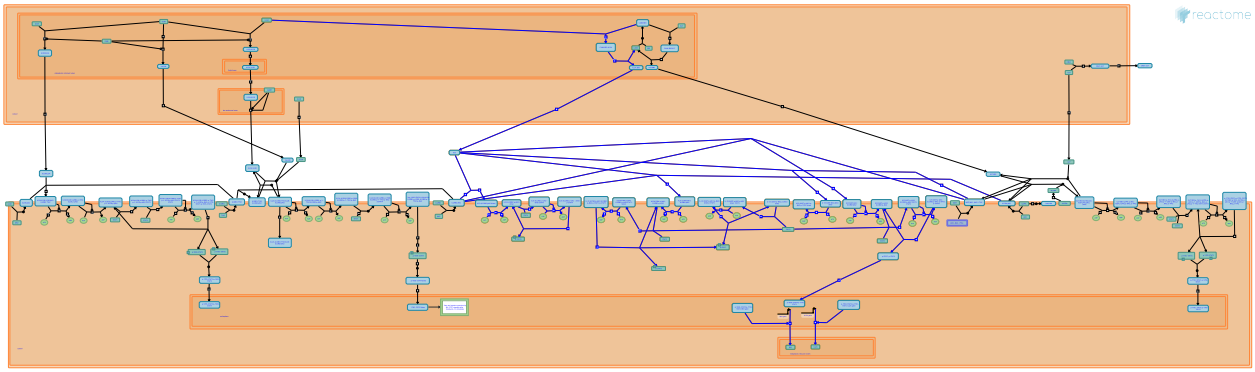
Interleukin-35 Signalling



Duenas, C., Garapati, P V., Jupe, S., Narazaki, M., Pylayeva-Gupta, Y., Singh, K., Tanaka, M., Varusai, TM., van de Vosse, E.

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

15/09/2021

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. ↗

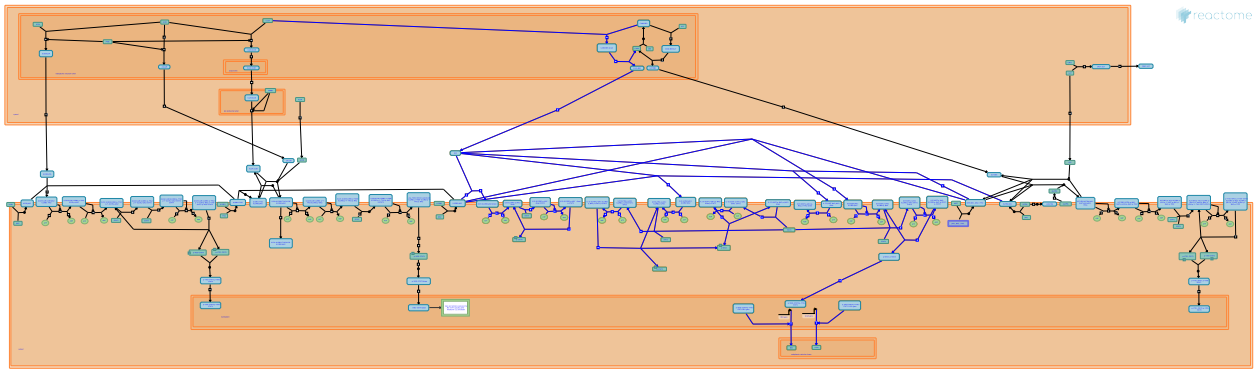
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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-35 Signalling ↗

Stable identifier: R-HSA-8984722



Interleukin 35 (IL35) is an IL12 family cytokine produced by regulatory but not effector T-cells. It is a dimeric protein composed of IL-12RB2 and IL27RA chains. IL35 suppresses inflammatory responses of immune cells.

Literature references

Egwuagu, CE., Yu, CR., Sun, L., Wang, R. (2015). Interleukin 35: Critical regulator of immunity and lymphocyte-mediated diseases. *Cytokine Growth Factor Rev., 26*, 587-93. ↗

Editions

2009-11-25	Authored	Jupe, S.
2015-11-09	Reviewed	Narazaki, M., Tanaka, M.
2017-05-11	Edited	Jupe, S.

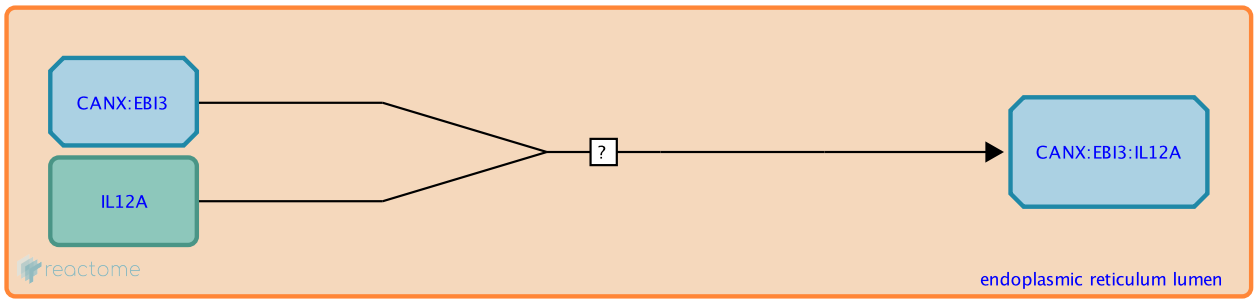
EBI3:CANX binds IL12A ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8950362

Type: uncertain

Compartments: endoplasmic reticulum lumen



Interleukin-35 is a heterodimer of Interleukin-27 subunit beta (EBI3) and Interleukin-12 subunit alpha (IL12A or IL12-p35) (Devergne et al. 1997). It is required for maximal T regulatory cell activity (Collison et al. 2007).

Site directed mutagenesis of IL12A identified mutations that disrupt formation of Interleukin 12 and Interleukin 27 heterodimeric complexes but not Interleukin 35. IL12A appears to pair with EBI3 entirely differently from IL27. (Jones et al. 2012). In the absence of IL12A, EBI3 is retained in the endoplasmic reticulum, associated with the chaperone Calnexin (CANX) (Devergne et al. 1997).

This is a Black Box event because we know that EBI3 is retained as a complex with CANX and the co expression of EBI3 and IL12A enables their secretion, but we don't have evidence about the mechanism of dissociation of CANX from EBI3 (Devergne et al. 1997).

Followed by: CANX dissociates from IL12A:EBI3

Literature references

Collison, LW., Workman, CJ., Kuo, TT., Boyd, K., Wang, Y., Vignali, KM. et al. (2007). The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature, 450*, 566-9. ↗

Devergne, O., Birkenbach, M., Kieff, E. (1997). Epstein-Barr virus-induced gene 3 and the p35 subunit of interleukin 12 form a novel heterodimeric hematopoietin. *Proc. Natl. Acad. Sci. U.S.A., 94*, 12041-6. ↗

Jones, LL., Chaturvedi, V., Uyttenhove, C., Van Snick, J., Vignali, DA. (2012). Distinct subunit pairing criteria within the heterodimeric IL-12 cytokine family. *Mol. Immunol., 51*, 234-44. ↗

Editions

2016-12-02	Authored	Duenas, C.
2017-05-11	Edited	Duenas, C.
2017-05-12	Reviewed	van de Vosse, E.

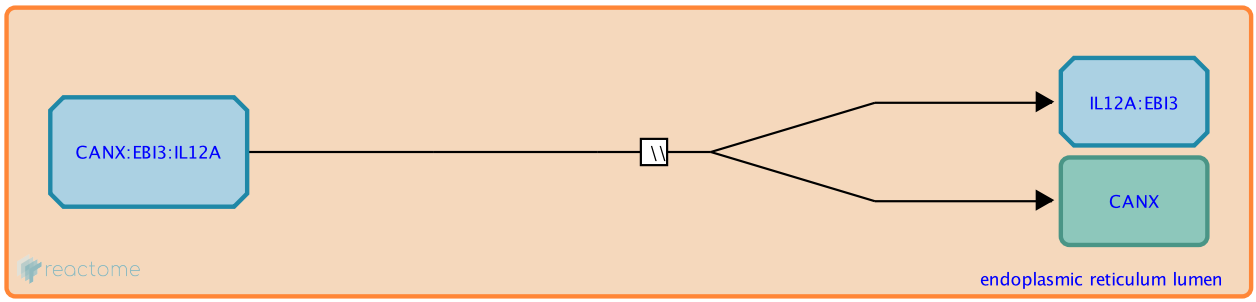
CANX dissociates from IL12A:EBI3

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8950740

Type: omitted

Compartments: endoplasmic reticulum lumen



Interleukin-12 subunit alpha (IL12A, IL12p35) binds Interleukin-27 subunit beta (EBI3) forming the Interleukin-35 heterodimeric complex (IL12A:EBI3)(Devergne et al.). When expressed alone, human EBI3 is associated with the endoplasmic reticulum (ER) resident molecular chaperone calnexin (CANX) and is retained in the ER (Devergne et al. 1997). Co-expression of IL27 and EBI3 enables formation of IL27:EBI3, allowing secretion (Pflanz et al. 2002).

This is a Black Box event because there is not reported wich reaction occurs first: the association of IL12A to EBI3:CANX and later the Interleukin-35 heterodimeric protein formation.

Preceded by: EBI3:CANX binds IL12A

Followed by: Interleukin-35 translocates from the ER lumen to the extracellular region

Literature references

Devergne, O., Birkenbach, M., Kieff, E. (1997). Epstein-Barr virus-induced gene 3 and the p35 subunit of interleukin 12 form a novel heterodimeric hematopoietin. *Proc. Natl. Acad. Sci. U.S.A., 94*, 12041-6.

Pflanz, S., Timans, JC., Cheung, J., Rosales, R., Kanzler, H., Gilbert, J. et al. (2002). IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity, 16*, 779-90.

Editions

2016-12-02	Authored	Duenas, C.
2017-05-11	Edited	Duenas, C.
2017-05-12	Reviewed	van de Vosse, E.

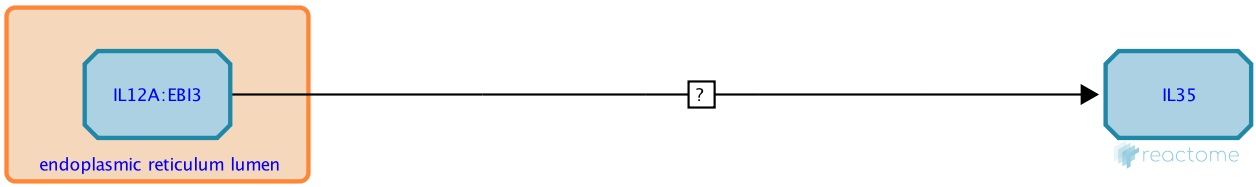
Interleukin-35 translocates from the ER lumen to the extracellular region ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-448627

Type: uncertain

Compartments: extracellular region, endoplasmic reticulum lumen



Interleukin-35 heterodimer is formed by interleukin-12 alpha (IL12A or IL12p35) and Interleukin 27 subunit beta (EBI3).

EBI3 monomer can be found at the endoplasmic reticulum and is not secreted since it remains associated to the protein calnexin (CANX). So is suggested EBI3 needs the association with another subunit to be released to the extracellular region (Devergne et al. 1996).

Interleukin-35 affects and is specifically produced by regulatory T cells and regulatory B cells (Niedbala et al. 2007, Wang et al. 2014, Egwuagu et al. 2015, Fonseca-Camarillo et al. 2015). This interleukin is secreted and inhibits T cell proliferation (Collison et al. 2007).

This reaction is a black box event because we know the Interleukin-35 heterodimeric protein is secreted but there is no reported evidence from which compartment and which mechanism is involved in the traslocation.

Preceded by: CANX dissociates from IL12A:EBI3

Followed by: IL35 binds IL6ST:IL6ST receptor, IL35 binds IL27RA:IL12RB2 receptor, IL35 binds IL-12RB2:IL6ST receptor, IL35 binds IL12RB2:IL12RB2 receptor

Literature references

Devergne, O., Birkenbach, M., Kieff, E. (1997). Epstein-Barr virus-induced gene 3 and the p35 subunit of interleukin 12 form a novel heterodimeric hematopoietin. *Proc. Natl. Acad. Sci. U.S.A., 94*, 12041-6. ↗

Niedbala, W., Wei, XQ., Cai, B., Hueber, AJ., Leung, BP., McInnes, IB. et al. (2007). IL-35 is a novel cytokine with therapeutic effects against collagen-induced arthritis through the expansion of regulatory T cells and suppression of Th17 cells. *Eur J Immunol, 37*, 3021-9. ↗

Collison, LW., Workman, CJ., Kuo, TT., Boyd, K., Wang, Y., Vignali, KM. et al. (2007). The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature, 450*, 566-9. ↗

Egwuagu, CE., Yu, CR., Sun, L., Wang, R. (2015). Interleukin 35: Critical regulator of immunity and lymphocyte-mediated diseases. *Cytokine Growth Factor Rev., 26*, 587-93. ↗

Editions

2009-11-25	Authored	Jupe, S.
2015-07-21	Authored, Edited	Garapati, P V.
2015-11-09	Reviewed	Narazaki, M., Tanaka, M.

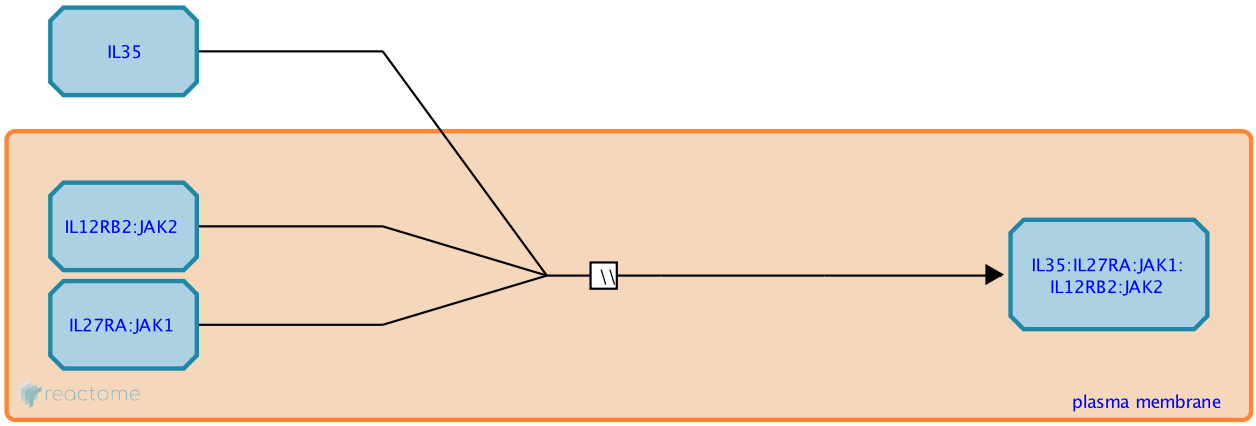
IL35 binds IL27RA:IL12RB2 receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984001

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol



Interleukin 35 (IL35) is a heteromeric complex of Interleukin 12 subunit alpha (IL12A) and Interleukin 27 subunit alpha (IL27). IL35 can trigger the activation of the Janus Kinase (JAK) bound heterodimeric receptor composed of Interleukin 27 receptor subunit alpha (Il27RA) and Interleukin 12 recetor subunit beta 2 (IL12RB2). JAKs are believed to be associated with the receptor before receptor activation (Behrmann et al., 2004). Consequently, IL12RB2:IL27RA facilitates the phosphorylation of STAT1:STAT3 heteromer downstream. Physiologically, this may result in the expansion of regulatory B cells and suppression of T and B cell proliferation. As it is not clear whether the dimeric receptor can form in the absence of ligand, formation of the receptor dimer is represented here as a black box event.

Preceded by: Interleukin-35 translocates from the ER lumen to the extracellular region

Followed by: JAK1,JAK2 bound to IL27RA:IL12RB2 receptor are phosphorylated

Literature references

Shen, P., Roch, T., Lampropoulou, V., O'Connor, RA., Stervbo, U., Hilgenberg, E. et al. (2014). IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature, 507*, 366-70. ↗

Wang, RX., Yu, CR., Dambuza, IM., Mahdi, RM., Dolinska, MB., Sergeev, YV. et al. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med., 20*, 633-41. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

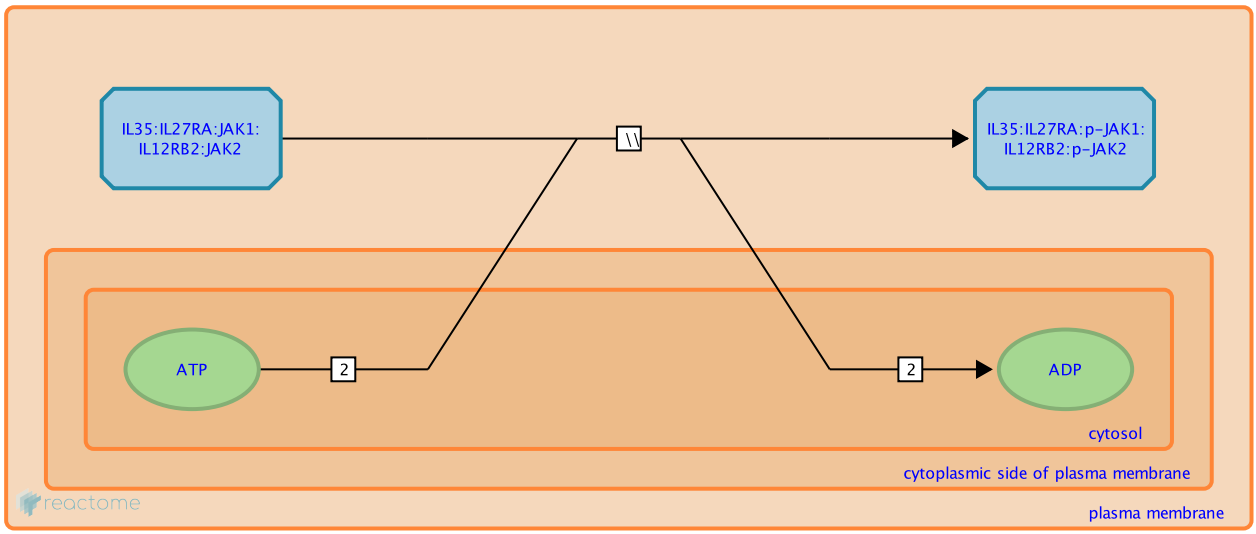
JAK1,JAK2 bound to IL27RA:IL12RB2 receptor are phosphorylated ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984012

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) presumably signal via a complex that includes Interleukin 27 receptor subunit alpha (Il27RA), Interleukin 12 receptor subunit beta 2 (IL12RB2) and the associated Tyrosine protein kinase JAK1 (JAK1) and JAK2 (Wang et al. 2014). Downstream, these JAKs are believed to phosphorylate Signal transducer and activator of transcription 1 (STAT1) and STAT3 (Stark GR and Darnell JE, 2012). As the series of events that induces JAK/STAT phosphorylation events in response to IL35 are not clear, this event is represented as a black box.

Preceded by: IL35 binds IL27RA:IL12RB2 receptor

Followed by: STAT1,STAT3 associate with IL27RA:IL12RB2 receptor

Literature references

Shen, P., Roch, T., Lampropoulou, V., O'Connor, RA., Stervbo, U., Hilgenberg, E. et al. (2014). IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature, 507*, 366-70. ↗

Wang, RX., Yu, CR., Dambuza, IM., Mahdi, RM., Dolinska, MB., Sergeev, YV. et al. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med., 20*, 633-41. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

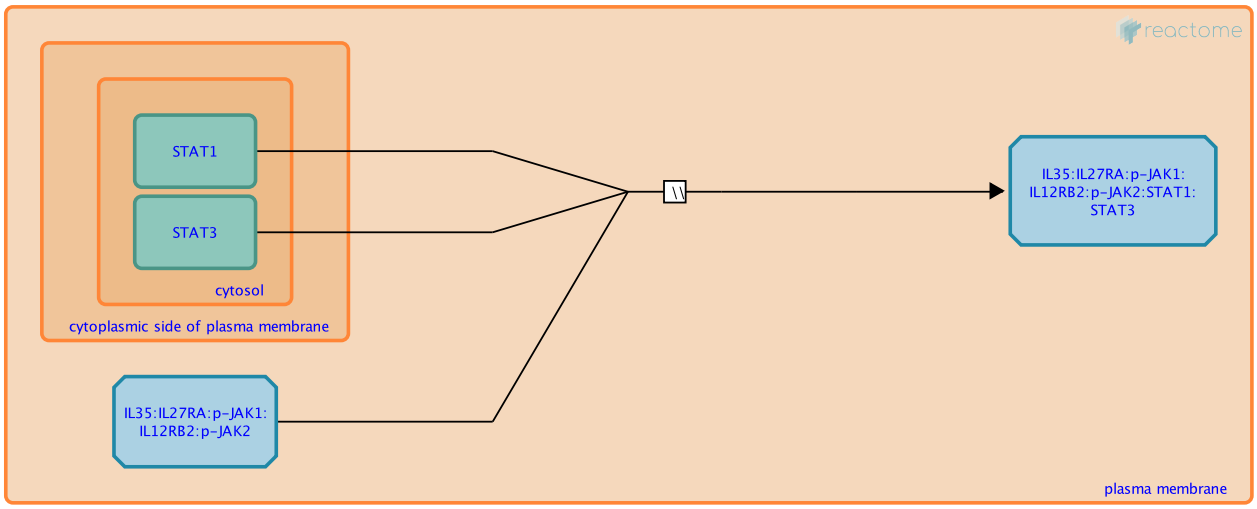
STAT1,STAT3 associate with IL27RA:IL12RB2 receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984021

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) binding activates the IL35 receptor complex and facilitates JAKs phosphorylation. Subsequently, Signal transducer and activator of transcription 1 alpha/beta (STAT1) and Signal transducer and activator of transcription 3 alpha/beta (STAT3) bind to the receptor complex and are activated by tyrosine phosphorylation (Wang et al. 2014). This is a black box event because the receptor subunit responsible for STAT1 and STAT3 binding to the receptor is unclear.

Preceded by: JAK1,JAK2 bound to IL27RA:IL12RB2 receptor are phosphorylated

Followed by: JAK1,JAK2 bound to IL27RA:IL12RB2 receptor phosphorylate STAT1,STAT3

Literature references

Shen, P., Roch, T., Lampropoulou, V., O'Connor, RA., Stervbo, U., Hilgenberg, E. et al. (2014). IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature, 507*, 366-70. ↗

Wang, RX., Yu, CR., Dambuza, IM., Mahdi, RM., Dolinska, MB., Sergeev, YV. et al. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med., 20*, 633-41. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

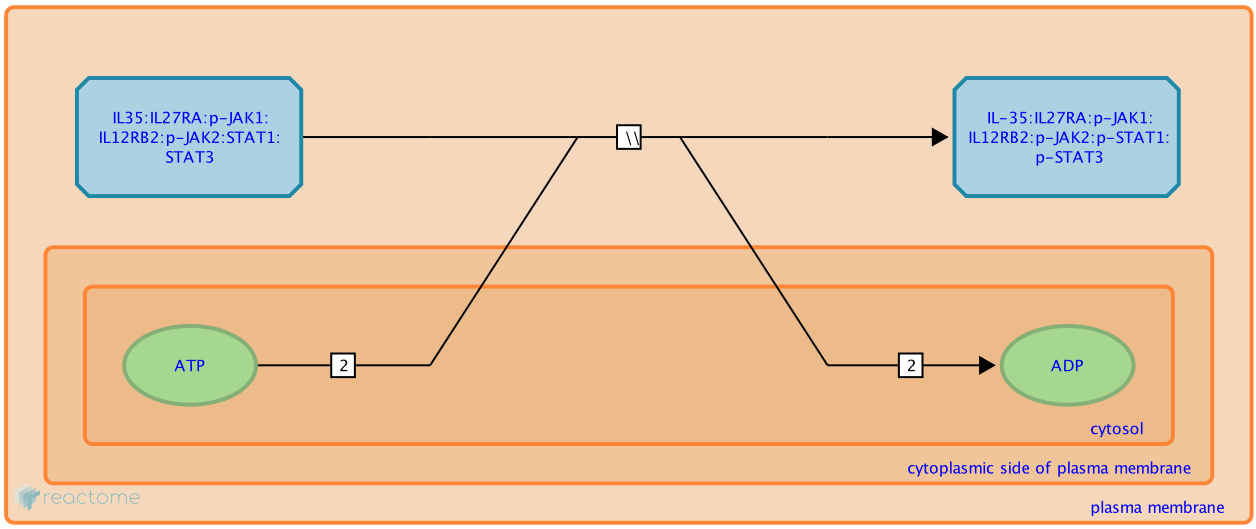
JAK1,JAK2 bound to IL27RA:IL12RB2 receptor phosphorylate STAT1,STAT3 ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984014

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) binding activates the IL35 receptor complex and may presumably facilitate Tyrosine protein kinase JAK (JAK) phosphorylation. Subsequently, Signal transducer and activator of transcription 1 alpha/beta (STAT1) and Signal transducer and activator of transcription 3 alpha/beta (STAT3) may bind to the receptor complex and are activated by tyrosine phosphorylation. Although it is known that JAKs are involved in STATs phosphorylation (Stark GR and Darnell JE, 2012), it is not clear how other components of the IL35 receptor complex contribute to STAT1/STAT3 phosphorylation. For this reason, this event is assigned a black box status.

Preceded by: STAT1,STAT3 associate with IL27RA:IL12RB2 receptor

Followed by: p-STAT1, p-STAT3 dissociate from IL27RA:IL12RB2 receptor

Literature references

Shen, P., Roch, T., Lampropoulou, V., O'Connor, RA., Stervbo, U., Hilgenberg, E. et al. (2014). IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature, 507*, 366-70. ↗

Wang, RX., Yu, CR., Dambuza, IM., Mahdi, RM., Dolinska, MB., Sergeev, YV. et al. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med., 20*, 633-41. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

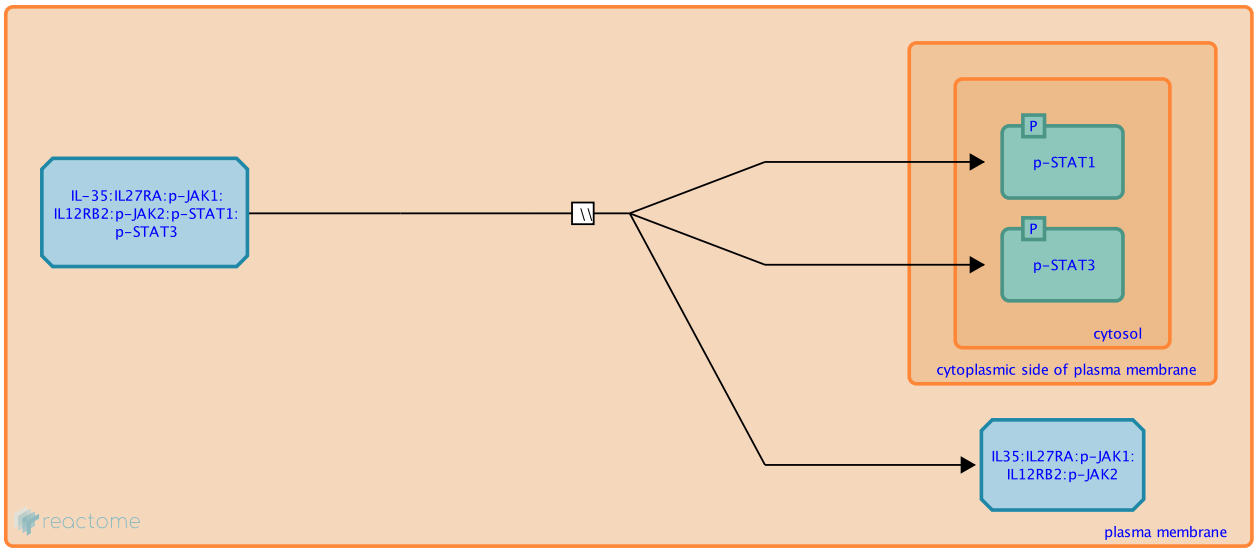
p-STAT1, p-STAT3 dissociate from IL27RA:IL12RB2 receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984023

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) can signal via IL35 receptors triggering the JAK/STAT pathway downstream. Signal transducer and activator of transcription 1 alpha/beta (STAT1) and Signal transducer and activator of transcription 3 alpha/beta (STAT3) bind to the JAK associated IL35 receptor complex and are activated via phosphorylations. Subsequently, phosphorylated p STAT1:p STAT3 dissociates from the receptor complex (Wang et al. 2014). This is a black box event because there is no literature evidence about the exact mechanism of the release of STAT1 and STAT3 from the receptor complex.

Preceded by: JAK1,JAK2 bound to IL27RA:IL12RB2 receptor phosphorylate STAT1,STAT3

Literature references

Shen, P., Roch, T., Lampropoulou, V., O'Connor, RA., Stervbo, U., Hilgenberg, E. et al. (2014). IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases. *Nature, 507*, 366-70. ↗

Wang, RX., Yu, CR., Dambuza, IM., Mahdi, RM., Dolinska, MB., Sergeev, YV. et al. (2014). Interleukin-35 induces regulatory B cells that suppress autoimmune disease. *Nat. Med., 20*, 633-41. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

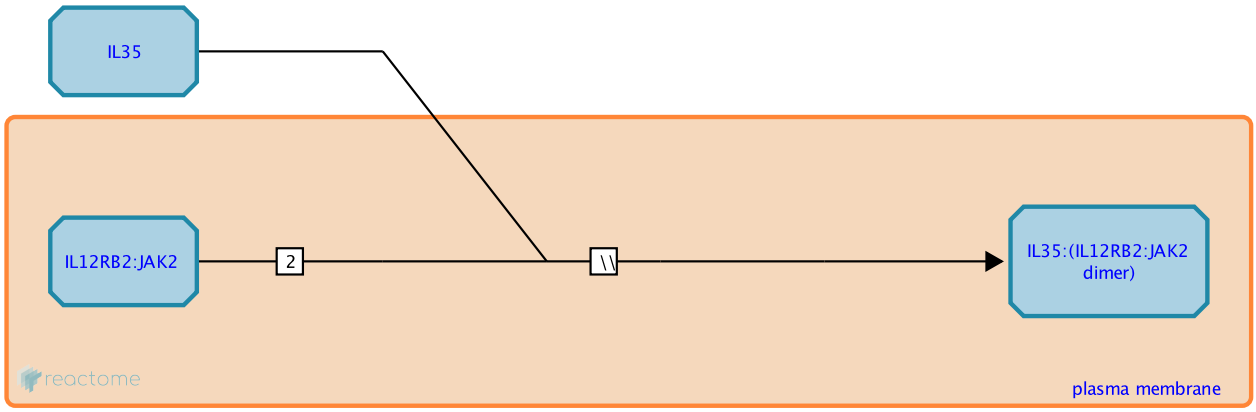
IL35 binds IL12RB2:IL12RB2 receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983519

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol



Interleukin 35 (IL35) is a heteromeric complex conformed by Interleukin 12 subunit alpha (IL12A) and Interleukin 27 subunit alpha (IL27). IL35 may presumably stimulate Janus Kinase (JAK) bound homodimers of Interleukin 12 receptor beta 2 (IL12RB2). JAKs are believed to be associated with the receptor before receptor activation (Behrmann et al., 2004). Subsequently, this triggers the phosphorylation of STAT4 downstream. The physiological consequence of this signalling is the suppression of T cell response. The event is represented as a black box due to the incomplete knowledge about the ligand binding to monomers followed by dimerization or binding directly to the dimers.

Preceded by: Interleukin-35 translocates from the ER lumen to the extracellular region

Followed by: JAK2 in IL12RB2:IL12RB2 receptor is phosphorylated

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Boulanger, MJ., Chow, DC., Brevnova, EE., Garcia, KC. (2003). Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science, 300*, 2101-4. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

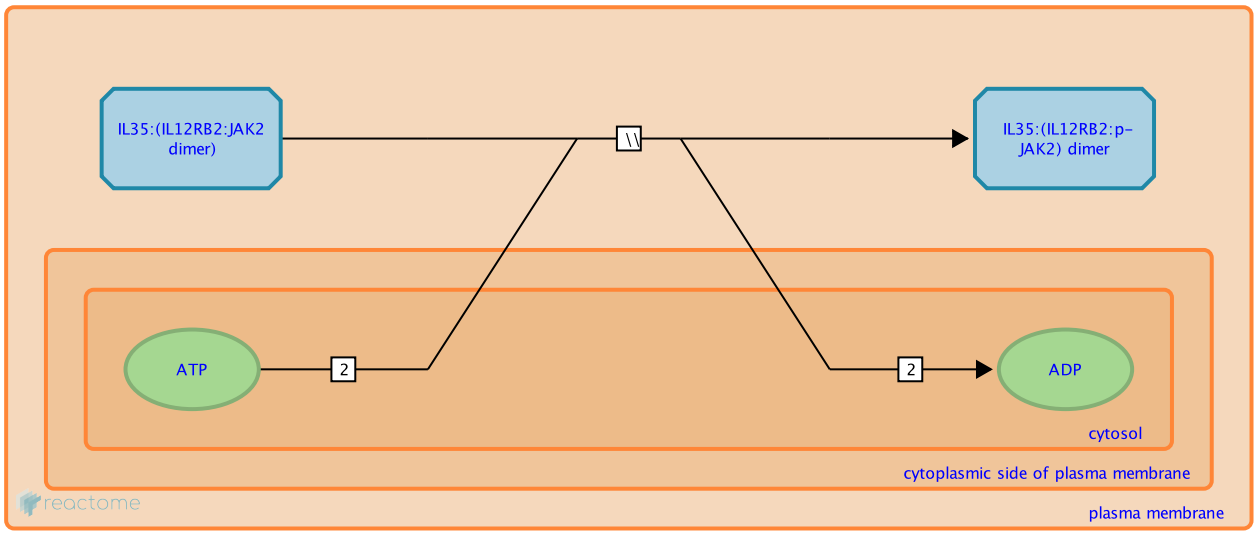
JAK2 in IL12RB2:IL12RB2 receptor is phosphorylated ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983870

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) may presumably signal via a complex that includes Tyrosine protein kinase JAK2 (JAK2) associated with Interleukin 12 receptor beta 2 (IL12RB2) dimers (Collison et al. 2012). JAKs are believed to phosphorylate Signal transducers and activator of transcription (STATs) (Stark GR and Darnell JE, 2012). As the series of events that induce JAK/STAT phosphorylation events in response to IL35 are not clear, this event is represented as a black box.

Preceded by: IL35 binds IL12RB2:IL12RB2 receptor

Followed by: STAT4 binds IL12RB2:IL12RB2

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
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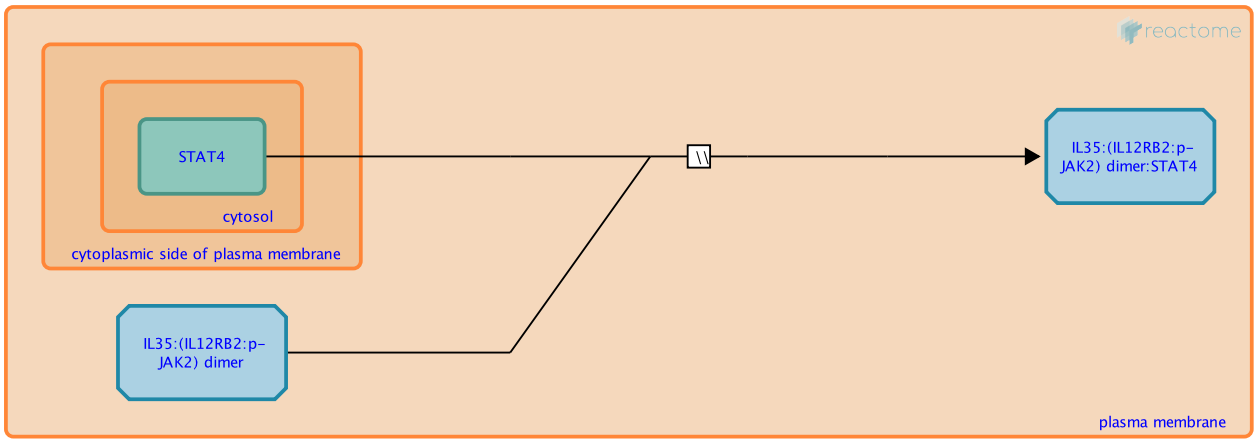
STAT4 binds IL12RB2:IL12RB2 ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983876

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) binding activates the IL35 receptor complex and facilitates JAKs phosphorylation. Subsequently, Signal transducer and activator of transcription 4-alpha/beta (STAT4) binds to the receptor complex and is activated by tyrosine phosphorylation (Collison et al. 2012). This is a black box event because the receptor subunit responsible for STAT4 binding to the receptor is unclear.

Preceded by: JAK2 in IL12RB2:IL12RB2 receptor is phosphorylated

Followed by: JAK2 bound to IL12RB2:IL12RB2 phosphorylate STAT4

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

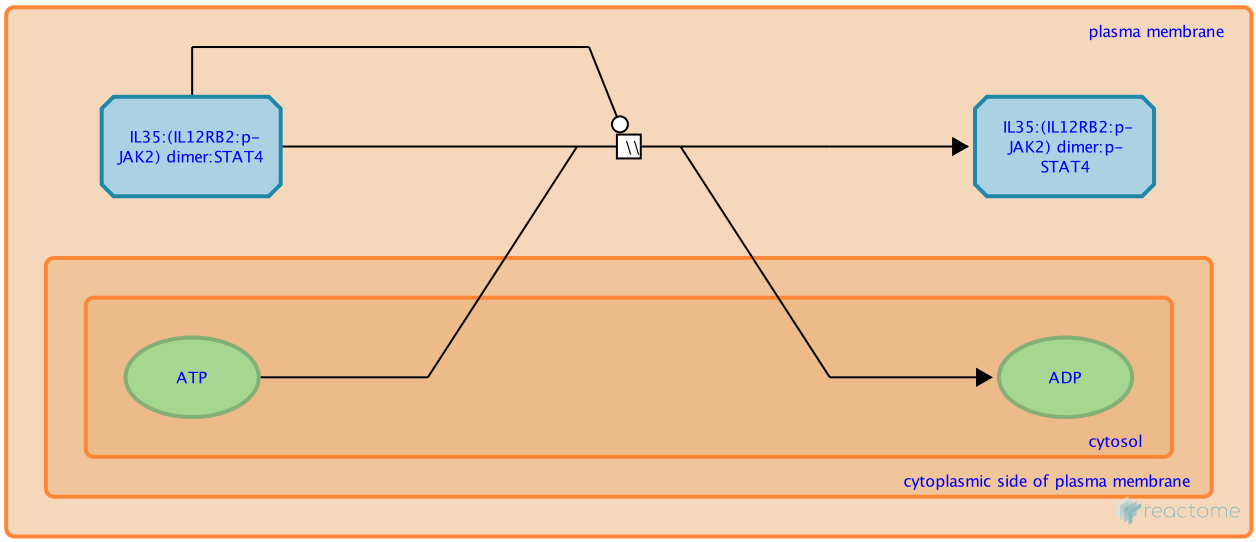
JAK2 bound to IL12RB2:IL12RB2 phosphorylate STAT4 ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983872

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) binding activates the IL35 receptor complex and may facilitate Tyrosine protein kinase JAK (JAK) phosphorylation. Subsequently, Signal transducer and activator of transcription 4 alpha/beta (STAT4) may bind to the receptor complex and is activated by tyrosine phosphorylation (Collison et al. 2012). JAK2 is known to be involved in the phosphorylation of STAT1 (Higashi T et al., 2005).

Preceded by: STAT4 binds IL12RB2:IL12RB2

Followed by: p-STAT4 dissociates from IL12RB2:IL12RB2 receptor

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Higashi, T., Tsukada, J., Yoshida, Y., Mizobe, T., Mouri, F., Minami, Y. et al. (2005). Constitutive tyrosine and serine phosphorylation of STAT4 in T-cells transformed with HTLV-I. *Genes Cells, 10*, 1153-62. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

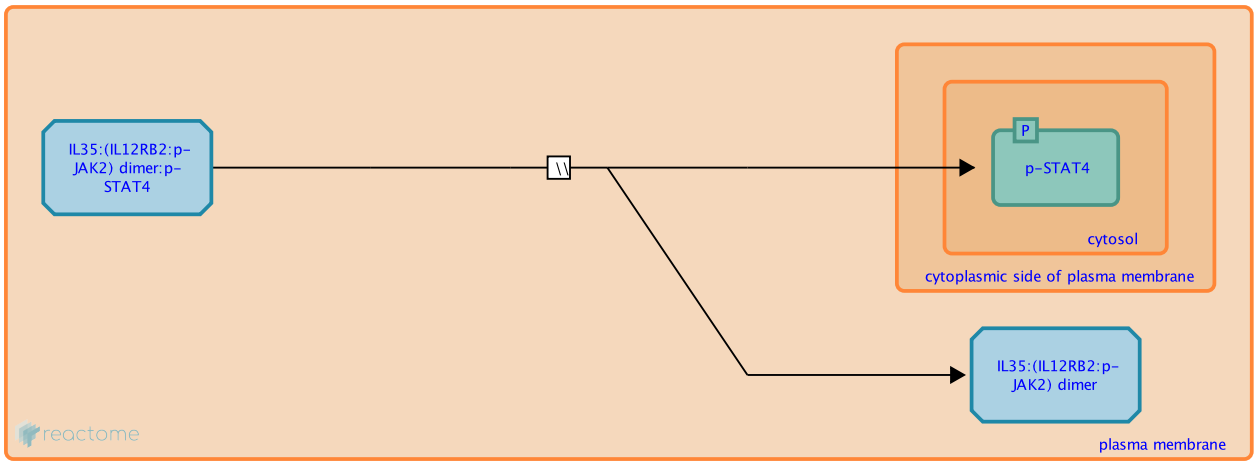
p-STAT4 dissociates from IL12RB2:IL12RB2 receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983878

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) can signal via IL35 receptors triggering the JAK/STAT pathway downstream. Signal transducer and activator of transcription 4-alpha/beta (STAT4) binds to the JAK associated-IL35 receptor complex and are activated via phosphorylations. Subsequently, phosphorylated p-STAT4 dissociates from the receptor complex (Collison et al. 2012). This is a black box event because there is no literature evidence about the exact mechanism of the release of STAT4 from the receptor complex.

Preceded by: JAK2 bound to IL12RB2:IL12RB2 phosphorylate STAT4

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

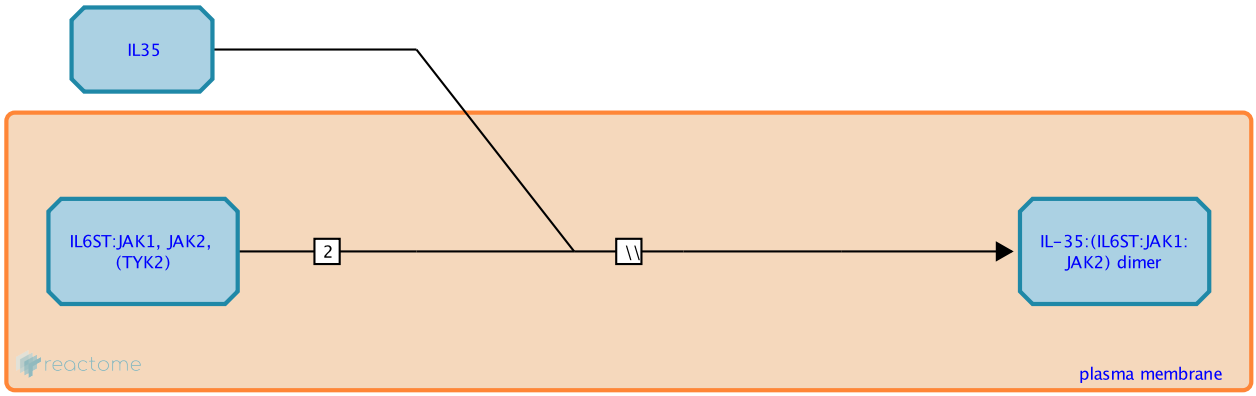
IL35 binds IL6ST:IL6ST receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983518

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol



Interleukin-35 (IL35) is a heteromeric complex conformed by Interleukin-12 subunit alpha (IL12A) and Interleukin-27 subunit alpha (IL27). IL35 can stimulate Janus Kinase (JAK)-bound homodimers of Interleukin-6 receptor beta precursor (IL6ST or gp130). JAKs are believed to be associated with the receptor before receptor activation (Behrmann et al., 2004). Subsequently, this triggers the phosphorylation of STAT1 downstream. The physiological consequence of this signalling is the suppression of T-cell response. The event is represented as a black box due to the incomplete knowledge about the ligand binding to monomers followed by dimerization or binding directly to the dimers.

Preceded by: Interleukin-35 translocates from the ER lumen to the extracellular region

Followed by: JAK1/JAK2/TYK2 bound to IL6ST:IL6ST are phosphorylated

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Boulanger, MJ., Chow, DC., Brevnova, EE., Garcia, KC. (2003). Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science, 300*, 2101-4. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

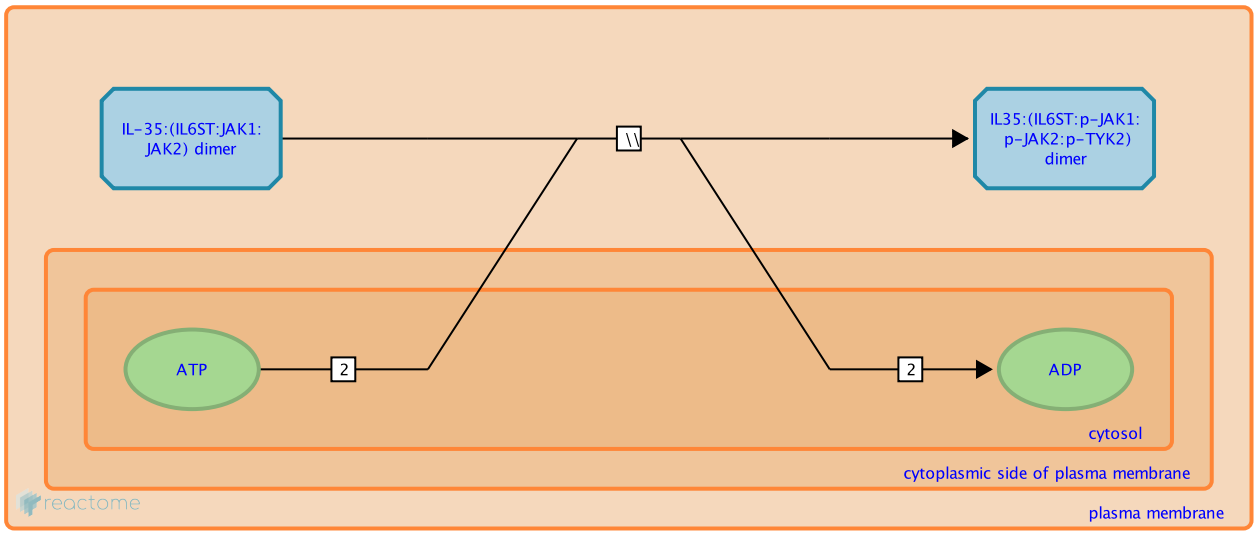
JAK1/JAK2/TYK2 bound to IL6ST:IL6ST are phosphorylated ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983834

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin 35 (IL35) may presumably signal via a complex that includes Tyrosine protein kinase JAK1 (JAK1) and JAK2 associated with Interleukin 6 receptor beta subunit (IL6ST) dimers (Collison et al. 2012). These JAKs are believed to phosphorylate Signal transducer and activator of transcription 1 (STAT) (Stark GR and Darnell JE, 2012). As the series of events that induces JAK/STAT phosphorylation events in response to IL35 are not clear, this event is represented as a black box.

Preceded by: IL35 binds IL6ST:IL6ST receptor

Followed by: STAT1 associates with IL6ST:IL6ST

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
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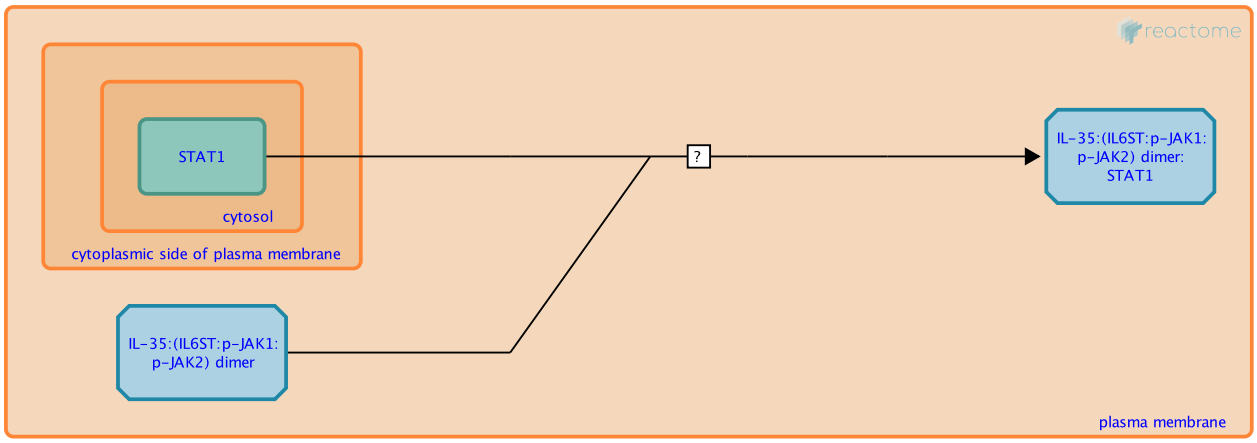
STAT1 associates with IL6ST:IL6ST ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983841

Type: uncertain

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) binding activates the IL35 receptor complex and facilitates JAKs phosphorylation. Subsequently, Signal transducer and activator of transcription 1-alpha/beta (STAT1) binds to the receptor complex and is activated by tyrosine phosphorylation (Collison et al. 2012). This is a black box event because the receptor subunit responsible for STAT1 binding to the receptor is unclear.

Preceded by: JAK1/JAK2/TYK2 bound to IL6ST:IL6ST are phosphorylated

Followed by: JAK1/JAK2/TYK2 bound to IL6ST:IL6ST phosphorylate STAT1

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13,* 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

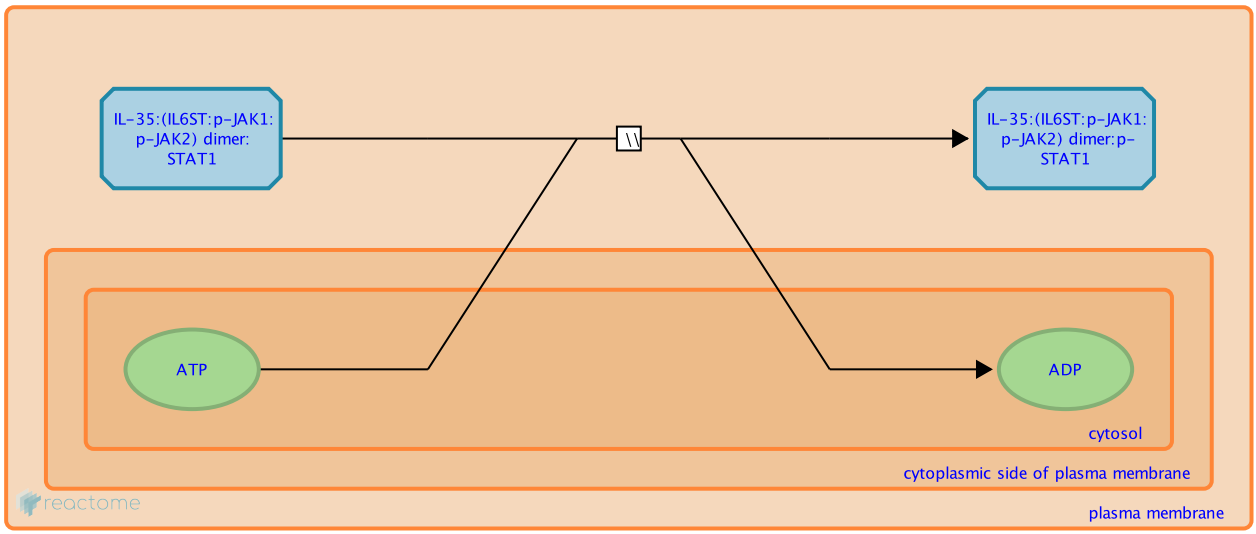
JAK1/JAK2/TYK2 bound to IL6ST:IL6ST phosphorylate STAT1 ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983835

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) binding activates the IL35 receptor complex and facilitates Tyrosine-protein kinase JAK (JAK) phosphorylation. Subsequently, Signal transducer and activator of transcription 1-alpha/beta (STAT1) binds to the receptor complex and is activated by tyrosine phosphorylation (Collison et al. 2012). Although it is known that JAKs are involved in STATs phosphorylation (Stark GR and Darnell JE, 2012), it is not clear how other components of the IL35 receptor complex contribute to STAT1 phosphorylation. For this reason, this event is assigned a black box status.

Preceded by: STAT1 associates with IL6ST:IL6ST

Followed by: p-STAT1 dissociates from IL6ST:IL6ST

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

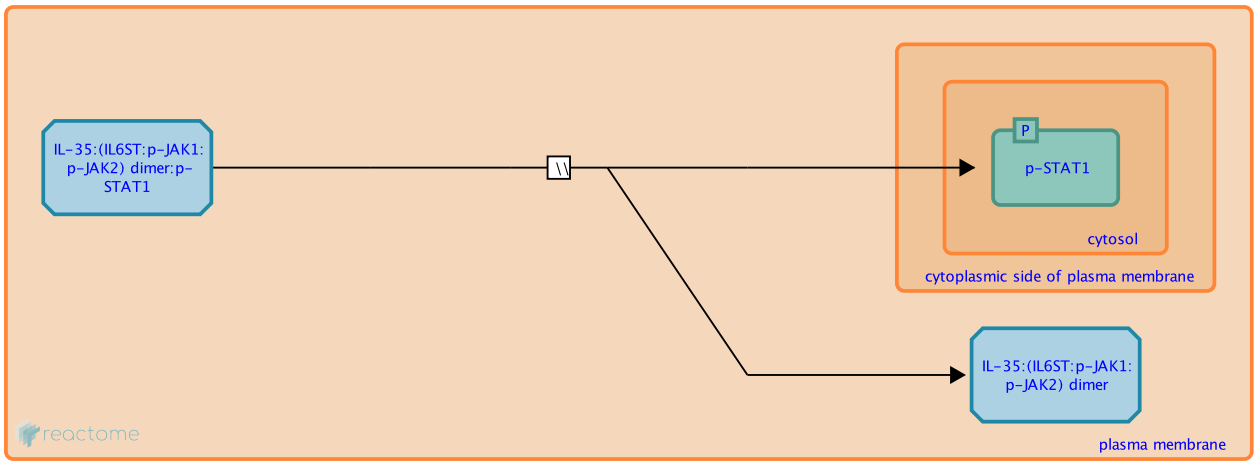
p-STAT1 dissociates from IL6ST:IL6ST ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983845

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) can signal via IL35 receptors triggering the JAK/STAT pathway downstream. Signal transducer and activator of transcription 1-alpha/beta (STAT1) binds to the JAK associated-IL35 receptor complex and is activated via phosphorylations. Subsequently, phosphorylated p-STAT1 dissociates from the receptor complex (Collison et al. 2012). This is a black box event because there is no literature evidence about the exact mechanism of the release of STAT1 from the receptor complex.

Preceded by: JAK1/JAK2/TYK2 bound to IL6ST:IL6ST phosphorylate STAT1

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

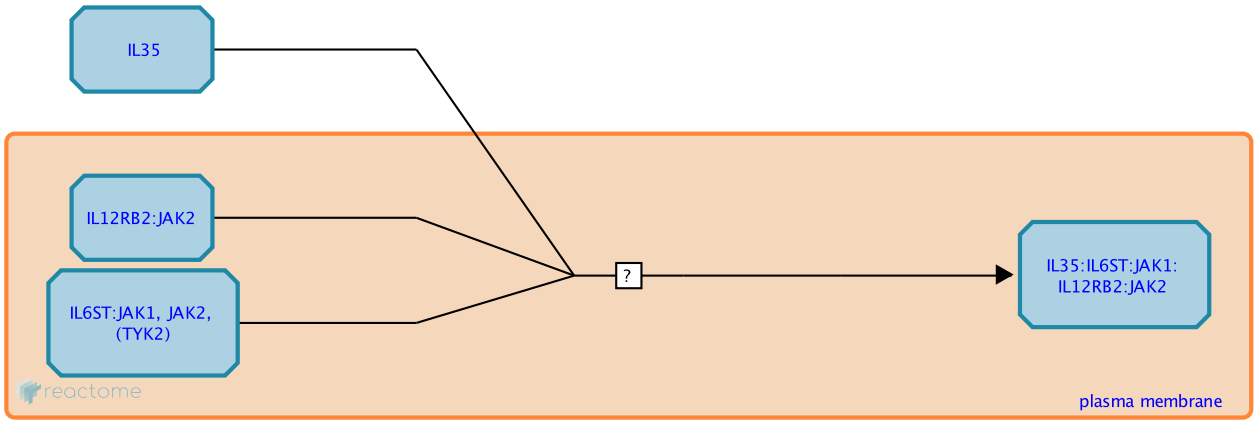
IL35 binds IL-12RB2:IL6ST receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-6809140

Type: uncertain

Compartments: plasma membrane, extracellular region, cytosol



Interleukin-35 (IL35) is a heteromeric complex of Interleukin-12 subunit alpha (IL12A) and Interleukin-27 subunit beta (EBI3, IL27B)) induces hetero and homodimers of Interleukin 6 receptor beta precursor (IL6ST, gp130) and Interleukin 12 receptor beta 2 (IL12RB2).

These results suggested that Interleukin 35 is bound to these three receptor subunits providing insight into the partial resistance to Interleukin 35 mediated suppression observed after the deletion of a single chain. Moreover there is the possibility of the assembly of higher structures by Interleukin 35, as has been suggested for Interleukin 6 receptor subunit beta precursor.

IL12RB2 and IL6ST represent the most plausible components of Interleukin 35 receptor. However, additional molecules might facilitate cytokine binding or downstream signaling, although this would be unprecedented in the Interleukin 6 receptor and Interleukin 12 receptor families (Collison et al. 2012)

Moreover Interleukin 35 (IL35) uses an unique heterodimer of receptor chains Interleukin 12 receptor subunit beta (IL 12RB2) and Interleukin 6 receptor subunit beta (gp130 or IL6ST) for its signal transduction.

The composition of Interleukin 35 heterodimeric receptor is not totally elucidated, but Interleukin 35–Interleukin 35 receptor interaction and assembly given the `site 1 2 3' follows an architectural paradigm originally established for Interleukin 6 (IL 6) (Boulanger et al. 2003).

Computational analysis suggests 3 potential conformations of Interleukin 35/Interleukin 35 Receptor complex:

First, IL6ST binds to site 2 in the Interleukin 6(IL 6), Ciliary neurotrophic factor (CNTF) and LIF (Leukemia inhibitory factor) complexes and thus could do so in the IL 35 IL35R complex, leaving IL12RB2 to bind site 3.

Second, the Interleukin 35–Interleukin 35 receptor complex could form symmetric homohexameric assemblies (2:2:2) analogous to the Interleukin 6 receptor complex, thus allowing IL 12RB2 and IL6ST to each bind to site 3 on IL12A.

Third, IL6ST and IL12RB2 could both be capable of binding to site 2 and site 3 and therefore exist in an interchanging equilibrium of heterotetrameric complexes (at a ratio of 1:1:1:1, IL6ST to IL12RB2 to Inter-

leukin 27 beta subunit (EBI3). Indeed, studies of the Interleukin 6 ligand receptor complex suggest that it may be able to signal as tetrameric or hexameric assembly.

Finally, a previously unknown mode of binding may exist that uses the site 1 2 3 model in a manner not predicted on the basis of the existing structural information for IL 6, LIF and CNTF (Collison et al. 2012).

As it is not clear whether the dimeric receptor can form in the absence of ligand, formation of the receptor dimer is represented here as a black box event.

Preceded by: Interleukin-35 translocates from the ER lumen to the extracellular region

Followed by: JAK1/JAK2 bound to IL35:IL6ST:IL12RB2 receptor are phosphorylated

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Boulanger, MJ., Chow, DC., Brevnova, EE., Garcia, KC. (2003). Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science, 300*, 2101-4. ↗

Editions

2015-07-21	Authored, Edited	Garapati, P V.
2015-11-09	Reviewed	Narazaki, M., Tanaka, M.

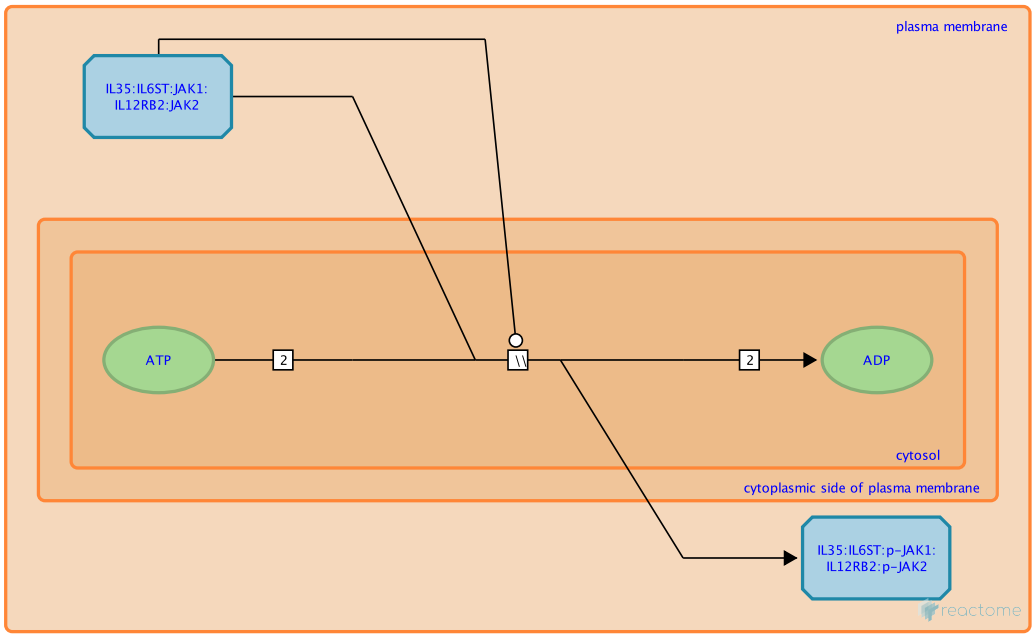
JAK1/JAK2 bound to IL35:IL6ST:IL12RB2 receptor are phosphorylated ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8950405

Type: omitted

Compartments: cytosol, plasma membrane, extracellular region



Interleukin 35 (IL35) may presumably signal via a complex that includes Tyrosine protein kinase JAK1 (JAK1) and JAK2 associated with Interleukin 6 receptor beta subunit (IL6ST) and Interleukin 12 receptor beta 2 subunit (IL12RB2) (Collison et al. 2012). These JAKs are believed to phosphorylate Signal transducer and activator of transcription 1 (STAT) (Stark GR and Darnell JE, 2012). As the series of events that induces JAK/STAT phosphorylation events in response to IL35 are not clear, this event is represented as a black box.

Preceded by: IL35 binds IL-12RB2:IL6ST receptor

Followed by: STAT1 and STAT4 associate with IL12RB2:IL6ST receptor

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Vignali, DA., Kuchroo, VK. (2012). IL-12 family cytokines: immunological playmakers. *Nat. Immunol., 13*, 722-8. ↗

Editions

2016-12-02	Authored	Duenas, C.
2016-12-15	Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

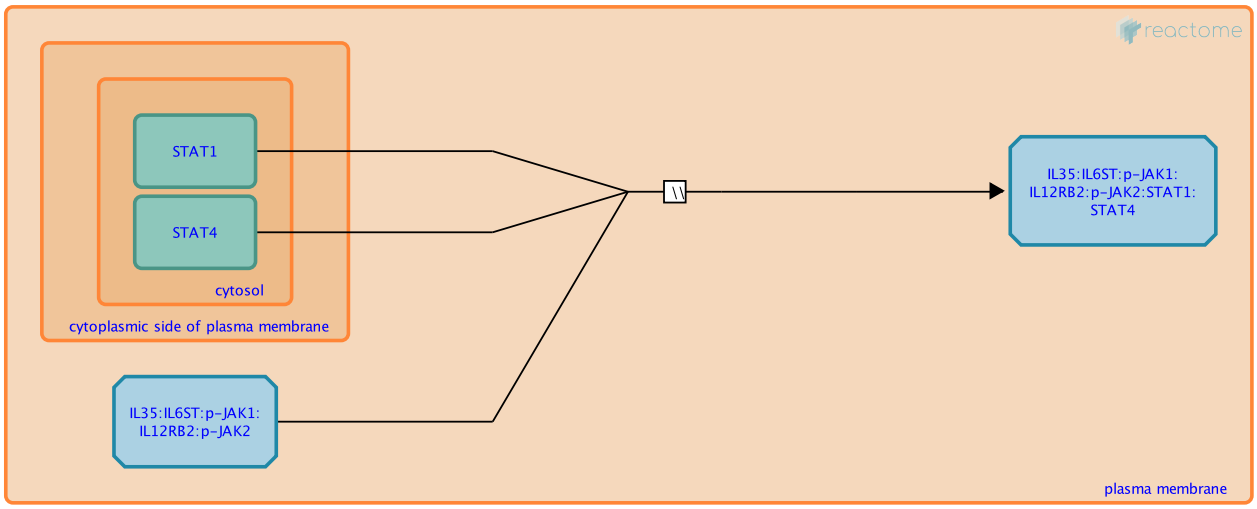
STAT1 and STAT4 associate with IL12RB2:IL6ST receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983996

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Interleukin-35 (IL35) binding activates the IL35 receptor complex and facilitates JAKs phosphorylation. Subsequently, Signal transducer and activator of transcription 1-alpha/beta (STAT1) and STAT4 bind to the receptor complex and are activated by tyrosine phosphorylation (Collison et al. 2012). This is a black box event because the receptor subunit responsible for STAT4 binding to the receptor is unclear. However, it is reported that simultaneous activation of IL12RB2 or IL6ST homodimer receptors do not promote the formation of pSTAT1:pSTAT4 and only the activation of the IL12RB2:IL6ST heteromeric receptor favours pSTAT1:pSTAT4 formation. For this reason, STAT1 and STAT4 are simultaneously considered in the binding, activation and release events.

Preceded by: JAK1/JAK2 bound to IL35:IL6ST:IL12RB2 receptor are phosphorylated

Followed by: JAK1/JAK2 bound to IL12RB2:IL6ST receptor phosphorylates STAT1 and STAT4

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

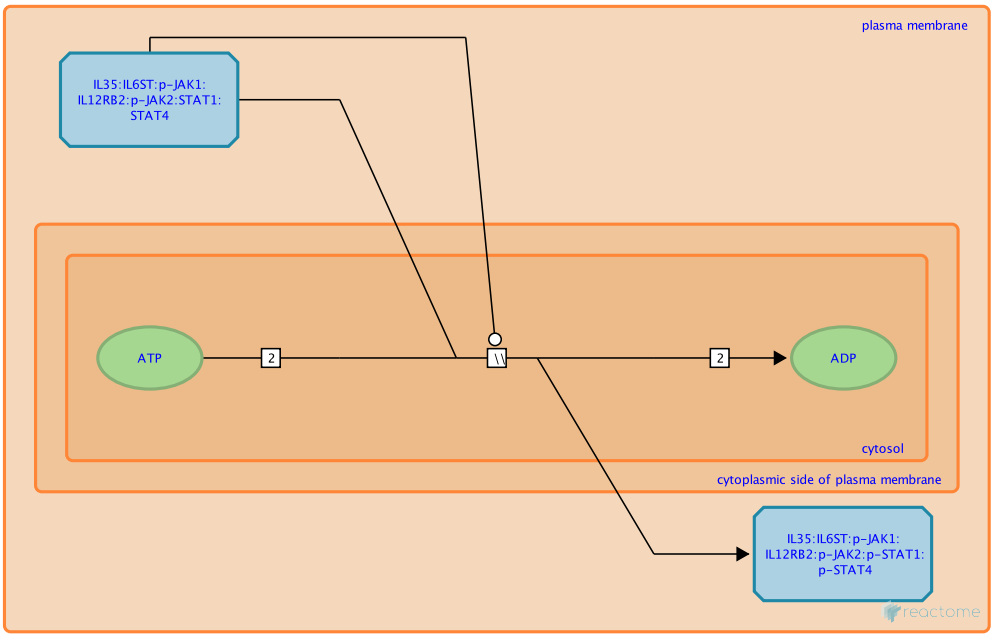
JAK1/JAK2 bound to IL12RB2:IL6ST receptor phosphorylates STAT1 and STAT4 ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8950453

Type: omitted

Compartments: cytosol, plasma membrane, extracellular region



Interleukin-35 (IL35) binding activates the IL35 receptor complex and facilitates Tyrosine-protein kinase JAK (JAK) phosphorylation. Subsequently, Signal transducer and activator of transcription 1-alpha/beta (STAT1) and STAT4 bind to the receptor complex and are activated by tyrosine phosphorylation (Collison et al. 2012). Although it is known that JAKs are involved in STATs phosphorylation (Stark GR and Darnell JE, 2012), it is not clear how other components of the IL35 receptor complex contribute to STAT1/STAT4 phosphorylation. For this reason, this event is assigned a black box status.

Preceded by: STAT1 and STAT4 associate with IL12RB2:IL6ST receptor

Followed by: p-STAT1 and p-STAT4 dissociate from IL12RB2:IL6ST receptor

Literature references

Delgoffe, GM., Vignali, DA. (2013). STAT heterodimers in immunity: A mixed message or a unique signal?. *JAKSTAT, 2*, e23060. ↗

Editions

2016-12-02	Authored	Duenas, C.
2016-12-15	Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

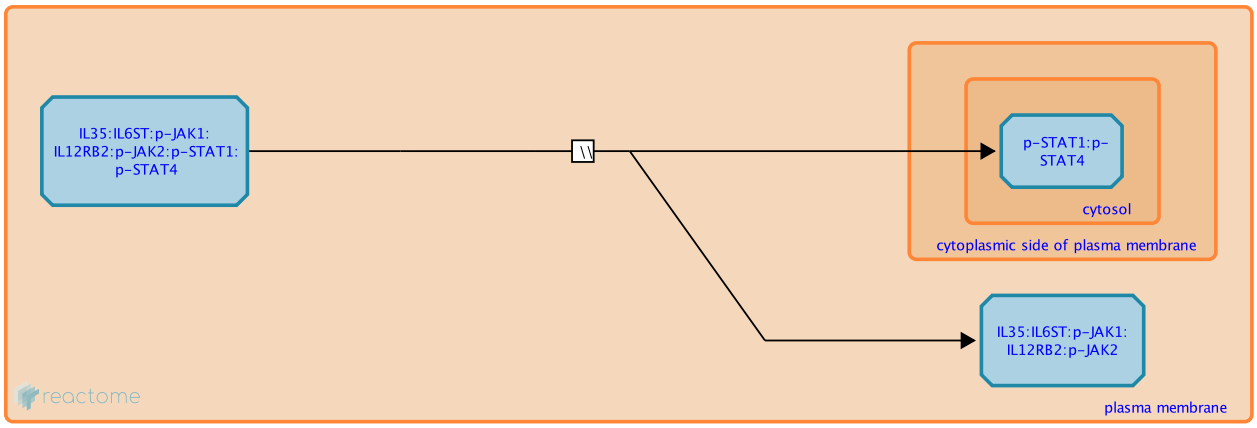
p-STAT1 and p-STAT4 dissociate from IL12RB2:IL6ST receptor ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8983983

Type: omitted

Compartments: plasma membrane, cytosol, extracellular region



Signal transducer and activator of transcription 1-alpha/beta(STAT1) and Signal transducer and activator of transcription 4 (STAT4) after phosphorylation dissociates from the complex of ligand receptor and will dimerize (Delgoffe & Vignali 2013). This is a Black Box event because the mechanism of the release of STAT1 and STAT4 from the receptor complex is unclear. However, it is reported that simultaneous activation of IL12RB2 or IL6ST homodimer receptors do not promote the formation of pSTAT1:pSTAT4 and only the activation of the IL12RB2:IL6ST heteromeric receptor favours pSTAT1:pSTAT4 formation. For this reason, STAT1 and STAT4 are simultaneously considered in the binding, activation and release events.

Preceded by: JAK1/JAK2 bound to IL12RB2:IL6ST receptor phosphorylates STAT1 and STAT4

Followed by: p-STAT1:p-STAT4 translocates to the nucleus

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

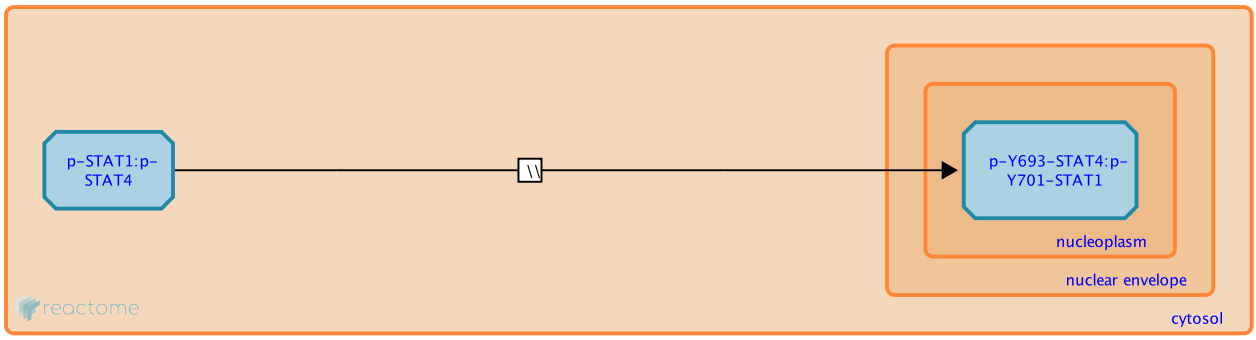
p-STAT1:p-STAT4 translocates to the nucleus ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8950522

Type: omitted

Compartments: cytosol, nucleoplasm



Interleukin-35 (IL-35) uses a unique Signal transducer and activator of transcription 1-alpha/beta - Signal transducer and activator of transcription 4 (STAT1:STAT4) heterodimer (Collinson et al. 2012) for signaling. Several cytokine receptors activate STAT1 and STAT4 to drive proinflammatory T helper 1 type responses, so it is unclear how their activation via the interleukin-35 receptor gives rise to a unique STAT dimer.

T cells stimulated with Interleukin-12 plus IFN-gamma (IFNG) induce minimal interaction of a STAT1:STAT4 with consensus STAT-binding sites in the IL12A and EBI3 promoters. However, T cells stimulated with Interleukin-35 showed considerable enrichment for the binding of STAT1 and STAT4 to IL12A position 250 and EBI3 position 500, as well as other sites in their promoters.

This reaction is presented as a black box because the exact mechanism of traslocation to the nucleus is unclear.

Preceded by: p-STAT1 and p-STAT4 dissociate from IL12RB2:IL6ST receptor

Followed by: IL12A gene transcription and translation, EBI3 gene transcription and translation

Literature references

Vignali, DA., Kuchroo, VK. (2012). IL-12 family cytokines: immunological playmakers. *Nat. Immunol., 13*, 722-8. ↗

Editions

2016-12-02	Authored	Duenas, C.
2016-12-15	Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

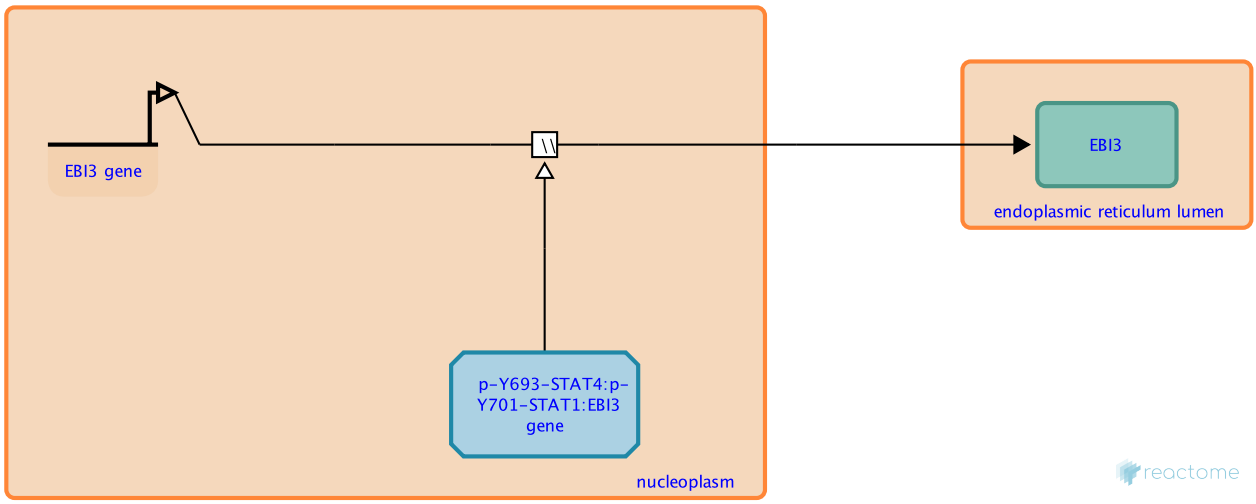
EBI3 gene transcription and translation ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984963

Type: omitted

Compartments: nucleoplasm, endoplasmic reticulum lumen



Interleukin-35 (IL35) is a complex conformed by Interleukin-12 subunit alpha (IL12A) and Interleukin-27 subunit alpha (IL27). IL35 can induce heterodimers of Interleukin-6 receptor beta precursor (IL6ST) and Interleukin-12 receptor beta 2 (IL12RB2). Consequently, heteromeric Signal transducer and activator of transcription 1-alpha/beta (STAT1) and Signal transducer and activator of transcription 4 (STAT4) are phosphorylated. Subsequently, this STAT1:STAT4 complex can translocate into the nucleus and bind to promoter regions of IL27 thereby facilitating the protein expression. Thus, by inducing the expression of itself, a positive feedback regulation is achieved in the IL35 signalling pathway. This is a black box event because the intermediate steps of IL27 transcription/translation are omitted.

Preceded by: p-STAT1:p-STAT4 translocates to the nucleus

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

2016-12-15	Authored, Edited	Varusai, TM.
2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

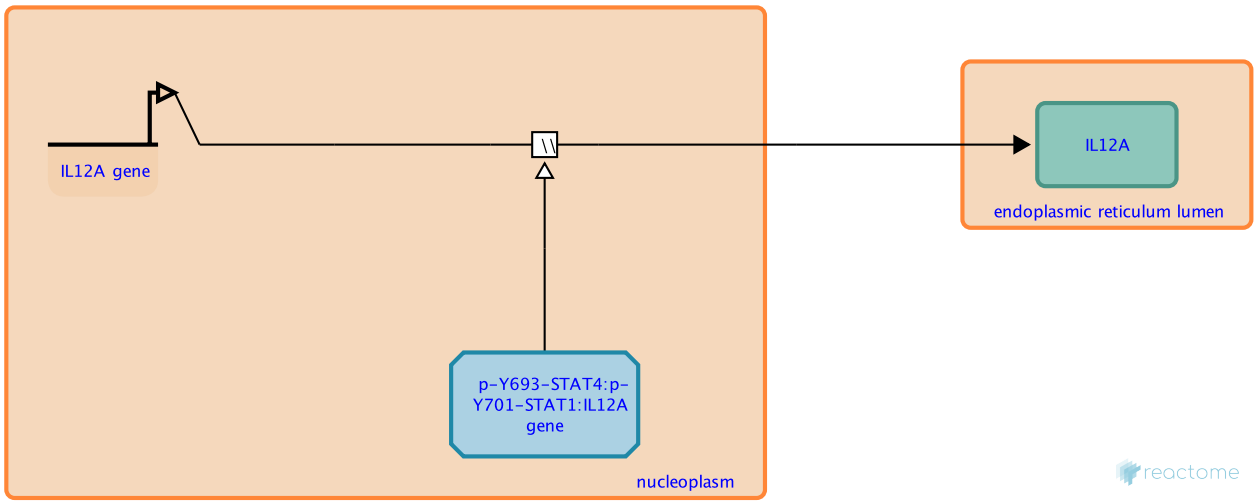
IL12A gene transcription and translation ↗

Location: Interleukin-35 Signalling

Stable identifier: R-HSA-8984964

Type: omitted

Compartments: nucleoplasm, endoplasmic reticulum lumen



Interleukin-35 (IL35) is a complex conformed by Interleukin-12 subunit alpha (IL12A) and Interleukin-27 subunit alpha (IL27). IL35 can induce heterodimers of Interleukin-6 receptor beta precursor (IL6ST) and Interleukin-12 receptor beta 2 (IL12RB2). Consequently, heteromeric Signal transducer and activator of transcription 1-alpha/beta (STAT1) and Signal transducer and activator of transcription 4 (STAT4) are phosphorylated. Subsequently, this STAT1:STAT4 complex can translocate into the nucleus and bind to promoter regions of IL12A thereby facilitating the protein expression. Thus, by inducing the expression of itself, a positive feedback regulation is achieved in the IL35 signalling pathway. This is a black box event because the intermediate steps of IL12A transcription/translation are omitted.

Preceded by: p-STAT1:p-STAT4 translocates to the nucleus

Literature references

Collison, LW., Delgoffe, GM., Guy, CS., Vignali, KM., Chaturvedi, V., Fairweather, D. et al. (2012). The composition and signaling of the IL-35 receptor are unconventional. *Nat. Immunol., 13*, 290-9. ↗

Editions

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2017-07-05	Reviewed	Singh, K.
2017-08-09	Reviewed	Pylayeva-Gupta, Y.

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