**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**


Reactome database release: 68

This document contains 1 pathway and 5 reactions (see Table of Contents)
Interleukin-21 (IL21) is a pleiotropic cytokine with four alpha-helical bundles. It is produced primarily by natural killer T cells, T follicular helper cells and TH17 cells, with lower levels of production by numerous other populations of lymphohaematopoietic cells (Spolski & Leonard 2014). IL21 binds Interleukin-21 receptor (IL21R, NILR) and Cytokine receptor common subunit gamma (IL2RG, GammaC).

IL21R has significant homology with the class I cytokine receptors Interleukin-2 receptor subunit beta (IL2RB) and Interleukin-4 receptor subunit alpha (IL4R) and was predicted to similarly form a complex with IL2RG. IL21R dimers can weakly bind and signal in response to IL21 but IL21 generates a much stronger response when IL21R is combined with IL2RG, which is required for a fully signaling capable IL21 receptor complex (Ozaki et al. 2000, Asao et al. 2001, Habib et al. 2002). IL21R can bind Janus kinase 1 (JAK1) (Ozaki et al. 2000) but IL2RG is required for IL21 induced signaling (Asao et al. 2001). The hetero-meric IL21 receptor complex can activate JAK1, JAK3, Signal transducer and activator of transcription 1 (STAT1), STAT3, STAT4 and STAT5, depending on the cell type. In cultured T-cells IL21 induced phosphorylation of JAK1, JAK3, STAT1, STAT3 and weakly STAT5 (Asao et al. 2001). In primary CD4+ T cells IL21 induced the phosphorylation of STAT1 and STAT3 but not STAT5, whereas IL2 induced the phosphorylation of STAT5 and STAT1 but not STAT3 (Bennet et al. 2003). IL21 stimulation of primary splenic B cells and the pro-B-cell line Ba-F3 induced the activation of JAK1, JAK3 and STAT5 (Habib et al. 2002). In primary human NK cells or the NK cell line NK-92, IL21 induced the activation of STAT1, STAT3, and STAT4 but not STAT5 (Strengell et al. 2002, 2003). IL21 activated STAT1 and STAT3 in human monocyte-derived macrophages (Vallières & Girard 2017).

Literature references
## Editions

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IL21 binds IL21R::JAK1

Location: Interleukin-21 signaling

Stable identifier: R-HSA-9005980

Type: omitted

Compartments: extracellular region, plasma membrane

Interleukin-21 (IL21) is a pleiotropic cytokine with four alpha-helical bundles. It is produced primarily by natural killer T cells, T follicular helper cells and TH17 cells, with lower levels of production by numerous other populations of lymphohaematopoietic cells (Spolski & Leonard 2014). IL21 binds Interleukin-21 receptor (IL21R, NILR) and Cytokine receptor common subunit gamma (IL2RG, GammaC).

IL21R has significant homology with the class I cytokine receptors Interleukin-2 receptor subunit beta (IL2RB) and Interleukin-4 receptor subunit alpha (IL4R) and was predicted to similarly form a complex with IL2RG. IL21R dimers can weakly bind and signal in response to IL21 but IL21 generates a much stronger response when IL21R is combined with IL2RG, which is required for a fully signaling capable IL21 receptor complex (Ozaki et al. 2000, Asao et al. 2001, Habib et al. 2002). IL21R can bind Janus kinase 1 (JAK1) (Ozaki et al. 2000) but IL2RG is required for IL21 induced signaling (Asao et al. 2001). The heteromeric IL21 receptor complex can activate JAK1, JAK3, Signal transducer and activator of transcription 1 (STAT1), STAT3, STAT4 and STAT5, depending on the cell type. In cultured T-cells IL21 induced phosphorylation of JAK1, JAK3, STAT1, STAT3 and weakly STAT5 (Asao et al. 2001). In primary CD4+ T cells IL21 induced the phosphorylation of STAT1 and STAT3 but not STAT5, whereas IL2 induced the phosphorylation of STAT5 and STAT1 but not STAT3 (Bennet et al. 2003). IL21 stimulation of primary splenic B cells and the pro-B-cell line Ba-F3 induced the activation of JAK1, JAK3 and STAT5 (Habib et al. 2002). In primary human NK cells or the NK cell line NK-92, IL21 induced the activation of STAT1, STAT3, and STAT4 but not STAT5 (Strengell et al. 2002, 2003). IL21 activated STAT1 and STAT3 in human monocyte-derived macrophages (Vallières & Girard 2017).

This is a black-box event because the pre-association of IL21R with JAK1 is inferred from the constitutive association of JAKs with other interleukin receptor subunits such as IL2R.

Followed by: IL21::IL21R::JAK1 binds IL2RG::JAK3

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IL21:IL21R:JAK1 binds IL2RG:JAK3

**Location:** Interleukin-21 signaling

**Stable identifier:** R-HSA-9006844

**Type:** omitted

**Compartments:** cytosol, extracellular region, plasma membrane

Interleukin-21 receptor (IL21R, NILR) can bind Janus kinase 1 (JAK1) (Ozaki et al. 2000) but little or no signaling occurs (Asao et al. 2001) unless IL21R is combined with IL2RG, which is required for a fully signaling capable IL21 receptor complex (Ozaki et al. 2000, Asao et al. 2001, Habib et al. 2002). The heteromeric IL21 receptor complex can activate JAK1 and JAK3.

This is a black box event because the pre-association of IL21R with JAK1 and of IL2RG with JAK3 is inferred from the mechanism of IL2 signaling.

**Preceded by:** IL21 binds IL21R:JAK1

**Followed by:** IL21 receptor JAK phosphorylation

**Literature references**


Habib, T., Senadheera, S., Weinberg, K., Kaushansky, K. (2002). The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. *Biochemistry, 41*, 8725-31.

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IL21 receptor JAK phosphorylation

Location: Interleukin-21 signaling

Stable identifier: R-HSA-9006850

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane

The IL21 heteromeric receptor complex can activate JAK1 and JAK3 in response to Interleukin-21 (IL21), leading to JAK tyrosine phosphorylation (Asao et al. 2001, Habib et al. 2002).

This is a black box event because the mechanism leading to JAK phosphorylation is not established for this receptor complex.

Preceded by: IL21:IL21R:JAK1 binds IL2RG:JAK3

Followed by: IL21 receptor STAT binding

Literature references


Habib, T., Senadheera, S., Weinberg, K., Kaushansky, K. (2002). The common gamma chain (gamma c) is a required signaling component of the IL-21 receptor and supports IL-21-induced cell proliferation via JAK3. Biochemistry, 41, 8725-31.

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https://reactome.org
**IL21 receptor STAT binding**

**Location:** Interleukin-21 signaling

**Stable identifier:** R-HSA-9006873

**Type:** omitted

**Compartments:** cytosol, extracellular region, plasma membrane

The IL21 receptor complex can activate Signal transducer and activator of transcription 1 (STAT1), STAT3, STAT4 and STAT5, depending on the cell type. In cultured T-cells IL21 induced phosphorylation of JAK1, JAK3, STAT1, STAT3 and weakly STAT5 (Asao et al. 2001). In primary CD4+ T cells IL21 induced the phosphorylation of STAT1 and STAT3 but not STAT5, whereas IL2 induced the phosphorylation of STAT5 and STAT1 but not STA3 (Bennet et al. 2003). IL21 stimulation of primary splenic B cells and the pro-B-cell line Ba-F3 induced the activation of JAK1, JAK3 and STAT5 (Habib et al. 2002). In primary human NK cells or the NK cell line NK-92, IL21 induced the activation of STAT1, STAT3, and STAT4 but not STAT5 (Strengell et al. 2002, 2003). IL21 activated STAT1 and STAT3 in human monocyte-derived macrophages (Vallières & Girard 2016).

This is a black-box event because STAT phosphorylation is assumed to involve STAT binding though this has not been demonstrated for this receptor complex. In addition the mechanism that brings about STAT binding to the receptor, which presumably involves receptor tyrosine phosphorylation, is unclear.

**Preceded by:** IL21 receptor JAK phosphorylation

**Followed by:** IL21 receptor STAT phosphorylation

**Literature references**


IL21 receptor STAT phosphorylation

Location: Interleukin-21 signaling

Stable identifier: R-HSA-9006870

Type: omitted

Compartments: cytosol, extracellular region, plasma membrane

The IL21R:IL2RG complex can activate Signal transducer and activator of transcription 1 (STAT1), STAT3, STAT4 and STAT5, depending on the cell type. In cultured T-cells IL21 induced phosphorylation of JAK1, JAK3, STAT1, STAT3 and weakly STAT5 (Asao et al. 2001). In primary CD4+ T cells IL21 induced the phosphorylation of STAT1 and STAT3 but not STAT5, whereas IL2 induced the phosphorylation of STAT5 and STAT1 but not STAT3 (Bennet et al. 2003). IL21 stimulation of primary splenic B cells and the pro-B-cell line Ba-F3 induced the activation of JAK1, JAK3 and STAT5 (Habib et al. 2002). In primary human NK cells or the NK cell line NK-92, IL21 induced the activation of STAT1, STAT3, and STAT4 but not STAT5 (Strengell et al. 2002, 2003). IL21 activated STAT1 and STAT3 in human monocyte-derived macrophages (Vallières & Girard 2016).

Preceded by: IL21 receptor STAT binding

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