diacylglycerol (DAG) and inositol triphosphate (IP3). Both are potent second messengers. IP3 diffuses into the cytosol, but as DAG is a hydrophobic lipid it remains within the plasma membrane. IP3 stimulates the release of calcium ions from the smooth endoplasmic reticulum, while DAG activates the conventional and unconventional protein kinase C (PKC) isoforms, facilitating the translocation of PKC from the cytosol to the plasma membrane. The effects of DAG are mimicked by tumor-promoting phorbol esters. DAG is also a precursor for the biosynthesis of prostaglandins, the endocannabinoid 2-arachidonoylglycerol and an activator of a subfamily of TRP-C (Transient Receptor Potential Canonical) cation channels 3, 6, and 7.

Literature references

Carrasco, S., Mérida, I. (2007). Diacylglycerol, when simplicity becomes complex. *Trends Biochem Sci, 32*, 27-36. ↗

Mellor, H., Parker, PJ. (1998). The extended protein kinase C superfamily. *Biochem J, 332*, 281-92. ↗

Editions

2009-09-09	Edited	Jupe, S.

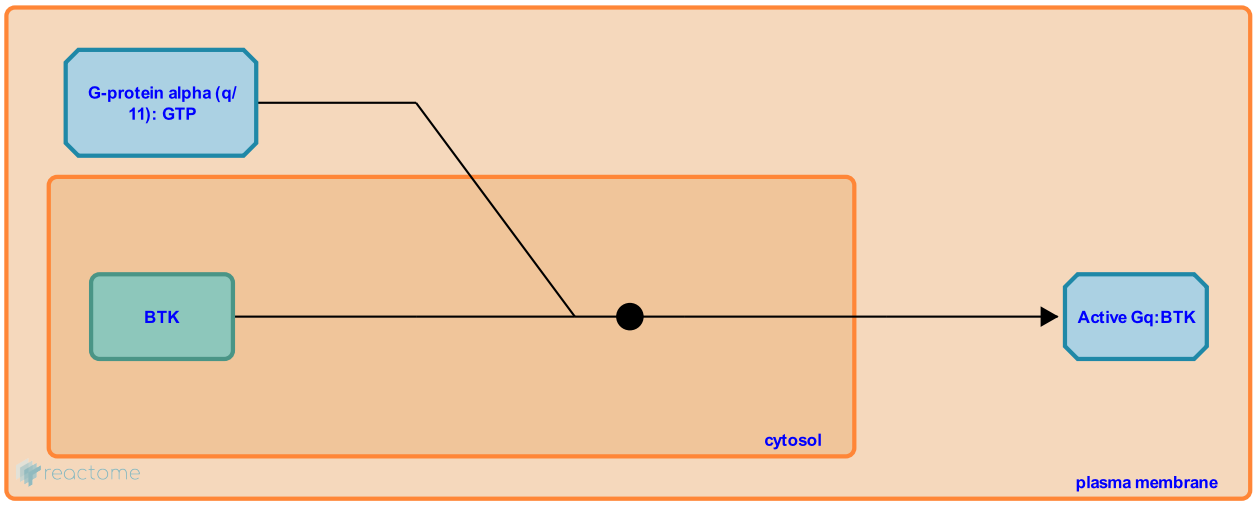
Active Gq binds BTK ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8964280

Type: binding

Compartments: cytosol, plasma membrane



G-Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins. Upon activation, the Guanine nucleotide-binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15) can bind directly to the THSH3 domain of the non-receptor Tyrosine-protein kinase BTK in vitro and in vivo. This binding results in a conformational change in BTK, which leads to its activation. Physiologically, BTK plays a key role in B lymphocyte development, differentiation and signalling.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Followed by: BTK in active Gq-BTK complex is activated

Literature references

Bence, K., Ma, W., Kozasa, T., Huang, XY. (1997). Direct stimulation of Bruton's tyrosine kinase by G(q)-protein alpha-subunit. *Nature, 389*, 296-9. ↗

Ma, YC., Huang, XY. (1998). Identification of the binding site for Gqalpha on its effector Bruton's tyrosine kinase. *Proc. Natl. Acad. Sci. U.S.A., 95*, 12197-201. ↗

Laederach, A., Cradic, KW., Brazin, KN., Zamoon, J., Fulton, DB., Huang, XY. et al. (2002). Competing modes of self-association in the regulatory domains of Bruton's tyrosine kinase: intramolecular contact versus asymmetric homodimerization. *Protein Sci., 11*, 36-45. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-13	Reviewed	Huang, X.

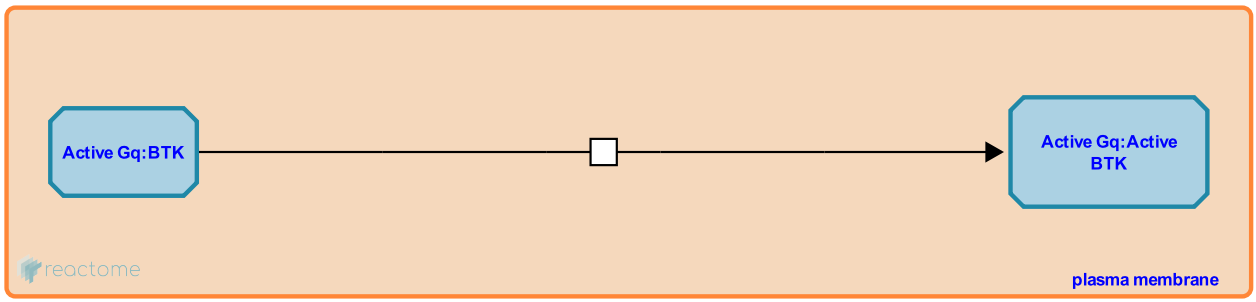
BTK in active Gq-BTK complex is activated ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8964284

Type: transition

Compartments: plasma membrane



G-Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins. Upon activation, the Guanine nucleotide-binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15) can bind directly to the non-receptor Tyrosine-protein kinase BTK. This binding breaks intramolecular interactions in BTK thereby making the kinase domain available for substrates. Physiologically, BTK plays a key role in B lymphocyte development, differentiation and signalling.

Preceded by: Active Gq binds BTK

Followed by: Gq-BTK complex dissociates to Active BTK and Gq

Literature references

Bence, K., Ma, W., Kozasa, T., Huang, XY. (1997). Direct stimulation of Bruton's tyrosine kinase by G(q)-protein alpha-subunit. *Nature, 389*, 296-9. ↗

Ma, YC., Huang, XY. (1998). Identification of the binding site for Gqalpha on its effector Bruton's tyrosine kinase. *Proc. Natl. Acad. Sci. U.S.A., 95*, 12197-201. ↗

Laederach, A., Cradic, KW., Brazin, KN., Zamoon, J., Fulton, DB., Huang, XY. et al. (2002). Competing modes of self-association in the regulatory domains of Bruton's tyrosine kinase: intramolecular contact versus asymmetric homodimerization. *Protein Sci., 11*, 36-45. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-13	Reviewed	Huang, X.

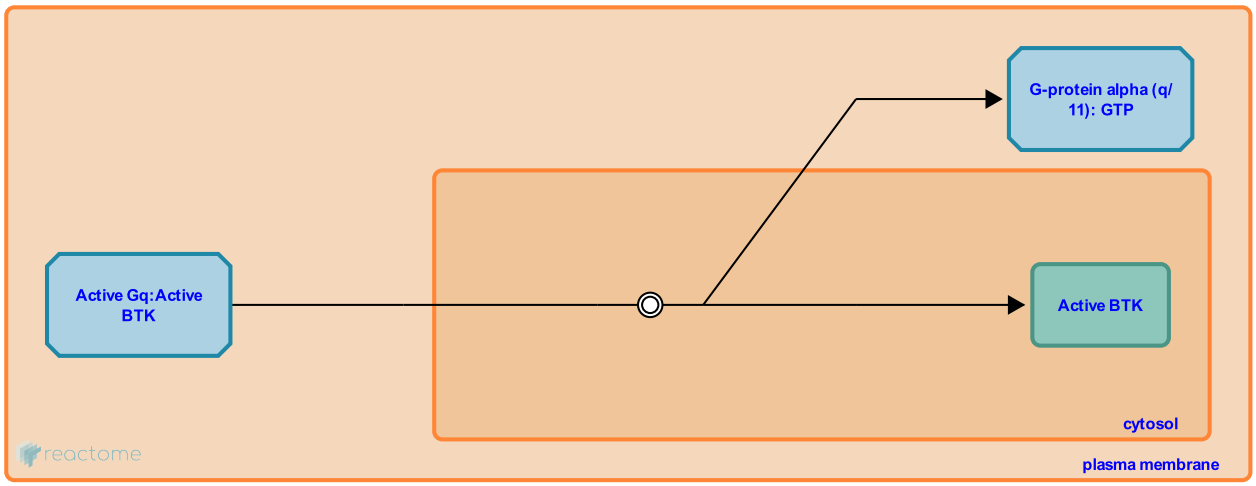
Gq-BTK complex dissociates to Active BTK and Gq ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8964340

Type: dissociation

Compartments: cytosol



G-Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins. Upon activation, the Guanine nucleotide-binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15) can bind to the non-receptor Tyrosine-protein kinase BTK. This binding results in a conformational change in BTK. Subsequently, the structurally modified BTK is released from GNAQ and is now catalytically active. Active BTK can trigger the downstream MAPK p38 pathway. Physiologically, BTK plays a key role in B lymphocyte development, differentiation and signalling.

Preceded by: BTK in active Gq-BTK complex is activated

Literature references

Bence, K., Ma, W., Kozasa, T., Huang, XY. (1997). Direct stimulation of Bruton's tyrosine kinase by G(q)-protein alpha-subunit. *Nature, 389*, 296-9. ↗

Ma, YC., Huang, XY. (1998). Identification of the binding site for Gqalpha on its effector Bruton's tyrosine kinase. *Proc. Natl. Acad. Sci. U.S.A., 95*, 12197-201. ↗

Laederach, A., Cradic, KW., Brazin, KN., Zamoon, J., Fulton, DB., Huang, XY. et al. (2002). Competing modes of self-association in the regulatory domains of Bruton's tyrosine kinase: intramolecular contact versus asymmetric homodimerization. *Protein Sci., 11*, 36-45. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-13	Reviewed	Huang, X.

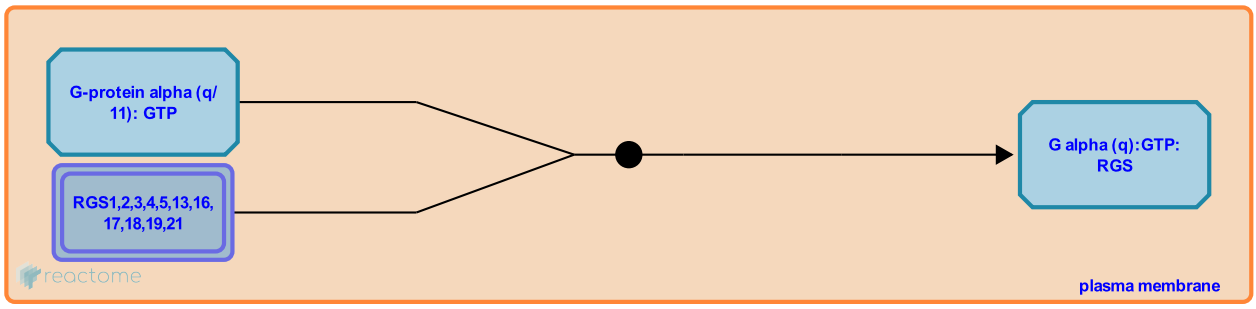
Active G alpha (q) binds RGS proteins ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8982017

Type: binding

Compartments: plasma membrane, cytosol



G Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins (G proteins). Upon activation, GPCRs can replace the GDP with GTP in the alpha subunit of G proteins. GTP binding modifies the conformation of G alpha proteins and activates them. The Regulator of G protein Signalling (RGS) are GTPase Accelerating Proteins (GAPs) that can directly inhibit the G alpha subunit activity. There are at least 25 different types of RGS proteins known. Several of these RGS proteins (1, 2, 3, 4, 5, 8, 13, 16, 17, 18, 19, 21) can bind and stabilize the transition state for GTP hydrolysis of Guanine nucleotide binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15). Subsequently, this leads to GTP hydrolysis and inactivation of G alpha (q) and terminating downstream signalling (Neubig RR and Siderovski DP et al. 2002, Kach J et al., 2012). The primary function of G alpha (q) is activation of phospholipase C beta thereby triggering phosphoinositide hydrolysis, calcium mobilization and protein kinase C activation.

Preceded by: The Ligand:GPCR:Gq complex dissociates

Followed by: G alpha (q) in G (q):RGS complex is inactivated

Literature references

Soundararajan, M., Willard, FS., Kimple, AJ., Turnbull, AP., Ball, LJ., Schoch, GA. et al. (2008). Structural diversity in the RGS domain and its interaction with heterotrimeric G protein alpha-subunits. *Proc. Natl. Acad. Sci. U.S.A., 105* , 6457-62. ↗

Neubig, RR., Siderovski, DP. (2002). Regulators of G-protein signalling as new central nervous system drug targets. *Nat Rev Drug Discov, 1*, 187-97. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-03	Reviewed	Siderovski, D.

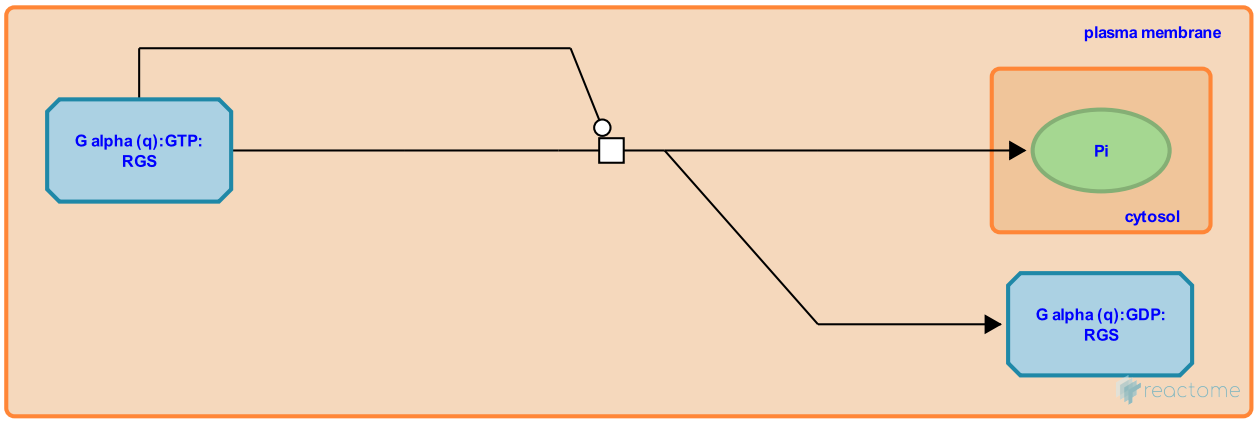
G alpha (q) in G (q):RGS complex is inactivated ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8982025

Type: transition

Compartments: plasma membrane, cytosol



G Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins (G proteins). Upon activation, GPCRs can replace the GDP with GTP in the alpha subunit of G proteins. GTP binding modifies the conformation of G alpha proteins and activates them. The Regulator of G protein Signalling (RGS) are GTPase Accelerating Proteins (GAPs) that can directly inhibit the G alpha subunit activity. There are at least 25 different types of RGS proteins known. Several of these RGS proteins (1, 2, 3, 4, 5, 8, 13, 16, 17, 18, 19, 21) can bind and stabilize the transition state of Guanine nucleotide binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15). Following this, the RGS domain of the proteins exert GAP activity on G alpha (q) and allosterically modulate residues within G-alpha subunit to accelerate the intrinsic GTPase activity that hydrolyses GTP to GDP. This inactivates G alpha (q) and terminates downstream signalling (Neubig & Siderovski 2002, Kach et al. 2012). The primary function of G alpha (q) is activation of phospholipase C beta thereby triggering phosphoinositide hydrolysis, calcium mobilization and protein kinase C activation.

Preceded by: Active G alpha (q) binds RGS proteins

Followed by: G alpha (q):RGS dissociates to inactive G alpha (q)

Literature references

Soundararajan, M., Willard, FS., Kimple, AJ., Turnbull, AP., Ball, LJ., Schoch, GA. et al. (2008). Structural diversity in the RGS domain and its interaction with heterotrimeric G protein alpha-subunits. *Proc. Natl. Acad. Sci. U.S.A., 105* , 6457-62. ↗

Neubig, RR., Siderovski, DP. (2002). Regulators of G-protein signalling as new central nervous system drug targets. *Nat Rev Drug Discov, 1*, 187-97. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-03	Reviewed	Siderovski, D.

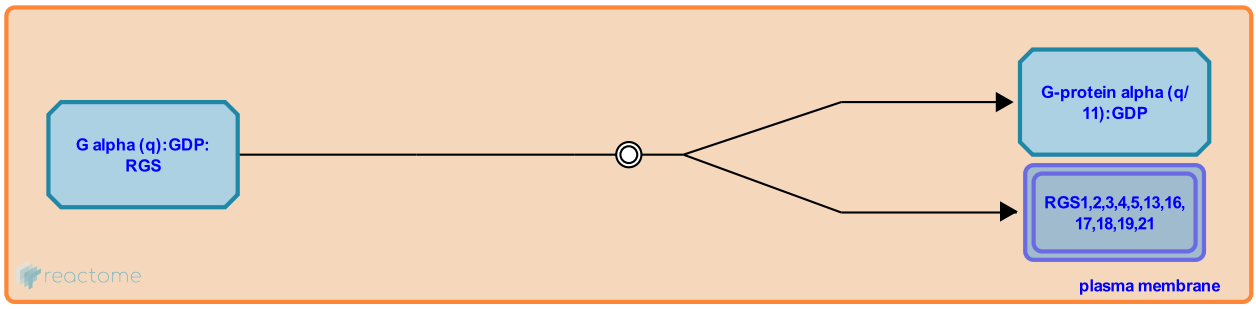
G alpha (q):RGS dissociates to inactive G alpha (q) ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-8982026

Type: dissociation

Compartments: plasma membrane



G Protein Coupled Receptors (GPCR) sense extracellular signals and activate different Guanine nucleotide binding proteins (G proteins). Upon activation, GPCRs can replace the GDP with GTP in the alpha subunit of G proteins. GTP binding modifies the conformation of G alpha proteins and activates them. The Regulator of G protein Signalling (RGS) are GTPase Accelerating Proteins (GAPs) that can directly inhibit the G alpha subunit activity. There are at least 25 different types of RGS proteins known. Several of these RGS proteins (1, 2, 3, 4, 5, 8, 13, 16, 17, 18, 19, 21) can bind and stabilize the transition state of Guanine nucleotide binding protein G(q) subunit alpha class (GNAQ/GNA11/GNA14/GNA15). Subsequently, the RGS domain in the complex facilitates the hydrolyses of G alpha (q):GTP to G alpha (q):GDP. Following this, the complex dissociates releasing inactive G alpha (q) (Neubig & Siderovski 2002, Kach et al. 2012). The primary function of G alpha (q) is activation of phospholipase C beta thereby triggering phosphoinositide hydrolysis, calcium mobilization and protein kinase C activation.

Preceded by: G alpha (q) in G (q):RGS complex is inactivated

Literature references

Soundararajan, M., Willard, FS., Kimple, AJ., Turnbull, AP., Ball, LJ., Schoch, GA. et al. (2008). Structural diversity in the RGS domain and its interaction with heterotrimeric G protein alpha-subunits. *Proc. Natl. Acad. Sci. U.S.A., 105* , 6457-62. ↗

Neubig, RR., Siderovski, DP. (2002). Regulators of G-protein signalling as new central nervous system drug targets. *Nat Rev Drug Discov, 1*, 187-97. ↗

Editions

2017-07-27	Authored, Edited	Varusai, TM.
2018-09-03	Reviewed	Siderovski, D.

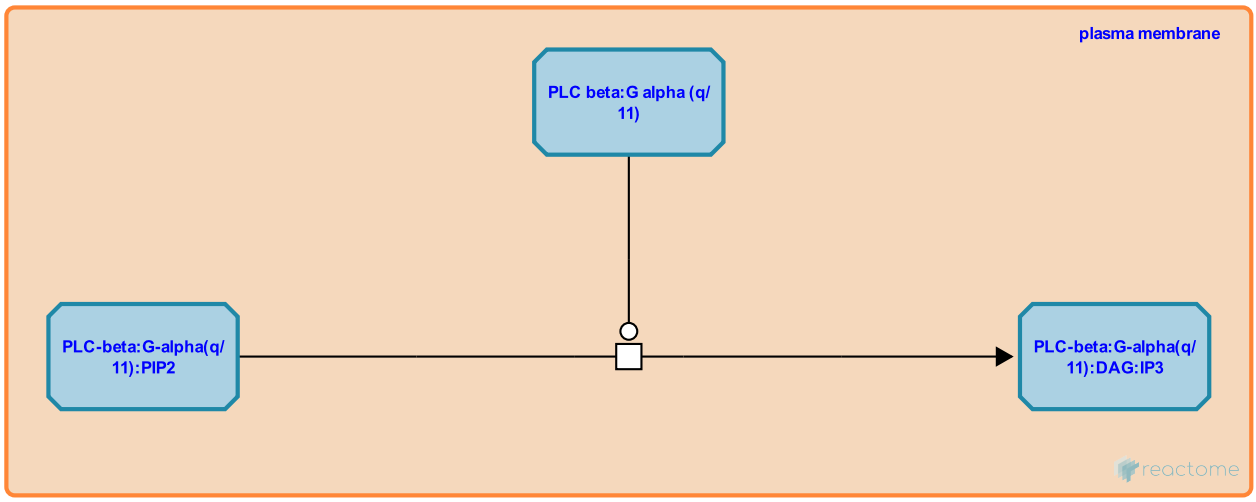
PLC-beta hydrolyses PIP2 to DAG and IP3 ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-114688

Type: transition

Compartments: plasma membrane



Phospholipase C (PLC) isozymes are a group of related proteins that cleave the polar head group from inositol phospholipids, typically in response to signals from cell surface receptors. They hydrolyze the highly phosphorylated lipid phosphatidylinositol 4,5-bisphosphate (PIP2) generating two products: inositol 1,4,5-trisphosphate (IP3), a universal calcium-mobilizing second messenger, and diacylglycerol (DAG), an activator of protein kinase C. PLC-beta isoforms are regulated by heterotrimeric GTP-binding proteins. PLC-beta 1 and 3 are widely expressed, with the highest concentrations found in (differing) specific regions of the brain. PLC-beta 2 is expressed at highest levels in cells of hematopoeitic origin; it is involved in leukocyte signaling and host defense. PLC-beta 4 is highly concentrated in cerebellar Purkinje and granule cells, the median geniculate body, whose axons terminate in the auditory cortex, and the lateral geniculate nucleus, where most retinal axons terminate in a visuotopic representation of each half of the visual field.

Literature references

Banno, Y., Yada, Y., Nozawa, Y. (1988). Purification and characterization of membrane-bound phospholipase C specific for phosphoinositides from human platelets. *J Biol Chem, 263*, 11459-65. ↗

Rebecchi, MJ., Pentyala, SN. (2000). Structure, function, and control of phosphoinositide-specific phospholipase C. *Physiol Rev, 80*, 1291-335. ↗

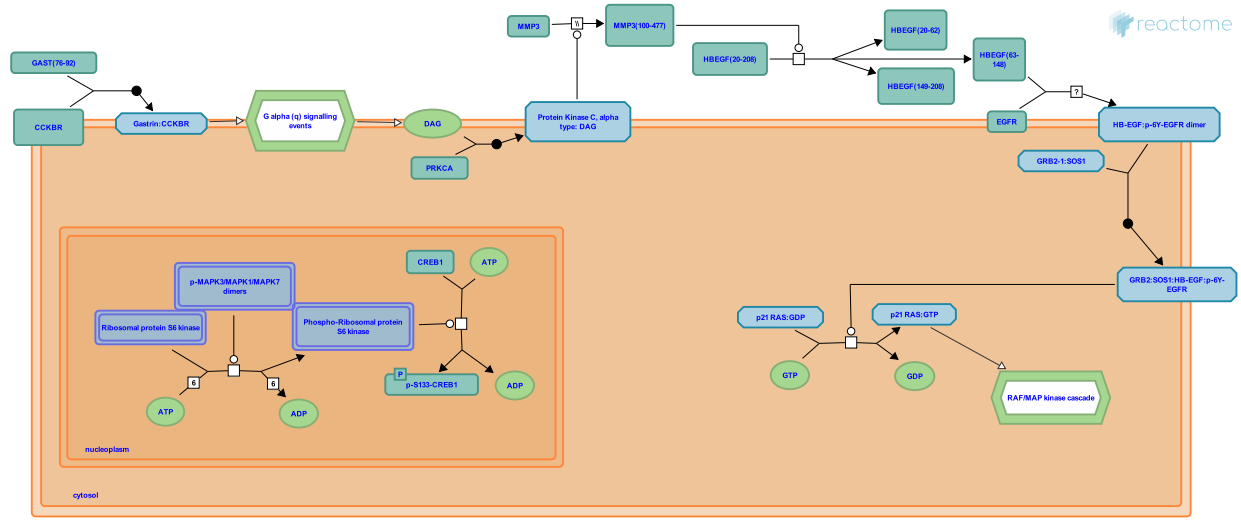
Editions

2009-09-09	Edited	Jupe, S.
2017-07-10	Revised	Varusai, TM.

Gastrin-CREB signalling pathway via PKC and MAPK ↗

Location: G alpha (q) signalling events

Stable identifier: R-HSA-881907



Gastrin is a hormone whose main function is to stimulate secretion of hydrochloric acid by the gastric mucosa, which results in gastrin formation inhibition. This hormone also acts as a mitogenic factor for gastrointestinal epithelial cells. Gastrin has two biologically active peptide forms, G34 and G17.Gastrin gene expression is upregulated in both a number of pre-malignant conditions and in established cancer through a variety of mechanisms. Depending on the tissue where it is expressed and the level of expression, differential processing of the polypeptide product leads to the production of different biologically active peptides. In turn, acting through the classical gastrin cholecystokinin B receptor CCK-BR, its isoforms and alternative receptors, these peptides trigger signalling pathways which influence the expression of downstream genes that affect cell survival, angiogenesis and invasion (Wank 1995, de Weerth et al. 1999, Grabowska & Watson 2007)

Literature references

Wank, SA. (1995). Cholecystokinin receptors. *Am J Physiol, 269*, G628-46. ↗

de Weerth, A., Bläker, M., von Schrenck, T. (1999). [Receptors for cholecystokinin and gastrin]. *Z Gastroenterol, 37*, 389-401. ↗

Grabowska, AM., Watson, SA. (2007). Role of gastrin peptides in carcinogenesis. *Cancer Lett, 257*, 1-15. ↗

Editions

2012-04-04	Authored, Edited	Jassal, B., Tripathi, S.
2012-04-23	Reviewed	D'Eustachio, P.

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