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.

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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


Reactome database release: 77

This document contains 1 pathway and 19 reactions (see Table of Contents)
Signaling by Leptin

Stable identifier: R-HSA-2586552

Compartments: plasma membrane, cytosol


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-RI) 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 (LEPRα, 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**


**Editions**

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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**


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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.

**Preceded by:** Leptin Binds Leptin Receptor

**Followed by:** JAK2 Phosphorylates LEPR

**Literature references**


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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**


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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

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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)

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**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

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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**

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**


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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**


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**STAT5 dimers translocate to the nucleus**

**Location:** Signaling by Leptin

**Stable identifier:** R-HSA-507937

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

**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**


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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 Phosphorylates STAT3 in Response to Leptin

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JAK2 Phosphorylates 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**


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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 Phosphorylates STAT3 in Response to Leptin

**Followed by:** Phosphorylated STAT3 Forms Dimers

**Literature references**


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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

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Phosphorylated STAT3 Dimer Translocates to the Nucleus

Location: Signaling by Leptin

Stable identifier: R-HSA-2730599

Type: omitted

Compartments: cytosol, nucleoplasm

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

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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)


**Preceded by:** JAK2 Phosphorylates LEPR

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

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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


Editions

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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**


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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

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