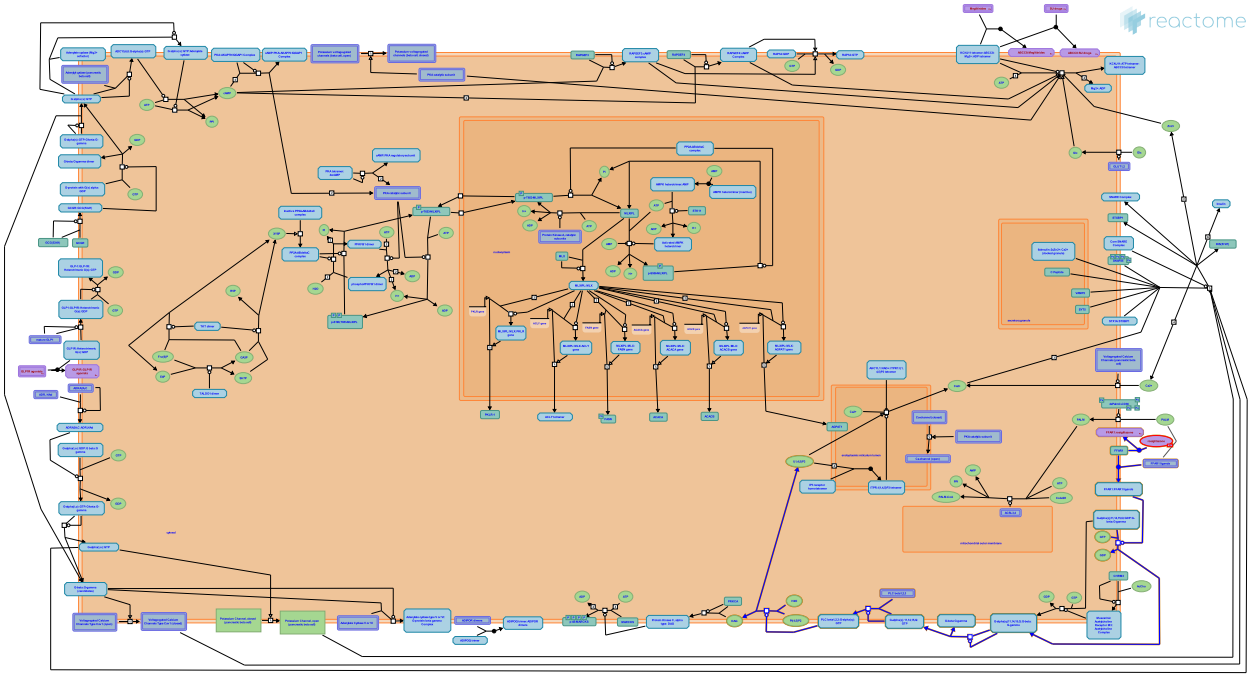
Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion



D'Eustachio, P., Gillespie, ME., Huddart, R., Jassal, B., Kebede, M., Madiraju, MS., Matthews, L., May, B., Poitout, V.

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

04/05/2024

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. ↗

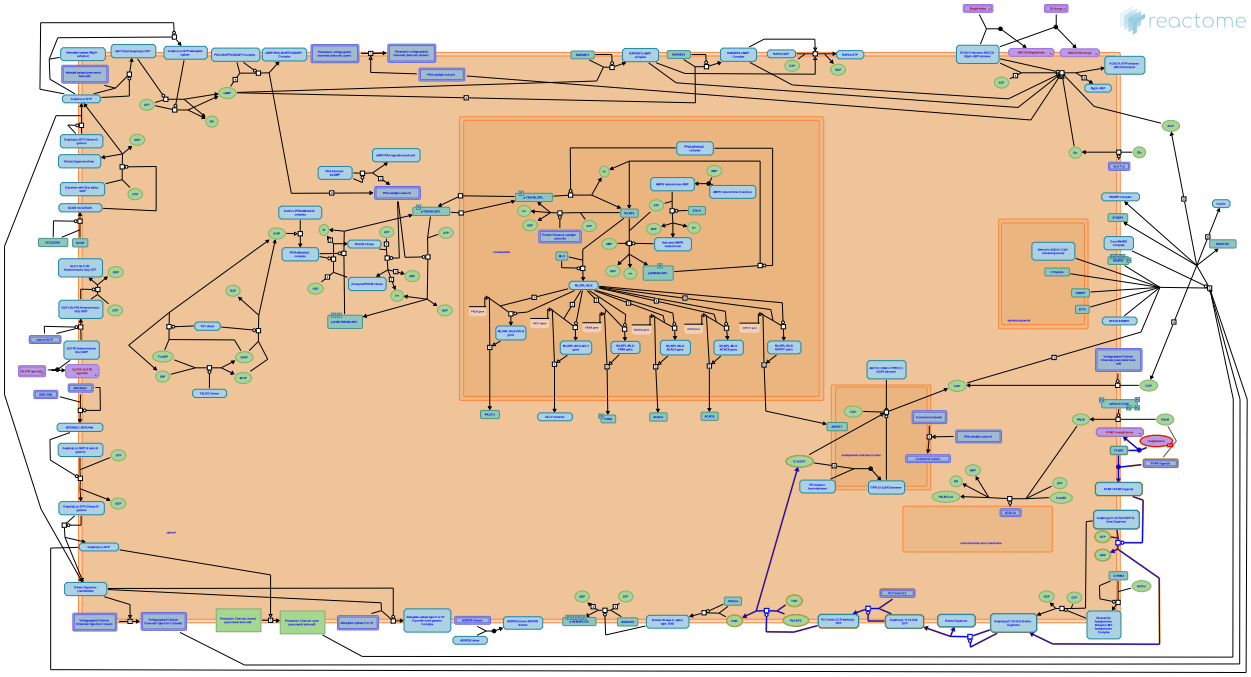
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion ↗

Stable identifier: R-HSA-434316

Compartments: cytosol, plasma membrane



Fatty acids augment the glucose triggered secretion of insulin through two mechanisms: intracellular metabolism and activation of FFAR1 (GPR40), a G-protein coupled receptor. Based on studies with inhibitors of G proteins such as pertussis toxin FFAR1 is believed to signal through Gq/11. Binding of free fatty acids by FFAR1 activates the heterotrimeric Gq complex which then activates Phospholipase C, producing inositol 1,4,5-trisphosphate and eventually causing the release of intracellular calcium into the cytosol. From experiments in knockout mice it is estimated that signaling through FFAR1 is responsible for about 50% of the augmentation of insulin secretion produced by free fatty acids.

Literature references

Shimada, Y., Masuzaki, H., Nakao, K., Kawamura, J., Tanaka, T., Fujikura, J. et al. (2005). GPR40 gene expression in human pancreas and insulinoma. *Biochem Biophys Res Commun, 338*, 1788-90. ↗

Minnick, DT., Ignar, DM., Muir, AI., Strum, JC., Goetz, AS., Elshourbagy, NA. et al. (2003). The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *J Biol Chem, 278*, 11303-11. ↗

Olde, B., Flodgren, E., Owman, C., Kotarsky, K., Nilsson, NE. (2003). A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biochem Biophys Res Commun, 301*, 406-10. ↗

Matsumura, F., Shinohara, T., Okubo, S., Tanaka, Y., Komatsu, H., Itoh, Y. et al. (2003). Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature, 422*, 173-6. ↗

Mosca, F., D'Aleo, V., Filipponi, F., Del Guerra, S., Bugliani, M., Lupi, R. et al. (2009). G-protein-coupled receptor 40 (GPR40) expression and its regulation in human pancreatic islets: The role of type 2 diabetes and fatty acids. *Nutr Metab Cardiovasc Dis.* ↗

Editions

2009-08-28	Authored, Edited	May, B.
2009-09-09	Reviewed	Poitout, V., Kebede, M.
2009-10-02	Reviewed	Madiraju, MS.

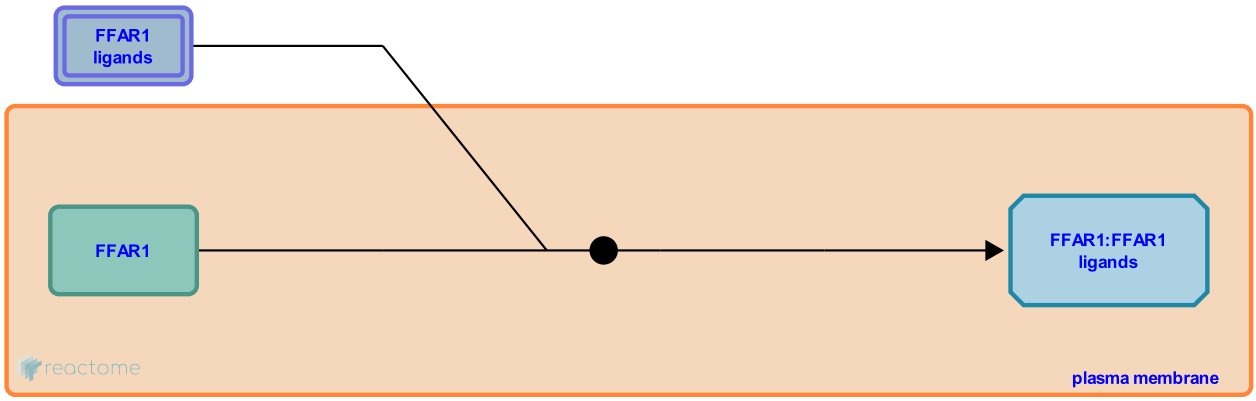
FFAR1 binds fatty acids ↗

Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-400434

Type: binding

Compartments: plasma membrane, extracellular region



Free fatty acid receptor 1 (FFAR1), also known as GPR40, is a G-protein coupled receptor located in the plasma membrane of pancreatic beta cells. FFAR1/GPR40 binds medium and long chain free fatty acids (free fatty acids having more than 12 carbon groups).

Followed by: FFAR1:FFAR1 ligands activate Gq

Literature references

Shimada, Y., Masuzaki, H., Nakao, K., Kawamura, J., Tanaka, T., Fujikura, J. et al. (2005). GPR40 gene expression in human pancreas and insulinoma. *Biochem Biophys Res Commun, 338*, 1788-90. ↗

Minnick, DT., Ignar, DM., Muir, AI., Strum, JC., Goetz, AS., Elshourbagy, NA. et al. (2003). The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *J Biol Chem, 278*, 11303-11. ↗

Olde, B., Flodgren, E., Owman, C., Kotarsky, K., Nilsson, NE. (2003). A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biochem Biophys Res Commun, 301*, 406-10. ↗

Matsumura, F., Shinohara, T., Okubo, S., Tanaka, Y., Komatsu, H., Itoh, Y. et al. (2003). Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature, 422*, 173-6. ↗

Mosca, F., D'Aleo, V., Filipponi, F., Del Guerra, S., Bugliani, M., Lupi, R. et al. (2009). G-protein-coupled receptor 40 (GPR40) expression and its regulation in human pancreatic islets: The role of type 2 diabetes and fatty acids. *Nutr Metab Cardiovasc Dis.* ↗

Editions

2009-06-08	Authored, Edited	May, B.
2009-09-09	Reviewed	Poitout, V., Kebede, M.
2009-10-02	Reviewed	Madiraju, MS.

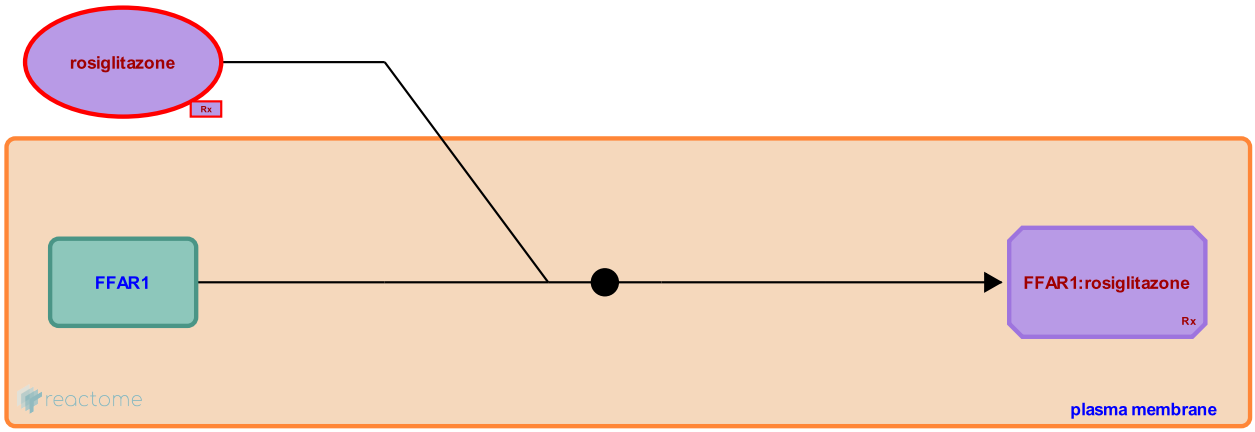
FFAR1 binds rosiglitazone ↗

Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-9732527

Type: binding

Compartments: plasma membrane, extracellular region



Free fatty acid receptor 1 (FFAR1, aka GR40) is a G-protein coupled receptor that plays an important role in glucose homeostasis. Fatty acid binding to FFAR1 increases glucose-stimulated insulin secretion. FFA1 is found in high concentrations in the pancreas and the brain.

Both preclinical and clinical studies have demonstrated that activation of FFAR1 improves glycaemic control by stimulating glucose-dependent insulin secretion. Rosiglitazone is an anti-diabetic drug of the thiazolidinedione class. Like other thiazolidinediones, rosiglitazone acts via activation of peroxisome proliferator-activated receptors (PPARs), specifically PPARγ. FFAR1 has also been shown to mediate responses to antidiabetic drugs of the thiazolidinedione class (Kotarsky et al. 2003).

Attempts to develop new FFAR1 agonists have so far been unsuccessful (Governa et al. 2021). Fasiglifam (TAK-875) was a novel antidiabetic drug (Yabuki et al. 2013) but phase 3 clinical trials were terminated due to potential liver toxicity (Otieno et al. 2018).

Literature references

Maeda, R., Mori, M., Takeuchi, K., Matsuda-Nagasumi, K., Habata, Y., Ito, R. et al. (2013). A novel antidiabetic drug, fasiglifam/TAK-875, acts as an ago-allosteric modulator of FFAR1. *PLoS One, 8*, e76280. ↗

Olde, B., Flodgren, E., Owman, C., Kotarsky, K., Nilsson, NE. (2003). A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biochem Biophys Res Commun, 301*, 406-10. ↗

Editions

2021-05-27	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

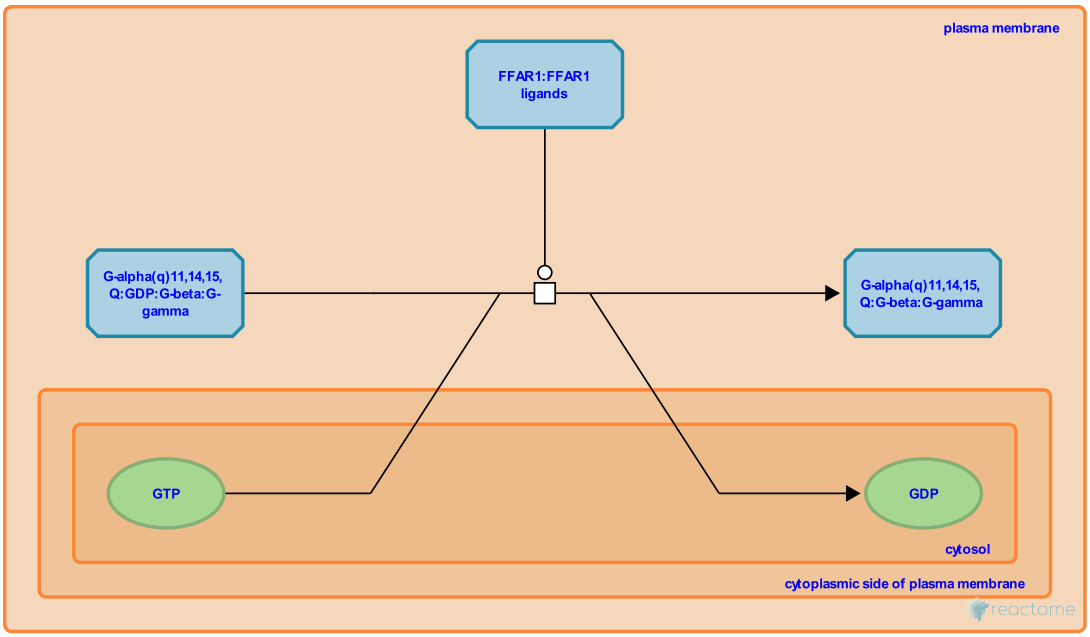
FFAR1:FFAR1 ligands activate Gq ↗

Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-416530

Type: transition

Compartments: plasma membrane, cytosol



FFAR1 (GPR40) is a G-protein coupled receptor. Based on studies with inhibitors of G proteins such as pertussis toxin FFAR1 is believed to signal through Gq/11. Binding of free fatty acids by FFAR1 activates the heterotrimeric Gq complex, which then activates Phospholipase C. From experiments in knockout mice it is estimated that signaling through FFAR1 is responsible for about 50% of the augmentation of insulin secretion produced by free fatty acids. The rest of the augmentation is due to metabolism of the free fatty acids within the pancreatic beta cell.

Preceded by: FFAR1 binds fatty acids

Followed by: Gq alpha:G beta:G gamma dissociates to Gq alpha:GTP and G beta:G gamma

Literature references

Lin, DC., Tremblay, C., Alquier, T., Poitout, V., Oseid, E., Jetton, TL. et al. (2007). GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes, 56*, 1087-94. ↗

Nolan, CJ., Peyot, ML., Delghingaro-Augusto, V., Prentki, M., Madiraju, MS. (2006). Fatty acid signaling in the beta-cell and insulin secretion. *Diabetes, 55*, S16-23. ↗

Maekawa, F., Fujiwara, K., Yada, T. (2005). Oleic acid interacts with GPR40 to induce Ca2+ signaling in rat islet beta-cells: mediation by PLC and L-type Ca2+ channel and link to insulin release. *Am J Physiol Endocrinol Metab, 289*, E670-7. ↗

Shachar, S., Hershfinkel, M., Shapiro, H., Sekler, I., Walker, MD. (2005). Role of GPR40 in fatty acid action on the beta cell line INS-1E. *Biochem Biophys Res Commun, 335*, 97-104. ↗

Hirasawa, A., Katsuma, S., Hara, T., Adachi, T., Tsujimoto, G. (2008). Free fatty acid receptors and drug discovery. *Biol Pharm Bull, 31*, 1847-51. ↗

Editions

2009-06-08	Authored, Edited	May, B.
2009-09-09	Reviewed	Poitout, V., Kebede, M.
2009-10-02	Reviewed	Madiraju, MS.

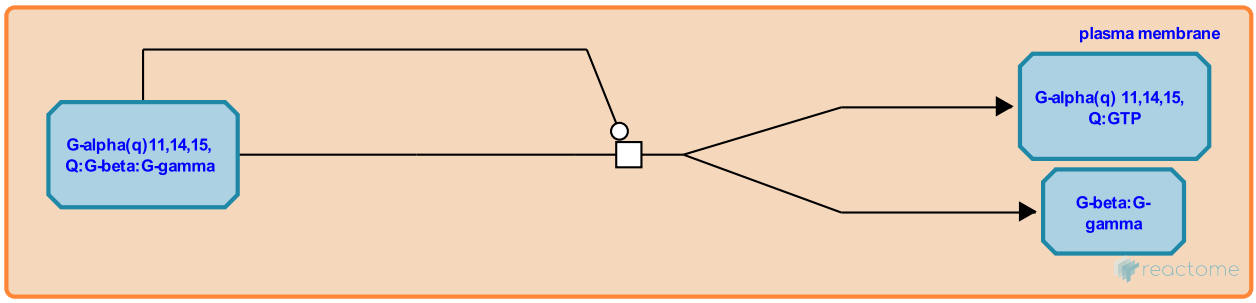
Gq alpha:G beta:G gamma dissociates to Gq alpha:GTP and G beta:G gamma ↗

Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-400027

Type: transition

Compartments: plasma membrane



In the non-activated state heterotrimeric G proteins exist at membranes as heterotrimeric complexes of alpha, beta, and gamma subunits, with the alpha subunit bound to GDP. Upon activation by a receptor coupled to the heterotrimer, exchange of GDP for GTP by the Gq alpha subunit causes the alpha subunit to lose affinity for the beta and gamma subunits. The alpha subunit with bound GTP then dissociates from the beta and gamma subunits.

Preceded by: FFAR1:FFAR1 ligands activate Gq

Followed by: Gq alpha activates Phospholipase C beta

Literature references

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

Azpiazu, I., Kalyanaraman, V., Akgoz, M., Gautam, N. (2006). G protein betagamma11 complex translocation is induced by Gi, Gq and Gs coupling receptors and is regulated by the alpha subunit type. *Cell Signal, 18*, 1190-200. ↗

Lambert, NA., Digby, GJ., Sethi, PR., Lober, RM. (2006). Some G protein heterotrimers physically dissociate in living cells. *Proc Natl Acad Sci U S A, 103*, 17789-94. ↗

Neuwald, AF. (2007). Galpha Gbetagamma dissociation may be due to retraction of a buried lysine and disruption of an aromatic cluster by a GTP-sensing Arg Trp pair. *Protein Sci, 16*, 2570-7. ↗

Kalyanaraman, V., Akgoz, M., Gautam, N. (2004). Receptor-mediated reversible translocation of the G protein betagamma complex from the plasma membrane to the Golgi complex. *J Biol Chem, 279*, 51541-4. ↗

Editions

2009-05-28	Authored, Edited	May, B.
2009-06-02	Reviewed	Gillespie, ME.
2024-01-29	Reviewed	D'Eustachio, P.

Gq alpha activates Phospholipase C beta ↗

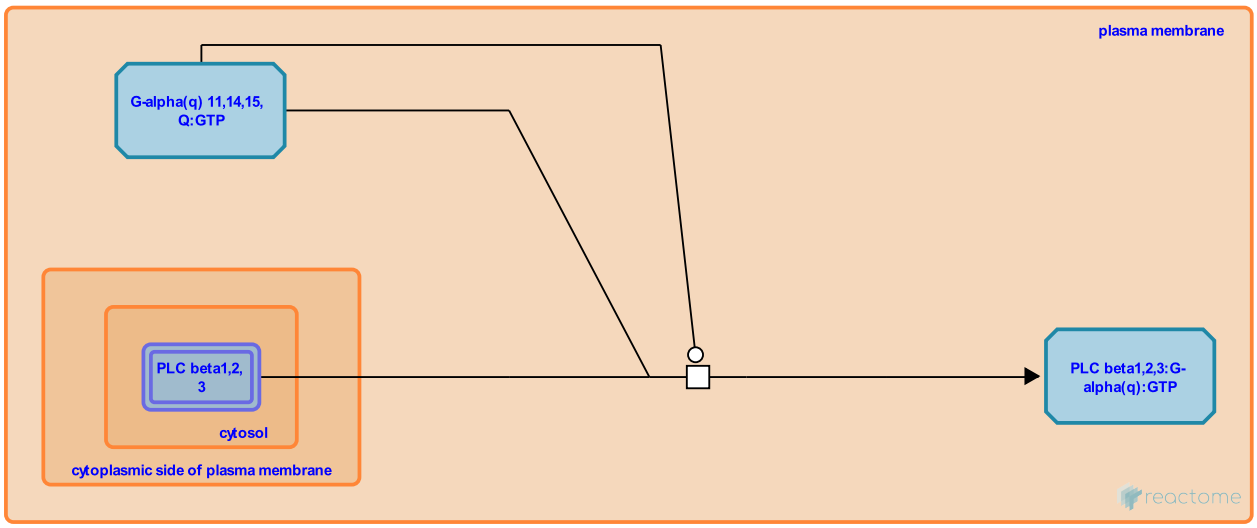
Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-400023

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Activation of Phospholipase C beta1 by G(q)alpha:GTP (Mus musculus)



The Gq alpha:GTP complex activates Phospholipase C beta-1 through protein interaction (inferred from homologues in Bos taurus). The activation by Gq alpha is insensitive to pertussis toxin whilst activation of PLC beta by the G beta-gamma complex is sensitive to pertussis toxin.

Preceded by: Gq alpha:G beta:G gamma dissociates to Gq alpha:GTP and G beta:G gamma

Followed by: Activated Phospholipase C beta-1 hydrolyzes 1-Phosphatidyl-D-myo-inositol 4,5-bisphosphate

Literature references

Smrcka, AV., Sternweis, PC., Hepler, JR., Brown, KO. (1991). Regulation of polyphosphoinositide-specific phospholipase C activity by purified Gq. *Science, 251*, 804-7. ↗

Ahren, B., Winzell, MS. (2007). G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes. *Pharmacol Ther, 116*, 437-48. ↗

Gilon, P., Henquin, JC. (2001). Mechanisms and physiological significance of the cholinergic control of pancreatic beta-cell function. *Endocr Rev, 22*, 565-604. ↗

Editions

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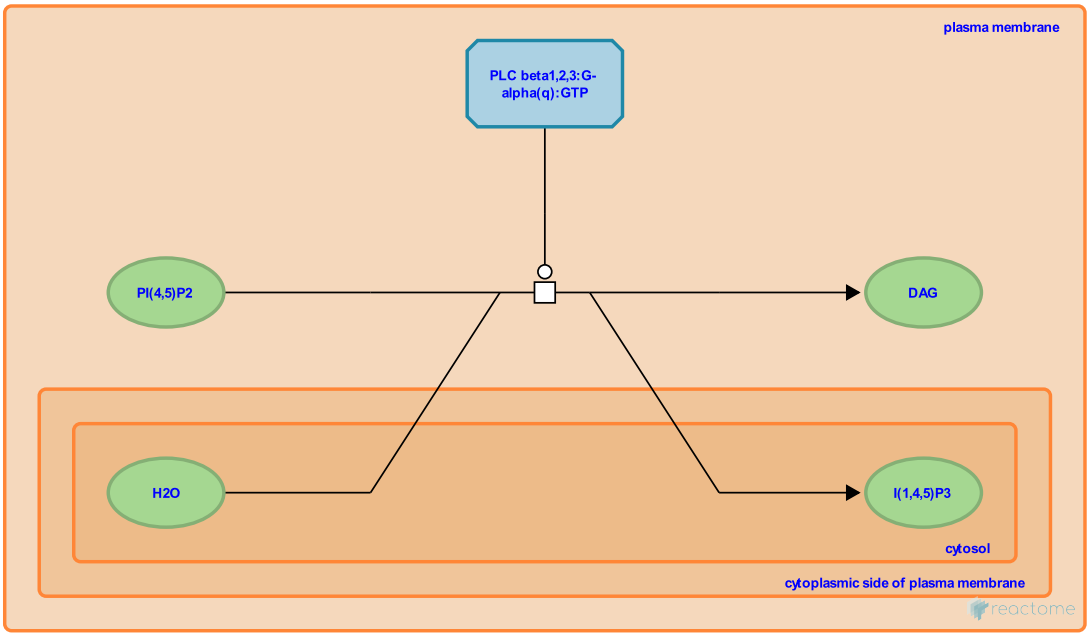
Activated Phospholipase C beta-1 hydrolyzes 1-Phosphatidyl-D-myo-inositol 4,5-bisphosphate ↗

Location: Fatty Acids bound to GPR40 (FFAR1) regulate insulin secretion

Stable identifier: R-HSA-399998

Type: transition

Compartments: plasma membrane, cytosol



Phospholipase C beta-1 associated with the G(q) complex in the plasma membrane catalyzes the hydrolysis of 1-Phosphatidyl-D-myo-inositol 4,5-bisphosphate to yield D-myo-Inositol 1,4,5-trisphosphate and 1,2-Diacylglycerol.

Preceded by: Gq alpha activates Phospholipase C beta

Literature references

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

Gilon, P., Henquin, JC. (2001). Mechanisms and physiological significance of the cholinergic control of pancreatic beta-cell function. *Endocr Rev, 22*, 565-604. ↗

Editions

2009-05-28	Authored, Edited	May, B.
2009-06-02	Reviewed	Gillespie, ME.

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