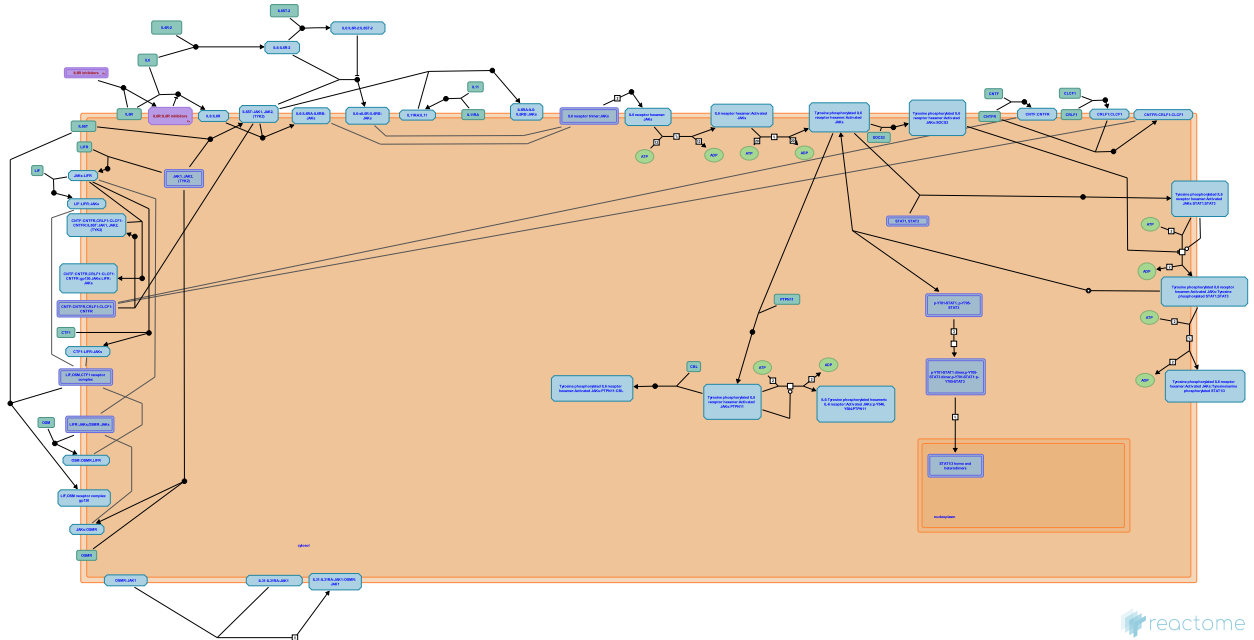


Interleukin-6 family signaling



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

19/04/2024

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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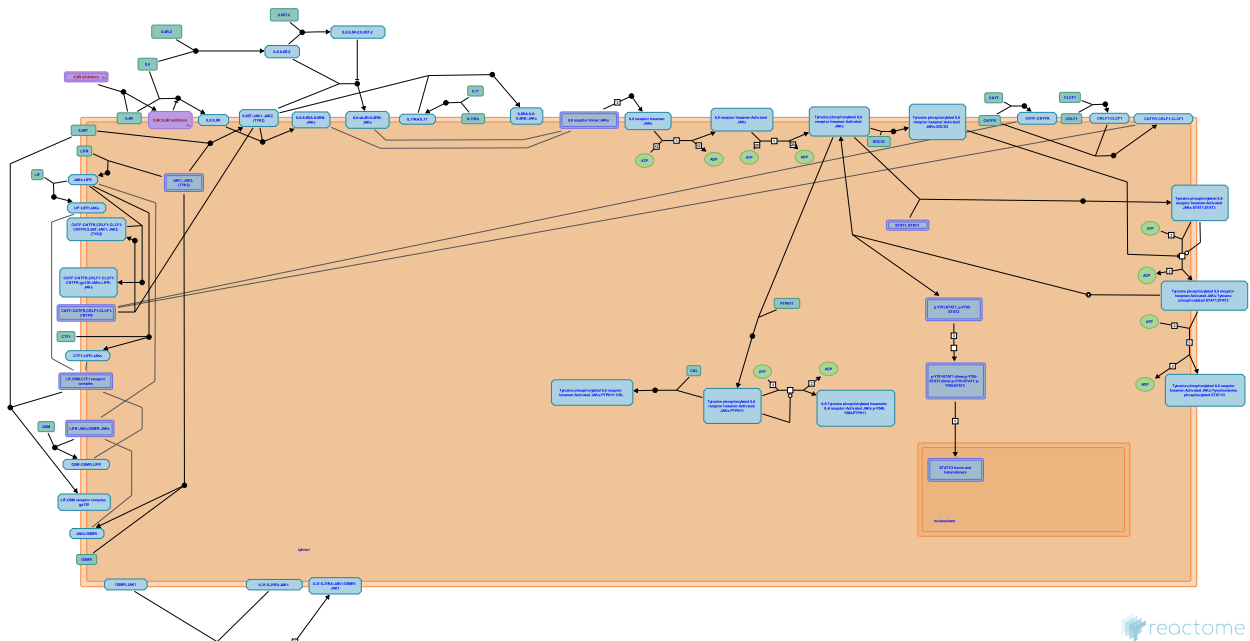
Reactome database release: 88

This document contains 3 pathways ([see Table of Contents](#))

Interleukin-6 family signaling ↗

Stable identifier: R-HSA-6783589

Compartments: plasma membrane, extracellular region



The interleukin-6 (IL6) family of cytokines includes IL6, IL11, IL27, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 and 2 (CT-1) and cardiotrophin-like cytokine (CLC) (Heinrich et al. 2003, Pflanz et al. 2002). The latest addition to this family is IL31, discovered in 2004 (Dillon et al. 2004). The family is defined largely by the shared use of the common signal transducing receptor Interleukin-6 receptor subunit beta (IL6ST, gp130). The IL31 receptor uniquely does not include this subunit, instead it uses the related IL31RA. The members of the IL6 family share very low sequence homology but are structurally highly related, forming anti-parallel four-helix bundles with a characteristic “up-up-down-down” topology (Rozwarski et al. 1994, Cornelissen et al. 2012).

Although each member of the IL6 family signals through a distinct receptor complex, their underlying signaling mechanisms are similar. Assembly of the receptor complex is followed by activation of receptor-associated Janus kinases (JAKs), believed to be constitutively associated with the receptor subunits. Activation of JAKs initiates downstream cytoplasmic signaling cascades that involve recruitment and phosphorylation of transcription factors of the Signal transducer and activator of transcription (STAT) family, which dimerize and translocate to the nucleus where they bind enhancer elements of target genes leading to transcriptional activation (Nakashima & Taga 1998).

Negative regulators of IL6 signaling include Suppressor of cytokine signals (SOCS) family members and PTPN11 (SHP-2).

IL6 is a pleiotropic cytokine with roles in processes including immune regulation, hematopoiesis, inflammation, oncogenesis, metabolic control and sleep.

IL6 and IL11 bind their corresponding specific receptors IL6R and IL11R respectively, resulting in dimeric complexes that subsequently associate with IL6ST, leading to IL6ST homodimer formation (in a hexameric or higher order complex) and signal initiation. IL6R alpha exists in transmembrane and soluble forms. The transmembrane form is mainly expressed by hepatocytes, neutrophils, monocytes/macrophages, and some lymphocytes. Soluble forms of IL6R (sIL6R) are also expressed by these cells. Two major mechanisms for the production of sIL6R have been proposed. Alternative splicing generates a transcript lacking the transmembrane domain coding region. This also introduces a frameshift leading to the incorporation of 10 additional amino acids at the C terminus of sIL6R. A second mechanism for the generation of sIL6R is the proteolytic cleavage or 'shedding' of membrane-bound IL-6R. Two proteases ADAM10 and ADAM17 are thought to contribute to this (Briso et al. 2008). sIL6R can bind IL6 and stimulate cells that express gp130 but not IL6R alpha, a process that is termed trans-signaling. This explains why many cells, including hematopoietic progenitor cells, neuronal cells, endothelial cells, smooth muscle cells, and embryonic stem cells, do not respond to IL6 alone, but show a remarkable response to IL6/sIL6R. It is clear that the trans-signaling pathway is responsible for the pro-inflammatory activities of IL6 whereas the membrane bound receptor governs regenerative and anti-inflammatory IL6 activities

LIF, CNTF, OSM, CTF1, CRLF1 and CLCF1 signal via IL6ST:LIFR heterodimeric receptor complexes (Taga & Kishimoto 1997, Mousa & Bakhiet 2013). OSM signals via a receptor complex consisting of IL6ST and OSMR. These cytokines play important roles in the regulation of complex cellular processes such as gene activation, proliferation and differentiation (Heinrich et al. 1998).

Antibodies have been developed to inhibit IL6 activity for the treatment of inflammatory diseases (Kopf et al. 2010).

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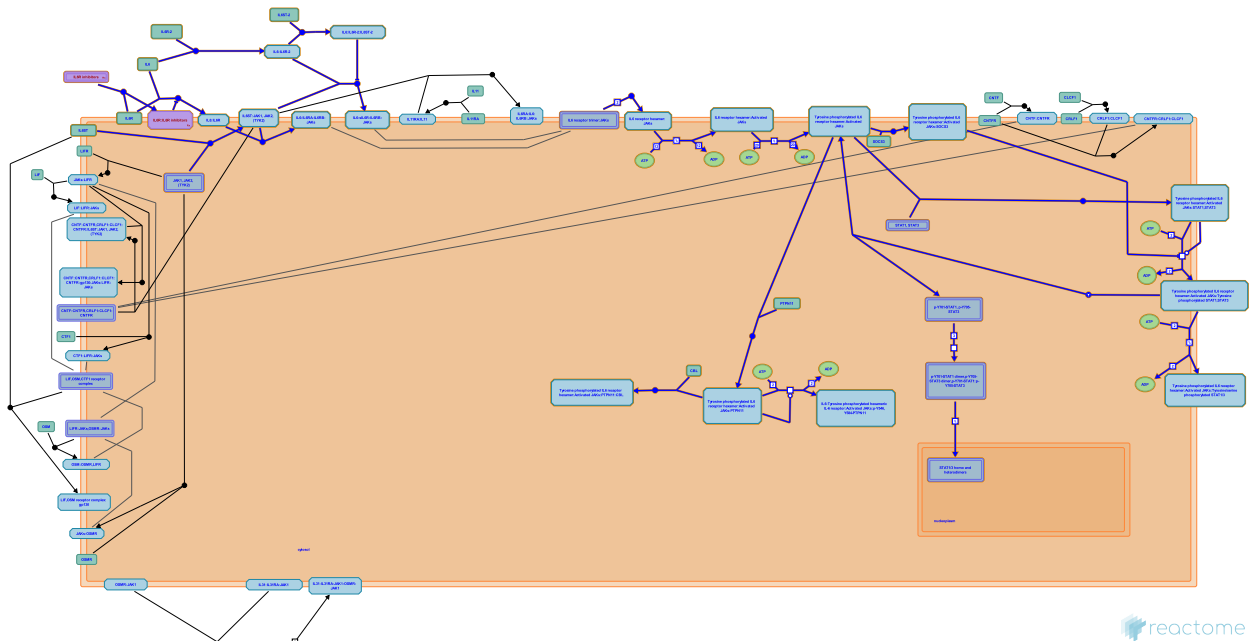
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Interleukin-6 signaling ↗

Location: [Interleukin-6 family signaling](#)

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Interleukin-6 (IL-6) is a pleiotropic cytokine with roles in processes including immune regulation, hematopoiesis, inflammation, oncogenesis, metabolic control and sleep. It is the founding member of a family of IL-6-related cytokines such as IL-11, IL-27 leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and oncostatin M.

The IL-6 receptor (IL6R) consists of an alpha subunit that specifically binds IL-6 and a beta subunit, IL6RB or gp130, which is the signaling component of all the receptors for cytokines related to IL-6. IL6R alpha exists in transmembrane and soluble forms. The transmembrane form is mainly expressed by hepatocytes, neutrophils, monocytes/macrophages, and some lymphocytes. Soluble forms of IL6R (sIL6R) are also expressed by these cells. Two major mechanisms for the production of sIL6R have been proposed. Alternative splicing generates a transcript lacking the transmembrane domain by using splicing donor and acceptor sites that flank the transmembrane domain coding region. This also introduces a frameshift leading to the incorporation of 10 additional amino acids at the C terminus of sIL6R. A second mechanism for the generation of sIL6R is the proteolytic cleavage or 'shedding' of membrane-bound IL-6R. Two proteases ADAM10 and ADAM17 are thought to contribute to this (Briso et al. 2008). sIL6R can bind IL6 and stimulate cells that express gp130 but not IL6R alpha, a process that is termed trans-signaling. This explains why many cells, including hematopoietic progenitor cells, neuronal cells, endothelial cells, smooth muscle cells, and embryonic stem cells, do not respond to IL6 alone, but show a remarkable response to IL6/sIL6R. It is clear that the trans-signaling pathway is responsible for the pro-inflammatory activities of IL-6 whereas the membrane bound receptor governs regenerative and anti-inflammatory IL-6 activities

IL6R signal transduction is mediated by two pathways: the JAK-STAT (Janus family tyrosine kinase-signal transducer and activator of transcription) pathway and the Ras-MAPK (mitogen-activated protein kinase) pathway. Negative regulators of IL-6 signaling include SOCS (suppressor of cytokine signals) and SHP2. Within the last few years different antibodies have been developed to inhibit IL-6 activity, and the first such antibodies have been introduced into the clinic for the treatment of inflammatory diseases (Kopf et al. 2010).

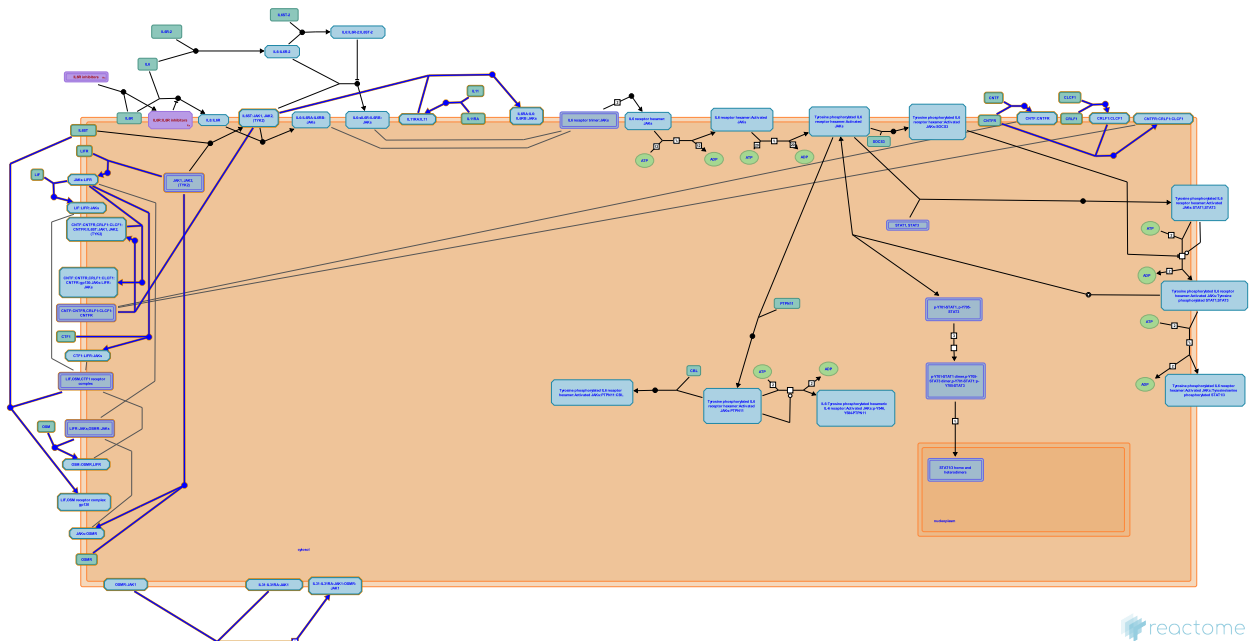
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IL-6-type cytokine receptor ligand interactions ↗

Location: [Interleukin-6 family signaling](#)

Stable identifier: R-HSA-6788467



The members involved in (interleukin)-6-type cytokine signalling are the IL-6, IL-11, LIF (leukaemia inhibitory factor), OSM (oncostatin M), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CTF1) and cardiotrophin-like cytokine factor 1 (CLCF1). Receptors involved in recognition of the IL-6-type cytokines can be subdivided in the non-signalling alpha-receptors (IL6R, IL 11R, and CNTFR) and the signal transducing receptors (gp130, LIFR, and OSMR). The latter associate with JAKs and become tyrosine phosphorylated in response to cytokine stimulation (Heinrich et al. 1998, 2003). IL27 and IL35 belongs to IL12 cytokine family but they share gp130 as a component of signalling receptor, along with IL-6, IL-11, LIF, OSM, CNTF, CTF1 and CLCF1.

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Garapati, P V.

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