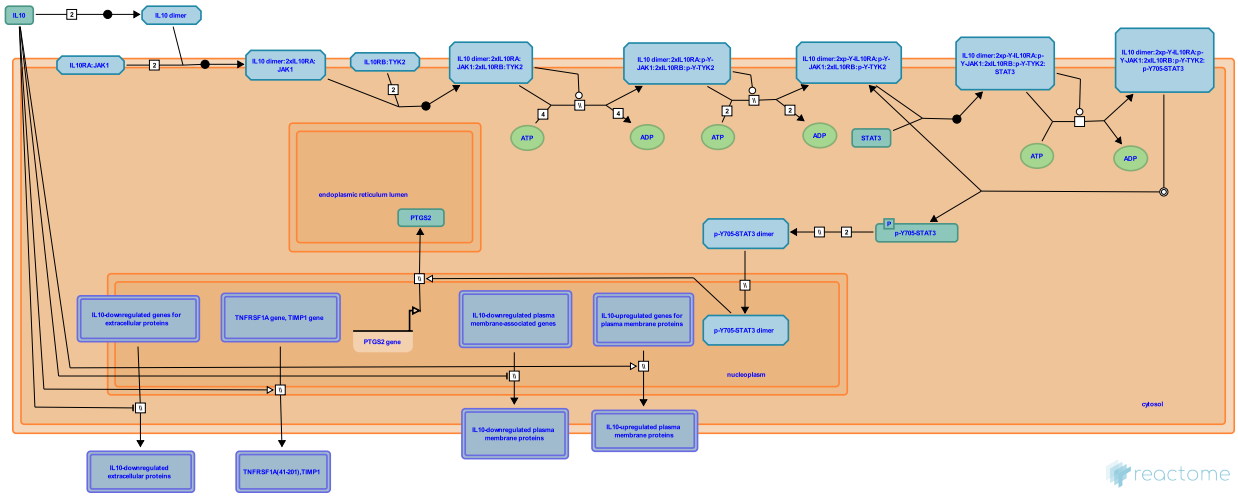
Interleukin-10 signaling



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24/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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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. ↗

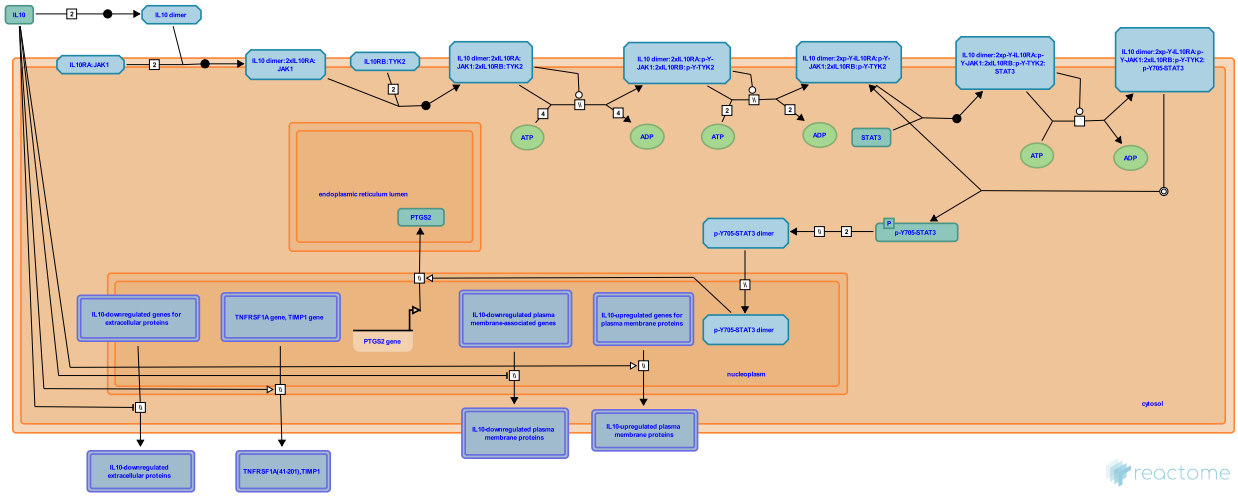
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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-10 signaling ↗

Stable identifier: R-HSA-6783783



Interleukin-10 (IL10) was originally described as a factor named cytokine synthesis inhibitory factor that inhibited T-helper (Th) 1 activation and Th1 cytokine production (Fiorentino et al. 1989). It was found to be expressed by a variety of cell types including macrophages, dendritic cell subsets, B cells, several T-cell subpopulations including Th2 and T-regulatory cells (Tregs) and Natural Killer (NK) cells (Moore et al. 2001). It is now recognized that the biological effects of IL10 are directed at antigen-presenting cells (APCs) such as macrophages and dendritic cells (DCs), its effects on T-cell development and differentiation are largely indirect via inhibition of macrophage/dendritic cell activation and maturation (Pestka et al. 2004, Mocellin et al. 2004). T cells are thought to be the main source of IL10 (Hedrich & Bream 2010). IL10 inhibits a broad spectrum of activated macrophage/monocyte functions including monokine synthesis, NO production, and expression of class II MHC and costimulatory molecules such as IL12 and CD80/CD86 (de Waal Malefyt et al. 1991, Gazzinelli et al. 1992). Studies with recombinant cytokine and neutralizing antibodies revealed pleiotropic activities of IL10 on B, T, and mast cells (de Waal Malefyt et al. 1993, Rousset et al. 1992, Thompson-Snipes et al. 1991) and provided evidence for the in vivo significance of IL10 activities (Ishida et al. 1992, 1993). IL10 antagonizes the expression of MHC class II and the co-stimulatory molecules CD80/CD86 as well as the pro-inflammatory cytokines IL1Beta, IL6, IL8, TNFalpha and especially IL12 (Fiorentino et al. 1991, D'Andrea et al. 1993). The biological role of IL10 is not limited to inactivation of APCs, it also enhances B cell, granulocyte, mast cell, and keratinocyte growth/differentiation, as well as NK-cell and CD8+ cytotoxic T-cell activation (Moore et al. 2001, Hedrich & Bream 2010). IL10 also enhances NK-cell proliferation and/or production of IFN-gamma (Cai et al. 1999).

IL10-deficient mice exhibited inflammatory bowel disease (IBD) and other exaggerated inflammatory responses (Kuhn et al. 1993, Berg et al. 1995) indicating a critical role for IL10 in limiting inflammatory responses. Dysregulation of IL10 is linked with susceptibility to numerous infectious and autoimmune diseases in humans and mouse models (Hedrich & Bream 2010).

IL10 signaling is initiated by binding of homodimeric IL10 to the extracellular domains of two adjoining IL10RA molecules. This tetramer then binds two IL10RB chains. IL10RB cannot bind to IL10 unless bound to IL10RA (Ding et al. 2001, Yoon et al. 2006); binding of IL10 to IL10RA without the co-presence of IL10RB fails to initiate signal transduction (Kotenko et al. 1997).

IL10 binding activates the receptor-associated Janus tyrosine kinases, JAK1 and TYK2, which are constitutively bound to IL10R1 and IL10R2 respectively. In the classic model of receptor activation assembly of the receptor complex is believed to enable JAK1/TYK2 to phosphorylate and activate each other. Alternatively the binding of IL10 may cause conformational changes that allow the pseudokinase inhibitory domain of one JAK kinase to move away from the kinase domain of the other JAK within the receptor dimer-JAK complex, allowing the two kinase domains to interact and trans-activate (Waters & Brooks 2015).

The activated JAK kinases phosphorylate the intracellular domains of the IL10R1 chains on specific tyrosine residues. These phosphorylated tyrosine residues and their flanking peptide sequences serve as temporary docking sites for the latent, cytosolic, transcription factor, STAT3. STAT3 transiently docks on the IL10R1 chain via its SH2 domain, and is in turn tyrosine phosphorylated by the receptor-associated JAKs. Once activated, it dissociates from the receptor, dimerizes with other STAT3 molecules, and translocates to the nucleus where it binds with high affinity to STAT-binding elements (SBEs) in the promoters of IL-10-inducible genes (Donnelly et al. 1999).

Literature references

Moore, KW., O'Garra, A., Coffman, RL., de Waal Malefyt, R. (2001). Interleukin-10 and the interleukin-10 receptor. *Annu. Rev. Immunol., 19*, 683-765. ↗

Editions

2015-06-17	Authored	Jupe, S.
2016-09-05	Reviewed	Meldal, BH.
2016-11-14	Edited	Jupe, S.

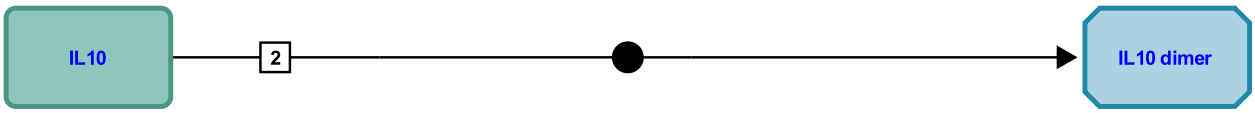
IL10 dimerizes ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-449855

Type: binding

Compartments: extracellular region



Interleukin-10 is predominantly a noncovalent homodimer with structural similarities to interferon-gamma.

Followed by: IL10 dimer binds IL10RA:JAK1

Literature references

Wlodawer, A., Schalk-Hihi, C., Zdanov, A. (1996). Crystal structure of human interleukin-10 at 1.6 A resolution and a model of a complex with its soluble receptor. *Protein Sci., 5*, 1955-62. ↗

Windsor, WT., Braswell, EH., Mui, P., Syto, R., Murgolo, NJ., Huang, E. (1998). Structural and biological stability of the human interleukin 10 homodimer. *Biochemistry, 37*, 16943-51. ↗

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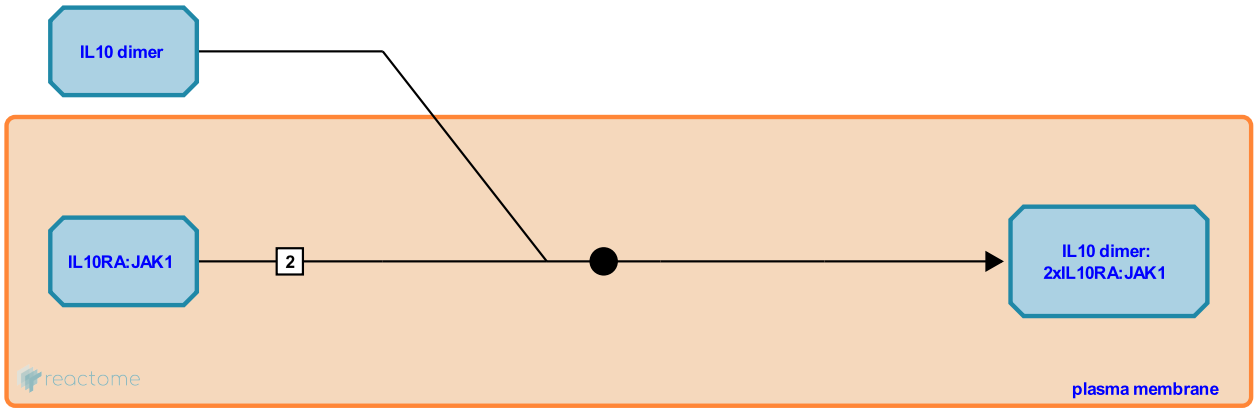
IL10 dimer binds IL10RA:JAK1 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-449803

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



The IL-10 receptor is composed of at least two subunits, both members of the interferon receptor (IFNR) family (Liu et al. 1994). Interferon-10 receptor alpha chain (IL10RA) is the ligand-binding subunit, binding IL-10 with high affinity (Kd 35-200 pM) (Tan et al. 1993). IL10RA is constitutively associated with JAK1 (Moore et al. 2001, Usacheva et al. 2002). This association is dependent on a membrane-proximal part of the receptor (amino acids 269-274) which contain a region designated the box 2B motif, characterized by a core of four hydrophobic residues flanked by a serine and charged residues (Usacheva et al. 2002).

Preceded by: IL10 dimerizes

Followed by: IL10 dimer:2xIL10RA1:JAK1 binds IL10RB:TYK2

Literature references

Wei, SH., Liu, Y., Ho, AS., Moore, KW., de Waal Malefyt, R. (1994). Expression cloning and characterization of a human IL-10 receptor. *J Immunol, 152*, 1821-9. ↗

Editions

2015-06-17	Authored	Jupe, S.
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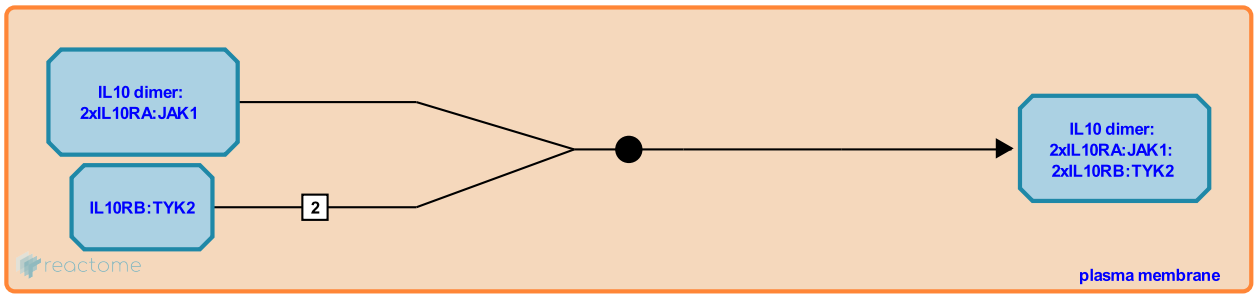
IL10 dimer:2xIL10RA1:JAK1 binds IL10RB:TYK2 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-449811

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



Interleukin-10 receptor chain B (IL10RB, IL10R2, CRF2-4) binds the IL1-10:IL10RA complex, causing conformational changes that allow it to bind IL-10 (Yoon et al. 2010). IL10RB is essential for signal transduction (Kotenko et al. 1997). It is constitutively bound to the JAK family kinase TYK2 (Kotenko et al. 1997, Spencer et al. 1998).

IL10RB can also combine with either IL-22R1, IFN-lambdaR1 or IL-20R1 to assemble the IL-22, IFN-lambda or IL-26 receptor complexes, respectively (Kotenko & Langer 2004).

Preceded by: IL10 dimer binds IL10RA:JAK1

Followed by: JAK1,TYK2 phosphorylate JAK1,TYK2

Literature references

Logsdon, NJ., Yoon, SI., Sheikh, F., Donnelly, RP., Walter, MR. (2006). Conformational changes mediate interleukin-10 receptor 2 (IL-10R2) binding to IL-10 and assembly of the signaling complex. *J. Biol. Chem., 281,* 35088-96. ↗

Pollack, BP., Izotova, LS., Wu, W., Krause, CD., Kotenko, SV., Pestka, S. (1997). Identification and functional characterization of a second chain of the interleukin-10 receptor complex. *EMBO J, 16,* 5894-903. ↗

Editions

2015-06-17	Authored	Jupe, S.
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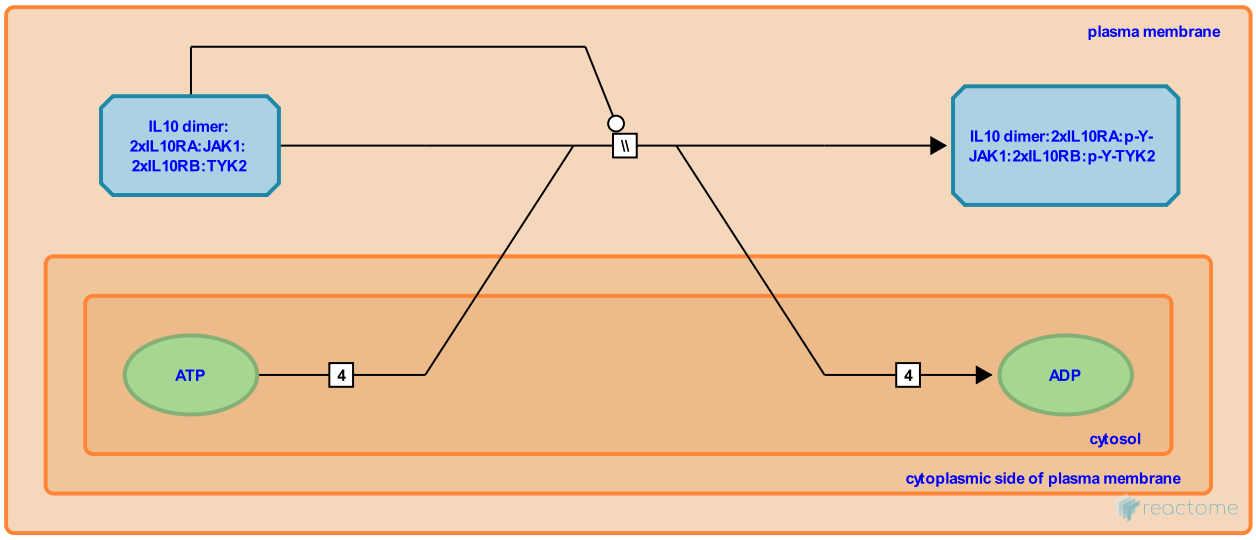
JAK1,TYK2 phosphorylate JAK1,TYK2 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784319

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol



Binding of IL-10 to its receptor causes phosphorylation and activation of the receptor-associated Janus tyrosine kinases, JAK1 and TYK2 (Finbloom & Winestock 1995), leading to phosphorylation of two conserved tyrosine residues (Y446 and Y496) within the intracellular domain of IL10RA, which serve as redundant docking sites for STAT3 (Ho et al. 1995, Weber-Nordt et al. 1996).

The details of JAK kinase activation are unclear. The classical model suggests that receptor dimerization, induced by ligand binding, brings the two JAK family kinases into proximity, so that they are able to trans-activate (phosphorylate) each other (Donnelly et al. 1999, Waters et al. 2015) but it is also possible that ligand binding causes a conformational change in a pre-existing receptor dimer that withdraws trans pseudo-kinase inhibition for paired kinases, which then autophosphorylate (Waters et al. 2014, Waters & Brooks 2015). JAK1, like all JAK kinases, has two adjacent tyrosines in its activation loop (Y1034, Y1035). It is not known which of these becomes phosphorylated in response to IL10 binding, or if phosphorylation at one site rather than the other has functional consequences. In vitro, phosphorylation at Y1034 has a greater enhancing effect on JAK1 catalytic ability (Wang et al. 2003) and is the more commonly observed phosphorylation site (see PhosphoSitePlus). Similarly TYK2 has two adjacent tyrosines, the first (Y1054) is the more commonly observed (see PhosphoSitePlus).

Preceded by: IL10 dimer:2xIL10RA1:JAK1 binds IL10RB:TYK2

Followed by: p-Y-JAK1,p-Y-TYK2 phosphorylate IL10RA

Literature references

Winestock, KD., Finbloom, DS. (1995). IL-10 induces the tyrosine phosphorylation of tyk2 and Jak1 and the differential assembly of STAT1 alpha and STAT3 complexes in human T cells and monocytes. *J. Immunol., 155*, 1079-90. ↗

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2015-06-17	Authored	Jupe, S.
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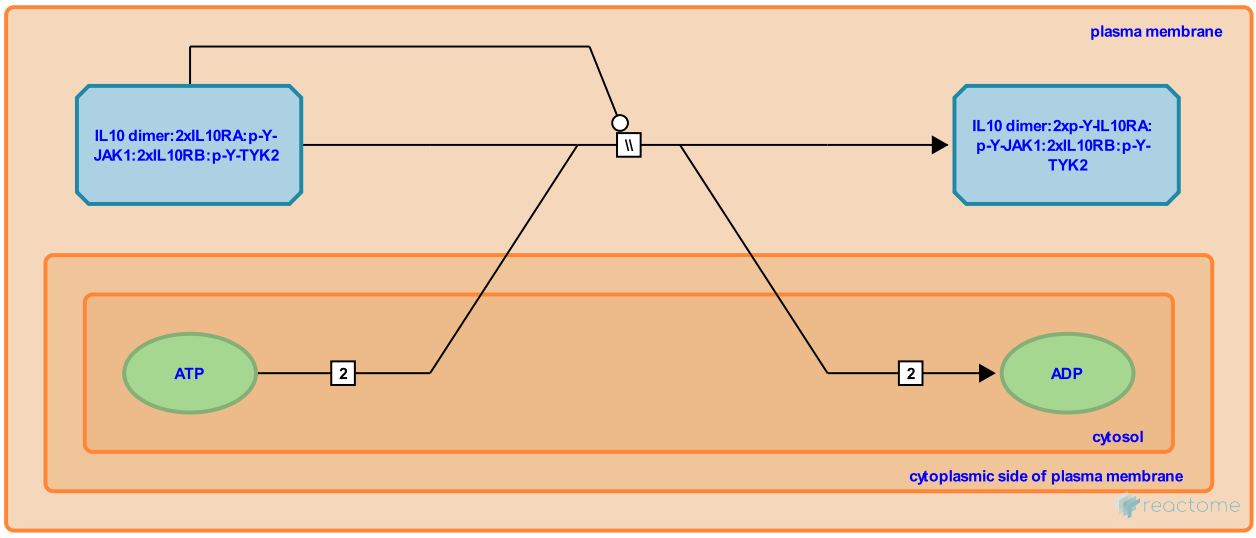
p-Y-JAK1,p-Y-TYK2 phosphorylate IL10RA ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784324

Type: omitted

Compartments: plasma membrane, extracellular region, cytosol



Binding of IL-10 leads to activation of the receptor-associated Janus tyrosine kinases, JAK1 and TYK2 (Finbloom & Winestock 1995), leading to phosphorylation of IL10RA at two conserved intracellular tyrosine residues (Y446 and Y496) that serve as docking sites for STAT molecules (Ho et al. 1995, Weber-Nordt et al. 1996).

The details of receptor phosphorylation are unclear. Most descriptions of IL10 receptor tyrosine phosphorylation (Donnelly et al. 1999, Carey et al. 2012) suggest that JAK1 and TYK2 are responsible for IL10RA phosphorylation but it is not clear whether one or both kinases are responsible for phosphorylating IL10RA.

Preceded by: JAK1,TYK2 phosphorylate JAK1,TYK2

Followed by: IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2 binds STAT3

Literature references

Winestock, KD., Finbloom, DS. (1995). IL-10 induces the tyrosine phosphorylation of tyk2 and Jak1 and the differential assembly of STAT1 alpha and STAT3 complexes in human T cells and monocytes. *J. Immunol., 155*, 1079-90. ↗

Moore, KW., Greenlund, AC., Weber-Nordt, RM., Riley, JK., Schreiber, RD., Darnell, JE. (1996). Stat3 recruitment by two distinct ligand-induced, tyrosine-phosphorylated docking sites in the interleukin-10 receptor intracellular domain. *J. Biol. Chem., 271*, 27954-61. ↗

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2015-06-17	Authored	Jupe, S.
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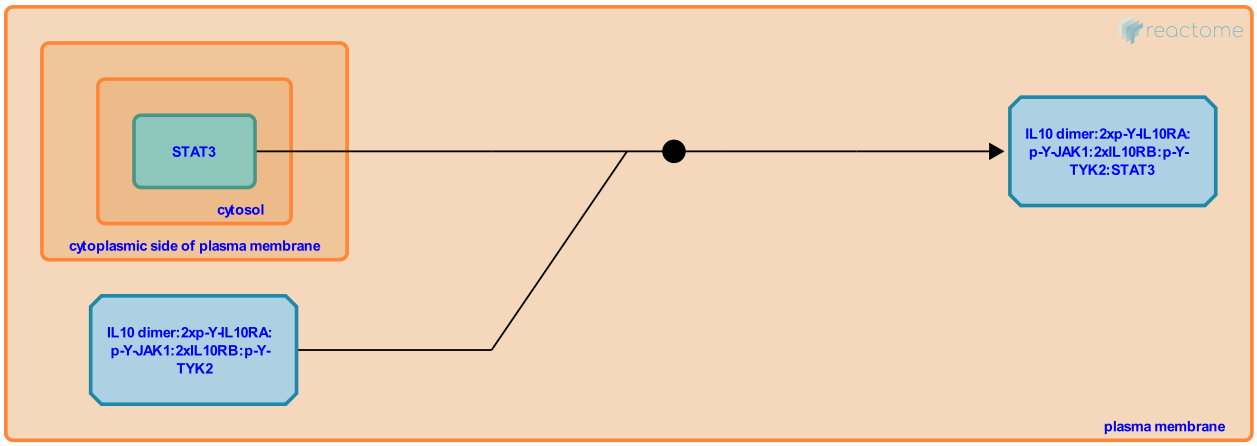
IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2 binds STAT3 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784323

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



STAT3 is recruited directly to the receptor complex via either of the two tyrosine residues in the IL10R1 cytoplasmic domain (Y446 and Y496) that become phosphorylated in response to IL-10 (Weber-Nordt et al. 1996, Riley et al. 1999). Overexpression of a dominant negative mouse Stat3 mutant or an inducibly-active form of mouse Stat3 demonstrated that Stat3 activation is necessary and sufficient to mediate inhibition of macrophage proliferation by IL-10 (O'Farrell et al. 1998) at least in part via enhancement of CDKN2D (INK4d) and CDKN1A (CIP1) expression (O'Farrell et al. 2000). In contrast, the Stat3 mutant did not detectably impair IL-10's ability to inhibit LPS-induced monokine production suggesting that IL10 inhibition of macrophage proliferation and monokine production are the result of two distinct signaling pathways (O'Farrell et al. 1998). Stat3 conditional knockout mice develop chronic enterocholitis and have macrophages that show no response to IL10 (Riley et al. 1999, Takeda et al. 1999).

Preceded by: p-Y-JAK1,p-Y-TYK2 phosphorylate IL10RA

Followed by: STAT3 is phosphorylated by p-Y-JAK1,P-Y-TYK2

Literature references

Caligiuri, MA., Jurlander, J., Kordula, T., Hawley, TS., Hawley, RG., Carson, WE. et al. (1996). Receptors for interleukin (IL)-10 and IL-6-type cytokines use similar signaling mechanisms for inducing transcription through IL-6 response elements. *J. Biol. Chem., 271*, 13968-75. ↗

Editions

2015-06-17	Authored	Jupe, S.
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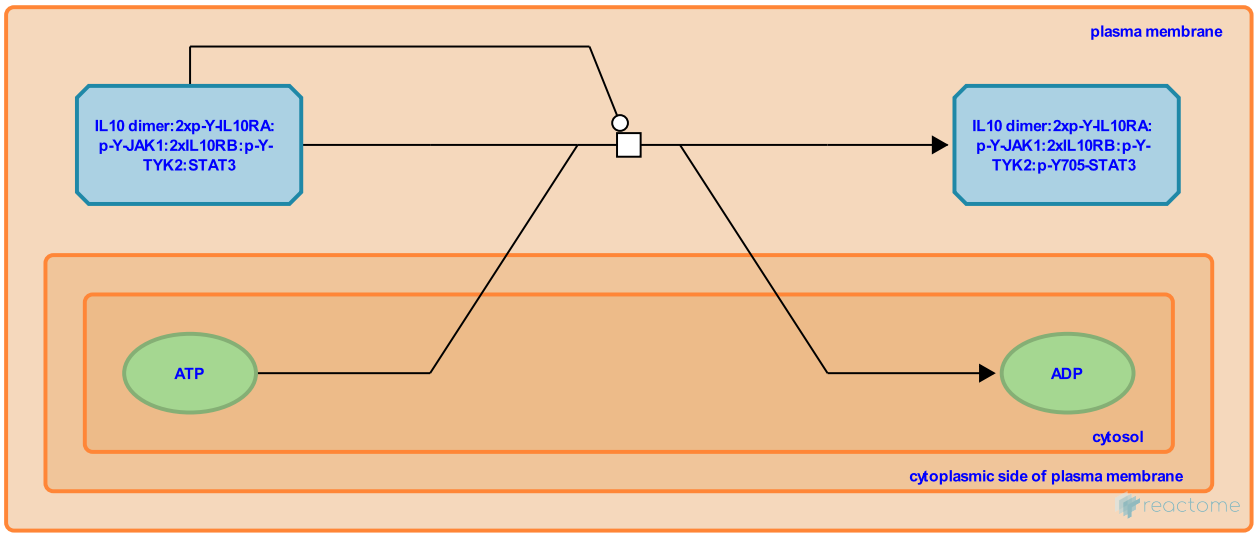
STAT3 is phosphorylated by p-Y-JAK1,P-Y-TYK2 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784006

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



STAT3 bound to IL10RA is tyrosine phosphorylated by the receptor-associated JAKs (Niemand et al. 2003, Liu et al. 2005).

Preceded by: IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2 binds STAT3

Followed by: p-Y705-STAT3 dissociates from IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2:p-Y705-STAT3

Literature references

Schaper, F., Nimmesgern, A., Haan, S., Müller-Newen, G., Rossaint, R., Fischer, P. et al. (2003). Activation of STAT3 by IL-6 and IL-10 in primary human macrophages is differentially modulated by suppressor of cytokine signaling 3. *J. Immunol., 170*, 3263-72. ↗

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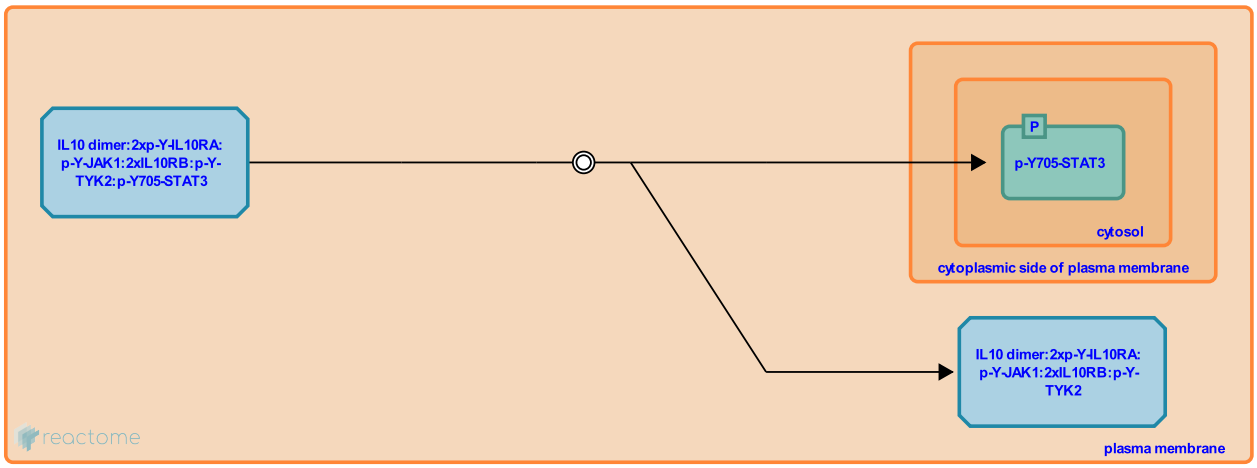
p-Y705-STAT3 dissociates from IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2:p-Y705-STAT3

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784791

Type: dissociation

Compartments: plasma membrane, extracellular region, cytosol



Once phosphorylated, STAT3 dissociates from the receptor, dimerizes with other STAT3 molecules, and translocates to the nucleus where it binds with high affinity to STAT-binding elements (SBEs) in the promoters of IL-10-inducible genes (Donnelly et al. 1999).

Preceded by: STAT3 is phosphorylated by p-Y-JAK1,P-Y-TYK2

Followed by: p-Y705-STAT3 dimerizes

Literature references

Dickensheets, H., Donnelly, RP., Finbloom, DS. (1999). The interleukin-10 signal transduction pathway and regulation of gene expression in mononuclear phagocytes. *J. Interferon Cytokine Res., 19*, 563-73.

Editions

2015-06-17	Authored	Jupe, S.
2016-09-05	Reviewed	Meldal, BH.
2016-11-14	Edited	Jupe, S.

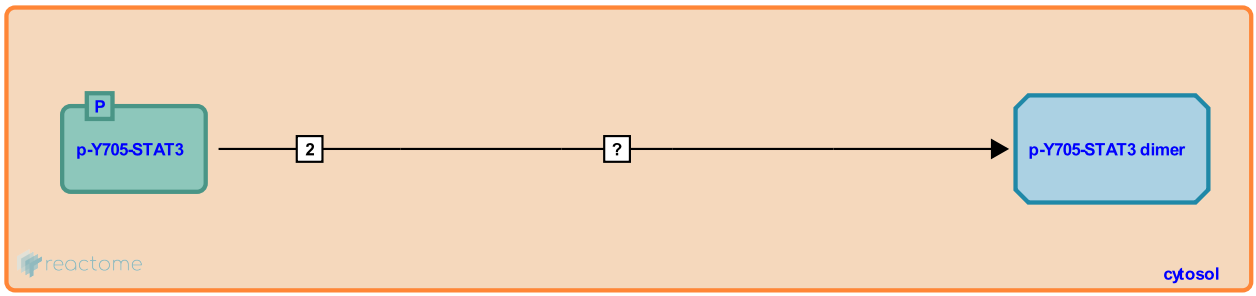
p-Y705-STAT3 dimerizes ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784765

Type: uncertain

Compartments: cytosol



Phosphorylated Signal transducer and activator of transcription 3 (STAT3) dimerizes after dissociating from the interleukin-19 (IL19) receptor complex (Akira et al. 1994) or Interleukin-22 (IL22) receptor complex (Lagos-Quintana et al. 2003, Sestito et al. 2011).

According to the classical model, phosphorylated Signal transducer and activator of transcription (STAT) monomers associate in an active dimer form, which is stabilized by the reciprocal interactions between a phosphorylated tyrosine residue of one and the SH2 domain of the other monomer (Shuai et al. 1994). These dimers then translocate to the nucleus (Akira et al. 1994). Recently an increasing number of studies have demonstrated the existence of STAT dimers in unstimulated cell states and the capability of STATs to exert biological functions independently of phosphorylation (Braunstein et al. 2003, Li et al. 2008, Santos & Costas-Pereira 2011). As phosphorylation of STATs is not unequivocally required for its subsequent translocation to the nucleus, this event is shown as an uncertain process.

Preceded by: p-Y705-STAT3 dissociates from IL10 dimer:2xp-Y-IL10RA:p-Y-JAK1:2xIL10RB:p-Y-TYK2:p-Y705-STAT3

Followed by: p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm

Literature references

Kishimoto, T., Naruto, M., Wang, XJ., Yoshida, K., Nishio, Y., Wei, S. et al. (1994). Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. *Cell, 77*, 63-71. ↗

Cowburn, D., Horvath, CM., Huang, LH., Darnell JE, Jr., Qureshi, SA., Shuai, K. (1994). Interferon activation of the transcription factor Stat91 involves dimerization through SH2-phosphotyrosyl peptide interactions. *Cell, 76*, 821-8 . ↗

Lagos-Quintana, M., Tuschl, T., Borkhardt, A., Meyer, J., Rauhut, R. (2003). New microRNAs from mouse and human . *RNA, 9*, 175-9. ↗

Olson, R., Schindler, C., Braunstein, J., Brutsaert, S. (2003). STATs dimerize in the absence of phosphorylation. *J. Biol. Chem., 278*, 34133-40. ↗

Editions

2015-06-17	Authored	Jupe, S.
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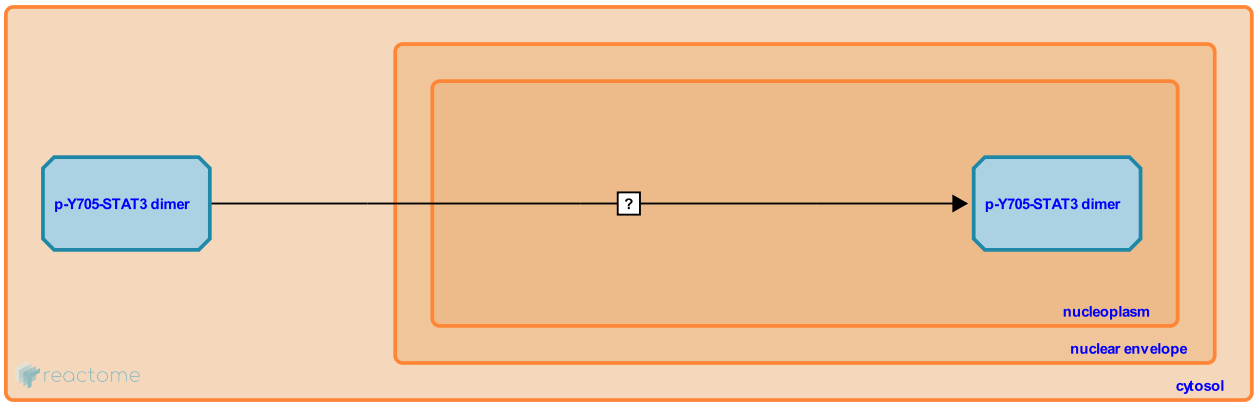
p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784763

Type: uncertain

Compartments: nucleoplasm, cytosol



The classical model of JAK-STAT signaling suggests that phosphorylated Signal transducer and activator of transcription 3 (STAT3) translocates to the nucleus (Akira et al. 1994) where it binds DNA to mediate the effects of Interleukin-10 (IL10) on expression of cytokines, soluble mediators and cell surface molecules by cells of myeloid origin, with important consequences for their ability to activate and sustain immune and inflammatory responses. STAT3 is able to shuttle freely between the cytoplasm and the nucleus, independent of tyrosine phosphorylation (Liu et al. 2005, Li 2008, Reich 2013). Binding of unphosphorylated STAT3 to DNA has been reported (Nkansah et al. 2013). As it is not clear what triggers nuclear accumulation of STAT3 in response to IL10 this event is shown as an uncertain process.

Preceded by: p-Y705-STAT3 dimerizes

Followed by: IL10 positively regulates plasma membrane-associated inflammatory mediators, IL10 positively regulates extracellular inflammatory mediators, IL10 negatively regulates plasma membrane-associated inflammatory mediators, IL10 negatively regulates extracellular inflammatory mediators

Literature references

Reich, NC., McBride, KM., Liu, L. (2005). STAT3 nuclear import is independent of tyrosine phosphorylation and mediated by importin-alpha3. *Proc. Natl. Acad. Sci. U.S.A., 102*, 8150-5. ↗

Kishimoto, T., Naruto, M., Wang, XJ., Yoshida, K., Nishio, Y., Wei, S. et al. (1994). Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. *Cell, 77*, 63-71. ↗

Lagos-Quintana, M., Tuschl, T., Borkhardt, A., Meyer, J., Rauhut, R. (2003). New microRNAs from mouse and human . *RNA, 9*, 175-9. ↗

Editions

2015-06-17	Authored	Jupe, S.
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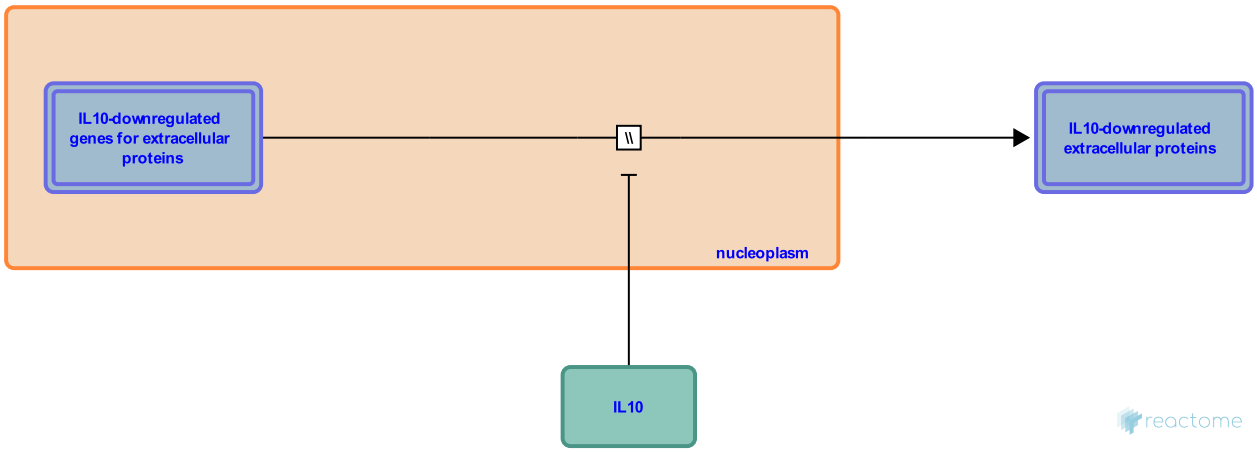
IL10 negatively regulates extracellular inflammatory mediators ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6784160

Type: omitted

Compartments: nucleoplasm, extracellular region



IL10 modulates the expression of cytokines, soluble mediators and cell surface molecules by cells of myeloid origin, with important consequences for their ability to activate and sustain immune and inflammatory responses. The effects of IL10 on cytokine production and function of human macrophages are generally similar to those on monocytes, although less pronounced (Moore et al. 2001). IL10 inhibits production of Interleukin-1 alpha (IL1A), IL1B, IL6, IL12, IL18, CSF2 (GM-CSF), CSF3 (G-CSF), CSF1 (M-CSF), TNF, LIF, PAF and itself by activated monocytes/macrophages (de Waal Malefyt et al. 1991, 1993, Fiorentino et al. 1991, D'Andrea et al. 1993, Gruber et al. 1994). The effect of IL10 on IL-1 and TNF production is particularly important as these cytokines often have synergistic effects on inflammatory processes, amplifying their effect by inducing secondary mediators such as chemokines, prostaglandins and PAF. IL10 also inhibits activated monocyte production of inducible chemokines that are involved in inflammation, namely CCL2 (MCP1), Ccl12 (MCP-5, in mice), CCL3, CCL3L1 (Mip-1alpha), CCL4 (Mip-1beta), CCL20 (Mip-3alpha), CCL19 (Mip-3beta), CCL5 (Rantes), CCL22 (MDC), CXCL8 (IL-8), CXCL10 (IP-10), CXCL2 (MIP-2) and CXCL1 (KC, Gro-alpha) (Berkman et al. 1995, Rossi et al. 1997, Marfaing-Koka et al. 1996, Kopydlowski et al. 1999). These are involved in the recruitment of monocytes, dendritic cells, neutrophils, and T cells, and affect both Th1 and Th2 responses. CXCL1 is induced by IFNgamma and attracts Th1 cells; CCL22 is induced by IL-4 and attracts Th2 cells.

IL10 inhibits expression of IL1R1 and IL-1RII (de Waal Malefyt et al. 1991, Jenkins et al. 1994, Dickensheets & Donnelly 1997).

Both transcriptional and posttranscriptional mechanisms have been implicated in the inhibitory effects of IL10 on cytokine and chemokine production (Bogdan et al. 1991, Clarke et al. 1998, Brown et al. 1996). IL10 regulates production of certain cytokines, such as CXCL1, by destabilizing mRNA via AU-rich elements in the 3'-UTR of sensitive genes (Kim et al. 1998, Kishore et al. 1999). IL-10 also enhances IL-1RA expression via inhibition of mRNA degradation (Cassatella et al. 1994).

IL10 indirectly inhibits production of prostaglandin E2 (PGE2) by downregulating PTGS2 (cyclooxygenase 2) expression (Niiro et al. 1994, 1995, Mertz et al. 1994), which also reduces expression of Matrix metalloproteinase 2 (MMP2) and MMP9, thereby modulating extracellular matrix turnover.

Preceded by: p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm

Literature references

Gruber, MF., Williams, CC., Gerrard, TL. (1994). Macrophage-colony-stimulating factor expression by anti-CD45 stimulated human monocytes is transcriptionally up-regulated by IL-1 beta and inhibited by IL-4 and IL-10. *J. Immunol., 152*, 1354-61. ↗

Mosmann, TR., Zlotnik, A., O'Garra, A., Howard, M., Fiorentino, DF. (1991). IL-10 inhibits cytokine production by activated macrophages. *J. Immunol., 147*, 3815-22. ↗

Donnelly, RP., Dickensheets, HL. (1997). IFN-gamma and IL-10 inhibit induction of IL-1 receptor type I and type II gene expression by IL-4 and IL-13 in human monocytes. *J. Immunol., 159*, 6226-33. ↗

Roesems, G., Barnes, PJ., Jose, PJ., John, M., Chung, KF., Berkman, N. (1995). Inhibition of macrophage inflammatory protein-1 alpha expression by IL-10. Differential sensitivities in human blood monocytes and alveolar macrophages. *J. Immunol., 155*, 4412-8. ↗

Huijbens, R., Mohan-Peterson, S., Dang, W., Zurawski, G., Figdor, CG., Bennett, B. et al. (1993). Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-gamma or IL-10. *J. Immunol., 151*, 6370-81. ↗

Editions

2015-06-17	Authored	Jupe, S.
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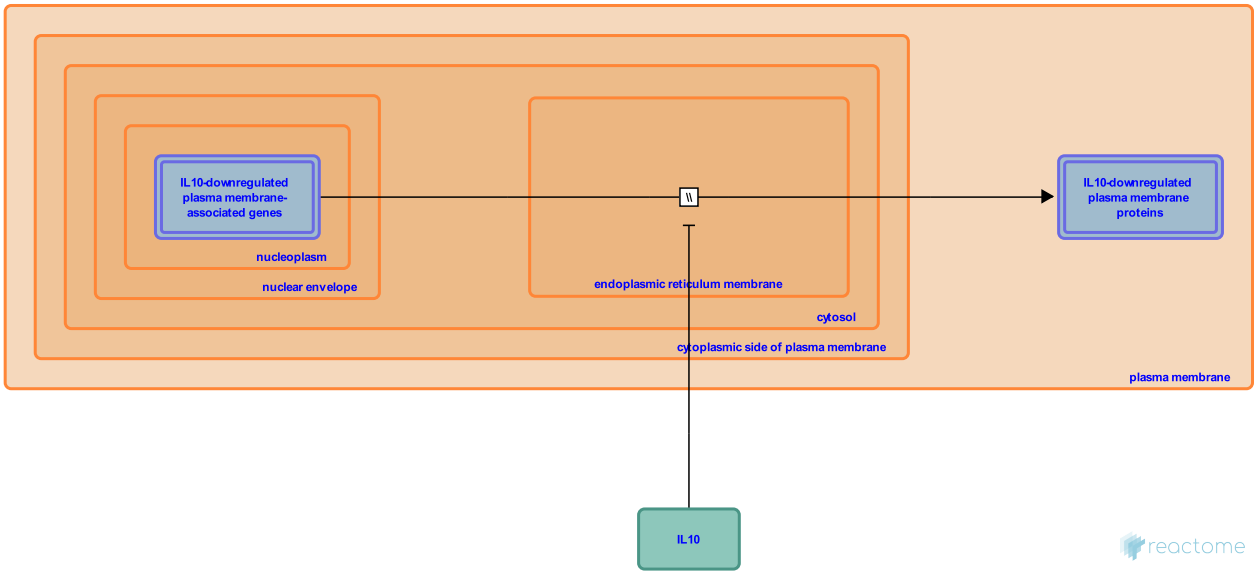
IL10 negatively regulates plasma membrane-associated inflammatory mediators ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-8937656

Type: omitted

Compartments: endoplasmic reticulum membrane, plasma membrane, nucleoplasm, extracellular region



IL10 modulates the expression of cytokines, soluble mediators and cell surface molecules by cells of myeloid origin, with important consequences for their ability to activate and sustain immune and inflammatory responses. The effects of IL10 on cytokine production and function of human macrophages are generally similar to those on monocytes, although less pronounced (Moore et al. 2001). IL10 inhibits expression of IL1R1 and IL-1RII (de Waal Malefyt et al. 1991, Jenkins et al. 1994, Dickensheets & Donnelly 1997).

Both transcriptional and posttranscriptional mechanisms have been implicated in the inhibitory effects of IL10 on cytokine and chemokine production (Bogdan et al. 1991, Clarke et al. 1998, Brown et al. 1996). IL10 inhibits monocyte expression of MHC class II antigens, ICAM1 (CD54), CD80 (B7), CD86 (B7.2) and FCER2 (CD23), countering the induction of these molecules by IL-4 or IFNgamma (de Waal Malefyt et al. 1991, Ding et al. 1993, Kubin et al. 1994, Willems et al. 1994, Morinobu et al. 1996). Downregulated expression of these molecules significantly decreases the T cell-activating capacity of monocyte APCs (de Waal Malefyt et al. 1991, Fiorentino et al. 1991, Ding et al. 1993).

Preceded by: p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm

Literature references

Mosmann, TR., Zlotnik, A., O'Garra, A., Howard, M., Fiorentino, DF. (1991). IL-10 inhibits cytokine production by activated macrophages. *J. Immunol., 147*, 3815-22. ↗

Huijbens, R., Mohan-Peterson, S., Dang, W., Zurawski, G., Figdor, CG., Bennett, B. et al. (1993). Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-gamma or IL-10. *J. Immunol., 151*, 6370-81. ↗

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Yodoi, J., Matsui, M., Ota, H., Kumagai, S., Nakao, K., Ishida, H. et al. (1996). IL-10 suppresses cell surface CD23/Fc epsilon RII expression, not by enhancing soluble CD23 release, but by reducing CD23 mRNA expression in human monocytes. *J. Clin. Immunol., 16*, 326-33. ↗

Figdor, CG., Bennett, B., de Waal Malefyt, R., de Vries, JE., Abrams, J. (1991). Interleukin 10(IL-10) inhibits cytokine synthesis by human monocytes: an autoregulatory role of IL-10 produced by monocytes. *J. Exp. Med., 174*, 1209-20. ↗

Editions

2015-06-17	Authored	Jupe, S.
2016-09-05	Reviewed	Meldal, BH.
2016-11-14	Edited	Jupe, S.

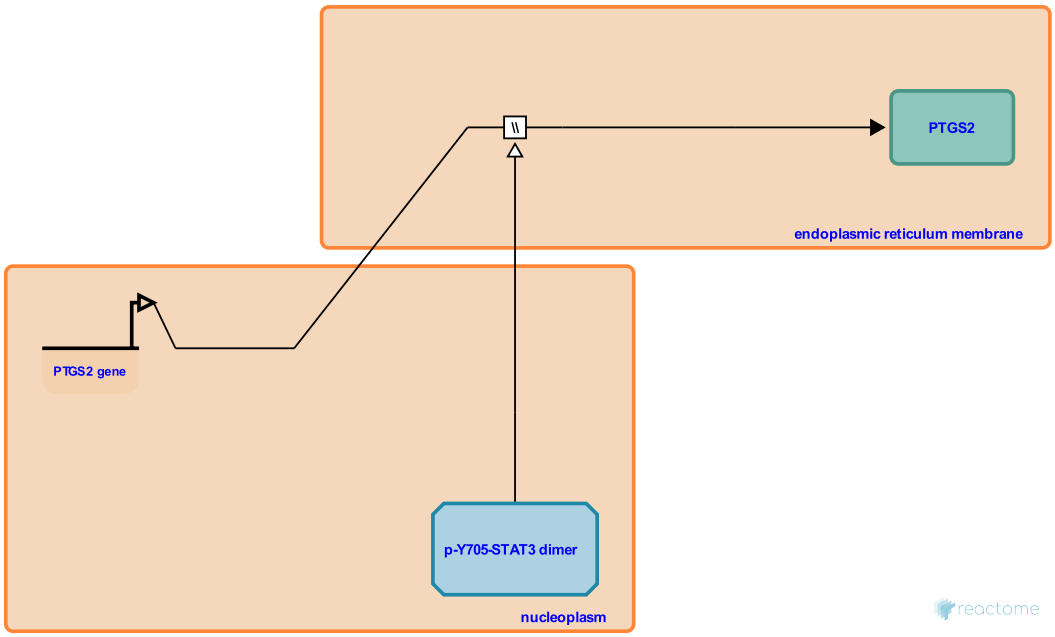
Expression of PTGS2 ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6790029

Type: omitted

Compartments: endoplasmic reticulum membrane, nucleoplasm



Signal transducer and activator of transcription 3 (STAT3) is a key regulator of gene expression in response to signaling of many cytokines including interleukin-6 (IL6), Oncostatin M, and leukemia inhibitory factor. Using microarray techniques, hundreds of genes have been reported as potential STAT3 target genes (Dauer et al. 2005, Hsieh et al. 2005). Some of these genes have been proven to be direct STAT3 targets using genome-wide chromatin immunoprecipitation screening (Snyder et al. 2008, Carpenter & Lo 2014), including the gene which encodes the endoplasmic reticulum membrane protein Prostaglandin G/H synthase 2 (PTGS2, COX2) (Lo et al. 2010).

Literature references

Zhu, H., Lo, HW., Ali-Osman, F., Cao, X. (2010). Cyclooxygenase-2 is a novel transcriptional target of the nuclear EGFR-STAT3 and EGFRvIII-STAT3 signaling axes. *Mol. Cancer Res., 8*, 232-45. ↗

Lo, HW., Carpenter, RL. (2014). STAT3 Target Genes Relevant to Human Cancers. *Cancers (Basel), 6*, 897-925. ↗

Editions

2015-07-01	Authored	Jupe, S.
2016-09-02	Reviewed	Leibovich, SJ.
2016-11-14	Edited	Jupe, S.

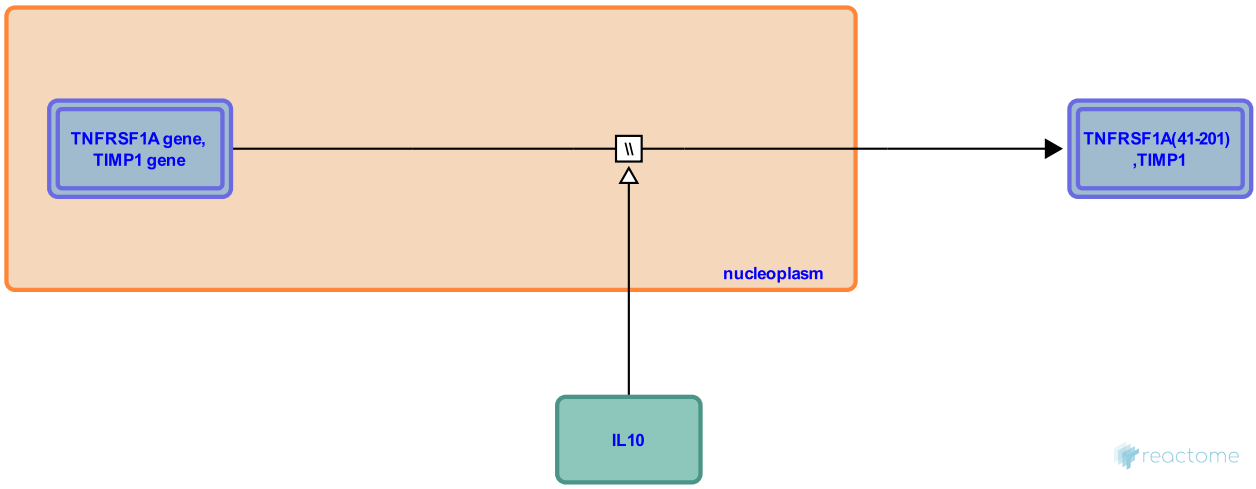
IL10 positively regulates extracellular inflammatory mediators ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-6785047

Type: omitted

Compartments: nucleoplasm, extracellular region



IL10 enhances activated monocyte expression of the natural antagonists interleukin-1 receptor antagonist (IL1RN), TNFRSF1A (soluble p55 TNFR) and TNFRSF1B (p75 TNFR) (Cassatella et al 1994, Hart et al. 1996, Joyce & Steer 1996, Linderholm et al. 1996, Dickensheets et al. 1997).

IL10 enhances production of tissue inhibitor of metalloproteinases (TIMP1) and hyaluronectin, which bind and inhibit the angiogenic- and migration-promoting activities of hyaluronic acid (Mertz et al. 1994, Lacraz et al. 1995, Stearns et al. 1999, Girard et al. 1999).

Preceded by: p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm

Literature references

Settergren, B., Ahlm, C., Tärnvik, A., Waage, A., Linderholm, M. (1996). Elevated plasma levels of tumor necrosis factor (TNF)-alpha, soluble TNF receptors, interleukin (IL)-6, and IL-10 in patients with hemorrhagic fever with renal syndrome. *J. Infect. Dis., 173*, 38-43. ↗

Bonder, CS., Finlay-Jones, JJ., Watson, CJ., Hart, PH., Hunt, EK. (1996). Regulation of surface and soluble TNF receptor expression on human monocytes and synovial fluid macrophages by IL-4 and IL-10. *J. Immunol., 157*, 3672-80. ↗

Lacraz, S., Welgus, HG., Chicheportiche, R., Dayer, JM., Nicod, LP. (1995). IL-10 inhibits metalloproteinase and stimulates TIMP-1 production in human mononuclear phagocytes. *J. Clin. Invest., 96*, 2304-10. ↗

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Freeman, SL., Smith, MF., Donnelly, RP., Dickensheets, HL. (1997). Interleukin-10 upregulates tumor necrosis factor receptor type-II (p75) gene expression in endotoxin-stimulated human monocytes. *Blood, 90*, 4162-71. ↗

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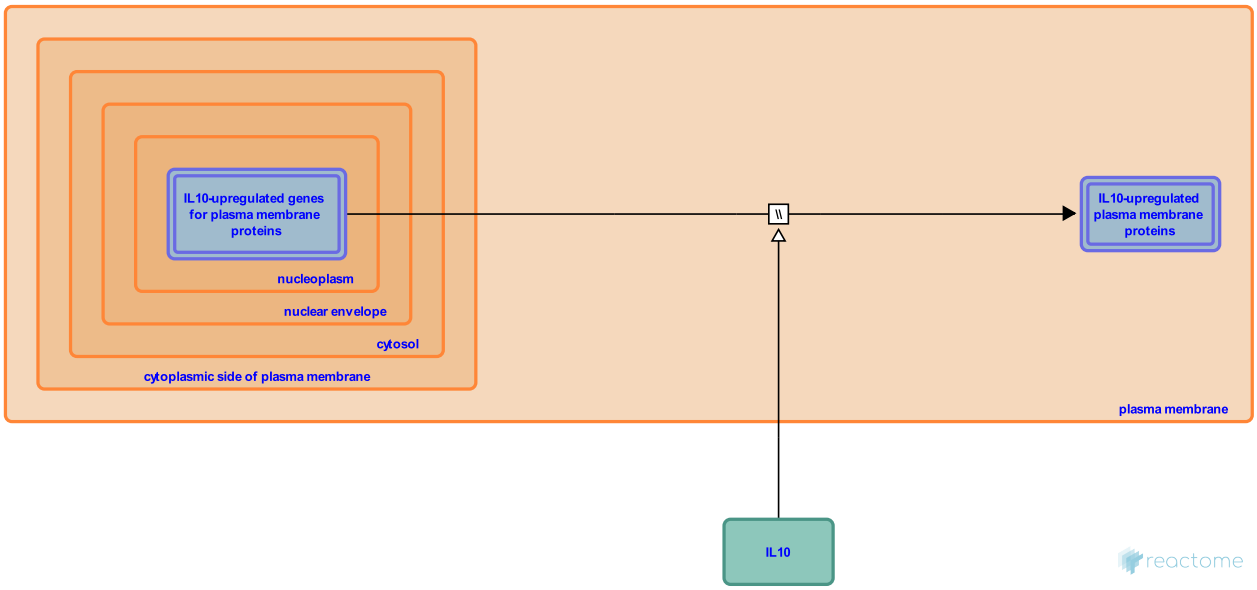
IL10 positively regulates plasma membrane-associated inflammatory mediators ↗

Location: Interleukin-10 signaling

Stable identifier: R-HSA-8937654

Type: omitted

Compartments: plasma membrane, nucleoplasm, extracellular region



IL10 upregulates monocyte expression of FPR1 (fMLP receptor), PTAFR (PAF receptor), CCR1, CCR2, and CCR5, making them more responsive to chemotactic factors (Andrew et al. 1998, Sozzani et al. 1998, Thivierge et al. 1999) and more susceptible to HIV infection (Andrew et al. 1998, Sozzani et al. 1998).
IL10 enhances activated monocyte expression of the natural antagonists interleukin-1 receptor antagonist (IL1RN) and TNFRSF1B (p75 TNFR) (Cassatella et al 1994, Hart et al. 1996, Joyce & Steer 1996, Linderholm et al. 1996, Dickensheets et al. 1997).

IL10 enhances production of tissue inhibitor of metalloproteinases (TIMP1) and hyaluronectin, which bind and inhibit the angiogenic- and migration-promoting activities of hyaluronic acid (Mertz et al. 1994, Lacraz et al. 1995, Stearns et al. 1999, Girard et al. 1999).

IL10 enhances expression of CD16 and CD64 FcgammaR on monocytes (te Velde et al. 1992, de Waal Malefyt et al. 1993, Calzada-Wack et al. 1996).

Preceded by: p-Y705-STAT3 dimer translocates from cytosol to nucleoplasm

Literature references

Yssel, H., de Waal Malefyt, R., de Vries, JE. (1993). Direct effects of IL-10 on subsets of human CD4+ T cell clones and resting T cells. Specific inhibition of IL-2 production and proliferation. *J. Immunol., 150*, 4754-65. ↗

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Table of Contents