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: 74

This document contains 2 pathways and 12 reactions (see Table of Contents)

https://reactome.org
Interferon-gamma signaling

Stable identifier: R-HSA-877300

Interferon-gamma (IFN-gamma) belongs to the type II interferon family and is secreted by activated immune cells—primarily T and NK cells, but also B-cells and APC. INFG exerts its effect on cells by interacting with the specific IFN-gamma receptor (IFNGR). IFNGR consists of two chains, namely IFNGR1 (also known as the IFNGR alpha chain) and IFNGR2 (also known as the IFNGR beta chain). IFNGR1 is the ligand binding receptor and is required but not sufficient for signal transduction, whereas IFNGR2 do not bind IFNG independently but mainly plays a role in IFNG signaling and is generally the limiting factor in IFNG responsiveness. Both IFNGR chains lack intrinsic kinase/phosphatase activity and thus rely on other signaling proteins like Janus-activated kinase 1 (JAK1), JAK2 and Signal transducer and activator of transcription 1 (STAT-1) for signal transduction. IFNGR complex in its resting state is a preformed tetramer and upon IFNG association undergoes a conformational change. This conformational change induces the phosphorylation and activation of JAK1, JAK2, and STAT1 which in turn induces genes containing the gamma-interferon activation sequence (GAS) in the promoter.

Literature references


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The IFNG receptor complex is a pre-assembled entity, as constitutive interactions are seen between IFNGR1 and IFNGR2, and between two IFNGR2 chains in the absence of ligand IFNG. JAK1 and JAK2 constitutively associate with the intracellular domains of the subunits of the IFNG receptor complex, providing it with tyrosine kinase activity. In unstimulated cells JAK1 preferentially associates with IFNGR1 and while JAK2 associates with IFNGR2 chains. JAK1 enhances the interaction between IFNGR1 and IFNGR2 chains, and thus has a major role in the pre-assembly of the IFNGR complex, in contrast the kinase activity of JAK2 is required to observe any signaling by IFNG.

IFNG binds directly to both the receptor chains IFNGR1 and IFNGR2. IFNGR1 is a high affinity receptor and binds directly to IFNG whereas IFNGR2 binds to IFNG in presence of IFNGR1. According to Krause et al. model IFNG binds to IFNGR1 chains first and then IFNGR2 chains interact with the IFNGR1:IFNG:IFNGR1 complex.

Followed by: Phosphorylation of JAK2

**Literature references**


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Janus Kinase 2 (JAK2) binds and is inhibited by several small molecule drugs (Clark et al. 2014, Fridman et al. 2010, Hanan et al. 2012). The Janus kinases (JAKs) are a family of intracellular tyrosine kinases that play an essential role in the signaling of numerous cytokines that have been implicated in the pathogenesis of inflammatory diseases. Drugs that inhibit these kinases such as baricitinib, tofacitinib and ruxolitinib are thus plausible candidates for treatment of severe host inflammatory reactions to viral infection (Peterson et al. 2020, Richardson et al. 2020).

Literature references


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Phosphorylation of JAK2

Location: Interferon gamma signaling

Stable identifier: R-HSA-873919

Type: transition

Compartments: cytosol, plasma membrane

IFN-gamma binding to the receptor complex, induces JAK2 autophosphorylation and activation. Like all protein tyrosine kinases (PTKs) JAK2 activity also depends on the phosphorylation of tandem tyrosine residues within the activation loop that results in the removal of the activation loop from the active site. Multiple phosphorylation sites have been identified in JAK2 (tyrosines 221, 570, 868, 966, 972, 1007 and 1008) of which phosphorylation of tyrosine 1007 is essential for kinase activity. Tyrosine 1007 is in the activation loop and phosphorylation allows access of the catalytic loop to the ATP in the ATP binding domain. Of all the predicted phosphorylation sites only tyrosine 1007 is represented in the reaction.

Preceded by: IFNG dimer binds IFNGR

Followed by: Transphosphorylation of JAK1

Literature references


Argetsinger, LS., Stuckey, JA., Robertson, SA., Koleva, RL., Cline, JM., Marto, JA. et al. (2010). Tyrosines 868, 966, and 972 in the kinase domain of JAK2 are autophosphorylated and required for maximal JAK2 kinase activity. Mol Endocrinol, 24, 1062-76.


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The initial phosphorylation of JAK1 and JAK2 is mediated by JAK2. Autophosphorylated JAK2 may transphosphorylate JAK1 bound to IFNGR1 chain. Tyrosine 1033 in the activation loop of the JAK1 kinase domain may be the target for transphosphorylation (phosphorylation site mentioned here is based on sequence similarity with all the other JAK kinases).

**Preceded by:** Phosphorylation of JAK2

**Followed by:** Phosphorylation of IFNGR1 by JAK kinases

**Literature references**

Phosphorylation of IFNGR1 by JAK kinases

Location: Interferon gamma signaling

Stable identifier: R-HSA-873924

Type: transition

Compartments: cytosol, plasma membrane

The phosphorylated active JAK1 kinase inturn phosphorylates tyrosine residue 440 on each of the IFNGR1 chains to form two adjacent docking sites for the latent STAT1 SH2 domains.

Preceded by: Transphosphorylation of JAK1

Followed by: Binding of STAT1 to p-IFNGR1

Literature references


Binding of STAT1 to p-IFNGR1

**Location:** Interferon gamma signaling

**Stable identifier:** R-HSA-873921

**Type:** binding

**Compartments:** cytosol, plasma membrane

The phosphorylated tyrosine residue 440 in the 440YDKPH444 motif on IFNGR1 chain serves as a docking site and recruits STAT1, an SH2 domain-containing transcription factor to the functional receptor unit.

**Preceded by:** Phosphorylation of IFNGR1 by JAK kinases

**Followed by:** Phosphorylation of STAT1 by JAK kinases

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Phosphorylation of STAT1 by JAK kinases

Location: Interferon gamma signaling

Stable identifier: R-HSA-873922

Type: transition

Compartments: cytosol, plasma membrane

STAT1 pair recruited to the receptor complex is phosphorylated near the C-terminus at residue Y701, probably by JAK2. This phosphorylation enables the STAT1 homodimer formation which is further phosphorylated on residue S727.

Preceded by: Binding of STAT1 to p-IFNGR1

Followed by: Phosphorylation of STAT1 at Ser727

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Phosphorylation of STAT1 at Ser727

**Location:** Interferon gamma signaling

**Stable identifier:** R-HSA-909552

**Type:** transition

**Compartments:** cytosol, plasma membrane

Kinases like Protein kinase C delta (PKC-delta) and Calcium/calmodulin-dependent protein kinase II (CaMK II ) can phosphorylate STAT1 at serine 727 (S727). This phosphorylation is not required for STAT1 homodimer formation, nuclear translocation and DNA binding. However, it is essential for the full transcriptional activation of STAT1.

**Preceded by:** Phosphorylation of STAT1 by JAK kinases

**Followed by:** Release of STAT1 dimer from active receptor unit

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Release of STAT1 dimer from active receptor unit

Location: Interferon gamma signaling

Stable identifier: R-HSA-873927

Type: dissociation

Compartments: cytosol, plasma membrane

The phosphorylated STAT1 on IFNGR1 chains homodimerize through reciprocal SH2-phosphotyrosine interactions to form p-STAT1 homodimer called gamma-activated-factor (GAF). This phosphorylated STAT1 homodimer disassociates from the receptor complex and translocates to the nucleus.

Preceded by: Phosphorylation of STAT1 at Ser727

Followed by: Translocation of STAT1 dimer to nucleus

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Translocation of STAT1 dimer to nucleus

**Location:** Interferon gamma signaling

**Stable identifier:** R-HSA-873917

**Type:** transition

**Compartments:** nuclear envelope

Released GAF complex translocates to the nucleus and binds to the gamma-activated sequence (GAS) element present in the promoters of IFNG-regulated genes and induces the transcription of IFNG-responsive genes.

**Preceded by:** Release of STAT1 dimer from active receptor unit

**Followed by:** GAF binds the GAS promoter elements in the IFNG-regulated genes

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GAF binds the GAS promoter elements in the IFNG-regulated genes

**Location:** Interferon gamma signaling

**Stable identifier:** R-HSA-1031713

**Type:** binding

**Compartments:** nucleoplasm

GAF transcription factor translocated into nucleus binds to defined DNA sequence called GAS (gamma activated sequence) elements in the promoters of IFN-gamma responsive elements and initiate transcription.

**Preceded by:** Translocation of STAT1 dimer to nucleus

**Followed by:** Expression of IFNG-stimulated genes

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Expression of IFNG-stimulated genes

Location: Interferon gamma signaling

Stable identifier: R-HSA-1031716

Type: omitted

Compartments: cytosol

IFN-gamma stimulates gene expression of about 200 genes which include the primary response genes like IRFs, Fc-gamma receptor (FCGR), GBP (guanylate-binding proteins) and also major histocompatibility complex (MHC) class I and class II molecules, proteins involved in antigen presentation, antiviral proteins like PKR, OAS proteins etc. A wonderful list of most of the IFN-gamma inducible proteins with corresponding literature are mentioned in the review article and the supplementary document by Boehm et al 1997.

Preceded by: GAF binds the GAS promoter elements in the IFNG-regulated genes

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Regulation of IFNG signaling

Location: Interferon gamma signaling

Stable identifier: R-HSA-877312

At least three different classes of negative regulators exist to control the extent of INFG 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.

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