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


Reactome database release: 69

This document contains 5 pathways (see Table of Contents)
Interleukin-12 family signaling

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


## Editions

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Interleukin 12 (IL-12) is heterodimeric cytokine produced by dendritic cells, macrophages and neutrophils. It is encoded by the genes Interleukin-12 subunit alpha (IL12A) and Interleukin-12 subunit beta (IL12B), which encode a 35-kDa light chain (p35) and a 40-kDa heavy chain (p40), respectively. The active IL12 heterodimer is sometimes referred to as p70. The p35 component has homology to single-chain cytokines, while p40 is homologous to the extracellular domains of members of the haematopoietic cytokine-receptor family. The IL12 heterodimer therefore resembles a cytokine linked to a soluble receptor.

IL12 is involved in the differentiation of naive T cells into Th1 cells and sometimes known as T cell-stimulating factor. IL12 enhances the cytotoxic activity of Natural Killer cells and CD8+ cytotoxic T lymphocytes. IL12 also has anti-angiogenic activity, mediated by increased production of CXCL10 via interferon gamma.

The IL12 receptor is a heterodimer formed by Interleukin-12 receptor subunit beta-1 (IL12RB1) and Interleukin-12 receptor subunit beta-2 (IL12RB2), both of which have extensive homology to IL6ST (gp130), the signal transducing receptor subunit of the IL6-like cytokine superfamily. IL-12RB2 is considered to play the key role in IL12 function, in part because its expression on activated T cells is stimulated by cytokines that promote Th1 cell development and inhibited by those that promote Th2 cells development. In addition, IL12 binding leads to IL12RB2 tyrosine phosphorylation, which provides binding sites for the kinases Non-receptor tyrosine-protein kinase TYK2 and Tyrosine-protein kinase JAK2. These activate transcription factor proteins in the Signal transducer and activator of transcription (STAT) family, particularly STAT4.

Literature references

Interleukin-23 signaling

Location: Interleukin-12 family signaling

Stable identifier: R-HSA-9020933

Interleukin-23 (IL23) is a heterodimer of Interleukin-12 subunit beta (IL12B, IL-12p40), which is shared with IL12, and Interleukin-23 subunit alpha IL23A (IL-23p19) subunit. The functional receptor for IL23 consists of Interleukin-12 receptor subunit beta-1 (IL12RB1), which is shared with the IL12 receptor, and Interleukin-23 receptor (IL23R). IL23R is mainly expressed on activated memory T cells, Natural Killer cells, monocytes/macrophage and at low levels on dendritic cells (DCs). IL23 is mainly secreted by activated macrophages and DCs in peripheral tissues such as skin, intestinal mucosa and lung.

IL23 is proinflammatory and implicated in several autoimmune inflammatory disorders such as colitis, gastritis, psoriasis and arthritis. It is similar to IL-12 both in structure and its ability to memory T cells to increase interferon-γ (IFN-γ) production and proliferation, the ability of IL-23 to induce IL-17.

IL23 activates the Janus kinases JAK2 and TYK2, resulting in phosphorylation of the receptor complex, which forms the docking sites for Signal transducer and activator of transcription 3 (STAT3) and STAT4 to bind and become phosphorylated.

Literature references


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https://reactome.org
Interleukin-27 signaling

Location: Interleukin-12 family signaling

Stable identifier: R-HSA-9020956

Interleukin-27 (IL27) is a heterodimeric cytokine that contains Epstein-Barr virus–induced gene 3 (EBI3) and IL27p28 (IL27). It signals through a receptor composed of Interleukin-6 receptor subunit beta (IL6ST, gp130), which is utilized by many cytokines, and Interleukin-27 receptor subunit alpha (IL27RA, WSX-1, TCCR) (Yoshida & Hunter 2015).

Literature references


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Interleukin-35 Signalling

**Location:** Interleukin-12 family signaling

**Stable identifier:** R-HSA-8984722

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

**Literature references**


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