Regulation of IFNG 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.

17/01/2023
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: 83

This document contains 1 pathway and 4 reactions (see Table of Contents)
At least three different classes of negative regulators exist to control the extent of IFNG stimulation and signaling. These include the feedback inhibitors belonging to protein family suppressors of cytokine signaling (SOCS), the Scr-homology 2 (SH2)-containing protein tyrosine phosphatases (SHPs), and the protein inhibitors of activated STATs (PIAS). The induction of these regulators seems to be able to stop further signal transduction by inhibiting various steps in IFNG cascade.

**Literature references**


**Editions**

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SOCS-1 and SOCS-3 binds to p-JAK2

**Location:** Regulation of IFNG signaling

**Stable identifier:** R-HSA-877269

**Type:** binding

**Compartments:** plasma membrane, cytosol

SOCS-1 and SOCS-3 coprecipitates with JAK kinases upon IFNG stimulation and are able to inhibit the JAK-STAT pathway, although with different affinity and kinetics. SOCS1 and SOCS3 binds to phosphorylated JAK1/2 and prevent the tyrosine kinase activity of JAKs through their kinase inhibitory region (KIR), thereby inhibiting downstream IFNG signaling. SOCS1 may also prevent IFNG signaling by targeting the signaling machinery to ubiquitin-proteasomal degradation pathway.

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Dephosphorylation of JAKs by PTPs

Location: Regulation of IFNG signaling

Stable identifier: R-HSA-877308

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Dephosphorylation of Jaks by Ptps (Mus musculus)

Protein tyrosine phosphatases (PTPs) SHP1 and SHP2 down regulate the IFNG signaling by dephosphorylating the tyrosine residues critical to the activation of JAK kinases. PTP1B interacts directly with JAK2 but not JAK1 and dephosphorylate the tyrosine Y1007 on JAK2.

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PIAS1 protein interacts directly with phosphorylated STAT1 dimers and inhibit the transcriptional activity of STAT1 by blocking the DNA-binding domain of STAT1. It has also been suggested that PIAS proteins might regulate transcription by promoting small ubiquitin-related modifier (SUMO1) conjugation of STAT1. The significance of STAT1 sumoylation in regulating STAT1 activity is controversial and needs to be clarified.

**Literature references**


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Dephosphorylation of p-STAT1 dimer by nuclear isoform of TCPTP

**Location:** Regulation of IFNG signaling

**Stable identifier:** R-HSA-997326

**Type:** transition

**Compartments:** nucleoplasm

The nuclear isoform of T cell protein tyrosine phosphatase (TC-PTP) referred as TC45 (or TC-PTPa) dephosphorylates p-STAT1 dimer in the nucleus. It can also dephosphorylate p-JAK1/3 in IFNG stimulated cells.

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