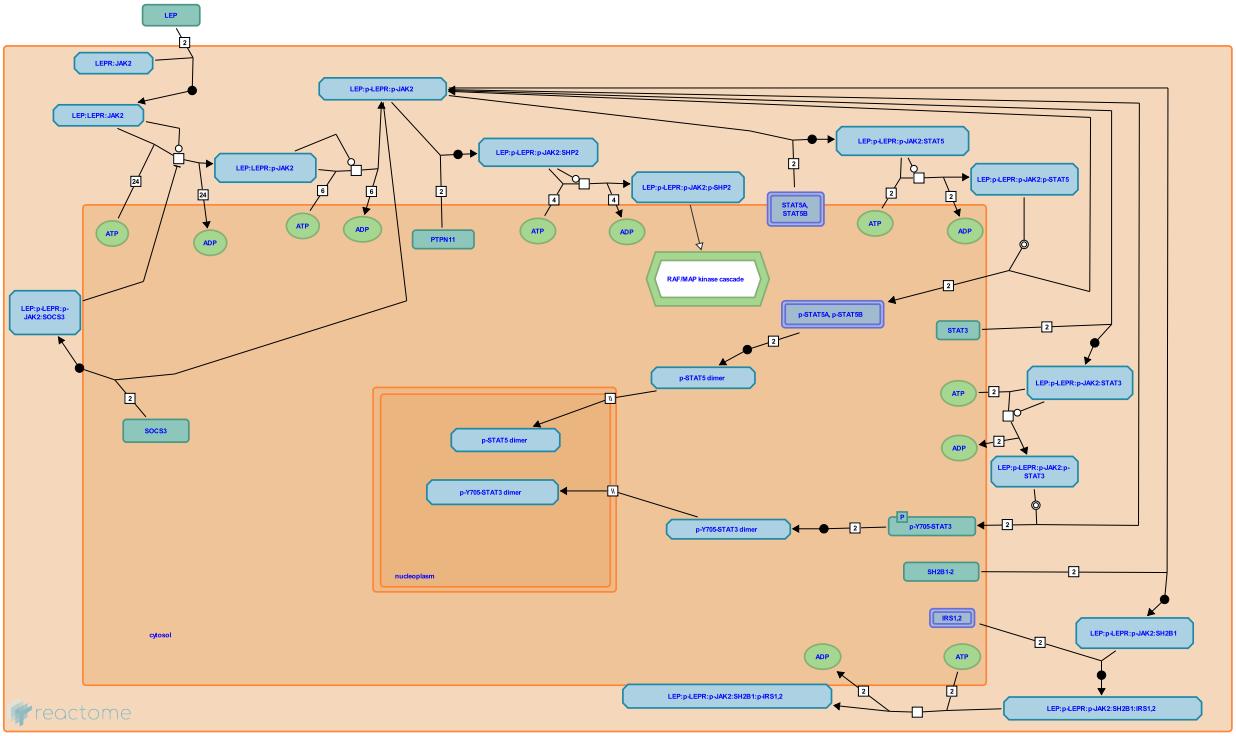
Signaling by Leptin



Birchmeier, W., Dooms, H., Gonzalez-Perez, RR., Heynen, G., Jupe, S., May, B., Pires, IM., Ray, KP., Scherer, T., Villarino, A., Waters, MJ.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

23/04/2024

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. ↗

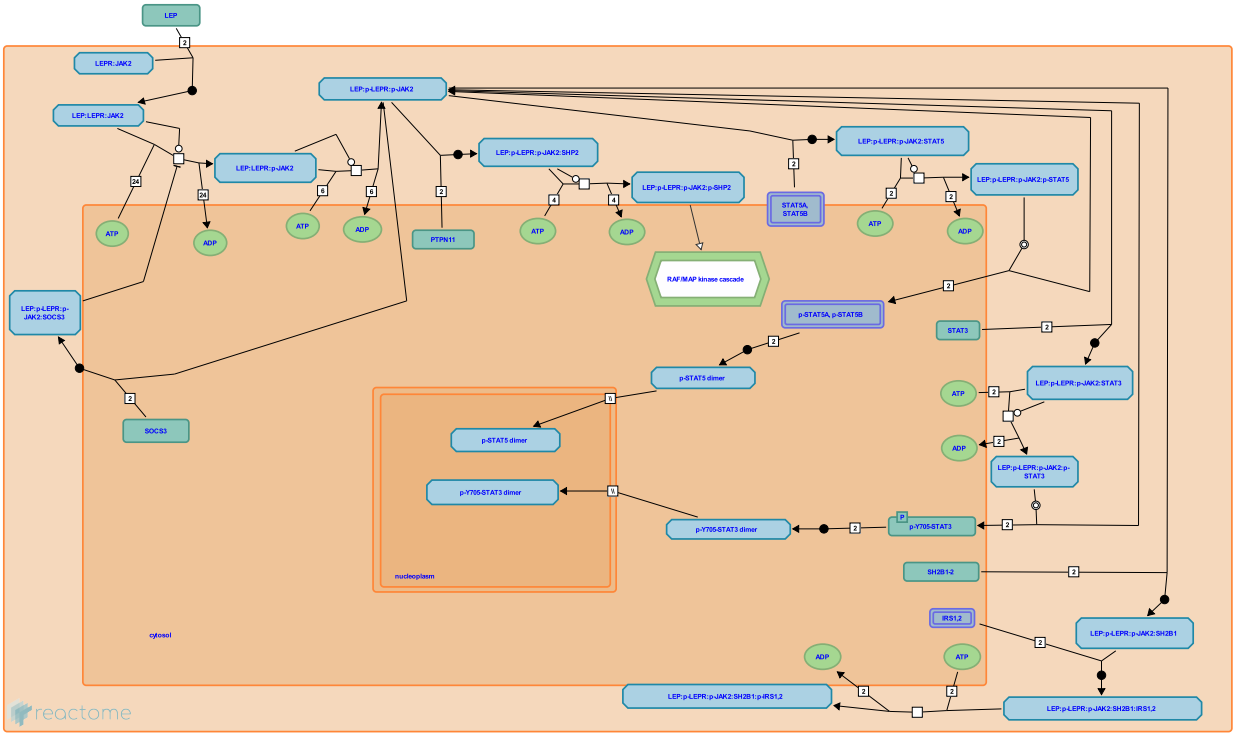
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Signaling by Leptin ↗

Stable identifier: R-HSA-2586552

Compartments: plasma membrane, cytosol



Leptin (LEP, OB, OBS), a circulating adipokine, and its receptor LEPR (DB, OBR) control food intake and energy balance and are implicated in obesity-related diseases (recently reviewed in Amitani et al. 2013, Dunmore and Brown 2013, Cottrell and Mercer 2012, La Cava 2012, Marroqui et al. 2012, Paz-Filho et al. 2012, Denver et al. 2011, Lee 2011, Marino et al. 2011, Morton and Schwartz 2011, Scherer and Buettner 2011, Shan and Yeo 2011, Wauman and Tavernier 2011, Dardeno et al. 2010, Bjorbaek 2009, Morris and Rui 2009, Myers et al. 2008), including cancer (Guo et al. 2012), inflammation (Newman and Gonzalez-Perez 2013, Iikuni et al. 2008), and angiogenesis (Gonzalez-Perez et al. 2013).

The identification of spontaneous mutations in the leptin gene (ob or LEP) and the leptin receptor gene (Ob-R, db or LEPR) genes in mice opened up a new field in obesity research. Leptin was discovered as the product of the gene affected by the ob (obesity) mutation, which causes obesity in mice. Likewise LEPR is the product of the gene affected by the db (diabetic) mutation. Leptin binding to LEPR induces canonical (JAK2/STATs; MAPK/ERK 1/2, PI-3K/AKT) and non-canonical signaling pathways (PKC, JNK, p38 MAPK and AMPK) in diverse cell types. The binding of leptin to the long isoform of LEPR (OB-Rl) initiates a phosphorylation cascade that results in transcriptional activation of target genes by STAT5 and STAT3 and activation of the PI3K pathway(not shown here), the MAPK/ERK pathway, and the mTOR/S6K pathway. Shorter LEPR isoforms with truncated intracellular domains are unable to activate the STAT pathway, but can transduce signals by way of activation of JAK2, IRS-1 or ERKs, including MAPKs.

LEPR is constitutively bound to the JAK2 kinase. Binding of LEP to LEPR causes a conformational change in LEPR that activates JAK2 autophosphorylation followed by phosphorylation of LEPR by JAK2. Phosphorylated LEPR binds STAT3, STAT5, and SHP2 which are then phosphorylated by JAK2. Phosphorylated JAK2 binds SH2B1 which then binds IRS1/2, resulting in phosphorylation of IRS1/2 by JAK2. Phosphorylated STAT3 and STAT5 dimerize and translocate to the nucleus where they activate transcription of target genes (Jovanovic et al. 2010). SHP2 activates the MAPK pathway. IRS1/2 activate the PI3K/AKT pathway which may be the activator of mTOR/S6K.

Several isoforms of LEPR have been identified (reviewed in Gorska et al. 2010). The long isoform (LEPRb, OBRb) is expressed in the hypothalamus and all types of immune cells. It is the only isoform known to fully activate signaling pathways in response to leptin. Shorter isoforms (LEPRa, LEPRc, LEPRd, and a soluble isoform LEPRe) are able to interact with JAK kinases and activate other pathways, however their roles in energy homeostasis are not fully characterized.

Literature references

Cowley, MA., Münzberg, H., Myers, MG. (2008). Mechanisms of leptin action and leptin resistance. *Annu. Rev. Physiol., 70*, 537-56.

Gonzalez-Perez, RR., Liu, M., Guo, S., Wang, G., Torroella-Kouri, M. (2012). Oncogenic role and therapeutic target of leptin signaling in breast cancer and cancer stem cells. *Biochim. Biophys. Acta, 1825*, 207-22.

Bonett, RM., Denver, RJ., Boorse, GC. (2011). Evolution of leptin structure and function. *Neuroendocrinology, 94*, 21-38 .

Mercer, JG., Cottrell, EC. (2012). Leptin receptors. *Handb Exp Pharmacol*, 3-21.

Iikuni, N., Matarese, G., Lam, QL., Lu, L., La Cava, A. (2008). Leptin and Inflammation. *Curr Immunol Rev, 4*, 70-79.

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Leptin Binds Leptin Receptor ↗

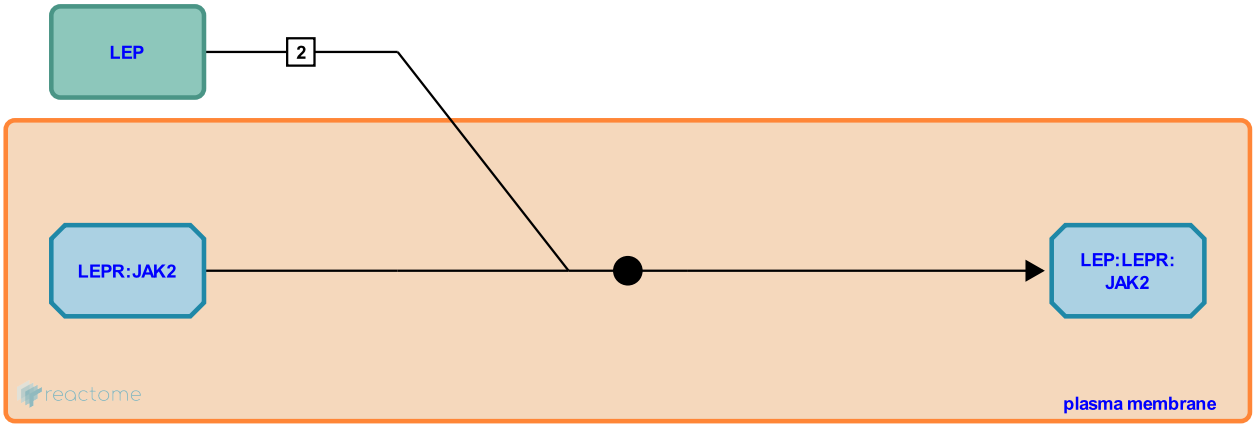
Location: Signaling by Leptin

Stable identifier: R-HSA-2586559

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Leptin Binds Leptin Receptor (Mus musculus)



Analysis of a structural model of the Leptin-LEPR complex using as a basis the complex formed by granulocyte-colony stimulator factor (GCSF) and its receptor G-CSF R (Hiroike et al., 2000) suggested that helices I and III of the human leptin structure were likely sites of interaction with the cytokine binding domain of leptin receptor (Gonzalez and Leavis, 2003). It is believed that the Leptin receptor (LEPR) is a dimer constitutively bound in a complex with JAK2 kinase (Couturier and Jockers 2003). It has been proposed that one molecule of Leptin binds each monomer of LEPR (Luoh et al. 1997, Mistrik et al. 2004), however these suggestions need further proof becasue the structure of the Leptin:LEPR complex has not yet been solved.

Followed by: JAK2 Autophosphorylates in Response to Leptin

Literature references

Leavis, PC., Gonzalez, RR. (2003). A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. *Endocrine, 21*, 185-95. ↗

Moreau, F., Mistrík, P., Allen, JM. (2004). BiaCore analysis of leptin-leptin receptor interaction: evidence for 1:1 stoichiometry. *Anal. Biochem., 327*, 271-7. ↗

Luoh, SM., Spencer, SA., Williams, M., de Sauvage, FJ., Nelson, C., Bennett, GL. et al. (1997). Cloning and characterization of a human leptin receptor using a biologically active leptin immunoadhesin. *J. Mol. Endocrinol., 18*, 77-85 . ↗

Toh, H., Hiroike, T., Jingami, H., Higo, J. (2000). Homology modeling of human leptin/leptin receptor complex. *Biochem. Biophys. Res. Commun., 275*, 154-8. ↗

Jockers, R., Couturier, C. (2003). Activation of the leptin receptor by a ligand-induced conformational change of constitutive receptor dimers. *J. Biol. Chem., 278*, 26604-11. ↗

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JAK2 Autophosphorylates in Response to Leptin ↗

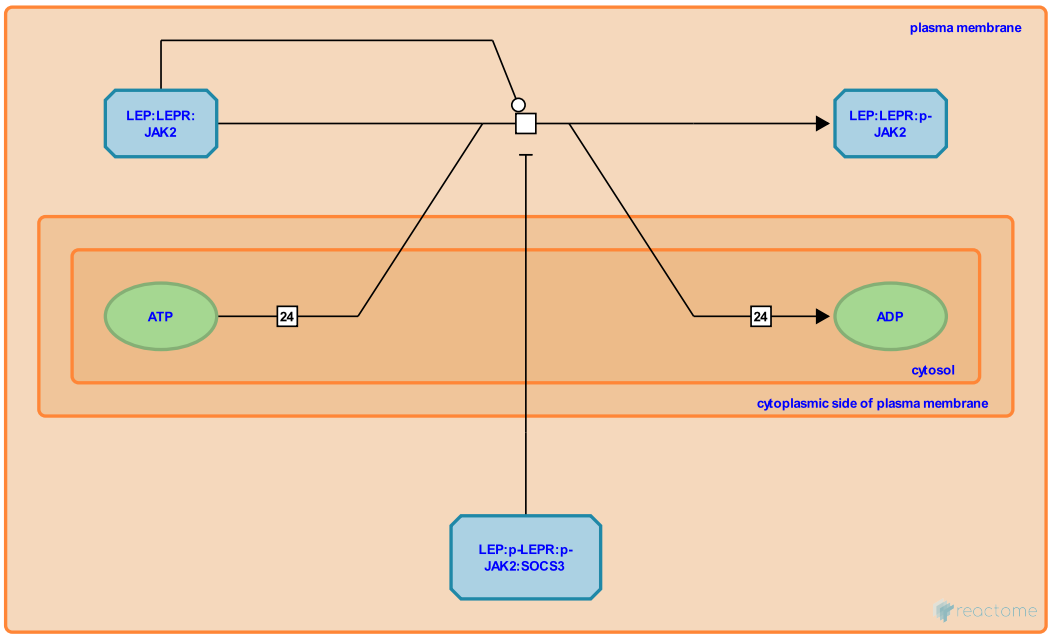
Location: Signaling by Leptin

Stable identifier: R-HSA-2586555

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Autophosphorylates in Response to Leptin (Mus musculus)



As inferred from mouse, binding of Leptin (LEP) to the Leptin receptor (LEPR) causes a conformational change in LEPR that activates autophosphorylation of JAK2 at multiple tyrosine residues. Phosphorylated JAK2 has much higher kinase activity than unphosphorylated JAK2.
As inferred from mouse, the kinase inhibitory domain of SOCS3 interacts with the activation loop of jAK2 and inhibits the phosphorylation of JAK2.

Preceded by: Leptin Binds Leptin Receptor

Followed by: JAK2 Phosphorylates LEPR

Literature references

Frantz, JD., Flier, JS., El-Haschimi, K., Bjørbaek, C. (1999). The role of SOCS-3 in leptin signaling and leptin resistance. *J. Biol. Chem., 274*, 30059-65. ↗

Editions

2012-11-15	Authored	May, B.
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2013-10-26	Reviewed	Gonzalez-Perez, RR.

JAK2 Phosphorylates LEPR ↗

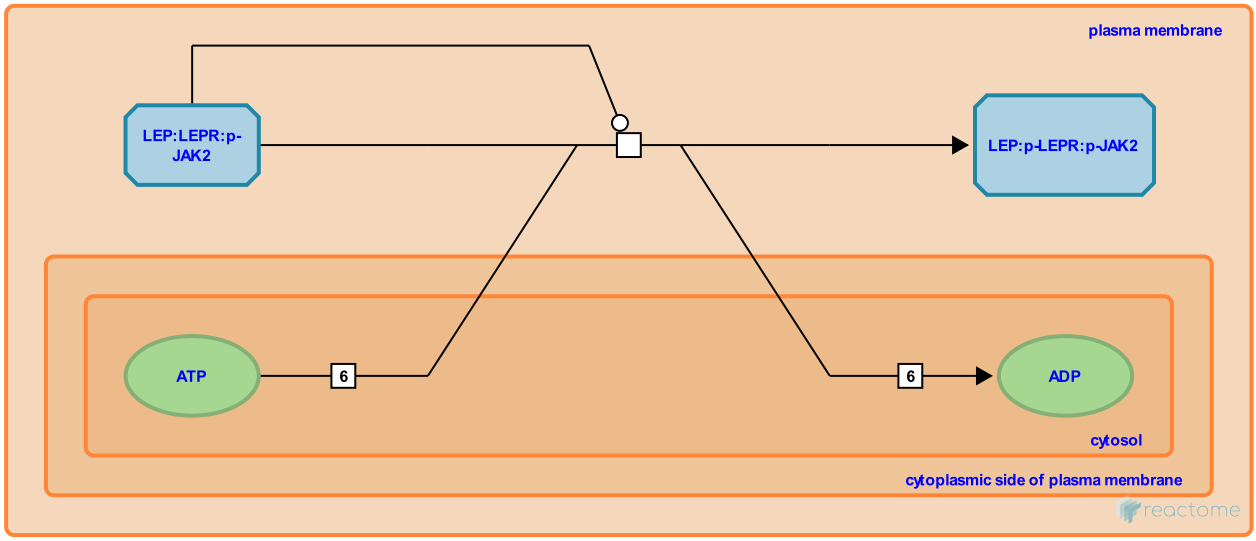
Location: Signaling by Leptin

Stable identifier: R-HSA-2586553

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Phosphorylates Lepr (Mus musculus)



Phosphorylated JAK2 phosphorylates the Leptin receptor (LEPR or OB-Rl, long isoform) at multiple tyrosine residues in the C-terminal, cytoplasmic domain (Bjorbaek et al. 1997, White et al. 1997, Ghilardi and Skoda 1997, Carpenter et al. 1998). The phosphotyrosines residues of LEPR then act as docking sites for downstream effectors STAT5, STAT3, SHP2, SH2B1, and SOCS3.

Preceded by: JAK2 Autophosphorylates in Response to Leptin

Followed by: Phosphorylated LEPR Binds SHP2 (PTPN11), Phosphorylated LEP:LEPR:JAK2 Binds SH2B1, Phosphorylated LEPR Binds STAT5, Phosphorylated LEPR Binds SOCS3, Phosphorylated LEPR Binds STAT3

Literature references

White, DW., Kuropatwinski, KK., Baumann, H., Devos, R., Tartaglia, LA. (1997). Leptin receptor (OB-R) signaling. Cytoplasmic domain mutational analysis and evidence for receptor homo-oligomerization. *J. Biol. Chem., 272*, 4065-71. ↗

da Silva, B., Uotani, S., Flier, JS., Bjørbaek, C. (1997). Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J. Biol. Chem., 272*, 32686-95. ↗

Ghilardi, N., Skoda, RC. (1997). The leptin receptor activates janus kinase 2 and signals for proliferation in a factor-dependent cell line. *Mol. Endocrinol., 11*, 393-9. ↗

Symes, A., Stahl, N., Farruggella, TJ., Yancopoulos, GD., Carpenter, LR., Karow, ML. (1998). Enhancing leptin response by preventing SH2-containing phosphatase 2 interaction with Ob receptor. *Proc. Natl. Acad. Sci. U.S.A., 95*, 6061-6. ↗

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2012-11-15	Authored	May, B.
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Phosphorylated LEPR Binds SHP2 (PTPN11) ↗

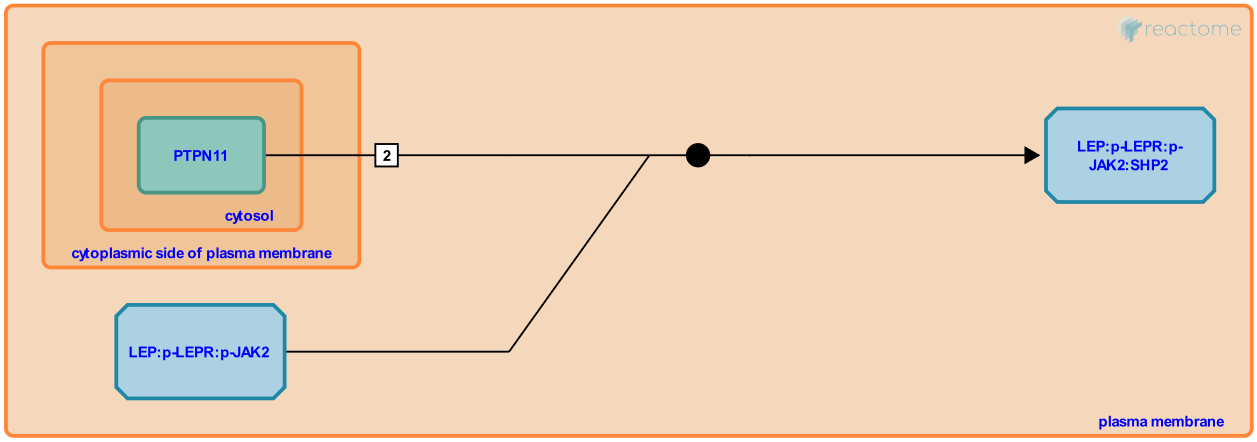
Location: Signaling by Leptin

Stable identifier: R-HSA-2671747

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Lepr Binds Shp2 (Mus musculus)



SHP2 (PTPN11) interacts with phosphotyrosine-986 of the phosphorylated Leptin receptor (LEPR) (Carpenter et al. 1998). The corresponding site in mouse is phosphotyrosine-985 and in rat phosphotyrosine-986.
SHP2 and SOCS3 compete for the same binding site on LEPR. SHP2 activates MAPK signaling, probably by recruiting GRB2:SOS which activates RAS.

Preceded by: JAK2 Phosphorylates LEPR

Followed by: JAK2 Phosphorylates SHP2 (PTPN11) in Response to Leptin

Literature references

Symes, A., Stahl, N., Farruggella, TJ., Yancopoulos, GD., Carpenter, LR., Karow, ML. (1998). Enhancing leptin response by preventing SH2-containing phosphatase 2 interaction with Ob receptor. *Proc. Natl. Acad. Sci. U.S.A., 95* , 6061-6. ↗

Editions

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2013-10-26	Reviewed	Gonzalez-Perez, RR.

JAK2 Phosphorylates SHP2 (PTPN11) in Response to Leptin ↗

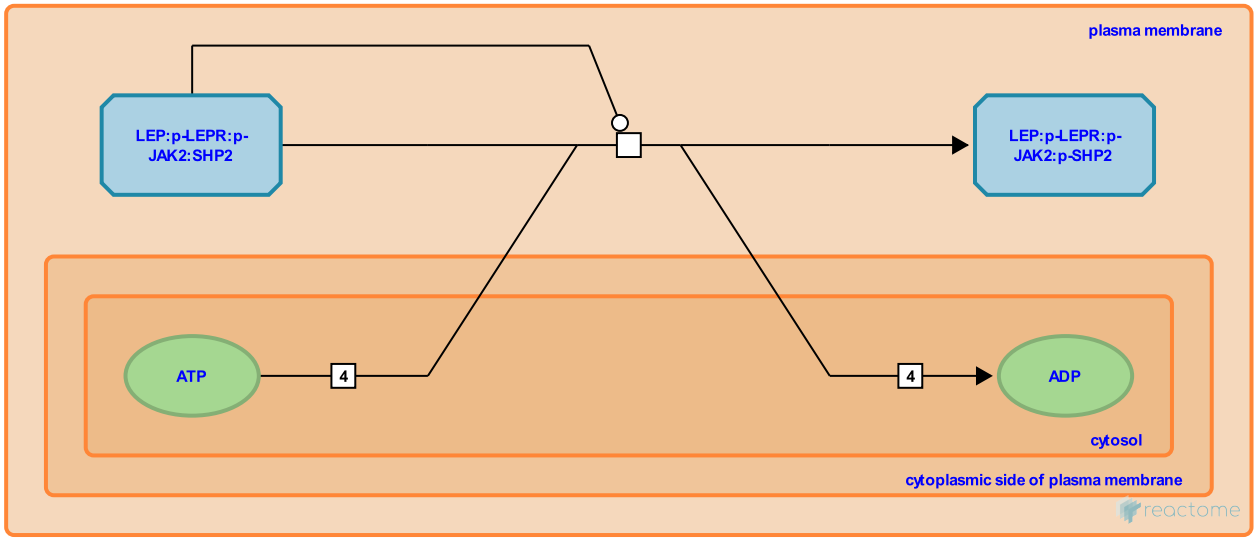
Location: Signaling by Leptin

Stable identifier: R-HSA-2671742

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Phosphorylates Shp2 in Response to Leptin (Mus musculus)



Phosphorylated JAK2 in the LEP:LEPR:JAK2:SHP2 complex phosphorylates SHP2 (Carpenter et al. 1998). Phosphorylated SHP2, in turn, activates the RAS-MAPK signaling pathway, possibly via GRB2:SOS.

Preceded by: Phosphorylated LEPR Binds SHP2 (PTPN11)

Literature references

Symes, A., Stahl, N., Farruggella, TJ., Yancopoulos, GD., Carpenter, LR., Karow, ML. (1998). Enhancing leptin response by preventing SH2-containing phosphatase 2 interaction with Ob receptor. *Proc. Natl. Acad. Sci. U.S.A., 95* , 6061-6. ↗

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2012-11-15	Authored	May, B.
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2013-10-26	Reviewed	Gonzalez-Perez, RR.

Phosphorylated LEPR Binds STAT5 ↗

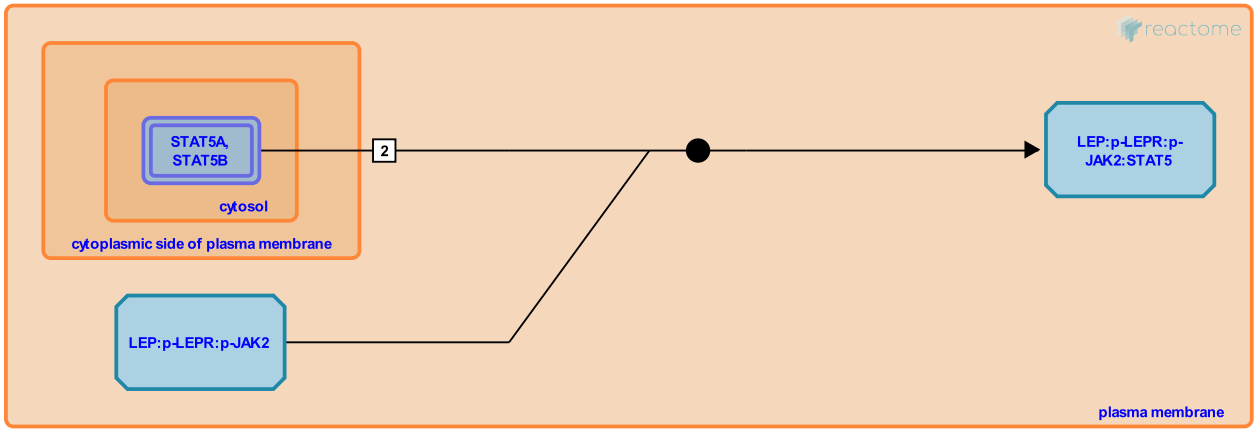
Location: Signaling by Leptin

Stable identifier: R-HSA-2671855

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Lepr Binds Stat5 (Mus musculus)



STAT5 interacts with phosphotyrosine-1079 of LEPR in the LEP:LEPR:JAK2 complex, bringing STAT5 in proximity to the JAK2 kinase (Briscoe et al. 2001).

Preceded by: JAK2 Phosphorylates LEPR

Followed by: JAK2 Phosphorylates STAT5 in Response to Leptin

Literature references

Tadayyon, M., Arch, JR., Briscoe, CP., Hanif, S. (2001). Leptin receptor long-form signalling in a human liver cell line . *Cytokine, 14*, 225-9. ↗

Editions

2012-11-15	Authored	May, B.
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2013-08-31	Reviewed	Scherer, T.
2013-10-26	Reviewed	Gonzalez-Perez, RR.

JAK2 Phosphorylates STAT5 in Response to Leptin ↗

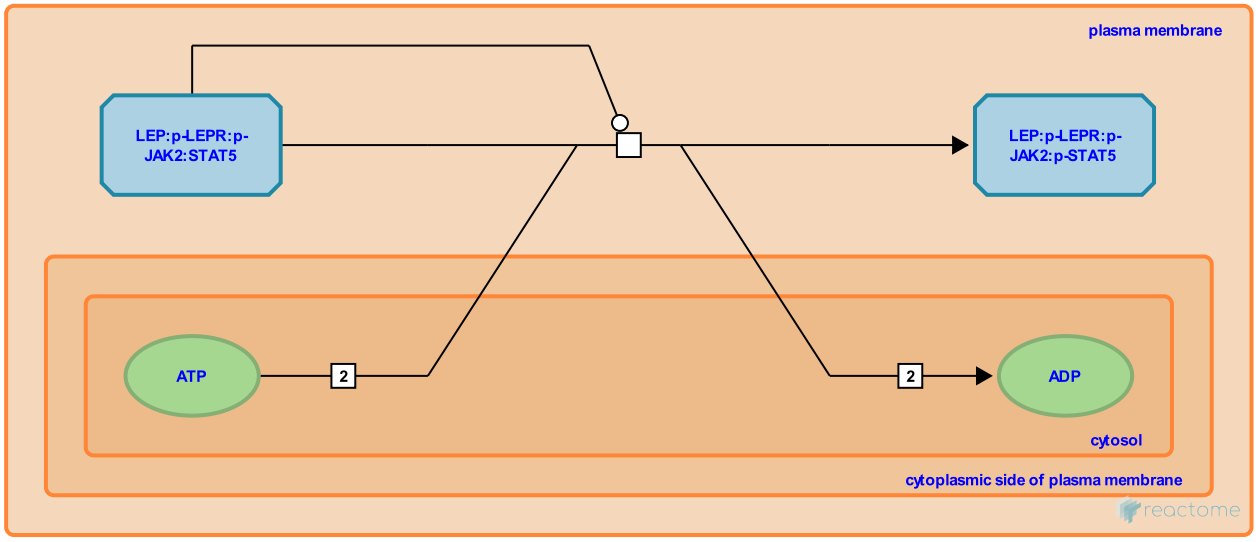
Location: Signaling by Leptin

Stable identifier: R-HSA-2671829

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Phosphorylates Stat5 in Response to Leptin (Mus musculus)



Phosphorylated JAK2 phosphorylates STAT5 (at phosphotyrosine-694 of STAT5A and probably at the homologous residue in STAT5B) while STAT5 and JAK2 are bound to LEPR (Briscoe et al. 2001).

Preceded by: Phosphorylated LEPR Binds STAT5

Followed by: Phosphorylated STAT5 Dissociates from Leptin Receptor

Literature references

Tadayyon, M., Arch, JR., Briscoe, CP., Hanif, S. (2001). Leptin receptor long-form signalling in a human liver cell line . *Cytokine, 14*, 225-9. ↗

Editions

2012-11-15	Authored	May, B.
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Phosphorylated STAT5 Dissociates from Leptin Receptor ↗

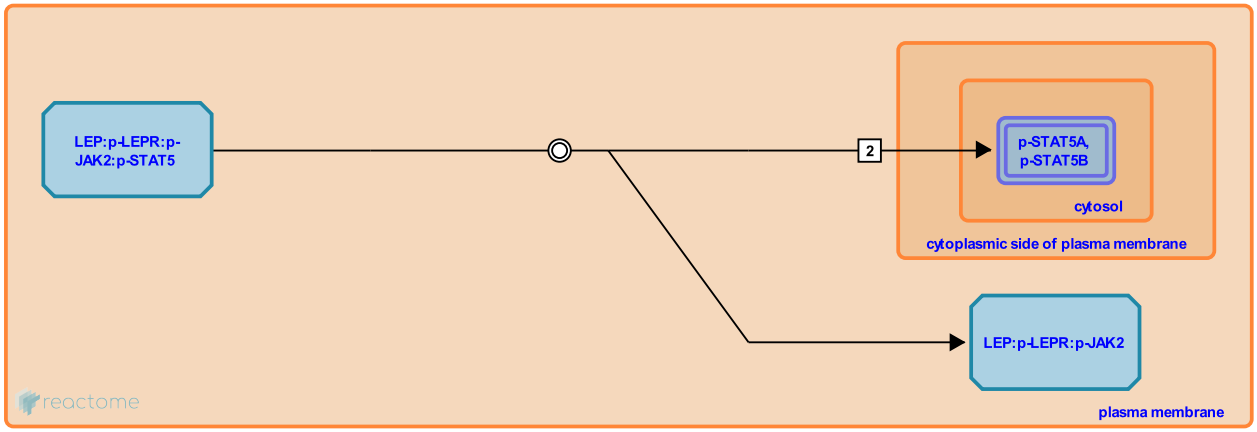
Location: Signaling by Leptin

Stable identifier: R-HSA-2671876

Type: dissociation

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Stat5 Dissociates from Leptin Receptor (Mus musculus)



Phosphorylated STAT5 dissociates from LEPR, dimerizes, and then translocates to the nucleus.

Preceded by: JAK2 Phosphorylates STAT5 in Response to Leptin

Literature references

Tadayyon, M., Arch, JR., Briscoe, CP., Hanif, S. (2001). Leptin receptor long-form signalling in a human liver cell line . *Cytokine, 14*, 225-9. ↗

Editions

2012-11-24	Authored, Edited	May, B.
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p-STAT5 dimerizes ↗

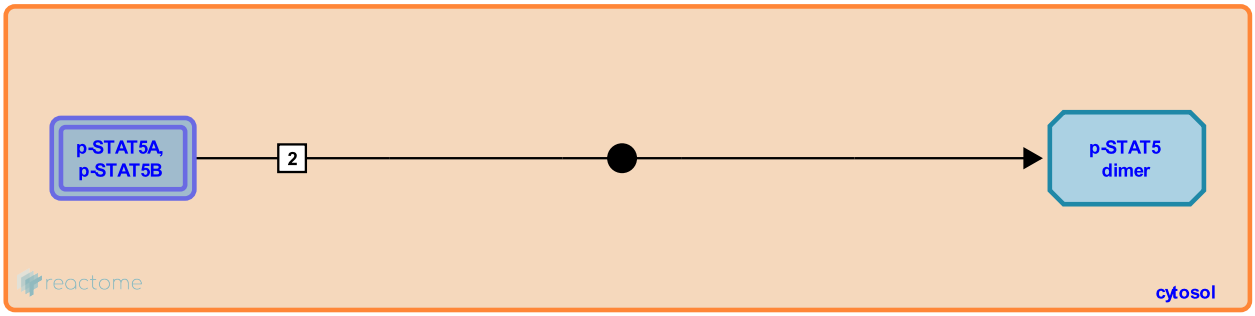
Location: Signaling by Leptin

Stable identifier: R-HSA-452102

Type: binding

Compartments: cytosol

Inferred from: Phosphorylated Stat5 dimerizes (Mus musculus)



Phosphorylated STAT5A and STAT5B form homodimers and heterodimers in the cytosol (Gaffen et al. 1996, Rosenthal et al. 1997, also inferred from mouse homologs). Phosphorylation of a critical tyrosine residue in the SH domain (Y694 in STAT5A and Y699 in STAT5B) and intramolecular interactions between hydrophobic residues in the SH domain are required for dimerization (inferred from mouse homologs).

Followed by: STAT5 dimers translocate to the nucleus

Literature references

Finbloom, DS., Rosenthal, LA., Winestock, KD. (1997). IL-2 and IL-7 induce heterodimerization of STAT5 isoforms in human peripheral blood T lymphoblasts. *Cell Immunol, 181*, 172-81. ↗

Goldsmith, MA., Liu, X., Hennighausen, L., Greene, WC., Gaffen, SL., Ha, M. et al. (1996). Distinct tyrosine residues within the interleukin-2 receptor beta chain drive signal transduction specificity, redundancy, and diversity. *J Biol Chem, 271*, 21381-90. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2011-02-11	Reviewed	Villarino, A.
2011-03-17	Reviewed	Dooms, H.

STAT5 dimers translocate to the nucleus ↗

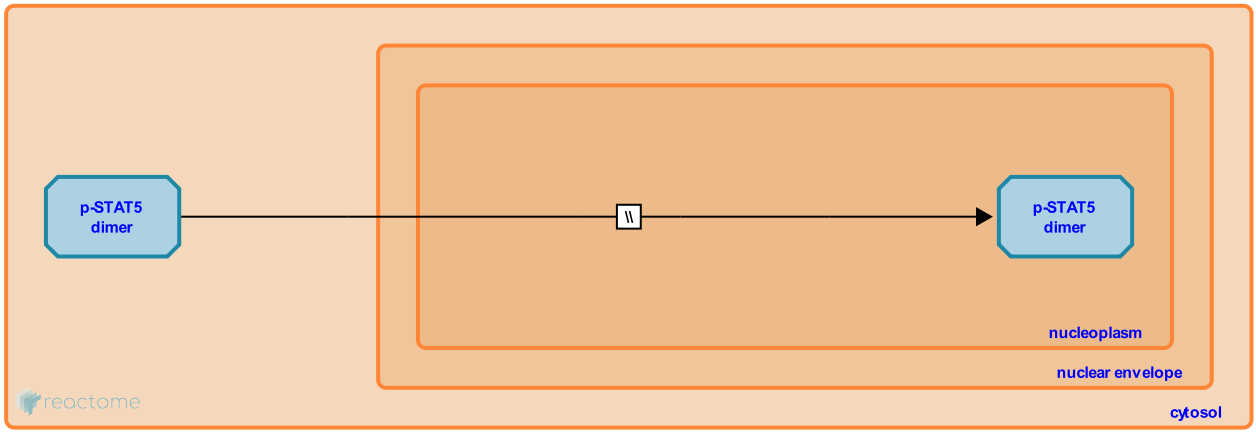
Location: Signaling by Leptin

Stable identifier: R-HSA-507937

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Phosphorylated Stat5 Dimer Translocates to the Nucleus (Mus musculus)



Interleukin-7 (IL7)-activated Signal transducer and activator of transcription 5A or 5B (typically referred to as STAT5) is recruited rapidly to the promoters of IL7-regulated genes (Ye et al. 2001, Stanton & Brodeur 2005).

Preceded by: p-STAT5 dimerizes

Literature references

Honjo, T., Kurooka, H., Agata, Y., Ikuta, K., Kitamura, T., Lee, HC. et al. (2001). The IL-7 receptor controls the accessibility of the TCRgamma locus by Stat5 and histone acetylation. *Immunity, 15*, 813-23. ↗

Stanton, ML., Brodeur, PH. (2005). Stat5 mediates the IL-7-induced accessibility of a representative D-Distal VH gene. *J. Immunol., 174*, 3164-8. ↗

Editions

2010-05-17	Authored	Ray, KP.
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2011-06-23	Reviewed	Waters, MJ.

Phosphorylated LEPR Binds STAT3 ↗

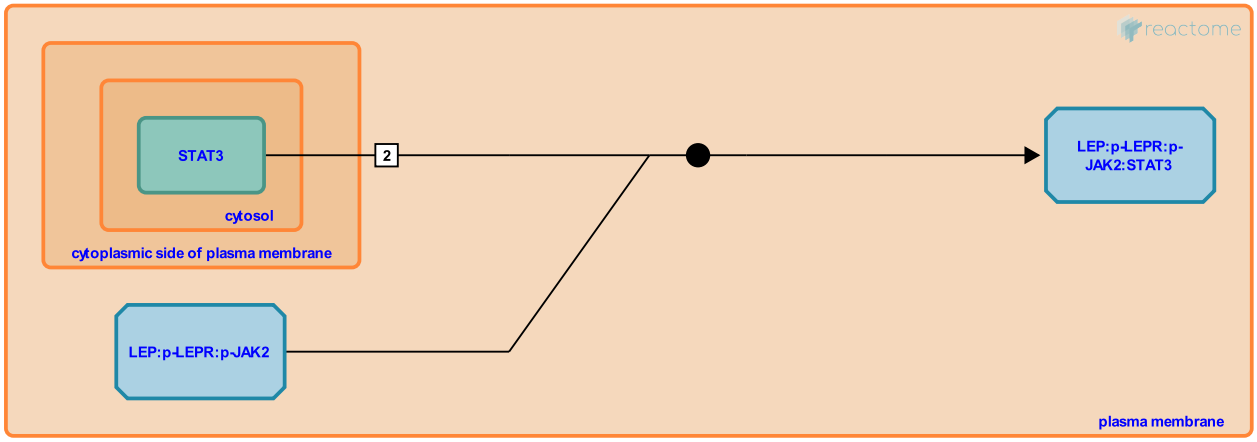
Location: Signaling by Leptin

Stable identifier: R-HSA-2671868

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Lepr Binds Stat3 (Mus musculus)



STAT3 binds phosphotyrosine-1141 of the C-terminal, cytoplasmic region of LEPR (Bjorbaek et al. 1997). Only the long isoform of LEPR has tyrosine-1141 and consequently only the long isoform of LEPR activates STAT3. Short isoforms of LEPR exist but their function is uncertain. Shorter LEPR isoforms bind JAK2 and can signal through IRS-1 or ERKs, including MAPKs (Bjorbaek et al. 1997).

Preceded by: JAK2 Phosphorylates LEPR

Followed by: JAK2 Phosphoryates STAT3 in Response to Leptin

Literature references

da Silva, B., Uotani, S., Flier, JS., Bjørbaek, C. (1997). Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J. Biol. Chem., 272*, 32686-95. ↗

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JAK2 Phosphoryates STAT3 in Response to Leptin ↗

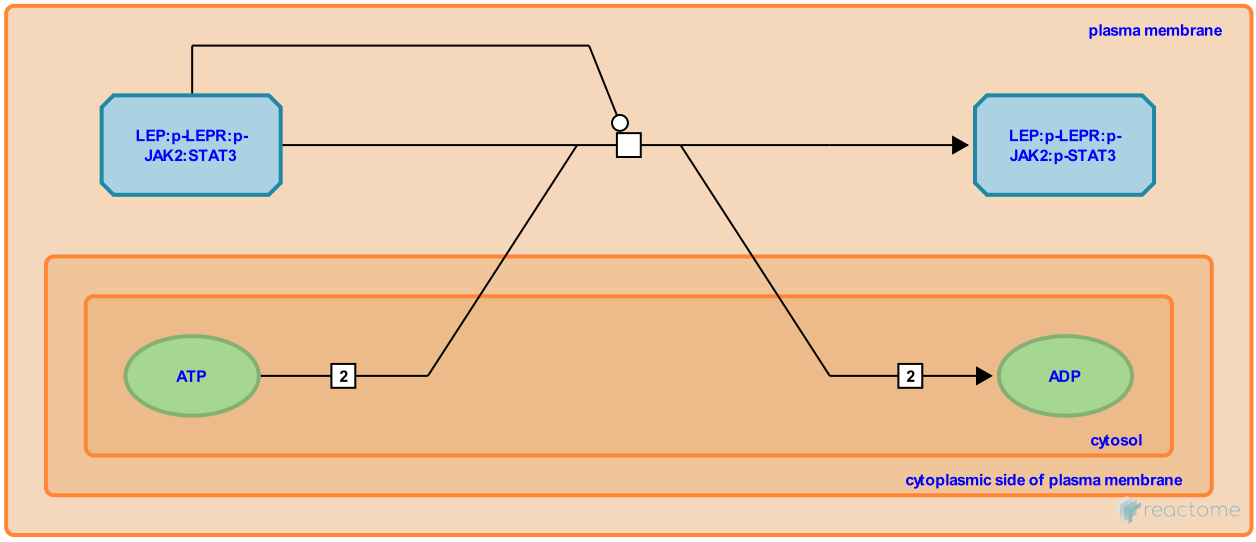
Location: Signaling by Leptin

Stable identifier: R-HSA-2671850

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Phosphorylates Stat3 in Response to Leptin (Mus musculus)



Phosphorylated JAK2 in the LEP:LEPR:JAK2:STAT3 complex phosphorylates STAT3 at tyrosine-705 (Bjorbaek et al. 1997).

Preceded by: Phosphorylated LEPR Binds STAT3

Followed by: Phosphorylated STAT3 Dissociates from Leptin Receptor

Literature references

da Silva, B., Uotani, S., Flier, JS., Bjørbaek, C. (1997). Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J. Biol. Chem., 272*, 32686-95. ↗

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Phosphorylated STAT3 Dissociates from Leptin Receptor ↗

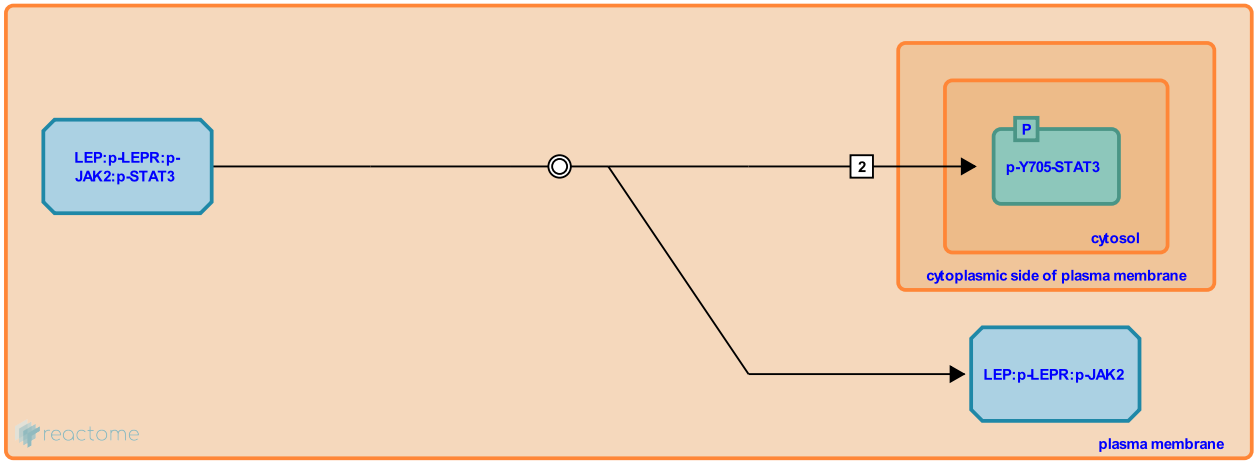
Location: Signaling by Leptin

Stable identifier: R-HSA-2671839

Type: dissociation

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Stat3 Dissociates from Leptin Receptor (Mus musculus)



Phosphorylated STAT3 dissociates from LEPR in the LEP:LEPR:JAK2 complex, dimerizes, and translocates to the nucleus.

Preceded by: JAK2 Phosphoryates STAT3 in Response to Leptin

Followed by: Phosphorylated STAT3 Forms Dimers

Literature references

da Silva, B., Uotani, S., Flier, JS., Bjørbaek, C. (1997). Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J. Biol. Chem., 272*, 32686-95. ↗

Editions

2012-11-24	Authored, Edited	May, B.
2013-08-31	Reviewed	Scherer, T.
2013-10-26	Reviewed	Gonzalez-Perez, RR.

Phosphorylated STAT3 Forms Dimers ↗

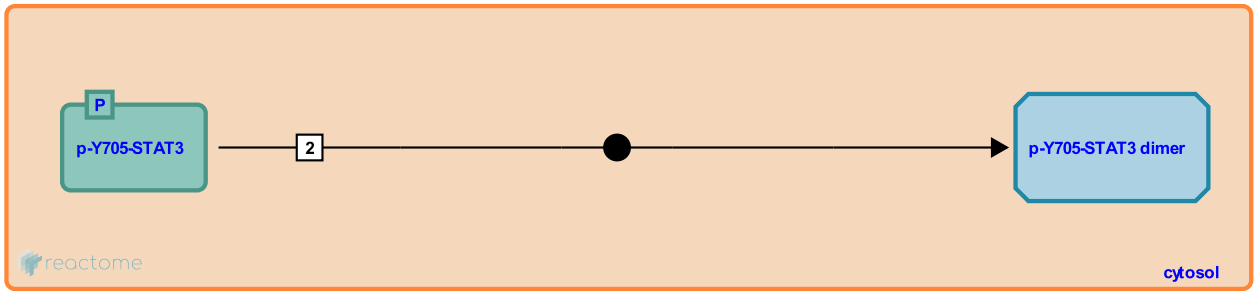
Location: Signaling by Leptin

Stable identifier: R-HSA-2730595

Type: binding

Compartments: cytosol

Inferred from: Phosphorylated Stat3 Forms Dimer (Mus musculus)



As inferred from mouse, both non-phosphorylated and phosphorylated STAT3 can form dimers and enter the nucleus. Phosphorylation of STAT3 appears to change the equilibrium between these states, causing accumulation of phosphorylated STAT3 in the nucleus. Phosphorylated STAT3 dimers also activate transcription more efficiently.

Preceded by: Phosphorylated STAT3 Dissociates from Leptin Receptor

Followed by: Phosphorylated STAT3 Dimer Translocates to the Nucleus

Editions

2012-12-03	Authored, Edited	May, B.
2013-08-31	Reviewed	Scherer, T.
2013-10-26	Reviewed	Gonzalez-Perez, RR.
2016-02-07	Revised	Pires, IM.
2016-07-11	Reviewed	Birchmeier, W., Heynen, G.

Phosphorylated STAT3 Dimer Translocates to the Nucleus ↗

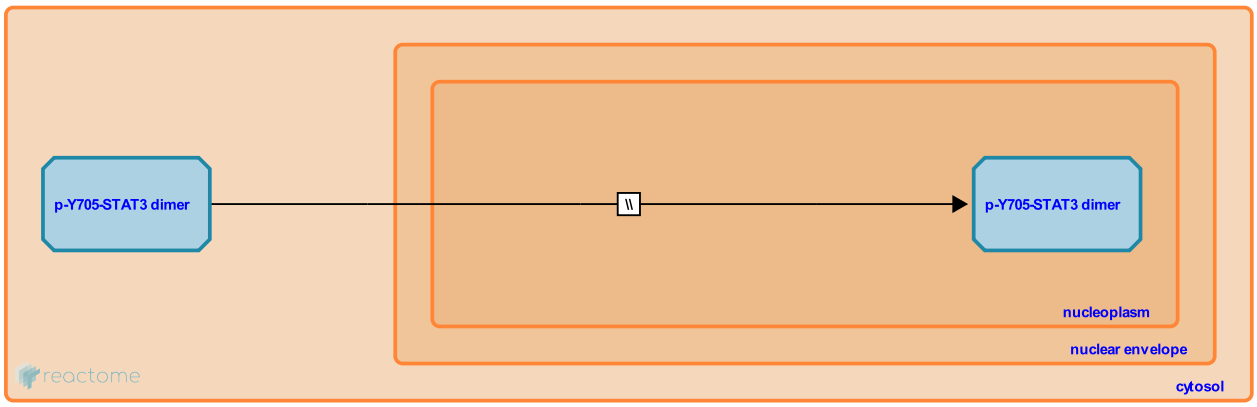
Location: Signaling by Leptin

Stable identifier: R-HSA-2730599

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Phosphorylated Stat3 Dimer Translocates to the Nucleus (Mus musculus)



As inferred from mouse, both non-phosphorylated and phosphorylated STAT3 are imported and exported from the nucleus. Phosphorylation shifts the equilibrium distribution of STAT3 to the nucleus.

Preceded by: Phosphorylated STAT3 Forms Dimers

Editions

2012-12-03	Authored, Edited	May, B.
2013-08-31	Reviewed	Scherer, T.
2013-10-26	Reviewed	Gonzalez-Perez, RR.
2016-02-07	Reviewed	Pires, IM.
2016-07-11	Reviewed	Birchmeier, W., Heynen, G.

Phosphorylated LEP:LEPR:JAK2 Binds SH2B1 ↗

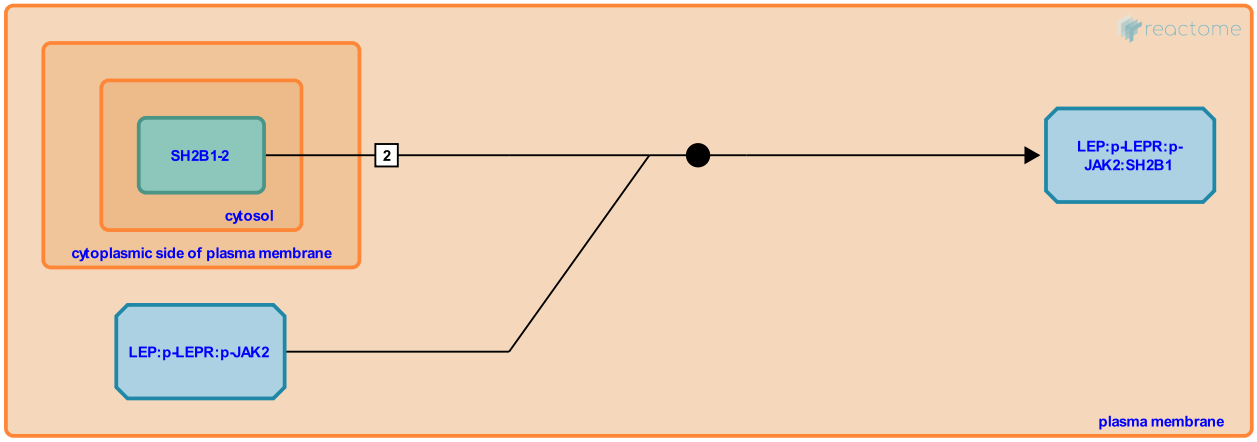
Location: Signaling by Leptin

Stable identifier: R-HSA-2671872

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphoryated Lep:Lepr:Jak2 Binds Sh2b1 (Mus musculus)



The SH2 domain of SH2B1 binds phosphotyrosine-813 of JAK2 (Nishi et al. 2005, Li et al. 2007). Binding of SH2B1 to JAK2 enhances leptin-induced JAK2 activity. SH2B1 also recruits IRS1 for phosphorylation by JAK2 (Li et al. 2007).

Preceded by: JAK2 Phosphorylates LEPR

Followed by: Phosphorylated LEP:LEPR:JAK2:SH2B1 Binds IRS1/2

Literature references

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

Li, Z., Zhou, Y., Carter-Su, C., Rui, L., Myers, MG. (2007). SH2B1 enhances leptin signaling by both Janus kinase 2 Tyr813 phosphorylation-dependent and -independent mechanisms. *Mol. Endocrinol., 21*, 2270-81. ↗

Editions

2012-11-24	Authored, Edited	May, B.
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2013-10-26	Reviewed	Gonzalez-Perez, RR.

Phosphorylated LEP:LEPR:JAK2:SH2B1 Binds IRS1/2 ↗

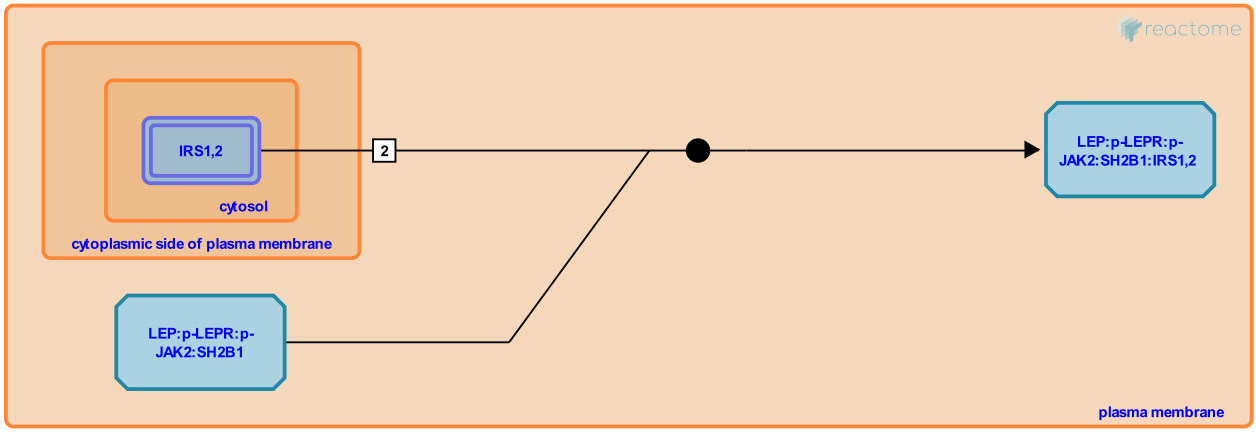
Location: Signaling by Leptin

Stable identifier: R-HSA-2671873

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Lep:Lepr:Jak2:Sh2b1 Binds Irs1/2 (Mus musculus)



SH2B1 in the LEP:LEPR:JAK2:SH2B1 complex can bind either IRS1 or IRS2 (Duan et al. 2004, Li et al. 2007). The binding brings IRS1/2 into proximity with JAK2 for phosphorylation.

Preceded by: Phosphorylated LEP:LEPR:JAK2 Binds SH2B1

Followed by: JAK2 Phosphorylates IRS in Response to Leptin

Literature references

Duan, C., Li, M., Rui, L. (2004). SH2-B promotes insulin receptor substrate 1 (IRS1)- and IRS2-mediated activation of the phosphatidylinositol 3-kinase pathway in response to leptin. *J Biol Chem, 279*, 43684-91. ↗

Li, Z., Zhou, Y., Carter-Su, C., Rui, L., Myers, MG. (2007). SH2B1 enhances leptin signaling by both Janus kinase 2 Tyr813 phosphorylation-dependent and -independent mechanisms. *Mol. Endocrinol., 21*, 2270-81. ↗

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2012-11-24	Authored, Edited	May, B.
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2013-10-26	Reviewed	Gonzalez-Perez, RR.

JAK2 Phosphorylates IRS in Response to Leptin ↗

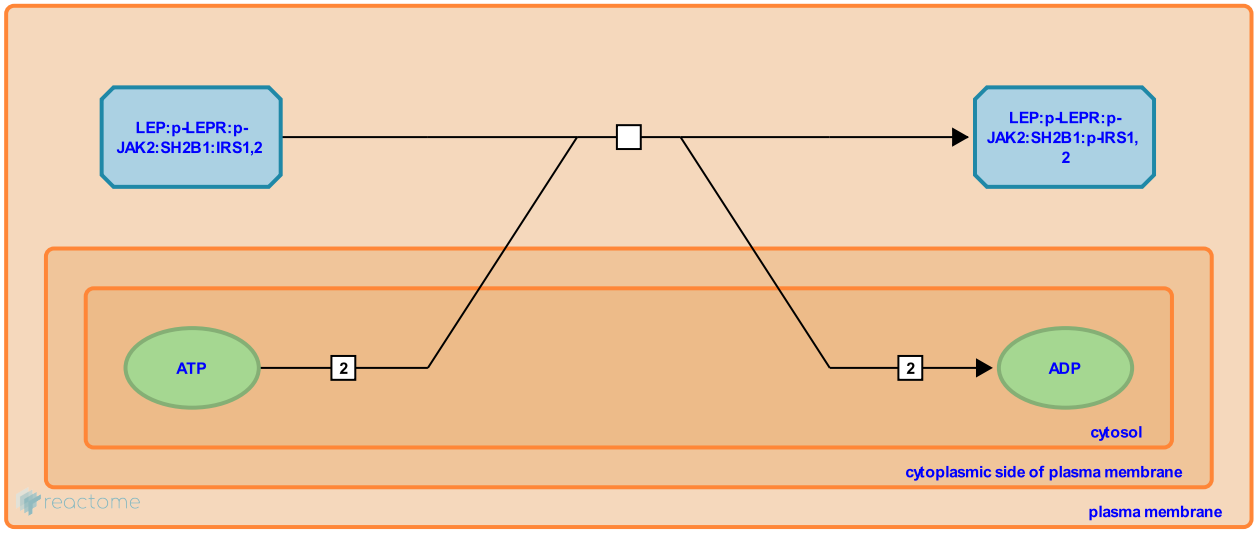
Location: Signaling by Leptin

Stable identifier: R-HSA-2671862

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Jak2 Phosphorylates Irs1/2 in Response to Leptin (Mus musculus)



JAK2 phosphorylates IRS1/2 after IRS1/2 binds SH2B1 in the LEP:LEPR:JAK2:SH2B1 complex (Martin-Romero and Sanchez-Margalet 2001, Li et al. 2007). However, in some cells leptin may only affect phosphorylation of IRS1/2 when insulin signaling subsequently occurs (Szanto and Kahn 2000). As inferred from mouse and rat (Buettner et al. 2008, Hill et al. 2008) phosphorylated IRS1/2 then activates PI3K independently of STAT3 signaling.

Preceded by: Phosphorylated LEP:LEPR:JAK2:SH2B1 Binds IRS1/2

Literature references

Szanto, I., Kahn, CR. (2000). Selective interaction between leptin and insulin signaling pathways in a hepatic cell line. *Proc. Natl. Acad. Sci. U.S.A., 97*, 2355-60. ↗

da Silva, B., Uotani, S., Flier, JS., Bjørbaek, C. (1997). Divergent signaling capacities of the long and short isoforms of the leptin receptor. *J. Biol. Chem., 272*, 32686-95. ↗

Martín-Romero, C., Sánchez-Margalet, V. (2001). Human leptin activates PI3K and MAPK pathways in human peripheral blood mononuclear cells: possible role of Sam68. *Cell. Immunol., 212*, 83-91. ↗

Li, Z., Zhou, Y., Carter-Su, C., Rui, L., Myers, MG. (2007). SH2B1 enhances leptin signaling by both Janus kinase 2 Tyr813 phosphorylation-dependent and -independent mechanisms. *Mol. Endocrinol., 21*, 2270-81. ↗

Elmquist, JK., Ye, C., Balthasar, N., Lowell, BB., Cantley, LC., Luo, J. et al. (2008). Acute effects of leptin require PI3K signaling in hypothalamic proopiomelanocortin neurons in mice. *J. Clin. Invest., 118*, 1796-805. ↗

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2012-11-24	Authored, Edited	May, B.
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Phosphorylated LEPR Binds SOCS3 ↗

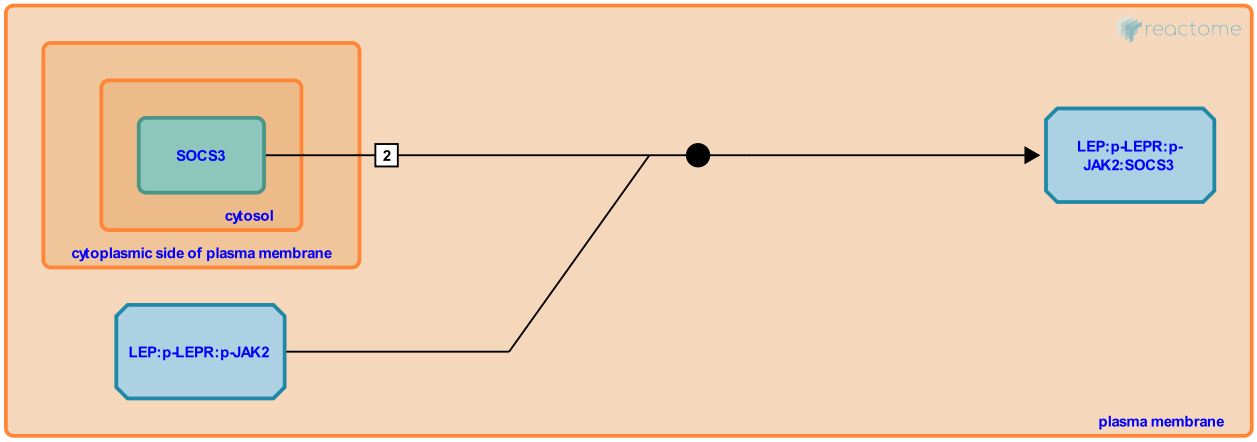
Location: Signaling by Leptin

Stable identifier: R-HSA-2672302

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylated Lepr Binds Socs3 (Mus musculus)



As inferred from mouse, SOCS3 binds LEPR at phosphotyrosine-986 and phosphotyrosine-1079. SOCS3 competes with SHP2 (PTPN11) for phosphotyrosine-986 and with STAT5 for phosphotyrosine-1079. SOCS3 expression is upregulated by leptin and SOCS3 downregulates prolonged leptin signaling, providing a feedback loop to limit leptin's action.

Preceded by: JAK2 Phosphorylates LEPR

Editions

2012-11-27	Authored, Edited	May, B.
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2013-10-26	Reviewed	Gonzalez-Perez, RR.

Table of Contents