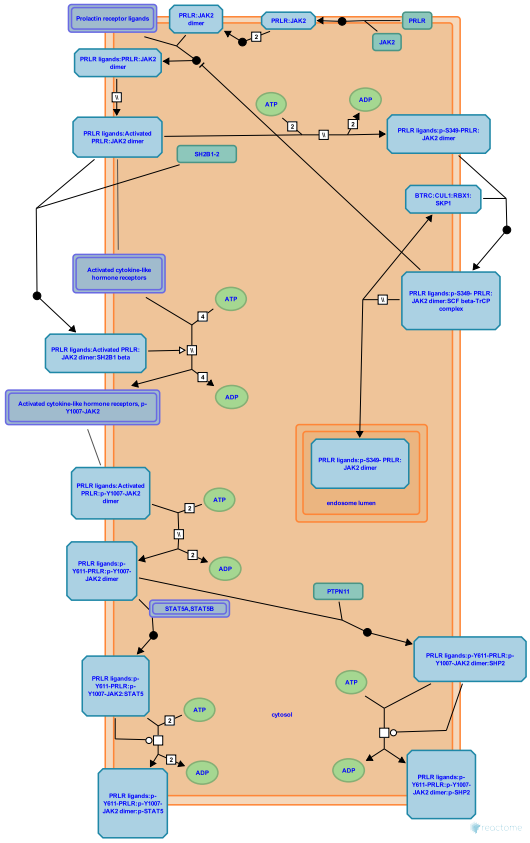
Prolactin receptor signaling



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18/11/2019

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. ↗

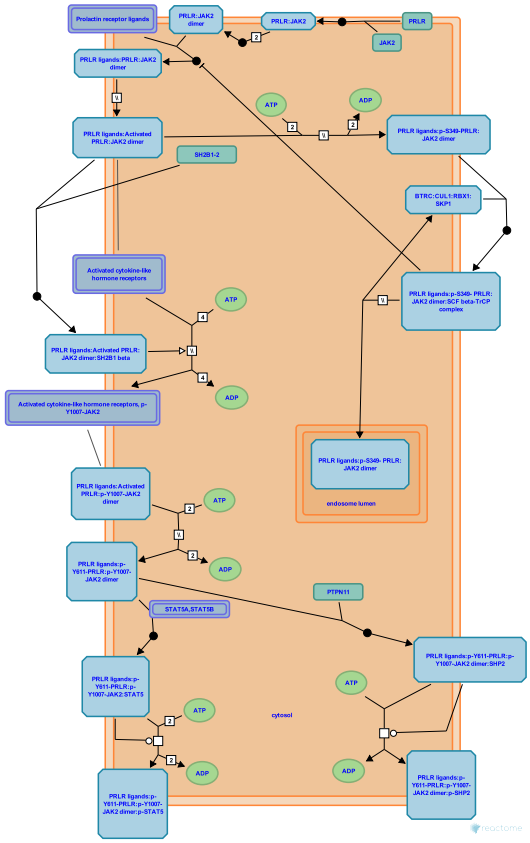
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Prolactin receptor signaling ↗

Stable identifier: R-HSA-1170546



Prolactin (PRL) is a hormone secreted mainly by the anterior pituitary gland. It was originally identified by its ability to stimulate the development of the mammary gland and lactation, but is now known to have numerous and varied functions (Bole-Feysot et al. 1998). Despite this, few pathologies have been associated with abnormalities in prolactin receptor (PRLR) signaling, though roles in various forms of cancer and certain autoimmune disorders have been suggested (Goffin et al. 2002). A vast body of literature suggests effects of PRL in immune cells (Matera 1996) but PRLR KO mice have unaltered immune system development and function (Bouchard et al. 1999). In addition to the pituitary, numerous other tissues produce PRL, including the decidua and myometrium, certain cells of the immune system, brain, skin and exocrine glands such as the mammary, sweat and lacrimal glands (Ben-Jonathan et al. 1996). Pituitary PRL secretion is negatively regulated by inhibitory factors originating from the hypothalamus, the most important of which is dopamine, acting through the D2 subclass of dopamine receptors present in lactotrophs (Freeman et al. 2000). PRL-binding sites or receptors have been identified in numerous cells and tissues of adult mammals. Various forms of PRLR, generated by alternative splicing, have been reported in several species including humans (Kelly et al. 1991, Clevenger et al. 2003).

PRLR is a member of the cytokine receptor superfamily. Like many other members of this family, the first step in receptor activation was generally believed to be ligand-induced dimerization whereby one molecule of PRL bound to two molecules of receptor (Elkins et al. 2000). Recent reports suggest that PRLR pre-assembles at the plasma membrane in the absence of ligand (Gadd & Clevenger 2006, Tallet et al. 2011), suggesting that ligand-induced activation involves conformational changes in preformed PRLR dimers (Broutin et al. 2010).

PRLR has no intrinsic kinase activity but associates (Lebrun et al. 1994, 1995) with Janus kinase 2 (JAK2) which is activated following receptor activation (Campbell et al. 1994, Rui et al. 1994, Carter-Su et al. 2000, Barua et al. 2009). JAK2-dependent activation of JAK1 has also been reported (Neilson et al. 2007). It

is generally accepted that activation of JAK2 occurs by transphosphorylation upon ligand-induced receptor activation, based on JAK activation by chimeric receptors in which various extracellular domains of cytokine or tyrosine kinase receptors were fused to the IL-2 receptor beta chain (see Ihle et al. 1994). This activation step involves the tyrosine phosphorylation of JAK2, which in turn phosphorylates PRLR on specific intracellular tyrosine residues leading to STAT5 recruitment and signaling, considered to be the most important signaling cascade for PRLR. STAT1 and STAT3 activation have also been reported (DaSilva et al. 1996) as have many other signaling pathways; signaling through MAP kinases (Shc/SOS/Grb2/Ras/Raf/MAPK) has been reported as a consequence of PRL stimuilation in many different cellular systems (see Bole-Feysot et al. 1998) though it is not clear how this signal is propagated. Other cascades non exhaustively include Src kinases, Focal adhesion kinase, phospholipase C gamma, PI3 kinase/Akt and Nek3 (Clevenger et al. 2003, Miller et al. 2007). The protein tyrosine phosphatase SHP2 is recruited to the C terminal tyrosine of PRLR and may have a regulatory role (Ali & Ali 2000). PRLR phosphotyrosines can recruit insulin receptor substrates (IRS) and other adaptor proteins to the receptor complex (Bole-Feysot et al. 1998).

Female homozygous PRLR knockout mice are completely infertile and show a lack of mammary development (Ormandy et al. 1997). Hemizogotes are unable to lactate following their first pregnancy and depending on the genetic background, this phenotype can persist through subsequent pregnancies (Kelly et al. 2001).

Literature references

Tsai-Morris, C., Dufau, M. (n.d.). PRLR (Prolactin receptor). Retrieved from http://AtlasGeneticsOncology.org/Genes/PRLRID42891ch5p14.html

Kelly, PA., Binart, N., Freemark, M., Lucas, B., Goffin, V., Bouchard, B. (2001). Prolactin receptor signal transduction pathways and actions determined in prolactin receptor knockout mice. *Biochem Soc Trans, 29*, 48-52.

Bole-Feysot, C., Goffin, V., Edery, M., Binart, N., Kelly, PA. (1998). Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr Rev, 19*, 225-68.

Goffin, V., Binart, N., Touraine, P., Kelly, PA. (2002). Prolactin: the new biology of an old hormone. *Annu Rev Physiol, 64*, 47-67.

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

PRLR associates with JAK2 ↗

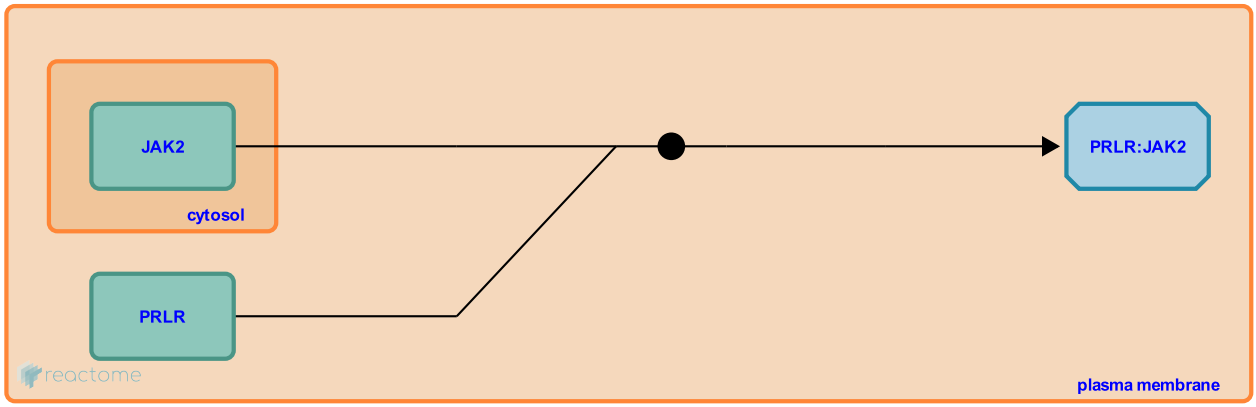
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1302698

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Prlr associates with Jak2 (Rattus norvegicus)



PRLR has no intrinsic kinase activity but associates with Janus kinase 2 (JAK2) (Lebrun et al. 1994, 1995, Campbell et al. 1994, Rui et al. 1994). PRLR to JAK2 binding has been described as constitutive but a recent computational model suggests that roughly half of dimerized Growth Hormone receptors are bound with JAK2 (Barua et al. 2009), a model that may apply to other receptors that promote JAK2 trans-activation. The box 1 region of PRLR is a membrane proximal proline-rich region in the intracellular domain, conserved in all members of the growth hormone rereptor family. This region is critical for JAK2 association; deletion of box 1 virtually abolishes PRLR signaling (Edery et al. 1994). Alanine substitutions of individual residues within box 1 of rat PRLR have shown that the most C-terminal proline (P269 in the Uniprot canonical sequence, 250 in the mature peptide) is critical for association with and subsequent activation of JAK2 (Pezet et al. 1997). It is not known whether the interaction of JAK2 with PRLR is direct or involves an adaptor protein.

When the receptor is activated by ligand binding JAK2 (receptor pre-bound or recruited after ligand binding) becomes activated and phosphorylates the dimerized receptor preferentially at Y611 (position 587 in the mature peptide), a consensus tyrosine phosphorylation site. This is followed by the phosphorylation, dimerization and nuclear translocation of STAT5. There are nine other tyrosines in the cytoplasmic domain, some of which may undergo phosphorylation and may participate in signal transduction.

Followed by: PRLR:JAK2 dimerizes

Editions

2011-06-13	Authored	Jupe, S.
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2011-11-08	Reviewed	Goffin, V.

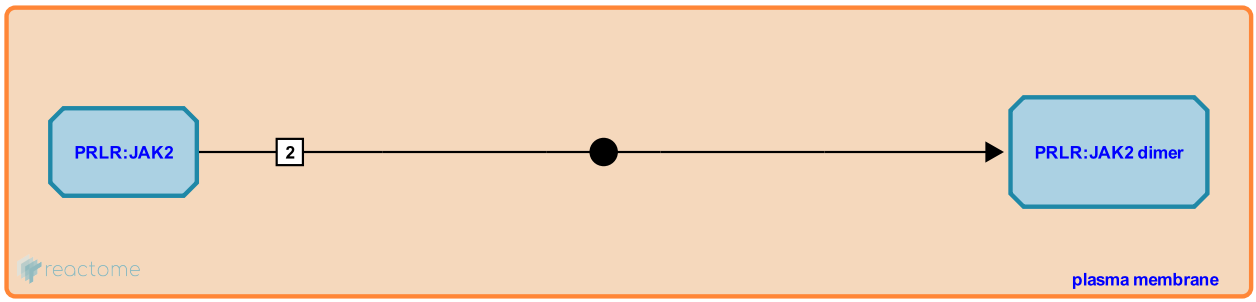
PRLR:JAK2 dimerizes ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1364044

Type: binding

Compartments: plasma membrane



The prolactin receptor (PRLR) peptide is a single transmembrane domain protein that functions as a dimer. Recent reports suggest that like many other cytokine receptors, the prolactin receptor (PRLR) preassembles at the plasma membrane in the absence of ligand (Gadd & Clevenger 2006, Tallet et al. 2011), suggesting that ligand-induced activation involves conformational changes in the preformed receptor dimer (Broutin et al. 2010).

Preceded by: PRLR associates with JAK2

Followed by: Prolactin receptor ligands bind the prolactin receptor

Literature references

Gadd, SL., Clevenger, CV. (2006). Ligand-independent dimerization of the human prolactin receptor isoforms: functional implications. *Mol Endocrinol, 20*, 2734-46. ↗

Tallet, E., Fernandez, I., Zhang, C., Salsac, M., Gregor, N., Ayoub, MA. et al. (2011). Investigation of prolactin receptor activation and blockade using time-resolved fluorescence resonance energy transfer. *Front Endocrinol (Lausanne), 2*, 29. ↗

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

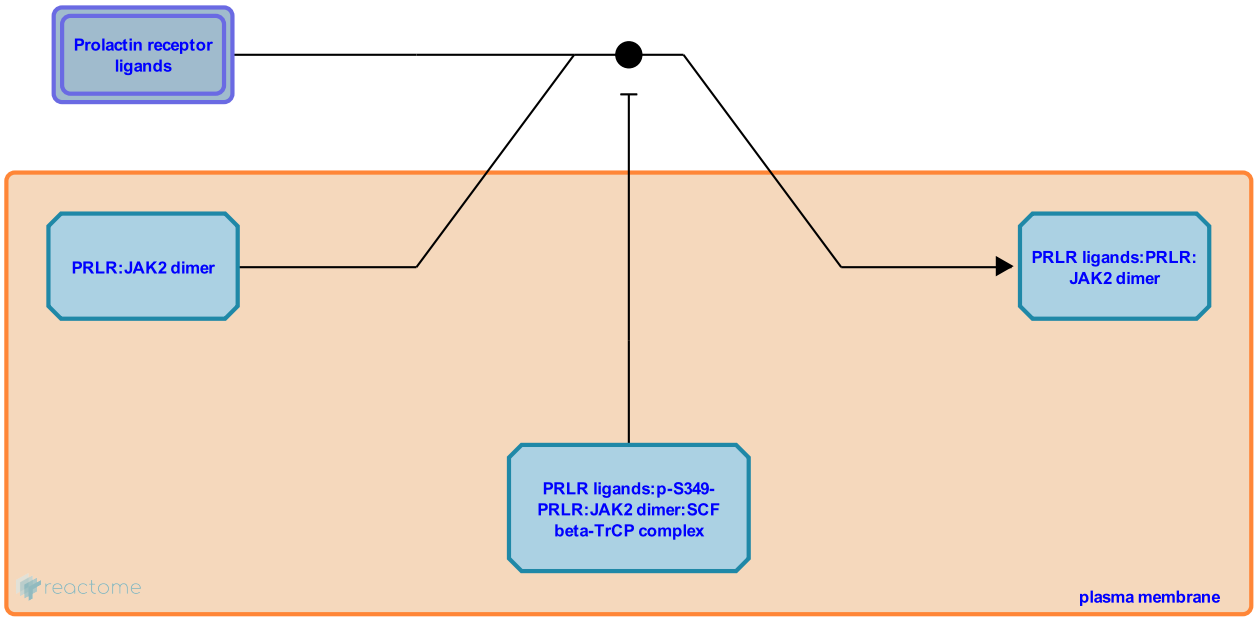
Prolactin receptor ligands bind the prolactin receptor ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-976991

Type: binding

Compartments: extracellular region, plasma membrane



Human PRLR binds at least 3 related peptide ligands namely prolactin, placental lactogen (PL) and growth hormone (GH). In non primates, GH is not able to bind the PRLR. Human GH binding to the PRLR is zinc-dependent (Cunningham et al. 1990). All three ligands bind the extracellular domain and have apparently identical actions. Two disulfide-linked cysteines in the D1 subdomain are involved in ligand binding while the WSXWS motif in the D2 subdomain is probably required for folding and cellular trafficking.

Preceded by: PRLR:JAK2 dimerizes

Followed by: PRLR activation

Literature references

Walsh, ST., Kossiakoff, AA. (2006). Crystal structure and site 1 binding energetics of human placental lactogen. *J Mol Biol, 358*, 773-84. ↗

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

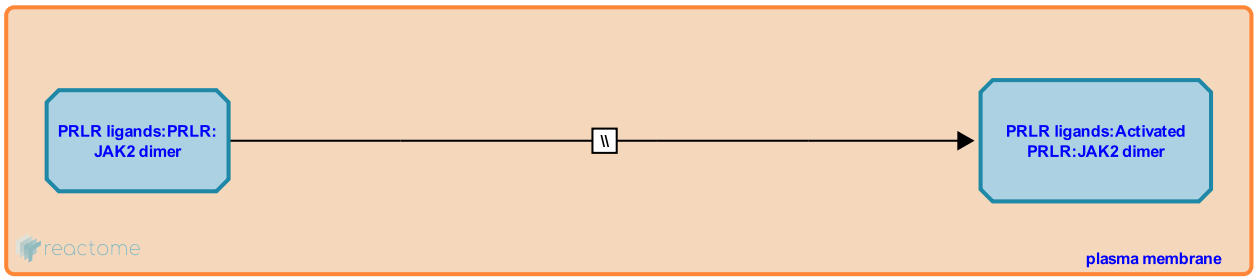
PRLR activation ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1671687

Type: omitted

Compartments: plasma membrane



Ligand binding activates the PRLR, probably by causing a subtle conformational change (Broutin et al. 2010).

Preceded by: Prolactin receptor ligands bind the prolactin receptor

Followed by: PRLR is phosphorylated at Ser-349, SH2B binds JAK2, JAK2 phosphorylation

Literature references

Broutin, I., Jomain, JB., Tallet, E., van Agthoven, J., Raynal, B., Hoos, S. et al. (2010). Crystal structure of an affinity-matured prolactin complexed to its dimerized receptor reveals the topology of hormone binding site 2. *J Biol Chem, 285*, 8422-33. ↗

Editions

2011-06-13	Authored	Jupe, S.
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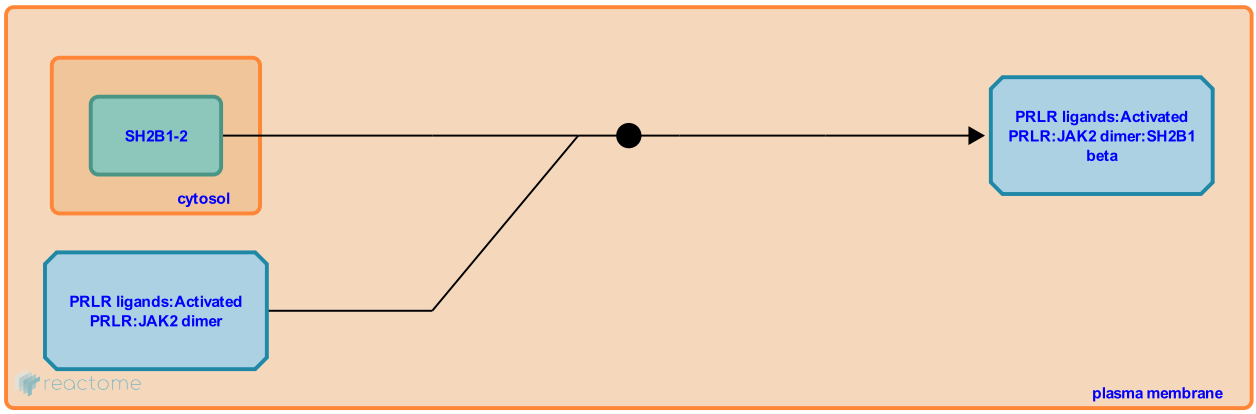
SH2B binds JAK2 ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1675473

Type: binding

Compartments: plasma membrane, cytosol



The SH2 domains of SH2B beta (Uniprot isoform Q9NRF2-2) binds JAK2 at Tyr813. SH2B beta is able to homodimerize while bound to JAK2 molecules, suggesting that SH2B binding and dimerization may help induce JAK2 transactivation (Nishi et al. 2005). Computational modeling suggests that SH2B beta can enhance Jak2 activation (Barua et al. 2009). The relevance of this for PRLR signalling has yet to be demonstrated.

Preceded by: PRLR activation

Literature references

Nishi, M., Werner, ED., Oh, BC., Frantz, JD., Dhe-Paganon, S., Hansen, L. et al. (2005). Kinase activation through dimerization by human SH2-B. *Mol Cell Biol, 25*, 2607-21. ↗

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
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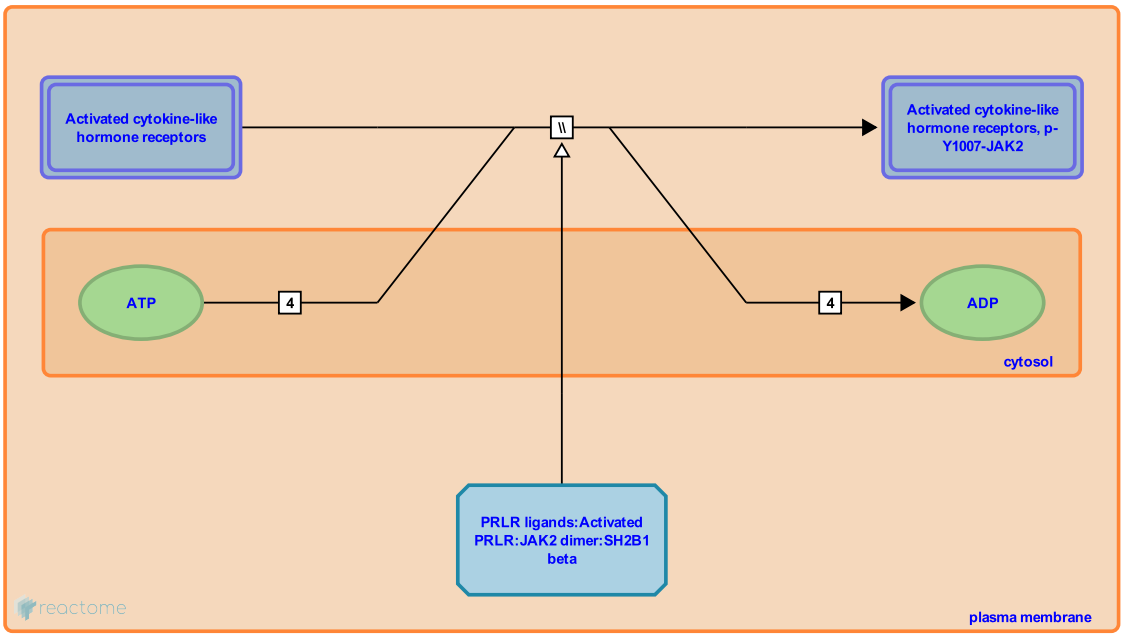
JAK2 phosphorylation ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-982810

Type: omitted

Compartments: plasma membrane, cytosol



Similar models explain JAK activation by the cytokine-like hormone receptors (GHR and PRLR) and interleukin receptors. JAK2 activation is believed to occur as mutual transactivation whereby JAK2 bound to one receptor chain phosphorylates JAK2 bound to the other receptor chain in the dimeric receptor. Transactivation is widely accepted (Herrington & Carter-Su 2001) having been originally proposed in the 1990's (Quelle et al. 1994, Hou et al. 2002). JAK phosphorylation is thought to lock the kinase domain in an active state; prior to this JAK2 is held in an inactive state by interactions between its kinase and pseudokinase domains (Giordanetto & Kroemer 2002). Although there are structures of JAK kinase domains (e.g. Lucet et al. 2006), no complete JAK structures are available and the activation mechanism remains poorly understood (Brooks & Waters 2010). The trigger for JAK activation is believed to be a conformational change in the receptor when ligand is bound, leading to a rotation of the cytoplasmic regions which brings the catalytic domains of bound JAK2 molecules into close proximity and frees them from inhibition by the pseudokinase domains. Supporting observations for cytokine-like hormone receptors include: JAK2 becomes tyrosine phosphorylated as a consequence of GHR activation by GH (Argetsinger et al. 1993); JAK2 is activated following PRLR activation (Campbell et al. 1994, Rui et al. 1994); forced dimerization of GH receptor domains is sufficient to activate signaling (Behncken et al. 2000); phosphorylation of JAK2 at Y1007 is critical for kinase activation (Feng et al. 1997, Lucet et al. 2006); JAK autophosphorylation at several other sites appears to regulate activity (e.g. Feener et al. 2004, Argetsinger et al. 2004, 2010). Only the Y1007 phosphorylation is represented in this reaction.

Preceded by: PRLR activation

Followed by: Tyrosine phosphorylation of PRLR

Literature references

Argetsinger, LS., Campbell, GS., Yang, X., Witthuhn, BA., Silvennoinen, O., Ihle, JN. et al. (1993). Identification of JAK2 as a growth hormone receptor-associated tyrosine kinase. *Cell, 74*, 237-44. ↗

Lebrun, JJ., Ali, S., Sofer, L., Ullrich, A., Kelly, PA. (1994). Prolactin-induced proliferation of Nb2 cells involves tyrosine phosphorylation of the prolactin receptor and its associated tyrosine kinase JAK2. *J Biol Chem, 269*, 14021-6. ↗

Editions

2010-10-14	Authored	Jupe, S.
2011-06-10	Edited	Jupe, S.
2011-06-13	Reviewed	Herington, AC.
2011-06-23	Reviewed	Waters, MJ.

Tyrosine phosphorylation of PRLR ↗

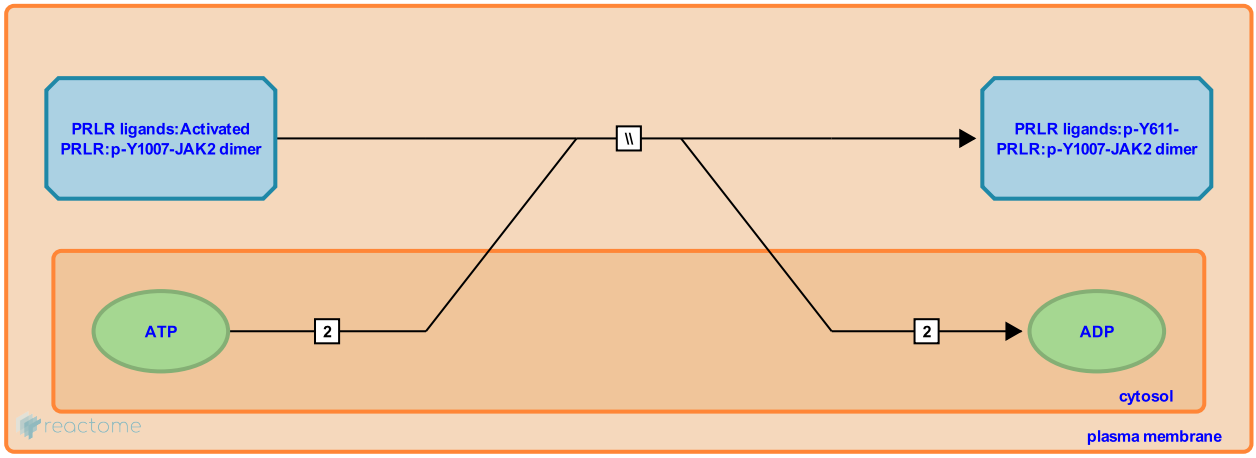
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1364043

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: Tyrosine phosphorylation of Prlr (Rattus norvegicus)



The model for PRL-induced PRLR activation suggests that JAK2 phosphorylates PRLR on specific tyrosine residues. Consistent with this, JAK2 and PRLR are phosphorylated in response to activating ligand (Lebrun et al. 1994) and PRLR tyrosine phosphorylation is required for subsequent Stat signaling (Pezet et al. 1997). Though this evidence is consistent with a role for JAK2, it has not been formally demonstrated that JAK2 is the kinase responsible for PRLR tyrosine phosphorylation.

Preceded by: JAK2 phosphorylation

Followed by: PRLR binds SHP2 (PTPN11), PRLR binds STAT5

Editions

2011-06-13	Authored	Jupe, S.
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PRLR binds STAT5 ↗

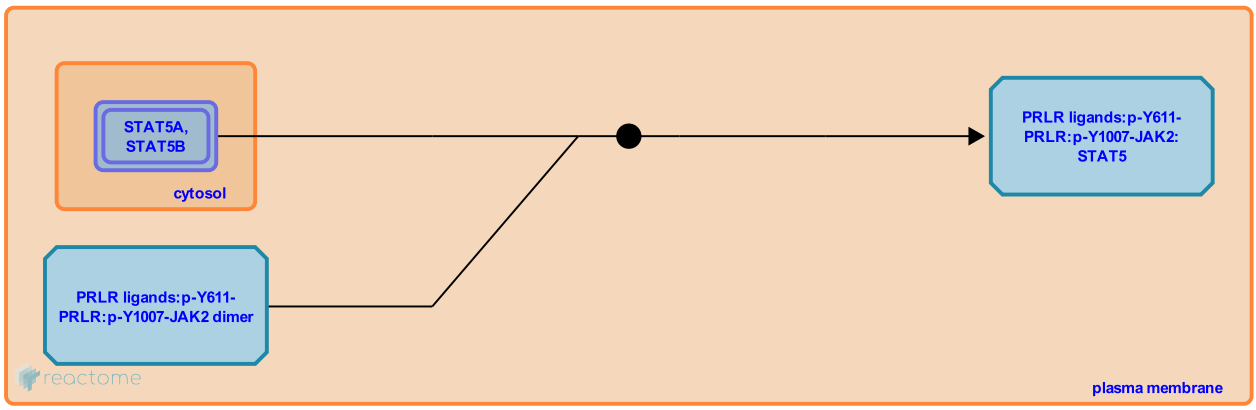
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1369080

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Prlr binds Stat5 (Rattus norvegicus)



PRLRs contain intracellular phosphorylated tyrosine residues that are able to bind and activate STATs, demonstrated by the co-immunoprecipitation of rat Stat5 and Prlrs mutated to have a single intracellular tyrosine (Pezet et al. 1997). Prlr mutants with a single tyrosine residue at positions 599, 498 or 492 (reported according to their position in the mature peptide as 580, 479 or 473 in Pezet et al. 1997) were all able to activate Stat5; Y599 gave a much stronger response. Short forms of PRLR lacking these tyrosines did not bind STAT5. The equivalent human tyrosine residues are Y509 and Y611; Y492 is not conserved in humans.

Activation of STAT1 and STAT3 by PRLR has been reported (Da Silva et al. 1996) but the interaction has been suggested to be indirect and possibly mediated by JAK2.

Preceded by: Tyrosine phosphorylation of PRLR

Followed by: PRLR-bound STAT5 is phosphorylated

Editions

2011-06-13	Authored	Jupe, S.
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PRLR-bound STAT5 is phosphorylated ↗

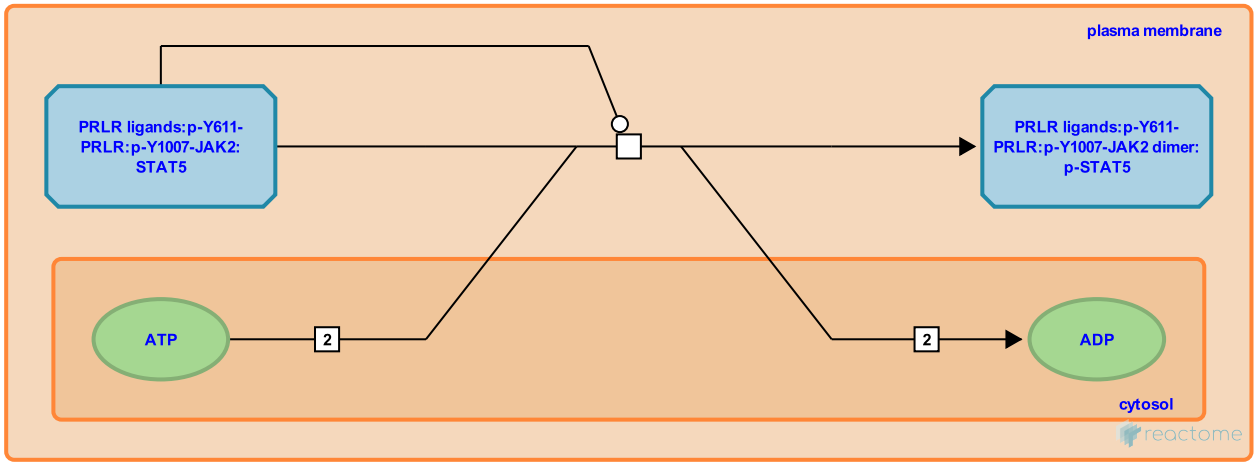
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1671691

Type: transition

Compartments: plasma membrane, cytosol, extracellular region

Inferred from: Prlr-bound Stat5 is phosphorylated (Rattus norvegicus)



Co-immunoprecipitation of rat Stat5 and Prlrs mutated to have a single intracellular tyrosine suggests that phosphorylation of these tyrosines is required for Stat5 binding and leads to Stat5 tyrosine phosphorylation (Pezet et al. 1997). STAT1 and STAT3 have both been reported to be activated by PRLR (DaSilva et al. 1996), but the region(s) of PRLR required for activation of these Stats remains poorly documented.

Preceded by: PRLR binds STAT5

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

PRLR binds SHP2 (PTPN11) ↗

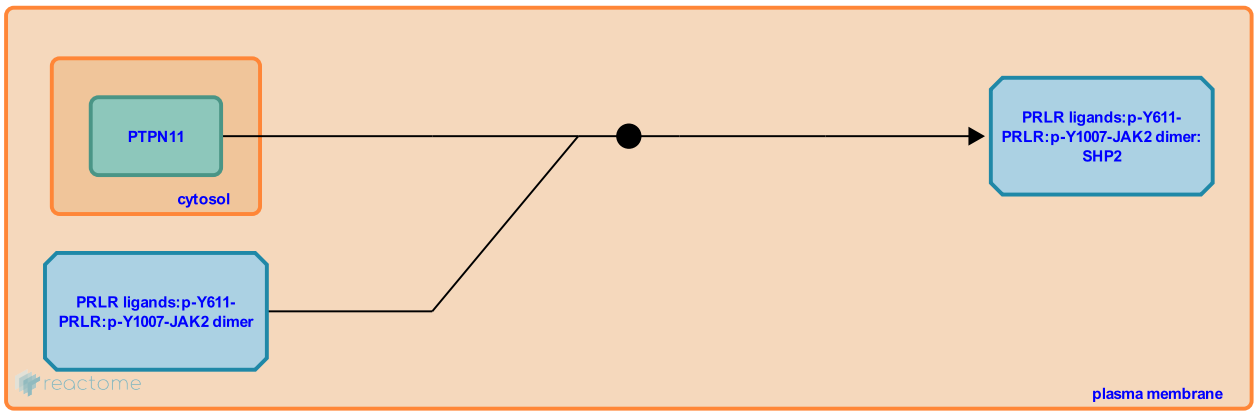
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1369114

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Prlr binds Shp2 (Rattus norvegicus)



Tyrosine-phosphorylated PRLR can bind the protein-tyrosine Phosphatase SHP2 (PTPN11) via its C-terminal SH2 Domain. This binding does not occur when the most C-terminal PRLR tyrosine residue (residue 611 in the human canonical Uniprot sequence, equivalent to 587 in the mature protein with signal peptide removed) is mutated to alanine (Ali & Ali 2000).

Preceded by: Tyrosine phosphorylation of PRLR

Followed by: SHP2 is phosphorylated

Editions

2011-06-13	Authored	Jupe, S.
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2011-11-08	Reviewed	Goffin, V.

SHP2 is phosphorylated ↗

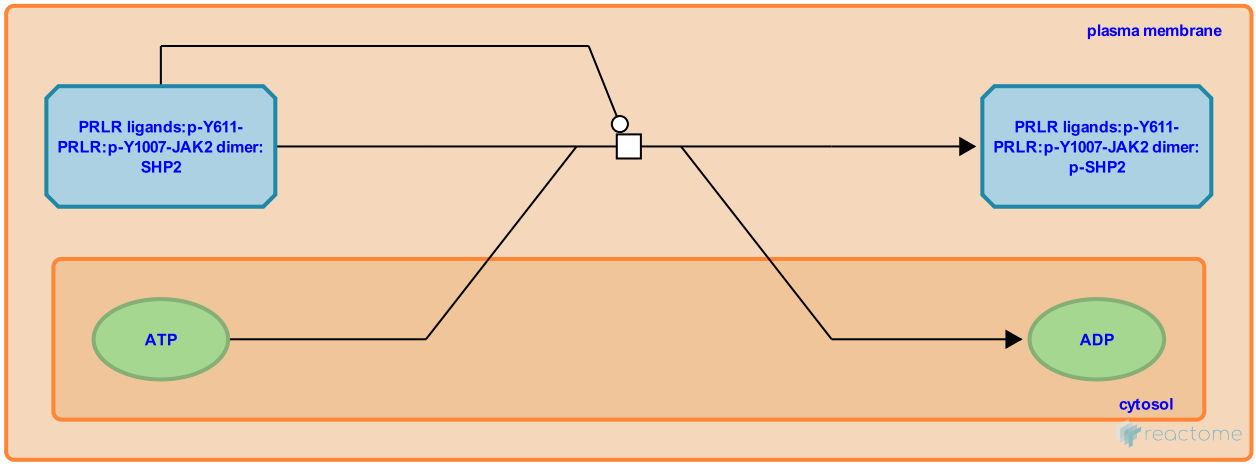
Location: Prolactin receptor signaling

Stable identifier: R-HSA-1369115

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Shp2 is phosphorylated (Rattus norvegicus)



Prolactin stimulation leads to tyrosine phosphorylation of the C-terminal SH2 domain of SHP2 and requires JAK2 (Ali et al. 1996). This has a positive regulatory influence on PRLR signaling. SHP2 has a number of signaling-capable interactors such as signal regulatory proteins (SIRPs, Kharitonenkov et al. 1997), SH2-containing inositol phosphatase (SHIP, Liu et al. 1997), insulin receptor substrates 1 and 2 (Myers et al. 1998), JAK2 (Jiao et al. 1996) and GRB2 associated binder 2 (GAB2) an adaptor protein that links activated receptor tyrosine kinase and cytokine receptors to downstream signaling molecules. PRL stimulation leads to SHP2-GAB2 association, GAB2 tyrosine phosphorylation, and GAB2-PI3K p85 subunit association, though it is not clear that this is the order of events, nor that SHP2 serves as a link between PRLR and GAB2 (Ali & Ali 2000).

Preceded by: PRLR binds SHP2 (PTPN11)

Editions

2011-06-13	Authored	Jupe, S.
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2011-11-08	Reviewed	Goffin, V.

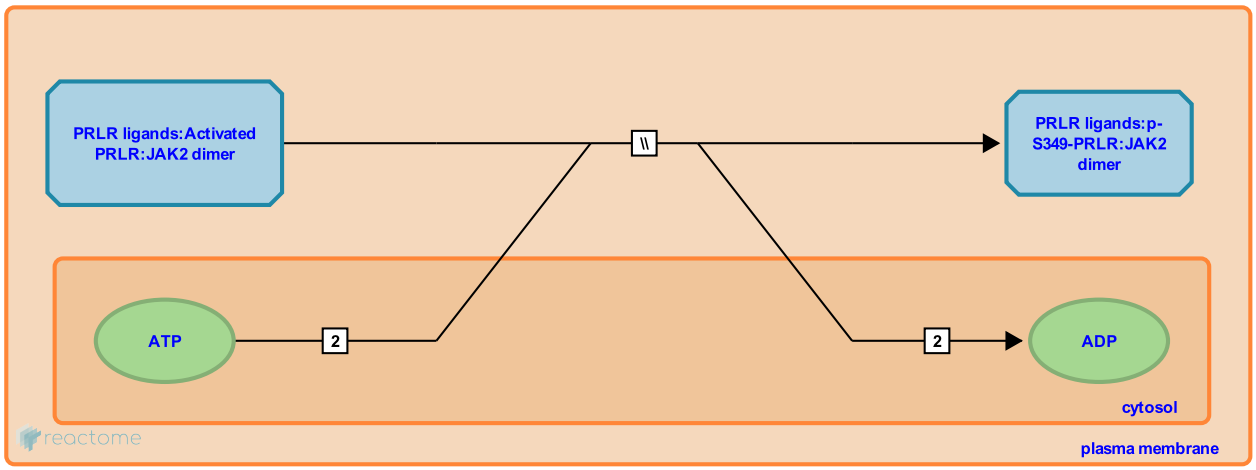
PRLR is phosphorylated at Ser-349 ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1370505

Type: omitted

Compartments: plasma membrane



The PRL responsiveness of target cells is negatively regulated by receptor internalization, ubiquitination and degradation, which limit the duration and intensity of receptor signaling (Djiane et al. 1981, 1982, Lu et al. 2002). The PRLR is phosphorylated on Ser-349 by an unidentified kinase (Li et al. 2006) enabling subsequent recruitment of the SCF beta-TrCP ubiquitin ligase complex (Li et al. 2004).

Preceded by: PRLR activation

Followed by: PRLR binds SCF beta-TrCP complex

Literature references

Li, Y., Kumar, KG., Tang, W., Spiegelman, VS., Fuchs, SY. (2004). Negative regulation of prolactin receptor stability and signaling mediated by SCF(beta-TrCP) E3 ubiquitin ligase. *Mol Cell Biol, 24*, 4038-48. ↗

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

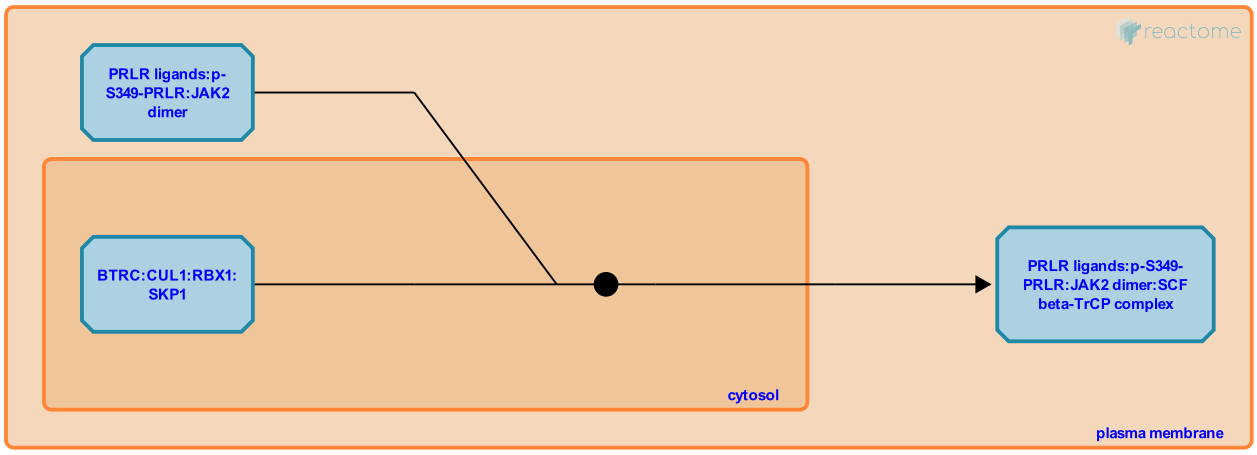
PRLR binds SCF beta-TrCP complex ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1370500

Type: binding

Compartments: cytosol, plasma membrane



Phosphorylation of PRLR on Ser-349 by an unidentified kinase enables recruitment of the SCF beta-TrCP ubiquitin ligase complex, which catalyzes ubiquitination of the receptor (Li et al. 2004). This downregulation mechanism is impaired in some forms of breast cancer (Li et al. 2006).

Preceded by: PRLR is phosphorylated at Ser-349

Followed by: Prolactin receptor is internalized

Literature references

Li, Y., Kumar, KG., Tang, W., Spiegelman, VS., Fuchs, SY. (2004). Negative regulation of prolactin receptor stability and signaling mediated by SCF(beta-TrCP) E3 ubiquitin ligase. *Mol Cell Biol, 24*, 4038-48. ↗

Editions

2011-06-13	Authored	Jupe, S.
2011-10-17	Edited	Jupe, S.
2011-11-08	Reviewed	Goffin, V.

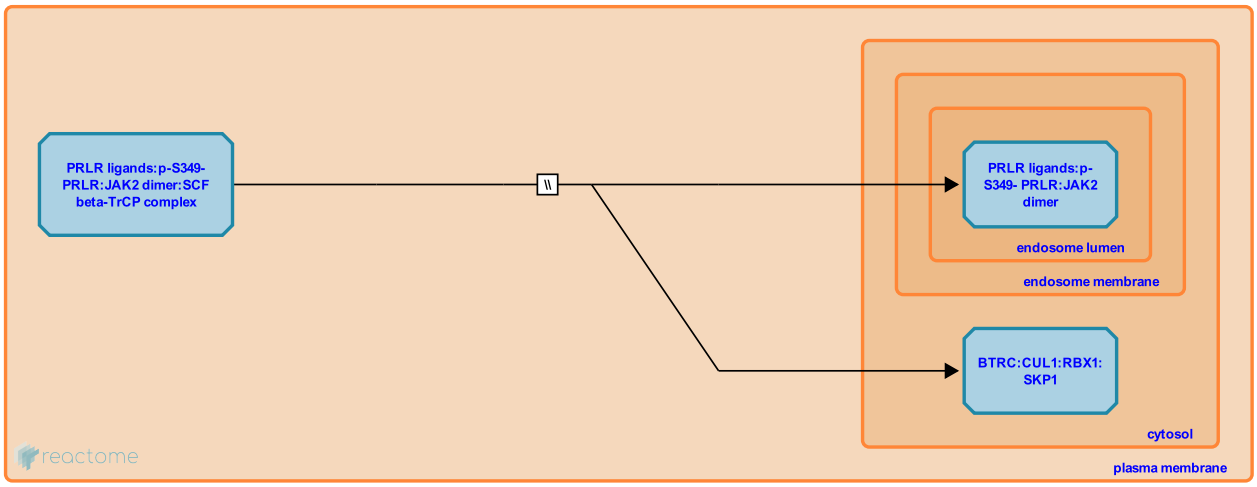
Prolactin receptor is internalized ↗

Location: Prolactin receptor signaling

Stable identifier: R-HSA-1170539

Type: omitted

Compartments: plasma membrane, cytosol, endosome lumen, extracellular region



PRLR is regulated by ubiquitination of the activated receptor, leading to lysosomal degradation (Djiane et al. 1981, 1982, Lu et al. 2002). Recruitment of the SCFbeta-TrCP ubiquitin ligase complex enables receptor ubiquitination and internalization (Li et al. 2004). This limits the duration and intensity of receptor signaling. Deregulation of this negative control lead to pathological conditions including cancer (Swaminathan et al. 2008).

Preceded by: PRLR binds SCF beta-TrCP complex

Literature references

Li, Y., Kumar, KG., Tang, W., Spiegelman, VS., Fuchs, SY. (2004). Negative regulation of prolactin receptor stability and signaling mediated by SCF(beta-TrCP) E3 ubiquitin ligase. *Mol Cell Biol, 24*, 4038-48. ↗

Editions

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