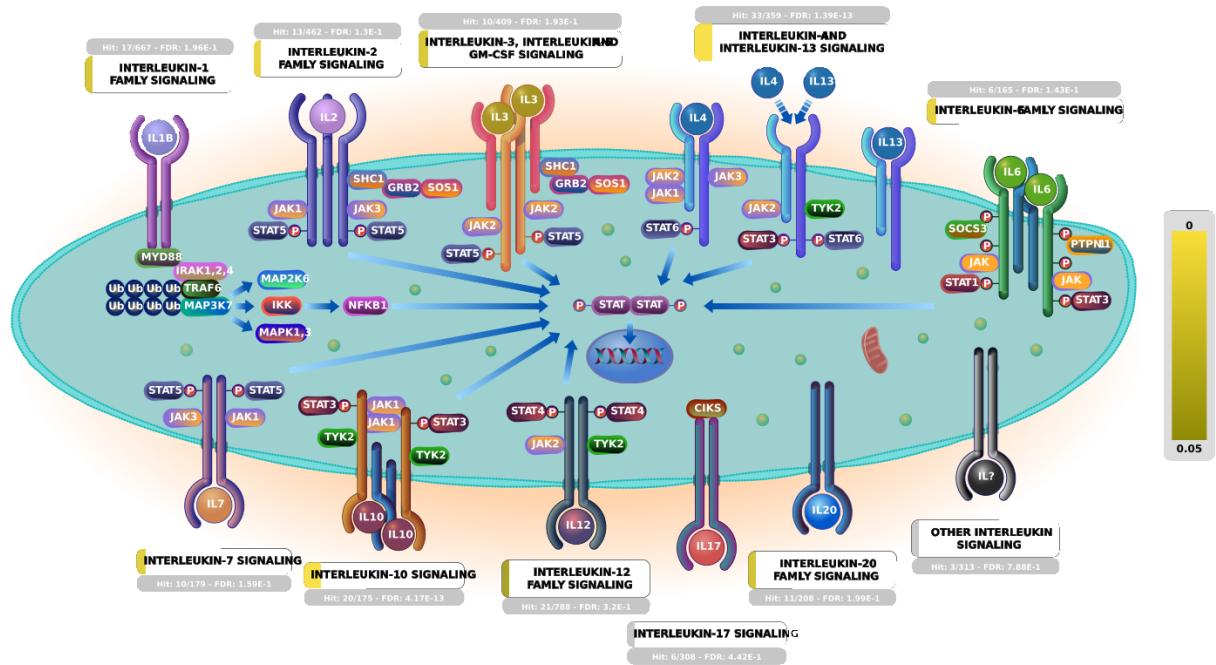


# Signaling by Interleukins



Datta, SK., Dooms, H., Garapati, P V., Goronzy, JJ., Hercus, TR., Jupe, S., Kumar, U., Leibovich, SJ., Lopez, AF., Mandal, M., Meldal, BH., Narazaki, M., Orlic-Milacic, M., Pinteaux, E., Puck, J., Ray, KP., Tanaka, M., Villarino, A.

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

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# Introduction

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

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

## Literature references

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. [↗](#)

Reactome database release: 81

This document contains 12 pathways (see [Table of Contents](#))

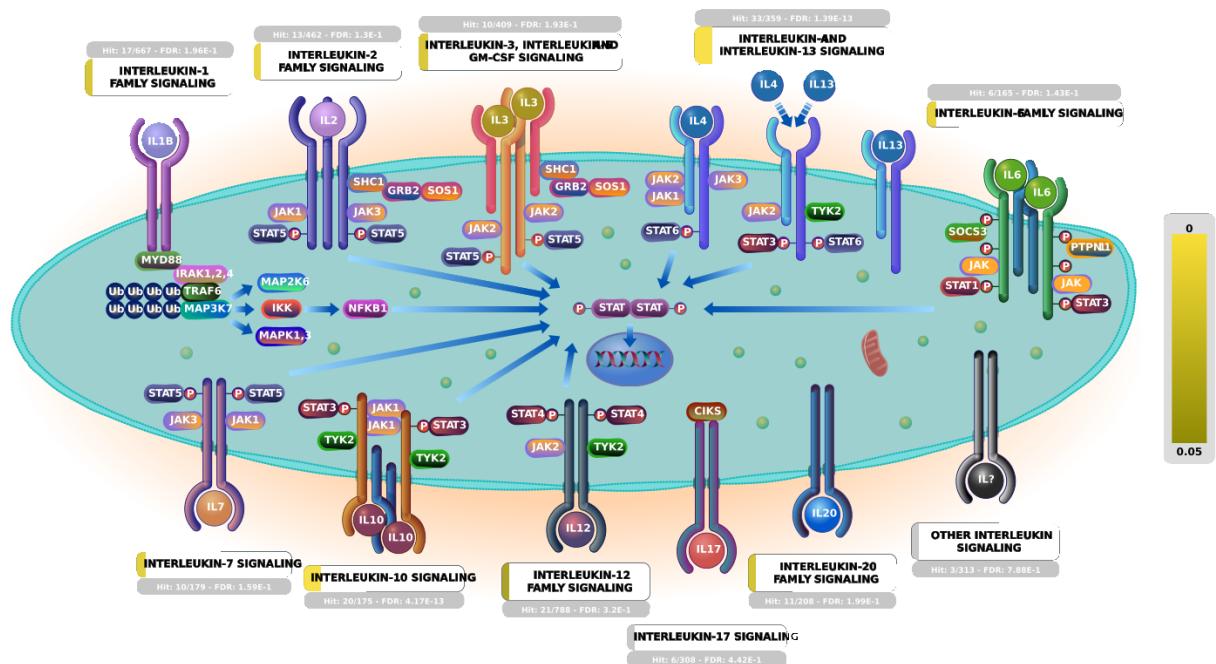
## Analysis properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method. [See more](#)
- 39 out of 39 identifiers in the sample were found in Reactome, where 1141 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent. [↗](#)
- IntAct interactors were included to increase the analysis background. This greatly increases the size of Reactome pathways, which maximises the chances of matching your submitted identifiers to the expanded pathway, but will include interactors that have not undergone manual curation by Reactome and may include interactors that have no biological significance, or unexplained relevance.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'all resources'.
- The unique ID for this analysis (token) is MjAyMjA5MDEwNDA3MzZfMzEyNTc%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

## Signaling by Interleukins ↗

Stable identifier: R-HSA-449147

Compartments: plasma membrane



Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

## Literature references

Dinarello, CA. (2009). Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*, 27, 519-50. [↗](#)

Komlosi, Z., Kucuksezer, UC., Frei, R., Huitema, C., Garbani, M., Pezer, M. et al. (2016). Interleukins (from IL-1 to IL-38), interferons, transforming growth factor  $\beta$ , and TNF- $\alpha$ : Receptors, functions, and roles in diseases. *J. Allergy Clin. Immunol.*, 138, 984-1010. [↗](#)

Vossenrich, CA., Di Santo, JP. (2002). Interleukin signaling. *Curr Biol*, 12, R760-3. [↗](#)

## Editions

2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.
2010-05-26	Edited	Jupe, S.

## 26 submitted entities found in this pathway, mapping to 41 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BCL2	P10415	IFNG	P01579	IL10	P22301
IL12B	P29460	IL13	P35225	IL17	Q16552
IL1B	P01583, P01584, Q8WWZ1	IL2	P60568	IL4	P05112
IL5	P05113	IL6	P05231	IL7	P13232

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL8	P10145	JAK1	P23458	JAK2	O60674
JAK3	P52333	MAPK	P28482	MUC1	P15941
Myc	P01106	NFKB1	P19838	PIK3CA	P42336
PTGS2	P35354	STAT	P40763	STAT3	P40763
TNF	P01375	p53	P04637		
Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
BCL2	ENSG00000171791	IFNG	ENSG00000111537	IL10	ENSG00000136634
IL12B	ENSG00000113302	IL17	ENSG00000112115	IL1B	ENSG00000125538
IL6	ENSG00000136244	IL8	ENSG00000169429	MUC1	ENSG00000185499
Myc	ENSG00000136997	PTGS2	ENSG00000073756	TNF	ENSG00000232810
p53	ENSG00000141510				

## Interactors found in the analysis (22)

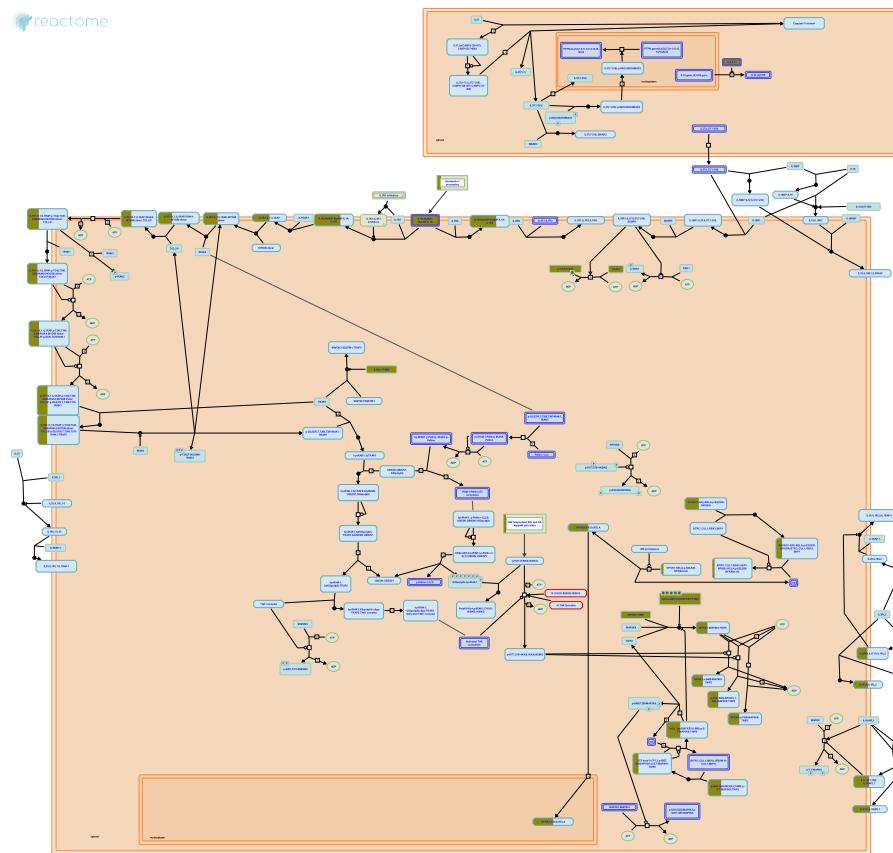
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BCL2	P10415	P00441	BRAF	P15056	P63104, P38646
EGFR	P00533	P29353, P22681, P14625, Q13905, Q06124, P38646, Q9UQC2, P15498, P42224, O00170, P62993, P14174, Q9Y6K9, P23528, P45983, O14543, P63104, P07355, P40763	IL10	P22301	Q08334
IL12B	P29460	P29460, Q9NPF7, P29459	IL13	P35225	P78552, Q14627
IL2	P60568	P01589, P14784	IL4	P05112	P24394, P78552, P31785
IL5	P05113	Q01344, P32927	IL6	P05231	P40189, P08887
IL7	P13232	P16871	JAK1	P23458	P42224, O60674, P40763
JAK2	O60674, Q62120	Q01344, Q5VWK5, O60674, P32927, P23458	JAK3	P52333	P17987
Myc	P01106, EBI-1265559	O15111, Q9Y6K9, P23771, P40763	NFKB1	P25799-1, P19838, P19838-1	P41279, O15111, P19838, Q9Y6K9, Q8NFZ5, O14920, P25963
PARP1	P09874	Q13007	PIK3CA	P42336	P62993, P01100
STAT	P35610, EBI-10097350, EBI-10952519	P42224, Q14765, P27824, P40763	STAT3	EBI-9914958, P42227, P40763	P42224, P40189, P43405, P62993, P22681, P23458, P49137, Q99062, P40763
TNF	P01375	Q16623, Q9Y6K9	p53	P04637	P17987, O14920, P63104, P38646

## Interleukin-1 family signaling ↗

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-446652

**Compartments:** plasma membrane



The Interleukin-1 (IL1) family of cytokines comprises 11 members, namely Interleukin-1 alpha (IL1A), Interleukin-1 beta (IL1B), Interleukin-1 receptor antagonist protein (IL1RN, IL1RA), Interleukin-18 (IL18), Interleukin-33 (IL33), Interleukin-36 receptor antagonist protein (IL36RN, IL36RA), Interleukin-36 alpha (IL36A), Interleukin-36 beta (IL36B), Interleukin-36 gamma (IL36G), Interleukin-37 (IL37) and Interleukin-38 (IL38). The genes encoding all except IL18 and IL33 are on chromosome 2. They share a common C-terminal three-dimensional structure and with apart from IL1RN they are synthesized without a hydrophobic leader sequence and are not secreted via the classical reticulum endoplasmic-Golgi pathway.

IL1B and IL18, are produced as biologically inactive propeptides that are cleaved to produce the mature, active interleukin peptide.

The IL1 receptor (IL1R) family comprises 10 members: Interleukin-1 receptor type 1 (IL1R1, IL1RA), Interleukin-1 receptor type 2 (IL1R2, IL1RB), Interleukin-1 receptor accessory protein (IL1RAP, IL1RAcP, IL1R3), Interleukin-18 receptor 1 (IL18R1, IL18RA), Interleukin-18 receptor accessory protein (IL18RAP, IL18RB), Interleukin-1 receptor-like 1 (IL1RL1, ST2, IL33R), Interleukin-1 receptor-like 2 (IL1RL2, IL36R), Single Ig IL-1-related receptor (SIGIRR, TIR8), Interleukin-1 receptor accessory protein-like 1 (IL1RAPL1, TIGGIR2) and X-linked interleukin-1 receptor accessory protein-like 2 (IL1RAPL2, TIGGIR1). Most of the genes encoding these receptors are on chromosome 2.

IL1 family receptors heterodimerize upon cytokine binding. IL1, IL33 and IL36 bind specific receptors, IL1R1, IL1RL1, and IL1RL2 respectively. All use IL1RAP as a co-receptor. IL18 binds IL18R1 and uses

IL18RAP as co-receptor.

The complexes formed by IL1 family cytokines and their heterodimeric receptors recruit intracellular signaling molecules, including Myeloid differentiation primary response protein MyD88 (MYD88), members of the IL1R-associated kinase (IRAK) family, and TNF receptor-associated factor 6 (TRAF6), activating Nuclear factor NF-kappa-B (NF $\kappa$ B), as well as Mitogen-activated protein kinase 14 (MAPK14, p38), c-Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs) and other Mitogen-activated protein kinases (MAPKs).

## Literature references

Dinarello, CA. (2009). Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*, 27, 519-50. [↗](#)

Martin, P., Dietrich, D., Gabay, C., Palomo, J., Palmer, G. (2015). The interleukin (IL)-1 cytokine family--Balance between agonists and antagonists in inflammatory diseases. *Cytokine*, 76, 25-37. [↗](#)

Arend, WP., Gabay, C., Palmer, G. (2008). IL-1, IL-18, and IL-33 families of cytokines. *Immunol. Rev.*, 223, 20-38. [↗](#)

Moynagh, PN. (2009). The Pellino family: IRAK E3 ligases with emerging roles in innate immune signalling. *Trends Immunol*, 30, 33-42. [↗](#)

## Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

## 6 submitted entities found in this pathway, mapping to 8 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL13	P35225	IL1B	P01583, P01584, Q8WWZ1	IL4	P05112
NFKB1	P19838	STAT3	P40763	p53	P04637

## Interactors found in the analysis (8)

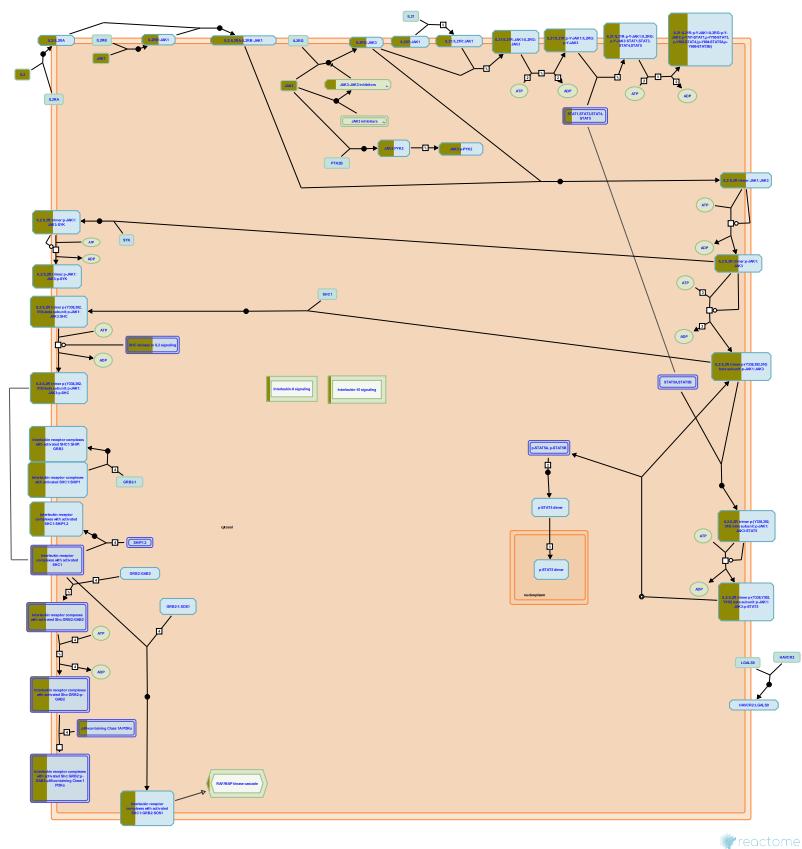
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q9Y6K9, P45983, P40763	JAK1	P23458	P40763
Myc	EBI-1265559, P01106	O15111, Q9Y6K9, P40763	NFKB1	P25799-1, P19838, P19838-1	P41279, O15111, P19838, Q9Y6K9, Q8NFZ5, O14920, P25963
STAT	EBI-10952519	P40763	STAT3	EBI-9914958, P40763	P40763
TNF	P01375	Q9Y6K9	p53	P04637	O14920

# Interleukin-2 family signaling ↗

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-451927

**Compartments:** plasma membrane



The interleukin-2 family (also called the common gamma chain cytokine family) consists of interleukin (IL)2, IL9, IL15 and IL21. Although sometimes considered to be within this family, the IL4 and IL7 receptors can form complexes with other receptor chains and are represented separately in Reactome. Receptors of this family associate with JAK1 and JAK3, primarily activating STAT5, although certain family members can also activate STAT1, STAT3 or STAT6.

## Literature references

Sim, GC., Radvanyi, L. (2014). The IL-2 cytokine family in cancer immunotherapy. *Cytokine Growth Factor Rev.*, 25, 377-90. ↗

Wang, X., Laporte, SL., Lupardus, P., Garcia, KC. (2009). Structural biology of shared cytokine receptors. *Annu Rev Immunol*, 27, 29-60. ↗

Spolski, R., Leonard, WJ., Rochman, Y. (2009). New insights into the regulation of T cells by gamma(c) family cytokines. *Nat Rev Immunol*, 9, 480-90. ↗

## Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2011-02-11	Reviewed	Villarino, A.
2011-03-17	Reviewed	Dooms, H.

## 7 submitted entities found in this pathway, mapping to 7 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL2	P60568	IL5	P05113	JAK1	P23458
JAK2	O60674	JAK3	P52333	PIK3CA	P42336
STAT3	P40763				

## Interactors found in the analysis (9)

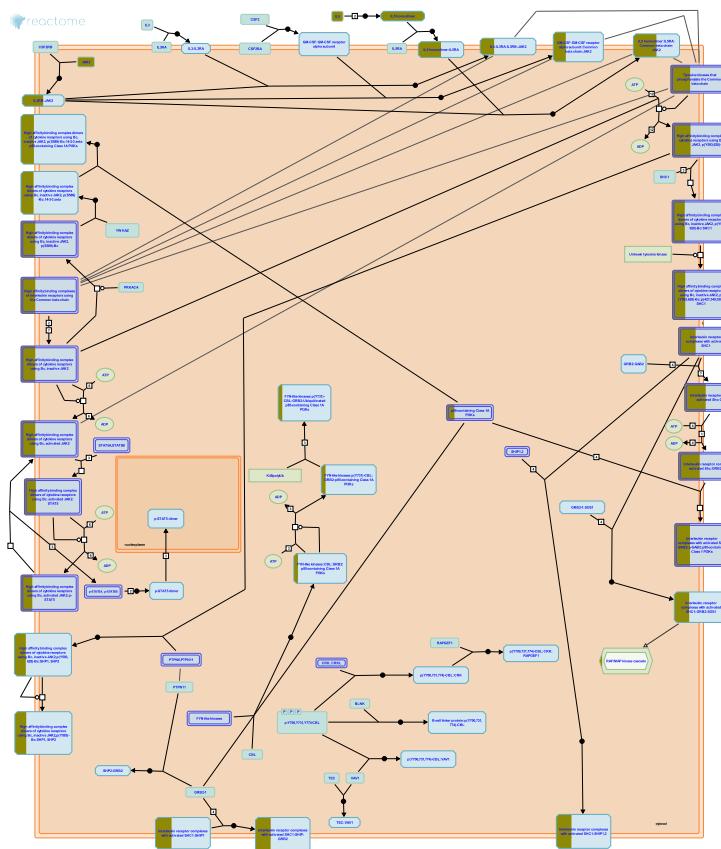
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	Q9UQC2, P42224, P62993, P29353, P40763	IL2	P60568	P01589, P14784
IL4	P05112	P31785	JAK1	P23458	P42224, P40763
JAK2	O60674	P23458	Myc	EBI-1265559	P40763
PIK3CA	P42336	P62993	STAT	EBI-10097350, EBI-10952519	P42224, P40763
STAT3	EBI-9914958, P40763	P42224, P43405, P62993, P23458, P40763			

## Interleukin-3, Interleukin-5 and GM-CSF signaling ↗

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-512988

**Compartments:** plasma membrane



The Interleukin-3 (IL-3), IL-5 and Granulocyte-macrophage colony stimulating factor (GM-CSF) receptors form a family of heterodimeric receptors that have specific alpha chains but share a common beta sub-unit, often referred to as the common beta (Bc). Both subunits contain extracellular conserved motifs typical of the cytokine receptor superfamily. The cytoplasmic domains have limited similarity with other cytokine receptors and lack detectable catalytic domains such as tyrosine kinase domains.

IL-3 is a 20-26 kDa product of CD4+ T cells that acts on the most immature marrow progenitors. IL-3 is capable of inducing the growth and differentiation of multi-potential hematopoietic stem cells, neutrophils, eosinophils, megakaryocytes, macrophages, lymphoid and erythroid cells. IL-3 has been used to support the proliferation of murine cell lines with properties of multi-potential progenitors, immature myeloid as well as T and pre-B lymphoid cells (Miyajima et al. 1992). IL-5 is a hematopoietic growth factor responsible for the maturation and differentiation of eosinophils. It was originally defined as a T-cell-derived cytokine that triggers activated B cells for terminal differentiation into antibody-secreting plasma cells. It also promotes the generation of cytotoxic T-cells from thymocytes. IL-5 induces the expression of IL-2 receptors (Kuro & Takatsu 2009). GM-CSF is produced by cells (T-lymphocytes, tissue macrophages, endothelial cells, mast cells) found at sites of inflammatory responses. It stimulates the growth and development of progenitors of granulocytes and macrophages, and the production and maturation of dendritic cells. It stimulates myeloblast and monoblast differentiation, synergises with Epo in the proliferation of erythroid and megakaryocytic progenitor cells, acts as an autocrine mediator of growth for some types of acute myeloid leukemia, is a strong chemoattractant for neutrophils and eosinophils. It enhances the activity of neutrophils and macrophages. Under steady-state conditions GM-CSF

is not essential for the production of myeloid cells, but it is required for the proper development of alveolar macrophages, otherwise, pulmonary alveolar proteinosis (PAP) develops. A growing body of evidence suggests that GM-CSF plays a key role in emergency hematopoiesis (predominantly myelopoiesis) in response to infection, including the production of granulocytes and macrophages in the bone marrow and their maintenance, survival, and functional activation at sites of injury or insult (Hercus et al. 2009).

All three receptors have alpha chains that bind their specific ligands with low affinity (de Groot et al. 1998). Bc then associates with the alpha chain forming a high affinity receptor (Geijsen et al. 2001), though the *in vivo* receptor is likely be a higher order multimer as recently demonstrated for the GM-CSF receptor (Hansen et al. 2008).

The receptor chains lack intrinsic kinase activity, instead they interact with and activate signaling kinases, notably Janus Kinase 2 (JAK2). These phosphorylate the common beta subunit, allowing recruitment of signaling molecules such as Shc, the phosphatidylinositol 3-kinases (PI3Ks), and the Signal Transducers and Activators of Transcription (STATs). The cytoplasmic domain of Bc has two distinct functional domains: the membrane proximal region mediates the induction of proliferation-associated genes such as c-myc, pim-1 and oncostatin M. This region binds multiple signal-transducing proteins including JAK2 (Quelle et al. 1994), STATs, c-Src and PI3 kinase (Rao and Mufson, 1995). The membrane distal domain is required for cytokine-induced growth inhibition and is necessary for the viability of hematopoietic cells (Inhorn et al. 1995). This region interacts with signal-transducing proteins such as Shc (Inhorn et al. 1995) and SHP and mediates the transcriptional activation of c-fos, c-jun, c-Raf and p70S6K (Reddy et al. 2000).

Figure reproduced by permission from Macmillan Publishers Ltd: Leukemia, WL Blalock et al. 13:1109-1166, copyright 1999. Note that residue numbering in this diagram refers to the mature Common beta chain with signal peptide removed.

## Literature references

Bagley, CJ., Berndt, MC., Stomski, FC., Lopez, AF., Woodcock, JM., Thomas, D. et al. (1998). Mechanism of activation of the GM-CSF, IL-3, and IL-5 family of receptors. *Stem Cells*, 16, 301-13. [↗](#)

McCubrey, JA., Hoyle, PE., Steelman, LS., Franklin, RA., Weinstein-Oppenheimer, C., Wang, XY. et al. (1999). Signal transduction, cell cycle regulatory, and anti-apoptotic pathways regulated by IL-3 in hematopoietic cells: possible sites for intervention with anti-neoplastic drugs. *Leukemia*, 13, 1109-66. [↗](#)

## Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

## 6 submitted entities found in this pathway, mapping to 6 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL2	P60568	IL5	P05113	JAK1	P23458
JAK2	O60674	JAK3	P52333	PIK3CA	P42336

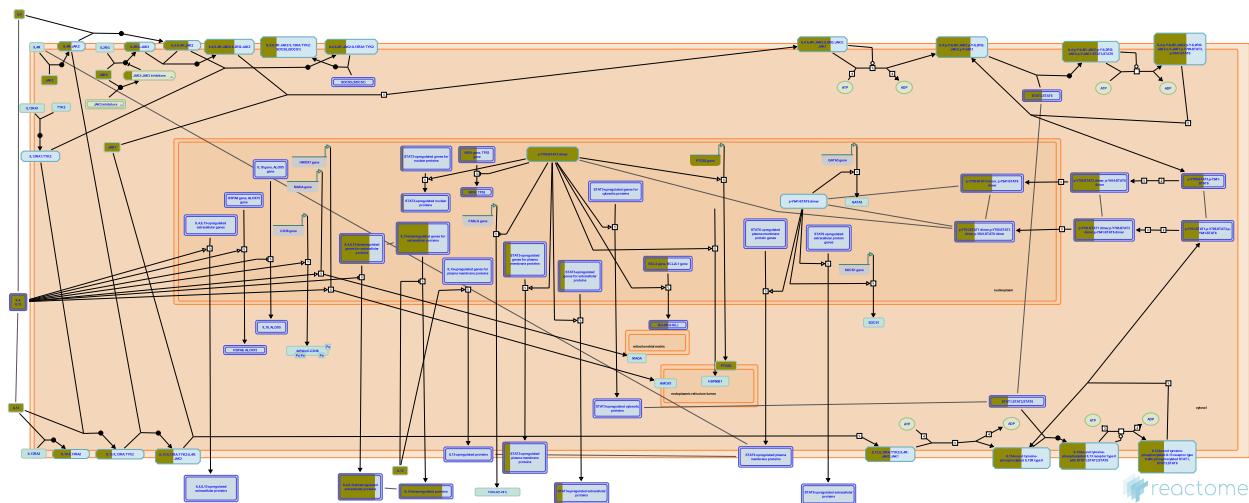
## Interactors found in the analysis (7)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BRAF	P15056	P63104	EGFR	P00533	P15498, P29353, P22681, Q13905, Q06124, P63104
IL5	P05113	Q01344, P32927	JAK1	P23458	O60674
JAK2	O60674	Q01344, O60674, P32927	STAT3	P40763	P22681
p53	P04637	P63104			

## Interleukin-4 and Interleukin-13 signaling ↗

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-6785807



Interleukin-4 (IL4) is a principal regulatory cytokine during the immune response, crucially important in allergy and asthma (Nelms et al. 1999). When resting T cells are antigen-activated and expand in response to Interleukin-2 (IL2), they can differentiate as Type 1 (Th1) or Type 2 (Th2) T helper cells. The outcome is influenced by IL4. Th2 cells secrete IL4, which both stimulates Th2 in an autocrine fashion and acts as a potent B cell growth factor to promote humoral immunity (Nelms et al. 1999).

Interleukin-13 (IL13) is an immunoregulatory cytokine secreted predominantly by activated Th2 cells. It is a key mediator in the pathogenesis of allergic inflammation. IL13 shares many functional properties with IL4, stemming from the fact that they share a common receptor subunit. IL13 receptors are expressed on human B cells, basophils, eosinophils, mast cells, endothelial cells, fibroblasts, monocytes, macrophages, respiratory epithelial cells, and smooth muscle cells, but unlike IL4, not T cells. Thus IL13 does not appear to be important in the initial differentiation of CD4 T cells into Th2 cells, rather it is important in the effector phase of allergic inflammation (Hershey et al. 2003).

IL4 and IL13 induce “alternative activation” of macrophages, inducing an anti-inflammatory phenotype by signaling through IL4R alpha in a STAT6 dependent manner. This signaling plays an important role in the Th2 response, mediating anti-parasitic effects and aiding wound healing (Gordon & Martinez 2010, Loke et al. 2002)

There are two types of IL4 receptor complex (Andrews et al. 2006). Type I IL4R (IL4R1) is predominantly expressed on the surface of hematopoietic cells and consists of IL4R and IL2RG, the common gamma chain. Type II IL4R (IL4R2) is predominantly expressed on the surface of nonhematopoietic cells, it consists of IL4R and IL13RA1 and is also the type II receptor for IL13. (Obiri et al. 1995, Aman et al. 1996, Hilton et al. 1996, Miloux et al. 1997, Zhang et al. 1997). The second receptor for IL13 consists of IL4R and Interleukin-13 receptor alpha 2 (IL13RA2), sometimes called Interleukin-13 binding protein (IL13BP). It has a high affinity receptor for IL13 ( $K_d = 250$  pmol/L) but is not sufficient to render cells responsive to IL13, even in the presence of IL4R (Donaldson et al. 1998). It is reported to exist in soluble form (Zhang et al. 1997) and when overexpressed reduces JAK-STAT signaling (Kawakami et al. 2001). Its function may be to prevent IL13 signalling via the functional IL4R:IL13RA1 receptor. IL13RA2 is overexpressed and enhances cell invasion in some human cancers (Joshi & Puri 2012).

The first step in the formation of IL4R1 (IL4:IL4R:IL2RB) is the binding of IL4 with IL4R (Hoffman et al. 1995, Shen et al. 1996, Hage et al. 1999). This is also the first step in formation of IL4R2

(IL4:IL4R:IL13RA1). After the initial binding of IL4 and IL4R, IL2RB binds (LaPorte et al. 2008), to form IL4R1. Alternatively, IL13RA1 binds, forming IL4R2. In contrast, the type II IL13 complex (IL13R2) forms with IL13 first binding to IL13RA1 followed by recruitment of IL4R (Wang et al. 2009).

Crystal structures of the IL4:IL4R:IL2RG, IL4:IL4R:IL13RA1 and IL13:IL4R:IL13RA1 complexes have been determined (LaPorte et al. 2008). Consistent with these structures, in monocytes IL4R is tyrosine phosphorylated in response to both IL4 and IL13 (Roy et al. 2002, Gordon & Martinez 2010) while IL13RA1 phosphorylation is induced only by IL13 (Roy et al. 2002, LaPorte et al. 2008) and IL2RG phosphorylation is induced only by IL4 (Roy et al. 2002).

Both IL4 receptor complexes signal through Jak/STAT cascades. IL4R is constitutively-associated with JAK2 (Roy et al. 2002) and associates with JAK1 following binding of IL4 (Yin et al. 1994) or IL13 (Roy et al. 2002). IL2RG constitutively associates with JAK3 (Boussiotis et al. 1994, Russell et al. 1994). IL13RA1 constitutively associates with TYK2 (Umeshita-Suyama et al. 2000, Roy et al. 2002, LaPorte et al. 2008, Bhattacharjee et al. 2013).

IL4 binding to IL4R1 leads to phosphorylation of JAK1 (but not JAK2) and STAT6 activation (Takeda et al. 1994, Ratthe et al. 2007, Bhattacharjee et al. 2013).

IL13 binding increases activating tyrosine-99 phosphorylation of IL13RA1 but not that of IL2RG. IL4 binding to IL2RG leads to its tyrosine phosphorylation (Roy et al. 2002). IL13 binding to IL4R2 leads to TYK2 and JAK2 (but not JAK1) phosphorylation (Roy & Cathcart 1998, Roy et al. 2002).

Phosphorylated TYK2 binds and phosphorylates STAT6 and possibly STAT1 (Bhattacharjee et al. 2013).

A second mechanism of signal transduction activated by IL4 and IL13 leads to the insulin receptor substrate (IRS) family (Kelly-Welch et al. 2003). IL4R1 associates with insulin receptor substrate 2 and activates the PI3K/Akt and Ras/MEK/Erk pathways involved in cell proliferation, survival and translational control. IL4R2 does not associate with insulin receptor substrate 2 and consequently the PI3K/Akt and Ras/MEK/Erk pathways are not activated (Busch-Dienstfertig & González-Rodríguez 2013).

## Literature references

Ryan, JJ., Nelms, K., Paul, WE., Zamorano, J., Keegan, AD. (1999). The IL-4 receptor: signaling mechanisms and biologic functions. *Annu. Rev. Immunol.*, 17, 701-38. [↗](#)

Hershey, GK. (2003). IL-13 receptors and signaling pathways: an evolving web. *J. Allergy Clin. Immunol.*, 111, 677-90; quiz 691. [↗](#)

## Editions

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

## 18 submitted entities found in this pathway, mapping to 31 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
BCL2	P10415	IL10	P22301	IL12B	P29460
IL13	P35225	IL17	Q16552	IL1B	P01583, P01584
IL4	P05112	IL6	P05231	IL8	P10145
JAK1	P23458	JAK2	O60674	JAK3	P52333
MUC1	P15941	Myc	P01106	PTGS2	P35354
STAT3	P40763	TNF	P01375	p53	P04637

Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
BCL2	ENSG00000171791	IL10	ENSG00000136634	IL12B	ENSG00000113302
IL17	ENSG00000112115	IL1B	ENSG00000125538	IL6	ENSG00000136244
IL8	ENSG00000169429	MUC1	ENSG00000185499	Myc	ENSG00000136997
PTGS2	ENSG00000073756	TNF	ENSG00000232810	p53	ENSG00000141510

### Interactors found in the analysis (7)

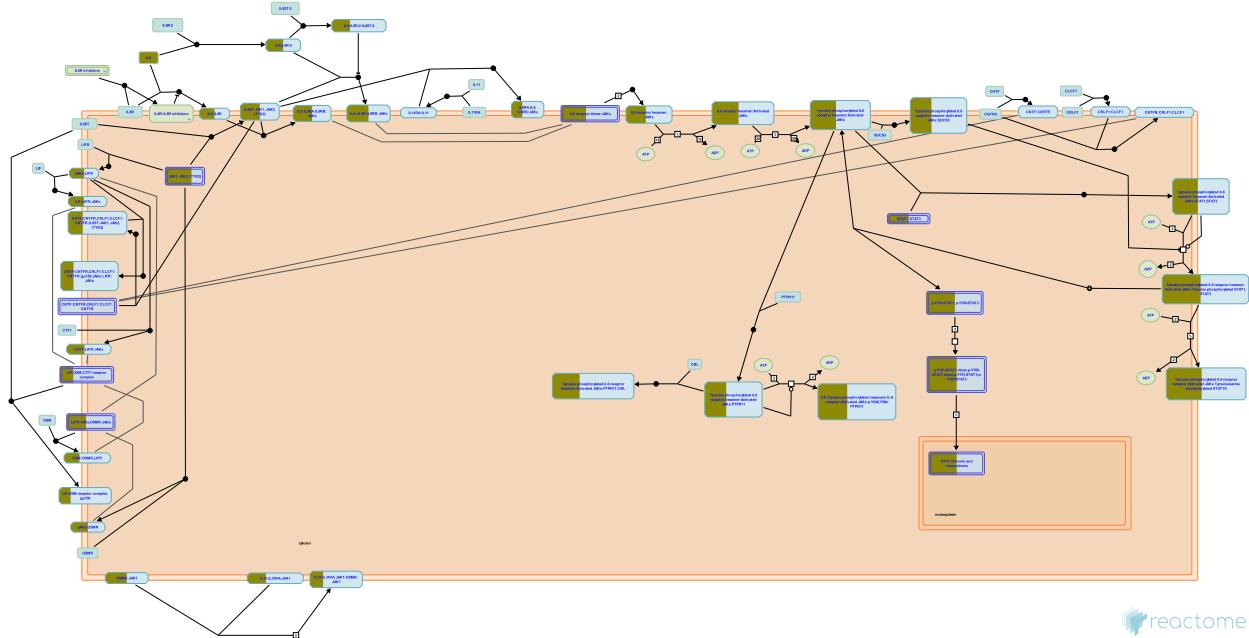
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P14625	IL13	P35225	P78552, Q14627
IL4	P05112	P24394, P78552, P31785	JAK1	P23458	O60674
JAK2	O60674	O60674, P23458	Myc	EBI-1265559	P23771
STAT3	P40763	P23458			

## Interleukin-6 family signaling ↗

**Location:** Signaling by Interleukins

**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 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 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 & Bakhet 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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Garbers, C., Lokau, J., Aparicio-Siegmund, S., Nitz, R., Scheller, J. (2015). Modular organization of Interleukin-6 and Interleukin-11  $\alpha$ -receptors. *Biochimie*, 119, 175-82. [↗](#)

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Kishimoto, T., Taga, T. (1997). Gp130 and the interleukin-6 family of cytokines. *Annu. Rev. Immunol.*, 15, 797-819. [↗](#)

## Editions

2015-06-16	Authored, Edited	Garapati, P V.
2015-11-09	Reviewed	Narazaki, M., Tanaka, M.

## 4 submitted entities found in this pathway, mapping to 4 Reactome entities

Input	UniProt Id	Input	UniProt Id
IL6	P05231	JAK1	P23458
JAK2	O60674	STAT3	P40763

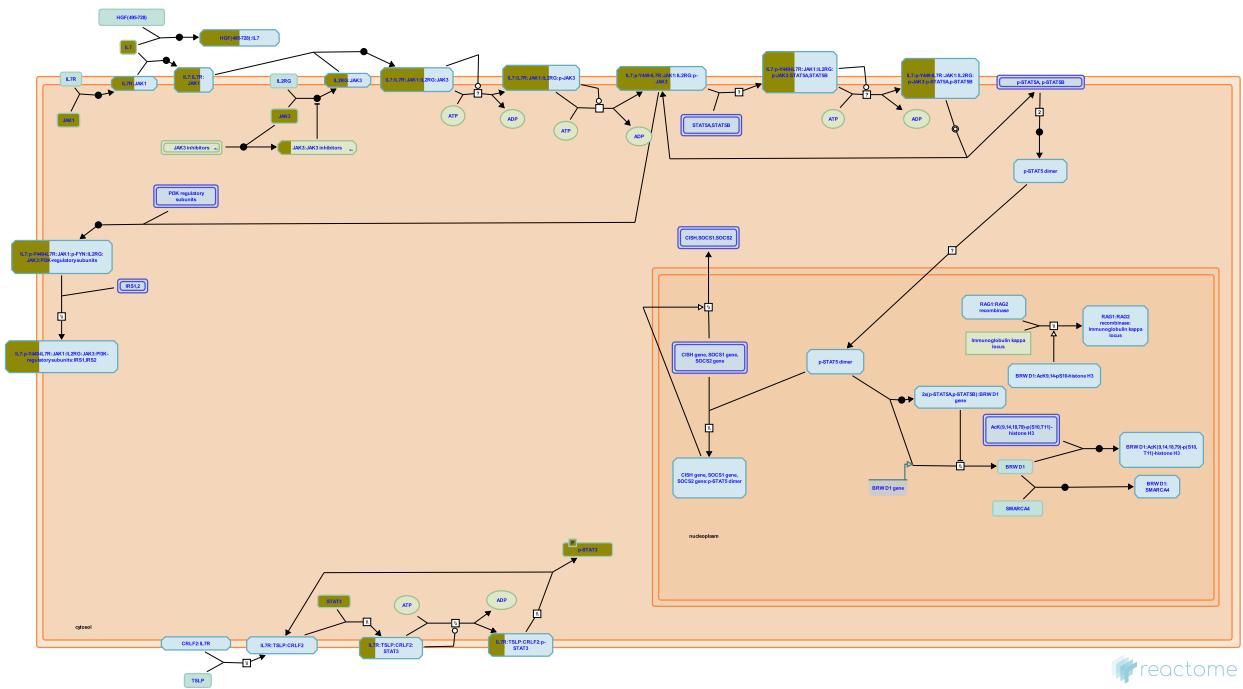
## Interactors found in the analysis (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P22681, Q06124, O14543	IL6	P05231	P40189, P08887
STAT3	P42227, P40763	P40189, P22681			

## Interleukin-7 signaling ↗

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-1266695



Interleukin-7 (IL7) is produced primarily by T zone fibroblastic reticular cells found in lymphoid organs, and also expressed by non-hematopoietic stromal cells present in other tissues including the skin, intestine and liver. It is an essential survival factor for lymphocytes, playing a key anti-apoptotic role in T-cell development, as well as mediating peripheral T-cell maintenance and proliferation. This dual function is reflected in a dose-response relationship that distinguishes the survival function from the proliferative activity; low doses of IL7 (<1 ng/ml) sustain only survival, higher doses (>1 ng/ml) promote survival and cell cycling (Kittipatarin et al. 2006, Swainson et al. 2007).

The IL7 receptor is a heterodimeric complex of the common cytokine-receptor gamma chain (IL2RG, CD132, or Gc) and the IL7-receptor alpha chain (IL7R, IL7RA, CD127). Both chains are members of the type 1 cytokine family. Neither chain is unique to the IL7 receptor as IL7R is utilized by the receptor for thymic stromal lymphopoitin (TSLP) while IL2RG is shared with the receptors for IL2, IL4, IL9, IL15 and IL21. IL2RG consists of a single transmembrane region and a 240aa extracellular region that includes a fibronectin type III (FNIII) domain thought to be involved in receptor complex formation. It is expressed on most lymphocyte populations. Null mutations of IL2RG in humans cause X-linked severe combined immunodeficiency (X-SCID), which has a phenotype of severely reduced T-cell and natural killer (NK) cell populations, but normal numbers of B cells. In addition to reduced T- and NK-cell numbers, Il2rg knockout mice also have dramatically reduced B-cell populations suggesting that Il2rg is more critical for B-cell development in mice than in humans. Patients with severe combined immunodeficiency (SCID) phenotype due to IL7R mutations (see Puel & Leonard 2000), or a partial deficiency of IL7R (Roifman et al. 2000) have markedly reduced circulating T cells, but normal levels of peripheral blood B cells and NK cells, similar to the phenotype of IL2RG mutations, highlighting a requirement for IL7 in T cell lymphopoiesis. It has been suggested that IL7 is essential for murine, but not human B cell development, but recent studies indicate that IL7 is essential for human B cell production from adult bone marrow and that IL7-induced expansion of the progenitor B cell compartment is increasingly critical for human B cell production during later stages of development (Parrish et al. 2009).

IL7 has been shown to induce rapid and dose-dependent tyrosine phosphorylation of JAKs 1 and 3, and concomitantly tyrosine phosphorylation and DNA-binding activity of STAT5a/b (Foxwell et al. 1995). IL7R was shown to directly induce the activation of JAKs and STATs by van der Plas et al. (1996). Jak1 and Jak3 knockout mice displayed severely impaired thymic development, further supporting their importance in IL7 signaling (Rodig et al. 1998, Nosaka et al. 1995).

The role of STAT5 in IL7 signaling has been studied largely in mouse models. Tyr449 in the cytoplasmic domain of IL7RA is required for T-cell development in vivo and activation of JAK/STAT5 and PI3k/Akt pathways (Jiang et al. 2004, Pallard et al. 1999). T-cells from an IL7R Y449F knock-in mouse did not activate STAT5 (Osbourne et al. 2007), indicating that IL7 regulates STAT5 activity via this key tyrosine residue. STAT5 seems to enhance proliferation of multiple cell lineages in mouse models but it remains unclear whether STAT5 is required solely for survival signaling or also for the induction of proliferative activity (Kittipatarin & Khaled, 2007).

The model for IL7 receptor signaling is believed to resemble that of other Gc family cytokines, based on detailed studies of the IL2 receptor, where IL2RB binds constitutively to JAK1 while JAK3 is pre-associated uniquely with the IL2RG chain. Extending this model to IL7 suggests a similar series of events: IL7R constitutively associated with JAK1 binds IL7, the resulting trimer recruits IL2RG:JAK3, bringing JAK1 and JAK3 into proximity. The association of both chains of the IL7 receptor orients the cytoplasmic domains of the receptor chains so that their associated kinases (Janus and phosphatidylinositol 3-kinases) can phosphorylate sequence elements on the cytoplasmic domains (Jiang et al. 2005). JAKs have low intrinsic enzymatic activity, but after mutual phosphorylation acquire much higher activity, leading to phosphorylation of the critical Y449 site on IL7R. This site binds STAT5 and possibly other signaling adapters, they in turn become phosphorylated by JAK1 and/or JAK3. Phosphorylated STATs translocate to the nucleus and trigger the transcriptional events of their target genes.

The role of the PI3K/AKT pathway in IL7 signaling is controversial. It is a potential T-cell survival pathway because in many cell types PI3K signaling regulates diverse cellular functions such as cell cycle progression, transcription, and metabolism. The ERK/MAPK pathway does not appear to be involved in IL7 signaling (Crawley et al. 1996).

It is not clear how IL7 influences cell proliferation. In the absence of a proliferative signal such as IL7 or IL3, dependent lymphocytes arrest in the G0/G1 phase of the cell cycle. To exit this phase, cells typically activate specific G1 Cyclin-dependent kinases/cyclins and down regulate cell cycle inhibitors such as Cyclin-dependent kinase inhibitor 1B (Cdkn1b or p27kip1). There is indirect evidence suggesting a possible role for IL7 stimulated activation of PI3K/AKT signaling, obtained from transformed cell lines and thymocytes, but not confirmed by observations using primary T-cells (Kittipatarin & Khaled, 2007). IL7 withdrawal results in G1/S cell cycle arrest and is correlated with loss of cdk2 activity (Geiselhart et al. 2001), both events which are known to be regulated by the dephosphorylating activity of Cdc25A. Expression of a p38 MAPK-resistant Cdc25A mutant in an IL-7-dependent T-cell line as well as in peripheral, primary T-cells was sufficient to sustain cell survival and promote cell cycling for several days in the absence of IL7 (Khaled et al. 2005). Cdkn1b is a member of the CIP/KIP family of cyclin-dependent cell cycle inhibitors (CKIs) that negatively regulates the G1/S transition. In IL7 dependent T-cells, the expression of Cdkn1b was sufficient to cause G1 arrest in the presence of IL7. Withdrawal of IL7 induced the upregulation of Cdkn1b and arrested cells in G1 while siRNA knockout of Cdkn1b enhanced cell cycle progression. However, adoptive transfer of Cdkn1b-deficient lymphocytes into IL7 deficient mice indicated that loss of Cdkn1b could only partially compensate for the IL7 signal needed by T-cells to expand in a lymphopenic environment (Li et al. 2006), so though Cdkn1b may be involved in negative regulation of the cell cycle through an effect on cdk2 activity, its absence is not sufficient to fully induce cell cycling under lymphopenic conditions.

## Editions

2010-05-17	Authored	Ray, KP.
2011-05-06	Edited	Jupe, S.
2011-11-03	Reviewed	Puck, J.
2016-03-23	Edited	Orlic-Milacic, M.
2016-05-11	Revised	Mandal, M.
2017-07-26	Reviewed	Kumar, U.
2017-08-21	Reviewed	Goronzy, JJ.

## 5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL7	P13232	JAK1	P23458	JAK3	P52333
STAT	P40763	STAT3	P40763		

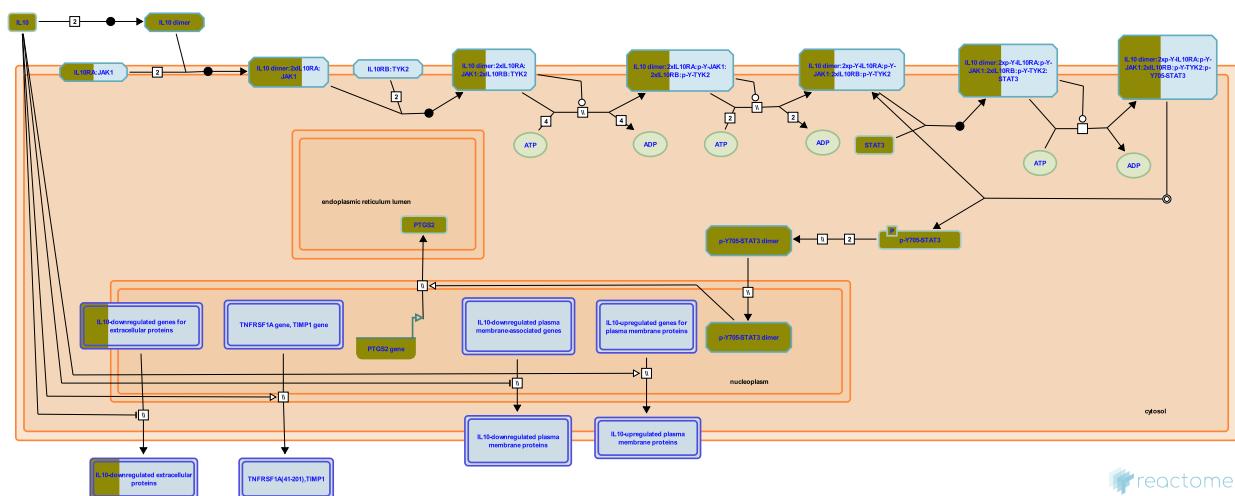
## Interactors found in the analysis (8)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P40763	IL4	P05112	P31785
IL7	P13232	P16871	JAK1	P23458	P40763
JAK2	O60674	P23458	Myc	EBI-1265559	P40763
STAT	EBI-10952519	P40763	STAT3	EBI-9914958, P40763	P23458, P40763

## Interleukin-10 signaling ↗

## **Location:** Signaling by Interleukins

**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 con-

stitutively 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.

## 9 submitted entities found in this pathway, mapping to 16 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL10	P22301	IL12B	P29460	IL1B	P01583, P01584
IL6	P05231	IL8	P10145	JAK1	P23458
PTGS2	P35354	STAT3	P40763	TNF	P01375
Input	Ensembl Id	Input	Ensembl Id	Input	Ensembl Id
IL12B	ENSG00000113302	IL1B	ENSG00000125538	IL6	ENSG00000136244
IL8	ENSG00000169429	PTGS2	ENSG00000073756	TNF	ENSG00000232810

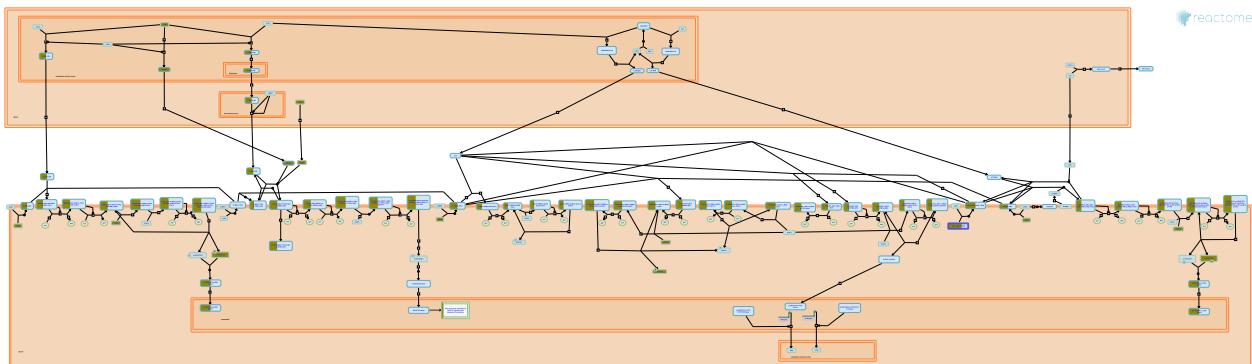
## Interactors found in the analysis (5)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P40763	JAK1	P23458	P40763
Myc	EBI-1265559	P40763	STAT	EBI-10952519	P40763
STAT3	EBI-9914958, P40763	P40763			

## Interleukin-12 family signaling [↗](#)

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-447115



Interleukin-12 (IL-12) is a heterodimer of interleukin-12 subunit alpha (IL12A, IL-12p35) and interleukin-12 subunit beta (IL12B, IL-12p40). It is a potent immunoregulatory cytokine involved in the generation of cell mediated immunity to intracellular pathogens. It is produced by antigen presenting cells, including dendritic cells, macrophages/monocytes, neutrophils and some B cells (D'Andrea et al. 1992, Kobayashi et al. 1989, Heufler et al. 1996). It enhances the cytotoxic activity of natural killer (NK) cells and cytotoxic T cells, stimulating proliferation of activated NK and T cells and induces production of interferon gamma (IFN gamma) by these cells (Stern et al. 1990). IL-12 also plays an important role in immunomodulation by promoting cell mediated immunity through induction of a class 1 T helper cell (Th1) immune response. IL-12 may contribute to immunopathological conditions such as rheumatoid arthritis (McIntyre et al. 1996).

The receptor for IL-12 is a heterodimer of IL-12Rbeta1 (IL12RB1) and IL-12Rbeta2 (IL12RB2), both highly homologous to Interleukin-6 receptor subunit beta (IL6ST, gp130). Each has an extracellular ligand binding domain, a transmembrane domain and a cytosolic domain containing box 1 and box 2 sequences that mediate binding of Janus family tyrosine kinases (JAKs). IL-12 binding is believed to bring about the heterodimerization and generation of a high affinity receptor complex capable of signal transduction. In this model, receptor dimerization leads to juxtaposition of the cytosolic domains and subsequent tyrosine phosphorylation and activation of JAK2 and TYK2. These activated kinases, in turn, tyrosine phosphorylate and activate several members of the signal transducer and activator of transcription (STAT) family, mainly STAT4, while also STAT1, STAT3 and STAT5 have been reported to be activated (Bacon et al. 1995, Jacobson et al. 1995, Yu et al. 1996, Gollob et al. 1995). The STATs translocate to the nucleus to activate transcription of several genes, including IFN gamma. The production of IFN gamma has a pleiotropic effect in the cell, stimulating production of molecules important to cell mediated immunity. In particular, IFN gamma stimulates production of more IL-12 and sets up a positive regulation loop between IL-12 signaling and IFN gamma (Chan et al. 1991). The importance of IL-12 for this loop is demonstrated by IL-12 and STAT4 knockout mice that are severely compromised in IFN-gamma production (Kaplan et al. 1996; Magram et al. 1996), as well as by patients with IL12B mutations that are severely compromised in IFN-gamma production (Altare et al. 1998).

### Literature references

Aste, M., Chehimi, J., Rengaraju, M., Kubin, M., Chan, SH., Valiante, NM. et al. (1992). Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. *J Exp Med*, 176, 1387-98. [↗](#)

Behzadi, E., Ranjbar, R., Behzadi, P. (2016). IL-12 Family Cytokines: General Characteristics, Pathogenic Microorganisms, Receptors, and Signalling Pathways. *Acta Microbiol Immunol Hung*, 63, 1-25. [↗](#)

Nair, L., He, C., Yeung, J., Egwuagu, CE., Sun, L. (2015). Interleukin 12 (IL-12) family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease. *Cytokine*, 75, 249-55. [↗](#)

## Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.

**7 submitted entities found in this pathway, mapping to 9 Reactome entities**

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IFNG	P01579	IL10	P22301	IL12B	P29460
JAK1	P23458	JAK2	O60674	STAT	P40763
STAT3	P40763				
Input	Ensembl Id		Input	Ensembl Id	
IFNG	ENSG00000111537		IL10	ENSG00000136634	

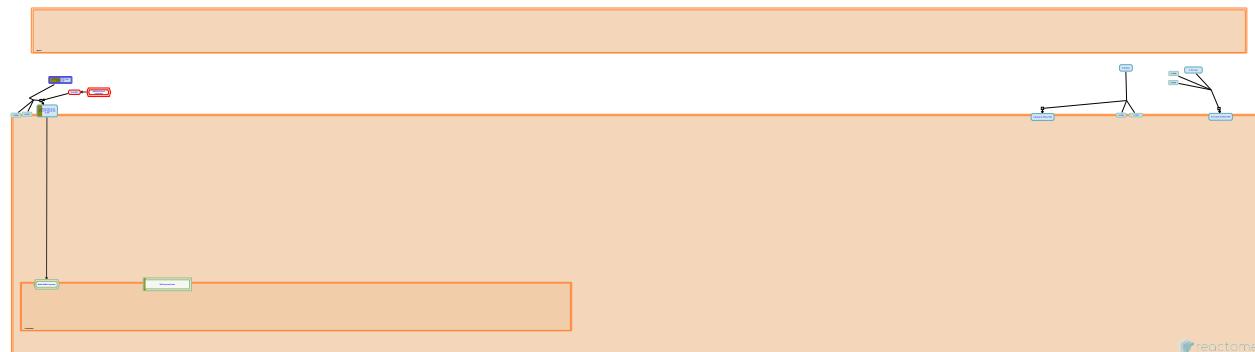
**Interactors found in the analysis (12)**

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
BCL2	P10415	P00441	BRAF	P15056	P38646
EGFR	P00533	P42224, O00170, P14174, P23528, P07355, P40763, P38646	IL12B	P29460	P29460, Q9NPF7, P29459
IL6	P05231	P40189	JAK1	P23458	P42224, O60674, P40763
JAK2	O60674, Q62120	Q5VWK5, O60674, P23458	JAK3	P52333	P17987
Myc	EBI-1265559	P40763	STAT	P35610, EBI-10097350, EBI-10952519	Q14765, P42224, P27824, P40763
STAT3	EBI-9914958, P42227, P40763	P42224, P40189, P23458, P40763	p53	P04637	P17987, P38646

## Interleukin-17 signaling [↗](#)

**Location:** [Signaling by Interleukins](#)

**Stable identifier:** R-HSA-448424



Interleukin-17 (IL17) is a family of cytokines (Kawaguchi et al. 2004, Gu et al. 2013). IL17A, the founding member of the family is able to induce the production of other cytokines and chemokines, such as IL6, IL8, and granulocyte colony-stimulating factor (G-CSF) in a variety of cell types, including activated T-cells. It plays a pivotal role in host defenses in response to microbial infection and is involved in the pathogenesis of autoimmune diseases and allergic syndromes. IL17 activates several downstream signaling pathways including NFkB, MAPKs and C/EBPs, inducing the expression of antibacterial peptides, proinflammatory chemokines and cytokines and matrix metalloproteases (MMPs). IL17 can stabilize the mRNA of genes induced by TNF-alpha. IL17 signal transduction is mediated by the cytosolic adaptor molecule ACT1 (also known as CIKS).

The receptor for IL17D is unknown (Gu et al. 2013).

### Literature references

Li, X., Gu, C., Wu, L. (2013). IL-17 family: cytokines, receptors and signaling. *Cytokine*, 64, 477-85. [↗](#)

### Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.

### 3 submitted entities found in this pathway, mapping to 3 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
IL17	Q16552	MAPK	P28482	NFKB1	P19838

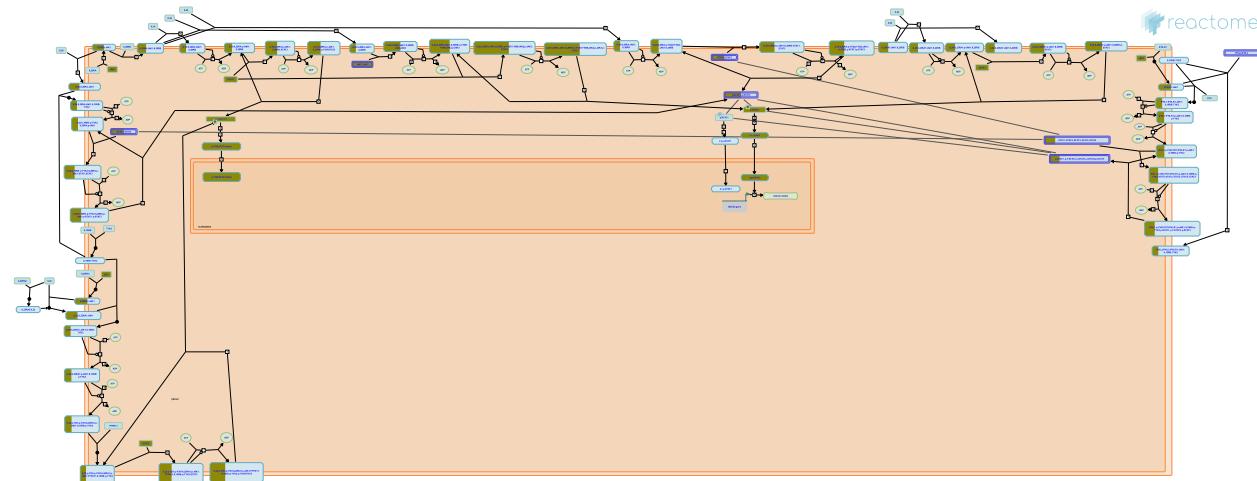
### Interactors found in the analysis (3)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
NFKB1	P19838, P19838-1	P41279, P19838, Q8NFZ5	PIK3CA	P42336	P01100
STAT3	P40763	P49137			

## Interleukin-20 family signaling [↗](#)

**Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-8854691



The interleukin 20 (IL20) subfamily comprises IL19, IL20, IL22, IL24 and IL26. They are members of the larger IL10 family, but have been grouped together based on their usage of common receptor subunits and similarities in their target cell profiles and biological functions. Members of the IL20 subfamily facilitate the communication between leukocytes and epithelial cells, thereby enhancing innate defence mechanisms and tissue repair processes at epithelial surfaces. Much of the understanding of this group of cytokines is based on IL22, which is the most studied member (Rutz et al. 2014, Akdis M et al. 2016, Longsdon et al. 2012).

### Literature references

Logsdon, NJ., Rajashankar, KR., Harris, BD., Deshpande, A., Walter, MR. (2012). Structural basis for receptor sharing and activation by interleukin-20 receptor-2 (IL-20R2) binding cytokines. *Proc. Natl. Acad. Sci. U.S.A.*, 109, 12704-9. [↗](#)

Komlosi, Z., Kucuksezer, UC., Frei, R., Huitema, C., Garbani, M., Pezer, M. et al. (2016). Interleukins (from IL-1 to IL-38), interferons, transforming growth factor  $\beta$ , and TNF- $\alpha$ : Receptors, functions, and roles in diseases. *J. Allergy Clin. Immunol.*, 138, 984-1010. [↗](#)

Wang, X., Rutz, S., Ouyang, W. (2014). The IL-20 subfamily of cytokines--from host defence to tissue homeostasis. *Nat. Rev. Immunol.*, 14, 783-95. [↗](#)

### Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.
2017-11-15	Reviewed	Datta, SK.

### 5 submitted entities found in this pathway, mapping to 5 Reactome entities

Input	UniProt Id	Input	UniProt Id	Input	UniProt Id
JAK1	P23458	JAK2	O60674	JAK3	P52333
STAT	P40763	STAT3	P40763		

### Interactors found in the analysis (8)

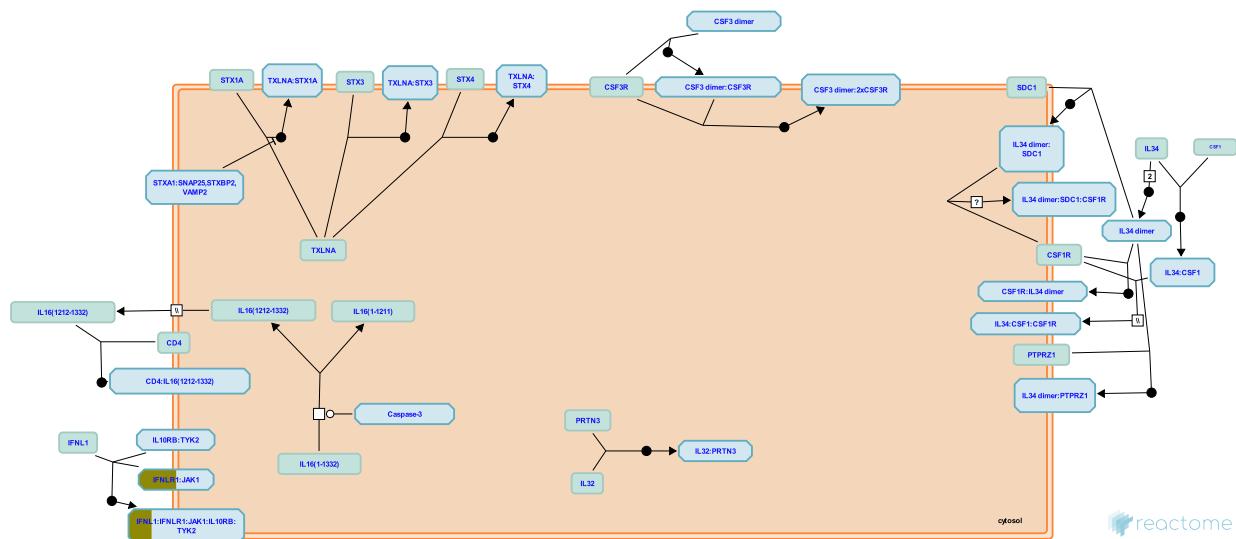
Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
EGFR	P00533	P42224, Q06124, P40763	IL10	P22301	Q08334

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
JAK1	P23458	P42224, P40763	JAK2	O60674	P23458
Myc	EBI-1265559	P40763	PARP1	P09874	Q13007
STAT	EBI-10097350, EBI-10952519	P42224, P40763	STAT3	EBI-9914958, P40763	P42224, P23458, P40763

## Other interleukin signaling ↗

## **Location:** Signaling by Interleukins

**Stable identifier:** R-HSA-449836



Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

## Literature references

Meyer, N., Akdis, M., Zimmermann, M., Ouaked, N., O'Mahony, L., Quaked, N. et al. (2011). Interleukins, from 1 to 37, and interferon- $\gamma$ : receptors, functions, and roles in diseases. *J. Allergy Clin. Immunol.*, 127, 701-21.e1-70. [\[CrossRef\]](#)

## Editions

2014-06-04	Authored	Jupe, S.
2016-01-28	Edited	Jupe, S.
2016-01-28	Reviewed	Meldal, BH.

**1 submitted entities found in this pathway, mapping to 1 Reactome entities**

Input	UniProt Id
JAK1	P23458

## Interactors found in the analysis (2)

Input	UniProt Id	Interacts with	Input	UniProt Id	Interacts with
STAT3	P40763	Q99062	TNF	P01375	Q16623

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