Interferon alpha/beta signaling

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30/01/2019
**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: 67

This document contains 2 pathways and 15 reactions (see Table of Contents)
Interferon alpha/beta signaling

Stable identifier: R-HSA-909733

Type I interferons (IFNs) are composed of various genes including IFN alpha (IFNA), beta (IFNB), omega, epsilon, and kappa. In humans the IFNA genes are composed of more than 13 subfamily genes, whereas there is only one IFNB gene. The large family of IFNA/B proteins all bind to a single receptor which is composed of two distinct chains: IFNAR1 and IFNAR2. The IFNA/B stimulation of the IFNA receptor complex leads to the formation of two transcriptional activator complexes: IFNA-activated-factor (AAF), which is a homodimer of STAT1 and IFN-stimulated gene factor 3 (ISGF3), which comprises STAT1, STAT2 and a member of the IRF family, IRF9/P48. AAF mediates activation of the IRF-1 gene by binding to GAS (IFNG-activated site), whereas ISGF3 activates several IFN-inducible genes including IRF3 and IRF7.

Literature references


Editions

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<tr>
<th>Date</th>
<th>Event</th>
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IFN alpha/beta binds to IFNAR2

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909720

Type: binding

Compartments: extracellular region, plasma membrane

The ligand IFNalpha/beta (IFNA/B), interacts independently with the two interferon receptor subunits. Based on detailed binding studies with the extracellular domains of the receptor subunits tethered onto solid-supported membranes, a two-step binding mechanism was experimentally confirmed, where the ligand binds first to one of the receptor subunits and then recruits the second subunit (Gavutis et al. 2005). The efficiency of recruitment of the IFNA receptor subunits by the IFN ligand depends on the absolute and relative concentration of the receptor subunits.

IFNAR2 chain constitutively associates with JAK1 kinase in its cytoplasmic domain. In addition IFNAR2 also binds STAT2 in a constitutive manner and this interaction is biochemically different from the interaction of STAT2 with phosphorylated IFNAR1. Although this interaction facilitates the recruitment of STAT2 to the receptors, the biological significance of this constitutive STAT2 interaction to IFNAR2 remains unclear (Nguyen et al, 2002). IFNAR2 not only associates with STAT2, but also with STAT1 and this binding of STAT1 to IFNAR2 depends on the presence of STAT2 but not vice versa.

IFNA/B may first bind to the high-affinity subunit IFNAR2 and subsequently recruit IFNAR1 in a transient fashion (Lamken et al. 2004). Different type I IFNs interact differently with the two IFNA receptor (IFNAR) subunits, IFNB generates a more stable signaling complex than IFNA subtypes. The interaction between IFNalpha2 (IFNA2) and IFNAR2 has an affinity in the nM range, whereas the affinity of the interaction with INFB is about tenfold tighter.

Followed by: Recruitment of IFNAR1

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Recruitment of IFNAR1

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909724

Type: binding

Compartments: plasma membrane

The extracellular domain of IFNAR1 is atypical, consisting of a tandem array of four FNIII domains and the first three N-terminal FNIII domains are involved in ligand recognition. IFNAR1 is recruited to the binary complex (IFNA/B:IFNAR2) on the membrane to form the ternary complex (IFNA/B:IFNAR2:IFNAR1). TYK2 kinase is pre-associated with IFNAR1 and JAK1 with IFNAR2. The binding of IFNA/B to IFNA receptors brings these JAK kinase together, allowing cross-phosphorylation and kinase activation.

Preceded by: IFN alpha/beta binds to IFNAR2

Followed by: Activation of JAK kinases

Literature references


Editions

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Activation of JAK kinases

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909729

Type: transition

Compartments: cytosol, plasma membrane

The two chains IFNAR1 and IFNAR2 are pre-associated with the JAK kinases TYK2 and JAK1, respectively. Receptor heterodimerization brings these JAK kinases into close proximity and they are activated by reciprocal trans-phosphorylation. Tyr-1054 and Tyr-1055 within the activation loop of TYK2 sub-domain VII are critical for TYK2 activation. For JAK1 two tyrosine residues within the KEYY motif (Tyr 1034 and Tyr 1035) of the kinase domain are thought to be transphosphorylated.

Preceded by: Recruitment of IFNAR1

Followed by: Phosphorylation of INFAR1 by TYK2

Literature references


Phosphorylation of INFAR1 by TYK2

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909730

Type: transition

Compartments: cytosol, plasma membrane

TYK2 functions as part of a receptor complex to trigger intracellular signaling in response to IFNA/B. TYK2 bound to IFNAR1 subunit is activated in response to IFNA/B treatment and this in turn phosphorylates two tyrosine residues Y466 and Y481 in the juxta-membrane region of IFNAR1.

Preceded by: Activation of JAK kinases

Followed by: Recruitment of STAT2 to p-IFNAR1

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Recruitment of STAT2 to p-IFNAR1

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909719

Type: binding

Compartments: cytosol, plasma membrane

Phosphorylated tyrosine residue 466 on IFNAR1 acts as a docking site for STAT2. Latent STAT2 is recruited to this phosphotyrosine residue via its SH2 domain.

Preceded by: Phosphorylation of INFAR1 by TYK2

Followed by: Phosphorylation of STAT2

Literature references

Yan, H., Krishnan, K., Greenlund, AC., Gupta, S., Lim, JT., Schreiber, RD. et al. (1996). Phosphorylated interferon-alpha receptor 1 subunit (IFNaR1) acts as a docking site for the latent form of the 113 kDa STAT2 protein. EMBO J, 15, 1064-74.

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Phosphorylation of STAT2

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909732

Type: transition

Compartments: cytosol, plasma membrane

STAT2 recruited to the IFNAR1 subunit then becomes tyrosine phosphorylated on residue 690 by TYK2 kinase. This phosphotyrosine provides a docking site for recruitment of STAT1 to IFNAR1, which is then tyrosine phosphorylated and activated.

Preceded by: Recruitment of STAT2 to p-IFNAR1

Followed by: Formation of p-STAT1 homodimer, Phosphorylation of STAT1

Literature references


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Phosphorylation of STAT1

**Location:** Interferon alpha/beta signaling

**Stable identifier:** R-HSA-909726

**Type:** transition

**Compartments:** cytosol, plasma membrane

Phosphotyrosine on STAT2 acts as docking site for STAT1 molecules. STAT1 binds to phosphorylated STAT2 and this is followed by STAT1 phosphorylation on tyrosine residue 701 (Y701). These STATs recruited to the phosphorylated IFNAR1 form two distinct transcriptional activator complexes, namely, IFN-alpha-activated factor (AAF) and IFN-stimulated gene factor 3 (ISGF3). AAF is a homodimer of STAT1, whereas ISGF3 is a heterotrimeric complex of STAT1, STAT2 and IRF9 (also known as p48 or ISGF3gamma) (Honda et al. 2005).

**Preceded by:** Phosphorylation of STAT2

**Followed by:** Release of p-STAT2:p-STAT1 dimer

**Literature references**


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The phosphorylated STAT2:STAT1 heterodimers thus formed disassociate from the IFNAR1 subunit and translocates to the nucleus.

**Preceded by:** Phosphorylation of STAT1

**Followed by:** Interaction of IRF9 with p-STAT2:p-STAT1

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Interaction of IRF9 with p-STAT2:p-STAT1

**Location:** Interferon alpha/beta signaling

**Stable identifier:** R-HSA-909725

**Type:** binding

**Compartments:** cytosol

The phosphorylated STAT2:STAT1 heterodimer associates with interferon-regulating factor 9 (IRF9) to form the interferon-stimulated gene factor 3 (ISGF3) complex.

**Preceded by:** Release of p-STAT2:p-STAT1 dimer

**Followed by:** Translocation of ISGF3 complex to nucleus

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Translocation of ISGF3 complex to nucleus

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909721

Type: transition

Compartments: nuclear envelope

The resultant ISGF3 trimeric complex then migrates to the nucleus and binds to interferon-stimulated response elements (ISREs). IRF9 is the DNA binding part of this ISGF3 complex. These ISREs are present in the promoters of a subset of ISGs (interferon stimulated genes), such as promyelocytic leukemia (PML), ISG15 ubiquitin-like modifier (ISG15), interferon-induced protein with tetratricopeptide repeats 2 (ISG54) and interferon alpha-inducible protein 6 (IFI6) to elicit an antiviral response.

Preceded by: Interaction of IRF9 with p-STAT2:p-STAT1

Followed by: ISGF3 binds the ISRE promoter elements in IFN-stimulated genes

Literature references


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Formation of p-STAT1 homodimer↗

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-909718

Type: transition

Compartments: cytosol, plasma membrane

Under certain conditions type I IFNs, IFNA/B are able to activate genes through a second STAT-based signaling cascade enabling the formation of p-STAT1:p-STAT1 homodimers called IFNA-activated-factor (AAF).

Preceded by: Phosphorylation of STAT2

Followed by: Translocation of p-STAT1:p-STAT1 dimer to nucleus

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Translocation of p-STAT1:p-STAT1 dimer to nucleus

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-913529

Type: transition

Compartments: nuclear envelope

IFNA-activated-factor (AAF) translocates to nucleus and then promotes the expression of a distinct set of gamma activated sequence (GAS)-driven genes like IRF1. IRF1, in turn, induces the transcription of ISG15, ISG54 and IFI6 genes. This second pathway of STAT1 homodimer formation is primarily activated by IFNG and is likely to account for some of the functional overlap between type I and type II IFNs.

Preceded by: Formation of p-STAT1 homodimer

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ISGF3 binds the ISRE promoter elements in IFN-stimulated genes

**Location:** Interferon alpha/beta signaling

**Stable identifier:** R-HSA-1015699

**Type:** binding

**Compartments:** nucleoplasm

Effects of IFNs result from induction of a subset of genes, called IFN stimulated genes (ISGs). These ISGs are mainly implicated in anti-viral, anti-angiogenic, immunomodulatory, cell cycle inhibitory effects and apoptotic functions. All IFNA/B-stimulated genes have a conserved region of about 15bp in their promoter called the Interferon Stimulation Response Element (ISRE). The transcription factor ISGF3 binds to this ISRE and induces the transcription of these genes by IFN.

**Preceded by:** Translocation of ISGF3 complex to nucleus

**Followed by:** Expression of IFN-induced genes

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Expression of IFN-induced genes

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-1015702

Type: omitted

Compartments: nucleoplasm

Around 300 IFN-induced genes have been identified from different oligonucleotide microarray studies in melanoma (WM9) and fibrosarcoma (HT1080) cell lines as well as from human dendritic cells treated with IFN. Only the proteins which are well studied and their function characterized are represented here.

Preceded by: ISGF3 binds the ISRE promoter elements in IFN-stimulated genes

Literature references


Editions

2010-07-07 Authored, Edited Garapati, P V.
2010-08-17 Reviewed Schindler, C., Abdul-Sater, AA.
There are several proteins and mechanisms involved in controlling the extent of ligand stimulation of IFNA/B signaling. These mechanisms can effect every step of the IFNA/B cascade. Dephosphorylation of JAK and STAT by SHP protein phosphatases, inhibition of STAT function in the nucleus by protein inhibitors of activated STATs (PIAS) proteins, inhibition of tyrosine kinase activity of JAKs by SOCS as well as inhibition of JAK and IFNAR2 interaction by UBP43 are few of the negative regulation mechanisms in controlling type I IFN signaling.

**Literature references**


ABCE1 binds RNASEL, inhibiting it

Location: Interferon alpha/beta signaling

Stable identifier: R-HSA-5223305

Type: binding

Compartments: mitochondrial matrix

2-5A-dependent ribonuclease (RNASEL) is an endoribonuclease that is activated in the interferon (IFN) antiviral response. Its anti-viral effects are probably a combination of induction of apoptosis, cleavage of viral mRNA and induction of other anti-viral genes. ATP-binding cassette sub-family E member 1 (ABCE1, aka RNase L inhibitor, RLI) directly interacts with RNASEL and inhibits its endoribonuclease activity, thus antagonising the anti-viral effect of the IFN-regulated 2-5A/RNase L pathway (Martinand et al. 1998, Martinand et al. 1999, Le Roy et al. 2001).

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</tbody>
</table>
Table of Contents

Introduction 1

Interferon alpha/beta signaling 2

IFN alpha/beta binds to IFNAR2 3

Recruitment of IFNAR1 5

Activation of JAK kinases 6

Phosphorylation of INFAR1 by TYK2 7

Recruitment of STAT2 to p-IFNAR1 8

Phosphorylation of STAT2 9

Phosphorylation of STAT1 10

Release of p-STAT2:p-STAT1 dimer 11

Interaction of IRF9 with p-STAT2:p-STAT1 12

Translocation of ISGF3 complex to nucleus 13

Formation of p-STAT1 homodimer 14

Translocation of p-STAT1:p-STAT1 dimer to nucleus 15

ISGF3 binds the ISRE promoter elements in IFN-stimulated genes 16

Expression of IFN-induced genes 17

Regulation of IFNA signaling 18

ABCE1 binds RNASEL, inhibiting it 19

Table of Contents 20