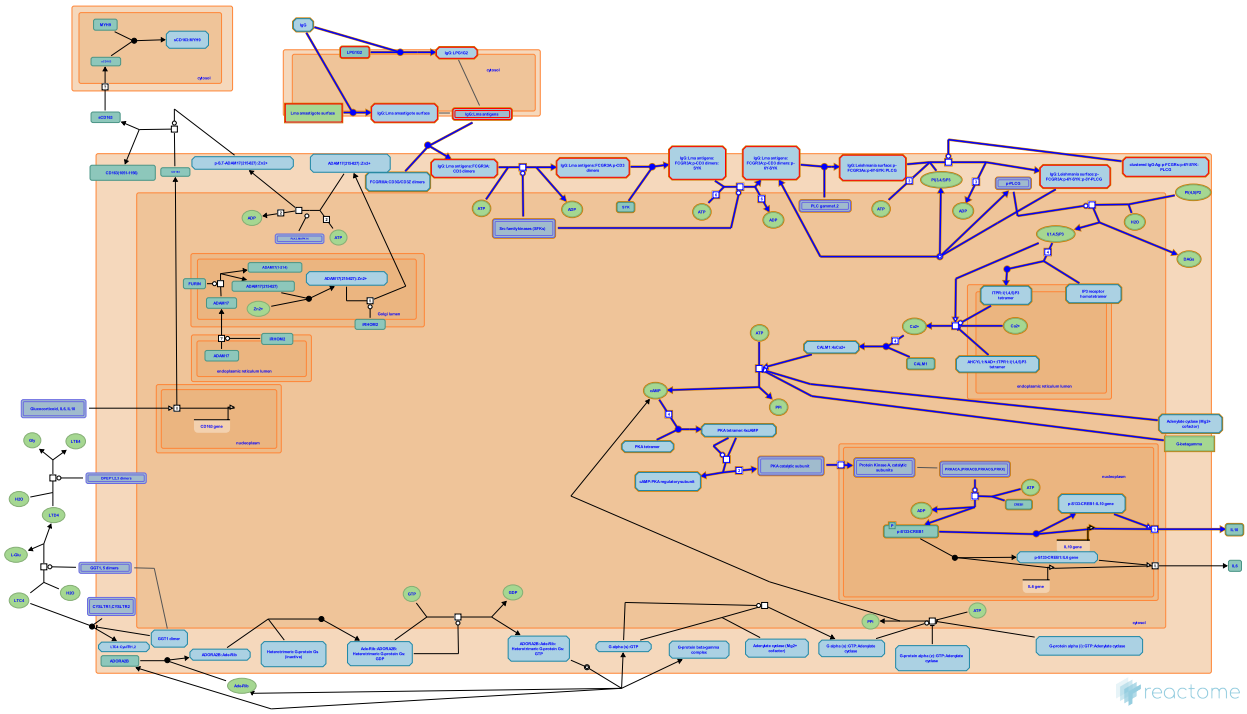
FCGR3A-mediated IL10 synthesis



Castagnoli, L., D'Eustachio, P., Garapati, P V., Gillespie, ME., Gregory, DJ., Hansen, KB., Jassal, B., Jupe, S., Le Novere, N., Mahajan, SS., Murillo, JI., Orlic-Milacic, M., Rudd, C.E.., Rush, MG., Trowsdale, J., Tukey, D., Yi, F., de Bono, B.

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

27/04/2024

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. ↗

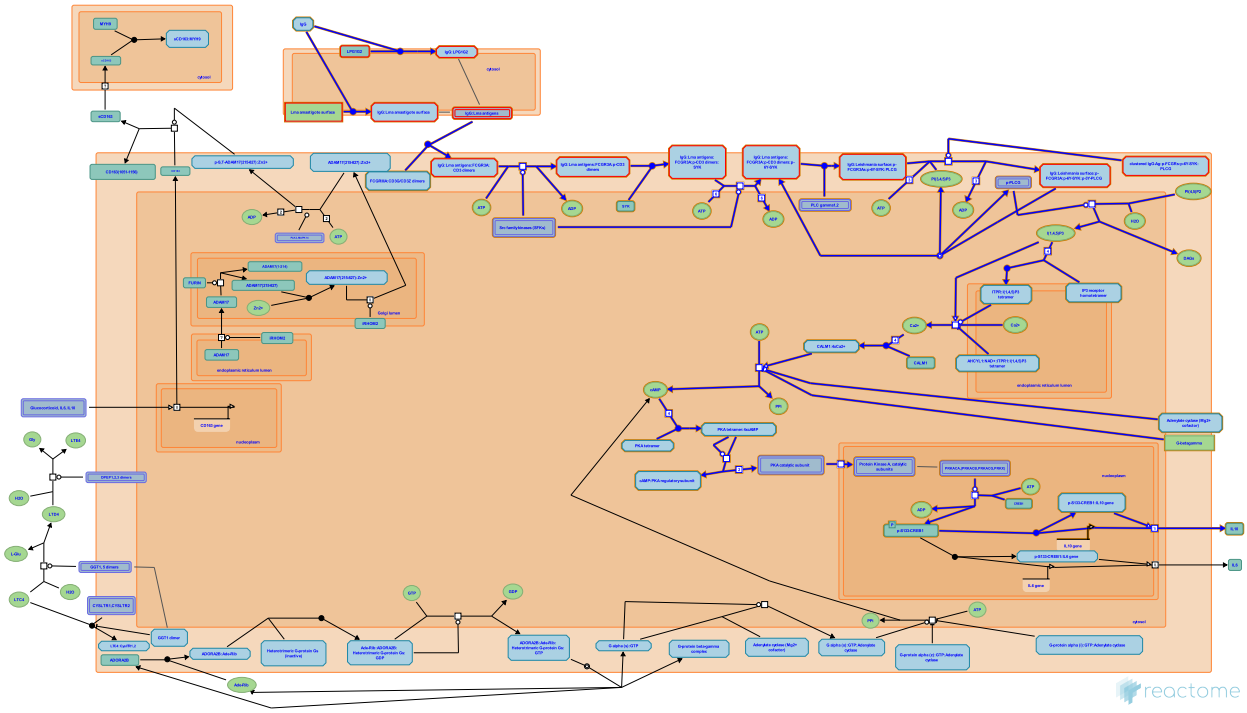
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

FCGR3A-mediated IL10 synthesis ↗

Stable identifier: R-HSA-9664323

Diseases: cutaneous leishmaniasis



Interleukin 10 (IL-10) is an important immunoregulatory cytokine produced by many cell populations; in macrophages it is induced after the stimulation of TLRs, Fcγ receptors or by the TLR-FcγR crosstalk (Vogelpoel et al. 2014 & Saninet al. 2015). Classically, its function is considered to be the limitation and termination of inflammatory responses and the regulation of differentiation of several immune cells (Asadullah et al. 2003). There is increasing evidence of the role of IL-10 in parasite infection outcomes either as a protective or a pathological mediator (Asadullah et al. 2003). In the context of the parasitic disease cutaneous leishmaniasis, Leishmania amastigotes opsonized by IgG induce IL-10 response through FcγRs, which in turn supresses the killing mechanisms in phagocytic cells. (Chu et al. 2010).

Literature references

Prendergast, CT., Mountford, AP., Sanin, DE. (2015). IL-10 Production in Macrophages Is Regulated by a TLR-Driven CREB-Mediated Mechanism That Is Linked to Genes Involved in Cell Metabolism. *J. Immunol., 195*, 1218-32. ↗

Sterry, W., Volk, HD., Asadullah, K. (2003). Interleukin-10 therapy--review of a new approach. *Pharmacol. Rev., 55*, 241-69. ↗

Kapsenberg, ML., Rispens, T., Vos, JB., Hansen, IS., Turina, MC., Baeten, DL. et al. (2014). Fc gamma receptor-TLR cross-talk elicits pro-inflammatory cytokine production by human M2 macrophages. *Nat Commun, 5*, 5444. ↗

Thomas, BN., Chu, N., Patel, SR., Buxbaum, LU. (2010). IgG1 is pathogenic in Leishmania mexicana infection. *J. Immunol., 185*, 6939-46. ↗

Editions

2020-01-07	Authored	Jassal, B., Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Murillo, JI.

IgG binds LPG1G2 in the amastigote form of Leishmania ↗

Location: FCGR3A-mediated IL10 synthesis

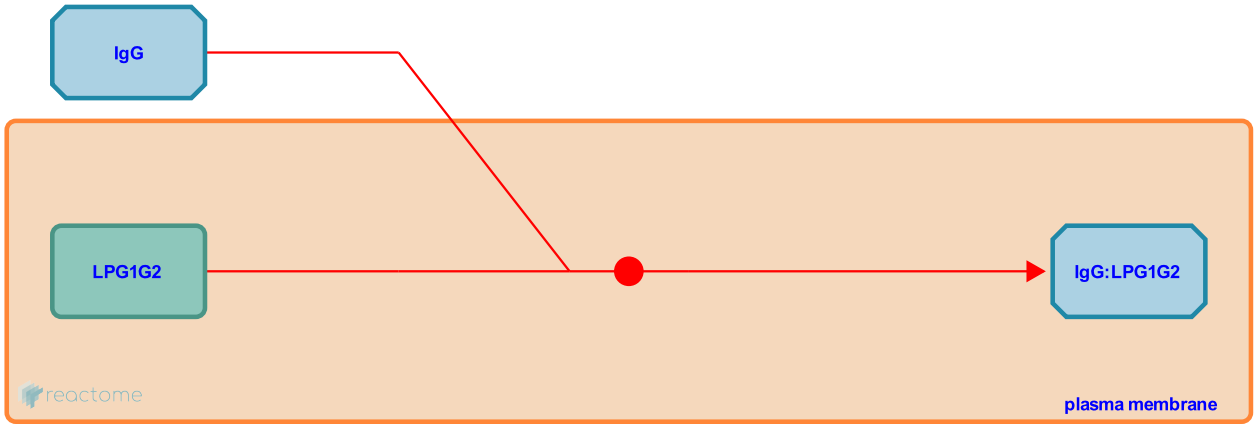
Stable identifier: R-HSA-9664397

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: cutaneous leishmaniasis

Inferred from: Mouse IgG binds LPG1G2 in the amastigote form of Leishmania (Mus musculus)



The internalization of Leishmania amastigotes by macrophages is thought to be mediated mainly through opsonization with immunoglobulins (Igs) which bind FcγRs, stimulating the uptake (Morehead et al 2002 & Padigel et al. 2005). Glycoinositol phospholipids (GIPLs) are the most abundant glycolipids on the surface of the amastigote form of Leishmania parasites and Buxbaum and colleagues showed that IgG1 in mice, binds the GIPL molecules on the amastigote stage of L. mexicana to subsequently induced the phagocytosis through FcγRs (Buxbaum 2013).

Followed by: Opsonized leishmania amastigote binds FCGR3

Literature references

Morehead, J., Coppens, I., Andrews, NW. (2002). Opsonization modulates Rac-1 activation during cell entry by Leishmania amazonensis. *Infect. Immun., 70*, 4571-80. ↗

Buxbaum, LU. (2013). Leishmania mexicana infection induces IgG to parasite surface glycoinositol phospholipids that can induce IL-10 in mice and humans. *PLoS Negl Trop Dis, 7*, e2224. ↗

Padigel, UM., Farrell, JP. (2005). Control of infection with Leishmania major in susceptible BALB/c mice lacking the common gamma-chain for FcR is associated with reduced production of IL-10 and TGF-beta by parasitized cells. *J. Immunol., 174*, 6340-5. ↗

Editions

2019-10-22	Authored	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Jassal, B., Murillo, JI.

IgG binds the surface of the amastigote form of Leishmania ↗

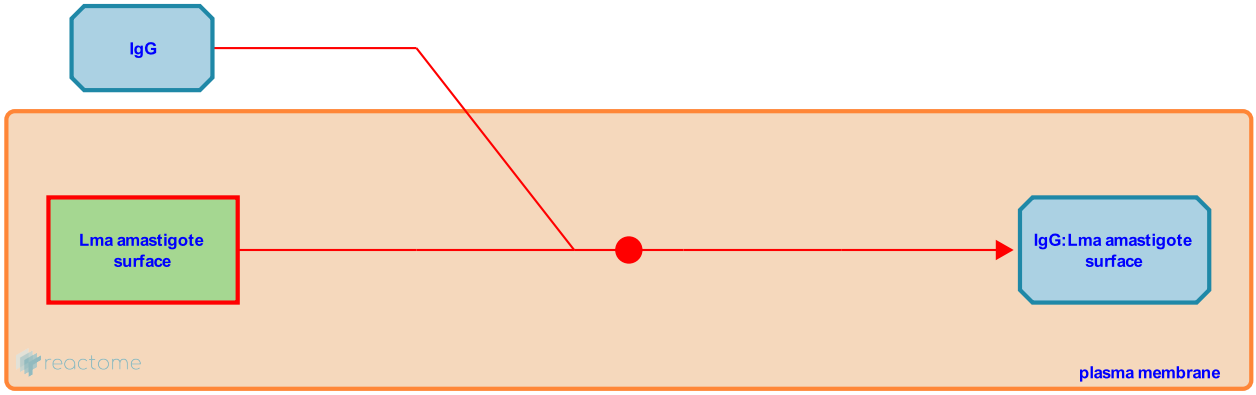
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664285

Type: binding

Compartments: plasma membrane, extracellular region

Diseases: cutaneous leishmaniasis



The internalization of Leishmania amastigotes by macrophages is thought to be mediated mainly through opsonization with immunoglobulins (Igs) which bind Fc gamma receptors (FCGRs), stimulating their uptake (Morehead et al 2002 & Padigel et al. 2005). Glycoinositol phospholipids (GIPLs) are the most abundant glycolipids on the surface of the amastigote form of Leishmania parasites and Buxbaum and colleagues showed that IgG1 in mice binds GIPL molecules on the amastigote stage of L. mexicana to subsequently induce phagocytosis through FCGRs (Buxbaum 2013).

Followed by: Opsonized leishmania amastigote binds FCGR3

Literature references

Thomas, BN., Buxbaum, LU. (2008). FcgammaRIII mediates immunoglobulin G-induced interleukin-10 and is required for chronic Leishmania mexicana lesions. *Infect. Immun., 76*, 623-31. ↗

Buxbaum, LU. (2013). Leishmania mexicana infection induces IgG to parasite surface glycoinositol phospholipids that can induce IL-10 in mice and humans. *PLoS Negl Trop Dis, 7*, e2224. ↗

Thomas, BN., Chu, N., Patel, SR., Buxbaum, LU. (2010). IgG1 is pathogenic in Leishmania mexicana infection. *J. Immunol., 185*, 6939-46. ↗

Editions

2020-01-07	Authored, Edited	Jassal, B.
2020-01-07	Authored, Edited	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.

Opsonized leishmania amastigote binds FCGR3

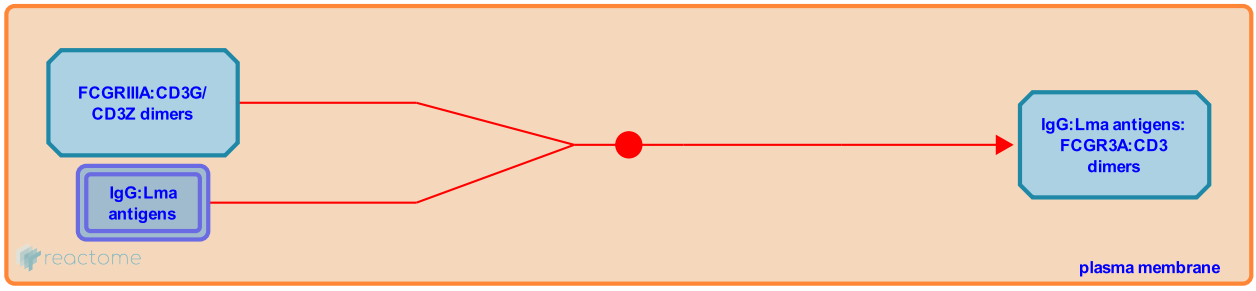
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664268

Type: binding

Compartments: plasma membrane

Diseases: cutaneous leishmaniasis



Leishmania amastigotes parasites opsonized by IgG are more susceptible to be phagocytosed through FcγRs. Nevertheless, besides the phagocytosis induction, the interaction IgG-FcγRs has been implicated in the synthesis induction, of several cytokines (Buxbaum 2013; Chu et al. 2010; Thomas and Buxbaum 2008). In particular, Buxbaum et al. in 2008 showed that IgGs bound glycoinositol phospholipids (GIPLs) of L. Mexicana and that IgG:GIPLs induces the synthesis of IL-10 through FcγRIII.

Preceded by: IgG binds LPG1G2 in the amastigote form of Leishmania, IgG binds the surface of the amastigote form of Leishmania

Followed by: Src phosphorylates CD3 dimers in IgG:Lma antigens:FCGR3A:CD3 dimers

Literature references

Thomas, BN., Buxbaum, LU. (2008). FcgammaRIII mediates immunoglobulin G-induced interleukin-10 and is required for chronic Leishmania mexicana lesions. *Infect. Immun., 76*, 623-31.

Buxbaum, LU. (2013). Leishmania mexicana infection induces IgG to parasite surface glycoinositol phospholipids that can induce IL-10 in mice and humans. *PLoS Negl Trop Dis, 7*, e2224.

Thomas, BN., Chu, N., Patel, SR., Buxbaum, LU. (2010). IgG1 is pathogenic in Leishmania mexicana infection. *J. Immunol., 185*, 6939-46.

Editions

2020-01-07	Authored, Edited	Jassal, B.
2020-01-07	Authored, Edited	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.

Src phosphorylates CD3 dimers in IgG:Lma antigens:FCGR3A:CD3 dimers ↗

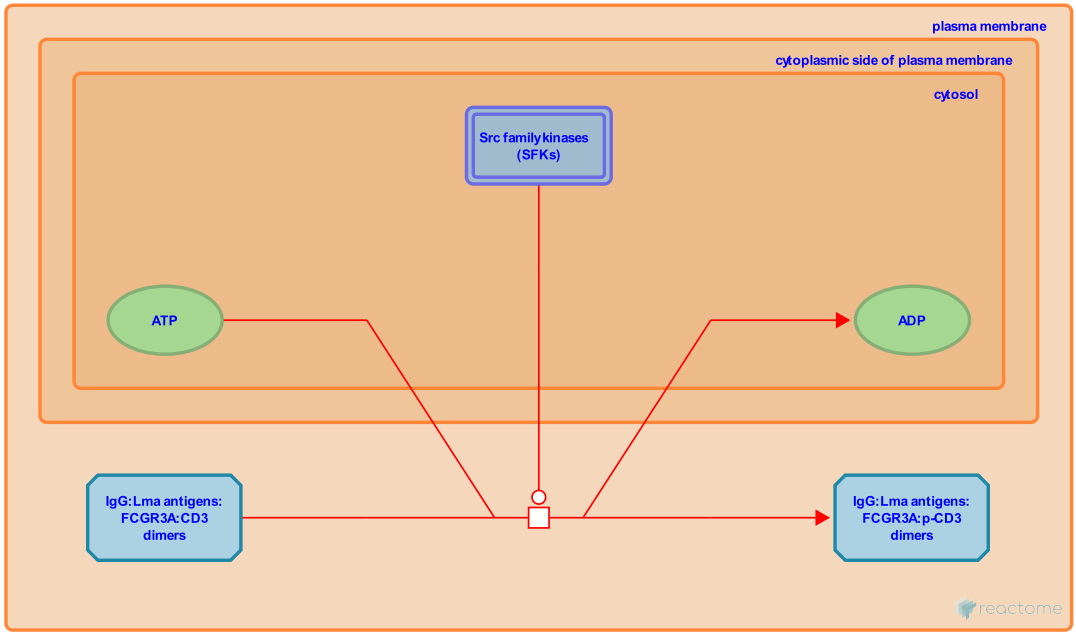
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664275

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



After cross linking, Fc gamma receptors are sequestered to lipid rafts where they are complexed with some of the tyrosine kinases of Src family and undergo phosphorylation on the tyrosine residues contained in conserved ITAM sequences. At least six out of nine members of the Src family kinases (SRC, FYN, FGR, HCK, YES and LYN) have been identified in the phagocytic cells and are implicated in the initiation of Fc gamma mediated signaling. (Suzuki et al. 2000, Majeed et al. 2001, Kwiatkowska et al. 2003). Some of these kinases have been found associated with specific receptors. In monocytes HCK and LYN have been found associated with FCGRI (Durden et al. 1995), whereas only HCK with FCGRIIA (Ghazizadeh et al. 1994) while FGR in neutrophils (Hamada et al. 1993) and LCK in NK cells with FCGRIIIA (Pignata et al. 1993)
The implication of Src kinases in phosphorylation was first supported by pharmacological findings that herbimycin A, a tyrosine kinase inhibitor relatively specific for Src-family kinases, potently suppressed Fc receptor mediated functions (Greenberg et al. 1993, Suzuki et al. 2000). However, their particular involvement in phagocytosis remains unclear, as targeted disruption of single or multiple Src family genes did not result in significant alterations in phagocytosis (Hunter et al. 1993, Fitzer Attas et al. 2000, Suzuki et al. 2000). HCK, FGR and LYN triple-deficient (-/-) macrophages have shown significant delays in FCGR mediated phagocytosis, but these deficiencies do not completly disrupt the process (Fitzer Attas et al. 2000).
Tyrosine residues Y288 and Y304 (Y282 and Y298 according to the literature reference, it is 6 residues shorter compared to uniprot entry due to an alternate initiation codon usage), within ITAM sequence in the cytoplasmic domain of FCGRIIA are the key target sites that are phosphorylated by Src family kinases (Mitchell et al, 1994). In case of FCGRIA and FCGRIIIA the specific tyrosine residues within ITAMs of the associated gamma/zeta chains are phosphorylated by activated Src family kinases (SFKs) (Park et al. 1993).

Preceded by: Opsonized leishmania amastigote binds FCGR3

Followed by: SYK binds IgG:Lma antigens:FCGR3A:p-CD3 dimers

Literature references

Okada, M., Honda, Z., Hirose, N., Yamamoto, T., Suzuki, T., Kono, H. et al. (2000). Differential involvement of Src family kinases in Fc gamma receptor-mediated phagocytosis. *J Immunol, 165*, 473-82. ↗

Huang, MM., Brugge, JS., Hoxie, JA., Indik, Z., Brass, LF., Schreiber, AD. (1992). Activation of Fc gamma RII induces tyrosine phosphorylation of multiple proteins including Fc gamma RII. *J Biol Chem, 267*, 5467-73. ↗

Indik, ZK., Worth, RG., Kim, MK., Barreda, DR., Huang, ZY., Chien, P. et al. (2006). Differential kinase requirements in human and mouse Fc-gamma receptor phagocytosis and endocytosis. *J Leukoc Biol, 80*, 1553-62. ↗

Strzelecka, A., Kwiatkowska, K., Sobota, A. (1997). Tyrosine phosphorylation and Fcgamma receptor-mediated phagocytosis. *FEBS Lett, 400*, 11-4. ↗

Editions

2019-10-22	Authored	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Jassal, B., Murillo, JI.

SYK binds IgG:Lma antigens:FCGR3A:p-CD3 dimers ↗

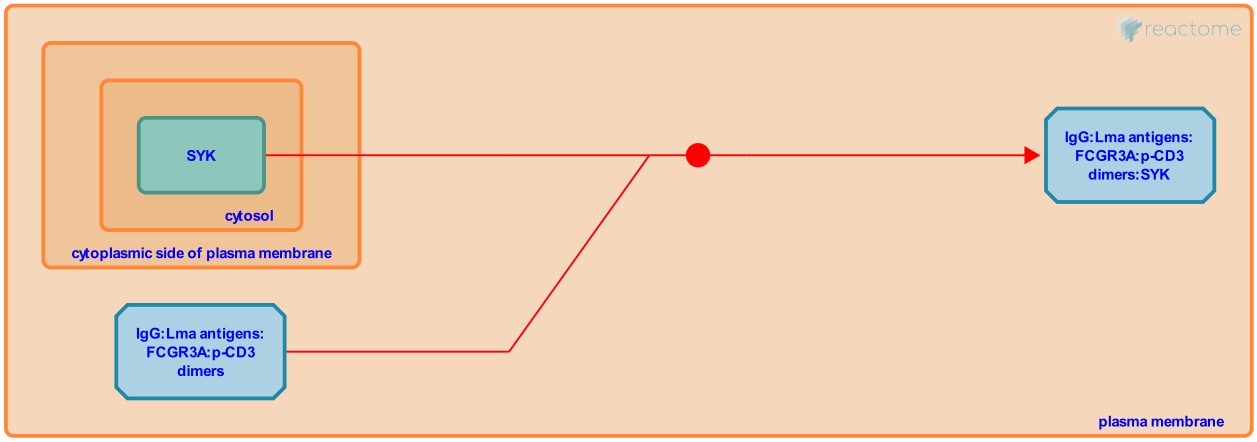
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664273

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



SYK is a tyrosine kinase related to ZAP70 that is expressed in all hematopoietic cells and coimmunoprecipitates with the gamma chain associated with FCGRIIIA in macrophages and with FCERI in mast cells. SYK is very important for FCGR phagocytosis and is recruited to these phosphorylated ITAM residues through its two SRC homology 2 (SH2) domains (Agarwal et al. 1993). When SYK kinase expression is inhibited with antisense oligonucleotides both in vitro and in vivo, phagocytosis and inflammation are abolished (Matsuda et al. 1997). The domain structure of SYK comprises a regulatory region at the N-terminus consisting of a pair of SH2 domains separated by an inter-SH2 linker called interdomain A, an SH2-domain-kinase linker termed interdomain B, and a C-terminal kinase domain (Arias-Palomo et al. 2009). In resting state SYK exists in an auto-inhibited conformation by the interactions between the SH2-SH2 regulatory region and the inter-SH2 linker and the catalytic domain. This interdomain interaction reduces the conformational flexibility required by the kinase domain for catalysis (Arias-Palomo et al. 2007). Changes in the orientation of the SH2 domains could control the disruption of the auto inhibitory interactions and the activation of SYK. These movements could be totally or partially induced by the binding to phosphorylated ITAMs and/or phosphorylation of tyrosine residues in interdomain A or B (Arias-Palomo et al. 2009). Tsang et al. suggested that SYK functions as an OR-gate switch with respect to phosphorylation and ITAM binding, as either one stimulus OR the other is sufficient to cause full activation (Tsang et al. 2008).

Preceded by: Src phosphorylates CD3 dimers in IgG:Lma antigens:FCGR3A:CD3 dimers

Followed by: Src phosphorylate SYK in IgG:Leishmania surface:p-FCGR3A:SYK

Literature references

Matsuda, M., Hunter, S., Wang, DC., Chien, P., Schreiber, AD., Park, JG. (1996). Abrogation of the Fc gamma receptor IIA-mediated phagocytic signal by stem-loop Syk antisense oligonucleotides. *Mol Biol Cell, 7*, 1095-106. ↗

Fleit, HB., Bolen, JB., Ghazizadeh, S. (1995). Tyrosine phosphorylation and association of Syk with Fc gamma RII in monocytic THP-1 cells. *Biochem J, 305*, 669-74. ↗

Robbins, KC., Salem, P., Agarwal, A. (1993). Involvement of p72syk, a protein-tyrosine kinase, in Fc gamma receptor signaling. *J Biol Chem, 268*, 15900-5. ↗

Rankin, BM., Gilliland, LK., Schieven, GL., Bolen, JB., Kiener, PA., Burkhardt, AL. et al. (1993). Cross-linking of Fc gamma receptor I (Fc gamma RI) and receptor II (Fc gamma RII) on monocytic cells activates a signal transduction pathway common to both Fc receptors that involves the stimulation of p72 Syk protein tyrosine kinase. *J Biol Chem, 268*, 24442-8. ↗

Lowell, C., Costello, PS., Turner, M., Tybulewicz, VL., DeFranco, AL., Meng, F. et al. (1997). A critical role for Syk in signal transduction and phagocytosis mediated by Fcgamma receptors on macrophages. *J Exp Med, 186*, 1027-39. ↗

Editions

2019-10-22	Authored	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Murillo, JI.

Src phosphorylate SYK in IgG:Leishmania surface:p-FCGR3A:SYK ↗

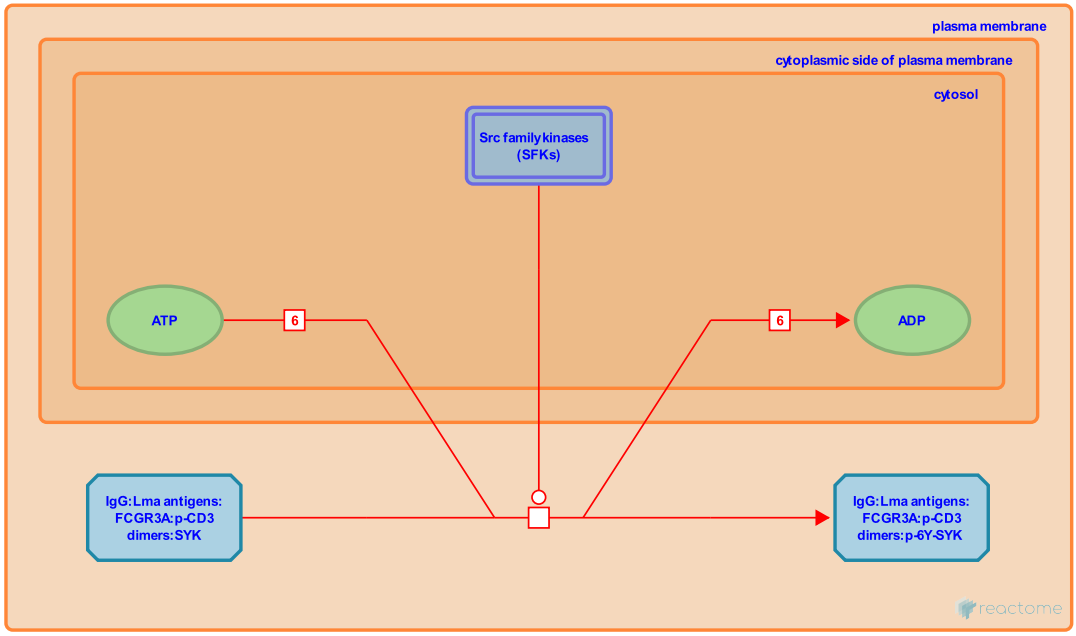
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664261

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



Multiple sites of phosphorylation are known to exist in SYK, which both regulate its activity and also serve as docking sites for other proteins. Some of these sites include Y131 of interdomain A, Y323, Y348, and Y352 of interdomain B, and Y525 and Y526 within the activation loop of the kinase domain and Y630 in the C-terminus (Zhang et al. 2002, Lupher et al. 1998, Furlong et al. 1997). Phosphorylation of these tyrosine residues disrupts autoinhibitory interactions and results in kinase activation even in the absence of phosphorylated ITAM tyrosines (Tsang et al. 2008). SYK is primarily phosphorylated by Src family kinases and this acts as an initiating trigger by generating few molecules of activated SYK which are then involved in major SYK autophosphorylation (Hillal et al. 1997).

Preceded by: SYK binds IgG:Lma antigens:FCGR3A:p-CD3 dimers

Followed by: Recruitment of PLCgamma to membrane due to FCGR3A effect

Literature references

Ashendel, CL., Furlong, MT., Geahlen, RL., Harrison, ML., Kim, KH., Mahrenholz, AM. (1997). Identification of the major sites of autophosphorylation of the murine protein-tyrosine kinase Syk. *Biochim Biophys Acta, 1355*, 177-90. ↗

Zhang, J., Berenstein, E., Siraganian, RP. (2002). Phosphorylation of Tyr342 in the linker region of Syk is critical for Fc epsilon RI signaling in mast cells. *Mol Cell Biol, 22*, 8144-54. ↗

Shaw, D., Papp, E., Gandhi, S., Tsang, E., Giannetti, AM., Tse, JK. et al. (2008). Molecular mechanism of the Syk activation switch. *J Biol Chem, 283*, 32650-9. ↗

Yamamura, H., El-Hillal, O., Kinet, JP., Kurosaki, T., Scharenberg, AM. (1997). syk kinase activation by a src kinase-initiated activation loop phosphorylation chain reaction. *Proc Natl Acad Sci U S A, 94*, 1919-24. ↗

Rao, N., Miyake, S., Lupher ML, Jr., Lill, NL., Andoniou, CE., Druker, B. et al. (1998). Cbl-mediated negative regulation of the Syk tyrosine kinase. A critical role for Cbl phosphotyrosine-binding domain binding to Syk phosphotyrosine 323. *J Biol Chem, 273*, 35273-81. ↗

Editions

2019-10-22	Authored	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Murillo, JI.

Recruitment of PLCgamma to membrane due to FCGR3A effect ↗

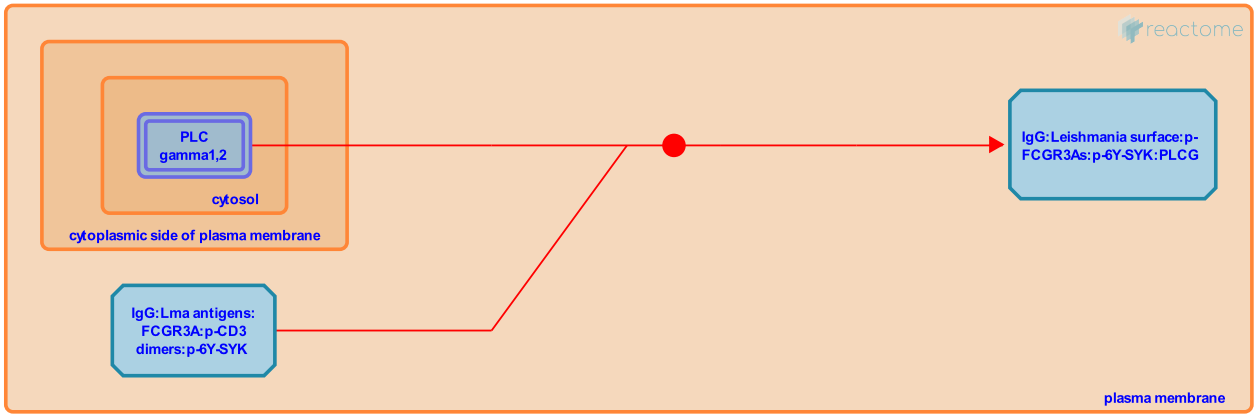
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664270

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



PLCgamma (PLCG) is recruited to FCGR and the phosphorylated Y342 and Y346 in SYK have been reported to be involved in the interaction of PLCG (Law et al. 1996). PLCG accumulates at the phagocytic cup during FCGR, but the exact role of PLCG in the regulation of phagocytosis is not clear. It may be involved in FCGR signaling by activating PKC through DAG production (Garcia-Garcia & Rosales 2002)

Preceded by: Src phosphorylate SYK in IgG:Leishmania surface:p-FCGR3A:SYK

Followed by: Phosphorylation and activation of PLCG due to FCGR3A effect

Literature references

Dusi, S., Donini, M., Della Bianca, V., Rossi, F. (1994). Tyrosine phosphorylation of phospholipase C-gamma 2 is involved in the activation of phosphoinositide hydrolysis by Fc receptors in human neutrophils. *Biochem Biophys Res Commun, 201*, 1100-8. ↗

Chandran, KA., Law, CL., Clark, EA., Sidorenko, SP. (1996). Phospholipase C-gamma1 interacts with conserved phosphotyrosyl residues in the linker region of Syk and is a substrate for Syk. *Mol Cell Biol, 16*, 1305-15. ↗

Editions

2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Authored, Edited	Murillo, JI.

Phosphorylation and activation of PLCG due to FCGR3A effect ↗

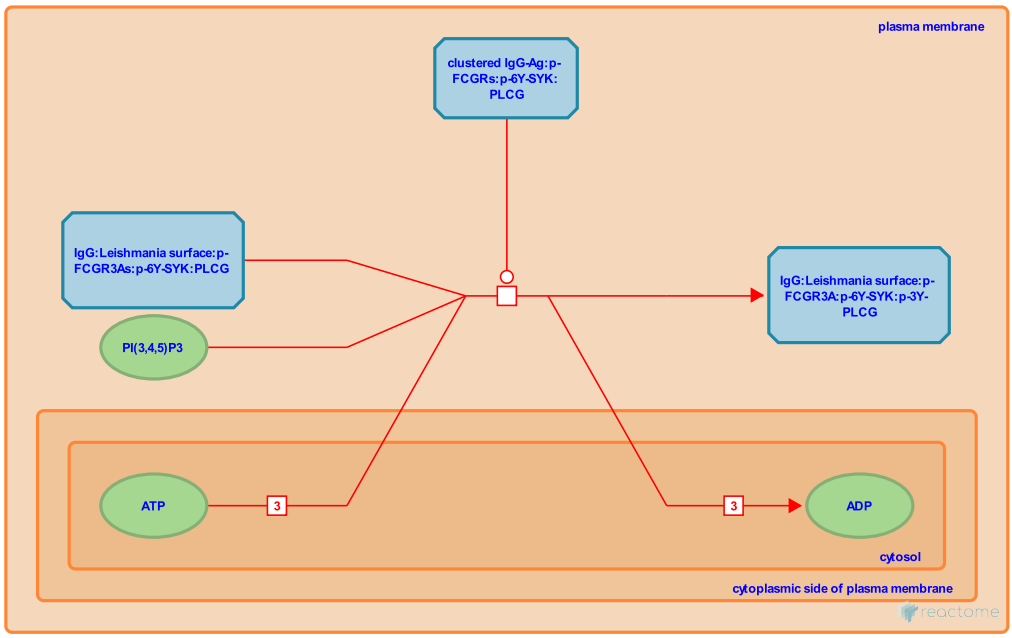
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664278

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



PLCG is tyrosine phosphorylated by either SYK or Src kinases on three tyrosine residues and this phosphorylation enhances the activity of PLCG. Although maximal activation requires binding of PLCG to PIP3 with its plecstrin homology (PH) domain.

Preceded by: Recruitment of PLCgamma to membrane due to FCGR3A effect

Followed by: Release of PLCG from FCGR3A

Literature references

Dusi, S., Donini, M., Della Bianca, V., Rossi, F. (1994). Tyrosine phosphorylation of phospholipase C-gamma 2 is involved in the activation of phosphoinositide hydrolysis by Fc receptors in human neutrophils. *Biochem Biophys Res Commun, 201*, 1100-8. ↗

Chandran, KA., Law, CL., Clark, EA., Sidorenko, SP. (1996). Phospholipase C-gamma1 interacts with conserved phosphotyrosyl residues in the linker region of Syk and is a substrate for Syk. *Mol Cell Biol, 16*, 1305-15. ↗

Kim, YJ., Rhee, SG., Sekiya, F., Poulin, B. (2004). Mechanism of tyrosine phosphorylation and activation of phospholipase C-gamma 1. Tyrosine 783 phosphorylation is not sufficient for lipase activation. *J Biol Chem, 279*, 32181-90. ↗

Editions

2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Authored, Edited	Murillo, JI.

Release of PLCG from FCGR3A ↗

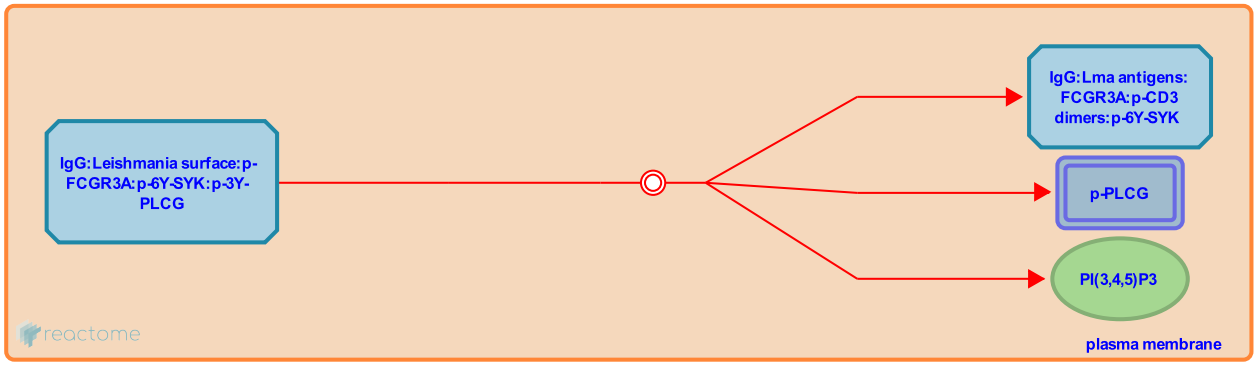
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664271

Type: dissociation

Compartments: plasma membrane, extracellular region, cytosol

Diseases: cutaneous leishmaniasis



Activated PLCG translocates to the plasmamembrane and interacts with the inositol ring of the membrane bound phosphatidylinositol 4,5-bisphosphate (PIP2) with its PH domain. The active enzyme promotes intracelllular signaling by catalysing the hydrolysis of PIP2 to generate the second messengers IP3 and DAG.

Preceded by: Phosphorylation and activation of PLCG due to FCGR3A effect

Followed by: PLC-gamma1 hydrolyses PIP2

Literature references

Ji, Q., Carpenter, G. (1999). Phospholipase C-gamma as a signal-transducing element. *Exp Cell Res, 253*, 15-24. ↗

Editions

2020-01-07	Authored	Jassal, B.
2020-01-13	Authored	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.
2020-02-05	Edited	Murillo, JI.

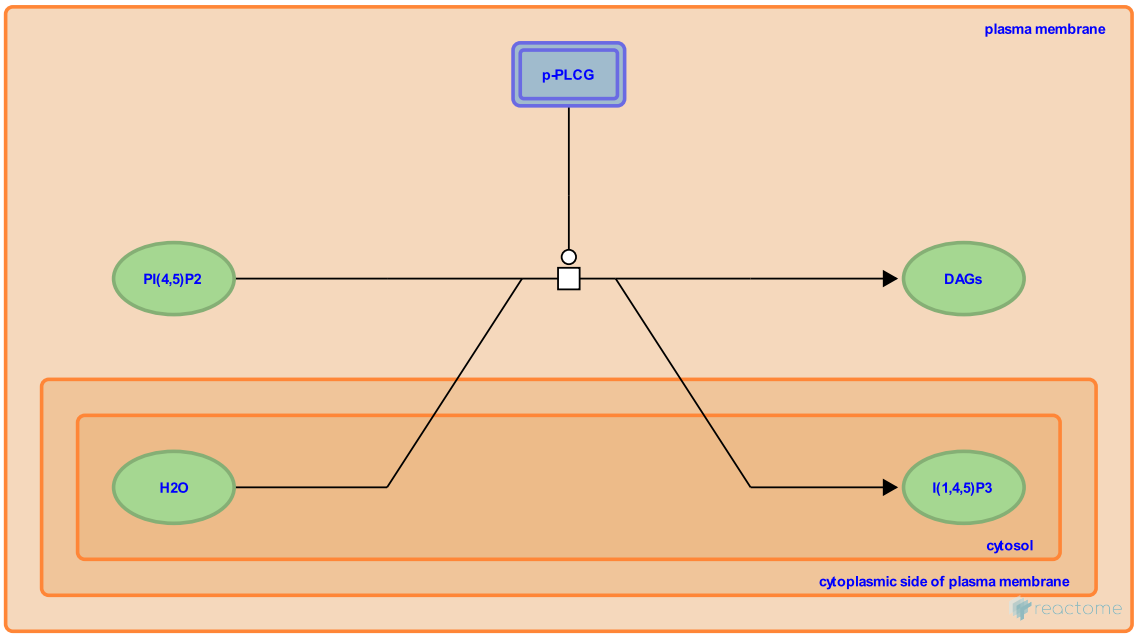
PLC-gamma1 hydrolyses PIP2 ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-202407

Type: transition

Compartments: plasma membrane, cytosol



On recruitment to plasma membrane PLC-gamma1 then hydrolyses PIP2 producing two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 induces a transient increase in intracellular free Ca++, while DAG is a direct activator of protein kinase C (PKC theta). These process have been implicated in many cellular physiological functions like cell proliferation, cell growth and differentiation.

Preceded by: Release of PLCG from FCGR3A

Followed by: IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.
2020-02-05	Edited	Murillo, JI.

IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel ↗

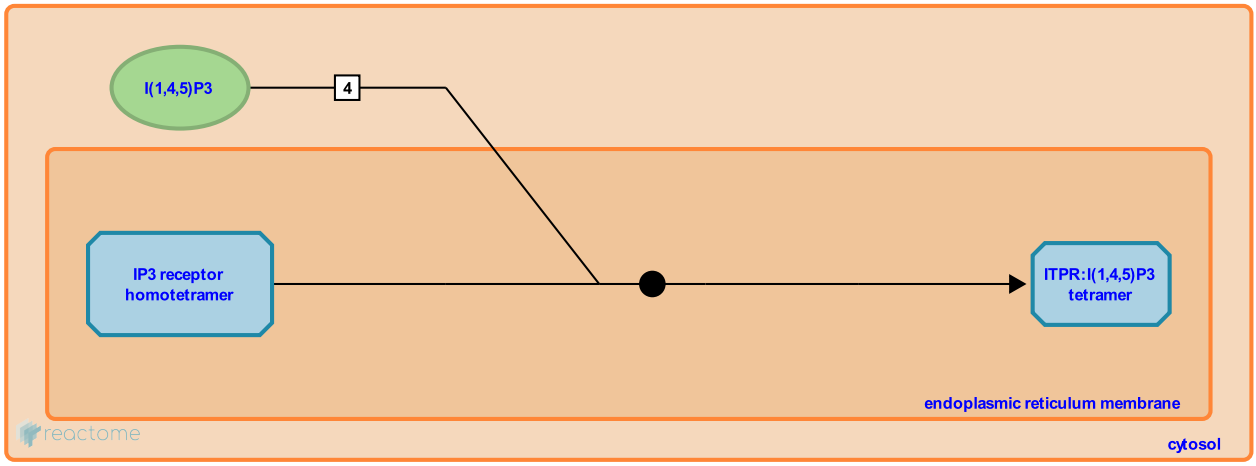
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-169680

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol

Inferred from: IP3 binds to the IP3 receptor, opening the Ca2+ channel (Rattus norvegicus)



The IP3 receptor (IP3R) is an IP3-gated calcium channel. It is a large, homotetrameric protein, similar to other calcium channel proteins such as ryanodine. The four subunits form a 'four-leafed clover' structure arranged around the central calcium channel. Binding of ligands such as IP3 results in conformational changes in the receptor's structure that leads to channel opening.

Preceded by: PLC-gamma1 hydrolyses PIP2

Followed by: IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2006-10-10	Edited	Jassal, B.
2009-06-02	Reviewed	Gillespie, ME.

IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol ↗

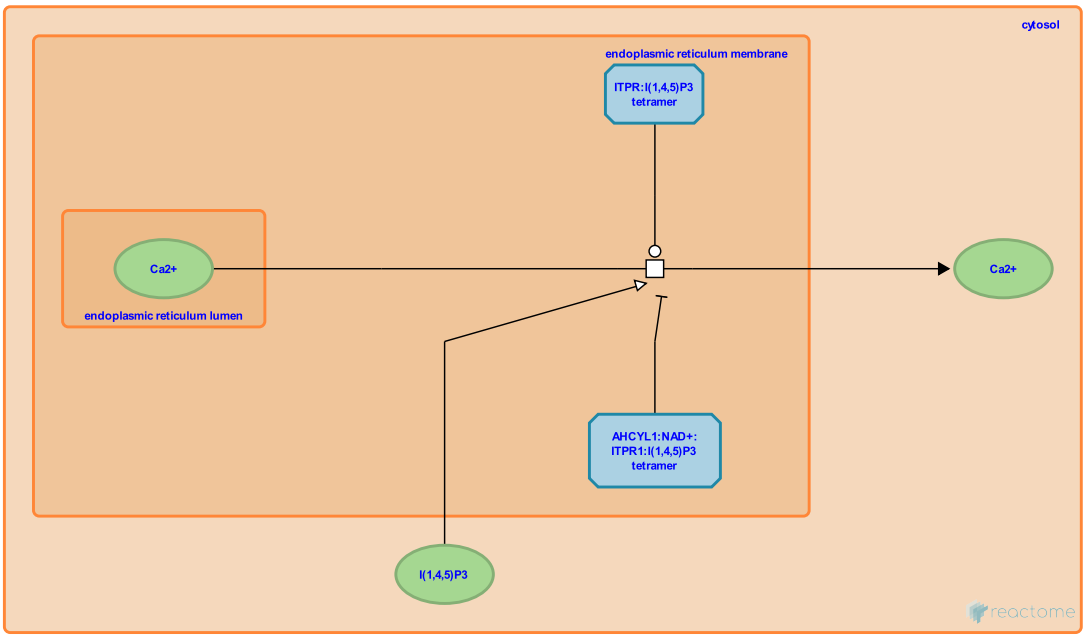
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-169683

Type: transition

Compartments: endoplasmic reticulum membrane

Inferred from: Calcium release from intracellular stores by IP3 receptor activation (Rattus norvegicus)



IP3 promotes the release of intracellular calcium.

Preceded by: IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2006-10-10	Edited	Jassal, B.
2009-06-02	Reviewed	Gillespie, ME.

Calcium binds calmodulin ↗

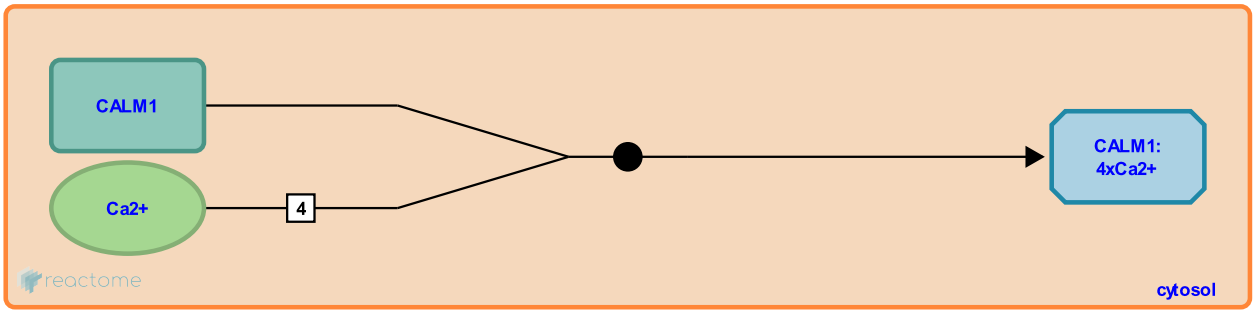
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-74448

Type: binding

Compartments: cytosol

Inferred from: Calcium binds calmodulin (Bos taurus)



Upon increase in calcium concentration, calmodulin (CaM) is activated by binding to four calcium ions (Crouch and Klee 1980).

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-01-11	Reviewed	Rush, MG.
2008-11-06	Edited	Jassal, B.

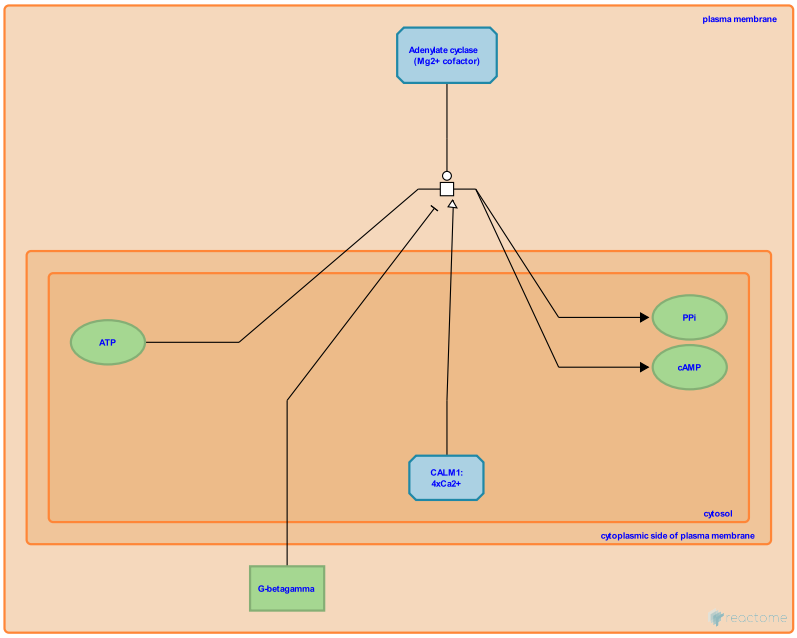
Adenylate cyclase produces cAMP ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-111930

Type: transition

Compartments: plasma membrane, cytosol



Adenylate cyclase is responsive to calcium and calmodulin and produces cAMP. One important physiological role for Calmodulin is the regulation of adenylylcyclases. Four of the ten known adenylylcyclases are calcium sensitive, in particular type 8 (AC8).

Followed by: cAMP binds PKA tetramer

Literature references

Gu, C., Cooper, DM. (1999). Calmodulin-binding sites on adenylyl cyclase type VIII. *J Biol Chem, 274*, 8012-21. ↗

Ciruela, A., Simpson, RE., Cooper, DM. (2006). The role of calmodulin recruitment in Ca2+ stimulation of adenylyl cyclase type 8. *J Biol Chem, 281*, 17379-89. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.

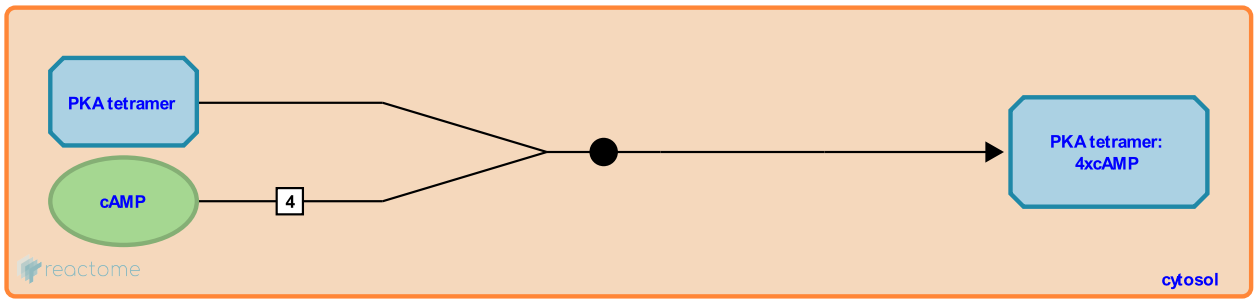
cAMP binds PKA tetramer ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-8951727

Type: binding

Compartments: cytosol



Protein kinase A (PKA) regulatory subunit isoforms differ in their tissue specificity and functional characteristics. The isoform activated in response to glucagon signaling is not known.

PKA kinase is a tetramer of two regulatory and two catalytic subunits. The regulatory subunits block the activity of the catalytic subunits.

cAMP binds the regulatory subunits, which leads to dissociation of the tetramer into two active dimers made up of a regulatory and a catalytic subunit.

Preceded by: Adenylate cyclase produces cAMP

Followed by: cAMP induces dissociation of inactive PKA tetramers

Literature references

Kim, C., Taylor, SS., McCammon, JA., Gullingsrud, J. (2006). Dynamic binding of PKA regulatory subunit RI alpha. *Structure, 14*, 141-9. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2016-11-25	Edited	Jupe, S.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

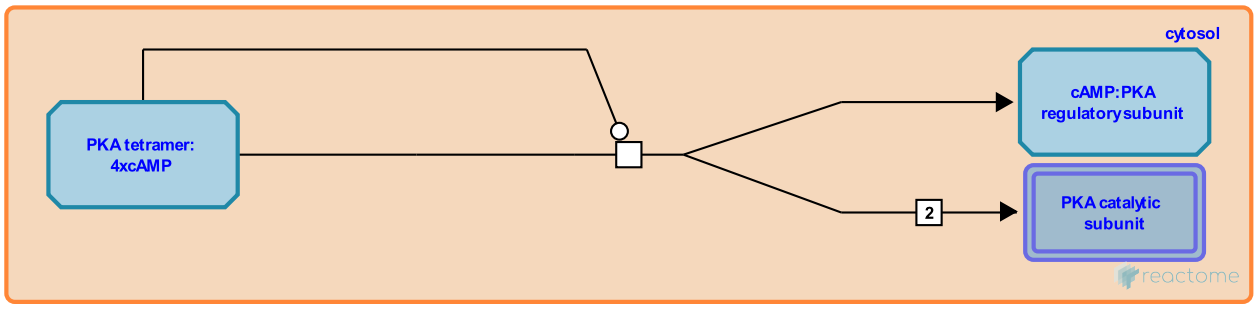
cAMP induces dissociation of inactive PKA tetramers ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-111925

Type: transition

Compartments: cytosol



The protein kinase A (PKA) regulatory subunit isoforms differ in their tissue specificity and functional characteristics. The specific isoform activated in response to glucagon signaling is not known. The PKA kinase is a tetramer of two regulatory and two catalytic subunits. The regulatory subunits block the catalytic subunits. Binding of cAMP to the regulatory subunit triggers dissociation of the tetramer into two active dimers made up of a regulatory and a catalytic subunit.

Preceded by: cAMP binds PKA tetramer

Followed by: PKA catalytic subunit translocates to the nucleus

Literature references

Kim, C., Taylor, SS., McCammon, JA., Gullingsrud, J. (2006). Dynamic binding of PKA regulatory subunit RI alpha. *Structure, 14*, 141-9. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.
2024-01-29	Reviewed	D'Eustachio, P.

PKA catalytic subunit translocates to the nucleus ↗

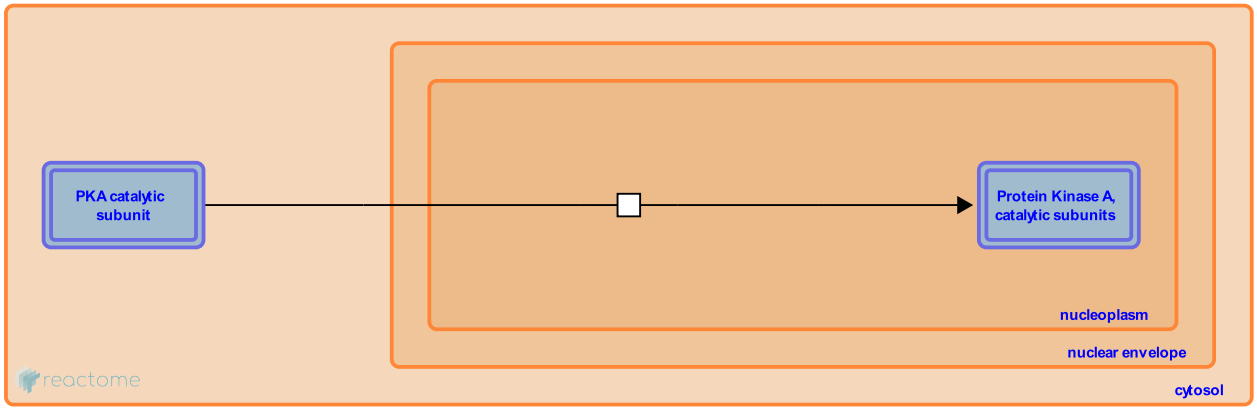
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-111924

Type: transition

Compartments: nucleoplasm, cytosol

Inferred from: PKA catalytic subunit translocates to the nucleus (Rattus norvegicus)



When cAMP level rises, the PKA catalytic subunit (C subunit) released from the holoenzyme enters the nucleus by passive diffusion whereas termination of signaling to the nucleus involves an active mechanism. In the nucleus, the C subunit binds to the heat-stable protein kinase inhibitor (PKI), and this binding not only inactivates the C subunit but also by conformational change unveils a nuclear export signal in PKI which leads to export of the C-PKI complex from the nucleus.

Preceded by: cAMP induces dissociation of inactive PKA tetramers

Followed by: PKA phosphorylates CREB1

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

PKA phosphorylates CREB1 ↗

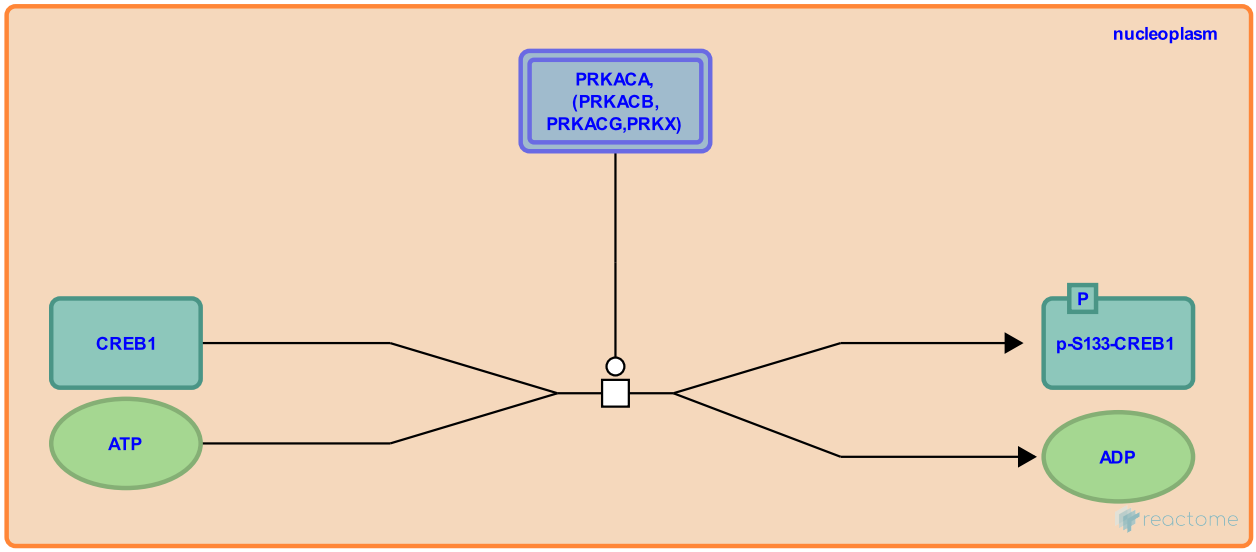
Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-111919

Type: transition

Compartments: nucleoplasm

Inferred from: Prkaca phosphorylates Creb1 (Rattus norvegicus)



Protein kinase A (PKA) has two regulatory subunits and two catalytic subunits which are held together to form the holoenzyme and is activated upon binding of cAMP to the regulatory subunits. Once cAMP binds the regulatory subunits, the catalytic subunits are released to carry out phosphorylation of CREB1 at serine residue S133. Only the PKA catalytic subunit alpha, PRKACA, was directly demonstrated to phosphorylate CREB1 at S133, using recombinant mouse and rat proteins, respectively (Gonzalez and Montminy 1989). PKA catalytic subunits beta and gamma (PRKACB and PRKACG) are candidate CREB1 kinases based on indirect evidence and sequence similarity (Nagakura et al. 2002, Liang et al. 2007, James et al. 2009). PRKX is the catalytic subunit of the cAMP dependent protein kinase X, which shares the regulatory subunits and functional properties with the PKA. PRKX is highly expressed in the mouse fetal brain (Li et al. 2005) and is implicated in CREB1 phosphorylation through indirect evidence (Di Pasquale and Stacey 1998, Li et al. 2002).

Preceded by: PKA catalytic subunit translocates to the nucleus

Followed by: CREB1 binds IL-10 promoter

Literature references

Yu, ZX., Li, W., Kotin, RM. (2005). Profiles of PrKX expression in developmental mouse embryo and human tissues. *J. Histochem. Cytochem., 53*, 1003-9. ↗

Montminy, MR., Gonzalez, GA. (1989). Cyclic AMP stimulates somatostatin gene transcription by phosphorylation of CREB at serine 133. *Cell, 59*, 675-80. ↗

Vikis, HG., Lu, Y., Liu, Y., You, M., James, MA. (2009). RGS17, an overexpressed gene in human lung and prostate cancer, induces tumor cell proliferation through the cyclic AMP-PKA-CREB pathway. *Cancer Res, 69*, 2108-16. ↗

Grundke-Iqbal, I., Iqbal, K., Gong, CX., Liang, Z., Liu, F. (2007). Down-regulation of cAMP-dependent protein kinase by over-activated calpain in Alzheimer disease brain. *J Neurochem, 103*, 2462-70. ↗

Takeo, S., Takagi, N., Nagakura, A. (2002). Impairment of cerebral cAMP-mediated signal transduction system and of spatial memory function after microsphere embolism in rats. *Neuroscience, 113*, 519-28. ↗

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-11-06	Reviewed	Castagnoli, L.
2008-11-06	Edited	Jassal, B.
2009-06-02	Edited	Gillespie, ME.
2009-10-29	Authored	Mahajan, SS.
2009-11-18	Reviewed	Tukey, D.
2018-11-02	Reviewed	Hansen, KB., Yi, F.
2018-11-07	Edited	Orlic-Milacic, M.

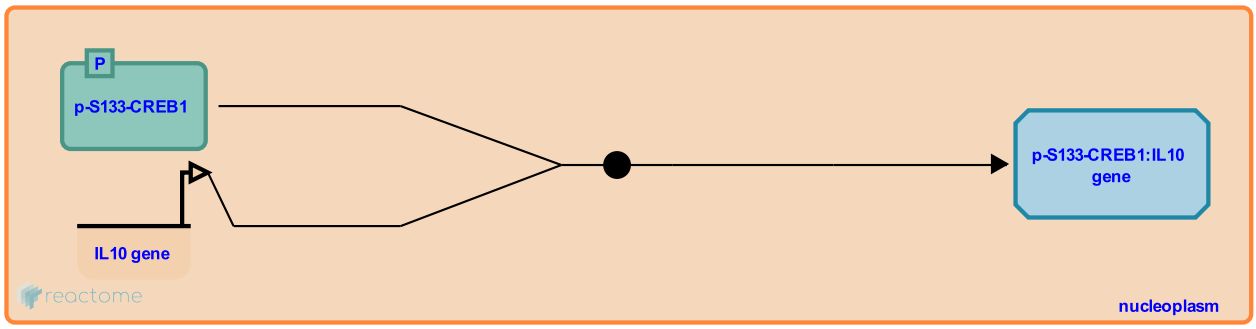
CREB1 binds IL-10 promoter ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664332

Type: binding

Compartments: nucleoplasm



The IL-10 promoter contains several transcription factor-responsive elements. (Asadullah et al 2003). In macrophages, the major source of IL-10, several receptor-mediated cytokine transcription end up in the activation of IL10 transcription factors, such as CREB (Platzer et al. 1995, Kelly et al 2010 & Sanin et al 2015)

Preceded by: PKA phosphorylates CREB1

Followed by: IL10 gene produces IL10 protein

Literature references

Prendergast, CT., Mountford, AP., Sanin, DE. (2015). IL-10 Production in Macrophages Is Regulated by a TLR-Driven CREB-Mediated Mechanism That Is Linked to Genes Involved in Cell Metabolism. *J. Immunol., 195*, 1218-32. ↗

Sterry, W., Volk, HD., Asadullah, K. (2003). Interleukin-10 therapy--review of a new approach. *Pharmacol. Rev., 55*, 241-69. ↗

Ivashkiv, LB., Kelly, EK., Wang, L. (2010). Calcium-activated pathways and oxidative burst mediate zymosan-induced signaling and IL-10 production in human macrophages. *J. Immunol., 184*, 5545-52. ↗

Meisel, C., Platzer, M., Vogt, K., Volk, HD., Platzer, C. (1995). Up-regulation of monocytic IL-10 by tumor necrosis factor-alpha and cAMP elevating drugs. *Int. Immunol., 7*, 517-23. ↗

Editions

2020-01-07	Authored, Edited	Jassal, B.
2020-01-07	Authored, Edited	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.

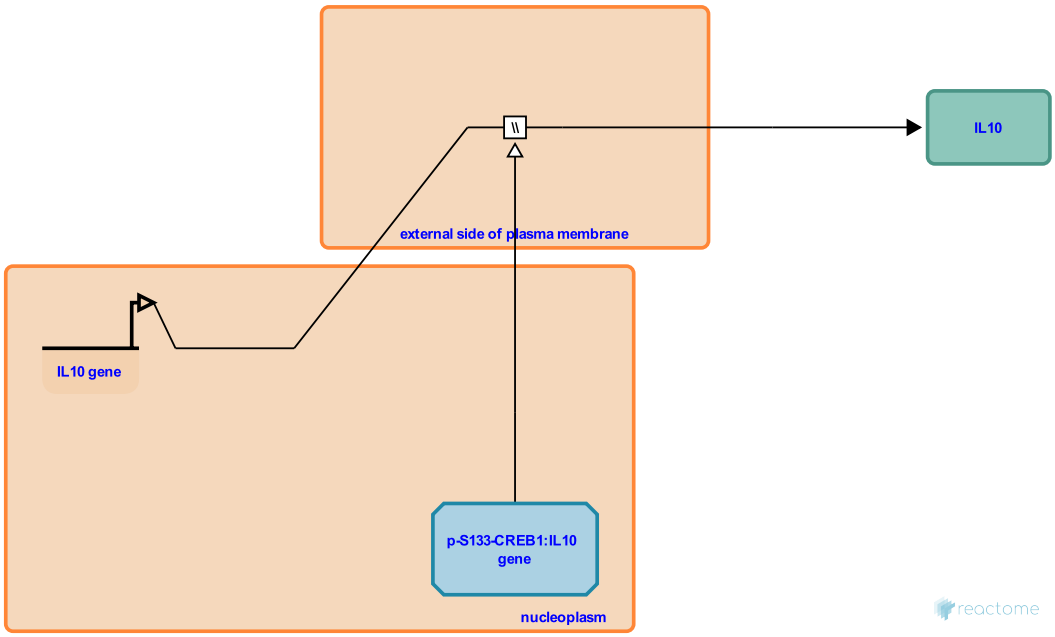
IL10 gene produces IL10 protein ↗

Location: FCGR3A-mediated IL10 synthesis

Stable identifier: R-HSA-9664346

Type: omitted

Compartments: external side of plasma membrane, nucleoplasm



The Interleukin 10 (IL10) gene is located at chromosome 1q31-32. It encodes for a protein with the same name that acts as a pleiotropic cytokine expressed primarily by monocytes and to a smaller degree by lymphocytes. IL10 down-regulates the expression of Th1 cytokines, MHC class II and costimulatory molecules on macrophages (Eskdale et al. 1997).

Preceded by: CREB1 binds IL-10 promoter

Literature references

Kube, D., Gallagher, G., Tesch, H., Eskdale, J. (1997). Mapping of the human IL10 gene and further characterization of the 5' flanking sequence. *Immunogenetics, 46*, 120-8. ↗

Editions

2020-01-07	Authored, Edited	Jassal, B.
2020-01-07	Authored, Edited	Murillo, JI.
2020-02-04	Reviewed	Gregory, DJ.

Table of Contents