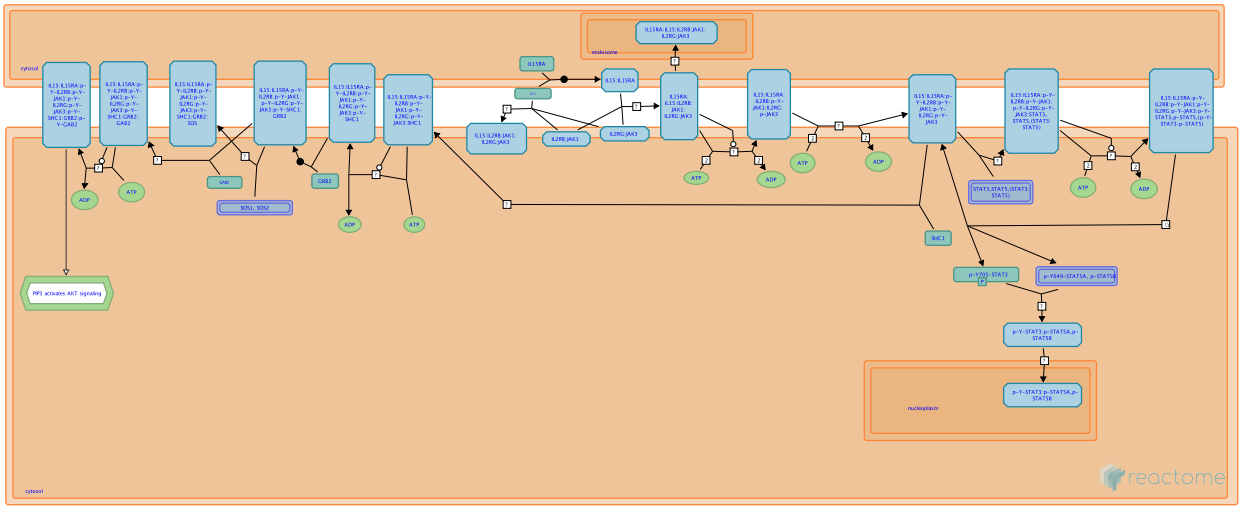
Interleukin-15 signaling



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11/09/2021

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. ↗

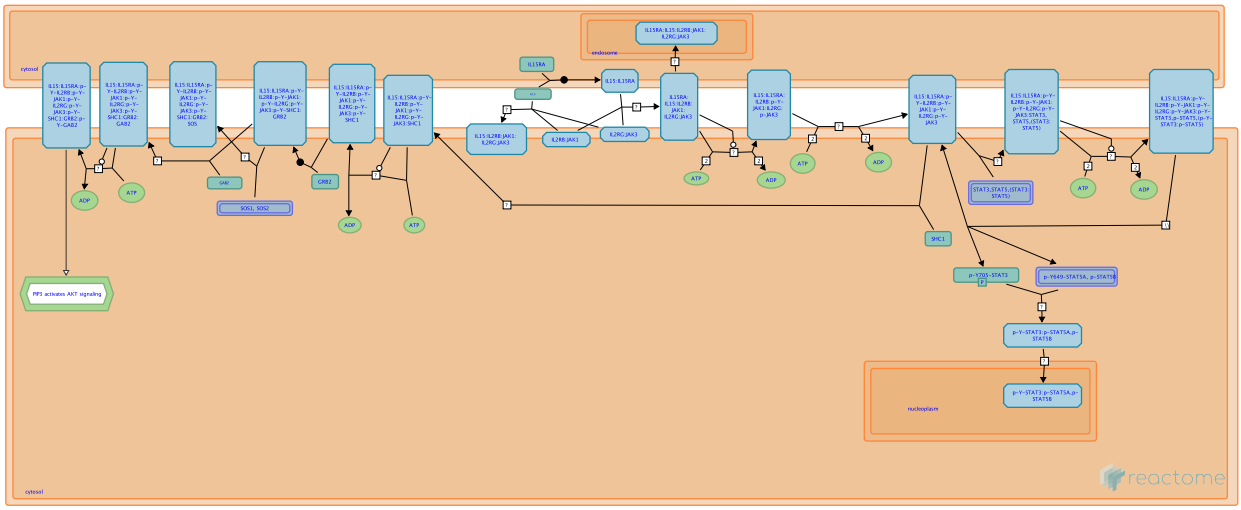
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Interleukin-15 signaling ↗

Stable identifier: R-HSA-8983432



The high affinity Interleukin-15 receptor is a heterotrimer of Interleukin-15 receptor subunit alpha (IL15RA), Interleukin-2 receptor subunit beta (IL2RB, CD122) and Cytokine receptor common subunit gamma (IL2RG, CD132). IL2RB and IL2RG are also components of the Interleukin-2 (IL2) receptor. Treatment of human T cells with Interleukin-15 (IL15) results in tyrosine phosphorylation of Tyrosine-protein kinase JAK1 (JAK1, Janus kinase 1) and Tyrosine-protein kinase JAK3 (JAK3, Janus kinase 3) (Johnston et al. 1995, Winthrop 2017). IL15 can signal by a process termed 'trans presentation', where IL15 bound by IL15 on one cell is trans-presented to IL2RB:IL2RG on another cell (Dubois et al. 2002) but can also participate in more 'traditional' cis signaling (Wu et al. 2008, Mishra et al. 2014) where all the three receptors are present on the same cell.

Stimulation of lymphocytes by IL15 release MAPK activation through GAB2/SHP2/SHC (GRB2-associated-binding protein 2/Tyrosine-protein phosphatase non-receptor type 11/SHC transforming protein 1 or 2) cascade activation (Gadina et al. 2000).

Literature references

Winthrop, KL. (2017). The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol, 13*, 234-243. ↗

Gadina, M., Sudarshan, C., Visconti, R., Zhou, YJ., Gu, H., Neel, BG. et al. (2000). The docking molecule gab2 is induced by lymphocyte activation and is involved in signaling by interleukin-2 and interleukin-15 but not other common gamma chain-using cytokines. *J. Biol. Chem., 275*, 26959-66. ↗

Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.
2017-05-11	Edited	Jupe, S.
2017-08-07	Reviewed	Patidar, M.

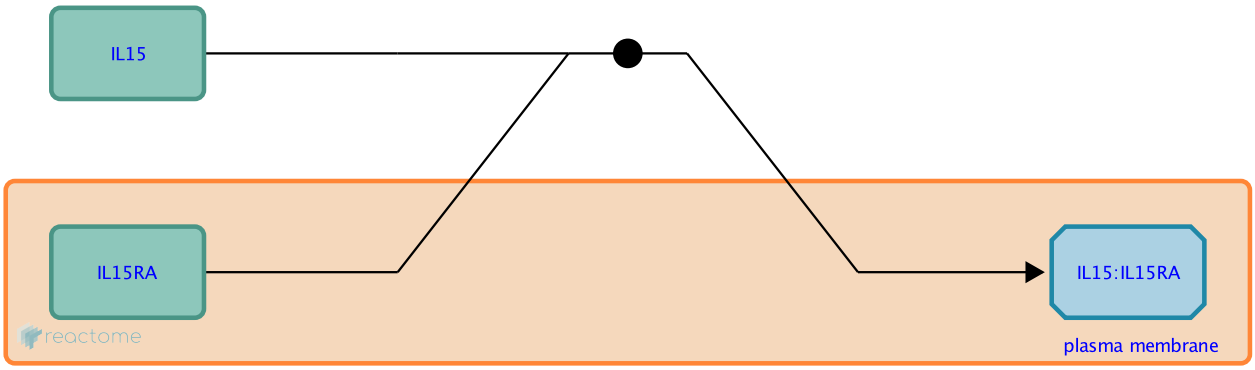
IL15 binds IL15RA ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983307

Type: binding

Compartments: extracellular region, plasma membrane



Interleukin 15 (IL15) binds Interleukin 15 receptor subunit alpha (IL15RA, IL15Rα). The high affinity Interleukin 15 receptor is a heterotrimer of IL15RA, Interleukin 2 receptor subunit beta (IL2RB, IL2Rβ, IL15RB) and Cytokine receptor common subunit gamma (IL2RG, IL2Rγ). IL15RA is structurally related to the alpha subunit of the Interleukin-2 receptor and determines high affinity binding for Interleukin 15 (IL15) (Giri et al. 1994, 1995, Anderson et al. 1995, Dubois et al. 2002). More in detail, IL15RA binds specifically to IL15 with high affinity (Kd=30-100 pM), whereas IL2RA specifically binds to IL2 with a comparatively lower affinity (Kd=10-30 nM) (Bernard et al. 2004).

Followed by: IL15:IL15RA binds IL2RB:JAK1 and IL2RG:JAK3

Literature references

Dubois, S., Mariner, J., Waldmann, TA., Tagaya, Y. (2002). IL-15Ralpha recycles and presents IL-15 In trans to neighboring cells. *Immunity, 17*, 537-47. ↗

Giri, JG., Kumaki, S., Ahdieh, M., Friend, DJ., Loomis, A., Shanebeck, K. et al. (1995). Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. *EMBO J, 14*, 3654-63 . ↗

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

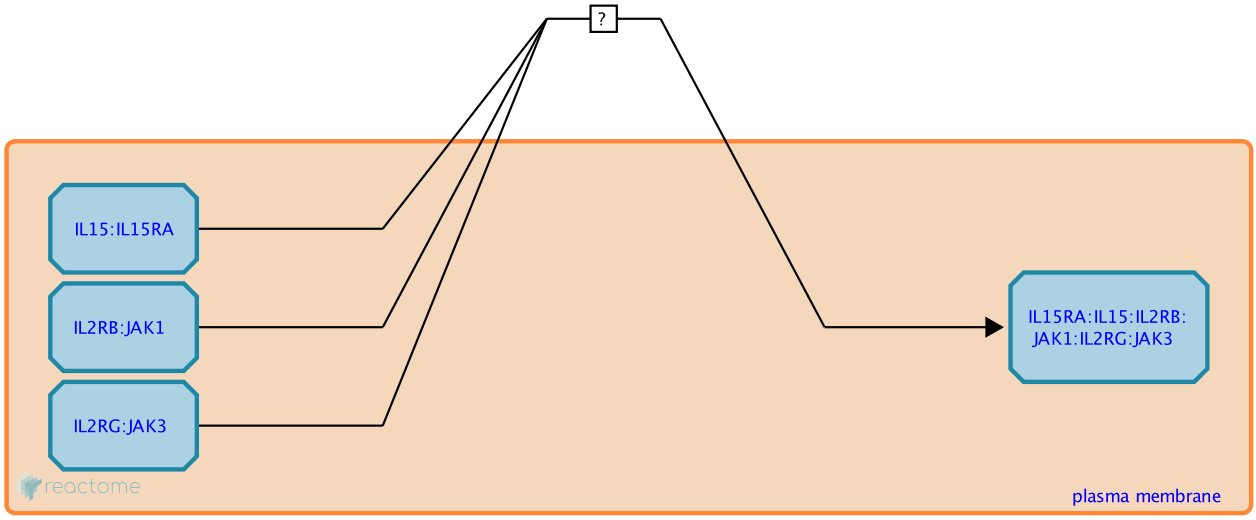
IL15:IL15RA binds IL2RB:JAK1 and IL2RG:JAK3 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-449115

Type: uncertain

Compartments: extracellular region, plasma membrane, cytosol



The Interleukin-15 (IL15) / Interleukin-15 receptor subunit alpha (IL15RA, IL15Rα) complex binds Interleukin-2 receptor subunit beta (IL2RB, IL2Rβ), which is associated with Tyrosine-protein kinase JAK1 (JAK1) and Cytokine receptor common subunit gamma (IL2RG, IL2Rγ), which is associated with Tyrosine-protein kinase JAK3 (JAK3) (Johnston et al. 1995). The heterodimer of IL2RB and IL2RG can bind IL15 with low affinity but high affinity binding requires a third component, IL15RA (Giri et al. 1994, 1995, Anderson et al. 1995). This is a Black Box Event because it is not clear whether the beta and gamma subunits pre-associate before binding IL15:IL15RA.

Preceded by: IL15 binds IL15RA

Followed by: IL15RA:IL15:IL2RB:JAK1:IL2RG:JAK3 phosphorylates JAK3 and JAK1

Literature references

Giri, JG., Kumaki, S., Ahdieh, M., Friend, DJ., Loomis, A., Shanebeck, K. et al. (1995). Identification and cloning of a novel IL-15 binding protein that is structurally related to the alpha chain of the IL-2 receptor. *EMBO J, 14*, 3654-63 . ↗

Anderson, DM., Kumaki, S., Ahdieh, M., Bertles, J., Tometsko, M., Loomis, A. et al. (1995). Functional characterization of the human interleukin-15 receptor alpha chain and close linkage of IL15RA and IL2RA genes. *J Biol Chem, 270*, 29862-9. ↗

Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

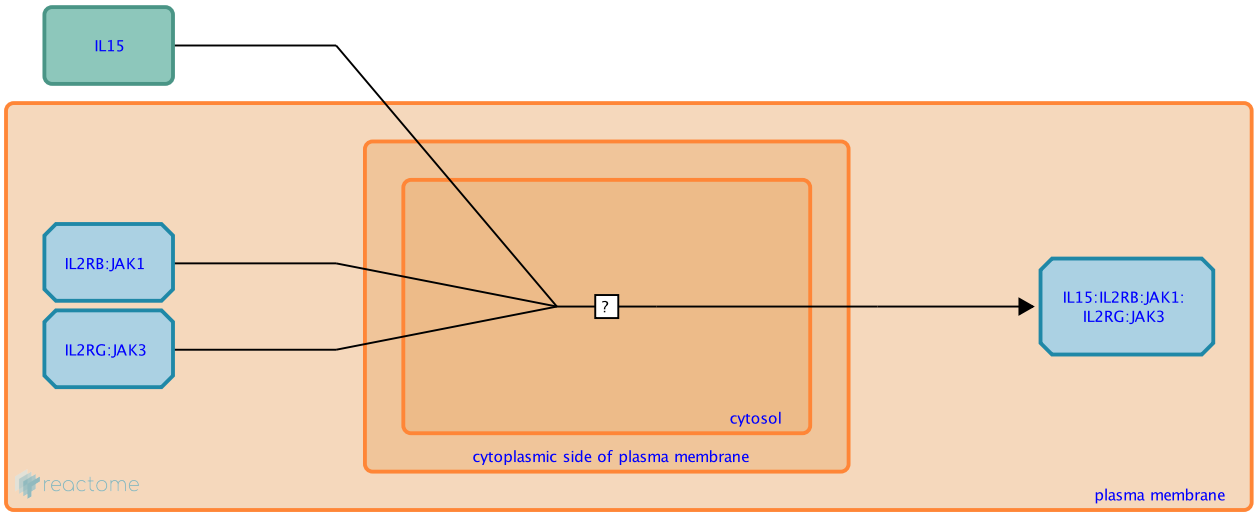
IL15 binds IL2RB:JAK1 and IL2RG:JAK3 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983298

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane



The Interleukin-15 (IL15) / Interleukin-15 receptor subunit alpha (IL15RA, IL15Rα) complex binds Interleukin-2 receptor subunit beta (IL2RB, IL2Rβ), which is associated with Tyrosine-protein kinase JAK1 (JAK1) and Cytokine receptor common subunit gamma (IL2RG, IL2Rγ), which is associated with Tyrosine-protein kinase JAK3 (JAK3) (Johnston et al. 1995). The heterodimer of IL2RB and IL2RG can bind IL15 with low affinity but high affinity binding requires a third component, IL15RA (Giri et al. 1994, 1995, Anderson et al. 1995). This is a Black Box Event because it is not clear whether the β and γ subunits pre-associate before binding IL15:IL15RA.

Literature references

Johnston, JA., Bacon, CM., Finbloom, DS., Rees, RC., Kaplan, D., Shibuya, K. et al. (1995). Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci U S A, 92*, 8705-9. ↗

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

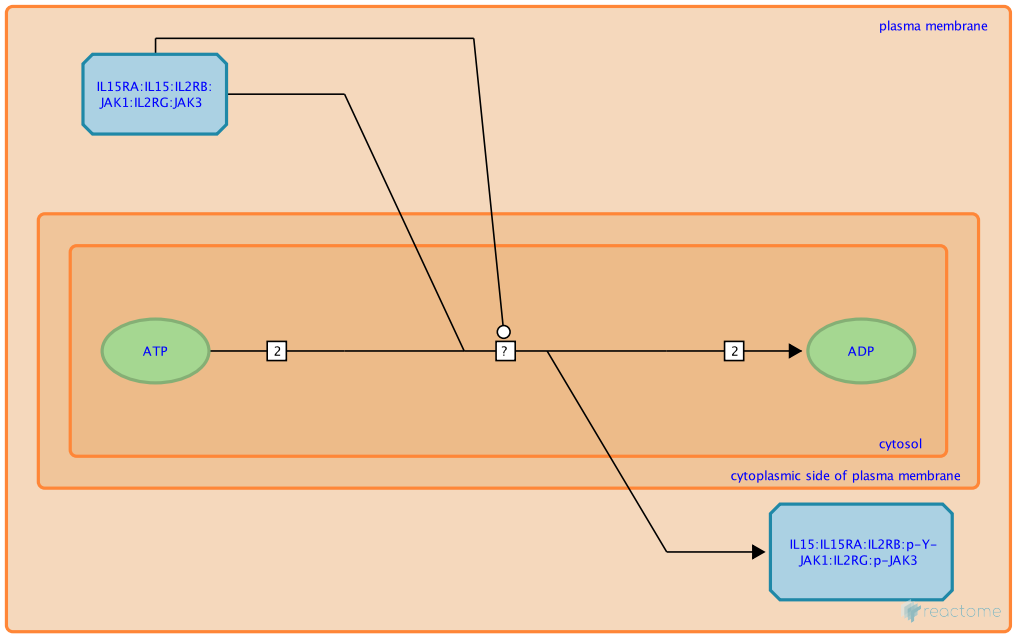
IL15RA:IL15:IL2RB:JAK1:IL2RG:JAK3 phosphorylates JAK3 and JAK1 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983300

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane



Tyrosine-protein kinase JAK1(JAK1) and Tyrosine-protein kinase JAK3 (JAK3) are believed to be phosphorylated after stimulation of the Interleukin-15 receptor complex by Interleukin-15 (IL15) (Johnston et al. 1995), though it has been reported that only JAK3 phosphorylation increases in response to IL15 (Krolopp et al. 2016). The Interleukin-15 receptor complex consists of IL15, Interleukin-15 receptor alpha subunit (IL15RA, IL15Rα), Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ), which is associated with JAK1 and Interleukin receptor gamma subunit, which is associated with JAK3 (Johnston et al. 1995). This is a black box event since the mechanism by which IL15 promotes JAK phosphorylation is unclear.

Preceded by: IL15:IL15RA binds IL2RB:JAK1 and IL2RG:JAK3

Followed by: IL2RB and IL2RG are phosphorylated

Literature references

Johnston, JA., Bacon, CM., Finbloom, DS., Rees, RC., Kaplan, D., Shibuya, K. et al. (1995). Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci U S A, 92*, 8705-9. ↗

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

IL2RB and IL2RG are phosphorylated ↗

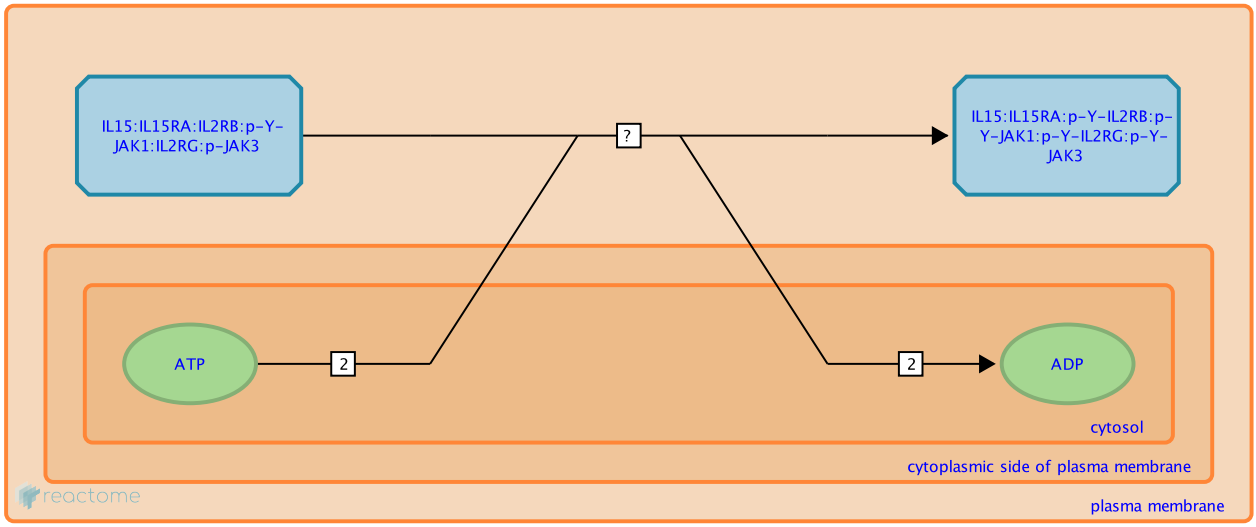
Location: Interleukin-15 signaling

Stable identifier: R-HSA-9009700

Type: uncertain

Compartments: plasma membrane, cytosol, extracellular region

Inferred from: Il2rb and Il2rg are phosphorylated (Mus musculus)



Inferred from mouse: Interleukin-2 receptor subunit beta (IL2RB, IL2Rβ) and Cytokine receptor common subunit gamma (IL2RG, IL2Rγ) is tyrosine phosphorylated after Interleukin-15 (IL15) / IL15 receptor complex interaction (Adunyah et al. 1997, Zambricki et al. 2005). More in detail, human and mouse IL15 have 70.2% amino acid sequence similarity and exhibit similar trans-presentation mechanism, signal transduction machinery and biological activities. Similarly, human IL15 shows cross-reactivity with mouse cells and it was demonstrated that human and mouse IL15 showed similar responses in mouse models (Stoklasek et al. 2006) (Patidar et al. data not published). This is a black box event because more evidence to support this reaction is needed.

Preceded by: IL15RA:IL15:IL2RB:JAK1:IL2RG:JAK3 phosphorylates JAK3 and JAK1

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds SHC1, IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds STAT3 and STAT5

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

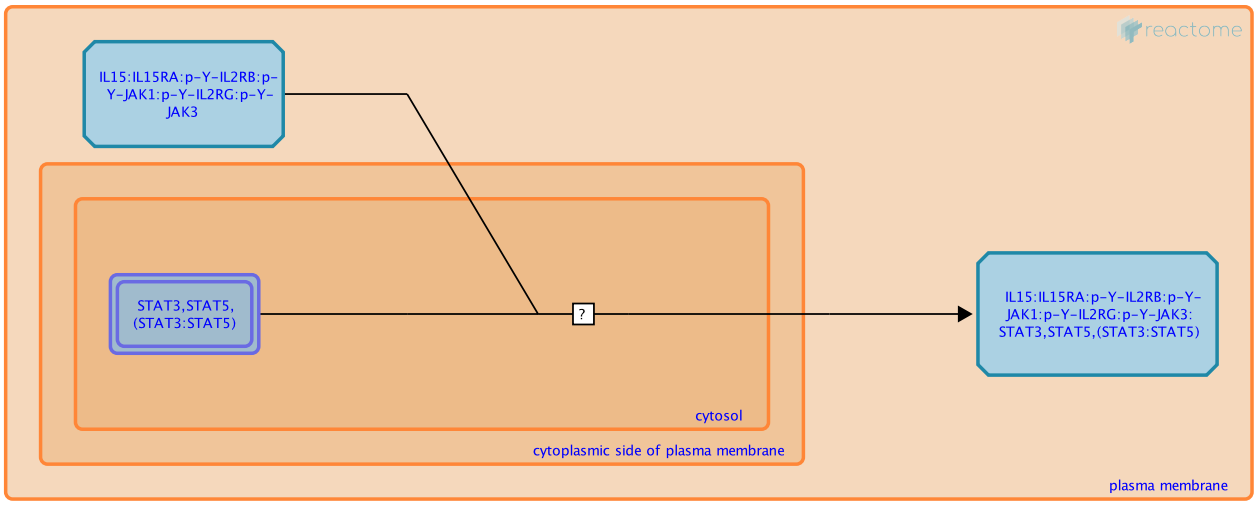
IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds STAT3 and STAT5 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983378

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane



Signal transducer and activator of transcription 3 (STAT3), Signal transducer and activator of transcription 5A and 5B (STAT5) are believed to bind the Interleukin-15 (IL15) receptor complex, which consists of IL15, Interleukin-15 receptor alpha subunit (IL15RA, IL15Rα), Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ), which is associated with JAK1 and Interleukin receptor gamma subunit, which is associated with JAK3 (Johnston et al. 1995). This is a black-box event because STAT binding is inferred from their subsequent phosphorylation.

Preceded by: IL2RB and IL2RG are phosphorylated

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates STAT3 and STAT5

Literature references

Johnston, JA., Bacon, CM., Finbloom, DS., Rees, RC., Kaplan, D., Shibuya, K. et al. (1995). Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci U S A, 92*, 8705-9. ↗

Editions

2017-08-07	Authored	Duenas, C.
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2017-08-09	Edited	Duenas, C.

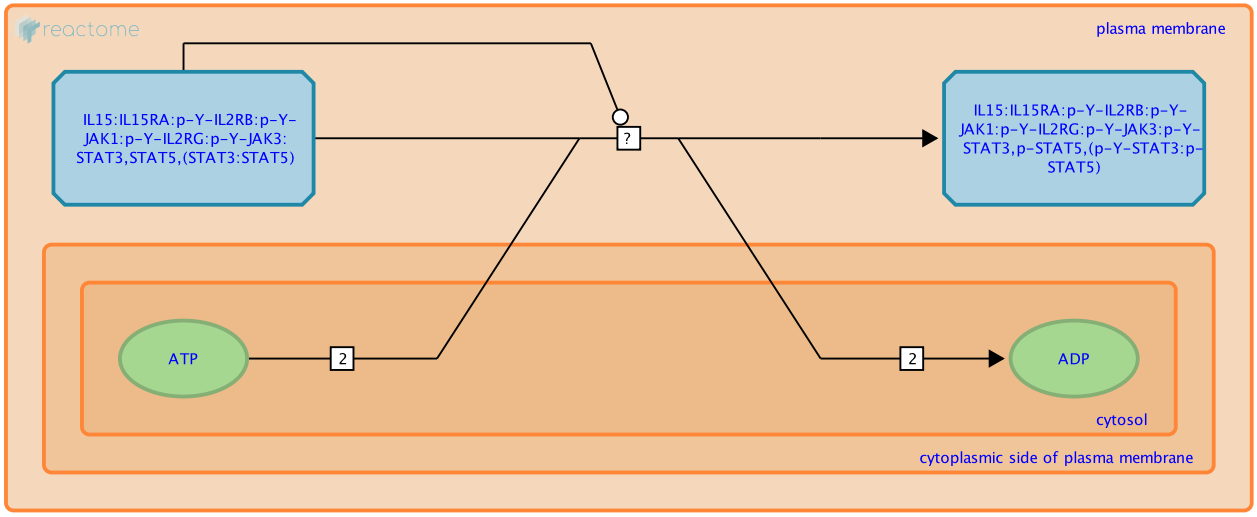
IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates STAT3 and STAT5 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983371

Type: uncertain

Compartments: plasma membrane, cytosol, extracellular region



Signal transducer and activator of transcription 3 (STAT3) and Signal transducer and activator of transcription 5A or 5B (STAT5A,STAT5B or STAT5) are phosphorylated after Interleukin 15 (IL15) stimulation of the IL15 receptor complex (Johnston et al. 1995, Lin et al. 1995, Okada et al. 2015, Cooley et al. 2015, Krolopp et al. 2016), which consists of IL15, Interleukin-15 receptor subunit alpha (IL15RA, IL15Rα), Interleukin 2 receptor beta subunit (IL2RB, IL2Rβ), Tyrosine protein kinase JAK1 (JAK1), Cytokine receptor common subunit gamma (IL2RG, IL2Rγ) and Tyrosine protein kinase JAK3 (JAK3).
Treatment of human T cells with Interleukin 15 (IL15) and Interleukin 2 (IL2) resulted in the tyrosine phosphorylation of JAK1 and JAK3. Additionally, there was a rapid induction of DNA binding complexes that contained STAT3 and STAT5, both of which were tyrosine phosphorylated (Johnston et al. 1995).This is a black-box event because it is not clear which receptor-associated kinase is responsible for STAT phosphorylation.

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds STAT3 and STAT5

Followed by: p-Y-STAT3 and p-STAT5 dissociates from IL15:IL15RA:IL2RB:p-JAK1:IL2RG:p-JAK3:p-Y-STAT3:p-STAT5

Literature references

Johnston, JA., Bacon, CM., Finbloom, DS., Rees, RC., Kaplan, D., Shibuya, K. et al. (1995). Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci U S A, 92,* 8705-9. ↗

Editions

2017-08-07	Authored	Duenas, C.
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2017-08-09	Edited	Duenas, C.

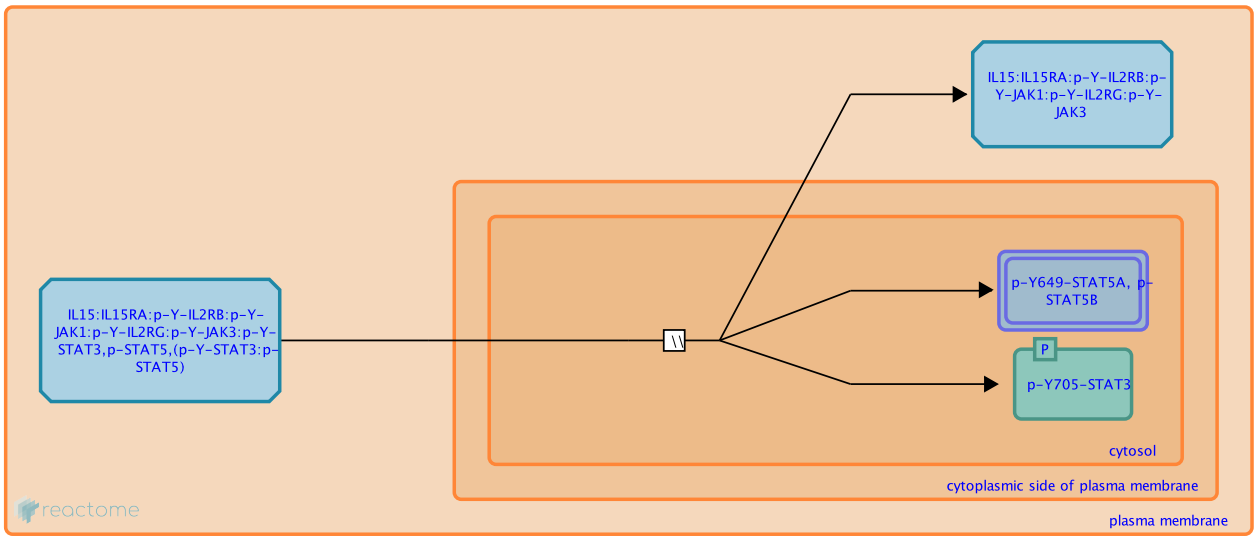
p-Y-STAT3 and p-STAT5 dissociates from IL15:IL15RA:IL2RB:p-JAK1:IL2RG:p-JAK3:p-Y-STAT3:p-STAT5 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983374

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane



Phosphorylated Signal transducer and activator of transcription 3 (STAT3) and Signal transducer and activator of transcription 5A/5B (STAT5A and STAT5B, respectively, or STAT5) dissociate from the Interleukin-15 (IL15) receptor complex, which consists of IL15, Interleukin-15 receptor subunit alpha (IL15RA, IL15Rα), Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ), Tyrosine-protein kinase JAK1 (JAK1), Cytokine receptor common subunit gamma (IL2RG, IL2Rγ) and Tyrosine-protein kinase JAK3 (JAK3). Recombinant IL15 (10 ng/mL) induces the translocation of pSTAT3 to the nucleus (Giron Michel et al. 2003). In mast cells, IL15-stimulated STAT5 activation has been suggested to involve Tyrosine protein kinase JAK2 (JAK2) rather than JAK1/JAK3 signaling (Waldman & Tagaya 1999). More in detail, mast cells have unique receptors for IL15 i.e., IL15 Receptor X (IL15RX). Binding of IL15 with IL15 RX (Tagaya et al. 1996) on mast cells induces mast cell growth by activation of JAK2/STAT5 pathways and mast cell differentiation by Non-receptor tyrosine-protein kinase TYK2/Signal transducer and activator of transcription 6/Interleukin-4 pathway(TYK2/STAT6/IL4 pathway) (Jackson et al. 2005). This is black box event because dissociation is inferred from the identification of STAT3 and STAT5 in DNA binding complexes after IL15 stimulation (Johnston et al. 1995, Giron Michel et al. 2003).

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates STAT3 and STAT5

Followed by: p-Y-STAT3 binds p-STAT5

Literature references

Waldmann, TA., Tagaya, Y. (1999). The multifaceted regulation of interleukin-15 expression and the role of this cytokine in NK cell differentiation and host response to intracellular pathogens. *Annu. Rev. Immunol., 17*, 19-49. ↗

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

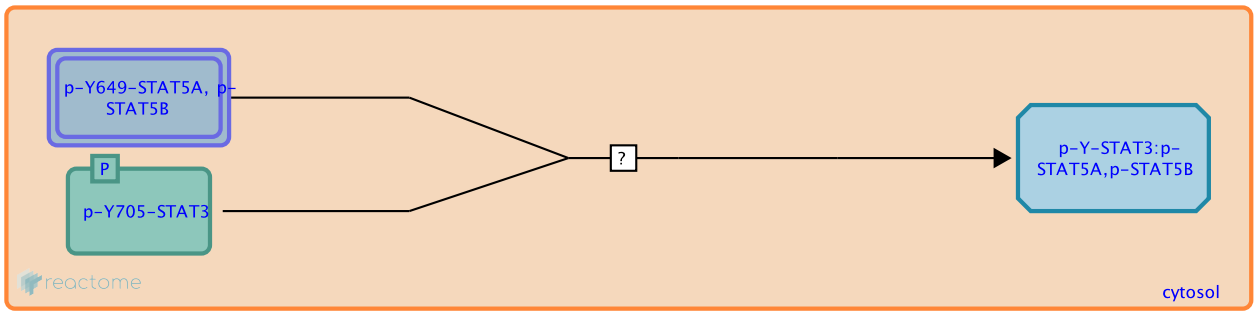
p-Y-STAT3 binds p-STAT5 ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983373

Type: uncertain

Compartments: cytosol



Signal transducer and activator of transcription 3 (STAT3) is believed to bind Signal transducer and activator of transcription 5A/5B (STAT5). IL15 stimulation leads to the formation of DNA binding complexes that contain STAT3 and STAT5 (Johnston et al. 1995, Giron-Michel et al. 2003). This is a black box event because dimer formation is inferred from STAT3 and STAT5 co-occurrence in DNA binding complexes.

Preceded by: p-Y-STAT3 and p-STAT5 dissociates from IL15:IL15RA:IL2RB:p-JAK1:IL2RG:p-JAK3:p-Y-STAT3:p-STAT5

Followed by: p-Y-STAT3:p-STAT5 translocates to the nucleus

Literature references

Giron-Michel, J., Caignard, A., Fogli, M., Brouty-Boyé, D., Briard, D., van Dijk, M. et al. (2003). Differential STAT3, STAT5, and NF-kappaB activation in human hematopoietic progenitors by endogenous interleukin-15: implications in the expression of functional molecules. *Blood, 102*, 109-17. ↗

Johnston, JA., Bacon, CM., Finbloom, DS., Rees, RC., Kaplan, D., Shibuya, K. et al. (1995). Tyrosine phosphorylation and activation of STAT5, STAT3, and Janus kinases by interleukins 2 and 15. *Proc Natl Acad Sci U S A, 92*, 8705-9. ↗

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

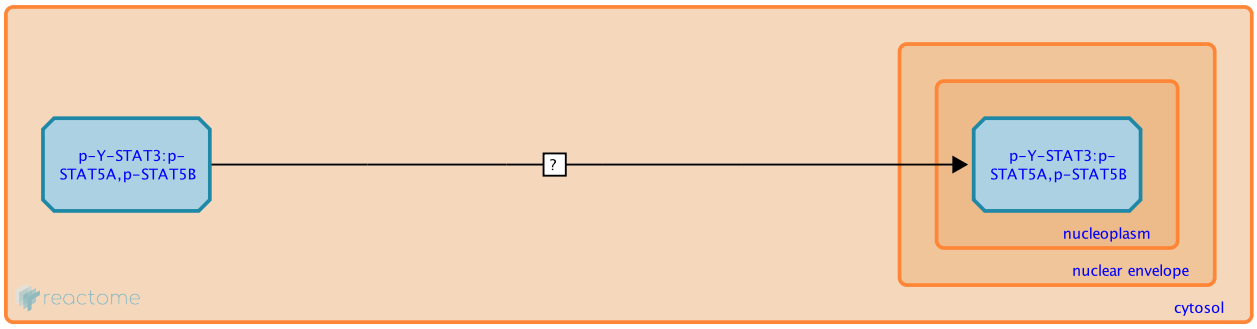
p-Y-STAT3:p-STAT5 translocates to the nucleus ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983379

Type: uncertain

Compartments: cytosol, nucleoplasm



Signal transducer and activator of transcription 3 (STAT3) and Signal transducer and activator of transcription 5A/5B (STAT5A and STAT5B respectively or STAT5) dimers translocate from the cytosol to the nucleoplasm. 10 ng/mL Interleukin-15 (IL15) induces the nuclear localization of phosphorylated STAT3, unless inhibited by neutralizing anti-IL15 or anti-Interleukin receptor alpha subunit (IL15RA, IL15Rα) mAbs (Giron Michel et al.2003, Johnston et al. 1995).This is a black box event because nuclear translocation of phosphorylated STAT3:STAT5 dimers has not been demonstrated but is inferred from other Jak-Stat signaling events.

Preceded by: p-Y-STAT3 binds p-STAT5

Literature references

Giron-Michel, J., Caignard, A., Fogli, M., Brouty-Boyé, D., Briard, D., van Dijk, M. et al. (2003). Differential STAT3, STAT5, and NF-kappaB activation in human hematopoietic progenitors by endogenous interleukin-15: implications in the expression of functional molecules. *Blood, 102*, 109-17. ↗

Editions

2017-08-07	Authored	Duenas, C.
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2017-08-09	Edited	Duenas, C.

IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds SHC1 ↗

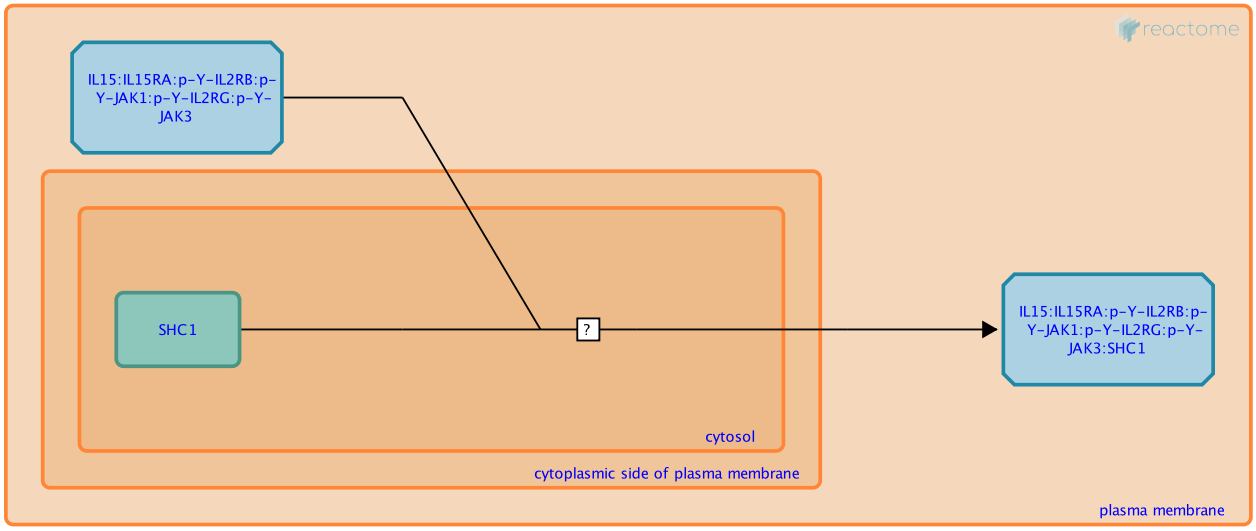
Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983299

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane

Inferred from: Il15:Il15ra:p-Y-Il2rb:p-Y-Jak1:p-Y-Il2rg:p-Y-Jak3 binds Shc1 (Mus musculus)



Inferred from mouse: Coimmunoprecipitation studies show that SHC transforming protein 1 (SHC1) associates with Interleukin-2 receptor subunit beta (IL2RB, IL2Rβ) as part of the Interleukin-2 (IL2) receptor complex (Gadina et al. 2000). Similar binding in IL15 receptor complex can be inferred from IL15 stimulates SHC1 phosphorylation (Zambricki et al. 2005). More in detail, human and mouse IL15 have 70.2% amino acid sequence similarity and exhibit similar trans-presentation mechanism, signal transduction machinery and biological activities. Similarly, human IL15 shows cross-reactivity with mouse cells and it was demonstrated that human and mouse IL15 showed similar responses in mouse models (Stoklasek et al. 2006) (Patidar et al. data not published). IL15 helps in B cell proliferation via two pathways: IL15–STAT5 and IL15–SHC–Ras–Raf–ERK pathway (Patidar et al. 2016).This is a black box event because there is no direct evidence of SHC1 binding after IL15 stimulation.

Preceded by: IL2RB and IL2RG are phosphorylated

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates SHC1

Editions

2017-08-07	Authored	Duenas, C.
2017-08-07	Reviewed	Patidar, M.
2017-08-09	Edited	Duenas, C.

IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates SHC1 ↗

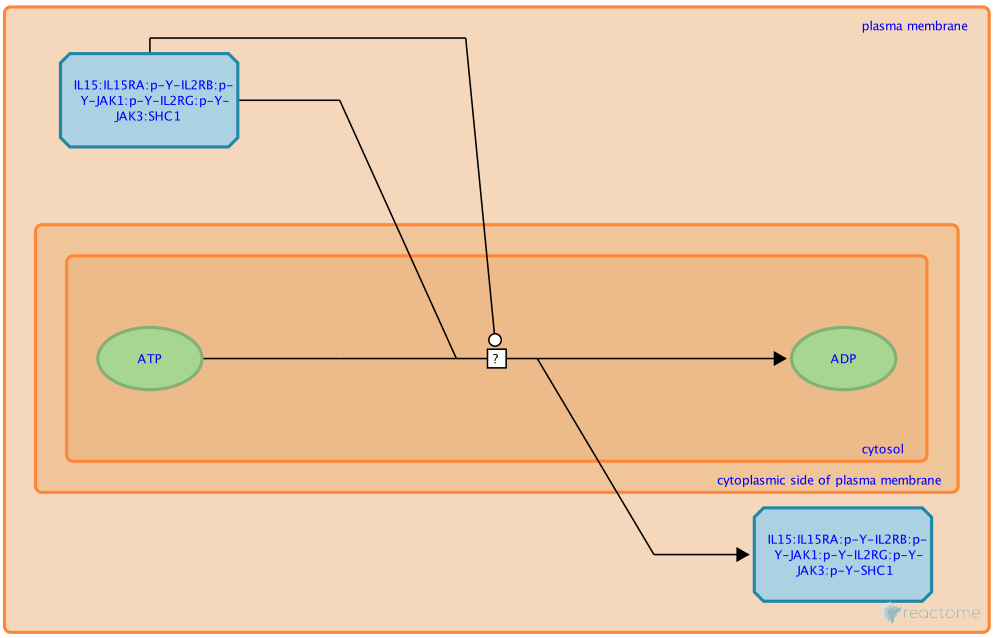
Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983309

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane

Inferred from: Il15ra:Il15:p-Y-Il2rb:p-Y-Jak1:p-Y-Il2rg:p-Y-Jak3 phosphorylates Shc1 (Mus musculus)



Inferred from mouse: Interleukin-15 (IL15) stimulates the phosphorylation of SHC1 bound to Interleukin-2 receptor subunit beta (IL2RB, IL2Rβ) (Zambricki et al 2005), which is a component of the IL15 and IL2 receptor complexes (Bennet et al. 1994, Li et al. 1994). More in detail, human and mouse IL15 have 70.2% amino acid sequence similarity and exhibit similar trans-presentation mechanism, signal transduction machinery and biological activities. Similarly, human IL15 shows cross reactivity with mouse cells and it was demonstrated that human and mouse IL15 showed similar responses in mouse models (Stoklasek et al. 2006) (Patidar et al. data not published).

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 binds SHC1

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1 binds GRB2

Editions

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2017-08-09	Edited	Duenas, C.

IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1 binds GRB2 ↗

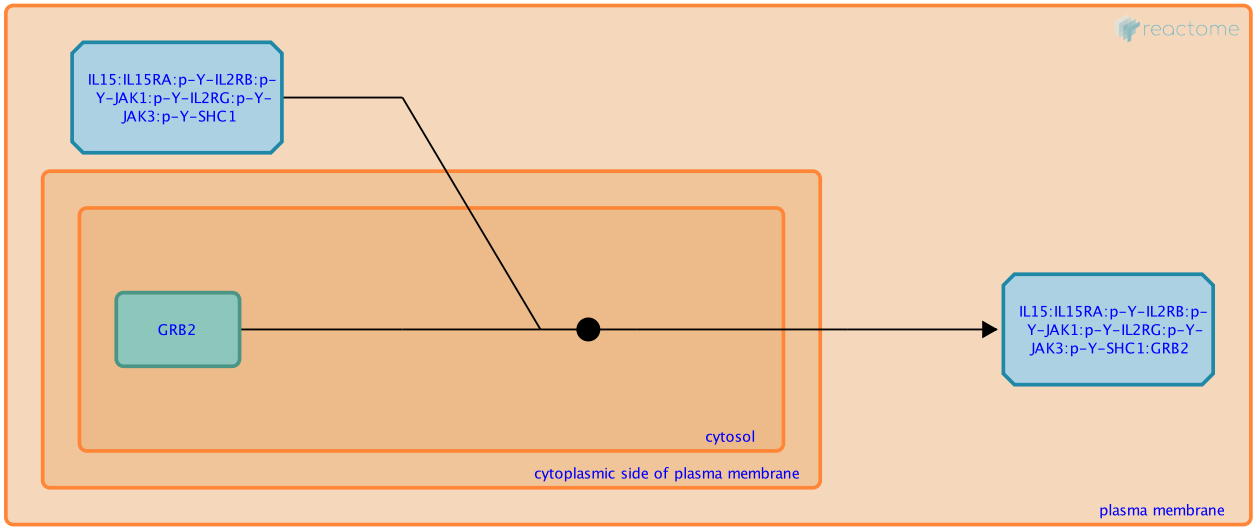
Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983394

Type: binding

Compartments: cytosol, extracellular region, plasma membrane

Inferred from: Il15:Il15ra:p-Y-Il2rb:p-Y-Jak1:p-Y-Il2rg:p-Y-Jak3:p-Y-Shc1 binds Grb2 (Mus musculus)



Inferred from mouse:GRB2 is recruited by phosphorylated SHC1 in the IL15 receptor complex (Zambricki et al. 2005, Gadina et al. 2000), as it is in the Interleukin-2 receptor complex (Li et al. 1994, Bennett et al. 1994).More in detail, human and mouse IL15 have 70.2% amino acid sequence similarity and exhibit similar trans-presentation mechanism, signal transduction machinery and biological activities. Similarly, human IL15 shows cross-reactivity with mouse cells and it was demonstrated that human and mouse IL15 showed similar responses in mouse models (Stoklasek et al. 2006) (Patidar et al. data not published).

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3 phosphorylates SHC1

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1:GRB2 binds SOS1,SOS2, IL15:IL15RA:IL2RB:JAK1:IL2RG:p-JAK3:p-Y-SHC1:GRB2 binds GAB2

Editions

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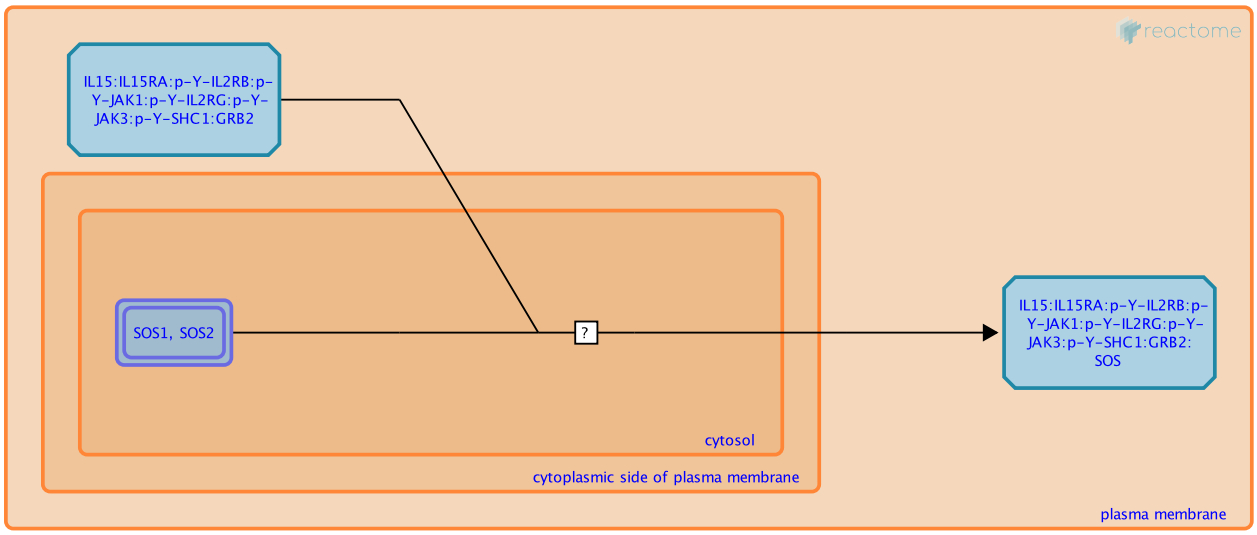
IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1:GRB2 binds SOS1,SOS2

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983384

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane



Son of sevenless homolog 2 (SOS2) is believed to bind the Interleukin-15 (IL15) receptor complex (Mishra et al. 2014). This is inferred from the binding of GRB2 to Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ) in the IL15 receptor complex (Zambricki et al. 2005) and Interleukin-2 receptor complex (Zhu et al. 1994) and from events that follow SHC-GRB2 association in IL2 receptor signaling. The Interleukin-15 (IL15) receptor complex consists mainly of IL15, Interleukin-15 receptor alpha subunit (IL15RA, IL15Rα), Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ), which is associated with JAK1 and Interleukin receptor gamma subunit, which is associated with JAK3 (Johnston et al. 1995). In IL2 signaling, the resulting GRB2:SOS complex activates the Ras-Raf pathway (Zhu et al. 1994) and is believed to participate in similar events in IL15 signaling (Anduyah et al. 1997, Mishra et al. 2014). This is a black box event because SOS1 binding to GRB2 in response to IL15 has not been demonstrated.

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1 binds GRB2

Literature references

Adunyah, SE., Wheeler, BJ., Cooper, RS. (1997). Evidence for the involvement of LCK and MAP kinase (ERK-1) in the signal transduction mechanism of interleukin-15. *Biochem. Biophys. Res. Commun., 232*, 754-8.

Mishra, A., Sullivan, L., Caligiuri, MA. (2014). Molecular pathways: interleukin-15 signaling in health and in cancer. *Clin. Cancer Res., 20*, 2044-50.

Zambricki, E., Shigeoka, A., Kishimoto, H., Sprent, J., Burakoff, S., Carpenter, C. et al. (2005). Signaling T-cell survival and death by IL-2 and IL-15. *Am. J. Transplant., 5*, 2623-31.

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IL15:IL15RA:IL2RB:JAK1:IL2RG:p-JAK3:p-Y-SHC1:GRB2 binds GAB2 ↗

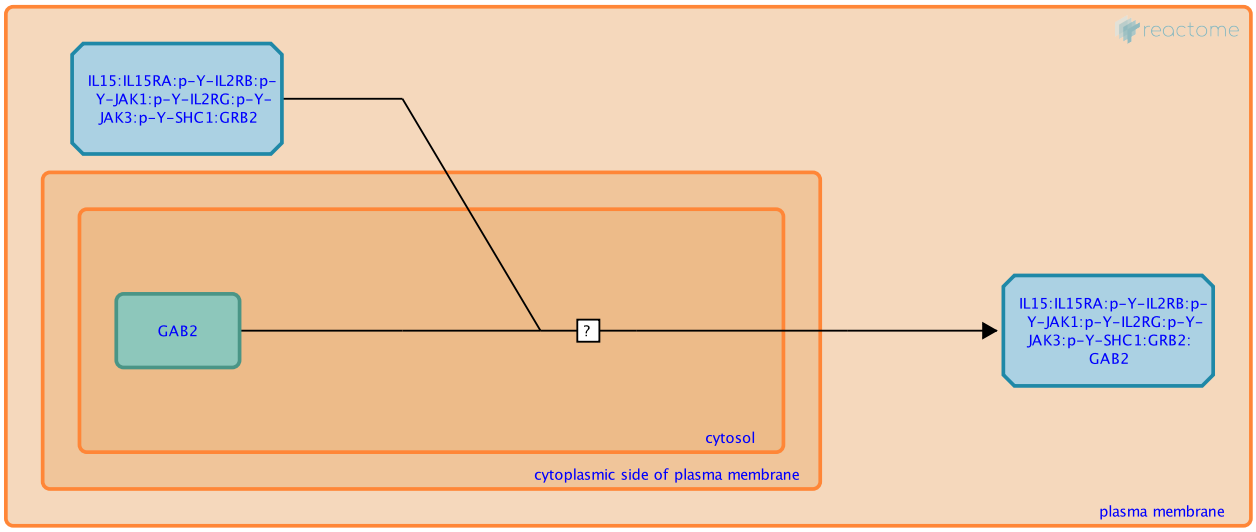
Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983425

Type: uncertain

Compartments: cytosol, extracellular region, plasma membrane

Inferred from: Il15:Il15ra:p-Y-Il2rb:p-Y-Jak1:p-Y-Il2rg:p-Y-Jak3:p-Y-Shc1:Grb2 binds Gab2 (Mus musculus)



Inferred from mouse: GRB2 associated binding protein 2 (GAB2) is believed to bind and be phosphorylated in response to Interleukin-2 (IL2) and Interleukin-15 (IL15) stimulation. Its phosphorylation is greatly diminished by mutation of the site in the Interleukin-2 Receptor beta chain (Y338F) (IL2RB, IL2Rβ) that recruits SHC transforming protein 1 (SHC1) (Gadina et al.2000, Wöhrle et al.2009, Gesbert et al. 1998, Brockdorff et al. 2001). GAB2 is a phosphoprotein that is suggested to associates with PI3kinase, Growth factor receptor-bound protein 2 (GRB2) and Tyrosine protein phosphatase non-receptor type 11 (PTPN11 or SHP2) in T and Natural Killer (NK) cells (Gu et al. 2000).This is a black box event because GAB2 binding is inferred from IL15 stimulation of GAB2 phosphorylation (Brockdorff et al. 2001). More in detail, human and mouse IL15 have 70.2% amino acid sequence similarity and exhibit similar trans-presentation mechanism, signal transduction machinery and biological activities. Similarly, human IL15 shows cross-reactivity with mouse cells and it was demonstrated that human and mouse IL15 showed similar responses in mouse models (Stoklasek et al. 2006) (Patidar et al. data not published).

Preceded by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1 binds GRB2

Followed by: IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1:GRB2:GAB2 phosphorylates GAB2

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IL15:IL15RA:p-Y-IL2RB:p-Y-JAK1:p-Y-IL2RG:p-Y-JAK3:p-Y-SHC1:GRB2:GAB2 phosphorylates GAB2 ↗

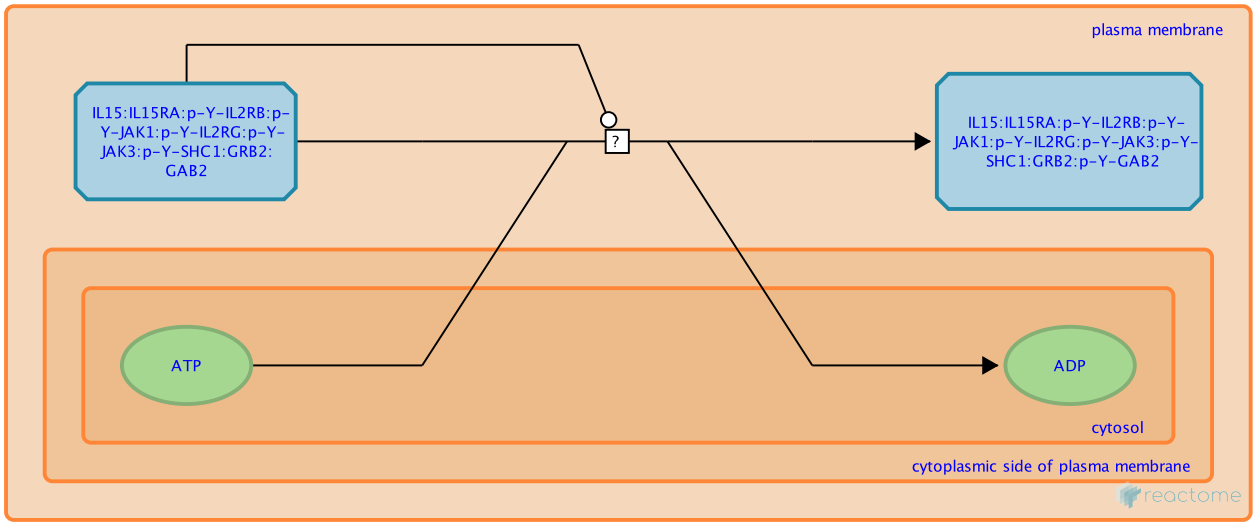
Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983424

Type: uncertain

Compartments: plasma membrane, cytosol, extracellular region

Inferred from: Il15:Il15ra:p-Y-Il2rb:p-Y-Jak1:p-Y-Il2rg:p-Y-Jak3:p-Y-Shc1:Grb2:Gab2 phosphorylates Gab2 (Mus musculus)



Inferred from mouse: GRB2 associated binding protein 2 (GAB2) is phosphorylated in response to Interleukin-2 (IL2) and Interleukin-15 (IL15) stimulation. Its phosphorylation is greatly diminished by mutation of the Y338 site in Interleukin-2 Receptor beta chain (IL2RB, IL2Rβ) that recruits SHC transforming protein 1 (SHC1) (Gadina et al. 2000, Wöhrle et al. 2009, Gesbert et al. 1998, Brockdorff et al. 2001). The core Interleukin-15 (IL15) receptor complex consists of IL15, Interleukin-15 receptor alpha subunit (IL15RA, IL15Rα), Interleukin-2 receptor beta subunit (IL2RB, IL2Rβ), which is associated with JAK1 and Interleukin-2 receptor gamma subunit (IL2RG, IL2Rγ), which is associated with JAK3 (Johnston et al. 1995). In this event, the IL15 receptor complex also includes phosphorylated SHC1, GRB2 and GAB2. This is a black box event because the kinase responsible for GAB2 phosphorylation has not been demonstrated.

Preceded by: IL15:IL15RA:IL2RB:JAK1:IL2RG:p-JAK3:p-Y-SHC1:GRB2 binds GAB2

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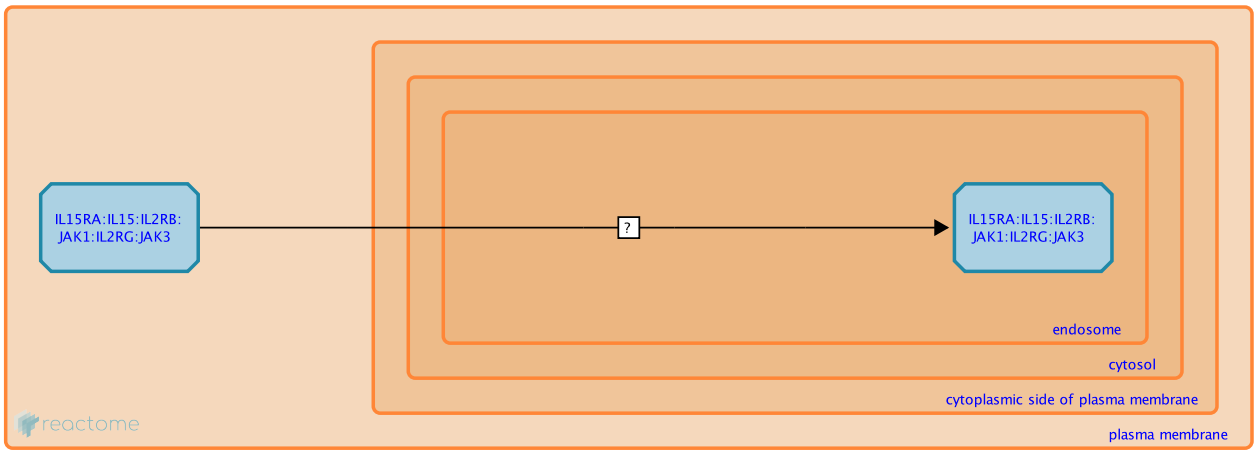
IL15:IL15RA:IL2RB:JAK1:IL2RG:JAK3 translocates from the plasma membrane to the endosome ↗

Location: Interleukin-15 signaling

Stable identifier: R-HSA-8983335

Type: uncertain

Compartments: endosome, extracellular region, plasma membrane



The formation of Interleukin-15/Interleukin-15 receptor alpha complexes (IL15:IL15RA or IL15: IL15Rα) on cell surfaces induce a trans-endosomal recycling of IL15 leading to the persistence of surface-bound IL15 due to the constant reappearance of IL15 on plasma membranes. This complex contributes to the long survival of T cells expressing IL15RA after IL15 withdrawal (Dubois et al. 2000). This is a black box event since the details of other potential receptors and proteins participating in this event, remain unclear. It is shown similar patterns for other interleukins (i.e: Interleukin-12, Chiaruttini et al. 2016).

Literature references

Dubois, S., Mariner, J., Waldmann, TA., Tagaya, Y. (2002). IL-15Ralpha recycles and presents IL-15 In trans to neighboring cells. *Immunity, 17*, 537-47. ↗

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